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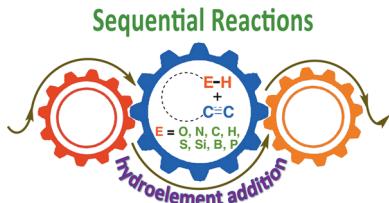
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## Recent Advances in Catalytic Sequential Reactions Involving Hydroelement Addition to Carbon–Carbon Multiple Bonds

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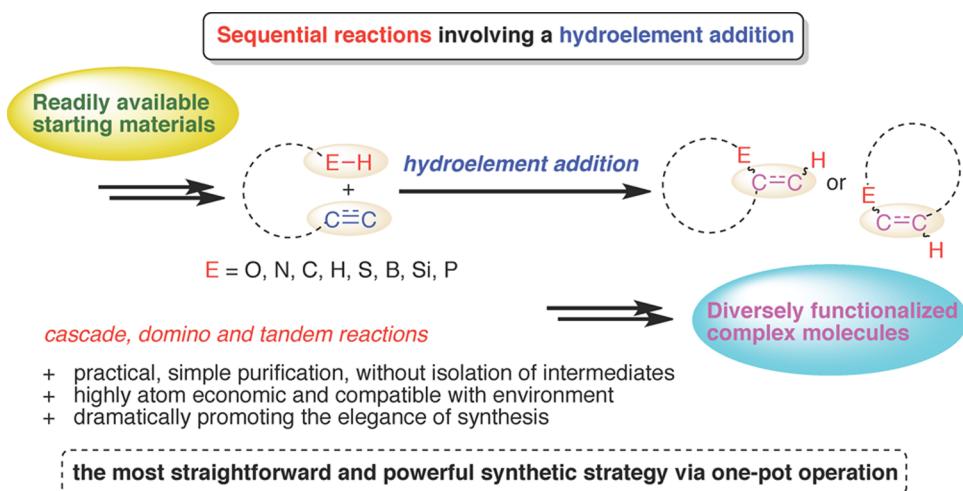
### 1. INTRODUCTION

Sequential reactions, through the incorporation of several distinct transformations into one single sequence, are one of the most powerful synthetic tools in modern organic chemistry. Compared with traditional stepwise-mediated synthetic approaches, sequential transformations (e.g., cascade,<sup>1</sup> domino,<sup>2</sup> and tandem reactions<sup>3</sup>) possess unique step economy features and significant advantages. In general, inexpensive, relatively simple and readily available starting materials can be employed to construct more sophisticated targeted molecules. Meanwhile, combining several distinct transformations into one single sequence greatly increases the complexity of the resulting compounds. Most important of all, such a practically useful “one-pot” operation simplifies purification of the products, as well as decreasing the cost and effort of synthesis. Clearly, this methodology is highly atom economic and environmentally benign in a practical fashion.<sup>4</sup> It dramatically promotes the elegance of synthesis and meets the demands for the continuing development of green chemistry.<sup>5</sup>

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**Scheme 1.** Schematic Illustration of Catalytic Sequential Reactions Involving Hydroelement Addition to Carbon–Carbon Multiple Bond



Carbon–element (C–E) bonds such as C–C, C–H, C–O, and C–N bonds are the most basic fragments of organic scaffolds. Undoubtedly, the construction of these chemical bonds is the central mission of organic synthesis. The direct addition of a nucleophilic element–hydrogen (E–H) bond to an unsaturated C–C bond is the most straightforward and powerful strategy for producing a C–E bond.<sup>6–14</sup> Obviously, incorporating such a transformation into a compatible reaction sequence makes it even more powerful in the rapid construction of synthetically useful molecules (Scheme 1).

Indeed, over the past decade, significant efforts have been addressed in the design and development of compatible synthetic sequences, through the incorporation of an attractive hydroelement addition reaction into a rationally designed consecutive transformation, resulting in the formation of diversely functionalized complex molecules via a one-pot procedure.

In 1996, a thematic issue of *Chemical Reviews* entitled “Frontiers in Organic Synthesis” was published, in which the advances in sequential transformations such as cascade, domino and tandem reactions were demonstrated.<sup>15</sup> Thirteen years later, another issue summarizing the applications of these reactions in total synthesis appeared in *Chemical Society Reviews*.<sup>16</sup> Even more specifically, a focus on transition metal catalysis,<sup>17</sup> organocatalysis,<sup>2b,c,3b,18</sup> and heterocycle synthesis<sup>1a,b,19</sup> also provides valuable perspectives for future development. With the tremendous advances in synthetic methodologies and strategies, especially transition metal-catalyzed organic reactions,<sup>20</sup> a comprehensive survey to cover recent progress with a specific topic is again necessary.

Given the important application values in synthesis, the significant practical advantages, and the absence of a comprehensive summary to date, recent advances in catalytic sequential reactions involving hydroelement addition to carbon–carbon multiple bonds will be highlighted in the current Review.

### 1.1. Scope and Organization of This Review

This Review is planned to provide a survey of catalytic sequential transformations involving hydroelement addition to unsaturated C–C bonds, not including the related redox transformation cascades (e.g., aminobromination, dehydrogenative coupling reactions). However, to have a comprehensive

overview of the advances in these sequential reactions, it is inevitable that there will be some overlap in the selected examples with previous reviews.<sup>1a,2b,c,18b,19</sup> It will cover examples of catalytic sequential reactions involving addition of E–H bonds to unsaturated C–C bonds that were published up to August 2012. Remarkable differences in reaction pathways resulting from diverse reactants and combination sequences will be comprehensively addressed, with a focus on discussion of the mechanism for insight into the design and development of novel reaction sequences.

This review is organized by the addition of distinct E–H bonds (including O–H, N–H, C–H, H–H, S–H, B–H, Si–H, and P–H bonds) to unsaturated C–C bonds (e.g., alkyne, olefin and diene substrates). Further division in each subsection will emphasize the diverse combination sequences for detailed discussion. Examples of sequential reactions involving the O–H bond transformation will be initially outlined. Then, the description will be expanded to the scope of N–H, C–H, H–H, S–H, B–H, Si–H, and P–H bonds.

## 2. THROUGH THE ADDITION OF AN O–H BOND TO AN UNSATURATED C–C BOND

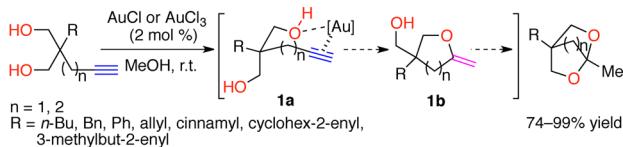
The C–O bond frequently serves as one of the key moieties found in numerous biologically active natural products, pharmaceuticals, and agrochemicals. Sequential reactions involving a hydroalkylation/hydroarylation process,<sup>7,9</sup> obviously, are among the most straightforward and fascinating synthetic approaches for C–O bond formation. Importantly, other chemical bonds, such as C–C and C–N bonds can be constructed simultaneously via a one-pot procedure. The related advances will be outlined in this section.

