

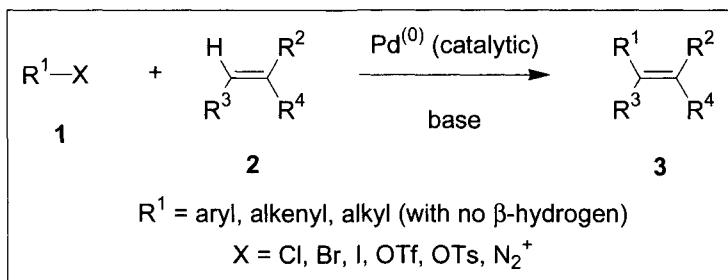
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## 1.1.1 Heck Reaction

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### 1.1.1.1 Description

The Heck reaction is the palladium-catalyzed alkenylation or arylation of olefins.<sup>1-24</sup> It has become one of the most widely used C–C bond forming tools in organic synthesis.

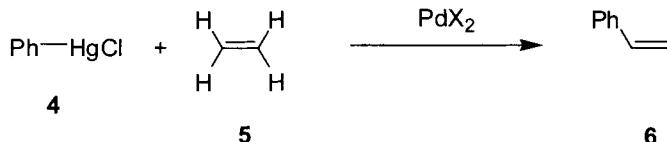


An extensive range of functional groups and substitution patterns on the olefin **2** are tolerated and aryl, alkenyl and some alkyl (lacking  $\beta$ -hydrogen atoms) electrophiles **1** are suitable reaction partners. The active catalyst is generated *in situ* from a variety of available palladium(0) or palladium(II) precatalysts ( $\text{Pd}(\text{OAc})_2$ ,  $\text{Pd}_2(\text{dba})_3$ , *etc.*). A large number of ligands have been employed including phosphines, palladacycles and carbenes and even “ligand-free” conditions are commonly exploited.<sup>16</sup> By using enantiomerically pure chiral ligands, the reaction can be rendered stereoselective (at centres adjacent to the newly formed olefin). A stoichiometric amount of base is needed, but in practice 3-5 molar equivalents are often used. Tertiary amine bases (for example  $\text{Et}_3\text{N}$  or PMP) or inorganic bases such as  $\text{K}_2\text{CO}_3$  can be employed. Halide-scavenging additives (such as  $\text{Ag}_3\text{PO}_4$ ) can be useful for aryl/alkenyl halide substrates, especially in the case of asymmetric Heck reactions. The reaction tolerates a range of solvents, however polar aprotic solvents such as DMF or NMP are most frequently utilized. The reaction most commonly takes place at elevated temperatures.

### 1.1.1.2 Historical Perspective

In the early 1970s, T. Mizoroki and R. F. Heck independently discovered that aryl, benzyl and styryl halides react with olefinic compounds and elevated temperature in the presence of a hindered amine base and a catalytic amount

of palladium.<sup>25,26</sup> This was based on the previous work of Heck when he was at the Hercules Powder Company, Delaware in 1968. He discovered that when palladium(II) chloride (interestingly the use of palladium was inspired by a colleague studying the Wacker reaction) was dissolved in acetonitrile with phenylmercuric chloride (**4**) and ethylene gas (**5**), the presumed transient phenylpalladium chloride rapidly absorbed one equivalent of ethylene to produce styrene (**6**) in high yield.<sup>27</sup>

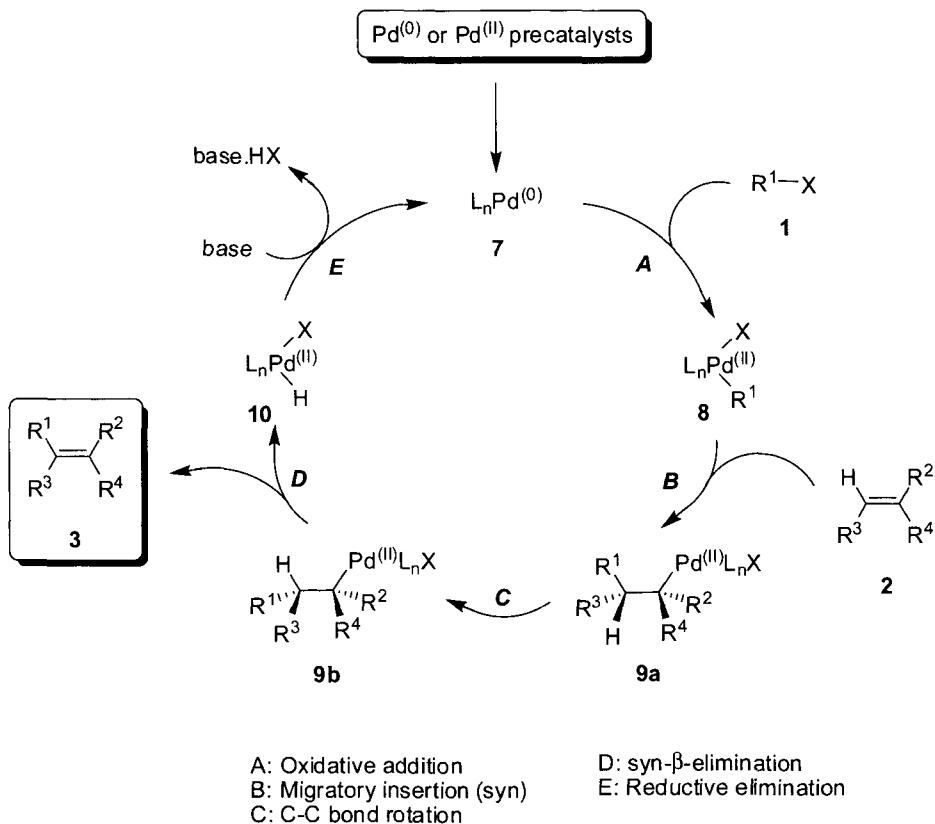


As reports began to appear on the formation of halo(aryl)palladium-phosphine complexes, Heck hypothesized that these intermediates could replace the arylmercurial-palladium combination. Crucially, he also reasoned that the use of a base to quench the hydrogen halide generated would render the reaction catalytic. In the 1970s the use of palladium was considered exotic and the reaction a mere curiosity, which meant its importance was underestimated for decades. In 1982, Heck published a review that contained all known examples in a mere 45 pages.

Today however, the paramount importance of organopalladium chemistry has propelled the Heck reaction into one of the most widely used catalytic C–C bond forming reactions. This was driven by its operational simplicity, unprecedented functional group compatibility and wide applicability. Indeed, from materials science to enantioselective organic synthesis, nearly every sub-discipline of modern organic chemistry has embraced the Heck reaction. It is hard to overstate its importance and in fact, this reaction may also be considered as a forerunner to all other widely used palladium-catalyzed couplings (Stille, Suzuki, Negishi, Hiyama, *etc.*). Perhaps the greatest social impact of the Heck reaction has been its use in the coupling of alkynes to aryl halides; a reaction which was used to couple fluorescent dyes to DNA bases, allowing the automation of DNA sequencing and the elucidation of the human genome.

### 1.1.1.3 Mechanism

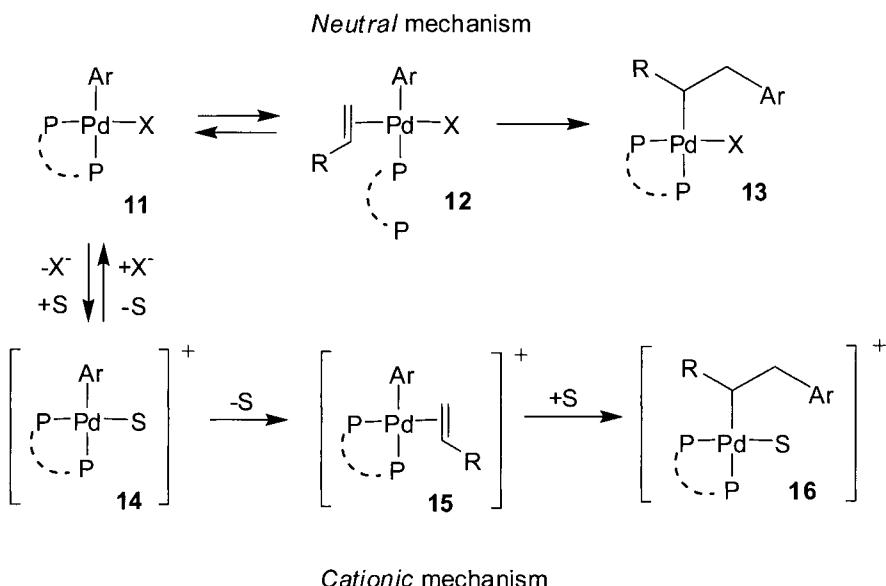
The general mechanism for the Heck reaction has been accepted for many years however numerous recent studies have shown the active catalytic species to vary dramatically depending on the ligands, reaction conditions and substrates.



formal charge on the palladium and therefore several more detailed mechanistic scenarios have been reported.

### Cationic versus “Neutral” Pathways

Historically, the Heck reaction was the functionalization of olefins by aryl iodides, bromides, aroyl chlorides, or the corresponding vinyl halides, carried out without ligands in the case of aryl iodides or in the presence of monodentate phosphines (e.g.,  $\text{Ph}_3\text{P}$ ).<sup>2</sup> Under these reaction conditions a square planar palladium(II) oxidative addition complex with a weak Pd–PR<sub>3</sub> bond (or Pd–solvent in the case of iodides) and a strong Pd–X bond is generated.<sup>6</sup> Dissociation of one of these neutral ligands gives a free coordination site to which the alkene can bind. In this context, Heck reported that chelating phosphines “in general do not form useful catalysts”.<sup>31</sup> Indeed, in the case of reactions employing aryl halide substrates and bidentate ligands, suppression of the reaction is observed due to competitive coordination of the chelating ligand, shifting the equilibrium of **11/12** to the left.<sup>6</sup>

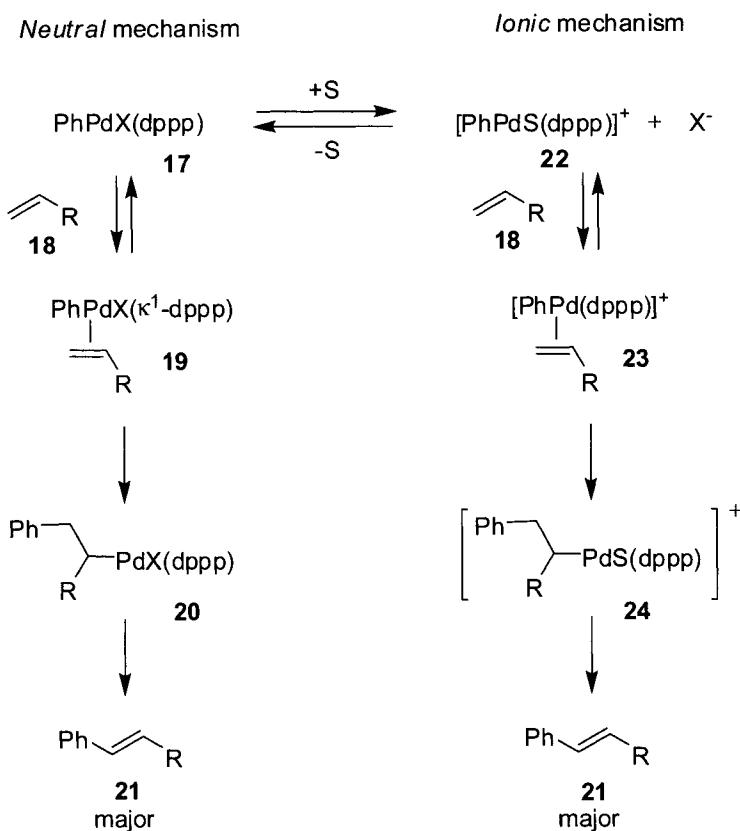


The cationic reaction manifold was first reported independently by Capri<sup>32</sup> and Hayashi<sup>33</sup> to describe the Heck reaction of aryl triflates in the presence of palladium-diphosphine catalytic systems. This scenario arises from the lability of the Pd–OTf bond present in complex **11** ( $X = \text{OTf}$ ).<sup>6</sup> Dissociation of the anionic counterion ( $^-\text{OTf}$ ) affords cationic complex **14** with a vacant coordination site (transiently occupied by a solvent molecule,

S), thus allowing binding of the olefin without decomplexation of either phosphorus atom of the bidentate ligand. The ability to use chelating ligands was crucial to the development of asymmetric Heck reactions employing chiral diphosphines, first pioneered independently by Shibasaki and Overman in 1989.<sup>17</sup> Partial dissociation of the chiral bidentate ligand under “neutral” conditions would diminish the rigidity of the ligand and could lead to erosion of the enantioselectivity. As well as the use of aryl (alkenyl) triflates, aryl (alkenyl) halides can be used in the presence of Ag(I) or Tl(I) additives. These additives mediate halide extraction from complex **11**,<sup>17</sup> facilitating the cationic pathway. Furthermore, the reactivity of complexes **11** and **14** depends on the charge density of the unsaturated system. Competition studies have shown electron-poor olefins (good  $\pi$ -acceptors and poor  $\sigma$ -donors) react faster with neutral complex **11**, whereas electron-rich olefins (poor  $\pi$ -acceptors and good  $\sigma$ -donors) react faster with cationic complex **14**.<sup>6</sup>

Cabri has used the cationic pathway to explain the regioselectivity of the Heck reaction. Moreover, the use of triflates or halide scavenging additives (cationic conditions) in the asymmetric Heck reaction has become widespread. However, recent studies have shown the employment of either “neutral” conditions or cationic conditions may not lead to the expected reaction pathway. In 1992, Overman reported a Pd/BINAP catalyzed Heck cyclization of aryl halides in high enantioselectivity *without halide scavengers* (i.e. “neutral” conditions).<sup>34</sup> Since monodentate analogues used to mimic a partially dissociated BINAP gave products of low enantiopurity, it was rationalized that both phosphorus atoms remain coordinated to the palladium in the enantio-discriminating step, despite the “neutral” reaction conditions. Whilst Overman has suggested the reaction proceeds via an associative process involving a pentacoordinated palladium species, theoretical and experimental data has largely dismissed this due to high activation energies of the subsequent migratory insertion.<sup>17</sup>

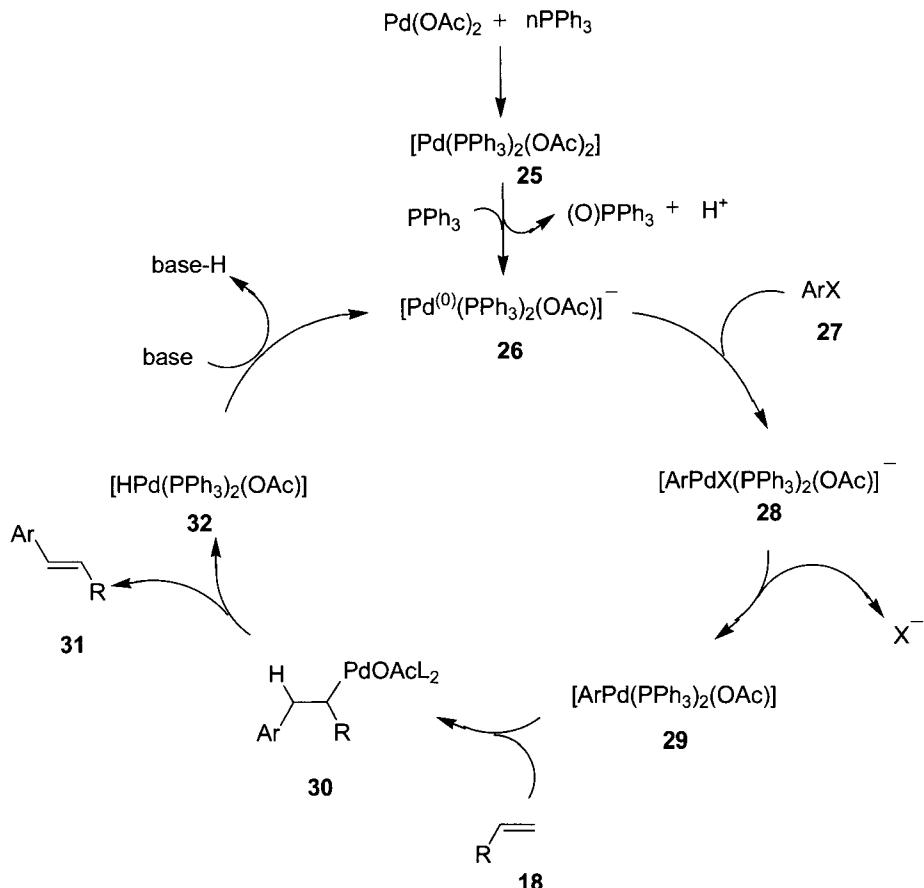
Recent work by Amatore and Jutand on the Heck reaction of aryl palladium complexes ligated by 1,3-bis(diphenylphosphino)propane (dppp) offers some fascinating new insight into the “neutral” *versus* cationic pathways.<sup>30</sup> Based on kinetic studies, they suggest the reactions of electron-rich alkenes (isobutyl vinyl ether) *always* proceed via a cationic mechanism, despite the use of so-called “neutral” conditions. The ability of the base to deliver anions (acetate, carbonate) is often overlooked, and regardless of the medium cationic complex **22** is always the most intrinsically reactive. As such, the regioselectivity of the Heck reaction of electron rich alkenes, as well as asymmetric Heck reactions under “neutral” conditions can be rationalized by considering the rates and equilibria constants of all palladium species under a given set of reaction conditions (concentration, ionic strength of the solvent, additives, counterions, substrates, *etc.*).<sup>30</sup>



### Anionic Pathways

In many palladium-mediated reactions, the exact role of the precatalyst is ignored and simply seen as a means to provide the active palladium(0) catalytic species. However, studies by Amatore and Jutand have shown the counterions of the precatalyst can be non-innocent and dramatically influence the reaction mechanism.<sup>35</sup>  $\text{Pd(OAc)}_2$  is the most common precatalyst used in the Heck reaction and previous studies have considered the acetate anion as an innocent bystander. Experimental evidence now suggests that the  $\text{Pd(OAc)}_2/\text{phosphine}$  systems initiate a catalytic cycle involving anionic palladium(0) and palladium(II) complexes.<sup>35</sup> The active catalyst generated is anionic species **26**, which undergoes oxidative addition to afford a pentacoordinated palladium species **28**, where both the acetate and iodide anions remain ligated to the palladium(II) centre. This short-lived species rapidly loses the halide ion to yield a new palladium(II) complex, *trans*- $[\text{ArPd(OAc)}(\text{PPh}_3)_2]$  (**29**). The increased reactivity of complex **29** compared to  $[\text{ArPdI}(\text{PPh}_3)_2]$  has been attributed to the bidentate nature of the acetate ligand, which may assist in phosphine release to open a coordination site for

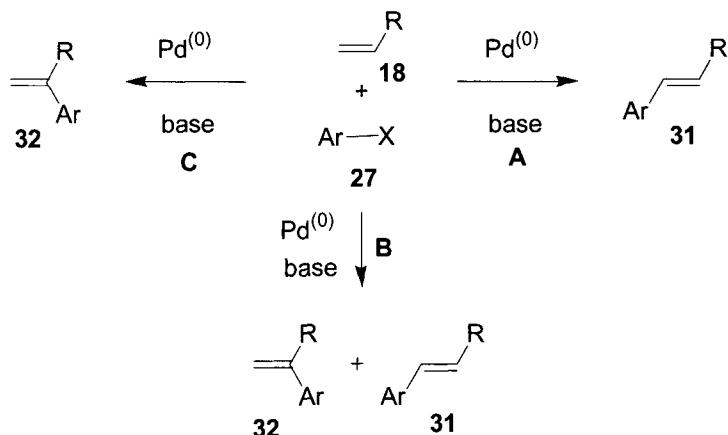
the alkene substrate. Migratory insertion, followed by  $\beta$ -hydride elimination provides olefin **31** and hydridopalladium complex **32**. Base-mediated conversion to palladium(0) species **26** completes the catalytic cycle. This proposed mechanism not only details the crucial role of acetate ions in many Heck reactions, but also provides an explanation of the beneficial effects of additives such as KOAc in certain cases.<sup>17</sup>



Related studies on the formation of active catalytic species' derived from Pd(OAc)<sub>2</sub> and bidentate phosphine ligands has also been reported.<sup>36</sup> A stable palladium(0) complex is formed in the presence of Pd(OAc)<sub>2</sub>, dppp, water and triethylamine. In this case oxidative addition to PhI gives the cationic complex **[PhPd(dppp)(dppp(O))]<sup>+</sup>**, in which the oxidized dppp(O) ligand is monodentate. The complex **[PhPd(OAc)(dppp)]** is only formed on addition of excess acetate anions. These results suggest that the anionic

pathway could be relevant to systems employing chelating phosphines, in the presence of acetate additives.

### *Regioselectivity and Stereoselectivity*



A: Where R = Aryl, alkyl,  $\text{CO}_2\text{R}$ , CN, etc.

B: Where R = OR,  $\text{NR}_2$ , etc.

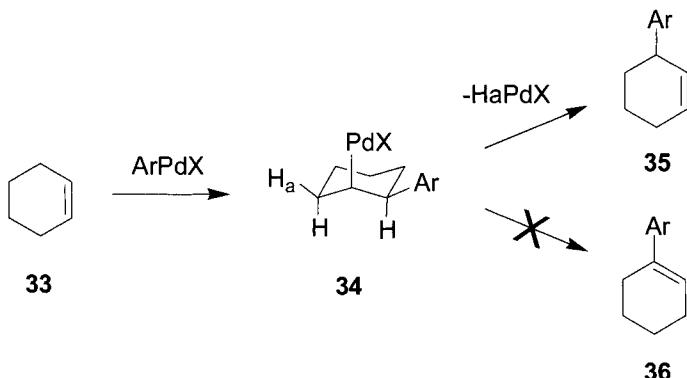
C: Where R = OR,  $\text{NR}_2$ , etc. and X = OTf

The direction of addition of the organopalladium species to the olefin is almost exclusively sterically controlled, i.e. addition will take place at the least substituted carbon to provide the linear product **31**.<sup>2</sup> In the case of alkenes containing electron withdrawing double bonds, once again, addition predominantly gives the linear product **31**. For alkenes appended with electron donating groups however, mixtures are often obtained with the sterically favoured isomer predominating. Work by Cabri using aryl triflates or aryl halides with halide scavengers (cationic pathway) has demonstrated, under these conditions, the branched product **32** is obtained in high selectivity for electron-rich olefins.<sup>6</sup> A recent mechanistic rationale for this effect has been reported.<sup>30</sup> While this is a useful guide, it is possible to override this intrinsic regioselectivity bias using other factors such as chelation control. Electron-rich olefins bearing pendant heteroatom functionalized substituents can form linear products exclusively by exploiting neighbouring-group effects.<sup>23</sup>

Other selectivity issues can arise during  $\beta$ -hydride elimination. If there is more than one  $\text{sp}^3$ -bonded hydrogen atom beta to the palladium group in the olefin adduct, then a mixture of geometric isomers may result.<sup>2</sup> Also, if the hydridopalladium(II) species is not scavenged fast enough by the

base, re-addition to the double bond may occur and once again, a mixture of geometric isomers may result.<sup>16</sup> The hydridopalladium(II) species can also be potentially scavenged by the starting olefin; a process which results in isomerization of the starting alkene and therefore leads to the formation of isomeric Heck products.<sup>16</sup> In certain cases it has been demonstrated that the use of low temperatures<sup>37</sup> or additives such as silver salts can minimize this type of alkene isomerization.<sup>38</sup>

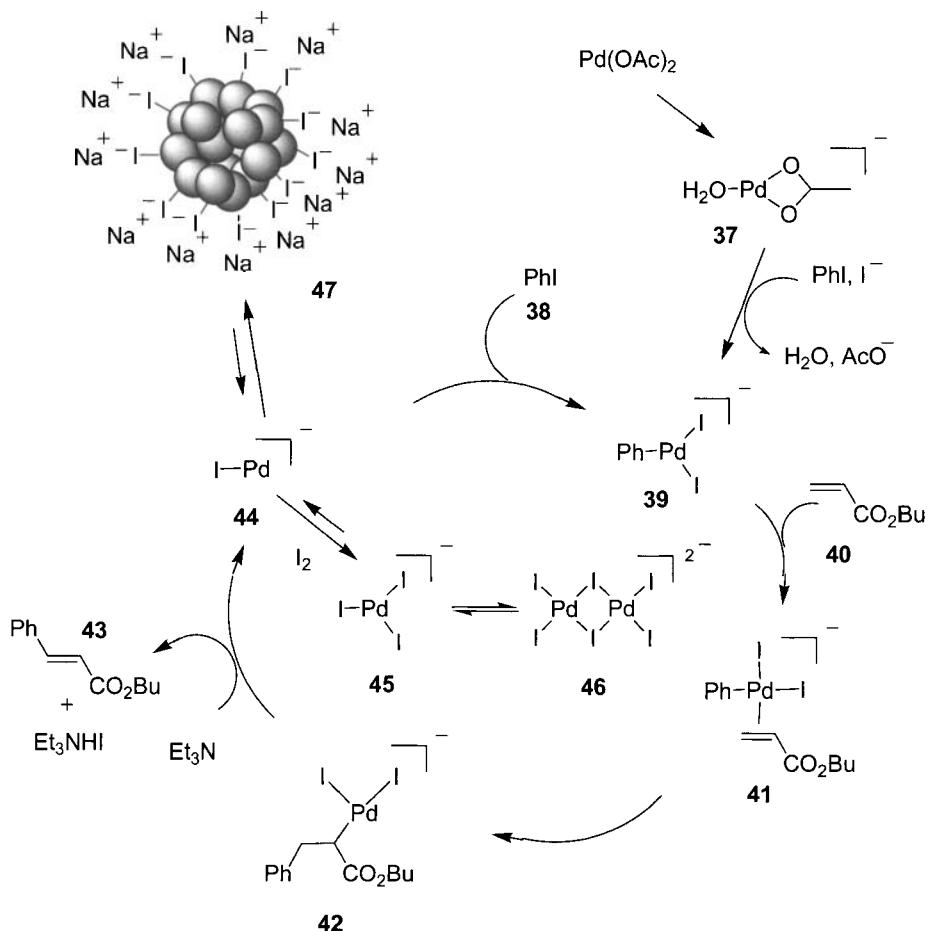
The stereoselectivity of the Heck reaction is governed by *syn*- $\beta$ -hydride elimination. In the majority of cases, the elimination obeys the Curtin–Hammett kinetic control principle<sup>39</sup> and the ratio of *E*- and *Z*-isomers reflects the relative energy of the respective transition states. Unless R (see **18**) is very small (for example CN), the *E*-isomer is predominant and the reaction is highly stereoselective.<sup>16</sup>



Selectivity issues noted above are largely irrelevant for intramolecular reactions. In these cases, regiocontrol in the migratory insertion is largely governed by the size of the ring being formed with *5-exo* and *6-exo* cyclizations being particularly favoured.<sup>17</sup> The use of cyclic olefin substrates also aids the regioselectivity of the reaction. Stereospecific *syn* addition of an arylpalladium species to a cyclic alkene, such as cyclohexene (**33**) produces  $\sigma$ -alkylpalladium(II) intermediate **34**, bearing a single *syn*- $\beta$ -hydrogen (H<sub>a</sub>). *Syn* elimination of this hydrogen provides product **35** exclusively (providing no isomerization of the product occurs under the reaction conditions, *vide supra*).<sup>17</sup> As a notable alternative, Tietze has used allyl silanes to control  $\beta$ -elimination in acyclic systems.<sup>40</sup> The additional elements of control in the intramolecular Heck reaction of cyclic substrates is the reason for its huge success in asymmetric, complex molecule synthesis.<sup>17</sup>

*“Ligand-free” Catalysts*

In some of his original work, Heck demonstrated that the reaction of aryl iodides can be carried out using  $\text{Pd}(\text{OAc})_2$  in the absence of additional ligands.<sup>2</sup> It was subsequently shown by Jeffery that this works particularly well in the presence of tetraalkyl ammonium salts.<sup>7</sup> A detailed mechanism for the “ligand-free” Heck reaction has been reported by de Vries.<sup>24</sup>



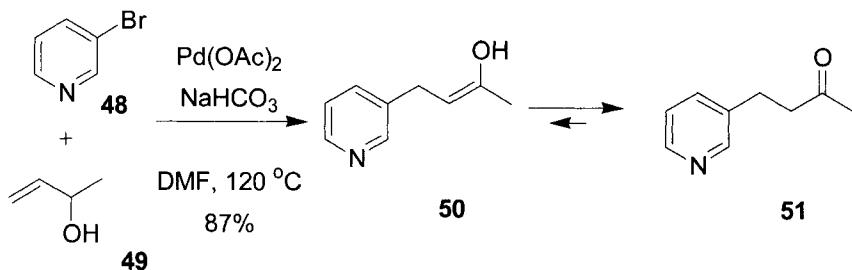
The reaction of iodobenzene (**38**) and olefin **40** was studied under “ligand-free” conditions in the presence of sodium halide additives. As in the generalized mechanism,  $\text{Pd}(\text{OAc})_2$  is reduced to transient palladium(0) complex **37**. This undergoes oxidative addition and ligand exchange to form anionic species **39** (potentially containing additional solvent ligands). Olefin complexation, migratory insertion and  $\beta$ -hydride elimination furnish the

product **43** along with highly underligated species **44**. At this stage complex **44** can do one of three things: (a) react with traces of iodine (arising from aerobic oxidation), to give **45** or dimer **46**; (b) form soluble palladium nanoparticles **47**; or (c) react with iodobenzene (**38**). Since oxidative addition is fast for reactive aryl iodides, (c) is the primary pathway observed. Once the substrate is consumed, rapid formation of palladium nanoparticles **47** occurs, which in turn conglomerate to form palladium black.<sup>24</sup>

For the less-reactive aryl bromides, the situations change. Since oxidative addition of these substrates is slower, formation of palladium nanoparticles is prevalent.<sup>24</sup> If these particles grow beyond a certain size, they precipitate as palladium black and the reaction stops. This is the reason aryl iodides were initially reported to be the only substrates to undergo the Heck reaction under “ligand-free” conditions. Therefore, one explanation of the success of Jeffery’s conditions<sup>7</sup> is that the tetraalkyl ammonium additives stabilize the palladium nanoparticles/colloids, preventing formation of palladium black. Indeed, the pioneering work of Reetz<sup>70</sup> and Hermann<sup>71</sup> has shown that pre-formed stabilized palladium colloids can be used as active catalysts in the reaction. This unifying mechanism can be extended to other high-temperature Heck reactions (solid-supported palladium, palladacycles) in the absence of strongly coordinating ligands.<sup>24</sup> Of perhaps the most experimental significance is that, while most groups have sort stabilizing agents to prevent aggregation of colloidal palladium in these reactions, de Vries has demonstrated that simply maintaining a low substrate/catalyst ratio allows the Heck reaction to compete with colloid formation. Using these conditions he has successfully used aryl bromides under “ligand-free” Heck reactions, in the absence of any additional stabilising agents.<sup>24</sup>

#### 1.1.1.4 Synthetic Utility

In his initial review on the scope of the reaction, Heck reported the use of a variety of relatively simple aryl, heteroaryl and vinyl halides.<sup>2</sup> For example, exposure of bromopyridine **48** to alcohol **49** gave ketone **51** in good yield, following tautomerization of the initial Heck adduct **50**.



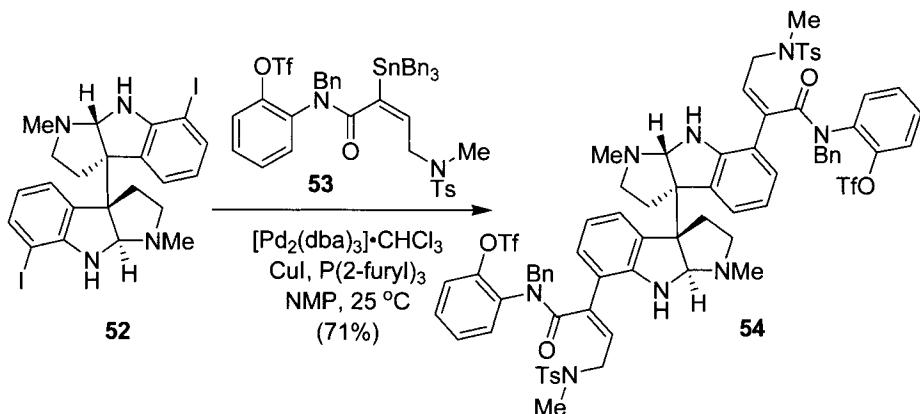
Nowadays however, the Heck reaction is one of the most widely used catalytic C–C bond forming reactions and there are numerous examples in nearly every sub-discipline of modern organic chemistry. The proceeding section will highlight some of the most accomplished uses of this flexible synthetic method.

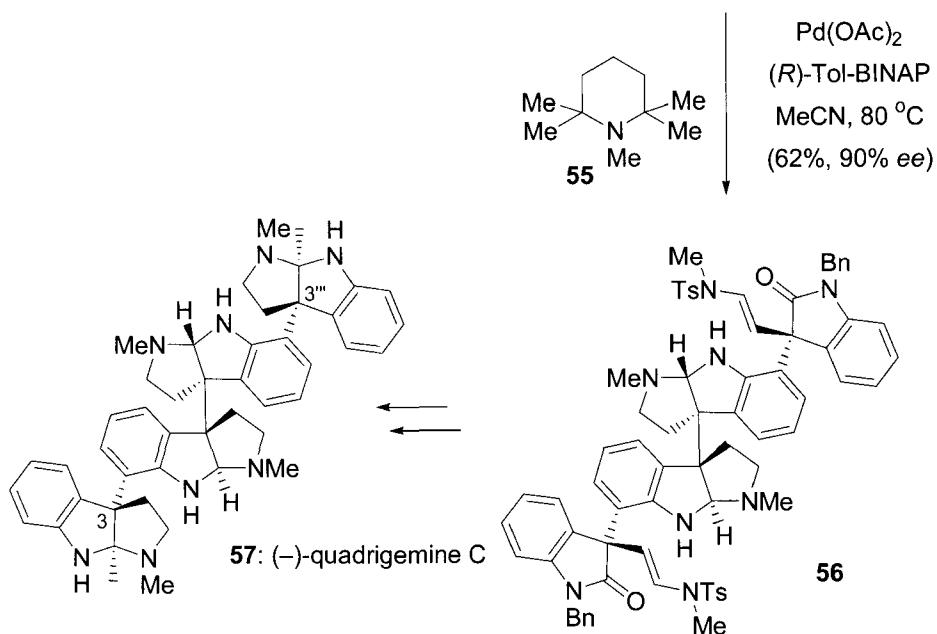
#### *Asymmetric Intramolecular Heck reaction*

Perhaps one of the most challenging aspects of complex molecule synthesis is control of the absolute sense of stereochemistry for the preparation of optically-active compounds. In 1989, Shibasaki and Overman independently reported the first examples of asymmetric Heck reactions.<sup>17</sup> These efforts focused on intramolecular cyclization reactions, which display extra elements of regiocontrol. To date, the asymmetric intramolecular Heck has been exploited in the synthesis of terpenoids, alkaloids and polyketides, forging key tertiary and quaternary stereocentres.<sup>17</sup>

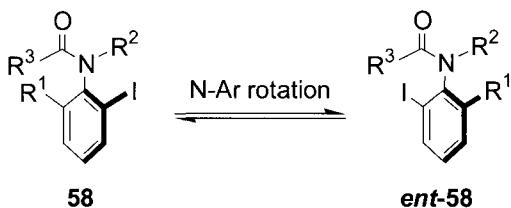
Some of the most spectacular examples have come from the laboratories of Overman at the University of California, Irvine. In his synthesis of (–)-quadrigemine C (**57**), Overman noted that the C3 and C3''' quaternary stereocentres have the same absolute stereochemistry. Therefore, following a Stille reaction to prepare key substrate **54**, a double asymmetric Heck reaction was performed, yielding decacyclic system **56** in good yield and in 90% ee.<sup>41</sup> This example truly displays the synthetic power of the Heck reaction in forging quaternary, crowded stereocentres.

Interestingly, the Heck cyclization of anilides, such as **54**, has constituted a frequent strategy in the asymmetric synthesis of alkaloids.<sup>17</sup> While it is often assumed that migratory insertion of the arylpalladium(II) species into the carbon–carbon double bond is the stereocontrolling step, recent studies by Curran have offered an alternative explanation.<sup>42</sup>



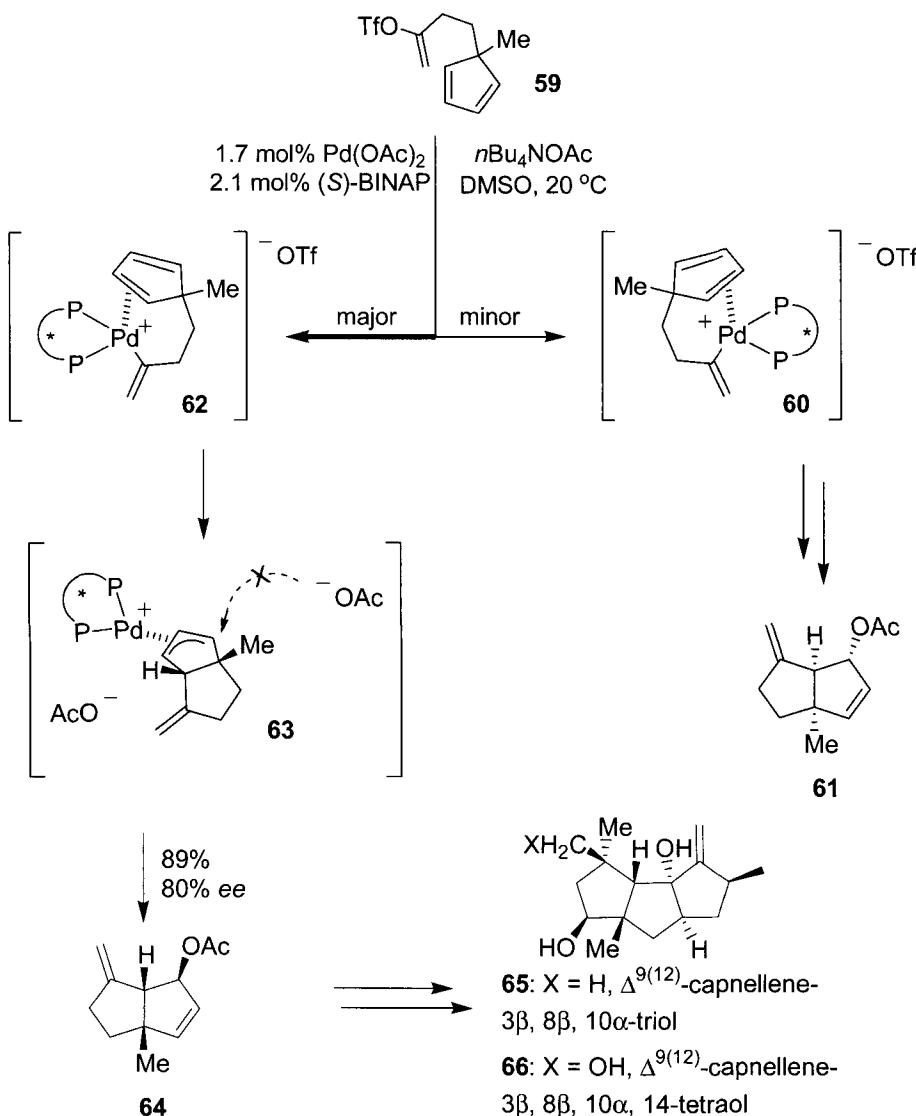


For iodoanilides, such as **58**, hindered rotation around the N–Ar bond renders these molecules axially chiral. Curran showed that low-temperature Heck reactions of chiral anilines **58** with an achiral palladium catalyst occur with efficient transfer of chirality from the chiral axis of the precursor to the stereocentre of the product. Since at high temperature the two axially chiral enantiomers will be rapidly equilibrating, this suggests that the stereocontrolling step in the asymmetric Heck reaction of similar substrates is, in fact, a dynamic kinetic resolution (oxidative addition to the aryl–X bond).

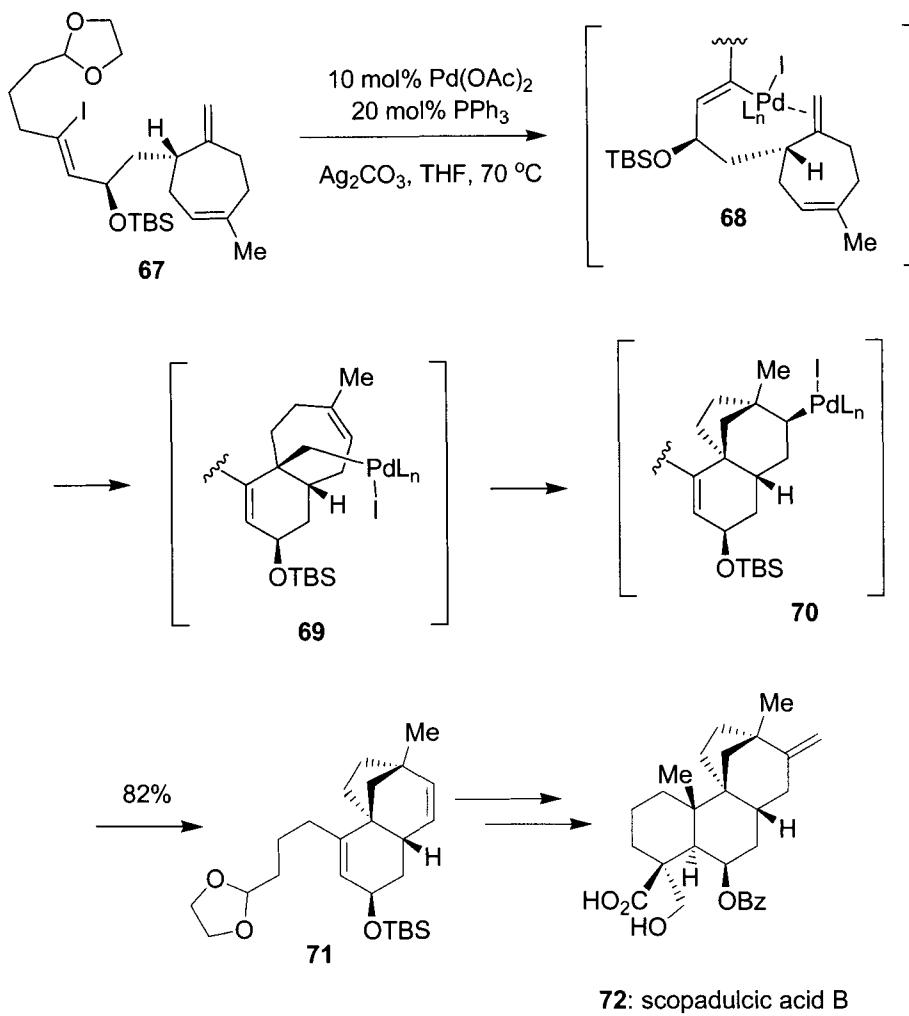


Exposure of prochiral cyclopentadiene **59** to catalytic  $\text{Pd}(\text{OAc})_2$ ,  $(S)$ -BINAP and  $n\text{-BuNOAc}$  furnished diquinane **64** in 89% yield and 80% *ee*. The mechanism presumably involves oxidative addition, followed by coordination of either enantiotopic double bond to yield diastereomeric intermediates **60** and **62**. The energetically favoured complex **62** undergoes insertion followed by rapid  $\sigma$ – $\pi$  isomerization to generate the  $\pi$ -allyl palladium species **63**. Trapping of the intermediate with an acetate anion

proceeds with good control of the regioselectivity (attack at the least hindered terminus of the  $\pi$ -allyl complex **63**) and stereoselectivity (attack on the opposite face to palladium) to yield **64**.<sup>43</sup>



Shibasaki has also reported impressive applications of the asymmetric intramolecular Heck reaction. For example, the Shibasaki group have applied their chemistry to the synthesis of compound **64**, a key intermediate in the total synthesis of two complex trquinane sesquiterpenes **65** and **66**, by making use of a Heck reaction/anion capture cascade sequence.<sup>43</sup>

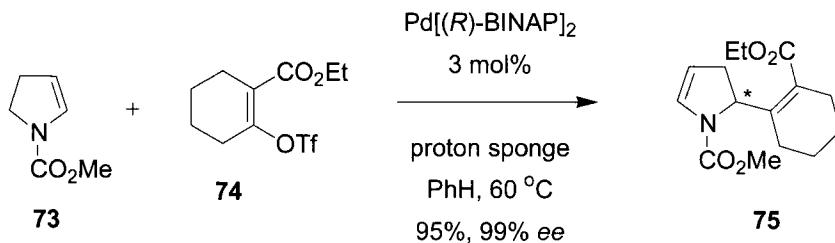


One of the most enabling features of the Heck reaction is the ability to facilitate polyene cyclizations in the synthesis of complex multiple ring systems. In the context of natural product synthesis, Overman pioneered this approach towards the synthesis of the scopadulcic acid family of diterpenes.<sup>44</sup> This inventive strategy formed three out of the four ring systems, including a sterically congested bridged bicyclic and two of the three quaternary stereocentres from a simple monocyclic precursor, employing an Heck cyclization cascade. In this case the stereochemistry of the product was under substrate control (i.e. there was no need for chiral ligands). Thus, compound 67 was converted into tricyclic intermediate 71 in one step, using catalytic  $\text{Pd(OAc)}_2$ ,  $\text{PPh}_3$  and a silver additive. Oxidative addition of the palladium(0) species into the C–I bond of compound 67 followed by the first

cyclization, gave intermediate **69**, which was unable to undergo  $\beta$ -hydride elimination due to the lack of suitably disposed hydrogen atoms. A second migratory insertion furnished intermediate **70**, which rapidly underwent  $\beta$ -hydride elimination to yield key intermediate **71**. Compound **71** was subsequently elaborated to scopadulcic acid B (**72**).

#### *Asymmetric intermolecular Heck reaction*

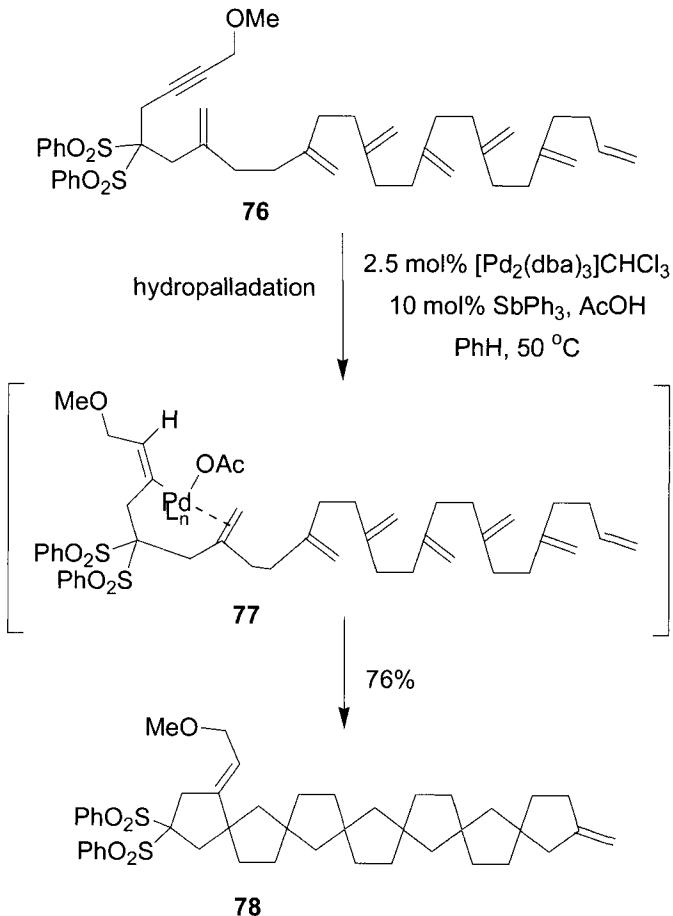
Perhaps the ultimate goal in the application of the asymmetric Heck reaction is to control both regio- and stereoselectivity in *intermolecular* reactions, which lack the extra elements of regiocontrol, compared to their intramolecular counterparts. Hayashi et al. reported the first example of an asymmetric intermolecular Heck reaction in 1991.<sup>45</sup> In their study, the use of aryl triflates was essential to achieve high levels of enantioinduction. Numerous examples have subsequently been reported in the literature with limited success.<sup>19</sup> In one impressive example, Hayashi reported the Heck reaction of dihydropyrrole **73** and alkenyl triflate **74** using (*R*)-BINAP as the chiral ligand. The product **75** was isolated in high yield and excellent enantioselectivity as the sole regiosomer.<sup>46</sup>



The majority of asymmetric Heck reactions reported employ BINAP as the chiral ligand, however initial reports suggest other ligating molecules may offer some benefits.<sup>19</sup> A dramatic example of this was the introduction of oxazoline-based *P,N*-ligands by Pfaltz. Using these ligands, several previously reported cases of asymmetric Heck reactions were improved, giving excellent enantioselectivities (> 99% ee). Other studies have reported the use of alternative *P,N*-ligands, *N,N*-ligands and bidentate phosphines.<sup>19</sup>

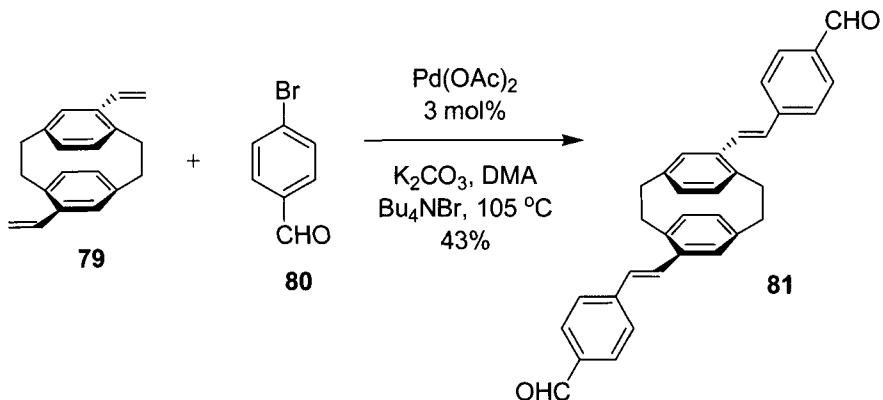
### *Zipper reactions*

In 1990, Negishi reported an impressive example of a domino Heck cascade reaction, where an acyclic polyunsaturated precursor was transformed into the tetracyclic steroidal ring framework in a single step.<sup>48</sup> Following this work, the Trost group reported several alternative examples of impressive cascade cyclizations.<sup>49</sup> For example, heptacyclic compound **78** was generated in a single synthetic step from precursor **76**. The first step of this cyclization cascade differs slightly from the traditional Heck mechanism, involving hydropalladation of an alkyne to give intermediate **77**. Subsequently, seven consecutive intramolecular Heck reactions furnished the polycyclic product **78** in good yield (76%). These cascade cyclizations were termed “zipper reactions” and nicely illustrate the power of this methodology.

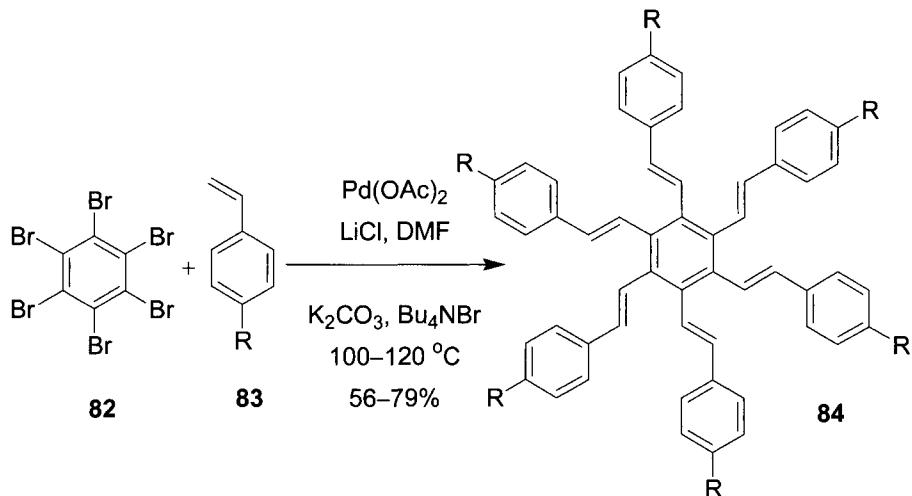


### *Highly conjugated systems*

The Heck reaction has also proved extremely useful in the synthesis of highly conjugated organic materials.<sup>4,16</sup> For example, using Jeffery's conditions, extended derivatives of paracyclophane **79** were prepared.<sup>50</sup>



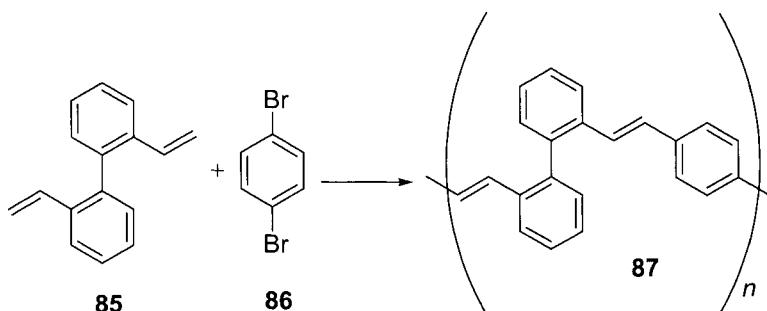
Although the preparation of hexaalkynylbenzenes had been reported in the 1980s, the synthesis of the corresponding hexaalkenyl derivatives was largely unknown. Studies by de Meijere demonstrated that the Heck reaction could be used to prepare conjugated molecules, such as **84** in good yields.<sup>4</sup> Interestingly once again the application of Heck's original procedure failed to initiate the reaction, whereas Jeffery's modified conditions successfully furnished the desired product **84**.



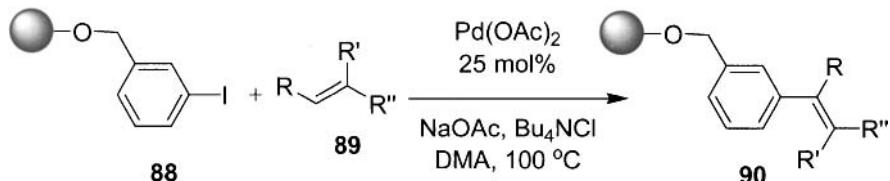
### *Polymers*

Due to its mildness and efficiency the Heck reaction has been explored for polymerization chemistry.<sup>4</sup> For example, oligomeric stilbenes, such as **87** were successfully prepared and studied in the context of photochemically induced reactions.<sup>51</sup>

Likewise, poly(*p*-phenylenevinylene) polymers are of particular interest in the field of organoelectronics and the Heck reaction has proved a useful tool in their construction.<sup>52</sup>



The use of resin-bound substrates in combinatorial chemistry is often essential to creating diverse chemical libraries. Such polymer-supported reagents are suitable for Heck-type chemistry; for example resin-bound iodobenzyl alcohol **88** was found to undergo reaction with a large range of olefins.<sup>53</sup>



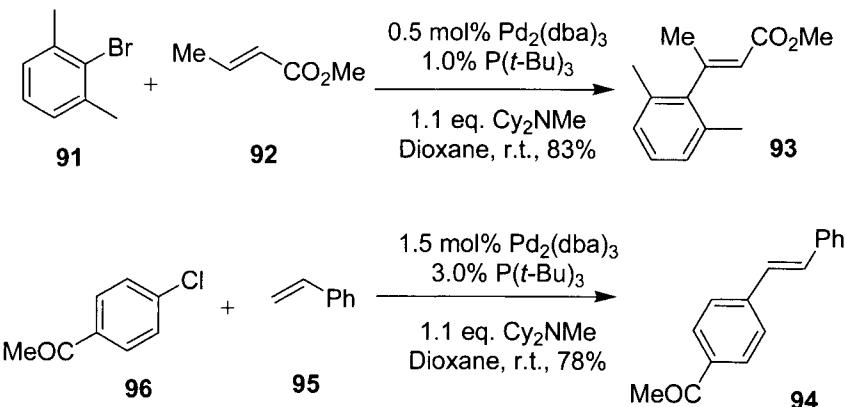
#### 1.1.1.5 *Variations and Improvements*

##### *Ligands with the highest activity*

Numerous ligands have been applied successfully to the Heck reaction, including phosphines, phosphites, palladacycles and carbenes.<sup>16</sup> Of the reported ligands however, several stand out for their high activity and substrate scope. Perhaps the greatest advance of this chemistry was the discovery of ligands which enable the Heck reaction of aryl chlorides.<sup>16</sup> Aryl

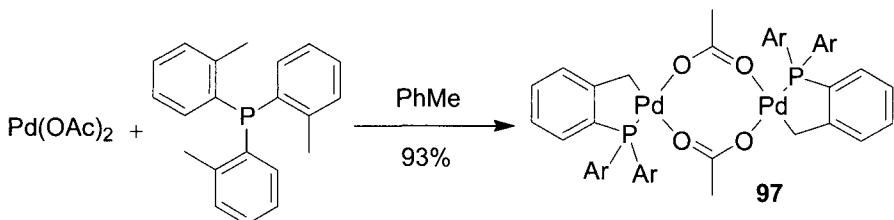
chlorides are more readily available and less expensive than their aryl bromide and aryl iodide counterparts and therefore the ability to use them in palladium-mediated transformations vastly improves the industrial relevance of these processes. Several of the most active catalysts are highlighted below.

**Phosphines:** Spencer demonstrated vast improvements in the phosphine-assisted Heck reaction in the early 1980s.<sup>54</sup> He showed that the use of  $\text{P}(o\text{-Tol})_3$  in polar aprotic solvents can give high turn-over number (TON) processes. Heck first reported the use of  $\text{P}(o\text{-Tol})_3$ <sup>2</sup> and interestingly this ligand is a key precursor to a highly active palladacycle (*vide supra*). Following these early efforts, in 1992 Milstein reported the use of bulky, electron-rich chelating phosphines (1,3-bis(diisopropylphosphino)propane) in the Heck reaction of aryl chlorides at high temperatures.<sup>55</sup> In this case a highly reactive monochelated palladium(0) species is formed which can undergo oxidative addition to aryl chlorides. Following subsequent de-ligation of the chloride ligand, the complex undergoes migratory insertion via the cationic route. Perhaps the greatest discovery however, was the use of the electron-rich, bulky monophosphine, tri-*tert*-butylphosphine ( $\text{P}(t\text{-Bu})_3$ ) by G. Fu at MIT in 1999.<sup>56</sup> In this study, he demonstrated that aryl chlorides could be effectively used in the Heck reaction at 100 °C. He subsequently reported a slightly modified procedure in 2001 where aryl bromides and aryl chlorides could undergo the Heck reaction at room temperature.<sup>57</sup> Amongst the impressive results in this publication, Fu demonstrated that bulky, *ortho*-substituted aryl bromides (for example **91**) and activated (electron-poor) aryl chlorides, such as **96** can undergo the Heck reaction at room temperature in high yield. He also demonstrated unactivated (electron-rich) aryl chlorides can undergo Heck coupling at relatively low, elevated temperatures (70 °C), and at higher temperatures (120 °C), the loading of palladium can be reduced to 0.1 mol%.<sup>57</sup> Hartwig has also reported active bulky phosphine catalysts for the Heck reaction under mild conditions.<sup>58</sup>



Traditionally, aryl chlorides are usually regarded as unreactive due to their reluctance to oxidatively add to palladium(0) complexes.<sup>59</sup> While intuitively it would seem bulky, electron-rich phosphines such as (*P*(*t*-Bu)<sub>3</sub>) facilitate this reaction by increasing the electron density on palladium, studies have shown the most likely explanation due to the formation of a highly reactive monoligated palladium species (PdL).<sup>60</sup> These heavily underligated complexes show a vastly increased reactivity towards oxidative addition. Additional studies by Fu have highlighted a dichotomy however, since other bulky phosphines, such as tricyclohexylphosphine (PCy<sub>3</sub>), do not furnish active catalysts in the Heck reaction (whereas they do in the case of other palladium-mediated cross coupling reactions).<sup>61</sup> He has attributed this to the base-mediated palladium(0) regeneration step (L<sub>2</sub>Pd<sup>(II)</sup>HX → Pd<sup>(0)</sup>L<sub>2</sub>) of the catalytic cycle being kinetically slow and thermodynamically unfavourable in certain cases. This suggests the difference in reactivity between *P*(*t*-Bu)<sub>3</sub> and PCy<sub>3</sub> is due to highly sensitive steric effects effecting the ability of the corresponding L<sub>2</sub>PdHX complexes to reductively eliminate.

**Palladacycles:** As mentioned previously, the use of *P*(*o*-Tol)<sub>3</sub> as a ligand was pioneered by Spencer, however it was Herrmann who demonstrated its true potential.<sup>62</sup> He discovered that treatment of Pd(OAc)<sub>2</sub> with *P*(*o*-Tol)<sub>3</sub> in toluene actually affords a cyclometallated palladacycle **97**, now known as Herrmann's catalyst. When this complex was employed in the Heck reaction, efficient coupling of aryl bromides and activated aryl chlorides was observed at high temperatures.



This highly active catalyst was the cause of much controversy however, in regards to a mechanistic understanding of its chemistry.<sup>20</sup> In Herrmann's original paper he hypothesized that since the catalyst is recovered unchanged from the reaction, the active species must be palladium(II), therefore invoking a Pd(II)/Pd(IV) catalytic cycle. This was further compounded by Shaw's speculations on exactly how this mechanistic cycle could operate.<sup>63,64</sup> However, despite these suggestions, elegant studies by Hartwig set the record straight.<sup>65</sup> He demonstrated that upon treatment with an amine base, palladacycle **97** fragmented to form a palladium(0) species, Pd[*(o*-Tol)<sub>3</sub>P]<sub>2</sub>. It therefore became apparent that the original speculations on the reactivity of *P*(*o*-Tol)<sub>3</sub> were most likely correct; the

active catalyst is an underligated palladium species caused by the large cone angle of the ligand.<sup>20</sup> Hartwig's experiments also suggest that species **97** may lead, upon activation to colloidal palladium(0), and the mechanism therefore follows an analogous path to "ligand-free" reactions.<sup>24</sup> Further support for this mechanism can be gleamed from the fact that the Heck reaction of aryl chlorides with Herrmann's catalyst **97** required a tetraalkyl ammonium salt additive ( $[\text{Bu}_4\text{N}]\text{Br}$ ),<sup>62</sup> and such additives are frequently employed to facilitate "ligand-free" reactions. Herrmann's pioneering studies sparked the synthesis of numerous other palladacycles and pincer-type complexes.<sup>16</sup>

**Carbenes:** The use of stable carbene ligands in palladium mediated processes was also pioneered by Herrmann,<sup>66</sup> however mechanistically, their role in the catalysis is unclear. Heterocyclic carbenes are strong  $\sigma$ -donor ligands and have stronger binding to palladium(II) than phosphines, therefore dissociative ligand processes are unlikely.<sup>20</sup> For this reason, olefin insertion has been postulated to occur via either a pentacoordinated complex or a cationic pathway (following halide decomplexation), both of which are unfavoured.<sup>16,20</sup> The enhancement of TONs by tetraalkyl ammonium salts however, suggests the presence of palladium colloids.<sup>16</sup> Therefore it would seem that, as in the case of Herrmann's palladacycle (**97**), the carbene complexes simply provide a source of palladium(0) colloids, which undergo the Heck reaction under "ligand-free" conditions.

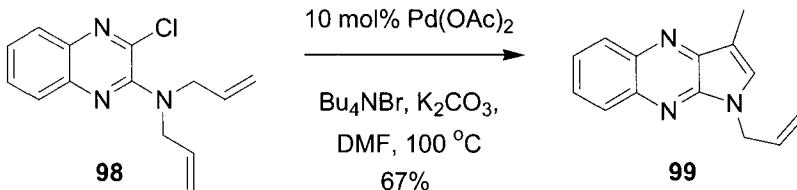
### *"Ligand-free" and Supported Catalysts*

As mentioned previously, Heck reported the ability to carry out the reaction of aryl iodides using  $\text{Pd}(\text{OAc})_2$  in the absence of additional ligands.<sup>2</sup> Indeed, it has been known for several decades that the Heck reaction using "naked" palladium can exhibit very high turnover frequencies (TOF), but short lifetimes, due to the lack of stabilizing ligands to prevent the formation of palladium black.<sup>21</sup> It was the seminal work of Jeffery which established the use of tetraalkyl ammonium salts to expand the applicability of "ligand-free" Heck reactions.<sup>7</sup> In fact the use of quaternary ammonium salts in the Heck reaction is often now referred to as Jeffery's conditions. The protocol gained popularity when, in 1987, Larock utilized these conditions in the intramolecular cyclization to form nitrogen heterocycles, demonstrating its potential in complex molecule synthesis.<sup>67</sup>

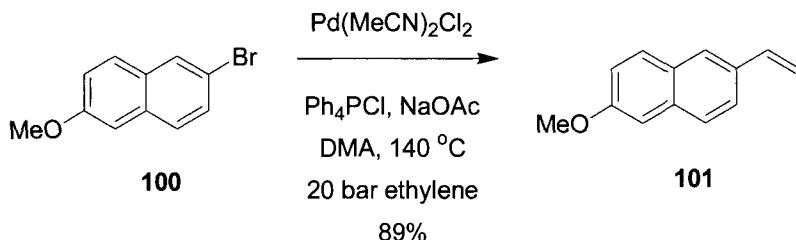
There have been numerous explanations for the beneficial effect of the quaternary ammonium salts including their ability to act as phase-transfer agents solubilizing inorganic bases, their role as a source of anions which can promote the reaction and their capacity to act as ion exchangers.<sup>16</sup> While these processes may be of relevance, their primary role appears to be as a stabilizing agent of the palladium nanoparticles formed in "ligand-free"

reactions. Indeed, these salts are known to be active colloid stabilizers.<sup>21</sup> Further work by Reetz demonstrated that there is an induction period of approximately one hour in the Heck reaction of iodobenzene and ethyl acrylate.<sup>68</sup> After this period both catalysis and the formation of palladium colloids was observed.

Regardless of the active species, importantly, Jeffery's conditions allowed the reaction to be carried out at < 100 °C, at least in the case of aryl iodides.<sup>16</sup> This protocol has therefore been embraced in the synthesis of a diverse range of molecular targets. For example, the preparation of pyrroloquinoxaline **99**, described by the editor of this book, in high yield using Jeffery's conditions was achieved in just two hours.<sup>69</sup> As a comparison, the phosphine-assisted conditions only gave marginal yields due to the strong binding of the reagents and product to the catalyst.



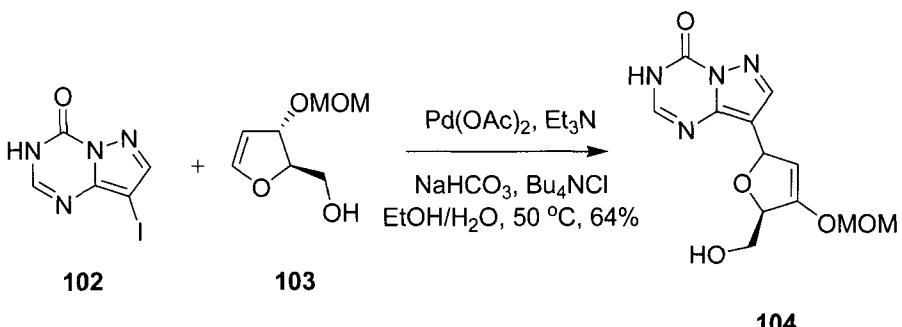
Since it is hypothesized that Jeffery's conditions are a means of utilizing palladium nanoparticles/colloids in the Heck reaction, it seems reasonable to suggest that pre-formed palladium colloids should also be catalytically active. Indeed, this idea has mostly been developed thanks to the seminal works of Reetz.<sup>70</sup> In 1996 he reported the preparation of uniform propylene carbonate stabilized palladium clusters (diameter 8–10 nm) which were stable up to 155 °C and catalytically active in the Heck reaction.<sup>70</sup> While Reetz's early colloids displayed some catalytic activity, it was the colloids reported by Beller and Herrmann, stabilized by tetraoctylammonium bromide, that started to show good activity.<sup>71</sup> Further dramatic improvements were made by Reetz, who reported the use of the stabilizing ligand *N,N*-dimethylglycine (DMG).<sup>72</sup> Impressive TON of 106,700 were achieved for the Heck reaction of bromobenzene with styrene using only 0.0009 mol% of palladium precatalyst and a 20-fold amount of DMG. In his continuing studies, Reetz later noted the use of tetraarylphosphonium salts as an additional additive, enabling the coupling of chlorobenzene with styrene in 96% conversion.<sup>73,16</sup> Also using these colloidal systems, the challenging olefination of **100** with ethylene was achieved in good yield.



In his preliminary work, Heck reported that the heterogeneous palladium on carbon ( $\text{Pd/C}$ ) could function as an effective catalyst at high temperatures.<sup>2</sup> Since this report, there have been numerous examples of palladium immobilized on a plethora of supports including polystyrene, silica, carbon, porous glass or encapsulated in zeolites and dendrimers.<sup>16,20,24</sup> Unfortunately in many cases, relatively low TON are observed. The main mechanistic issue in all these cases is whether catalysis is truly heterogeneous (i.e. the whole catalytic cycle takes place on the supported catalyst) or whether it operates in solution, through leaching of palladium(0). Indeed, there is a growing body of evidence suggesting in almost all cases, it is homogenous catalysis via active palladium(0) anionic species resulting from palladium nanoparticles/colloids.<sup>24</sup> The main goal for using such supported systems is to prevent leaching of palladium into commercially valuable products. However, on the contrary, it would appear a small degree of leaching is necessary for effective catalysis. This therefore fundamentally limits this approach.

### *Alternative Solvents*

**Aqueous media:** Following the discovery that the Heck reaction could be accomplished under phase transfer conditions, it was demonstrated that it could also be efficiently carried out in the aqueous phase using palladium salts in the presence of inorganic bases.<sup>74</sup> In these reactions, miscible co-solvents such as DMF or HMPA are often employed as a means to solubilize lipophilic organic reactants. Whereas the reaction of bromobenzene with acrylic acid catalyzed by  $\text{Pd}(\text{OAc})_2$ , in the presence of  $\text{P}(o\text{-Tol})_3$  and  $\text{K}_2\text{CO}_3$  gave only 12% yield of cinnamic acid in DMF, the addition of 10 % (v/v) or more of water increased the yield to quantitative.<sup>16</sup> Indeed, for water-soluble iodoarene substrates, full conversion was observed with 0.0005 mol% palladium, which corresponds to 200,000 catalytic cycles. It is thought the addition of water promotes the formation of palladium nanoparticles, which mediate the reaction under “ligand-free” conditions.<sup>16</sup>



Another beneficial effect of water was observed for the synthesis of C-nucleosides, for example **104**. Whereas the Heck reaction could not be achieved under standard conditions, the use of “ligand-free” conditions in aqueous ethanol (1:1, v/v) furnished the product in good yield.<sup>75</sup> Interestingly suppression of double bond migration in the product was also observed (a common issue in these substrates).

Phosphine-assisted catalysis under aqueous conditions requires the use of water-soluble phosphines, for example sulfonated derivatives.<sup>21</sup> Of particular note is the fact that for several cyclization reactions, a reversal of regioselectivity was observed; whereas standard Heck conditions furnish the *exo* cyclization adduct preferentially, the phosphine-assisted aqueous conditions gave the *endo* product predominantly.<sup>76,16</sup>

**Ionic liquids:** The use of ionic liquids (or molten salts) in the Heck reaction has mainly been to allow easy recycling of the catalytic system. There is some evidence however that this medium can activate the catalyst in certain cases.<sup>16</sup> Ionic liquids are highly polar and therefore facilitate the cationic mechanism, and can also contribute to the stabilization of underligated palladium(0) species through the formation of anionic complexes with halide ions.<sup>16</sup> Indeed, in some examples which generally require halide scavenging agents for the Heck reaction to proceed efficiently, the use of ionic liquids has been shown to negate the need for these additives. This has been attributed to the ease of dissociation of the halide, to give a cationic palladium complex in this highly polar medium.<sup>30</sup> Numerous ionic liquids have been employed including  $n\text{-Bu}_4\text{NBr}$ ,  $\text{Ph}_3\text{MePCl}$ ,  $\text{Ph}_3\text{MePBr}$ ,  $n\text{-Bu}_3\text{-}n\text{-C}_{16}\text{H}_{33}\text{NBr}$  and 1-methylimidazolium bromide. It must be noted however, that in general, imidazolium salts cannot be used in the absence of phosphine ligands below  $100^\circ\text{C}$  due to their ability to form carbene complexes (which release catalytically active palladium only at higher temperatures, *vide infra*).<sup>16,21</sup> In the presence of  $\text{Ph}_3\text{P}$ , a system of 1-butyl-3-methylimidazolium• $\text{PF}_6^-$  and  $\text{Et}_3\text{N}$  gave quantitative yield in the coupling of iodobenzene with ethyl acrylate at  $100^\circ\text{C}$ .<sup>77</sup> Importantly, the reaction could be rejuvenated without any loss of activity by extracting triethylammonium

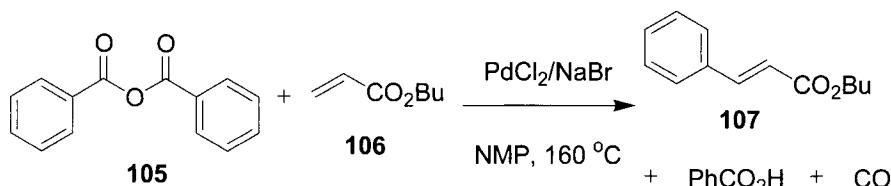
iodide with water, the product with cyclohexane and recharging the system with fresh reagents and base.

**Supercritical fluids:** Carbon dioxide forms a supercritical phase under relatively low temperatures and pressures and it therefore has been explored as a solvent for the Heck reaction.<sup>16,21</sup> Following the reaction, the gas can be collected and recycled, allowing the design of true waste-free technology. The dielectric constant of supercritical CO<sub>2</sub> is similar to pentane and therefore modified catalytic systems are often required to aid solubility.<sup>16,21</sup> Unusually, one of the best catalytic precursors in supercritical CO<sub>2</sub> is Pd(OCOF<sub>3</sub>)<sub>2</sub>, a strong electrophile and oxidant. Heck reactions in supercritical water have also been investigated.<sup>16,21</sup>

**Fluorous Systems:** Fluorous systems employ fluorinated compounds in perfluorinated solvents, which are immiscible with organic solvents. This allows the design of biphasic systems, where product is extracted from a reusable catalytic fluorous phase with organic solvents. Such systems have recently been applied to the Heck reaction with limited success.<sup>16,21</sup>

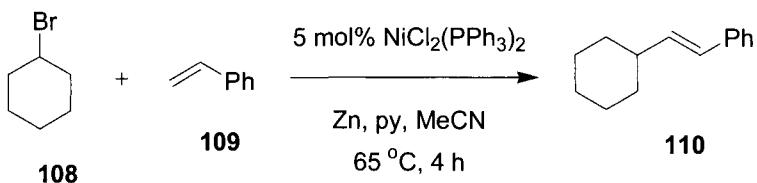
### *Less Usual Leaving Groups*

Besides halides and triflates, other electrophiles can be applied to Heck reactions. The first classical alternative was diazonium salts.<sup>20</sup> Reactions proceed in the absence of phosphine (partly due to the fact that phosphines result in uncontrolled decomposition of the diazonium salt). The Heck reaction using these species can be useful in cases when mild conditions are required. Alternatively, iodonium salts behave in a similar manner to diazonium salts and show better tolerance to bases.<sup>20</sup> The reactions take place at ambient temperature and so are once again most useful in situations when mild conditions are required. Some main group metallic compounds such as lead(IV) and thallium(III) have also been shown to undergo Heck-type chemistry and can be useful in specific cases.<sup>20</sup> Of particular interest is the fact that acid chlorides and anhydrides can be employed in Heck chemistry, the use which was pioneered by Blaser and Spencer in 1982.<sup>78,20</sup> The process involves oxidative addition of palladium into the C–X bond followed by decarbonylation to yield the intermediate ArPdX species. de Vries has exploited this reaction, demonstrating the use of benzoic anhydride (**105**) as an effective arylating agent.<sup>79,24</sup>



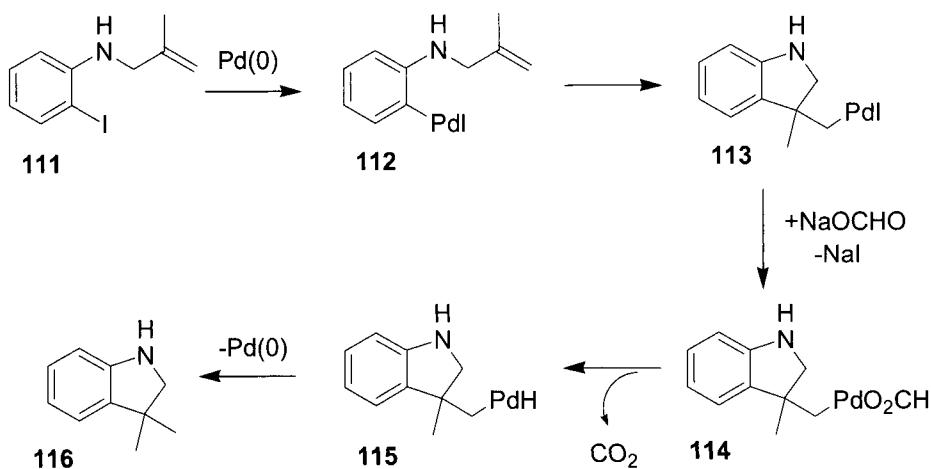
## *Other Metal Catalysts*

Other metals can catalyze Heck-type reactions, although none thus far match the versatility of palladium. Copper salts have been shown to mediate the arylation of olefins, however this reaction most probably differs from the Heck mechanistically.<sup>20</sup> Likewise, complexes of platinum(II), cobalt(I), rhodium(I) and iridium(I) have all been employed in analogous arylation chemistry, although often with disappointing results.<sup>20</sup> Perhaps the most useful alternative is the application of nickel catalysis. Unfortunately, due to the persistence of the nickel(II) hydride complex in the catalytic cycle, the employment of a stoichiometric reductant, such as zinc dust is necessary, however the nickel-catalyzed Heck reaction does offer one distinct advantage. Unlike its palladium counterpart, it is possible to use aliphatic halides.<sup>20</sup> For example, cyclohexyl bromide (**108**) was coupled to styrene to yield product **110**.

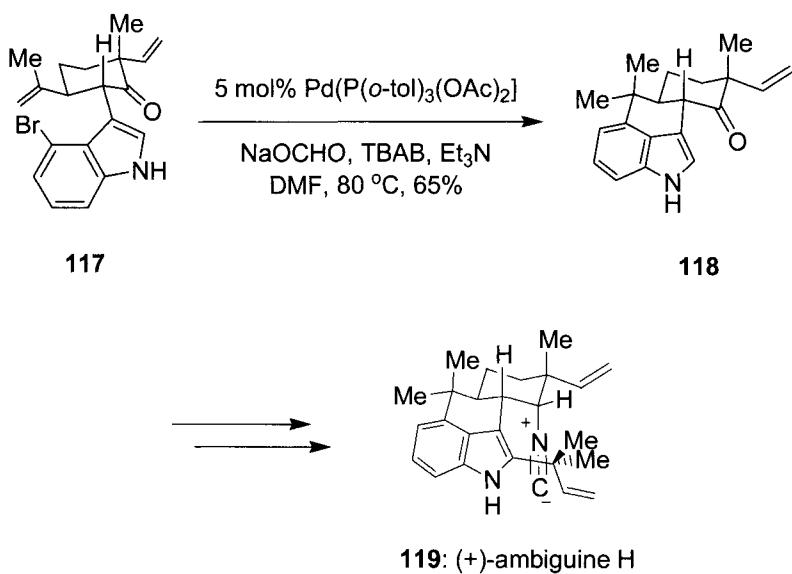


## *Reductive Heck Reaction*

In 1987, Larock published a paper on the palladium-mediated synthesis of nitrogen heterocycles.<sup>67</sup> For one example, he noted the cyclization of iodoaniline **111** in the presence of one equivalent of sodium formate gave indoline **116** in good yield. The use of sodium formate was based on previous precedent for the reduction of aryl halides.<sup>80</sup> Mechanistically he proposed the reaction proceeded via oxidative addition and migratory insertion to give intermediate **113**, which lacks a  $\beta$ -hydrogen atom, and therefore cannot undergo  $\beta$ -hydride elimination. Instead, ligand exchange with the formate anion gives species **114**, which can decarboxylate, providing hydridopalladium complex **115**. Reductive elimination provides indoline **116**, regenerating the palladium(0) catalyst. Similar reports on the use of formate as a hydride source in Heck-type reactions was published soon after by Grigg.<sup>81</sup>



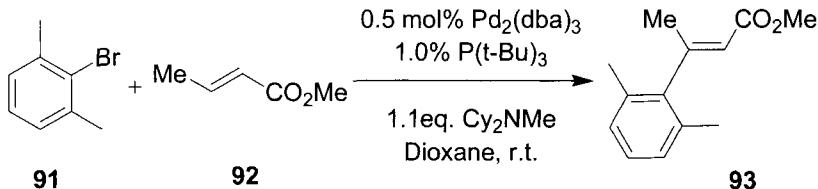
This reductive Heck reaction has become a useful tool in cyclization reactions for complex molecule synthesis. In his “protecting group free” synthesis of ambiguine H (**119**), Baran successfully applied this strategy.<sup>82</sup> Slow addition of Herrmann’s catalyst (**97**)<sup>62</sup> to substrate **117** provided intermediate **118** in a reliable 65% yield. This chemistry proved both robust and scalable, providing gram quantities of **118**.



### 1.1.1.6 Experimental

The proceeding examples highlight active modifications of Heck's original conditions. For the preliminary conditions, readers are directed to Heck's initial review article.<sup>2</sup>

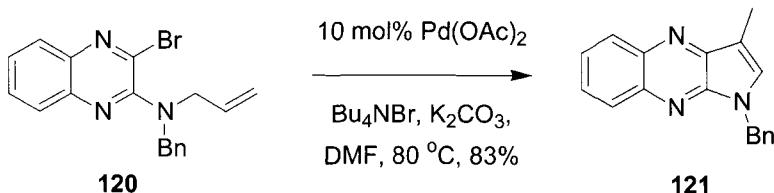
#### *Heck Reaction Using Fu's Conditions*



#### (E)-3-(2,6-Dimethylphenyl)-3-methyl Acrylic Acid Methyl Ester (93).<sup>57</sup>

To a solution of  $\text{Pd}_2(\text{dba})_3$  (11.9 mg, 0.013 mmol), 2-bromo-*m*-xylene (**91**, 0.115 mL, 0.863 mmol), methyl crotonate (**92**, 0.100 mL, 0.943 mmol) and  $\text{Cy}_2\text{NMe}$  (0.200 mL, 0.934 mmol) in anhydrous dioxane (0.60 mL) was added  $\text{P}(t\text{-Bu})_3$  (0.10 M solution in dioxane; 0.26 mL, 0.026 mmol) under argon. The resulting mixture was stirred at ambient temperature for 49 h. The mixture was diluted with  $\text{EtOAc}$ , filtered through a pad of silica gel with copious washings and concentrated *in vacuo*. Flash column chromatography ( $\text{SiO}_2$ ;  $\text{Et}_2\text{O}/\text{hexanes}$ , 5 : 95) furnished compound **93** (150 mg, 85%) as a clear, colorless liquid.

#### *Heck Reaction Using Jeffery's Conditions*



#### 1-Benzyl-3-methyl-1*H*-pyrrolo[2,3-*b*]quinoxaline (121).<sup>69</sup>

To a solution of allylbenzyl-(3-bromoquinoxalin-2-yl)amine (**120**, 500 mg, 1.42 mmol) in DMF (15 mL) was added  $\text{Pd}(\text{OAc})_2$  (32 mg, 0.14 mmol),  $\text{K}_2\text{CO}_3$  (580 mg, 4.25 mmol), and  $\text{Bu}_4\text{NBr}$  (456 mg, 1.42 mmol). The resulting mixture was stirred at 80 °C for 30 min and cooled to room temperature. The mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (100 mL), washed with water (3 × 20 mL) and brine (20 mL), dried ( $\text{Na}_2\text{SO}_4$ ), and filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by flash

chromatography to furnish 1-benzyl-3-methylpyrrolo[2,3-*b*]quinoxaline (**121**) as a yellow solid (321 mg, 83% yield).

### 1.1.1.7 References

1. [R] Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4.
2. [R] Heck, R. F. *Org. React. (N. Y.)* **1982**, 27, 345.
3. [R] Daves, G. D.; Hallberg, A. *Chem Rev.* **1989**, 89, 1433.
4. [R] de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 2379.
5. [R] de Meijere, A.; Braese, S. In *Transition Metal Catalyzed Reactions*; Davies S. G., Murahashi, S.-I., Eds.; Blackwell Science: Oxford, 1999.
6. [R] Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, 28, 2.
7. [R] Jeffery, T. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; Jai Press Inc: Greenwich, CT, 1996; Vol. 5.
8. [R] Crisp, G. T. *Chem. Soc. Rev.* **1998**, 27, 427.
9. [R] Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diedrich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.
10. [R] Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron*, **1997**, 53, 7371.
11. [R] Overman, L. E. *Pure Appl. Chem.* **1994**, 66, 1423.
12. [R] Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-Coupling Reactions*; Diedrich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998.
13. [R] Link, J. T.; Overman, L. E. *Chemtech* **1998**, 28, 19.
14. [R] Gibson, S. E.; Middleton, R. J. *Contemp. Org. Synth.* **1996**, 3, 447.
15. [R] Reetz, M. T. In *Metal-Catalyzed Reactions*; Davies, S. G., Murahashi, S.-I., Eds.; Blackwell Sci.: Oxford, 1999.
16. [R] Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, 100, 3009.
17. [R] Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, 103, 2945.
18. [R] Biffs, A.; Zecca, M.; Basato, M. *J. Mol. Catal. A: Chem.* **2001**, 173, 249.
19. [R] Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, 346, 1533.
20. [R] Farina, V. *Adv. Synth. Catal.* **2004**, 346, 1553.
21. [R] Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron*, **2005**, 61, 11771.
22. [R] Trzeciak, A. M.; Ziolkowski, J. J. *Coord. Chem. Rev.* **2005**, 249, 2308.
23. [R] Oestreich, M. *Eur. J. Org. Chem.* **2005**, 783.
24. [R] de Vries, J. G. *Dalton Trans.* **2006**, 421.
25. Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, 44, 581.
26. Heck, R. F.; Nolley, J. P. Jr. *J. Org. Chem.* **1972**, 37, 2320.
27. Heck, R. F. *J. Am. Chem. Soc.* **1968**, 90, 5518.
28. [R] Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, 254.
29. [R] Hegedus, L. S. In *Transition Metals in the Synthesis of Complex Organic Molecules*, 1<sup>st</sup> ed.; University Science Books: Mill Valley, CA, 1994; p 87.
30. Amatore, C.; Godin, B.; Jutand, A.; Lemaître, F. *Organometallics*, **2007**, 26, 1757.
31. [R] Heck, R. F. *Acc. Chem. Res.* **1979**, 12, 146.
32. Cabri, W.; Candiani, I.; DeBernardis, S.; Francalance, F.; Penco, S. *J. Org. Chem.* **1991**, 56, 5796.
33. Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, 113, 1417.
34. Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, 57, 4571.
35. Amatore, C.; Jutand, A. *Acc. Chem. Res.* **2000**, 33, 314.
36. Amatore, C.; Jutand, A.; Thuilliez, A. *Organometallics*, **2001**, 20, 3241.
37. Overman, L. E.; Rucker, P. V. *Tetrahedron Lett.* **1998**, 39, 4643.
38. Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, 52, 4130.
39. [R] Hammett, L. P. *Physical Organic Chemistry: Reaction Rates, Equilibria and Mechanisms*, 2<sup>nd</sup> ed.; McGraw-Hill: New York, 1970.
40. Tietze, L. F.; Schimpf, R. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 1089.

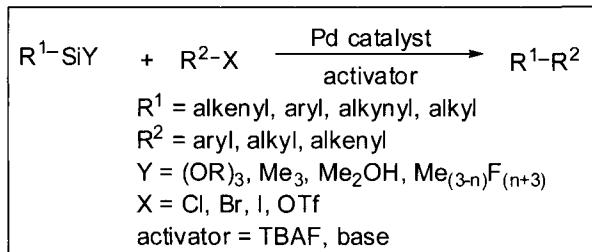
41. Lebsack, A. D.; Link, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008.
42. Lapierre, A. J. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2007**, *129*, 494.
43. a) Kagechika, K.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 4093; b) Kagechika, K.; Ohshima, T.; Shibasaki, M. *Tetrahedron* **1993**, *49*, 1773.
44. a) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042; b) Kucera, D. J.; O'Connor, S. J.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 5304.
45. Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417.
46. Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505.
47. Loiseleur, O.; Meijer, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 200.
48. Zhang, Y.; Wu, G.; Angel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590.
49. a) Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 701; b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259.
50. a) Koenig, B.; Knieriem, B.; de Meijere, A. *Chem. Ber.* **1993**, *126*, 1643; b) Bazan, G. C.; Oldham, W. J.; Lachicotte, R. J.; Tretiak, S.; Chernyak, V.; Mukamel, S. *J. Am. Chem. Soc.* **1998**, *120*, 9188.
51. Scherf, U.; Müllen, K. *Synthesis*, **1992**, 23.
52. Lee, Y.; Liang, Y.; Yu, L. *Synlett* **2006**, 2879.
53. Berteina, S.; Wendeborn, S.; Brill, W. K. D.; Mesmacker, A. D. *Synlett* **1998**, *6*, 676.
54. Spencer, A. *J. Organomet. Chem.* **1983**, 258, 101.
55. Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734.
56. Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10.
57. Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989.
58. Stambuli, J. P.; Stauffer, S. R.; Shaughnessy, K. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 2677.
59. [R] Grushin, V. V.; Alper, H. *Chem. Rev.* **1994**, *94*, 1047.
60. Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366.
61. Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 13178.
62. Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1844.
63. Shaw, B. L. *New. J. Chem.* **1998**, *22*, 77.
64. Shaw, B. L.; Petera, S. D.; Staley, E. A. *Chem. Commun.* **1998**, 1361.
65. Louie, J.; Hartwig, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2359.
66. Herrmann, W. A.; Elison, M.; Fischer, J.; Koecher, G. R.; Artus, J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2371.
67. Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291.
68. Reetz, M. T.; Westermann, *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 165.
69. Li, J. J. *J. Org. Chem.* **1999**, *64*, 8425.
70. Reetz, M. T.; Lohmer, G. *Chem. Commun.* **1996**, 1921.
71. Beller, M.; Fischer, H.; Kuehlein, K.; Reisinger, C.-P.; Herrmann, W. A. *J. Organomet. Chem.* **1996**, *520*, 257.
72. Reetz, M. T.; Westermann, E.; Lohmer, R.; Lohmer, G. *Tetrahedron Lett.* **1998**, *39*, 8449.
73. Reetz, M. T.; Lohmer, G.; Schwickardi, R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 481.
74. Zhao, F.; Shirai, M.; Arai, M.; *J. Mol. Cat. (A)* **2000**, *154*, 39.
75. Zhang, H. C.; Daves, G. D.; *Organometallics*, **1993**, *12*, 1499.
76. Lemaire-Audoire, S.; Savignac, M.; Dupuis, C.; Genet, J. P. *Tetrahedron Lett.* **1996**, *37*, 2003.
77. Carmichael, A. J.; Earle, M. J.; Holbrey, J. D.; McCormac, P. B.; Seddon, K. R. *Org. Lett.* **1999**, *1*, 997.
78. Blaser, H.-U.; Spencer, A. *J. Organomet. Chem.* **1982**, *233*, 267.
79. Stephan, M. S.; Teunissen, A. J. J. M.; Verzijl, G. K. M.; de Vries, J. G. *Angew. Chem., Int. Ed.* **1998**, *37*, 662.
80. Pri-Bar, I.; Buchman, O. *J. Org. Chem.* **1986**, *51*, 734.
81. Burns, B.; Grigg, R.; Ratananukul, P.; Visuvanathar, S.; Stevenson, P.; Tanachat, W. *Tetrahedron Lett.* **1988**, *29*, 4329.
82. Baran, P. S.; Maimone, T. J.; Richter, J. M. *Nature*, **2007**, *446*, 404.

## 1.1.2 Hiyama Cross-Coupling Reaction

Larry Yet

### 1.1.2.1 Description

The palladium-catalyzed reaction of alkenyl-, aryl-, alkynyl- and alkylsiloxanes with aryl, alkyl, and alkenyl halides and triflates in the presence of activators is known as the Hiyama cross-coupling reaction and several reviews have been published.<sup>1-8</sup> This chapter will present major developments and examples of recent carbon–carbon bond formation methodology and improvements as well as their use in natural products synthesis in the last few years.



Organotin, organoboron, and organozinc reagents have become useful reagents for palladium-catalyzed cross-coupling reactions, which have found widespread applications in modern synthetic organic chemistry applications. The low molecular weight of organosilanes as well as the lack of toxicity, ease of activation, and high stability in most chemical reactions makes them ideal for use as nucleophilic partners in the cross-coupling reaction with organic halides and pseudohalides.

### 1.1.2.2 Historical Perspective

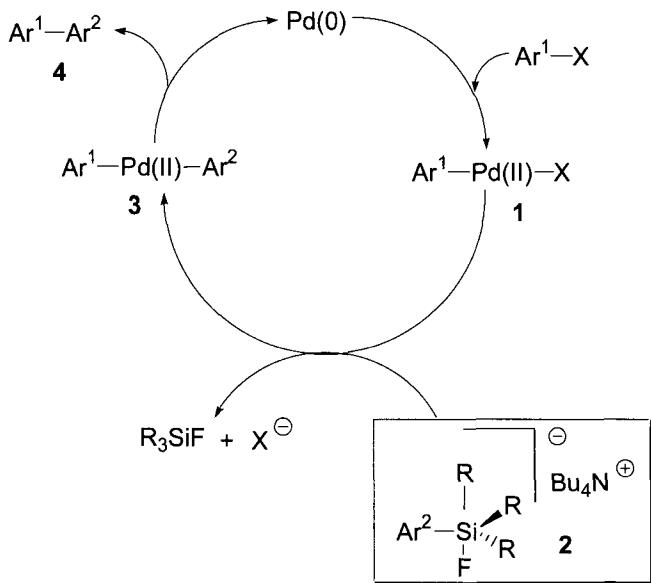
In the early 1980's, Hiyama started his academic research at the Sagami Chemical Research Center focusing on the activation of C–Si and Si–Si bonds using fluoride ion to generate the corresponding naked anion species that were otherwise destabilized by metallic counter ions.<sup>9</sup> Typical examples included synthetic reactions of  $\text{Me}_3\text{Si-SiMe}_3$  with 1,3-butadienes<sup>10</sup>, reduction of ketones with  $\text{HSiMe}_2\text{Ph}$ ,<sup>11</sup> and carbonyl addition of carbenoid-type carbanions  $^-\text{CX}_n\text{R}_{3-n}$ ,<sup>12</sup> all mediated at room temperature by tetrabutylammonium fluoride (TBAF) or by  $[(\text{Et}_2\text{N})_3\text{S}^+(\text{Me}_3\text{SiF}_2^-)]$  (TASF).

Hiyama then wondered what would happen if a palladium complex was present in the reaction mixture. The questions he asked, “Does a

fluoride ion simply attack the Pd(II) to deactivate the catalyst?" Hiyama then found through experimentation that a fluoride ion was found to preferentially attack the silicon to generate the anionic species that were later proved to be the pentacoordinated silicates, and the involvement of this species was shown to be essential for smooth transmetallation of the organosilicon reagents to complete the catalytic cycle of the cross-coupling reaction.<sup>13-15</sup> These initial observations then created a slew of palladium-catalyzed silicon-based reactions known today as the Hiyama cross-coupling reaction.

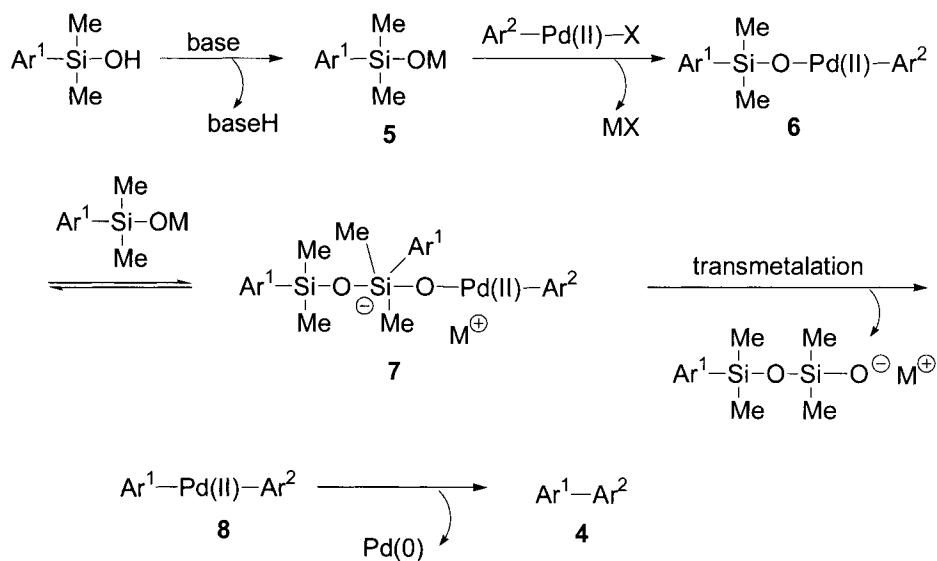
### 1.1.2.3 Mechanism

The most commonly accepted mechanism for this coupling was initially proposed by Hiyama and Hatanaka, which involves three steps.<sup>16</sup> The first step is the oxidative addition of the aryl halide to the palladium(0) catalyst to give arylpalladium complex **1**. The second step involves the transmetallation of the arylpalladium complex **1** with the anionic arylsilicate **2** to give bis(aryl)palladium complex **3**. Finally, the cross-coupled product **4** is produced and the palladium(0) catalyst is regenerated through reductive elimination of the bis(aryl)palladium(II) complex **3**. The key intermediate to this process is the requirement for the pentacoordinate arylsilicate anion **2**, typically formed by treatment of the tetracoordinate silane with the activating anion, such as tetrabutylammonium fluoride (TBAF).



To overcome the limitations of using TBAF as an activating reagent in sensitive compounds containing silicon protecting groups, Denmark

reported that simple deprotonation of the silanol might open a new pathway for activation.<sup>17</sup> In this mechanism, the conjugate base of the silanol served two roles. First, the silanolate **5** displaces the halide ion on the organopalladium–X species to generate a palladium silanolate complex **6**. Then another silanolate molecule activates the palladium silanolate complex through the formation of a pentacoordinate siliconate complex **7**, which undergoes transmetalation to give **8**. Finally, reductive elimination of **8** gives the product **4**. Bases that can be used include potassium trimethylsilanoate, cesium carbonate, sodium hydride, and sodium *tert*-butoxide.



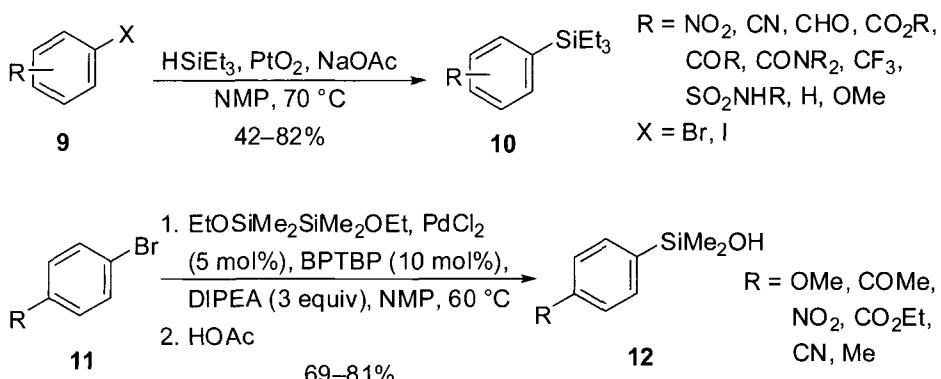
#### 1.1.2.4 Variations and Improvements

Several reviews have shown variations and improvements in the scope and limitations of the Hiyama cross-coupling reaction.<sup>1–8</sup> This section reports the recent advancements in this area over the last few years.

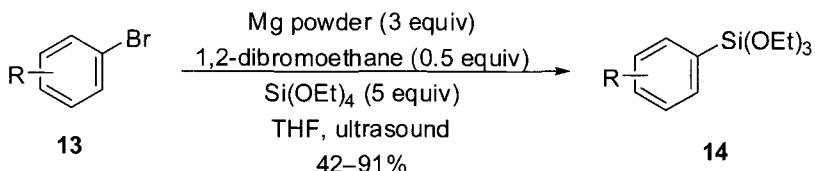
##### *Preparation of the Organosiloxanes*

Classical synthetic routes to arylsilanes consist of the reaction of aryl Grignard or aryllithium compounds with silicon electrophiles and many of these routes are presented in the various reviews. Recently, metal-catalyzed reactions of aryl halides with silanes have proven to be useful routes to functionalized arylsilanes. Alami reported the first platinum-catalyzed selective silylation of aryl iodides and bromides **9** having electron-withdrawing group to give arylsilanes **10** with triethylsilane and sodium

acetate in NMP.<sup>18</sup> Heteroaromatic halides were also readily silylated. Previous palladium-catalyzed methods were limited due to the difficult synthesis where only electron-rich, para-substituted aryl iodides afforded good yields of the arylsiloxanes. Denmark demonstrated a mild and general palladium-catalyzed insertion of 1,2-diethoxy-1,1,2,2-tetramethyldisilane to a variety of para-substituted aryl bromides **11** to afford the aryldimethylsilanols **12**.<sup>19</sup>



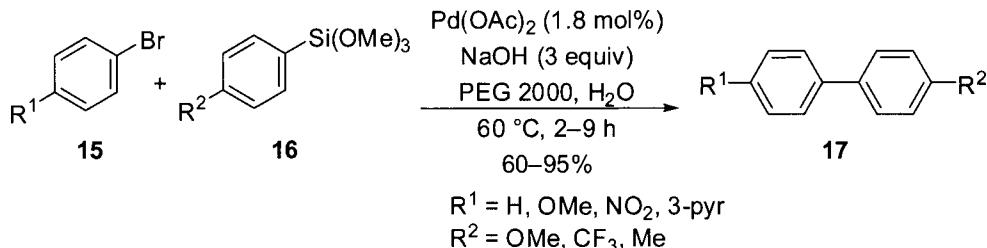
A series of aryltriethoxysilanes **14** were synthesized from the reaction of aryl bromides **13** with magnesium powder, 1,2-dibromoethane and tetraethylorthosilicate in tetrahydrofuran via sonochemical Barbier-type conditions.<sup>20</sup> DeShong previously reported the preparation of aryltrialkoxysilanes via treatment of aryl Grignard or lithium reagents with tetralkylorthosilicates.<sup>21</sup> DeShong also synthesized a selection of *ortho*-substituted aryltriethoxysilanes by directed orthometallation protocols.<sup>22</sup>



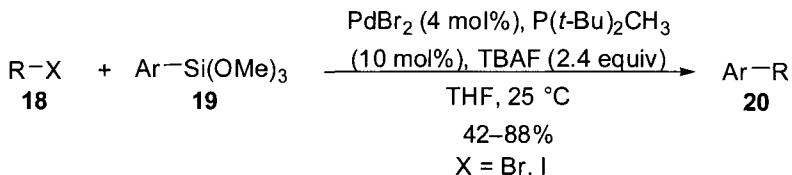
#### *Hiyama Cross-Coupling Improvements*

Zhang developed mild conditions for the palladium-catalyzed fluoride-free cross-coupling between aryl bromides **15** and aryltrimethoxysilanes **16** in good to high yields to afford biaryls **17** in the presence of poly(ethylene glycol) and sodium hydroxide.<sup>23</sup> Significant increase in substrate reactivity and reduction in reaction times were noted. Hiyama reported the use of triallyl(aryl)silanes as stable and easily accessible arylsilanes for the cross-

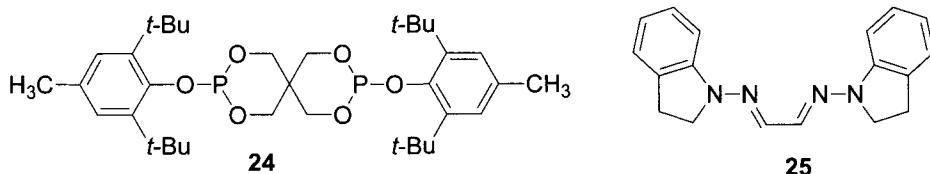
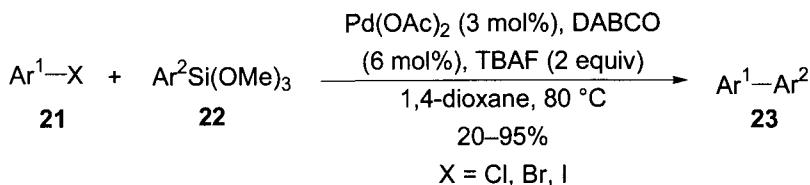
coupling reactions of aryl bromides in the presence of palladium catalyst ( $\text{PdCl}_2/\text{PCy}_3$ ) and TBAF.<sup>24</sup>



To date, nearly all studies of the Hiyama reaction have focused on couplings of  $\text{C}_{\text{sp}}^2\text{-X}$  electrophiles. Fu developed the first method for achieving the room-temperature Hiyama couplings of unactivated alkyl bromides and iodides.<sup>25</sup> Palladium-catalyzed reactions of alkyl bromides and iodides **18** with aryltrimethoxysilanes **19** in the presence of phosphorus ligand and TBAF afforded coupled products **20** in moderate to good yields.



The use of ligands has found beneficial use in the promotion of Hiyama cross-coupling reactions. Li has showed that palladium(II) acetate/DABCO was an inexpensive and efficient catalytic system for the Hiyama cross-coupling reactions of aryl halides **21** with aryltrimethoxysilanes **22** to give biaryls **23**.<sup>26</sup> He also reported the improved palladium-catalyzed Hiyama cross-coupling reaction of aryl halides with aryltrimethoxysilanes under solvent-free conditions with  $\text{PdCl}_2(\text{CH}_3\text{CN})_2$  and  $\text{P}(o\text{-tol})_3$  and tetrabutylammonium fluoride.<sup>27</sup> Phosphite ligand **24** was utilized in the palladium-catalyzed Hiyama cross-coupling reactions of trimethoxysilylbenzene with aryl bromides and chlorides in the presence of  $\text{Pd}(\text{acac})_2$  in *p*-xylene at  $80^\circ\text{C}$  with tetrabutylammonium fluoride.<sup>28</sup> Hydrazone **25** was a good ligand in the  $\text{PdCl}_2$ -catalyzed Hiyama reaction of aryl bromides with aryltriethoxysilanes with tetrabutylammonium fluoride in toluene at  $80^\circ\text{C}$ .<sup>29</sup>



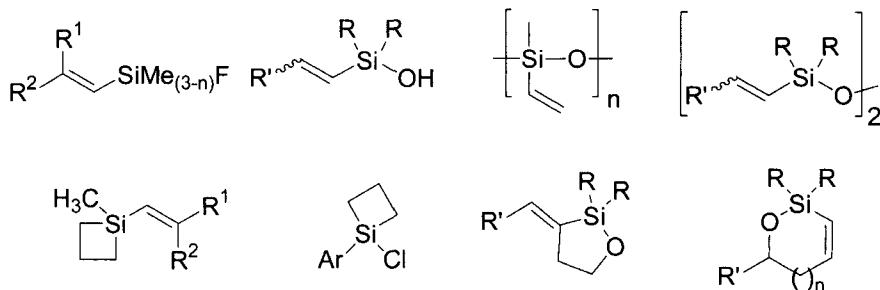
A colloidal palladium nanoparticle prepared from a Fischer carbene complex of tungsten with  $\text{K}_2\text{PdCl}_4$  as the reductant and PEG as the capping agent, efficiently catalyzed the Hiyama cross-coupling reactions in air.<sup>30</sup>

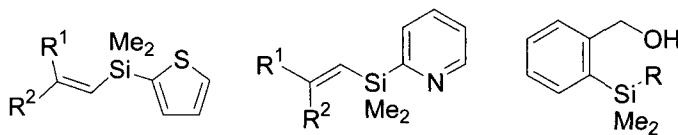
### 1.1.2.5 Synthetic Utility

Many reviews have been published in the last few years on the applications of the Hiyama cross-coupling reaction in organic synthesis.<sup>1–8</sup> In general, preparation of biaryls or heterobiaryls is the most common application of this reaction since new methodology development is based on examples of these. The most prevalent applications of the aryl and heteroaryl halides with organosilane precursors involve reactions such as vinylations, alkenylations, and alkynylations. The reader is encouraged to consult these key reviews. This section will describe some of the more recent applications published in the last few years.

#### *Range of Organosilyl Precursors*

The organosilyl precursors for the Hiyama cross-coupling reaction is not limited to the aryltrialkoxysilanes but can include the following structures shown below, where their applications are numerous.<sup>1–8</sup>

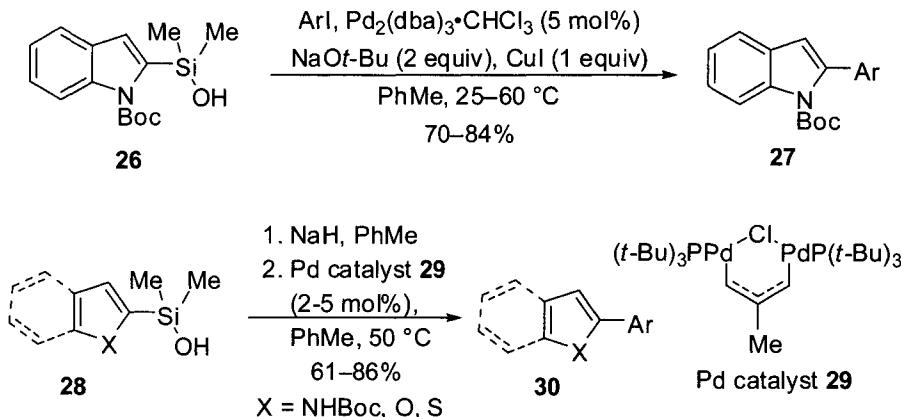


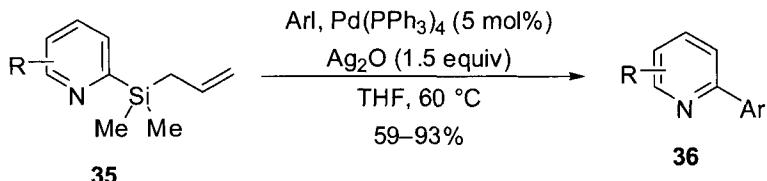
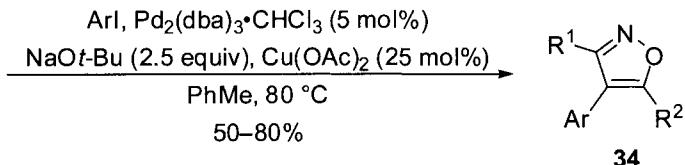
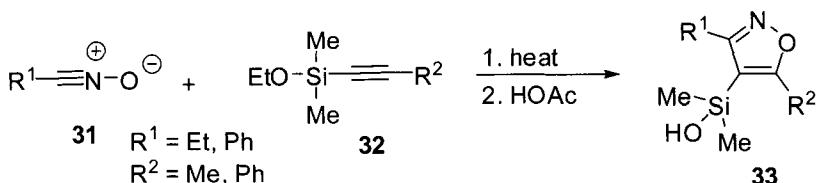


### Heterocycle Examples

The applications of aryltrialkoxysilanes in Hiyama cross-couplings with heteroaryl halides have been documented in a review by DeShong.<sup>7</sup> The Hiyama cross-coupling has now been widened to include heterocyclic silanlates.

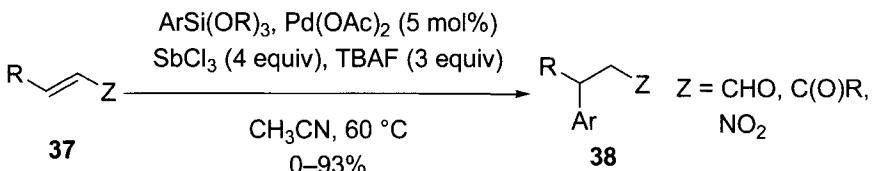
Denmark reported a mild and general palladium-catalyzed cross-coupling reaction of 2-indolylsilanols **26** with aryl iodides in the presence of stoichiometric copper(I) iodide and sodium *tert*-butoxide to afford coupled products **27** in good yields.<sup>31</sup> In a different protocol, Denmark showed that sodium silanoates derived from a number of heterocyclic (pyrrole, thiophene, furan, indole) silanols **28** underwent cross-coupling reactions with a variety of aryl iodides and bromides to give products **30** with palladium catalyst **29**.<sup>32</sup> Denmark reported that isoxazolylsilanols **33**, prepared from a [3 + 2] cycloaddition reaction between alkynyldimethylsilyl ether **32** and aryl and alkyl nitrile oxides **31**, cross-coupled with aryl iodides to give 3,4,5-trisubstituted isoxazoles **34**.<sup>33</sup> Yoshida demonstrated that (2-pyridyl)allyldimethylsilanes **35** were found to be novel pyridyl transfer reagents in the palladium-catalyzed reactions of aryl iodides to give 2-arylpyridines **36** in the presence of silver(I) oxide as an activator.<sup>34</sup>

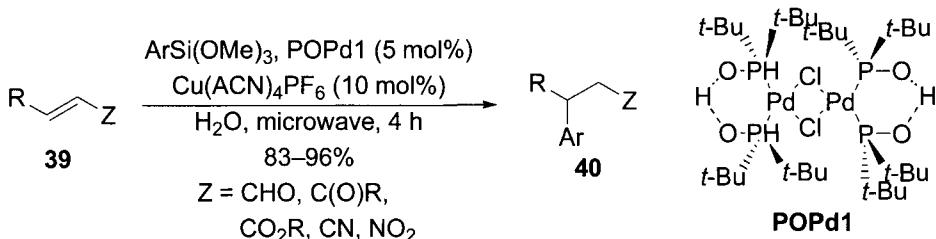




### Conjugate Additions

Aryltrialkoxysilanes can participate not only in palladium-catalyzed cross-coupling reactions but also in palladium-catalyzed conjugate addition reactions to  $\alpha,\beta$ -unsaturated compounds. Denmark showed that addition of aryltrialkoxysilanes to  $\alpha,\beta$ -unsaturated compounds (ketones, aldehydes) and nitroalkenes **37** in the presence of  $SbCl_5$ , TBAF, acetic acid, and palladium(II) acetate in acetonitrile gave the conjugate addition product **38** in variable yields depending on the substrates.<sup>35</sup> Wolf also reported the conjugate addition of aryltrimethoxysilanes to  $\alpha,\beta$ -unsaturated compounds (ketones, aldehydes, esters, nitroalkanes, and nitriles) **39** in the presence of POPd1 gave conjugate product **40** in water under microwave irradiation.<sup>36</sup> This method eliminated the need for stoichiometric additives such as TBAF and an excess of arylsiloxane, and does not require an inert atmosphere.

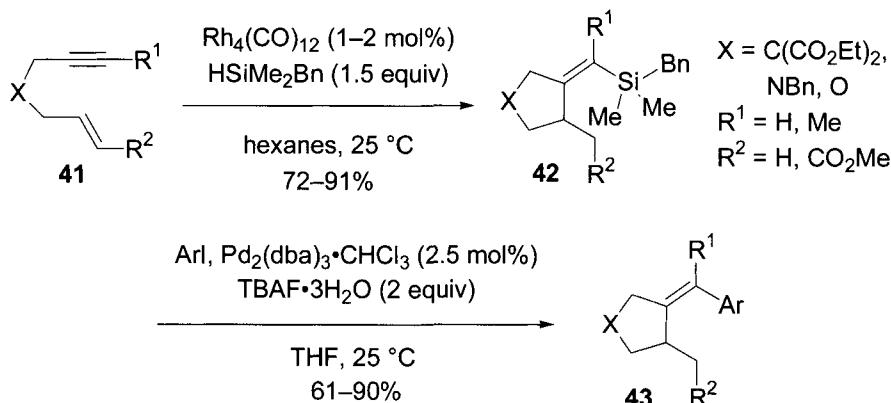




### Tandem Reactions

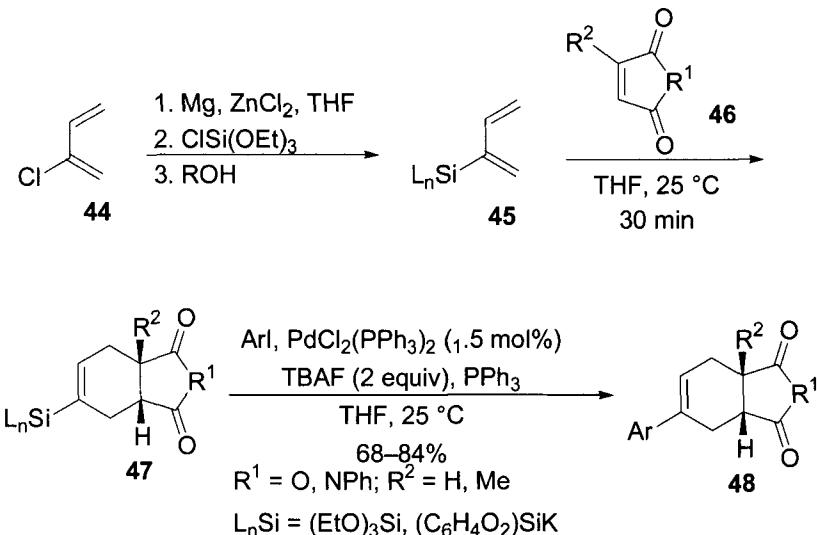
Multistep or tandem reactions have been employed in the use of the organosilicon moiety to create complex structures rapidly. These tandem reactions terminate with the palladium-catalyzed cross-coupling reactions. Tandem reactions have been involved in processes such as intermolecular and intramolecular hydrosilylation/cross-coupling, silylformylation/cross-coupling, Mizoroki–Heck reaction/cross-coupling, ring-closing metathesis/cross-coupling, and Alder–ene/cross-coupling reactions. Examples of these tandem reactions are represented in Denmark's review.<sup>5</sup>

Denmark published a sequential rhodium-catalyzed silylcarbocyclization of enynes parlayed with a palladium-catalyzed silicon-based cross-coupling reaction for the synthesis of highly substituted cyclopentanes.<sup>37</sup> 1,6-Enynes **41** reacted with benzylidemethylsilane in the presence of rhodium catalysts to afford five-membered rings **42** bearing a (*Z*)-alkylidenylbenzylsilyl group. A variety of substitution patterns and heteroatom substituents were compatible. Cyclopentenes **42** then underwent Hiyama cross-coupling reaction with aryl iodides in the presence of TBAF to give coupled products **43** in good yields.

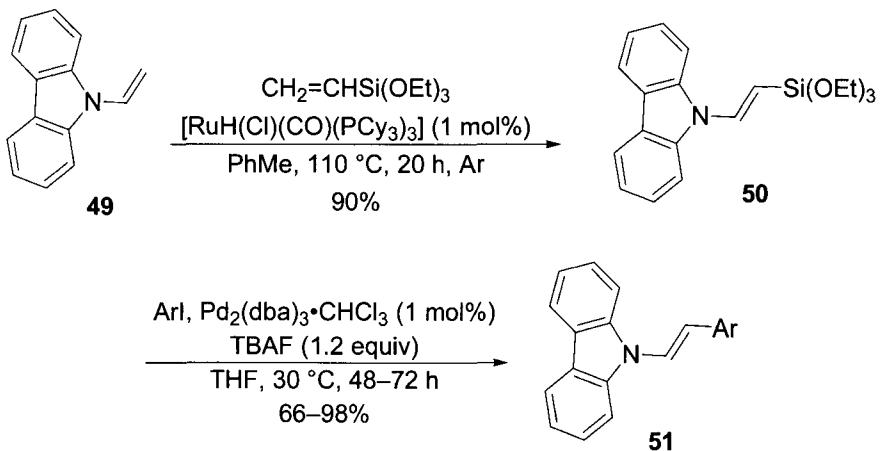


Welker reported the preparation of 2-triethylsiloxy-substituted 1,3-butadienes **45** from 2-chlorobutadiene (**44**) via a Grignard reaction, addition to triethoxysilyl chloride and alcoholysis.<sup>38</sup> These dienes **45** then

participated in a Diels–Alder/cross-coupling reaction, respectively with dienophiles **46** to give cycloadducts **47** and then Hiyama cross-couplings with aryl iodides to give final product **48**.

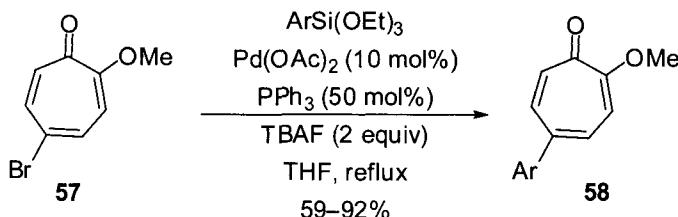
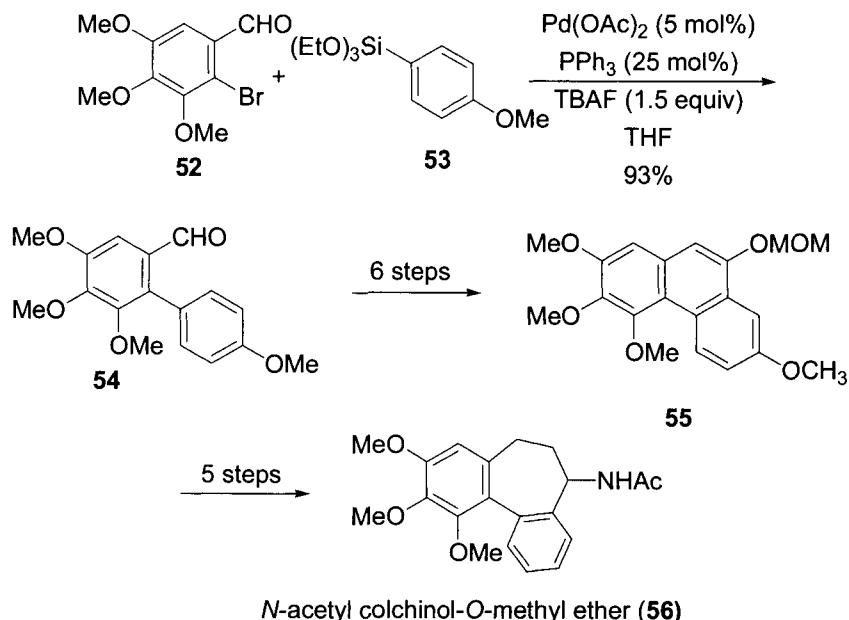


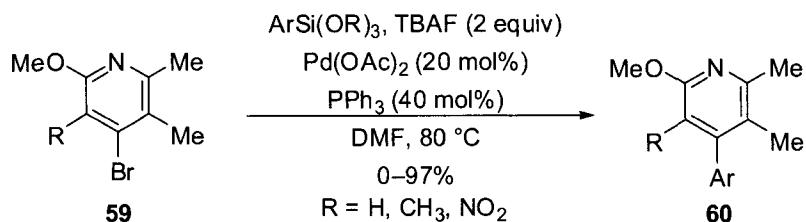
Marciniec demonstrated that 9-vinylcarbazole (**49**) can undergo cross-metathesis with vinyltriethoxysilane with the ruthenium catalyst to give vinylsiloxane carbazole **50** which then participated in a Hiyama palladium-catalyzed reaction with aryl iodides to furnish (*E*)-*N*-styrylcarbazoles **51**.<sup>39</sup>



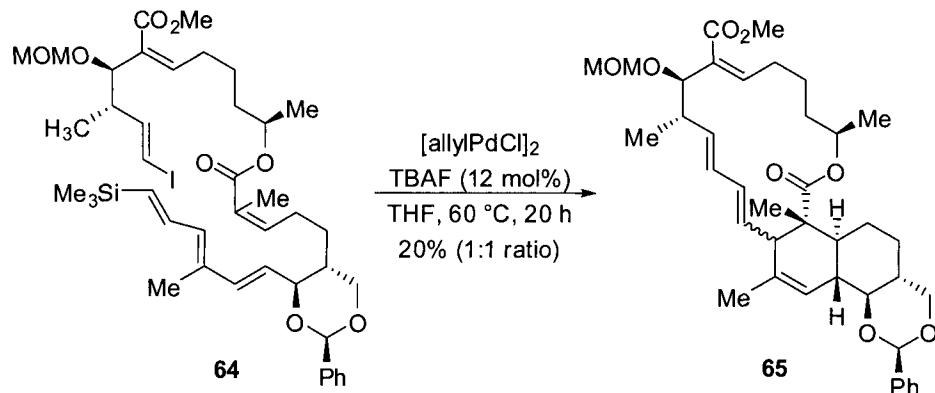
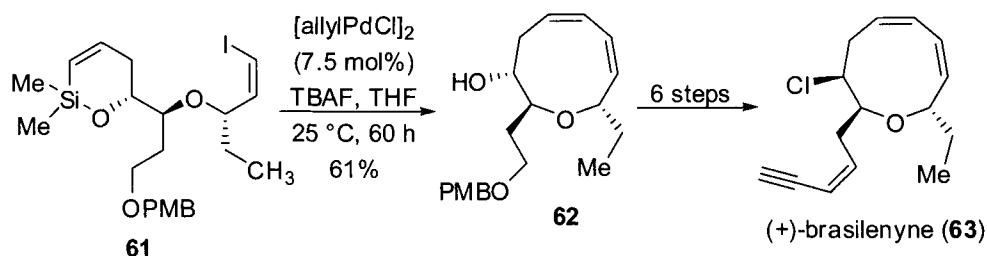
### *Applications in Natural Products*

The Hiyama cross-coupling reaction has not been highly represented in the preparation of natural products compared to the Negishi, Stille, and Suzuki reactions. DeShong utilized this key step in synthetic studies towards several natural products. For example, the Hiyama cross-coupling reaction was employed in the early synthesis of sterically-hindered biaryl **54** from 2-bromo-3,4,5-trimethoxybenzaldehyde (**52**) and arylsiloxane **53**.<sup>40</sup> Elaboration of **54** to phenanthrol **55** was accomplished in six steps. Finally phenanthrol ring expansion provided racemic *N*-acetyl colchinol-*O*-methyl ether (**56**). Similarly, DeShong approached the studies towards colchicine via palladium-catalyzed siloxane cross-coupling of 5-bromotropolone (**57**) to give aryltropolone **58**.<sup>41</sup> Siloxane-based cross-coupling of highly functionalized 4-bromopyridines **59** with aryltrialkylsilanes furnished sterically demanding biaryls **60** towards studies for the synthesis of streptonigrin and lavendamycin.<sup>42</sup>





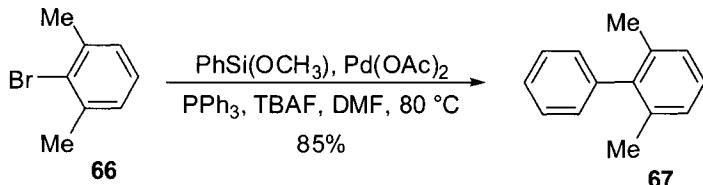
Denmark showcased the intramolecular silicon-assisted cross-coupling reaction of vinyl iodide **61** to give oxecene **62** in the first total synthesis of (+)-brasilenyne (**63**).<sup>43</sup>



Tadano utilized the Hiyama reaction in a formal synthesis of the antimicrobial tricyclic macrolides tubelactomycins.<sup>44</sup> The intramolecular Hiyama cross-coupling reaction of **64** aided in the synthesis of a 24-membered macrolactone equipped with all the requisite functionalities, which then triggered the transannular Diels–Alder reaction to give **65**. The 24-membered lactone formation was also achieved by the intramolecular ring-closing metathesis reaction.

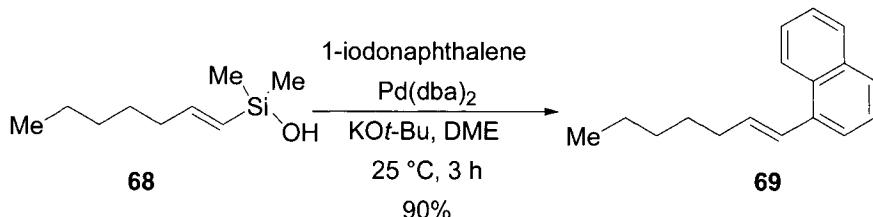
### 1.1.2.6 Experimental

#### 2,6-Dimethylbiphenyl (67)<sup>45</sup>



Phenyltrimethoxysilane (2.18 g, 10.9 mmol) was added to 2-bromo-*m*-xylene (**66**, 1.00 g, 5.43 mmol), Pd(OAc)<sub>2</sub> (119 mg, 0.530 mmol) and triphenylphosphine (283 mg, 1.08 mmol) in DMF (40 mL). TBAF (10.8 mL, 10.8 mmol, 1.0 M in THF) was added dropwise via a syringe. The reaction mixture was degassed with argon and was heated at 80 °C for 24 h. The reaction was quenched with water (50 mL) and extracted with diethyl ether (4 × 50 mL). The organic layers were dried over MgSO<sub>4</sub> and concentrated in vacuo. Purification by flash chromatography eluting with pentane afforded **67** (825 mg, 85%) as a colorless oil.

#### (E)-(Hept-1-enyl)naphthalene (69).<sup>46</sup>



A mixture of potassium *tert*-butoxide (449 mg, 4.0 mmol), (*E*)-**68** (344 mg, 2.0 mmol), 1-iodonaphthalene (292 μL, 2.0 mmol) and Pd(dba)<sub>2</sub> (58 mg, 0.1 mmol) was stirred in DME (4 mL) at room temperature for 3 h, and then was filtered through a pad of silica gel. Purification by column chromatography (RP C18, MeOH/H<sub>2</sub>O, 9/1) afforded 403 mg (90%) of (*E*)-**69** (403 mg, 90%) as a colorless oil.

### 1.1.2.7 References

- [R] Hiyama, T. In *Metal Catalyzed Cross-coupling Reactions*, Chapter 10, Ed. By Diederich, F.; Stang, P. J., Wiley-VCH, Weinheim, 1998, pg 421.
- [R] Hiyama, T.; Shirakwa, E., *Topics in Current Chemistry* **2002**, *219*, 61.
- [R] Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835.
- [R] Denmark, S. E.; Sweis, R. F. *Chem. Pharm. Bull.* **2002**, *50*, 1531.

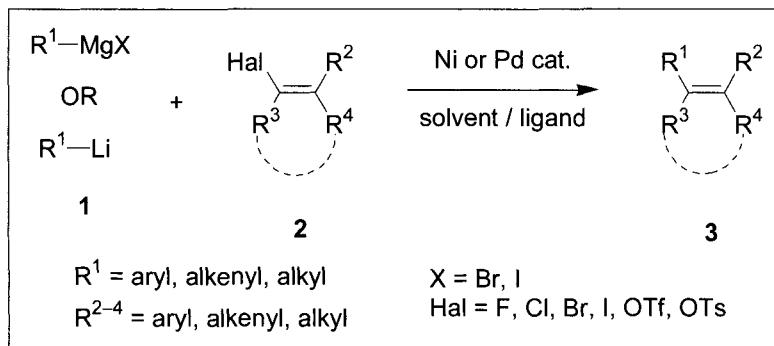
5. [R] Denmark, S. E.; Ober, M. H. *Aldrichimica Acta* **2003**, *36*, 75.
6. [R] Spivey, A. C.; Gripton, C. J. G.; Hannah, J. P. *Curr. Org. Synth.* **2004**, *1*, 211.
7. [R] Handy, C. J.; Manoso, A. S.; McElroy, W. T.; Seganish, W. M.; DeShong, P. *Tetrahedron* **2005**, *61*, 12201.
8. [R] Denmark, S. E.; Baird, J. D. *Chem. Eur. J.* **2006**, *12*, 4954.
9. Hiyama, T. *J. Organometal. Chem.* **2002**, *653*, 58.
10. Hiyama, T.; Obayashi, M.; Mori, H.; Nozaki, H. *J. Org. Chem.* **1983**, *48*, 912.
11. Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5415.
12. Fujita, M. Obayashi, M.; Hiyama, T. *Tetrahedron* **1988**, *44*, 4135.
13. Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.
14. Hatanaka, Y.; Hiyama, T. *Synlett* **1994**, 845.
15. Hiyama, T.; Hatanaka, Y. *Pure Appl. Chem.* **1994**, *66*, 1471.
16. Hatanaka, Y.; Goda, K.; Hiyama, T. *J. Organomet. Chem.* **1994**, *465*, 97.
17. Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439.
18. Hamze, A.; Provot, O.; Alami, M.; Brion, J.-D. *Org. Lett.* **2006**, *8*, 931.
19. Denmark, S. E.; Kallmeyn, J. M. *Org. Lett.* **2003**, *5*, 3483.
20. Lee, A. S.-Y.; Chang, Y.-T.; Chu, S.-F.; Tsao, K.-W. *Tetrahedron Lett.* **2007**, *47*, 7085.
21. Manoso, A. S.; Ahn, C.; Soheili, A.; Handy, C. J.; Correia, R.; Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 8305.
22. Seganish, W. M.; DeShong, P. *J. Org. Chem.* **2004**, *69*, 6790.
23. Shi, S.; Zhang, Y. *J. Org. Chem.* **2007**, *72*, 5927.
24. Nakao, Y.; Oda, T.; Sahoo, A. K.; Hiyama, T. *J. Organomet. Chem.* **2003**, *687*, 570.
25. Lee, J.-Y.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 5616.
26. Li, J.-H.; Deng, C.-L.; Liu, W.-J.; Xie, Y.-X. *Synthesis* **2005**, 3039.
27. Li, J.-H.; Deng, C.-L.; Xie, Y.-X. *Synthesis* **2006**, 969.
28. Ju, J.; Nam, H.; Jung, H. M.; Lee, S. *Tetrahedron Lett.* **2006**, *47*, 8673.
29. Mino, T.; Shirae, Y.; Saito, T.; Sakamoto, M.; Fujita, T. *J. Org. Chem.* **2006**, *71*, 9499.
30. Srimani, D.; Sawoo, S.; Sarkar, A. *Org. Lett.* **2007**, *9*, 3639.
31. Denmark, S. E.; Baird, J. D. *Org. Lett.* **2004**, *6*, 3649.
32. Denmark, S. E.; Baird, J. D. *Org. Lett.* **2006**, *8*, 793.
33. Denmark, S. E.; Kallmeyn, J. M. *J. Org. Chem.* **2005**, *70*, 2839.
34. Nokami, T.; Tomida, Y.; Kamei, T.; Itami, K.; Yoshida, J.-i. *Org. Lett.* **2006**, *8*, 729.
35. Denmark, S. E.; Amishiro, N. *J. Org. Chem.* **2003**, *68*, 6997.
36. Lerebours, R.; Wolf, C. *Org. Lett.* **2007**, *9*, 2737.
37. Denmark, S. E.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2007**, *129*, 3737.
38. Pidaparthi, R. R.; Welker, M. E.; Day, C. S.; Wright, M. W. *Org. Lett.* **2007**, *9*, 1623.
39. (a) Marciniec, B.; Majchrzak, M.; Prukala, W.; Kubicki, M.; Chadyniak, D. *J. Org. Chem.* **2005**, *70*, 8550. (b) Prukala, W.; Marciniec, B.; Majchrzak, M.; Kubicki, M. *Tetrahedron* **2007**, *63*, 1107.
40. Seganish, W. M.; DeShong, P. *Org. Lett.* **2006**, *8*, 3951.
41. Seganish, W. M.; Handy, C. J.; DeShong, P. *J. Org. Chem.* **2005**, *70*, 8948.
42. McElroy, W. T.; DeShong, P. *Org. Lett.* **2003**, *5*, 4779.
43. (a) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 15196. b) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2004**, *126*, 12432.
44. Anzo, T.; Suzuki, A.; Sawamura, K.; Motozaki, T.; Hatta, M.; Takao, K.-i.; Tadano, K.-i. *Tetrahedron Lett.* **2007**, *48*, 8442.
45. Mowery, M. E.; DeShong, P. *Org. Lett.* **1999**, *1*, 2137.
46. Denmark, S. E.; Sweis, R. F. *J. Am. Chem. Soc.* **2001**, *123*, 6439.

## 1.1.3 Kumada Cross-Coupling Reaction

Mathew J. Fuchter

### 1.1.3.1 Description

The Kumada cross-coupling reaction was originally reported as the nickel-catalyzed cross-coupling of Grignard reagents with aryl- or alkenyl halides. It has subsequently been developed to encompass the coupling of organolithium or organomagnesium compounds with aryl-, alkenyl or alkyl halides, catalyzed by nickel or palladium.<sup>1-8</sup>

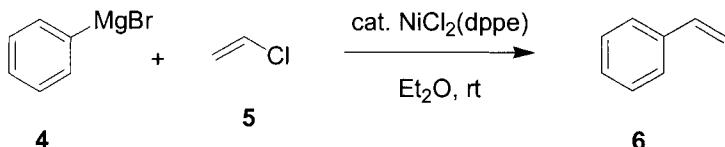


In the nickel-catalyzed process, catalytic activity depends on the phosphine ligand employed and the following trend is observed:  $\text{Ni}(\text{dppp})\text{Cl}_2 > \text{Ni}(\text{dppe})\text{Cl}_2 > \text{Ni}(\text{PPR}_3)_2\text{Cl}_2 \sim \text{Ni}(\text{dppb})\text{Cl}_2$ . Even alkyl Grignard reagents (with  $\beta$ -hydrogen atoms) can undergo nickel-catalyzed cross coupling without  $\beta$ -hydride elimination. Chlorinated aromatic compounds (**2**,  $\text{Hal} = \text{Cl}$ ) react with ease and even fluorobenzene (**2**,  $\text{Hal} = \text{F}$ ) can be utilized. The coupling is stereoselective and the stereochemistry of the alkenyl halide reagent **2** is preserved. While organolithium reagents cannot be used in the nickel-catalyzed reaction, they are suitable reaction partners for the palladium-catalyzed process, which is more stereo- and chemoselective. More reactive aryl halide substrates **2** are required ( $\text{Hal} = \text{Br, I}$ , and under modified conditions  $\text{Cl}$ ) however, for the palladium-catalyzed process. By using enantiomerically pure chiral ligands, the reaction can be rendered stereoselective (for saturated coupling partners). The reaction tolerates a range of non-protic solvents including  $\text{Et}_2\text{O}$ , THF, DME and toluene. The reaction most commonly takes place at ambient or slightly elevated temperatures. Side-reactions including homocoupling and reduction can be avoided by: 1) slow addition of organolithiums (to avoid rearrangement of

transient  $\alpha$ -bromo alkenyllithiums into lithium acetylides); 2) the use of high purity catalyst; and 3) avoiding the use of excess reagents.<sup>5</sup>

### 1.1.3.2 Historical Perspective

The discovery of the stereoselective cross-coupling reaction between aryl- or alkenyl halides and Grignard reagents under nickel catalysis is attributed to two independent publications in 1972. The first report, from the laboratories of R. J. P. Corriu in Montpellier, France, detailed the coupling of  $\beta$ -bromostyrene with phenylmagnesium bromide in the presence of several nickel salts, for example nickel(II) acetylacetone.<sup>9</sup> The second, from the laboratories of M. Kumada in Kyoto, Japan, described the coupling of Grignard reagents, such as phenylmagnesium bromide (**4**) with aryl- or vinyl chloride (**5**), catalyzed by  $\text{NiCl}_2(\text{dppe})$ .<sup>10</sup> Interestingly, this research was carried out by a graduate student, K. Sumitani, alongside M. Kumada's research associate K. Tamao, who has made significant contributions in the field of organosilicon chemistry (for example, the Tamao–Kumada–Flemming oxidation). In the following years, Kumada and co-workers fully explored the scope of the reaction and thus the transformation is now referred to as the Kumada cross-coupling.<sup>11,4</sup>



It would be incorrect however, to state that these initial reports were the first examples of this type of chemistry being performed. Indeed, as early as 1923, a French chemist, largely unrecognized today, A. Job and co-workers reported that “a solution of  $\text{C}_6\text{H}_5\text{MgBr}$  in diethyl ether gives in the presence of  $\text{NiCl}_2$  a derivative able to absorb  $\text{CO}$ ,  $\text{NO}$ ,  $\text{C}_2\text{H}_4$ ,  $\text{C}_2\text{H}_2$  and  $\text{H}_2$ ”.<sup>12</sup> He subsequently went on to detail the catalytic effect of the nickel salt and its use in several chemical reactions.<sup>13</sup> Several years later in 1939, H. Gilman and co-workers from the chemical laboratory of Iowa State College reported the homocoupling of phenylmagnesium iodide in the presence of catalytic nickel(II) bromide, to yield biphenyl in quantitative yield.<sup>14</sup> Most importantly however, a publication by M. S. Kharasch and co-workers from the George Herbert Jones Laboratory of the University of Chicago in 1941, reported the coupling of phenylmagnesium bromide with bromobenzene using 4 mol% of nickel(II) chloride, amongst a variety of other salts.<sup>15</sup> Perhaps in part due to his work on organocobalt chemistry,<sup>16,17</sup> the mechanism of this reaction was attributed to homocoupling of phenyl radicals derived from the Grignard

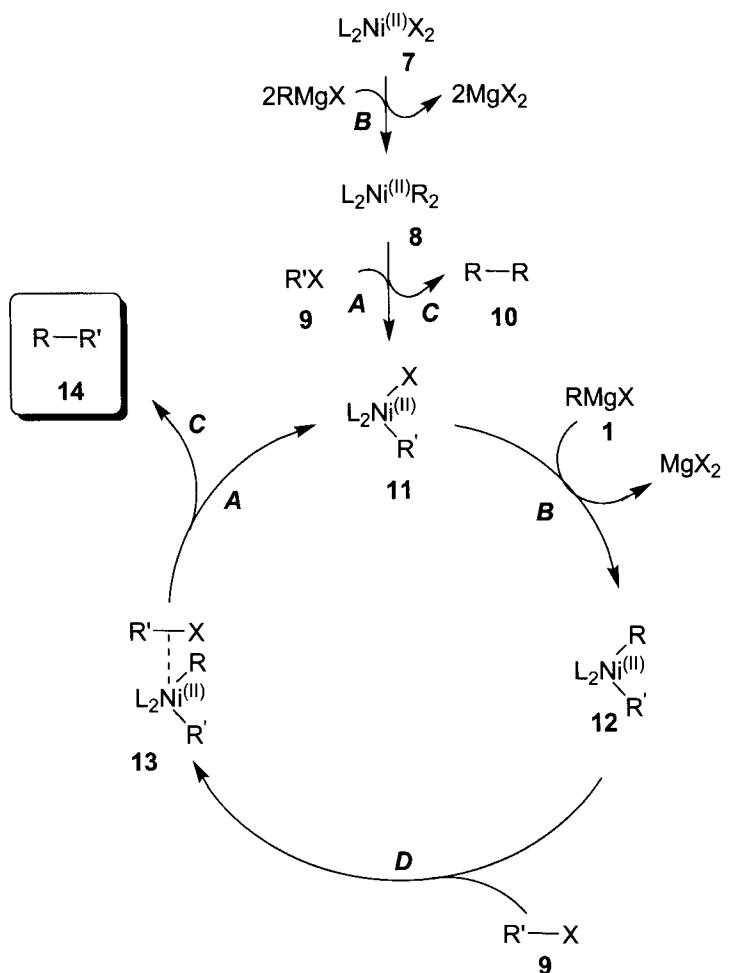
reagent, however, it remains uncertain whether a radical or polar pathway is occurring in the case of the nickel salt. Even the independent reports by Corriu and Kumada, published in 1972, followed a flurry of activities on the transition metal-catalyzed C–C bond forming reactions of unreactive alkenyl and aryl halides.<sup>18–23</sup>

Key to the publication of Kumada and co-workers, was the use of a nickel(II)–phosphine complex. Indeed, they subsequently demonstrated that the catalytic activity of the complex strongly depends on the nature of the phosphine ligand.<sup>4</sup> In 1973, it was reported that the use of an optically active phosphine ligand could induce asymmetric induction in the related reaction of secondary alkyl Grignard reagents and vinyl chloride, under nickel catalysis.<sup>24,6</sup> Perhaps the most notable development however, was a publication by S.-I. Murahashi and co-workers, which detailed the ability of the Kumada cross-coupling to be carried out under palladium, as apposed to nickel catalysis.<sup>25,5</sup> One distinct advantage of this procedure, was that it allowed versatile organolithium reagents to be used as an alternative to Grignard reagents.

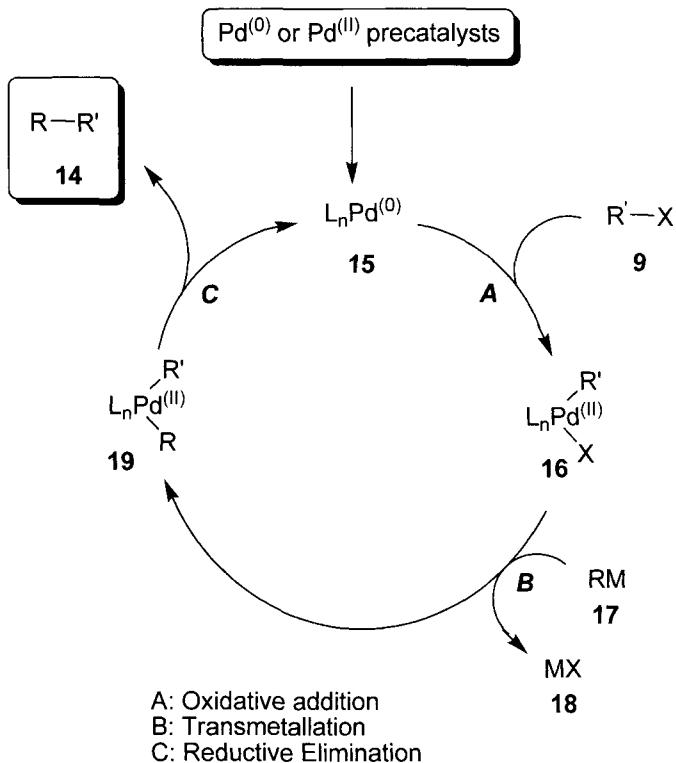
Following this early activity, application of the Kumada cross-coupling reaction in synthesis dwindled somewhat in latter years. This was a result of issues with functional group compatibility: The high basicity of Grignard and organolithium reagents prohibits the use of base-sensitive functional groups. Alternative protocols using less nucleophilic (and basic) coupling reagents such as organozinc (Negishi), organoboron (Suzuki–Miyaura), organotin (Stille) and organosilicon (Hiyama) became more widespread.<sup>26</sup> However, since many of the alternative coupling reagents are synthetically prepared from Grignard or organolithium reagents, these alternative procedures are less direct and experimentally straightforward than the Kumada coupling. Thus this procedure has seen a slight renaissance lately.<sup>27,28</sup>

### 1.1.3.3 Mechanism

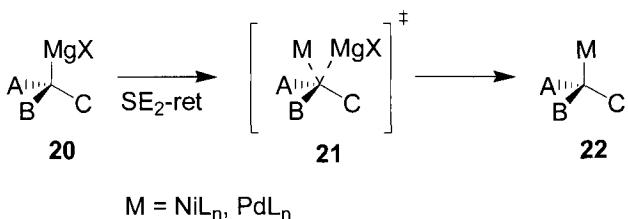
The general mechanism of the nickel-catalyzed process can be described as follows: The initial nickel(II) complex **7** undergoes transmetallation with the Grignard reagent **1** to form a diorganonickel species **8**. Reaction of complex **8** with an organohalide **9** forms the homocoupled product **10** and the nickel(II) species **11**, which enters the catalytic cycle. This preliminary sequence can be viewed as initiation of the nickel complex, and is negligible in the overall reaction due to the catalytic quantity of nickel. The first step of the catalytic cycle is transmetallation of the active nickel(II) complex **11** with Grignard reagent **1**. Coordination of the organohalide **9** to the diorganonickel species **12**, gives complex **13** which subsequently undergoes oxidative addition of organohalide **9**, releasing the coupled product **14**.<sup>29</sup>



In the basic mechanism for the palladium-catalyzed process, organohalide **9** undergoes oxidative addition to a palladium(0) catalyst **15** to afford a  $\sigma$ -organopalladium(II) complex **16**. All palladium precatalysts are converted to the active palladium(0) catalyst **15** *in situ*, most commonly by phosphine in phosphine assisted catalytic cycles. Transmetalation of the palladium(II) complex **16** with organometallic reagent **17** gives diorganopalladium complex **19**. Reductive elimination of the product **14** regenerates the active palladium(0) catalyst.<sup>29</sup>



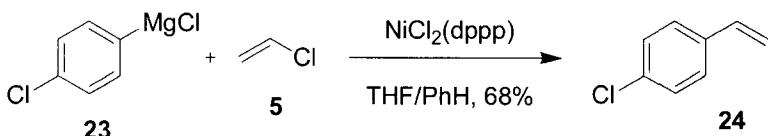
While useful in explaining the discrete mechanistic steps of the Kumada cross-coupling reaction this generalized scheme ignores the precise coordination number, geometry and formal charge of the nickel or palladium centres. Indeed, readers are referred to more detailed mechanistic studies for further information.<sup>30,31</sup> For example, in the palladium catalyzed reaction, Murahashi has pointed out the benefit of using  $\text{Pd}(\text{PPh}_3)_2\text{LiCl}$ , formed upon addition of methyl lithium to  $\text{PdCl}_2(\text{PPh}_3)_2$ .<sup>5</sup> Following their publication of this synthetic method in 1984,<sup>32</sup> Negishi confirmed the presence of  $\text{Pd}(\text{PPh}_3)_2\text{LiCl}$  in the reaction.<sup>33</sup> It has since been established in elegant studies by Amatore and Jutand, that anions can play a vital role in palladium mediated cross-couplings, and that in many cases, the active catalytic species may involve a formally anionic palladium centre.<sup>31</sup> This situation is most likely further complicated by the presence of strongly nucleophilic Grignard or organolithium reagents. Indeed, Knochel has postulated that an organopalladate of the type  $[\text{MgX}]^+[\text{RPdL}_2]^-$  may be involved in certain coupling processes.<sup>34</sup>



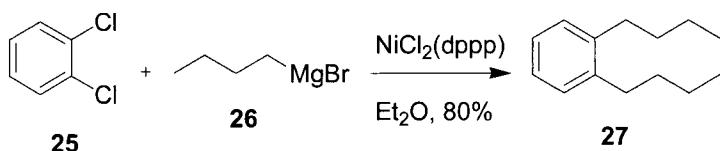
For given systems it is possible to render the Kumada cross-coupling stereoselective. Elegant studies by Hoffmann and co-workers have provided details on the stereochemical course of the transmetallation step when using saturated reaction partners.<sup>35</sup> Utilizing a chiral Grignard reagent as a probe, they determined that transmetallation of the Grignard reagent **20** by nickel or palladium, proceeds with retention of configuration to give **22**; a concerted S<sub>E2</sub>-ret process.<sup>36</sup> Since virtually all examples of asymmetric Kumada cross-coupling reactions use racemic secondary Grignard reagents (the Grignard reagents usually undergo racemization on a rate comparable to cross-coupling), they can be viewed as a dynamic kinetic resolution, with transmetallation as the enantiodiscriminating step.<sup>6</sup>

#### 1.1.3.4 Synthetic Utility

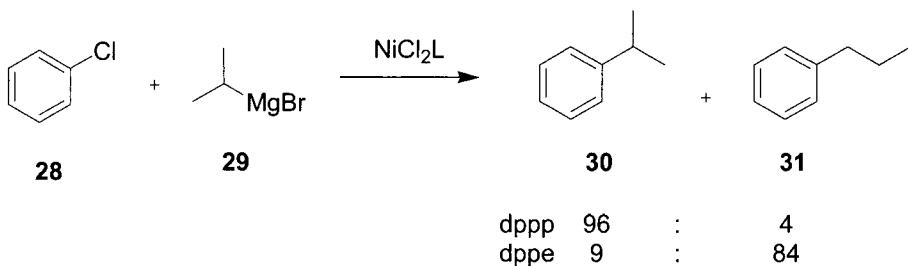
Despite its historical significance, the application of the Kumada cross-coupling reaction in synthesis dwindled somewhat in recent years due to due issues with functional group compatibility, and thus alternative cross-coupling protocols have flourished.<sup>26</sup> In certain cases however, the Kumada cross-coupling offers distinct advantages. For example, in many palladium-mediated cross-coupling reactions, the use of aryl or alkenyl bromides, iodides or tosylates are required as a cross-coupling partner. The use of readily available and cheap aryl or alkenyl chloride reagents is problematic, due to their low reactivity towards oxidative addition to Pd(0).<sup>26</sup> On the other hand, for the nickel-catalyzed Kumada cross-coupling, aryl or alkenyl chlorides are the reagent of choice in view of their high reactivity and high yields.<sup>4</sup> Indeed, the Hokko Chemical Industry Company Ltd., Japan, industrialized a process involving a Kumada coupling of aryl Grignard reagents (for example, **23**) and vinyl chloride (**5**) to give styrene compounds in good yields. In 2002, it was reported that styrene **24** was being prepared at approximately 5000 kg per year using this process.<sup>37</sup>



Kumada, Tamao and co-workers demonstrated another important aspect of the Kumada cross-coupling reaction prior to 1982.<sup>38</sup> They demonstrated that even alkyl Grignard reagents containing  $\beta$ -hydrogen atoms can selectively undergo cross-coupling. For example, *o*-dibutylbenzene (**27**) can be prepared in good yield from butyl Grignard reagent **26** and dichlorobenzene **25**.

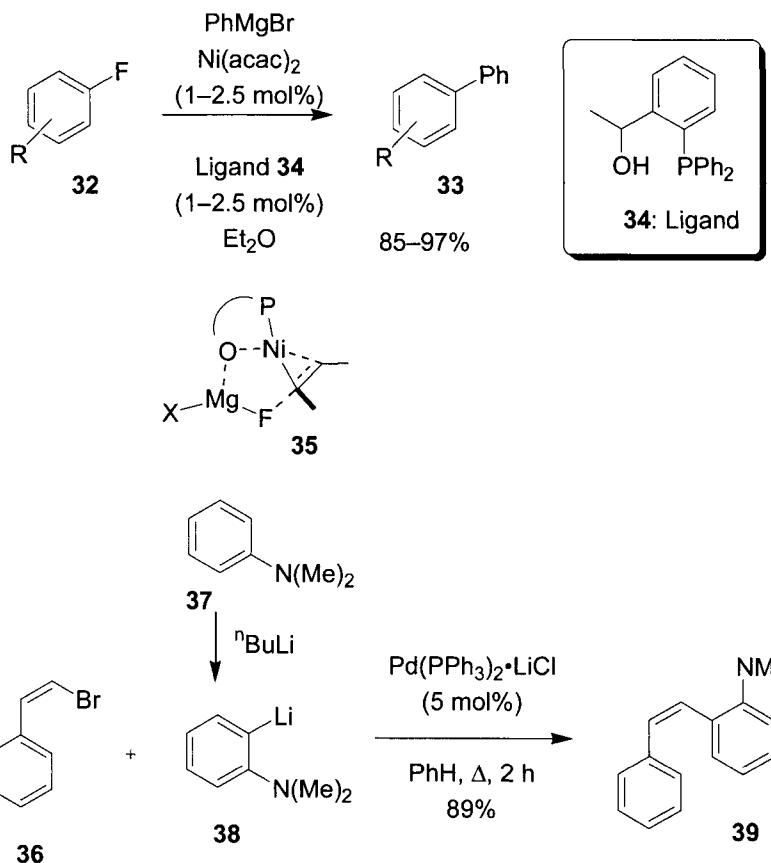


The use of secondary alkyl Grignard reagents however, can result in product mixtures. This is due to alkyl group isomerization from secondary to primary, and has been shown to be highly dependent on the basicity of the phosphine ligands, as well as the electronic nature of the aromatic halides.<sup>39,40</sup> For example, cross-coupling of *sec*-propyl Grignard reagent **29** with chlorobenzene (**28**), results in the desired product **30** in a 96 : 4 ratio when 1,3-bis(diphenylphosphino)propane (dppp) is used as a ligand, whereas isomerization is the major mechanistic pathway when 1,3-bis(diphenylphosphino)ethane (dppe) is employed.



The importance of the seminal paper by Kumada, Tamao and co-workers lies in the use of nickel-phosphine complexes, rather than nickel salts in the Kumada cross-coupling reaction.<sup>10</sup> As the example above already demonstrates, the ability to tune the reactivity of the system by modifying the group which ligates the nickel is of prime importance, and results in a versatile catalytic procedure. As already discussed, the use of aryl or alkenyl chloride reagents is problematic in palladium-mediated cross-coupling reactions,<sup>26</sup> and aryl fluorides are highly inert due to the strength of the C–F bond. While Kumada and Tamao first demonstrated that aryl fluorides are suitable reagents for the nickel-catalyzed Kumada cross-coupling (albeit in poor yields),<sup>4</sup> Herrmann and co-workers demonstrated, that in the presence of suitably stabilizing ligands (*N*-heterocyclic carbenes in this case), aryl

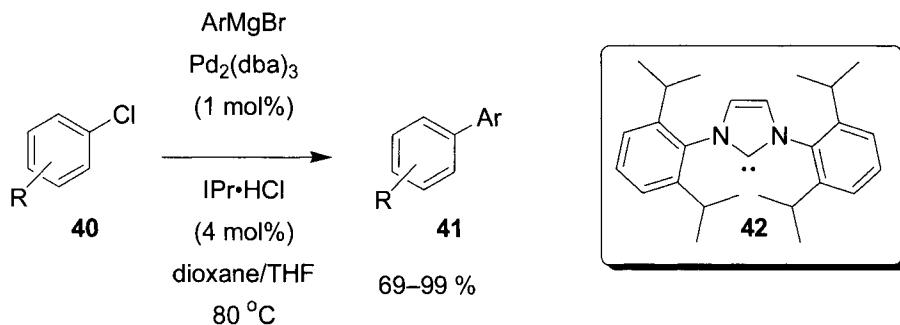
fluorides and aryl Grignard reagents can be coupled at ambient temperature.<sup>38</sup> Similarly, Ackermann and co-workers have disclosed a phosphine oxide ligand which can mediate an analogous reactivity profile.<sup>39</sup> In an alternative, but related approach, a fascinating report by Nakamura and co-workers detailed the use of bimetallic cooperation to realize this transformation. They reported the efficient coupling of aryl fluorides **32** with phenylmagnesium bromide, catalyzed by nickel ligated to **34**.<sup>40</sup> Computational studies indicated that a bimetallic synergy facilitates C–F bond activation in the oxidative addition step, and the oxidative addition transition state can be represented by structure **35**.



While the nickel-catalyzed reaction facilitates oxidative addition of substrates problematic to palladium-mediated processes, there is still a great deal of interest in the palladium-catalyzed Kumada cross-coupling reaction due to its enhanced chemoselectivity.<sup>25,5</sup> Also, as mentioned previously, one distinct advantage of the palladium-catalyzed procedure, is that it allows versatile organolithium reagents to be used as an alternative to Grignard

reagents. The strongest merit of organolithium reagents is their preparation by direct lithiation of hydrocarbons, particularly when directed by neighbouring heteroatoms. Thus, lithiated aniline derivative **38**, prepared *in situ* from *ortho*-lithiation of **37** can be coupled directly to vinyl bromide **36** in good yield.<sup>5</sup> Clearly, this procedure is extremely experimentally straightforward and therefore highly useful for given cases.

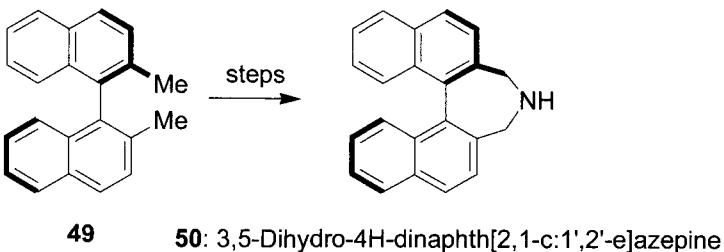
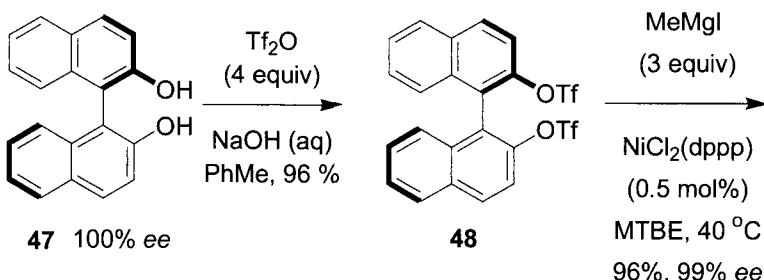
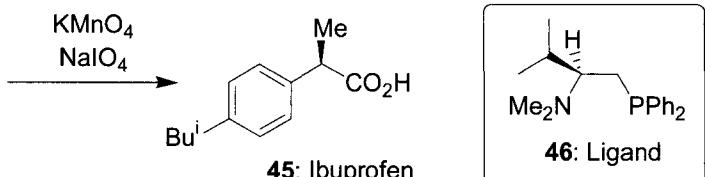
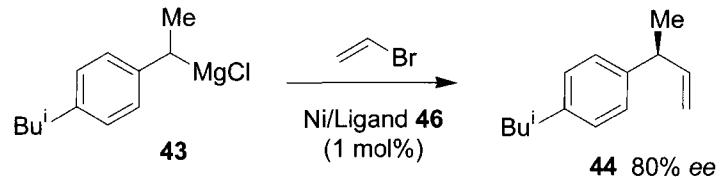
As discussed above however, a switch from nickel to palladium renders the use of aryl or alkenyl chloride reagents problematic, due to their low reactivity towards oxidative addition to Pd(0).<sup>26</sup> To overcome this issue, in 1999 Nolan and co-workers reported the palladium-catalyzed Kumada cross-coupling of aryl chlorides using *N*-heterocyclic carbenes as ligands for the palladium centre.<sup>41</sup> Using *N*-heterocyclic carbene **42** (prepared *in situ* from the imidazolium salt, IPr•HCl), the biaryl products **41** were isolated in moderate to good yields. A subsequent publication from Li in 2002 detailed the use of a phosphine oxide ligand to mediate an analogous process.<sup>42</sup> Finally, other *N*-heterocyclic carbene-based precatalysts have been reported to mediate this transformation.<sup>43</sup>



### Asymmetric Kumada Cross-Coupling

Asymmetric synthesis using the Kumada cross-coupling reaction has most frequently been studied using racemic secondary Grignard reagents.<sup>3</sup> Since such reagents usually undergo racemization on a rate comparable to cross-coupling, the reaction process can be viewed as a dynamic kinetic resolution to produce enantioenriched products. The first example of an asymmetric, nickel-catalyzed Kumada cross-coupling reaction utilized (−)-DIOP as a ligand, although the products were only isolated in 13–17% *ee*.<sup>24,3</sup> Subsequent studies have surveyed a large number of optically active phosphines in the quest for improved enantioselectivities. Two of the best ligand systems are the ferrocenylphosphines containing (dialkylamino)alkyl sidechains and β-(dialkylamino)alkylphosphines.<sup>3</sup> For example, in the latter class of ligands, Valphos (**46**) was shown to mediate the asymmetric Kumada

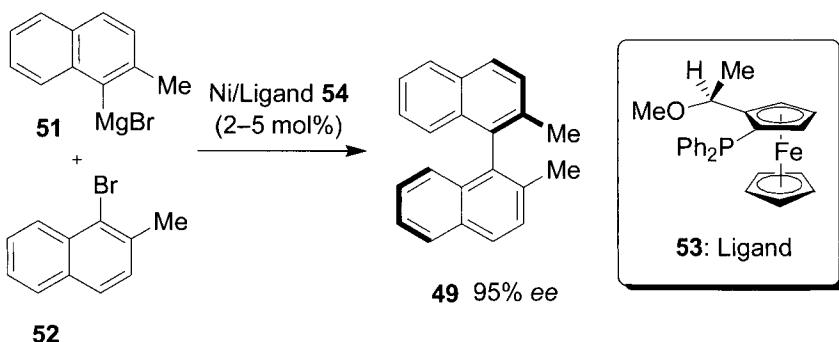
cross-coupling of racemic Grignard reagent **43** with vinyl bromide to give **44** in 80% *ee*. Oxidative cleavage of the double bond gave a short synthesis of the anti-inflammatory agent Ibuprofen (**45**).<sup>44</sup>



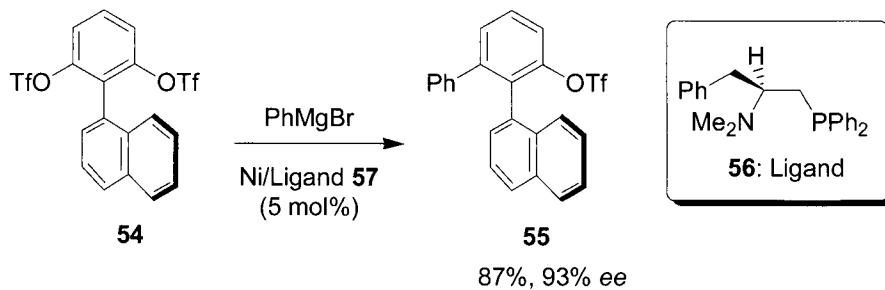
Unfortunately, despite significant work,<sup>3</sup> there are very few reports detailing the asymmetric Kumada cross-coupling of racemic secondary Grignard reagents, to give truly exception levels of enantioselection (> 95% *ee*). One area that has shown promise however, is in the synthesis of axially chiral biaryls.<sup>3</sup> Indeed, control of atropisomeric selectivity in asymmetric cross coupling reactions is an exciting and challenging field.<sup>45</sup> In order to prepare azepine **50**, a precursor to C<sub>2</sub>-symmetric chiral quaternary ammonium salts, that can serve as asymmetric phase-transfer catalysts,

Ikunaka *et al.* employed a Kumada cross-coupling reaction.<sup>46</sup> Conversion of commercially available (*R*)-BINOL (**47**) to the bistriflate **48**, followed by Kumada cross-coupling with methylmagnesium iodide, gave access to methyl derivative **49** in good yield. The synthesis proved reliable and scalable as apposed to other cited reports.

For the above example however, the Kumada cross-coupling is not stereoselective and the source of chiral information lies in the commercially available, but relatively expensive (*R*)-BINOL (**47**). An impressive alternative was reported 15 years previous to this by Hayashi and co-workers.<sup>47</sup> Asymmetric cross-coupling of aryl Grignard **51** with napthyl bromide **52**, gave the desired product **49** in an impressive 95% *ee*. While other ligands had proved less successful in mediating an analogous transformation,<sup>3</sup> the use of ferrocenylphosphine (*S*)-(R)-**53** dramatically improved the selectivity.<sup>47</sup>

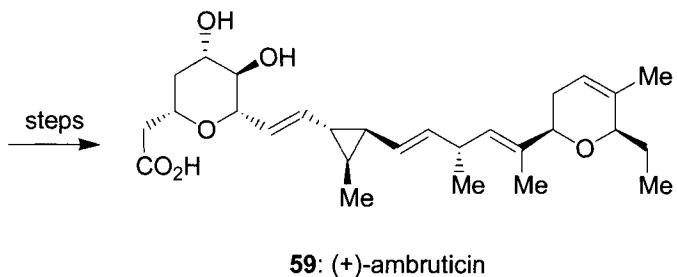
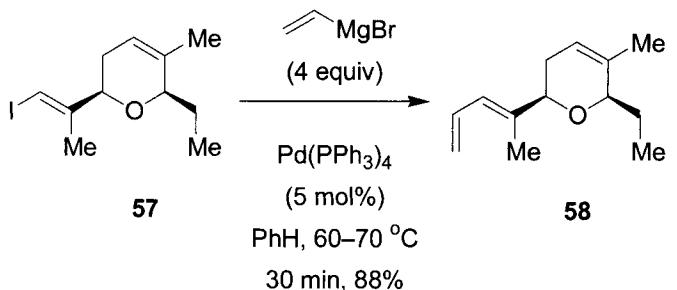


In another example of the enantioselective synthesis of axially chiral molecules, Hayashi and co-workers reported the successful enantioselective asymmetric Kumada cross-coupling, for the preparation of **55**. Indeed, using (*S*)-phenphos (**56**) as a ligand, the Kumada cross-coupling of bistriflate **54** gave the desired product **55** in good yield and a high level of asymmetric induction.<sup>48</sup>

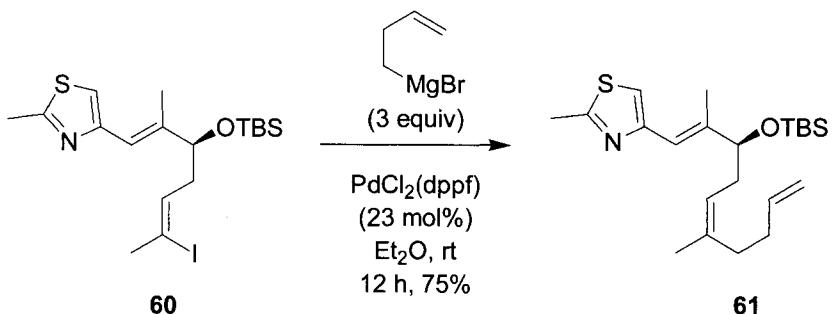


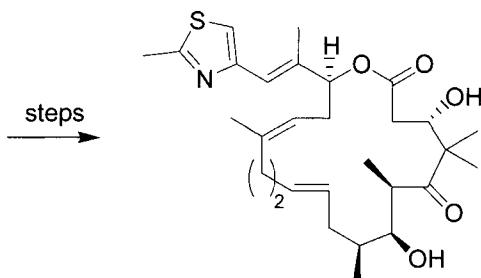
*Natural Product Synthesis*

There are several examples of the synthesis of naturally isolated, complex molecular architectures utilizing the Kumada cross-coupling as a key step. For example, the enantioselective synthesis of (+)-ambruticin (**59**) was reported from the laboratories of Jacobsen.<sup>49</sup> Conversion of an (*E*)-vinyl iodide **57** to diene **58** was achieved in good yield using a Kumada cross-coupling. The stereochemistry of the vinyl iodide **57** was conserved in the transformation.



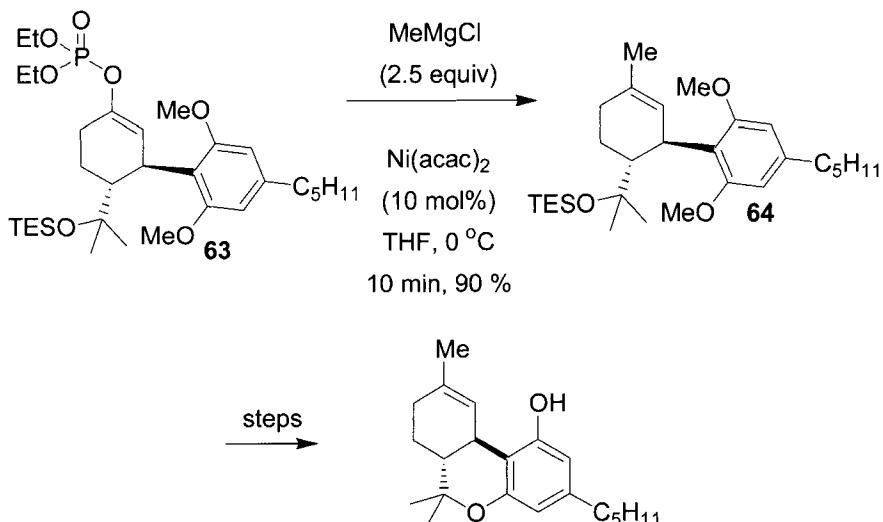
**59:** (+)-ambruticin



**62:** [18]-dehydrodesoxyepothilone B

In 2002, Danishefsky and co-workers reported a highly concise synthesis of [18]-dehydrodesoxyepothilone B (**62**).<sup>50</sup> The synthetic approach was based on a key ring-closing metathesis reaction, and the precursor to this was prepared by a Kumada cross-coupling reaction. Coupling of vinyl iodide **60** with allylmagnesium bromide, under palladium-catalyzed conditions gave key intermediate **61** in good yield.

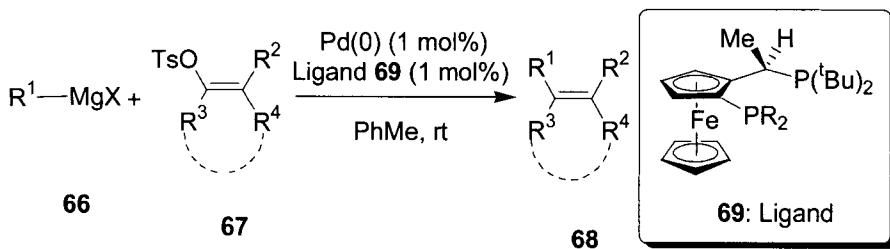
The synthesis of tetrahydrocannabinol **65** by Kobayashi and co-workers employed a Kumada cross-coupling in its final stages, utilizing an unusual enol phosphate as the substrate.<sup>51</sup> The synthetic sequence employed a three-step 1,4-addition strategy to functionalize an  $\alpha$ -iodinated cyclohexanone via the conjugate addition of a cuprate. The resulting enolate was trapped as the corresponding phosphate **63** and engaged in a Kumada cross-coupling reaction with methylmagnesium chloride.

**65:**  $\Delta^9$ -Tetrahydrocannabinol

### 1.1.3.5 Variations and Improvements

#### Kumada Cross-Coupling of Aryl Tosylates

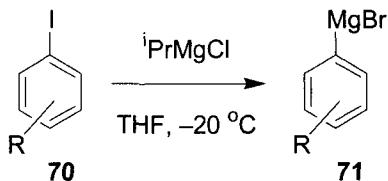
As described above, many electrophiles can be utilized in the Kumada cross-coupling including aryl and alkenyl iodides, bromides, chlorides and fluorides. To enable oxidative addition of a carbon–oxygen bond, it is usual to convert it to an aryl or vinyl triflate. Aryl or vinyl tosylates on the other hand are used much less frequently employed, despite the fact that they are readily prepared and cheaper than the corresponding triflates. They are also more stable to water and often crystalline. This greater stability however, renders them less-reactive towards oxidative addition, and therefore catalytic procedures with an enhanced activity must be applied. Studies by Hartwig and co-workers have demonstrated that aryl and alkenyl tosylates are suitable reaction partners in the palladium-catalyzed Kumada cross-coupling.<sup>52,53</sup> Using sterically hindered ligands from the Josiphos family **69**, efficient coupling of aryl or alkenyl tosylates **67** with Grignard reagents **66** was observed in good to excellent yields at ambient temperature. Additional studies by Ackermann and co-workers have demonstrated that phosphine oxides are also suitable ligands for the Kumada cross-coupling of aryl tosylates.<sup>54</sup>



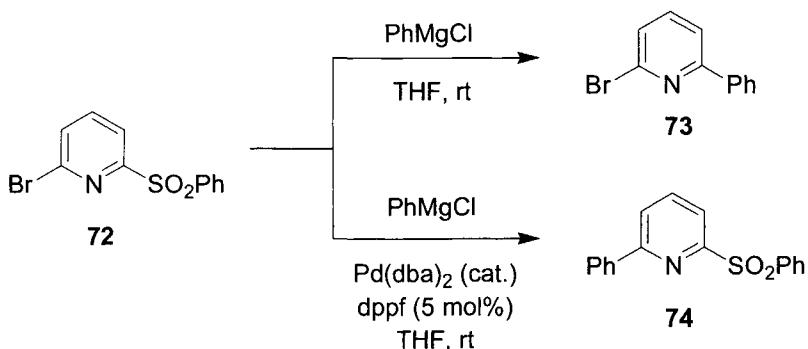
#### Cross-Coupling of Knochel-type Grignard Reagents and Triarylmagnesiates

Traditionally, the palladium-catalyzed Kumada cross-coupling was developed to allow the use of organolithium reagents. The attractiveness of these reagents in synthesis stems from their ease of preparation, either by direct lithiation of hydrocarbons or low temperature lithium halogen exchange.<sup>55</sup> The downside of their use however, is that the high polarity of the carbon–lithium bond precludes the presence of sensitive functional groups. Classically, Grignard reagents are prepared by direct reaction of magnesium metal with organic halides at elevated temperatures. Unfortunately, this method is also not compatible with sensitive functionality. In recent years, pioneering work by Knochel has demonstrated the power of the magnesium-

halogen exchange reaction. Using *i*-propylmagnesium chloride at temperatures below 0 °C, Knochel has published extensively on the synthesis of functionalized Grignard reagents **71** from the magnesium–halogen exchange of aryl iodides **70**.<sup>56,57</sup> Since only reactive electrophiles such as aldehydes and ketones react with Grignard reagents rapidly at temperatures below 0 °C, a whole host of Grignard reagents can be prepared bearing sensitive functional groups.<sup>56,57</sup>

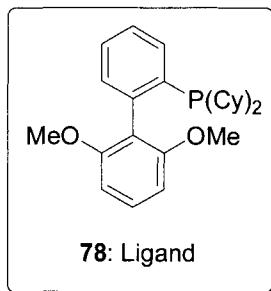
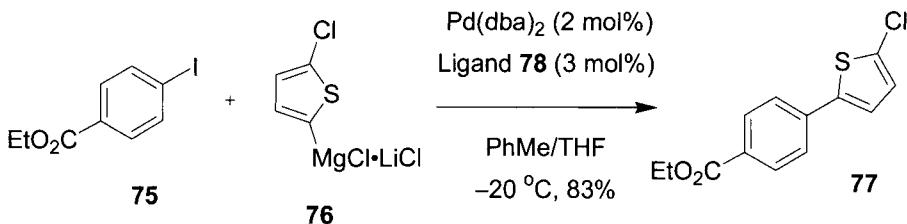


These elegant studies by Knochel and co-workers have reinvigorated the use of Grignard reagents in synthesis, due to the ready availability of reagents bearing previously unobtainable functionality. Also, due to the more covalent nature of the carbon-magnesium bond, these reagents are, in general, more functional group compatible than the corresponding organolithium reagents.<sup>57</sup> A large body of Knochel's work focuses on the functionalization of heteroaromatics.<sup>56,57</sup> For example, during their studies Knochel and co-workers noticed an interesting selectivity in the synthesis of pyridine derivatives using a Kumada cross-coupling. Exposure of bromopyridine derivative **72** to phenylmagnesium chloride results in the direct substitution of the phenyl sulfonyl group in 77% yield, whereas under Kumada conditions, smooth cross-coupling of the Grignard reagent with the aryl bromide moiety results in the production of biaryl **74**.<sup>58</sup>

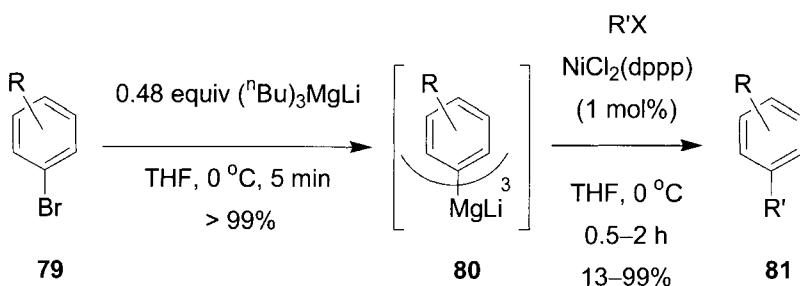


Despite the synthetic flexibility of the magnesium–halogen exchange using *i*-propylmagnesium chloride, the reaction is still considerably slow, especially with substrates other than organic iodides. Knochel and co-

workers have recently reported an improved system however, which employs one equivalent of lithium chloride.<sup>59</sup> Thus, magnesium–halogen exchange is mediated by *i*-PrMgCl•LiCl, which has a greatly enhanced reactivity profile, allowing the exchange of aryl bromides at low temperature. It is postulated that enhanced reactivity upon addition of LiCl stems from breaking down of the aggregated *i*-PrMgCl, in addition to the reactive nature of the magnesiate [*i*-PrMgCl<sub>2</sub><sup>-</sup>Li<sup>+</sup>].<sup>59</sup> This method has allowed the preparation of Grignard reagents bearing highly sensitive functionality. Despite this success, in the context of the Kumada cross-coupling, temperatures above 0 °C are required, at which unfortunately, these sensitive magnesiate reagents are often unstable. Recent work by Buchwald and co-workers however, has recently opened up the possibility of utilizing Knochel's magnesiates in the Kumada cross-coupling reaction. Utilizing the most active ligand systems developed in his laboratories (such as **78**), Buchwald and co-workers demonstrated the effective Kumada cross coupling of aryl iodides and Knochel-type magnesiates at temperatures ranging from -20 to -62 °C.<sup>60</sup> For example, Kumada cross-coupling of functionalized thiophene **76** with aryl iodide **75** gave access to **77** in good yield.



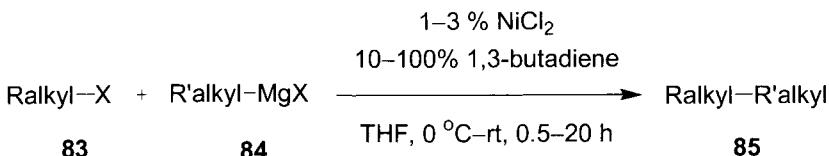
One of the remaining major drawbacks in the synthesis of functionalized aryl Grignard reagents is that magnesium insertion or halogen–magnesium exchange on electron-rich aryl halides is often problematic.



Recent work by Lau and co-workers has addressed this issue in the synthesis of electron-rich biaryls. While magnesium–halogen exchange of **79** using Knochel’s conditions failed to give the desired Grignard reagents, Lau and co-workers found that conversion to the triaryl magnesiate **80** proceeded in high yield in five minutes.<sup>61</sup> They subsequently found that such magnesiates undergo efficient nickel-catalyzed Kumada cross-coupling reactions in mostly high yield.

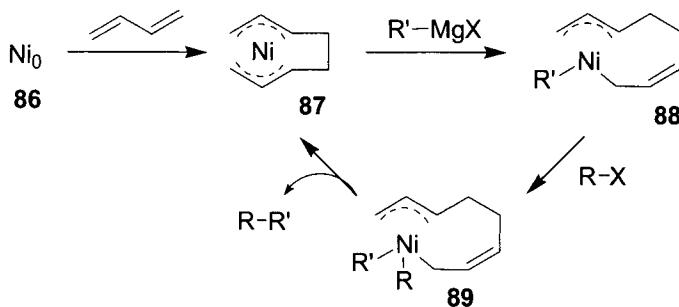
#### *Kumada Cross-Coupling of Alkyl Halides*

While aryl and vinyl electrophiles have been thoroughly investigated as cross-coupling partners over the last 30 years or so, the use of alkyl halides as electrophiles has remained largely unknown until recently.<sup>62</sup> Firstly, since the  $\text{C}(\text{sp}^3)\text{—X}$  bond in alkyl halides is more electron rich than the  $\text{C}(\text{sp}^2)\text{—X}$  bond in aryl and vinyl halides, these substrates are much less reactive to oxidative addition to a low-valent transition metal complex. Furthermore, the resultant alkyl metal complex is highly reactive owing to the absence of stabilizing electronic interactions with the metal d orbitals.<sup>62</sup> As such, the fast and thermodynamically favoured  $\beta$ -hydride elimination leads predominantly to olefinic by-products in the majority of catalytic systems. Finally, the relatively slow reductive elimination of the cross-coupling product increases the likelihood of further side-reactions (elimination, hydrodehalogenation).<sup>62</sup>



Although the first report of this type of coupling appeared in the 1970s from the laboratories of J. K. Kochi,<sup>21,22</sup> only a few subsequent publications emerged until the early 1990s. In 1992, Suzuki demonstrated the ability of alkyl halides to be used in the cross-coupling of organoboron reagents,<sup>63</sup> whereas in 1995 Knochel reported the use of organozinc

reagents.<sup>64</sup> In terms of the Kumada cross-coupling however, Kambe and co-workers first reported the nickel-catalyzed cross-coupling of alkyl bromides, chlorides and tosylates **83** with Grignard reagents **84** in 2002.<sup>65</sup> It is important to note that prior to this study, several other publications on a similar theme had emerged using other metallic catalysts. Fascinatingly, Kambe and co-workers reported the beneficial addition of 1,3-butadiene as opposed to phosphine ligands. Cross-coupling of alkyl bromides and tosylates was observed quantitatively at 0 °C in the presence of the diene, whereas reduction and/or elimination of the electrophile were mainly observed in its absence. Mechanistically, they postulated that nickel (0), generated from reduction of nickel(II) by the Grignard reagent, undergoes reaction with 2 equivalents of butadiene to generate **87**. Transmetallation with the Grignard reagent gives the formally anionic species **88**, which undergoes alkylation and reductive elimination to give the product and regenerate the catalyst.<sup>65</sup> It is important to note however, that this postulation, inferring nickel(IV) intermediate, contradicts mechanistic interpretations of similar nickel-catalyzed cross coupling reactions.<sup>62</sup>



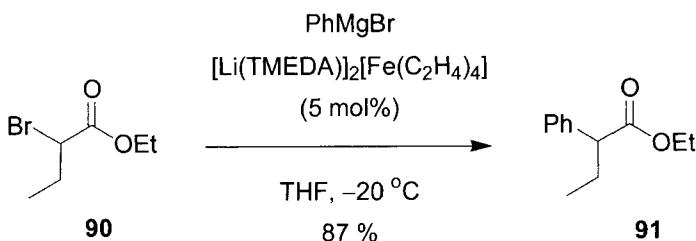
The following year, Kambe and co-workers reported an analogous strategy using a palladium catalyst,  $[\text{Pd}(\text{acac})_2]$ .<sup>66</sup> Once again, the need for 1,3-butadiene was highlighted and the palladium-catalyzed system exhibited higher chemoselectivity. Another report emerged from the same group highlighting the use of nickel or copper catalysts in the alkyl–alkyl cross-coupling reaction of alkyl fluorides.<sup>67</sup> As well as these pioneering efforts, reports have emerged from the laboratories of M. Beller which highlight the Kumada cross-coupling of alkyl chlorides under palladium catalysis.<sup>68,69</sup>

#### *Other Metallic Catalysts*

Numerous other metallic salts have been shown to exhibit similar reactivity profiles in the Kumada coupling, although not necessarily via the same mechanistic pathway. Even in the early studies of Kharasch, Kochi, Gilman and a variety of others, cobalt and iron salts displayed similar reactivity to

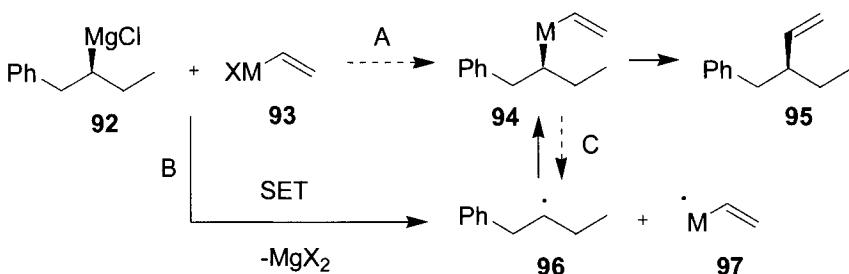
nickel and palladium. Perhaps as a result of this, the use of cobalt and iron salts has been resurrected in cross-coupling reactions. For example, Knochel has demonstrated that catalytic cobalt(II) chloride is able to mediate a Kumada cross-coupling of chloroheteroaromatics with aryl Grignard reagents in good yield.<sup>70</sup> Likewise, Oshima and co-workers have reported the use of cobalt(III) acetylacetonate in the catalyzed Kumada cross-coupling of alkyl halides with 1-(trimethylsilyl)ethenylmagnesium, although large catalytic loadings of the cobalt complex were required.<sup>71</sup>

With the growing importance of sustainable chemistry however, iron-catalyzed cross-coupling reactions are becoming more-widespread, owing to the fact iron is inexpensive and more environmentally friendly than palladium, cobalt, or nickel. While important breakthroughs have been made in the laboratories of Cahiez and Nakamura, the use of iron in the Kumada cross-coupling has been pioneered by A. Fürstner and co-workers.<sup>72</sup> Using  $\text{FeX}_n$  ( $n = 2, 3$ ;  $X = \text{Cl}, \text{acac}$ ) as a precatalyst, Fürstner and co-workers observed the effective cross-coupling of a variety of substrates with Grignard reagents. It was postulated that the active catalysts were highly reduced iron-magnesium clusters of formal composition  $[\text{Fe}(\text{MgX})_2]_n$ , in which the iron is in its -2 oxidation state.<sup>72</sup> To probe this hypothesis, they utilized a structurally defined iron(-II) complex,  $[\text{Li}(\text{tmEDA})_2][\text{Fe}(\text{C}_2\text{H}_4)_4]$  in the Kumada cross-coupling of alkyl halides with Grignard reagents.<sup>72</sup> Pleasingly, this catalyst was extremely effective, and since the iron-catalyzed reaction turned out to be significantly faster than the uncatalyzed version, the process tolerated other polar groups present in the substrates. For example,  $\alpha$ -bromoester **90** was converted to its phenylated derivative in high yield within minutes.<sup>72</sup>



Although the mechanism of this reaction is not entirely understood, studies by Hoffmann and co-workers have provided some interesting insight.<sup>35</sup> Utilizing a chiral Grignard reagent as a probe, they observed a significant loss of optical purity of the cross-coupling product, when mediated by low-valent iron or cobalt. They attribute this to the transmetalation step, which may involve a radical pathway, i.e. pathway B. However, since the actual oxidation state of the metal is unknown (and hence its ability to oxidize a Grignard reagent), they also mention another potential

mechanistic scenario, whereby reversible carbon–metal bond homolysis could lead to racemisation.<sup>35</sup>

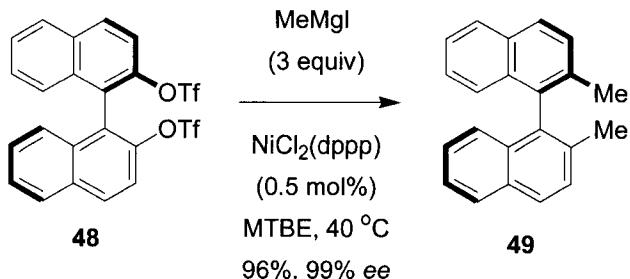


M = Fe or Co species of unknown oxidation state

Fürstner has also reported the loss of optical purity in the iron-catalyzed cross-coupling of optically-pure secondary alkyl halides, as well as the cyclization of alkyl iodides bearing unsaturation, both of which suggest the presence of radical intermediates.<sup>72</sup> Numerous substrates however, do not undergo analogous 5-*exo*-trig cyclizations and tertiary halides remain unchanged and thus caution should be taken in generalizing the exact mechanistic pathway for all substrates.<sup>72</sup> Mechanistic studies are ongoing in the laboratories of A. Fürstner. For example, recently he has reported the isolation and structural characterization of a homoleptic “super-ate” complex of iron, which has implications in the iron-catalyzed Kumada cross-coupling reaction.<sup>73</sup>

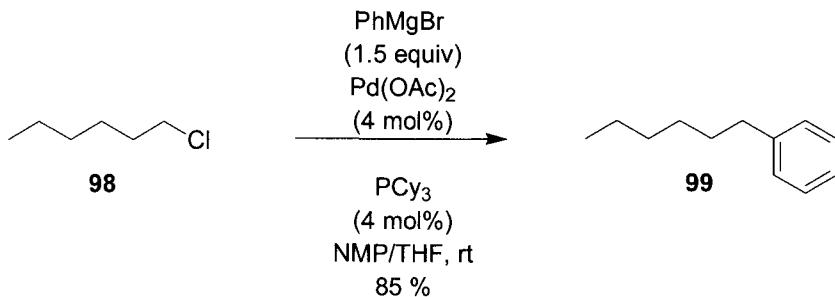
### 1.1.3.6 Experimental

#### Standard Nickel-Catalyzed Procedure



**(R)-2,2'-Dimethyl-1,1'-binaphthyl (49).**<sup>46</sup>

Under an atmosphere of nitrogen, a solution of MeI (3.90 g, 27.5 mmol) in *tert*-butyl methyl ether (MTBE, 4.0 mL) was added dropwise to a stirred suspension of Mg turnings (660 mg, 27.1 mmol) in MTBE (7.0 mL) such that gentle reflux was maintained throughout the addition. The mixture was allowed to cool to 30 °C where MTBE (5.0 mL) and NiCl<sub>2</sub>(dppp) (250 mg, 0.46 mmol) were added in sequence. A solution of crude (R)-48 (5.00 g, 9.08 mmol) in MTBE (20 mL) was added dropwise, and the mixture was stirred and heated under reflux (at 55 °C) for 30 min. Consumption of (R)-48 was confirmed by TLC [AcOEt/*n*-hexane (1:4); *Rf* 0.46 for (R)-48, 0.79 for (R)-49]. The mixture was allowed to cool to room temperature (20–25 °C). PhMe (30 mL) was added, and the mixture was poured into ice-chilled water (50 mL). To the mixture was added 35% aqueous HCl (50 mL). The layers were separated, and the organic layer was washed with H<sub>2</sub>O (30 mL × 2) and saturated aqueous NaCl solution (30 mL × 1). The organic solution was dried (MgSO<sub>4</sub>) and concentrated in vacuo [40–50 °C (bath temperature), 50–60 mmHg]. The solid residue (2.60 g) was mounted on a short pad of silica gel (Merck Kieselgel 60, 7.8 g). Elution with AcOEt/*n*-hexane (1 : 4; 200 mL) gave (R)-49 (2.46 g, 96.1%) as white crystals: 99.6% ee.

*Highly-Active Palladium-Catalyzed Procedure.***Hexylbenzene (99).**<sup>68</sup>

A 25-mL Schlenk flask was charged with Pd(OAc)<sub>2</sub> (0.0180 g, 0.080 mmol) and PCy<sub>3</sub> (0.0224 g, 0.080 mmol), sealed with a septum, and purged with argon for 15 min. NMP (5 mL) and **98** (0.27 mL, 2 mmol) were added by syringe. Then, phenylmagnesium bromide (3 mL, 3 mmol, 1 M in THF) was added dropwise over 1 min to the stirred mixture. After 20 h at room temperature, the reaction was quenched with MeOH (1 mL) and water (1 mL). The solution was concentrated to about 6 mL by rotary evaporation, and subjected to silica gel column chromatography (heptane) to give a colorless liquid (0.276 g, 1.7 mmol, 85% yield).

## 1.1.3.7

## References

1. [R] Negishi, E.-I.; Liu, F. *Palladium- or Nickel-Catalyzed Cross-Coupling With Organometals Containing Zinc, Magnesium, Aluminium and Zirconium*. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 1998, 1.
2. [R] Anastasia, L.; Negishi, E.-I. *Palladium-catalyzed Aryl-Aryl Coupling*. In *Handbook of Organopalladium Chemistry for Organic Synthesis*: 2002, Vol. 1, 311.
3. [R] Hayashi, T. *Palladium-catalyzed Asymmetric Cross-Coupling*. In *Handbook of Organopalladium Chemistry for Organic Synthesis*: 2002, Vol. 1, 791.
4. [R] Tamao, K. *J. Organomet. Chem.* **2002**, *653*, 23.
5. [R] Murahashi, S.-I. *J. Organomet. Chem.* **2002**, *653*, 27.
6. [R] Hayashi, T. *J. Organomet. Chem.* **2002**, *653*, 41.
7. [R] Hiller, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69.
8. [R] Huo, S.; Negishi, E.-I. *Palladium-catalyzed Alkenyl-Aryl, Aryl-Alkenyl, And Alkenyl-Alkenyl Coupling Reactions*. In *Handbook of Organopalladium Chemistry for Organic Synthesis*: 2002, Vol. 1, 335.
9. Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144.
10. Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.
11. Tamao, K.; Sumitani, K.; Kiso, Y.; Zemayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 1958.
12. Job, A.; Reich, R. *Compt. Rend.* **1923**, *177*, 1439.
13. Job, A.; Reich, R. *Compt. Rend.* **1924**, *179*, 330.
14. Gilman, H.; Lichtenwalter, M. *J. Am. Chem. Soc.* **1939**, *61*, 957.
15. Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316.
16. Kharasch, M. S.; Fuchs, C. F. *J. Am. Chem. Soc.* **1943**, *65*, 504.
17. Kharasch, M. S.; Lewis, D. W.; Reynolds, W. B. *J. Am. Chem. Soc.* **1943**, *65*, 493.
18. Chuit, C.; Felkin, H.; Frajerman, C.; Roussi, G.; Swierczewski, G.; *Chem. Commun.* **1968**, 1604.
19. [R] Collman, J. P. *Acc. Chem. Res.* **1968**, *1*, 126.
20. Uchino, M.; Yamamoto, A.; Ikeda, S. *J. Organomet. Chem.* **1970**, *24*, C63.
21. Kochi, J. K.; Tamura, M. *J. Am. Chem. Soc.* **1971**, *93*, 1483.
22. Kochi, J. K.; Tamura, M. *J. Am. Chem. Soc.* **1971**, *93*, 1485.
23. Tamura, M.; Kochi, J. K. *J. Organomet. Chem.* **1972**, *42*, 205.
24. Consiglio, G.; Botteghi, C. *Helv. Chim. Acta.* **1973**, *56*, 460.
25. Yamamura, M.; Moritani, I.; Murahashi, S.-I. *J. Organomet. Chem.* **1975**, *91*, C39.
26. [R] *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, Germany, 2004.
27. Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364.
28. Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3822.
29. [R] *Strategic Applications of Named Reactions in Organic Synthesis*; Kurti, L., Czako, B.; Academic Press, 2005.
30. Faivarque, J.-F.; Pflüger, F.; Troupel, M. *J. Organomet. Chem.* **1981**, *208*, 419.
31. Amatore, C.; Jutand, A. *J. Organomet. Chem.* **1999**, *576*, 254.
32. Murahashi, S.-I.; Naota, T.; Tanigawa, Y. *Org. Synth.* **1984**, *62*, 39.
33. Negishi, E.-I.; Takahashi, T.; Akiyoshi, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1338.
34. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.
35. Hölder, B.; Hoffman, R. W. *Chem. Commun.* **2003**, 732.
36. Gawler, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297.
37. [R] Banno, T.; Hayakawa, Y.; Umeno, M. *J. Organomet. Chem.* **2002**, *653*, 288.
38. Böhm, V. P.; Gstöttmayr, C. W. K.; Weskamp, T.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3387.
39. Ackermann, L.; Born, R.; Spatz, J. H.; Meyer, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 7216.
40. Yoshikai, N.; Mashima, H.; Nakamura, E. *J. Am. Chem. Soc.* **2005**, *127*, 17978.

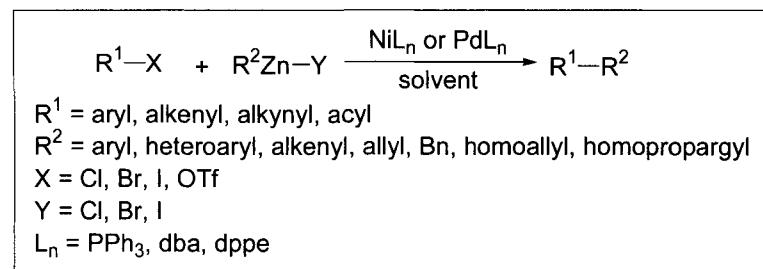
41. Huang, J.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889.
42. Li, G. Y. *J. Organomet. Chem.* **2002**, *653*, 63.
43. Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem. Eur. J.* **2007**, *13*, 150.
44. Hayashi, T.; Konishi, M.; Fukushima, M.; Kanemura, T.; Hioki, M.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2195.
45. Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384.
46. Ikenaka, M.; Maruoka, K.; Okuda, Y.; Ooi, T. *Org. Process Res. Dev.* **2003**, *7*, 644.
47. Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153.
48. Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101.
49. Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772.
50. Rivkin, A.; Njardarson, J. T.; Biswas, K.; Chou, T.-C.; Danishefsky, S. J. *J. Org. Chem.* **2002**, *67*, 7737.
51. William, A. D.; Kobayashi, Y. *J. Org. Chem.* **2002**, *67*, 8771.
52. Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704.
53. Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364.
54. Ackermann, L.; Althämmer, A. *Org. Lett.* **2006**, *8*, 3457.
55. Wittig, G.; Pockels, U.; Dröge, H. *Chem. Ber.* **1938**, *71*, 1903.
56. Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.
57. Ilia, H.; Baron, O.; Wagner, A. J.; Knochel, P. *Chem. Commun.* **2006**, 583.
58. Bonnet, V.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Knochel, P. *Tetrahedron*, **2002**, *58*, 4429.
59. Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.
60. Martin, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3844.
61. Lau, S. Y. W.; Hughes, G.; O'Shea, P. D.; Davies, I. W. *Org. Lett.* **2007**, *9*, 2239.
62. Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 674.
63. Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691.
64. Devasagayaraj, A.; Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2723.
65. Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222.
66. Terao, J.; Naitoh, Y.; Kuniyasu, H.; Kambe, N. *Chem. Lett.* **2003**, *32*, 890.
67. Terao, J.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2003**, *125*, 5646.
68. Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *114*, 4056.
69. Frisch, A. C.; Rataboul, F.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2003**, *687*, 403.
70. Korn, T. J.; Cahiez, G.; Knochel, P. *Synlett*, **2003**, 1893.
71. Ohmiya, H.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2006**, *8*, 3093.
72. Martin, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3955. And references therein.
73. Fürstner, A.; Krause, H.; Lehmann, C. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 440.

## 1.1.4 Negishi Cross-Coupling Reaction

Larry Yet

### 1.1.4.1 Description

The Negishi cross-coupling reaction is the versatile nickel- or palladium-catalyzed coupling of organozinc compounds with various halides or triflates (aryl, alkenyl, alkynyl, acyl).<sup>1</sup>



Both nickel- and palladium-phosphine complexes work well as catalysts. However, Pd catalysts tend to give somewhat higher yields and better stereoselectivity, and their functional group tolerance is better. The active catalysts are relatively unstable Ni(0)- and Pd(0)-complexes but these can be generated *in situ* from more stable Ni(II)- and Pd(II)-complexes with a reducing agent such as 2 equivalents of DIBAL-H or *n*-BuLi. The most widely used ligand is PPh<sub>3</sub>, but other achiral and chiral phosphine ligands have been successfully used. The various organozinc reagents can be prepared either by direct reaction of the organic halide with zinc metal or activated zinc metal or by transmetallation of the corresponding organolithium or Grignard reaction with a zinc halide. The use of organozinc reagents allow for a much greater functional group tolerance in both coupling partners than in the Kumada cross-coupling where organolithiums and Grignard reagents are utilized as coupling partners. Other advantages of the use of organozincs include: high regio- and stereoselectivity, wide scope and applicability, few side reactions and almost no toxicity. The reaction is mostly used for the coupling of two C(sp<sup>2</sup>) carbons but C(sp<sup>2</sup>)-C(sp), C(sp<sup>2</sup>)-C(sp<sup>3</sup>), and C(sp<sup>3</sup>)-C(sp<sup>3</sup>) couplings are well-known. Of all the various organometals (Al, Zr, B, Sn, Cu, Zn), organozincs are usually the most reactive in palladium-catalyzed cross-coupling reactions and do not require the use of additives such as bases as in Suzuki reactions to boost the reactivity.

### 1.1.4.2 Historical Perspective

In 1972, after the discovery of nickel-catalyzed coupling of alkenyl and aryl iodides with Grignard reagents (Kumada cross-coupling), it became apparent in order to improve the functional group tolerance of the process, the organometallic coupling partners should contain less electropositive metals than lithium and magnesium. In 1976, E. Negishi reported the first stereospecific nickel-catalyzed alkenyl–alkenyl and alkenyl–aryl cross-coupling of alkenylalanes (organoaluminums) with alkenyl- or aryl halides.<sup>2</sup> Extensive research by Negishi showed that the best results (reaction rate, yield, and stereoselectivity) were obtained when organozincs are coupled in the presence of Pd(0) catalysts.<sup>3–5</sup>

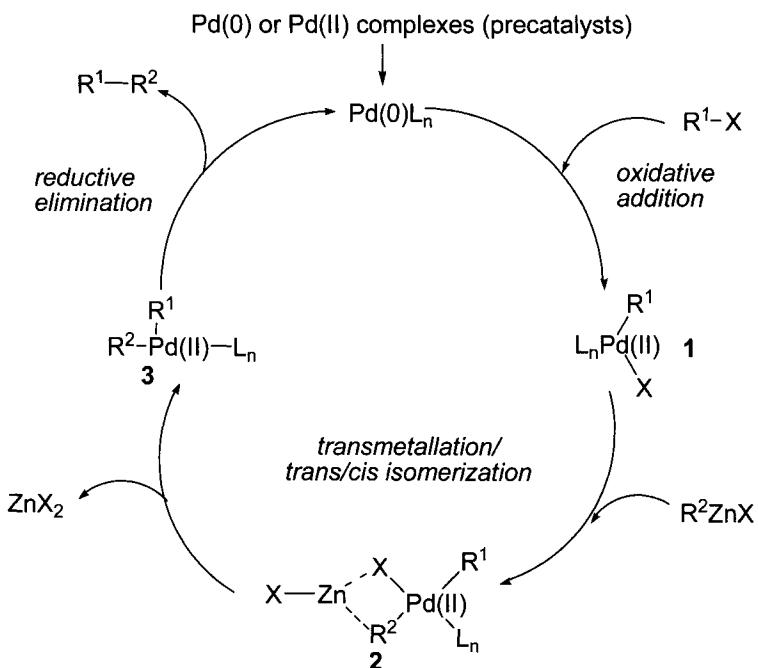
Negishi's group published seminal papers on the palladium- or nickel-catalyzed cross-coupling reactions between 1976–1978.<sup>6–13</sup> The palladium-catalyzed reaction of alkynylzinc chlorides with alkenyl halides<sup>8</sup> along with the related alkynyl–aryl,<sup>9</sup> aryl–aryl,<sup>10</sup> and benzyl–aryl<sup>10</sup> coupling reactions provided some of the earliest examples of the palladium-catalyzed cross-coupling of organozincs, and showed superior reactivity of organozincs under the palladium-catalyzed cross-coupling conditions relative to the ten or so other types of organometals. The first examples of the palladium-catalyzed carboalumination–cross-coupling tandem reaction were also reported in 1978.<sup>13</sup> The use of Zn salts, such as ZnCl<sub>2</sub> or ZnBr<sub>2</sub>, as additives or cocatalysts in the coupling step of this tandem reaction was shown to be highly desirable or even essential to observing satisfactory results. This study demonstrated, for the first time, the concept of double metal catalysis and the favorable effects of additives on the palladium- or nickel-catalyzed cross-coupling.<sup>13</sup> These findings reported established that the palladium- or nickel-catalyzed cross-coupling can be achieved with organometals containing various metal counteractions other than Mg, which had previously been used almost exclusively.

### 1.1.4.3 Mechanism

The palladium-catalyzed Negishi cross-coupling reaction follows a general pathway common to other palladium-catalyzed type reactions.<sup>14</sup> The active catalyst in this reaction is the Pd(0) species which proceeds through an oxidative addition step of the organic halide to give the Pd(II) species **1**, which then undergoes transmetalation with the zinc halides to afford *trans*-adduct Pd(II) species **2**. Isomerization of **2** to the *cis*-adduct Pd(II) species **3** followed by reductive elimination affords the product R<sup>1</sup>–R<sup>2</sup> and the regenerated Pd(0) catalyst, which then continues with the catalytic cycle.

Compared to other palladium-catalyzed cross-coupling reactions such as Stille and Suzuki, mechanistic proposals on the transmetalation step in

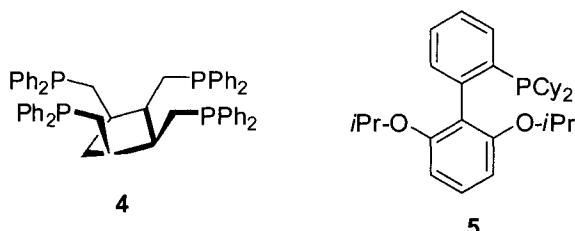
Negishi cross-couplings are purely speculative, and the essential stereochemical and kinetic aspects remain obscure. Casares and Espinet have studied the *cis-trans* isomerization of this transmetalation reaction with  $\text{ZnMe}_2$  and  $\text{ZnMeCl}$  using  $[\text{PdRfCl}(\text{PPh}_3)_2]$  ( $\text{Rf} = 3,5\text{-dichloro-2,4,6-trifluorophenyl}$ ) with  $^{19}\text{F}$  NMR spectroscopy as a tool for the mechanistic probes.<sup>15</sup> They found that each methylating reagent afforded stereoselectively a different isomer (*cis* or *trans*) of the  $[\text{PdRfCl}(\text{PPh}_3)_2]$  coupling intermediate. The key point they found was that the choice of the organozinc reagent could strongly affect the outcome of the Negishi cycle. The mechanism of the nickel-catalyzed Negishi cross-coupling reactions mirrors that of the palladium-catalyzed processes.<sup>16</sup>



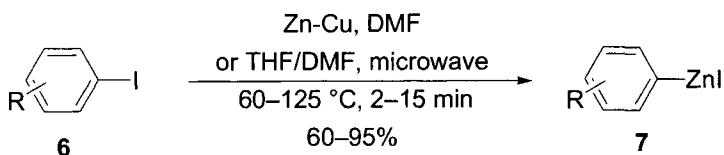
#### 1.1.4.4 Variations and Improvements

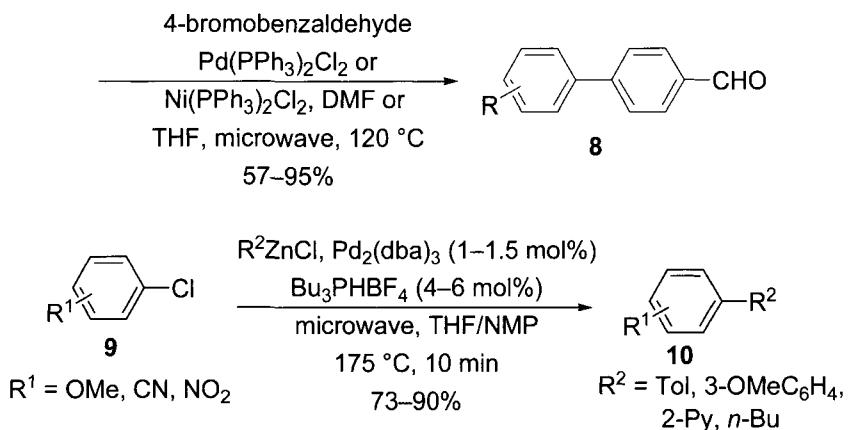
Phosphine-type ligands have been utilized in the acceleration of Negishi cross-coupling reactions. Santelli published a procedure where the system combining the tetraphosphine *cis,cis,cis*-1,2,3,4-tetrakis(diphenylphosphino-methyl)cyclopentane (**4**, Tedicyp) and  $[\text{Pd}(\text{C}_3\text{H}_5)\text{Cl}]_2$  was found to be a very active catalyst for the cross-coupling of aryl bromides with alkyl- or arylzinc derivatives.<sup>17</sup> Buchwald reported a new catalyst system for the palladium-catalyzed cross-coupling of organozinc reagents with aryl halides with  $\text{Pd}_2(\text{dba})_3$  and biphenyl ligand **5**.<sup>18</sup> This system permitted efficient

preparation of hindered biaryls (tri- and tetra-*ortho*-substituted) and functioned effectively at low levels of catalyst, and tolerated a wide range of functional groups and heterocyclic substrates. Fu showed that commercially available  $\text{Pd}(\text{P}(t\text{-Bu})_3)_2$  effected the first general method for the Negishi cross-coupling of a wide range of aryl and vinyl chlorides with aryl- and alkylzinc reagents.<sup>19</sup> The process tolerated nitro groups, and it efficiently generated sterically hindered biaryls. In addition, a high turnover number ( $> 3000$ ) could be achieved.

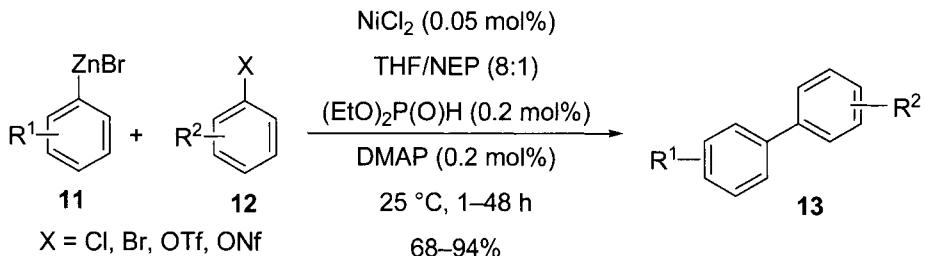


In the last few years, the use of microwave irradiation has appeared in several reports for the Negishi cross-coupling reactions. Suna reported that arylzinc reagents 7 could be readily prepared from aryl iodides 6 using a zinc–copper couple in a microwave environment followed by a Negishi cross-coupling with 4-bromobenzaldehyde under palladium- or nickel-catalyzed conditions to give biphenyl aldehydes 8.<sup>20</sup> Furthermore, Suna published a report where arylmagnesium species could be efficiently generated from magnesium turnings and aryl chlorides or aryl bromides under microwave irradiation, followed by transmetalation with  $\text{ZnCl}_2$ –TMEDA to give the corresponding arylzinc reagents.<sup>21</sup> Finally these arylzinc reagents underwent efficient Negishi cross-coupling reactions with aryl bromides. Kappe reported a general and efficient protocol for high-speed microwave-assisted Negishi cross-coupling reactions of aryl chlorides.<sup>22</sup> A range of electron-rich and electron-deficient aryl chlorides 9 participated in this accelerated reaction to give aryls 10. The use of  $\text{Ni}(\text{acac})_2$  catalyst was also successful in these reactions. An example of a solid-phase Negishi cross-coupling reaction was also shown.



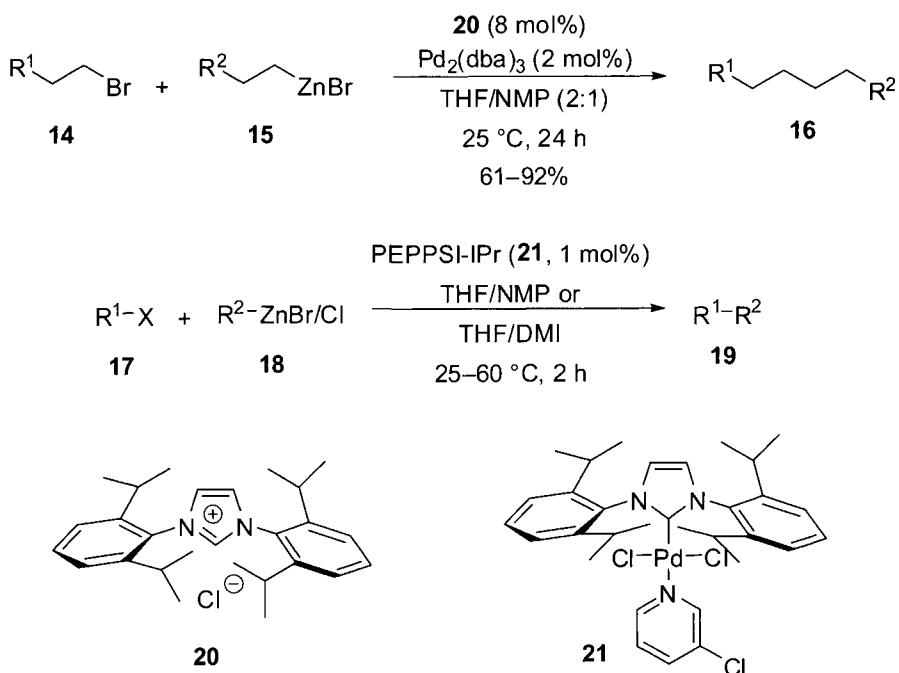


Knochel reported that a combination of diethyl phosphite–DMAP and Ni(II) salts formed a very effective catalytic system for the cross-coupling reactions of arylzinc halides with aryl, heteroaryl, alkenyl bromides, chlorides, triflates, and nonaflates.<sup>23</sup> The choice of solvent was quite important and the mixture of THF–*N*-ethylpyrrolidinone (NEP) (8:1) was found to be optimal in the synthesis of biaryls **13** with arylzinc bromides **11** with aryl halides **12**.



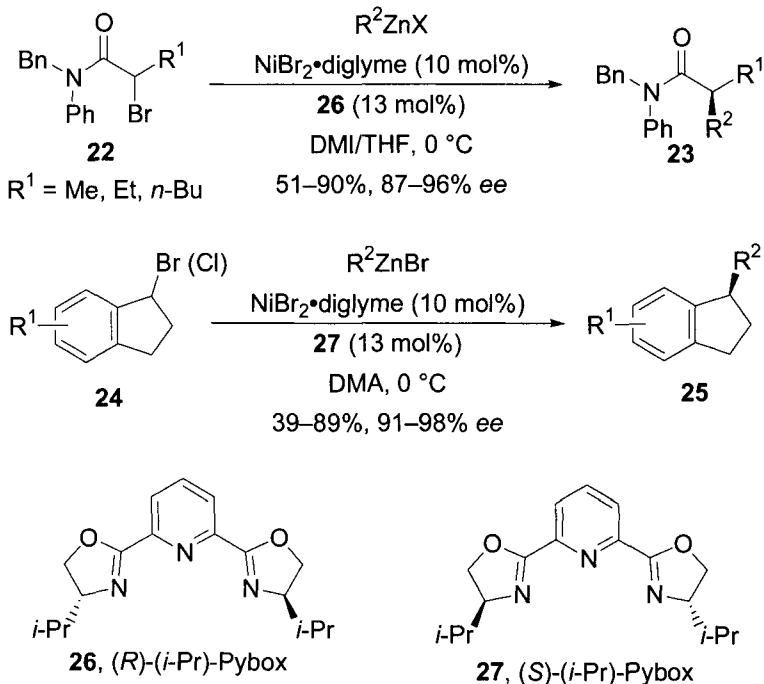
Organ reported the high-yielding Negishi cross-coupling reaction of unactivated alkyl bromides possessing  $\beta$ -hydrogens with alkylzinc bromides utilizing a Pd/*N*-heterocyclic carbene (NHC) catalyst **20** at room temperature.<sup>24</sup> Under optimal conditions, a number of alkyl bromides **14** and alkylzinc bromides **15** possessing common functional groups such as amide, nitrile, ester, acetal, and alkyne were effectively cross-coupled to give **16**. It was noteworthy that  $\beta$ -substituted alkyl bromides and alkylzinc bromides successfully underwent cross-coupling. Organ has also developed the first user-friendly Negishi protocol capable of routinely cross-coupling all combinations of alkyl and aryl centers.<sup>25</sup> The use of an easily synthesized, air stable, highly active, well-defined precatalyst PEPPSI–IPr (**21**; PEPPSI = pyridine-enhanced precatalyst preparation, stabilization and initiation; IPr =

diisopropylphenylimidazolium derivative) substantially increased the scope, reliability, and ease-of-use of the Negishi reaction. All organohalides and routinely used pseudohalides **17** were excellent coupling partners such as the use of chlorides, bromides, iodides, triflates, tosylates, and mesylates with aryl chlorides **18** resulting in high yield of the coupled product **19**. Furthermore, all reactions were performed by using general laboratory techniques with no glovebox necessary as the precatalyst was weighed and stored in air. Utilization of this methodology allowed for the easy synthesis of an assortment of sterically encumbered biaryls and druglike heteroaromatics, demonstrating the value of the PEPPSI-IPr system. Furthermore, this was also the first time Pd–NHC methodology surpassed the related phosphine-ligated Negishi processes both in activity and use.

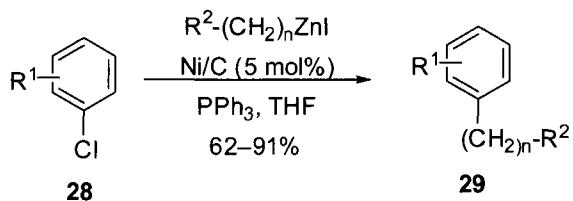


Fu reported the first catalytic enantioselective cross-couplings of secondary alkyl electrophiles such as the Negishi cross-coupling reaction of a range of  $\alpha$ -bromo amides **22** with an array of organozinc reagents with a pyridinyl oxazoline ligand **26** to afford  $\alpha$ -substituted amides **23**.<sup>26</sup> This asymmetric carbon–carbon bond formation proceeded smoothly in the presence of groups such as an olefin, a benzyl ether, an acetal, an imide and a nitrile. Fu described also the first highly enantioselective Negishi cross-coupling reactions of racemic secondary benzylic bromides and chlorides **24** with organozinc reagents with the opposite pyridinyl oxazoline ligand **27** to

give substituted indanes **25** in high enantiomeric excesses. Functionalized organozinc reagents, including those that bear a cyano or a chloride group, coupled with 1-bromoindanes in very good enantiomeric excesses.<sup>27</sup> Fu also established that  $\text{Ni}(\text{cod})_2$ -*s*-Bu-Pybox catalyzed Negishi cross-coupling reactions of an array of functionalized alkyl bromides and iodides at room temperature.<sup>28</sup> This represented the first nickel- or palladium-catalyzed method for cross-coupling of unactivated,  $\beta$ -hydrogen-containing secondary alkyl halides. A single method (2%  $\text{Pd}_2(\text{dba})_3$ /8%  $\text{PCy}_3/\text{NMI}$  in THF/NMP at 80 °C) achieved the cross-coupling of a range of  $\alpha$ -hydrogen-containing primary alkyl iodides, bromides, chlorides, and tosylates with an array of alkyl-, alkenyl-, and arylzinc halides.<sup>29</sup> The process was compatible with a variety of functional groups, which included esters, amides, imides, nitriles, and heterocycles.



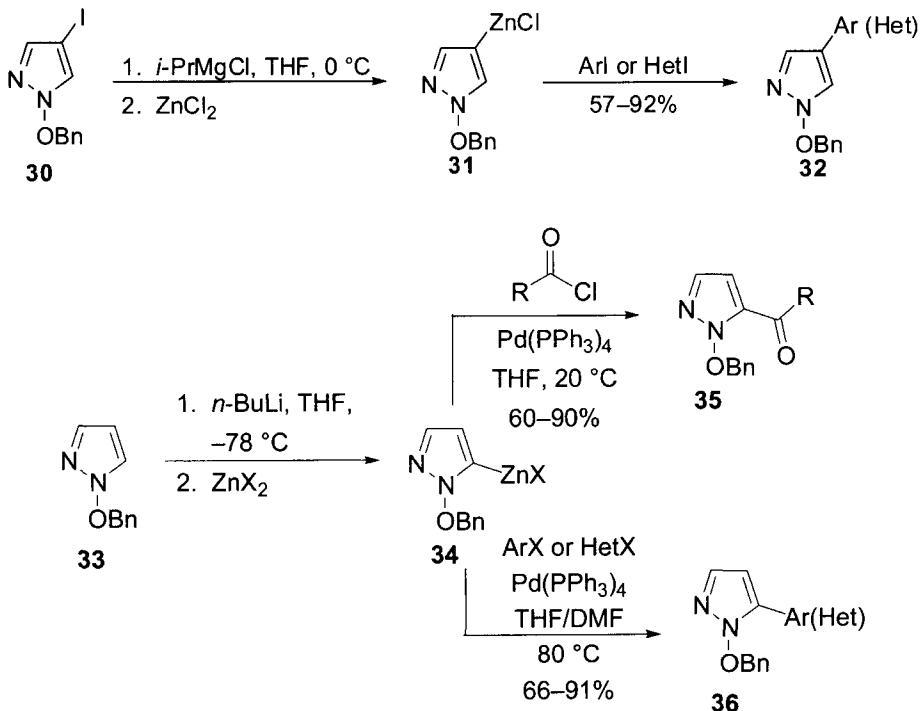
Lipshutz showed that nickel on charcoal (“Ni/C”) was found to be an efficient heterogeneous catalyst for mediating carbon-carbon bond constructions involving chloroarenes **28** and functionalized organozinc reagents to give **29**.<sup>30</sup> Importantly retention of nickel on the solid support offers control over such critical parameters as waste disposal and toxicity.



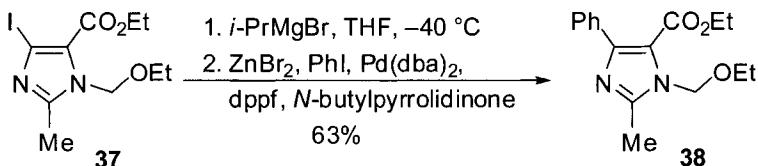
### 1.1.4.5 Synthetic Utility

#### Five-Membered Heterocycles

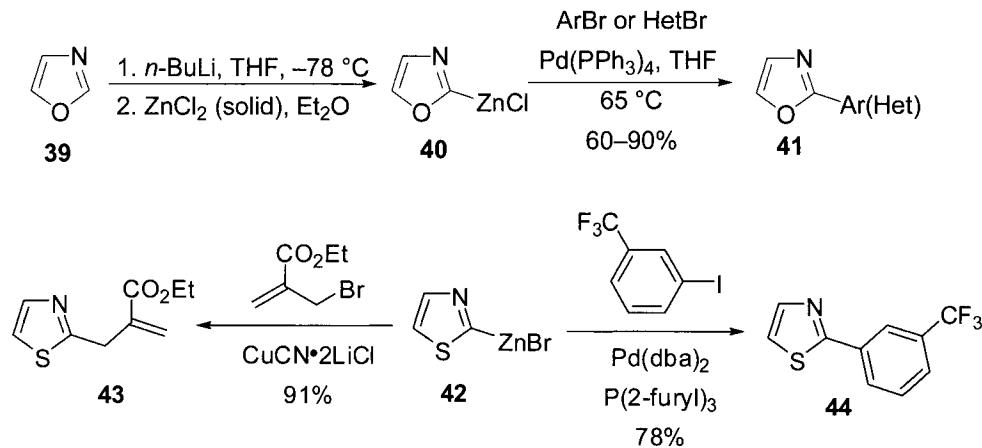
1-(Benzyl)-4-iodopyrazole (**30**) could be metalated by using *isopropylmagnesium chloride*, transmetallated with zinc chloride and Negishi cross-coupling of intermediate **31** with aryl and heteroaryl iodides to give the corresponding products **32** in good to excellent yields.<sup>31</sup> The reaction worked well with both electron-donating and electron-withdrawing substituents. Experiments with 1-(benzyl)-4-(tributylstannyl)pyrazole (prepared via pyrazolylmagnesium bromide) in a Stille reaction or the Grignard intermediate directly in a Kumada–Corriu reaction failed. Cross-coupling reactions of zinc organyls **34** in the 5-position with acid chlorides to **35** and aryl halides to **36** were accomplished in generally good yields.<sup>32</sup>



5-Iodoimidazole **37** readily underwent halogen–magnesium exchange followed by transmetallation with zinc bromide and subsequent Negishi cross-coupling with iodobenzene to give product **38**.<sup>33</sup> A Negishi reaction in the 2-position of imidazole has been reported on the solid phase.<sup>34</sup>

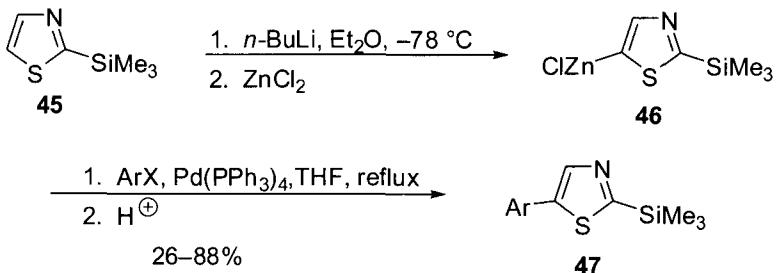


The Merck process chemists found that 2-oxazolylzinc species **40**, successfully prepared from oxazole **39** subsequently cross-coupled with aryl or heteroaryl bromides to oxazoles **41**.<sup>35</sup> The use of solid zinc chloride helped the transmetallation; however, long reaction times were required for good yields. Anderson also reported 2-oxazolylzinc species **40** was successfully cross-coupled with aryl iodides and triflates to compounds **41**.<sup>36</sup> This methodology was employed in the synthesis of oxazole-containing partial ergot alkaloids.<sup>37</sup>

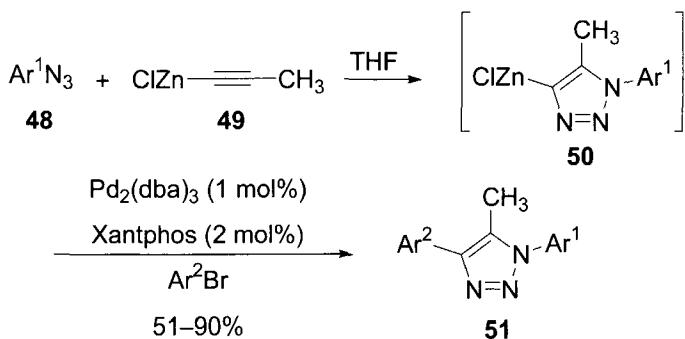


Knochel showed that 2-thiazolylzinc species **42** cross-coupled with aromatic or aliphatic electrophiles to give the corresponding products **43** and **44**, respectively, in the presence of copper and palladium catalysts.<sup>38</sup> 2,4-Dibromothiazole has been used as halide in Negishi reactions; the cross-coupling took place selectively in the 2-position in 50–62% yield.<sup>39</sup> The formation of zinc species in the 5-position of thiazole can also be prepared if the 2-position was protected with a trimethylsilyl group as in **45** before the organozinc derivative **46** was formed in the 5-position. The subsequent

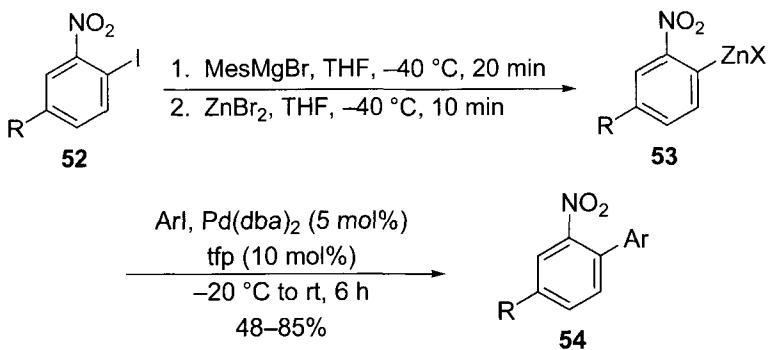
Negishi cross-coupling reaction and deprotection gave the desired products **47** with substituted aryl and heteroaryl halides.<sup>40</sup>



Several derivatives of 4-aryl-1,5-disubstituted-1,2,3-triazole **51** were synthesized in good yields via 1,3-dipolar cycloaddition of aryl azides **48** and alkynylzinc species **49** followed by Negishi reaction of **50** under new conditions.<sup>41</sup> Of all the combinations screened, Pd/xantphos was found to be superior. Kumada coupling was not as effective as the Negishi coupling in this reaction.

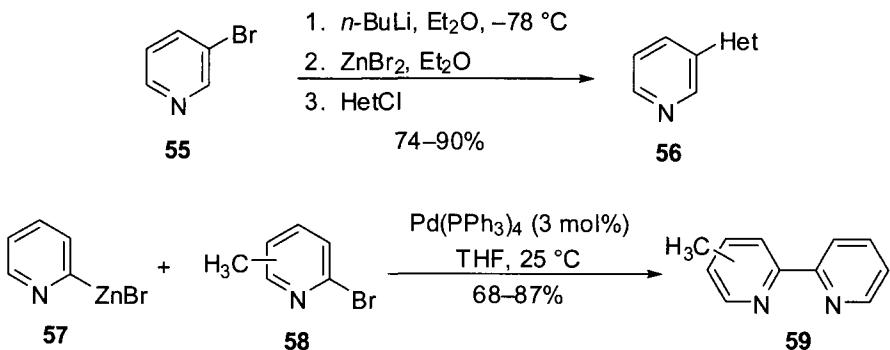


Six-Membered Rings

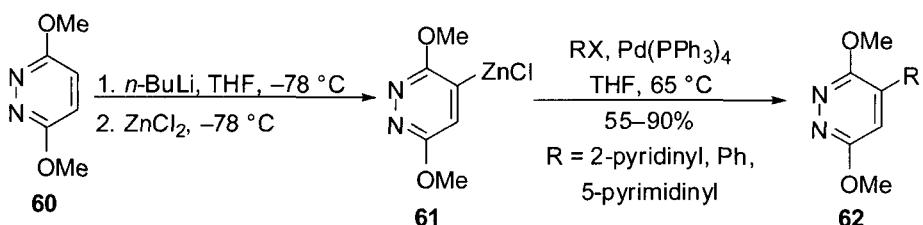


Knochel reported that various ortho nitro-substituted arylmagnesium reagents prepared by an iodine–magnesium exchange reaction starting from the corresponding aryl iodides **52** and mesitylmagnesium bromide are readily transmetallated to the corresponding organozinc compounds **53**.<sup>42</sup> These nitro-containing organometallics underwent a smooth Negishi cross-coupling reaction with various aryl iodides to give highly functionalized nitrosubstituted biphenyls **54**.

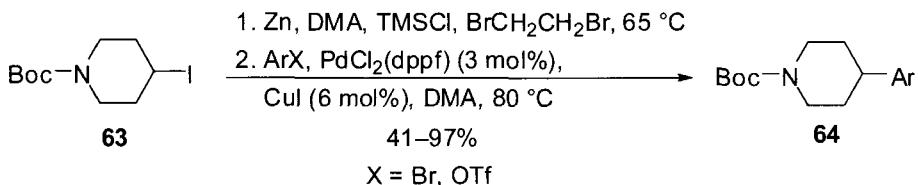
Pyridines have been employed as substrates for Negishi cross-coupling reactions. An efficient procedure for cross-coupling of 3-bromopyridine (**55**) with various mono- and dichloroheteroaryl compounds giving the corresponding biaryls **56** has been described.<sup>43</sup> The Negishi reaction also gave a mild and efficient method for the conversion of bromopyridines **58** into functionalized 2,2'-bipyridines **59** using commercially available 2-pyridylzinc bromide (**57**).<sup>44</sup> This method was also extended to the conversion of dibromopyridines to 5- and 6-bromobipyridines, which are powerful synthons for incorporation into larger supramolecular systems. A similar protocol for the efficient, modified Negishi cross-coupling strategy for substituted 2,2'-bipyridines from 2-bromo- and 2-chloropyridines has also been reported.<sup>45</sup> A convenient scalable synthesis of 6,6'-dimethyl-2,2'-bipyridine-4-ester based on modified Negishi cross-coupling conditions from substituted 2-chloro and 2-bromopyridines has been disclosed.<sup>46</sup>



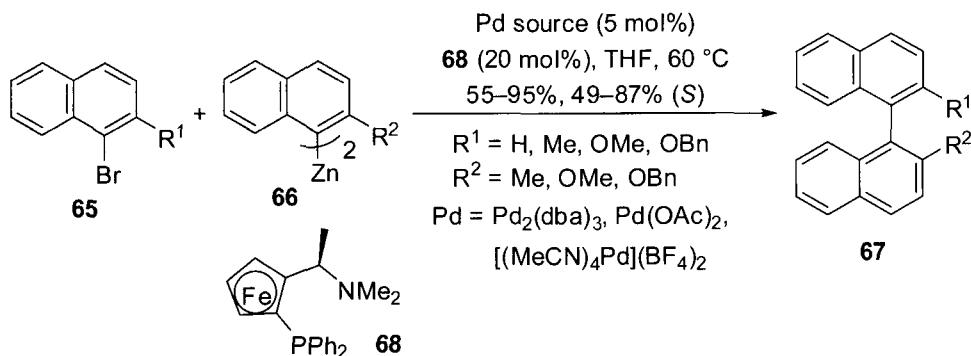
Queguiner prepared the first Negishi cross-coupling reaction of a pyridazine. 3,6-Dimethoxypyridazine (**60**) was lithiated and transmetallated with zinc chloride at the 4-position to give zinc species **61**, which underwent smooth cross-couplings with a few halides to give pyridazinyl compounds **62**.<sup>47</sup> Negishi cross-coupling reactions of pyridazines have also been utilized in the synthesis of analogs of nicotinic acetylcholine receptor agonists<sup>48</sup> and anxiolytic drugs with improved side-effect profiles.<sup>49</sup>



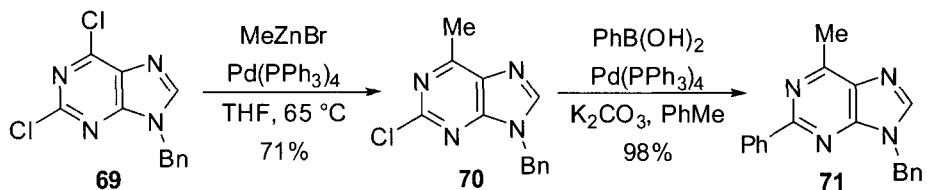
A general procedure for the synthesis of 4-arylpiperidines **64** via the coupling of 4-(*N*-BOC-piperidyl)zinc iodide, generated from zinc insertion of **63** with improved conditions, with aryl halides and triflates in the presence of palladium/copper cocatalysis has been reported.<sup>50</sup>



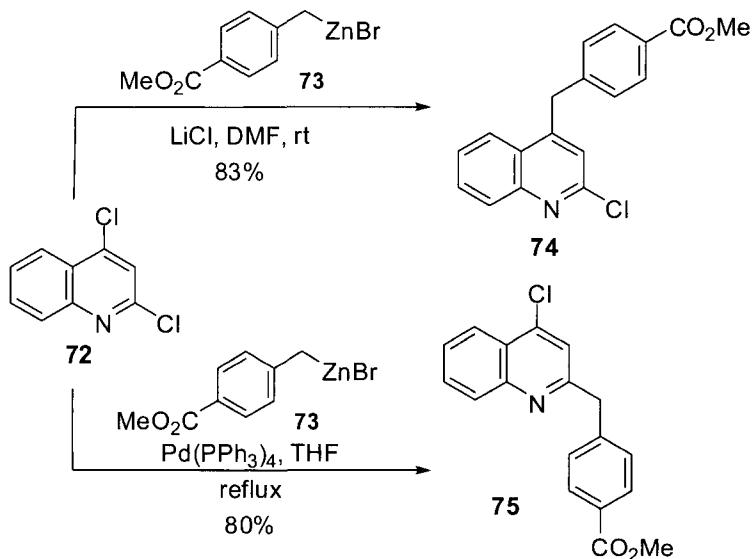
Chiral binaphthalenes are amongst the most useful chiral ligands and auxiliaries employed in asymmetric synthesis. Although the Stille and Suzuki–Miyaura reactions are very efficient for aryl–aryl carbon bond formation, sterically congested coupling partners such as naphthyls have the problems of poor yields and extensive deboronation in the Suzuki couplings. The naphthyl–naphthyl Negishi cross-coupling reaction was a possible alternative to overcome this problem. A new synthetic approach affording for the first time chiral binaphthalene derivatives **67** via an asymmetric Negishi reaction with 1-naphthyl bromides **65** and 2-naphthyl zinc species **66** with ligand **68** in good yields and good enantioselectivities was reported.<sup>51</sup>



Sequential cross-coupling reactions of 2,4-dichloropurine **69** have been conducted.<sup>52a</sup> 2,6-Disubstituted purine **69** was cross-coupled with MeZnBr to give monosubstituted purine **70**, which underwent Suzuki cross-coupling with phenylboronic acid to furnish disubstituted purine **71**. Recently, the synthesis of 6-(2-hydroxyethyl)purines was developed based on the Negishi palladium-catalyzed cross-coupling reactions of 6-chloropurines with the Reformatsky reagent followed by reduction by sodium borohydride and treatment with manganese(IV) oxide.<sup>52b</sup>



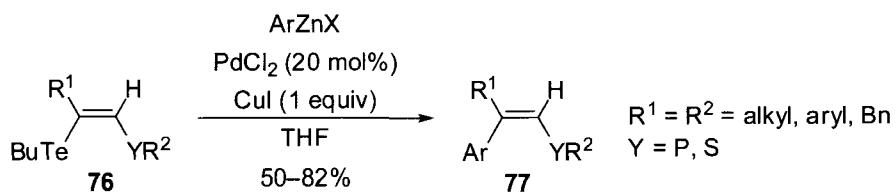
Strategies for controlling the regioselective reactions between 2,4-dichloroquinoline (**72**) and organozinc reagents have been reported.<sup>53</sup> 2,4-Dichloroquinoline (**72**) has been found to react with benzylic zinc reagent **73** in the presence of catalytic amounts of palladium complexes to exclusively give  $\alpha$ -substituted products such as **75**. Several metal salts were examined as an additive for  $\chi$ -selective coupling reactions. The most effective additive for selective coupling reaction at the  $\chi$ -position has been found to be LiCl to give products such as **74**.



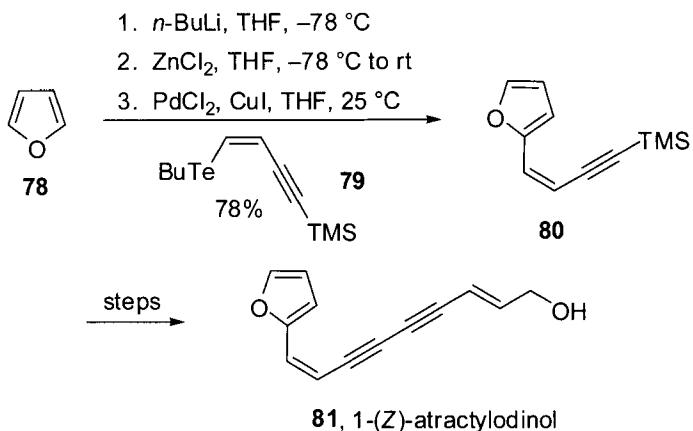
### Alkenes, Alkynes, Polyenes, Enynes

Polysubstituted alkenes, alkynes, polyenes, and enynes are present in many naturally occurring biologically active compounds such as terpenoids, pheromones, etc. They are also key intermediates in a number of transformations leading to natural products and have remained an active area of research for organic chemists.

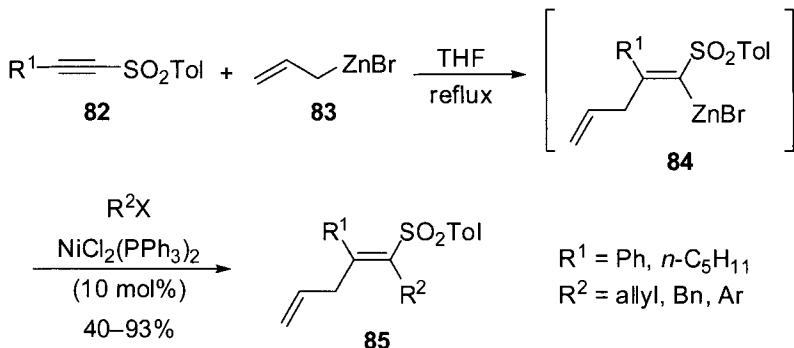
The Negishi cross-coupling reaction of arylzinc chlorides and bromides with functionalized vinylic tellurides **76** in the presence of a catalytic amount of  $\text{PdCl}_2$  in THF at room temperature was reported.<sup>54</sup> This cross-coupling reaction was general and permitted the synthesis of functionalized substituted alkenes **77** in good yields and high stereoselectivity. In this way, there were some advantages to use vinylic tellurides instead of the other methods, such as the easy access by stereoselective reactions to either (*Z*)- or (*E*)-vinylic tellurides, no isomerization of the double bond and the enhanced stability of these compounds. The use of vinylic tellurides in cross-coupling reactions tolerated many sensitive functional groups and provided mild reaction conditions. The Negishi cross-coupling reaction of vinylic- and aryltellurides with heteroarylzinc chlorides catalyzed by  $\text{PdCl}_2/\text{CuI}$  was reported. This cross-coupling reaction was general and permitted the formation of a new  $\text{sp}^2\text{-sp}^2$  carbon bond in good yields and high stereoselectivity.



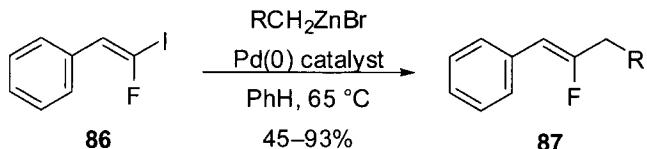
The application of this methodology in the synthesis of 1-(*Z*)-atractylodinol (**81**), a natural product isolated from the dried rhizomes of *Atractylodes lancea* De Candolle widely used in China and Japan against rheumatic diseases, digestive disorders, night blindness, and influenza.<sup>55</sup> The total synthesis of 1-(*Z*)-atractylodinol, a natural polyacetylenic alcohol with several biological activities, has been achieved using a newly developed telluride synthon and a novel use for the Negishi type coupling reaction employing vinyl tellurides. The protection of the alkyne terminus as its trimethylsilyl derivative **79** followed by a cross-coupling reaction with an excess 2-furylzinc chloride from furan (**78**) gave **80**, precursor to **81**.



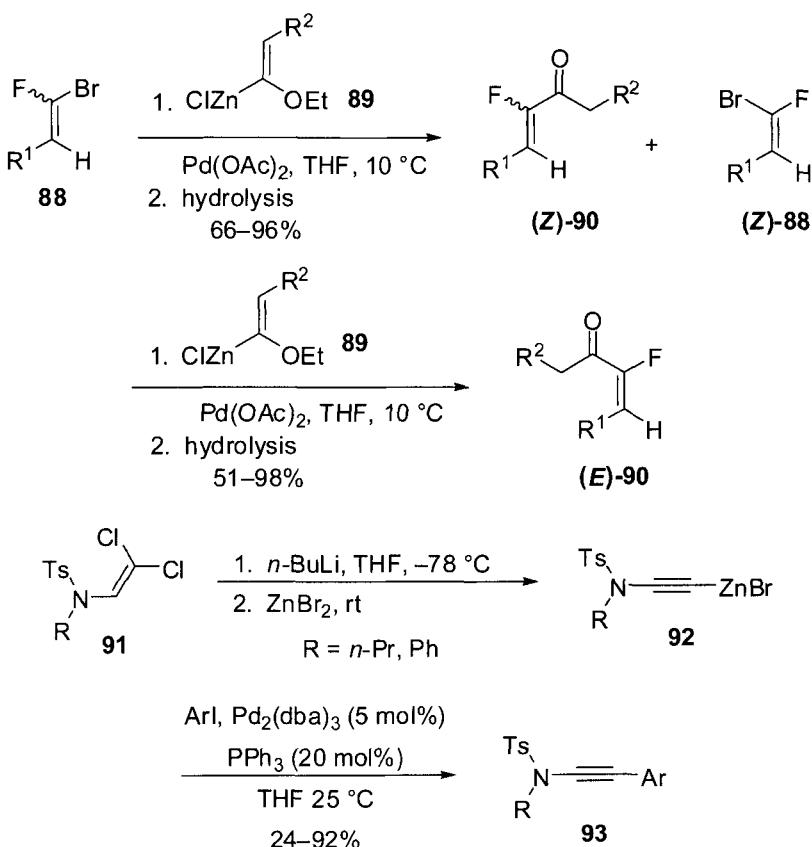
Tetrasubstituted olefins containing a 1,4-diene structural unit as in **85** can be regio- and stereoselectively constructed in one pot by the allylzincation of acetylenic sulfones **82** with **83**, followed by Negishi cross-coupling of intermediate **84** with halohydrocarbons in the presence of catalytic nickel.<sup>56</sup>



The 1-fluoro-1-haloalkenes **86** undergo palladium-catalyzed Negishi cross-couplings with primary alkylzinc bromides to give multisubstituted fluoroalkenes.<sup>57</sup> The alkylation was transselective giving pure *Z*-fluoroalkenes **87** in most cases. The highest yields were obtained with Pd<sub>2</sub>(dba)<sub>3</sub> and PdCl<sub>2</sub>(dppb) catalysts but the best stereochemical outcome was obtained with less reactive Pd(PPh<sub>3</sub>)<sub>4</sub>. The tertiary alkylzincs also produced the desired fluoroalkenes in high yields.

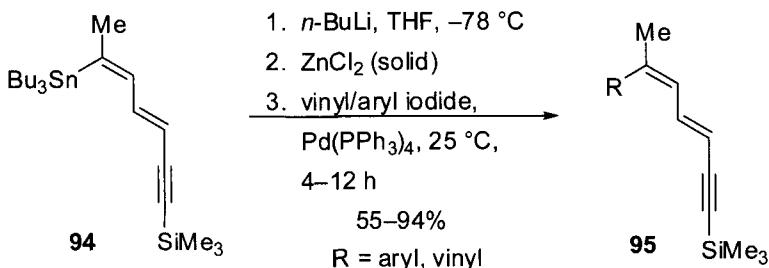


A highly stereospecific synthesis of (*E*)- or (*Z*)- $\alpha$ -fluoro- $\alpha,\beta$ -unsaturated ketones **90**, via a kinetically controlled Negishi palladium-catalyzed coupling reaction was developed providing an easy and general access to valuable fluorinated intermediates.<sup>58</sup> The synthesis involved a reaction between *E/Z* *gem*-bromofluoroolefins **88** and alkoxyvinylzinc species **89** under controlled reaction temperature. At 10 °C, (*Z*)-**90** was obtained along with unreacted (*Z*)-**88**. At THF reflux, the recovered olefin was transformed into (*E*)-**90**.

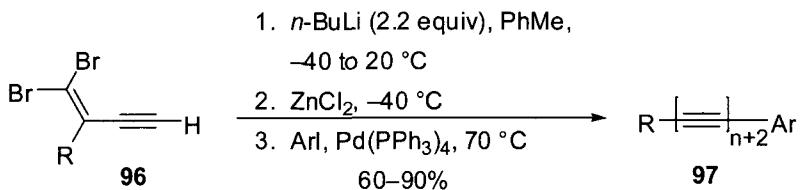


Negishi coupling of *N*-ethynylzinc tosylamides derivatives **92**, prepared from 1,1-dichlorovinylamide **91** with aryl iodides in the presence of Pd<sub>2</sub>(dba)<sub>3</sub> and triphenylphosphine afforded *N*-aryl and *N*-alkyl arylynamides **93**.<sup>59</sup>

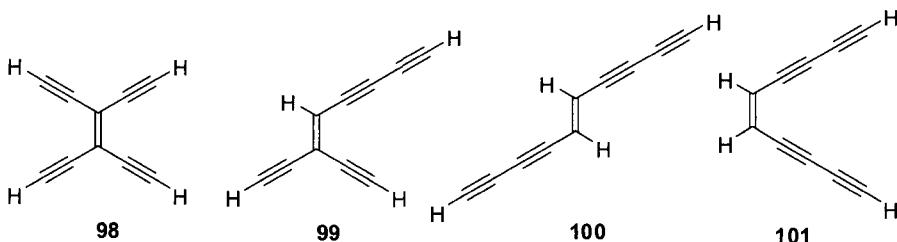
New conjunctive reagents **94** can be used, after transmetalation, in Negishi cross-couplings with vinyl and aryl iodides to give **95**.<sup>60</sup> The subsequently unmasked terminal alkynes could be further manipulated to obtain retinoid-like products.



A one-pot synthesis and derivatization of diarynes and triynes is reported.<sup>61</sup> The polyyne framework was formed from a dibromoolefin precursor **96** based on a carbenoid rearrangement, and the resulting Li-acetylide is then transmetallated with zinc chloride which then allowed for the divergent preparation of aryl polyynes **97** via Negishi palladium-catalyzed cross-coupling reactions.

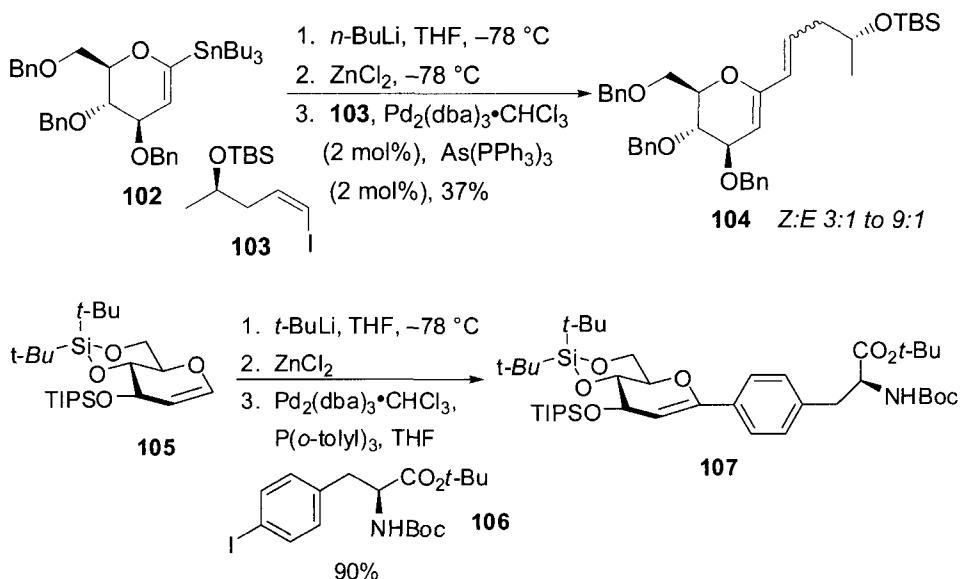


Three isomers of tetraethynylethene (**98**,  $\text{C}_{10}\text{H}_4$ ) have been prepared by palladium-catalyzed Negishi coupling of a trimethylsilylbutadiynyl zinc reagent with a bromoalkene, followed by mild deprotection with potassium carbonate in methanol.<sup>62</sup> The unsubstituted enynes, 3-ethynylcyclooct-3-ene-1,5,7-triyne (**99**), *trans*-dec-5-ene-1,3,7,9-tetrayne (**100**), and *cis*-dec-5-ene-1,3,7,9-tetrayne (**101**), exhibit modest stability at  $-20\text{ }^\circ\text{C}$  but decomposed rapidly at room temperature.