### 2.1. Double Hydroalkylation

**2.1.1. Double Intramolecular Hydroalkylation.** The pioneering work on double hydroalkylation was reported by Utimoto and co-workers in 1983.<sup>21</sup> From then on, numerous reports became available on the application of this method for accessing oxygen-containing heterocycles. In particular, with the rapid expansion of  $\pi$ -acid-mediated catalysis,<sup>22</sup> noble metals such as gold, silver and platinum complexes have been widely utilized to promote this transformation, leading to the related spiroketals and bicyclic acetals via consecutive addition of two alcohol nucleophiles to alkynes.

Genêt and Michelet demonstrated that simple gold salts, including  $\text{AuCl}$  and  $\text{AuCl}_3$ , promote the biscyclization of bis-homopropargylic diols.<sup>23</sup> Strained bicyclic ketals were formed in methanol (Scheme 2). Notably, the related addition of

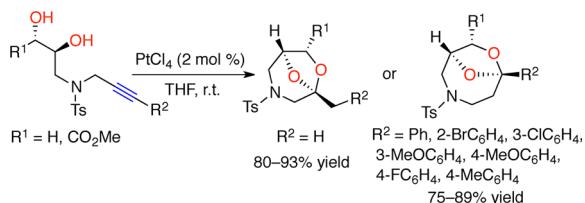
**Scheme 2. Biscyclization of Bis-homopropargylic Diols<sup>23</sup>**



methanol to olefin intermediates did not occur under standard conditions. Substituents including benzyl, phenyl, allyl, and *n*-butyl can be introduced to the backbone of ketals. An analogue using a mixture of  $\text{Ph}_3\text{PAuCl}$  and  $\text{AgOTf}$  was reported by Xue and Li.<sup>24</sup> Bisbenzannelated spiroketals, an important scaffold of natural bioactive rubromycins, are easily accessible from 2-alkynyl phenols.

Recently, Ley and co-workers described an example of Pt(IV)-promoted double cyclization of alkyne diols.<sup>25</sup> The substituents on the alkyne partners were found to influence strongly the regioselectivity of this reaction. Terminal-alkyne-containing diols give rise to [3.2.1]bicyclic acetals as the sole products via a 6-exo-cyclization. The corresponding [4.2.1]-bicyclic compounds can be generated from the internal compounds by a 7-endo-cyclic process (Scheme 3). However,

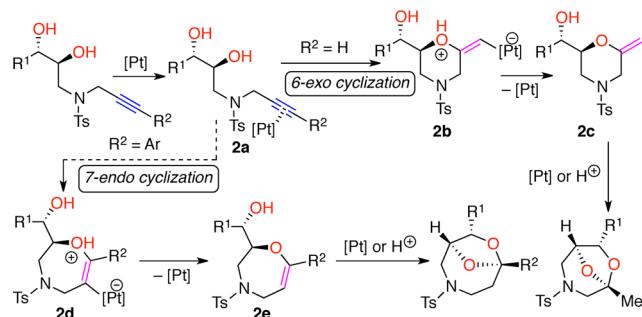
**Scheme 3. Pt-Catalyzed Double Hydroalkoxylation of Alkyne Diols<sup>25</sup>**



using  $\text{CF}_3^-$ - and  $\text{NO}_2^-$ -substituted reactants resulted in a mixture of regioisomers. The reaction may proceed initially via a 6-exo- or 7-endo-cyclization, followed by the addition of the residual hydroxyl moiety to the double bond leading to acetals (Scheme 4). Notably, in this case, the corresponding *para*- $\text{CF}_3$ -containing 6-exo-dig and 7-endo-dig enol intermediates can be detected by *in situ* NMR analysis.

The conversion of bis-homopropargylic diols to substituted bicyclic ketals can be achieved using the  $\text{AgOTf}$  salt.<sup>26</sup> It should be noted that dyne-substituted diols provide access to cis-

**Scheme 4. Proposed Mechanism**



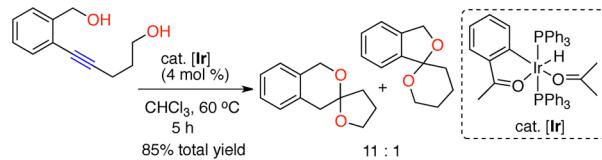
oriented adducts while leaving one triple bond intact. Interestingly, an alkynyl-incorporated carboxylic acid results in the formation of a bicyclic dione via a double hydrocarboxylation (Scheme 5).

**Scheme 5. Synthesis of Bicyclic Dione<sup>26</sup>**



Crabtree's group showed that an air- and moisture-insensitive Ir(III) hydride complex enables the double cyclization of alkynyl diols to proceed, leading to spiroacetals with high 6-endo-dig regioselectivities (Scheme 6).<sup>27</sup> Messerle,<sup>28</sup> Chai,<sup>29</sup>

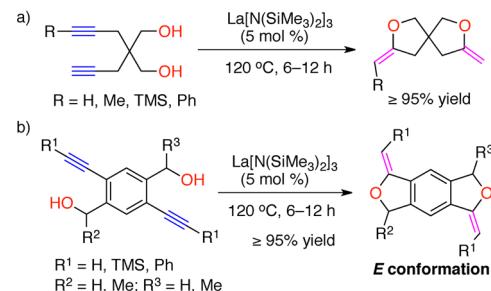
**Scheme 6. Iridium-Catalyzed Double Intramolecular Hydroalkoxylation<sup>27</sup>**



and Fensterbank<sup>30</sup> independently reported analogous transformations for the formation of spiroketal motifs. In addition, a  $[\text{Rh}(\text{cod})_2]\text{PF}_6$  complex also displays catalytic activity in this reaction, although with lower performance than for the related Ir(I) catalysts.<sup>29</sup>

On the other hand, organolanthanide complexes were proved to be suitable precatalysts in the double hydroalkoxylation. Marks and Seo described an interesting lanthanide-mediated catalytic protocol using dialkynyl dialcohol substrates (Scheme 7).<sup>31</sup> This reaction occurs with excellent stereoselectivity with

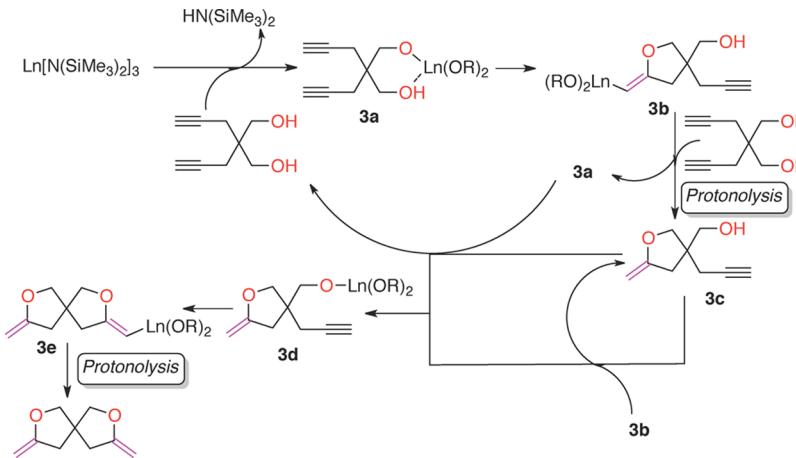
**Scheme 7. Lanthanide-Promoted Double Hydroalkoxylation of Dialkynyl Dialcohols<sup>31</sup>**



the formation of an absolute E-conformational O-heterocycle via a double 5-exo-cyclic pathway (Scheme 7b). Benzylic alcohols are more prone to undergo this transformation than linear alcohols, while secondary alkynyl-substituted alcohols were found to facilitate the reaction.

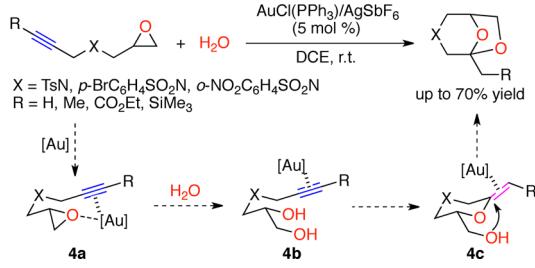
The proposed mechanism indicates that an oxygen-coordinated lanthanide (**3a**) derived from a ligand exchange may be the actual catalytic species (Scheme 8). Subsequent insertion of an alkyne into the O–Ln bond gives the related alkenyllanthanide complex, which then undergoes a rapid protonolysis, leading to the final product. Mechanistic studies by rate law and kinetic isotope effect show that the insertion

Scheme 8. Proposed Mechanism



reaction would be the turnover-limiting step in the transformation.

Shi's group reported that a mixture of  $\text{AuCl}(\text{PPh}_3)$  and  $\text{AgSbF}_6$  allows the direct addition of water to epoxy alkynes leading to fused bicyclic ketals (Scheme 9).<sup>32</sup> Electron-

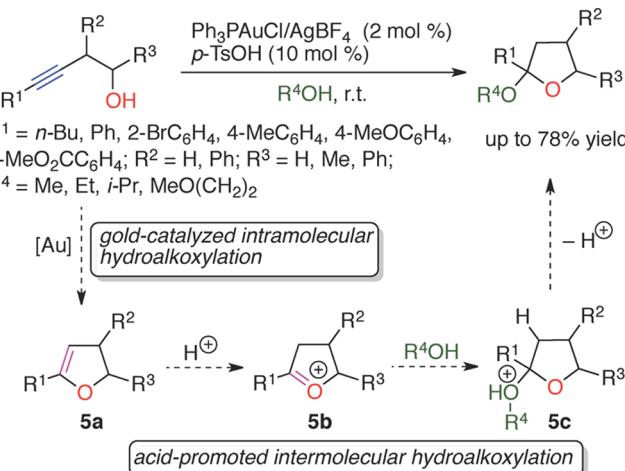
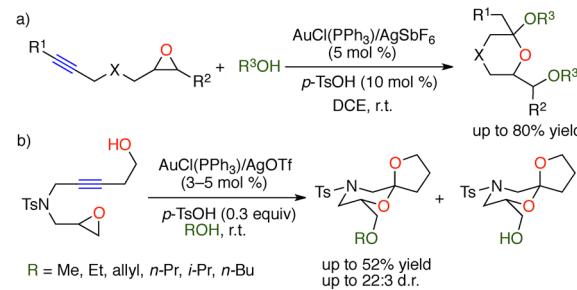
Scheme 9. Direct Addition of Water to Epoxy Alkynes<sup>32</sup>

withdrawing substituents on alkynes facilitate this transformation. The reaction may involve a consecutive three-membered ring-opening/double hydroalkoxylation pathway. Using alcohol nucleophiles, monocyclic ketals can be prepared by a gold/Brønsted acid cocatalysis.

**2.1.2. Intra- and Intermolecular Double Hydroalkoxylation.** Although a procedure for the double intermolecular hydroalkoxylation was reported as early as 1991,<sup>33</sup> to date, related reports on this field remain rare.<sup>34</sup> In contrast, the double hydroalkoxylation via intra- and intermolecular reaction pathways has been widely studied for formation of diversely functionalized O-heterocycles.

Using a simple alcohol as solvent, the conversion of homopropargylic alcohols to substituted tetrahydrofuranyl ethers, an important scaffold found in many natural products, was achieved at room temperature (Scheme 10).<sup>35</sup> In this case, a cationic gold complex was proposed to promote the intramolecular hydroalkoxylation of homopropargylic alcohols, and a Brønsted acid may be responsible for the nucleophilic attack of alcohol on the resulting enol ethers. Note that the transformation is sensitive to the steric hindrance of substrates. Bulky *tert*-butyl and trimethylsilyl substituents were found to shut down this reaction.

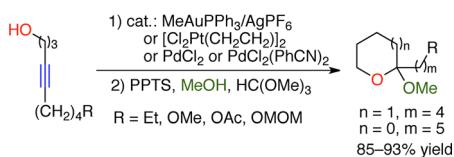
The related ketal compounds can be produced by replacing homopropargylic alcohols with epoxy alkynes (Scheme 11a).<sup>36</sup> Notably, this reaction proceeds effectively in 1,2-dichloroethane and does not need an alcohol solvent. By treatment of

Scheme 10. Synthesis of Tetrahydrofuranyl Ether Derivatives<sup>35</sup>Scheme 11. Au(I)/Brønsted Acid Catalyzed Reaction of Epoxy Alkynes and Alcohols<sup>36</sup>

hydroxyl-tethered reactants with alcohols, formation of two spiroketals as a mixture of products was observed (Scheme 11b).