### Carbohydrates

The Negishi cross-coupling reactions could also be applied to functionalized carbohydrate precursors. For example, Negishi and Stille coupling reactions of 3,4,6-tri-*O*-benzyl-2-(tri-*n*-butylstannyl)-*D*-glucal (**102**) with (*Z*)-vinyl iodide **103** provided access to functionalized spiroketal **104**.<sup>63</sup> With the Stille reaction, erosion of alkene chemistry (3 : 1) was noticed plus it was sluggish requiring higher temperatures but no erosion of alkene geometry occurred when the Negishi reaction was performed.

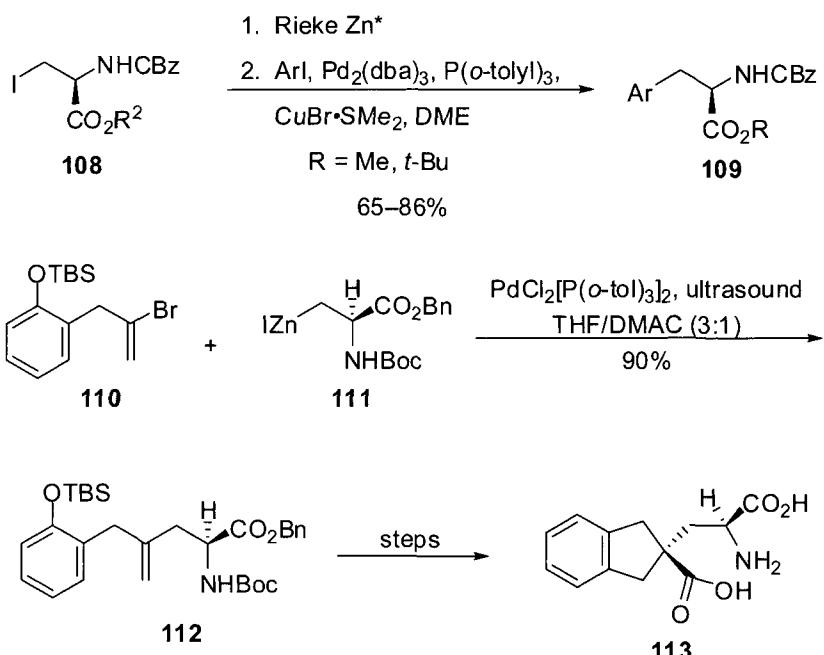


A *p*-(*C*-glucopyranosyl)-*L*-phenylalanine derivative, protected to be directly incorporated into a peptidic chain, was prepared from glucose on a gram scale, with a Negishi cross-coupling reaction as the key step.<sup>64</sup> The zinctated glucal **105** and *p*-iodo-*L*-phenylalanine **106** were involved in this organometallic coupling, which gave rise to a link between the sugar and amino acid moieties; the  $\beta$ -gluco configuration of the *C*-glycopyranosyl amino acid **107** was ascertained by a stereoselective hydroboration of the double bond of the glucal.

### Amino Acids

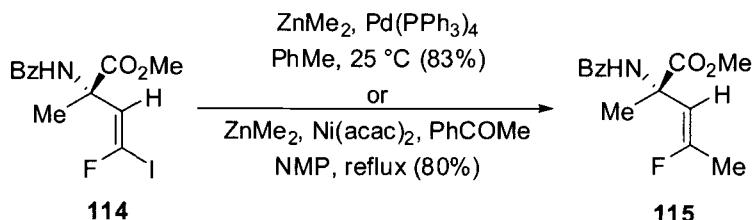
Protected amino acids have also participated in Negishi cross-coupling reactions. Protected *L*-serine iodides were converted under Rieke conditions to iodozinc species of **108**, which were efficiently coupled to give

phenylalanine-derived chiral amino acids **109** in the presence of palladium and copper catalysts.<sup>65</sup>



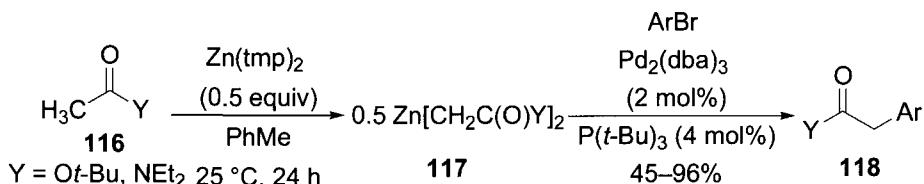
A general route to excitatory amino acid analogues has been developed. The key reactions involved were a Negishi coupling of Jackson's organozinc reagent **111** with vinyl bromide **110** and subsequent ring closure of **112** using the Mitsunobu reaction as the key step to **113**.<sup>66</sup> The efficient and direct synthesis of protected biaryl amino acids, including dityrosine by Negishi cross-coupling of the Jackson's reagent **111** with iodo- and diiodobiaryls, is also reported.<sup>67</sup>

Quaternary,  $\alpha$ -vinyl amino acids are potential mechanism-based inactivators of pyridoxal phosphate (PLP) dependent enzymes, particularly amino acid decarboxylases (AADC's). Protected  $\alpha$ -formyl amino acids, themselves available from the corresponding  $\alpha$ -vinyl amino acids, are stereoselectively transformed into the (*Z*)-configured  $\alpha$ -(2'-fluoro)vinyl amino acids via a three-step sequence.<sup>68</sup> Palladium-mediated Negishi-type coupling with Me<sub>2</sub>Zn or the analogous Ni-mediated procedure of Knochel could be applied to the synthesis of **115** from **114**, an unusual analogue of  $\alpha$ -methylleucine in which a fluorine atom takes the place of a methyl group.

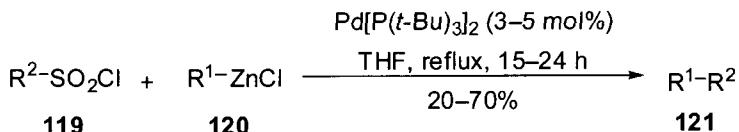


### Miscellaneous

Simple amides and esters **116** were conveniently deprotonated by  $\text{Zn}(\text{tmp})_2$  ( $\text{tmp} = 2,2,6,6$ -tetramethylpiperidinyl anion) to generate zinc enolates **117**.<sup>69</sup> The zinc enolates **117** were readily coupled with aryl bromides using typical palladium-catalyzed Negishi cross-coupling reactions to give arylketones **118**. Enolates formed by this method were suitable for use in aldol reactions that tolerate base-sensitive functional groups.

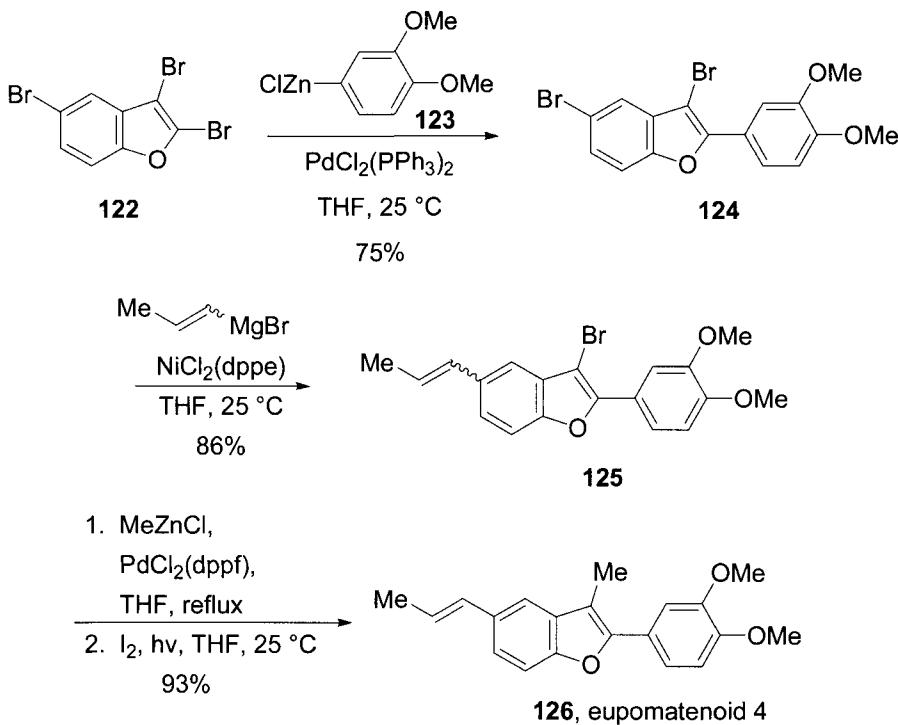


Arene-, phenylmethane- and alkenesulfonyl chlorides are suitable electrophilic reagents in desulfinylative carbon–carbon bond formation cross-coupling reactions with organozinc reagents.<sup>70</sup> Organozinc reagents **120** underwent desulfinylative Negishi C–C cross-coupling reactions with sulfonyl chlorides **119**. However, in the presence of 1–5 mol% of Pd(0) catalyst such as  $\text{Pd}[\text{P}(t\text{-Bu})_3]_2$ , smooth reactions occurred with elimination of  $\text{SO}_2$  and formation of products **121** of C–C cross-coupling. All reactions were accompanied with the concurrent formation of homocoupling product  $\text{R}^1-\text{R}^1$  of organozinc chloride as minor by-products.



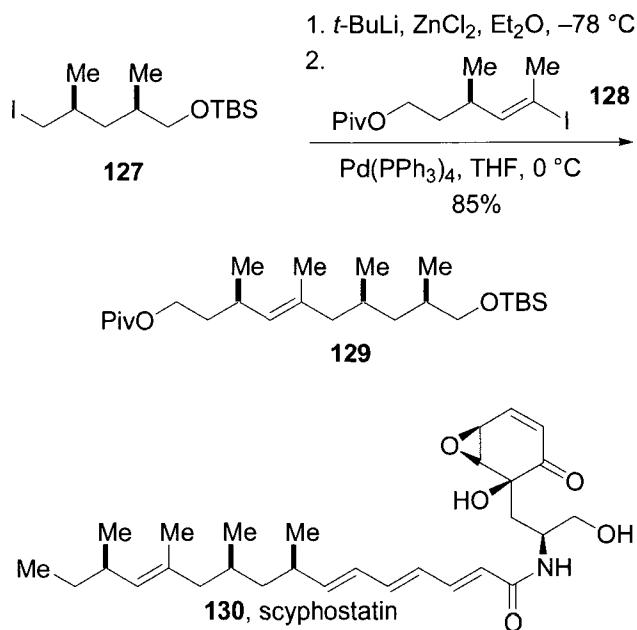
### Natural Products

The Negishi cross-coupling reactions have been showcased as key steps in the synthesis of many natural products and in structure-activity relationship drug discovery programmes.

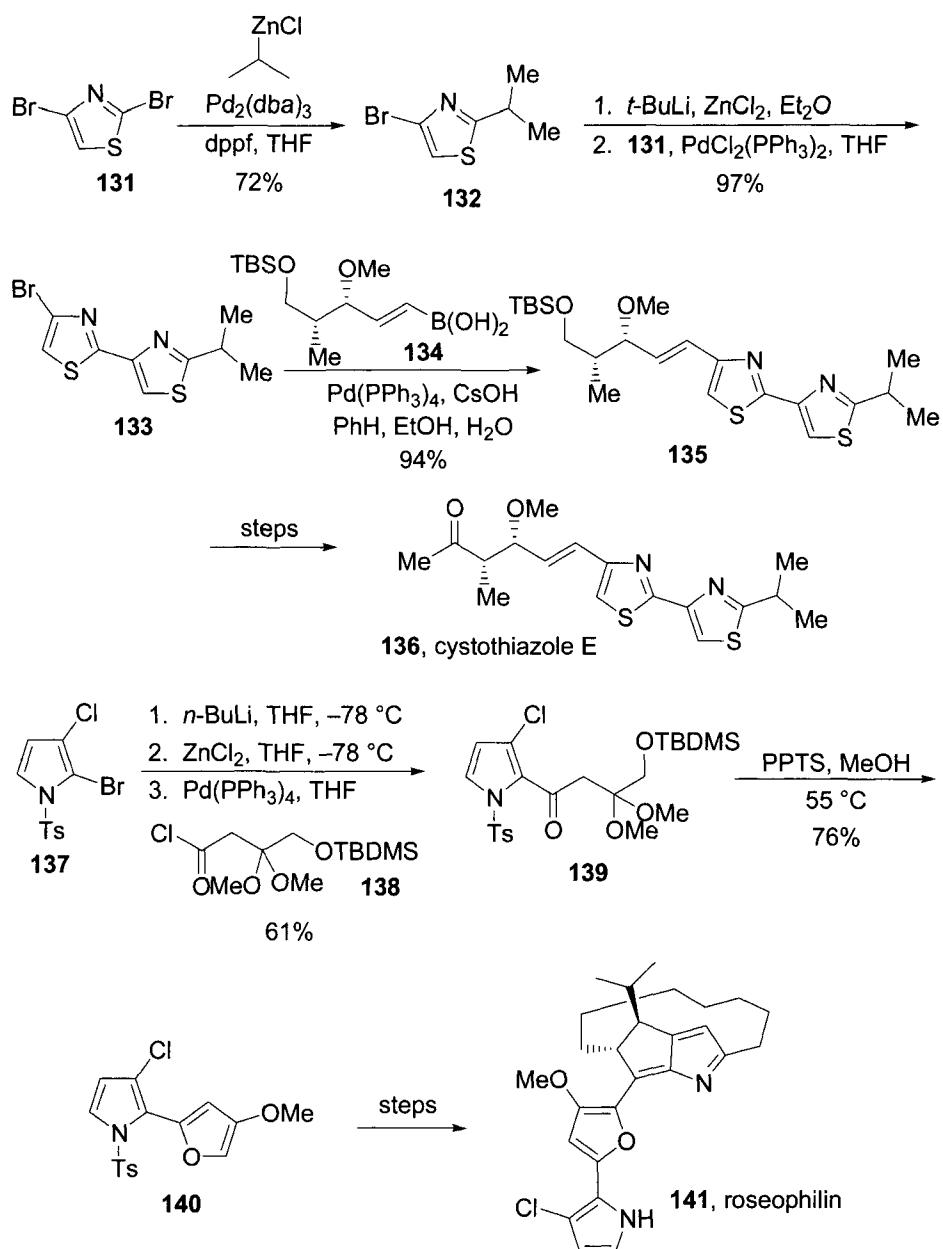


Bach has developed a synthetic approach to the trisubstituted benzofurans of the neolignan eupomatenoid family of natural products based on the regioselective transition metal-catalyzed cross-coupling reactions on the easily available 2,3,5-tribromobenzofuran (122).<sup>71</sup> The sequence commenced with 2,3,5-tribromobenzofuran (122) with zinc species 123, which underwent regioselective Negishi cross-coupling to yield dibromide 124. The Kumada cross-coupling was the method of choice to differentiate between the sterically different, but electronically similar, positions C-3 and C-5. A 1-prop-1-enyl group was established by this means to yield the monobromide 125. Finally, the least reactive position at carbon atom C-3 was addressed in a Negishi cross-coupling with an excess of methylzinc chloride. Quantitative isomerization of the double bond in compounds 125 led exclusively to the more stable naturally occurring (*E*)-configurated eupomatenoid (126).

Scyphostatin (**130**) has been isolated as a potent inhibitor of neutral sphingomyelinase (N-Smase) from the mycelial extract of *Dasyscyphus mollissima*. The hydrophobic side chain of scyphostatin was synthesized by the construction of the C12'-C13' trisubstituted *E*-olefin moiety by Negishi coupling.<sup>72</sup> Treatment of iodide **127** with *tert*-butyllithium (3 equiv) in the presence of zinc chloride afforded the organozinc species *in situ* and Negishi palladium-catalyzed cross-coupling with vinyl iodide **128** afforded the hydrophobic side chain of scyphostatin **129**. Another similar report utilizing the Negishi cross-coupling reaction for the side-chain has been disclosed.<sup>73</sup>



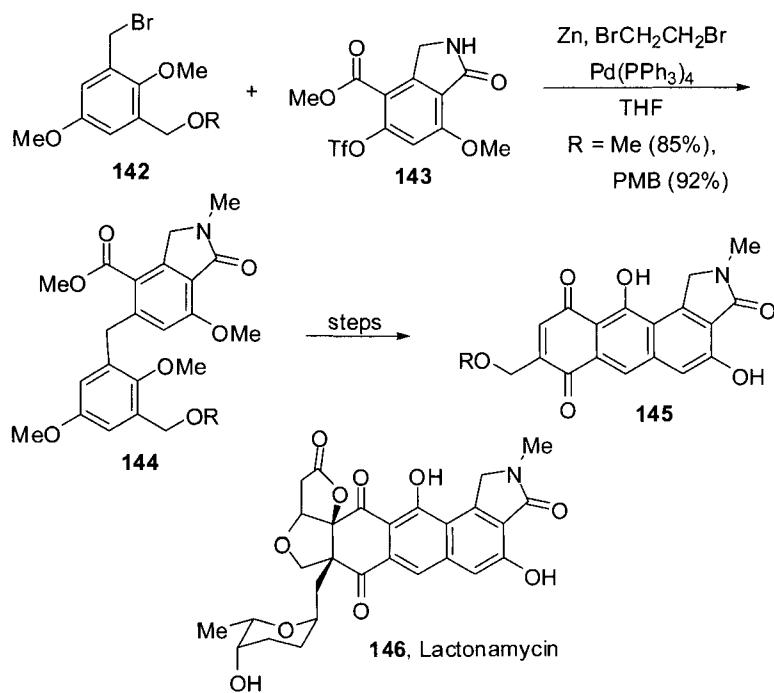
2',4-Disubstituted-2,4'-bithiazoles are prevalent in several natural products which exhibit antiinfective and cytotoxic properties. Regioselective Negishi cross-coupling of 2,4-dibromothiazole (**131**) delivered 4-bromothiazole **132**, which was converted into a nucleophile by bromine–lithium exchange and transmetallation to zinc.<sup>74</sup> The 4-thiazolylzinc chloride underwent another cross-coupling with another equivalent of 2,4-dibromothiazole (**131**) to yield the bithiazole **133**, which bore a residual bromine atom at the 4-position. Subsequent cross-coupling with boronic acid **134** led to **135**, an immediate precursor to the natural product, cystothiazole E (**136**).



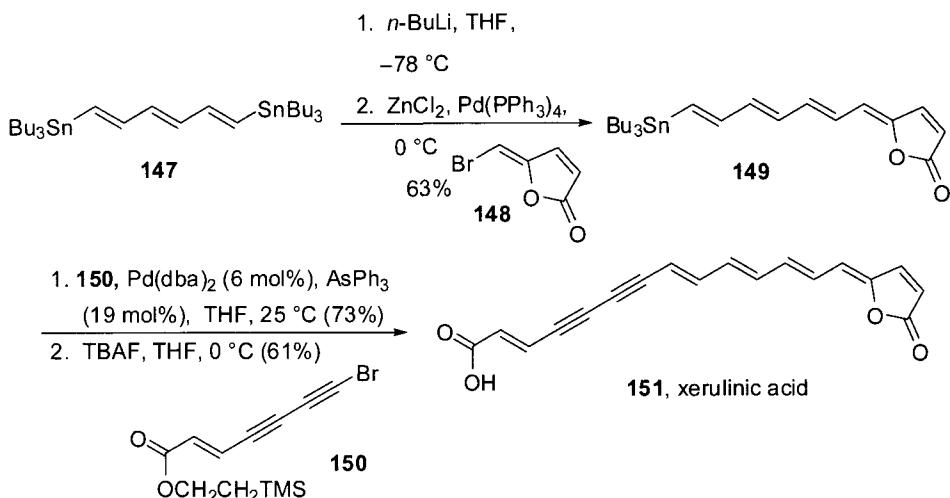
The first total synthesis of roseophilin (**141**), a novel antibiotic isolated from *Streptomyces griseoviridis*, employed the Negishi cross-coupling reaction in the early steps.<sup>75</sup> Thus, Fürstner demonstrated that the selective conversion of the C2-bromo–C3-chloro system **137**, via successive formation of the zinc intermediate, then cross-coupling with acid chloride **138**, into the corresponding C2-acylated product **139**. The silyl group of **139**

was cleaved upon exposure to pyridinium *p*-toluenesulfonate (PPTS) in methanol followed by spontaneous cyclization to the pyrrolylfuran derivative **140**, precursor to roseophilin (**141**).

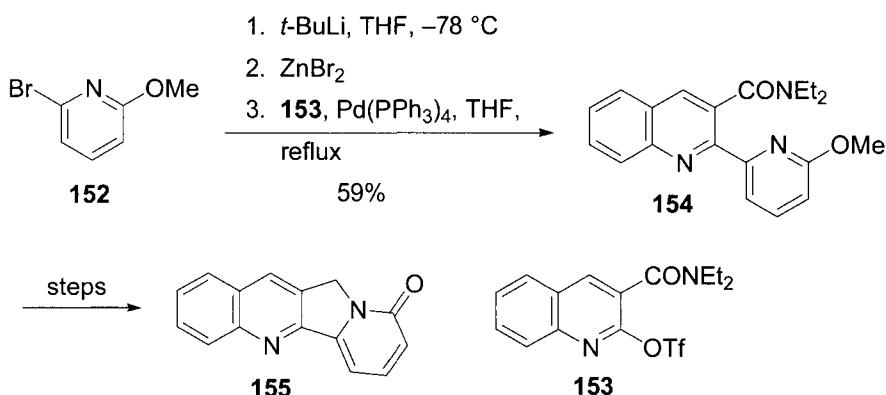
Lactonamycin (**146**) showed significant levels of antimicrobial activity toward Gram-positive bacteria, being especially effective against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE). In addition, lactonamycin (**146**) showed significant levels of cytotoxicity against various tumor cell lines. The synthesis of **146** was carried out using a high-yielding Negishi coupling of organozinc species of benzyl bromide **142** with triflate **143** to obtain coupled product **144**, which was further elaborated to the tetracyclic CDEF ring system **145** of lactonamycin (**146**).<sup>76</sup>



Xerulinic acid (**151**) inhibited the biosynthesis of cholesterol in HeLa S3 cells by blocking HMG-CoA synthase. Bisstannane **147** was transmetallated to the zincate intermediate and was Negishi cross-coupled with butenolide **148** to give the all *trans*-polyene **149**.<sup>77</sup> The Stille reaction of **149** with enediyne **150** followed by deprotection of the silyl group with tetrabutylammonium fluoride afforded xerulinic acid (**151**).

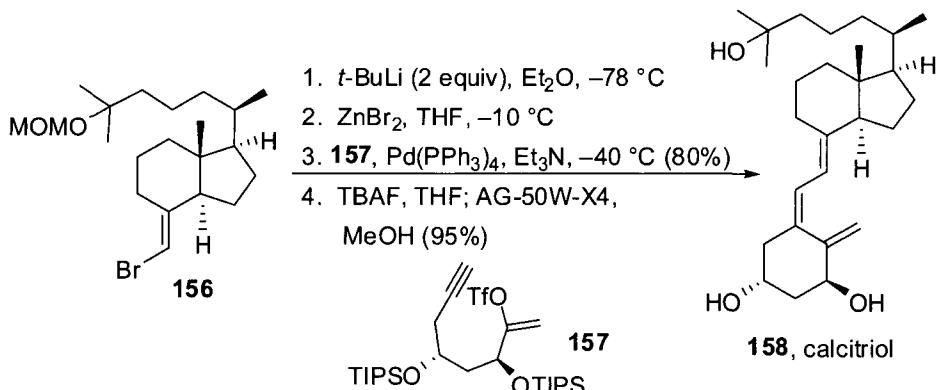


The tetracyclic A/B/C/D ring core of (20*S*)-camptothecin, one of the most potent antitumor natural products isolated from *Camptotheca acuminata*, was prepared by a combined directed ortho metallation/cross-coupling strategy.<sup>78</sup> Snieckus showed that 2-bromo-6-methoxypyridine (152) could be sequentially treated with *tert*-butyllithium (2 equiv) at  $-78\text{ }^{\circ}\text{C}$  and anhydrous zinc bromide. The resulting organozinc species was then subjected to palladium-catalyzed cross-coupling reaction with triflate 153 to afford the biaryl 154, a precursor to the tetracyclic A/B/C/D ring core 155.



The steroid hormone *1R,25-dihydroxyvitamin D*<sub>3</sub> (*1R,25-(OH)*<sub>2</sub>-D<sub>3</sub>, calcitriol, 158) is the bioactive metabolite of vitamin D<sub>3</sub>. This B-ring-seco-steroid plays an important role in the regulation of mineral metabolism and finds application in the treatment of osteodystrophy due to renal failure, rickets, osteoporosis, and psoriasis. The bromoolefin 156 was subjected to sequential metallation and transmetallation to give the corresponding

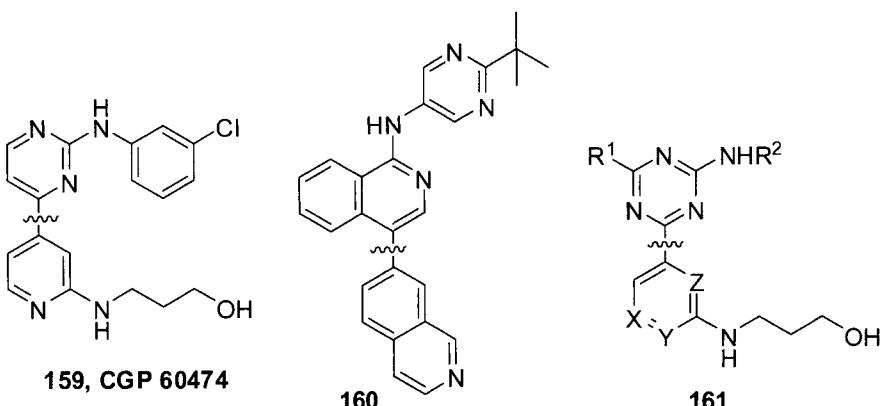
organozinc derivative, which was treated with vinyl triflate **157** to give, by the palladium-catalyzed cascade and deprotection, the desired hormone calcitriol (**158**).<sup>79</sup>



One of the current approaches to the treatment of cancer involves the disruption of kinase activity and signal transduction pathways. For example, protein kinase C (PKC) plays a crucial role in signal transductions, cellular proliferation, and differentiation. PKC is the term for a whole family of cytosolic serine/threonine kinases. Phenylamino-pyrimidines like 3-{4-[2-(3-chlorophenylamino)-pyrimidin-4-yl]pyridin-2-yl-amino}propanol (**159**, CGP 60474) represent a promising class of inhibitors of PKC with a high degree of selectivity versus other serine/threonine and tyrosine kinases and show competitive kinetics relative to ATP.<sup>80</sup> Analogs of CGP 60474 were synthesized as useful models for the evaluation of structure–activity relationships of phenylamino-pyrimidine-type protein kinase C inhibitors.

The signal transduction pathway in which Raf kinase operates has long been implicated in oncogenesis and is critical for proliferation, survival, and angiogenesis in various cancer models. [4,7']Bis-isoquinolinyl-1-yl-(2-*tert*-butyl-pyrimidine-5-yl)amine (**160**) was identified as effective inhibitors of B-Raf kinase and was ultimately promoted for development as a drug candidate for the treatment of melanoma.<sup>81</sup> The key step in the synthesis was the palladium-catalyzed Negishi coupling of 4-bromo-1-chloroisoquinoline with trifluoromethanesulfonic acid isoquinoline-7-yl ester to yield 1-chloro-[4,7']bis-isoquinolinyl.

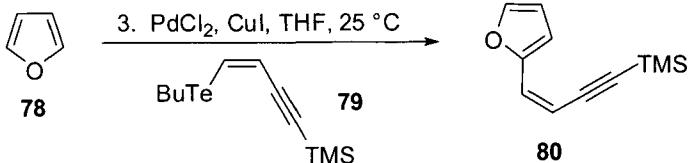
Cyclin-dependent kinases (CDKs) play a key role in regulating cell cycle machinery. This family of kinases requires association with a cyclin regulatory subunit for activity. Different CDK/cyclin pairs are active during each phase of the cell cycle. Negishi cross-coupling reactions were the key steps in the synthesis of [1,3,5]triazine-pyridine biheteroaryls **161** as a novel series of potent cyclin-dependent kinase inhibitors.<sup>82</sup>



#### **1.1.4.7      *Experimental***

Negishi Cross-Coupling in the Preparation of a Furanoenyne

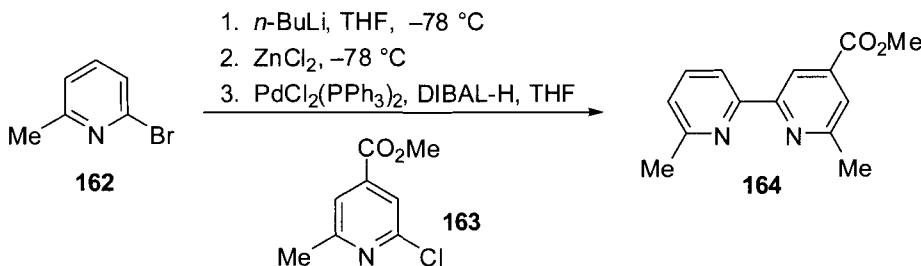
1. *n*-BuLi, THF, -78 °C
  2. ZnCl<sub>2</sub>, THF, -78 °C to rt



(Z)-[4-(Furan-2-yl)buten-3-en-1-ynyl]trimethylsilane (80).<sup>55</sup>

*n*-Butyllithium (12 mmol, 1.43 M in hexane, 8.40 mL) was added to a solution of freshly distilled furan (**78**, 0.87 mL, 12 mmol) in THF (12 mL) at -78 °C and stirred for 45 min. After this time, a suspension of anhydrous ZnCl<sub>2</sub> (1.22 g, 9.0 mmol) in THF (9 mL) was added and the mixture was warmed up to room temperature. A pale yellow solution was observed. Another two-necked, round-bottomed flask equipped with a magnetic stirring bar, rubber septum, under argon was charged sequentially with PdCl<sub>2</sub> (0.105 g; 0.60 mmol), CuI (0.57 g; 3.0 mmol), THF (3 mL), and compound **79** (0.924 g; 3.0 mmol). The mixture was stirred at room temperature for 10 min; then 2-furylzinc chloride was transferred dropwise from other flask via cannula. The dark solution was stirred at room temperature for 32 h. After this time, the mixture was filtered through a pad of silica gel/Celite and treated with aqueous ammonium chloride (30 mL) and CH<sub>2</sub>Cl<sub>2</sub> (3 × 20 mL). The organic phase was separated, dried over MgSO<sub>4</sub> and concentrated under vacuum. The residue was purified by flash chromatography to give **80** (0.40 g, 78%) as a yellow oil.

### Negishi Cross-Coupling in the Preparation of a Bipyridine



#### Methyl 6,6'-Dimethyl-2,2'-bipyridine-4-carboxylate (**164**).<sup>83</sup>

A solution of  $n\text{-BuLi}$  (1.5 M in hexane, 1.1 equiv) was slowly added to a stirred solution of 2-bromo-6-picoline (1.02 g, 5.93 mmol) in anhydrous THF (10 mL) at  $-78^\circ\text{C}$ , and the resulting mixture was stirred for 15 min at this temperature. Then, a 0.44 M solution of anhydrous  $\text{ZnCl}_2$  (1.1 equiv) in THF was added and the stirring was continued for 30 min at room temperature. In a separate flask, a solution of methyl 3-chloro-5-methylbenzoate (**163**, 715 mg, 3.85 mmol) in anhydrous THF (5 mL) was added to a solution containing 5 mol % of a catalyst prepared by reaction of a 0.014 M solution of  $\text{PdCl}_2(\text{PPh}_3)_2$  with diisobutylaluminium hydride (1.0 M in hexane, 2 equiv) and the mixture was stirred at room temperature for 10 min. The pyridylzinc chloride solution **162** prepared above was then added dropwise, and the resulting mixture was heated at reflux for 1.5 h, cooled, and poured into saturated aqueous  $\text{NaHCO}_3$ . The aqueous phase was extracted with  $\text{Et}_2\text{O}$  and the organic extracts were concentrated to give a solid residue which was purified by flash chromatography over alumina (petroleum ether/ether 90 : 10), to yield **164** (827 mg, 84%) as a white solid.

#### 1.1.4.8 References

1. (a) [R] Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340. (b) [R] Negishi, E. In *Metal-Catalyzed Cross Coupling*, Eds. Diederich, F.; Stang, P. J., Wiley, New York, **1998**. (c) Negishi, E. *J. Organomet. Chem.* **2002**, *653*, 34. (d) [R] Negishi, E.; Zeng, X.; Tan, Z.; Mingxing, Q.; Hu, Q.; Huang, Z. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed., Vol. 2; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: Weinheim, **2004**, 815. (e) [R] Negishi, E.; Hu, Z.; Huang, M. Q.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71.
2. Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729.
3. King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683.
4. Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.
5. Negishi, E. In *Aspects Mech. Organometal. Chem., [Proc. Symp.]*, Ed. Brewster, J. H., Plenum, New York, **1978**, 285.
6. Negishi, E.; Baba, S. *J. Chem. Soc., Chem. Commun.* **1976**, 597.
7. Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729.
8. King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683.
9. King, A. O.; Negishi, E.; Villani, F. J., Jr.; Silveira, A., Jr. *J. Org. Chem.* **1978**, *43*, 358.
10. Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.

11. Negishi, E.; van Horn, D. E. *J. Am. Chem. Soc.* **1977**, *99*, 3168.
12. Okukado, N.; van Horn, D. E.; Klima, W. L.; Negishi, E. *Tetrahedron Lett.* **1978**, *19*, 1027.
13. Negishi, E.; Okukado, N.; King, A. O.; van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254.
14. (a) Espinet, P.; Echavarren, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4704. (b) Casado, A. L.; Espinet, P. *Organometallics* **1998**, *31*, 852.
15. Casares, J. A.; Espinet, P.; Fuentes, B.; Salas, G. *J. Am. Chem. Soc.* **2007**, *129*, 3508.
16. Takahashi, T.; Kanno, K.-i. In *Modern Organonickel Chemistry*; Tamaru, Y., Ed.; Wiley-VCH: Weinheim, **2005**, 41.
17. Kondolff, I.; Doucet, H.; Santelli, M. *Organometallics* **2006**, *25*, 5219.
18. Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.
19. Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719.
20. Mutule, I.; Suna, E. *Tetrahedron Lett.* **2004**, *45*, 3909.
21. Mutule, I.; Suna, E. *Tetrahedron* **2005**, *61*, 11168.
22. Walla, P.; Kappe, C. O. *J. Chem. Soc., Chem. Commun.* **2004**, 564.
23. (a) Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Org. Lett.* **2005**, *7*, 4871. (b) Gavryushin, A.; Kofink, C.; Manolikakes, G.; Knochel, P. *Tetrahedron* **2006**, *62*, 7521.
24. (a) Hadei, N.; Kantchev, E. A. B; O'Brien, C. J.; Organ, M. G. *J. Org. Chem.* **2005**, *70*, 8503. (b) Hadei, N.; Kantchev, E. A. B; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805. (c) O'Brien, C. J.; Kantchev, E. A. B.; Chass, G. A.; Hadei, N.; Hopkinson, A. C.; Organ, M. G.; Setiadi, D. H.; Tang, T.-H.; Fang, D.-C. *Tetrahedron* **2005**, *61*, 9723.
25. Organ, M. G.; Avola, S.; Dubovsky, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. *Chem.-Eur. J.* **2006**, *12*, 4749.
26. Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594.
27. Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482.
28. Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726.
29. Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527.
30. Lipshutz, B. H.; Blomgren, P. A. *J. Am. Chem. Soc.* **1999**, *121*, 5819.
31. (a) Felding, J.; Kristensen, J.; Bjerregaard, T. B.; Sander, L.; Vedsø, P.; Begtrup, M. *J. Org. Chem.* **1999**, *64*, 4196. (b) Pawlas, J.; Vedsø, P.; Jakobsen, P.; Huusfeldt, P. O.; Begtrup, M. *J. Org. Chem.* **2000**, *65*, 9001.
32. Kristensen, J.; Begtrup, M.; Vedsø, P. *Synthesis* **1998**, 1604.
33. Abarbri, M.; Thibonnet, J.; Berillon, L.; Dehmel, F.; Rottlander, M.; Knochel, P. *J. Org. Chem.* **2000**, *65*, 4618.
34. Havez, S.; Begtrup, M.; Vedsø, P.; Andersen, K.; Ruhland, T. *Synthesis* **2001**, 909.
35. Reeder, M. R.; Gleaves, H. E.; Hoover, S. A.; Imbordino R. J.; Pangborn, J. *J. Org. Process Res. Dev.* **2003**, *7*, 696.
36. Anderson, B. A.; Harn, N. K. *Synthesis* **1996**, 583.
37. Anderson, B. B.; Becke, L. M.; Booher, R. N.; Flaugh, M. E.; Harn, N. K.; Kress, T. J.; Varie, D. L.; Wepsiec, J. P. *J. Org. Chem.* **1997**, *62*, 8634.
38. Prasad, A. S. B.; Stevenson, T. M.; Citineni, J. R.; Nyzam, V.; Knochel, P. *Tetrahedron* **1997**, *53*, 7237.
39. Bach, T.; Heuser, S. *Tetrahedron Lett.* **2000**, *41*, 1707.
40. Jensen, J.; Skjaerbaek, N.; Vedsø, P. *Synthesis* **2001**, 128.
41. Akao, A.; Tsuritani, T.; Satoshi K. S; Sato, K.; Nonoyama, N.; Mase, T.; Yasuda, N. *Synlett* **2007**, 31.
42. Sapountzis, I.; Dube, H.; Knochel, P. *Adv. Synth. Catal.* **2004**, *346*, 709.
43. Simkovsky, N. M.; Ermann, M.; Roberts, S. M.; Parry, D. M.; Baxter, A. D. *J. Chem. Soc., Perkin Trans. 1*, **2002**, 1847.
44. Fang, Y.-Q.; Hanan, G. S. *Synlett* **2003**, 852.
45. Kiehne, U.; Bunzen, J.; Staats, H.; Lutzen, A. *Synthesis* **2007**, 1061.
46. Havas, F.; Danel, M.; Galaup, C.; Tisnes, P.; Picard, C. *Tetrahedron Lett.* **2007**, *48*, 999.
47. Turck, A.; Ple, N.; Lepretre-Gaquerre, A.; Queguiner, G. *Heterocycles* **1998**, *49*, 205.
48. Sharples, C. G. V.; Karig, G.; Simpson, G. L.; Spencer, J. A.; Wright, E.; Millar, N. S.; Wonnacott, S.; Gallager, T. *J. Med. Chem.* **2002**, *45*, 3235.
49. Collins, I.; Castro, J. L.; Street, L. J. *Tetrahedron Lett.* **2000**, *41*, 781.

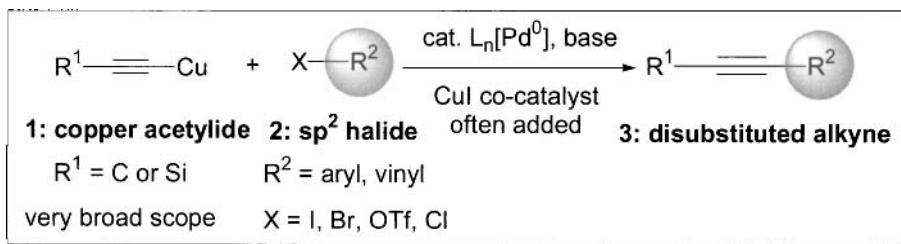
50. Gorley, E. G.; Conrad, K.; Murry, J. A.; Savarin, C.; Holko, J.; Boice, G. *J. Org. Chem.* **2004**, *69*, 5120.
51. (a) Genov, M.; Fuentes, B.; Espinet, P.; Pelaz, B. *Tetrahedron: Asymmetry* **2006**, *17*, 2593.  
(b) Genov, M.; Almorin, A.; Espinet, P. *Tetrahedron: Asymmetry* **2007**, *18*, 625.
52. (a) Hocek, M.; Dvorakova, H. *J. Org. Chem.* **2003**, *68*, 5773. (b) Hasnik, Z.; Silhar, P.; Hocek, M. *Tetrahedron Lett.* **2007**, *48*, 5589.
53. Shiota, T.; Yamamori, T. *J. Org. Chem.* **1999**, *64*, 453.
54. (a) Alves, D.; Schumacher, R. F.; Brandao, R.; Nogueira, C. W.; Zeni, G. *Synlett* **2006**, 1035.  
(b) Zeni, G.; Alves, D.; Braga, A. L.; Stefani, H. A.; Nogueira, C. W. *Tetrahedron Lett.* **2004**, *45*, 4823.
55. Oliveira, J. M.; Zeni, G.; Malvestiti, I.; Menezes, P. H. *Tetrahedron Lett.* **2006**, *47*, 8183.
56. Xie, M.; Wang, J.; Gu, X.; Sun, Y.; Wang, S. *Org. Lett.* **2006**, *8*, 431.
57. Andrei, D.; Wnuk, S. F. *J. Org. Chem.* **2006**, *71*, 405.
58. Dutheuil, G.; Paturel, C.; Lei, X.; Couve-Bonnaire, S.; Pannecoucke, X. *J. Org. Chem.* **2006**, *71*, 4316.
59. (a) Rodriguez, D.; Castedo, L.; Saa, C. *Synlett* **2004**, 783. (b) Martinez-Esperon, M. F.; Rodriguez, D.; Castedo, L.; Saa, C. *Tetrahedron* **2006**, *62*, 3843.
60. Lipshutz, B. H.; Clososki, G. C.; Chrisman, W.; Chung, D. W.; Ball, D. B.; Howell, J. *Org. Lett.* **2005**, *7*, 4561.
61. Morisaki, Y.; Luu, T.; Tykwienski, R. R. *Org. Lett.* **2006**, *8*, 689.
62. Bowling, N. P.; McMahon, R. J. *J. Org. Chem.* **2006**, *71*, 5841.
63. Conway, J. C.; Urch, C. J.; Quayle, P.; Xu, J. *Synlett* **2006**, 776.
64. Ousmer, M.; Boucard, V.; Lubin-Germain, N.; Uziel, J.; Auge, J. *Eur. J. Org. Chem.* **2006**, 1216.
65. Kruppa, M.; Imperato, G.; Konig, B. *Tetrahedron* **2006**, *62*, 1360.
66. Goundry, W. R. F.; Lee, V.; Baldwin, J. E. *Synlett* **2006**, 2407.
67. Moreno, E.; Nolasco, L. A.; Caggiano, L.; Jackson, R. F. W. *Org. Biomol. Chem.* **2006**, *4*, 3639.
68. Berkowitz, D. B.; de la Salud-Bea, R.; Jahng, W.-J. *Org. Lett.* **2004**, *6*, 1821.
69. Hlavinka, M. L.; Hagadorn, J. R. *Tetrahedron Lett.* **2006**, *47*, 5049.
70. Dubbaka, S. R.; Vogel, P. *Tetrahedron Lett.* **2006**, *47*, 3345.
71. Bach, T.; Bartels, M. *Tetrahedron Lett.* **2002**, *43*, 9125.
72. Takagi, R.; Tsuyumine, S.; Nishitani, H.; Miyanaga, W.; Ohkata, K. *Aust. J. Chem.* **2004**, *57*, 439.
73. Inoue, M.; Yokota, W.; Katoh, T. *Synthesis* **2007**, 622.
74. (a) Bach, T.; Heuser, S. *Agnew. Chem. Int. Ed.* **2001**, *40*, 3184. (b) Bach, T.; Heuser, S. *Chem.-Eur. J.* **2002**, *8*, 5585.
75. Fürstner, A.; Weintritt, H. *J. Am. Chem. Soc.* **1998**, *120*, 2817.
76. Wehlan, H.; Jezek, E.; Lebrasseur, N.; Pave, G.; Roulland, E.; White, A. J. P.; Burrows, J. N.; Barrett, A. G. M. *J. Org. Chem.* **2006**, *71*, 8151.
77. Sorg, A.; Bruckner, R. *Angew. Chem., Int. Ed.* **2004**, *43*, 4523.
78. Nguyen, T.; Wicki, M. A.; Snieckus, V. *J. Org. Chem.* **2004**, *69*, 7816.
79. Gomez-Reino, C.; Vitale, C.; Maestro, M.; Mourino, A. *Org. Lett.* **2005**, *7*, 5885.
80. (a) Stanetty, P.; Rohrling, J.; Stanetty, P.; Hatinger, G.; Schnurch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2005**, *70*, 5215. (b) Stanetty, P.; Rohrling, J.; Hatinger, G.; Schnurch, M.; Mihovilovic, M. D. *Tetrahedron* **2006**, *62*, 2380.
81. Denni-Discher, D.; Marterer, W.; Banziger, M.; Yusuff, N.; Batt, D.; Ramsey, T.; Geng, P.; Michael, W.; Wang, R.-M.; Taplin, F., Jr.; Versace, R.; Cesarz, D.; Perez, L. B. *Org. Proc. Res. & Dev.* **2006**, *10*, 70.
82. Kuo, G.-H.; DeAngelis, A.; Emanuel, S.; Wang, A.; Zhang, Y.; Connolly, P. J.; Chen, X.; Gruninger, R. H.; Rugg, C.; Fuentes-Pesquera, A.; Middleton, S. A.; Jolliffee, L.; Murray, W. V. *J. Med. Chem.* **2005**, *48*, 4535.
83. Havas, F.; Danel, M.; Galaup, C.; Tisnes, P.; Ficard, C. *Tetrahedron Lett.* **2007**, *48*, 999.

## 1.1.5 Sonogashira Reaction

David L. Gray

### 1.1.5.1 Description

The palladium catalyzed C–C bond formation processes that couples the terminal  $sp$  hybridized carbon from an alkyne (**1**) with an  $sp^2$  carbon of an aryl or vinyl halide **2** to afford a disubstituted alkyne (**3**) is commonly referred to as a Sonogashira coupling.<sup>1–6</sup> As with many palladium-mediated coupling processes, there are numerous variants of this name reaction, including the analogous entirely copper-mediated process (see Stevens–Castro reaction, section 1.2.1), but the most common version uses catalytic copper as a co-promoter. The Sonogashira coupling has found broad utility in complex molecule synthesis, and truly excels in certain transformations for which it is particularly suited. The generic reaction equation does not visually capture the impressive diversity of compounds which have successfully undergone Sonogashira coupling. Among the over 1000 articles which report on Sonogashira couplings are a number of recent and comprehensive reviews of this reaction, its application, and ongoing advancements in the field.<sup>7–21</sup>

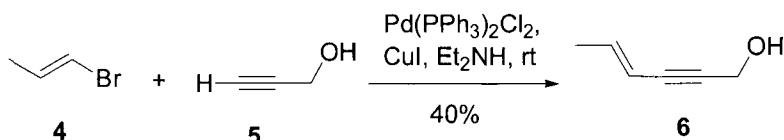


A difference between the Sonogashira coupling and many other palladium-mediated C–C bond forming reactions covered in this chapter is the fact that one of the coupling partners (the terminal alkyne) does not need to be activated with a halide or other metal, the alkyne itself being a sufficiently good ligand for the palladium by virtue of its *d*-orbital structure and inherent lack of steric bulk. In early embodiments, the coupling was primarily observed with activated (electron deficient) aryl/vinyl iodides or bromides, and functional group compatibility was shown to be excellent. An examination of successful substrates reveals examples of Sonogashira coupling in the presence of nearly any common functional group.<sup>7,22–25</sup> In fact, this coupling process is among the most tolerant in terms of other functionalities, making it particularly effective for the synthesis of complex

molecules and large supramolecular constructs.<sup>26,27</sup> Key requirements for reliable reactivity include an alkyne that is not highly electron deficient (conjugation with a carbonyl dramatically slows the reaction rates, though this can be overcome) and the familiar activation constraints on the halide coupling partner, with electron rich aryl bromides, and particularly aryl chlorides, necessitating more forcing conditions and specially tuned catalyst systems.<sup>15</sup> Steric bulk around the reacting alkyl halide and significant bulk on the alkyne are normally tolerated. The Sonogashira coupling reaction is usually complete within 8 hours and often within 30 minutes. Palladium loading varies widely, however in a large percentage of synthetic application, between 0.5 and 5 mol% of the metal is used.

In its early form, the reactions were generally run in amine bases as solvent with co-catalytic CuI.<sup>1</sup> The functional palladium catalyst can be added to the reaction mixtures either as a Pd(0) species such as [Pd(PPh<sub>3</sub>)<sub>4</sub>], or as a Pd(II) precatalyst like [Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub>]. This latter pre-catalyst was the palladium source for the cross-coupling of 1-bromopropene (**4**) and propargyl alcohol (**5**) to form ene-yne **6**, which was demonstrated in Sonogashira's original disclosure.<sup>1</sup> More recent advances include powerful "copper-free" conditions capable of coupling notoriously unreactive aryl chlorides, and a host of developments in the areas of heterogeneous catalyst systems, novel solvents, ligands, and palladium sources, though the early CuI, Pd/PPh<sub>3</sub>-based systems remain as the methods chosen for the majority of synthetic application.<sup>7,28–36</sup> One caveat to the use of the Sonogashira coupling is the ready formation of copper-promoted alkyne homo-dimers. A number of protocols have been developed to minimize the formation of these products and some of these techniques will be discussed in section 1.1.5.3.<sup>37–39</sup>

The union of an sp<sup>2</sup> and an sp center does not create any new stereochemistry, making for an attractive retrosynthetic disconnection in certain situations. In cases where E- or Z-geometry exists in the aryl halide component (e.g., **4**), the stereochemical integrity of the olefin is retained during a Sonogashira coupling.<sup>9</sup>

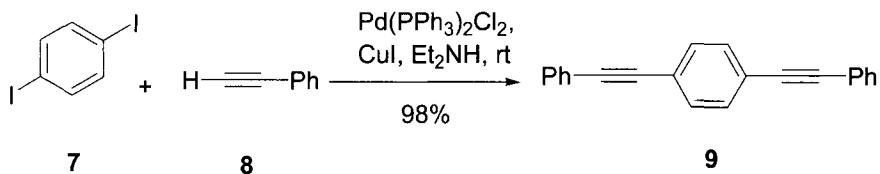


A large number of ligands for palladium have been employed, though the largest and most important class is the monodentate phosphines. Multidentate phosphanes, palladacycles, and *N*-heterocyclic carbenes are emerging areas of ligand development and application.<sup>8</sup> A stoichiometric amount of base is necessary to turn the catalytic system over, but in practice two or

more molar equivalents are normally used. Organic amine bases (for example Et<sub>3</sub>N or *i*-Pr<sub>2</sub>NH) were used as solvent in much of the early investigation of this reaction, and later, inorganic bases such as K<sub>2</sub>CO<sub>3</sub> or Cs<sub>2</sub>CO<sub>3</sub> were shown to be effective in many cases. While reaction solvent is a parameter that has been varied in many studies with effect, when taken collectively, any of the solvents used in Pd-based cross coupling chemistry have functioned well in the appropriate Sonogashira system. Apart from the aforementioned components, (Pd<sup>0</sup>, Cu<sup>I</sup>, ligand for Pd, solvent, and base), additional additives are uncommon save for phase transfer agents used in aqueous systems, and tetra-alkyl amines which accelerate ligand-free protocols.<sup>42–44</sup> Many successful Sonogashira transformations occur at room temperature, but reaction have been reported as low as –20 °C and in excess of 150 °C.<sup>7–45</sup>

### 1.1.5.2 *Historical Perspective*

The Sonogashira coupling has its origins in the extension of copper-catalyzed processes that were being described in the late 1950's.<sup>6</sup> Conceptually, it is related to the Castro–Stephens coupling (see 1.2.1) and shares mechanistic connection to other productive Pd-mediated cross couplings in common use today (See sections 1.1.1–1.1.4), with many of the same pioneers in organometallic chemistry making important contributions to the advancement of this reaction in parallel with their studies of other cross-coupling methodologies. In consecutive *Journal of Organometallic Chemistry* articles in 1975, Heck and Cassar independently described Pd-catalyzed conditions for the union of alkynes and aryl iodides under basic conditions at high temperature, Heck's procedure using amine bases as solvent, and Cassar's protocol featuring sodium methoxide in DMF.<sup>2,3</sup> As part of a program directed toward characterizing alkyne reactivity with metals, Kenkichi Sonogashira and co-workers had previously observed that copper acetylides effectively transmetalated to platinum and that the resulting Pt-alkyne intermediates went on to react at the unactivated alkyne terminus.<sup>7,8</sup> Sonogashira's insight was to combine the copper-mediated transmetalation of alkynes that his group was studying with a metal that offered more in terms of catalyst tenability, namely palladium. Several months after the Heck and Cassar disclosures, Sonogashira reported on 15 examples of Pd-catalyzed cross coupling between terminal alkynes and aryl/alkenyl halides that proceeded *at room temperature* in amine solvent when co-catalytic CuI was added. It was this extension of Heck and Cassar's results that yielded a productive and robust C–C bond formation with especially mild reaction conditions.<sup>1</sup>

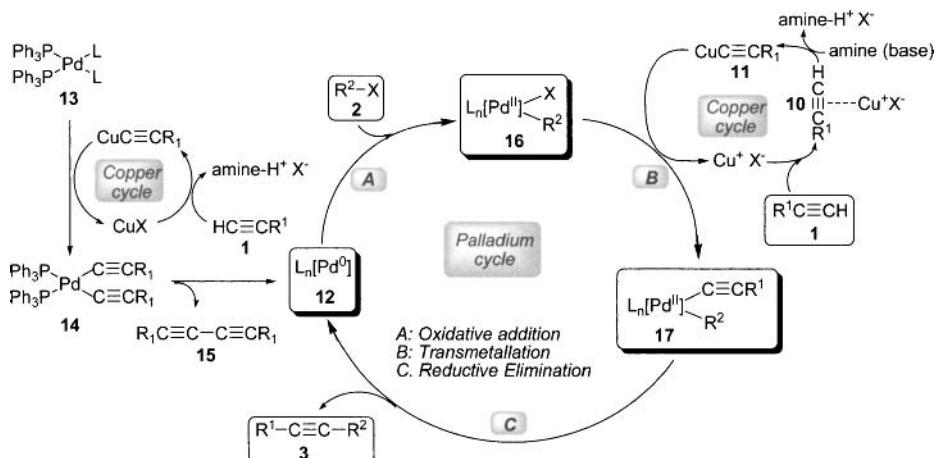


Typical of the reactions exemplified in Sonogashira, Todha, and Hagihara's 1975 report is the double coupling of 1,4-diiodobenzene (**7**) with phenylacetylene (**8**), which proceeded to give a remarkably high yield of linear triphenyl compound **9** using 0.5 mol% of a Pd(II) precatalyst and 1 mol% cuprous iodide in diethylamine. The same initial publication also described the formation of symmetrically disubstituted alkynes from aryl iodides and bubbled-in acetylene gas under the same conditions (coupling at both acetylene termini).<sup>1</sup> The striking mildness of the copper-promoted coupling conditions (when compared to the similar Heck and Cassar palladium-only conditions for the same transformation) spurred significant research into the application of this reaction and later, into the broadening of its scope. It was quickly established that the original Sonogashira protocol was very tolerant of functional groups and steric bulk within the reacting partners, and could therefore be adapted to complex molecule synthesis with little modification. It is likely these features which contribute the current popularity of the Sonogashira reaction.<sup>49</sup> Of course, while the addition of copper yielded tangible benefits in terms of reaction mildness, there were a number of challenges with the methodology which provided fertile ground for organometallic research.<sup>8,10,13,15</sup> These initial shortcomings included relatively high catalyst loadings with aryl bromide coupling partners, significant alkyne homocoupling (Glaser reaction – see 1.2.2), inertness of unactivated aryl bromide and chlorides, complexity of two-metal systems, and the need for a large excess of amine base. These challenges have all been addressed to a certain extent, and in some cases, a solution has been to eliminate the copper in so called "copper-free" Sonogashira conditions (which could just as easily have been termed Heck–Cassar couplings). The term "Sonogashira coupling" however, is now a blanket description commonly applied to the Pd(0) mediated union of a terminal alkyne and an  $sp^2$  (or even  $sp^3$ ) halide or triflate, regardless of whether copper(I) salts are present. The ene-yne moiety of Sonogashira products has found applicability in diverse and highly useful ways spanning everything from self-assembly and guest-host constructs, to dyes, sensors, biomolecule conjugates, polymers, and heterocycle synthesis.<sup>27,49–63</sup>

### 1.1.5.3 Mechanism

#### Mechanism of Sonogashira Reaction with Copper Co-Catalyst

It has been generally accepted that the copper co-catalyzed Sonogashira coupling proceeds via a dual catalytic cycle- a palladium cycle which is similar to that which is postulated for the Heck and Suzuki couplings, and an ancillary copper cycle which facilitates the transfer of an un-activated acetylynic group to the palladium metal center.<sup>6</sup> There are similarities between key steps of the postulated Pd catalytic cycle for the Sonogashira coupling, and those elements in Heck and Suzuki couplings which unify many of the considerations that have driven progress in the palladium-mediated C–C bond formation area. The difficulty of unequivocally “proving” the details of a complex catalytic cycle leave room for additional insight into the precise nature of the various intermediates, however, as a basis for informing progress in the field, the basic 3-step catalytic cycle consisting of A) oxidative addition, B) transmetalation, and C) reductive elimination has been fruitful.<sup>9</sup> There is more uncertainty surrounding the Cu cycle, as the putative intermediates (e.g., **10** and **11**) have not been directly characterized and there is less analogy with other well-studied systems. There are excellent resources which provide insight into mechanistic subtleties as presently understood, however this scheme outlines a suitable framework for practical mechanistic discussion.<sup>8–10,16</sup>



The requisite entry into the main catalytic cycle is a Pd(0) species (**12**) which can either be added as  $[\text{Pd}^0(\text{PPh}_3)_4]$  or similar, or generated *in situ* from a Pd(II) pre-catalyst and excess phosphine or alkyne. In Sonogashira's original condition, it is likely that the active Pd(0) catalyst **12** was generated

from  $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$  (**13**, L = Cl) via reductive coupling of sacrificial alkyne as outlined.<sup>6</sup> Thus, the “copper cycle” and a base facilitate the sequential transfer of two alkyne ligands (**1**) onto Pd(II) to afford intermediate **14**. Reductive C–C bond formation then expels diacetylene species **15** and generates low valent palladium **12**. The classical Pd cycle then begins with the oxidative addition (step A) of this Pd(0) species into the C–X bond of the aryl or vinyl halide component **2** to afford a Pd(II) complex (**16**). The L<sub>n</sub> designation within **16** is purposefully ambiguous in that a number of factors are thought to determine the coordination chemistry and charge state of this Pd(II) intermediate complex, with counterions, main ligand properties, and solvent effects typically proposed as the major players. Regardless of its exact structure, progress towards eventual product occurs in step B when the electron deficient metal center accepts a terminal alkyne donor ligand in a transmetalation event, leading to intermediate **17**. A co-catalytic copper cycle is postulated to form a transient copper acetylide **11**, which transfers alkyne to palladium. Activation of the alkyne starting material **1** likely precedes formation of **11** via the intermediacy of the  $\pi$ -alkyne copper complex **10**. In step C, complex **17** reductively eliminates disubstituted alkyne product **3**, forming a new carbon–carbon bond and re-generating the Pd(0) **12**. A minimum of one equivalent of base (frequently an amine) is required to remove the net acid (HX) generated in the reductive elimination step, and this action is often thought to be focused within the copper cycle when copper salts are present.

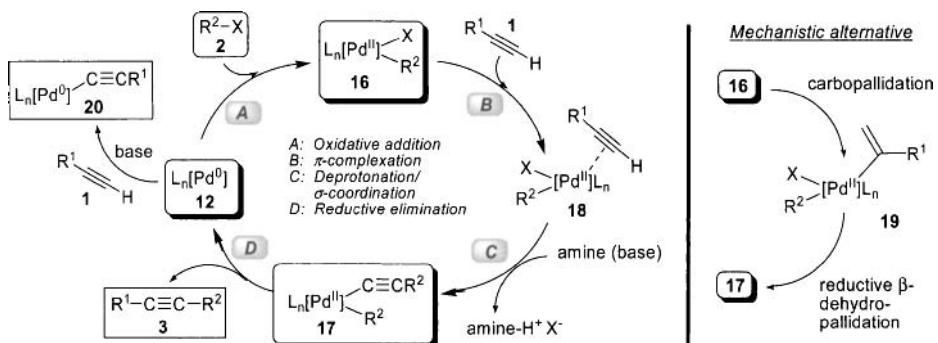
Similar to other Pd-promoted C–C bond formations, the ligand plays a key role in funnelling the course of the reaction into a productive manifold. In favourably biased reactions, most any Pd(0)-based catalyst/ligand system can be coerced to afford useful yields of product. However, the importance of the ligand is particularly apparent with more recalcitrant systems, where slow steps need to be accelerated by ligand effects in order to avoid side reactions and the plating out of palladium black, which limits turnover.<sup>13</sup> Certainly, the optimization of phosphine ligands is the single biggest development contributing to the increasing scope of the Sonogashira coupling. Not surprisingly, the order of reactivity for halide substrates **2** parallels their propensity to undergo oxidative addition, namely X = I > OTf > Br >> Cl.<sup>9</sup> For iodides and electron deficient bromides or triflates, the oxidative addition is generally fast and is not rate limiting.<sup>16</sup> Transmetalation from the copper acetylide is typically the slower event unless electron rich bromides, and particularly aryl chlorides are employed, in which case the situation changes considerably and the oxidative addition may be rate limiting.<sup>15</sup>

Under Sonogashira reaction conditions, the propensity of terminal alkynes to form dimerized products (**15**) is often attributed to oxidation of

copper(I), which is well known to reductively dimerize terminal alkynes in its higher oxidation state (see section 1.2.2, Glaser coupling). The mechanistic scheme also points to a second, minor pathway for the formation of **15** mediated by palladium. The homocoupled side product is a unique issue to the Sonogashira coupling among the reactions covered in this chapter.

As is the case with many other Pd-mediated coupling processes, there can be varying coordination states at the metal center at each stage of the catalytic cycle, depending upon the conditions. Familiar  $\text{Pd}(0)\text{L}_2$  (**12**) seems likely with ligands like  $\text{PPh}_3$ , but evidence suggests that very bulky phosphanes shift **12** to a singly ligated  $\text{Pd}(0)\text{L}$  catalyst species, a condition which promotes oxidative addition to less reactive aryl bromides and chlorides.<sup>15</sup> On the other end of that spectrum, heterogeneous catalyst conditions lead to a weakly or transiently coordinated  $\text{Pd}(0)$  catalyst **12**.<sup>13,64</sup> Jutand advocates that **12** can also be an anionic  $\text{Pd}(0)\text{L}_2\text{X}^-$  complex, particularly with certain precatalysts like  $\text{Pd}(\text{OAc})_2$  or with aryl chloride substrates, where the acetate or Cl anion can serve as a ligand to drive formation of pentacoordinate palladium species.<sup>16</sup>

#### *Mechanism of “Copper-Free” Sonogashira Reaction*



Recent publications concerning “Ligand-free” and “copper-free” conditions for the Sonogashira coupling raise additional points about the reactivity pathway.<sup>65</sup> In copper free variants, several mechanistic possibilities have been proposed, one of which is presented here. Laying aside specifics about the  $\text{Pd}(0)$  entry into the catalytic cycle, palladium complex **12** again oxidatively inserts into  $\text{sp}^2$  halide **2** (step A) to give rise to complex **16**. In step B,  $\pi$ -complexation of **1** with **16** would acidify the acetylinic proton in species **18** and facilitate its removal by an amine base (step C) with coordination of the now (formally) anionic acetylene ligand to the metal

center. Palladium(II) species **17** is now set up for step D – reductive elimination of product **3** and reformation of active catalyst **12**.

One might envision that the base plays a direct role in deprotonating the alkyne, with the resulting acetylide anion coordinating to the palladium, however, activation of the acetylynic proton in an  $\eta^2$  complex **18** seems to be required, because the employed amine and inorganic bases are not sufficiently strong to directly deprotonate the alkyne, though the pKa of the acetylinic proton has been shown to influence reaction outcome and rate.<sup>66</sup> When amine bases are used under “copper-free” conditions, the influence of specific amines is more pronounced than with standard copper co-promoted reactions.<sup>68</sup> Perhaps surprisingly, while copper(I) salts have robust acceleration effects most Sonogashira couplings with iodides and electron-poor bromides regardless of ligand/catalysts system, the protocols that have demonstrated the capability to successfully couple deactivated aryl bromides and chlorides are mainly “copper-free” and the addition of CuI to these reactions has a deleterious effect on both rate and yield.<sup>8,28,67</sup> Clearly, the copper-free Sonogashira coupling is less well characterized, though surely it proceeds via oxidative addition and reductive elimination. A detailed understanding of the process for coordination of the alkyne remains elusive. In fact, at least one leading researcher recently suggested that a carbopallidation/reductive  $\beta$ -dehydropallidation sequence advancing through transient vinyl palladium **19** cannot be ruled out owing to the lack of palladium-derived structural information translating to Sonogashira products. This latter pathway may be more relevant when there is no amine base in solution.<sup>9,69</sup>

#### *Additional Mechanistic Considerations*

One interesting observation is that the oxidative addition of palladium(0)-tetrakis(triphenylphosphine) to iodobenzene is slowed when performed in the presence of phenylacetlyene, with the rate of the overall reaction having an inversely proportional relationship to alkyne concentration.<sup>16</sup> This strongly suggests that a portion of the active Pd(0) catalyst **12** is coordinated to the alkyne in the form of deactivated  $[(\eta^2\text{-R}^1\text{C}\equiv\text{CH})\text{Pd}^0\text{L}_2]$  **20**, and helps to explain inconsistent effects on rate due to alkyne concentration. With an alkyne ligand on Pd(0), the oxidative addition will be slowed. Oxidative addition is typically not considered to be the rate-limiting step in this postulated catalytic cycle, but this slowing can have divergent consequences. Slowing of step A can actually lead to favourable effects on turnover numbers (TONs) when there is a significant rate mismatch between a fast oxidative addition and a slower transmetalation. The coordination of the alkyne to the Pd can move the relative rates closer to unity, the ideal situation

for maximum catalytic efficiency. Much effort has been devoted to the coupling of propiolic acid derivatives because the products would have broad utility.<sup>70,71</sup> Success in this area has been limited, likely due to the affinity of Pd(0) for propiolates, which affinity would increase the contribution of a significantly deactivated species **20** [ $(\eta^2\text{-RC}\equiv\text{CH})\text{Pd}^0\text{L}_2$ ], R = CO<sub>2</sub>H.<sup>16</sup> To further obscure the details, many of the amine bases used in the Sonogashira reaction can themselves be transient ligands for the Pd metal, displacing phosphine to form [Pd<sup>0</sup>L<sub>n</sub>(amine)] complexes in a reversible process that should be a more significant contributor to reaction outcome when the amine base is used as solvent.<sup>13,16,69</sup>

### *Regioselectivity and Stereoselectivity*

The Sonogashira coupling is regio- and stereochemically straightforward. The aryl or vinyl halide component always couples with retention of any *E,Z* stereochemical information contained within the starting materials, and no additional stereocenters are generated, nor are migrations observed. The alkyne component couples at the unsubstituted terminus and affords an expected product. Information derived from stereochemical outcomes of other Pd coupling reactions has been invaluable in establishing the mechanistic underpinnings of those processes. Conversely, the lack of such clues in the product has hampered efforts to more fully define the mechanistic course of the Sonogashira coupling.

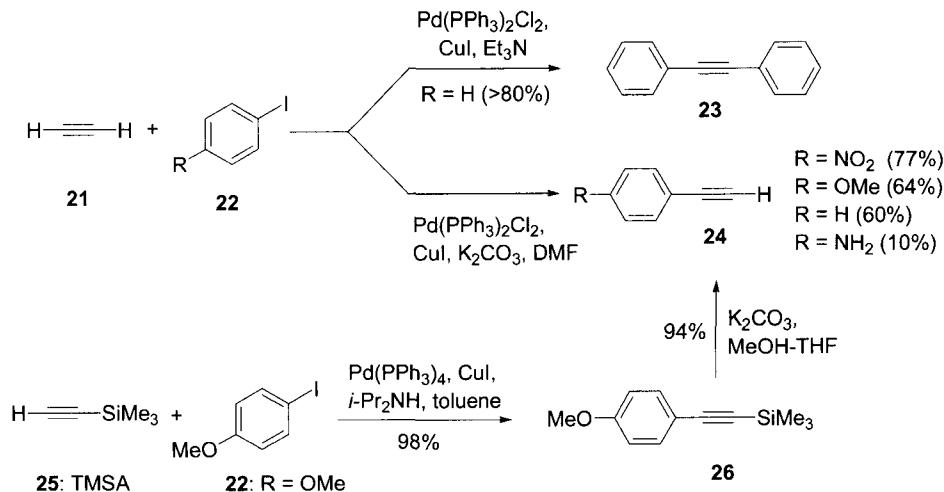
### *“Ligand-free” Catalysis*

Background and general mechanistic considerations for “ligand-free” catalysis are covered in previous sections, and many of the same concepts apply to the Sonogashira coupling. The term “ligand-free” is meant to convey the absence of traditional “strong” ligands (like PPh<sub>3</sub>) rather than a truly naked Pd(0) species. Basic amines or solvents are assumed to serve as weak ligands for the palladium center in these protocols. Owing to the transient nature of the interactions, it is difficult to glean much structural information on weakly coordinated palladium species or to make mechanistic generalizations across brand of catalysis. Nanoparticulate or soluble molecular palladium has been shown to be the operant catalyst in some “ligand-free” systems. Aryl iodides (e.g., **7**) couple so readily with terminal alkynes that Pd(OAc)<sub>2</sub> has been shown to catalyze this transformation without the addition of any traditional ligand.<sup>42–44,72,73</sup> There is an ongoing debate as to the nature of the active species when classical ligands are absent, but it is clear that poorly ligated palladium can demonstrate interesting catalytic activity.<sup>74</sup>

### Heterogeneous Catalysis

Heterogeneous catalysis encompasses a broad and active area of cross coupling research. Similar to ligand-free catalysis, the chemistries and mechanistic proposals surrounding productively harnessed heterogeneous palladium-based cross coupling are complex and evolving.<sup>75</sup> For palladium nanoparticles, a well accepted relationship exists between particle size, accessible surface area, and activity. Preparations that maximize accessible metal surface area lead to enhanced reactivity. At present, mechanistic work is primarily focused on the characterization of reactive surface metal.<sup>76</sup> The strategies used to increase turnover with these reactive, but inherently unstable catalyst species are somewhat generally applicable to Heck, Stille, or Sonogashira protocols and include addition of ionic liquids or quaternary ammonium salts, reservoir strategies where soluble palladium is thought to slowly release into solution, capture of palladium in peroskovites or other mesoporous matrices, and the use of palladium coated particles which maximize the amount of surface-accessible reactive catalyst.<sup>74</sup> Each of these approaches aims to maximize operant Pd(0) while mitigating against the expected aggregations of the low valent metal. One must be careful to differentiate between truly insoluble metal, and catalysis which occurs via low ppm leaching of palladium into solution. A great challenge in this area is proving unequivocally that catalysis is occurring exclusively in the heterogeneous phase. Even so, the expected progression for Sonogashira couplings in the heterogeneous phase is via intermediates like **14** and **15** with undefined ligands L<sub>n</sub>.

### Alkyne Homocoupling and Reactivity of Acetylene



Acetylene is ideally a very useful reagent for Sonogashira coupling, however, this gas poses selectivity problems in this reaction owing to the propensity for the product to couple with additional halide to form symmetrical constructs. In fact, under the typical conditions, the bis-coupled acetylene **23** has been reported to be the major isolated product from reaction of acetylene (**21**) and iodobenzene (**22**: R = H).<sup>39,77</sup>

The common work-around for this reactivity problem is to use TMS acetylene (**25**). This reagent is easily handled and the silyl group is readily removed upon treatment with mild base (**26** → **24**: R = OMe).<sup>78</sup> Productive monocoupling of **22** and acetylene (**21**) to afford the terminal alkynes (**24**) has been achieved by judicious choice of DMF as a reaction solvent. The proposal is that acetylene has high solubility in DMF, and that the high molarity of acetylene compared to starting halide statistically drives the reaction equilibrium toward formation of the desired monocoupled alkyne **24**. Use of TMS acetylene is a general solution to the synthesis of monosubstituted alkynes, while the reactions with acetylene itself afforded products (**24**) in good yield only when aryl iodides were coupled.<sup>77</sup>

Separate from the issue with acetylene, the homocoupling of alkynes is a reaction shunt that is usually undesired and arises chiefly via copper redox chemistry. This end to end union of two of the same alkynes is also known as a Glaser coupling (see 1.2.2). In order to minimize the formation of these dimers, the alkyne is often added slowly to keep its relative concentration low.<sup>37</sup> Oxygen has been identified as a promoter for the unwanted homocoupling of alkynes, and most procedures now actively remove this gas from reaction solvents and are run under inert atmospheres to minimize Glaser products. Running Sonogashira coupling under an atmosphere of H<sub>2</sub> suppresses the oxidative pathway, but most experimental procedures simply call for degassed solvents and reaction under nitrogen.<sup>38</sup> A more recent development is the “sila-Sonogashira” wherein the Glaser pathway is completely avoided by effecting direct coupling of trimethylsilylacetylenes (reaction occurring on the silyl-bearing carbon).<sup>79,80</sup>

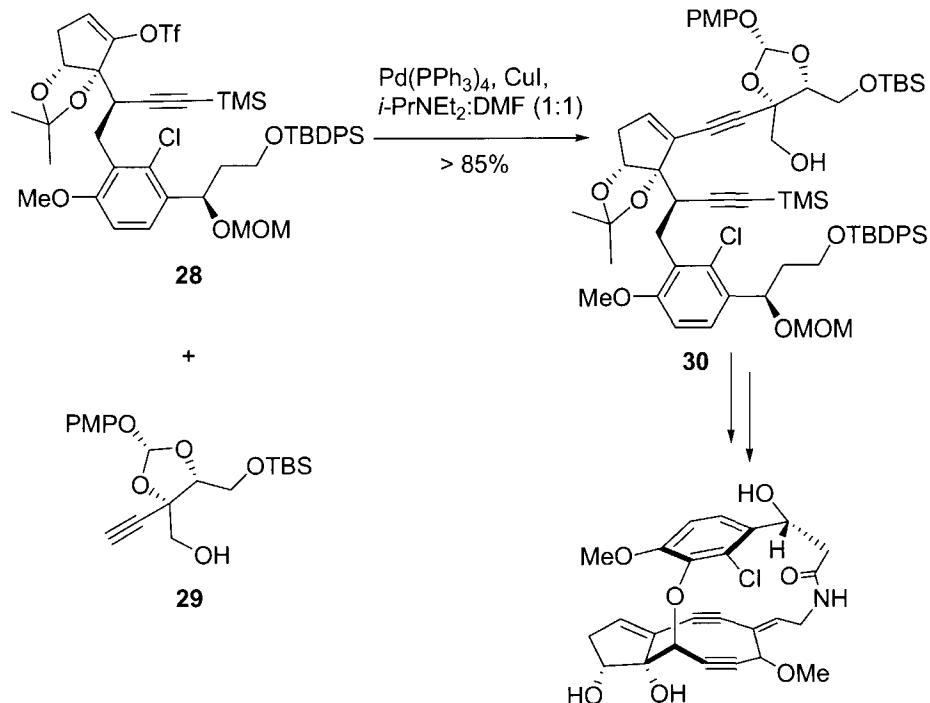
#### 1.1.5.4 *Synthetic Utility*

The Sonogashira finds frequent application in nearly every area of synthetic chemistry, and consequently, a dizzying array of diverse compound classes are represented among the successful products of this reaction. Though the product structures may look quite distinct, the reason that the Sonogashira coupling is typically chosen is often the same – either the mild reaction conditions and corresponding functional group tolerance or incorporation of the useful alkyne moiety. Despite the significant work on copper-free conditions, heterogeneous catalyst systems, advanced phosphanes, aqueous reaction, and other “improved” protocols, the vast majority of the literature

on actual application of the Sonogashira coupling still uses the CuI promoted conditions with simple Pd/PPh<sub>3</sub>-based catalyst systems and reaction conditions that are not too dissimilar from early versions of the reaction, the main difference being that amines are rarely used neat as solvent.<sup>7</sup> Despite the preponderance of the “old” conditions in synthetic application, there is recently a trend of uptake which indicates that newer procedures are indeed more powerful, and general. Strategically, some larger classes of applications emerge:

- Cross-coupling of advanced and precious fragments in total synthesis
- Construction of long saturated or polyunsaturated alkyl chains in target molecules
- Synthesis of rigid polyalkynyl–polyaryl products
- Synthesis of organomaterials where the electrooptical properties of arylalkynes themselves are of interest
- Heterocycle synthesis

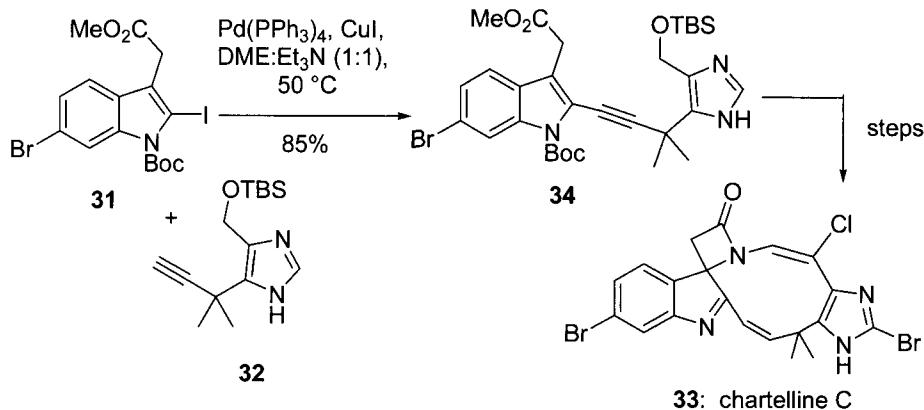
### *Complex Fragment Coupling*



**27:** maduropeptin chromophore aglycon

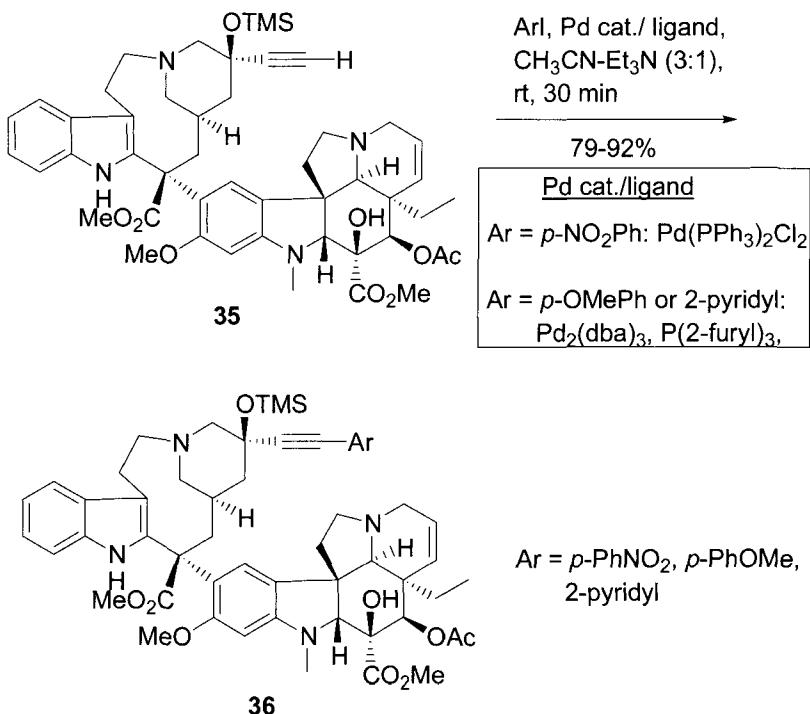
Each year, dozens of published syntheses of natural products feature a Sonogashira coupling. A recent example of coupling large and precious (and potentially sensitive) fragments can be found in Hirama and Inoue's synthesis of the maduropeptin chromophore.<sup>81</sup> Some of the more spectacular applications of this reaction have come in the area of ene-dyne natural products of which maduropeptin chromophore (**27**) is an example.<sup>82</sup> Sonogashira coupling gives direct access to the namesake ene-dyne functionality and maintains the mildness necessary for handling such energetically loaded systems. The coupling between vinyl triflate **28** and hindered alkyne **29** was effected using 5 mol% Pd(0) tetrakis(triphenylphosphine) and 10 mol% CuI in DMF and Hunig's base (1 : 1). This union proceeds to give an 85% yield of **30**, despite the presence of a free hydroxyl and multiple protecting groups. The high yield is particularly gratifying when the individual fragments represent dozens of linear steps.

Another example which demonstrates the high tolerance of the Sonogashira coupling for heteroatoms is the joining of substituted iodoindole **31** and imidazole alkyne **32** in Baran's elegant biomimetic synthesis of chartelline C (**33**). In this case, the cross coupling to synthetic intermediate **34** is accomplished in a 1:1 mixture of DME and Et<sub>3</sub>N and is complete after 7 hours at 50 °C.<sup>83</sup>

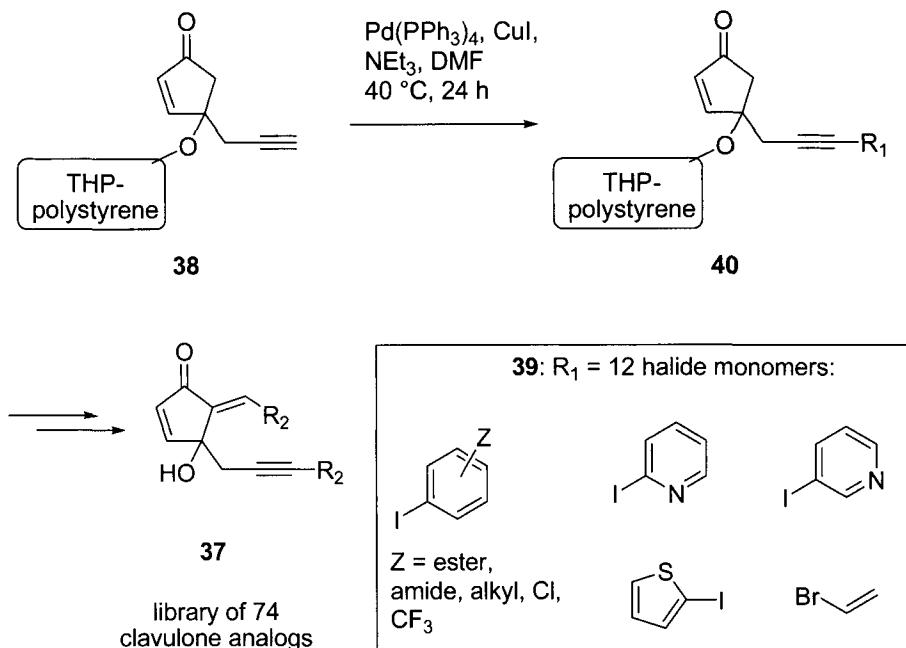


Fukuyama *et al.* accomplished penultimate step analoging of vinblastine via Sonogashira coupling. In this example, the union is carried out on the completed molecule arraying nearly a dozen different functional groups.<sup>84</sup> Three aryl iodides were coupled to **35** in good to excellent yields and the derived vinblastine analogs **36** screened for anti-cancer activity after removal of the TMS protecting group. When *p*-nitroiodobenzene was the coupling partner, standard copper-promoted Sonogashira conditions were adequate to afford high yield of product **36** (Ar = *p*-PhNO<sub>2</sub>). In contrast,

attempted coupling with *p*-methoxyiodobenzene and 2-iodopyridine afforded significant quantities of homodimerized **35**. An effective solution which conserved precious alkyne **35** was to switch to a more active catalytic system. The ability to execute this reaction at room temperature without the need for protection of these moieties showcases the mildness and generality of the Sonogashira coupling process and the effectiveness of modern conditions using tri-2-furyl-phosphine and Pd<sub>2</sub>(dba)<sub>3</sub> with catalytic CuI in a mixture acetonitrile and triethylamine.

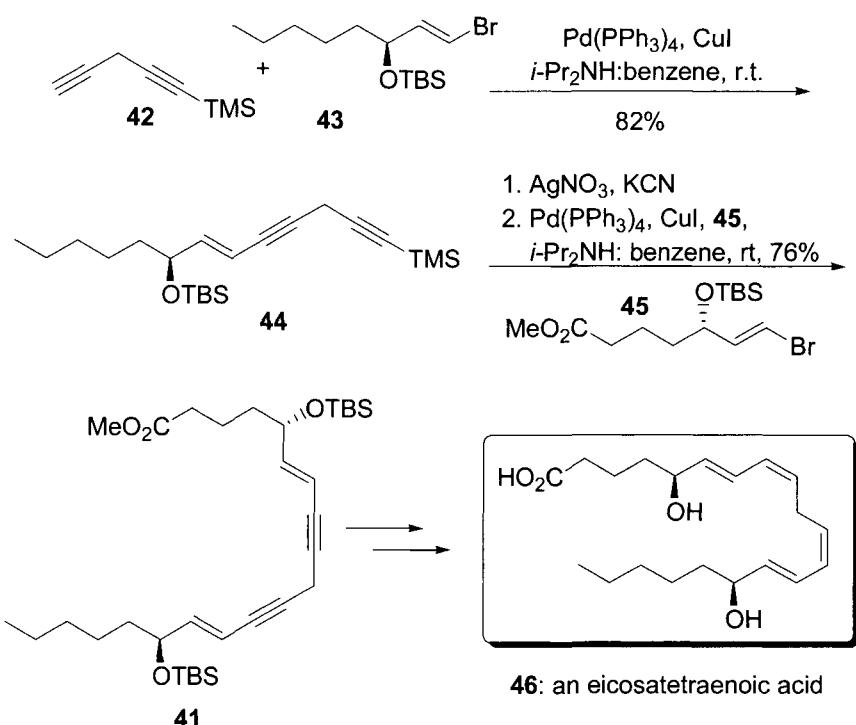


The Sonogashira coupling also finds regular use in combinatorial library synthesis protocols. Takahashi's library of clavulone analogs (**37**) was synthesized beginning with the union terminal alkyne **38** to a collection of 12 halide monomers (**39**) while the alkyne portion was bound to polystyrene resin via a THP linker. Standard Sonogashira coupling conditions in DMF at 40 °C were successful in this case, and after 24 hours, the functionalized alkynes **40** were isolated by filtration and rinse of the resin. Additional diversity was added to the immobilized cross coupling products **40** in a subsequent step, and the derived analogs cleaved from resin and purified to yield a set of 74 compounds with general structure **37**.<sup>85</sup>

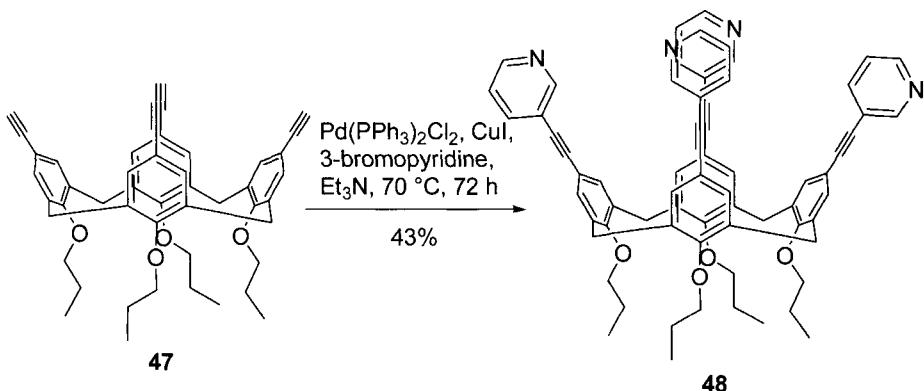


### Fatty Acids and Polyunsaturated Systems

From the early 1980s to the present day, the Sonogashira coupling has constituted a frequent strategy for the synthesis of long saturated and polyunsaturated alkyl chains by coupling vinyl halides and alkynes. The product ene–yne (e.g., **41**) can be reduced to afford dienes of defined geometry, controlled by choice appropriate reduction reagents. Hydrogenation of alkynes to *Z*-olefins is often done with poisoned palladium catalysts such as Lindlar's catalyst.<sup>86</sup> The *E*-olefins can be accessed with various complementary chemical reductions, with one of the more recent methodologies being hydrosilation/protodesilation reactions employing ruthenium catalyst and a trialkoxysilane.<sup>87,88</sup> Nicolaou's group completed several syntheses of biologically important members of the eicosatetraenoic acid family. A representative portion of this work, published within a decade of Sonogashira's initial report, features two key ene–yne couplings using modified original conditions ( $[\text{Pd}(\text{PPh}_3)_4]$ ,  $\text{CuI}$ , amine base) in benzene at room temperature. Initially, bis-alkyne **42** was united with *Z*-vinyl bromide **43** to deliver **44**. Removal of the terminal TMS set the stage for the second high-yielding Sonogashira, this time with ester-bearing vinyl bromide **45**. From bis-alkyne **41**, a double Lindlar reduction generated the targeted *cis*-diene system and further manipulation led to the arachidonic acid metabolite **46**.<sup>89</sup>



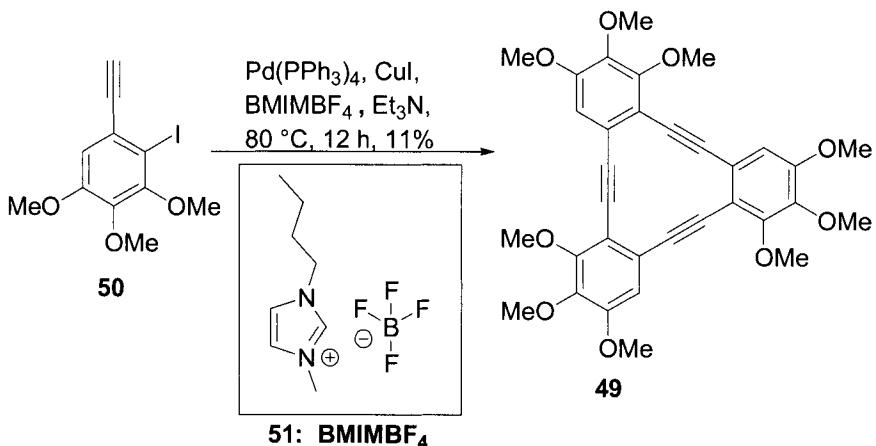
### *Self-assembly Subunits, Dendrimers, and Biopolymers*



Dyker *et al.* studied the properties of cone calixarenes with aryl and pyridyl head groups. The fourfold Sonogashira coupling of **47** with several different aryl bromides was more sluggish than most, and went to completion over 72 hours under standard conditions in 24–95% yield depending on the aryl halide employed. In one example **47** was tetra-coupled with 3-bromopyridine, which reaction yielded 43% yield of host **48**, and this

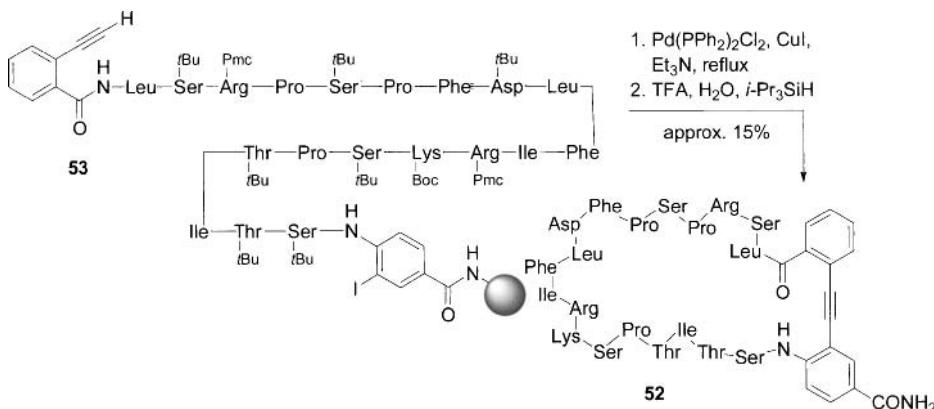
molecule was studied for its ability to sequester *N*-methylpyridinium and tetramethyl ammonium ions.<sup>90</sup>

Nanostructures formed from spontaneous assembly of extended arylene-ethylene macrocycles (e.g., **49**) have special properties by virtue of the non-collapsible and highly delocalized nature of this bond connection.<sup>91</sup> The individual macrocycle units can get quite complex, containing a dozen or more alkynes, so not surprisingly, many synthetic routes to molecules in this classification feature the Sonogashira coupling. In a relatively simple example, She, Pan, and co-workers found that the strongly deactivated aryl iodide **50** would only afford unwanted alkyne–alkyne coupling material in THF and DMF. Switching solvents to the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate **51** had a pronounced accelerating effect on the cross coupling and allowed the copper loading to be reduced to 1 mol%, which, in turn, reduced the formation of alkyne dimers and allowed for isolation of desired cyclic product **49**, albeit in low yield. With less electron-rich aryl iodides, coupling yields were greatly improved, and in such cases, THF as solvent delivered the product in modest yields in the absence of the molten salt.<sup>92</sup>



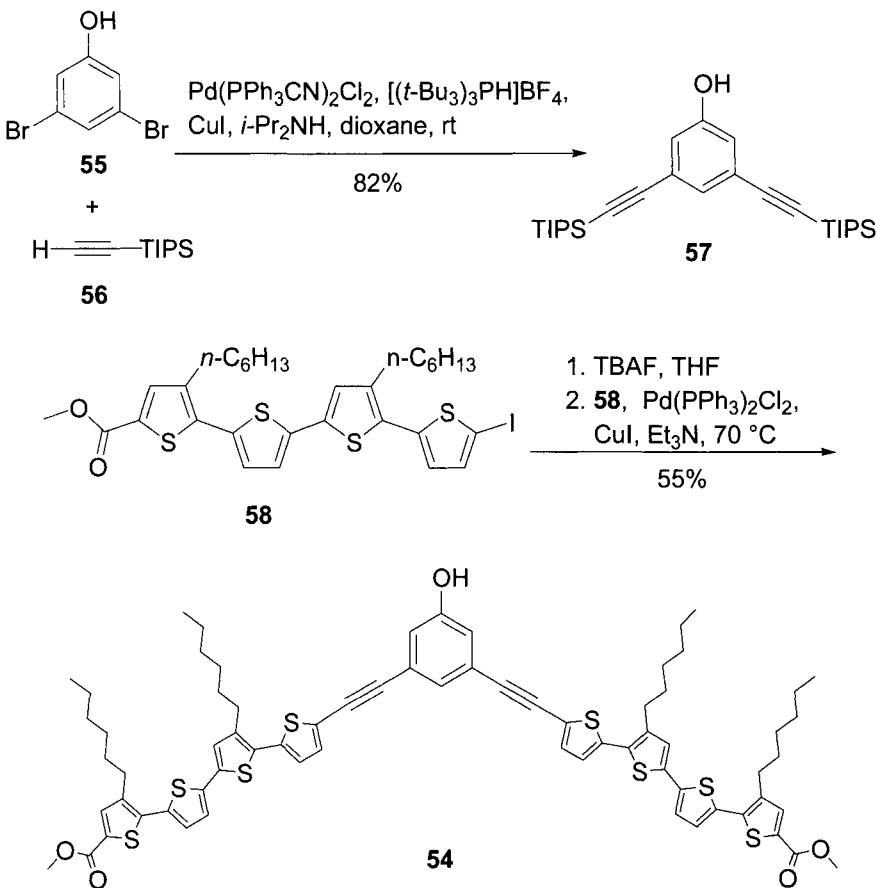
The compatibility of the Sonogashira coupling with multiple functionalities has provided some unique applications for conjugating organic compounds with biopolymers. One of the motivations for an ongoing push to extend Sonogashira coupling to systems which function well in water, is the desire to apply this reaction to the derivatization of biological molecules.<sup>19</sup> The large ring in the 21 amino acid cyclic peptide **52** was closed via an intramolecular Sonogashira coupling of **53**. The peptide (**53**) was synthesized on RINK-resin using a combination of solution phase and resin-bound peptide synthesis techniques. Immobilization of **53** served an additional purpose of preventing intermolecular reactivity in the coupling of

the large ring. In fact, attempted off-resin macrocyclization of the same peptide was unsuccessful. Exposure of **53** to typical Sonogashira conditions in refluxing triethylamine followed by global peptide deprotection (with concomitant release off the bead) and HPLC purification, gave the desired product **52**. This compound (**52**) was designed to be a loop mimic of human immunoglobulin E with potential therapeutic application.<sup>93</sup>



### Compounds with Electronic and Optical Properties

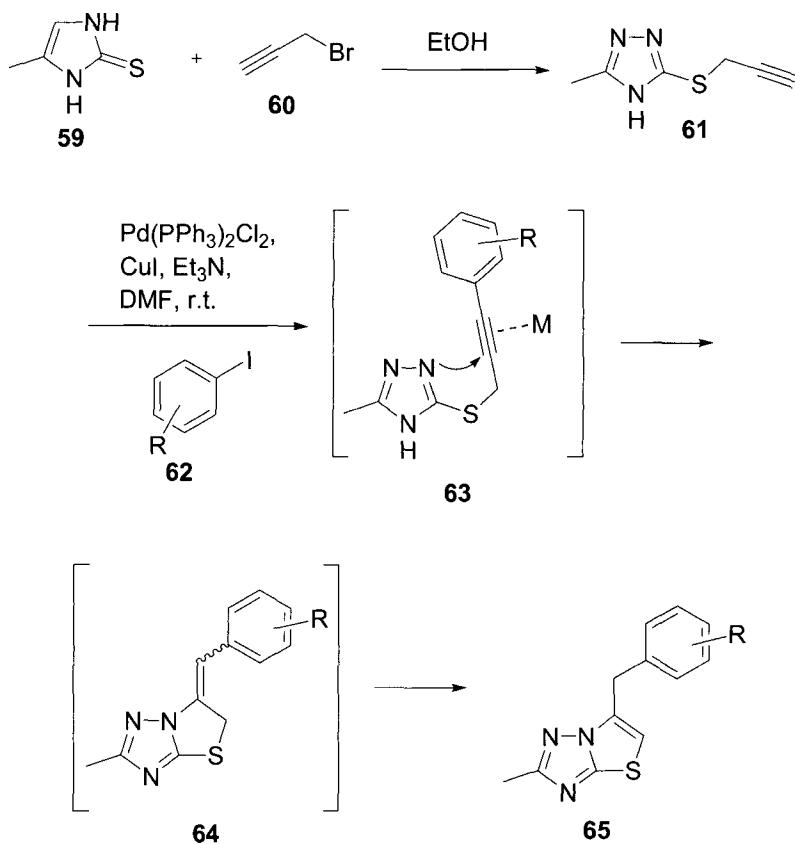
A highly enabling aspect of the Songashira reaction is its ready applicability to classes of rigid, extended phenylene alkynes. These highly conjugated compounds have intriguing electronic and optical characteristics deriving from the extended delocalization of the rigid  $\pi$ -system. Frequently, multiple arene groups are arrayed in series to obtain specific properties. A representative example is the synthesis of polythiophene **54**, which relies upon two Sonogashira couplings for key bond formations. In the first coupling, dibromophenol **55** is a challenging substrate, but it was cleanly bis-coupled to TIPS-acetylene **56** at room temperature using Fu's phosphane salt conditions—tri-*t*-butyl phosphine tetrafluoroborate salt and  $[\text{Pd}(\text{PPh}_3\text{CN})_2\text{Cl}_2]$  with  $\text{CuI}$  and  $i\text{-Pr}_2\text{NH}$  in dioxane, providing phenol intermediate **57**. The advantage of the phosphine salt is that it is air stable and more easily handled than the oxygen-sensitive tri-*t*-butyl phosphine.<sup>94</sup> Following base-promoted removal of the silyl groups, a second double Sonogashira with polythiophene iodide **58** was accomplished using more traditional conditions. Compound **54** and several similar constructs were then characterized for their absorption, fluorescence, quantum yield, and lifetime.<sup>95</sup> Facile modular construction is advantageous when looking to fine tune these semi-empirical properties.



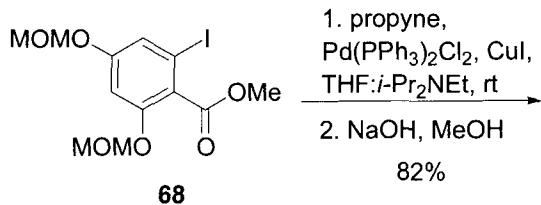
### Heterocycle Synthesis

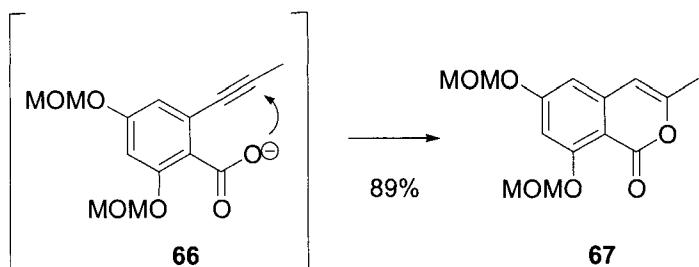
The Sonogashira coupling is firmly entrenched as an integral reaction for heterocycle formation.<sup>52-54</sup> The coupling of an alkyne to an appropriately functionalized molecule can set it up for intermolecular heterocyclization (**61** → **65**) where the employed metals can serve to activate the alkyne toward the cyclization event and yield operationally simple one-pot procedures. The most general application of this approach forms a new 5-membered aromatic system, often fused to another ring system. After standard reaction of **59** and **60**, the transformation from **61** to thiazolo-1,2,4-triazole **65** occurs in one pot following an initial standard condition Sonogashira coupling with **62**, and in this instance, the heterocyclization did not occur in the absence of copper salt. A plausible mechanism might involve engagement of a metal-activated alkyne (**63**), followed by favourable base-promoted isomerisation of **64**.<sup>96</sup> Owing to broad toleration for unprotected heteroatoms, the Sonogashira is

well suited for the task of installing the requisite alkyne with a minimal protecting groups.

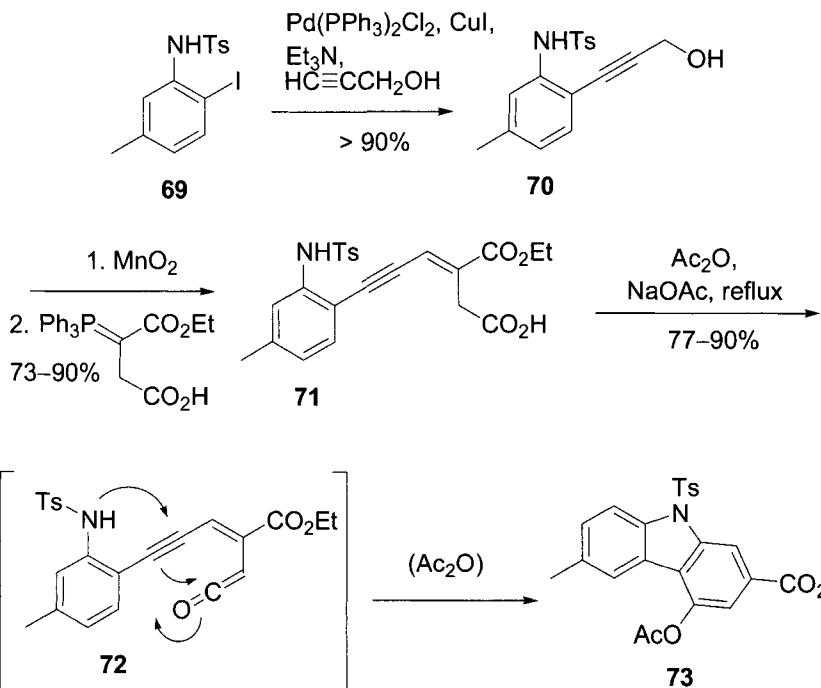


For some of the fused heterocycles, the coupling/cyclization protocol affords one of the easiest entries into that particular substituted heterocycle.





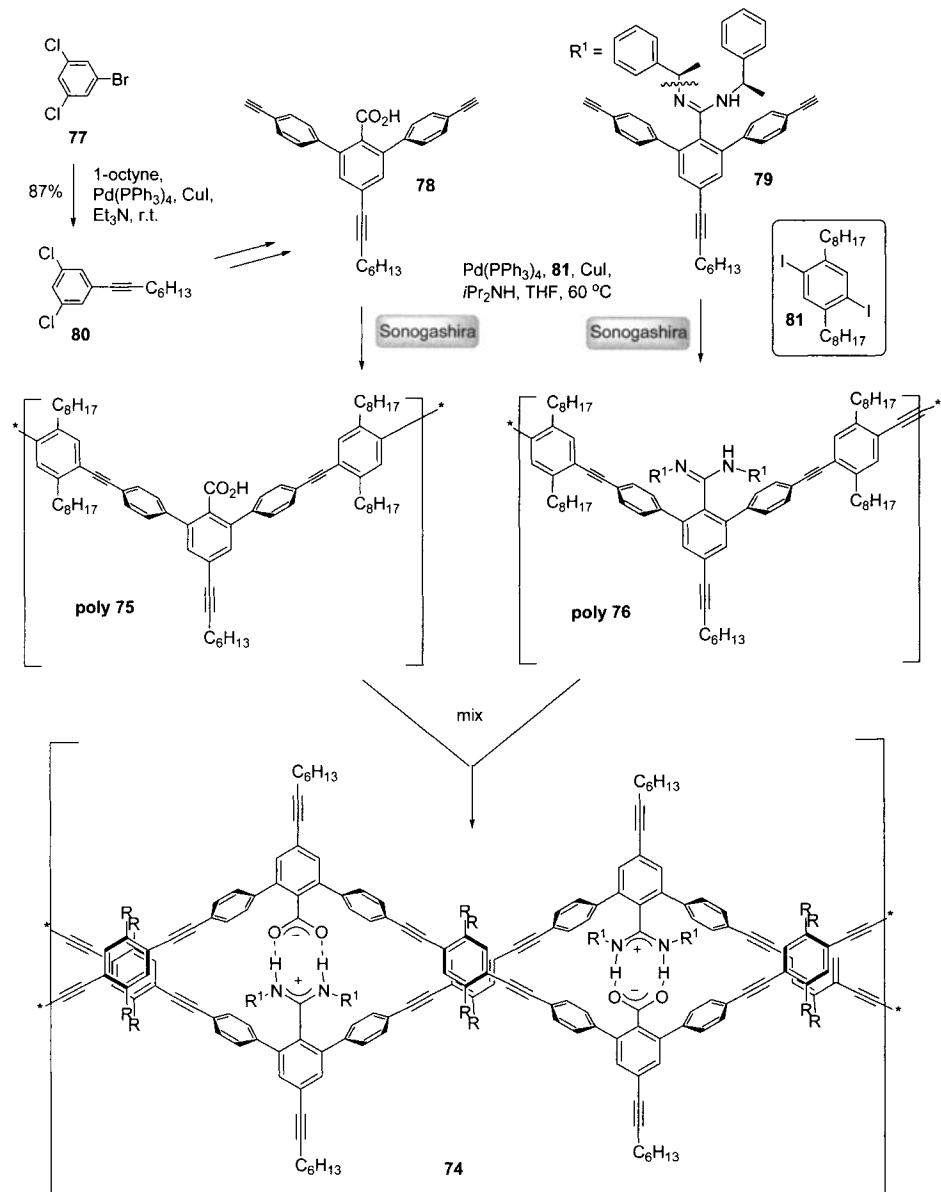
Recent work on the synthesis of Cassarin demonstrates the formation of an isocoumarin (**67**) in a base-promoted 6-*endo*-dig cyclization of acid **68** onto the just-coupled alkyne. The stage is set for this reaction when aryl iodide **68** reacts with *in situ* generated propyne in a Sonogashira coupling catalyzed by  $[\text{Pd}(\text{PPh}_3)_2\text{Cl}_2]$  and cuprous iodide in THF–*i*-Pr<sub>2</sub>NH at room temperature.<sup>97</sup>



A nice substituted carbazole synthesis begins with installation of propargyl alcohol via its Sonogashira coupling with aryl iodide **69**. Subsequent oxidation of propargylic alcohol **70** to the aldehyde, followed by stabilized Wittig reaction, affords a conjugated intermediate ene–yne **71**,

which undergoes a cascade cyclization upon treatment with acetic anhydride, proceeding via ketene ene–yne **72** to carbazole **73** in 76% overall yield.<sup>98</sup>

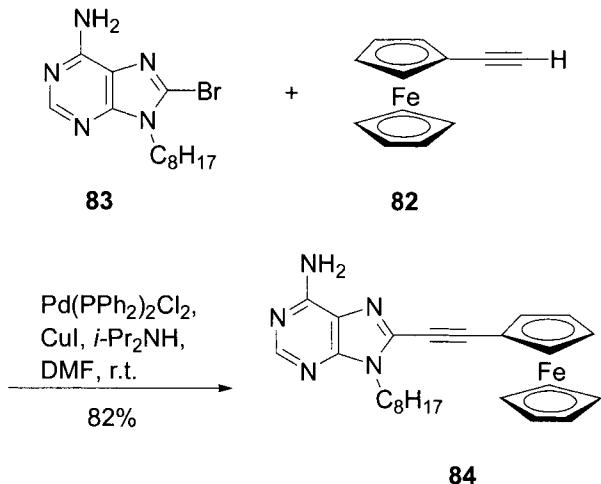
### *Emerging Applications – Bioconjugates*



The structurally impressive DNA mimic **74** was designed around a pair of oligomeric constructs (poly-**75** and poly-**76**) that hold complementary

sets of lipophilic and hydrogen bonding interactions. The Sonogashira reaction features prominently in the construction of these large molecules, serving first to attach octynyl chains to trihalo precursor **77**. The dichloro product **78** is further functionalized to monomers **79** and chiral monomer **80**. The oligomerization is accomplished by cross-linking these monomers in a series of double Sonogashira couplings between diiodophenyl linker **81** and bisacetylene **79** (and, in a separate pot, **80**). The oligomers **75** and **76** were found to have average molecular weights of 24,000 and 38,000 respectively and formed a chiral helical structure (**74**) upon mixing under controlled conditions. The Sonogashira couplings were performed under very typical reaction conditions employing Pd-tetrakis(triphenylphosphine) and CuI with mixtures of triethylamine and either toluene or THF as solvent.<sup>99</sup>

There are numerous examples of harnessing ene–yne coupling chemistry to assist with the characterization a biological system such as the Sonogashira coupling of ferrocene acetylene chromophore **82** to a uracil-derived bromide **83**. This reaction proceeded smoothly in DMF at room temperature under otherwise standard conditions. After isolation, the tagged uracil–ferrocene conjugate **84** could conceivably serve as a component of a bioelectronic gene-sensing system.<sup>100</sup>



### Polymers

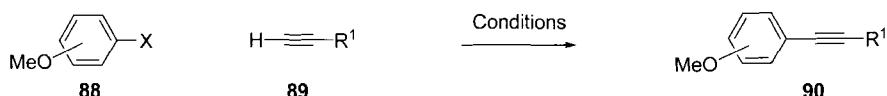
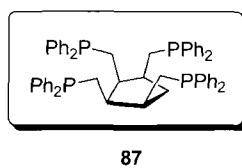
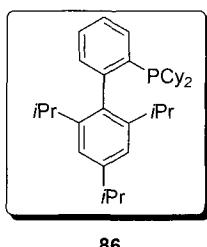
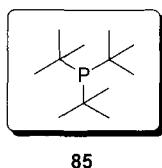
Designer polyene/yne oligomers of the types exemplified by compounds **54** and poly-**75** and poly-**76** are often synthesized in sequences containing Sonogashira couplings. Applications for rigid, polymeric structures based on polyaryleneethynylanes are emerging, however, true industrial scale polymer synthesis has not been achieved, due either to lack of demand or unavailability of the extremely high TON catalyst systems and ultra clean

reactions that are typically necessary for cost-effective large-scale polymerization. Polyphenylene–ethynylene with average molecular weight of 4300 was synthesized by polymerization of diiodobenzene and acetylene gas in a 3:1 mixture of acetonitrile and water under  $\text{Pd}(\text{OAc})_2/\text{PPh}_3/\text{CuI}/\text{Et}_3\text{N}$  conditions, but overall, these conditions are not ready for serious polymer synthesis.<sup>101</sup>

### 1.1.5.5 Variations and Improvements

For the majority of applications, the chemist is looking to the Sonogashira coupling to afford mild, reliable bond construction. In this context, the basic CuI-promoted conditions worked out early in the evolution of this reaction remain a viable option. Key areas for additional development are increasing catalyst turnover, maintaining lower reaction temperatures with less activated systems, and developing generally effective recyclable catalysts.<sup>8</sup>

#### Ligands with the Highest Activity



Entry	Ligand	X	88	89	Pd	CuI?	Base	Solvent	Temp °C	% Yield	TON
1	85	Br	p-OMe	nBu	$\text{Na}_2[\text{PdCl}_4]$	Yes	$i\text{Pr}_2\text{NH}$	$i\text{Pr}_2\text{NH}$	80	85	850
2	85	Br	o-OMe	Ph	$\text{Na}_2[\text{PdCl}_4]$	Yes	$i\text{Pr}_2\text{NH}$	$i\text{Pr}_2\text{NH}$	80	87	17400
3	85	Cl	p-OMe	Ph	$\text{Na}_2[\text{PdCl}_4]$	Yes	$\text{Na}_2\text{CO}_3$	xylene	120	75	41
4	86	Cl	p-OMe	tBu	$\text{PdCl}_2(\text{MeCN})_2$	No	$\text{Cs}_2\text{CO}_3$	MeCN	95	89	870
5	86	Cl	o-OMe	Ph	$\text{PdCl}_2(\text{MeCN})_2$	No	$\text{Cs}_2\text{CO}_3$	MeCN	95	93	950
6	87	Br	p-OMe	$\text{CH}(\text{OBn})_2$	$(\text{Pd}(\text{C}_5\text{H}_5)\text{Cl})_2$	Yes	$\text{K}_2\text{CO}_3$	DMF	130	>50	8200
7	87	Cl	p-OMe	Ph	$(\text{Pd}(\text{C}_5\text{H}_5)\text{Cl})_2$	No	$\text{K}_2\text{CO}_3$	DMF	140	31	155

Much of the ligand evolution that has occurred in the field of Pd catalyzed cross couplings was done without, perhaps, the Sonogashira coupling as a main focus. The mechanistic insights which led to the introduction of phosphanes with large cone angles and high  $\sigma$ -donating ability for promoting Heck and Suzuki couplings of aryl chlorides at room temperature were also successfully applied to the similarly recalcitrant Sonogashira with aryl

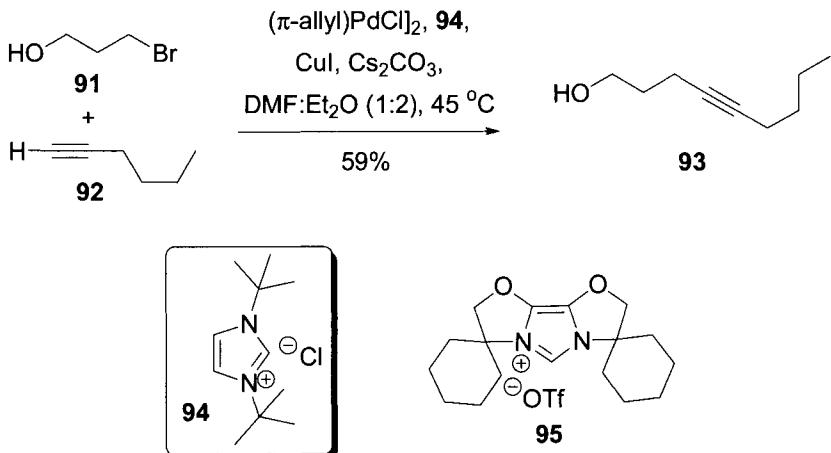
chlorides.<sup>28,102–104</sup> Among the more successful of these monodentate phosphanes for the Sonogashira coupling is tri-*t*-butylphosphine (**85**) which is able to handle traditionally difficult electron-rich aryl bromides like 4-bromoanisole (entry 1) as well as aryl chlorides at elevated reaction temperatures (entries 2 and 3). Buchwald's hindered biphenyl dicyclohexyl phosphine (X-Phos, **86**) is perhaps even more capable, giving good turnover even with electron rich aryl chlorides (entries 4 and 5) and the first example of Sonogashira reaction with aryl tosylates.<sup>28</sup> With this latter catalyst, the addition of CuI was found to hamper the reaction, a finding which has been duplicated in other catalytic systems for the Sonogashira couplings of aryl chlorides (see "CuI?" column in the table).

The effectiveness of ligands **85** and **86** derives from acceleration of slow oxidative addition to aryl halides. As an additional benefit, these powerful ligands form product rapidly and can essentially shut down the homodimerization pathway even in the presence of CuI.

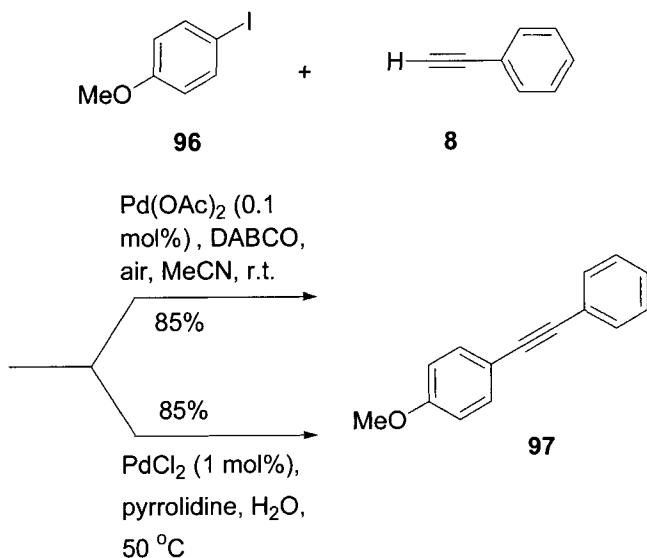
Apart from the ability to couple previously inaccessible substrates, a valuable measure of ligand effectiveness is derived by comparing turn-over numbers (TONs) for a benchmark reaction such as the Sonogashira coupling of 4-bromoanisole and phenylacetylene. It is by this measure that these two catalysts really distinguish themselves. An examination of the table highlights the precipitous drop in TON that occurs with nearly all catalytic systems in going from more reactive halides to less reactive substrates. It is important to recognize that very few catalytic systems are capable of accessing **90** via Sonogashira coupling of substrates **88** (X = Br, Cl) and **89**. For favourable reactions such as the coupling of diiodobenzene and phenylacetylene (**7** and **8**), a number of catalytic systems including mono- and multidentate phosphanes, palladacycles, carbene ligands, and ligandless procedures are able to reach TON's of 100,000 or more. With more difficult substrates, however, the validated bulky monophosphines such as **85** and **86**, together with a few similar ligands stand in a class by themselves.<sup>8</sup>

The tetradentate phosphine **87** is of note, recording high TONs for the coupling of 4-bromo- and 4-chloroanisole (see table entries 6 and 7). Beyond the various phosphanes, *N*-heterocyclic carbenes ligands (NHC's) have also received much attention and have been successfully demonstrated in both typical and challenging Sonogashira couplings, though in general, these ligands have not demonstrated advantages over **85** or **86**.<sup>105,106</sup> One notable example of the budding potential of the strongly donating carbene ligands is the reaction of *alkyl* bromide **91**, and 1-hexyne (**92**) in a DMF–Et<sub>2</sub>O mixture to afford alkynol **93**. To achieve this impressive result, 7.5 mol% of Pd and CuI were required. Interestingly, Fu showed that imidazolium carbene ligand **94** was uniquely able to minimize competing (undesired) β-hydride elimination from the Pd(II) complex where other high-

performance phosphanes ligands failed.<sup>29</sup> Glorius similarly showed that the NHC ligand **95** also promotes Sonogashira coupling of alkyl halides under mild conditions.<sup>107</sup>



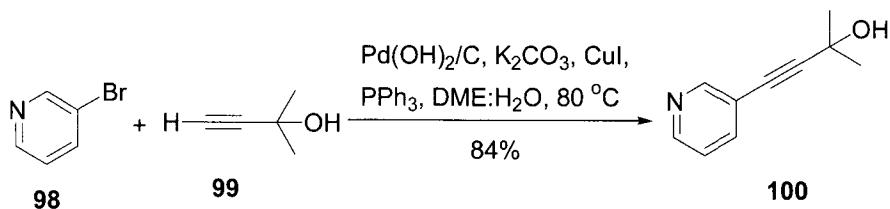
#### *“Ligand-free” Catalysts*



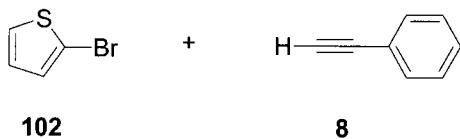
While there are open questions about the exact nature and processing of the molecular or colloidal Pd which may operate under the so called “ligand-free” conditions, there is no doubt that stabilized Pd nanoparticles are highly capable of catalyzing Sonogashira couplings. Li reported that DABCO is a superior amine additive when compared to tetrabutylammonium salts in widespread use for stabilizing Pd(0) in “ligand-free” cross couplings.<sup>33,34</sup> For

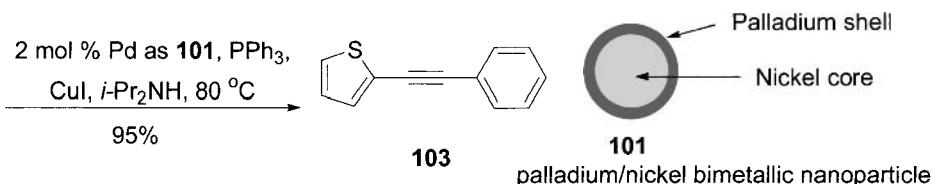
example, *p*-idoanisole (**96**) reacts with phenylacetylene (**8**) in the presence of 0.1 mol% Pd(OAc)<sub>2</sub> and DABCO in acetonitrile to afford the coupled product **97** in 85% yield. Similarly, 1 mol% PdCl<sub>2</sub> catalyzes the same reaction in water at 50 °C when 5 equivalents of pyrrolidine are added.<sup>32</sup> This result if of interest, however, the reaction fails with more challenging aryl bromides. The potential advantages of lower cost and simpler work-up procedures are mitigated by the limited scope, higher palladium loadings, and the stabilizing additives (PPh<sub>3</sub>, tetraalkylammonium salts) that have been necessary for with many ligand-free protocols reported to date.

Heterogeneous “ligand-free” reagent systems have been employed with some success, though they too have yet to demonstrate the power and generality of the bulky phosphanes in coupling alkynes to unreactive halides. Common palladium sources including Pd/C and Pd(OH)<sub>2</sub> provide an environmentally friendlier way to accomplish the Sonogashira transformation because the majority of the catalyst can be recovered and often recycled after filtration from the reaction mixture. For the coupling of 3-bromopyridine (**98**) and butyne-ol **99**, a mixture of Pd(OH)<sub>2</sub>, CuI, K<sub>2</sub>CO<sub>3</sub>, and PPh<sub>3</sub> in DME-water at 80°C for 21 hours resulted in an 84% yield of the pyridyl alkyne **100**. The elevated temperature and longer reaction time is evidence of the lower level of activity often seen with the heterogeneous catalysts. In this system, the role of the copper salt and phosphane have not been fully elucidated.<sup>34</sup>



One approach towards more efficient use of precious metals is to engineer surfaces coated with palladium. In one embodiment of this concept, chemically-controlled deposition of Pd and Ni results in defined particles with Pd-rich shells built up on inexpensive nickel cores (**101**).<sup>108</sup>

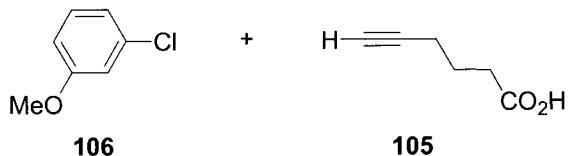


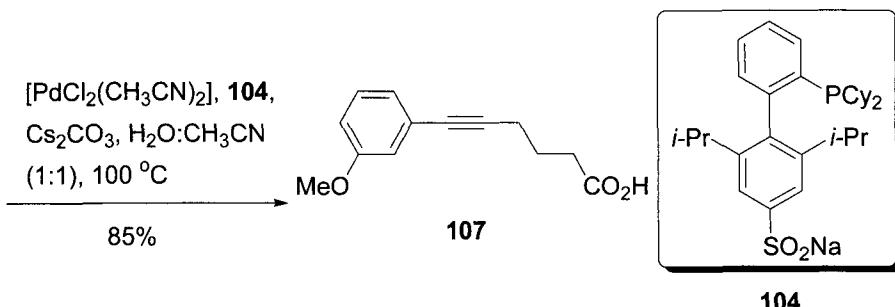


This technology has been applied to aryl-alkyne cross coupling, where thiophene bromide **102** couples with phenylacetylene (**8**) in a reaction mix consisting of Pd/Ni bimetallic nanoparticulate catalyst **101** (approximately 2 mol% palladium),  $\text{PPh}_3$ , and  $\text{CuI}$  in  $i\text{-Pr}_2\text{NH}$ . Coupling occurs in two hours at  $80^\circ\text{C}$  in high yield, and the nanoparticles can be filtered and recycled. It is not always clear which heterogeneous catalysts merely constitute a reservoir for slow release of colloidal/soluble Pd into solution and which actually have catalytically active sites immobilized.<sup>74</sup> An important application of truly immobilized catalyst would be in the synthesis of active drug ingredients, with the potential to eliminate contamination of product by low ppm quantities of toxic metal. If, however, if the true active catalysts are some type of soluble palladium, there will be limited pharmaceutical application for those ligand-free protocols.