In addition, Liu and De Brabander found that acetals can also be generated from internal alkynols using a Pd, Pt, or Au catalytic system (Scheme 12).<sup>37</sup> It is worth noting that the regioselectivity of this reaction strongly depends on the catalytic species. A gold(I) complex was found to favor a 5-exo-cyclic transformation. In contrast, forming 6-exo-acetals as major products was observed using Zeise's dimer ( $[\{\text{PtCl}_2(\text{CH}_2=\text{CH}_2)\}_2]$ ). Mechanistic studies indicate that

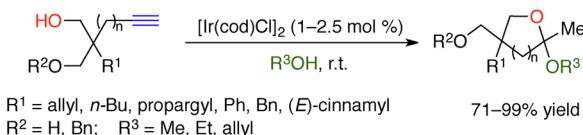
**Scheme 12. Transition Metal-Catalyzed Oxy-Functionalization of 4-Alkynols<sup>37</sup>**



an oxocarbenium species may serve as an activated intermediate in this case. Six-membered cyclic acetals are also accessible using an analogous synthetic protocol.<sup>38</sup>

Genêt's group described an example of an iridium catalytic protocol.<sup>39</sup> Bis-homopropargylic alcohols were reacted with alcohols, including methanol, ethanol and allyl alcohol, leading to 5-exo-cyclic ketals with high regioselectivities (Scheme 13). The alkynyl dialcohols are suitable substrates, and the related double intramolecular cyclization did not take place.

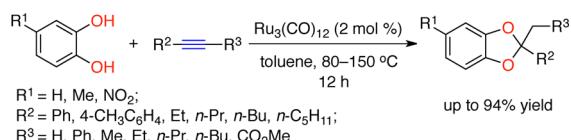
**Scheme 13. Iridium(I)-Catalyzed Intra- and Intermolecular Hydroalkoxylation<sup>39</sup>**



Macgregor and Messerle investigated the mechanism of iridium(I)-mediated double hydroalkoxylation between 4-pentyn-1-ol and methanol.<sup>40</sup> Computational studies showed that C–O bond formation would be the rate-determining step in the reaction. Meanwhile, an external H-bonded methanol may stabilize the related iridium-alkenyl intermediate, followed by a reductive elimination of alkyl(hydrido)metal species giving the final acetal product.

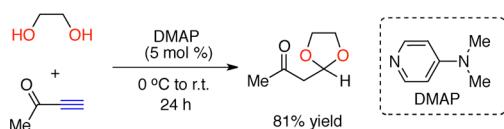
Ruthenium-catalyzed reaction between catechols and alkynes was demonstrated by Hua for the synthesis of 2,2-disubstituted 1,3-benzodioxoles (Scheme 14).<sup>41</sup> It was noted that formation

**Scheme 14. Ruthenium-Catalyzed Reaction of Catechols and Alkynes<sup>41</sup>**



of Markovnikov adducts was observed when using terminal alkynes. Besides transition metal catalysis, 4-(dimethylamino)-pyridine (DMAP) also displays good catalytic activity in a double hydroalkoxylation.<sup>42</sup> Ethylene glycol selectively adds to the terminus of an  $\alpha$ -carbonyl-substituted alkyne to give the corresponding ketal (Scheme 15).

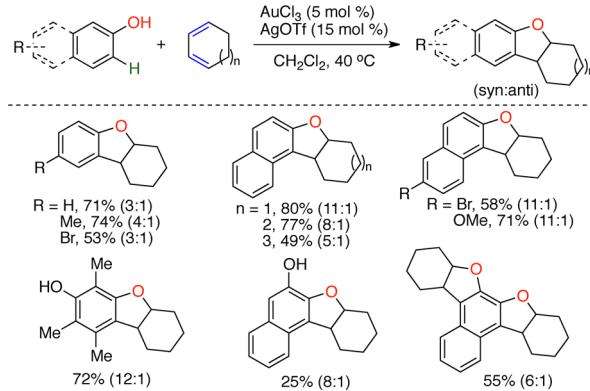
**Scheme 15. Amine-Promoted Double Hydroalkoxylation<sup>42</sup>**



## 2.2. With Hydroarylation

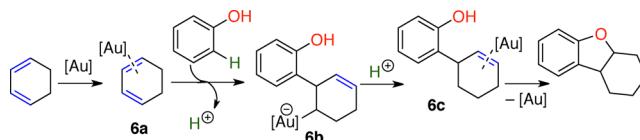
Li's group reported an annulation between phenols and cyclic dienes in the formation of benzofurans (Scheme 16).<sup>43</sup> In

**Scheme 16. Au(III)-Catalyzed Annulation of Phenols with Dienes<sup>43</sup>**



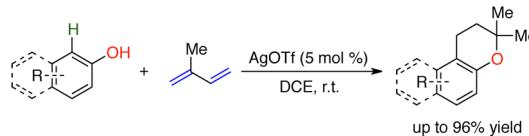
combination with AgOTf, the gold(III) salt AuCl<sub>3</sub> enables this reaction to proceed efficiently under mild conditions. Phenols bearing electron-donating substituents on the benzene ring facilitate the transformation. Notably, synthetically useful macrocyclic and fused benzofurans can be prepared by this method. However, an acyclic diene was found to be unsuitable in this case. The proposed mechanism involves an initial addition of an ortho-C–H bond of phenols to activated dienes, followed by an intramolecular cyclization leading to benzofurans (Scheme 17).

**Scheme 17. Proposed Mechanism for the Synthesis of Benzofurans**



Interestingly, using the simple AgOTf salt, acyclic dienes can react with phenols giving rise to dihydrobenzopyran and -furan derivatives (Scheme 18).<sup>44</sup> Other silver salts, including AgSbF<sub>6</sub>,

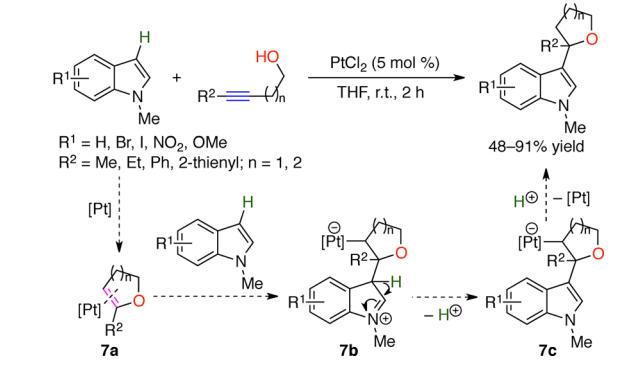
**Scheme 18. Annulation of Acyclic Dienes with Phenols<sup>44</sup>**



AgBF<sub>4</sub>, and AgClO<sub>4</sub>, also display catalytic activity in this reaction. However, CF<sub>3</sub>CO<sub>2</sub>Ag, AgNO<sub>3</sub>, and AgOTs do not give the desired products. An analogous synthetic strategy has also been reported by Hii using a recyclable Cu(OTf)<sub>2</sub>/2,2'-bipyridine catalytic system.<sup>45</sup> Notably, the reaction temperature strongly affects the transformation. Without the 2,2'-bipyridine ligand, the reaction between 4-methoxyphenol and isoprene occurs smoothly at 50 °C, with the formation of benzopyran in 45% yield. However, at room temperature, the desired product was not detected.<sup>44</sup>

Cheng's group demonstrated a platinum(II)-promoted reaction between alkynyl alcohols and indoles.<sup>46</sup> C3-furanyl and pyranyl-functionalized indole frameworks were constructed at room temperature (Scheme 19). Electron-donating N-

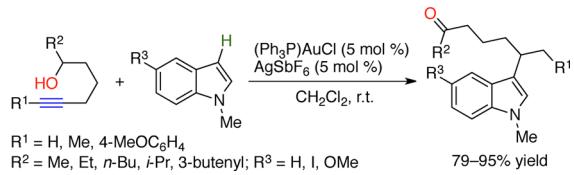
**Scheme 19.** Pt(II)-Catalyzed Synthesis of Furanyl or Pyranyl-Substituted Indoles<sup>46</sup>



methyl indoles were found to favor this transformation. In addition, extending this method to the synthesis of C2-substituted indoles was successful by using pyrrole partners. The mechanism proposes that an intramolecular addition of the OH moiety to the activated triple bond may occur initially, and then the resulting exo-cyclic enol ethers (**7a**) further react with indoles giving the final products via a hydroarylation process. A similar transformation can also be promoted by the Cu(OTf)<sub>2</sub> salt.<sup>47</sup>

Using an alternative cationic gold complex, unusual indolyl-incorporated ketones were formed in good yields (Scheme 20).<sup>48</sup> Mechanistic studies indicate that tetrahydropyranylinc-

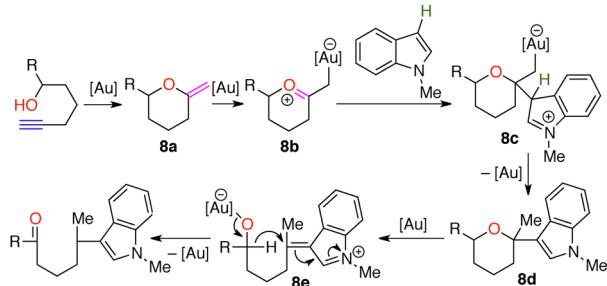
**Scheme 20.** Synthesis of Indolyl-Substituted Ketones<sup>48</sup>



doles (**8d**) may be generated initially, which may undergo an Oppenauer-type oxidative process, followed by a formal 1,5-hydride migration giving the acyclic products (Scheme 21). This type of hydride transfer reaction pathway was proved by deuterium-labeling studies.

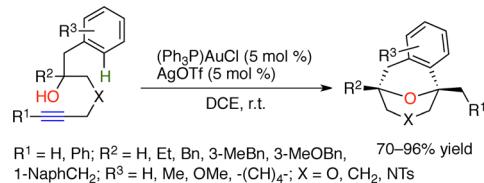
Starting from benzyl-substituted alkynols, the related intramolecular reaction provides facile access to benzofused

**Scheme 21.** Proposed Mechanism



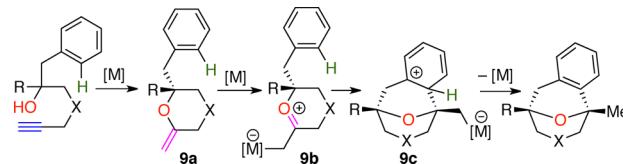
bicyclo[3.3.1]nonanes with high diastereoselectivities (Scheme 22).<sup>49</sup> Soft Lewis π-acid catalysts including Au(I) and Pt(II)

**Scheme 22.** Au(I)-Promoted Intramolecular Hydroalkoxylation/Hydroarylation<sup>49</sup>



complexes can be used to promote the transformation. As shown in Scheme 23, the mechanism involves the formation of

**Scheme 23.** Proposed Reaction Pathway

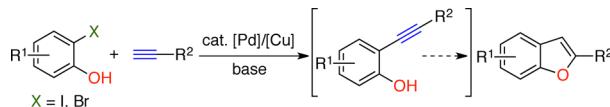


cyclic enol ethers (**9a**) initially, and then a nucleophilic attack and rearomatization could take place giving bicyclic products. It is noteworthy that such a transformation has been successfully employed as a key step in the total synthesis of the natural product bruguierol A.<sup>50</sup>

### 2.3. With Coupling Reactions

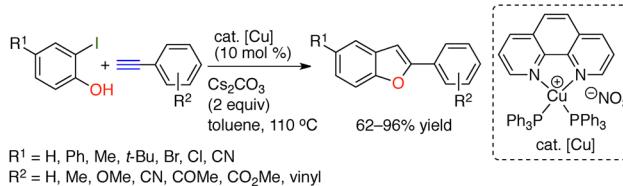
Sonogashira cross-coupling reactions are important and ubiquitous synthetic tools in the construction of functionalized internal alkynes.<sup>51</sup> As early as 1986, Marinelli and Cacchi demonstrated that such a reaction can combine with a hydroalkoxylation to produce a compatible sequence, yielding the corresponding benzofurans via a one-pot protocol (Scheme 24).<sup>52</sup> Then, Torii,<sup>53</sup> Arcadi<sup>54</sup> and Fancelli<sup>55</sup> reported analogous synthetic procedures using palladium and copper cocatalytic systems.