#### *Alternative Solvents – Aqueous Reactions*

The Sonogashira reaction proceeds in an admirably wide range of solvents given the correct catalytic system, and water is no exception. Numerous reports have surfaced showcasing this coupling in water using phase transfer agents, or microwave heating. To date, the best reactivity is seen in mixed solvent systems and substrate scope if limited, however, the potential advantage of facile catalyst recovery continues to drive progress in this area. An interesting extension of substrate scope came with the introduction of biarylphosphine ligand **104** bearing a solubilising sulphate salt. The non-sulfonylated version of this ligand was able to promote Sonogashira couplings with aryl chlorides, and the addition of the sulphate allows for the coupling of water soluble alkynes in aqueous mixtures. Thus, acid **105** and 3-chloroanisole (**106**) unite to generate acid **107** in high yield when heated to  $100^\circ\text{C}$  in a 1:1  $\text{MeCN}-\text{H}_2\text{O}$  mixture with ligand **104**,  $[\text{PdCl}_2(\text{MeCN})_2]$ , and  $\text{Cs}_2\text{CO}_3$ .<sup>109</sup>





### *Non-traditional Coupling Partners*

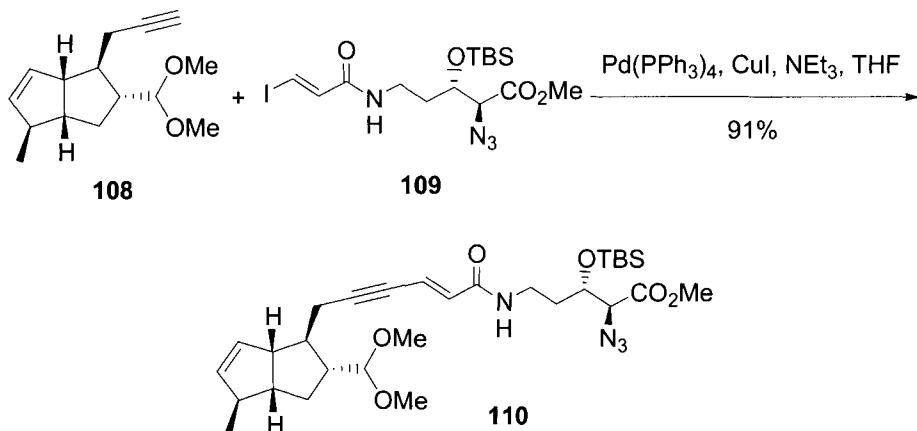
Under the broad umbrella of the Sonogashira coupling, less common substrates for both the alkyne and halide partners have been described. There are examples of Sonogashira-type coupling of terminal acetylenes to benzylic and primary bromides and iodides, and even secondary bromides. There are also limited examples of aryl tosylates and sulfonates (so called pseudo-halides) entering into Sonogashira reaction.<sup>107,110</sup> The union of phenylacetylene and acid chlorides (e.g., benzoyl chloride) catalyzed by Pd/C in refluxing toluene–Et<sub>3</sub>N has been reported to proceed in excellent yield.<sup>111,112</sup> For the alkyne component, Mori demonstrated that terminal silanes can couple with a range of aryl halides using 5 mol% [Pd(PPh<sub>3</sub>)<sub>4</sub>] and CuCl in DMF at moderately elevated temperature.<sup>113–115</sup> One can envision an effective strategy for sequential coupling of different halides using this sila-Sonogashira. Molander's alkyne tetrafluoroborate salts afford an alternative related entry into mild reaction systems.<sup>116</sup> Beyond the examples discussed here, there are additional isolated examples of unusual reaction partners.<sup>8</sup>

### *Other Metal Catalysts*

Aluminium, Zinc, Nickel, Ruthenium, and other metal acetylides will transmetalate to Pd to afford a species which can productively couple to aryl and vinyl halides.<sup>8</sup> There is a surge in methods which do not require expensive palladium, in particular, copper- and nickel-based methodologies.<sup>117</sup> The so called “palladium-free” Sonogashira begins to look like a Castro–Stephens coupling when promoted by copper. Indeed a host of other methods are available to effect the net transformation of generating an ene-yne from an acetylide and aryl or vinyl halide. These processes begin to stray from the already large categorical umbrella of the Sonogashira coupling and will not be discussed in this chapter.

### 1.1.5.6 Experimental

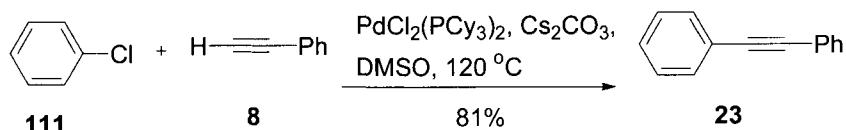
#### Sonogashira Reaction using Modification of Original Conditions



#### Cylindramide intermediate (**110**).<sup>118</sup>

Under argon gas, a solution of compound **108** (630 mg, 1.3 mmol) and compound **109** (276 mg, 1.18 mmol) in anhydrous THF (1.6 mL) was added to a stirred suspension of  $[\text{Pd}(\text{PPh}_3)_4]$  (19 mg, 0.016 mmol, 1.3 mol%) and copper(I) iodide (9 mg, 0.047 mmol, 4 mol %) in  $\text{Et}_3\text{N}$  (2.8 mL) and the reaction mixture stirred at room temperature. After 1 hour, the solvent was removed under vacuum and the residue purified by silica gel chromatography (petroleum ether/EtOAc, 3:1) to give compound **110** (630 mg, 91%, > 95% NMR purity) as a yellow resin.

#### Sonogashira Reaction using Bulky Phosphine Ligand and Copper-Free Conditions



#### Diphenylacetylene (**23**).<sup>119</sup>

A mixture of chlorobenzene (**111**, 75.0 mg, 0.66 mmol), phenyl acetylene (**8**, 61.5 mg, 0.6 mmol),  $\text{Cs}_2\text{CO}_3$  (230.0 mg, 0.66 mmol),  $[\text{PdCl}_2(\text{PCy}_3)_2]$  (15.4 mg, 0.02 mmol), and DMSO (0.8 mL) under nitrogen in a sealed tube was heated with stirring at 120 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  to 1.5 mL total volume and octadecane (45 mg, 0.18 mmol) was added as an internal standard for GC.

analysis. After GC–MS analysis, the solvents and volatiles were removed under vacuum and the residue was subjected to preparative TLC isolation (silica, eluted with cyclohexane). Compound **23** was obtained (85.5 mg, 0.48 mmol, 81%) as a white solid.

### 1.1.5.7 References

1. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
2. Cassar, L. J. *Organomet. Chem.* **1975**, *93*, 253.
3. Dieck, H.; Heck, F. J. *Organomet. Chem.* **1975**, *93*, 259.
4. [R] Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; de Meijere, A., Eds.; Wiley-VCH: Weinheim, **2004**; Vol. 1, 319.
5. [R] Sonogashira, K. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, **1991**; Vol. 3, p 521.
6. [R] Sonogashira, K. J. *Organomet. Chem.* **2002**, *653*, 46.
7. [R] Chinchilla, R.; Najera, C. *Chem. Rev.* **2007**, *107*, 874.
8. [R] Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834.
9. [R] Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.
10. [R] Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566.
11. [R] Brandsma, L. *Synthesis of Acetylenes, Allenes and Cumulenes: Methods and Techniques*; Elsevier: Oxford, **2004**; p293.
12. [R] Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proced. Int.* **1995**, *27*, 127.
13. [R] Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553.
14. [R] Herrmann, W.; Öfele, K.; von Preysing, D.; S.; Schneider, S. *J. Organomet. Chem.* **2003**, *687*, 229.
15. [R] Fu, G.; Littke, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.
16. [R] Jutand, A. *Pure Appl. Chem.* **2004**, *76*, 565.
17. [R] Shi Shun, A.; Tykwinski, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1034.
18. [R] Hermann, W. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.
19. [R] Gauthier, M.; Klok, H.-A. *Chem. Commun.* **2008**, *23*, 2591.
20. [R] Singh, B.; Kaval, N.; Tomar, S.; Van der Eycken, E.; Parmar, V. *Org. Proc. R&D.* **2008**, *12*, 468.
21. [R] Peris, E.; Crabtree, R-H. *Coord. Chem. Rev.* **2004**, *248*, 2239.
22. Zheng, S.-L.; Reid, S.; Lin, N.; Wang, B. *Tetrahedron Lett.* **2006**, *47*, 2331.
23. Organ, M. G.; Ghasemi, H. *J. Org. Chem.* **2004**, *69*, 695.
24. Raju, S.; Batchu, V. R.; Swamy, N. K.; Dev, R. V.; Babu, J. M.; Kumar, P. R.; Mukkanti, K.; Pal, M. *Tetrahedron Lett.* **2006**, *47*, 83.
25. Huang, Q.; Hunter, J.; Larock, R. *J. Org. Chem.* **2002**, *67*, 3437.
26. [R] Nicolaou, K. C.; Bulger, P.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442.
27. [R] Bunz, U. *Chem. Rev.* **2000**, *100*, 1605.
28. Gelman, D.; Buchwald, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993.
29. Eckhardt, M.; Fu, G. *J. Am. Chem. Soc.* **2003**, *125*, 13642.
30. Shi, S.; Zhang, Y. *Synlett* **2007**, *12*, 1843
31. Liang Bo; D.; Mingji; C.-J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 391.
32. Urgaonkar, S.; Verkade, J. *J. Org. Chem.* **2004**, *69*, 5752.
33. Li, J.; Zhang, X.; Xie, Y. *Synthesis* **2005**, 804.
34. Li, J.; Hu, X.; Liang, Y.; Xie, Y. *Tetrahedron* **2006**, *62*, 31.
35. Alami, M.; Crousse, B.; Ferri, F. *J. Organomet. Chem.* **2001**, *624*, 114.
36. Mori, Y.; Seki, M. *J. Org. Chem.* **2003**, *68*, 1571.
37. Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551.
38. Elangovan, A.; Wang, Y.-H.; Ho, T.-I. *Org. Lett.* **2003**, *5*, 1841.
39. Traschsel, D. *Helv. Chim. Acta* **2003**, *86*, 2754.
40. Nguefack, J.-F.; Bolitt, V.; Sinou, D. *Tetrahedron Lett.* **1996**, *37*, 5527
41. Rossi, R.; Carpita, A.; Lezzi, A. *Tetrahedron* **1984**, *40*, 2773
42. Bhattacharya, S.; Sengupta, S. *Tetrahedron Lett.* **2004**, *45*, 8733

43. Rossi, R.; Carpita, A.; Lezzi, A. *Tetrahedron* **1984**, *40*, 2773.
44. Bhattacharya, S.; Sengupta, S. *Tetrahedron Lett.* **2004**, *45*, 8733.
45. Nakamura, K.; Okubo, H.; Yamaguchi, M. *Synlett*, **1999**, 549.
46. Masai, H.; Sonogashira, K.; Hagiwara, N. *J. Organomet. Chem.* **1971**, *26*, 271.
47. Sonogashira, K.; Takahashi, S.; Hagiwara, N. *Macromolecules* **1977**, *10*, 879.
48. Hong, P.; Sonogashira, K.; Hagiwara, N. *Tetrahedron Lett.* **1970**, 1633.
49. Böhm, V.; Herrmann, W. *Eur. J. Org. Chem.* **2000**, 3679.
50. Genêt, J.-P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305.
51. [R] (a) *Electronic Materials: The Oligomer Approach*; Müllen, K., Wegner, G., Eds.; Wiley-VCH: Weinheim, 1998. [R] (b) Nalwa, H. S.; Miyata, S. *Nonlinear Optics of Organic Molecules and Polymers*; CRC Press: Boca Raton, FL, 1997.
52. Sorensen, U. S.; Pombo-Villar, E. *Tetrahedron* **2005**, *61*, 2697.
53. Bach, T.; Bartels, M. *Synthesis* **2003**, 925.
54. Zoppellaro, G.; Baumgarten, M. *Eur. J. Org. Chem.* **2005**, 2888.
55. Martin, R. E.; Diederich, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 1350.
56. Breitenkamp, R. B.; Arnt, L.; Tew, G. N. *Polym. Adv. Technol.* **2005**, *16*, 189.
57. Zhou, N.; Merschrod, E. F.; Zhao, Y. *J. Am. Chem. Soc.* **2005**, *127*, 14154.
58. Sugiura, H.; Nigorikawa, Y.; Saiki, Y.; Nakamura, K.; Yamaguchi, M. *J. Am. Chem. Soc.* **2004**, *126*, 14858.
59. Meier, H.; Mühlung, B.; Oehlhof, A.; Theisinger, S.; Kirsten, E. *Eur. J. Org. Chem.* **2006**, 405.
60. Nagy, A.; Novak, Z.; Kotschy, A. *J. Organomet. Chem.* **2005**, *690*, 4453.
61. Corona, C.; Bryant, B. K.; Arterburn, J. B. *Org. Lett.* **2006**, *8*, 1883.
62. Toyota, S.; Iida, T.; Kunizane, C.; Tanifushi, N.; Yoshida, Y. *Org. Biomol. Chem.* **2003**, *1*, 2298.
63. [R] Testero, S.; Mata, E. *J. Comb. Chem.*, **2008**, *10*, 487.
64. Urgaonkar, S.; Verkade, J. G. *J. Org. Chem.* **2004**, *69*, 5752.
65. Ljungdahl, T.; Bennur, T.; Dallas, A.; Emtenaes, H.; Maartensson, J. *Organometallics* **2008**, *27*, 2490.
66. Jutand, A.; Negri, S.; Principaul, A. *Eur. J. Org. Chem.* **2005**, 631.
67. Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2004**, *45*, 8443.
68. Amatore, C.; Bensalem, S.; Ghalem, S.; Jutand, A. *J. Organomet. Chem.* **2004**, *689*, 4642.
69. Amatore, C.; Bensalem, S.; Ghalem, S.; Jutand, A.; Medjour, Y. *Eur. J. Org. Chem.* **2004**, 366.
70. Moon, J.; Jeong, M.; Nam, H.; Ju, J.; Moon, J.-H.; Jung, H.-M.; Lee, S. *Org. Lett.*, **2008**, *10*, 945.
71. Dobler, M. R. *Tetrahedron Lett.* **2003**, *44*, 7115.
72. Li, J.-H.; Liang, Y.; Xie, Y.-X. *J. Org. Chem.* **2005**, *70*, 4393.
73. Jana, S.; Dutta, B.; Bera, R.; Koner, S. *Inorg. Chem.* **2008**, *12*, 5512.
74. Reetz, R. T.; Westermann, E. *Angew. Chem., Int. Ed.* **2000**, *39*, 165.
75. Reetz, M. T.; Masse, M. *Adv. Mater.* **1999**, *11*, 773.
76. Choudary, B. M. Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127.
77. Vasilevsky, S.; Klyatskaya, S.; Elguero, J. *Tetrahedron*, **2004**, *60*, 6685.
78. Walker, W. H. IV; Rokita, S. E. *J. Org. Chem.* **2003**, *68*, 1563.
79. Alonso, D.; Botella, L.; Najera, C.; Pacheco, M. *Synthesis*, **2004**, *10*, 1713.
80. Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chem. Lett.*, **1997**, *12*, 1233.
81. Komano, K.; Shimamura, S.; Inoue, M.; Hirama, M. *J. Am. Chem. Soc.* **2007**, *129*, 14184.
82. Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1377.
83. Baran, P.; Shenvi, R. *J. Am. Chem. Soc.* **2006**, *128*, 14028.
84. Miyazaki, T.; Yokoshima, S.; Simizu, S.; Osada, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2007**, *23*, 4737.
85. Kitade, M.; Tanaka, H.; Oe, S.; Iwashima, M.; Iguchi, K.; Takahashi, T. *Chem. Eur. J.* **2006**, *12*, 1368.
86. Lindlar, H.; Dubuis, R. *Org. Syn.* **1966**, *46*, 89.
87. Fürstner, A.; Radkowski, K. *Chem. Commun.* **2002**, 2182.
88. Trost, B. M.; Ball, Z. T.; Jöge, T. *J. Am. Chem. Soc.* **2002**, *124*, 7922.

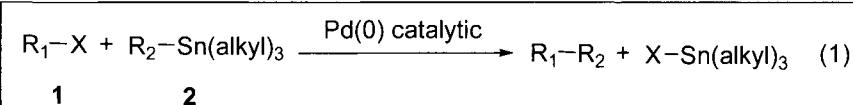
89. Nicolaou, K. C.; Webber, S. *J. Am. Chem. Soc.* **1984**, *106*, 5734.  
90. Dyker, G.; Mastalerz, M.; Müller, I. M. *Eur. J. Org. Chem.* **2005**, 3801.  
91. Xia, Y.; Yang, P.; Sun, Y.; Wu, Y.; Mayers, B.; Gates, B.; Yin, Y.; Kim, F.; Yan, H. *Adv. Mat.*, **2003**, *15*, 353.  
92. Li, Y.; Zhang, J.; Wang, W.; Miao, Q.; She, X.; Pan, X. *J. Org. Chem.* **2005**, *70*, 3285.  
93. Spivey, A.; McKendrick, J.; Srikanan. *J. Org. Chem.* **2003**, *68*, 1843.  
94. Netherton, M.; Fu, G. *Org. Lett.* **2001**, *3*, 4295.  
95. Zhang, Y.; Zhao, C.; Yang, J.; Kapiamba, M.; Haze, O.; Rothberg, L.; Ng, M.-K. *J. Org. Chem.* **2006**, *71*, 9473.  
96. Heravi, M.; Kivanloo, A.; Rahimzadeh, M.; Bakavoli, M.; Ghassemzadeh, M.; Neumuller, B. *Tetrahedron Lett.* **2005**, *46*, 1607.  
97. Rudyanto, M.; Tomizawa, Y.; Morita, H.; Honda, T. *Org. Lett.*, **2008**, *10*, 1921.  
98. Serra, S.; Fuganti, C. *Synlett*, **2005**, 809.  
99. Maeda, T.; Furusho, Y.; Sakurai, S.; Kumaki, J.; Okoshi, K.; Yashima, E. *J. Am. Chem. Soc.* **2008**, *130*, 7938.  
100. Coutouli-Argyropoulou, E.; Tsitabani, M.; Petrantonakis, G.; Terzis, A.; Raptopoulou, C. *Org. Biomol. Chem.* **2003**, *1*, 1382.  
101. Li, C.-J.; Slaven, W.; John, V.; Banerjee, S. *J. Chem. Soc., Chem. Commun.* **1997**, 1569.  
102. Hundertmark, T.; Littke, A.; Buchwald, S.; Fu, G. *Org. Lett.* **2000**, *2*, 1729.  
103. Hierso, J.-C.; Fihri, A.; Amardeil, R.; Meunier, P.; Doucet, H.; Santelli, M.; Ivanov, V. *Org. Lett.* **2004**, *6*, 3473.  
104. (a) Köllhofer, A.; Plenio, H. *Adv. Synth. Catal.* **2005**, *347*, 1295. (b) A. Köllhofer, H. Plenio, *Chem. Eur. J.* **2003**, *9*, 1416.  
105. Fukuyama, T.; Shimmen, M.; Nishitani, S.; Sato, M.; Ryu, I. *Org. Lett.* **2002**, *4*, 1691.  
106. Hierso, J.-C.; Boudon, J.; Picquet, M.; Meunier, P. *Eur. J. Org. Chem.* **2007**, *4*, 583.  
107. Altenhoff, G.; Wurtz, S.; Glorius, F. *Tetrahedron Lett.* **2006**, *47*, 2925.  
108. Son, S.; Jang, Y.; Park, J.; Na, H.-B.; Park, H.-M.; Yun, H.-J.; Lee, J.; Hyeon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5026.  
109. Anderson, K.; Buchwald, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173.  
110. Dubbaka, S. R.; Vogel, P. *Adv. Synth. Catal.* **2004**, *346*, 1793.  
111. (a) Likhar, P.; Subhas, M.; Roy, M.; Roy, S.; Kantam, M. *Helvetica Chim. Acta*, **2008**, *91*, 259; (b) Collett, M.; Jones, D.; Renyard, S. *J. Chem. Soc. Perkin Trans. I*, **1986**, 1471.  
112. Karpov, A. S.; Müller, T. J. *J. Org. Lett.* **2003**, *5*, 3451.  
113. Nishihara, Y.; Ikegashira, K.; Mori, A.; Hiyama, T. *Chem. Lett.* **1997**, 1233.  
114. Yang, C.; Nolan, S. P. *Organometallics* **2002**, *21*, 1020.  
115. Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780.  
116. Molander, G.; Katona, B. W.; Machroubi, F. *J. Org. Chem.* **2002**, *67*, 8416.  
117. Wang, L.; Pinhua, L.; Zhang, Y.; *Chem Commun.* **2004**, 514.  
118. Cramer, N.; Buchweitz, M.; Laschat, S.; Frey, W.; Baro, A.; Mathieu, D.; Richter, C.; Schwalbe, H. *Chem. Eur. J.* **2006**, *12*, 2488.  
119. Hua, R.; Yi, C. *J. Org. Chem.* **2006**, *71*, 2536.

## 1.1.6 Stille Coupling

Vincent Mascitti

### 1.1.6.1 Description

The reaction between an organic electrophile **1** and an organostannane **2** mediated by a transition metal catalyst (originally palladium) to form a new sigma carbon carbon bond is referred to as the Stille cross-coupling reaction (equation 1).



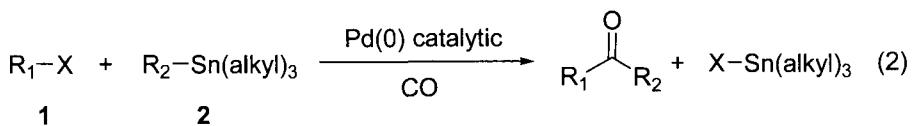
Commonly used organic electrophiles involve  $\text{C}(\text{sp}^2)$  hybridized carbon as coupling partners like in acid chlorides<sup>1</sup>, (hetero)aryl halides (Cl, Br, I) and triflates, alkenyl halides and triflates; activated  $\text{C}(\text{sp}^3)$  hybridized carbon like allyl halides and acetates, benzyl halides are also used. Recently the use of unactivated alkyl halides has also been reported<sup>2</sup>. Aryl sulphonyl chlorides<sup>3</sup> and arenediazonium salts<sup>4</sup> have also been used as organic electrophiles.

Organotin reagents involving  $\text{C}(\text{sp}^2)$  or  $\text{C}(\text{sp})$  hybridized carbons, like in alkenyl, aryl, heteroaryl, alkynyl organostannanes, are the most widely used. Examples of use of allyl and alkyl organotin compounds are also reported. The relative order of ligand transfer from the organostannane is: alkynyl > alkenyl > aryl > allyl ~ benzyl >> alkyl.

The catalyst used is often palladium (0) (like  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Pd}_2(\text{dba})_3$ ), or a source of palladium (II) (like  $\text{Pd}(\text{OAc})_2$ ,  $\text{BnPdCl}(\text{PPh}_3)_2$  to name a few), that gets reduced to the active species palladium(0) *in situ*. Methods using other metals like manganese, copper, and nickel have been reported; the latter has been applied for instance in the successful Stille coupling of unreactive aryl chlorides as well as in the coupling of unactivated primary and secondary alkyl halides.<sup>2</sup>

The Stille coupling is usually carried out in a dipolar solvent (like DMF, DMSO or NMP) or in an ethereal solvent (like THF or dioxane).

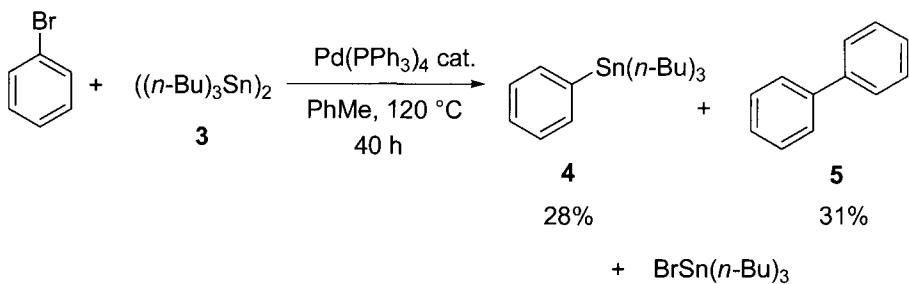
When the above reaction is performed under an atmosphere of carbon monoxide, CO insertion occurs with the concomitant formation of two sigma carbon carbon bonds to give a ketone as product. This reaction is referred to as the Stille carbonylative coupling reaction (see equation 2 below).



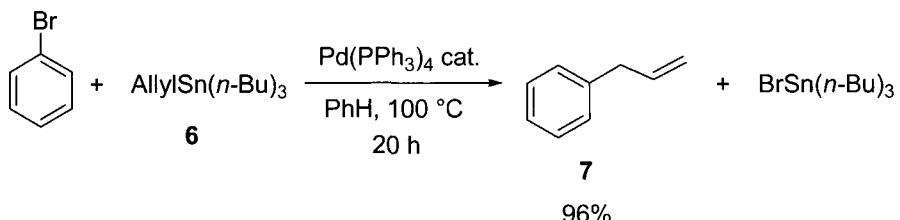
The Stille coupling is one of the most powerful tools available to synthetic chemists to date for the formation of sigma carbon carbon bonds. This is clearly demonstrated by the impressive amount of syntheses involving this transformation.<sup>5</sup> One advantage of this reaction is that it can be performed under very mild and neutral conditions (on the contrary to other cross coupling reactions, like the Suzuki coupling, which are done under basic conditions) compatible with sensitive motifs and functional groups found for instance in natural products. Furthermore, the organostannane precursors are usually easily accessible, easily purified and stored under normal conditions (on the contrary to other air- or moisture-sensitive reagents required for other types of palladium mediated cross couplings) and tolerate many functional groups<sup>6</sup> (properties mainly due to the low polarity of the carbon tin bond compared to other organometallic reagents like Grignards and organozincs respectively used in Kumada and Negishi cross couplings). Last but not least, the reaction has usually a high rate of success and the numerous precedents found in literature as well as the numerous options available to tune a particular coupling (solvent, catalyst, ligand, additives, ability to change the pair electrophile/organostannane to the other possible combination, *etc.*) allow for a quick screening of the most optimal set of conditions for a particular motif.<sup>7</sup> The extensive use of the Stille coupling in total syntheses, not only to build small fragments but also to combine together advanced intermediates harboring very elaborated carbon frameworks is no stranger to that and should be regarded as a testimony of the power of this method. One drawback however is the generation of toxic tin-containing by-products (often in stoichiometric amounts), which renders the reaction potentially problematic on scale-up. Elegant solutions to this problem have emerged in the literature.<sup>8</sup>

### 1.1.6.2 *Historical Perspective*

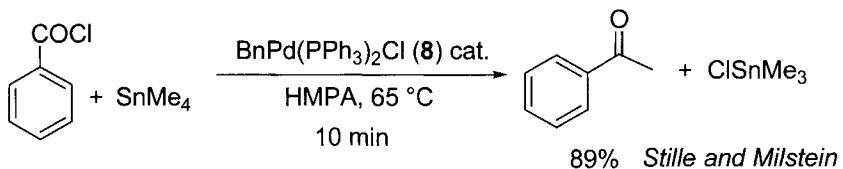
The reaction between an organic electrophile and a tin reagent (hexaalkyldistannane) was first reported by Colin Eaborn and co-workers<sup>9</sup> in 1976. For instance reaction of a stoichiometric amount of bromobenzene and hexabutyldistannane **3** in toluene in a sealed tube heated at 120 °C for 40 hours in presence of a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub> led to the formation of tributyl(phenyl)stannane **4** and biphenyl **5** in respectively 28 and 31% yield.

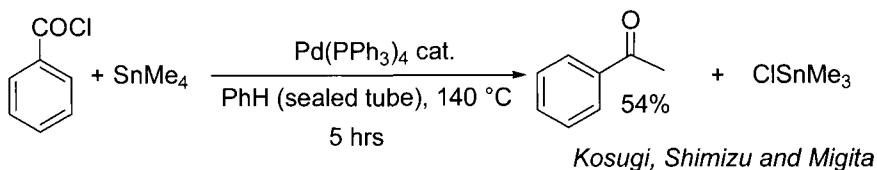


A year later, Kosugi, Shimizu and Migita reported the first palladium-catalysed sigma carbon-carbon bond formation from an organic electrophile (acid chloride<sup>10</sup> or aryl halide<sup>11</sup>) and an organostannane. Thus, heating a mixture of allyltributyltin **6** and bromobenzene in a sealed tube at 100 °C for 20 hours in presence of a catalytic amount of  $\text{Pd}(\text{PPh}_3)_4$  led to the clean formation of allylbenzene **7** in high yield.<sup>11</sup>



The first report by Stille was published in 1978 and dealt with the formation of ketones, mediated by a palladium(II) catalyst, starting from acid chlorides and organostannanes.<sup>12</sup> For instance acetophenone was produced in 89% isolated yield upon treatment of a solution of benzoyl chloride and tetramethylstannane in HMPA at 65 °C for 10–15 minutes in presence of benzylchlorobis(triphenylphosphine)palladium(II) (**8**). The experimental conditions reported in this article proved to be milder and higher yielding than the ones reported by Kosugi, Shimizu and Migita (see below).

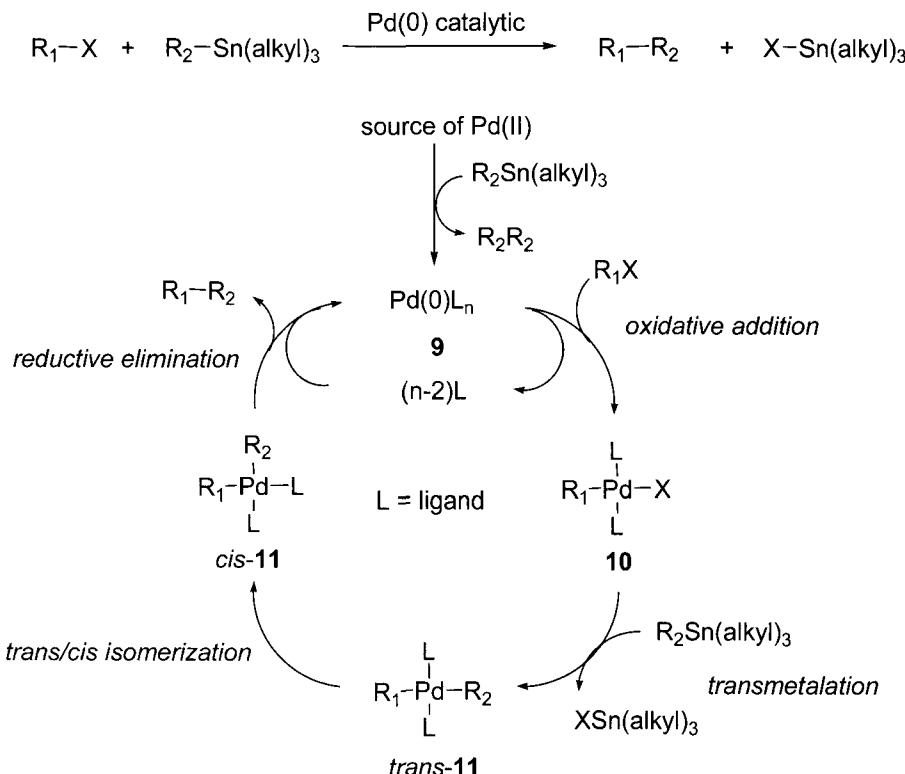




Stille then studied extensively this reaction<sup>13</sup> and in recognition of Stille's contribution, this reaction is now referred to as the Stille coupling.<sup>14</sup>

### 1.1.6.3 Mechanism

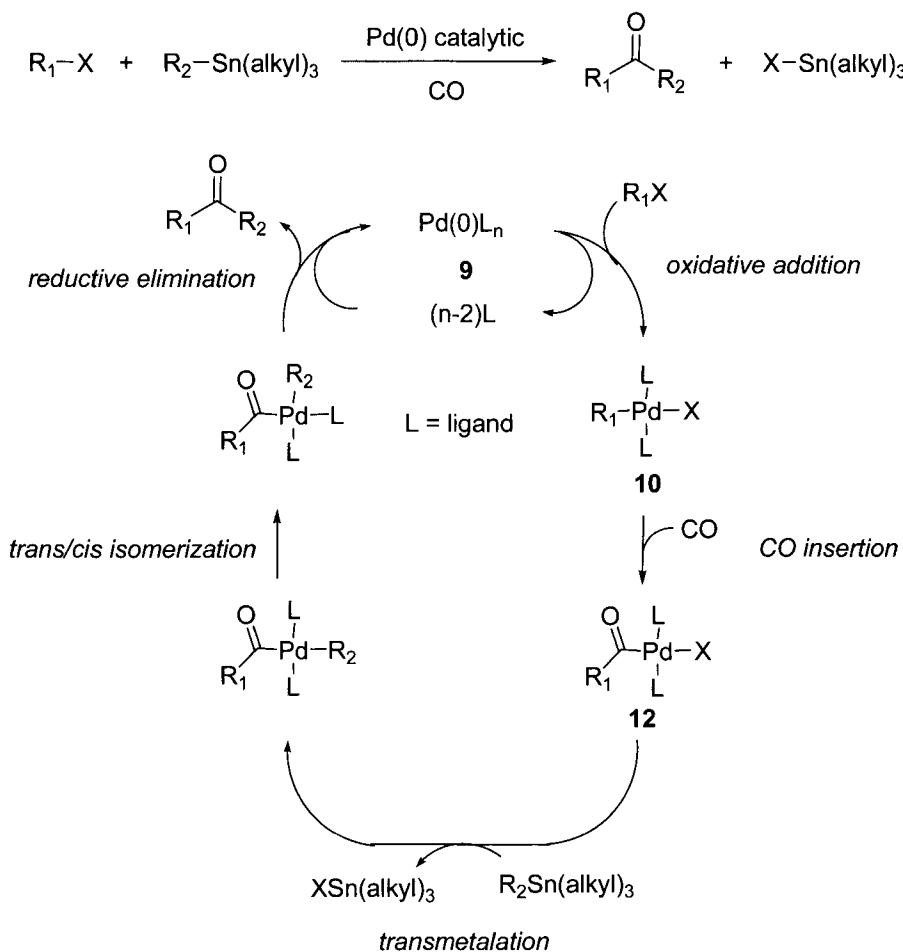
The mechanism of the Stille coupling presented by Stille as a working model in his 1986 review,<sup>13</sup> is represented below.



If using a palladium(II) catalyst, the catalytic active species palladium(0) **9** is generated *in situ* from reduction of the palladium(II) precursor with the organostannane present in the medium. Oxidative addition of the organic electrophile then generates a 16-electron palladium(II) complex intermediate **10**, which then undergoes a transmetalation step to

produce *trans*-**11**. A rapid *trans/cis*-isomerization to produce *cis*-**11** followed by a reductive elimination to generate the carbon carbon bond in the product and to regenerate the active catalytic palladium(0) species **9** complete the catalytic cycle.

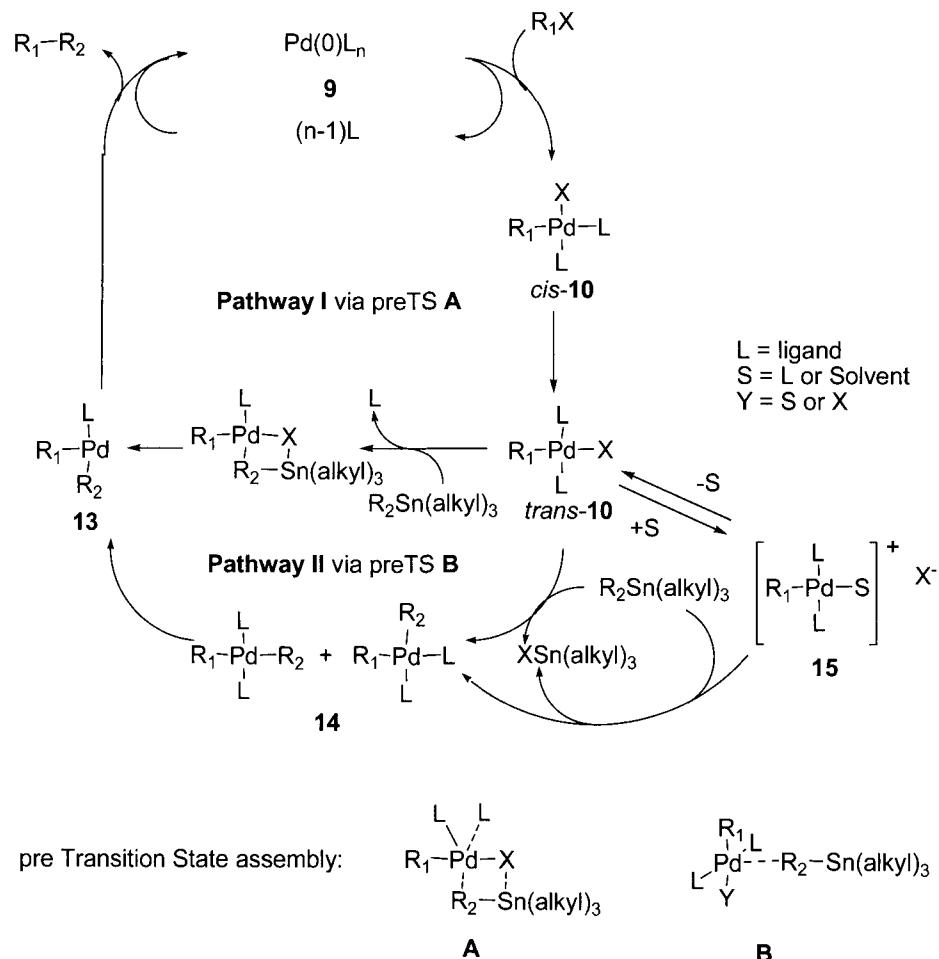
The carbonylative Stille coupling obeys to the same catalytic loop except that there is a carbon monoxide insertion into intermediate **10** to produce **12**, which undergoes the transmetalation step (carbonyl insertion into **12** is faster than transmetalation).



The mechanism deserves some additional comments. It is admitted that the transmetalation step is the rate-limiting step in most cases.<sup>15</sup> However, at times either the oxidative addition<sup>16</sup> or the reductive elimination<sup>17</sup> could be the rate-limiting step. As it will be seen in the next paragraph, knowing that

the transmetalation step is the rate-determining step in most cases is of key importance when trying to fine-tune the reaction.

The mechanism of the reaction has been the subject of considerable attention over the past twenty years and very detailed physicochemical studies aiming at decoding this mechanistic black box have been published<sup>18</sup>. A very detailed review on the subject has been published in 2004 by Espinet and Echavarren<sup>15</sup> in which a more detailed view of the pathways that may be involved in the catalytic loop of the Stille coupling was proposed. It is presented below.



Oxidative addition of the organic electrophile leads to **cis-10** (relative to  $\text{R}_1$  and  $\text{X}$ ), which is the kinetic addition product. This product rapidly isomerises to the thermodynamically more stable **trans-10** (by virtue of the transphobia effect<sup>19</sup> between a phosphane ligand and a *trans* C-donor ligand);

two transmetalation pathways are then suggested depending of the reaction conditions.

In **pathway I**, *trans*-**10** leads to **13** via a cyclic transition state (see **A**) in an *associative L-for-R<sub>2</sub>* substitution. Reductive elimination then completes the catalytic loop.

In **pathway II**, *trans*-**10** leads to **14** (either directly or by the intermediary of **15**) via an acyclic transition state (see **B**) in an *associative Y-for-R<sub>2</sub>* substitution. Reductive elimination then completes the catalytic loop. Espinet and Echavarren have proposed that **pathway I** is favored for conditions involving organic halides as electrophiles and a solvent with moderate coordinative ability towards palladium. **Pathway II** would be favored for good leaving groups like triflates and in presence of solvents with good coordinative ability for palladium.

Postulating a universal mechanism more detailed than the working models presented above seems to be a very ambitious endeavour since clearly reaction mechanisms are very dependent of each parameter (catalyst, nature of the ligand, nature of the counter ion in the electrophile, nature of the organostannane, presence of additives like lithium chloride<sup>20</sup> or copper salts<sup>21</sup>). The next paragraph will give us an additional flavour of this.

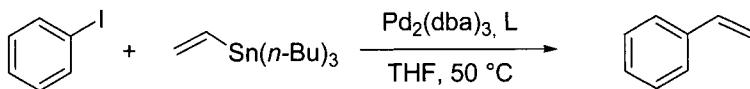
#### 1.1.6.4 *Variations and Improvements*

The variations and improvements of the Stille coupling are numerous in literature and each of the parameters that can potentially influence the mechanism of the reaction has been studied. In this paragraph, we do not have the pretension to give an exhaustive list of the numerous modifications that have been published but instead we will focus on presenting a representative set of examples. This will allow emphasis on the logical path taken to bring the reaction to where it stands now, 30 years after its discovery.

##### *Influence of the ligand*

Based on the working models presented in the mechanism section it is easily conceivable that each parameter prone to modify the sphere of coordination of the metal will have an influence on the course of the reaction.

The ligand is no exception to this. Indeed, it was found by Farina and Krishnan that changing the ligand triphenylphosphine PPh<sub>3</sub> for ligands like tri-2-furylphosphine (TFP) or triphenylarsine AsPh<sub>3</sub> led to large rate enhancements in the Stille coupling<sup>22</sup> (see below).



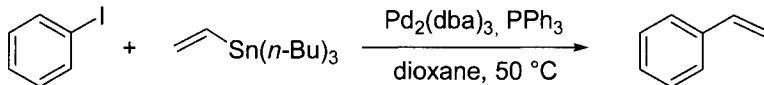
Ligand <sup>a</sup> L	rel rate	yield <sup>b</sup> (%)
PPh <sub>3</sub>	1	15
TFP	105	> 95
AsPh <sub>3</sub>	1100	> 95

a. Pd:L ratio = 1:4. b. HPLC yield after 72 hrs.

It was proposed that in this case, ligands like TFP and AsPh<sub>3</sub> were increasing the rate of the reaction because of their ability to readily dissociate from Pd(II) intermediate and therefore increase the rate of the rate limiting transmetalation step.

#### Influence of additives

It is reported in literature that additives like LiCl<sup>20</sup> or Cu(I)<sup>23</sup> salts can have a dramatic influence on the coupling. The “copper effect” in Stille coupling reactions was investigated by Farina and Liebeskind and coworkers<sup>21</sup>. For instance in the reaction of iodobenzene and vinyltributyltin in dioxane at 50 °C catalyzed by Pd<sub>2</sub>(dba)<sub>3</sub> in presence of a strong ligand like PPh<sub>3</sub>, it was found that the addition of 2 molar equivalents of CuI per mol of catalyst led to a > 100 fold increase in reaction rate.



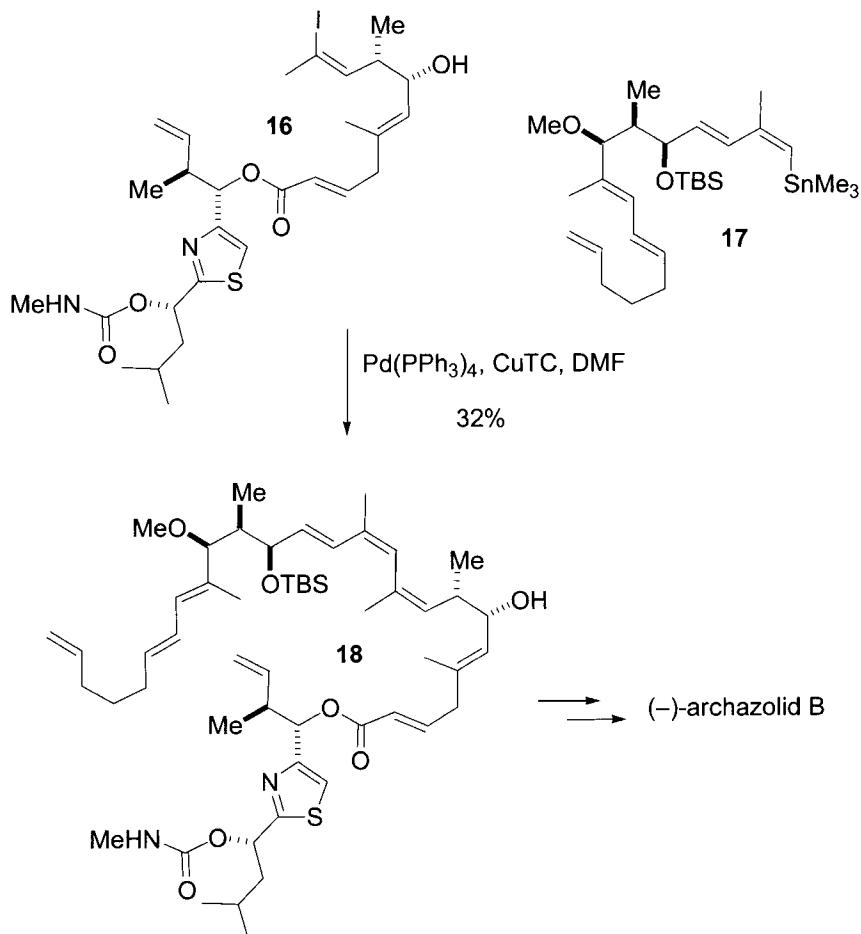
Pd:L:CuI	rel rate	yield <sup>a</sup> (%)
1:4:0	1	85
1:4:1	5	91
<b>1:4:2</b>	<b>114</b>	<b>&gt; 95</b>

a. HPLC yield determined after catalyst had decomposed.

Based on NMR studies it was proposed that in this case the rate increase was due to the ability of CuI to scavenge the strong ligand PPh<sub>3</sub> free in solution. Indeed, strong ligands in solution are known to inhibit the rate-limiting transmetalation step.

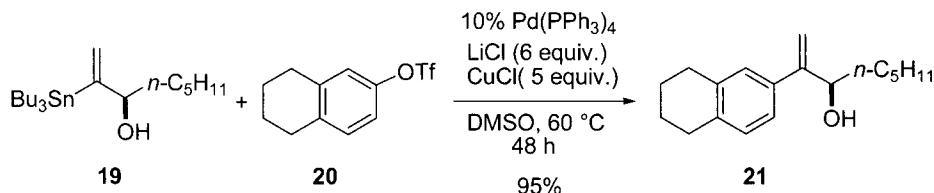
Following on this discovery, in 1996 Liebeskind reported that copper(I) thiophene-2-carboxylate (CuTC) was able to promote the Stille coupling between organic iodides (mainly vinyl and activated aryl) and organostannanes in the absence of palladium, at or below room temperature in NMP as solvent.<sup>24</sup>

CuTC proved to be crucial in the successful late stage Stille coupling involved in the recent total synthesis of (-)-archazolid B reported by the Trauner group<sup>25</sup> (**16** + **17** → **18**). Palladium and copper were required to promote this coupling.



Cuprous chloride proves to be an ally of choice in fine tuning tricky Stille coupling reactions. This was demonstrated by the Corey group while working towards the total synthesis of natural product nicandrenone.<sup>26</sup> One step in the synthetic scheme required the Stille coupling between a 1-substituted vinylstannane and an aryl triflate (or nonaflate). However, 1-substituted vinylstannes are notoriously known for being poor coupling partners in Stille reactions mainly for steric reasons, leading to poor yields of desired coupling product with competing formation of products resulting from *cine* substitution. This prompted the study of new conditions for this particular type of systems.

It was found that the coupling between vinylstannane **19** and aryltriflate **20** mediated by Pd(PPh<sub>3</sub>)<sub>4</sub> proceeded in high yield when performed in polar solvent DMSO at 60 °C for 48 hours in the presence of 6 equivalents of LiCl and 5 equivalents of CuCl to produce **21** in 95% isolated yield.



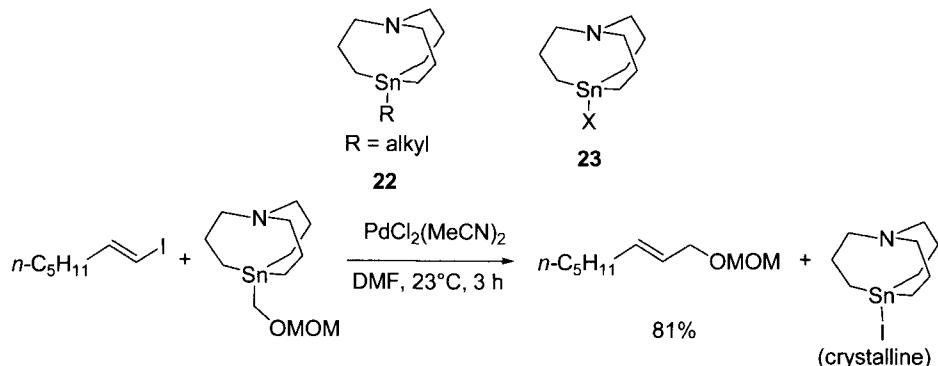
It was proposed that the influence of CuCl was to promote the formation of a more reactive metalloid (RCu or RCuLiCl) than the starting organostannane. This reactive metalloid then participates in the transmetalation step with palladium (II) intermediate to yield to the desired product after reductive elimination. The conditions developed by Corey were successfully applied later on by the Tanner group in their studies towards the total synthesis of zoanthamine.<sup>27</sup>

Other transition metals, like manganese<sup>28</sup> and nickel,<sup>29</sup> have been used in the Stille coupling (as additive or as replacement of palladium). As we will see later, nickel proved to be very powerful in replacing palladium as catalyst and is very promising in terms of expanding the scope of the reaction.

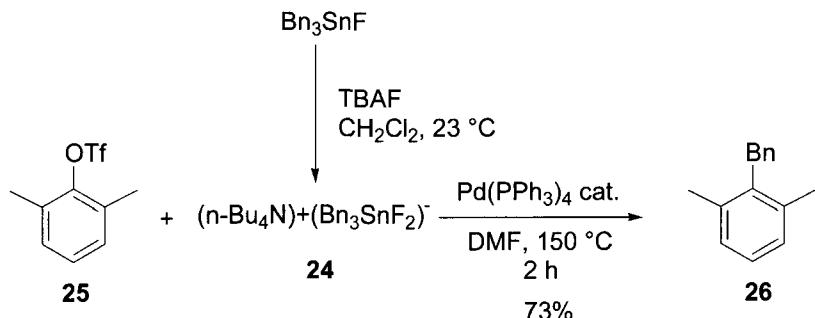
#### *Activation of the organostannane*

As seen with the previous example, activation of the organostannane to promote the transmetalation step has a dramatic and positive influence on the outcome of the reaction. In 1992, Vedejs *et al.* showed that intramolecular coordination of tin by a nucleophilic center like a nitrogen can considerably increase the rate of the transmetalation step in the Stille coupling<sup>30</sup>. Derivatives like **22** proved to be more reactive than their analogue trialkyl tin

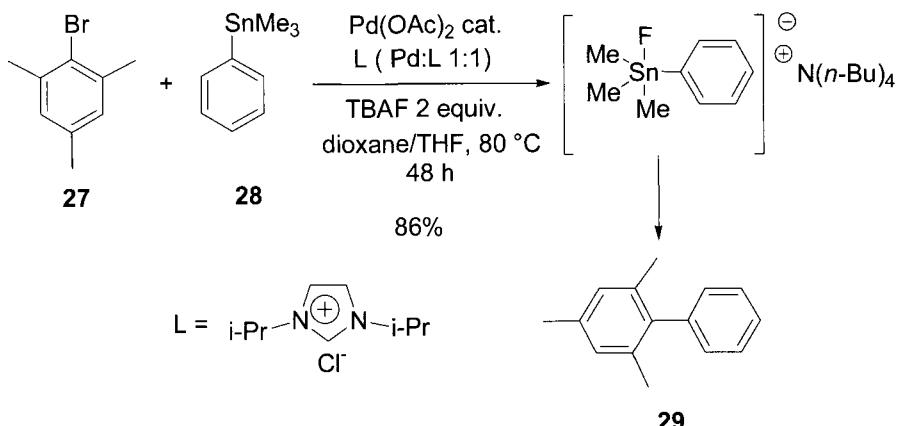
derivatives and the by product halide **23** can be easily removed and recycled from the crude since it crystallizes in the course of the reaction.



Other methods of activating organostannanes have been reported in literature. These methods capitalize on the use of fluoride ions and the formation in situ or not of activated hypervalent stannate intermediates. For instance, Garcia Martinez has used the hypervalent tin reagent tetrabutylammonium difluorotribenzylstannate **24** (prepared in quantitative yield from Bn<sub>3</sub>SnF) in the synthesis of unsymmetrical diarylmethanes starting from aryl triflates (e.g., **24** + **25** → **26**).<sup>31</sup>

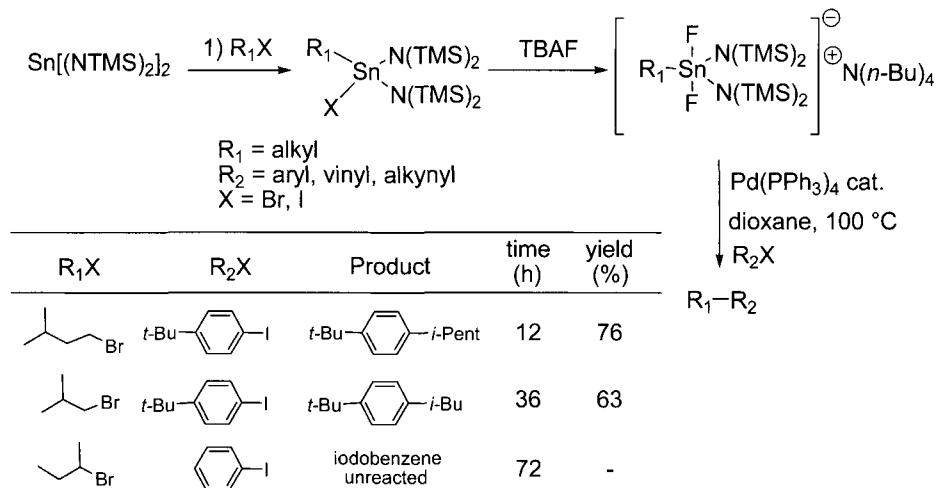


Nolan has also taken advantage of hypervalent organostannate (generated in situ) in Stille coupling catalyzed by a Palladium/imidazolium salt system (e.g., **27** + **28** → **29**).<sup>32</sup>



Four examples were also reported where aryl chlorides were used as substrate, best yields and shorter reaction times being obtained with activated aryl chlorides (like 1-(4-chlorophenyl)ethanone).

Fouquet developed an interesting methodology using activated alkyl tin reagents which allows for the formation of C(sp<sup>3</sup>)–C(sp<sup>2</sup>) sigma carbon bonds starting from primary alkyl bromides or iodides.<sup>33</sup> The reaction is limited to the use of primary alkyl halides ( $\beta$  and  $\gamma$  substitution is tolerated).



reagents <sup>a</sup>	yield <sup>b</sup> (%)
Pd(PPh <sub>3</sub> ) <sub>4</sub>	2
Pd(PPh <sub>3</sub> ) <sub>4</sub> , CsF	8
Pd(PPh <sub>3</sub> ) <sub>4</sub> , CuI	46
<b>Pd(PPh<sub>3</sub>)<sub>4</sub>, CsF, CuI</b>	<b>98</b>
CsF, CuI	0

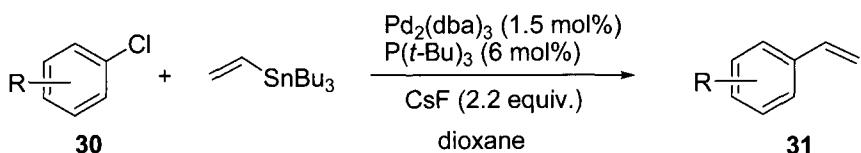
a. Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol%), CuI (20 mol%), CsF (2 equiv.).

b. isolated yield.

Taking advantage of the “copper” and “fluoride” effects, Baldwin and co-workers have developed conditions (Pd(PPh<sub>3</sub>)<sub>4</sub>/CuI/CsF) that allow the Stille coupling of electronically unfavourable and/or sterically hindered substrates.<sup>34</sup>

#### *Development of powerful catalytic systems: the aryl chloride case.*

In 1999, the Fu group reported the first general method for the Stille cross coupling of aryl chlorides<sup>35</sup> (**30**→**31**). On the contrary to previously reported methods involving the coupling of aryl chlorides, the Fu conditions allowed for the coupling in good yield of not only electron poor but also electron neutral and electro rich aryl chlorides. The conditions involved the use of 1.5 mol% of Pd<sub>2</sub>(dba)<sub>3</sub>, 6 mol% of the electron rich and sterically demanding phosphine P(*t*-Bu)<sub>3</sub> as ligand and 2.2 equivalents of CsF.



aryl chloride	temp. (°C)	time (h)	yield <sup>a</sup> (%)
	80	12	87
	100	23	80
	100	48	82
	100	48	61
	100	36	71

a. isolated yield.

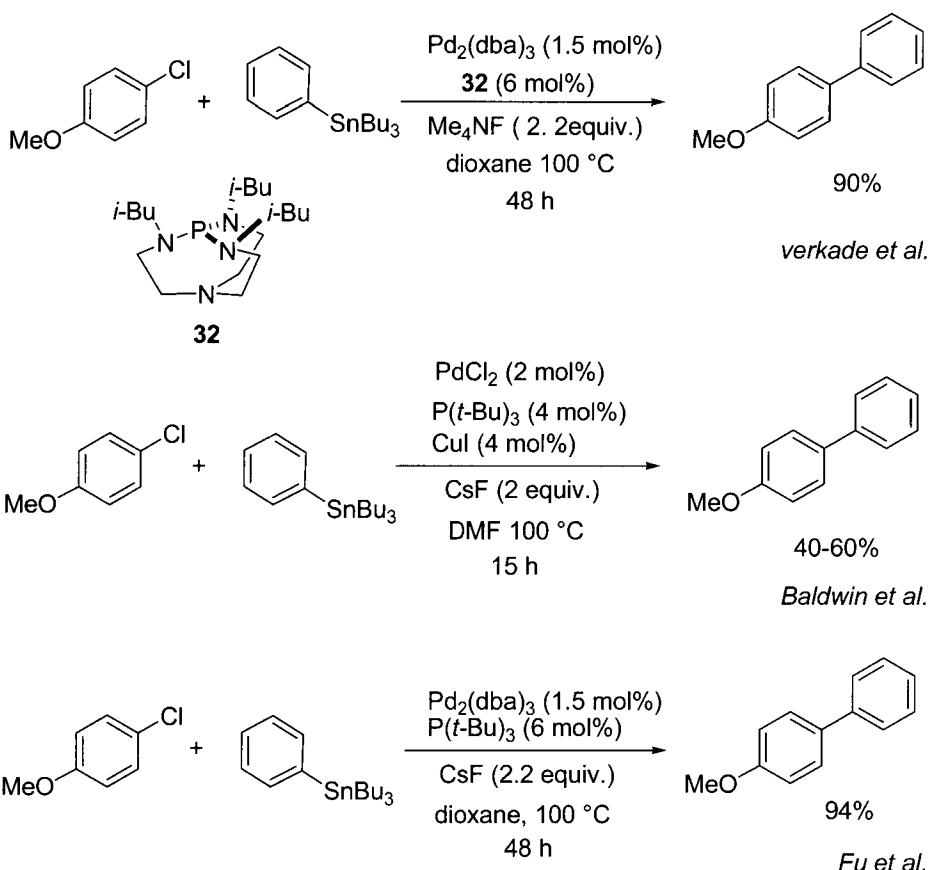
Additional advantages of this methodology are:

- Allow Stille coupling with aryl bromides at room temperature;
- Very hindered biaryl can be synthesized (like tetra ortho substituted biaryls);
- Aryl chlorides can be coupled in presence of aryl triflates.<sup>36</sup>

This method should be regarded as a method of choice when looking to perform a Stille coupling on a sensitive substrate potentially prone to decomposition under the more classical Stille conditions which require higher temperature.

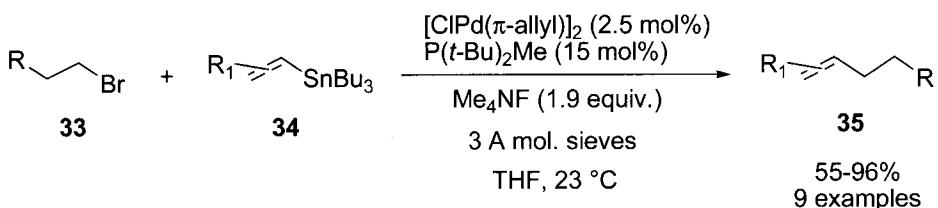
In 2004 Verkade and co-workers reported a catalyst system of general applicability for the Stille coupling of aryl chlorides at 110 °C in dioxane and the coupling of aryl bromides at room temperature in THF. The catalyst system uses  $\text{Pd}_2(\text{dba})_3$ , the bulky proazaphosphatrane ligand **32** in presence of  $\text{CsF}$  (or  $\text{Me}_4\text{NF}$ ).

The same year Baldwin also reported conditions capable of coupling electron rich aryl chlorides.

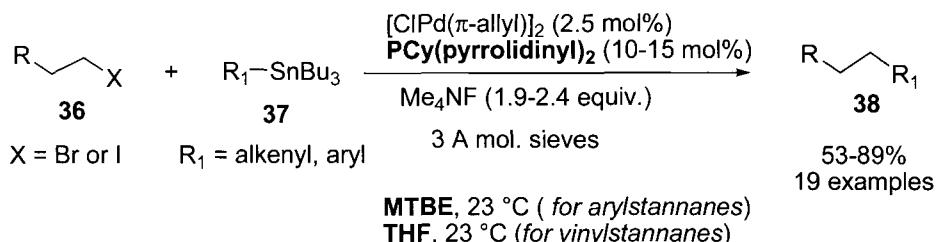


*Development of powerful catalytic systems: the alkyl halide case.*

After having proposed a general solution to the Stille coupling of unactivated aryl chlorides, the Fu laboratories reported in 2003 a general method for the coupling of unactivated primary alkyl bromides with vinylstannanes<sup>37</sup> (**33** + **34** → **35**). It is a real tour de force since these substrates harbor β-hydrogens and therefore the spectre of undesired β-hydride elimination loomed as a real threat.<sup>38</sup> At that time only 5 successes had been reported in literature but only on specific substrates.<sup>39</sup>

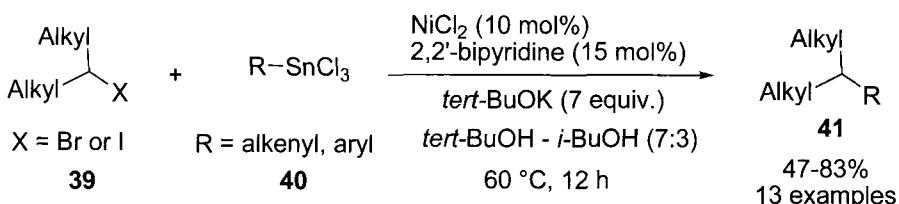


It is worth noting from a practical point of view that the air sensitive phosphine  $P(t\text{-Bu})_2\text{Me}$  can be replaced by the commercially available, air- and moisture- stable salt  $[\text{HP}(t\text{-Bu})_2\text{Me}]BF_4$  without decrease in yield. The drawback of this methodology was that it is limited to the use of vinylstannanes and that arylstannanes were ineffective partners. The solution came a few months later with the discovery that electron-rich alkyldiaminophosphane  $\text{PCy}(\text{pyrrolidinyl})_2$  was a superior ligand compared to  $P(t\text{-Bu})_2\text{Me}$  (**36** + **37** → **38**).<sup>40</sup>



Besides the role of the ligand, the solvent plays a key role, methyl *tert*-butyl ether (MTBE) being the solvent of choice for the coupling with arylstannanes. Other solvents like acetonitrile, *tert*-amyl alcohol, or dichloromethane proved to be not suitable. From a synthetic point of view it is worth mentioning that these conditions are compatible with a wide range of functionalities like, ester, amide, nitrile, benzyl, terminal olefin, tetrahydropyran, 1,3-dioxolane. For an alternative method, see also the work of Fouquet mentioned above.<sup>33,41</sup>

The Stille coupling involving secondary alkyl electrophiles still remained an unmet challenge...but not for long since in 2005 the Fu group published a landmark communication reporting the first catalytic system able to perform Stille cross couplings of unactivated secondary alkyl halides (bromide and iodide) with electronically and sterically diverse monoorganotin reagents<sup>42</sup> (**39** + **40** → **41**).



A key was the realization that Ni, the neighbour of Pd in the groupVIII, was superior in such coupling. Nickel catalysts have already been used in the Stille coupling for the generation of  $C(\text{sp}^2)\text{-}C(\text{sp}^2)$  sigma carbon–carbon bonds. For instance Shirakawa and Hiyama had shown that  $\text{Ni}(0)$  catalyst

(formed by the in situ reduction of Ni(acac)<sub>2</sub> by DIBAL-H) combined with PPh<sub>3</sub> could catalyze the Stille coupling of aryl halides with vinyl-, aryl- or allyl-stannanes<sup>43</sup>.

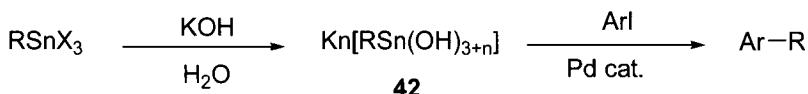
Fu's methodology is impressive for several reasons:

- It uses unactivated secondary alkyl halides (bromide and iodide, cyclic or acyclic).
- It works equally well using unactivated primary alkyl halides (bromide and iodide).
- It uses inexpensive and air stable NiCl<sub>2</sub> as catalyst.
- Palladium (Pd<sub>2</sub>(dba)<sub>3</sub> or Pd(OAc)<sub>2</sub>) was ineffective as a catalyst.
- Reaction conditions are mild.
- Preliminary results suggest that the coupling may be done with retention of configuration.
- Mechanism may proceed through the initial formation of an alkyl radical.
- It works on electronically and sterically diverse aryl- and alkenyl-monoorganostannanes (easily accessible starting from alkenyl- or aryl- trialkylstannanes by redistribution with SnCl<sub>4</sub>).
- This process does not generate toxic triorganotin compound (XSn(alkyl)<sub>3</sub>) in stoichiometric amount but instead inorganic tin-based by-products which are less toxic and easier to eliminate in the work-up<sup>44,45</sup>.

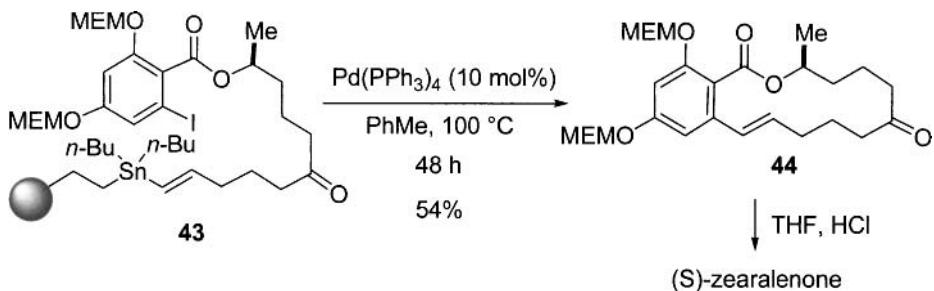
*Reduction of the potential toxicity associated with tin compounds.*

Tin reagents particularly trialkyl organostannanes are toxic chemicals<sup>44,45</sup> and extreme care should be exercised when manipulating them (avoiding inhalation and contact as well as working in a well ventilated hood is very important). In most cases the Stille reaction will produce toxic halotrialkylstannane XSn(alkyl)<sub>3</sub> (in stoichiometric amount) which are also difficult to remove (for instance ClSnBu<sub>3</sub> is high boiling, non polar and tends to streak when purifying a crude by flash chromatography over silica gel). Fortunately methods have appeared in literature that generate less toxic and easier to eliminate tin-containing by-products. The Fu methodology using monoorganostannanes of general formula RSnCl<sub>3</sub> is one of them.

Other methods have appeared in literature that capitalize on the use of alkyltrichlorostannanes to perform Stille couplings in aqueous solutions (via an organostanoate intermediate **42**)<sup>46</sup>. The by products are inorganic tin by products, less toxic and easily eliminated in the work-up.<sup>44,45</sup>

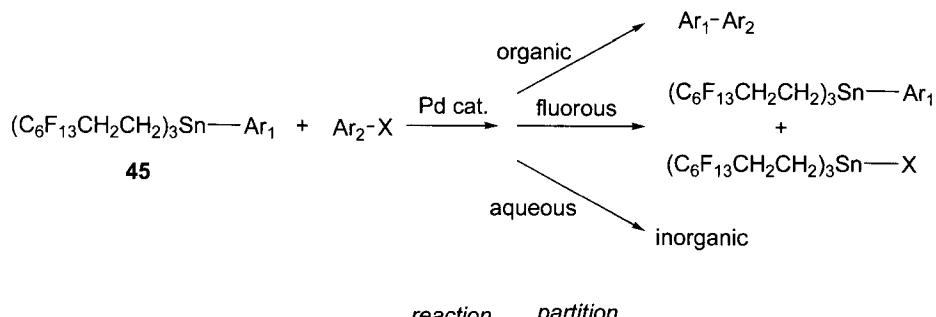


Solid Phase chemistry has also been used to help solving this problem by immobilizing one of the partners (organic electrophile or organostannane) on the solid support to help purification<sup>47</sup>. An example of this approach is found in Nicolaou's total synthesis of (S)-zearealenone<sup>48</sup> (**43** → **44**).



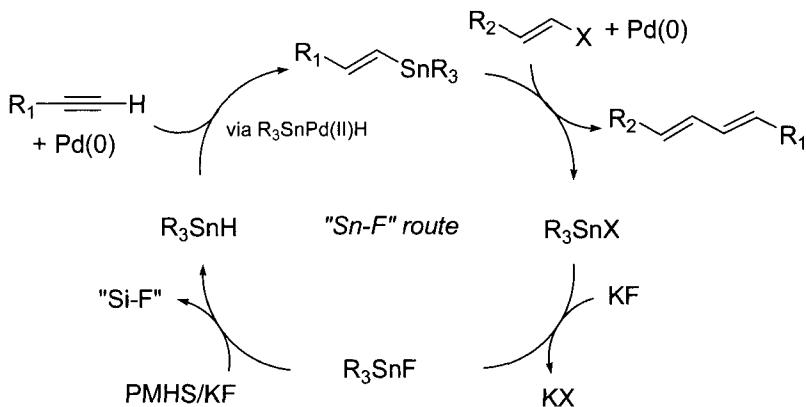
The application of modern solid-phase chemistry to metal catalyzed cross coupling reaction (including the Stille coupling) has been the subject of a very recent review by Testero and Matta.<sup>47a</sup> Ionic liquid supported tin reagents have also been developed.<sup>49</sup>

Curran has used fluorous tin reactants (**45**) to facilitate the separation of the desired product from tin by-products via a three-phase (aqueous/organic/fluorous) extraction protocol as presented below.<sup>50</sup> This also allows for easy isolation and recycling of the tin fluorous compound.



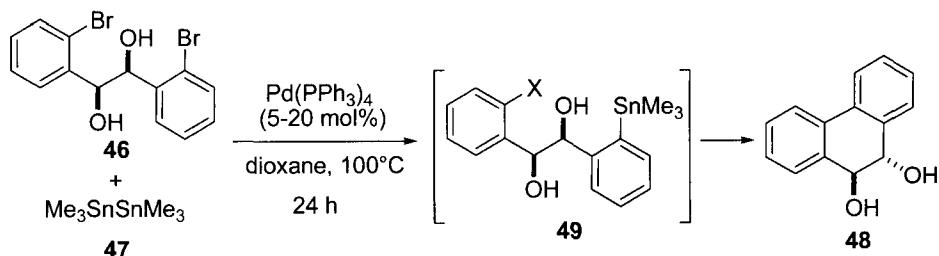
Curran and Hallberg also applied this method in combination with the rapid microwave assisted Stille coupling of simple organic halides or triflates.<sup>51</sup> Stille couplings under microwave irradiation conditions usually leads to shorter reaction time compared to classical conditions and have been the subject of a very recent review.<sup>52</sup>

Maleczka proposed an ingenious approach (the ‘Sn–F’ route), catalytic in tin, for the Stille coupling involving alkenylstannanes.<sup>53,54</sup> The alkenylstannane is formed in situ from the corresponding terminal alkyne and a catalytic amount of trialkyltinhydride as depicted on the catalytic loop below.



Polymethylhydrosiloxane (PMHS) made hypercoordinate by KF is responsible for the regeneration of the tin hydride. These conditions were successfully applied to the C(sp<sup>2</sup>)–C(sp<sup>2</sup>) carbon–carbon bond formation involving aryl iodides, alkenyl halides (bromide or iodide) or benzyl bromide. Aryl nonaflate and allyl bromide proved to be ineffective partners under these conditions.

#### *The Stille–Kelly reaction.*

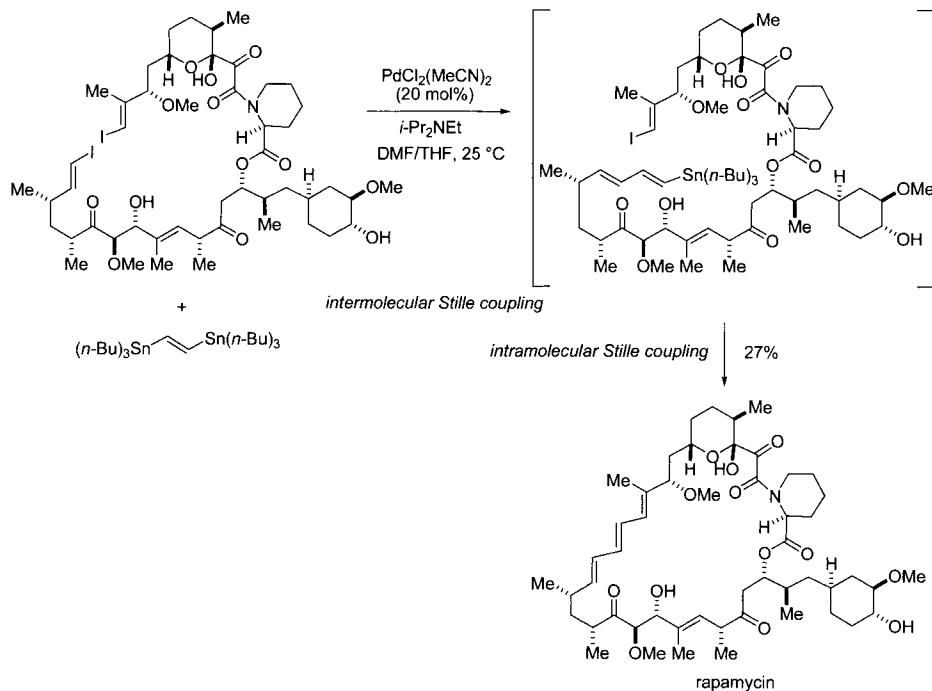


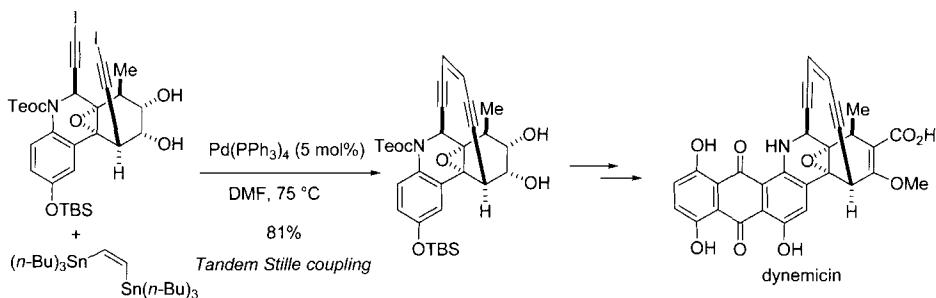
In 1990, while working on the total synthesis of pradimicin, Kelly discovered that the treatment of a biaryl halide (**46**) or triflate in presence of hexaalkyldistannane (**47**) and a catalytic amount of Pd(PPh<sub>3</sub>)<sub>4</sub> led to the clean intramolecular biaryl coupling to produce **48** in 80% isolated yield.<sup>55</sup> This reaction can be regarded as the transmetalation with the distannane mediated by palladium to afford the intermediate organostannane **49** which then

intramolecularly reacts in a classical Stille fashion to produce the desired biaryl product.

### 1.1.6.5 Synthetic Utility

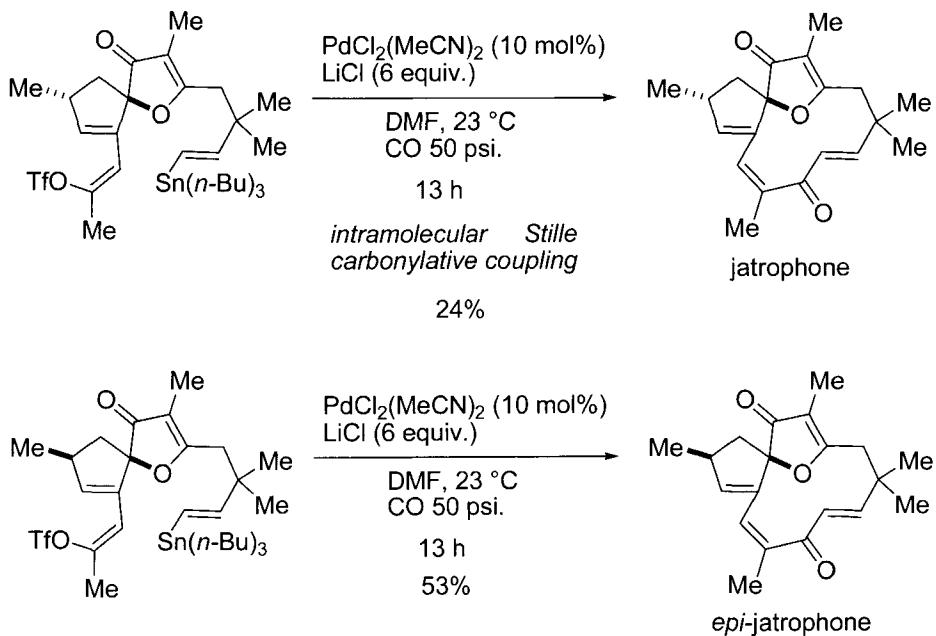
As mentioned already in the description, the Stille coupling is one of the most powerful **and reliable** tool available to synthetic chemists to form a sigma carbon carbon bond ( $C(sp^2) - C(sp^2)$  or  $C(sp^2) - C(sp^3)$ ). There are countless examples reported in literature over the past 30 years. Not only this reaction found an abundant application in the synthesis of small molecules but it has also been widely used in total syntheses of complex natural products; sometimes as a key step! The “stitching” approaches used by the Nicolaou and Danishefsky groups to respectively close at a late stage of the synthesis the 29-membered ring macrocycle found in rapamycin,<sup>56</sup> and to form the enediyne motif found in dynemicin<sup>57</sup> constitute perfect examples of the power of the Stille coupling.



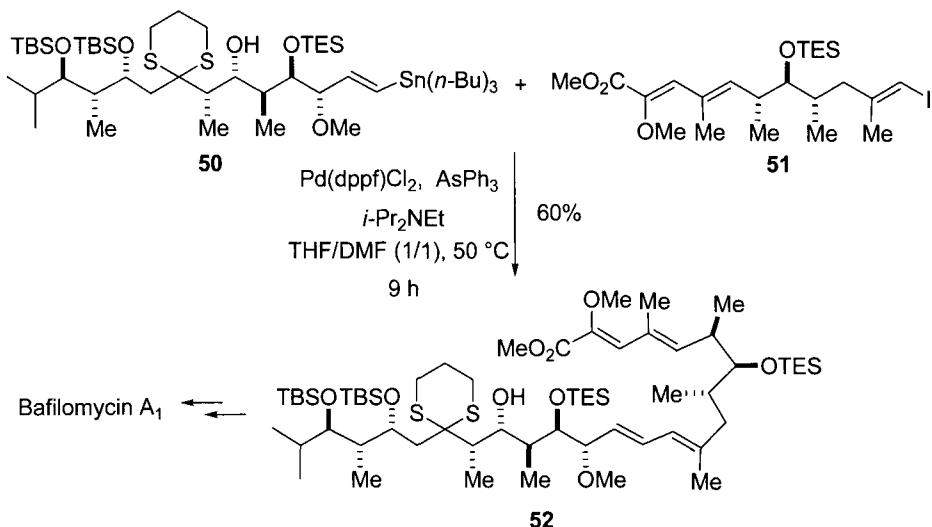


The use of the Stille reaction (cross coupling and carbonylative variation) has been the subject of numerous excellent reviews<sup>58</sup> and books<sup>7</sup> over the past few years and we will mention in this part only a few examples to illustrate the power and broad applicability of the method.

The Stille–Hegedus synthesis of the diterpene jatropheone took advantage of an intramolecular carbonylative Stille coupling between a vinyl triflate and a vinylstannane motif to forge the macrocycle found in the natural product (see below).<sup>59</sup>

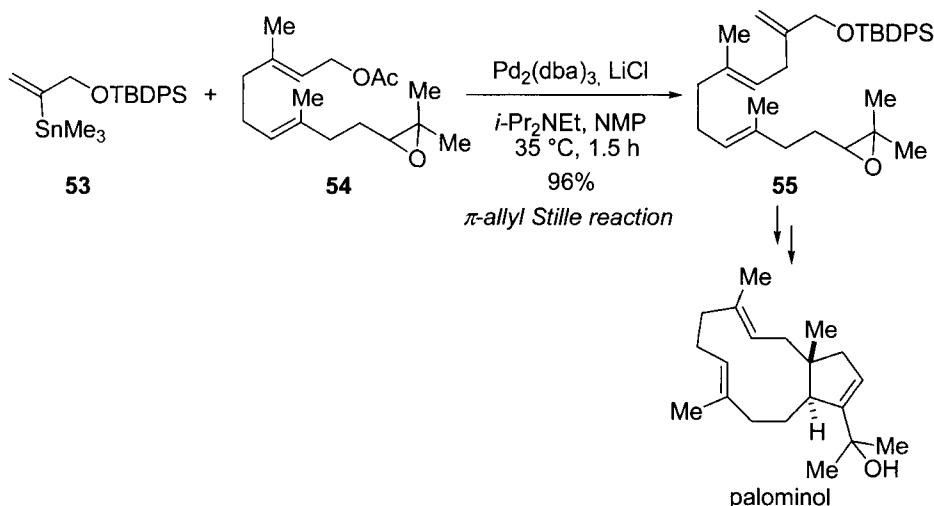


As often in organic synthesis, a remotely placed stereocenter had a profound influence on the course of the reaction (probably due to a conformational change).



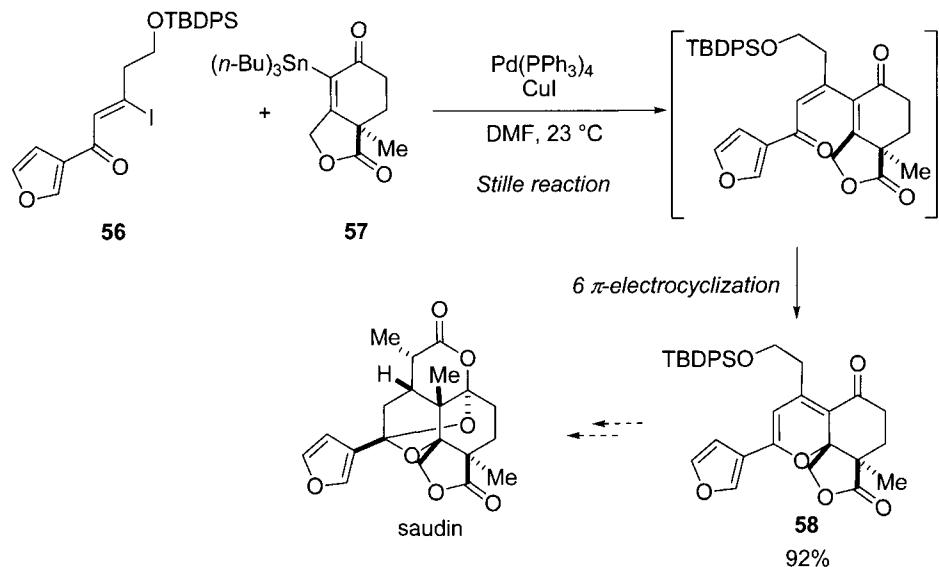
In their total synthesis of baflomycin A<sub>1</sub> Hanessian and co-workers used a Stille coupling to forge the carbon carbon bond between two advanced intermediates **50** and **51**.<sup>60</sup> The coupling was catalyzed by  $\text{Pd}(\text{dppf})\text{Cl}_2$  in presence of triphenylarsine as ligand and proceeded cleanly at  $50^\circ\text{C}$  in a mixture of THF/DMF as solvent to afford the desired advanced intermediate **52** possessing all the carbon backbone of the natural product.

In their total synthesis of palominol, Corey and Snyder capitalized on a  $\pi$ -allyl Stille reaction early in the synthesis between 1-substituted vinylstannane **53** and allyl acetate **54** to produce intermediate **55** in excellent yield.<sup>61</sup>

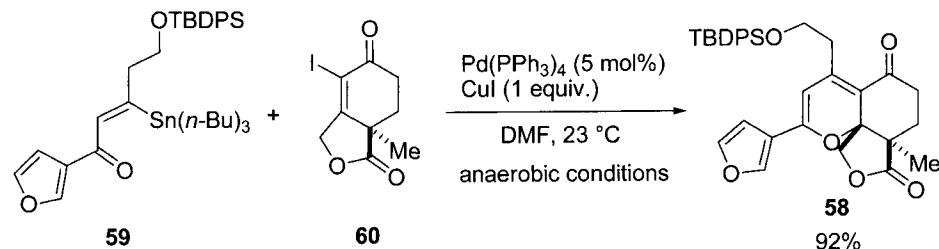


It is worth noting that under these conditions, the 1-substituted vinylstannane behaved well (1-substituted vinylstannanes tend to behave poorly in Stille reactions due to steric hindrance) and that no isomeric mixture of products was obtained (palladium mediated couplings on farnesyl substrates had led in the past to isomeric mixtures of products). The newly formed carbon C(sp<sup>3</sup>)–C(sp<sup>2</sup>) bond resulted from the attack at the less hindered terminus of the π-allyl intermediate (which is a usual trend in this type of couplings).

Recently, in the course of studies directed towards the total synthesis of saudin, the Stoltz group developed a tandem Stille-oxa-electrocyclization reaction to access substituted pyran systems (**56** + **57** → **58**)<sup>62</sup>.



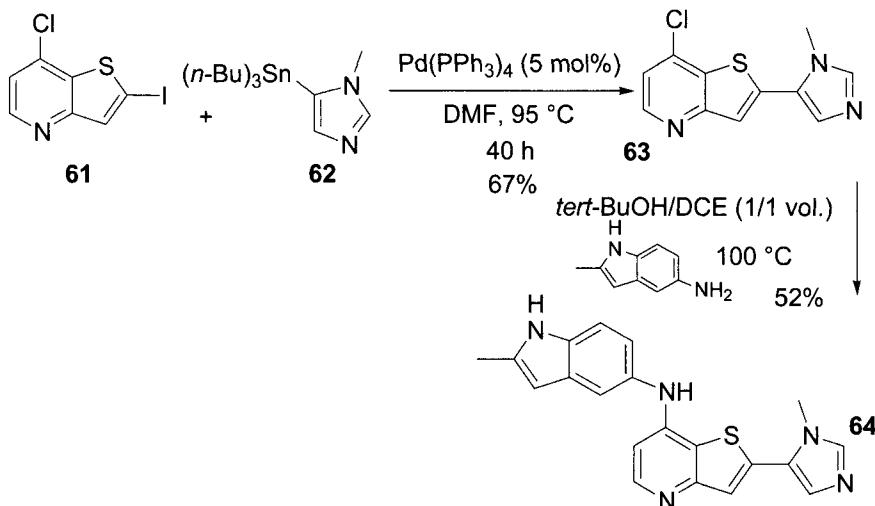
It is interesting to note that if the coupling partners were reversed (**59** + **60** → **58**), the coupling was more tricky; the use of a stoichiometric amount of CuI under anaerobic conditions proved to be crucial to get high yields of the desired product.



It was postulated that in presence of air copper (I) is oxidized to copper (II) and promotes the homocoupling<sup>63</sup> of the vinylstannane **59** to the detriment of the formation of the desired product.

One pot cascade sequences involving a Stille coupling (Heck/Stille, Heck/ carbonylative Stille, Stille/Diels Alder, Stille/electrocyclization, *etc.*) have been reported in literature.<sup>58,64</sup>

Process chemists at Pfizer took advantage of the Stille coupling reaction between an iodothienopyridine **61** and 5-(tributylstanny)-1-imidazole **62** to produce **63**, an intermediate in the synthesis of a cGMP bulk lot of VEGFR kinase inhibitor **64**.<sup>65</sup>



From all the palladium cross coupling conditions tried (Suzuki–Miyaura, Heck, Negishi, Hiyama, Kumada–Tamao, Kobayashi, DeShong), only the Stille coupling proved to be reliable on scale over 50 g. It is also interesting to note that adequate work-up allowed for getting below the acceptable upper limit of 20 ppm of stannane content (analytically determined by ICP).

### 1.1.6.6 *Experimental*

*Caution:* Tin reagents particularly trialkyl organostannanes are toxic chemicals<sup>44,45</sup> and extreme care should be exercised when manipulating them (avoiding inhalation and contact as well as working in a well ventilated hood is very important).

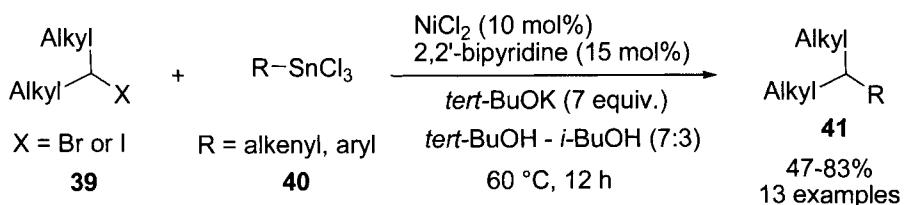
A useful trick when doing the work up of a Stille coupling (or of any reaction involving formation of non polar tin by-products) is to do a biphasic

MeCN/hexanes extraction if solubility of the desired organic product allows.  $(n\text{-Bu}_3)\text{SnCl}$  is soluble in hexanes but not in MeCN.

$(n\text{-Bu})_3\text{SnX}$  can also be removed by washing with aqueous KF solution to form polymeric  $(n\text{-Bu})_3\text{SnF}$  which can be removed by filtration.

Washing with a dilute aqueous solution of ammonium hydroxide also helps making trialkyltin halides more water soluble.

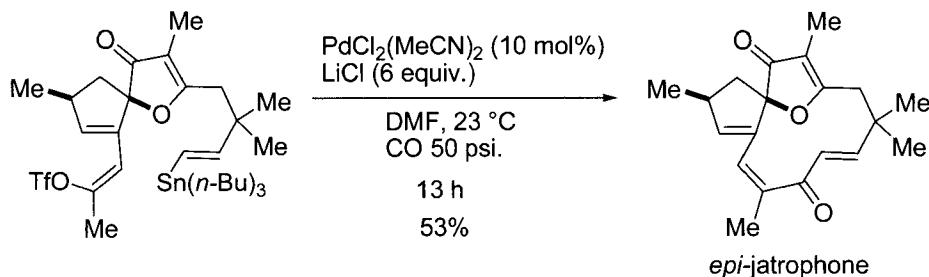
*General procedure for the Stille coupling of unactivated secondary alkyl halides reported by Fu:<sup>42</sup>*



Into a 20 mL sample vial was added  $\text{NiCl}_2$  (13 mg, 0.10 mmol) and 2,2'-bipyridine (23 mg, 0.15 mmol); these compounds were weighed in air, and no special handling precautions were employed. The vial was sealed with a septum screw-cap and purged under a steady stream of argon (nitrogen may also be used) for 20 min. A 1.0 M stock solution of *tert*-BuOK in *tert*-BuOH:*i*-BuOH (7.0 mL, 7.0 mmol of *tert*-BuOK) was added, followed by the aryltrichlorotin reagent (**40**, 1.2 mmol) and the alkyl halide (**39**, 1.0 mmol). The reaction mixture was heated in an oil bath to 60 °C for 12 h, with vigorous stirring under an argon atmosphere (the reaction mixture typically turns deep purple within 1 h of heating). Then, the cooled reaction mixture was poured into a separatory funnel that contained an aqueous 1 M HCl solution (50 mL), and the mixture was extracted with  $\text{Et}_2\text{O}$  (3 × 20 mL). The combined organic layers were washed with brine (40 mL), dried over  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The resulting crude reaction mixture was purified by column chromatography.

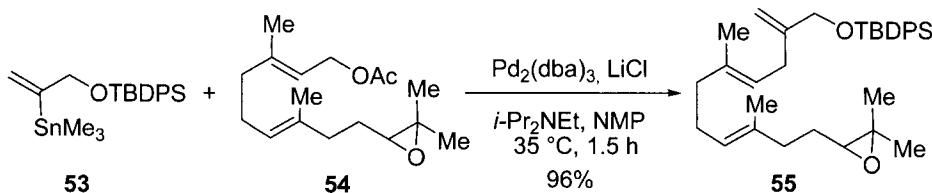
Note: the reaction is air- and moisture-sensitive. The *tert*-BuOK solution and the tin reagent should be handled/stored under nitrogen or argon.

*Stille carbonylative coupling:*<sup>59</sup>



To a Fisher–Porter tube were added the vinylic triflate (30 mg, 0.042 mmol) in 10 mL of DMF and LiCl (11 mg, 0.26 mmol). The solution was bubbled with carbon monoxide for 30 min. This was followed by the addition of  $\text{PdCl}_2(\text{MeCN})_2$  (1 mg, 0.004 mmol) in 3 mL of DMF. The tube was then pressurized to 50 psi and the mixture stirred at room temperature for 13 h, after which time palladium black had precipitated out of solution. The tube was vented and the solution taken up in ether and washed with water. The organic layer was dried over  $\text{Na}_2\text{SO}_4$ . Filtration and removal of solvent under reduced pressure afforded an oily residue that was purified by column chromatography on silica gel with 25% EtOAc/hexanes to give 7 mg (53%) of product as a white solid.

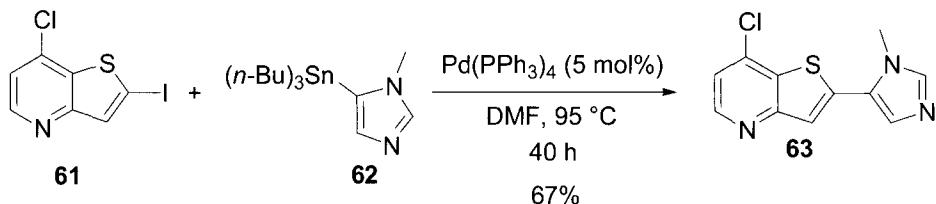
*$\pi$ -Allyl Stille coupling:*<sup>61</sup>



A solution of epoxy acetate **54** (2.07 g, 7.39 mmol, 1.2 equiv.) in 2-methyl-*N*-pyrrolidinone (17 mL) was added via cannula to a reaction vessel containing  $\text{Pd}_2(\text{dba})_3$  (677 mg, 0.739 mmol, 0.12 equiv) and flame dried LiCl (1.25 g, 29.6 mmol, 4.7 equiv.) at 25 °C. A 3 mL wash of 2-methyl-*N*-pyrrolidinone was used to quantitate the transfer. A solution of stannane **53** (2.90 g, 6.31 mmol, 1.0 equiv) and *i*-Pr<sub>2</sub>NEt (2.58 mL, 14.8 mmol, 2.3 equiv.) in 2-methyl-*N*-pyrrolidinone (17 mL) was then added via cannula, again using a 3 mL wash of 2-methyl-*N*-pyrrolidinone to quantitate the transfer. The resultant dark red solution was stirred at 25 °C for 10 min, and then was warmed to 35 °C and stirred for an additional 1.5 h. Upon completion, the reaction contents were cooled to 25 °C, poured into saturated

aqueous NH<sub>4</sub>Cl (100 mL), and extracted with EtOAc ( $3 \times 50$  mL). The combined organic layers were then washed with water (50 mL) and brine (50 mL), dried over MgSO<sub>4</sub> and concentrated. The resultant red-brown residue was purified by flash chromatography over silica gel (hexanes/EtOAc, 1:0 to 4:1) to give Stille coupling product **55** (3.12 g, 96% yield).

*Large scale Stille coupling.*<sup>65</sup>



A 22-L, three-neck, round-bottom flask equipped with a mechanical stirrer was charged with stannane **62** (672 g, 1.81 mol), **61** (535 g, 1.81 mol), Pd(PPh<sub>3</sub>)<sub>4</sub> (105 g, 0.091 mol, 5 mol%) and DMF (2.7 L), and heated to 95 °C under nitrogen. After 40 h, HPLC analysis indicated complete conversion. The reaction mixture was cooled to 10 °C and quenched by the addition of 1 N HCl (5.3 L). EtOAc (4.2 L) was added, and the mixture was filtered. The layers were separated, and the aqueous phase was extracted with two 4-L portions of EtOAc. The combined organic layers were washed with water (3 L). The aqueous extracts were combined, the pH was adjusted to 10–10.5 as needed. HPLC analysis indicated essentially complete extraction of product from the aqueous phase at this point. The organic extracts were combined, washed with water (three portions of 4 L each) and brine (2 L), and concentrated under vacuum to provide a tacky solid. MTBE (4 L) was added, and the mixture was concentrated under vacuum. An additional 3 L of MTBE was then added, and the resulting slurry was stirred for 2 h. The solids were collected by filtration, rinsing with MTBE. After drying at 40 °C under vacuum, the product (**63**) was obtained as an off-white solid (302 g, 1.21 mol, 67% yield).

### 1.1.6.7 References

1. The original report by Stille was between an acid chloride and an organostannane; see section 1.1.6.2.
2. See section 1.1.6.4.
3. Dubbaka, S. R.; Vogel, P. *J. Am. Chem. Soc.* **2003**, *125*, 15292.
4. (a) Kikiukawa, K.; Kono, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* **1983**, *48*, 1333. (b) Kikiukawa, K.; Idemoto, T.; Katayama, A.; Kono, K.; Wada, F.; Matsuda, T. *J. Chem. Soc. Perkin Trans. I* **1987**, 1511. (c) Dughera, S. *Synthesis* **2006**, 1117. For a review on the use of diazonium salts in palladium catalyzed cross-coupling reactions see [R] Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. *Chem. Rev.* **2006**, *106*, 4622.

5. See section 1.1.6.5.
6. [R] (a) Farina, V.; Krishnamurthy, V.; Scott, W. K. *Organic Reactions*, vol. 50, Wiley, New York 1997. [R] (b) Lee, A. S.-Y.; Dai, W.-C. *Tetrahedron* **1997**, *53*, 859.
7. [R] A very thorough investigation organized by type of substrate has been reported in the following book: Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; John Wiley & Sons: New York 1998.
8. See section 1.1.6.4.
9. Azarian, D; Dua, S. S.; Eaborn, C.; Walton, D. R. M. *J. Organomet. Chem.* **1976**, *117*, C55–C57.
10. (a) Kosugi, M.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423. (b) Kosugi, M.; Shimizu, Y.; Migita, T. *J. Organomet. Chem.* **1977**, *129*, C36. For a historical note, see also Kosugi, M.; Fugami, K. *J. Organomet. Chem.* **2002**, *653*, 50.
11. Kosugi, M.; Sasazawa, K.; Shimizu, Y.; Migita, T. *Chem. Lett.* **1977**, 301.
12. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636.
13. For a review, see Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.
14. Also referred sometimes as the Migita-Kosugi-Stille coupling.
15. (a) Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books; Mill Valley, CA 1987. (b) Negishi, E.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393. For an excellent review on the mechanisms of the Stille reaction see: Espinet, P.; Echavarren, A. M. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 4704. See also: Casares, J. A.; Espinet, P.; Salas, G. *Chem. Eur. J.* **2002**, *8*, 4843.
16. Casado, A. L.; Espinet, P.; Gallego, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11771.
17. Casado, A. L.; Espinet, P.; Gallego, A. M.; Martinez-llarduya, J. M. *Chem. Commun.* **2001**, 339.
18. (a) Casado, A. L.; Espinet, P. *J. Am. Chem. Soc.* **1998**, *120*, 8978. (b) Casado, A. L.; Espinet, P.; Gallego, A. M. *J. Am. Chem. Soc.* **2000**, *122*, 11771. (c) Casado, A. L.; Espinet, P.; Gallego, A. M.; Martinez-llarduya, J. M. *Chem. Commun.* **2001**, 339. (d) Amatore, C.; Bahsoun, A. A.; Jutand, A.; Meyer, G.; Ntepe, A. N.; Ricard, L. *J. Am. Chem. Soc.* **2003**, *125*, 4212. (e) Santos, L. S.; Rosso, G. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2007**, *72*, 5809. (f) Perez-Temprano, M H.; Nova, A.; Casares, J. A.; Espinet, P. *J. Am. Chem. Soc.* **2008**, *130*, 10518.
19. Vicente, J.; Arcas, A.; Bautista, D.; Jones, P. G. *Organometallics* **1997**, *16*, 2127.
20. For a review on the influence of chloride ions in palladium catalysed reaction see: Jutand, A. *Appl. Organometal. Chem.* **2004**, *18*, 574.
21. Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.
22. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
23. (a) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973. (b) Takeda, T.; Matsunaga, K.-I.; Kabasawa, Y.; Fujiwara, T. *Chem Lett.* **1995**, 771. (c) Piers, E. Romero, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 1215. (d) Kang, S. K.; Kim, J. S.; Choi, S. C. *J. Org. Chem.* **1997**, *62*, 4208. (e) Kang, S. K.; Kim, J. S.; Yoon, S. K.; Lim, K. H.; Yoon, S. S. *Tetrahedron Lett.* **1998**, *39*, 3011. (f) Kang, S. K.; Kim, W. Y.; Jiao, X. G. *Synthesis* **1998**, 1252. (g) Naso, F.; Babudri, F.; Farinola, G. M. *Pure Appl. Chem.* **1999**, *71*, 1485.
24. Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.
25. Roethle, P. A.; Chen, I. T.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 8960.
26. Han, X.; Stoltz, B. M.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 7600.
27. Nielsen, T. E.; Le Quement, S.; Juhl, M.; Tanner, D. *Tetrahedron* **2005**, *61*, 8013.
28. Kang, S. K.; Kim, J. S.; Choi, S. C. *J. Org. Chem.* **1997**, *62*, 4208.
29. (a) Percec, V.; Bae, J. Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 6895. (b) Cui, D.-M.; Hashimoto, N.; Ikeda, S.-I.; Sato, Y. *J. Org. Chem.* **1995**, *60*, 5752. (c) Shirakawa, E.; Yamasaki, K.; Hiyama, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2449. (d) Shirakawa, E.; Yamasaki, K.; Hiyama, T. *Synthesis* **1998**, 1544.
30. Vedejs, E.; Haight, A. R.; Moss, W. O. *J. Am. Chem. Soc.* **1992**, *114*, 6556. See also Brown, J. M.; Pearson, M.; Jastrzebski, J. T. B. H.; van Koten, G. *J. Chem. Soc., Chem. Commun.* **1992**, 1440.

31. Garcia Martinez, A.; Osio Barcina, J.; del Rosario Colorado Heras, M.; de Fresno Cerezo, A. *Org. Lett.* **2000**, 2, 1377.
32. Grasa, G. A.; Nolan, S. P. *Org. Lett.* **2001**, 3, 119.
33. (a) Herve, A.; Rodriguez, A. L.; Fouquet, E. *J. Org. Chem.* **2005**, 70, 1953. See also Bourdier, T.; Huiban, M.; Huet, A.; Sobrio, F.; Fouquet, E.; Perrio, C.; Barré, L. *Synthesis* **2008**, 978.
34. (a) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed. Engl.* **2004**, 43, 1132. (b) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Chem. Eur. J.* **2005**, 11, 3294.
35. Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1999**, 38, 2411. For a review on the palladium catalyzed coupling reactions of aryl chlorides see [R] Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **2002**, 41, 4176.
36. Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, 124, 6343.
37. Menzel, K.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, 125, 3718.
38. [R] (a) Luh, T.-Y.; Leung, M.-K.; Wong, K.-T. *Chem. Rev.* **2000**, 100, 3187. (b) Cardenas, D. J. *Angew. Chem., Int. Ed. Engl.* **2003**, 42, 384.
39. (a) for  $\alpha$ -bromoketones see: Kosugi, M.; Takano, I.; Sakurai, M.; Sano, H.; Migita, T. *Chem. Lett.* **1984**, 1221. (b) for  $\alpha$ -halolactones see: Simpson, J. H.; Stille, J. K. *J. Org. Chem.* **1985**, 50, 1759. (c) for 1-bromo-1-phenylethane see: Sustmann, R.; Lau, J.; Zipp, M. *Tetrahedron Lett.* **1986**, 27, 5207. (d)  $\alpha$ -chloroether see: Bhatt, R. K.; Shin, D.-S.; Falck, J. R.; Mioskowski, C. *Tetrahedron Lett.* **1992**, 33, 4885. (e) for fluorinated alkyl iodides see: Shimizu, R.; Fuchikami, T. *Tetrahedron Lett.* **1996**, 37, 8405 and Shimizu, R.; Fuchikami, T. *Tetrahedron Lett.* **2001**, 42, 6891.
40. Tang, H.; Menzel, K.; Fu, G. C. *Angew. Chem. Int. Ed. Engl.* **2003**, 42, 5079.
41. For a review on the catalysts developed for the cross coupling of non activated alkyl halides see also: [R] Frisch, A. C.; Beller, M. *Angew. Chem., Int. Ed. Engl.* **2005**, 44, 674.
42. Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, 127, 510.
43. (a) Shirakawa, E.; Yamasaki, K.; Hiyama, T. *J. Chem. Soc., Perkin Trans. I* **1997**, 2449. (b) Shirakawa, E.; Yamasaki, K.; Hiyama, T. *Synthesis* **1998**, 1544. See also, Cui, D.-M.; Hashimoto, N.; Ikeda, S.-I.; Sato, Y. *J. Org. Chem.* **1995**, 60, 5752.
44. [R] Bulten, E. J.; Meinema, H. A. *Metals and their Compounds in the Environment*; Merian E.; Ed.; VCH: New York, **1991**; chapter II, 30, p1243.
45. [R] Davie, A. G.; Smith, P. G. *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A., Ed.; Pergamon, New York, **1982**, vol. 2, chapter 11.
46. See for example: (a) Roschchin, A.; Bumagin, N. A.; Beletskaya, I. P. *Tetrahedron Lett.* **1995**, 36, 125. (b) Rai, R.; Aubrecht, K. B.; Collum, D. B. *Tetrahedron Lett.* **1995**, 36, 3111. For a review on the developments of palladium catalyzed reactions in aqueous media see also: Genet, J.-P.; Savignac, M. *J. Organomet. Chem.* **1999**, 576, 305.
47. [R] (a) For a recent review see: Testero, S. A.; Mata, E. G. *J. Comb. Chem.* **2008**, 10, 487. (b) Gerlach, M.; Jordens, F.; Kuhn, H.; Neumann, W. P.; Peterseim, M. *J. Org. Chem.* **1991**, 56, 5971. (c) Kuhn, H.; Neumann, W. P. *Synlett* **1994**, 123. (d) Deshpande, M. S. *Tetrahedron Lett.* **1994**, 35, 5613. (e) Hernan, A. G.; Guillot, V.; Kuvshinov, A.; Kilburn, J. D. *Tetrahedron Lett.* **2003**, 44, 8601. (f) Chrétien, J.-M.; Mallinger, A.; Zammattio, F.; Le Grogne, E.; Paris, M.; Montavon, G.; Quintard, J.-P. *Tetrahedron Lett.* **2007**, 48, 1781. (g) Lau, K. C. Y.; Chiu, P. *Tetrahedron Lett.* **2007**, 48, 1813. (h) Zaho, H.; Wang, Y.; Sha, J.; Sheng, S.; Mingzhong, C. *Tetrahedron* **2008**, 64, 7517. (i) Charette, A. B.; Roy, M.-N. *Synthesis and Applications of New and Improved Tetraarylphosphonium-supported Tin Reagents*; abstract of the 236<sup>th</sup> ACS national meeting, Philadelphia, PA, August 17-21 2008.
48. Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Murphy, F. *Angew. Chem., Int. Ed. Engl.* **1998**, 37, 2534.
49. Vitz, J.; Mac, D. H.; Legoupy, S. *Green Chem.* **2007**, 9, 431. For a review on the use of ionic liquid in organometallic catalysis see: [R] Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, 102, 3667.
50. Hoshino, M.; Degenkolb, P.; Curran, D. P. *J. Org. Chem.* **1997**, 62, 8341.
51. Larhed, M.; Hoshino, M.; Hadida, S.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **1997**, 62, 5583.
52. Appukuttan, P.; Van der Eycken, E. *Eur. J. Org. Chem.* **2008**, 1133.

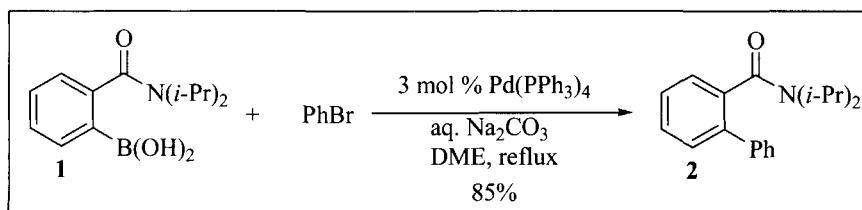
53. (a) Gallagher, W. P.; Maleczka, Jr. R. E. *J. Org. Chem.* **2005**, *70*, 841. (b) Maleczka, Jr. R. E.; Gallagher, W. P. *Org. Lett.* **2001**, *3*, 4173.
54. For the Sn–O route see: (a) Maleczka, Jr. R. E.; Gallagher, W. P.; Terstiege, I. *J. Am. Chem. Soc.* **2000**, *122*, 384. (b) Gallagher, W. P.; Terstiege, I.; Maleczka, Jr. R. E.; *J. Am. Chem. Soc.* **2001**, *123*, 3194.
55. Kelly, T. R.; Li, Q.; Bhushan, V. *Tetrahedron Lett.* **1990**, *31*, 161. For additional examples see: Mori, M.; Kaneta, N.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 3486. Fukuyama, Y.; Yaso, H.; Mori, T.; Takahashi, H.; Minami, H.; Kodama, M. *Heterocycles* **2001**, *54*, 259. Yue, W. S.; Li, J. *J. Org. Lett.* **2002**, *4*, 2201.
56. Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419.
57. Shair, M. D.; Yoon, T.-Y.; Mosny, K. K.; Chou, S. J.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1996**, *118*, 9509.
58. [R] (a) For a review on the Stille reaction in the synthesis of natural products see: De Souza, M. V. N. *Current Organic Synthesis* **2006**, *3*, 313. [R] (b) For a review on the palladium catalyzed cross coupling reactions in total synthesis see: Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 4442. [R] (c) For reviews on the intramolecular Stille reaction in synthesis see: Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235. Pattenden, G.; Sinclair, D. J. *J. Organomet. Chem.* **2002**, *653*, 261.
59. Gyorkos, A. C.; Stille, J. K.; Hegedus, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 8465.
60. Hanessian, S.; Ma, J.; Wang, W. *J. Am. Chem. Soc.* **2001**, *123*, 10200.
61. Snyder, S. A.; Corey, E. J. *J. Am. Chem. Soc.* **2006**, *128*, 740.
62. Tambar, U. K.; Kano, T.; Zepernick, J. F.; Stoltz, B. M. *Tetrahedron Lett.* **2007**, *48*, 345.
63. Han, X.; Corey, E. J. *Org. Lett.* **1999**, *1*, 1871.
64. For examples see: (a) Kosugi, M.; Tamura, H.; Sano, H.; Migita, T. *Chem. Lett.* **1987**, 193. (b) Larock, R. C.; Lee, N. H. *J. Org. Chem.* **1991**, *56*, 6253. (c) Grigg, R.; Redpath, J.; Sridharan, V.; Wilson, D. *Tetrahedron Lett.* **1994**, *35*, 4429.
65. Ragan, J. A.; Raggon, J. W.; Hill, P. D.; Jones, B. P.; McDermott, R. E.; Munchhof, M. J.; Marx, M. A.; Casavant, J. M.; Cooper, B. A.; Doty, J. L.; Lu, Y. *Org. Proc. Res. & Dev.* **2003**, *7*, 676.

## 1.1.7 The Suzuki Reaction

**John P. Wolfe and Josephine S. Nakhla**

### 1.1.7.1 Description

The Suzuki reaction (also referred to as the Suzuki–Miyaura reaction) is the palladium-catalyzed cross-coupling of an alkenyl-, aryl-, or heteroaryl halide or pseudohalide ( $R-X$ ) with an alkyl, alkenyl, aryl, or heteroaryl boron reagent ( $R'-BY_2$ ). This transformation leads to formation of a carbon–carbon bond with stereospecific and regiospecific replacement of  $X$  with  $R'$ .<sup>1–9</sup> In a representative example, boronic acid **1** was coupled with bromobenzene in the presence of aqueous  $Na_2CO_3$  and 3 mol%  $Pd(PPh_3)_4$  in refluxing DME to provide biaryl derivative **2** in 85% yield.<sup>10</sup>



### 1.1.7.2 General Trends

Through extensive experimentation, several reactivity trends have been established that hold true for most Suzuki coupling reactions.<sup>1–9</sup> In general, the order of reactivity of the electrophilic component is alkenyl–X > aryl–X > alkyl–X. The nature of the halogen also has an impact on reactivity, with the general trend of I > Br ~ OTf >> Cl. In addition, sterically hindered electrophiles are typically less reactive than unhindered derivatives. These trends can be exploited for selective coupling of substrates bearing two or more different halogens, and in some instances selectivity can be obtained in reactions of substrates that contain two or more of the same halogen.<sup>11</sup> In terms of the nucleophilic component, steric hindrance also leads to decreased reactivity, and the order of reactivity with respect to carbon hybridization is  $spC-B > sp^2C-B > sp^3C-B$ .

### 1.1.7.3 Comparison with Other Cross-Coupling Reactions

The Suzuki reaction is a member of a class of transformations that are typically referred to as cross-coupling reactions,<sup>12–15</sup> which involve the

coupling of an aryl halide or related electrophile with a main-group organometallic reagent. Many of these processes are also named reactions, and the most common variations employ Grignard reagents (Kumada coupling-chapter 1.1.3),<sup>16,17</sup> organotin reagents (Stille Coupling-chapter 1.1.6),<sup>18</sup> organozinc reagents (Negishi coupling-chapter 1.1.4),<sup>19,20</sup> or organosilicon reagents (Hiyama coupling-chapter 1.1.2)<sup>21,22</sup> as the main group organometallic species.

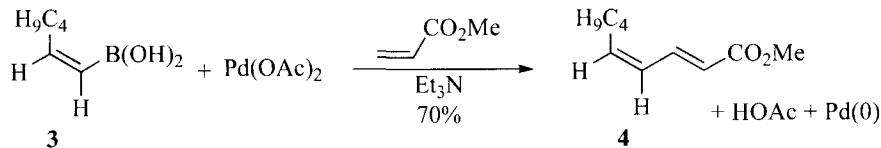
The Suzuki reaction has many advantages over these related cross-coupling reactions. A large number of organoboron coupling partners are commercially available, including a vast array of heteroaromatic derivatives. The preparation of organoboron compounds can also be accomplished through several different methods, the most common of which involves treatment of a Grignard or organolithium reagent with a trialkoxyboron derivative.<sup>6,23</sup> The synthesis of organoboron reagents can be achieved under mild conditions through Pd-catalyzed coupling reactions of aryl/heteroaryl halides with bis(pinacolato)diboron,<sup>24</sup> and alkylboron reagents can be generated *in situ* from readily available alkene precursors via hydroboration.<sup>3</sup> In addition, the synthesis of organoboron reagents has also been accomplished through C–H bond functionalization.<sup>25,26</sup> The organoboron reagents are relatively non-toxic, particularly in comparison to organotin reagents. Moreover, the boron-containing byproducts of the reactions can easily be separated from the desired product by extraction with aqueous base. In contrast, removal of tin-containing byproducts is frequently a problem in Stille coupling reactions.<sup>18</sup> The organoboron reagents do not react with most common functional groups, and Suzuki reactions can be conducted under relatively mild conditions. Thus, the functional group tolerance of Suzuki reactions is usually higher than related Kumada coupling or Negishi coupling processes. These features make the Suzuki reaction one of the most valuable and extensively used methods for C–C bond formation in organic synthesis.<sup>1–21</sup>

Although the Suzuki reaction has many advantages over other cross-coupling reactions, there are three principal limitations of this method. The Suzuki reaction requires the use of either an inorganic base or fluoride, which can be problematic with some functionalized substrates. However, use of anhydrous conditions can help to mitigate some of these complications. The organoboron reagents can be difficult to purify, although in many cases use of high-purity reagents is not essential. Finally, in contrast to organostannanes, which are relatively nonpolar, and can be carried several steps through a synthetic sequence, organoboron reagents are fairly polar, and react with many commonly used reagents (e.g., oxidants, nucleophiles, bases). Recent studies described below have led to the development of new

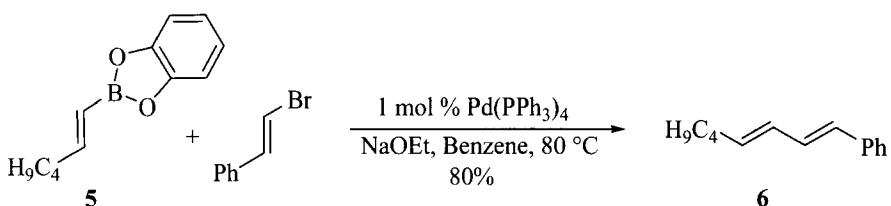
organoboron reagents that are more robust, and more amenable to use in multistep synthetic sequences.

#### 1.1.7.4 *Historical Perspective*

Two significant examples of Pd-catalyzed or mediated cross-coupling type reactions of organoboron compounds were reported prior to Suzuki's 1979 disclosure of what has become known as the Suzuki reaction. The first example was described by Heck in 1975 in the context of studies on the mechanism of Pd-catalyzed coupling reactions between alkenyl halides and activated alkenes. As shown below, treatment of alkenyl boronic acid **3** with methyl acrylate in the presence of stoichiometric  $\text{Pd}(\text{OAc})_2$  generated conjugated diene **4** in 70% yield.<sup>27</sup> This reaction likely proceeds via transmetalation of the boronic acid with  $\text{Pd}(\text{OAc})_2$ , insertion of the alkene into the Pd–C bond of the intermediate alkenyl palladium complex, and  $\beta$ -hydride elimination to provide the diene product. Importantly, the stereochemistry of the alkenylboronic acid was transferred to the diene products. A second example, which involved a Pd-catalyzed coupling of an alkynyl(tributyl)borate with iodobenzene was described at an American Chemical Society meeting by Negishi in 1977 and subsequently published in a book chapter on transition-metal catalyzed C–C bond formation.<sup>28</sup>

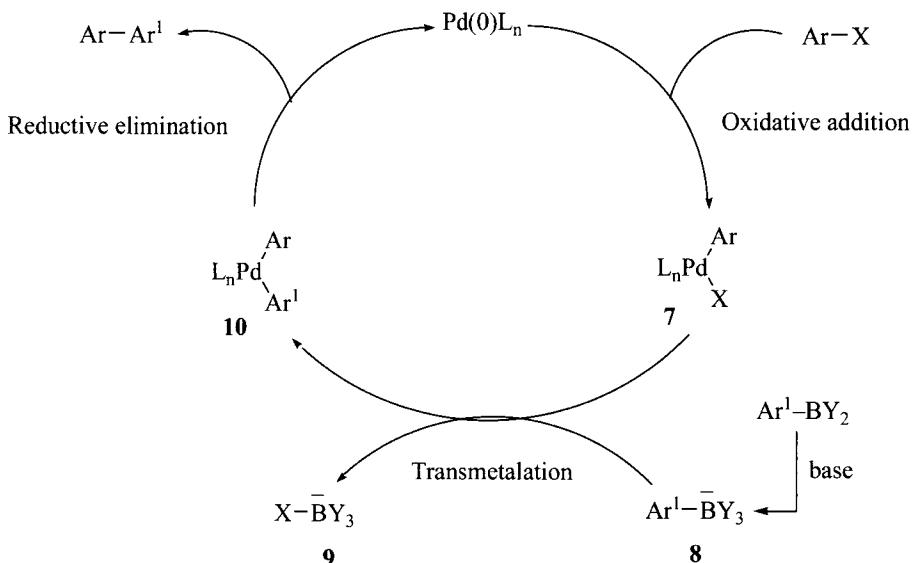


In 1979, Miyaura, Yamada, and Suzuki demonstrated that 1-alkenylboranes react with 1-alkenyl or 1-alkynyl halides in the presence of a base using  $\text{Pd}(\text{PPh}_3)_4$  as a catalyst to afford diene or enyne products.<sup>29</sup> For example, treatment of (*E*)- $\beta$ -bromostyrene with 1.1. equiv of alkenylboron reagent **5** in the presence of 2 equiv  $\text{NaOEt}$  and 1 mol%  $\text{Pd}(\text{PPh}_3)_4$  afforded diene **6** in 80% yield. The use of base was essential for the success of these transformations, as the weakly nucleophilic organoboronic acid or ester derivatives do not undergo transmetalation to  $\text{L}_n\text{Pd}(\text{Ar})(\text{X})$  complexes at sufficient rates to facilitate catalysis.<sup>29,30</sup> In contrast, the reaction of the organoboron reagent with base leads to generation of a highly nucleophilic boron “ate” complex, which undergoes facile transmetalation with Pd(II).



Since the initial communication by Suzuki and coworkers, the Suzuki reaction has evolved into one of the most commonly used methods for the construction of C–C bonds. The Suzuki reaction has found many applications in the synthesis of biologically active molecules<sup>3,31</sup> and useful materials.<sup>32,33</sup> The reactions are amenable to scale-up, and are broadly employed in the pharmaceutical industry.<sup>34</sup>

### 1.1.7.5 Mechanism

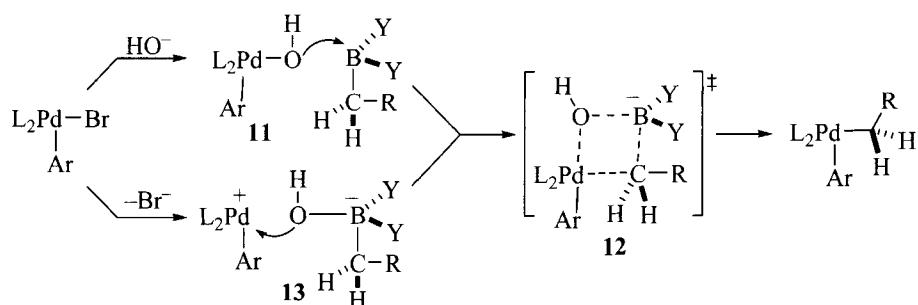


The mechanism of the Suzuki reaction is believed to be similar to that of other well-established Pd-catalyzed cross-coupling reactions.<sup>12–14,35</sup> The active  $\text{L}_n\text{Pd}(0)$  catalyst is often generated *in situ* by coordination of added phosphine ligands to a stable source of Pd(0), such as  $\text{Pd}_2(\text{dba})_3$ . In cases where Pd(II) complexes such as  $\text{Pd}(\text{OAc})_2$  are used as precatalysts, these species are converted to the active  $\text{L}_n\text{Pd}(0)$  species under the reaction conditions. The catalytic cycle then commences with oxidative addition of the aryl halide (or related electrophile) to Pd(0), which generates Pd(II) intermediate 7.<sup>36</sup> Reaction of the organoboron reagent with base leads to

formation of borate **8**,<sup>37</sup> which undergoes transmetalation with **7** to afford Pd(Ar)(Ar<sup>1</sup>) complex **10** and the boron-containing byproduct **9**. Reductive elimination from **10** forms the C–C bond with concomitant regeneration of the Pd(0) catalyst. Key intermediates **7** and **10** in this catalytic cycle have been observed in the coupling reaction of 3-bromopyridine with phenylboronic acid.<sup>38</sup> Detailed kinetic studies on the Pd-catalyzed Suzuki coupling reaction have also been conducted, and indicate that the turnover-limiting step of the catalytic cycle is substrate-dependent.<sup>39</sup>

As noted above, the principal difference between the Suzuki reaction and other Pd-catalyzed cross coupling processes (e.g., Stille coupling of organostannanes with aryl/alkenyl halides or Negishi coupling of organozinc reagents with similar electrophiles) is the use of an organoboron reagent as the main-group coupling partner. Although the mechanisms of the various Pd-catalyzed cross-coupling reactions share many common features, differences between these processes are apparent in the transmetalation steps of the catalytic cycles.

Several groups have conducted studies to elucidate specific details concerning the mechanism of transmetalation from boron to palladium. Evidence suggests that two different pathways may be operable in this process. The first involves exchange of hydroxide with halogen to generate palladium hydroxide **11**, which then undergoes transmetalation with the neutral organoboron reagent through a four-centered transition state (**12**).<sup>40</sup> Alternatively, transmetalation may occur through reaction of the borate complex **13** with a cationic Pd(II) intermediate that derives from dissociation of the halide from the oxidative addition complex **7** shown above.<sup>40,41</sup> The preference for reactivity via one path over another may depend on the Lewis acidity of the organoboron reagent, along with other parameters of individual reactions. When alkylboron reagents are employed transmetalation occurs with retention of stereochemistry.<sup>40,42</sup>



Interestingly, the relative reactivity of aryl bromides vs. aryl triflates in Suzuki coupling reactions differs from other Pd-catalyzed cross-coupling

processes.<sup>43</sup> Brown has demonstrated that 2- and 3-bromophenyl triflate derivatives undergo selective substitution of the triflate group in Stille, Negishi, and Kumada coupling reactions, as well as Pd-catalyzed Heck reactions and *N*-arylation reactions. In contrast, the bromide group is selectively replaced in the Suzuki coupling. The exact origin of this effect remains unclear, but could arise from differences in oxidative addition, or differences in transmetalation if oxidative addition is reversible under the reaction conditions.<sup>44</sup>

### 1.1.7.6 *Variations and Improvements*

#### *New, Highly Active Catalysts for Suzuki Coupling Reactions*

Since the initial report by Suzuki in 1979, the optimization of reaction parameters, such as base and solvent, has been explored by many different groups.<sup>1–6,31</sup> Replacement of the base with KF or CsF has been demonstrated to improve functional group tolerance in some systems.<sup>45</sup> Use of microwave heating,<sup>46–48</sup> water<sup>49</sup> or ionic liquids<sup>50,51</sup> as solvents, solid supports,<sup>52,53</sup> or other non-traditional conditions<sup>54</sup> can also provide advantages. However, the research that has arguably led to the broadest expansion of scope has been focused on catalyst development.

Although many Suzuki coupling reactions can be effected with triphenylphosphine-based catalysts, which were traditionally used in these transformations, these catalysts suffer from several key limitations. In general, the reactivity of  $\text{Pd}(\text{PPh}_3)_4$  and related triphenylphosphine palladium complexes is relatively low, and it is generally not feasible to employ these catalysts for transformations of unreactive substrates such as aryl chlorides, or very hindered aryl halides or boronic acids. In addition, it is difficult to carry out Suzuki reactions at low catalyst loadings with triphenylphosphine-derived catalysts, and reactions of many interesting heterocyclic compounds are also challenging. In order to address these limitations, many studies over the past ten years have focused on the development of new ligands and/or catalysts for palladium-catalyzed Suzuki coupling reactions. The description of every single ligand or catalyst that has been surveyed falls beyond the scope of this chapter. However, representative examples of several new catalysts and their utility in traditionally difficult Suzuki coupling reactions are outlined below.

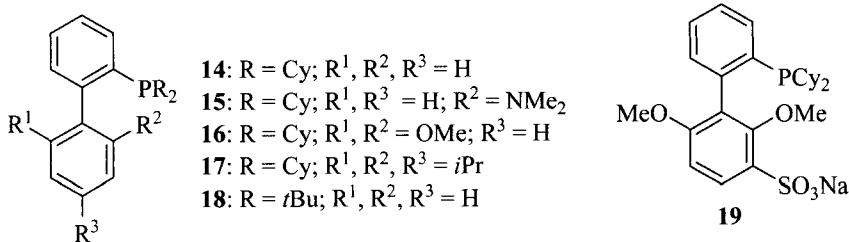
In addition to recent work on the development of new homogenous catalysts, several groups have also explored the utility of heterogeneous catalyst systems for Suzuki coupling reactions.<sup>55,56</sup> In some instances these catalysts can be recovered and reused after catalytic reactions. However, in many cases the use of added phosphine ligands is required, and it is not clear

these catalysts are effective with a similarly broad range of substrates as the homogenous catalysts described below.

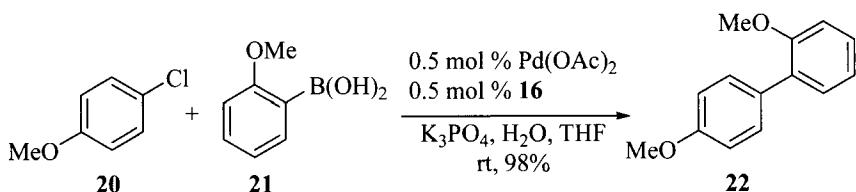
### *Suzuki Coupling Reactions of Aryl Chlorides*

The low reactivity of aryl chloride substrates, which are cheaper and often more readily available than the analogous aryl iodides or bromides, has been a longstanding problem in cross-coupling chemistry.<sup>57,58</sup> This problem arises from the fact that aryl chlorides undergo oxidative addition to Pd(0) much more slowly than aryl iodides or bromides. Although it has been known for some time that the rate of oxidative addition to Pd(0) can be accelerated by using electron-rich ligands, many of these ligands also slow the rate of the key C–C bond forming reductive elimination step of the catalytic cycle. A solution to this problem involves the use of electron-rich ligands that are also sterically bulky, as the size of the ligand can increase the rate of the reductive elimination step.<sup>59</sup> This concept has led to the development of several different new catalysts for Suzuki coupling reactions.

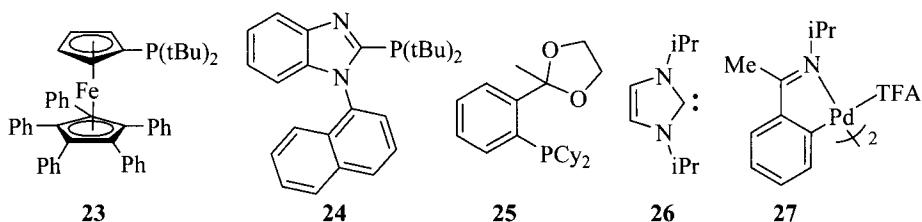
The first general catalyst for Suzuki coupling reactions of aryl chlorides was reported by Buchwald in 1998, and featured a new type of biaryl(dialkyl)phosphine ligand (**15**).<sup>59</sup> In subsequent years, Buchwald has expanded on this general structure to develop a family of ligands with broad utility in Suzuki coupling reactions (**14–19**).<sup>60–63</sup>



Ligand **19** is water soluble, and has been employed in Suzuki coupling reactions conducted in aqueous media.<sup>64</sup> Ligand **17** provides optimal results in Suzuki coupling reactions of aryl tosylates and aryl benzenesulfonates.<sup>65</sup> Ligand **16** is thought to have the greatest substrate scope of the Buchwald biaryl-phosphine derivatives, and is widely used in both academia and industry.<sup>62</sup> In a representative example, the reaction of 4-chloroanisole (**20**) with 2-methoxyphenyl boronic acid (**21**) using 0.5 mol% of a palladium catalyst ligated by **16** provided **22** in 98% yield in only 3 h at rt.<sup>62</sup>



Several other research groups have also explored the use of bulky, electron-rich phosphine ligands for Suzuki coupling reactions. Ligands **23** (Hartwig),<sup>66</sup> **24** (Beller),<sup>67</sup> **25** (Guram),<sup>68</sup> and Pt-Bu<sub>3</sub> (Fu)<sup>69</sup> also exhibit good reactivity in transformations involving aryl chloride substrates. Hartwig has also demonstrated that dimeric (LPdBr)<sub>2</sub> complexes (L = Pt-Bu<sub>3</sub> or PAd<sub>3</sub>) are effective catalysts for Suzuki coupling reactions of aryl chlorides.<sup>70</sup> In addition, *N*-heterocyclic carbene ligands (e.g., **26**) have been successfully employed in Pd-catalyzed Suzuki coupling reactions of aryl chlorides,<sup>71–73</sup> as have palladacyclic catalysts (e.g., **27**).<sup>74–76</sup>

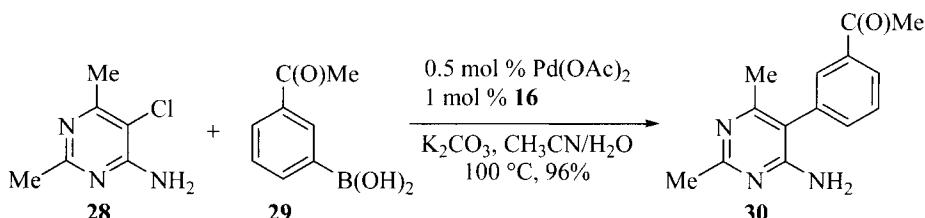


The new catalysts and ligands described above are also generally effective in Suzuki coupling reactions of aryl bromides and iodides. In addition, several of the catalysts derived from these ligands are sufficiently active and long-lived to allow for use of low levels of palladium (< 0.1 mol%), which is of great significance for large scale applications.<sup>60,73,74</sup>

#### Suzuki Coupling Reactions of Heteroaromatic Compounds

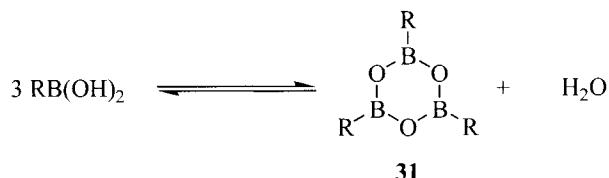
Suzuki coupling reactions of heteroaromatic halides and/or heteroaryl boronic acids are often challenging transformations. Although some transformations can be effected with triphenylphosphine-derived catalysts,<sup>77</sup> many heteroarenes can coordinate strongly to palladium, which often leads to catalyst poisoning or low reactivity. Fortunately, several of the catalyst systems/ligands described above are also highly effective for Suzuki coupling reactions of heteroaromatic systems, and the Buchwald ligands appear to have particularly good generality.<sup>78,79</sup> For example, the coupling of boronic acid **29** with **28** provided **30** in 96% yield when a catalyst composed of Pd(OAc)<sub>2</sub>/**16** was employed. In addition to the ligands noted above,

$\text{PCy}_3$ ,<sup>80</sup> *p*-substituted phenyl( $\text{PR}_2$ ) ligands ( $\text{R} = \text{Cy}$  or  $t\text{-Bu}$ ),<sup>81</sup> sulfonated fluorenyl dialkylphosphines,<sup>82</sup> and diaryl- or dialkylphosphine oxides<sup>83</sup> have also shown good reactivity in Suzuki reactions of heteroaryl halides/boronic acids.



### Organotrifluoroborate Reagents for Suzuki Coupling Reactions

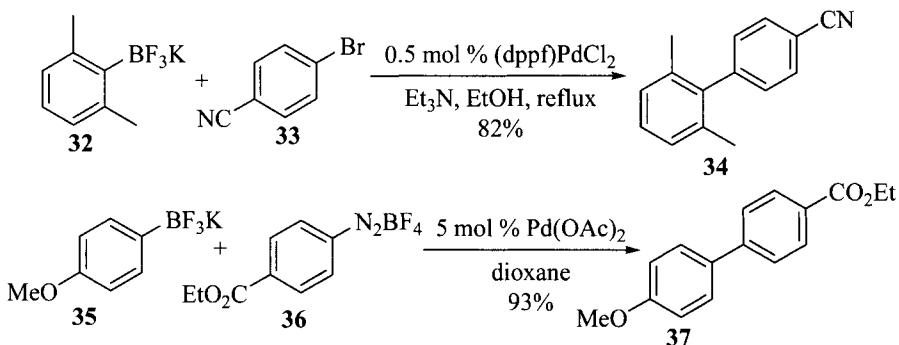
Classical Suzuki coupling reactions typically employ either boronic acids, or boronate esters or trialkylboranes (derived from hydroboration reactions) as the nucleophilic coupling partner. However, there are several problems associated with the use, purification, and/or handling of these reagents. For example, boronic acids can be quite difficult to purify, and can undergo relatively facile dehydration to generate less reactive cyclic trimers (e.g., 31). Boronic acids can also undergo protiodeboronation or homocoupling under typical Suzuki reaction conditions, and vinylboronic acid readily polymerizes. Some of these limitations may be overcome by use of pinacol boronate esters, which are generated by reaction of a boronic acid with pinacol. However, these reagents tend to be more expensive and less reactive than boronic acids, and their use is less atom-economical. Finally, it is challenging to carry trivalent boron compounds through multi-step syntheses due to their sensitivity to a variety of common reagents, such as oxidizing agents and Lewis bases.



In recent years, the use of organotrifluoroborate reagents ( $\text{RBF}_3\text{K}$ ) in Suzuki coupling reactions has been shown to solve many of the problems described above. These reagents were originally developed by Vedejs in 1995 as air-stable precursors to aryl(difluoro)boron Lewis acids,<sup>84</sup> and are typically prepared in high yield by treatment of boronic acids or esters with

$\text{KHF}_2$ .<sup>84–87</sup> These reagents are free-flowing solids that can easily be purified by crystallization. In addition, they have greatly increased stability to oxidants, nucleophiles, and bases, and are resistant to trimerization.

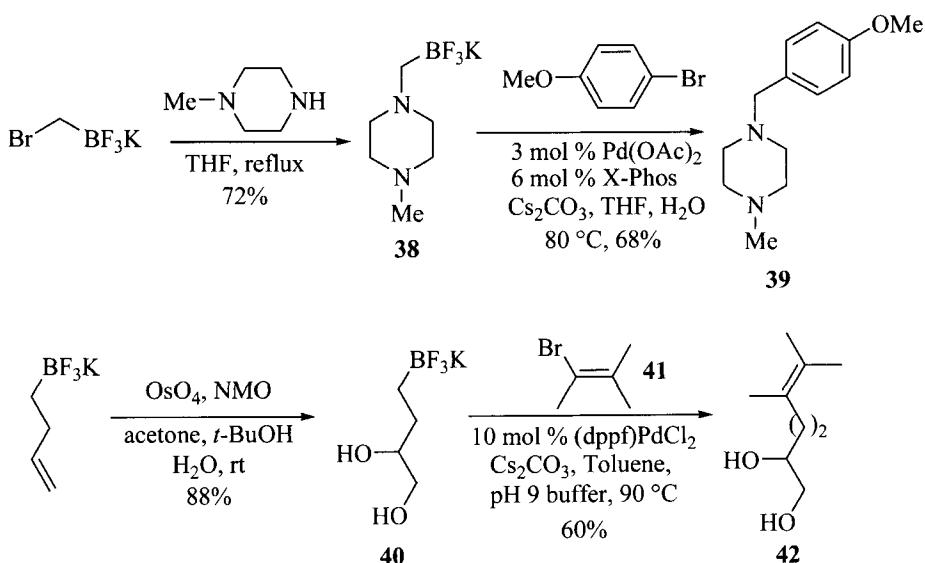
Organotrifluoroborate reagents were first employed in Suzuki coupling reactions of aryl diazonium salts by Genet<sup>86,88</sup> and diaryl iodonium salts by Xia and Chen.<sup>89</sup> Although these electrophiles can be efficiently transformed,<sup>90</sup> their use is relatively uncommon due to cost and safety issues. More recent studies by Molander have led to a significant expansion of the scope of this chemistry to include aryl/alkenyl halide and sulfonate electrophiles.<sup>87</sup> In representative examples, the coupling of **32** with **33** and **35** with **36** afforded **34** and **37** in good yields.<sup>86,91</sup> Interestingly, the coupling reactions of aryl halides require addition of base (e.g.,  $\text{Et}_3\text{N}$  or  $\text{K}_2\text{CO}_3$ ) to the reaction mixture, whereas transformations of the apparently more reactive aryl diazonium salts or diaryl iodonium salts are effective in the absence of base.



The scope of the Suzuki coupling reactions of organotrifluoroborate salts is quite broad, and examples of aryl–aryl, aryl–alkenyl, aryl–benzyl, aryl–alkyl, alkenyl–aryl, and alkenyl–alkenyl couplings have been described. These reactions can also be conducted with heteroaryl halides and/or heteroaryl trifluoroborates, and are highly tolerant of functional groups, such as ethers, nitriles, carbonyls, and halogens.<sup>87</sup> It is important to note that silyl ethers are also stable to the reaction conditions, even though fluoride ions may be present. The use of potassium vinyltrifluoroborate, which does not undergo polymerization that prohibits use of the analogous boronic acid, has also been realized. In addition, the transformations can be conducted using air stable, isolable alkyl trifluoroborate salts.<sup>92</sup> This allows for the installation of methyl groups via Suzuki coupling, which is not easily accomplished with other readily available organoboron reagents.

In addition to exhibiting excellent functional group tolerance, the organotrifluoroborate reagents are also stable towards many commonly used

reagents and transformations, including nucleophilic substitution reactions,<sup>93,94</sup> azide dipolar cycloaddition reactions,<sup>95</sup> lithiation/alkylation reactions,<sup>96</sup> oxidations,<sup>97</sup> epoxidations,<sup>98</sup> dihydroxylations,<sup>99</sup> and Wittig or Horner–Wadsworth–Emmons olefinations.<sup>100</sup> For example, treatment of bromomethylpotassium trifluoroborate with *N*-methylpiperazine afforded **38** in 72% yield. Subsequent cross-coupling of **38** with 4-bromoanisole provided **39** in 68% yield.<sup>94</sup> Similarly, treatment of potassium 3-buteneitrifluoroborate with OsO<sub>4</sub>/NMO gave diol **40**, which was coupled with alkenyl bromide **41** to generate **42** in 60% yield.<sup>99</sup> These transformations have great potential utility in multistep complex molecule synthesis.

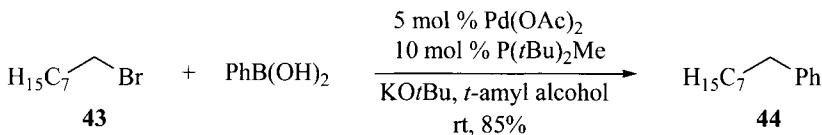


### Suzuki Coupling Reactions of Unactivated Alkyl Halides and Sulfonates

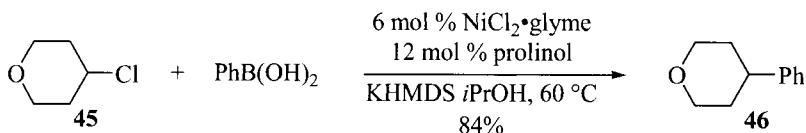
Although cross-coupling reactions of aryl and alkenyl halides have been broadly studied and applied to numerous synthetic challenges over the past thirty years, the use of alkyl halides as electrophiles in these reactions was seldom reported. Cross-coupling reactions of alkyl halides are quite challenging to effect due to the fact that they are less reactive than aryl/alkenyl halides towards oxidative addition to Pd(0), and the resulting alkylpalladium(II)halide species undergo relatively facile competing  $\beta$ -hydride elimination that leads to alkene formation rather than cross coupling. Prior to 2001, most examples of cross-coupling reactions of alkyl halides involved substrates that did not contain  $\beta$ -hydrogens and/or were activated towards oxidative addition, such as benzylic halides or iodocyclopropanes.<sup>101,102</sup> In 1992 the first examples of Suzuki coupling

reactions of alkyl halides were reported by Suzuki and Miyaura,<sup>103</sup> although the scope of these transformations was limited to primary alkyl iodide substrates.

In 2001 Fu described the first examples of Pd-catalyzed Suzuki coupling reactions of primary alkyl bromides with alkyl-9-BBN reagents.<sup>104</sup> The following year the scope of these transformations was extended to allow for use of aryl and alkenylboronic acids as nucleophiles,<sup>105</sup> and alkyl tosylates as electrophiles.<sup>106</sup> The key for the success of these reactions was use of either PCy<sub>3</sub> (alkyl-9-BBN reagents) or P(*t*-Bu)<sub>2</sub>Me (boronic acids) as ligands for palladium; other ligands provided unsatisfactory yields. In a representative example, *n*-octyl bromide (**43**) was coupled with phenylboronic acid to afford **44** in 85% yield using a catalyst composed of Pd(OAc)<sub>2</sub> and P(*t*-Bu)<sub>2</sub>Me. Subsequent studies have indicated that NHC-ligated palladium catalysts also provide good results for some of these transformations.<sup>107,108</sup>



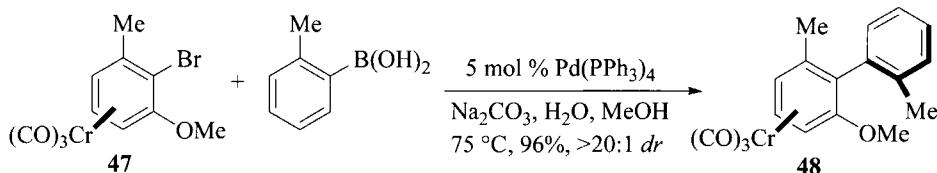
Suzuki Coupling reactions of secondary alkyl halides were not effective using the palladium catalysts described above. However, these latter transformations can be achieved using nickel catalyst systems.<sup>109–111</sup> For example the Ni/prolinol-catalyzed coupling of **45** with phenylboronic acid gave **46** in 84% yield.



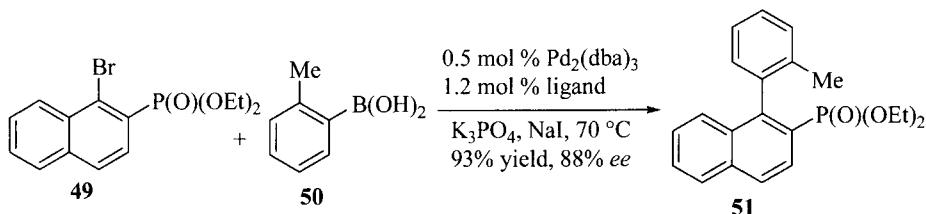
#### *Enantioselective Suzuki Coupling Reactions*

The asymmetric construction of axially chiral biaryl derivatives has been accomplished through enantioselective Suzuki coupling reactions, although these transformations remain relatively rare.<sup>112</sup> Two different strategies have been employed, the first of which involves diastereoselective reactions of chiral aryl halides. For example, Uemura has reported stereoselective couplings of Cr(CO)<sub>3</sub>-complexed aryl halides such as **47**, which yield diastereomerically pure biaryls (e.g., **48**).<sup>113</sup> Subsequent photolytic removal of the Cr-moiety affords enantiomerically pure compounds. Asymmetric

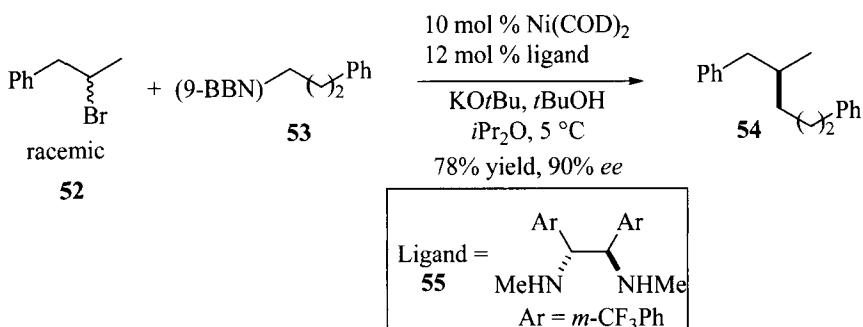
coupling reactions of arenes bearing  $sp^3$ -stereocenters have also been reported.<sup>114–116</sup>



Enantioselective Suzuki coupling reactions that employ chiral catalysts for the synthesis of nonracemic biaryl derivatives have also been explored by several groups.<sup>112</sup> The first examples of these transformations were reported independently by Buchwald<sup>117</sup> and Cammidge<sup>118</sup> in 2000, although related asymmetric desymmetrizations<sup>119,120</sup> and the use of chiral catalysts for diastereoselective reactions of chiral substrates had been previously described.<sup>121</sup> In a representative example,<sup>117</sup> boronic acid **50** was coupled with aryl bromide **49** to provide **51** in 93% yield and 88% *ee*; selectivities of up to 92% *ee* were obtained in some systems.



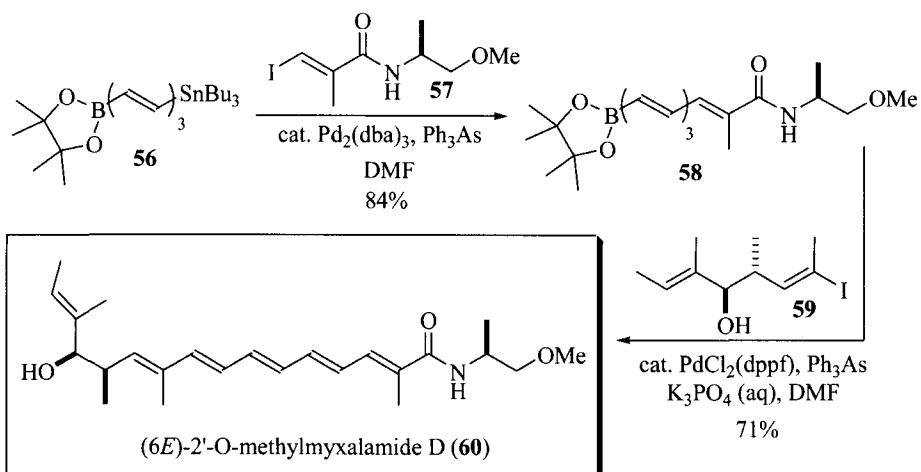
A very recent paper described the first examples of asymmetric Suzuki coupling reactions of unactivated alkyl halides.<sup>122</sup> These transformations take advantage of the fact that oxidative addition of secondary alkyl halides to  $\text{Ni}(0)$  proceeds through radical intermediates. This leads to scrambling of stereochemistry when achiral catalysts are employed, but can be exploited to achieve dynamic kinetic resolution with chiral catalysts. For example, use of a catalyst composed of  $\text{Ni}(\text{COD})_2$  and chiral 1,2-diamine ligand **55** for the coupling of **52** with **53** gave **54** in 78% yield and 90% *ee*.



### 1.1.7.7 Synthetic Utility

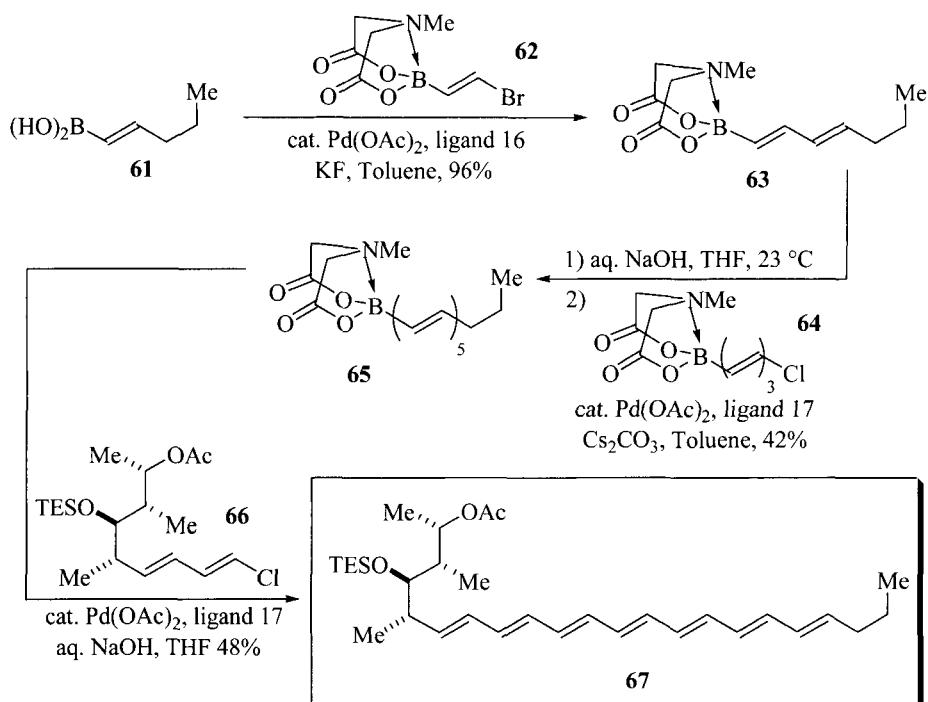
The Suzuki reaction has been frequently employed in the synthesis of natural products and other complex molecules.<sup>3,31</sup> A few recent, representative examples that illustrate the chemoselectivity and functional group tolerance of these transformations are described below.

Coleman and coworkers have reported a lynchpin synthesis of (*6E*)-2'-*O*-methylmyxalamide D (**60**) that employs a Suzuki coupling of pinacolboronate **58** with alkenyl iodide **59**.<sup>123</sup> The key intermediate alkenylboronate (**58**) was generated through chemoselective Stille coupling of vinylstananne **56** with **57**. This example further highlights the importance of base in the Suzuki coupling, and illustrates the utility of substrates bearing two different main-group elements that can undergo selective transmetalation under appropriate conditions.

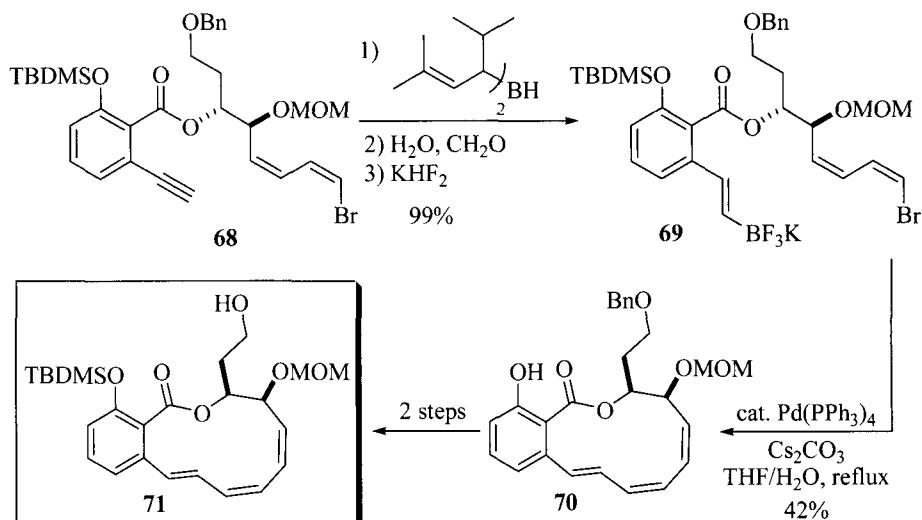


A different Suzuki-Coupling strategy for the lynchpin synthesis of polyene-containing natural products was recently described by Burke.<sup>124</sup> This

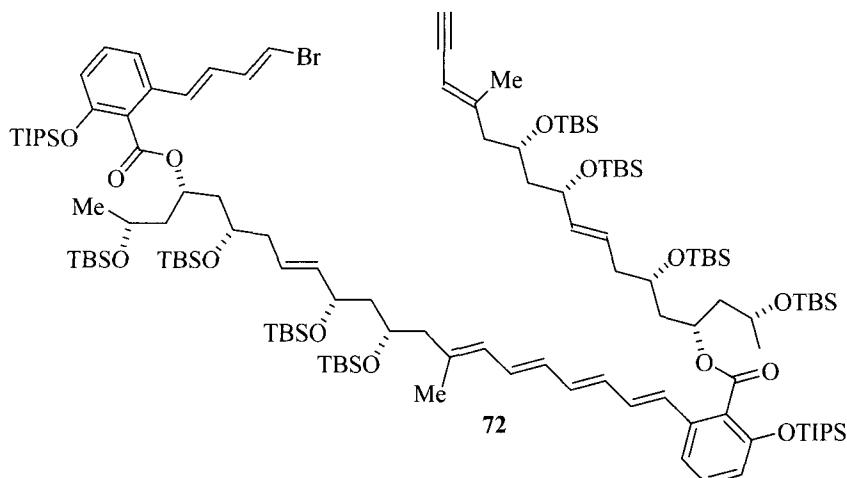
strategy is illustrated in the construction of the polyene fragment of amphotericin B, and employs a MIDA-protected  $\beta$ -bromovinylboronate ester (**62**, MIDA = *N*-methyliminodiacetic acid) as a key building block. The MIDA-protected boronate is unreactive under anhydrous conditions, which allows for chemoselective coupling of the alkenyl bromide with alkenylboronic acid **61**. The MIDA group was cleaved from the resulting product **63** with aqueous NaOH, and the resulting boronic acid was then treated with alkenyl chloride **64** to afford **65**. A second sequence involving *in situ* deprotection of **65** followed by cross coupling with dienyl chloride **66** provided **67**, which is a fragment of amphotericin B, in moderate overall yield. This strategy was also employed for the synthesis of retinal and  $\beta$ -parinarinic acid.

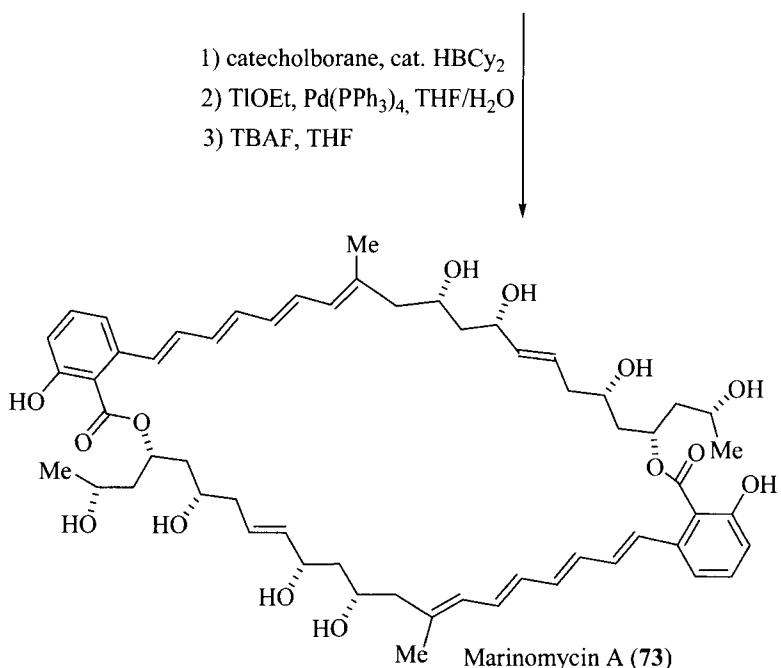


The utility of potassium organotrifluoroborate salts in natural product synthesis was demonstrated by Molander through a formal total synthesis of the macrolide oximidine II. Alkyne **68** was selectively hydroborated with di(isopropylprenyl)borane and then converted to the potassium trifluoroborate salt **69**. Formation of the macrocyclic ring was achieved through intramolecular Suzuki coupling of **69**, which generated **70** in a 42% yield.<sup>125</sup> Intermediate **70** was transformed to **71** in two steps to complete the formal synthesis.

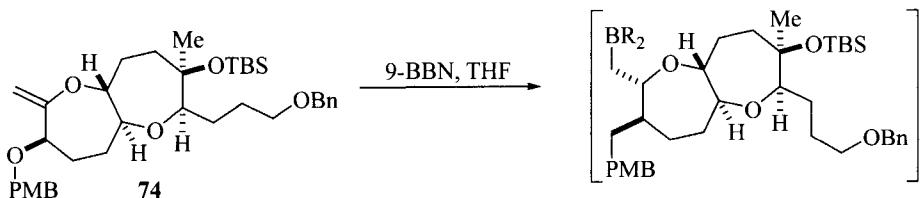


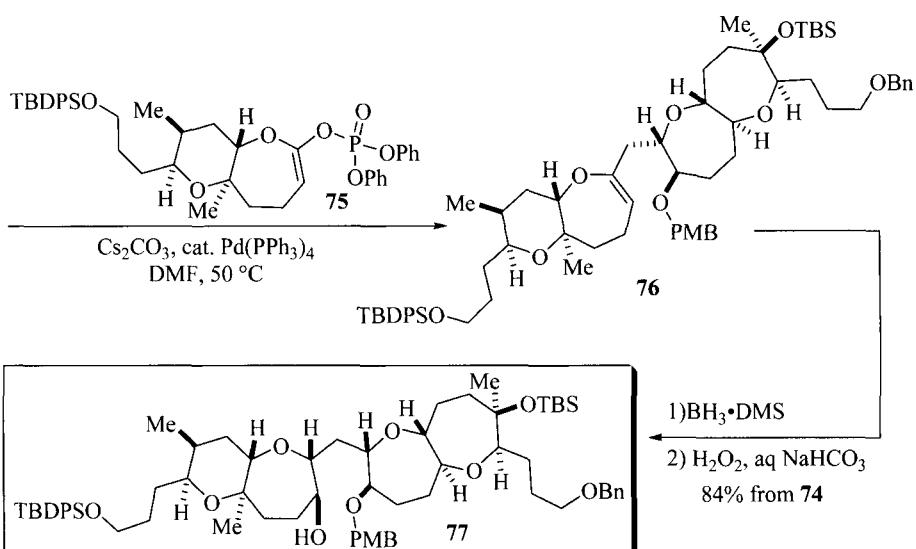
Nicolaou and coworkers recently employed an intramolecular Suzuki macrocyclization reaction in their total synthesis of the antibiotic marinomycin A (**73**).<sup>126</sup> The requisite organoboron reagent was generated *in situ* through treatment of enyne ester **72** with catecholborane in the presence of catalytic dicyclohexylborane, and the Pd-catalyzed Suzuki coupling effected closure of the 44-membered ring. The natural product was obtained in 23% yield over three steps from **72** after TBAF-mediated global deprotection.



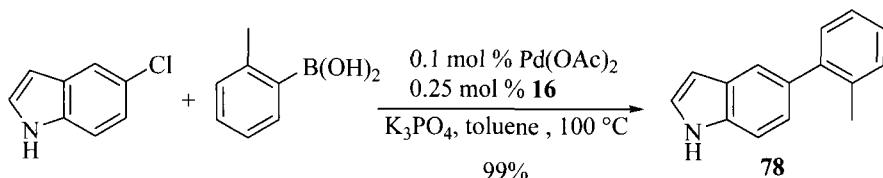


The Suzuki coupling of an *in situ*-generated alkyl-9-BBN reagent with a vinyl phosphonate was employed by Sasai for the synthesis of the skipped ladder polyether brevenal.<sup>127</sup> As shown below, treatment of **74** with 9-BBN followed by addition of **75**, Cs<sub>2</sub>CO<sub>3</sub>, and a palladium catalyst provided **76**. Hydroboration of the crude alkene product afforded alcohol **77** in 84% total yield over two steps. This intermediate was transformed to the natural product after several additional steps.



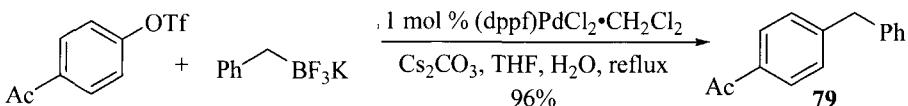


### 1.1.7.8 Experimental



#### 5-(2'-Methylphenyl)-1*H*-indole (78).<sup>62</sup>

An oven-dried resealable Schlenk tube was purged with argon and charged with 5-chloroindole (152 mg, 1.0 mmol), 2-methylphenylboronic acid (204 mg, 1.5 mmol),  $\text{K}_3\text{PO}_4$  (424 mg, 2.0 mmol). The tube was capped with a rubber septum, evacuated and backfilled with argon three times, and then toluene (3 mL), and 200  $\mu\text{L}$  of a catalyst solution composed of  $\text{Pd}(\text{OAc})_2$  (2.2 mg, 0.1 mmol), **16** (10.3 mg, 0.025 mmol), and THF (2 mL) were added via syringe. The septum was replaced with a Teflon screwcap, the tube was sealed, and the mixture was heated to 100 °C with stirring for 15 h. The mixture was then cooled to rt, diluted with ether (10 mL), filtered through a plug of silica gel, and concentrated. The crude product was purified by flash chromatography on silica gel using 9:1 hexanes:ether as the eluent to afford 207 mg (99%) of the title compound as a colorless oil.



### 1-(4-Benzylphenyl)ethanone (79).<sup>128</sup>

A round-bottom flask equipped with a stirbar and a reflux condenser was purged with argon and charged with potassium benzyltrifluoroborate (106 mg, 0.5 mmol),  $\text{Cs}_2\text{CO}_3$  (489 mg, 1.5 mmol),  $\text{PdCl}_2(\text{dppf})\cdot\text{CH}_2\text{Cl}_2$  (36 mg, 0.045 mmol), 4-acetylphenyltriflate (134 mg, 0.5 mmol), and THF (5 mL). Water (0.5 mL) was added, and the resulting mixture was heated to reflux for 18 h. The mixture was cooled to rt and diluted with water (10 mL). The organic layer was extracted with ether (50 mL  $\times$  3) and the ethereal extracts were washed with 1 M HCl (10 mL), and brine (20 mL). The organic layer was dried over anhydrous  $\text{MgSO}_4$ , filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 20:1 hexanes:ether as the eluent to afford 108 mg (96%) of the title compound as a colorless oil.

#### 1.1.7.8 References

- [R] Suzuki, A. in *Modern Arene Chemistry*, Astruc, D., Ed., Wiley, VCH: Weinheim, 2002, pp 53–106.
- [R] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
- [R] Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568.
- [R] Suzuki, A. in *Metal-Catalyzed Cross-Coupling Reactions*, Diederich, F.; Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998, Ch 2.
- [R] Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440.
- [R] Suzuki, A. Brown, H. C. in *Organic Syntheses via Boranes*, Aldrich Chemical Co: Milwaukee, WI, 2003, Vol 3.
- [R] Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695.
- [R] Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168.
- [R] Sasaki, M.; Fuwa, H. *Synlett* **2004**, 1851–1874.
10. Alo, B. I.; Kandil, A.; Patil, P. A.; Sharp, M. J.; Siddiqui, M. A.; Snieckus, V.; Josephy, P. D. *J. Org. Chem.* **1991**, *56*, 3763–3768.
11. [R] Schroter, S.; Stock, C.; Bach, T. *Tetrahedron* **2005**, *61*, 2245–2267.
12. [R] Negishi, E. -i. *B. Chem. Soc. Jpn.* **2007**, *80*, 233–257.
13. [R] Corbet, J.-P.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710.
14. [R] Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.
15. [R] Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303.
16. [R] Murahashi, S.-i. *J. Organomet. Chem.* **2002**, *653*, 27–33.
17. [R] Tamao, K. *J. Organomet. Chem.* **2002**, *653*, 23–26.
18. [R] Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1–652.
19. [R] Negishi, E.-i. *Acc. Chem. Res.* **1982**, *15*, 340–348.
20. [R] Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188.
21. [R] Hiyama, T.; Shirakwa, E. *Top. Curr. Chem.* **2002**, *219*, 61–85.
22. [R] Denmark, S. E.; Sweis, R. F. *Acc. Chem. Res.* **2002**, *35*, 835–846.
23. [R] Chauder, B.; Green, L.; Snieckus, V. *Pure. Appl. Chem.* **1999**, *71*, 1521–1529.
24. Murata, M.; Watanabe, S.; Masuda, Y. *J. Org. Chem.* **1997**, *62*, 6458–6459.

25. Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III. *Science* **2002**, *295*, 305–308.
26. Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995–1997.
27. Dieck, H. A.; Heck, R. F. *J. Org. Chem.* **1975**, *40*, 1083–1090.
28. Negishi, E. i. in *Aspects of Mechanism and Organometallic Chemistry*, Brewster, J. H., Ed., Plenum Press: New York, 1978, pp 285–317.
29. Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440.
30. Baba, S.; Negishi, E.-i. *J. Am. Chem. Soc.* **1976**, *98*, 6729–6731.
31. [R] Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442–4489.
32. [R] Schluter, A. D. *J. Polym. Sci. A* **2001**, *39*, 1533–1556.
33. [R] Schiedel, M.-S.; Briehn, C. A.; Bauerle, P. *J. Organomet. Chem.* **2002**, *653*, 200–208.
34. [R] Doucet, H.; Hierso, J.-C. *Curr. Opin. Drug Discov. Dev.* **2007**, *10*, 672–690.
35. [R] Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609–679.
36. [R] Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434–442.
37. [R] Leadbeater, N. E. *Chem. Commun.* **2005**, 2881–2902.
38. Aliprantis, A. O.; Canary, J. W. *J. Am. Chem. Soc.* **1994**, *116*, 6985–6986.
39. Smith, G. B.; Dezeny, G. C.; Hughes, D. L.; King, A. O.; Verhoeven, T. R. *J. Org. Chem.* **1994**, *59*, 8151–8156.
40. Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461–470.
41. Braga, A. A. C.; Morgan, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005**, *127*, 9298–9307.
42. Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458–460.
43. Espino, G.; Kurbangalieva, A.; Brown, J. M. *Chem. Commun.* **2007**, 1742–1744.
44. Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 13944–13945.
45. Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095–6097.
46. [R] Appukkuttan, P.; Van der Eycken, E. *Eur. J. Org. Chem.* **2008**, 1133–1155.
47. [R] Singh, B. K.; Kaval, N.; Tomar, S.; Van der Eycken, E.; Parmar, V. S. *Org. Proc. Res. Dev.* **2008**, *12*, 468–474.
48. Leadbeater, N. E.; Williams, V. A.; Barnard, T. M.; Collins, M. J., Jr. *Org. Proc. Res. Dev.* **2006**, *10*, 833–837.
49. [R] Genet, J. P.; Savignac, M. *J. Organomet. Chem.* **1999**, *576*, 305–317.
50. [R] DuPont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3667–3691.
51. Mathews, C. J.; Smith, P. J.; Welton, T. *Chem. Commun.* **2000**, 1249–1250.
52. [R] Franzen, R. *Can. J. Chem.* **2000**, *78*, 957–962.
53. [R] Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549–1581.
54. [R] Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2008**, *64*, 3047–3101.
55. [R] Yin, L. X.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133–173.
56. [R] Felpin, F.-X.; Ayad, T.; Mitra, S. *Eur. J. Org. Chem.* **2006**, 2679–2690.
57. [R] Bedford, R. B.; Cazin, C. S. J.; Holder, D. *Coord. Chem. Rev.* **2004**, *248*, 2283–2321.
58. [R] Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.
59. Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723.
60. [R] Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, Articles ASAP; DOI: 10.1021/ar800036s.
61. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
62. Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876.
63. Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
64. Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6173–6177.
65. Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818–11819.
66. Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553–5556.
67. Harkal, S.; Rataboul, F.; Zapf, A.; Fuhrmann, C.; Riermeier, T.; Monsees, A.; Beller, M. *Adv. Synth. Catal.* **2004**, *346*, 1742–1748.
68. Bei, X.; Turner, H. W.; Weinberg, W. H.; Guram, A. S.; Petersen, J. L. *J. Org. Chem.* **1999**, *64*, 6797–6803.
69. Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387–3388.

70. Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746–4748.
71. [R] Hiller, A. C.; Grasa, G. A.; Viciu, M. S.; Lee, H. M.; Yang, C.; Nolan, S. P. *J. Organomet. Chem.* **2002**, *653*, 69–82.
72. Fürstner, A.; Leitner, A. *Synlett* **2001**, 290–292.
73. Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101–4111.
74. [R] Bedford, R. B. *Chem. Commun.* **2003**, 1787–1796.
75. Schnyder, A.; Indolese, A. F.; Studer, M.; Blaser, H.-U. *Angew. Chem., Int. Ed.* **2002**, *41*, 3668–3671.
76. Roca, F. X.; Richards, C. *J. Chem. Commun.* **2003**, 3002–3003.
77. Thompson, A. E.; Hughes, G.; Batsanov, A. S.; Bryce, M. R.; Parry, P. R.; Tarbit, B. *J. Org. Chem.* **2005**, *70*, 388–390.
78. Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484–3488.
79. Billingsley, K.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 3358–3366.
80. Kudo, N.; Persegiani, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1282–1284.
81. Guram, A. S.; Wang, X.; Bunel, E. E.; Faul, M. M.; Larsen, R. D.; Martinelli, M. J. *J. Org. Chem.* **2007**, *72*, 5104–5112.
82. Fleckenstein, C. A.; Plenio, H. *Chem. Eur. J.* **2008**, *14*, 4267–4279.
83. Billingsley, K.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4695–4698.
84. Vedejs, E.; Chapman, R. W.; Fields, S. C.; Lin, S.; Schrimpf, M. R. *J. Org. Chem.* **1995**, *60*, 3020–3027.
85. Murphy, J. M.; Tzschucke, C. C.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 757–760.
86. Darses, S.; Michaud, G.; Genet, J.-P. *Eur. J. Org. Chem.* **1999**, 1875–1883.
87. [R] Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286.
88. Darses, S.; Genet, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* **1997**, *38*, 4393–4396.
89. Xia, M.; Chen, Z.-C. *Synth. Commun.* **1999**, *29*, 2457–2465.
90. [R] Roglans, A.; Pla-Quintana, A.; Moreno-Manas, M. *Chem. Rev.* **2006**, *106*, 4622–4643.
91. Molander, G. A.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 4302–4314.
92. Molander, G. A.; Yun, C. –S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* **2003**, *68*, 5534–5539.
93. Molander, G. A.; Canturk, B. *Org. Lett.* **2008**, *10*, 2135–2138.
94. Molander, G. A.; Gormisky, P. E.; Sandrock, D. L. *J. Org. Chem.* **2008**, *73*, 2052–2057.
95. Molander, G. A.; Ham, J. *Org. Lett.* **2006**, *8*, 2767–2770.
96. Molander, G. A.; Ellis, N. M. *J. Org. Chem.* **2006**, *71*, 7491–7493.
97. Molander, G. A.; Petrillo, D. E. *J. Am. Chem. Soc.* **2006**, *128*, 9634–9635.
98. Molander, G. A.; Ribagorda, M. *J. Am. Chem. Soc.* **2003**, *125*, 11148–11149.
99. Molander, G. A.; Figueroa, R. *Org. Lett.* **2006**, *8*, 75–78.
100. Molander, G. A.; Figueroa, R. *J. Org. Chem.* **2006**, *71*, 6135–6140.
101. [R] Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013–2030.
102. [R] Netherton, M. R.; Fu, G. C. *Top. Organomet. Chem.* **2005**, *14*, 85–108.
103. Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, *21*, 691–694.
104. Netherton, M. R.; Dai, C.; Neuschutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100.
105. Kirchhoff, J. H.; Netherton, M. R.; Hills, I. D.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 13662–13663.
106. Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3910–3912.
107. Arentsen, K.; Caddick, S.; Cloke, F. G. N.; Herring, A. P.; Hitchcock, P. B. *Tetrahedron Lett.* **2004**, *45*, 3511–3515.
108. Valente, C.; Baglione, S.; Candito, D.; O'Brien, C. J.; Organ, M. G. *Chem. Commun.* **2008**, 735–737.
109. Gonzalez-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360–5361.
110. Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340–1341.
111. Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602–9603.
112. [R] Baudoin, O. *Eur. J. Org. Chem.* **2005**, 4223–4229.
113. [R] Kamikawa, K.; Uemura, M. *Synlett* **2000**, 938–949.

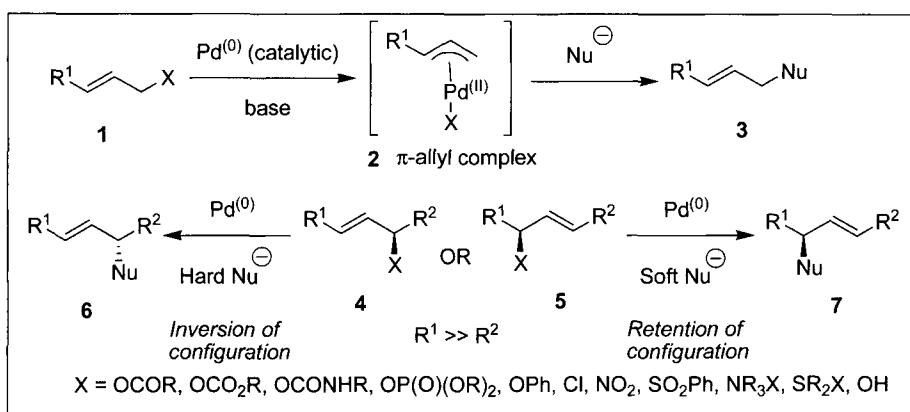
114. Lipshutz, B. H.; Keith, J. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3530–3533.
115. Baudoin, O.; Décor, A.; Cesario, M.; Gueritte, F. *Synlett* **2003**, 2009–2012.
116. Broutin, P.-E.; Colobert, F. *Org. Lett.* **2003**, *5*, 3281–3284.
117. Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051–12052.
118. Cammidge, A. N.; Crepy, K. V. L. *Chem. Commun.* **2000**, 1723–1724.
119. Uemura, M.; Nishimura, H.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 107–110.
120. Suk, Y. C.; Shibasaki, M. *Tetrahedron: Asymmetry* **1998**, *9*, 3751–3754.
121. Nicolaou, K. C.; Li, H.; Boddy, C. N. C.; Ramanjulu, J. M.; Yue, T.-Y.; Natarajan, S.; Chu, X.-J.; Brase, S.; Rubsam, F. *Chem. Eur. J.* **1999**, *5*, 2584–2601.
122. Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695.
123. Coleman, R. S.; Lu, X.; Modolo, I. *J. Am. Chem. Soc.* **2007**, *129*, 3826–3827.
124. Lee, S. J.; Gray, K. C.; Paek, J. S.; Burke, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 466–468 and references therein.
125. Molander, G. A.; Dehmel, F. *J. Am. Chem. Soc.* **2004**, *126*, 10313–10318.
126. Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S.; Cole, K. P.; Yamaguchi, J. *J. Am. Chem. Soc.* **2007**, *129*, 1760–1768.
127. Fuwa, H.; Ebine, M.; Sasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 9648–9650.
128. Molander, G. A.; Ito, T. *Org. Lett.* **2001**, *3*, 393–396.

## 1.1.8 Tsuji–Trost Reaction

Mathew J. Fuchter

### 1.1.8.1 Description

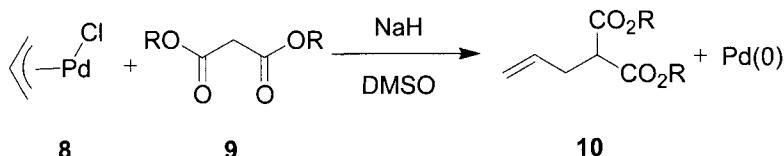
The Tsuji–Trost reaction is the palladium-catalyzed substitution of allylic leaving groups by carbon nucleophiles. These reactions proceed via  $\pi$ -allylpalladium intermediates **2**.<sup>1–18</sup>



A wide range of leaving groups (X) on the allylic reagent **1** can be utilized including halides, acetates, ethers, sulfones, carbonates, carbamates, epoxides and phosphates. The order of reactivity of the various leaving groups follows the trend: Cl > OCO<sub>2</sub>R > OAc >> OH. For most substrates **1**, a stoichiometric amount of base is required (to deprotonate the “soft” nucleophile). However, allylic carbonates undergo decarboxylation, generating a sufficiently basic alkoxide and therefore can be used under neutral conditions. Traditionally, only “soft” carbon nucleophiles were employed in the Tsuji–Trost reaction, the most common being active methylene compounds with two electron-withdrawing groups (RR'CH, where R,R' = CN, CO<sub>2</sub>R, NO<sub>2</sub>, etc.), enamines and enolates. It is equally possible however, to employ nitrogen-, oxygen-, and sulfur-based “soft” nucleophiles, as well as “hard” organometallic nucleophiles. In general, addition of the nucleophile occurs to the least hindered terminus of the  $\pi$ -allyl intermediate **2**, regardless of the position of the leaving group. For optically-active reagents **4** or **5**, substitution with “hard” nucleophiles occurs with overall inversion of configuration (to yield **6**). In the case of “soft” nucleophiles, substitution takes place with overall retention of configuration (to yield **7**).

### 1.1.8.2 Historical Perspective

In 1965, Jiro Tsuji and co-workers demonstrated that  $\pi$ -allylpalladium chloride (**8**) could be substituted with several nucleophiles including enamines and the anions derived from diethyl malonate.<sup>19</sup> This was an extension of their studies on the reaction of olefins activated by palladium(II) with “soft” nucleophiles.<sup>20</sup>

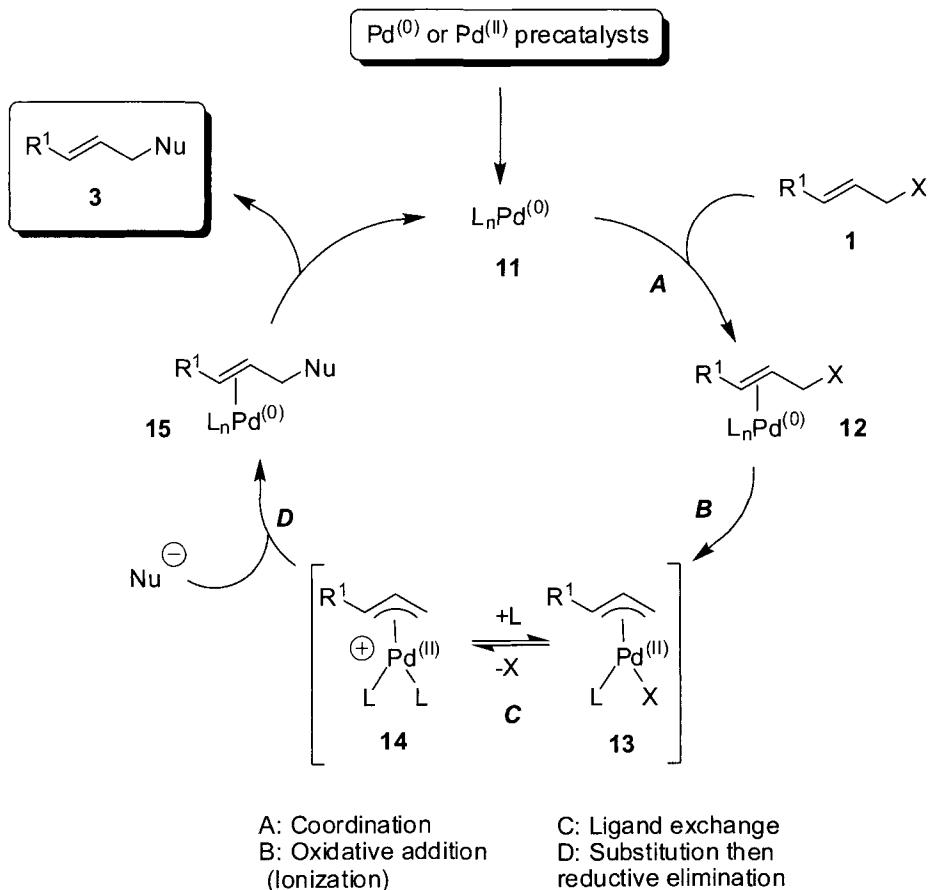


The reaction was found to require DMSO as the solvent and resulted in the formation of allylated product **10** and palladium black. Importantly, these studies constituted a conceptual shift in organometallic chemistry. Many organometallic compounds known at the time (for example Grignard reagents) were established as nucleophiles, however these studies demonstrated certain organometallic reagents could function as electrophiles.<sup>21</sup> The formation of palladium(0) in the reaction highlighted the potential for it to be rendered catalytic. Indeed, previously in 1964, Tsuji had developed the palladium-catalyzed carbonylation of allylic compounds.<sup>22</sup> In 1967, several other groups reported the palladium-catalyzed telomerization of butadiene with nucleophiles, which constituted the first examples of catalytic allylation reactions.<sup>23,24</sup> It was not until 1970 however the first examples of palladium-catalyzed allylation of nucleophiles using allylic compounds appeared.<sup>25,26</sup> In 1973, B. M. Trost reported that alkyl-substituted  $\pi$ -alkylpalladium complexes (often derived from the corresponding olefins) could be alkylated by “soft” carbon nucleophiles with complete regio- and stereoselectivity.<sup>27</sup> He subsequently published extensively on the use of this chemistry in complex molecule synthesis.<sup>28</sup> Nowadays this reaction is a powerful method of forging C–C bonds, particularly in the synthesis of intricate molecular architectures.

### 1.1.8.3 Mechanism

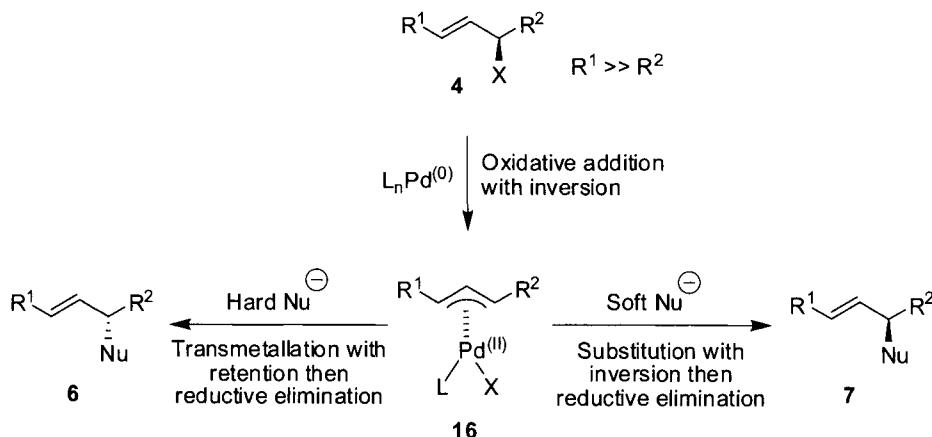
The basic mechanism of the Tsuji–Trost reaction is as follows: All palladium precatalysts are converted to the active palladium(0) catalyst **11** *in situ*, most commonly by phosphine in phosphine assisted catalytic cycles. Following coordination of the allylic reagent **1** to the palladium(0) catalyst **11**, oxidative addition occurs to give  $\pi$ -allylpalladium(II) complexes **13/14** (this step is also known as ionization). Complexes **13/14** can interconvert via ligand exchange

reactions. As mentioned previously, for most substrates **1**, a stoichiometric amount of base is required to deprotonate the “soft” nucleophile. However, allylic carbonates undergo decarboxylation, generating a sufficiently basic alkoxide and therefore can be used under neutral conditions. Nucleophilic attack of the anionic nucleophile on complex **13/14**, followed by reductive elimination gives the complexed product **15**. Ligand exchange regenerates **12** and releases the product **3**.



The regioselectivity of the process depends on several factors: (1) The charge distribution in the intermediate  $\pi$ -allyl palladium species, which favours attack at the more substituted allyl terminus; (2) steric hindrance to the approach of the nucleophiles, which favours attack at the less substituted allyl terminus; (3) electronic effects of substituents of the allyl unit; (4) the stability of the initial olefin–palladium(0) complex.<sup>7,29</sup> As a general rule of thumb however, in the case of palladium catalyzed reactions, steric control dominates and attack predominately occurs at the least hindered terminus.<sup>29</sup>

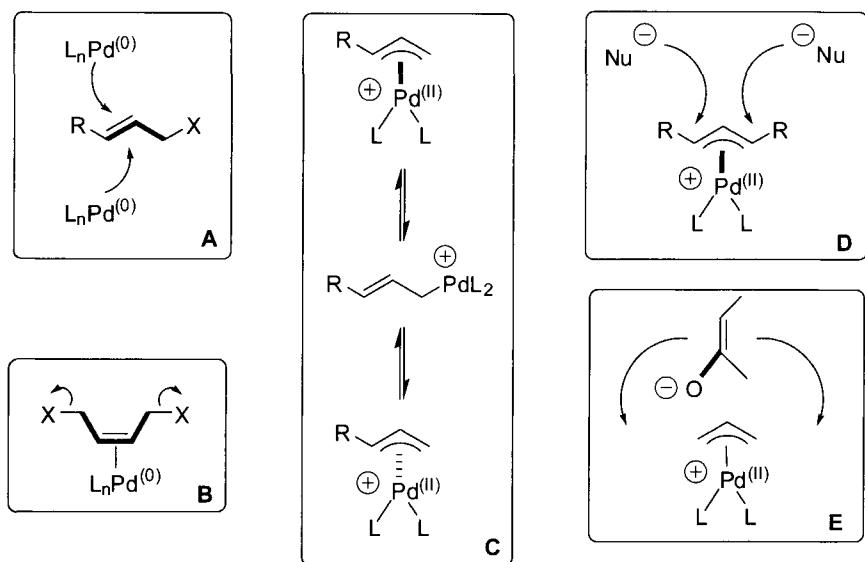
Another important consideration is the stereoselectivity of the reaction. Oxidative addition occurs under stereochemical control and one can think of this step as an  $S_N2$ -like displacement of the leaving group by the incoming palladium “nucleophile”.<sup>30</sup> In the case of a substrate such as **4**, oxidative addition occurs with inversion of stereochemistry, to give complex **16**.



Two different pathways subsequently occur for “soft” or “hard” nucleophiles. “soft” nucleophiles, such as those derived from conjugate acids with a  $pK_a < 25$  and most heteroatoms, directly attack the  $\pi$ -allyl unit (i.e. from outside the coordination sphere of the metal) from the opposite face of the palladium, resulting in a second inversion to give product **7**.<sup>12</sup> On the other hand, “hard” nucleophiles such as conjugate acids with a  $pK_a > 25$ , attack the metal centre directly (transmetallation), followed by reductive elimination. This gives products with inversion of configuration, **6**.<sup>12</sup>

### *The Asymmetric Allylic Alkylation*

In 1977, Trost published the first example of an asymmetric variant of the Tsuji–Trost reaction, termed the asymmetric allylic alkylation reaction (AAA).<sup>31</sup> Much of the subsequent development of the AAA reaction can be attributed to the dedicated work of Trost and co-workers.<sup>17,18</sup> There was a substantial time lag however, in the development of processes where high enantioselectivities were realized in a predictable fashion. This was due, in part, to the fact that chiral, asymmetrically pure ligands must create a chiral environment on the opposite face of the allyl fragment to the metal centre (a stereochemical requirement, *vide infra*).<sup>12</sup> This obviously represents a significant design challenge in the production of effective ligand systems.



A: Enantiotopic faces of olefin

B: Enantiotopic leaving groups

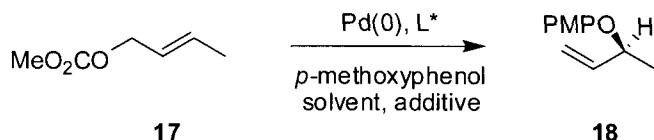
C: Enantiotopic faces of the allyl complex

D: Enantiotopic termini of the allyl complex

E: Enantiotopic faces of the nucleophile

Further intricacies of the AAA present both a sizeable challenge, but also a unique opportunity.<sup>12,17,18</sup> The general catalytic cycle offers at least five opportunities for enantiodiscrimination: In the olefin complexation step, if one complex leads to oxidative addition at a rate significantly faster than the other, and nucleophilic capture of that diastereomer is fast relative to  $\pi-\sigma-\pi$  equilibration, then enantiotopic olefin face coordination becomes the enantiodetermining step (mechanism A). In a case where there are two potential leaving groups on a *meso* or on an achiral *gem*-disubstituted system, enantiotopic ionization of the leaving groups is the enantiodetermining step (mechanism B). Where initial olefin coordination is rapid and reversible, two diastereomeric palladium complexes can form, which can interchange through a  $\pi-\sigma-\pi$  equilibration step. This form of equilibration involves a change in hapticity of the allyl ligand (from  $\eta^3$  to  $\eta^1$ ), carbon–carbon bond rotation, and a second change in hapticity (from  $\eta^1$  to  $\eta^3$ ).<sup>12</sup> Either the more abundant or the more reactive diastereomeric complex leads to the product (mechanism C). If the starting material is a chiral racemic moiety, but ionization leads to a *meso*  $\pi$ -allyl intermediate, differentiation of enantiotopic allyl termini is the enantioselection event (mechanism D). Finally, in the case of a prochiral nucleophile, enantioface discrimination of an achiral allyl complex can be enantiodetermining (mechanism E).

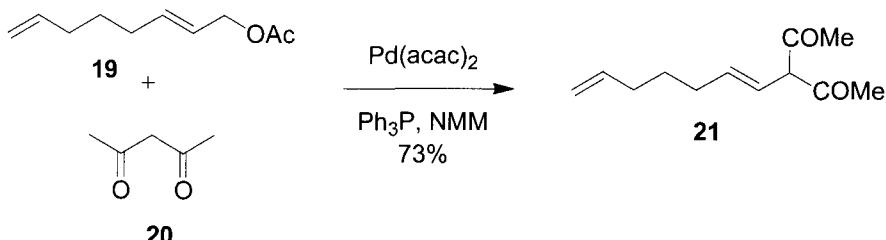
Trost has published several extensive reviews, which elegantly demonstrate examples of all these modes of enantioselection in operation.<sup>12,17,18</sup> Additives can be employed to distinguish between different selection modes. For example, in the AAA of substrate **17**, chloride ion additives rapidly increase the rate of  $\pi$ - $\sigma$ - $\pi$  equilibration and this, in turn, results in a decrease in the enantioselectivity.<sup>17</sup> Since this is not a base-catalyzed effect and lowering the concentration, increases the %ee, this suggests enantiotopic olefin face coordination is the enantiodetermining event in this AAA reaction. Further evidence is gained from the fact that changing to the equivalent chiral racemic branched substrate gives a branched product with low enantioselectivity.<sup>17</sup>



Perhaps the most important mechanistic implication of all is the very fact that the allylpalladium complexes can interconvert via  $\pi$ - $\sigma$ - $\pi$  equilibration. This enables chiral racemic material to be transformed into products of enantiopurity through a dynamic kinetic asymmetric transformation (DYKAT).<sup>17,18</sup> This powerful strategy has facilitated the construction of numerous complex, asymmetric molecules from simple racemic starting materials. Dynamic kinetic asymmetric transformations are extremely rare in other asymmetric reactions, highlighting the importance of the AAA reaction.

#### **1.1.8.4      *Synthetic Utility***

### *“Soft” carbon nucleophiles*

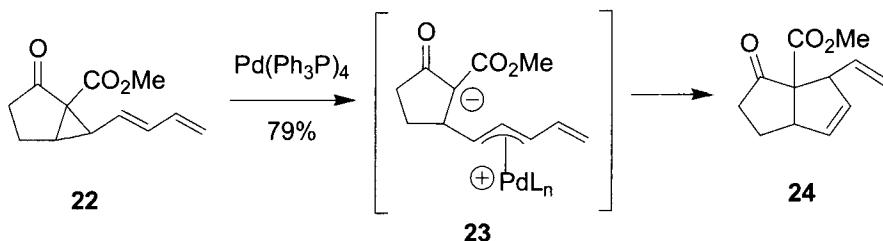


$\pi$ -Allyl palladium cations can be regarded as “soft” electrophiles, and react smoothly with “soft” nucleophiles. For carbon-based nucleophiles, “soft” methylene compounds (conjugate acids with a  $pK_a < 25$ ) with two electron-

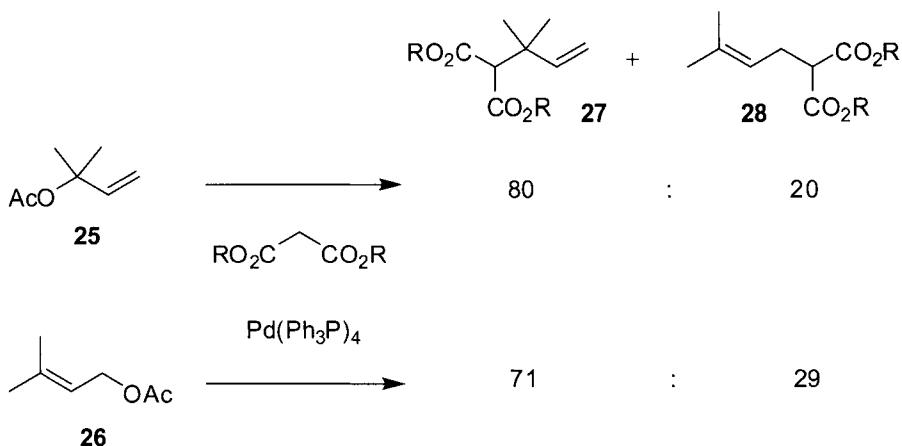
withdrawing groups ( $\text{RR}'\text{CH}$ , where  $\text{R}, \text{R}' = \text{CN}, \text{CO}_2\text{R}, \text{NO}_2$ , etc.) are most commonly employed.

In the first catalytic Tsuji–Trost reaction, allylic acetate **19** was readily converted into product **21** in good yield.<sup>26</sup> Following this precedent, numerous examples of this allylation reaction have been reported using activating groups such as carbonyl, sulfonyl, cyano, nitro, aryl, olefinic, imino, etc. Readers are referred to the many comprehensive reviews on the topic for extensive examples of the Tsuji–Trost reaction in synthesis.<sup>1–18</sup>

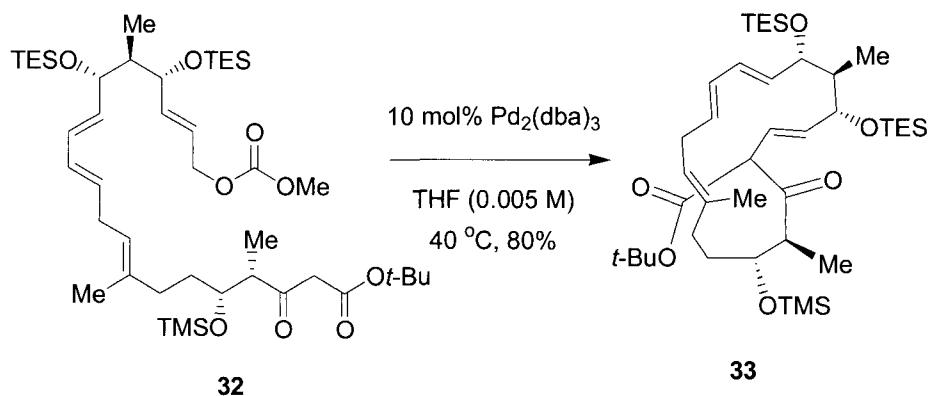
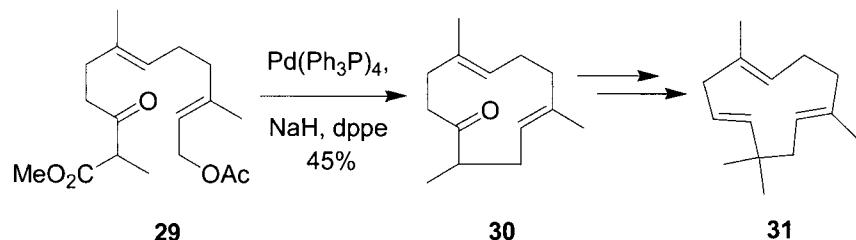
One interesting example of the Tsuji–Trost reaction is the ring-opening of a vinyl cyclopropane bearing two electron-withdrawing groups. Under palladium catalysis, substrate **22** undergoes ring-opening oxidative addition (cleaving a C–C bond in the process) to give  $\pi$ -allyl intermediate **23**. Subsequent cyclization furnishes the bicyclic compound **24** in good yield.<sup>32</sup>

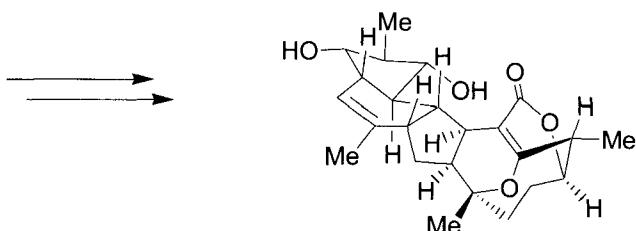


The regiochemistry of the Tsuji–Trost reaction warrants further consideration (see 1.1.8.3). While steric control often dominates, with nucleophilic attack occurring at the least hindered terminus of the allyl moiety, examples of branched adducts have been reported. In certain cases the electronic bias of a given substrate can give rise to attack at the more hindered terminus.<sup>12</sup> Other cases are less straightforward. It has been proposed that at low temperature and with short reaction times the reaction is under kinetic control, but at elevated temperature and prolonged reaction times the reaction is under thermodynamic control. Indeed, allyl malonates have been shown to rearrange to the more thermodynamically-stable (branched) regioisomer in the presence of palladium(0).<sup>33</sup> Regioselectivity can also be influenced by leaving groups, nucleophiles and ligands. For example, in studies of the Tsuji–Trost reaction of allylic acetates **25** and **26** in refluxing THF, the branched isomer **27** predominates.<sup>34</sup>



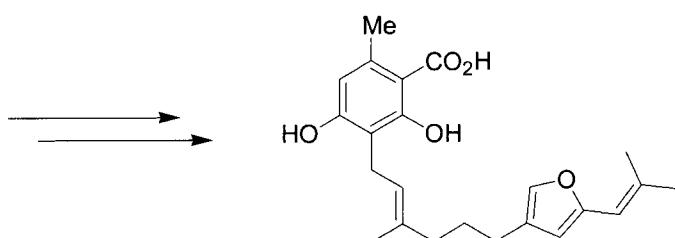
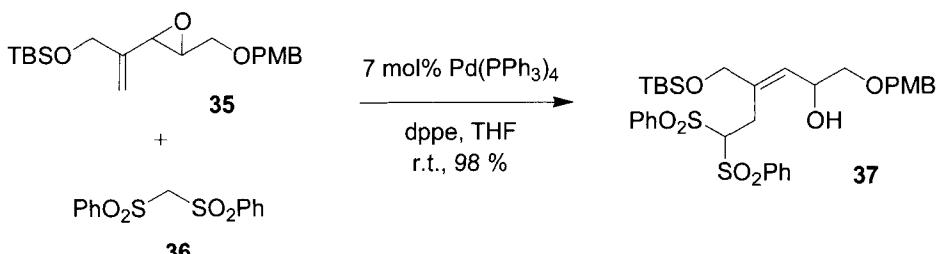
Intramolecular allylation has proved extremely useful in the synthesis of macrocyclic compounds. In 1977, Nozaki and co-workers reported the first example in the synthesis of humulene **31**.<sup>35</sup> Intramolecular Tsuji–Trost allylation provided key intermediate **30** in moderate yield.





34: (+)-FR182877

More recently, in 2003, Sorensen demonstrated an impressive, scalable synthesis of cytotoxic natural product (+)-FR182877 **34**, which employed an intramolecular Tsuji–Trost allylation reaction to prepare the 19-membered macrocycle **33**.<sup>36</sup> Exposure of allylic carbonate **32** to 10 mol% palladium catalyst under high dilution formed the key bond in good yield and complete diastereoselectivity. This key intermediate was subsequently converted to (+)-FR182877 **34** via an intramolecular Diels–Alder reaction.



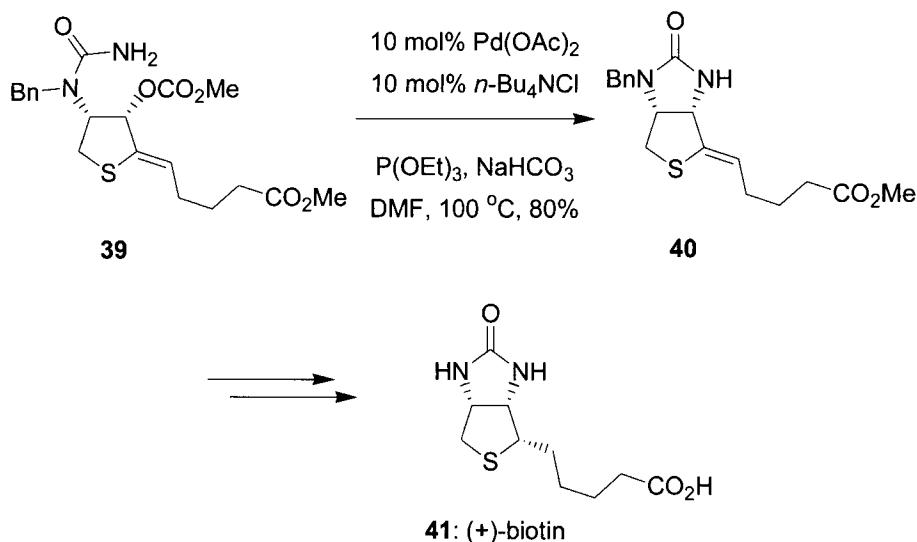
38: cristatic acid

Another potent cytotoxic compound cristatic acid (**38**) was prepared for the first time by A. Fürstner.<sup>37</sup> Allylation of vinyl epoxide **35** with bis(phenylsulfonyl)methane (**36**) gave 1,4-diol **37** in almost quantitative yield. This substrate was subsequently elaborated to cristatic acid (**38**). This example nicely highlights the use of the vinyl epoxide activating group in Tsuji–Trost reactions.

### *Nitrogen nucleophiles*

Amines are suitable nucleophiles in the Tsuji–Trost reaction, with the use of simple amines, imides, azides, sulfonamides and heterocyclic amines having been reported.<sup>11</sup> In fact, one of the first examples of the catalytic version of the Tsuji–Trost reaction involved the use of aliphatic amine nucleophiles.<sup>25</sup> Subsequently these important nucleophiles have been used extensively in synthesis.

The water soluble vitamin (+)-biotin (**41**) was prepared by Seki and co-workers from *L*-cysteine in only 11 steps.<sup>38</sup> The key ring-forming reaction was an intramolecular allylic amination of a *cis*-allylic carbonate **39**. As expected, the allylation took place with net retention and furnished key intermediate **40** in good yield.

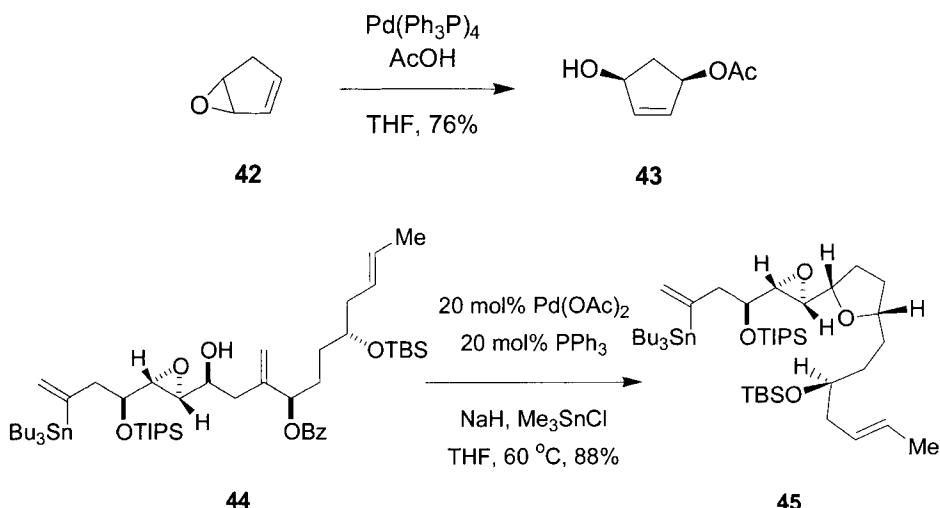


### *Oxygen nucleophiles*

Aliphatic alcohols are poor *O*-nucleophiles, and the allylation of alcohols to form alkyl allyl ethers is somewhat sluggish.<sup>11</sup> One method to overcome this issue is to use aliphatic carbonates as the leaving group. These substrates are decarboxylated upon oxidative addition, releasing an alkoxide moiety, which gives an allyl ether in the absence of any other nucleophiles.<sup>11</sup> Phenolic alcohols and carboxylates are far better substrates for the Tsuji–Trost reaction however, and have been used extensively. For example, the monoepoxide of cyclopentadiene **42** is readily attacked by acetic acid to give *cis*-dibsubstituted cyclopentene **43** in good yield.<sup>39</sup> Note how the reaction

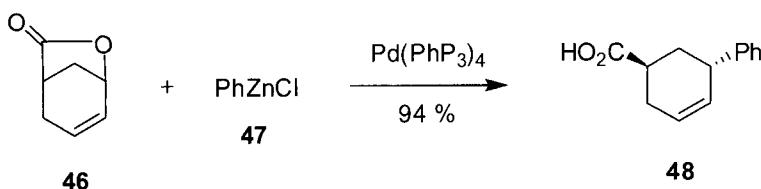
proceeds both regio- and stereoselectively (net retention) via a  $\pi$ -allyl intermediate.

While the reaction of aliphatic alcohols can be problematic, there are several examples reported in the synthesis of complex molecular targets. For example, the use of Tsuji–Trost reaction in the synthesis of *cis*-2,5-disubstituted tetrahydrofurans was reported by Williams and co-workers. They used a “soft” oxygen nucleophile in an intramolecular reaction to prepare the C7–C22 core of amphidinolide K **45**.<sup>40</sup> It was found the addition of  $\text{Me}_3\text{SnCl}$  was necessary to both suppress acyl migration and ensure the oxygen was strongly nucleophilic.



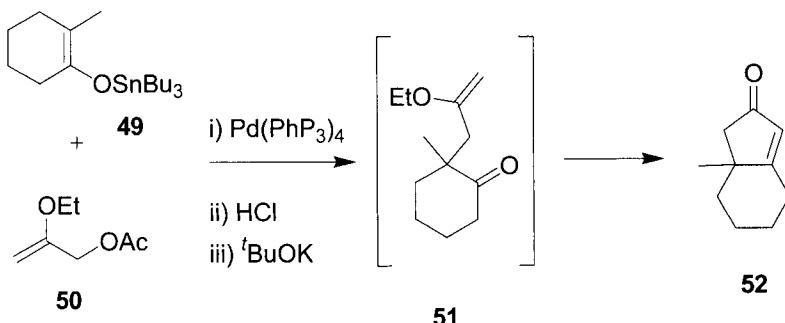
### “Hard” carbon nucleophiles

Various allylic compounds react with “hard” carbon nucleophiles ( $\text{pK}_a > 25$ ) including organometallic compounds of Zn, B, Al, Sn and Si via a transmetallation pathway (see 1.1.8.3).<sup>11</sup> For example, the reaction of allylic lactone **46** with phenylzinc chloride gave the product **48** in excellent yield.<sup>41</sup> Note the inversion of the stereochemistry at the allylic carbon (see 1.1.8.3).



Simple ketones cannot be allylated under standard Tsuji–Trost conditions however transmetallation via tin enolates has proven to be a useful

modification. For example, Trost reported the use of tin enolate **49** in the preparation of intermediate **51**, which was subsequently annulated to give bicyclic **52**.<sup>42</sup> Additionally by using enol acetates in the presence of Bu<sub>3</sub>SnOMe, the quantity of tin can be substoichiometric, allowing the allylation of simple ketones under bimetallic tin and palladium catalysis.<sup>11</sup>

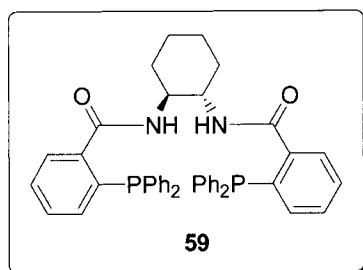
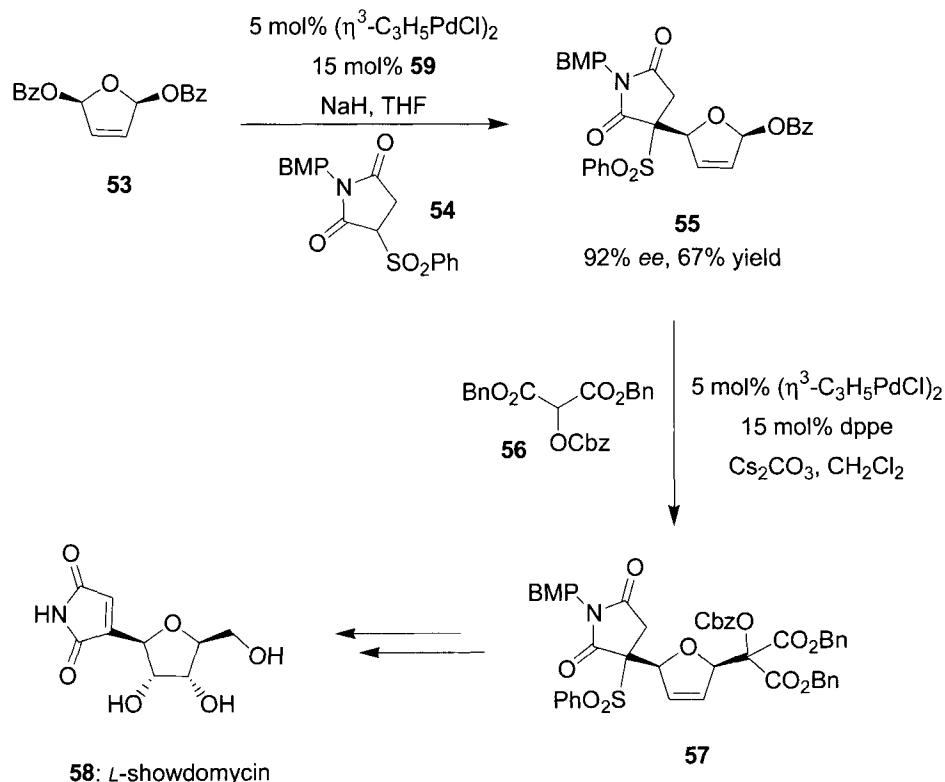


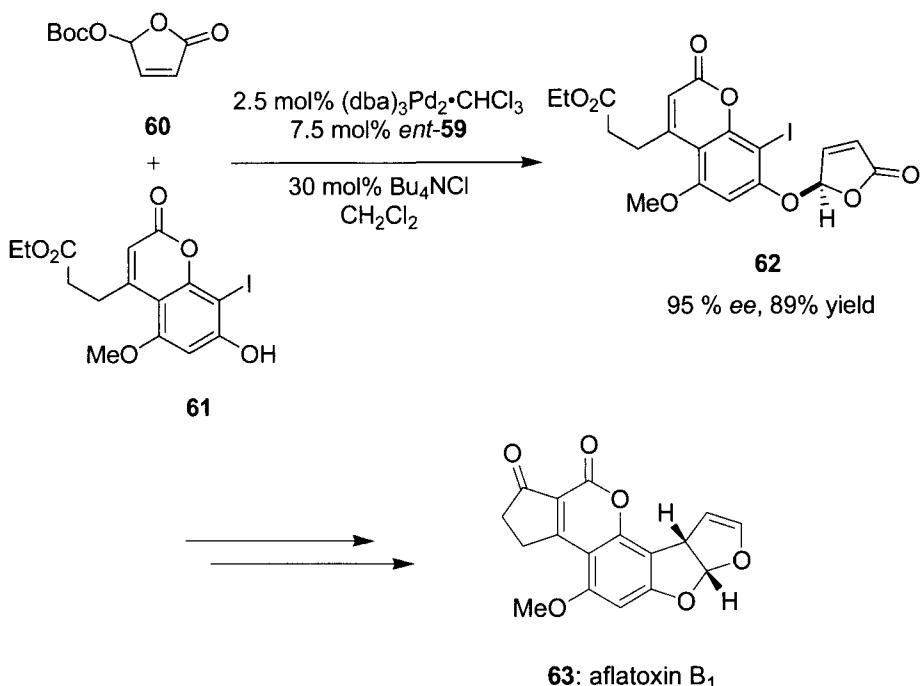
#### AAA Reaction: Carbon Nucleophiles

Asymmetric carbon-carbon bond formation is one of the ongoing challenges in synthetic organic chemistry. Good enantioselectivity at the nucleophile and electrophile has been achieved with “soft” carbon nucleophiles on both cyclic and acyclic electrophiles.<sup>12,17,18</sup> The majority of the reported examples in the AAA using carbon nucleophiles utilize cyclic electrophiles. One elegant example from the Trost laboratory was the synthesis of *L*-showdomycin (**58**).<sup>43</sup> The synthesis employed a desymmetrization of *meso*-substrate **53** as the first step (see mechanism B). Thus *meso*-dihydrofuran **53** was transformed into adduct **55** using imidosulfone **54** and ligand **59** in 67% yield and 92% *ee*. The resulting adduct was further alkylated using an achiral palladium complex with 1,3-bisdiphenyl-phosphinopropane (dppp) to yield key intermediate **57**, which was transformed to *L*-showdomycin (**58**) in eight further steps.

It is worth mentioning the huge success diphenylphosphino benzoic acid-based ligands (such as **59**), first pioneered by Trost and co-workers, have had in AAA reactions.<sup>12,17,18</sup> While many *C*<sub>2</sub>-symmetrical ligands such as BINAP, DIOP and CHIRAPHOS have proved extraordinarily successful in other asymmetric transformations, their performance in AAA reactions is somewhat lacklustre.<sup>12</sup> Trost has published a working model to act as a predictive tool on the outcome of a given AAA reaction using ligands such as **59**.<sup>44</sup> Due to the numerous potential coordination modes of ligand **59** however, the exact catalytic species for a given reaction may differ.<sup>45</sup> Other successfully employed ligands include *C*<sub>2</sub>-symmetric diamine ligands,<sup>46</sup>

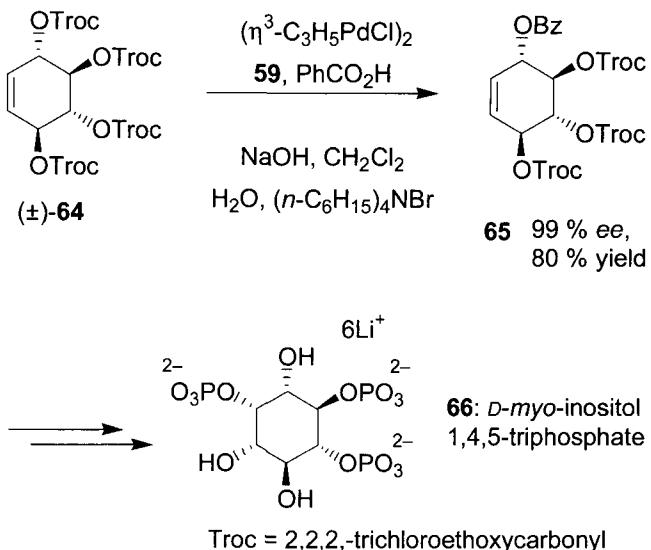
bisoxazoline ligands,<sup>47</sup> ferrocenyl ligands,<sup>48,49</sup> electronically differentiated *P,S*-<sup>50</sup> and *P,N*-based<sup>51</sup> ligands.



*AAA reaction: Oxygen Nucleophiles*

With over a dozen biologically-active, complex molecules prepared using oxygen nucleophiles in the AAA reaction, asymmetric formation of carbon-oxygen bonds is well precedented.<sup>12,17,18</sup> Phenolic oxygens are the most thoroughly explored nucleophiles and have been employed in a number of syntheses. For example, AAA of racemic butenolide **60** with coumarin **61** gave the product in high yield and enantiopurity.<sup>52</sup> Product **62** was a key intermediate in the synthesis of mycotoxin (–)-aflatoxin B (**63**). Facile  $\pi$ – $\sigma$ – $\pi$  equilibration (see mechanism C) of the allylpalladium species formed upon ionization of butenolide **60** enables a dynamic kinetic asymmetric transformation (DYKAT), furnishing product **62** in high enantiopurity from a racemic reagent.

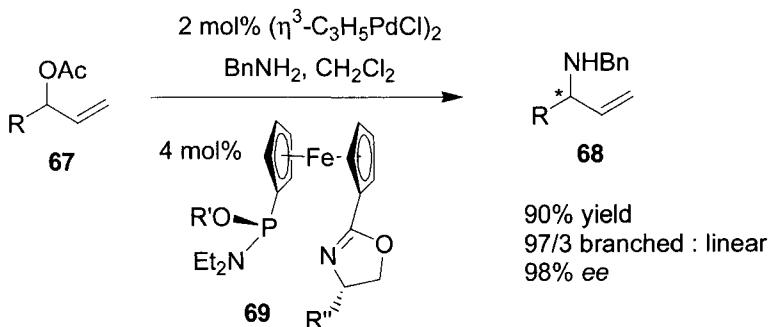
Carboxylates have also proven to be suitable nucleophiles in the AAA reaction, especially with cyclic electrophiles.<sup>17,18</sup> For example, DYKAT of conduritol B tetracarboxylate facilitated a synthesis of *D*-*myo*-inositol 1,4,5-triphosphate (**66**).<sup>53</sup> Racemic substrate **64** was transformed to the enantiopure disubstituted product **65** in 80% yield. This was a key intermediate in the preparation of *D*-*myo*-inositol 1,4,5-triphosphate (**66**), a key component of intracellular signalling.



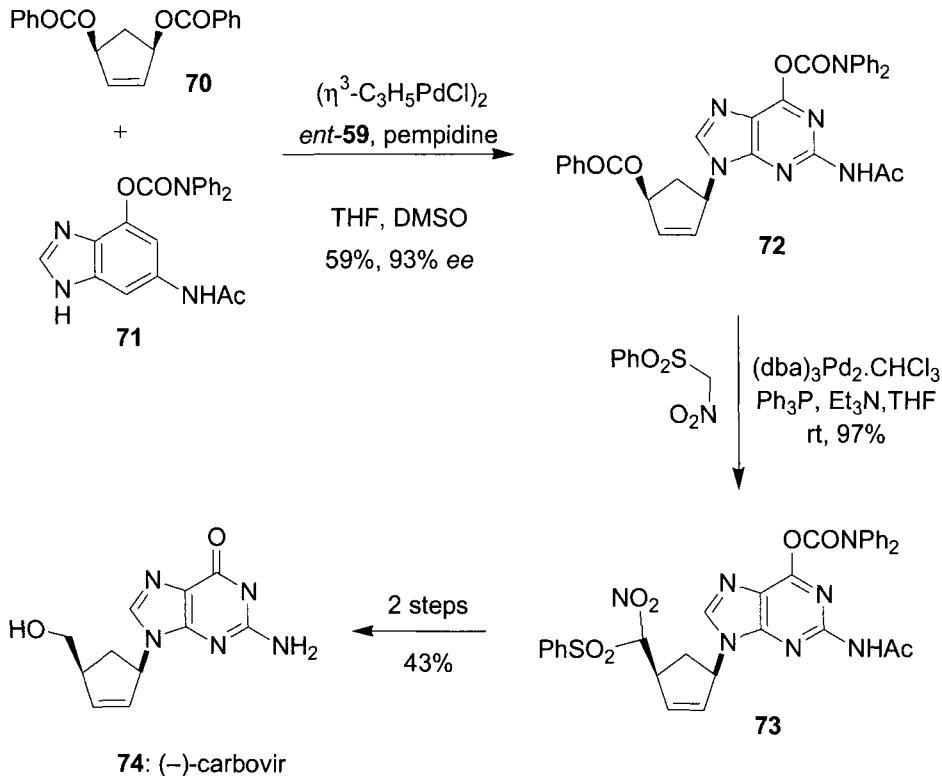
Aliphatic, primary alcohols can also be utilized in the AAA reaction and several examples have been reported.<sup>17,18</sup>

#### AAA Reaction: Amine Nucleophiles

Amines as nucleophiles in AAA have proven a challenge due to mono- vs. bisalkylation, regioselectivity issues and rate of nucleophilic addition vs allyl equilibration.<sup>17</sup> While no AAA-based total synthesis has been reported utilizing an alkylamine nucleophile, novel ligand systems are being developed which provide unprecedented selectivity. For example, novel *P,N*-ferrocene ligand **69** mediated a regio- and enantioselective amination of allylic acetates.<sup>54</sup> The product **68** was isolated predominantly as the branched isomer in 90% yield, 98% *ee*.

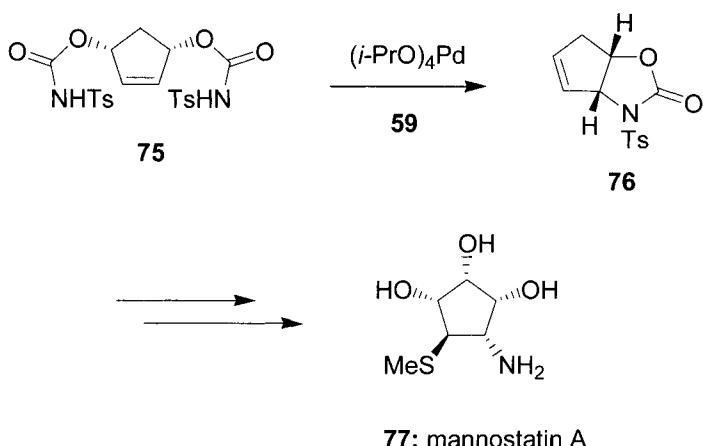


Numerous other amine nucleophiles have been used with great success in the AAA reaction including azides, imides, sulfonamides, and heterocycles.



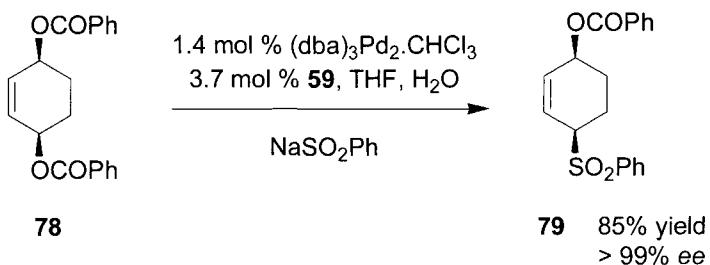
Trost reported an elegant and expedient preparation of the antiviral agent (-)-carbovir (74).<sup>55</sup> Desymmetrization of dibenzoate 70 with a purine base 71 gave product 72 in moderate yield and high enantioselectivity. A second Tsuji–Trost allylation with a carbon nucleophile proceeded with net retention to give adduct 73. This was converted to (-)-carbovir (74) in a two further steps.

In another example of the power of amine nucleophiles in the AAA reaction, Trost reported a highly enantioselective route to mannostatin A (77), a specific nanomolar inhibitor of  $\alpha$ -D-mannosidase. Once again a desymmetrization strategy was employed, cyclizing meso substrate 75 in an intramolecular AAA reaction to give adduct 76.<sup>56</sup> While other ligands provided inefficient in this task, the diphenylphosphino benzoic acid-based ligand 59 delivered key intermediate 76 in 97% *ee*, which was subsequently converted to mannostatin A (77).



### *AAA Reaction: Sulfur Nucleophiles*

Allylic sulfones are important and versatile intermediates in organic synthesis due to the ability of the sulfone to impart both nucleophilic and electrophilic properties to the  $\alpha$ -carbon. Pleasingly, the use of sodium benzenesulfinate in an AAA reaction of *meso* substrate **78** furnished the chiral adduct **79** in 85% yield and essentially asymmetrically pure.<sup>57</sup>



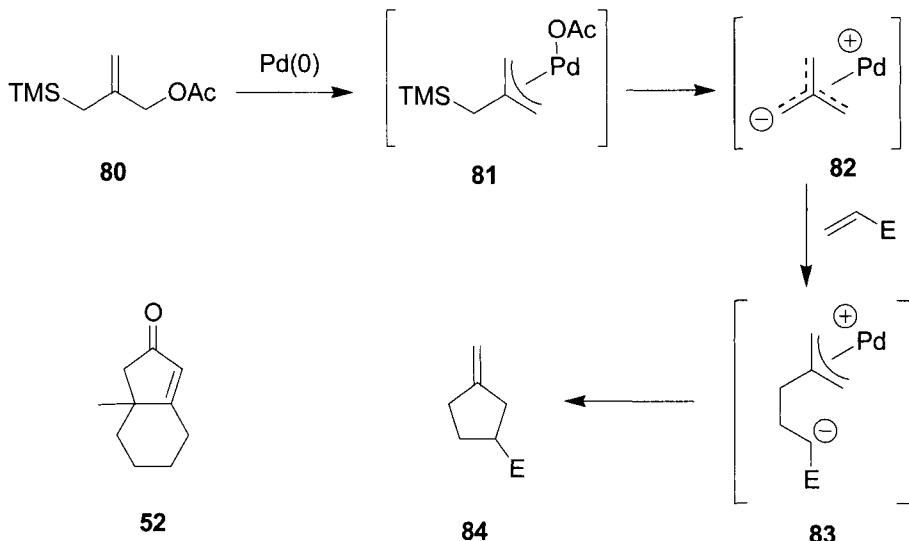
### **1.1.8.5 Variations and Improvements**

There are many variations on the Tsuji–Trost reaction whereby transient  $\pi$ -allylpalladium compounds are harnessed in a variety of pathways. Some examples are highlighted below.

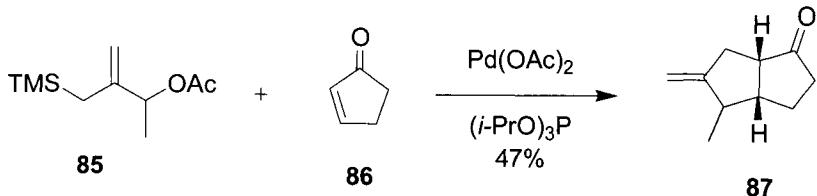
### *2-(Trimethylsilylmethyl)allyl Acetate.*

2-(Trimethylsilylmethyl)allyl acetate (**80**), which has a silyl group in the allylic position undergoes a formal [3 + 2] cycloaddition reaction with electron deficient alkenes to give methylenecyclopentane derivatives **84**.<sup>11</sup> Following oxidative addition, elimination of the TMS group, facilitated by

the proximal positive charge, generates dipolar intermediate **82**. The cyclization of reactive intermediate **82** proceeds by a Michael addition to the activated double bond to give **83**, followed by intramolecular allylation.<sup>11</sup> In general, tri-isopropyl phosphite is a particularly good ligand for this process a numerous cyclic compounds have been prepared.<sup>11</sup>

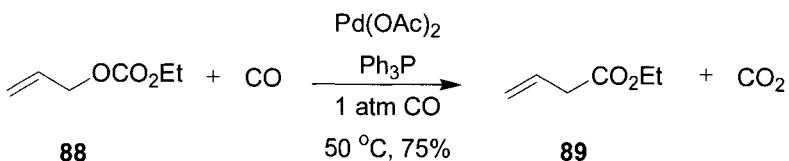


In their synthesis of the naturally occurring product loganin, Trost and co-workers prepared bicycle **87** as a key intermediate. Exposure of substrate **85** to cyclopentenone **86** under palladium catalysis, furnished the desired [3 + 2] cycloaddition adduct **87** in moderate yield.<sup>58</sup>



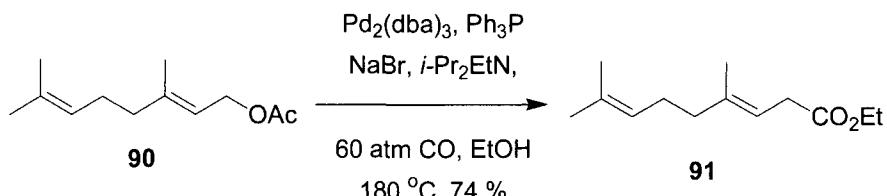
### *Carbonylation*

Carbonylation of allylic compounds in alcoholic solvent gives  $\beta,\gamma$ -unsaturated esters, however, these substrates are far less reactive to palladium-catalyzed carbonylation than aryl or alkenyl halides.<sup>11</sup> In general, a large positive pressure of carbon monoxide is necessary to drive these reactions forward.



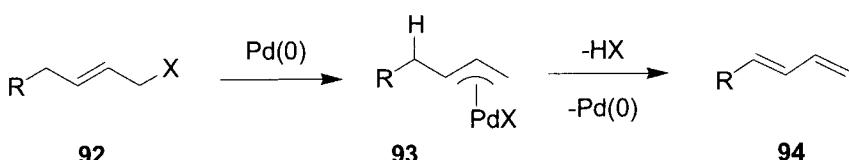
While carbonylation of allylic halides occurs with reasonable rates, allylic carbonates are the most reactive substrates. For example, carbonylation of carbonate **88** proceeds under relatively mild conditions to furnish allylic ester **89** in good yield.<sup>59</sup>

Since it is known that  $\pi$ -allylpalladium acetate is converted to allyl acetate by reductive elimination when treated by CO, it is understandable that carbonylation of allylic acetates is problematic.<sup>11</sup> Forcing conditions and additives such as NaBr can aid this reaction however. For example, under a high pressure of carbon monoxide and with NaBr as an additive, allylic acetate **90** was converted to allylic ester **91** in good yield.<sup>60</sup> It has been suggested this reaction could proceed via the allylic bromide.<sup>11,60</sup>

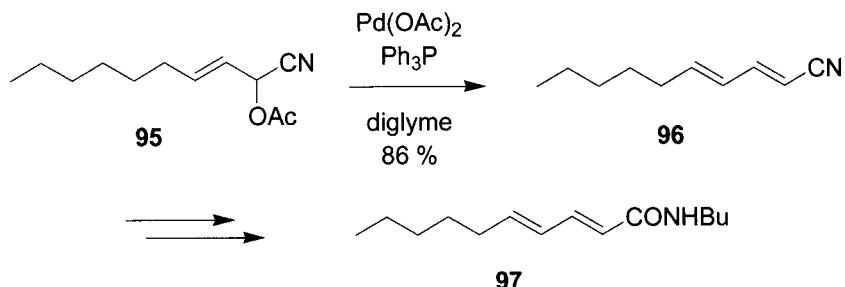


#### *Elimination to Form Conjugated Dienes*

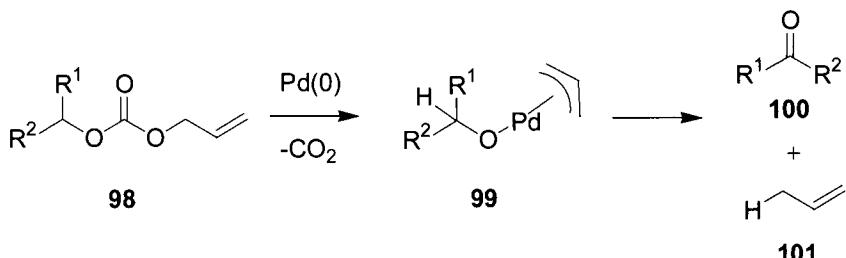
When allylic compounds are exposed to palladium(0) in the absence of any suitable nucleophiles, 1,4-elimination occurs to yield conjugated dienes.<sup>11</sup> Following oxidative addition, hydride elimination from  $\pi$ -allylpalladium compound **93** gives conjugated diene **94**, often as a mixture of *E*- and *Z*-isomers.<sup>11</sup>



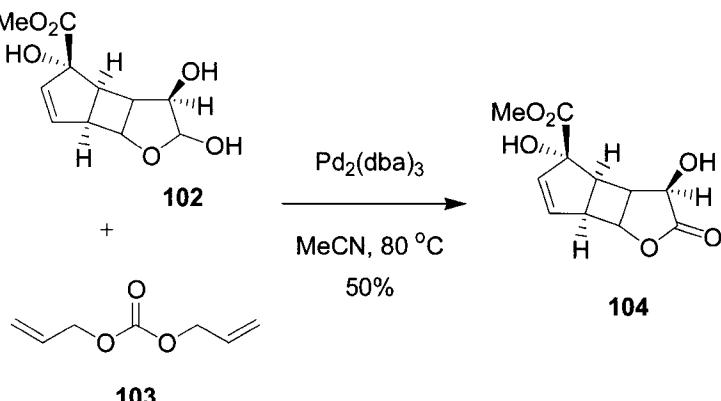
This strategy has been exploited in the synthesis of variety of naturally occurring compounds such as pheromones and steroids.<sup>11</sup> For example, selective elimination of the acetate moiety from cyanohydrin derivative **95** was used to prepare key intermediate **96**. Diene **96** was subsequently elaborated to pellitorine (**97**).<sup>61</sup>



*Oxidation of Alcohols*



Smooth oxidation of alcohols under mild, neutral conditions can be achieved via  $\pi$ -allylpalladium intermediates. The reaction of aliphatic allyl carbonate **98** with a palladium(0) catalyst generates palladium alkoxide species **99**, which subsequently undergoes  $\beta$ -hydride elimination to give carbonyl compound **100**. This reaction is very clean since the by-products are  $\text{CO}_2$  and propylene (**101**).<sup>62</sup> The reaction can readily be applied to secondary alcohols, allylic primary and secondary alcohols and benzylic alcohols. The oxidation of primary alcohols is prohibitively slow.

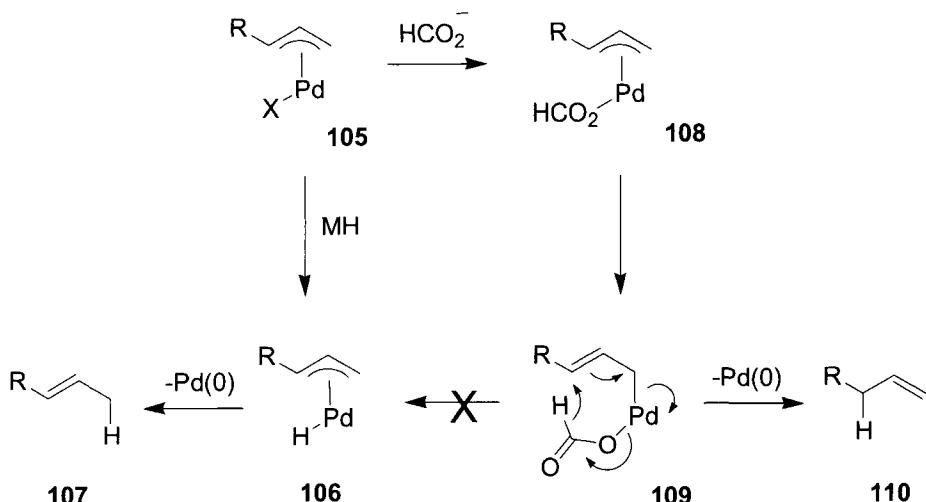


Indeed the slow oxidation of primary alcohols enables the use of external allylating agents as oxidants. For example, unprotected lactol **102** was selectively oxidized with diallyl carbonate **103** to yield lactone **104**.<sup>63</sup> Lactone **104** was subsequently used in the synthesis of echinosporin.

#### *Hydrogenolysis of Allylic Compounds.*

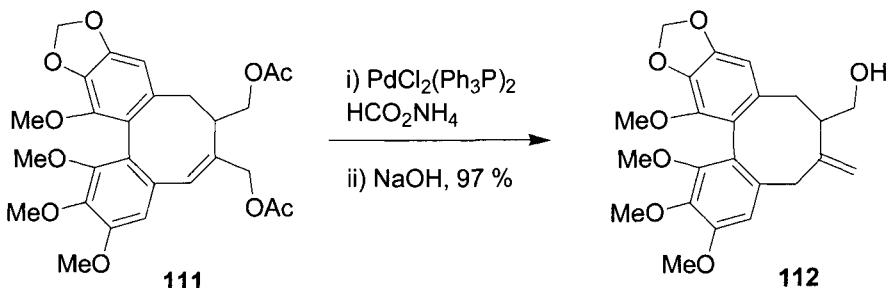
Palladium-catalyzed hydrogenolysis of allylic compounds gives access to alkene products. While initial studies focused on the use of ammonium formate as a hydride source, subsequent studies showed a plethora of metal hydride agents could be employed, including  $\text{LiAlH}_4$ ,  $\text{NaBH}_4$ , hydrosilanes, tin hydrides, *etc.*<sup>11</sup> These studies highlighted an interesting regiochemical issue. For all reducing agents apart from formate, the reduction of terminal allylic compounds gave the more substituted 2-alkenes, whereas for formate, the terminal 1-alkene is produced.<sup>11</sup>

Mechanistically, this can be rationalized as follows.<sup>11</sup> Exposure of  $\pi$ -allylpalladium complex **105** to a metal hydride species results in transmetallation to give palladium species **106**. The hydride is then transferred to the less hindered side of the allylic system by reductive elimination, furnishing the internal alkene **107**. In the presence of formate however, ligand exchange gives palladium complex **108**, which can undergo concerted decarboxylation and hydride transfer to give terminal alkene **110**. Formation of  $\pi$ -allylpalladium formate **108** in the hydrogenolysis was confirmed by NMR studies.<sup>64</sup>



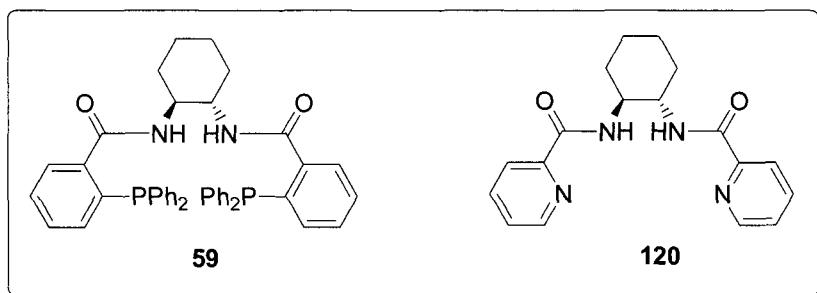
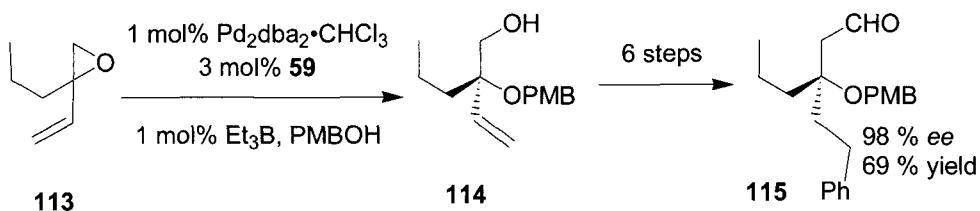
There are many examples of this reaction in the preparation of both cyclic and acyclic compounds.<sup>11</sup> For example, regioselective hydrogenolysis

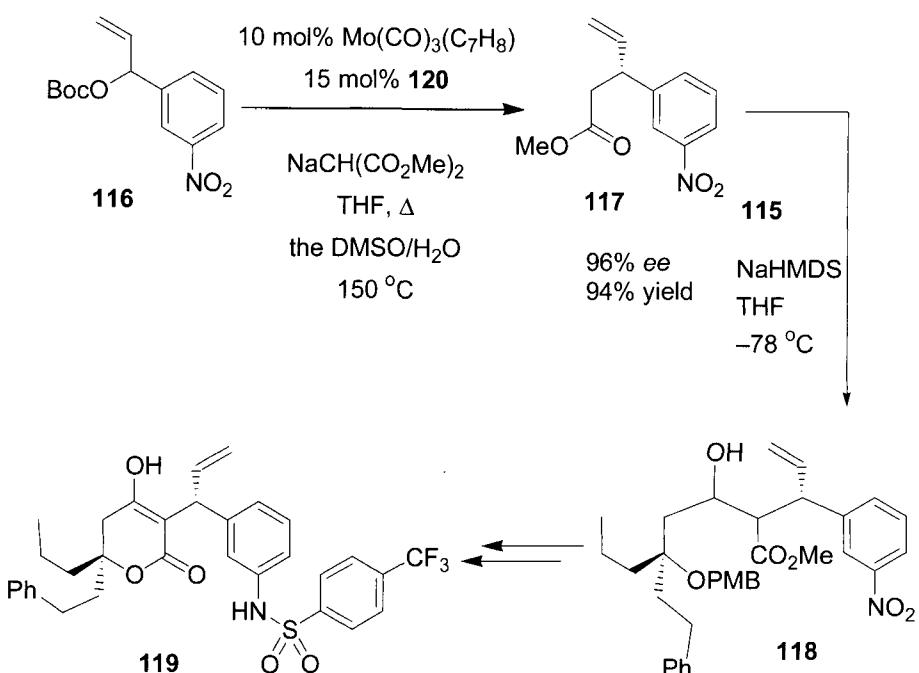
of compound **111** furnished the desired product **112** bearing an *exo*-methylene group in almost quantitative yield. This compound was subsequently used in the preparation of gomisin A and schizandrin.<sup>65</sup> Asymmetric reductions have also been reported using this reaction pathway.<sup>66</sup>



## *Other Metal Catalysts*

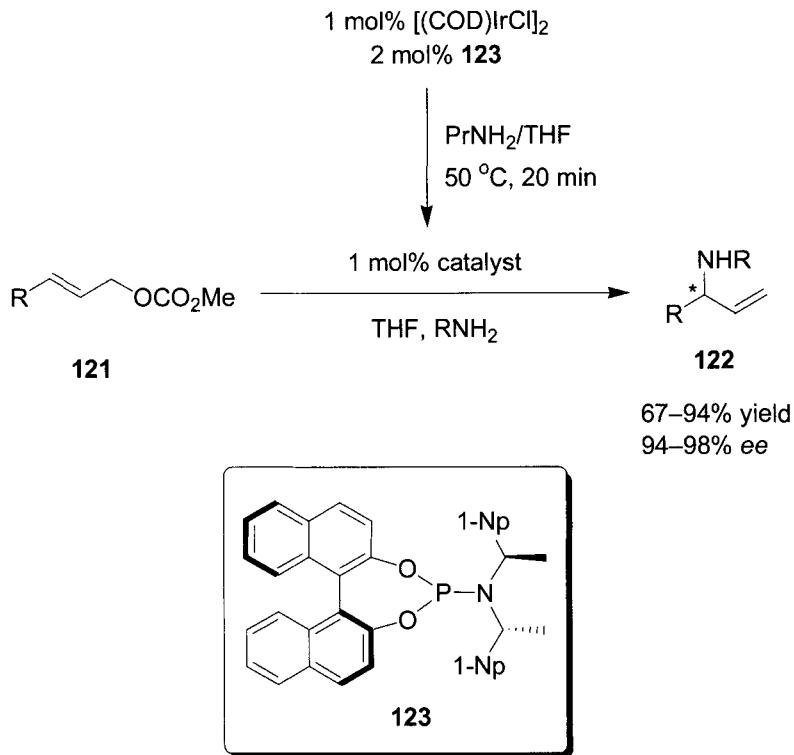
Several other metal catalysts have been shown to mediate the Tsuji–Trost reaction, with molybdenum being the most developed. Trost first reported the use of molybdenum for allylic alkylation in 1982.<sup>67</sup> The most important aspect of the use of this metal is its regiocomplementary with the palladium-catalyzed process. While palladium preferentially gives linear adducts (in the absence of electronic bias), molybdenum gives preferentially branched adducts.<sup>67,17</sup>





Just like palladium, the molybdenum-catalyzed reaction has been extended to an asymmetric variant. Following development of the reaction by Trost and co-workers,<sup>68</sup> they reported a concise and efficient synthesis of the HIV therapeutic tipranavir (**119**).<sup>69</sup> While the key tetrasubstituted centre in compound **115** was constructed by a palladium–boron co-catalyzed DYKAT reaction, the stereogenic centre in nitroaromatic **117** was installed in a molybdenum-catalyzed DYKAT reaction. Both compounds were subsequently elaborated to tipranavir (**119**). While it has been determined that the molybdenum-catalyzed reaction proceeds with overall retention, the stereochemistry of each step has not been extensively studied. Recent studies have suggested a retention–retention pathway may be in operation.<sup>70</sup>

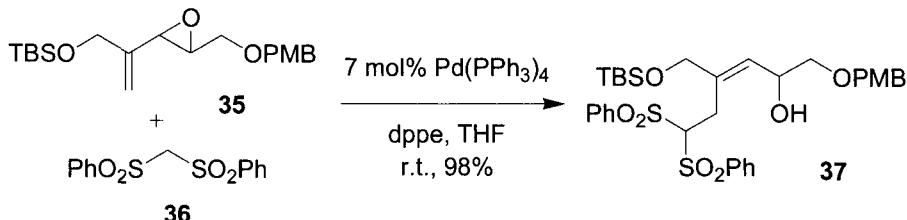
Progress has also been made in the use of other metals. For example, iridium-catalyzed processes have been developed for AAA reactions.<sup>17</sup> The regioselectivity of this reaction is analogous to molybdenum. Allylation of “soft” carbon nucleophiles has been reported using chiral iridium complexes, with the products isolated in high enantiomeric purity (> 91% *ee*).<sup>71,72</sup> Hartwig has reported the use of chiral iridium complexes derived from ligand **123** in the formation of chiral allylic amines.<sup>73</sup> The branched amines **122** were isolated in moderate to good yield and excellent enantiomeric purity (> 94% *ee*).



Nickel and platinum mediated allylation reactions have been reported and in terms of AAA reactions, perhaps the most useful processes have involved “hard” nucleophiles.<sup>17</sup> For example, high enantioselectivities have been realized in nickel-catalyzed processes employing Grignard reagents.<sup>74</sup> Tungsten has also been used in Tsuji–Trost type reactions, however it has thus far not been applied to complex molecule synthesis.<sup>17</sup>

### 1.1.8.6 *Experimental*

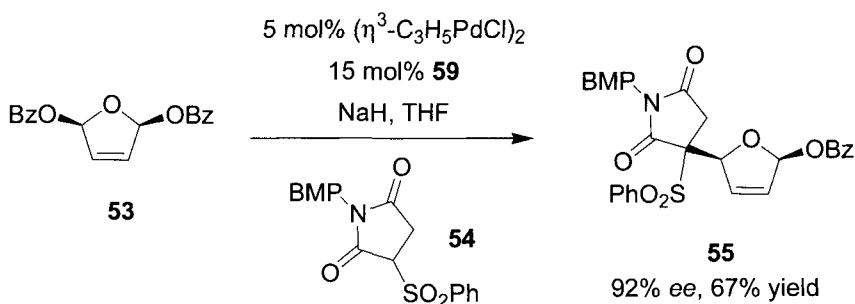
#### *Tsuji–Trost Reaction*



**6,6-Bis(phenylsulfonyl)-4-(tert-butyldimethylsilanyloxymethyl)-1-(4-methoxy-benzyl)-hex-3-en-2-ol (37).<sup>37</sup>**

To a solution of Pd(PPh<sub>3</sub>)<sub>4</sub> (280 mg, 0.24 mmol), dppe (182 mg, 4.6 mmol) and bis(phenylsulfonyl)methane (**36**) (1.007 g, 3.40 mmol) in THF (100 mL) was added epoxide **35** (1.25 g, 3.43 mmol) and the resulting mixture was stirred for 14 h at ambient temperature. An aqueous extractive work-up followed by flash chromatography of the crude material (hexane/EtOAc, 10/1 → 4/1) afforded product **37** as a colorless syrup (2.20 g, 98%, mixture of diastereoisomers).

*AAA reaction*



**Preparation of (2*S*,5*S*)-2-[3'-Phenylsulfonyl-*N'*-(4-methoxybenzyl)succinimid-3'-yl]-5-benzoyloxy-2,5-dihydrofuran (55).<sup>43</sup>**

To sodium hydride (68% oil, 3.9 mg, 0.097 mmol) in a cooled sonicator bath (0 °C) was added **54** (46 mg, 0.13 mmol) in THF (300 μL). The mixture was degassed with argon while bubbling ensued for 3–5 min. A prestirred solution of **53** (20 mg, 0.064 mmol), bis( $\eta^3$ -allyl)di- $\mu$ -chlorodipalladium (0.5 mg, 5 mol% Pd), and ligand **59** (3.0 mg, 15%) in THF (300 μL) under argon was cannulated into the solution of nucleophile in the sonicator. Additional THF was added to help wash all the material into the reactive flask (200 μL, 0.08M overall). The reaction mixture was degassed by bubbling with argon with sonication for 10 min. The mixture was sealed and stirred for 4 h at 0 °C. Direct application to flash chromatography (50 : 50 petroleum ether/ethyl acetate) gave a crude oil with a ratio of starting material to product of 8 : 92. The product was purified by flash chromatography (75 : 25 petroleum ether/ethyl acetate) to give 24 mg (67%) of **55** as a colorless oil. The diastereomeric ratio was 7 : 3 by proton NMR. The diastereomers were separated by flash chromatography (80 : 20 petroleum ether/ethyl acetate) for enantiomeric excess determination by chiral HPLC. The enantiomeric excess for both the major and minor diastereomers was 92%.