**Scheme 24.** Sonogashira Cross-Coupling/Hydroalkoxylation Reactions



In addition, a phenanthroline-ligated copper complex can be used as the sole catalytic species in this transformation (Scheme 25).<sup>56</sup> Note that sensitive groups, including chloride, bromide and vinyl, are well tolerated by the catalytic system. Mata's

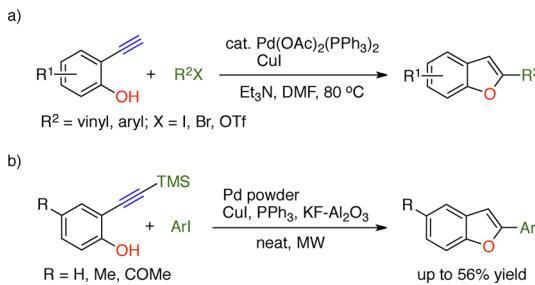
**Scheme 25.** Copper-Catalyzed Formation of Benzo[*b*]furans<sup>56</sup>



group found that an alternative Pd catalysis based on a N-heterocyclic carbene (NHC) ligand enables the reaction to proceed effectively.<sup>57</sup> Extending this method to the synthesis of tricyclic O-heterocycles was successful starting from 3-bromo-4-acetoxycoumarins and terminal alkynes.<sup>58</sup>

An alternative strategy using *ortho*-ethynylphenol and unsaturated halide substrates was established to produce benzo[*b*]furans (Scheme 26a).<sup>54</sup> Note that TMS-substituted

**Scheme 26. Use of 2-Hydroxy-Mediated Aromatic Alkynes as Substrates<sup>54,59</sup>**

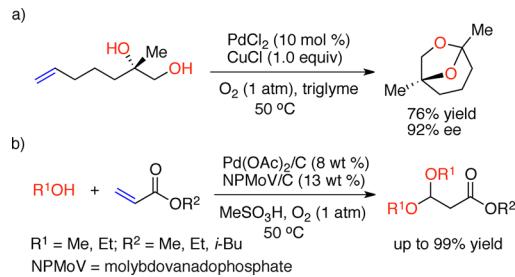


internal alkynes are suitable reactants in this reaction. A desilylation of TMS-protected alkynes is thought to occur with the formation of the related terminal alkynes, followed by a cross-coupling and cyclization process leading to the final products. A mixture of palladium powder, CuI and triphenylphosphine on KF-doped alumina also enables the reaction to take place under microwave conditions (Scheme 26b).<sup>59</sup> Interestingly, the treatment of a 2-iodoaryl alkyne with potassium hydroxide allows easy access to benzofuran via a copper-catalyzed hydroxylation/cyclization reaction.<sup>60</sup>

#### 2.4. Aerobic Dialkoxylation

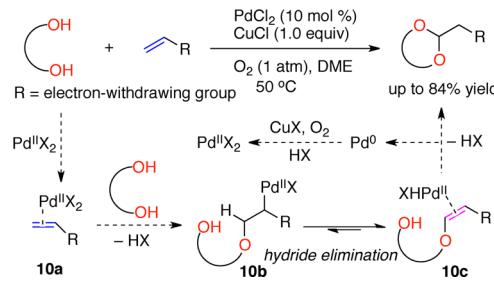
Aerobic dialkoxylation, by the treatment of alcohols with olefins under oxidative conditions, provides a unique and facile approach to the synthesis of oxygen-containing molecules. Lloyd demonstrated the example of Pd-catalyzed aerobic dialkoxylation in 1969.<sup>61</sup> Grigg described an analogous reaction for the preparation of *endo*-brevicomin.<sup>62</sup> Then Hosokawa greatly expanded the substrate scope using electron-deficient alkenes<sup>63</sup> and alkenyl-containing diols.<sup>64</sup> Formation of cyclic acetals with high regioselectivities was observed using optically active diols (Scheme 27a).<sup>64</sup> A consecutive oxypalladation/β-

**Scheme 27. Pd(II)-Catalyzed Aerobic Dialkoxylation<sup>64,66</sup>**



hydride elimination/cyclization transformation may be involved in the reaction pathway (Scheme 28).<sup>63b,65</sup> Mechanistic studies using deuterium-labeling experiments indicate that the related Pd–H elimination step would be reversible. In addition, a mixture of Pd(OAc)<sub>2</sub> and molybdovanadophosphate supported

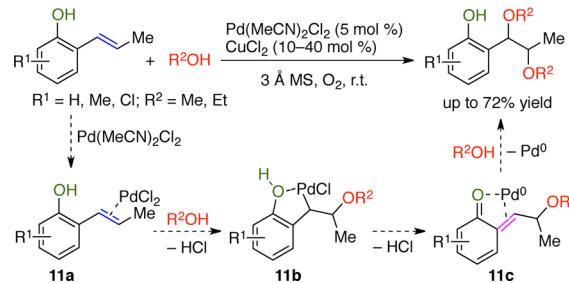
**Scheme 28. Proposed Mechanism<sup>63b,65</sup>**



on activated carbon also displays high efficiency in an intramolecular reaction (Scheme 27b).<sup>66</sup>

Sigman's group reported that a palladium salt enables the formation of dialkoxylation products under a balloon pressure of O<sub>2</sub> (Scheme 29).<sup>67</sup> The proposed mechanism involves that a

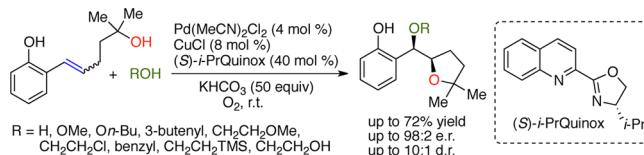
**Scheme 29. Aerobic Dialkoxylation of Styrenes Involving a Quinone Methide Intermediate<sup>67</sup>**



nucleopalladation of ortho-hydroxyl-substituted styrenes followed by rearomatization may occur initially, and then the resulting quinone methide species 11c can be attacked by nucleophilic alcohols leading to the final products. It is noteworthy that formation of allylic ether as side product was observed when using trisubstituted olefin in this reaction, which may arise from a competitive attack of alcohol at the α-position of styrene.

The same group extended this procedure to the synthesis of enantioenriched dialkoxylation compounds.<sup>68</sup> A combination of a palladium salt and chiral quinoline oxazoline ligand gives the best result in this reaction. In addition, optically active tetrahydrofuran derivatives can also be prepared using two different alcohols as nucleophiles (Scheme 30).<sup>69</sup>

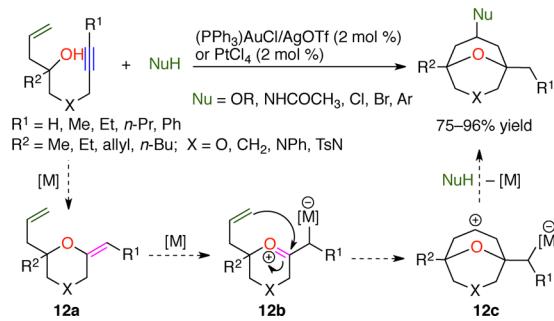
**Scheme 30. Asymmetric Synthesis of Tetrahydrofuran Derivatives<sup>69</sup>**



#### 2.5. With a Nucleophilic Ring Closure

For the synthesis of diversely functionalized heterocycles, sequential transformations involving a hydroalkoxylation followed by a nucleophilic ring closure have been extensively investigated. Barluenga's group reported that alkynols can react with various nucleophiles giving rise to bicyclic heterocycles (Scheme 31).<sup>70</sup> Lewis acids including gold and platinum

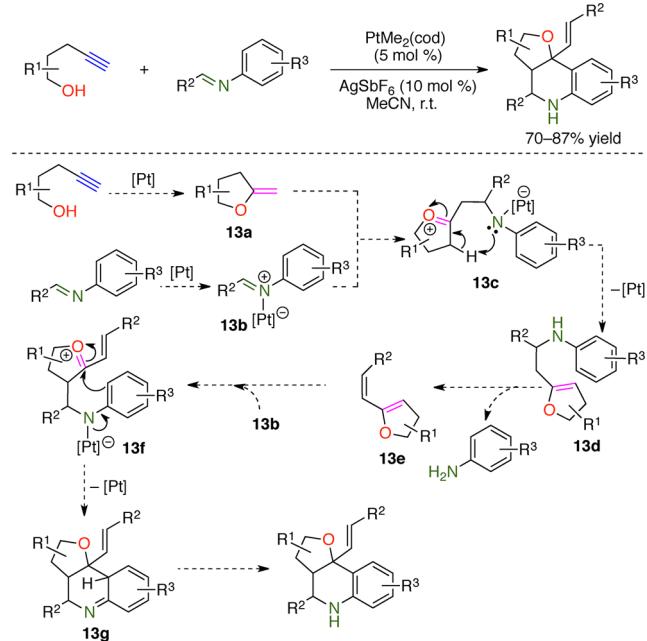
**Scheme 31.** Lewis Acid-Promoted Reaction of Alkynols with Various Nucleophiles<sup>70</sup>



complexes enable the reaction to proceed effectively. Alcohols, amides, acetonitrile, dichloromethane, and electron-rich arenes can be employed as nucleophiles. It is noteworthy that chiral alkynol reactants result in enantiomerically pure products in this reaction. A mechanism involving oxocarbenium ion (**12b**) formation can be considered, which then can be trapped by nucleophiles followed by a ring closure process leading to the final products.

Interestingly, using *N*-arylaldimines and alkynols, an alternative Pt catalysis results in the formation of vinyl-substituted spirofuranquinolines as a single diastereoisomer (Scheme 32).<sup>71</sup> In this reaction, a Mannich-type addition of

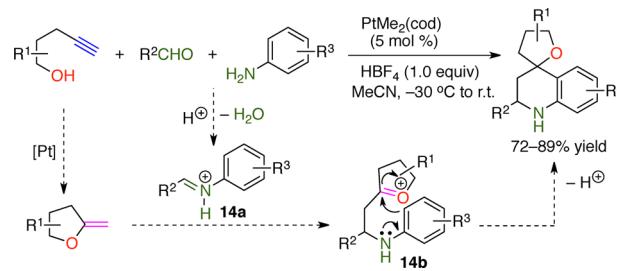
**Scheme 32.** Synthesis of Spirofuranquinolines<sup>71</sup>



enol ethers to a Pt-activated imine may occur leading to an oxocarbenium ion (**13c**), which easily undergoes the processes of proton transfer and aniline elimination giving the corresponding dienes **13e**. Subsequently, a nucleophilic attack to the activated imine can take place, followed by cyclization and rearomatization to yield the tricyclic products.

Replacing *N*-arylaldimines with aldehydes and anilines, spiroquinolines can be prepared using a PtMe<sub>2</sub>(cod) complex (Scheme 33).<sup>72</sup> A stoichiometric amount of HBF<sub>4</sub> is necessary for the transformation. The role of the Brønsted acid may be assigned to promote the conversion of aldehydes and anilines

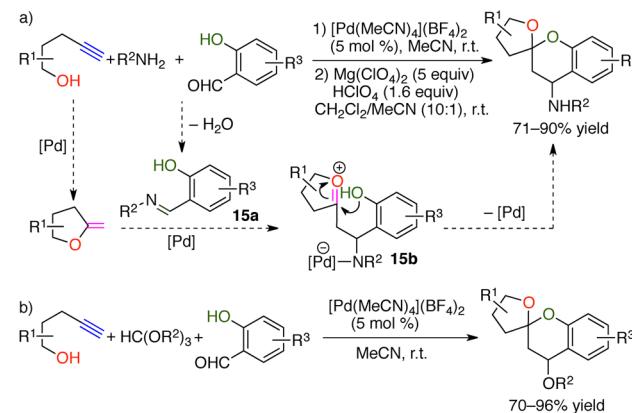
**Scheme 33.** Pt-Catalyzed Multicomponent Reaction Using Stoichiometric Amount of HBF<sub>4</sub><sup>72</sup>



to iminium salts (**14a**). Fluoride, chloride, alkoxy and alkoxycarbonyl are well tolerated. As compared with the related elimination reaction pathway, electron-rich arenes are superior in attacking the oxonium ions, followed by a rearomatization leading to the formation of spiroquinolines.

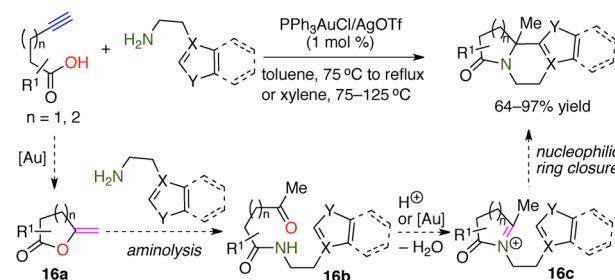
On the other hand, in the presence of a Pd(II) salt, the corresponding imines can be formed from salicylaldehydes and anilines, which may react with an oxonium ion derived from an alkynol, leading to functionalized spiroacetals (Scheme 34a).<sup>73</sup> Besides aniline substrates, orthoesters can also be employed in the formation of alkoxylated products with a single diastereoisomer (Scheme 34b).

**Scheme 34.** Pd(II)-Catalyzed Synthesis of Spiroacetals<sup>73</sup>



Dixon's group demonstrated a gold(I)-catalyzed sequential reaction between alkynoic acids and amine nucleophiles (Scheme 35).<sup>74</sup> Nitrogen-containing polycycles were prepared using a AuCl(PPh<sub>3</sub>)/AgOTf mixture. Nonterminal alkynoic reactants can also be employed to yield two regiosymmetric products in this case. The authors proposed a mechanism

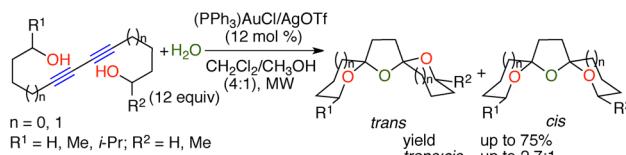
**Scheme 35.** Au(I)-Catalyzed Cascade Reaction of Alkynoic Acids with Amine Nucleophiles<sup>74</sup>



involving a hydrocarboxylation of alkynoic acids as the first step. Subsequently, a nucleophilic attack by amines may occur in the formation of keto amides **16b**, which can convert to the corresponding cyclic iminium salts with generation of water, followed by a ring closure giving polycycles. Control experiments indicate that a Lewis acid-assisted Brønsted acid catalysis may be responsible for the *N*-acyl iminium ion formation.