### 1.1.8.7 References

1. [R] Trost, B. M. In *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W., Sharpless, K. B., Eds.; VCH: New York, 1986.
2. [R] Trost, B. M. *Pure Appl. Chem.* **1981**, *53*, 2357.
3. [R] Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Ed.; Pergamon Press: Oxford, 1982; Vol. 8, Chapter 57.
4. [R] Tsuji, J. *Pure Appl. Chem.* **1982**, *54*, 197.
5. [R] Tsuji, J. *Tetrahedron*, **1986**, *42*, 4361.
6. [R] Trost, B. M. *Chemtracts: Org. Chem.* **1988**, *1*, 415.
7. [R] Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1173.
8. [R] Trost, B. M. *ACS Adv. Chem.* **1992**, *230*, 463.
9. [R] Godleski, S. A. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming, I., Semmerlack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, Chapter 3.3.
10. [R] Frost, C. G.; Howart, J.; Williams, J. M. J.; *Tetrahedron: Asymmetry*, **1992**, *3*, 1089.
11. [R] Tsuji, J. In *Palladium Reagents and Catalysts*; John Wiley & Sons: New York, 1995; Chapter 4.2.
12. [R] Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395.
13. [R] Moberg, C.; Bremberg, U.; Hallman, K.; Svensson, M.; Norrby, P.-O.; Hallberg, A.; Larhed, M.; Csoregh, I. *Pure Appl. Chem.* **1999**, *71*, 1477.
14. [R] Acemoglu, L.; Williams, J. M. J. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Eds.; John Wiley & Sons: New York, 2002; Vol. 2, 1689–1705.
15. [R] Mandai, T. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Eds.; John Wiley & Sons: New York, 2002; Vol. 2, 1845–1858.
16. [R] Tsuji, J. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Eds.; John Wiley & Sons: New York, 2002; Vol. 2, 1669–1687.
17. [R] Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921.
18. [R] Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813.
19. Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387.
20. Tsuji, J.; Takahashi, H. *J. Am. Chem. Soc.* **1965**, *87*, 3275.
21. Tsuji, J. *New. J. Chem.* **2000**, *24*, 127.
22. Tsuji, J.; Kiji, J.; Morikawa, M. *J. Am. Chem. Soc.* **1964**, *86*, 4350.
23. Takahashi, S.; Shibano, T.; Hagihara, N. *Tetrahedron Lett.* **1967**, 2451.
24. Smutny, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 6793.
25. Hata, G.; Takahashi, K.; Miyaka, J. *Chem. Soc., Chem. Commun.* **1970**, 1392.
26. Atkins, K. E.; Walker, W. E.; Manyik, R. M. *Tetrahedron Lett.* **1970**, 3821.
27. Trost, B. M.; Fullerton, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 292.
28. [R] Trost, B. M. *Acc. Chem. Res.* **1980**, *13*, 385.
29. Trost, B. M.; Hung, M.-H. *J. Am. Chem. Soc.* **1984**, *106*, 6837.
30. [R] Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747.
31. Trost, B. M.; Strege, P. E. *J. Am. Chem. Soc.* **1977**, *99*, 1650.
32. Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 2871.
33. Nilsson, Y. I. M.; Andersson, P. G.; Bäckvall, J. E. *J. Am. Chem. Soc.* **1993**, *115*, 6609.
34. Cuvigny, T.; Julia, M.; Rolando, C. *J. Organomet. Chem.* **1985**, *285*, 395.
35. Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3865.
36. Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorenson, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393.
37. Fürstner, A.; Gastner, T. *Org. Lett.* **2000**, *2*, 2467.
38. Seki, M.; Mori, Y.; Hatsuda, M.; Yamada, S. *J. Org. Chem.* **2002**, *67*, 5527.
39. Deardorff, D. R.; Myles, D. C.; MacFerrin, K. D. *Tetrahedron Lett.* **1985**, *26*, 5615.
40. Williams, D. R.; Meyer, K. G. *Org. Lett.* **1999**, *1*, 1303.
41. Matsushita, H.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1982**, 160.
42. Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2591.
43. Trost, B. M.; Kallander, L. S. *J. Org. Chem.* **1999**, *64*, 5427.

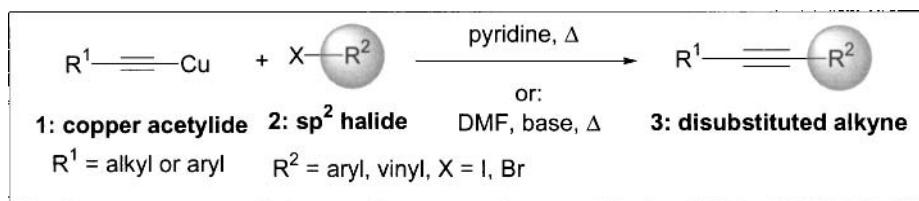
44. [R] Trost, B. M.; Machacek, M. R.; Aponick, A. *Acc. Chem. Res.* **2006**, *39*, 747.
45. Amatore, C.; Jutand, A.; Mensah, L.; Ricard, L. *J. Organomet. Chem.* **2007**, *692*, 1457.
46. Andersson, P. G.; Harden, A.; Tanner, D.; Norrby, P. D. *Chem. Eur. J.* **1995**, *1*, 12.
47. Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339.
48. Hayashi, T.; Yamamoto, A.; Ito, Y.; Hagiwara, T. *Tetrahedron Lett.* **1986**, *27*, 191.
49. Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.
50. Evans, D. A.; Campos, K. R. Tedrow, J. S.; Michael, F. E.; Gagne, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905.
51. Sprinz, J.; Kiefer, M.; Helmchen, G.; Reggelin, M.; Huttner, G.; Walter, O.; Zsolnai, L. *Tetrahedron Lett.* **1994**, *35*, 1523.
52. (a) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 3090; (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 3543.
53. Trost, B. M.; Patterson, D. E.; Hembre, E. *J. Am. Chem. Soc.* **1999**, *121*, 10834.
54. You, S. L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471.
55. (a) Trost, B. M.; Madsen, R.; Guile, S. D.; Brown, B. *J. Am. Chem. Soc.* **2000**, *122*, 5947; (b) Trost, B. M.; Madsen, R.; Guile, S. D.; Elia, A. E. H. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1569.
56. Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444.
57. Trost, B. M.; Organ, M. G.; O'Doherty, G. A.; *J. Am. Chem. Soc.* **1995**, *117*, 9662.
58. Trost, B. M.; Nanninga, T. N.; *J. Am. Chem. Soc.* **1985**, *107*, 1293.
59. Tsuji, J.; Sato, K.; Okumoto, H. *Tetrahedron Lett.* **1982**, *23*, 5189.
60. Murahashi, S.; Imada, Y.; Taniguchi, Y.; Higashiuira, *Tetrahedron Lett.* **1988**, *29*, 4945.
61. Mandai, T.; Gotoh, J.; Otera, J.; Kawada, M. *Chem. Lett.* **1980**, 313.
62. Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1984**, *25*, 279.
63. Smith, A. S.; Sulikowski, G. A.; Fujimoto, K. *J. Am. Chem. Soc.* **1989**, *111*, 8039.
64. Oshima, M.; Shimizu, I.; Yamamoto, A.; Ozawa, F. *Organometallics* **1991**, *10*, 1221.
65. Mukaiyama, C.; Mitsuhashi, H.; Wakamatsu, T. *Tetrahedron Lett.* **1992**, *33*, 4165.
66. Hayashi, T.; Iwamura, H.; Naito, M.; Matsumoto, Y.; Uozumi, Y.; Miki, M.; Yanagi, K. *J. Am. Chem. Soc.* **1994**, *116*, 775.
67. Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1982**, *104*, 5543.
68. Krsa, S. W.; Hughes, D. L.; Reamer, R. A.; Mathre, D. J.; Sun, Y.; Trost, B. M. *J. Am. Chem. Soc.* **2002**, *124*, 12656. And references therein.
69. Trost, B. M.; Anderson, N. G. *J. Am. Chem. Soc.* **2002**, *124*, 14320.
70. Hughes, D. L.; Lloyd-Jones, G.C.; Krsa, S. W.; Gourioua, L.; Bonnet, V. D.; Sun, Y.; Mathre, D. J.; Reamer, R. A. *Proc. Natl. Acad. Sci. USA.* **2004**, *101*, 5379.
71. Takeuchi, R.; Kashio, M. *J. Am. Chem. Soc.* **1998**, *120*, 8647.
72. Jannsen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025.
73. Leitner, A.; Shu, C.; Hartwig, J. F. *Org. Lett.* **2005**, *7*, 1093.
74. Gomez-Bengoa, E.; Heron, N. M.; Didiuk, M. T.; Luchaco, C. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 7649.

## 1.2.1 Castro–Stephens Reaction

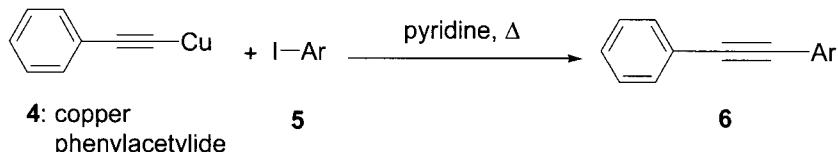
David L. Gray

### 1.2.1.1 Description

The Castro–Stephens reaction is the cross coupling of a copper acetylide (**1**) and an aryl or vinyl halide (**2**) to give a disubstituted alkyne (**3**).<sup>1</sup> The reaction, which shares some common elements with the Sonogashira, Cadiot–Chodkiewicz, Rosenmund–von Braun, Hay, and Glaser coupling reactions, was discovered by Stephens and Castro in the early 1960s and has found some applications in synthesis.<sup>2–5</sup>

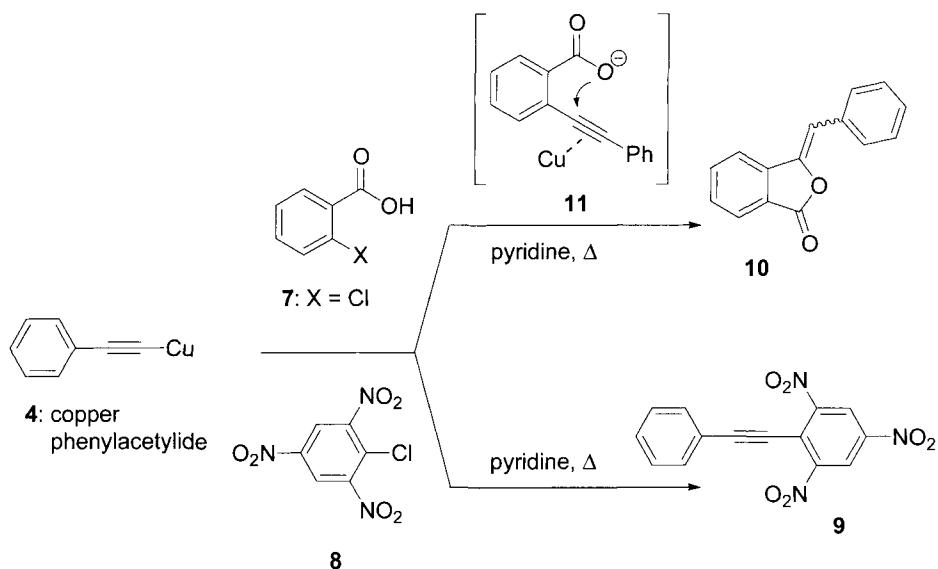


In many ways, the utility of the Castro–Stephens coupling has been supplanted by the more convenient Sonogashira coupling because the latter palladium-based reaction accesses the same target space with broader scope and functional group toleration, milder conditions, and greater operational simplicity (see 1.1.5).<sup>6</sup> There are a very few instances where the Castro–Stephens reaction is a superior option, but the need to pre-generate a air-sensitive and potentially explosive copper acetylide in the traditional protocol had made it a less popular choice for disubstituted alkyne synthesis. Perhaps 70% of published traditional Castro–Stephens couplings involve the union of copper (I) phenylacetylide (**4**) and an aryl iodide (**5**) to give linearly linked biphenyl compounds like **6**. Advancements in Castro–Stephens methodology have given the chemist simpler procedures for this reaction and have marginally broadened the scope of this process.



A somewhat limited range of coupling partners participates in Castro–Stephens coupling chemistry. Substrates tend to be simple, robust molecules that can stand up to basic copper salt solutions during prolonged

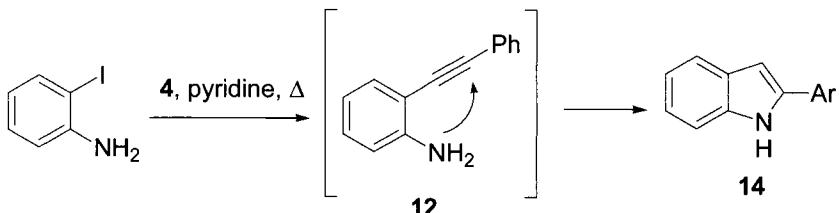
heating to 110 °C or more and many common functional groups are not tolerated. For the halide partner, examples of coupling to aryl bromides are extremely rare – limited to cases where the aryl ring is further activated by an electron withdrawing group.<sup>7</sup> The two published classical Castro–Stephens couplings of **4** to aryl or vinyl chlorides were exemplified in Castro and Owsley's follow-up work on the reaction's scope, and are the special cases where the aryl chloride is either *ortho* to a carboxylic acid (e.g., 2-chlorobenzoic acid, **7**, X = Cl) or extremely activated (picryl chloride, **8**). Reaction of **8** with **4** in refluxing pyridine gave the expected biarylalkyne **9**, while the same protocol with **7** led to phthalide **11**, by way of alkynylated intermediate **10**.<sup>8</sup>



By definition, the reaction of a pre-generated copper acetylide requires stoichiometric copper, and the process generates one equivalent of a by-product copper(I) salt (usually cuprous iodide). The majority of successful reactions are carried out either in refluxing pyridine, or in DMF at elevated temperature, and reaction times often extend to 24 hours. One of the reasons for the narrow solvent range is that copper acetylides are insoluble polymeric species which are unavailable for any coupling chemistry until heated in particular polar solvents which have affinity for copper(I). Oxygen must be rigorously excluded to avoid the copper-mediated Glaser homocoupling of alkynes (see 1.2.2). An important advancement in the methodology introduced *in situ* formation of the copper acetylidyde, and later, reaction conditions that are catalytic in copper.

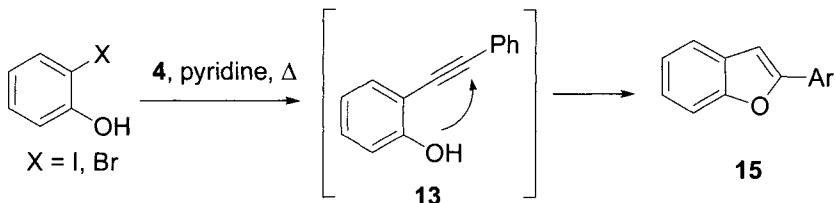
There is a great deal of nomenclature confusion in the Sonogashira/Castro–Stephens literature, with some authors calling palladium-based couplings “Castro–Stephens” reactions, and others calling copper-only procedures “palladium-free Sonogashira couplings”.<sup>9,10</sup> Presently, the term “Sonogashira reaction” has morphed to cover any coupling of a terminal alkyne and a halide, irrespective of metal catalyst or pre-activation requirements. A useful rule for distinction of the two name reactions is that the classical Castro–Stephens coupling is a copper-only process that utilizes a discrete, pre-formed copper acetylide, while the Sonogashira, as first conceived, features palladium (with co-catalytic cuprous halide) and starts from an unactivated alkyne.<sup>2</sup> Advances in both methodologies, particularly the *in situ* formation of copper acetylides for Castro–Stephens reactions, have blurred the lines between these two methodologies, and under some conditions, they share key mechanistic features. The substrate scope, reaction conditions, and postulated intermediates for the pre- and the *in situ*-generated copper acetylide coupling reactions are similar, therefore, the latter procedures will be considered Castro–Stephens-like couplings in this section. Owing to heightened sensitivity within the chemical community toward the depletion of non-renewable resources (like precious noble metals) and also because of cost considerations, there has been renewed interest in copper-based cross coupling for C–N, C–O, and C–C bond formation including a number of advancements in so-called “palladium-free” Sonogashira couplings.

### 1.2.1.2 *Historical Perspective*



C. E. Castro and R. D. Stephens were working at the University of California, Riverside in the Chemistry and Nematology Departments where they were studying metal-promoted reductions of alkynes as well as heterocycle formation from *ortho*-heteroatom substituted biaryl acetylenes. They found that some of the required precursors for this work could be prepared by “exposing aryl iodides to cuprous acetylides in refluxing pyridine”. In many cases, the coupled biaryl acetylenes (**11–13**) went on to cyclize with the *ortho*-oxygen or *ortho*-nitrogen atoms under those same conditions, thus the initial publications on this chemistry highlighted both the

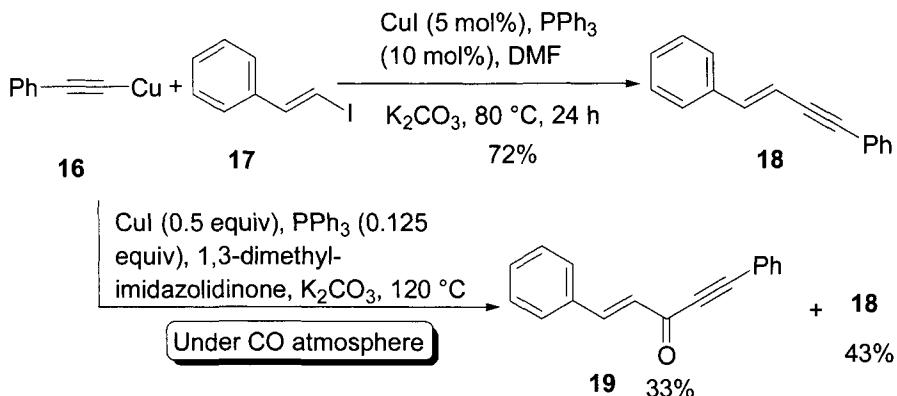
uncovered reactivity, and its utility in the synthesis of 2-arylindoles (**14**), 2-arylbenzofurans (**15**) and 3-benzylideneephthalides (**10**).



In their initial 1963 *Journal of Organic Chemistry* publication, Stephens and Castro proposed some potential reaction pathways and also noted the similarity of the reactivity they had uncovered to the much older Rosenmund von Braun displacement of aryl halides by copper cyanide.<sup>1</sup> In the next few years, Castro's laboratory did a relatively complete study of reaction scope for both the alkyne and halide components, exemplifying over 40 successful substrate pairs.<sup>8</sup> For the halide component, they included successful reactions with activated and deactivated aryl iodides, a pair of bromophenols, *o*-bromobenzoic acid, *o*-chlorobenzoic acid, picryl chloride, and an iodothiophene. On the alkyne side, they demonstrated that primarily phenyl, but also substituted phenyl, alkyl, pyridyl, propargyl alcohol, and propiolate acetylides would undergo productive reaction in pyridine or occasionally DMF. For some of the more reactive halides, room temperature reaction was demonstrated. Additionally, Castro showed that *in situ* formation of copper acetylides was possible for a half-dozen examples when *N*-ethylpiperidine was added to the reactions. This obviated the hassle of pre-forming the oxygen sensitive copper reagent for those substrates. Interestingly, in the intervening years, the scope they outlined in the mid 1960's has not expanded very much. Perhaps some of Castro's success can be attributed to a proficiency in generating, purifying, and handling cuprous acetylide reagents.

Copper acetylide ( $\text{Cu}\equiv\text{C}$ ) itself is highly explosive and other metal acetylides have explosive character.<sup>11</sup> Copper acetylides are generally synthesized by exposure of a terminal acetylene to  $\text{CuCl}$  in aqueous ammonia solution, and this treatment will cause the newly formed reagent to precipitate from the reaction mixture as a colourful, polymeric solid within minutes of adding the copper salt (see 1.2.1.6 for a preparation of copper(I) phenylacetylide **4**). It has been shown that successful Castro–Stephens coupling requires that this insoluble metal acetylide be carefully purified in an often lengthy process of rinsing and filtering. In 1993, Miura reported on a version of this reaction that was catalytic in copper salt and generated the required copper-bound alkyne *in situ* with a mixture of  $\text{CuI}$ ,  $\text{K}_2\text{CO}_3$ , and  $\text{PPh}_3$ .

in DMF at 120 °C.<sup>12,13</sup> The scope of this variant at least equalled what was available from pre-formed copper acetylide coupling, with aryl and vinyl iodides giving reliable coupling to copper acetylides generated *in situ*. For example, Miura reported that phenylacetylene (**16**) and *E*-vinyl iodide **17** unite to give **18** in 72% isolated yield at only 80 °C. Running the same reaction under carbon monoxide and in dimethylimidazolidinone with a slightly different phosphine/copper ratio yielded an appreciable amount (33%) of the carbonylated product **19** along with similar yields of expected ene-yne **18**.

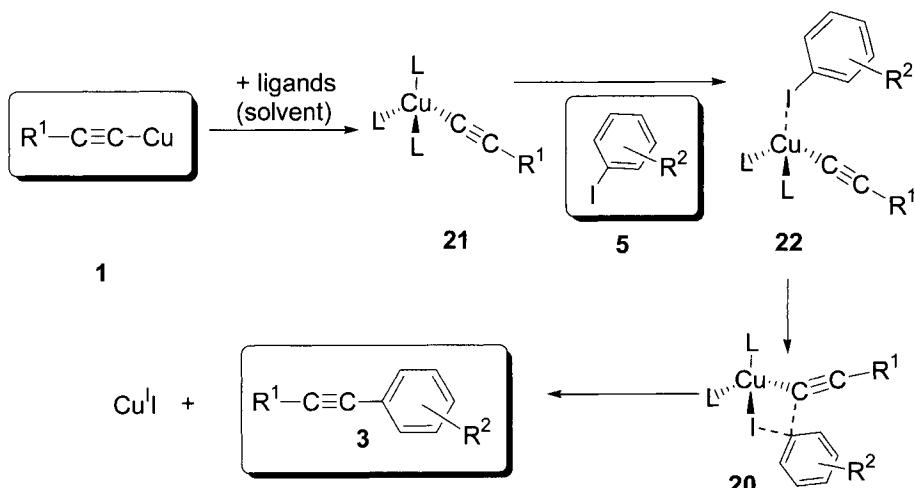


Modern extensions of Miura's work have yielded similarly simple *in situ* procedures which are also catalytic in copper and do not require pre-formation of a copper acetylide.<sup>14,15</sup> As a rule, regardless of Cu-acetylidyde origin, the scope of cross coupling with  $\text{sp}^2$  halides remains limited to activated (electron deficient) aryl bromides and vinyl, aryl, or activated heteroaryl iodides, and reaction temperatures below 100 °C or reaction times less than 3 hours are unusual. There are situations where the coupling of acetylene itself would be of interest. The formal product of acetylene coupling is obtained in other cross coupling methodology (e.g., Sonogashira reaction) by use of TMS–acetylene and later deprotection. That sequence is ineffective in the Castro–Stephens reaction because the copper acetylidyde of TMS–acetylene is inherently unstable and decomposes before it can react productively. It is uncertain if major advances in the traditional Castro–Stephens coupling methodology are on the horizon, however, there is significant contemporary effort going into developing copper-catalyzed reactions to synthesize disubstituted acetylenes (**3**) from **1** and **2**.

### 1.2.1.3 Mechanism

#### Mechanism of Classical Castro–Stephens Reaction

Copper is able to participate in cross coupling chemistry in ways that are similar to palladium. Indeed there are copper-promoted analogs to many of the common Pd-based coupling procedures. Distinct from palladium, however, is the more complex and dynamic redox chemistry of the copper metal center.<sup>16,17</sup> Copper exists in four stable oxidation states from 0 to +3, and is able to readily shuttle among oxidation states and access several coordination geometries in each oxidation state. For instance, Cu(I), is regularly observed in linear (2 ligand), trigonal (3 or 4 ligand), or T-shaped (3 ligand) geometries. To further complicate matters at the metal center, solvent effects on copper complexes are significant because organocopper compounds are found to be highly aggregated and frequently engage in three-center (bridging) copper-copper bonding. Where the discrete geometry and binary oxidation state of palladium has led to isolable intermediates and testable hypothesis for some palladium-based cross-coupling reaction mechanisms, the aforementioned fluidity and complexity of copper has hampered rigorous mechanistic studies of reactions like the Castro–Stephens.<sup>11</sup>



Copper acetylides have been characterized as polymeric species. They have notoriously poor solubility in organic solvents and are not completely soluble even in DMF at 100 °C, though this may be advantageous for cross-coupling because there is evidence that the reaction proceeded best under partially heterogenous conditions. The pKa of the acetylinic proton

does not seem to exert influence on reaction outcome, and this observation may make the Castro–Stephens coupling more attractive (vs. Sonogashira coupling) in certain systems. Stephens and Castro put forth a mechanistic hypothesis in 1963 that still has merit, and they provided some rationale for their proposed key transition state intermediate **20**. Building upon that framework, when a copper acetylide disassociates from its polymer state and goes into solution (**1**), it takes on additional solvent ligands to afford a tetrahedral complex **21**.

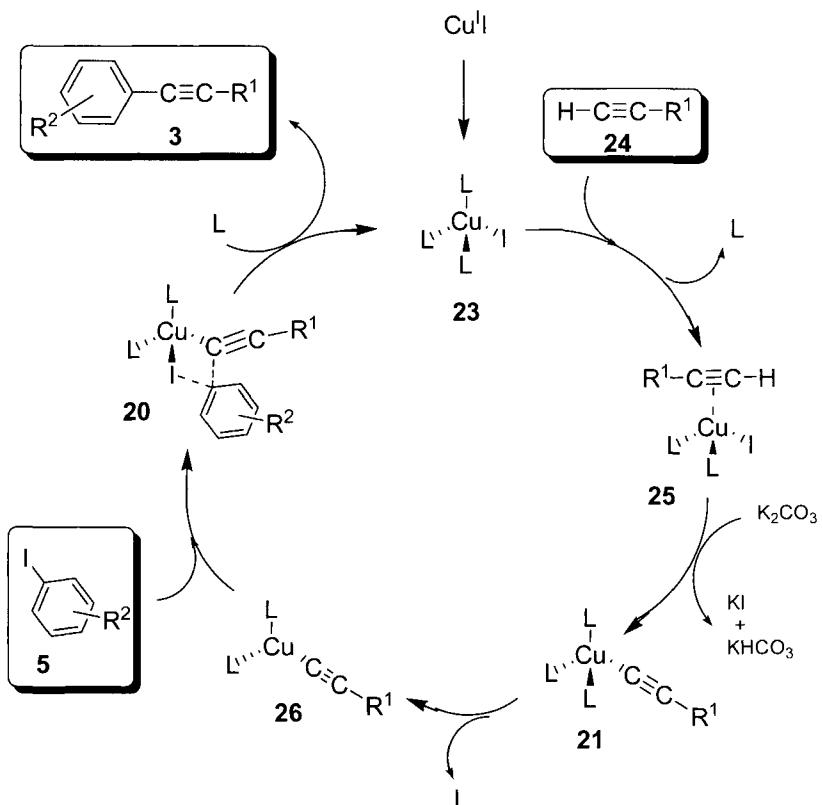
It is proposed that the coordination of this species with the halide component **5** occurs via a fleeting initial interaction of the copper and the halogen atom (complex **22**), which progressed to a bridging three-center bond with the halogen-bearing  $sp^2$  carbon in the transition state **20**. At this point, coupling of the two carbon ligands liberates the product **3** along with the favourable formation of CuI.

Hammett studies measuring the effect of ring substituents for copper promoted carbon substitution of aryl halides have demonstrated a weak positive correlation ( $\rho$ -values +0.1 to +1.1) which confirm the nucleophilic character of the copper reagent. The smaller  $\rho$ -values could indicate a weaker, through-atom-communication of the aryl ring's electronic information in the transition state. The three-center bonding represented in **20** is entirely consistent with the Hammett data as well as with the relative rate data for different halides, where the relative rates follow with the polarizability of the halides (e.g., I > Br > Cl), and aryl triflates do not react.<sup>11,16,17</sup> The very strong *ortho* effect of chelating heteroatom groups that Stephens and Castro noted (e.g., reaction of **7** → **10**) is also in line with intermediates like **20** and argues against mechanistically relevant  $\pi$ -complexation of copper to the arene.

#### *Catalytic Mechanism and in situ Acetylide Formation*

When Miura published the first example of a catalytic Castro–Stephens coupling, he made a number of careful mechanistic observations and proposed a catalytic cycle which incorporates many of the same intermediates (e.g., **20** and **21**) postulated for the non-catalytic reaction.<sup>13</sup> The entry into this catalytic cycle, copper iodide (**23**) is converted to the soluble, solvent ligated copper(I) species **24**. In this scheme, with the ligand PPh<sub>3</sub> present and no pyridine solvent to ligate copper, the ligands (L) could be phosphines. The metal activates a terminal alkyne (**25**), acidifying the proton for removal by base via a transient complex **26**. The mechanistic requirement for at least one equivalent of base is a difference between the stoichiometric copper reactions and the *in situ* catalytic methods. Following deprotonation, the copper acetylide **21** is proposed to lose a ligand to

generate a coordinatively unsaturated complex **27** which is predisposed to coordinate with the aryl halide component **5** in a halogen-centred 3-atom bond between copper and the aryl ring. Within this complex (**20**), bonding occurs between the alkyne and the aryl ring, ultimately leading to C–C bond formation, creation of coupled product **5**, and regeneration of the copper entry catalyst **24**. This proposal was based upon several important experimental results. First, when phenylacetylene (**16**) was treated with 0.5 equivalent of CuI in the presence of excess K<sub>2</sub>CO<sub>3</sub> in DMF at room temperature, the characteristic polymeric copper phenylacetylene **4** was quantitatively formed. This precipitate was a competent reagent and reacted with iodobenzene only at elevated temperature (where the polymer begins to dissolve into its soluble monomeric form) to deliver the desired coupling product. This result and the surrounding observations provided clear evidence that *in situ* formation of copper(I) acetylides was occurring under the reaction conditions, and that these acetylides were highly similar to pre-formed copper acetylide.



Second, Miura did a set of experiments to conclusively show that addition of  $\text{PPh}_3$  greatly accelerated the coupling reaction. This result was attributed to the ability of  $\text{PPh}_3$  to solubilise the copper acetylide (as species **21**). Using this observation, Miura reasoned that  $\text{PPh}_3$  must be coordinating to a copper(I) acetylide. He was able to isolate and partially characterize a labile complex which had spectral (FT-IR and X-ray fluorescence) properties consistent with **21** ( $\text{L} = \text{PPh}_3$ ). This complex was able to react with iodobenzene to afford coupling product **3** when heated with iodobenzene in DMF. In the course of studying this process, Miura examined the effects of varied ligands and found that stronger  $\sigma$ -donor ligands (stronger than  $\text{PPh}_3$ ) shut the reaction down. He hypothesized that accessing the coordinatively unsaturated species **27** might be difficult with very strongly donating ligands, thus providing some support for the putative complex **27**. Following Miura's work, publications using bidentate bipyridine and phenanthroline-based ligand systems have emerged.<sup>14</sup> The protocols that are catalytic in copper often use inorganic bases, and it is interesting to note that amine bases retard cross coupling in many of these catalytic reaction systems. Relative to the original Castro–Stephens conditions, all of these catalytic, *in situ* methods are more convenient, however, the reaction appears to have reached a reactivity wall with electron rich aryl bromides as these substrates are not coupled effectively by any of the newer procedures.

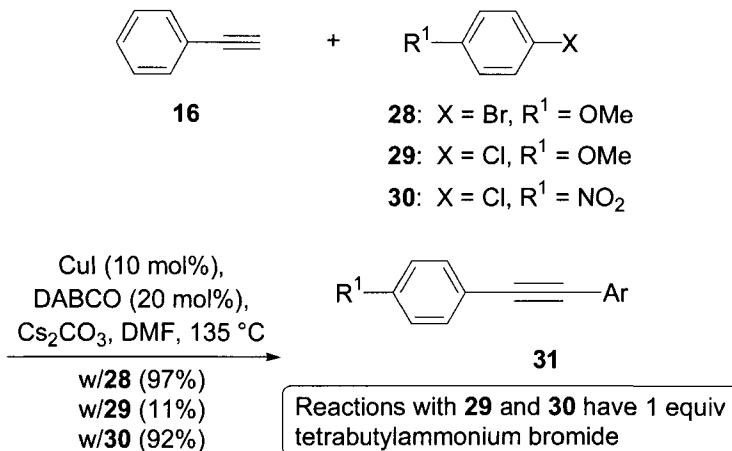
#### *Regioselectivity and Stereoselectivity*

Similar to the Sonogashira and related  $\text{sp}-\text{sp}^2$  couplings, there are no regio- or stereoselectivity complications in the Castro–Stephens coupling. Reaction conditions are quite vigorous, however, and where vinyl halides with defined geometry are used, the potential for olefin scrambling must be considered because there are rare cases where olefin isomerisation has been observed.<sup>18</sup>

#### *Ligand Effects*

Traditional Castro–Stephens couplings with pre-generated copper acetylides have not been aided by the addition of ligands for copper, and pyridine or other reaction solvent serves to fill coordination sites on the metal center. The general necessity to solubilise pre-formed (polymeric) copper acetylide with pyridine leads to a situation where a strong ligand for the copper (pyridine) is abundant and probably overrides any added ligand. For catalytic protocols, where copper acetylide can be accessed in a more soluble form (e.g., **21**,  $\text{L} = \text{PPh}_3$ ), monodentate phosphine, bidentate pyridine-based ligands, and low molecular weight PEG (polyethyleneglycol) have all been reported to be effective ligands in DMF or DMSO.<sup>14,19</sup> The most interesting

development along these lines is the methodology developed by J.-H. Li, which uses DABCO as a ligand under otherwise fairly typical Miyura conditions.<sup>20</sup>

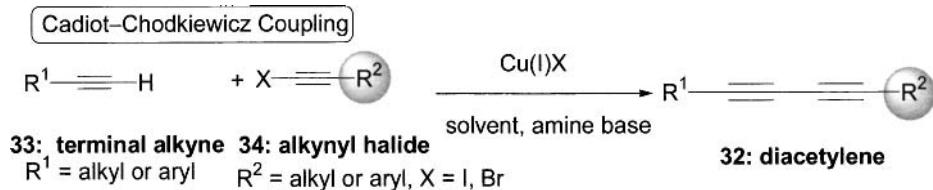


When 20 mol% of this base is added to 10 mol% CuI in DMF with 2 equivalents of Cs<sub>2</sub>CO<sub>3</sub>, the resulting catalyst is highly active for Castro–Stephens coupling of terminal alkynes and aryl bromides. For the reaction of **16** with *p*-bromoanisole **28**, the product **31** ( $\text{R}^1 = \text{OMe}$ ) is obtained in excellent yield after 24 hours at 140 °C. Most impressively, with the addition of one equivalent of tetrabutylammonium bromide, even *p*-methoxychlorobenzene **29** couples to **16** under these conditions, affording the desired product in 11% yield, while *p*-nitrochlorobenzene **30** couples with phenylacetylene in 92% yield (55% in the absence of the tetraalkylammonium salt). Alkyl alkynes also couple effectively to both aryl and vinyl iodides and bromides in this methodology. The DABCO ligand is highly effective for Castro–Stephens coupling, displaying a substrate scope not seen with any other copper-promoted Csp–Csp<sup>2</sup> coupling methodology. Interestingly, the same catalytic system (CuI, DABCO) is also effective for Suzuki couplings of aryl halides and boronic acids.<sup>20</sup>

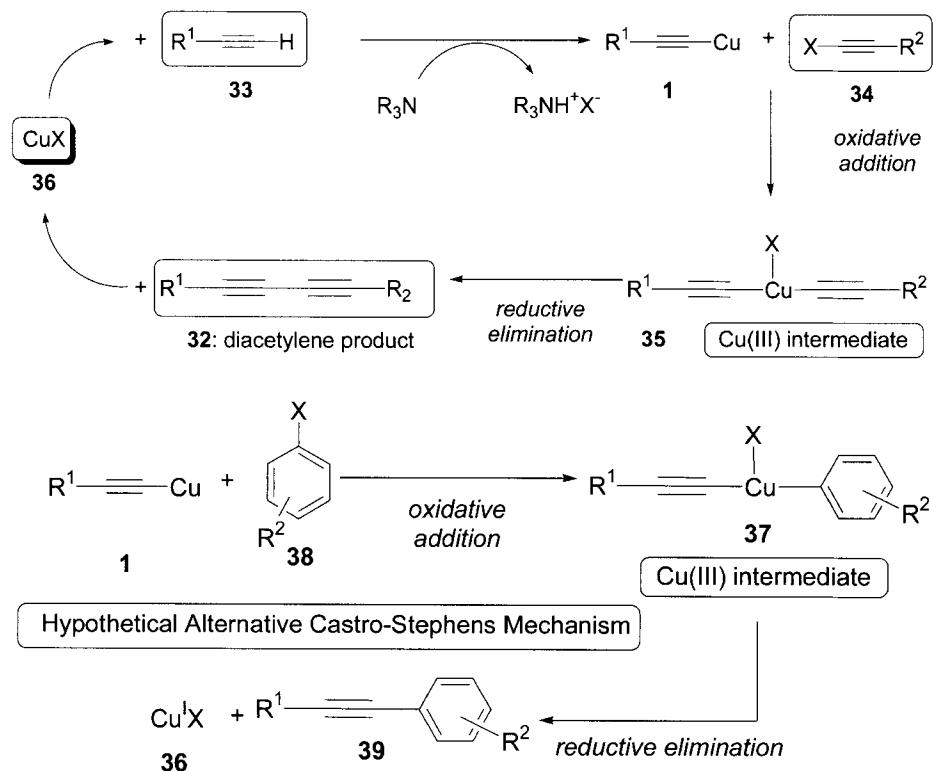
### Cadiot–Chodkiewicz Reaction

One of the reactions that has some mechanistic relationship to the Castro–Stephens coupling is the Cadiot–Chodkiewicz synthesis of unsymmetrical bis-alkynes (**32**).<sup>3</sup> This coupling reaction finds occasional use in modern synthesis. Like the Castro–Stephens, this cross coupling is promoted by cuprous halides and proceeds through a putative copper acetylide. The Cadiot–Chodkiewicz reaction requires a terminal alkyne (**33**), an alkynyl

halide (**34**), and a base, and typically goes to product under conditions which are considerably milder than Castro–Stephens couplings. Similar to most other copper-based homologation reactions, it is important to exclude oxygen to prevent the formation of copper(II).



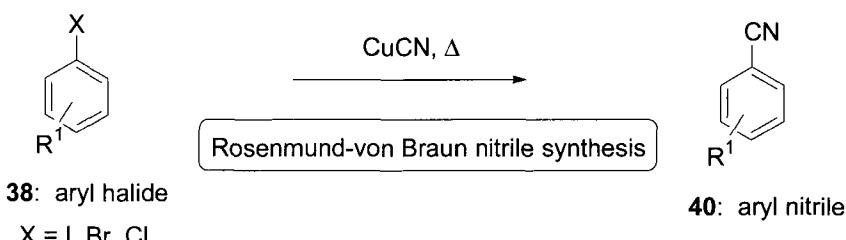
This reaction process takes advantage of the ease with which a copper acetylidyne will oxidatively insert into an alkynyl halide bond. The postulated mechanism begins with and *in situ* base- and Cu(I)-induced formation of a copper acetylidyne (**1**) from a terminal alkyne (**33**). This intermediate undergoes oxidative addition into the activated C–X bond of an alkynyl halide (**34**) to afford the copper(III) species **35**. Reductive elimination of the bis-alkyne **32** from complex **35** delivers the reaction product and regenerates the copper(I) halide **36** which may re-enter the catalytic cycle.



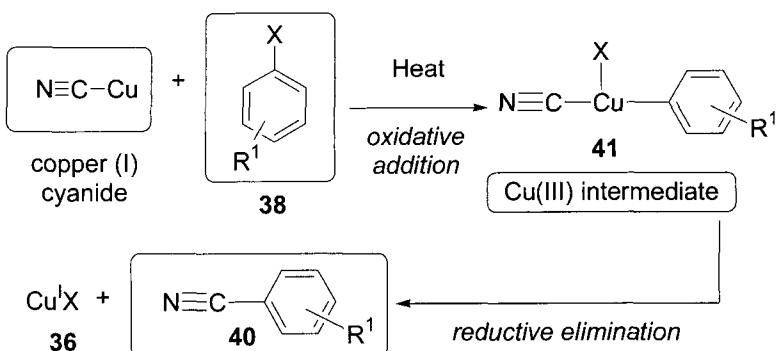
It is conceivable that a copper(III) intermediate like **35** could be involved in Castro–Stephens coupling, with copper acetylide **1** advancing through complex **37** after oxidative addition of the aryl halide (**5**). By analogy to the Cadiot–Chodkiewicz reaction, a reductive elimination event would liberate the disubstituted alkyne **39**. The evidences for the Castro–Stephens mechanism outlined in 1.2.1.3 are much more compelling at present, and experimental support for this alternate mechanism is lacking, but chemists working on copper-catalyzed cross coupling methodology would certainly benefit from additional mechanistic studies in this area.

### Rosenmund–von Braun Reaction

The Rosenmund–von Braun synthesis of aryl nitriles (**40**) from aryl halides (**38**) also shares some commonality with the Castro–Stephens reaction.<sup>4</sup> This transformation was discovered nearly a century ago, and was mentioned in the initial Castro–Stephens publication where the authors noted potential mechanistic similarity.



The typical Rosenmund–von Braun conditions are very harsh (200 °C neat), and product purification is generally troublesome, but the reaction is of historical interest and is occasionally used in the synthesis of simple aryl nitriles.

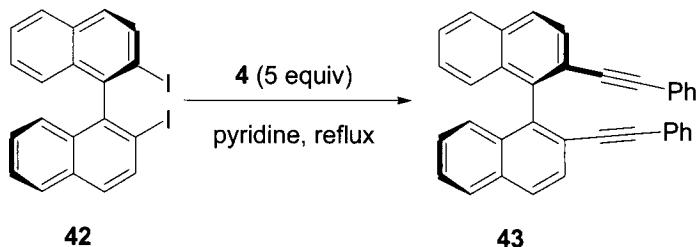


A possible mechanism for the conversion of aryl halides **38** to aryl nitriles **40** invokes a copper(III) intermediate **41**, which is reminiscent of the postulated key complex **35** in the Cadiot–Chodkiewicz mechanism outlined above. Despite the gross similarities among these three transformations, there is no clear evidence that the oxidative addition/elimination pathway and copper(III) intermediates which define the Cadiot–Chodkiewicz and Rosenmund–von Braun reaction mechanisms are operant in the typical Castro–Stephens coupling.

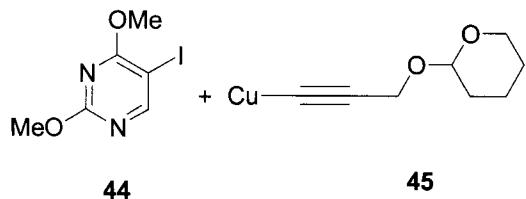
#### 1.2.1.4 Synthetic Utility

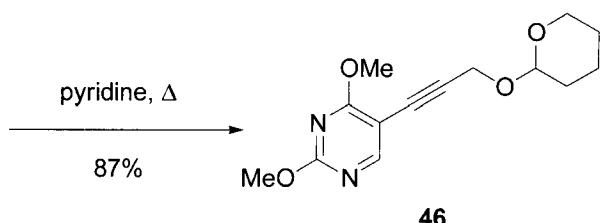
##### *Alkylation of Aryl Halides*

One example where Castro–Stephens reaction proved to be superior to other methods is the synthesis of the binaphthyl compound **43**. In this case, Sonogashira reaction on **42** afforded only an undesired helicene product, while the Castro–Stephens coupling with **4** gave the desired bis-alkyne **43** in 40% yield. Later a Negishi coupling approach was even more successful, delivering the same product in 90% yield.<sup>21</sup>



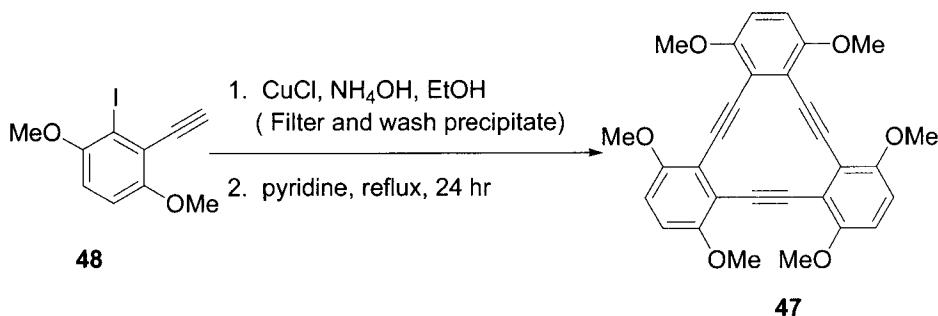
Copper acetylides of protected propargyl alcohols have been used as partners in Castro–Stephens couplings on multiple occasions. Coupling of iodopyrimidine **44** with the pre-formed copper reagent **45** was carried out in refluxing pyridine was complete in 2.5 hours, and gave the desired pyrimidine **46** in high yield. This intermediate was used to synthesize uracils with novel carbon substituents.<sup>22</sup>





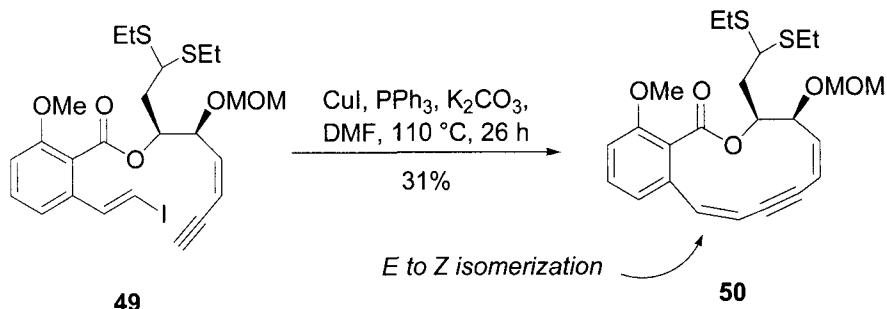
### Macrocycle Synthesis

Compounds like tribenzocyclotriyne **47** are of interest because they have the ability to form conducting complexes with low-valent nickel by virtue of their planar, anti-aromatic character and cavity size. Youngs *et al.* published a synthesis of **47** where cyclotrimerization of precursor **48** is accomplished by synthesizing and then purifying the copper acetylide of the latter iodo alkyne and then refluxing said material in pyridine for 24 hours. In this way, the desired cyclotrimer **47** is obtained in an impressive 80% yield. The palladium-based Sonogashira reaction was attempted for this same substrate (**48**) and was much less effective (5% yield of **47**). There are several examples where the Castro–Stephens approach was superior to other methods for creating cyclic arene/yne macrocycles.<sup>23,24</sup>



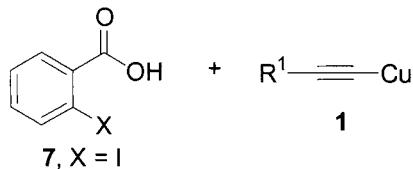
One of the few applications of the Castro–Stephens reaction to natural product synthesis is another example of the apparent suitability of the copper sp–sp<sup>2</sup> coupling for macrocyclic ring closure. As part of studies directed towards the synthesis of oximidine I, the copper-initiated coupling was mildly successful for the formation of a large ring via intramolecular closure of an *in situ*-formed copper acetylide and an *E*-vinyl iodide within **49**.<sup>18,25</sup> Thus following Miura's conditions, adding CuI, PPh<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, and compound **49** together in DMF and heating this mixture to 110 °C for 26 hours, provided a 31% yield of **50**. The obtained *cis/cis* diene geometry was postulated to arise via an isomerisation event caused by the high reaction temperature. Computational modelling of the **50** provided evidence that the

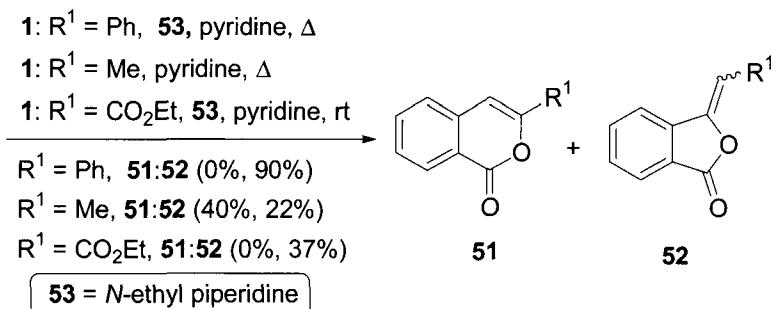
all *cis* arrangement was lower in energy than the initially formed *cis/trans* product.



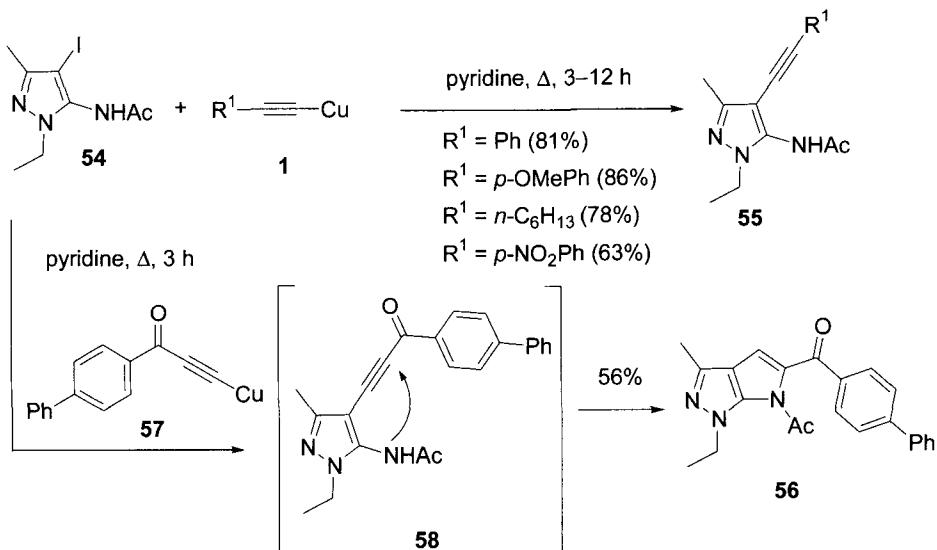
### Heterocycle Synthesis

In their first full disclosure of their reaction, Stephens and Castro reported that coupling acetylides to *ortho*-halobenzoic acids (**7**) led, via intermediate **11**, to isocoumarins **51**.<sup>1b</sup> Several years later, they corrected the structure of the product of this reaction, realizing that the post-coupling cyclization had occurred in a *5-exo*-dig arrangement to yield the benzylidene phthalide **52**. This reaction typifies the utility of the Castro–Stephens reaction in heterocycle synthesis, where examples are essentially limited to closure of *ortho*-heteroatoms onto a newly coupled alkyne, perhaps facilitated by the presence of copper. Castro did find one example where the small alkyl acetylidyde of propyne (**1**, R = Me) gave a quantity of the isocoumarin **51** in a mixture with **52**. The profound activation mediated by the *ortho* heteroatoms might come from a coordination of the heteroatom to the metal center, which would facilitate (by proximity) the formation of transition-state complex **20**. With iodobenzoic acid (**7**, X = I), unique examples of room temperature Castro–Stephens couplings were observed. Ethyl propiolate (**1**, R = CO<sub>2</sub>Et), **7**, and *N*-ethyl piperidine catalyst **53** in pyridine gave a 37% yield of phthalide **52** in a room temperature reaction.<sup>8</sup>



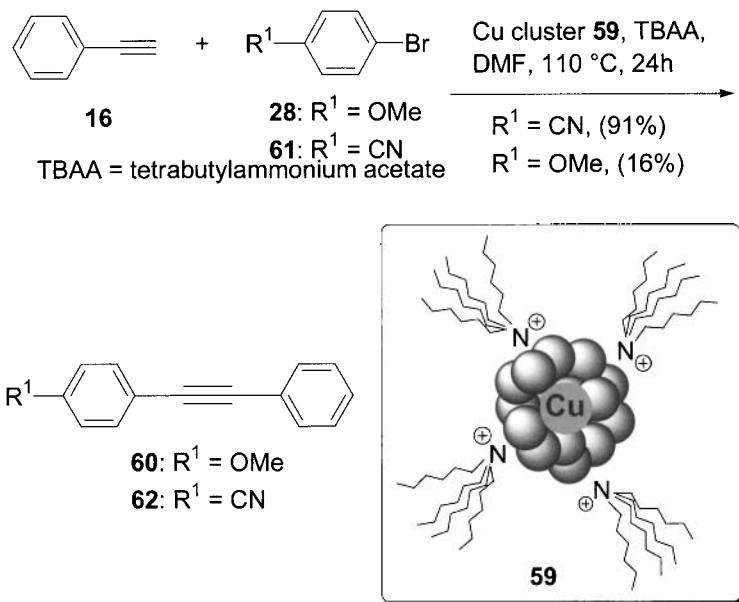


While attempting to couple iodopyrazine **54** to a terminal acetylene under Sonogashira conditions, Vasilevsky noted that the Castro–Stephens reaction was successful in some instances where Sonogashira reaction only gave starting material or side products, particularly with less acidic alkynes.<sup>26</sup> With limited examples, he concluded that for pyrazine iodides, the Sonogashira coupling doesn't work well above a pKa threshold for the alkyne. Others have noted pKa effects for the Sonogashira reaction.<sup>27</sup> A series of substituted copper phenylacetylides were reacted with **54** in refluxing pyridine. Good yields of products **55** were obtained with all groups. This synthesis could also be adapted to afford the heterocyclic derivative **56** from reaction with propiolic copper acetylidyde **57**. This cyclization is most likely occurring via homologated intermediate **58**, with ring closure aided by the presence of the ketone.



### 1.2.1.5 Variations and Improvements

#### Copper Nanoclusters – Heterogeneous Catalysis

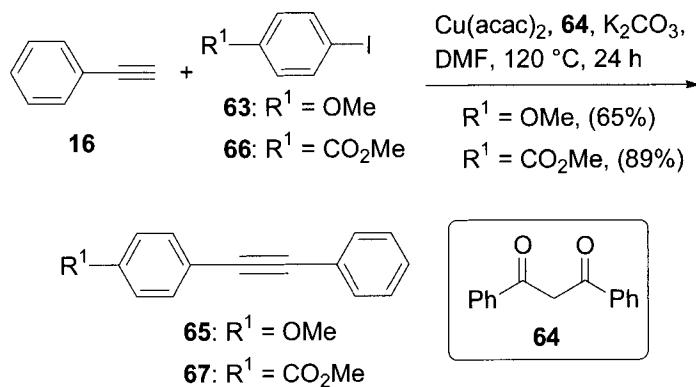


One of the driving forces behind the substitution of palladium for copper is a growing awareness of environmental and sustainable chemistry issues. Accordingly, the substitution of rare metals for more common elements and the use of protocols which allow for facile re-use of metal catalysts are important goals. The use of copper nanoclusters of 2–10 nM diameter (**59**) to catalyze Castro–Stephens reactions is a foothold into “green” arene–alkyne cross coupling.<sup>10</sup> The catalytic system consists of microscopic nanoclusters which are stabilized against self-aggregation by tetraalkylammonium salt additives. It is possible to conceptualize the entire nanoparticle as a substitute for a single copper atom, with developed charges shared across multiple copper centers and substrate ligands perhaps residing on different atoms. The nature of reacting species is poorly understood for nanoparticles, but the reactivity seen with these catalysts is promising. When alkyne **16** and *p*-bromoanisole (**28**) are heated to 110 °C for 24 hours with 5 mol% of these tiny copper clusters and tetrabutylammonium acetate as a base, a 16% yield of **60** was obtained. This reaction only proceeded with an alkylammonium aggregation inhibitor/stabilizer (tetraoctylammonium formate). The yield for the traditionally challenging reaction of **28** → **60** is unimpressive, however, with a handful of more favourable substrate pairs, such as the conversion of **61** to **62**, yields were excellent. One advantage for

such heterogeneous catalysts is that they can often be filtered and re-used. In this case, the catalysts began losing some activity after 3 recycles.

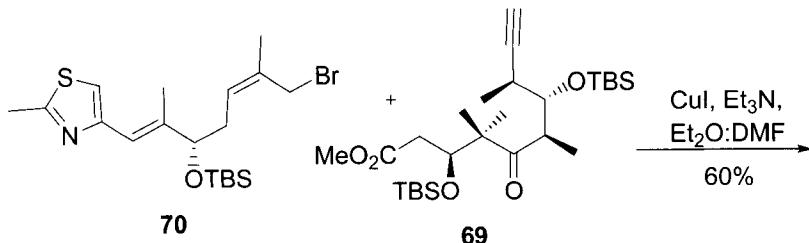
### Copper-Catalyzed Sonogashira

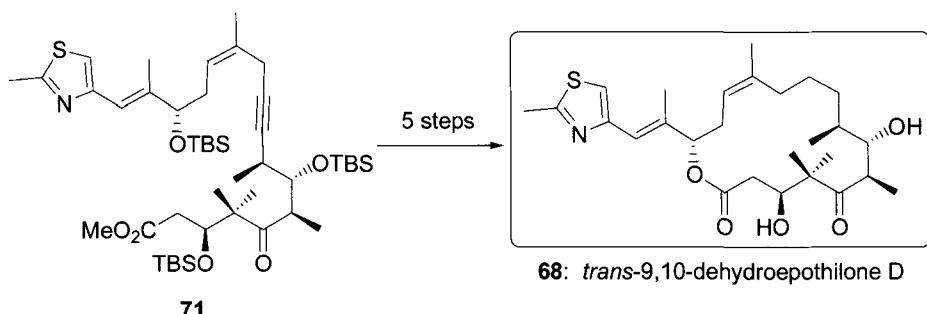
As efforts have accelerated to find copper-based methods for Csp<sup>2</sup>-O and Csp<sup>2</sup>-N bond formation, the developed ligands have found some application in Castro–Stephens type couplings of aryl iodides and terminal acetylenes. For example, phenylacetylene (**16**) was united to **63** under the influence of Cu(acac)<sub>2</sub> and the diketone ligand **64** in DMF. The product (**65**) was isolated in 65% yield. The more active iodoarene **66** yielded better yields of the expected disubstituted acetylene **67** when it was reacted under the same conditions.<sup>9</sup> Among the handful of bidentate ligands used to date in so called “palladium-free” Sonogashira coupling approaches, none have demonstrated robust coupling of aryl bromides to alkynes.



### Castro–Stephens-like Coupling with Allylic Halides

One of the other complex molecule examples which showcase a coupling under Castro–Stephens-like conditions appeared in the synthesis of dehydroepothilone D (**68**), an anti-mitotic agent of interest for its anti-proliferation activity.

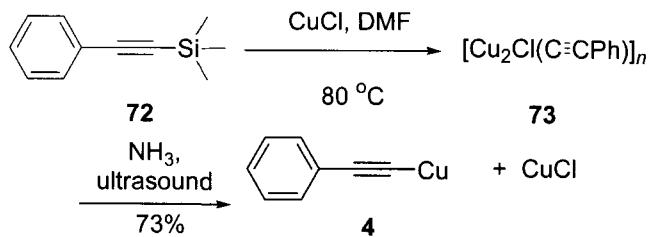




This synthesis included a Castro–Stephens-type coupling of two highly functionalized fragments, where **69**, and allylic bromide **70**, together with Et<sub>3</sub>N and CuI, were heated to 50 °C in an Et<sub>2</sub>O/DMF solvent system. With this treatment, a 60% yield of the coupled product **71** was obtained.<sup>28</sup> There are several other examples of allylic substitution with copper acetylides, and these reactions clearly occur under milder conditions than typical Castro–Stephens couplings.<sup>29</sup> This reaction may be more of an S<sub>N</sub>2 displacement, however, the net transformation and reaction conditions bear some similarity to the Castro–Stephens reaction.

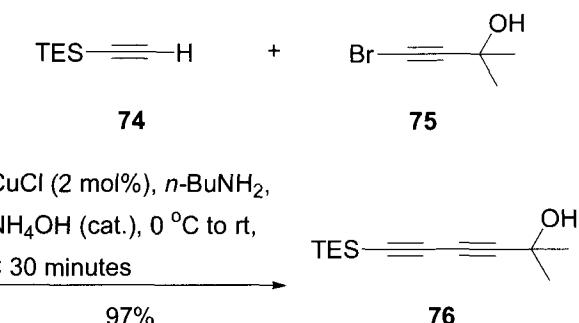
## *Silylated Alkynes*

Until recently, there has not been much of a role for silyl alkynes in Castro–Stephens reactions though they are ubiquitous in Pd-based alkyne couplings due to the extreme instability of TMS copper acetylide under typical reaction conditions. The stability of the acetylide increases as the alkyl group on silicon become larger. Advances in C–Si bond cleavage methodology has led to a few methods where silyl alkynes like **72** can be used as a reagent to generate reaction-competent copper(I) acetylides. In one such example, cuprous chloride in DMF is reported to cleave the C–Si bond in TMS–alkyne **72** to afford a discrete copper species **73**. This material was characterized and is not reactive as an acetylide, however, following additional processing, the desired reagent **4** is formed in good overall yield. The reagent thus obtained is viable in Castro–Stephens couplings.<sup>15,30</sup>

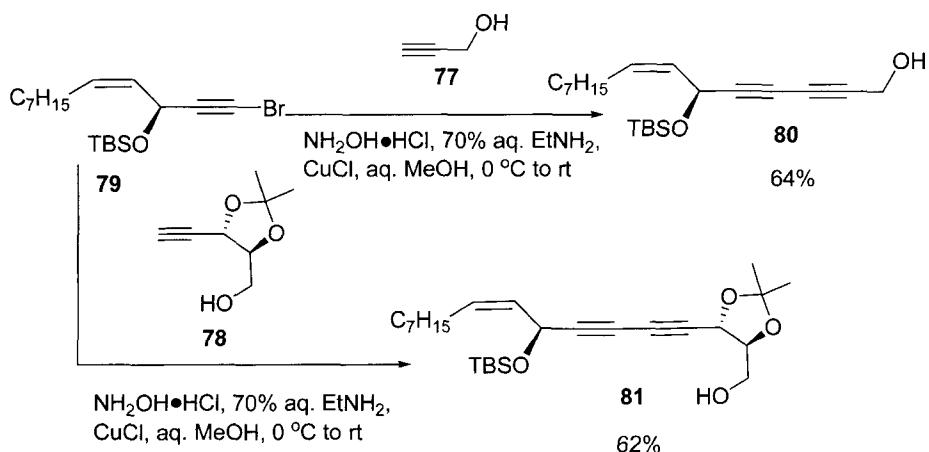


Related Processes—Cadiot-Chodkiewicz Reaction

The Cadiot–Chodkiewicz coupling typically proceeds under conditions which are considerably milder than Castro–Stephens reactions. Triethylsilylacetylene **74** rapidly undergoes Cadiot–Chodkiewicz coupling with alkynyl bromide **75** to generate the unsymmetrical bisalkyne **76** in nearly quantitative yield when those two reactants are treated with catalytic cuprous chloride and catalytic ammonium hydroxide in *n*-butylamine solution. This coupling process affords one of the best entries into compounds such as **76** and is permissive of TES and larger silylated copper acetylide species because of the lower reaction temperature.<sup>31</sup>

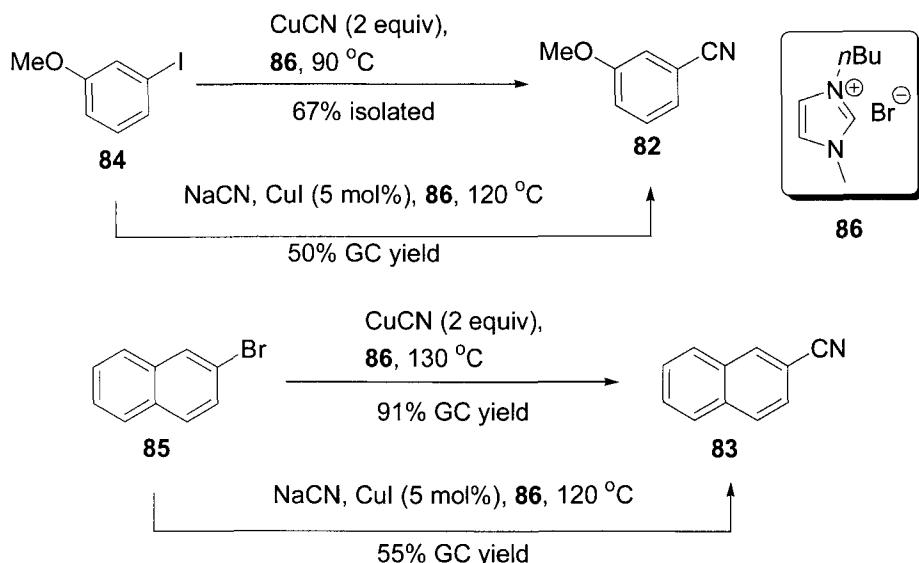


Similarly, exposure of propargyl alcohol **77** or alkyne **78** to hydroxylamine in aqueous MeOH with two equivalents of copper(I) chloride and excess diethylamine with under nitrogen atmosphere forms *in situ* copper acetylides that react with **79** to efficiently yield bisacetylenes **80** and **81**. These intermediate were used in a total synthesis of falcarindiol.<sup>32</sup>



*Related Processes: Rosenmund–von Braun Reaction*

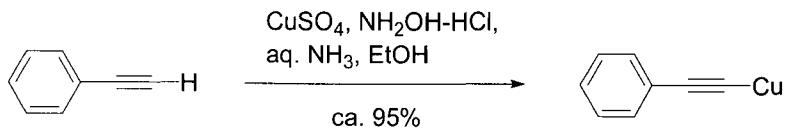
The application of ionic liquid solvent has led to Rosenmund–von Braun conditions which are considerably milder than previous variants.<sup>33,34</sup>



Aryl nitriles **82** and **83** were synthesized from the corresponding iodide **84** and bromide **85** in imidazolium bromide ionic solvent (**86**). The described protocol using either excess copper cyanide or catalytic copper(I) iodide and sodium cyanide, allows for these reaction to be run at between 90 and 130 °C. Isolation of the products is still somewhat problematic, however, the catalyst can be recycled from this medium and effectively reused.<sup>35</sup>

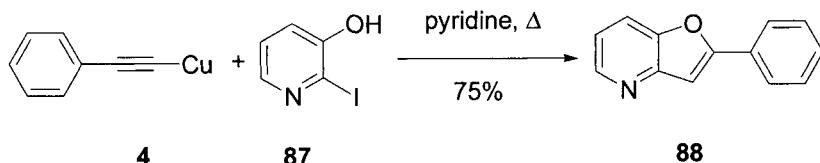
### 1.2.1.6 Experimental

#### Preparation of Copper(I) Acetylide



**Copper(I) phenylacetylide (4).<sup>36</sup>**

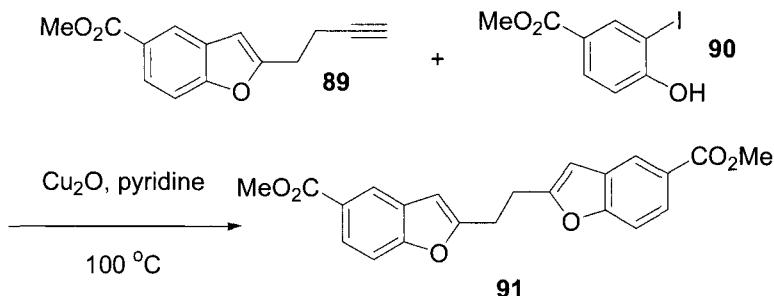
A solution of 25.0 g. (0.100 mole) of copper(II) sulfate pentahydrate in 100 mL of concentrated aqueous ammonia was placed in a large Erlenmeyer flask fitted with an effective magnetic stirbar and cooled to 0 °C. Stirring was maintained through the course of the reaction and the reaction is maintained under a constant stream of N<sub>2</sub>. Water (400 mL) is added followed by addition of solid hydroxylamine hydrochloride (13.9 g, 0.200 mole) over 10 minutes. A solution of 10.25 g (0.1005 mole) of phenylacetylene (**16**) in 500 mL of 95% ethanol is then added rapidly to the pale blue solution. The reaction flask is swirled by hand, copper(I) phenylacetylide separates as a copious yellow precipitate, and an additional 500 mL of water is added. After the mixture has been allowed to stand for 5 minutes, the precipitate is collected on a sintered glass filter and washed successively with five 100 mL portions of water, five 100 mL portions of absolute ethanol, and five 100 mL portions of anhydrous diethyl ether. The copper(I) acetylidyde **4** is dried in a 250 mL, round-bottom flask heated to 65 °C for 4 hours under reduced pressure on a rotary evaporator, yielding 14.8–16.4 g (90–99%) of a bright yellow solid. The dry acetylidyde may be stored under nitrogen in a brown bottle.

*Castro–Stephens Reaction and Heterocyclization***2-Phenylfuro[3,2-b]pyridine (88).<sup>36</sup>**

A 300-mL, three-necked flask fitted with a nitrogen inlet stopcock, a magnetic stirring bar, and a condenser attached to a nitrogen outlet bubbler is charged with 2.47 g (0.0150 mole) of copper(I) phenylacetylide (**4**). The system is purged with nitrogen for 20 minutes before 80 mL of pyridine is added. The resulting mixture is stirred for 20 minutes under a nitrogen atmosphere, and 3.30 g (0.0149 mole) of 3-hydroxy-2-iodopyridine (**87**) is added. The mixture, which changes in color from yellow to dark green as the acetylidyde dissolves, is warmed in an oil bath at 110–120 °C for 9 hours with continuous stirring under a nitrogen atmosphere. The reaction solution is transferred to a 500-mL, round-bottom flask and concentrated to a volume of 20 mL at 60–70 °C (20–80 mmHg) with a rotary evaporator. The pyridine solution is treated with 100 mL of concentrated aqueous ammonia, and the resulting deep-blue mixture is stirred for 10 minutes and extracted with five 100 mL portions of ether. The combined ethereal extracts are washed with

three 250 mL portions of water, dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The crude product, 2.6–2.76 g of orange semisolid, is dissolved in 100 mL of boiling cyclohexane. The solution is filtered, concentrated to a volume of about 30 mL, and cooled in an ice bath. The partially purified product **88** crystallizes as 2.3–2.7 g of orange solid, m.p. 83–89 °C. Further purification is effected by sublimation at 110–120° (0.01–0.2 mmHg), yielding 2.2–2.4 g (75–82%) of a yellow solid, m.p. 90–91°C.

#### *Castro–Stephens Reaction Using In situ Modification*



#### Methyl 2-(2-(5-(methoxycarbonyl)benzofuran-2-yl)ethyl)benzofuran-5-carboxylate (**91**).<sup>37</sup>

A mixture of **89** (7.6 g, 33.5 mmol), **90** (9.2 g, 33 mmol), and copper(I) oxide (3.2 g, 22.5 mmol) in dry pyridine (40 mL) was stirred under  $\text{N}_2$  at 110 °C overnight. The mixture was allowed to cool to ambient temperature, diluted with EtOAc (50 mL), filtered through a 5 cm Celite pad, and concentrated. The residue was dissolved in EtOAc (75 mL), washed with 2 M HCl (12.5 mL) and brine (25 mL), dried over  $\text{Na}_2\text{SO}_4$ , and concentrated. The residue was purified by column chromatography, eluting with (1 : 1) hexanes/diethyl ether to produce **91** as a white solid (5.24 g, 43%): mp 165–167 °C (hexanes/EtOAc).

#### 1.2.1.7 References

- (a) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 2163; (b) Stephens, R. D.; Castro, C. E. *J. Org. Chem.* **1963**, *28*, 3313–3315.
- Sonogashira, K.; Tohda, Y.; Hagiwara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
- (a) Chodkiewicz, W. *Ann. Chim. Paris* **1957**, *2*, 819–869; [R] (b) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, **1969**.
- Koelsch, C.; Whitney, A. J. *Org. Chem.* **1941**, *6*, 597–647.
- Hay, A. J. *Org. Chem.* **1962**, *27*, 3320–3321.
- Siemens, P.; Livingston, R.; Diederich, F. *Angew. Chem.* **2000**, *39*, 2632–2657.
- Gonzalez-Rojas, C.; Oprunenko, Y.; Morales, R. *Russ. Chem. Bull. Int. Ed.* **2004**, *53*, 474–475.
- Castro, C. E.; Gaughan, J.; Owsley, D. J. *Org. Chem.* **1966**, *31*, 4071–4078.
- Monnier, F.; Turtaut, F.; Duroure, L.; Taillefer, M. *Org. Lett.* **2008**, *10*, 3203–3206.

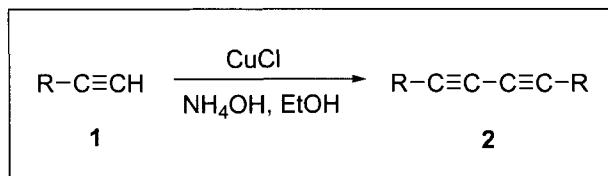
10. Thathagar, M.; Beckers, J.; Rothenberg, G. *Green Chem.* **2004**, *215–218*.
11. [R] (a) Jastrzebski, J.; van Koten, G. in *Modern Organocopper Chemistry* Ed. N. Krause. **2002** Wiley-VCH. Pp. 1–44; [R] (b) Mori, S.; Nakamura, E. in *Modern Organocopper Chemistry* Ed. N. Krause. 2002 Wiley-VCH pp 315–346.
12. Okura, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716–4721.
13. Okura, K.; Furuune, M.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **1992**, *37*, 5363–5364.
14. Gujadhur, R.; Bates, C.; Venkataraman, R. *Org. Lett.* **2001**, *3*, 4315–4317.
15. Marshall, J.; Chobanian, H.; Yanik, M. *Org. Lett.* **2001**, *3*, 4107–4110.
16. [R] Beletskaya, I.; Cheprakov, A. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364.
17. Lindey, J. *Tetrahedron* **1984**, *40*, 1433–1456.
18. Haack, T.; Kurtkaya, S.; Snyder, J.; Georg, G. *Org. Lett.* **2003**, *5*, 5019–5022.
19. Colacino, E.; Daich, L.; Martinez, J.; Lamaty, F. *Synlett* **2007**, 1279–1283.
20. Li, J.-H.; Li, J.-L.; Wang, D.-P.; Pi, S.-F.; Xie, Y.-X.; Zhang, M.-B.; Hu, X.-C. *J. Org. Chem.* **2007**, *72*, 2053–2057.
21. Juricek, M.; Kasak, P.; Stach, M.; Putala, M. *Tetrahedron Lett.* **2007**, *48*, 8869–8873.
22. Woon, E.; Dhami, A.; Mahon, M.; Threadgill, M. *Tetrahedron* **2006**, *62*, 4829–4837.
23. Kinder, J.; Tessier, C.; Youngs, W. *Synlett* **1993**, 149–150.
24. Staab, H.; Neuhoefner, K. *Synthesis* **1974**, 424.
25. Coleman, R.; Garg, R. *Org. Lett.* **2001**, *3*, 3487–3490.
26. Tretyakov, E.; Knight, D.; Vasilevsky, S. *J. Chem Soc., Perkin Trans. I* **1999**, 3713–3720.
27. (a) Jutand, A.; Negri, S.; Principaul, A. *Eur. J. Org. Chem.* **2005**, 631; (b) Suo, Q-L.; Ma, Y-Q.; Wang, Y-B.; Han, L.-M.; Bai, Y.-G.; Weng, L.-H. *J. Coord. Chem.*, **2008**, 1234–1243.
28. White, J.; Carter, R.; Sundermann, K.; Wartmann, M. *J. Am. Chem. Soc.* **2001**, *123*, 5407–5413.
29. Mignani, G.; Chevalier, C.; Grass, R.; Allmang, G.; Morel, D. *Tetrahedron Lett.* **1990**, *36*, 5161–5164.
30. Nishihara, Y.; Takemura, M.; Mori, A.; Osakada, K. *J. Organomet. Chem.* **2001**, *620*, 282–286.
31. Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841–6844.
32. Bandyopadhyay, A.; Varghese, B.; Sankararaman, S. *J. Org. Chem.* **2006**, *71*, 4544–4548.
33. Steffen, W.; Laskoski, M.; Collins, G.; Bunz, U. H. F. *J. Organomet. Chem.* **2001**, *630*, 132–138.
34. Zanon, J.; Klapars, A.; Buchwald, S. *J. Am. Chem. Soc.* **2003**, *125*, 2890–2891.
35. Wu, J.; Beck, B.; Ren, R. *Tetrahedron Lett.* **2002**, *43*, 387–389.
36. Owlsley, D.; Castro, C. *Org. Synth.* **1988**, *52*, 128–131.
37. Bakunova, A.; Bakunov, S.; Wenzler, T.; Barszcz, T.; Werbovetz, K.; Brun, R.; Hall, J.; Tidwell, R. *J. Med. Chem.* **2007**, *50*, 5807–5823.

## 1.2.2 Glaser Coupling

Gordon W. Gribble

### 1.2.2.1 Description

The Glaser Coupling reaction describes the oxidative coupling of terminal acetylenes, **1**→**2**, under the influence of copper(I) and base.<sup>1–6</sup> Several closely related acetylenic homocoupling variations are also discussed in this chapter.



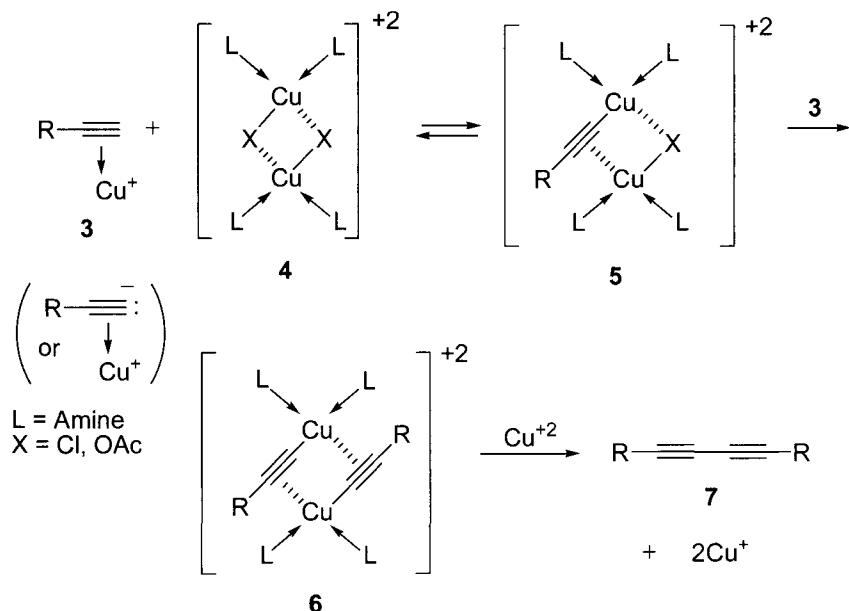
### 1.2.2.2 Historical Perspective

In 1869, Carl Glaser observed that an ethanolic ammonia solution of copper(I) phenylacetylidyne in the presence of air undergoes oxidative coupling to afford diphenyldiacetylene.<sup>7</sup> In 1956, Eglinton and Galbraith described an acetylenic oxidative dimerization using copper(II) acetate in methanolic pyridine.<sup>8</sup> In 1957, Cameron and Bennett demonstrated that some amines (*t*-butylamine, ethylenediamine, and pyridine) can substitute for ammonia in the original Glaser protocol.<sup>9</sup> In 1960, Hay reported a fourth variation involving copper(I) chloride, oxygen, and the bidentate amine *N,N,N',N'*-tetramethylethylenediamine (TMEDA) or pyridine.<sup>10</sup> Examples of all four methods — Glaser, Eglinton, Cameron, and Hay — are presented in the following sections, as will be other lesser well-known and newer modifications and variations. Whereas the Glaser, Cameron, and Hay coupling reactions are catalytic with copper(I), the Eglinton modification is stoichiometric (or with excess) in copper(II). The more recent palladium-catalyzed terminal alkyne homocouplings (e.g., Cadiot–Chodkiewicz and Sonogashira) are covered elsewhere.

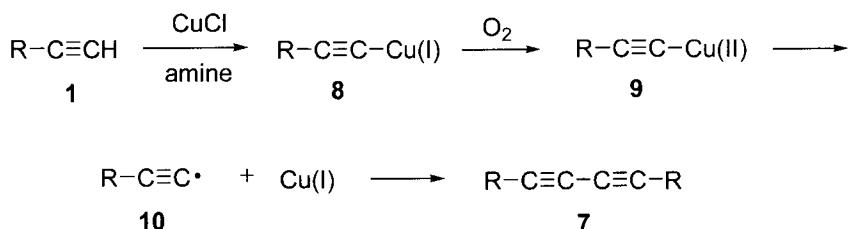
### 1.2.2.3 Mechanism

Glaser originally invoked a copper phenylacetylidyne dimer ( $\text{Ph}-\text{C}\equiv\text{C}-\text{Cu}-\text{Cu}-\text{C}\equiv\text{C}-\text{Ph}$ ) as the species that reacts with oxygen to form diphenyldiacetylene and  $\text{Cu}_2\text{O}$ .<sup>7a</sup> Subsequent studies by Salkind,<sup>11</sup> Vaitiekunas,<sup>12</sup> Bohlmann,<sup>13</sup> and others<sup>2</sup> provide further details on the mechanism of this alkyne coupling

reaction. Diederich *et al.*<sup>2</sup> conclude that the mechanism proposed by Bohlmann, which does not involve acetylenic radicals, is most consistent with the experimental data. Thus, copper–acetylene  $\pi$ -complex **3** (or a copper acetylid e $\pi$ -complex) and copper(II) complex **4** are in equilibrium with dimeric copper acetylid e **5**. Subsequent dimerization to **6** is followed by collapse to diacetylene **7**.<sup>13</sup>

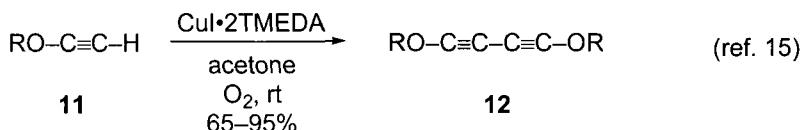


It should be noted that most presentations of the Glaser and related acetylene homocouplings show a simpler mechanism involving base-catalyzed formation of a copper(I) acetylid e **8**, oxidation to copper(II) acetylid e **9**, and homocoupling of the resultant acetylenic radical **10** to afford **7**.<sup>2,14</sup>

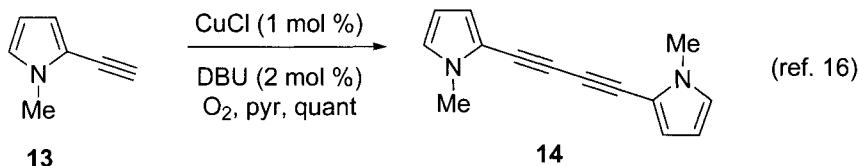


### 1.2.2.4 Variations and Improvements

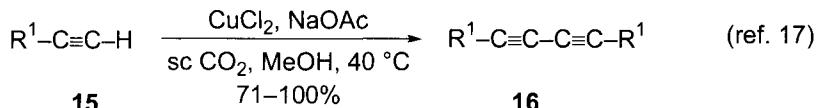
Several minor variations and practical improvements on the Glaser and related acetylenic coupling reactions have been developed. For example, when CuI is substituted for CuCl in the standard Hay conditions (TMEDA, O<sub>2</sub>, acetone) a greatly improved yield of **12** is obtained, which was ascribed to the more soluble CuI·2TMEDA in acetone.<sup>15</sup> The homocoupling of 2-ethynyl-1-methylpyrrole (**13**) only proceeds in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), which may be due to the decreased acidity of the acetylenic hydrogen.<sup>16</sup>



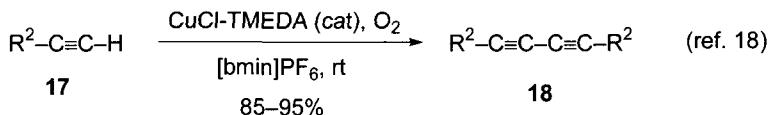
R = *t*-Bu, *n*-C<sub>10</sub>H<sub>21</sub>, 1-adamantyl, *c*-C<sub>6</sub>H<sub>13</sub>, L-menthyl, 2,6-diMeOPh



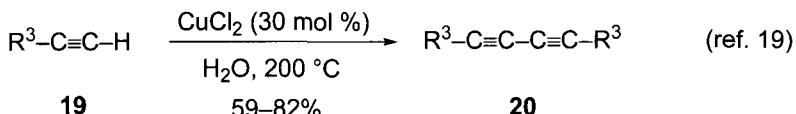
Glaser coupling can be carried out both in supercritical CO<sub>2</sub> using NaOAc as base, e.g., **15** to **16**,<sup>17</sup> and in ionic liquids, e.g., **17** to **18**.<sup>18</sup> Likewise, water near its critical point serves as a solvent for Glaser coupling, **19**→**20**.<sup>19</sup> Terminal alkynes **21** are effectively coupled to **22** with the recyclable system Cu(OAc)<sub>2</sub>–polyethyleneglycol (PEG)–NaOAc.<sup>20</sup> PEG 6000 afforded the highest efficiency and this catalyst system could be recycled more than five times. Recycling of the resulting Cu<sub>2</sub>O was accomplished by heating in acetic acid in air. A microwave solvent-free Glaser coupling in the presence of KF–Al<sub>2</sub>O<sub>3</sub> forms diacetylenes **24**.<sup>21</sup>



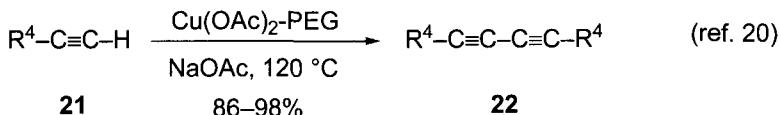
R = Ph, *n*-C<sub>5</sub>H<sub>11</sub>, *n*-C<sub>6</sub>H<sub>13</sub>, CH<sub>2</sub>OH, CH<sub>2</sub>OAc



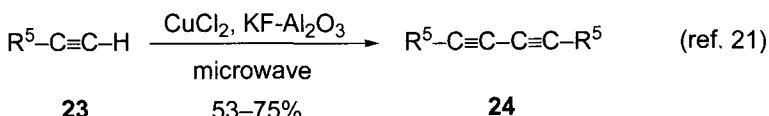
$\text{R}^2 = \text{Ph}, \text{CH}_2\text{OH}, n\text{-Bu}, \text{CH}_2\text{CH}_2\text{CN}, \text{CH}_2\text{CH}_2\text{OTHP}, \text{CH}_2\text{OMe}, \text{CH}_2\text{OTs}, (\text{CH}_2)_4\text{OH}$ , others



$\text{R}^3 = \text{Ph}, 4\text{-MePh}, 2\text{-ClPh}, 4\text{-FPh}, n\text{-C}_8\text{H}_{17}, n\text{-C}_6\text{H}_{13}$

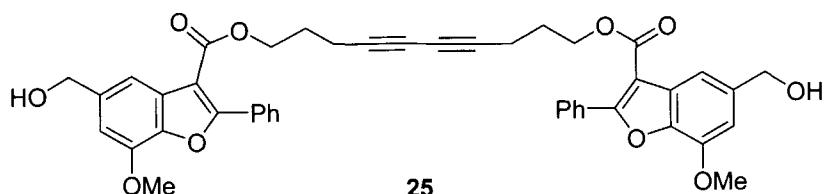


$\text{R}^4 = \text{Ph}, 4\text{-FPh}, 4\text{-EtPh}, \text{cyclohex-1-enyl}, n\text{-Bu}, n\text{-Hex}, \text{CH}_2\text{OH}$

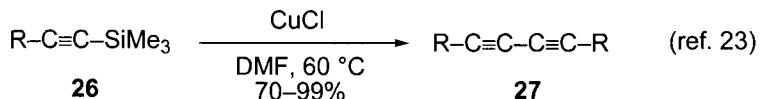


$\text{R}^5 = n\text{-C}_8\text{H}_{17}, n\text{-C}_6\text{H}_{13}, \text{Ph}, 4\text{-MePh}, 2\text{-ClPh}, 2\text{-FPh}, 4\text{-FPh}$

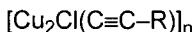
The novel catalytic system  $\text{AgOTs-CuCl}_2\text{-TMEDA}$  is reported to effect homocoupling in high yield of a series of benzo[*b*]furan alkynes on the solid phase.<sup>22</sup> For example, compound **25** is obtained after cleavage from the bead in high purity. The conventional Glaser, Hay, and Eglinton methods fared badly. This seems to be the first report of  $\text{Ag(I)}$  promoting a copper-mediated alkyne homocoupling.



Several methods have been reported involving Glaser-type homocoupling of alkynyltrialkylsilanes. Thus, exposure of various alkynyltrimethylsilanes **26** to CuCl in a polar solvent such as DMF affords good to excellent yields of dialkynes **27**.<sup>23</sup> Interestingly, whereas other silanes give good to excellent yields of coupled acetylenes **27** when R = *n*-C<sub>6</sub>H<sub>13</sub> (e.g., SiPhMe<sub>2</sub>, 83%; Si(OMe)<sub>3</sub>, > 99%; SiMe<sub>2</sub>OSiMe<sub>3</sub>, 92%; SiMe<sub>2</sub>(OH), 89%), both SiEt<sub>3</sub> and Si*i*-Pr<sub>3</sub> fail completely.<sup>23b</sup> In this study it was also possible to isolate the intermediate alkynylcopper complexes **28**, which upon further heating in DMF in air afford diacetylenes.<sup>23c</sup>



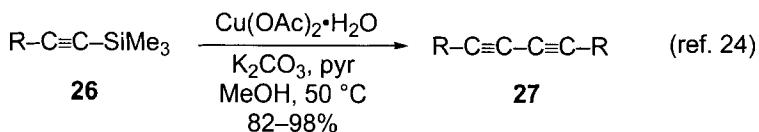
R = Ph, 4-MePh, 4-AcPh, 2-thienyl, *n*-C<sub>6</sub>H<sub>13</sub>



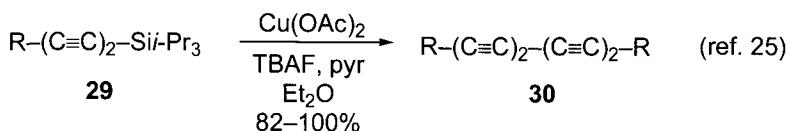
**28** (40–67%)

R = 4-AcPh, 4-MeOPh, 2-thienyl, 4-ClPh, 4-*n*-C<sub>8</sub>H<sub>17</sub>Ph, *n*-C<sub>6</sub>H<sub>13</sub>

The use of Cu(OAc)<sub>2</sub> under the Eglinton conditions also effects homocoupling of both alkynyltrimethylsilanes, **26**→**27**,<sup>24</sup> and dialkynyltrialkylsilanes, **29**→**30**.<sup>25</sup>

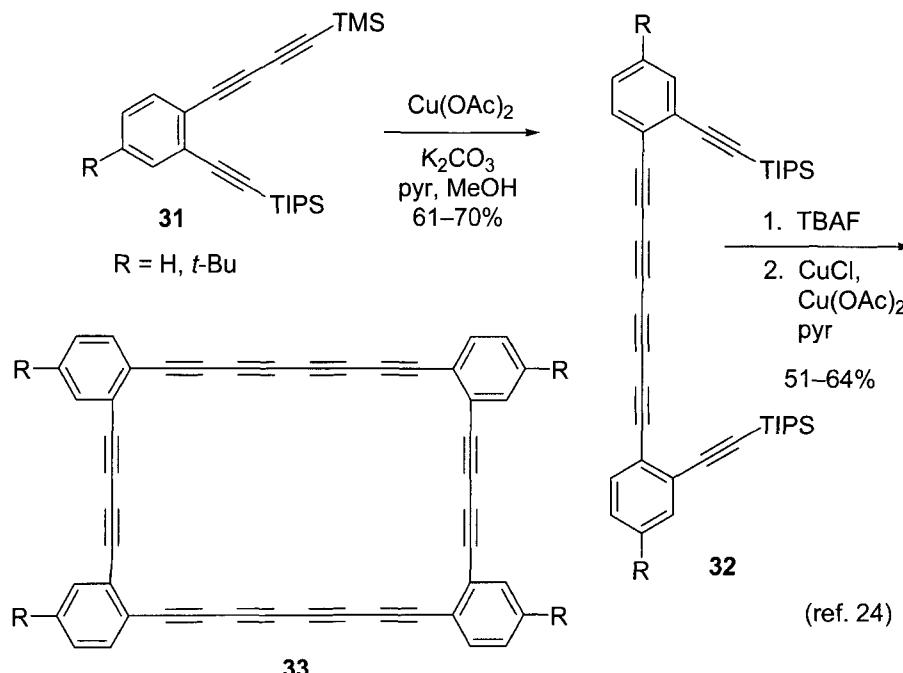


R = Ph, 2-BrPh, 2,6-diBrPh, PhC≡C

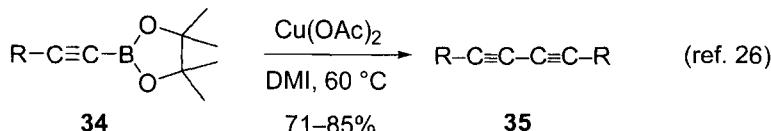


R = Ph, 2-BrPh, 3-Me<sub>2</sub>NPh, 1-naphthyl, *n*-C<sub>5</sub>H<sub>11</sub>, 2-thienyl

The former study was successfully applied to the synthesis of benzoannulenes **33** relying on the selective reactivity of the trialkylsilyl groups.<sup>24</sup>



Alkynylboronates may also be used in Glaser-type homocoupling as summarized in **34**→**35**.<sup>26</sup> Homocoupling of terminal alkynes that do not employ copper include  $\text{Co}_2(\text{CO})_8$ <sup>27</sup> and  $\text{NiCl}_2$ ,<sup>28</sup> but these are beyond the scope of the present chapter.



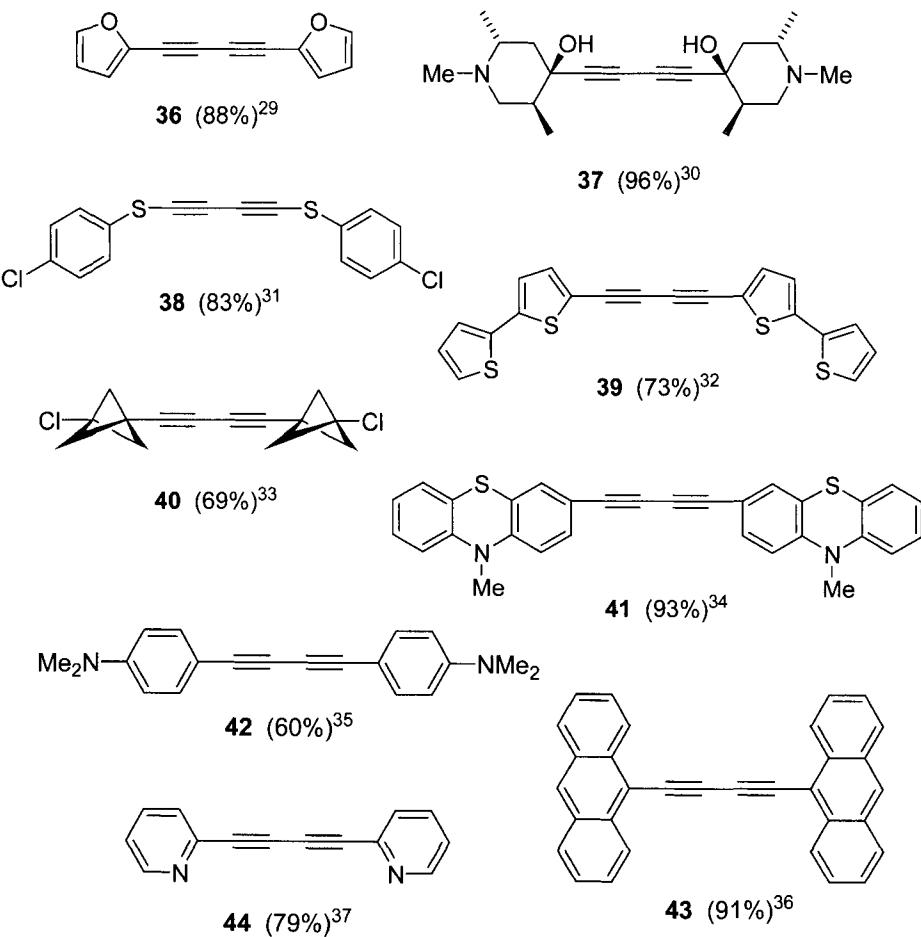
R = Ph, 4-MePh, 2-MePh, 4-MeOPh, 3-CF<sub>3</sub>Ph, 2-thienyl, 2-propenyl, CH<sub>2</sub>OMe, (EtO)<sub>2</sub>CH, *n*-C<sub>6</sub>H<sub>13</sub>, *t*-BuMe<sub>2</sub>SiO(CH<sub>2</sub>)<sub>4</sub>

### 1.2.2.5 Synthetic Utility

Virtually from the onset of its discovery by Glaser in 1869, the copper-catalyzed coupling of terminal acetylenes has seen enormous applications, far too many to be fully documented herein. Therefore, emphasis is on recent

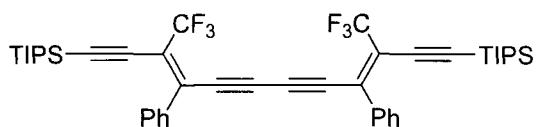
examples. In addition to the synthesis of straight-chain (literally!) dialkynes, the Glaser coupling reaction and its variants have been extensively employed in the synthesis of cyclic polyalkynes (annulenes, catenanes, knots, and others), and in the synthesis of polymeric alkynes.

A selection of diacetylenes that have been synthesized using Glaser coupling methodology is presented here. As can be seen, a myriad of diacetylenes are available, running the gamut of heterocyclic structures. Compound **46** was prepared from the corresponding trimethylsilyl acetylene using CuBr<sub>2</sub> under Eglinton conditions.<sup>38</sup> Interestingly, the attempted homocoupling of the ethylene precursor corresponding to that which afforded **48** failed completely, which may be due to copper–alkene complexation.<sup>40b</sup> In contrast, diacetylene **49** is obtained in modest yield.<sup>41</sup> The 1-alkynyl tosylamides **51** are best synthesized using CuI under classic Hay conditions.<sup>43</sup> Alkynes **52** are prepared from the corresponding trimethylsilyl acetylenes.<sup>44</sup>





**45** (90%)<sup>37</sup>



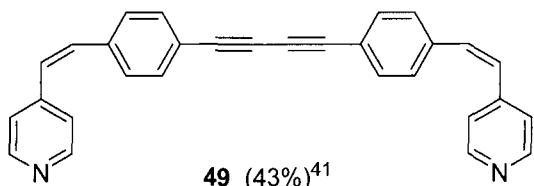
**46** (77%)<sup>38</sup>



**47** (72%)<sup>39</sup>



**48** (71%)<sup>40</sup>



**49** (43%)<sup>41</sup>

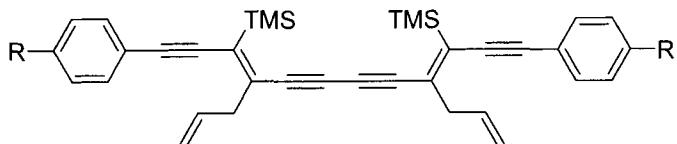


**50** (95%)<sup>42a</sup>



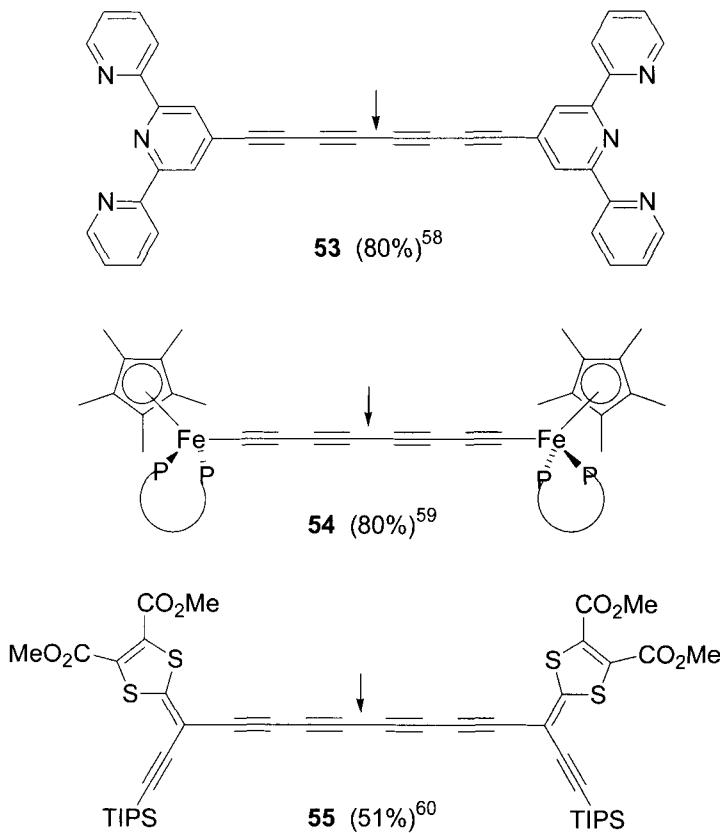
R = Ph, 4-MePh, *n*-Pr, allyl, Bn

**51** (84–100%)<sup>43</sup>

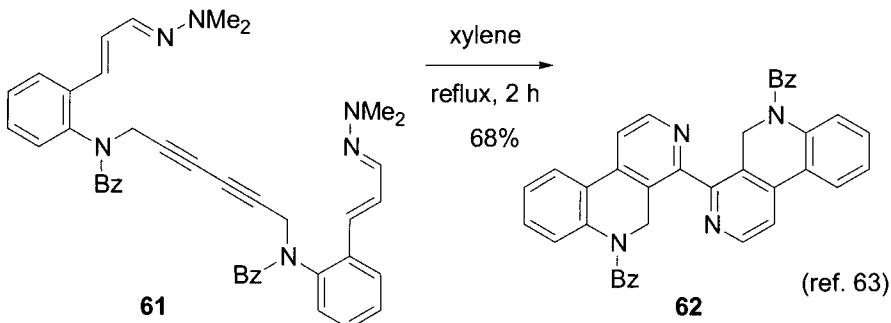
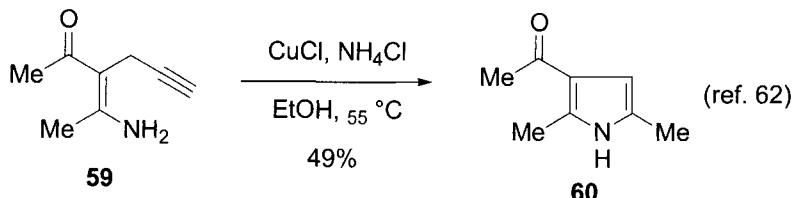
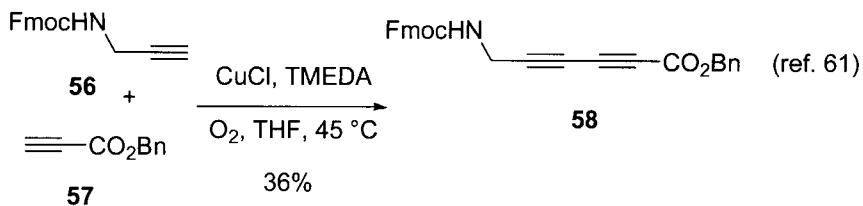


**52**, R = H, Cl, OMe (49–55%)<sup>44</sup>

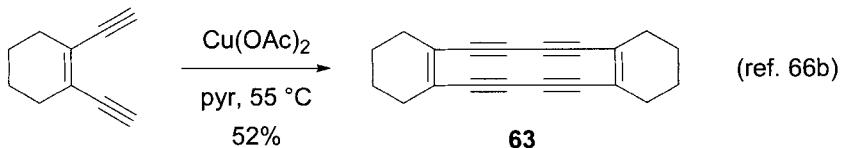
Other substituted diacetylenes that have been made via Glaser coupling methods include simple carbohydrates,<sup>45</sup> cyclooctaamyllose analogues,<sup>46</sup> nucleosides,<sup>47</sup> ferrocene-labeled amino acids,<sup>48</sup> phthalocyaninato complexes,<sup>49</sup>  $\beta$ -cyclodextrins,<sup>50</sup> novel lithium ion binding ionophores,<sup>51</sup> ruthenium “dumbbells”,<sup>52</sup> dendritic 1,1'-binaphthalene carbohydrate receptors,<sup>53</sup> calix[4]arenes,<sup>54</sup> a highly fluorescent pyrene,<sup>55</sup> trityl-based chemical sensors,<sup>56</sup> and novel phosphocholines.<sup>57</sup> A few examples of the Glaser homocoupling of diacetylenes to tetraacetylenes are known. For example, **53–55** can be fashioned in this manner.

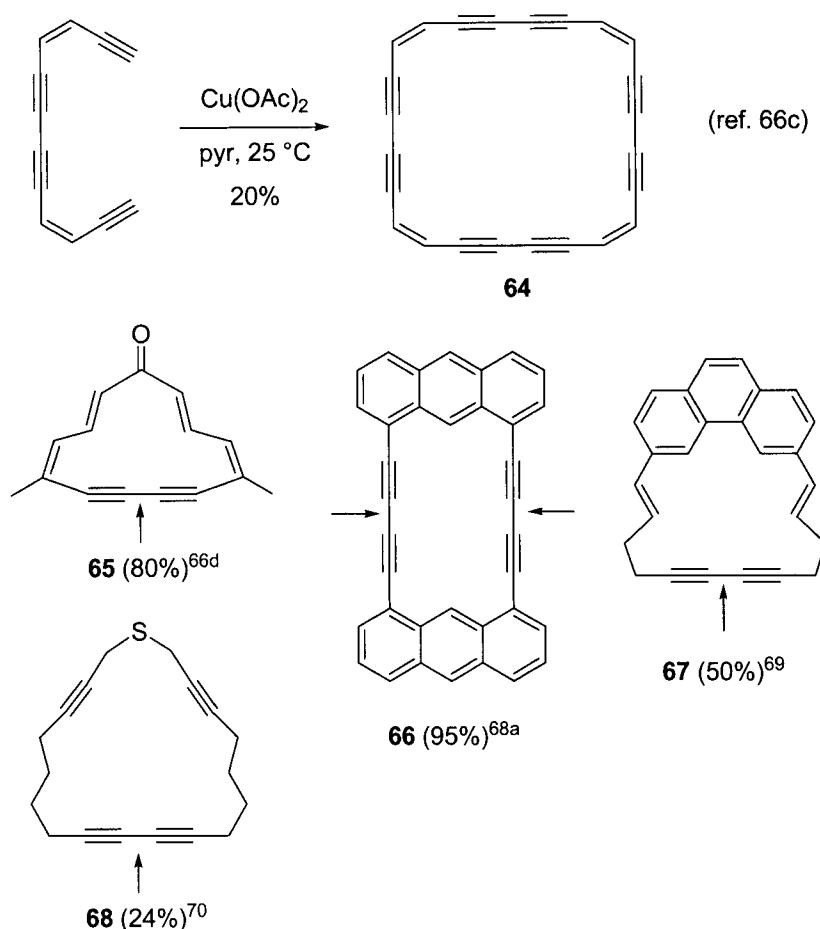


Rare are “mixed” Glaser heterocouplings, but an example is **56** plus **57** to give **58** in low yield.<sup>61</sup> An interesting, but not unexpected, side reaction in the attempted homocoupling of alkyne **59** is the copper-catalyzed formation of pyrrole **60**, which is the major product under all Glaser conditions.<sup>62</sup> An elegant application of copper-catalyzed homocoupling is the synthesis of diacetylene **61** (83% yield) and its conversion to bipyridine **62** via a double intramolecular Diels–Alder reaction.<sup>63</sup> Other examples were also described.

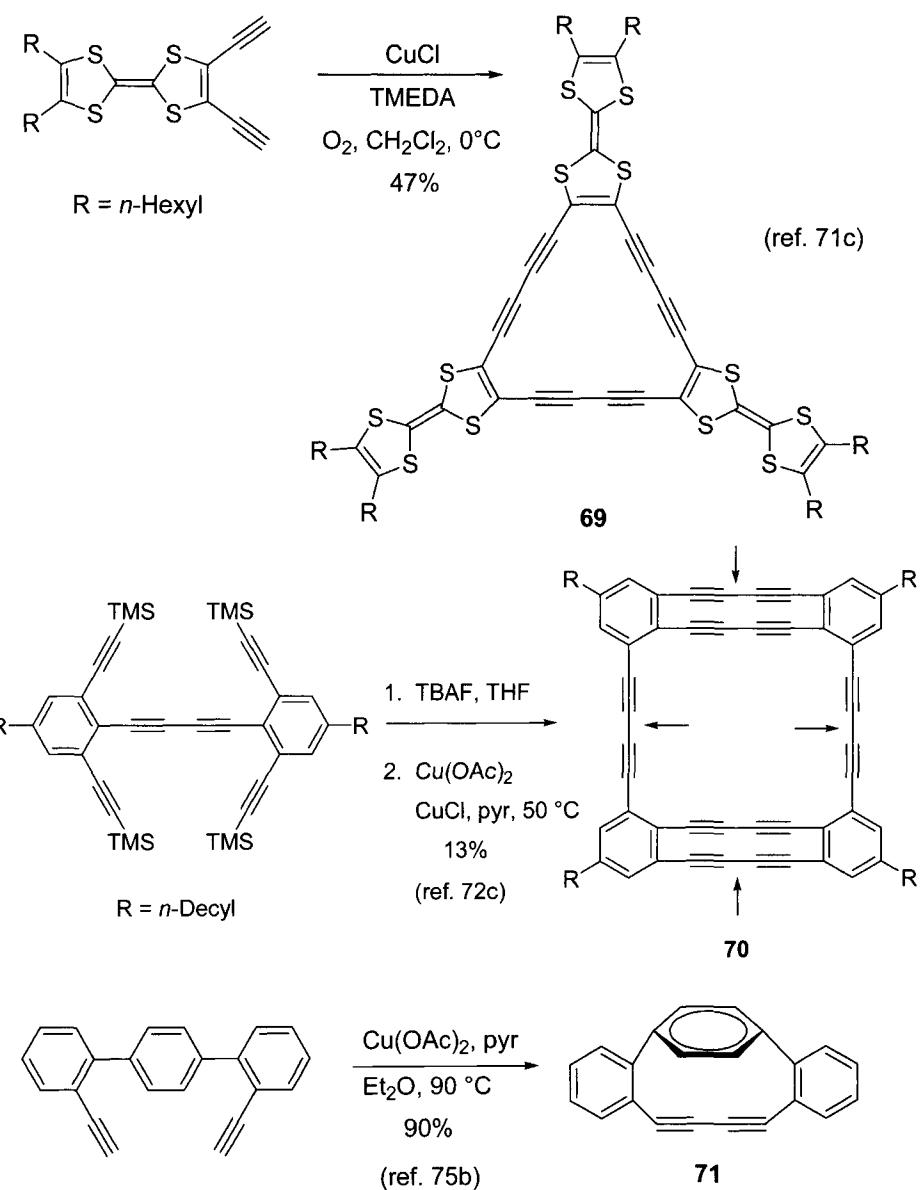


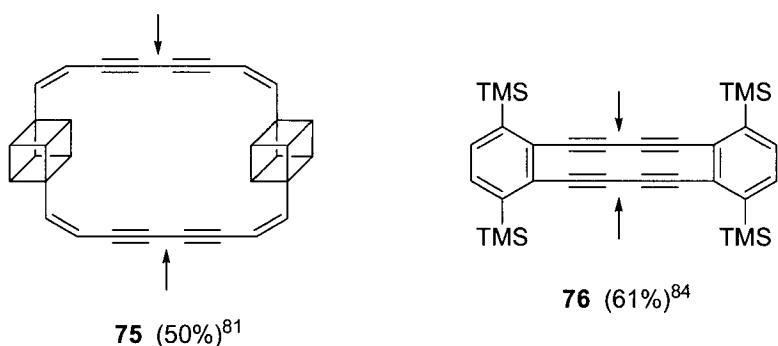
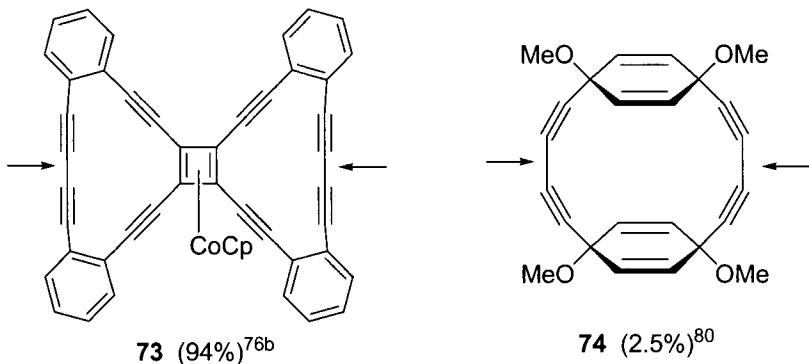
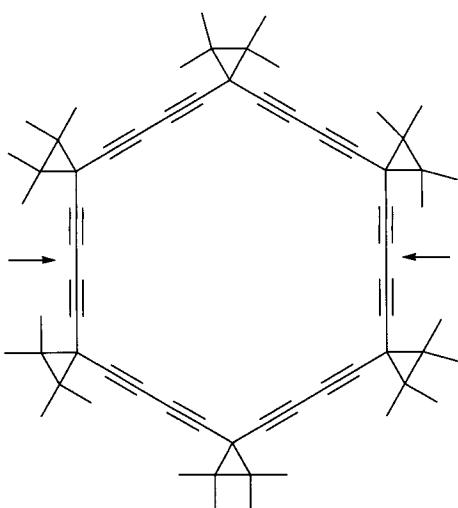
Another major application of Glaser couplings is the construction of cyclic polyalkynes, most notably annulenes<sup>64</sup> and catenanes.<sup>65</sup> The pioneering work of Sondheimer,<sup>66</sup> Eglinton,<sup>67</sup> Nakagawa,<sup>68</sup> and others, e.g., **63–68**, suggested that the Glaser coupling would be a general route to cyclic polyacetylenes.





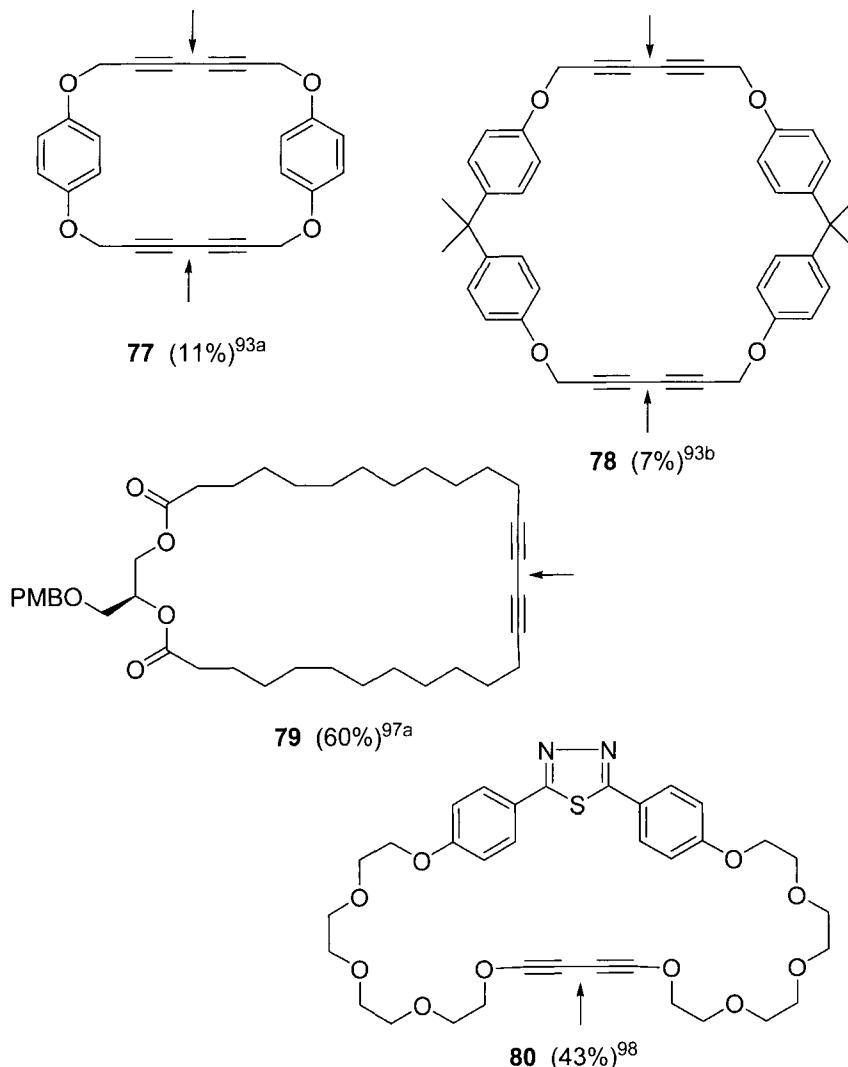
The recent work of Diederich,<sup>71</sup> Haley,<sup>72</sup> Höger,<sup>73</sup> de Meijere and Scott,<sup>74</sup> Fallis,<sup>75</sup> Bunz,<sup>76</sup> and several others<sup>77–85</sup> has established Glaser-type couplings as the preeminent synthetic route to a multitude of complex cyclic polyacetylenes. A limited selection of these molecules is illustrated here, **69–76**. Höger has pointed out that copper salts may act as a template in the intermolecular dimerization of functionalized bisacetylenes.<sup>73c</sup> The trimer corresponding to **74** is isolated in 9%.<sup>80</sup> Annulene **76** is unusually stable, being sterically protected by the bulky trimethylsilyl groups.<sup>84</sup>





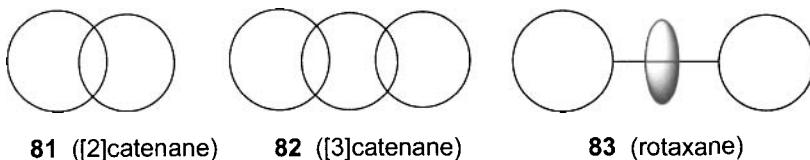
Glaser coupling methodologies have also been instrumental in the synthesis of cyclic polyacetylenes linked to porphyrins,<sup>86</sup> lipids,<sup>87–90</sup> carbohydrates,<sup>91</sup> cyclophane ethers (e.g., 77, 78),<sup>92–94</sup> dicationic aromatic

ether dyestuffs,<sup>95</sup> aromatic ether liquid crystals,<sup>96</sup> and macrocyclic glycerol lactones (e.g., **79**).<sup>97</sup> Several aromatic heterocycle-based macrocyclic polyacetylenes are available via Glaser coupling techniques. These include the 1,3,4-thiadiazole polyether **80**<sup>98</sup> and diethynylcarbazoles.<sup>99</sup>

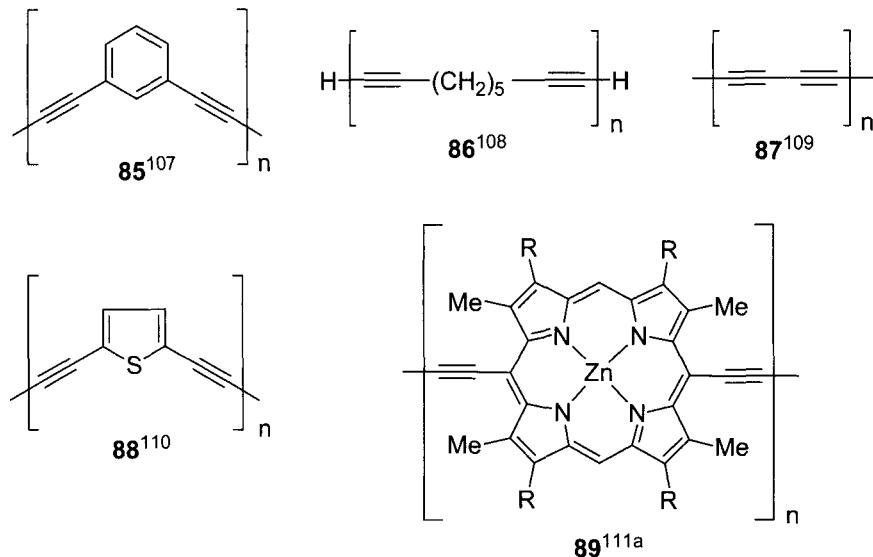


The Glaser homocoupling of terminal alkynes has proven a powerful method for constructing catenanes, molecules consisting of two ([2]catenanes) or more interlocking rings (e.g., **81**, **82**), rotaxanes (e.g., **83**), and knots (e.g., a trefoil knot **84** (not shown)).<sup>100</sup> Catenanes containing up to 147-membered rings are known using Glaser coupling to close the second ring.<sup>101</sup> Asymmetric [2]catenanes,<sup>102</sup> porphyrin [2]catenanes,<sup>103</sup> donor-

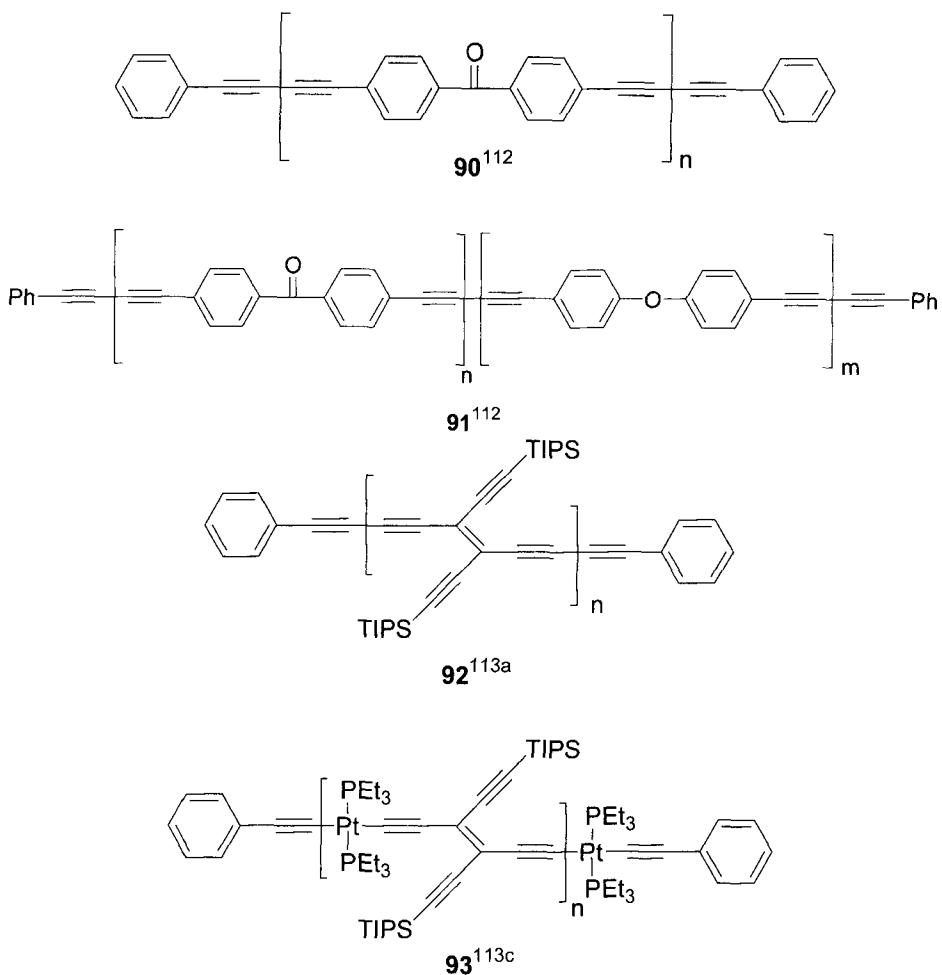
acceptor [2]catenanes,<sup>104</sup> and molecular composite knots<sup>105</sup> have also been synthesized via Glaser coupling.



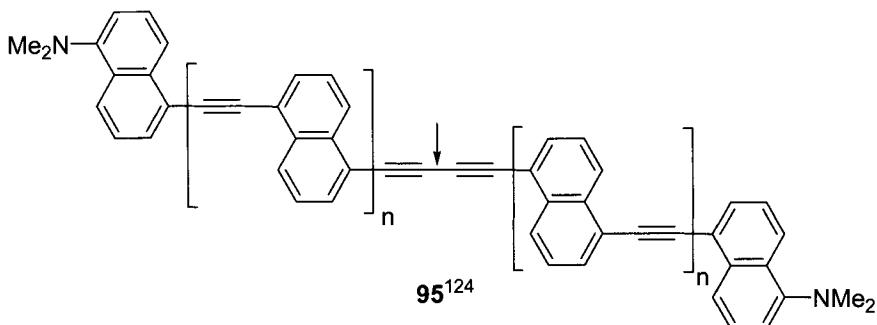
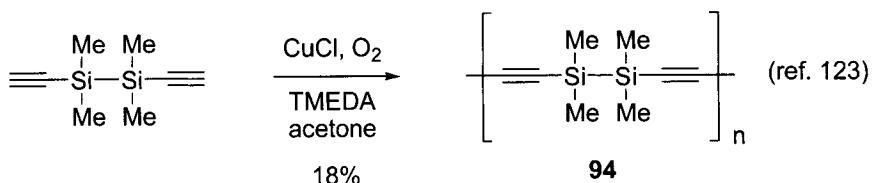
The final major application of Glaser-Type coupling of terminal dialkynes is the synthesis of polymeric acetylenes.<sup>106</sup> Following the seminal work of Hay<sup>107</sup> and others,<sup>106</sup> polymeric coupling of terminal bis-acetylenes has led to a myriad of polymeric acetylenes. Some pioneering examples are **85** (polymerization of *m*-diethynylbenzene),<sup>107</sup> **86** (polymerization of 1,8-nonadiyne),<sup>108</sup>  $\alpha$ -carbyne (polyyne) (**87**) (polymerization of dicopper acetylidyde),<sup>109</sup> **88** (polymerization of 2,5-diethynylthiophene),<sup>110</sup> and porphyrins (e.g., **89**).<sup>111</sup>



Mixed acetylenic polymerizations are also achievable via Glaser couplings. For example, coupling between 4,4'-diethynylbenzophenone and phenylacetylene affords polymer **90**.<sup>112</sup> Likewise, several soluble polymers of type **91** are prepared in quantitative yield using standard Hay conditions (CuCl, O<sub>2</sub>, TMEDA, pyridine, *o*-dichlorobenzene, 75 °C).<sup>112</sup> End-capping with phenylacetylene or 3,5-di(*tert*-butyl)phenylacetylene was also used to prepare "molecular rods" (e.g., **92**, **93**).<sup>113</sup>



Other polymeric acetylenic materials constructed using Glaser methodology include water-soluble rotaxanes as insulated molecular wires,<sup>114</sup> exceptionally long polymeric thiophenes as novel nanomaterials,<sup>115</sup> macrocyclic oligothiophenes with cavities in the nanometer region,<sup>116</sup> ruthenium-capped polyacetylenes,<sup>117</sup> crown-ether-capped polyacetylenes,<sup>118</sup> asymmetric polyacetylenic binaphthols,<sup>119</sup> hyperbranched polyacetylenes,<sup>120</sup> end-capped carbynes,<sup>121</sup> polyacetylenic oligoazulenes,<sup>112</sup> acetylenic polycarbosilanes (e.g., **94**),<sup>123</sup> and polymeric naphthylacetylenes (e.g., **95**).<sup>124</sup>



### 1.2.2.6      *Experimental*

The reader is referred to the syntheses of diphenyldiacetylene,<sup>125</sup> cyclooctadeca-1,3,7,9,13,15-hexayne,<sup>126</sup> and 1,4-bis(trimethylsilyl)buta-1,3-diyne<sup>127</sup> published in *Organic Syntheses*, 2,7-dimethyl-3,5-octadiyn-2,7-diol published in an undergraduate laboratory text,<sup>128</sup> and 3,5-octadiyne and 2,4-hexadiyn-1,6-diol published in *Preparative Acetylenic Chemistry*.<sup>129</sup>

#### **2,4-Hexadiyne-1,6-diol (Glaser Method):<sup>9</sup>**

Propargyl alcohol (11.2 g, 0.20 mol) was added with stirring to a mixture of copper(I) chloride (25 g, 0.13 mol), ammonium chloride (40 g, 0.75 mol), concentrated ammonium hydroxide (12.5 mL, 0.18 mol NH<sub>3</sub>), and water (200 mL). The mixture was stirred under a slight (30 Torr) positive pressure of oxygen for 20 h. The blue-green reaction mixture was acidified with dilute hydrochloric acid, diluted to 750 mL with water and extracted with ether in a continuous extractor for 24 h. Evaporation of ether from the extract left a solid which, when recrystallized from hot water, gave 9.1 g (83%) of the title compound, mp 111.5–112 °C.

#### **1,4-Di-(2'-quinoly)-1,3-butadiyne (Cameron Modification):<sup>130</sup>**

A solution of cuprous chloride (10 mg, 0.1 mmol) and 2-ethynylquinoline (85 mg, 0.55 mmol) in freshly distilled pyridine (30 mL), under oxygen at 40 °C was stirred for 150 min. Then, the solvent was removed at reduced atmosphere giving a brown solid, which was washed with an aqueous ammonium chloride solution and extracted with dichloromethane. The

combined extracts were dried with anhydrous sodium sulfate, filtered, and the solvent was evaporated affording a brown solid that was crystallized from acetonitrile-hexane (1:1). The title compound was isolated as a white solid (76 mg, 89%).

***N,N'-Phenylbuta-1,3-diyne-1,4-tosylamide (51, R = Ph) (Hay Modification with CuI):<sup>43</sup>***

TMEDA (5  $\mu$ L, 0.033 mmol) was added to a suspension of copper(I) iodide 93 mg, 0.017 mmol) in dry acetone (4 mL) under oxygen at rt. After 15 min, a solution of *N*-phenyl-*N*-tosyl ynamide (45 mg, 0.177 mmol) in acetone (4 mL) was added and the mixture was vigorously stirred until TLC showed complete consumption of the starting material (3 h). After removal of the solvent, the crude residue was purified by column chromatography on silica gel using hexanes-ethyl acetate (1 : 3) as eluent, yielding 41 mg (91%) of **51** (*R* = Ph) as white prisms.

***9,9'-Dianthryldiacetylene (43) (Eglinton Modification):<sup>36</sup>***

A mixture of 9-ethynylanthracene (0.02 g, 1.1 mmol), cupric acetate monohydrate (5.0 g, 25 mmol), pyridine (10 mL) and methanol (1 mL) was stirred for 3 h at 50 °C. The insoluble material was collected by filtration and washed with a small amount of methanol, water, and a small amount of ethanol, successively. The orange tiny cubes (0.20 g, 91%, mp 287–291 °C), thus obtained, were dissolved in toluene, and passed through a short column of alumina to give **43** as orange cubes, mp 290–292 °C, which was identical with an authentic sample.

### 1.2.2.7 References

1. [R] Cadiot, P.; Chodkiewicz, W. "Chemistry of Acetylenes," Ed. Viehe, H. G., Dekker, New York, 1979, pp 597–647.
2. [R] Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632–2657.
3. [R] Hay, A. S. *J. Polymer Sci. Part A: Polym. Chem.* **1998**, *36*, 505–517.
4. [R] Eglinton, G.; McCrae, W. *Adv. Org. Chem.* **1963**, *4*, 225–328.
5. [R] Nakagawa, M. "The Chemistry of the Carbon-Carbon Triple Bond, Part 2," Ed. Patai, S., John Wiley, New York, 1978, pp 635–712.
6. [R] Simádi, L. I. "The Chemistry of Triple-Bonding Functional Groups, Supplement C, Part 1," Ed. Patai, S.; Rappoport, Z., John Wiley, New York, 1983, pp 529–534.
7. a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422–424. b) Glaser, C. *Ann. Chem. Pharm.* **1870**, *154*, 137–171.
8. a) Eglinton, G.; Galbraith, A. R. *Chem. Ind. (London)* **1956**, 737–738. b) Eglinton, G.; Galbraith, A. R. *J. Chem. Soc.* **1959**, 889–896.
9. Cameron, M. D.; Bennett, G. E. *J. Org. Chem.* **1957**, *22*, 557–558.
10. a) Hay, A. S. *J. Org. Chem.* **1960**, *25*, 1275–1276. b) Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320–3321.
11. a) Zal'kind, Yu. S.; Aizikovich, M. A. *J. Gen. Chem. USSR*, **1937**, *7*, 227–233. b) Zal'kind, Yu. S.; Gverdtsiteli, I. M. *J. Gen. Chem. USSR* **1939**, *9*, 971–974. c) Zal'kind, Yu. S.;

- Fundyler, B. M. *J. Gen. Chem. USSR* **1939**, *9*, 1725–1728. d) Salkind, J. S. Fundyler, Fr. B. *Ber.* **1936**, *69*, 128–130.
12. Vaitiekunas, A.; Nord, F. F. *J. Am. Chem. Soc.* **1954**, *76*, 2733–2736.
  13. Bohlmann, F.; Schonowsky, H.; Inhoffen, E.; Grau, G. *Chem. Ber.* **1964**, *97*, 794–800.
  14. a) Clifford, A. A.; Waters, W. A. *J. Chem. Soc.* **1963**, 3056–3062. b) For a recent theoretical study of the coupling mechanism using DFT calculations, see Fomina, L.; Vazquez, B.; Tkatchouk, E.; Fomine, S. *Tetrahedron* **2002**, *58*, 6741–6747.
  15. Valenti, E.; Pericás, M. A.; Serratosa, F. *J. Am. Chem. Soc.* **1990**, *112*, 7405–7406.
  16. Vasilevsky, S. F.; Verkruisje, H. D.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas.* **1992**, *111*, 529–530.
  17. Li, J.; Jiang, H. *Chem. Commun.* **1999**, 2369–2370.
  18. Yadav, J. S.; Reddy, B. V. S.; Reddy, K. B.; Gayathri, K. U.; Prasad, A. R. *Tetrahedron Lett.* **2003**, *44*, 6493–6496.
  19. Li, P.-H.; Yan, J.-C.; Wang, M.; Wang, L. *Chin. J. Chem.* **2004**, *22*, 219–221.
  20. Lu, X.; Zhang, Y.; Luo, C.; Wang, Y. *Synth. Commun.* **2006**, *36*, 2503–2511.
  21. a) Kabalka, G. W.; Wang, L.; Pagni, R. M. *Synlett* **2001**, 108–110. For related conditions, see b) Sharifi, A.; Mirzaei, M.; Naimi-Jamal, M. R. *J. Chem. Res. (S)* **2002**, 628–630. c) Sharifi, A.; Mirzaei, M.; Naimi-Jamal, M. R. *Monatsh.* **2006**, *137*, 213–217.
  22. Liao, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2003**, *5*, 909–912.
  23. a) Ikegashira, K.; Nishihara, Y.; Hirabayashi, K.; Mori, A.; Hiyama, T. *Chem. Commun.* **1997**, 1039–1040. b) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.; Mori, A.; Hiyama T. *J. Org. Chem.* **2000**, *65*, 1780–1787. c) Nishihara Y.; Takemura, M.; Mori, A.; Osakada, K. *J. Organomet. Chem.* **2001**, *620*, 282–286.
  24. Haley, M. M.; Bell, M. L.; Brand, S. C.; Kimball, D. B.; Pak, J. J.; Wan, W. B. *Tetrahedron Lett.* **1997**, *38*, 7483–7486.
  25. Heuft, M. A.; Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2001**, *3*, 2883–2886.
  26. Nishihara, Y.; Okamoto, M.; Inoue, Y.; Miyazaki, M.; Miyasaka, M.; Takagi, K. *Tetrahedron Lett.* **2005**, *46*, 8661–8664.
  27. Krafft, M. E.; Hirosawa, C.; Dalal, N.; Ramsey, C.; Stiegman, A. *Tetrahedron Lett.* **2001**, *42*, 7733–7736.
  28. Li, P. H.; Wang, L.; Wang, M.; Yan, J. C. *Chin. Chem. Lett.* **2004**, *15*, 1295–1298.
  29. Carpita, A.; Rossi, R.; Veracini, C. A. *Tetrahedron* **1985**, *41*, 1919–1929.
  30. Abdulganeeva, S. A.; Grishina, G. V.; Potapov, V. M.; Erzhanov, K. B.; Shapovalov, A. A. *Chem. Het. Cpdns.* **1983**, 408–411.
  31. Sen, B. K.; Majumdar, K. C. *J. Indian Chem. Soc.* **LX**, 409–410.
  32. Kagan, J.; Arora, S. K. *J. Org. Chem.* **1983**, *48*, 4317–4320.
  33. Bunz, U.; Szeimies, G. *Tetrahedron Lett.* **1989**, *30*, 2087–2088.
  34. Müller, T. J. J. *Tetrahedron Lett.* **1999**, *40*, 6563–6566.
  35. Rodríguez, J. G.; Ramos, S.; Martín-Villamil, R.; Fonseca, I.; Albert, A. *J. Chem. Soc., Perkin Trans. I* **1996**, 541–543.
  36. Akiyama, S.; Ogura, F.; Nakagawa, M. *Bull. Chem. Soc. Japan* **1971**, *44*, 3443–3445.
  37. Fritzsche, U.; Hunig, S. *Tetrahedron Lett.* **1972**, *13*, 4831–4834.
  38. Jeon, H. H.; Son, J. B.; Choi, J. H.; Jeong, I. H. *Tetrahedron Lett.* **2007**, *48*, 627–631.
  39. Gilbertson, R. D.; Wu, H.-P.; Gorman-Lewis, D.; Weakley, T. J. R.; Weiss, H-C.; Boese, R.; Haley, M. M. *Tetrahedron* **2004**, *60*, 1215–1223.
  40. a) Rodríguez, J. G.; Lafuente, A.; Rubio, L. *Tetrahedron Lett.* **2004**, *45*, 5685–5688. b) Rodríguez, J. G.; Esquivias, J.; Lafuente, A.; Rubio, L. *Tetrahedron* **2006**, *62*, 3112–3122.
  41. Rodriguez, J. G.; Martín-Villamil, R.; Lafuente, A. *Tetrahedron* **2003**, *59*, 1021–1032.
  42. a) Müller, T. J. J.; Blümel, J. *J. Organomet. Chem.* **2003**, *683*, 354–367. b) Yagi, S.; Kitayama, H.; Takagishi, T. *J. Chem. Soc., Perkin Trans. I* **2000**, 925–932.
  43. Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, 377–379.
  44. Liu, Y.; Gao, H. *Org. Lett.* **2006**, *8*, 309–311.
  45. a) Murty, K. V. S. N.; Vasella, A. *Helv. Chim. Acta* **2001**, *84*, 939–963. b) Gan, Z.; Roy, R. *Tetrahedron Lett.* **2000**, *41*, 1155–1158.
  46. Hoffmann, B.; Zanini, D.; Ripoche, I.; Bürli, R.; Vasella, A. *Helv. Chim. Acta* **2001**, *84*, 1862–1888.
  47. Jung, F.; Burger, A.; Biellmann, J-F. *Org. Lett.* **2003**, *5*, 383–385.

48. Brosch, O.; Weyhermüller, T.; Metzler-Nolte, N. *Eur. J. Inorg. Chem.* **2000**, 323–330.
49. Maya, E. M.; Vásquez, P.; Torres, T.; Gobbi, L.; Diederich, F.; Pyro, S.; Echegoyen, L. *J. Org. Chem.* **2000**, 65, 823–830.
50. Faiz, J. A.; Spencer, N.; Pikramenou, Z. *Org. Biomol. Chem.* **2005**, 3, 4239–4245.
51. Paquette, L. A.; Tae, J. J. *Am. Chem. Soc.* **2001**, 123, 4974–4984.
52. Chen, W.-Z.; Ren, T. *Inorg. Chem.* **2006**, 45, 9175–9177.
53. Bähr, A.; Felber, B.; Schneider, K.; Diederich, F. *Helv. Chim. Acta* **2000**, 83, 1346–1376.
54. Al-Saraierh, H.; Miller, D. O.; Georgiou, P. E. *J. Org. Chem.* **2005**, 70, 8273–8280.
55. Benniston, A. C.; Harriman, A.; Lawrie, D. J.; Rostron, S. A. *Eur. J. Org. Chem.* **2004**, 2272–2276.
56. Raker, J.; Glass, T. E. *J. Org. Chem.* **2001**, 66, 6505–6512.
57. a) Patwardhan, A. P.; Thompson, D. H. *Org. Lett.* **1999**, 1, 241–243. b) Patwardhan, A. P.; Thompson, D. H. *Langmuir* **2000**, 16, 10340–10350.
58. Ziessel, R.; Suffert, J.; Youinou, M.-T. *J. Org. Chem.* **1996**, 61, 6535–6546.
59. Coat, F.; Lapinte, C. *Organometallics* **1996**, 15, 477–479.
60. Nielsen, M. B.; Utesch, N. F.; Moonen, N. N. P.; Boudon, C.; Gisselbrecht, J.-P.; Concilio, S.; Piotto, S. P.; Seiler, P.; Günter, P.; Gross, M.; Diederich, F. *Chem. Eur. J.* **2002**, 8, 3610–3613.
61. van Swieten, P. F.; Maehr, R.; van den Nieuwendijk, A. M. C. H.; Kessler, B. M.; Reich, M.; Wong, C.-S.; Kalbacher, H.; Leeuwenburgh, M. A.; Driessen, C.; van der Marel, G. A.; Ploegh, H. L.; Overkleef, H. S. *Bioorg. Med. Chem. Lett.* **2004**, 14, 3131–3134.
62. Vizer, S. A.; Yerzhanov, K. B.; Dembitsky, V. M. *Heteroatom. Chem.* **2006**, 17, 66–73.
63. Bushby, N.; Moody, C. J.; Riddick, D. A.; Waldron, I. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2183–2193.
64. [R] a) Spitzer, E. L.; Johnson, II, C. A.; Haley, M. M. *Chem. Rev.* **2006**, 106, 5344–5386. b) Haley, M. M.; Pak, J. J.; Brand, S. C. *Top. Curr. Chem.* **1999**, 201, 81–130. c) Diederich, F.; Gobbi, L. *Top. Curr. Chem.* **1999**, 201, 43–79.
65. [R] Godt, A. *Eur. J. Org. Chem.* **2004**, 1639–1654.
66. a) Sondheimer, F.; Amiel, Y. *J. Am. Chem. Soc.* **1957**, 79, 5817–5820. b) Pilling, G. M.; Sondheimer, F. *J. Am. Chem. Soc.* **1971**, 93, 1970–1977. c) McQuilkin, R. M.; Garratt, P. J.; Sondheimer, F. *J. Am. Chem. Soc.* **1970**, 92, 6682–6683. d) Cresp, T. M.; Ojima, J.; Sondheimer, F. *J. Org. Chem.* **1977**, 42, 2130–2134 e) [R] Huang, N. Z.; Sondheimer, F. *Acc. Chem. Res.* **1982**, 15, 96–102.
67. Behr, O. M.; Eglinton, G.; Galbraith, A. R.; Raphael, R. A. *J. Chem. Soc.* **1960**, 3614–3625.
68. a) Akiyama, S.; Misumi, S.; Nakagawa, M. *Bull. Chem. Soc. Japan* **1960**, 33, 1293–1298. b) Fukui, K.; Okamoto, T.; Nakagawa, M. *Tetrahedron Lett.* **1971**, 12, 3121–3124.
69. Meissner, U.; Meissner, B.; Staab, H. A. *Angew. Chem. Internat. Ed.* **1973**, 12, 916–918.
70. Carruthers, W.; Pellatt, M. G. *J. Chem. Soc. (C)* **1971**, 1485–1488.
71. a) Boldi, A. M.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 468–471. b) Kivala, M.; Mitzel, F.; Boudon, C.; Gisselbrecht, J.-P.; Seiler, P.; Gross, M.; Diederich, F. *Chem. Asian J.* **2006**, 1, 479–489. c) Andersson, A. S.; Kilsa, K.; Hassenkam, T.; Gisselbrecht, J.-P.; Boudon, C.; Gross, M.; Nielsen, M. B.; Diederich, F. *Chem. Eur. J.* **2006**, 12, 8451–8459.
72. a) Haley, M. M.; Langsdorf, B. L. *Chem. Commun.* **1997**, 1121–1122. b) Pak, J. J.; Weakley, T. J. R.; Haley, M. M. *J. Am. Chem. Soc.* **1999**, 121, 8182–8192. c) Marsden, J. A.; O'Connor, M. J.; Haley, M. M. *Org. Lett.* **2004**, 6, 2385–2388.
73. a) Höger, S.; Meckenstock, A.-D.; Pellen, H. *J. Org. Chem.* **1997**, 62, 4556–4557. b) Höger, S.; Meckenstock, A.-D. *Chem. Eur. J.* **1999**, 5, 1686–1691. c) Höger, S.; Bonrad, K.; Karcher, L.; Meckenstock, A.-D. *J. Org. Chem.* **2000**, 65, 1588–1589. d) Ziegler, A.; Mamdouh, W.; Ver Heyen, A.; Surin, M.; Uji-i, H.; Abdel-Mottaleb, M. M. S.; De Schryver, F. C.; De Feyter, S.; Lazzaroni, R.; Höger, S. *Chem. Mater.* **2005**, 17, 5670–5683.
74. a) de Meijere, A.; Kozhushkov, S.; Puls, C.; Haumann, T.; Boese, R.; Cooney, M. J.; Scott, L. T. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 869–871. b) de Meijere, A.; Kozhushkov, S.; Haumann, T.; Boese, R.; Puls, C.; Cooney, M. J.; Scott, L. T. *Chem. Eur. J.* **1995**, 1, 124–131. d) de Meijere, A.; Kozhushkov, S. I. *Chem. Eur. J.* **2002**, 8, 3195–3202.
75. a) Romero, M. A.; Fallis, A. G. *Tetrahedron Lett.* **1994**, 35, 4711–4714. b) Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Angew. Chem., Int. Ed.* **2000**, 39, 385–388.

76. a) Altmann, M.; Friedrich, J.; Beer, F.; Reuter, R.; Enkelmann, V.; Bunz, U. H. F. *J. Am. Chem. Soc.* **1997**, *119*, 1472–1473. b) Laskoski, M.; Roidl, G.; Ricks, H. L.; Morton, J. G. M.; Smith, M. D.; Bunz, U. H. F. *J. Organomet. Chem.* **2003**, *673*, 13–24.
77. Ohkita, M.; Ando, K.; Suzuki, T.; Tsuji, T. *J. Org. Chem.* **2000**, *65*, 4385–4390.
78. García-Frutos, E. M.; Fernández-Lázaro, F.; Maya, E. M.; Vázquez, P.; Torres, T. *J. Org. Chem.* **2000**, *65*, 6841–6846.
79. Tobe, Y.; Utsumi, N.; Kawabata, K.; Nagano, A.; Adachi, K.; Araki, S.; Sonoda, M.; Hirose, K.; Naemura, K. *J. Am. Chem. Soc.* **2002**, *124*, 5350–5364.
80. Srinivasan, M.; Sankararaman, S.; Hopf, H.; Varghese, B. *Eur. J. Org. Chem.* **2003**, *660*–665.
81. Moriarty, R. M.; Pavlović, D. *J. Org. Chem.* **2004**, *69*, 5501–5504.
82. a) Werz, D. B.; Gleiter, R.; Rominger, F. *J. Org. Chem.* **2004**, *69*, 2945–2952. b) Baier, M.; Gleiter, R.; Rominger, F. *Eur. J. Org. Chem.* **2006**, 5264–5278.
83. Iyoda, M.; Kuwatani, Y.; Yamagata, S.; Nakamura, N.; Todaka, M.; Yamamoto, G. *Org. Lett.* **2004**, *6*, 4667–4670.
84. Setaka, W.; Kanai, S.; Kabuto, C.; Kira, M. *Chem. Lett.* **2006**, *35*, 1364–1365.
85. a) Goichi, M.; Toyota, S. *Chem. Lett.* **2006**, *35*, 684–685. b) Goichi, M.; Miyahara, H.; Toyota, S. *Chem. Lett.* **2006**, *35*, 920–921.
86. a) Anderson, H. L. *Inorg. Chem.* **1994**, *33*, 972–981. b) Marvaud, V.; Vidal-Ferran, A.; Webb, S. J.; Sanders, J. K. M. *J. Chem. Soc., Dalton Trans.* **1997**, 985–990. c) Nakash, M.; Clyde-Watson, Z.; Feeder, N.; Davies, J. E.; Teat, S. J.; Sanders, J. K. M. *J. Am. Chem. Soc.* **2000**, *122*, 5286–5293.
87. a) Menger, F. M.; Chen, X. Y.; Broccolini, S.; Hopkins, H. P.; Hamilton, D. *J. Am. Chem. Soc.* **1993**, *115*, 6600–6608. b) Menger, F. M.; Chen, X. Y. *Tetrahedron Lett.* **1996**, *37*, 323–326.
88. Ladika, M.; Fisk, T. E.; Wu, W. W.; Jons, S. D. *J. Am. Chem. Soc.* **1994**, *116*, 12093–12094.
89. Taguchi, K.; Arakawa, K.; Eguchi, T.; Kakinuma, K.; Nakatani, Y.; Ourisson, G. *New J. Chem.* **1998**, *63*–69.
90. a) Miyawaki, K.; Takagi, T.; Shibakami, M. *Synlett* **2002**, 1326–1328. b) Miyawaki, K.; Goto, R.; Takagi, T.; Shibakami, M. *Synlett* **2002**, 1467–1470.
91. a) Bukownik, R. R.; Wilcox, C. S. *J. Org. Chem.* **1988**, *53*, 463–471. b) Belghiti, T.; Joly, J.-P.; Didierjean, C.; Dahaoui, S.; Chapleur, Y. *Tetrahedron Lett.* **2002**, *43*, 1441–1443.
92. a) Whitlock, B. J.; Jarvi, E. T.; Whitlock, H. W. *J. Org. Chem.* **1981**, *46*, 1832–1835. b) Jarvi, E. T.; Whitlock, H. W. *J. Am. Chem. Soc.* **1982**, *104*, 7196–7204. c) Cloninger, M. J.; Whitlock, H. W. *J. Org. Chem.* **1998**, *63*, 6153–6159.
93. a) Srinivasan, M.; Sankararaman, S.; Hopf, H.; Dix, I.; Jones, P. G. *J. Org. Chem.* **2001**, *66*, 4299–4303. b) Sankararaman, S.; Srinivasan, M.; Narayanan, V.; Varghese, B. *Ind. J. Chem.* **2004**, *43B*, 1499–1503.
94. Lehn, J.-M.; Schmidt, F.; Vigneron, J.-P. *Tetrahedron Lett.* **1988**, *29*, 5255–5258.
95. Berscheid, R.; Vögtle, F. *Synthesis* **1992**, 58–62.
96. Godt, A.; Duda, S.; Ünsal, O.; Thiel, J.; Härtel, A.; Roos, M.; Tschierske, C.; Diele, S. *Chem. Eur. J.* **2002**, *8*, 5094–5106.
97. a) Hébert, N.; Beck, A.; Lennox, R. B.; Just, G. *J. Org. Chem.* **1992**, *57*, 1777–1783. b) Bhattacharya, S.; Ghosh, S.; Easwaran, K. R. K. *J. Org. Chem.* **1998**, *63*, 9232–9242.
98. Hegmann, T.; Neumann, B.; Wolf, B.; Tschierske, C. *J. Mater. Chem.* **2005**, *15*, 1025–1034.
99. Zhao, T.; Liu, Z.; Song, Y.; Xu, W.; Zhang, D.; Zhu, D. *J. Org. Chem.* **2006**, *71*, 7422–7432.
100. [R] a) Schill, G. *Catenanes, Rotaxanes, and Knots*, Academic, New York, 1971. b) Dietrich-Buchecker, C. O.; Sauvage, J.-P. *Chem. Rev.* **1987**, *87*, 795–810. c) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725–2828.
101. a) Duda, S.; Godt, A.; *Eur. J. Org. Chem.* **2003**, 3412–3420. b) Ünsal, Ö.; Godt, A. *Chem. Eur. J.* **1999**, *5*, 1728–1733.
102. Hamilton, D. G.; Prodi, L.; Feeder, N.; Sanders, J. K. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1057–1065.
103. Gunter, M. J.; Farquhar, S. M. *Org. Biomol. Chem.* **2003**, *1*, 3450–3457.
104. Miljanić, O. S.; Dichtel, W. R.; Mortezaei, S.; Stoddart, J. F. *Org. Lett.* **2006**, *8*, 4835–4838.
105. Carina, R. F.; Dietrich-Buchecker, C.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1996**, *118*, 9110–9116.

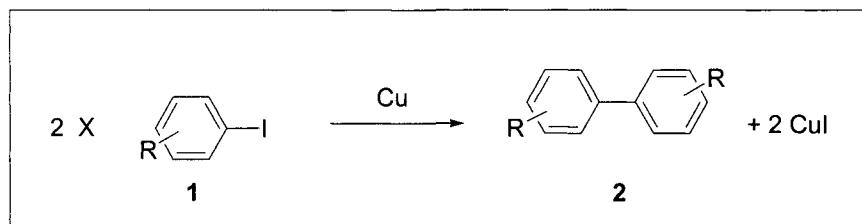
106. [R] a) Ogawa, T. *Prog. Polym. Sci.* **1995**, *20*, 943–985. b) Szafert, S.; Gladysz, J. A. *Chem. Rev.* **2006**, *106*, 1–33.
107. Hay, A. S. *J. Polym. Sci. A* **1969**, *7*, 1625–1634.
108. Knol, K. E.; van Horssen, L. W.; Challa, G.; Havinga, E. E. *Polym. Commun.* **1985**, *26*, 71–73.
109. Cataldo, F. *Polym. Int.* **1997**, *44*, 191–200.
110. Rutherford, D. R.; Stille, J. K.; Elliott, C. M.; Reichert, V. R. *Macromolecules* **1992**, *25*, 2294–2306.
111. a) Anderson, H. L.; Martin, S. J.; Bradley, D. D. C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 655–657. b) Screen, T. E. O.; Lawton, K. B.; Wilson, G. S.; Donley, N.; Ispasoiu, R.; Goodson III, T.; Martin, S. J.; Bradley, D. D. C.; Anderson, H. L. *J. Mater. Chem.* **2001**, *11*, 312–320.
112. Kwock, E. W.; Baird, Jr., T.; Miller, T. M. *Macromolecules* **1993**, *26*, 2935–2940.
113. a) Boldi, A. M.; Anthony, J.; Gramlich, V.; Knobler, C. B.; Boudon, C.; Gisselbrecht, J.-P.; Gross, M.; Diederich, F. *Helv. Chim. Acta* **1995**, *78*, 779–796. b) Schenning, A. P. H. J.; Arndt, J.-D.; Ito, M.; Stoddart, A.; Schreiber, M.; Siemsen, P.; Martin, R. E.; Boudon, C.; Gisselbrecht, J.-P.; Gross, M.; Gramlich, V.; Diederich, F. *Helv. Chim. Acta* **2001**, *84*, 296–334. c) Siemsen, P.; Gubler, U.; Bosshard, C.; Günter, P.; Diederich, F. *Chem. Eur. J.* **2001**, *7*, 1333–1341.
114. a) Anderson, S.; Aplin, R. T.; Claridge, T. D. W.; Goodson III, T.; Maciel, A. C.; Rumbles, G.; Ryan, J. F.; Anderson, H. L. *J. Chem. Soc., Perkin Trans. I* **1998**, 2383–2397. b) Taylor, P. N.; Hagan, A. J.; Anderson, H. L. *Org. Biomol. Chem.* **2003**, *1*, 3851–3856.
115. a) Sumi, N.; Nakanishi, H.; Ueno, S.; Takimiya, K.; Aso, Y.; Otsubo, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 979–988. b) Inouchi, K.; Kobashi, S.; Takimiya, K.; Aso, Y.; Otsubo, T. *Org. Lett.* **2002**, *4*, 2533–2536.
116. a) Krömer, J.; Rios-Carreras, I.; Fuhrmann, G.; Musch, C.; Wunderlin, M.; Debaerdemaeker, T.; Mena-Osteritz, E.; Bäuerle, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3481–3486. b) Fuhrmann, G.; Krömer, J.; Bäuerle, P. *Synth. Met.* **2001**, *119*, 125–126.
117. Xu, G.-L.; Wang, C.-Y.; Ni, Y.-H.; Goodson III, T. G.; Ren, T. *Organometallics* **2005**, *24*, 3247–3254.
118. Lee, L.-H.; Lynch, V.; Lagow, R. J. *J. Chem. Soc., Perkin Trans. I* **2000**, 2805–2809.
119. Xie, X.; Phuan, P.-W.; Kozlowski, M. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2168–2170.
120. Häussler, M.; Zheng, R.; Lam, J. W. Y.; Tong, H.; Dong, H.; Tang, B. Z. *J. Phys. Chem. B* **2004**, *108*, 10645–10650.
121. Gibtnner, T.; Hampel, F.; Gisselbrecht, J.-P.; Hirsch, A. *Chem. Eur. J.* **2002**, *8*, 408–432.
122. Elwahy, A. H. M.; Hafner, K. *Eur. J. Org. Chem.* **2006**, 3910–3916.
123. Kim, J. H.; Park, Y. T. *Bull. Korean Chem. Soc.* **2006**, *27*, 869–874.
124. Rodriguez, J. G.; Tejedor, J. L. *Tetrahedron* **2005**, *61*, 3033–3043.
125. Campbell, I. D.; Eglinton, G. *Org. Syn. Coll. Vol. V* **1973**, 517–520.
126. Stöckel, K.; Sondheimer, F. *Org. Syn. Coll. Vol. VI* **1991**, 68–75.
127. Jones, G. E. Kendrick, D. A.; Holmes, A. B. *Org. Syn. Coll. Vol. VIII* **1993**, 63–67.
128. [R] Williamson, K. L.; Minard, R.; Masters, K. M. *Macroscale and Microscale Organic Experiments*, 5th Ed. Houghton Mifflin, Boston, 2007, pp 399–403.
129. [R] Brandsma, L. *Preparative Acetylenic Chemistry*, 2nd Edition, Elsevier, Amsterdam, 1988, pp 220–223.
130. Rodriguez, J. G.; de los Rios, C.; Lafuente, A. *Tetrahedron* **2005**, *61*, 9042–9051.

### 1.2.3 Ullmann Coupling

Nadia M. Ahmad

#### 1.2.3.1 Description

The Ullmann reaction can be taken to refer to two different transformations. The first is the copper mediated coupling of two aryl groups to give a biaryl compound; this is the “classic” Ullmann reaction. The second, the Ullmann-type reaction, is the nucleophilic aromatic substitution between aryl nucleophiles and aryl halides, the most common of which is the Ullmann ether synthesis.<sup>1,2</sup> The classic Ullmann reaction will be reviewed in this chapter; the reader is referred to several excellent reviews for details on the Ullmann-type reaction.<sup>3,4</sup>



#### 1.2.3.2 Historical Perspective

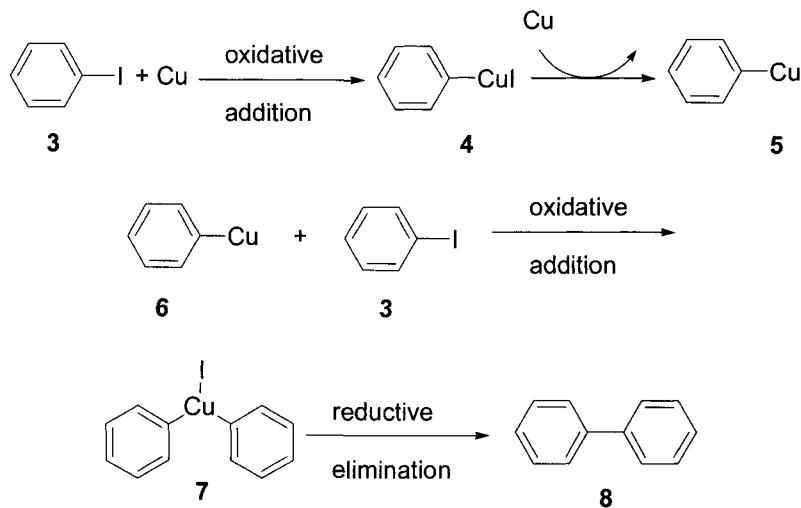
The reaction of aryl halides with stoichiometric copper to produce aryl–aryl bonds was reported by Fritz Ullmann in 1901 in series of papers in *Chemische Bericht*.<sup>5–8</sup> Ullmann, a German chemist, studied chemistry in Nuremberg and received his Ph.D. from the University of Geneva under the tutelage of Carl Gräbe in 1895. Ullmann has the honour of several reactions being named after him, including the Graebe–Ullmann reaction,<sup>9a,b</sup> and the Jourdan–Ullmann–Goldberg synthesis,<sup>8,10,11</sup> a reaction discovered with his wife, Irma Goldberg.

The reaction employing copper was utilized almost exclusively in the following decades for biaryl formation until the rising popularity of nickel, in an Ullmann-type coupling. This was followed by the use of zinc, tin, boron, and eventually, palladium, arguably the most commonly used transition metal in organic synthesis today for such transformations.

#### 1.2.3.3 Mechanism

The mechanism proceeds by oxidative addition of the copper into the aryl halide **3**. The copper(I)–aryl species **4** then undergoes another oxidative

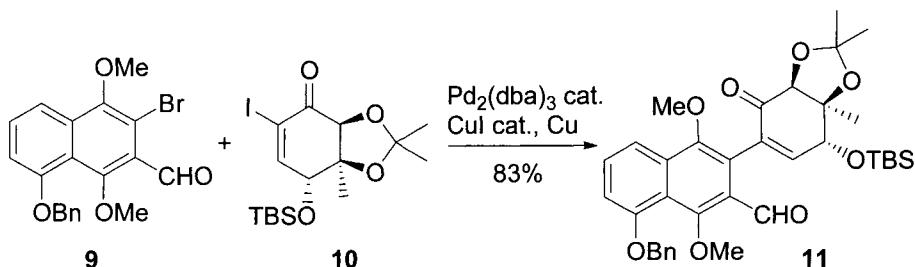
coupling with another equivalent of the aryl halide resulting in a biaryl copper compound **7**. Reductive elimination follows resulting in the formation of the carbon–carbon bond and a biaryl compound **8** is produced.



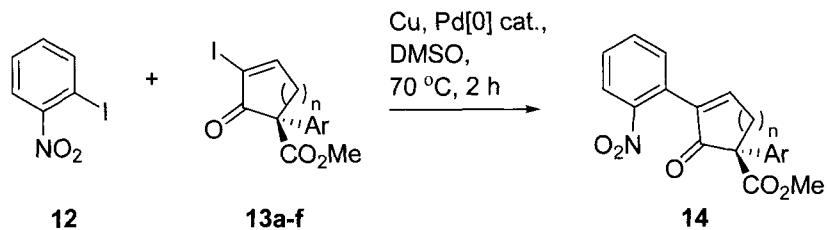
Thus it is clear that electron-withdrawing groups on the aromatic ring, particularly in the ortho position to the halogen, result in an activating effect on the reaction. Electron-donating groups on the other hand, hinder the reaction if not inhibiting it altogether. For obvious reasons, bulky substituents in the ortho positions can also decrease the effectiveness of the reaction, although exceptions exist.

#### 1.2.3.4 Variations, Improvements or Modifications

Variations in the Ullmann reaction centre mainly on the catalysts used to carry out the transformation and modifications to the conditions in order to improve yields. Additionally, although the Ullmann reaction is traditionally the reaction of aryl halides with copper, other metals have also been utilized, often to inhibit the formation of by-products.<sup>12–15</sup>



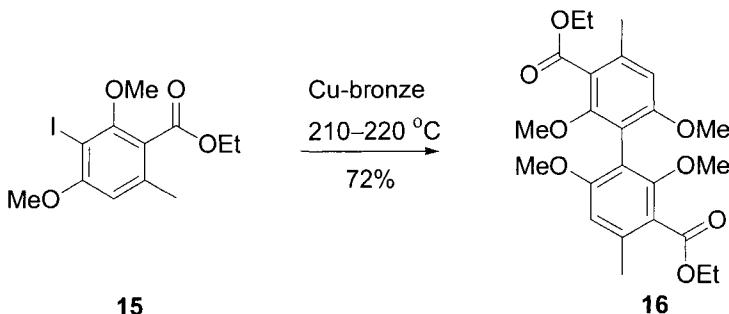
The replacement of copper by other metals in the Ullmann reaction usually results in milder and more efficient pathways. The common use of Pd in conjunction with copper in the Ullmann coupling can be seen in many examples. Nicolaou *et al.* utilized such modifications in their total synthesis of kinamycins C, F, and J.<sup>16</sup> Bromide **9** underwent coupling with iodide **10** to give aldehyde **11** in a satisfactory 83% yield.



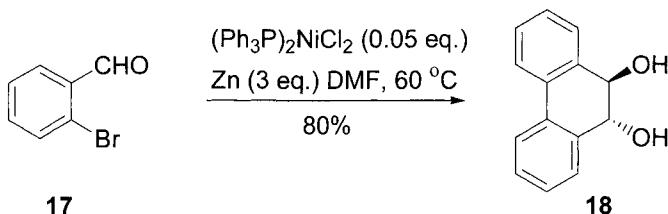
Substrate	n	Ar	Yield %
13a	1		60
13b	1		58
13c	1		86
13d	2		56
13e	22		56
13f	2		91

The synthesis of vincristine and vinblastine has received much attention over the years due to their use in cancer therapy, especially breast and testicular cancer, and acute leukemia. However due to their neurotoxicological side effects the identification and effective synthesis of analogues displaying improved therapeutic properties has been a pursuit of several research groups.<sup>17–19</sup> Accordingly, Banwell and coworkers have reported the use of a Pd[0]-catalyzed Ullmann cross-coupling between 2-iodonitrobenzene **12** and iodides **13** in their synthesis of the indole–indoline analogues.<sup>20</sup> Good to excellent yields were obtained. The Ullmann products then underwent reductive cyclisations to give the desired indole-indoline structures.

The use of copper bronze was used in the Ullmann coupling of protected iodoresorcinol **15** to give the symmetrical biphenyl **16**.<sup>21</sup> Despite the obvious steric hinderance afforded by the *ortho*-methoxy groups, the reaction took place in a good yield of 72%.

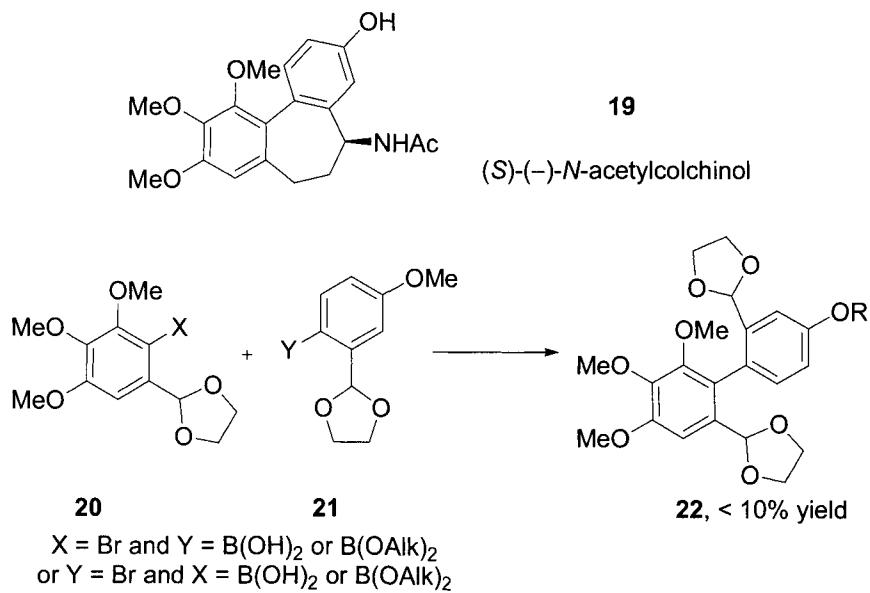


Nickel is a popular alternative to copper in the Ullmann reaction as the reaction conditions are mild and the nickel reagent is inexpensive. You and coworkers have reported the use of a nickel(0)-mediated Ullmann coupling in their reactions of *ortho*-carbonyl-substituted aryl halides **17**, with Zn powder used *in situ* as a reductant, to form *trans*-9,10-dihydroxy-9,10-dihydrophenanthrenes **18**.<sup>22</sup> These phenanthrenes could then be used as chiral ligands in asymmetric synthesis.

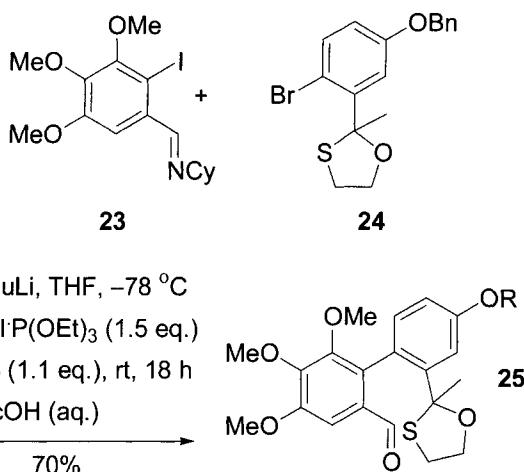


### 1.2.3.5 Synthetic Utility

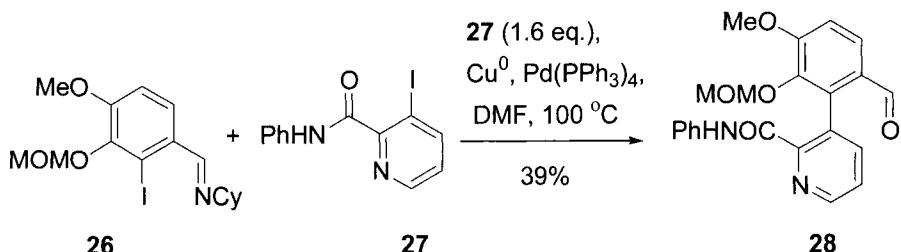
Occasionally, the Ullmann reaction is the only successful method of coupling two aryl groups when other, more prevalent coupling reactions fail. Broady and coworkers for example, attempted to synthesize the core of colchicine-based natural products (**19**) initially utilizing a Suzuki reaction to carry out the key intermolecular biaryl coupling (**20** and **21** → **22**).<sup>23</sup> However, despite significant efforts to optimise the reaction between **20** and **21**, the yields remained below 10%.



The Ziegler–Ullmann reaction was then attempted. This is the reaction devised by Ziegler in which an Ullmann reaction between aryl groups bearing certain substituents is particularly favoured.<sup>24–26</sup> Electron-rich aromatic systems bearing *ortho*-substituents capable of coordinating to copper work best, and thus a sulfur atom is typically preferred. Thus, aryl bromide **24** was converted to the diaryl system **25** in a satisfactory 70% yield, with concomitant conversion of the imine to the aldehyde during work-up. The thioacetal group was then further manipulated to form the 7-membered central colchicine ring. The method illustrates the synthetic utility of the Ullmann reaction which can be employed when other, perhaps more known procedures, fail.

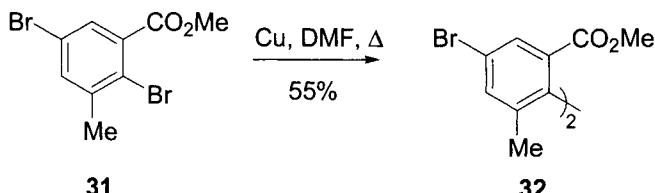
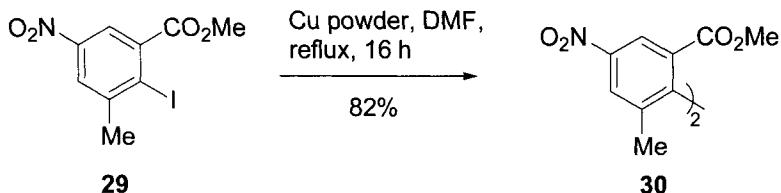


The coordinating effect of an *ortho*-substituent is further exemplified by Kelly and coworkers' synthesis of santiagonamine.<sup>27</sup> Although the yield of the reaction of imine 26 with iodide 27 was still poor, it was still significantly better than the reaction with the corresponding aldehyde (7%). This was partly attributed to the coordinating N lone pair and partly due to the precedent of success Ullmann reactions carried out with imines.<sup>28–29</sup>

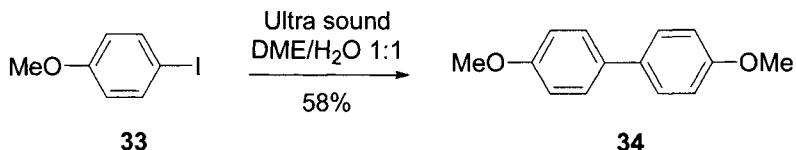


The Ullmann reaction can be used to selectively couple at one aromatic halogen than another depending on the substituents around it. As previously mentioned *ortho*-substituents can be used to direct the coupling and indeed, facilitate the reaction over a less hindered halogen substitute. Crudden and coworkers investigated the Ullmann reaction for the synthesis of biaryl 30.<sup>30</sup> The Ullmann homocoupling of the iodonitro derivative 29 proceeded with a high yield of 82%; however, the nitro group then had to be reduced and converted to the halogen *via* a Sandmeyer reaction. Conversely the Ullmann reaction of the dibromo derivative 31 gave the desired product 32 – due to the coordinating *ortho*-ester only one product was formed, albeit in lower yield (55%). However, the shortness of the second route compensated for the lower yield. The authors found the Ullmann to be a particularly useful reaction in this case as cross-coupling reactions forming

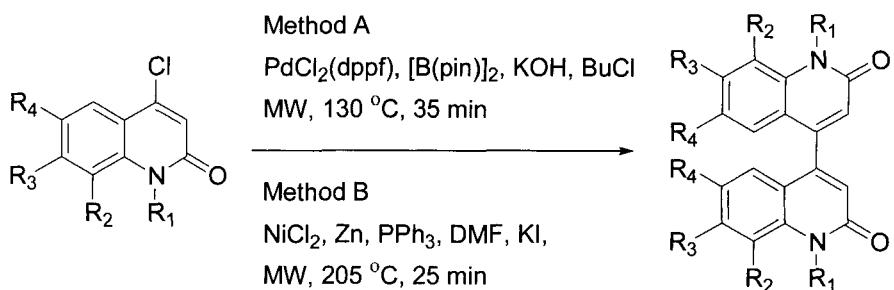
tetr subsituted biaryl systems are rarely effective. The biaryl systems were synthesized for use as chiral materials.



Symmetrical biaryl systems have been synthesised using high-intensity ultrasound (US). The zinc-mediated Ullmann coupling reaction of iodide 33 was carried out in aqueous solvent under bubbling CO<sub>2</sub> with Pd/C to give biaryl 34. The procedure has the advantage of fast reaction times and green credentials.<sup>31</sup>



Similarly, homocoupling reactions can also be carried out using microwave irradiation. Kappe and coworkers demonstrate such procedures, synthesizing bisquinolones 36 from quinolones 35 via both one-pot borylation/Suzuki reactions and Ni(0)-mediated Ullmann homocouplings.<sup>32</sup> In these examples, the yields and product distributions are comparable although the Ullmann benefits as the cheaper alternative to using a diboron reagent.

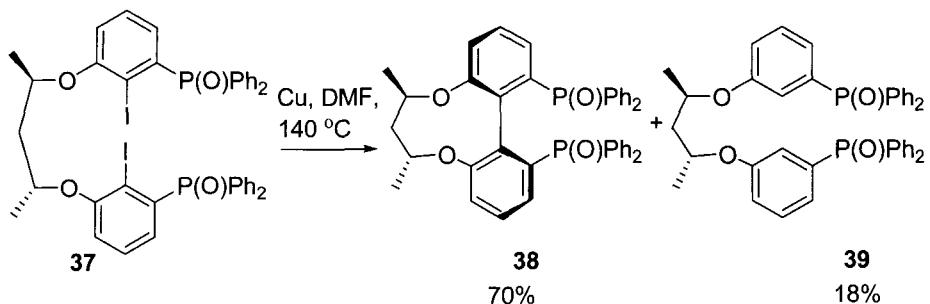


Substrate	Yield %	
	Method A	Method B
<b>xa</b> $R_1 = \text{Me}, R_2 = R_3 = R_4 = \text{H}$	85	90
<b>xb</b> $R_1-R_2 = (\text{CH}_2)_3, R_3 = R_4 = \text{H}$	68	68
<b>xc</b> $R_1 = \text{Ph}, R_2 = R_3 = R_4 = \text{H}$	83	39
<b>xd</b> $R_1 = \text{Me}, R_2 = R_3 = \text{H}, R_4 = \text{OMe}$	83	70
<b>xe</b> $R_1 = \text{Me}, R_2 = R_4 = \text{H}, R_3 = \text{OMe}$	70	74

### 1.2.3.6 Experimental

#### Asymmetric Ullmann Coupling Using Copper

#### Synthesis of (*S*)-[6,6'-(2*R*,4*R*-Pentadioxyl)]-(2,2')-bis(diphenylphosphoryl)-(1,1')-biphenyl (38)<sup>33</sup>

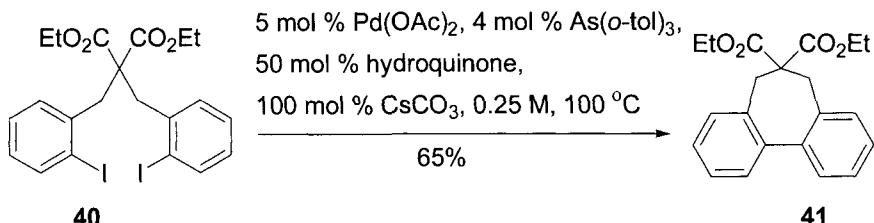


DMF (5 mL) was added into a flask containing Cu powder (0.215 g, 3.36 mmol) and 37 (0.382 g, 0.42 mmol). The resulting mixture was stirred at 140 °C for 12 h under a nitrogen atmosphere. After removal of the DMF solvent under reduced pressure, the residue was boiled for 5 min. with hot CH<sub>2</sub>Cl<sub>2</sub> (10 mL × 3). The insoluble solid was removed by filtration and washed with hot CH<sub>2</sub>Cl<sub>2</sub> (5 mL × 3). The combined filtrate was washed successively with

saturated aqueous ammonium chloride and brine and was dried over anhydrous  $\text{Na}_2\text{SO}_4$ . After removal of the solvent, the residue was purified by silica gel chromatography to give (*SRR*)-**38** as a white solid (194 mg, 0.296 mmol, 70.5%) and a recovered compound **39** (50 mg, 0.076 mmol, 18.1%).

Intramolecular Ullmann Coupling Using Palladium

**5,7-Dihydro-dibenzo[a,c]cycloheptane-6,6-dicarboxylic acid diethyl ester**



To a mixture of **40** (592 mg, 1 mmol), hydroquinone (55 mg, 0.5 mmol) and Cs<sub>2</sub>CO<sub>3</sub> (0.326 g, 1 mmol) was added a homogenous pre-stirred DMA solution (2.50 mL) of Pd(OAc)<sub>2</sub> (11.2 mg, 0.05 mmol) and tri-*o*-tolylarsine (17.4 mg, 0.05 mmol). The reaction mixture darkened immediately upon addition of the catalyst solution to the solid reagents. The mixture was degassed, using N<sub>2</sub> and house vacuum, and heated under N<sub>2</sub> at 100 °C for 24 h. The reaction mixture was cooled to room temperature, quenched with HCl (20 mL, 2 M), diluted with water (20 mL), and extracted with EtOAc (3 × 25 mL). The combined organics were washed with 10% NaOH (4 × 20 mL), brine, dried over MgSO<sub>4</sub>, concentrated under reduced pressure, and purified using flash column chromatography on silica gel (elution with hexanes:toluene:ether 30:10:1) to afford biaryl **41** as a colourless oil (221 mg, 65%) and recovered **40** (81 mg, 14%).

### **1.2.3.7 References**

- [R] Frlan, R.; Kikelj, D. *Synthesis* **2006**, *14*, 2271–2285.
  - [R] Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045–5065.
  - [R] Liang, Y.; Li, J-H. *Youji Huaxue* **2005**, *25*, 147–151.
  - [R] Beletskaya, I. P.; Cheprakov, A. V. *Coordination Chem. Rev.* **2004**, *248*, 2337–2364.
  - Ullmann, F.; Bielecki, J. *Chem. Ber.* **1901**, *34*, 2174–2178.
  - Ullmann, F. *Chem. Ber.* **1906**, *39*, 1693–1696.
  - Ullmann, F. *Chem. Ber.* **1905**, *38*, 2111–2112.
  - Ullmann, F. *Chem. Ber.* **1903**, *36*, 2382–2384.
  - (a) Graebe, C.; Ullmann, F. *Ann.* **1896**, *16*, 291; (b) Ullmann, F. *Ann.* **1904**, *82*, 332.
  - Jourdan, F. *Chem. Ber.* **1885**, *18*, 1444.
  - Goldberg, I. *Chem. Ber.* **1906**, *39*, 1691.
  - [R] Nelson, T. D.; Crouch, R. D. *Org. React.* **2004**, *63*, 265–555.

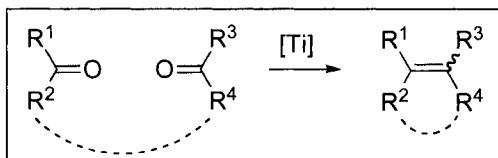
13. [R] Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.
14. [R] Fanta, P. E. *Chem. Rev.* **1964**, *61*–632.
15. [R] Fanta, P. E. *Synthesis* **1974**, *1*, 9–21.
16. Nicolaou, K. C.; Li, H.; Nold, A. L.; Pappo, D.; Lenzen, A. *J. Am. Chem. Soc.* **2007**, *129*, 10356–10357.
17. Miyazaki, T.; Yokoshima, S.; Simizu, S.; Osada, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2007**, *9*, 4737–4740.
18. Shao, Y.; Ding, H.; Tang, W.; Lou, L.; Hu, L. *Bioorg. Med. Chem.* **2007**, *15*, 5061–5075.
19. Li, W.; Shao, Y.; Hu, L.; Zhang, X.; Chen, Y.; Tong, L.; Li, C.; Shen, X.; Ding, J. *Cancer Biol. Ther.* **2007**, *6*, 787–794.
20. Harvey, M. J.; Banwell, M. G.; Lupton, D. W. *Tetrahedron Lett.* **2008**, *49*, 4780–4783.
21. Hauser, F. M.; Gauuan, P. J. F. *Org. Lett.* **1999**, *1*, 671–672.
22. You, T.-p.; Chen, Q.-a.; Lin, S.-z. *Synlett.* **2007**, *13*, 2101–2105.
23. Broady, S. D.; Golden, M. D.; Leonard, J.; Muir, J. C.; Maudet, M. *Tetrahedron Lett.* **2007**, *48*, 4627–4630.
24. Ziegler, F. E.; Chiliwner, I.; Fowler, K. W.; Kanfer, S. J.; Kuo, S. J.; Sinha, N. D. *J. Am. Chem. Soc.* **1980**, *102*, 790–798.
25. Ziegler, F. E.; Fowler, K. W.; Rodgers, W. B.; Wester, R. T. *Org. Synth.* **1987**, *65*, 108–118.
26. Stark, L. M.; Lin, X.-F.; Flippin, L. A. *J. Org. Chem.* **2000**, *65*, 3227–3230.
27. Markey, M. D.; Fu, Y.; Kelly, T. R. *Org. Lett.* **2007**, *9*, 3255–3257.
28. Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327–3359.
29. Stark, L. M.; Lin, X.-F.; Flippin, L. A. *J. Org. Chem.* **2000**, *65*, 3227–3230.
30. Montoya-Pelaez, P. J.; Uh, Y.-S.; Lata, C.; Thompson, M. P.; Lemieux, R. P.; Crudden, C. M. *J. Org. Chem.* **2006**, *71*, 5921–5929.
31. Cravotto, G.; Beggiato, M.; Penoni, A.; Palmisano, G.; Tollari, S.; Leveque, J.-M.; Bonrath, W. *Tetrahedron Lett.* **2005**, *46*, 2267–2271.
32. Hashim, J.; Glasnov, T. N.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2006**, *71*, 1707–1710.
33. Qui, L.; Kwong, F. Y.; Wu, J.; Wai, H. L.; Chan, S.; Yu, W.-Y.; Li, Y.-M.; Guo, R.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2006**, *128*, 5955–5965.
34. Hennings, D. D.; Iwama, T.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 1205–1208.

### 1.3.1 McMurry Coupling

Brian Goess

#### 1.3.1.1 Description

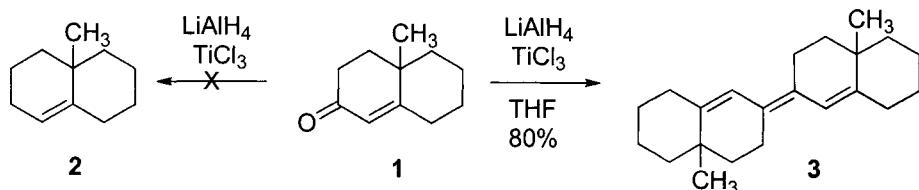
Alkenes may be generated via the intra- or intermolecular reductive coupling of carbonyl compounds in a titanium-mediated process known as the McMurry coupling.<sup>1</sup>



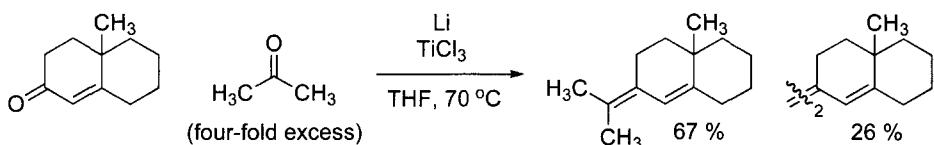
The reaction is a versatile strategy for carbon–carbon bond construction as evidenced by the large number of natural and non-natural compounds that have been synthesized using the McMurry reaction as a key step. Furthermore, the reaction has stimulated a significant number of theoretical studies, including examinations of the unique and often highly-strained molecules that can be prepared using the McMurry reaction and of the mechanism of the reaction itself.

#### 1.3.1.2 Historical Perspective

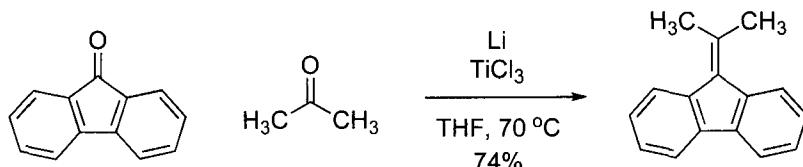
A titanium-induced carbonyl coupling reaction was discovered serendipitously by the McMurry group in 1974 during their search for a new, high-yielding reduction of  $\alpha,\beta$ -unsaturated carbonyl compounds such as **1** to the corresponding alkene (**2**).<sup>2</sup> Their plan was to conduct a hydride reduction of the carbonyl in the presence of an oxophilic transition metal, which they had hoped might coordinate strongly to the alkoxide intermediate and facilitate a second hydride reduction to yield the deoxygenated product (**2**). However, their experimental conditions, which employed LiAlH<sub>4</sub> as the strong hydride donor and TiCl<sub>3</sub> as the oxophile, instead generated the product of reductive dimerization (**3**).



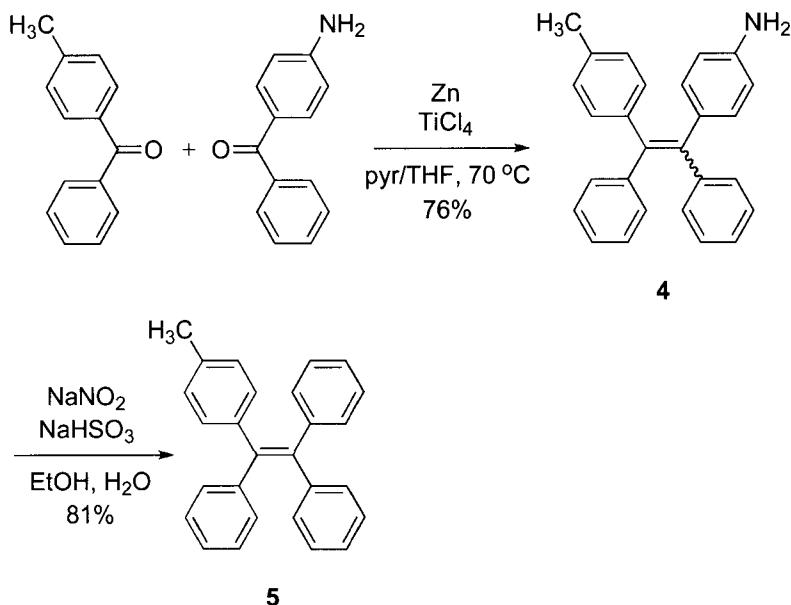
Two other groups made a similar discovery almost simultaneously,<sup>3,4</sup> and the potential value of these transformations was immediately apparent to the synthetic community. Early investigations into substrate scope led to the discovery that the reductive coupling was successful for a wide range of aldehydes and ketones, including saturated and unsaturated ketones and aldehydes, aryl ketones and aldehydes, and diaryl ketones.<sup>5</sup> In these early stages of reaction development, there were few techniques for overcoming the problems inherent with achieving selective reductive heterocoupling of two different carbonyl-containing compounds. Therefore, acyclic products were limited to symmetrical alkenes, although this limitation was overcome in specific cases when an excess of one reaction partner was used.<sup>5</sup>



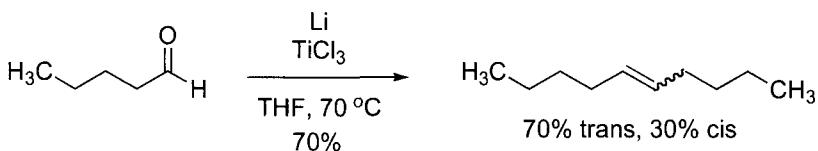
If both carbonyl substrates have sufficiently different redox potentials, a reasonable yield of crossed product is obtained without resorting to using one substrate in excess. This result was unexpected given the relative ease that a bisaromatic ketone should undergo ketyl formation followed by self pinacol coupling and was one of the first results that indicated more than one mechanism may be operative in McMurry couplings.<sup>5</sup> In this case, the diaryl ketone may be reduced selectively to a dianion, which then undergoes nucleophilic addition to the saturated ketone.



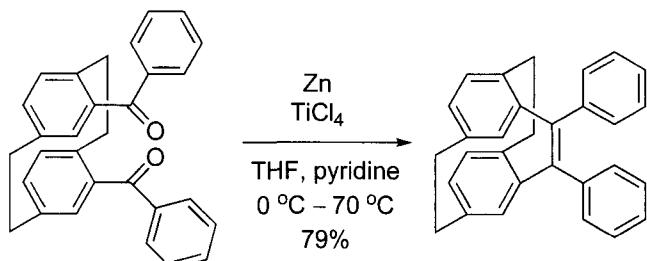
A more recent study has provided a strategy for heterocoupling structurally similar aryl or diaryl ketones.<sup>6</sup> Heteroatom directing groups are appended to one of the ketone reaction partners, thus giving it an enhanced affinity for the titanium surface on which the reaction proceeds. Binding of these substrates deactivates the titanium surface and retards the corresponding homocoupling reaction. The result is increased selectivity for the heterocoupled product (**4**). Removal of the directing group can then lead to more symmetrical heterocoupled products (**5**).



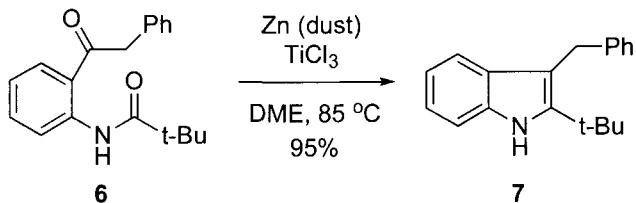
In cases where the formation of alkene geometrical isomers was possible the more stable isomer usually predominated. Notably, it was demonstrated that the stereoselectivity was kinetically-controlled; no alkene isomerization was observed when single geometrical isomers were resubmitted to the reaction conditions.<sup>2</sup>



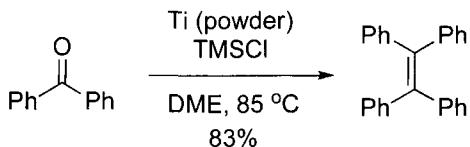
The robust nature of the coupling reaction was repeatedly demonstrated through the synthesis of unusual ring structures as exemplified by the key bond-forming step of Hopf's synthesis of triply-bridged cyclophanes.<sup>7</sup>



These examples also demonstrate another hallmark of the development of the McMurry coupling, namely the ongoing search for the best source of low-valent metal for reductive couplings. Early efforts by McMurry and Geise<sup>8</sup> to substitute other transition metals for titanium failed to uncover a suitable replacement. Various sources of low-valent titanium were also intensively investigated. McMurry's initial combination of  $\text{LiAlH}_4/\text{TiCl}_3$  proved difficult to reproduce consistently. He later reported improved variations on this reagent combination including  $\text{K/TiCl}_3$ ,<sup>9</sup>  $\text{Li/TiCl}_3$ ,<sup>10</sup> and  $\text{Zn-Cu/TiCl}_3(\text{DME})_{1.5}$ .<sup>11</sup> In each of these cases, the reaction was performed in two steps wherein the titanium chloride and reducing agent were combined prior to introduction of the carbonyl-containing substrate. A breakthrough in the convenience of low-valent titanium preparation came in 1994 when Fürstner described a single-step "instant" method for the purpose of indole synthesis.<sup>12</sup> Here, the active titanium species is generated upon coordination of the substrate carbonyl to  $\text{TiCl}_3$  followed by reduction of this complex *in situ* with zinc dust. This one-step procedure is effective only when the reducing agent is not strong enough to reduce the carbonyl. Using this methodology, indole (7) was prepared from oxo amide (6) in high yield. The method is also applicable to furans<sup>13</sup> and a number of other heterocycles.

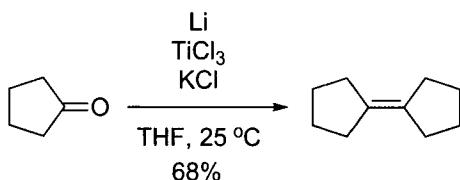


Importantly, this method was shown to be effective for many conventional McMurry reactions as well, and a catalytic variant, using commercially-available titanium powder, followed one year later.<sup>14</sup> The catalytic reaction relied on an admixed chlorosilane, which both activated the commercial titanium powder by destroying the tightly bound oxide layer and regenerated, via ligand exchange, the active titanium chloride from the inactive titanium oxychloride product.

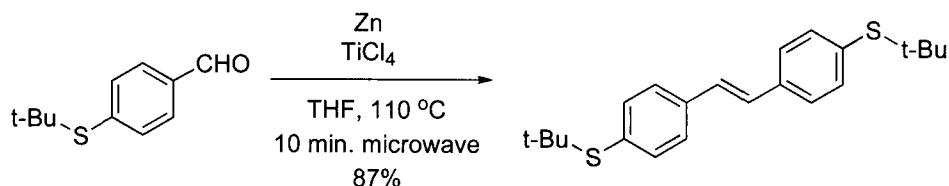


The high temperatures required for most McMurry reactions have prompted recent studies into activating the low-valent titanium reagents for

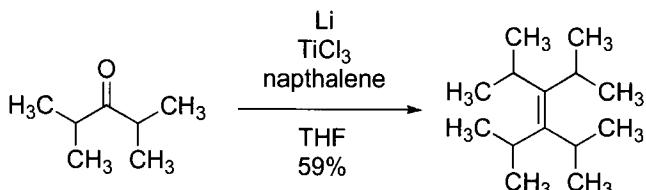
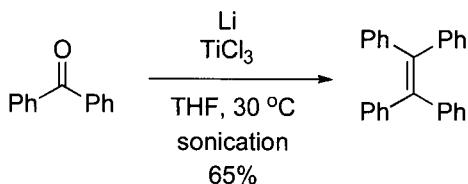
use in room temperature couplings with correspondingly increased functional group tolerance. For instance, addition of alkaline or alkaline earth metal salts was found to enhance the activity of the activated titanium reagent.<sup>15</sup> The authors suggest that exchange of lithium for more electropositive metal cations such as potassium increases the electron density on titanium, which may lead to higher activity for the titanium intermetallic complex.



Microwave heating was found to accelerate reaction times for conventional McMurry reactions, which ordinarily require refluxing for more than two hours.<sup>16</sup>



Sonication allows coupling aromatic aldehydes and ketones at lower temperatures.<sup>17</sup>

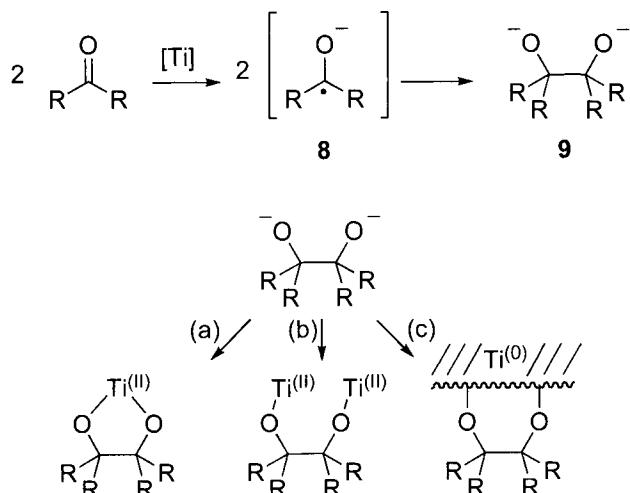


And the use of metal-arenes as single-electron reducing agents for  $\text{TiCl}_3$  allows the McMurry reaction between aromatic and aliphatic aldehydes and ketones to proceed at room temperature.<sup>18</sup>

### 1.3.1.3 Mechanism

The precise mechanism of the McMurry coupling is not known, though the details have been the subject of intense speculation since the discovery of the reaction. The reagent combinations used to perform McMurry couplings result in heterogeneous solutions, thus complicating the determination of both the structure of the reaction intermediates and of the oxidation states of titanium, which vary as the reaction progresses. Nonetheless, in recent years significant progress has been made in determining the identity of early reaction intermediates, and the results of these studies point to a context-dependent mechanism accommodating elements from a variety of mechanisms proposed since the early 1970s.

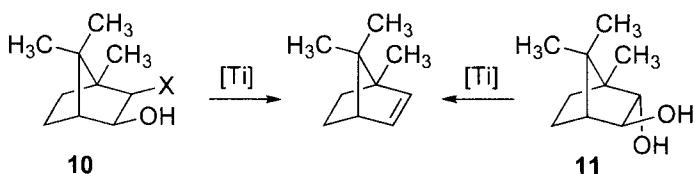
McMurry's original mechanistic proposal involved an initial pinacol coupling followed by a deoxygenation step.<sup>2a</sup> The pinacol step, involving a one-electron reduction from a titanium complex to generate a ketyl (**8**), followed by a carbon–carbon bond-forming dimerization to yield an intermediate pinacolate dianion (**9**), had significant circumstantial support. Reducing metals were known to react with aldehydes and ketones to generate radical anions that subsequently dimerized to form pinacols. Furthermore, pinacols could be isolated in high yields as products if the reaction mixtures were hydrolyzed before completion at temperatures well below reflux.<sup>2</sup>



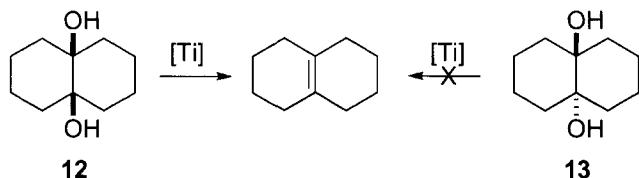
The deoxygenation step was both unprecedented at the time and unique to titanium, thus its mechanism was more challenging to probe. McMurry postulated three general mechanisms: (a) titanacycle formation, (b) an acyclic variant with two coordinated titaniums, and (c) a hybrid mechanism where both oxyanions coordinate to the surface of a finely

divided titanium particle presumably formed from the reduction of  $\text{TiCl}_3$ .<sup>5</sup> In each case, cleavage of the two carbon-oxygen bonds then occurs via a stepwise radical process to yield the product alkene and a titanium oxide. That this cleavage must be non-concerted was demonstrated when configurationally pure diols were found to yield mixtures of *E* and *Z* alkenes when treated under the reaction conditions.<sup>5</sup>

Two mechanistic probes were designed to distinguish the three pinacol pathways. When it was discovered that both *cis*-camphanediol (**10**), which can easily form a 5-membered metallacycle, and *trans*-camphanediol (**11**), which cannot, reacted at a similar rate to yield camphene, pathway (a) was ruled out.



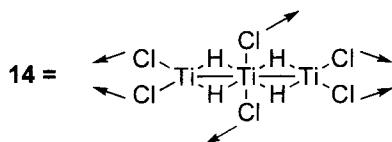
When it was discovered that *trans*-9,10-decalindiol (**13**) was inert to titanium under all conditions whereas *cis*-9,10-decalindiol (**12**) reacted as expected, pathway (b) was ruled out in favor of a pathway that required a common titanium surface for reaction.



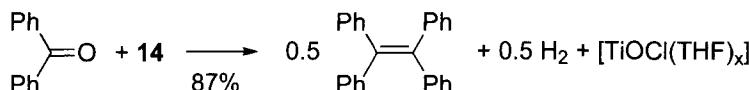
This left pathway (c) as the only reasonable alternative, and this mechanistic proposal received early independent experimental support.<sup>19</sup> The templating effect inherent in pathway (c) also nicely explained the unusual ease with which large rings could be formed using the McMurry protocol.<sup>20</sup> It was later suggested that coordination to the titanium surface might instead occur at the ketyl stage, in which case the carbon-carbon bond formation would also be facilitated by templating of the ketyl radicals.<sup>19</sup>

More recent studies have demonstrated that  $\text{Ti}(0)$  is not required for the McMurry reaction to proceed. Indeed, the assumption that zero-valent titanium is prerequisite for the McMurry reaction persisted even in spite of early evidence that pinacol couplings could be performed with well-characterized  $\text{Ti}(\text{II})$  species and without intervention of  $\text{Ti}(0)$  intermediates.<sup>21</sup> Furthermore, the reductive coupling of gas-phase benzaldehyde was effected

on  $\text{TiO}_2$  surfaces on which X-ray photoelectron spectroscopy detected no  $\text{Ti}(0)$ .<sup>22</sup> Finally, when the McMurry reagent was prepared by one of the traditional methods,  $\text{Ti}(\text{II})$  chlorohydride complex **14** (one possible structure shown) was produced according to the following equation:<sup>23</sup>

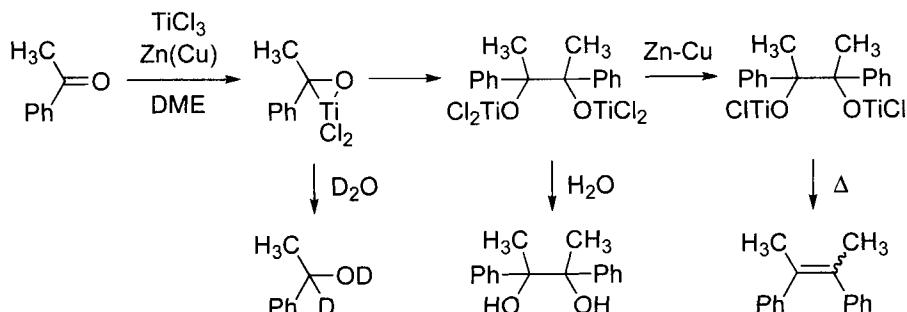


Complex **14** proved to be active in the reductive coupling of benzophenone according to the following equation, yielding a  $\text{Ti}(\text{III})$  oxychloride by-product:

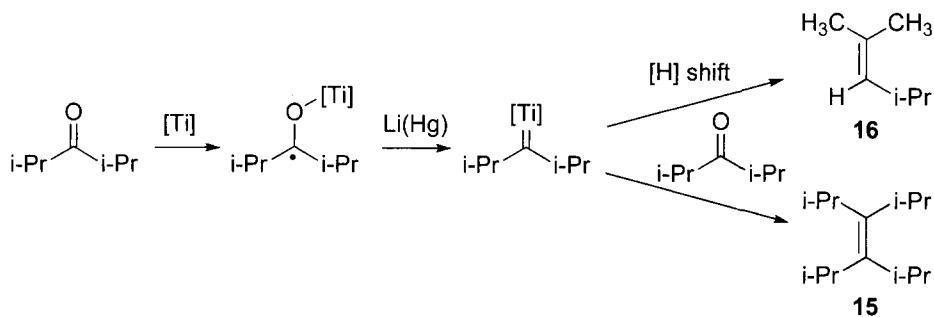


These results imply that the McMurry reaction, when performed with one of the most commonly applied reagent sets,  $\text{TiCl}_3\text{--LiAlH}_4\text{--THF}$ , involves changes in the oxidation state of titanium only between  $\text{Ti}^{1+}$ ,  $\text{Ti}^{2+}$  and  $\text{Ti}^{3+}$ . The necessity of finely divided  $\text{Ti}(0)$  seems to be precluded by these results.<sup>24</sup>

The established mechanism for pinacolate formation has also been challenged by an analysis of the reaction between acetophenone and  $\text{TiCl}_3(\text{DME})\text{--Zn}(\text{Cu})$ .<sup>25</sup> Aliquots quenched at various stages of the reaction revealed products from which a nucleophilic addition mechanism could be inferred. DFT calculations indicated that this reaction pathway is more energetically favorable than the corresponding ketyl pathway.

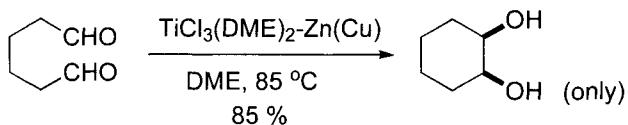


When sterically hindered systems are investigated, evidence has been found for a mechanistic pathway that proceeds not through pinacolate intermediates but through carbenes.<sup>26</sup> In the reaction between diisopropyl ketone and TiCl<sub>4</sub>-Li(Hg) two products were observed, the expected coupling product (**15**) and a product (**16**) that could only be explained through the existence of a carbenoid intermediate. Data supporting this mechanistic hypothesis include the lack of pinacol product and the observation that the titanium pinacolate intermediate is unstable and readily decomposes to carbonyl and titanium chloride. Similar evidence using di-*tert*-butyl ketone has also been obtained.<sup>27</sup>

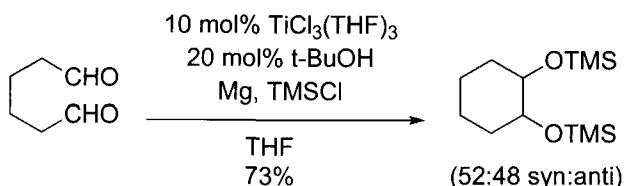


#### 1.3.1.4 Variations, Improvements and Modifications

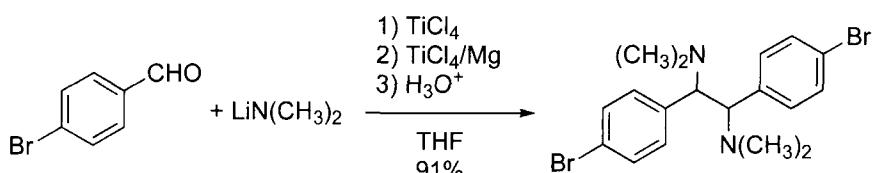
As reflux temperatures are usually required to effect the deoxygenation step of the McMurry reaction, pinacol intermediates can be isolated if the McMurry reaction is run below room temperature. Though a mixture of diol diastereomers is formed in intermolecular reactions, intramolecular reactions can be highly diastereoselective.<sup>28</sup>



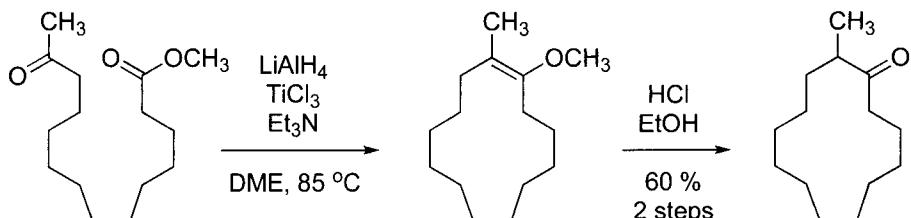
A catalytic version of this reaction has been developed, but diastereoselectivities are low to moderate.<sup>29</sup> Diastereoselectivities for catalytic pinacol coupling of aromatic aldehydes are usually much higher.<sup>30</sup> Recent work on catalytic, enantioselective aromatic aldehyde pinacol couplings have produced enantioselectivities above 90%.<sup>31</sup>



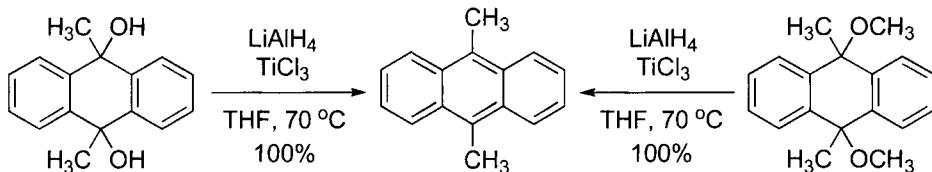
This reaction has been extended to the synthesis of vicinal arylamines,<sup>32</sup> and a one-pot reductive coupling of aryl aldehydes and amines has also been reported.<sup>33</sup>



One of the earliest variations on the traditional McMurry coupling is the McMurry keto ester coupling for the synthesis of enol ethers. Large rings can be prepared by this method, albeit in lower yields, and the cyclic enol ether can be hydrolyzed to yield a cyclic alkanone.<sup>34</sup>

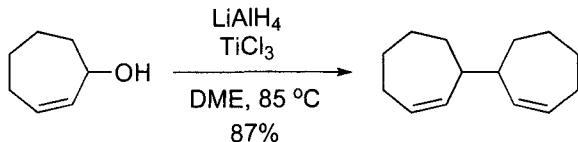


The titanium-mediated deoxygenation step has also been made more general. For example, allylic and benzylic 1,4-diols and 1,4-dimethyl ethers are transformed into more highly unsaturated products under McMurry conditions.<sup>35</sup>



Furthermore, epoxides<sup>36</sup> and halohydrins<sup>37</sup> are deoxygenated to alkenes, nitro compounds<sup>38</sup> and oximes<sup>39</sup> are reduced to imines, and sulfoxides are reduced to sulfides.<sup>40</sup>

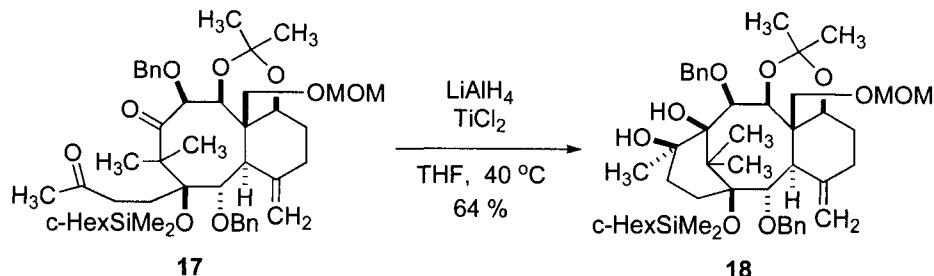
McMurry conditions have been used to self-couple allylic and benzylic alcohols, though this process has not been as successful in the intramolecular synthesis of large rings.<sup>41</sup>



### 1.3.1.5 Synthetic Utility

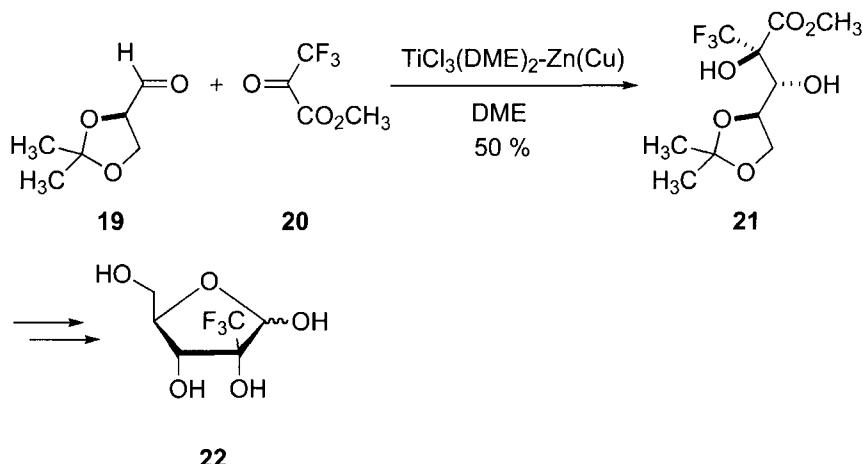
In addition to the numerous examples of the McMurry couplings described above, the following examples illustrate the power of the transformation in the synthesis of a broad range of natural products and non-natural molecules. Of particular note in the following examples is the impressive functional group tolerance of the McMurry conditions. In general, alcohols, tosyl alcohols, alkyl ethers, silyl ethers, alkyl silanes, vinyl silanes, amines, sulfides, and alkenes are inert to McMurry conditions. Acteals, halides, alkynes, nitriles, and carboxylic acids are semi-compatible.

In his recent synthesis of 19-hydroxytaxoid **18**, an intermediate in the synthesis of the anti-cancer agent 19-hydroxytaxol, Mukaiyama performed an intermolecular McMurry pinacol coupling on diketone **17**.<sup>42</sup> Note that the reaction temperature was sufficiently low to allow isolation of the diol intermediate.

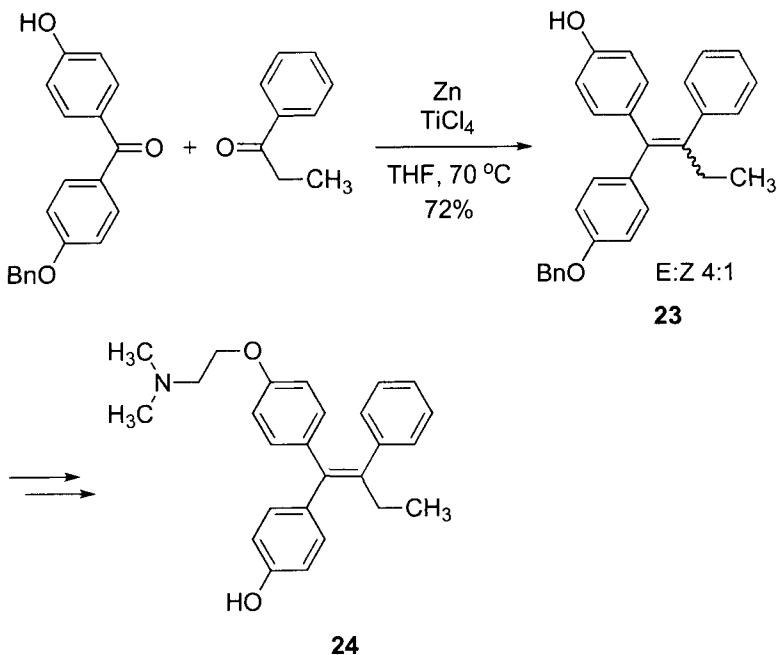


McMurry pinacol couplings can proceed with stereochemical induction from nearby stereogenic carbons. For example, diastereomer **21** was the major heterocoupled stereoisomer observed when aldehyde **19** and ketone **20** were treated under McMurry conditions.<sup>43</sup> A diastereomer of **21** was also produced in 22% yield along with the product of homocoupling of

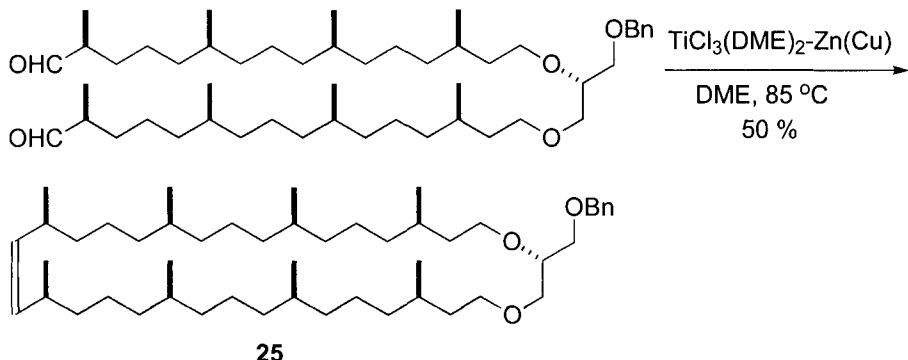
**19.** This route provides access to 2-C-trifluoromethyl-substituted-*D*-ribose (**22**).



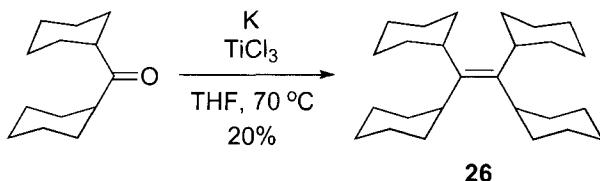
Calogeropoulou took advantage of the stereoselectivity of the McMurry coupling to prepare (*E*)-**23**, a synthetic intermediate en route to (*Z*)-4-hydroxytamoxifen (**24**), the active metabolite of the anti-cancer drug Tamoxifen.<sup>44</sup> A three-fold excess of propiophenone was used to account for unproductive reductive homocoupling.



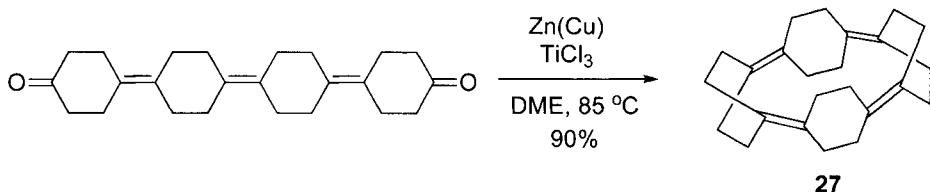
The use of the McMurry reaction to form large rings was aptly demonstrated by Eguchi in his synthesis of this 36-membered ring-containing precursor to an archaeabacterial diether lipid (**25**).<sup>45</sup>

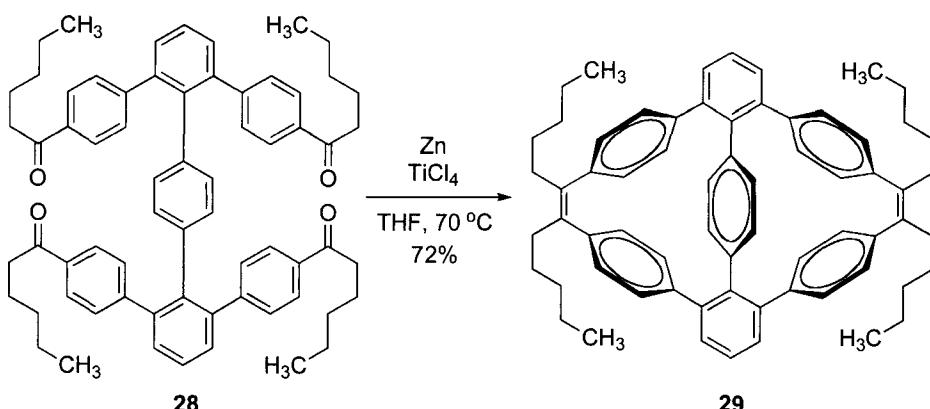


The McMurry reaction is often employed in the synthesis of highly-strained alkenes of theoretical interest. For instance, the rotational barrier of the cyclohexyl groups in **26** is 18.7 kcal/mol as determined by dynamic NMR.<sup>46</sup>



Spherand **27** has an inner surface of high electron density and was found to bind silver(I) ions in a static, square-planar, d<sup>10</sup> organometallic complex.<sup>47</sup> Receptor **28** was found to bind a single silver(I) ion which hops intramolecularly between the two adjoined cavities.<sup>48</sup>





### 1.3.1.6 Experimental

The examples presented illustrate two of the common ways McMurry reactions are run. The first uses the instant method and is intramolecular. The second uses a different order of addition and is intermolecular.

#### **Indole (7).<sup>12</sup>**

To a 100 mL two-necked flask, equipped with a Teflon-coated magnetic stirring bar and a reflux condenser connected to an argon line, was added keto-amide **6** (0.395 g, 1.34 mmol),  $\text{TiCl}_3$  (0.772 g, 5.00 mmol), and zinc dust (0.654 g, 10.00 mmol). The mixture was suspended in DME (50 mL), refluxed for 92 h, cooled to room temperature, and filtered through a short plug of silica. The inorganic residues were washed with ethyl acetate (50 mL), the filtrate was evaporated, and the residue was purified by flash column chromatography using 10% ethyl acetate in *n*-hexanes to yield indole **7** as a viscous oil (0.334 g, 95 %).

#### **Receptor (29).<sup>48</sup>**

To a Schlenck flask containing chilled ( $\sim 0^\circ\text{C}$ ) anhydrous THF (100 mL) was added  $\text{TiCl}_4$  (3 mL, 27 mmol) via a dropping funnel under an argon atmosphere. To this mixture was added Zn dust (2.2 g, 34 mmol) and dry pyridine (0.1 g, 1.3 mmol), and the resulting black suspension was warmed to room temperature and refluxed for 2 h. A solution of **28** (2.8 g, 3 mmol) in THF (200 mL) was added dropwise to the black reaction mixture over 4 h while refluxing, and the resulting mixture was refluxed for an additional 12 h. The reaction mixture was cooled to room temperature and quenched with 10 % aqueous  $\text{K}_2\text{CO}_3$  (50 mL). The organic layer was separated and the aqueous suspension was extracted with dichloromethane ( $5 \times 50$  mL). The combined organic extracts were dried over anhydrous  $\text{MgSO}_4$ , filtered and evaporated to afford a syrupy liquid which was purified by flash

chromatography on silica gel using 1: 9 mixture of ethyl acetate and hexanes to afford pure **29** as a crystalline solid (1.86 g, 72%).

### 1.3.1.7 References

1. a) [R] McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513–1524. b) [R] Lenoir, R. *Synthesis* **1989**, 883–897. c) [R] Fürstner, A.; Bogdanović, B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2443–2469. d) [R] Fürstner, A. *Pure Appl. Chem.* **1998**, *70*, 1071–1076. e) [R] Ephritikhine, M. *Chem. Commun.* **1998**, *6*, 2549–2554. f) [R] Hirao, T. *Synlett.* **1999**, 175–181. g) [R] Ladipo, F. T. *Curr. Org. Chem.* **2006**, *10*, 965–980.
2. [R] a) McMurry, J. E.; Fleming, M. P. *J. Am. Chem. Soc.* **1974**, *96*, 4708–4709. [R] b) McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405–411.
3. Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041–1044.
4. Tyrlík, S.; Wolochowicz, I. *Bull. Soc. Chim. Fr.* **1973**, 2147–2148.
5. McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krebski, L. R. *J. Org. Chem.* **1978**, *43*, 3255–3266.
6. Duan, X.-F.; Zeng, J.; Lü, J.-W.; Zhang, Z.-B. *J. Org. Chem.* **2006**, *71*, 9873–9876.
7. Hopf, H.; Mlynek, C. *J. Org. Chem.* **1990**, *55*, 1361–1363.
8. Dams, R.; Malinowski, M.; Geise, H. J. *Bull. Soc. Chim. Belg.* **1982**, *91*, 149–152.
9. McMurry, J. E.; Fleming, M. P. *J. Org. Chem.* **1976**, *41*, 896–897.
10. McMurry, J. E.; Krebski, L. R. *J. Org. Chem.* **1976**, *41*, 3929–3930.
11. McMurry, J. E.; Lectka, T.; Rico, J. G. *J. Org. Chem.* **1989**, *54*, 3748–3749.
12. Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215–5229.
13. Fürstner, A.; Jumbam, D. N. *Tetrahedron* **1992**, *48*, 5991–6010.
14. Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468–4475.
15. Rele, S.; Chattopadhyay, S.; Nayak, S. K. *Tetrahedron Lett.* **2001**, *42*, 9093–9095.
16. Stuhr-Hansen, N. *Tetrahedron Lett.* **2005**, *46*, 5491–5494.
17. Nayak, S. K.; Banerji, A. *J. Org. Chem.* **1991**, *56*, 1940–1942.
18. Rele, S.; Talukdar, S.; Banerji, A.; Chattopadhyay, S. *J. Org. Chem.* **2001**, *66*, 2990–2994.
19. Dams, R.; Malinowski, M.; Westdorp, I.; Geise, H. Y. *J. Org. Chem.* **1982**, *47*, 248–259.
20. McMurry, J. E.; Kees, K. L. *J. Org. Chem.* **1977**, *42*, 2655–2656.
21. Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260–265.
22. Idriss, H.; Pierce, K. G.; Barreau, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 3063–3074.
23. Aleandri, L. E.; Becke, S.; Bogdanović, B.; Jones, D. J. *J. Organomet. Chem.* **1994**, *472*, 97–112.
24. Bogdanović, B.; Bolte, A. *J. Organomet. Chem.* **1995**, *502*, 109–121.
25. Stahl, M.; Pidun, U.; Frenking, G. *Angew. Chem., Int. Ed.* **1997**, *36*, 2234–2237.
26. Villiers, C.; Ephritikhine, M. *Angew. Chem., Int. Ed.* **1997**, *36*, 2380–2382.
27. Villiers, C.; Vandais, A.; Ephritikhine, M. *J. Organomet. Chem.* **2001**, *617–618*, 744–747.
28. McMurry, J. E.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 1169–1172.
29. Lipski, T. A.; Hilfiker, M. A.; Nelson, S. G. *J. Org. Chem.* **1997**, *62*, 4566–4567.
30. Bandini, M.; Cozzi, P. G.; Morganti, S.; Umani-Ronchi, A. *Tetrahedron Lett.* **1999**, *40*, 1997–2000.
31. a) Chatterjee, A.; Bennur, T. H.; Joshi, N. N. *J. Org. Chem.* **2003**, *68*, 5668–5671. b) Li, Y.-G.; Tian, Q.-S.; Zhao, J.; Feng, Y.; Li, M.-J.; You, T. *Tetrahedron: Asymmetry* **2004**, *15*, 1707–1710.
32. Mangeney, P.; Grojean, F.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 2675–2676.
33. Betschart, C.; Schmidt, B.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1999–2021.
34. McMurry, J. E.; Miller, D. D. *J. Am. Chem. Soc.* **1983**, *105*, 1660–1661.
35. Walborsky, H. M.; Wüst, H. H. *J. Am. Chem. Soc.* **1982**, *104*, 5807–5808.
36. McMurry, J. E.; Fleming, M. P. *J. Org. Chem.* **1975**, *40*, 2555–2556.
37. McMurry, J. E.; Hoz, T. *J. Org. Chem.* **1975**, *40*, 3797–3798.

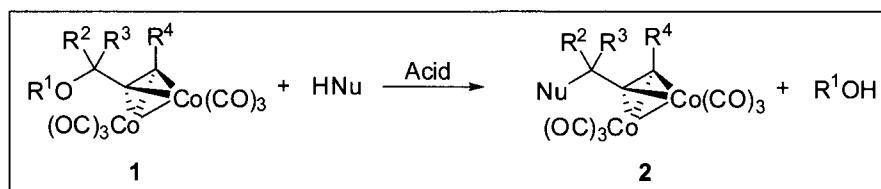
38. McMurry, J. E.; Melton, J. *J. Org. Chem.* **1973**, *38*, 4367–4373.
39. Timms, G. H.; Wildsmith, E. *Tetrahedron Lett.* **1971**, *2*, 195–198.
40. Ho, T-L.; Wong, C. M. *Synth. Commun.* **1973**, *3*, 37–38.
41. McMurry, J. E.; Silvestri, M. *J. Org. Chem.* **1975**, *40*, 2687–2688.
42. Mukaiyama, T.; Ogawa, Y.; Kuroda, K.; Matsuo, J.-I. *Chem. Lett.* **2004**, *33*, 1412–1413.
43. Eilitz, U.; Böttcher, C.; Sieler, J.; Gockel, S.; Haas, A.; Burger, K. *Tetrahedron*, **2001**, *57*, 3921–3925.
44. Detsi, A.; Koufaki, M.; Calogeropoulou, T. *J. Org. Chem.* **2002**, *67*, 4608–4611.
45. Eguchi, T.; Terachi, T.; Kakinuma, K. *J. Chem. Soc. Chem. Comm.* **1994**, *2*, 137–138.
46. Columbus, I.; Biali, S. *J. Org. Chem.* **1994**, *59*, 3402–3407.
47. McMurry, J. E.; Haley, G. J.; Matz, J. R.; Clardy, J. C.; Mitchell, J. *J. Am. Chem. Soc.* **1986**, *108*, 515–516.
48. Emond, S. J.; Debroy, P.; Rathore, R. *Org. Lett.* **2008**, *10*, 389–392.

### 1.3.2 The Nicholas Reaction

Kevin M. Shea

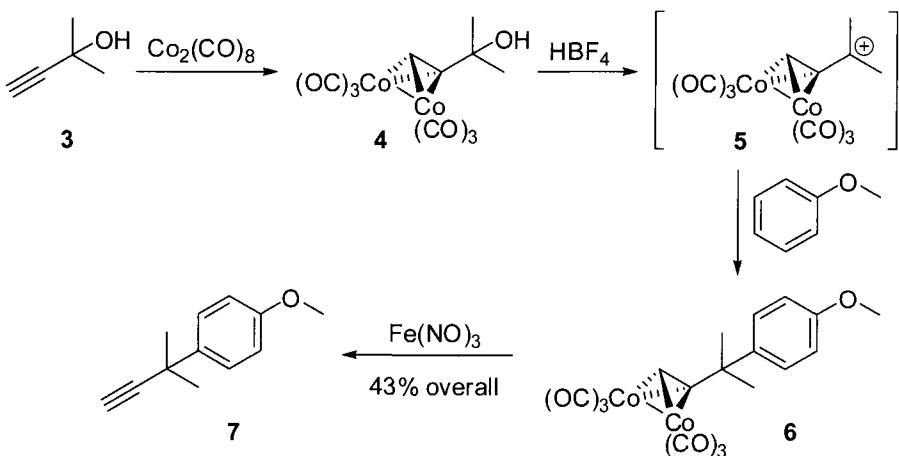
#### 1.3.2.1 Description

The Nicholas reaction enables efficient substitution reactions of propargyl alcohols, ethers, and acetates. Prior to the substitution step, dicobalt octacarbonyl reacts with the alkyne to yield cobalt-alkyne complex **1**. The resulting organometallic complex reacts with inter- or intramolecular nucleophiles in the presence of a Lewis or protic acid to furnish desired substitution products **2**. The cobalt-complexed alkyne can be oxidatively removed after this step or used to further functionalize the Nicholas reaction products.<sup>1</sup> The stereoselective synthesis of chiral products using the title reaction is also possible.<sup>2</sup>



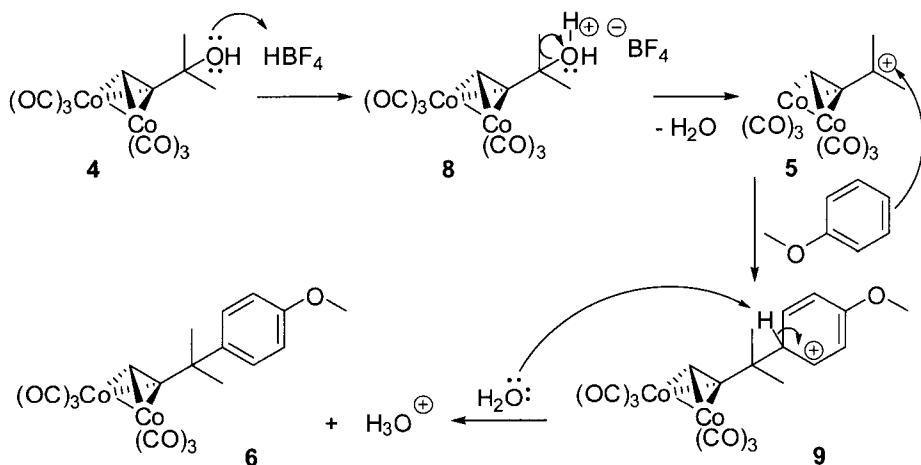
#### 1.3.2.2 Historical Perspective

Kenneth M. Nicholas, currently a professor at the University of Oklahoma, discovered the reaction that bears his name while a professor at Boston College.<sup>3</sup> He began the study of cobalt-complexed alkynes during his graduate research at the University of Texas, Austin under the direction of Rowland Pettit. In 1971 Nicholas and Petit demonstrated the use of a cobalt–alkyne complex as an alkyne protecting group,<sup>4</sup> and one year later they reported the enhanced stability of carbocations adjacent to cobalt-alkyne complexes.<sup>5</sup> In 1977, along with his graduate student Rosa Lockwood, Nicholas described the first propargylic substitution reactions of propargyl alcohols complexed with dicobalt hexacarbonyl in the presence of strong protic acids and electron rich benzene derivatives. For example, propargyl alcohol **3** can be cobalt-complexed to yield cobalt–alkyne complex **4**. Addition of tetrafluoroboric acid yields stabilized carbocation **5** that undergoes a Friedel–Crafts reaction with anisole to furnish *para* disubstituted benzene **6**. Oxidative decomplexation with iron(III) provides the target alkyne **7** in 43% overall yield.<sup>3</sup>



Nicholas continued his study of these propargylic substitution reactions for nearly the next twenty years<sup>1d,e</sup> and expanded his research to include the behavior of radicals stabilized by adjacent cobalt-complexed alkynes.<sup>6</sup>

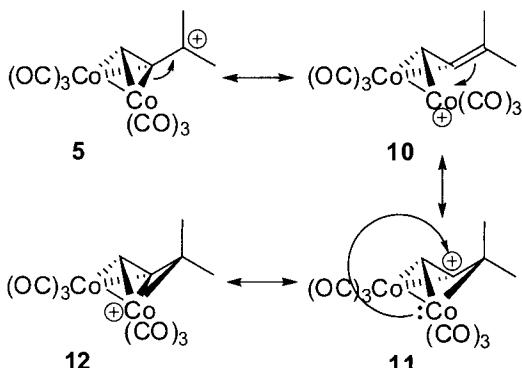
### 1.3.2.3 Mechanism



The mechanism of the Nicholas reaction is best described as an S<sub>N</sub>1 process. Protonation of the alcohol in **4** followed by loss of water from cation **5** yields cobalt-stabilized carbocation **5**. Friedel-Crafts reaction of this electrophile with anisole provides resonance-stabilized carbocation **9** which, upon removal of a proton, furnishes the substitution product **6**. In addition to electron rich aromatics like anisole, a variety of neutral carbo- and heterocyclic nucleophiles react successfully with the carbocation

intermediate. The most important advantage of this mechanism versus standard propargylic substitution reactions is that  $S_N1'$  and  $S_N2'$  reactions are impossible thus eliminating the pathway that yields allene byproducts.<sup>1</sup>

Stabilization of adjacent carbocations can be depicted by several resonance structures (**5**, **10–12**) which highlight opportunities for charge delocalization. Early NMR and IR studies by Nicholas on the isolable tetrafluoroborate salt of **5** and several analogs demonstrated measurable loss of electron density at cobalt (versus alcohol **4**), thus implicating structures like **10** and **12** in the stabilization of the positive charge.<sup>7</sup> Furthermore, Melikyan obtained an X-ray crystal structure of a carbocation stabilized by two adjacent cobalt-complexed alkynes that showed shortening of one cobalt  $\alpha$ -carbon distance like that shown in compound **12**.<sup>8</sup>

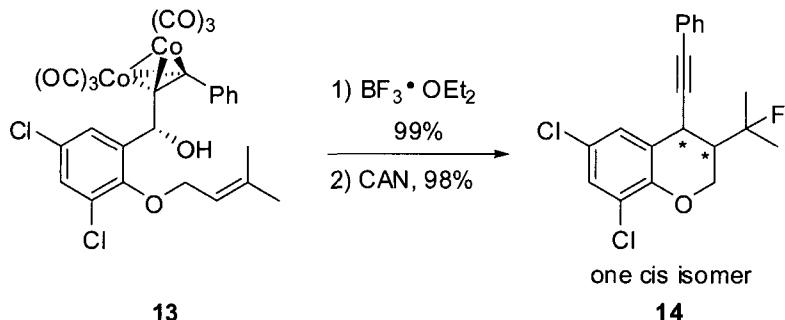


#### 1.3.2.4 Variations and Improvements

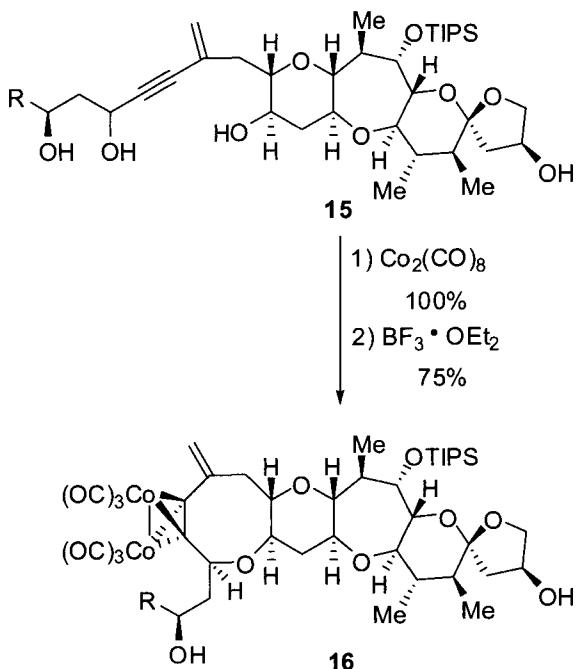
Modifications to the standard Nicholas reaction generally fall into the following categories: asymmetric reactions, use of heteroatom nucleophiles, use of metals other than cobalt, reactions of neutral electrophiles, reactions of carbocations not in the  $\alpha$ -position, cycloadditions, and rearrangements.

Numerous groups have investigated the asymmetric Nicholas reaction; studies focus on chiral nucleophiles, chiral cobalt-alkyne complexes, chiral cobalt ligands, and chirality transfer.<sup>1b,2a</sup> Two recent reports highlight examples of these strategies. Kann demonstrated that chiral phosphoramidite ligands effectively promote Nicholas reactions with moderate to good enantioselectivities.<sup>9</sup> Tyrrell reported a detailed study of asymmetric Nicholas reactions using a chiral auxiliary, chiral propargyl alcohols, and substrates derived from the chiral pool. In the best example, chiral non-racemic secondary alcohol **13** undergoes a boron trifluoride promoted intramolecular cyclization followed by cobalt decomplexation with ceric ammonium nitrate (CAN) to yield only one isomer of cyclic ether **14**.

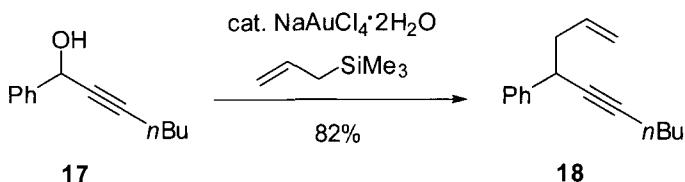
Although the absolute stereochemistry is unclear,  $^1\text{H}$  NMR analysis supports assignment of the relative stereochemistry as cis.<sup>10</sup>



The use of heteroatom nucleophiles is a very popular variation of the Nicholas reaction.<sup>1a</sup> Alcohols<sup>11</sup> and amines<sup>12</sup> are most prevalent, while examples of azides,<sup>13</sup> thiols,<sup>14</sup> carboxylic acids,<sup>15</sup> epoxides,<sup>16</sup> hydrides,<sup>17</sup> and fluorides<sup>18</sup> are known. Isobe has made extensive use of alcohol nucleophiles in the preparation of various sized cyclic ethers. In studies directed toward the synthesis of ciguatoxin, Isobe converted alcohol **15** into eight-membered ring cyclic ether **16** using the Nicholas reaction.<sup>19</sup>

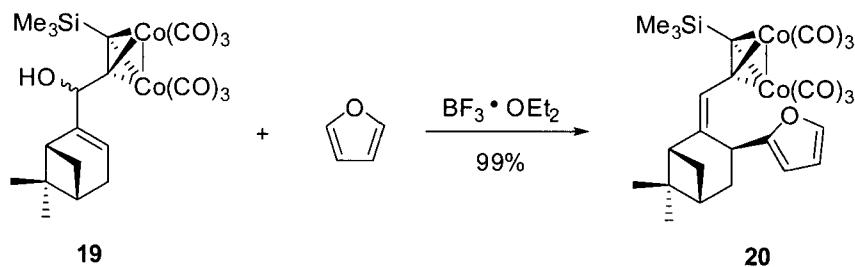


Many examples exist of alkynophylic metals other than cobalt that also promote propargylic substitution reactions; rhenium,<sup>20</sup> ruthenium,<sup>21</sup> and gold<sup>22</sup> can all be useful substitutes for cobalt. For example, Campagne synthesized enyne **18** upon treatment of propargyl alcohol **17** with allyltrimethylsilane and a Au(III) catalyst.<sup>22</sup>

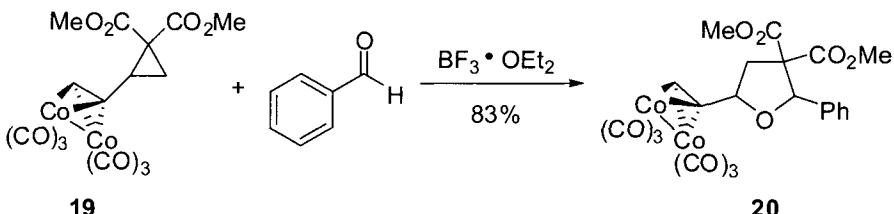


An interesting modification of the Nicholas reaction is an aldol reaction with an aldehyde adjacent to a cobalt-complexed alkyne. Chauvin reported a recent example of this strategy involving double addition of several carbon nucleophiles to cobalt-complexed acetylenedicarbaldehyde and comparison to the analogous Nicholas reactions with the corresponding diacetal. Depending on the reaction conditions, the products ranged from the expected addition product to unexpected oxygen heterocycles.<sup>23</sup>

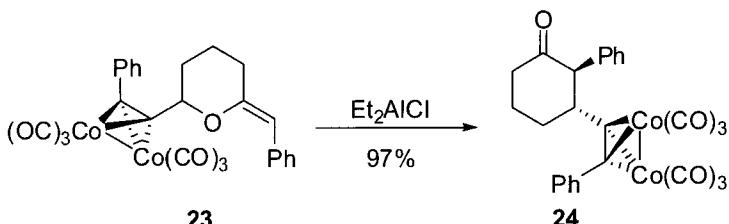
Carbocations adjacent to cobalt-alkyne complexes that are also conjugated to  $\pi$  bonds enable a variety of conjugate addition options. Sierra and de la Torre reported examples for the synthesis of terpene-based hybrids. Treatment of alcohol **19** with boron trifluoride and furan furnished addition product **20** via an  $S_N1'$  mechanism.<sup>24</sup> Green employed a similar strategy for the synthesis of substituted cycloheptenes.<sup>25</sup>



Christie and Jones first demonstrated in 2004 that appropriately substituted cyclopropanes adjacent to cobalt-alkyne complexes react with Lewis acids to yield 1,3-dipoles that are poised to participate in dipolar cycloadditions. Reaction of cyclopropane **21** with benzaldehyde and boron trifluoride provides tetrahydrofuran **22** in 83% yield.<sup>26</sup> Kerr subsequently applied this strategy to the synthesis of tetrahydro-1,2-oxazines upon combination of cyclopropanes like **21** with a variety of nitrones.<sup>27</sup>



Harrity exploited the carbocation stabilizing ability of cobalt–alkyne complexes to promote a novel O→C rearrangement reaction. Exposure of cyclic enol ether **23** to diethylaluminum chloride promotes ionization of the C–O bond to yield the stabilized carbocation and an enolate. Bond rotation followed by C–C bond formation provides cyclohexanone product **24**.<sup>28</sup>



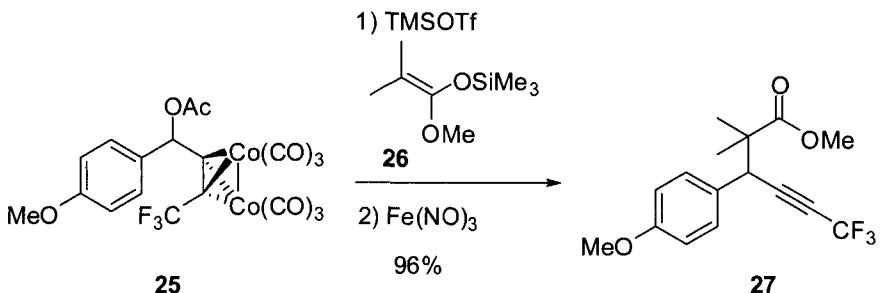
### 1.3.2.5 Synthetic Utility

Since its discovery just over thirty years ago, the Nicholas reaction has become a highly useful tool for the organic chemistry community. Applications of the Nicholas reaction fall into four categories: intermolecular reactions, endocyclic intramolecular reactions, exocyclic intramolecular reactions, and tandem reactions. For this discussion, endocyclic means that the cobalt-complexed alkyne is in the ring formed during the Nicholas reaction, while exocyclic indicates that the cobalt-alkyne complex is outside the newly generated ring.

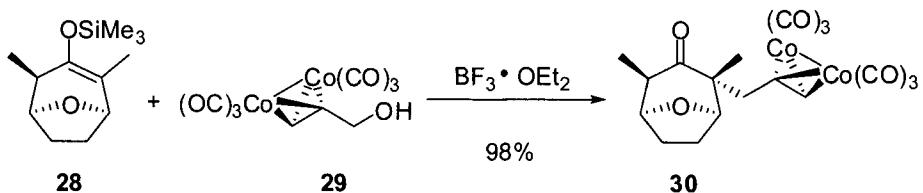
Numerous carbon nucleophiles participate in the Nicholas reaction; the most popular are electron rich aromatics, enamines, enol ethers, ketene acetals, alkenes, allylsilanes, allylstannanes, and organoaluminum compounds.<sup>1a,29</sup> Upon completion of the substitution reaction, the cobalt complex can be oxidatively removed with  $\text{I}_2$ ,  $\text{Fe}(\text{III})$ , or  $\text{Ce}(\text{IV})$ .<sup>1a</sup> Additional chemistry based on cobalt-complexed alkynes, like the Pauson-Khand reaction,<sup>30</sup> can also be performed to further increase molecular complexity.

### Intermolecular Reactions

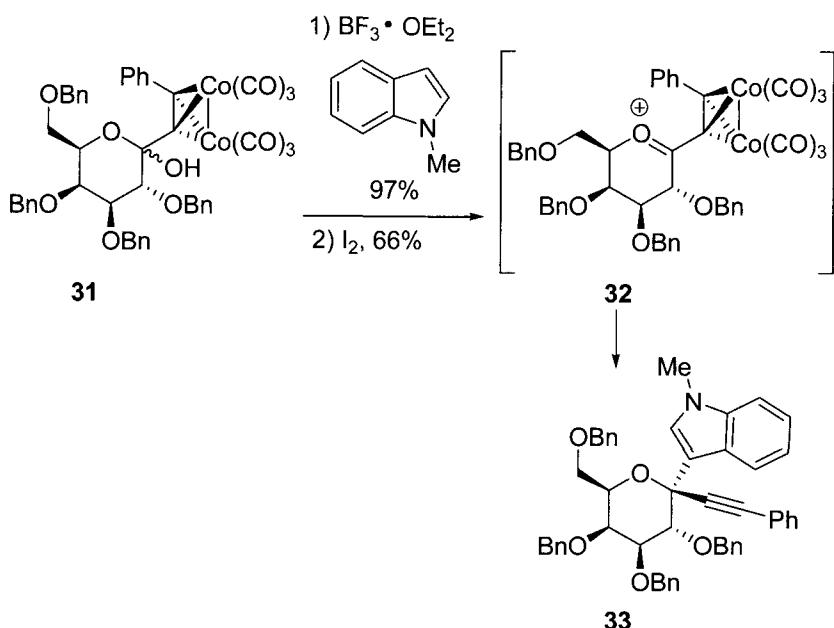
Konno reported a detailed study of the reaction of fluorine-containing propargyl acetates under Nicholas conditions with a variety of nucleophiles. Allylstannanes and allylsilanes provided moderate yields of the desired products, while enamines, silyl enol ethers, and silyl ketene acetals furnished the target compounds with excellent efficiency. In one example, cobalt-alkyne complex **25** reacts with silyl ketene acetal **26** in the presence of trimethylsilyl triflate to yield, after cobalt decomplexation, ester **27**.<sup>31</sup>



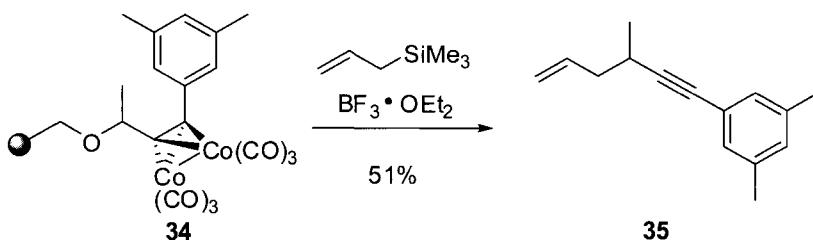
As part of his research into the synthesis of oxygen-bridged nine- and ten-membered cycloalkanes, Montaña introduced a key carbon fragment via the Nicholas reaction. Boron trifluoride promoted reaction between silyl enol ether **28** and cobalt-alkyne complexed propargyl alcohol **29** provides substitution product **30** in excellent yield.<sup>32</sup>



Gómez and López reported the synthesis of *C*-ketosides using Nicholas reactions with several nucleophiles. In addition to the standard stabilization by the adjacent cobalt-alkyne complex, the carbocations generated in this study were further stabilized as oxonium ions (e.g., **32**). Reaction of galacto sugar **31** with 1-methylindole, followed by iodine promoted decomplexation, furnishes compound **33** in 64% overall yield. Interestingly, in the gluco series of cobalt-complexed alkynes, similar conditions led to double addition of several nucleophiles resulting in products substituted at both C-1 and C-4.<sup>33</sup>



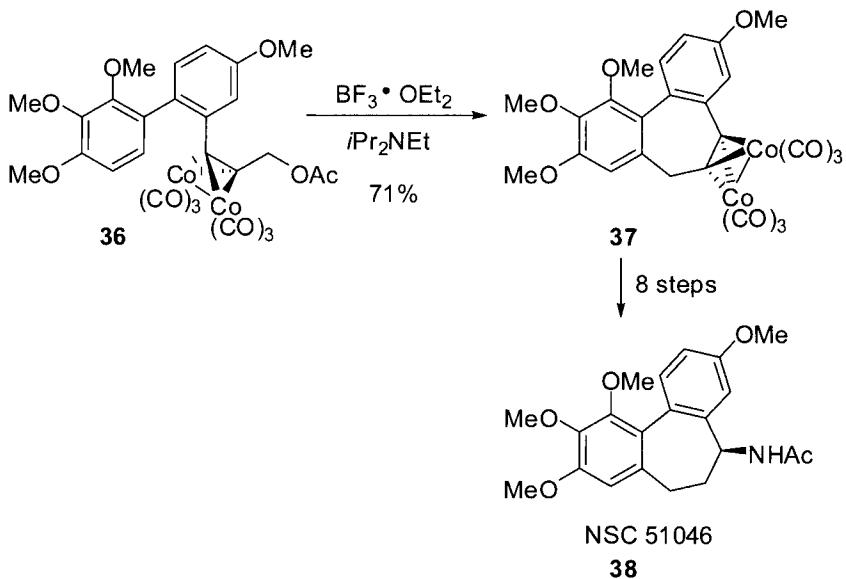
Kann recently investigated the intermolecular Nicholas reaction with substrates on the solid phase. In a detailed study with a variety of carbon and heteroatom nucleophiles, she demonstrated that the Nicholas reaction is a useful strategy for cleaving the substrate from the resin. Enyne **35** is available upon treatment of resin-bound cobalt–alkyne complex **34** with allyltrimethylsilane and boron trifluoride. Generation of the requisite carbocation results in cleavage from the polymer which is followed by a standard solution phase substitution reaction.<sup>18</sup> Subsequently, Kann applied this methodology for the synthesis of alkynylbenzyl galactosides which were evaluated as galectin inhibitors.<sup>34</sup>



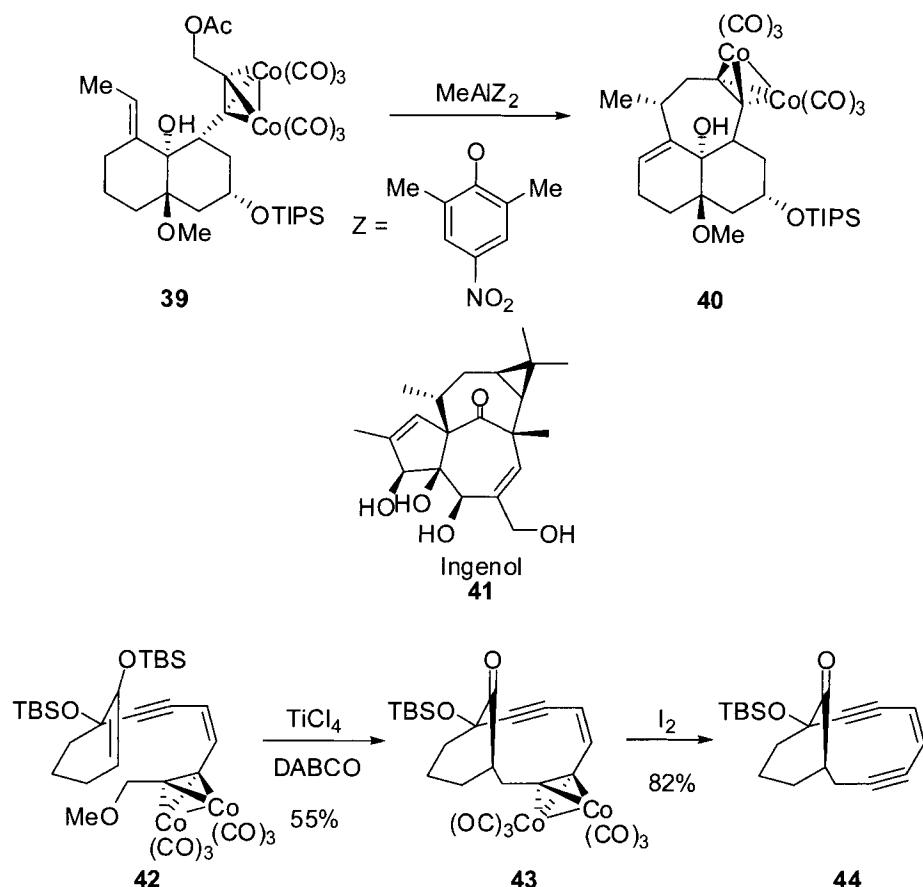
As highlighted in the *Variations and Improvements* section (**19→20**), de la Torre and Sierra use the Nicholas reaction to synthesize natural product hybrids. They reported standard transformations with electron rich aromatic nucleophiles in 2006.<sup>35</sup>

## *Endocyclic Intramolecular Reactions*

One of Green's many applications of the chemistry of cobalt–alkyne complexes in synthesis involved formation of a seven-membered ring via an endocyclic intramolecular Nicholas reaction. The key step in his successful synthesis of allocolchicine NSC 51046 (**38**) was production of cyclic cobalt–alkyne complex **37** from reaction of acetate **36** and boron trifluoride. Hydrosilylation of the organometallic complex followed by desilylation yielded the corresponding alkene that was ultimately transformed into the target tricycle.<sup>36</sup>

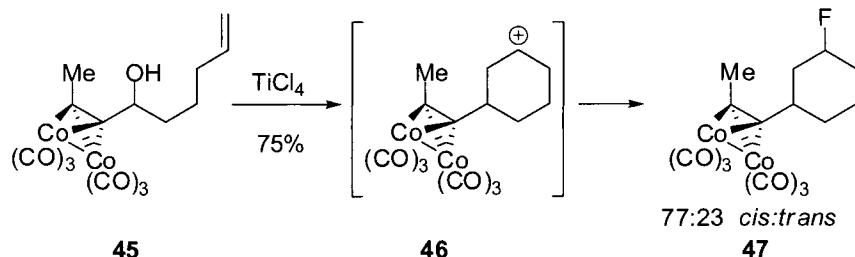


This type of Nicholas reaction has also been applied to the synthesis of ingenol and enediyne antitumor agents. Tanino and Kuwajima prepared the C ring of ingenol beginning with cobalt-alkyne complex **39**. Treatment with methylaluminum bis(2,6-dimethyl-4-nitrophenoxy) afforded target **40** which was ultimately transformed into ingenol (**41**).<sup>37</sup> Magnus targeted esperamicin, calicheamicin, dynemicin, and neocarzinostatin using the endocyclic intramolecular Nicholas reaction. For use in the syntheses of esperamicin and calicheamicin, he converted cobalt–alkyne complex **42** into enyne **43**. Subsequent exposure of **43** to iodine revealed the characteristic endiene structure (**44**) common to all of these antitumor compounds.<sup>38</sup>

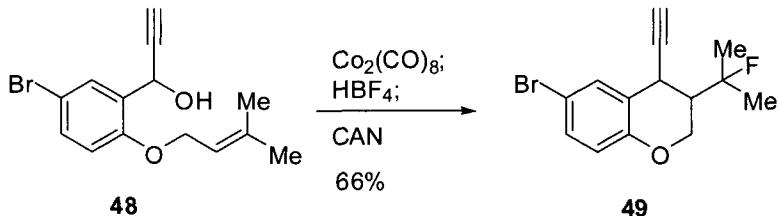


### Exocyclic Intramolecular Reactions

Bertrand recently generated six- and seven-membered rings using a terminal alkene nucleophile in exocyclic intramolecular Nicholas reactions. Depending on the nature of the Lewis acid, the carbocation intermediate formed upon cyclization (e.g., **46**) could be converted into a halide, amide, ester, or alkene. For example, alcohol **45** undergoes a 6-*endo*-cyclization to yield chlorocyclohexane **47** upon exposure to titanium tetrachloride.<sup>39</sup>

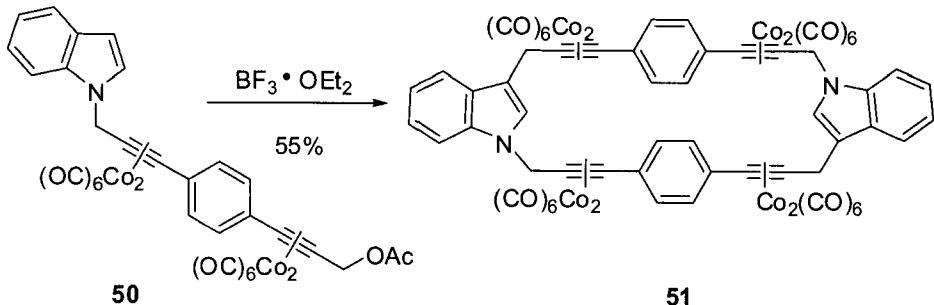


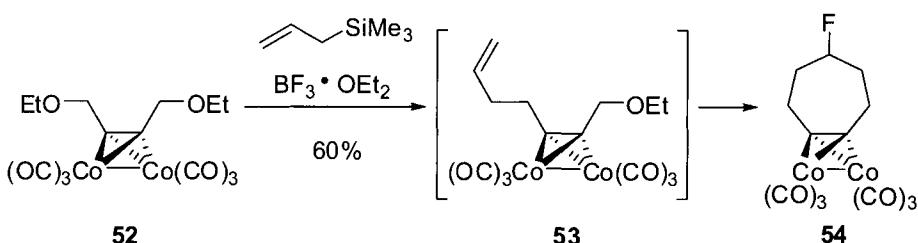
In addition to her studies on the asymmetric Nicholas reaction mentioned previously (13–14), Tyrrell investigated standard intramolecular cyclizations to generate benzopyrans. An important advance in this report is that Tyrrell performed the cobalt complexation, Nicholas reaction, and cobalt decomplexation using a one-pot procedure. The conversion of propargyl alcohol **48** into benzopyran **49** highlights this strategy.<sup>40</sup>



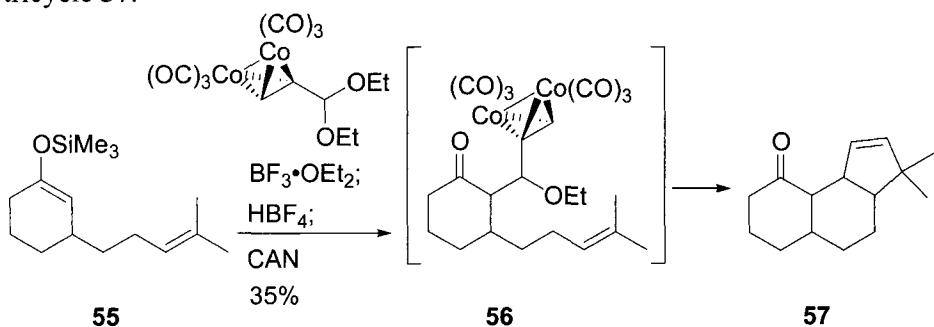
## *Tandem Reactions*

Several reports describe a tandem intermolecular Nicholas/intramolecular Nicholas reaction sequence for the synthesis of cyclic compounds. Green employed this strategy for the synthesis of indolophanetetrayne cobalt complexes. Dimerization of substituted indole **50** with boron trifluoride furnishes target **51** in 55% yield.<sup>41</sup> Green also prepared a cobalt-complexed cycloheptyne via tandem intermolecular Nicholas/intramolecular Nicholas reactions. Boron trifluoride promotes combination of cobalt–alkyne complex **52** with allyltrimethylsilane to first yield intermolecular product **53** and then the desired intramolecular product **54**.<sup>42</sup>

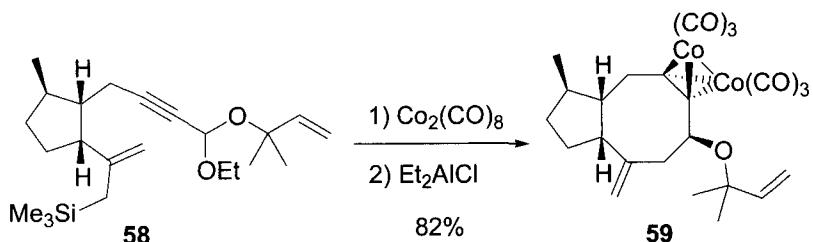


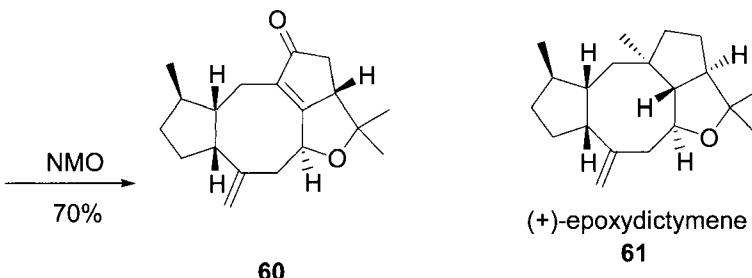


Tyrrell demonstrated a three step tandem sequence involving an intermolecular Nicholas reaction, intramolecular Nicholas reaction, and a cationic cyclization. Treatment of silyl enol ether **55** with hexacarbonyl(propionaldehyde diethyl acetal) dicobalt and boron trifluoride provides cobalt–alkyne complex **56**. Exposure of this material to tetrafluoroboric acid promotes an intramolecular Nicholas reaction to form the second six-membered ring. Alkyne decomplexation with ceric ammonium nitrate enables the final cyclization step to yield the target tricycle **57**.<sup>43</sup>



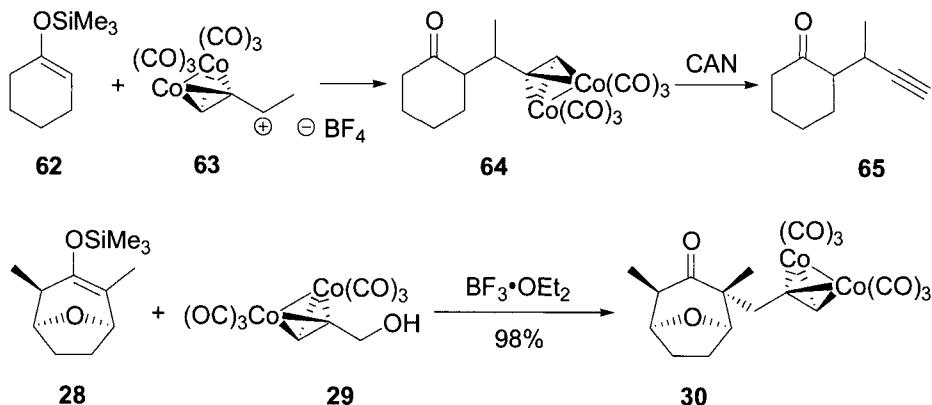
The most impressive use of a tandem strategy involving the Nicholas reaction in a total synthesis project is Schreiber's preparation of (+)-epoxydictyemene (**61**). Cobalt complexation of **58** followed by an endocyclic intramolecular Nicholas reaction with an allylsilane nucleophile yields Pauson–Khand precursor **59**. Treatment of **59** with *N*-methylmorpholine-*N*-oxide (NMO) promotes the Pauson–Khand reaction to furnish tetracycle **60** which was ultimately converted to the target natural product **61**.<sup>44</sup>





### 1.3.2.6 Experimental

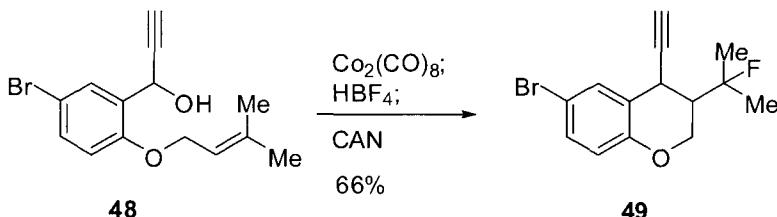
Nicholas published an *Organic Syntheses* paper highlighting the preparation of 2-(1-methyl-2-propynyl)cyclohexanone (**65**) from the reaction of 1-trimethylsiloxy cyclohexene (**62**) with hexacarbonyl (1-methyl-2-propynyl)dicobalt tetrafluoroborate (**63**) and subsequent decomplexation of cobalt complexed alkyne **64**. This report also includes procedures for the synthesis of the two starting materials (**62** and **63**).<sup>45</sup>



**Hexacarbonyl(μ-{η<sup>4</sup>-[2,4-dimethyl-2-(prop-2-yn-1-yl)-8-oxabicyclo-[3.2.1]octan-3-one]}dicobalt(Co-Co):**<sup>32</sup>

In a 50 mL flask fitted with a magnetic stirring bar, argon inlet, and septum, compound **29** (150 mg, 0.440 mmol) was dissolved in anhydrous dichloromethane (2 mL). Then, compound **28** (90 mg, 0.40 mmol), dissolved in anhydrous dichloromethane (2 mL), was added by cannula. The mixture was cooled to 0 °C, and  $\text{BF}_3 \cdot \text{OEt}_2$  (300 μL, 2.0 mmol) was added all at once. The reaction mixture was maintained at 0 °C for 5 min and then allowed to warm to room temperature. After 2 h (monitored by TLC), the reaction mixture was quenched at 0 °C by the addition of triethylamine (400 μL, 2.5 mmol) and washed with ice water. The organic solution was dried with anhydrous  $\text{MgSO}_4$ , filtered and then percolated through a short pad of

activated neutral alumina, eluting with dichloromethane. The organic solution was concentrated to dryness in a rotary evaporator (without heating!), giving **30** as a dark red oil (190 mg, 98%).



### **6-Bromo-4-ethynyl-3-(1-fluoro-1-methylethyl)chromane:<sup>41</sup>**

To a solution of propynyl alcohol **48** (0.80 g, 2.7 mmol) in anhydrous dichloromethane (12 mL), under an atmosphere of nitrogen, was added octacarbonyldicobalt (1.02 g, 3.0 mmol) and the reaction was stirred at ambient temperature. The progress of the reaction was monitored by observing the evolution of carbon monoxide from the reaction mixture. TLC analysis, after fifteen minutes, showed the presence of a faster moving compound ( $R_f$  0.45, 2:1 hexane:diethyl ether). The reaction mixture was then cooled to -10 °C whereupon tetrafluoroboric acid diethyl ether complex (0.52 mL, 3.0 mmol, 85% by volume) was added and the mixture left to stir. TLC analysis, after five minutes, showed the presence of a new compound ( $R_f$  0.65, 2:1 hexane:diethyl ether). To the reaction mixture, maintained at -10 °C, was added dropwise methanolic ceric ammonium nitrate (CAN, 6.67 g, 12.20 mmol, 30 mL) until the evolution of carbon dioxide ceased and the yellow color of CAN persisted (about fifteen minutes). TLC analysis of the reaction mixture revealed the presence of a new compound ( $R_f$  0.40, 3:1 hexane:diethyl ether). Residual methanol was removed *in vacuo* and the residue was partitioned between diethyl ether (25 mL) and water (25 mL). The aqueous phase was extracted with diethyl ether (3 × 20 mL) and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and the solvent removed *in vacuo* to afford an oil. Purification was effected by column chromatography on silica (3 : 1 hexane:diethyl ether) to afford the desired compound **49** (0.53 g, 66%) as a yellow oil.

#### 1.3.2.7         References

1. a) [R] Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133–4170. b) [R] Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809–826. c) [R] Welker, M. E. *Curr. Org. Chem.* **2001**, *5*, 785–807. d) [R] Caffyn, A. J. M.; Nicholas, K. M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Kidlington, 1995; Vol. 12, pp 685–702. e) [R] Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207–214.
2. a) [R] Diaz, D. D.; Betancort, J. M.; Martin, V. S. *Synlett* **2007**, 343–359. b) [R] Muller, T. J. J. *Eur. J. Org. Chem.* **2001**, 2021–2033.

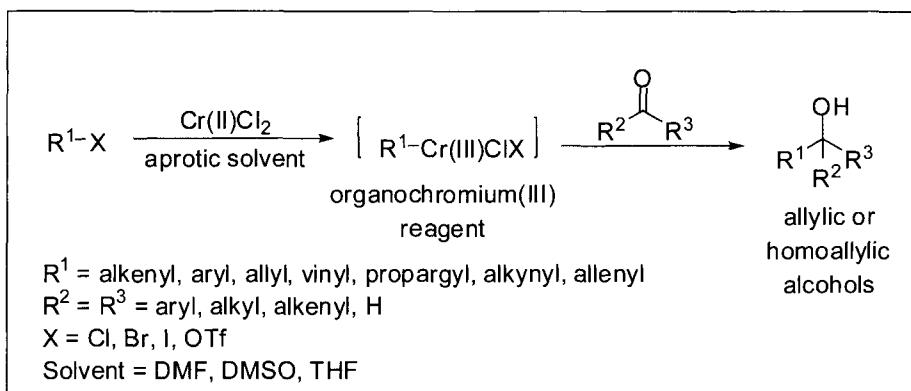
3. Lockwood, R. F.; Nicholas, K. M. *Tetrahedron Lett.* **1977**, 4163–4166.
4. Nicholas, K. M.; Pettit, R. *Tetrahedron Lett.* **1971**, 37, 3475–3478.
5. Nicholas, K. M.; Pettit, R. *J. Organomet. Chem.* **1972**, 44, C21–C24.
6. [R] Salazar, K. L.; Nicholas, K. M. *Tetrahedron* **2000**, 56, 2211–2224.
7. Connor, R. E.; Nicholas, K. M. *J. Organomet. Chem.* **1977**, 125, C45–C48.
8. Melikyan, G. G.; Bright, S.; Monroe, T.; Hardcastle, K. I.; Ciurash, J. *Angew. Chem., Int. Ed.* **1998**, 37, 161–164.
9. Ljungdahl, N.; Pera, N. P.; Andersson, K. H. O.; Kann, N. *Synlett* **2008**, 394–398.
10. Tyrrell, E.; Millet, J.; Tesfa, K. H.; Williams, N.; Mann, A.; Tillett, C.; Muller, C. *Tetrahedron* **2007**, 63, 12769–12778.
11. Quintal, M. M.; Closser, K. D.; Shea, K. M. *Org. Lett.* **2004**, 6, 4949–4952.
12. Hernández, J. N.; Ramírez, M. A.; Rodríguez, M. L.; Martín, V. S. *Org. Lett.* **2008**, 10, 2349–2352.
13. Shuto, S.; Ono, S.; Imoto, H.; Yoshii, K.; Matsuda, A. *J. Med. Chem.* **1998**, 41, 3507–3514.
14. Mohamed, A. B.; Green, J. R.; Masuda, J. *Synlett* **2005**, 1543–1546.
15. Shea, K. M.; Closser, K. D.; Quintal, M. M. *J. Org. Chem.* **2005**, 70, 9088–9091.
16. Pinacho Crisostomo, F. R.; Carrillo, R.; Leon, L. G.; Martin, T.; Padron, J. M.; Martin, V. S. *J. Org. Chem.* **2006**, 71, 2339–2345.
17. Díaz, D. D.; Ramírez, M. A.; Martín, V. S. *Chem.–Eur. J.* **2006**, 12, 2593–2606.
18. Gachkova, N.; Cassel, J.; Leue, S.; Kann, N. *J. Comb. Chem.* **2005**, 7, 449–457.
19. Hamajima, A.; Isobe, M. *Org. Lett.* **2006**, 8, 1205–1208.
20. Ohri, R. V.; Radosevich, A. T.; Hrovat, K. J.; Musich, C.; Huang, D.; Holman, T. R.; Toste, F. D. *Org. Lett.* **2005**, 7, 2501–2504.
21. [R] Nishibayashi, Y.; Uemura, S. *Curr. Org. Chem.* **2006**, 10, 135–150.
22. Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, 127, 14180–14181.
23. Soleilhavoup, M.; Maurette, L.; Lamirand, C.; Donnadieu, B.; McGlinchey, M. J.; Chauvin, R. *Eur. J. Org. Chem.* **2003**, 2003, 1652–1660.
24. Alvaro, E.; de la Torre, M. C.; Sierra, M. A. *Org. Lett.* **2003**, 5, 2381–2384.
25. DiMartino, J.; Green, J. R. *Tetrahedron* **2006**, 62, 1402–1409.
26. Christie, S. D. R.; Davoile, R. J.; Elsegood, M. R. J.; Fryatt, R.; Jones, R. C. F.; Pritchard, G. *J. Chem. Commun.* **2004**, 2474–2475.
27. Lebold, T. P.; Carson, C. A.; Kerr, M. A. *Synlett* **2006**, 364–368.
28. Meek, S. J.; Pradaux, F.; Carbery, D. R.; Demont, E. H.; Harrity, J. P. A. *J. Org. Chem.* **2005**, 70, 10046–10056.
29. [R] Tyrrell, E. *Chem. Ind.* **2006**, 22–23.
30. [R] Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, 56, 3263–3283.
31. Konno, T.; Nagai, G.; Ishihara, T. *J. Fluorine Chem.* **2006**, 127, 510–518.
32. Montana, A. M.; Ponzano, S.; Kociok-Koehn, G.; Font-Bardia, M.; Solans, X. *Eur. J. Org. Chem.* **2007**, 4383–4401.
33. Gomez, A. M.; Uriel, C.; Valverde, S.; Lopez, J. C. *Org. Lett.* **2006**, 8, 3187–3190.
34. Bergh, A.; Leffler, H.; Sundin, A.; Nilsson, U. J.; Kann, N. *Tetrahedron* **2006**, 62, 8309–8317.
35. Alvaro, E.; de la Torre, M. C.; Sierra, M. A. *Chem.–Eur. J.* **2006**, 12, 6403–6411.
36. Djurdjevic, S.; Green, J. R. *Org. Lett.* **2007**, 9, 5505–5508.
37. Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. *J. Am. Chem. Soc.* **2003**, 125, 1498–1500.
38. [R] Magnus, P. *Tetrahedron* **1994**, 50, 1397–1418.
39. Olier, C.; Gastaldi, S.; Christie, S. D. R.; Bertrand, M. P. *Synlett* **2007**, 423–426.
40. Mann, A.; Muller, C.; Tyrrell, E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1427–1438.
41. Gibe, R.; Green, J. R.; Davidson, G. *Org. Lett.* **2003**, 5, 1003–1005.
42. Lu, Y.; Green, J. R. *Synlett* **2001**, 243–247.
43. Tyrrell, E.; Tillett, C. *Tetrahedron Lett.* **1998**, 39, 9535–9538.
44. Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, 119, 4353–4363.
45. Varghese, V.; Saha, M.; Nicholas, K. M. *Org. Synth.* **1989**, 67, 141–148.

### 1.3.3 Nozaki–Hiyama–Kishi Reaction

Larry Yet

#### 1.3.3.1 Description

The one-pot Barbier-type addition of alkenyl, aryl, allyl, vinyl, propargyl, alkynyl, or allenylchromium compounds to aldehydes or ketones is known as the Nozaki–Hiyama–Kishi (NHK) reaction.<sup>1–3</sup> An excellent review by Fürstner published in 1999 detailed the exhaustive literature on the carbon–carbon bond formations involving organochromium(III) reagents. This chapter will present major developments and examples of recent carbon–carbon bond formation methodology and improvements as well as their use in natural products synthesis since 1999.



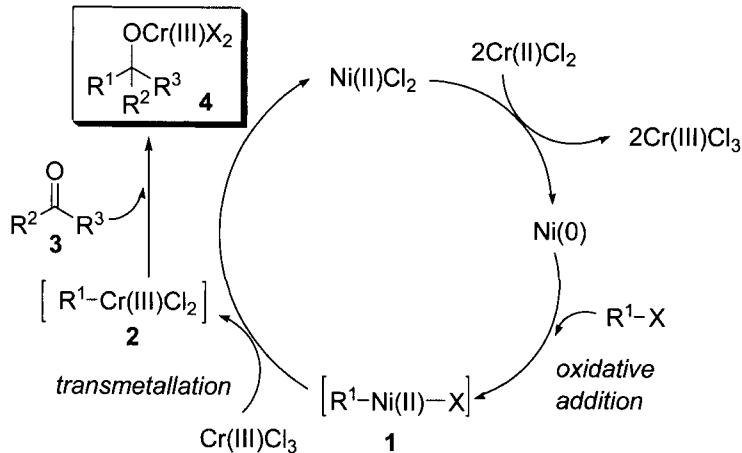
The NHK reaction has become a powerful synthetic tool for the chemoselective formation of carbon–carbon bonds under very mild conditions. The most notable feature of these reactions include: 1) Cr(II)Cl<sub>2</sub> or Cr(III)Cl<sub>3</sub> are inexpensive commercially available reagents; 2) the broad range of substrates amenable to insertion of Cr(II) under mild conditions; 3) reactions can take place intermolecularly or intramolecularly where the thermodynamically driving force is the formation of a strong O–Cr(III) bond; 4) aldehydes or ketones can react; however it is chemoselective for the aldehyde if a ketone is present in the same molecule; 5) a low basicity of the organochromium reagents allow compatibility of a wide range of sensitive functional groups in the same molecule; 6) distinct stereochemical preference of *anti* products in reactions of crotylchromium reagents; and 7) simple set up and excellent reliability of the reaction. However, drawbacks of the NHK reactions include the toxic chromium salts and their need for greater than stoichiometric quantities.

### 1.3.3.2 Historical Perspective

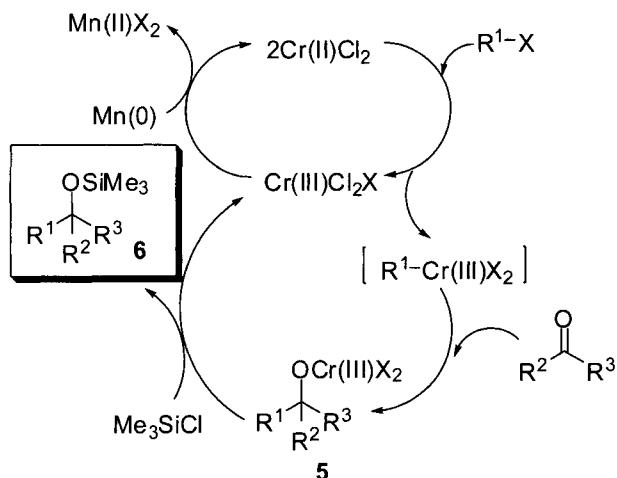
From 1977–1983, Nozaki and Hiyama published the first seminal papers that started an explosive development of this particular branch of organometallic chemistry.<sup>4</sup> Both research groups demonstrated in great detail that stoichiometric quantities of CrCl<sub>2</sub> readily inserted into allyl-, alkynyl-, propargyl-, and aryl halides or sulfonates under aprotic conditions to give the corresponding organochromium(III) reagents, which reacted with aldehydes and ketones to give various alcohol products with high chemoselectivity and stereoselectivity. In 1986, Kishi and Nozaki independently and almost simultaneously discovered that traces of nickel salts exerted a catalytic effect on the formation of the C–Cr(III) bond.<sup>5–6</sup> This aided in the reactions with less reactive substrates such as vinyl or aryl halides or triflates.

### 1.3.3.3 Mechanism

The CrCl<sub>2</sub>/NiCl<sub>2</sub> is the most widely employed synthetic tool in the Nozaki–Hiyama–Kishi reaction today and the generalized mechanism is outlined below.<sup>1–3</sup> In the nickel(II)-catalyzed NHK reaction, the first step in this cycle is the reduction of Ni(II) to Ni(0), which inserts into the carbon–halogen bond via an oxidative addition reaction to give organonickel species **1**. During this reduction, the Cr(II)Cl<sub>2</sub> is oxidized to Cr(III)Cl<sub>3</sub>. This organonickel species **1** is then transmetallated with Cr(III)Cl<sub>3</sub> to form the organochromium(III) nucleophile **2**, which then reacts with the carbonyl compounds **3** to give **4**, where the final product is obtained after work-up. It should be noted that Cr(II)Cl<sub>2</sub> is a one-electron donor and therefore ≥ 2 equivalents is required per equivalent of organic halide is needed for the formation of any organochromium(III) nucleophile. Only low catalyst loading of NiCl<sub>2</sub> (0.1–2%) is needed.



A chromium-catalyzed version has been developed by Fürstner which makes this process environmentally benign.<sup>7</sup> The key feature of this process uses chlorotrimethylsilane as an additive for the silylation of the chromium alkoxide species **5** in order to release the metal salt from the product **6**. The liberated Cr(III)Cl<sub>2</sub>X can then be reduced to the active species Cr(II)Cl<sub>2</sub> by means of a stoichiometric and nontoxic reducing agent as a manganese(0) metal.

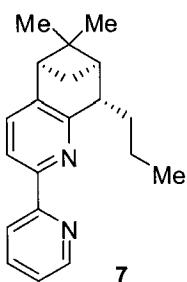


#### 1.3.3.4 Variations and Improvements

The most useful improvement in the last decade has been the catalytic use of the NHK reaction developed by Fürstner.<sup>7</sup> Most of the improvements in the last few years involved the asymmetric NHK reaction with the special use of ligands with good enantioselectivities up to 98%.<sup>8</sup> This section will outline the various ligands that have shown marked improvement in this area.

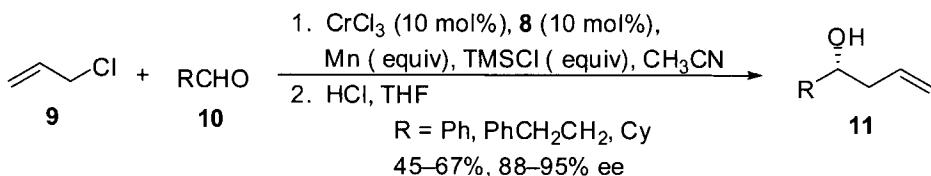
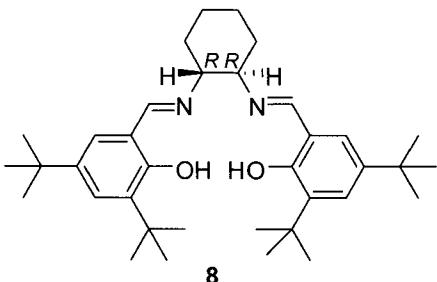
##### Bipyridyl Ligands

The first reports of the enantioselective NHK reaction was published by Kishi *et al.* in the chromium-mediated allylation and alkenylation reactions using specially designed bipyridyl ligands.<sup>9</sup> Bipyridine itself inhibited the cross-coupling. It was, however, possible to tune the complexation capacity by introducing substituents at the 6-position, with the best ligand being **7**. However, the bipyridine derivative must be used in (over)stoichiometric amounts along with (over)stoichiometric amounts of CrCl<sub>2</sub>, thus limiting the practicality of this method.

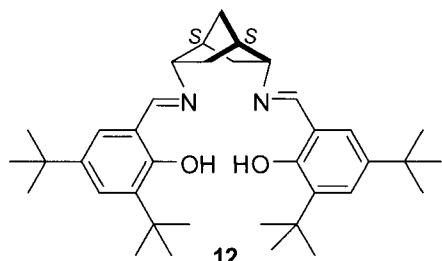


### Chiral Salen Ligands

Umani–Ronchi adapted the Fürstner protocol to achieve the first catalytic, enantioselective variant of this reaction.<sup>10</sup> The chiral chromium salen complex was prepared from the *in situ* reduction of the anhydrous CrCl<sub>3</sub> to CrCl<sub>2</sub> with an excess of manganese metal, followed by complexation with the salen ligand **8** in the presence of catalytic triethylamine.<sup>11</sup> Then the addition of allylic chloride (**9**) to aldehydes **10** to give the allylic alcohols **11** in moderate yields and in up to 95% ee. The same groups employed the same conditions for the addition of 2-butenyl bromides to aldehydes to achieve up to 83:17 *syn/anti* of allylic alcohol products<sup>12</sup> and for the addition of 1,3-dichloropropene to aromatic aldehydes to obtain the syn chlorohydrin adduct in modest yield which were further converted to optically active vinyl epoxides.<sup>13</sup> The [Cr(salen)]-catalyzed addition of propargyl halides to aromatic aldehydes allowed the synthesis of enantiomerically enriched homopropargyl alcohols in moderate yields with up to 56% ee.<sup>14</sup>

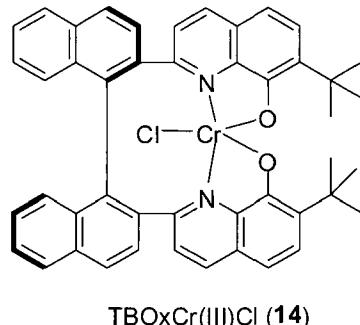
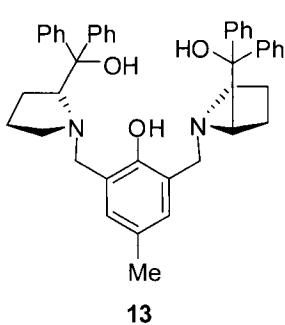


Berkessel *et al.* have demonstrated that salen ligand **12** based on *endo,endo*-2,5-diaminonorbornane (DIANANE) promoted efficient and highly enantioselective catalytic NHK reactions of various allylic and vinylic halides to aromatic and aliphatic aldehydes with up to 92% *ee*.<sup>15</sup>



### *Other Ligands*

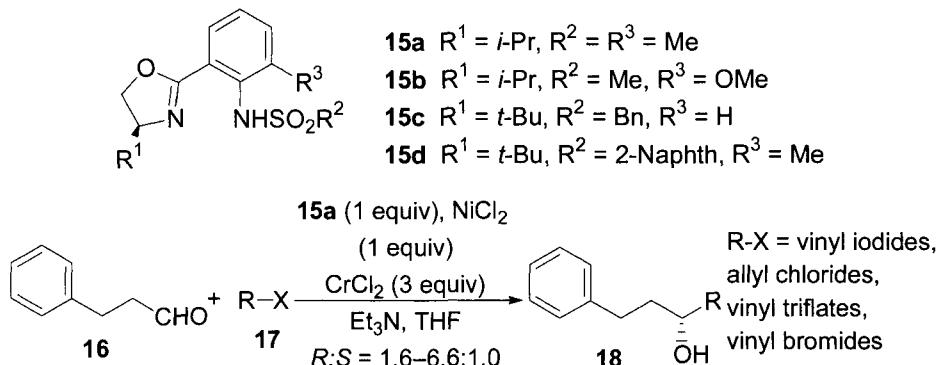
Asymmetric Nozaki–Hiyama allylation of benzaldehyde with a multidentate proline-derived amino alcohol ligand **13** showed good enantioselectivity up to 90% *ee*.<sup>16</sup> Yamamoto *et al.* showed that tethered bis-(8-quinolinolato)-(TBOx) chromium complex **14** participated in catalytic enantioselective Nozaki–Hiyama allylation, crotylation and allenylation reactions of aliphatic and aromatic aldehydes up to 97% *ee*.<sup>17</sup>



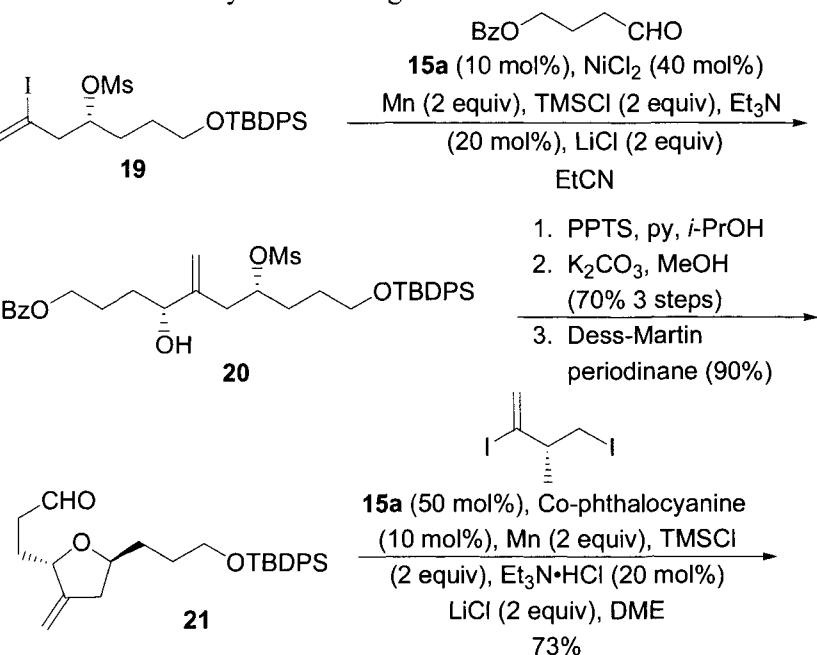
### *Chiral Oxazoline Ligands*

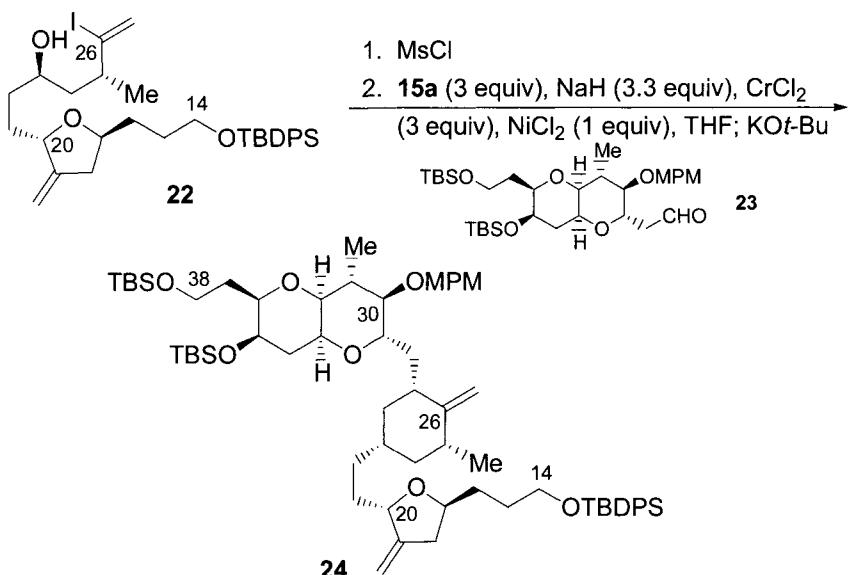
The most developed ligands for the asymmetric Nozaki–Hiyama–Kishi reaction have the chiral oxazoline-type structures. Kishi was the first to show that sulfonamide ligands **15** can effect asymmetric induction under both stoichiometric and catalytic conditions.<sup>18</sup> Sulfonamide ligand **15a** was found to be a suitable ligand, after several screening experiments, for the Ni/Cr mediated stoichiometric enantioselective coupling of dihydrocinnamaldehyde (**16**) with various vinyl and allyl halides and triflates **17** to give the (*R*)-

alcohols **18**. The catalytic application of ligand **15a** and **15b** was exploited in the same set of reactions with manganese metal (2 equiv) and chlorotrimethylsilane (2 equiv) in propionitrile or THF as solvents.<sup>19</sup> Ligand **15c** was utilized in the Fe/Cr- and Co/Cr-mediated catalytic asymmetric 2-haloallylations of aldehydes.<sup>20</sup> Ligands **15c** and **15d** were further exploited in several new catalytic reactions: 1) Ni/Cr-mediated alkenylation, alkynylation, and arylation; 2) Co/Cr-mediated 2-haloallylation, alkylation, and propargylation; and 3) Cr-mediated allylation.<sup>21</sup>

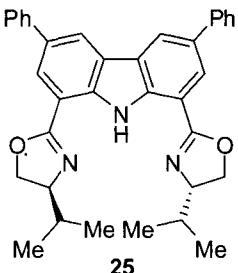


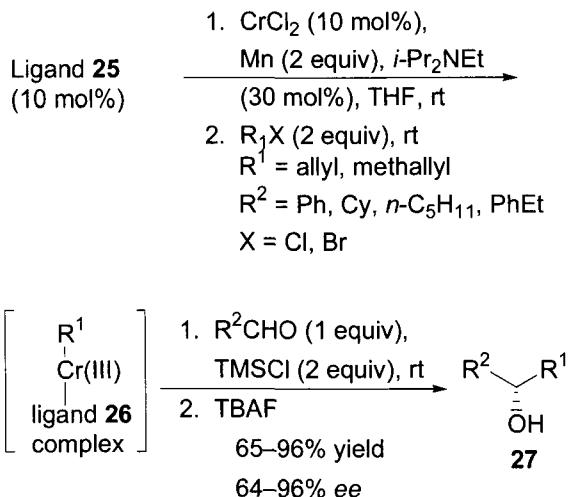
These discoveries were employed in the synthesis of the C14–C26 precursor **22** and C26–C38 segment of **24** of halicohondrins with stoichiometric and catalytic uses of ligand **15a**.<sup>18–19</sup>



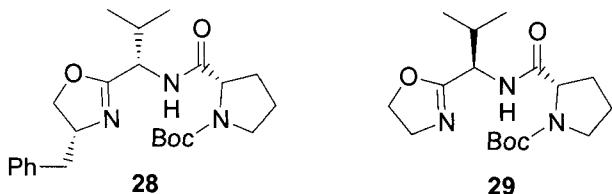


Nakada *et al.* designed and synthesized a  $C_2$ -symmetrical tridentate bis(oxazolinyl)carbazole ligand **25** for the asymmetric catalysis of Nozaki-Hiyama allylation and methallylation.<sup>22</sup> They reasoned that the allyl–Cr(III) ligand did not undergo significant dissociation due to the stabilization by three bonds: a  $\sigma$ -bond with the carbazole nitrogen and two coordination bonds with the oxazoline nitrogens, leaving a vacant coordination site at which an aldehyde can bind. Ligand **25**,  $\text{CrCl}_2$ , and Mn were all mixed in THF at room temperature; the Cr(II)-ligand **26** complex thus prepared *in situ* was then used for the enantioselective allylation.<sup>23</sup> Addition of allyl or methallyl halides afforded intermediate **26** which then reacted with aldehydes to give enantioenriched alcohols **27**. An allylation and methallylation reaction with this ligand was showcased in the enantioselective total synthesis of the potent HMG-CoA reductase inhibitor FR901512.<sup>24</sup> Furthermore, catalytic asymmetric Nozaki-Hiyama propargylation with ligand **25** proceeded with good to excellent enantioselectivity.<sup>25</sup> The first enantioselective NHK allenylation of terminally silylated propargyl halides using ligand **25** was also reported.<sup>26</sup>

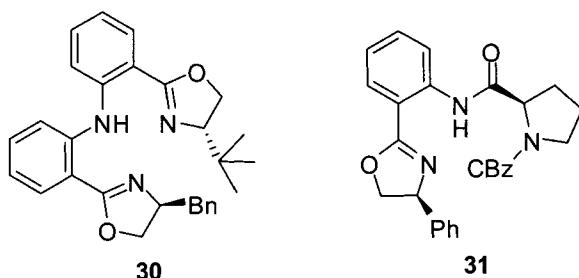




Sigman *et al.* identified a new set of stereochemically diverse oxazoline ligands derived from simple amino acids that promoted the Cr-catalyzed enantioselective addition of allylic halides to aldehydes in up to 95% *ee*.<sup>27</sup> Ligand diastereomer **28** was found to be the best general catalytic system for these reactions. Furthermore, diastereomer **29** was the ligand of choice for the enantioselective Cr-catalyzed addition of allyl bromide to ketones in up to 93% *ee*.<sup>28</sup>



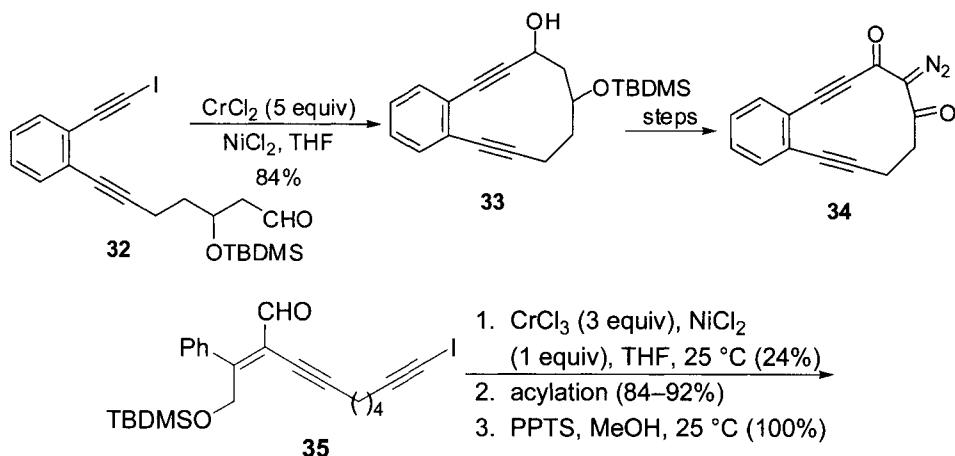
Guiry *et al.* found that the non-symmetric bis(oxazoline) ligand **30** was the optimal ligand in the allylation and crotylation of a range of aryl and aliphatic aldehydes.<sup>29</sup> The enantioselectivities obtained in the allylation reaction were up to 91% *ee* and in the crotylation reaction up to 92% *ee* with typical *syn:anti* ratios of up to 80:20. Sixteen members of a new ligand class incorporating an oxazoline ring linked by an amide bond to a chiral protected proline unit were reported; ligand **31** was found to be the best in the enantioselective allylation of benzaldehyde with 57% *ee*.<sup>30</sup>

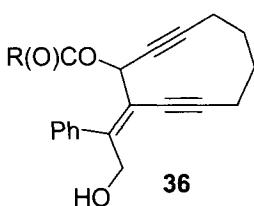


### **1.3.3.5 Synthetic Utility**

## *Cyclization to Large-Sized Ring Systems*

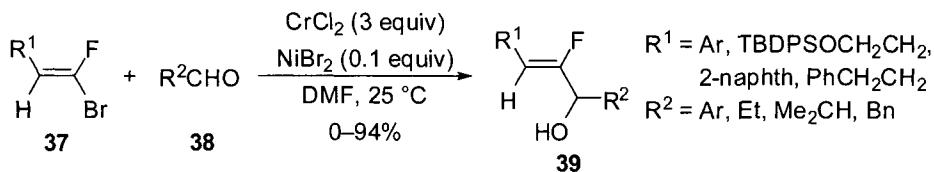
Popik reported the first example of triggering of the thermal Bergman cyclization by the photochemical ring contraction.<sup>31</sup> Thus, iododiyne **32** underwent NHK reaction in good yield to give cyclodeca-1,5-diyne **33**, which was further elaborated to 2-diazo-6,7-benzocycloundeca-4,8-diyne-1,3-dione (**34**). Upon irradiation **34** underwent Wolff rearrangement to produce reactive 10-membered enediynes followed by spontaneous Bergman cyclization. The synthesis and cytotoxicity of enediyne prodrugs with 3-hydroxy-4-arylmethylidene)cyclodeca-1,5-diyne scaffolds **36** were prepared from the NHK reaction of iododiyne **35** followed by esterification and silyl deprotection.<sup>32</sup> Pilli has reported the intramolecular NHK reaction for the construction of ten-membered lactones<sup>33</sup> and Bermejo has investigated the intramolecular NHK reaction for the preparation of the ten-membered ether of the eleutheside family of natural products.<sup>34</sup> Malacria has published an efficient preparation of a highly strained eleven-membered ring using the NHK reaction.<sup>35</sup>



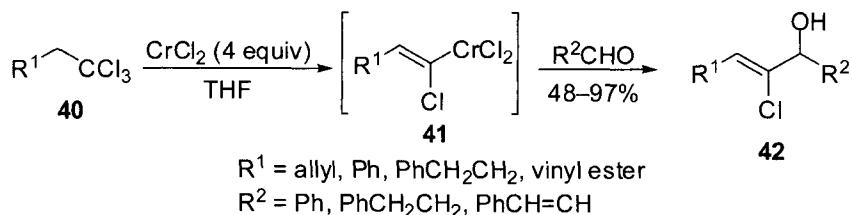


*(Z)-Haloallylic Alcohols*

Halogenated alkenols are versatile synthetic intermediates as well as critical structural units in a variety of biologically active natural products. Previous preparations of these structures are often hampered by multistep synthesis and by poor stereoselectivity. The Nozaki–Hiyama reaction has provided good synthetic entry to these structures. For example, a highly diastereoselective and straightforward synthesis for (*Z*)-2-fluoroallylic alcohols **39** via a Nozaki–Hiyama–Kishi type reaction with the corresponding bromofluoroolefins **37** with aliphatic and aromatic aldehydes **38** was developed.<sup>36</sup> Application of lithium, organoindium, organosamarium, organocupper, and organochromium carbenoid conditions failed to effect this transformation.



Mioskowski and Flack showed that (*Z*)-2-chloroalk-2-en-1-ols **42** were obtained in excellent yields from a wide variety of aldehydes by addition of (*E*)-chromium vinylidene carbenoids **41**, generated from trichloroalkanes **40** with CrCl<sub>2</sub> in THF at room temperature.<sup>37</sup> The same authors also reported CrCl<sub>2</sub>-mediated condensations of  $\gamma$ -chloro-*gem*-trichloroalkanes with aldehydes to give homallylic alcohols through a hydride rearrangement followed by a Nozaki–Hiyama allylation.<sup>38</sup>



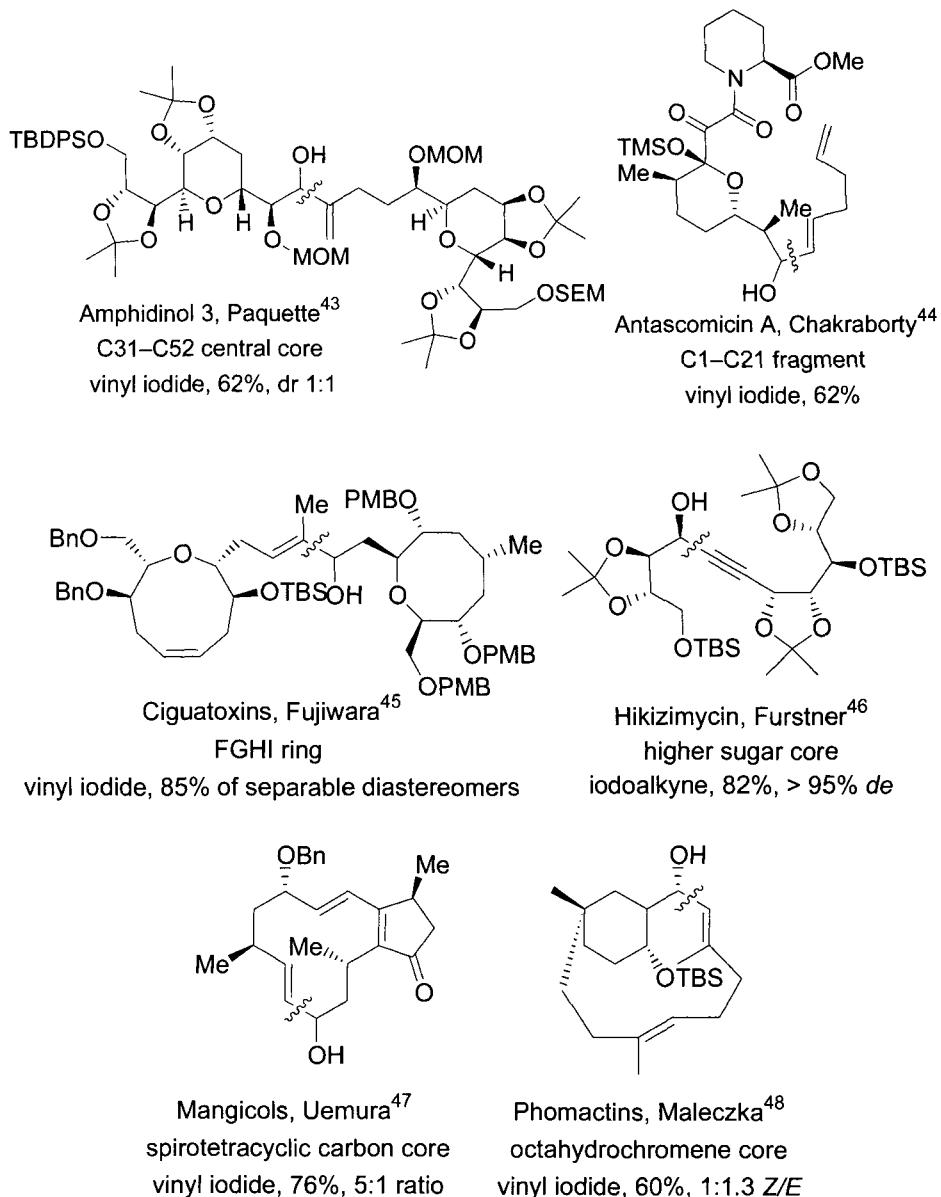
### Miscellaneous Reactions

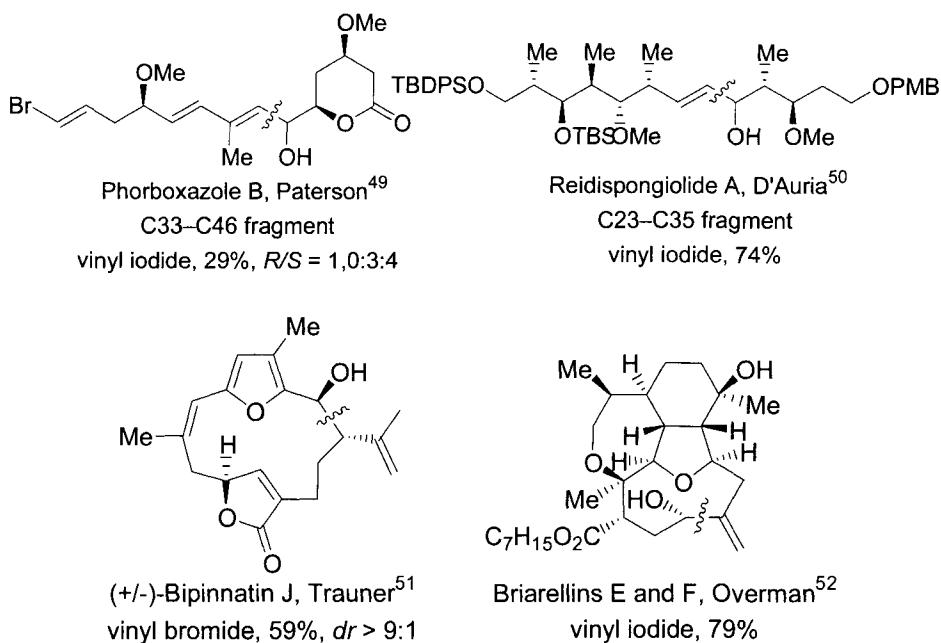
Cheng has published a convenient and synthetically useful alternative method to the NHK reaction for the arylation of aromatic aldehydes in a mild and selective way with nickel(II) bromide/zinc/dppe mediated protocol for the synthesis of diaryl carbinols.<sup>39</sup> Durandetti reported an electrochemical coupling of aryl halides with aldehydes for the synthesis of diaryl carbinols which was catalytic in chromium and nickel salts.<sup>40</sup> Comins utilized the NHK reaction to prepare 5-(1-hydroxyalkyl)-2,3-dihydro-4-pyridones, which were then explored in reductive, oxidative and substitutive reactions.<sup>41</sup> The first asymmetric catalytic synthesis of *syn*-alk-1-ene-3,4-diols was developed; the regio-, diastereo- and enantioselective addition of 3-chloropropenyl pivaloate to aldehydes was made possible by exploiting Salen-Cr(II) species in a catalytic version of the NHK reaction.<sup>42</sup>

### Applications in Natural Products

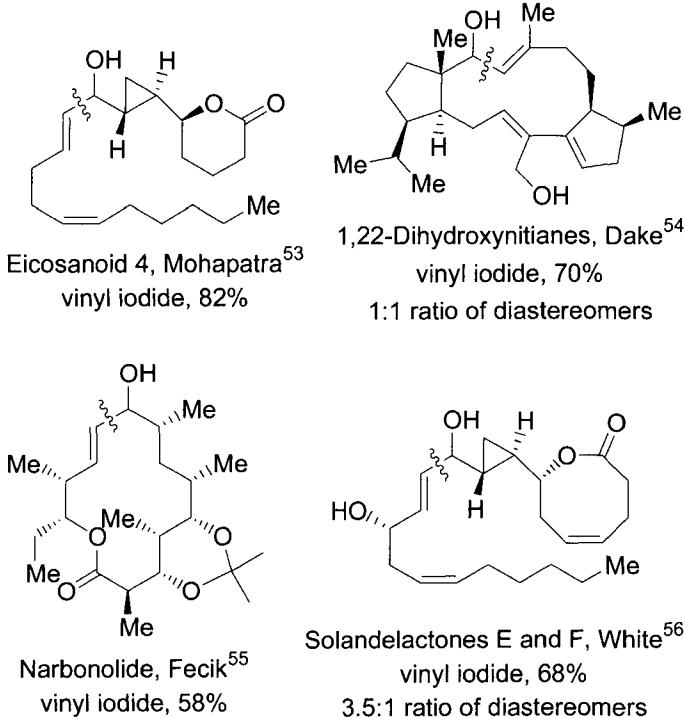
The unique features of the Nozaki–Hiyama–Kishi reaction make this an attractive methodology in the application to natural products synthesis, particularly the pronounced chemoselectivity and remarkable compatibility with an array of functional groups. However, there are very few reports published of the application of enantioselective NHK reactions in the total synthesis of natural products. This section is divided into three parts: 1) preparation of fragments with the NHK reaction in the synthesis of a portion of a natural product; 2) the NHK reaction in the final or second last step of a natural product; 3) the NHK reaction utilized anywhere in the total synthesis of a natural product. The next several pages show natural products where the NHK reaction have been employed in the syntheses of natural products since Fürstner's review published in 1999.<sup>1</sup>

The structures shown below are natural products where a portion of the target has been completed using the NHK reaction conditions. The swiggly lines denote the bond formed by the NHK reaction. Other information includes the natural products, the principal author, the halo or triflate precursor, the yields and ratio of isomers, enantiomers, or diastereomers from that step.

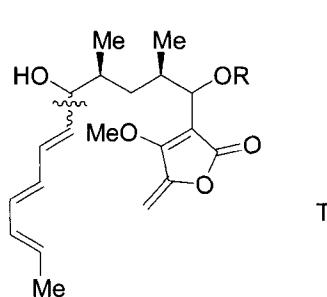




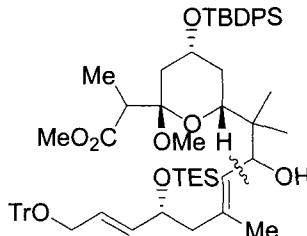
The structures below are natural products where the NHK reaction was used either in the second or last step of the synthesis where the natural product was completed.



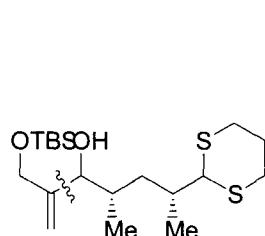
The structures below are the completed total syntheses of natural products where the NHK reaction is utilized in any part of the synthetic scheme.



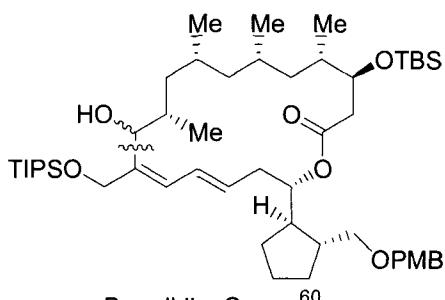
R = TBS, PMB  
vinyl iodide, 40%



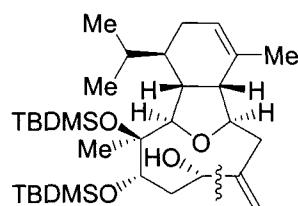
vinyl iodide, 90%  
2:1 ratio of diastereomers



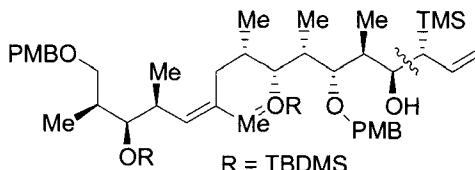
vinyl iodide, 95%



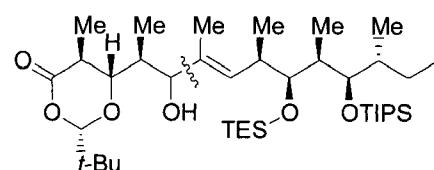
vinyl iodide, 55%; vinyl bromide, 13%



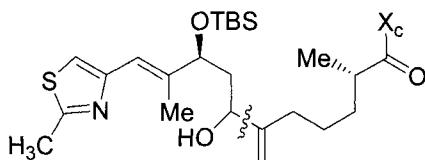
vinyl iodide, 55%, >20:1 ratio



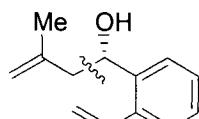
vinyl bromide, 81%



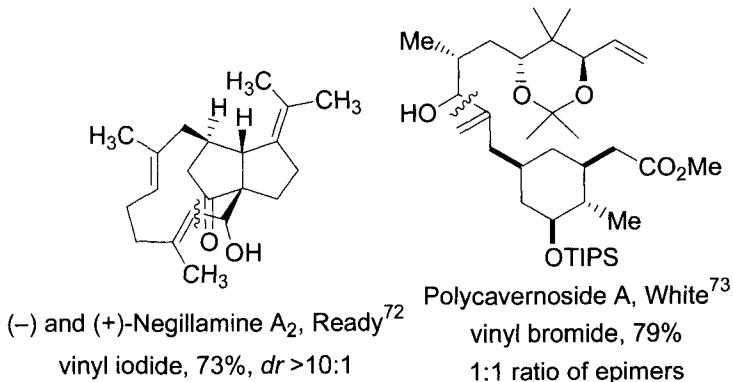
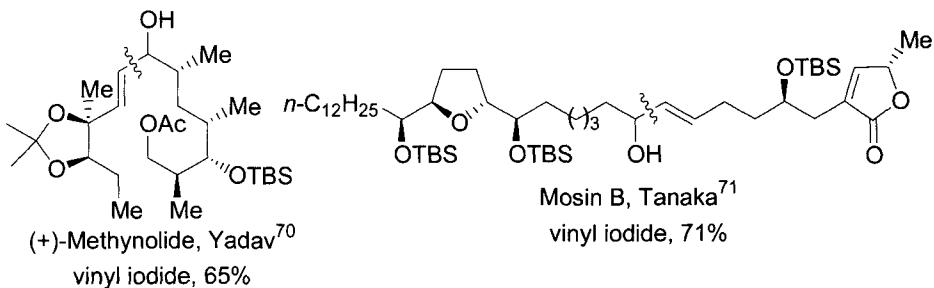
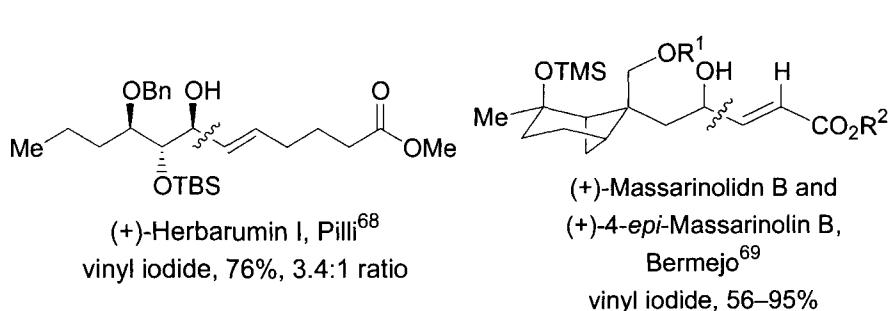
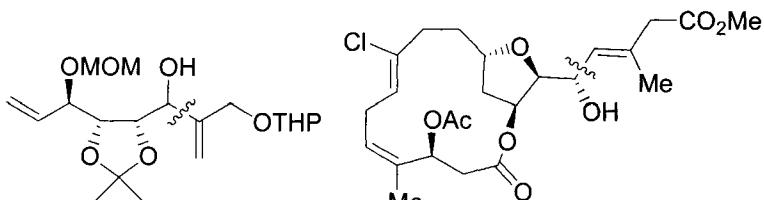
iodide, 41%, 77:23 ratio

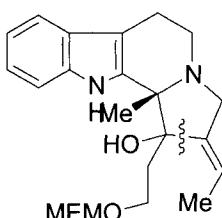


vinyl iodide, 93%

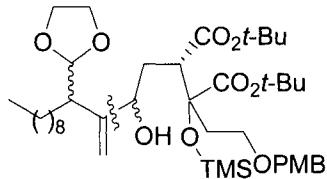


methallyl chloride, 93%, 92% ee  
with Nakada catalyst 25



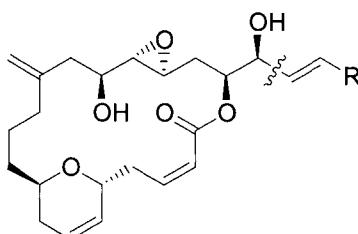


(*-*)-Subincanadines A and B, Takayama<sup>74</sup> ( $\pm$ )-Trachyspic Acid, Hatakeyama<sup>75</sup>  
vinyl iodide, 88% vinyl triflate, 83%  
1.7:1 separable diastereomers

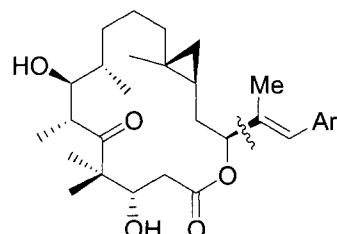


### NHK Reaction in Drug Discovery Analogues

The NHK reaction has also been reported in the syntheses of biologically active drug candidates such as analogues of laulimalide and epithilone B.



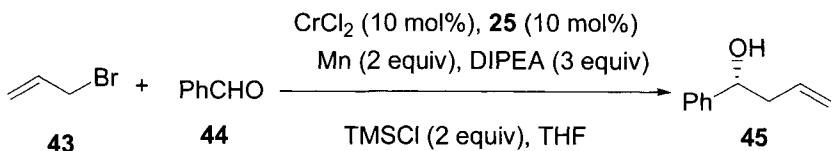
Laulimalide Analogue, Paterson<sup>76</sup>  
vinyl iodide, DIANNE catalyst **12**



*trans*-12,13-cyclopropyl  
Epothilone B analogue, Nicolaou<sup>77</sup>  
vinyl iodide

#### 1.3.3.6 Experimental

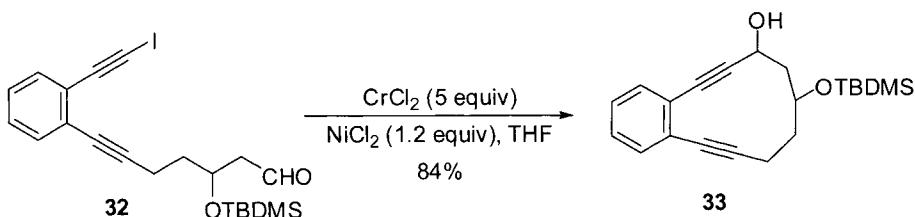
##### (*S*)-1-Phenyl-3-butene-1-ol (**45**)<sup>22</sup>



A mixture of ligand **25** (27.1 mg, 0.0500 mmol),  $\text{CrCl}_2$  (6.3 mg, 0.0510 mmol), and Mn (53.8 mg, 0.979 mmol) was azeotroped three times with toluene and dried under high vacuum, and was suspended in THF (2 mL). The color of the suspension immediately turned to brown. To the stirred suspension was added DIPEA (0.026 mL, 0.15 mmol), and after 5 min to the resulting mixture was added allyl bromide (**43**, 0.086 mL, 0.99 mmol). After stirring for 30 min, the color of the mixture turned to greenish brown. To the

stirred mixture was added benzaldehyde (**44**, 0.050 mL, 0.49 mmol), TMSCl (0.125 mL, 0.985 mmol) successively at 0 °C. After 12 h, the color of the reaction mixture turned to reddish brown. The reaction was quenched with saturated aqueous sodium bicarbonate (1 mL), filtered through a pad of Celite and the filtrate evaporated under vacuum. The crude product was dissolved in THF (2 mL) and the stirred mixture was treated with TBAF (1 mL, 1.0 mmol, 1.0 M in THF). The reaction was quenched with adding saturated aqueous ammonium chloride (2 mL), extracted with Et<sub>2</sub>O (4 × 10 mL), dried over sodium sulfate, and evaporated. The residue was purified by flash chromatography (hexanes/ethyl acetate 10:1) to afford (*S*)-1-phenyl-3-butene-1-ol (**45**, 64.7 mg, 89%, 93% *ee*):  $[\alpha]_D^{27} -46.2$  (*c* 0.94, benzene), *ee* was determined by HPLC (254 nm); Daicel Chiral Cell OD-H 0.46 cm × 25 cm; hexanes/isopropanol 19:1; flow rate = 0.3 mL/min; retention time: 26.4 min for (*R*)-1-phenyl-3-butene-1-ol, 28.7 min for (*S*)-1-phenyl-3-butene-1-ol.

**9-(*Tert*-butyldimethylsilyloxy)-5,6,12,13-tetrahydro-8,9,10,11-tetrahydro-7*H*-benzo[11]annulen-7-ol (**33**).<sup>31</sup>**



A solution of **32** (2.48 g, 5.33 mmol) in anhydrous THF (10 mL) was added to a vigorously stirred deoxygenated suspension of anhydrous CrCl<sub>2</sub> (3.28 g, 26.65 mmol) and anhydrous NiCl<sub>2</sub> (0.820 g, 6.33 mmol) in THF (700 mL) under argon and stirred for 4 h. The reaction mixture was concentrated to ~100 mL, diluted with ethyl acetate (300 mL) and washed with brine/saturated aqueous ammonium chloride (200 mL, 1:1) and brine (100 mL). The aqueous phase was back-extracted with ethyl acetate (100 mL). The combined organic phases were dried over magnesium sulfate and the solvents were removed under vacuum. The crude product was separated by column chromatography (ethyl acetate/dichloromethane 5:95) to yield two diastereomers, **33a** (0.364 g, 20%,  $R_f$  = 0.45) and **33b** (1.157 g, 64%,  $R_f$  = 0.40). **33a**: colorless solid.

### 1.3.3.7 References

- [R] Fürstner, A. *Chem. Rev.* **1999**, *99*, 991.
- [R] Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763.
- [R] Kishi, Y. *Pure Appl. Chem.* **1992**, *64*, 343.

4. a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. b) Okude, Y.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1977**, 3829. c) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561. d) Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037. e) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281.
5. Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.
6. Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048.
7. a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349. b) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533. c) Fürstner, A. *Chem. Eur. J.* **1998**, *4*, 567. d) Fürstner, A. *Pure Appl. Chem.* **1998**, *70*, 1071.
8. [R] Hargaden, G. C.; Guiry, P. J. *Adv. Synth. Catal.* **2007**, *349*, 2407.
9. Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386.
10. a) [R] Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Pure App. Chem.* **2001**, *73*, 325. b) [R] Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Chem. Commun.* **2002**, 919.
11. Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Agnew. Chem., Int. Ed.* **1999**, *38*, 3357.
12. a) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Agnew. Chem., Int. Ed.* **2000**, *39*, 2327. b) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Tetrahedron* **2001**, *57*, 835.
13. Bandini, M.; Cozzi, P. G.; Melchioore, P.; Morganti, S.; Umani-Ronchi, A. *Org. Lett.* **2001**, *3*, 1153.
14. Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Tino, R.; Umani-Ronchi, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1063.
15. Berkessel, A.; Menche, D.; Sklorz, C. A.; Schroder, M.; Paterson, I. *Agnew. Chem., Int. Ed. Engl.* **2003**, *42*, 1032.
16. Rozners, E.; Fontanez, J. *Lett. Org. Chem.* **2005**, *2*, 524.
17. a) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 2554. b) Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 496. c) Yamamoto, H.; Xia, G. *Chem. Lett.* **2007**, *36*, 1082.
18. Wan, Z.-K.; Choi, H.-w.; Kang, F.-A.; Nakajima, K.; Demeke, D.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4431.
19. Choi, H.-w.; Nakajima, K.; Demeke, D.; Kang, F.-A.; Jun, H.-S.; Wan, Z.-K.; Kishi, Y. *Org. Lett.* **2002**, *4*, 4435.
20. Kurosu, M.; Lin, M.-H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248.
21. Namba, K.; Kishi, Y. *Org. Lett.* **2004**, *6*, 5031.
22. Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc.* **2003**, *125*, 1140.
23. Suzuki, T.; Kinoshita, A.; Kawada, H.; Nakada, M. *Synlett* **2003**, 570.
24. Inoue, M.; Nakada, M. *J. Am. Chem. Soc.* **2007**, *129*, 4164.
25. Inoue, M.; Nakada, M. *Org. Lett.* **2004**, *6*, 2977.
26. Inoue, M.; Nakada, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 252.
27. Lee, J.-Y.; Miller, J. J.; Hamilton, S. S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 1837.
28. Miller, J. J.; Sigman, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 2752.
29. a) McManus, H. A.; Guiry, P. J. *J. Org. Chem.* **2002**, *67*, 8566. b) McManus, H. A.; Cozzi, P. G.; Guiry, P. J. *Adv. Synth. Catal.* **2006**, *348*, 551.
30. Hargaden, G. C.; Muller-Bunz, H.; Guiry, P. J. *Eur. J. Org. Chem.* **2007**, 4235.
31. Karpov, G. V.; Popik, V. V. *J. Am. Chem. Soc.* **2007**, *129*, 3792.
32. a) Dai, W.-M.; Wu, A.; Hamaguchi, W. *Tetrahedron Lett.* **2001**, *42*, 4211. b) Dai, W.-M.; Tachi, Y.; Nishimoto, S.-i.; Zhong, X.; Guo, Z. *Lett. Drug Des. Discov.* **2004**, *1*, 69. c) Tachi, Y.; Dai, W.-M.; Tanabe, K.; Nishimoto, S.-i. *Bioorg. Med. Chem.* **2006**, *14*, 3199. d) Dai, W.-M.; Li, K. W.; Wu, A.; Hamaguchi, W.; Lee, M. Y. H.; Zhou, L.; Ishii, A.; Nishimoto, S.-i. *J. Med. Chem.* **2002**, *45*, 758.
33. Pilli, R. A.; Victor, M. M. *Tetrahedron Lett.* **2002**, *43*, 2815.
34. Sandoval, C.; Lopez-Perez, J. L.; Bermejo, F. *Tetrahedron* **2007**, *63*, 11738.
35. Elliott, M. R.; Dhiman, A.-L.; Hamon, L.; Malacria, M. *Eur. J. Org. Chem.* **2000**, *1*, 155.
36. Dutheuil, G.; Lei, X.; Pannecoucke, X.; Quirion, J.-C. *J. Org. Chem.* **2005**, *70*, 1911.
37. a) Falck, J. R.; Barma, D. K.; Mioskowski, C.; Schlama, T. *Tetrahedron Lett.* **1999**, *40*, 2091. b) Barma, D. K.; Baati, R.; Valleix, A.; Mioskowski, C.; Falck, J. R. *Org. Lett.* **2001**, *3*, 4237.

38. Tisserand, S.; Bejot, R.; Billaud, C.; Li, D. R.; Falck, J. R.; Mioskowski, C. *Tetrahedron Lett.* **2006**, *47*, 5177.
39. Majumdar, K. K.; Cheng, C.-H. *Org. Lett.* **2000**, *2*, 2295.
40. Durandetti, M.; Nedelec, J.-V.; Perichon, J. *Org. Lett.* **2001**, *3*, 2073.
41. Comins, D. L.; Hiebel, A.-C.; Huang, S. *Org. Lett.* **2001**, *3*, 769.
42. Lombardo, M.; Licciulli, S.; Morganti, S.; Trombini, C. *Chem. Commun.* **2003**, 1762.
43. Bedore, M. W.; Chang, S.-K.; Paquette, L. A. *Org. Lett.* **2007**, *9*, 513.
44. Chakraborty, T. K.; Mohan, B. K. *Tetrahedron Lett.* **2006**, *47*, 4999.
45. a) Takizawa, A.; Fujiwara, K.; Doi, E.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2006**, *47*, 747. b) Takizawa, A.; Fujiwara, K.; Doi, E.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron* **2006**, *62*, 7408.
46. Fürstner, A.; Wuchrer, M. *Chem. Eur. J.* **2006**, *12*, 76.
47. Araki, K.; Saito, K.; Arimoto, H.; Uemura, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 81.
48. Mi, B.; Maleczka, R. E., Jr. *Org. Lett.* **2001**, *3*, 1491.
49. Paterson, I.; Steven, A.; Luckhurst, C. A. *Org. Biomol. Chem.* **2004**, *2*, 3026.
50. Zampella, A.; Sepe, V.; D'Orsi, R.; D'Auria, M. D. *Lett. Org. Chem.* **2004**, *1*, 308.
51. Roethle, P. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 345.
52. Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650.
53. Mohapatra, D. K.; Yellol, G. S. *Arkivoc* **2005**, *3*, 144.
54. Wilson, M. S.; Woo, J. C. S.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4237.
55. Venkatraman, L.; Aldrich, C. C.; Sherman, D. H.; Fecik, R. A. *J. Org. Chem.* **2005**, *70*, 7267.
56. White, J. D.; Martin, W. H. C.; Lincoln, C.; Yang, J. *Org. Lett.* **2007**, *9*, 3481.
57. Couladouros, E. A.; Bouzas, E. A.; Magos, A. D. *Tetrahedron* **2006**, *62*, 5272.
58. Suenaga, K.; Hoshino, H.; Yoshii, T.; Mori, K.; Sone, H.; Bessho, Y.; Sakakura, A.; Hayakawa, I.; Yamada, K.; Kigoshi, H. *Tetrahedron* **2006**, *62*, 7687.
59. Nicolaou, K. C.; Pinko, P. M.; Bernal, F.; Frederick M. O.; Qian, W.; Uesaka, N.; Diedrichs, N.; Hinrichs, J.; Koftis, T. V.; Loizidou, E.; Petrovic, G.; Rodriguez, M.; Sariah, D.; Zou, N. *J. Am. Chem. Soc.* **2006**, *128*, 2244.
60. Nagamitsu, T.; Takano, D.; Marumoto, K.; Fukuda, T.; Furuya, K.; Otoguro, K.; Takeda, K.; Kuwajima, I.; Harigaya, Y.; Omura, S. *J. Org. Chem.* **2007**, *72*, 2744.
61. a) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033. b) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *Org. Lett.* **2003**, *5*, 1543.
62. Mickel, S. J.; Sedelmeier, G. H.; Niederer, D.; Schuerch, F.; Seger, M.; Schreiner, K.; Dacfller, R.; Osmania, A.; Bixel, D.; Loiseleur, Loiseleur, O.; Cercus, J.; Stettler, H.; Schaer, K.; Gamboni, R.; Bach, A.; Chen, G.-P.; Chen, W.; Geng, P.; Lee, G. T.; Loeser, E.; McKenna, J.; Kinder, F. R.; Konigsberger, K.; Prasad, K.; Ramsey, T. M.; Reel, N.; Repic, O.; Rogers, L.; Shich, W.-C.; Wang, R.-M.; Waykole, L.; Xue, S. *Org. Proc. Res. Devel.* **2004**, *8*, 113.
63. Archibald, S. C.; Barden, D. J.; Bazin, J. F. Y.; Fleming, I.; Foster, C. F.; Mandal, A. K.; Mandal, A. K.; Parker, D.; Takaki, K.; Ware, A. C.; Williams, A. R. B.; Zwicky, A. B. *Org. Biomol. Chem.* **2004**, *2*, 1051.
64. Taylor, R. E.; Chen, Y. *Org. Lett.* **2001**, *3*, 2221.
65. Inoue, M.; Nakada, M. *J. Am. Chem. Soc.* **2007**, *129*, 4164.
66. Ramana, G. V.; Rao, B. V. *Tetrahedron Lett.* **2005**, *46*, 3049.
67. Kigoshi, H.; Kita, M.; Ogawa, S.; Itoh, M.; Uemura, D. *Org. Lett.* **2003**, *5*, 957.
68. Sabino, A. A.; Pilli, R. A. *Tetrahedron Lett.* **2002**, *43*, 2819.
69. Lopez, M. R.; Bermejo, F. A. *Tetrahedron* **2006**, *62*, 8095.
70. Yadav, J. S.; Pratap, T. V.; Rajender, V. J. *Org. Chem.* **2007**, *72*, 5882.
71. a) Maezaki, N.; Kojima, N.; Sakamoto, A.; Iwata, C.; Tanaka, T. *Org. Lett.* **2003**, *3*, 429. b) Maezaki, N.; Kojima, N.; Sakamoto, A.; Tominaga, H.; Iwata, C.; Tanaka, T.; Monden, M.; Damdinsuren, B.; Nakamori, S. *Chem. Eur. J.* **2003**, *9*, 389.
72. Bian, J.; Van Wingerden, M.; Ready, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 7428.
73. a) White, J. D.; Blakemore, P. R.; Browler, C. C.; Hong, J.; Lincoln, C. M.; Nagomyy, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 8593. b) Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagomyy, P. A.; Robarge, L. A.; Wardrop, D. J.; White, J. D. *J. Org. Chem.* **2005**, *70*, 5449.
74. Suzuki, K.; Takayama, H. *Org. Lett.* **2006**, *8*, 4605.

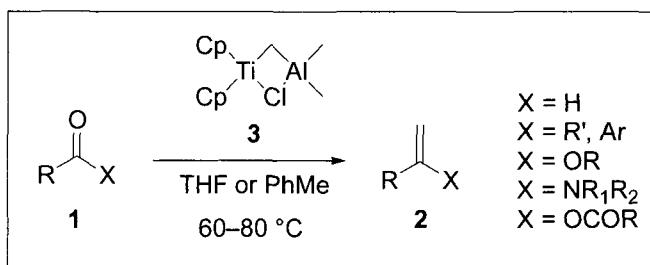
75. Hirai, K.; Ooi, H.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *3*, 857.
76. a) Paterson, I.; Bergmann, H.; Menche, D.; Berkessel, A. *Org. Lett.* **2004**, *6*, 1293. b)  
Paterson, I.; Menche, D.; Hakansson, A.; Longstaff, A.; Wong, D.; Barasoain, I.; Buey, R.  
M.; Diaz, J. F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2243.
77. a) Nicolaou, K. C.; Namoto, K.; Ritzen, A.; Ulven, T.; Shoji, M.; Li, J.; D'Amico, G.; Liotta,  
D.; French, C. T.; Wartmann, M.; Altmann, K.-H.; Giannakakou, P. *J. Am. Chem. Soc.* **2001**,  
*123*, 9313. b) Nicolaou, K. C.; Ritzen, A.; Namoto, K.; Buey, R. M.; Diaz, J. F.; Andreu, J.  
M.; Wartman,, M.; Altmann, K.-H.; O'Brate, A.; Giannakakou, P. *Tetrahedron* **2002**, *58*,  
6413.

### 1.3.4 Tebbe Methylenation

Ji Zhang

#### 1.3.4.1 Description

The Tebbe methylenation describes the conversion of carbonyl compound **1** into a terminal alkene **2** using titanium–aluminium complex **3** (the Tebbe reagent). Sterically encumbered carbonyl groups present in aldehydes, ketones, carboxylic acid derivatives (esters, lactones, and amides), and carbonates can be successfully methylenated utilizing this reagent. Several closely related titanium carbenoid reagents, including the Petasis, Takeda, and Takai reagents for carbonyl olefinations are also discussed here.<sup>1–4</sup>



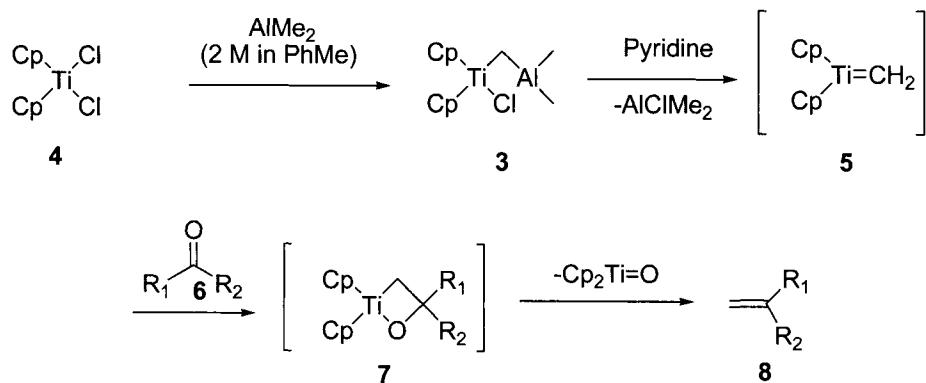
#### 1.3.4.2 Historical Perspective

In 1978, Tebbe and co-workers at du Pont prepared the titanium–aluminum methylidene complex **3** from titanocene dichloride **4** and trimethylaluminium in toluene.<sup>5</sup> This complex **3** is a versatile methylene transfer reagent for conversion of ketones to terminal olefins when it was treated with a Lewis base such as pyridine or THF. Later on, Grubbs developed a facile method for the *in situ* generation of Tebbe reagent **3**.<sup>6</sup> In 1990, Pine and co-workers observed that the Tebbe reagent is unique in the carbonyl groups of carboxylic acid derivatives which are readily methylenated.<sup>7</sup> Examples include the formation of vinyl enol ethers from esters and enamines from amides. This reagent also provides an excellent alternative to the Wittig reagent for the methylenation hindered or base sensitive ketones, which have proven to be difficult reactants. In 1991, Pine compared the Tebbe reagent with the Wittig reagent for ketone methylenation and demonstrated for a variety of ketones, especially with hindered substrates, that the Tebbe reagent gives superior product yields.<sup>8</sup> It was also noted that the Tebbe reaction accomplishes methylenation in a non-basic medium, thus racemization does not take place on substrates with enolizable chiral centers. Today, this titanium-based alkylidenating reagent has been employed to prepare

synthetic intermediates that cannot be access effectively using traditional alkenation methods.<sup>9</sup>

### 1.3.4.3 Mechanism

A highly reactive titanocene methylidene **5** is generated when the Tebbe reagent is treated with a Lewis base, even as mild as tetrahydrofuran (THF). Intermediate **5** efficiently methylenates a range of carbonyl groups, presumably via formation of oxatitanacyclobutane **7** by a [2 + 2] cycloaddition, which decomposes with elimination of  $\text{Cp}_2\text{Ti}=\text{O}$  to afford alkene **8** in a matter of minutes at mild conditions. The driving force of this reaction is presumably the irreversible formation of the strong titanium oxygen double bond. Titanocene methylidene **5** is a typical Schrock carbene,<sup>10</sup> being an electron-deficient (16e) complex of an early transition metal in a high formal oxidation state. Such Schrock carbenes are nucleophilic at the carbene carbon atom and electrophilic at titanium, with their reactivity towards carbonyl groups being dominated by their high energy HOMOs. Thus, titanium alkylidenes would be expected to react preferentially with the most electrophilic carbonyl groups. It is known that the Tebbe reagent reacts more rapidly with amides than esters in the absence Lewis base because amide itself is a better Lewis base than ester, therefore, it generates the reactive titanium methylidene **5** more effectively.<sup>7</sup>

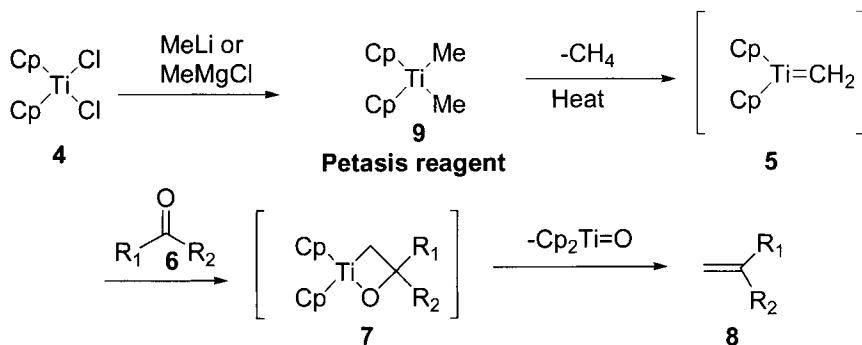


The main advantage of the Tebbe reagent **3** is for methylenating a range of carbonyl compounds and the reactive titanocene methylidene **5** is generated at mild conditions in the absence of strong base. The drawback of the Tebbe reagent is that it is capable for methylenation, to make  $\text{R}_1\text{R}_2\text{C}=\text{CH}_2$ , but unsuitable for the generation of other alkenes, such as  $\text{R}_1\text{R}_2\text{C}=\text{CHR}$  ( $\text{R} \neq \text{H}$ ). It should also be noted that the Tebbe reagent and the

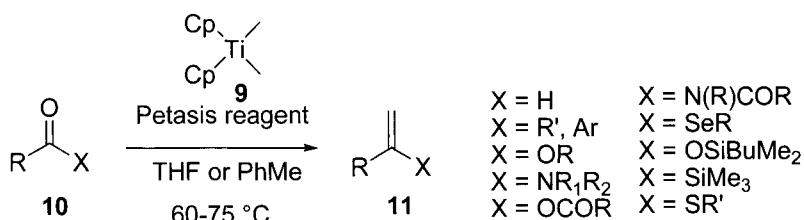
by-products formed by its decomposition are Lewis acidic and the handling of this reagent is hampered by its extreme sensitivity to air and moisture.

#### 1.3.4.4 Variations and Improvements: Petasis olefination

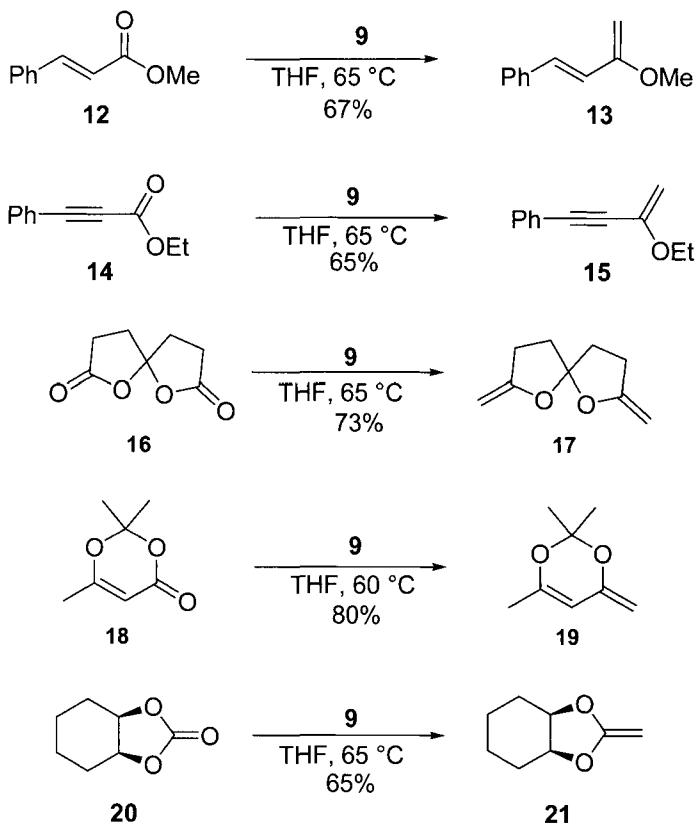
Despite the great synthetic utility of the Tebbe reagent, the presence of aluminium in its structure results in several drawbacks, such as Lewis-acidic aluminium byproducts, poor stability of the Tebbe reagent in air and water, as well as the tedious treatment in the separation which limits its application in organic synthesis. A more superior reagent that exhibits similar reactivity is dimethyl titanocene **9** (Petasis reagent). In 1990, Petasis reported that dimethyltitanocene, readily prepared from titanocene dichloride **4** and methylolithium, or more preferably methylmagnesium chloride, methylenated carbonyl compound when the reaction mixture was heated to 60–75 °C in either THF or toluene.<sup>11</sup> The Petasis reagent tolerates brief exposure to air and water and is stable at room temperature when kept in solution in the dark. This reagent serves as a mild and practical alternative to the Tebbe reagent for carbonyl methylenation.

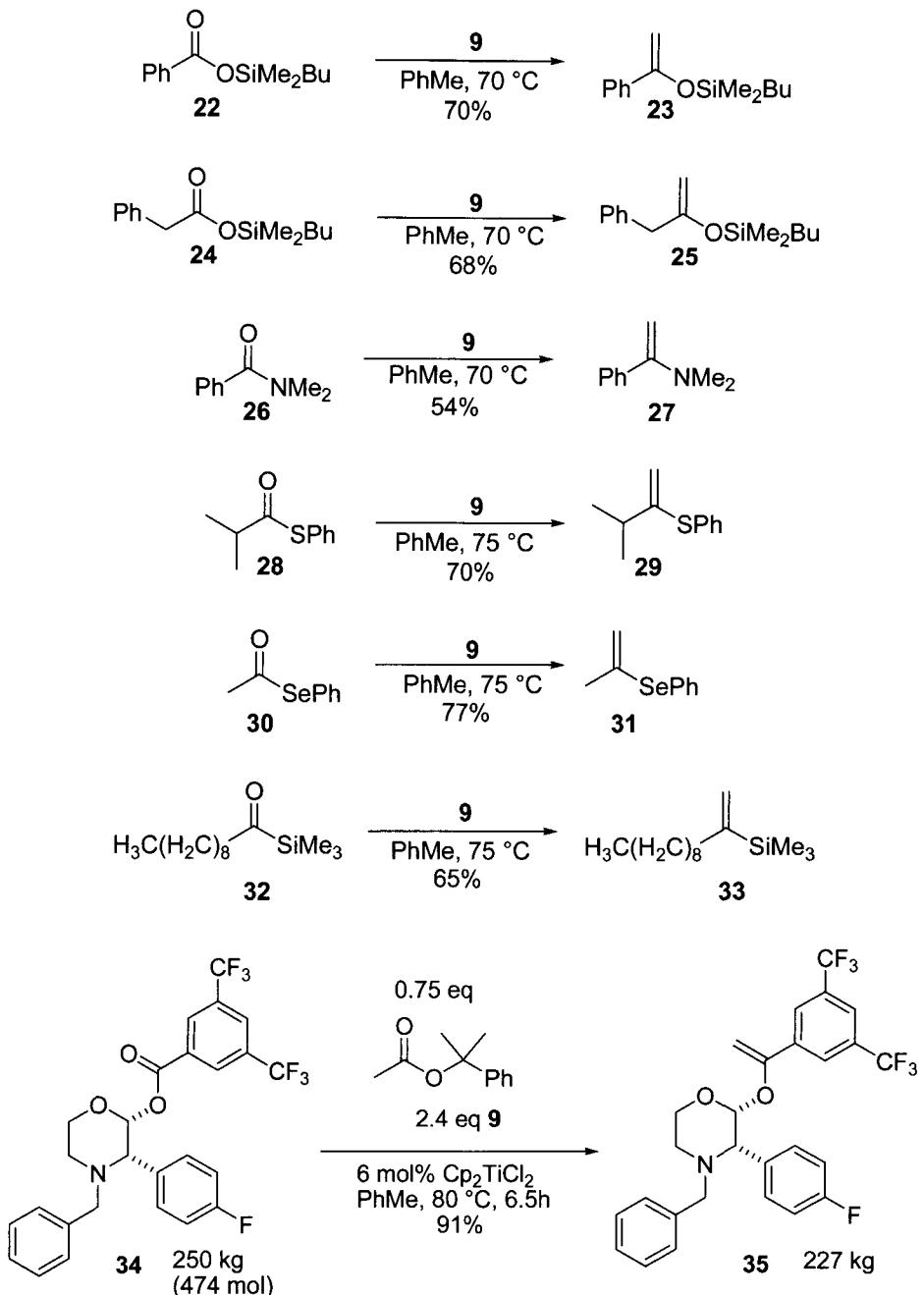


The common element between Tebbe and Petasis methylenation is that both share the same reactive intermediate, titanocene methyldiene **5**, in the reaction pathway. Hughes has provided a strong evidence that the Petasis reaction proceeds by the rate-determining generation of titanocene methyldiene **5** via an  $\alpha$ -elimination to remove of methane, followed by a rapid reaction with the carbonyl compound.<sup>12</sup>



The  $\alpha,\beta$ -unsaturated esters **12** and **14**, spirobislactone **16**, and vinylogous lactone **18** are smoothly methylenated by Petasis reagent. Silyl esters **22** and **24** are converted to silyl enol ethers **23** and **25**. Carbonate **20** can be methylenated to give ketene acetal **21**. Amide **26** and lactams can be methylenated, however the reaction is generally sluggish and the complete separation of Ti species is usually difficult. In a similar manner, thioester **28** and selenoester **30** are converted to alkenyl sulphide **29** and alkenyl selenide **31**, respectively. Additionally it has been demonstrated that acyl silanes can be converted to the corresponding alkenyl silanes.<sup>13,14</sup>

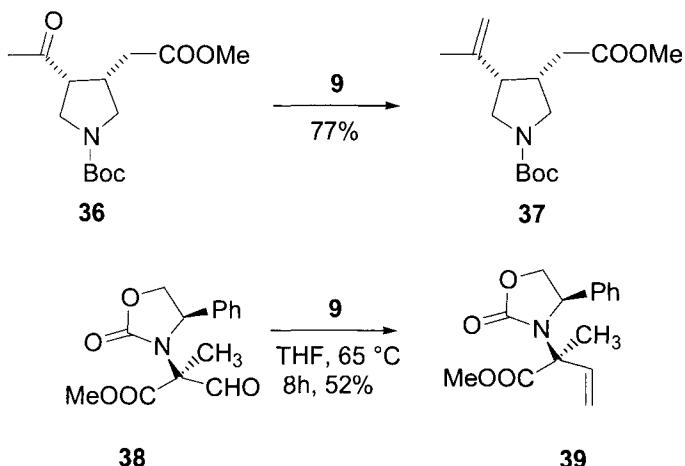




An elegant example of the preparation, storage, and use of the Petasis reagent for methylenation in multikilogram scale (250 kg, 474 mole) was provided by Payack and co-workers at Merck Process Chemistry Department in 2004.<sup>15</sup> The Petasis reagent should be stored refrigerated as a solution (in

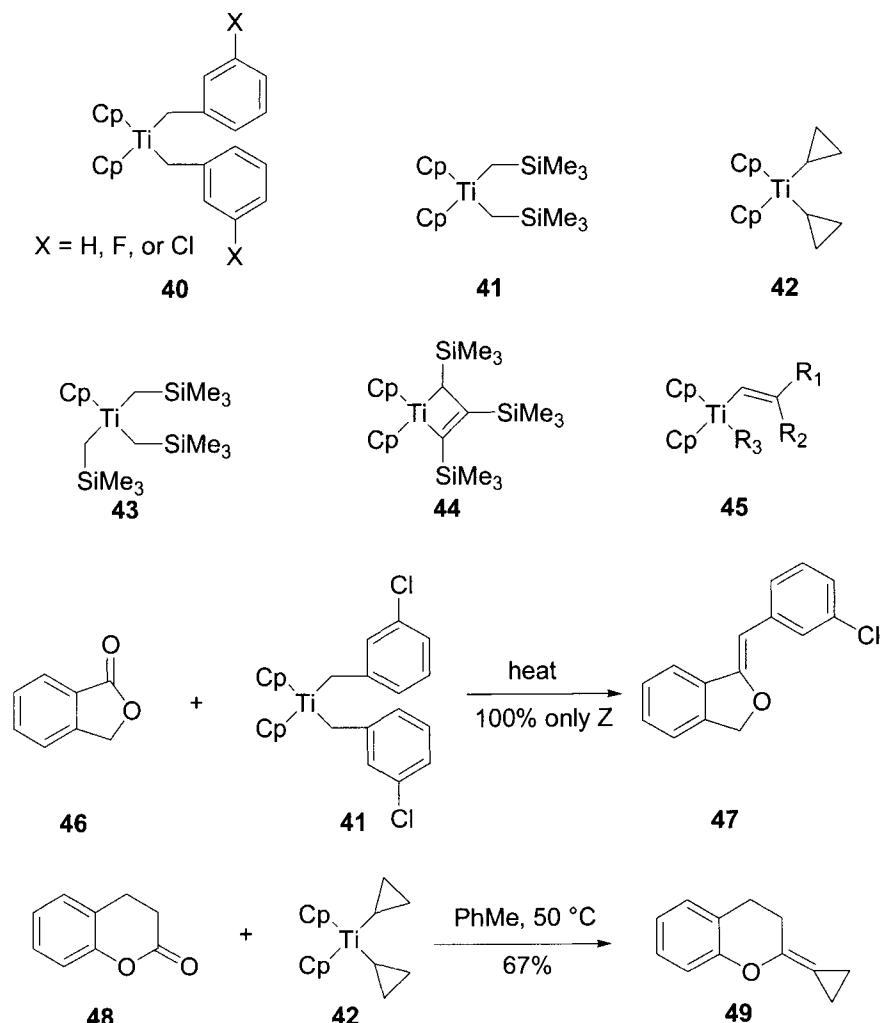
toluene or THF) because it is unstable in the solid state and decomposes, releasing heat and gas. Payack recommends quenching the methylenation reaction with a mixture of aqueous sodium bicarbonate and methanol while stirring at slightly elevated temperature ( $\sim 40^\circ\text{C}$ ) in order to convert titanium residues into insoluble waste that can be removed by filtration. On large scale it was demonstrated that ethanol can be used instead of methanol with the conversion being complete after stirring at  $60^\circ\text{C}$  for 6 h. Payack and co-workers successfully developed a practical process for converting ester **34** to give enol ether **35** in excellent yield using the Petasis reagent. On the other hand, it was found that the utilization of a Tebbe methylenation generates only a 15% yield of enol ether **35**. This process was used to make hundreds of kilograms of an advanced intermediate of Aprepitant (Emend), which is employed as a therapy to prevent chemotherapy-induced nausea and vomiting.

Aldehydes and ketones can be selectively methylenated in the presence of less electrophilic carbonyl groups such as esters, amides and carbamates using the Petasis reagent. In Parsons' model study towards kainic acid, selective methylenation of ketone **36** was achieved using the Petasis reagent, avoiding epimerization of the neighbouring stereocenters and reaction with the methyl ester.<sup>16</sup> In Hegedus's route to  $\alpha$ -alkyl- $\alpha$ -amino acid, key intermediate **39** was synthesized by the Petasis reagent.<sup>17</sup>

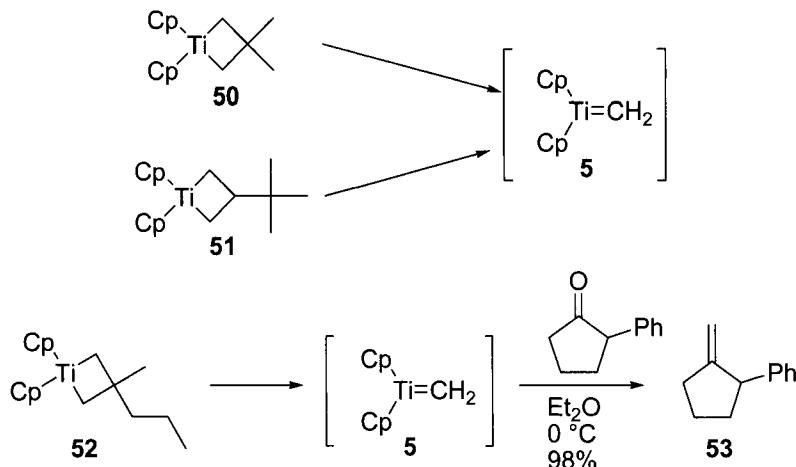


While homologated titanocene-aluminium complexes analogous to **3** are difficult to prepare; however, the corresponding dialkyl titanocenes of **5** can be readily prepared from titanocene dichloride and the appropriate organolithium or Grignard reagent. Therefore, Petasis-type reagents can be used not only for methylenation but also for olefination. Among these compounds that were shown to exhibit similar reactivity with **5** are the

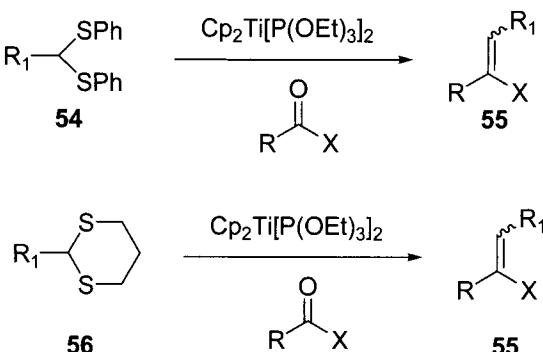
dibenzyl **40**,<sup>18</sup> bis(trimethyl-silylmethyl) **41**, bis(cyclopropyl) **42** and other titanocenes **43**, **44** and **45**.<sup>19–21</sup> It should be noted that these dialkyl titanocenes are only useful for alkylideneation of carbonyl groups that are not capable of undergoing a prohibitively fast  $\beta$ -elimination process.



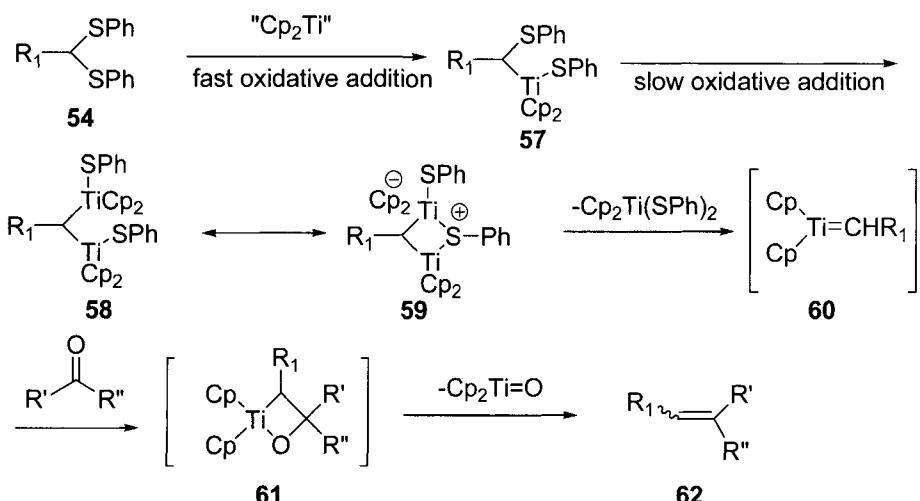
Grubbs reagents, titanacycles **50** and **51** were prepared by the reaction of Tebbe reagent with a terminal alkene in the presence of a Lewis base.<sup>22</sup> When these complexes are heated, reactive titanocene methyldiene **5** is regenerated and will methylenate carbonyl group (**49** to **53**).<sup>23</sup>



Takeda and co-workers discovered that the easily accessible thioacetals **54** and **56** can be reduced by a low-valent titanium reagent to give Schrock carbenes that are competent to alkylidenate aldehydes, ketones, esters, lactones, and thioesters.<sup>24</sup> This method has the advantage of tolerating hydrogen atoms on the β-carbon atom relative to the titanium atom of the Schrock carbene. The other distinct advantage of the Takeda olefination is that functionality can be incorporated into the titanium alkylidene complex from a range of functionalised thioacetals.<sup>25</sup>



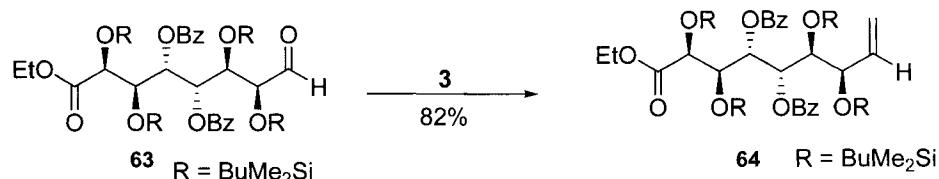
A plausible mechanism for the Takeda alkylideneation is given here.<sup>26</sup> The first oxidative addition to generate titanocene complex **57** is essentially instantaneous, while the second oxidative addition, giving bimetallic **58** or **59** is slower. By analogy with the Petasis reagent, the rate-determining step is likely to be the generation of the titanium(IV) alkylidene complex **60**, a Schrock carbene.

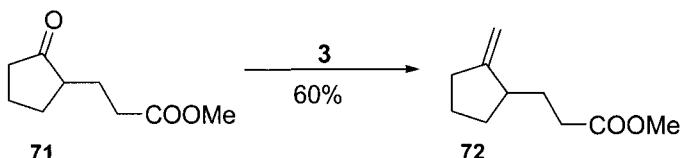
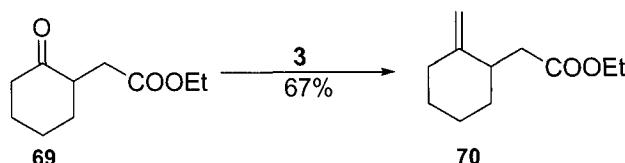
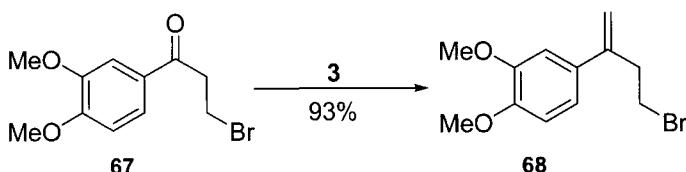
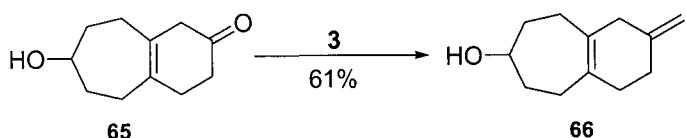


Takai reported a simple, general, and stereoselective method for the alkylideneation of ester to give Z-enol ethers.<sup>27</sup> The titanium carbene complex is easily prepared *in situ* by the reaction of RCHBr<sub>2</sub> with a low-valent titanium species generated by treatment of TiCl<sub>4</sub> with zinc and tetramethylenediamine (TMEDA) in THF. Without isolation, the complex is used for carbonyl alkenation.<sup>28</sup> It was reported that the presence of a small amount of lead in the zinc was crucial to the reaction.<sup>29</sup>

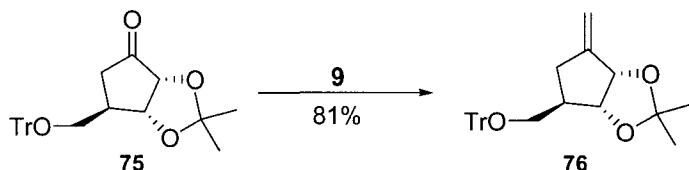
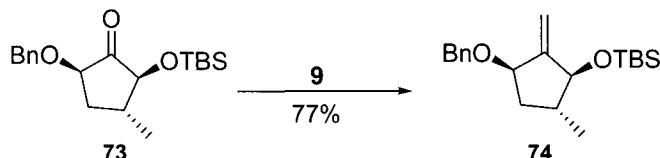
#### 1.3.4.5 Synthetic Utility

The Tebbe reagent has been used extensively for the methylenation of a variety of carbonyl groups in the presence of other functional groups. For example, the aldehyde group in **63** was selectively methylenated in the presence of the ester without epimerisation of the adjacent chiral centers.<sup>30</sup> Without the protection of the hydroxy group, methylenation of readily enolizable ketone **65** gave alkene **66** in 61% isolated yield.<sup>31</sup> Ketone **67** possessing a β-halide atom was successfully methylenated, giving the substituted styrene **68** in 93% isolated yield.<sup>32</sup> Keto esters **69** and **71** are efficiently methylenated using the Tebbe reagent to afford olefins **70** and **72** respectively.<sup>7,11</sup> Additionally, the methylenation of carbonates with Tebbe reagent generates ketene acetals.



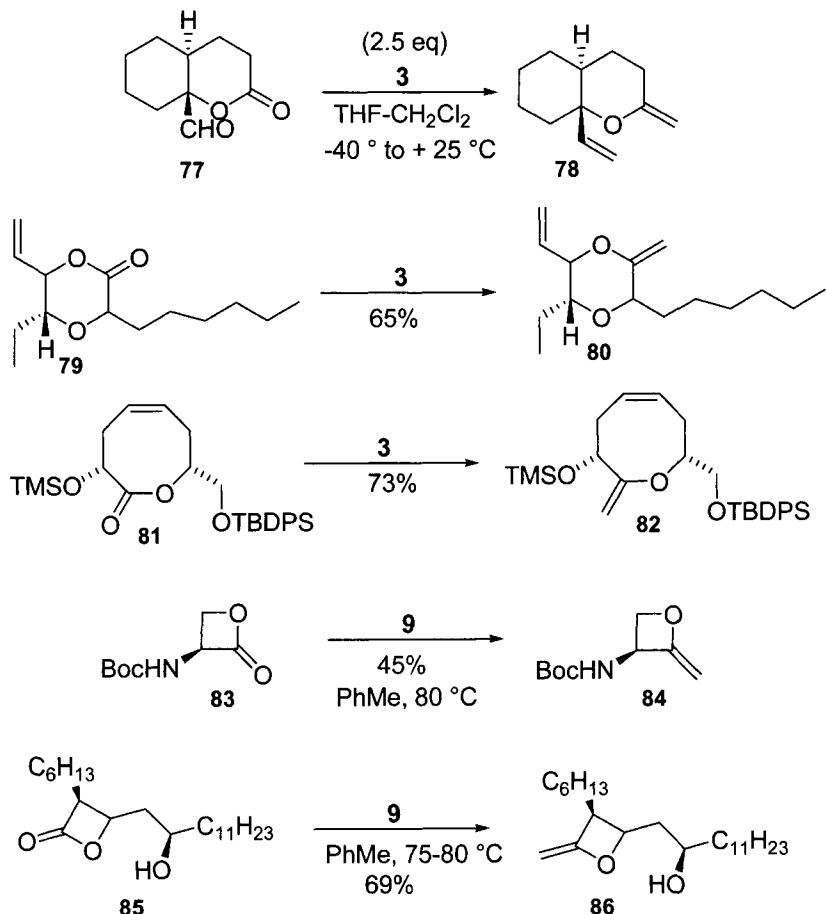


The Petasis reagent has been demonstrated to methylenate base-sensitive substrates without epimerization of sensitive stereocenters. For example the easily enolizable cyclopentanones **73** and **75** were converted to alkenes **74** and **76** in 77% and 81% isolated yield respectively.<sup>33</sup>



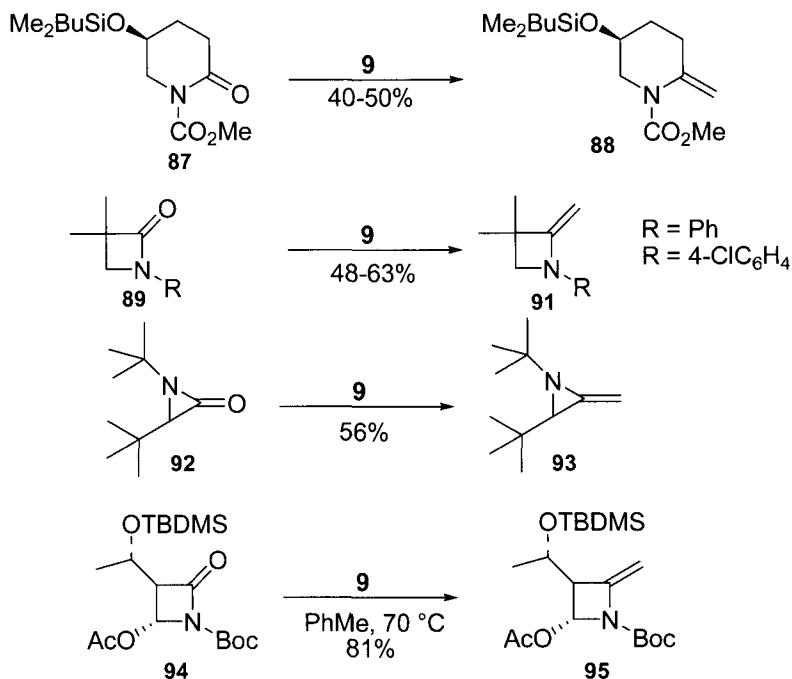
Using double Tebbe methylation (**77** to **78**) followed by a Claisen rearrangement, Paquette and co-workers developed a concise, reliable, and efficient scheme for 4-cyclooctenones.<sup>34</sup> Using this methodology, Paquette reported an alternate enantioselective route to a key bicyclic intermediate,

demonstrated the feasibility of a Tebbe–Claisen sequence for assembling the entire kalmanol backbone<sup>35</sup> and enantiomerically pure (+)-*cis*- and (+)-*trans*-lauthisan via a Claisen ring expansion.<sup>36</sup>

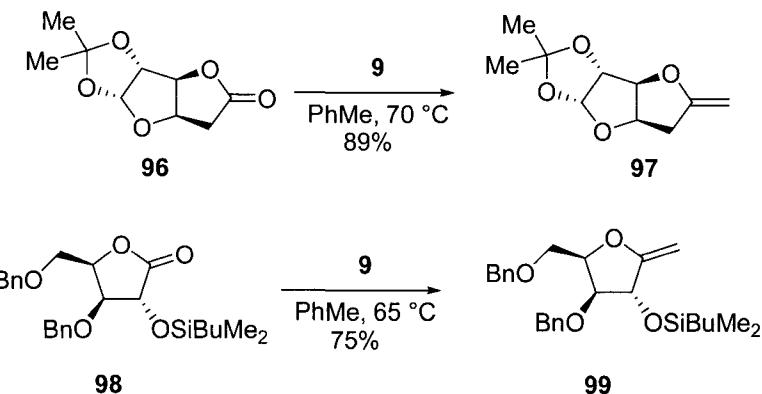


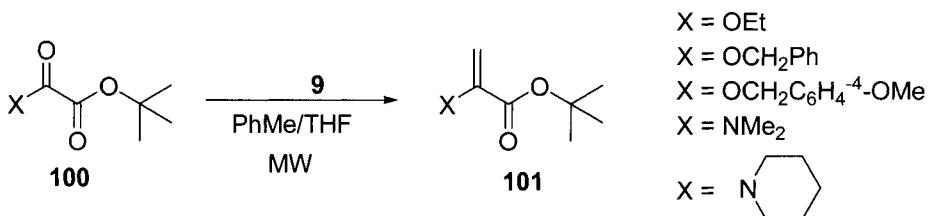
In the synthesis of (+)-laurencin, Holmes used Tebbe reagent converted ester to alkene in 71% yield.<sup>37</sup> Nicolaou developed a novel method for direct conversion of olefinic ester to cyclic enol ethers with Tebbe reagent.<sup>38</sup>

Methylenation of tertiary amides utilizing Petasis reagent, including *N*-acyl heterocycles, gives enamines.<sup>13,39a</sup> From the corresponding  $\alpha$ -lactam 92, and  $\beta$ -lactams 89, methyleneaziridine 93 and methylenetidine 91 were synthesized via Petasis olefination.<sup>39b</sup>

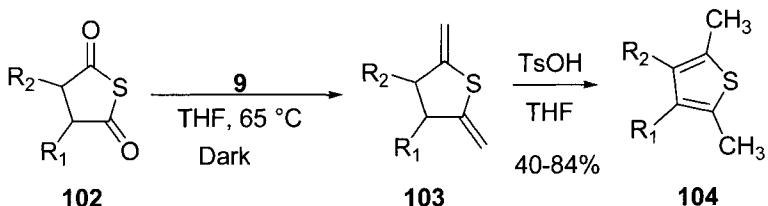


Petasis reagent was also effective for the methylenation of aldonolactones, **96**<sup>40</sup> and **98**.<sup>41</sup> Petasis olefination of unsymmetrical oxalates and oxalate monoesters or monoamides **100** under microwave-assisted, provides pyruvate-based enol ethers and enamines **101** in higher yields.<sup>42</sup>





Depending on the number of equivalents of Petasis reagent used, anhydrides, as well as thioanhydrides and imides can be methylenated one or both carbonyl groups. In the case of cyclic substrates, the bis-methylenation provides a novel method for accessing functionalized furans or thiophenes, such as **104** *via* subsequent isomerization of the newly generated olefin.<sup>43</sup>



#### 1.3.4.6 Experimental

##### The Tebbe Reaction; General Procedure:

To a solution of carbonyl (1.0 mmol) in THF (2–3 mL) at 0 °C is added a toluene solution of the Tebbe reagent (2 mL of 0.5 M solution, 1.0 mmol). The mixture is allowed to warm to rt, and after about 15 minutes, Et<sub>2</sub>O (15–20 mL) is added. Then 5–10 drops of aq NaOH (0.1 M) slowly added while stirring the mixture. After gas evolution ceases, the mixture is dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered using a celite pad. Rotary evaporation of the solvent provides the crude product which is purified by column chromatography using alumina and an eluent of 2% Et<sub>2</sub>O in pentane or petroleum ether.

##### The Petasis Reaction; General Procedure:

A 0.5 M toluene (or THF) solution of Cp<sub>2</sub>TiMe<sub>2</sub> (2–3 equiv) was mixed with the carbonyl compound (1 mmol) and stirred under argon in the dark at 65 °C. After the reaction was completed (12–26 h), the mixture was diluted with petroleum ether. The resulting yellow-orange precipitate was removed by filtration, and the filtrate was concentrated. The residue was purified by flash column chromatography on silica or basic alumina (for vinyl ethers).

### 1.3.4.7 References

1. [R] Pine, S. H. *Org. React.* **1993**, *43*, 1.
2. [R] Hartley, R. C.; McKiernan, G. J. *J. Chem. Soc., Perkin Trans. I* **2002**, 2763.
3. [R] Hartley, R. C.; Li, J.; Main, C. A.; McKiernan, G. J. *Tetrahedron* **2007**, *63*, 4825.
4. [R] Petasis, N. A. "Transition Metals for Organic Synthesis" Volume 1, Second Revised Ed. Beller M. and Bolm, C. Wiley-VCH, 2004, pp427–447.
5. Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611.
6. Cannizzo, L. F.; Grubbe, R. H. *J. Org. Chem.* **1985**, *50*, 2386.
7. Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212.
8. Pine, S. H.; Shen, G. S.; Hoang, H. *Synthesis* **1991**, 165.
9. [R] (a) Maercker, A. *Org. React. (N. Y.)* **1965**, *14*, 270. [R] (b) House, H. O. "Modern Synthetic Reactions"; Benjamin; Menlo Park, CA, **1972**; pp682–709. [R] (c) Bestman, H. J.; Vostrowsky, O. *Top. Cur. Chem.* **1983**, *109*, 65.
10. [R] Schrock, R. R. *Chem. Rev.* **2002**, *102*, 145.
11. (a) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392–6394. (b) Petasis, N. A.; Hu, Y. H.; Fu, D. K. *Tetrahedron Lett.* **1993**, *36*, 6001.
12. Hughes, D. L.; Payack, J. F.; Cai, D. W.; Verhoeven, T. R.; Reider, P. J. *Organometallics* **1996**, *15*, 663.
13. Petasis, N. A.; Lu, S. P. *Tetrahedron Lett.* **1995**, *36*, 2393.
14. Petasis, N. A.; Bzowej, E. I. *Tetrahedron Lett.* **1993**, *34*, 943–946.
15. (a) Payack, J. F.; Huffman, M. A.; Cai, D. W.; Hughes, D. L.; Collins, P. C.; Johnson, B. K.; Cottrell, I. F.; Tuma, L. D. *Org. Process Res. Dev.* **2004**, *8*, 256. (b) Payack, J. F.; Hughes, D. L.; Cai, D.; Cottrell, I. F.; Verhoeven, T. R. *Org. Synth.* **2002**, *79*, 19.
16. Greenwood, E. S.; Hitchcock, P. B.; Parsons, P. J. *Tetrahedron* **2003**, *59*, 3307.
17. Colson, P. J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 5918.
18. Petasis, N. A.; Bzowej, E. I. *J. Org. Chem.* **1992**, *57*, 1327.
19. Petasis, N. A.; Akritopoulou, I. *Synlett* **1992**, 665.
20. Petasis, N. A.; Staszewski, J. P.; Fu, D. K. *Tetrahedron Lett.* **1995**, *36*, 3619.
21. Petasis, N. A.; Bzowej, E. I. *Tetrahedron Lett.* **1993**, *34*, 943.
22. (a) Ott, K. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 5922. (b) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2386. (c) Cannizzo, L. F.; Grubbs, R. H. *J. Org. Chem.* **1985**, *50*, 2316. (d) Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1986**, *108*, 855.
23. (a) Clawson, L.; Buchwald, S. L.; Grubbs, R. H. *Tetrahedron Lett.* **1984**, *25*, 5733. (b) Anslyn, E. V.; Grubbs, R. H. *J. Am. Chem. Soc.* **1987**, *109*, 4880.
24. (a) Horikawa, Y.; Watanabe, M.; Fujiwara, T.; Takeda, T. *J. Am. Chem. Soc.* **1997**, *119*, 1127. (b) Takeda, T.; Saito, J.; Tsubouchi, A. *Tetrahedron Lett.* **2003**, *44*, 5571.
24. (a) Takeda, T.; Watanabe, M.; Rahim, M. A.; Fujiwara, T. *Tetrahedron Lett.* **1998**, *39*, 3753. (b) Rahim, A.; Taguchi, H.; Watanabe, M.; Fujiwara, T.; Takeda, T. *Tetrahedron Lett.* **1998**, *39*, 2153. (c) Takeda, T.; Sato, K.; Tsubouchi, A. *Synthesis* **2004**, 1457.
25. See reference 3, page 4830.
26. Okazoe, T.; Takai, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1987**, *52*, 4410.
27. [R] Tsuji, J. *Transition Metal Reagents and Catalysts, Innovations in Organic Synthesis*, John Wiley & Sons, **2000**, 326.
28. Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 2668.
29. Ikemoto, N.; Schreiber, L. S. *J. Am. Chem. Soc.* **1992**, *114*, 2524.
30. Clawson, L.; Buchwald, S. L.; Grubbs, R. H. *Tetrahedron Lett.* **1984**, *25*, 5733.
31. Winkler, J. D.; Muller, C. L.; Scott, R. D. *J. Am. Chem. Soc.* **1988**, *110*, 4831.
32. (a) Marschner, C.; Penn, G.; Griengl, H. *Tetrahedron Lett.* **1993**, *49*, 5067. (b) Matsuura, T.; Nishiyama, S.; Yamamura, S. *Chem. Lett.* **1993**, 1503.
33. Philippo, C. M. G.; Vo, N. H.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 2762.
34. Borrelly, S.; Paquette, L. A. *J. Am. Chem. Soc.* **1996**, *118*, 727.
35. Paquette, L. A.; Sweeney, T. J. *J. Org. Chem.* **1990**, *55*, 1703.
36. Robinson, R. A.; Clark, J. S.; Holmes, A. B. *J. Am. Chem. Soc.* **1993**, *115*, 10400.
37. Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565.

38. (a) Herdeis, C.; Heller, E. *Tetrahedron: Asymmetry*, **1993**, *4*, 2085. (b) Tehrani, K. A.; Kimpe, N. D. *Tetrahedron Lett.* **2000**, *41*, 1975.
39. Csuk, R.; Glanzer, B. I. *Tetrahedron* **1991**, *47*, 1655.
40. Faivre-Buet, V.; Eynard, I.; Nga, H. N.; Descotes, G.; Grouiller, A. *J. Carbohydr. Chem.* **1993**, *72*, 349.
41. Cook, M. J.; Fleming, D. W.; Gallagher, T. *Tetrahedron Lett.* **2005**, *46*, 297.
42. Kates, M. J.; Schauble, J. H. *J. Org. Chem.* **1994**, *59*, 494.