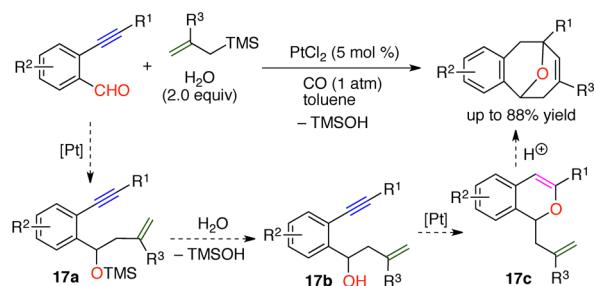
Lee and co-workers described a gold-catalyzed hydroalkoxylation/hydration procedure.<sup>75</sup> The conversion of diyne-diols into tricyclic bis(spiroketal)s was achieved in aqueous media (Scheme 36). In the presence of water and CO, the

**Scheme 36. Gold(I)-Catalyzed Hydroalkoxylation/Hydration Reaction<sup>75</sup>**



reaction between 2-alkynylbenzaldehydes and allylsilanes allows access to 9-oxabicyclo[3.3.1]nona-2,6-dienes (Scheme 37).<sup>76</sup> In

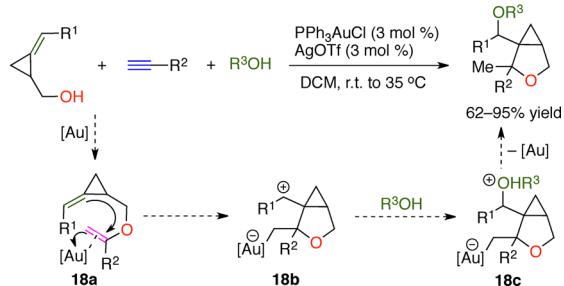
**Scheme 37. Pt(II)-Promoted Annulation of 2-Alkynylbenzaldehydes and Allylsilanes<sup>76</sup>**



this reaction, a siloxy compound (**17a**) can be formed by the addition of allylsilanes to aldehydes, and then converts to 1*H*-isochromenes through a consecutive hydrolysis and hydroalkoxylation process. Finally, a nucleophilic ring closure may take place leading to the products.

Shi's group reported an interesting three-component transformation for the synthesis of 3-oxabicyclo[3.1.0]hexanes (Scheme 38).<sup>77</sup> Functional groups, such as chloride, bromide, alkoxy, and vinyl, were tolerated by the catalytic system. The mechanism may involve an alkylgold ion (**18b**) being formed initially through a hydroalkoxylation and Prince-type ring

**Scheme 38. Synthesis of 3-Oxabicyclo[3.1.0]hexane Derivatives<sup>77</sup>**



closure, which then can be trapped with alcohols to give the final products.

The conversion of 4-bromo-3-yn-1-ols to  $\gamma$ -butyrolactones was achieved by using a AuCl<sub>3</sub> catalytic system (Scheme 39).<sup>78</sup>

**Scheme 39. Synthesis of  $\gamma$ -Butyrolactones<sup>78</sup>**



It is worth pointing out that the reaction can proceed effectively under aqueous and air conditions. A gold(III)-promoted intramolecular hydroalkoxylation may occur initially in this transformation. Then, the resulting bromo-containing enol ether **19a** can be attacked by water, followed by the elimination of HBr leading to the lactone.

Using hydroxyl-containing enyne, trioxadispiroketal, an important scaffold of azaspiracids, has been successfully prepared in a one-pot operation (Scheme 40).<sup>79</sup> A combination of AuCl and pyridinium *p*-toluenesulfonate (PPTS) facilitates this conversion. Other transition metal salts, including Ag<sub>2</sub>O, Ag<sub>2</sub>CO<sub>3</sub>, Pd(OAc)<sub>2</sub>, PdCl<sub>2</sub>, and HgCl<sub>2</sub>, were found to be unsuitable in this case. A 6-exo-cycloisomerization is thought to occur with the formation of enol ether (**20a**), which then may undergo the processes of protonation and ring closure giving the corresponding oxonium ion (**20c**), followed by a methyl transfer leading to the final bis(spiroketal).

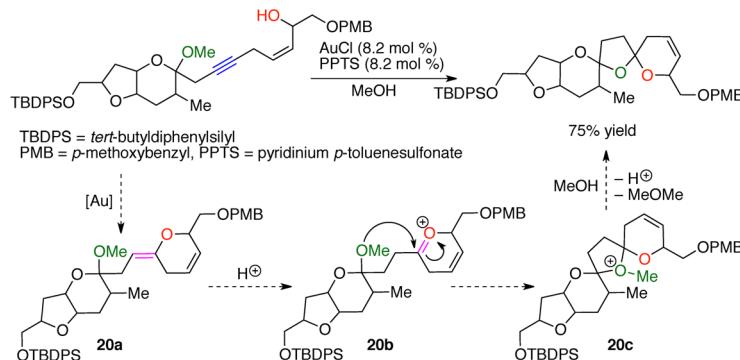
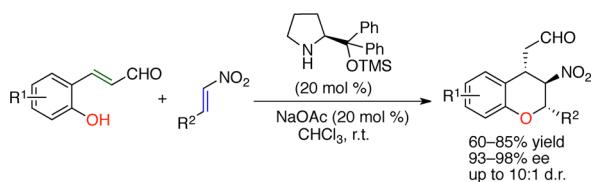
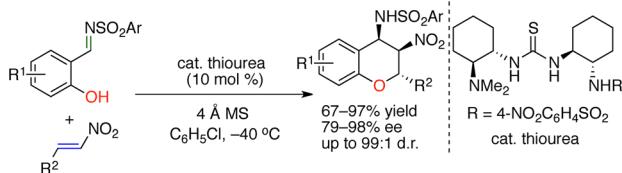
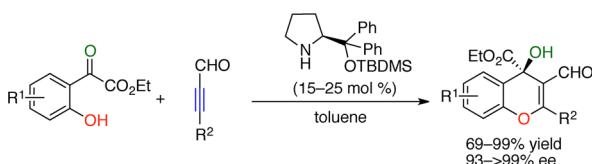
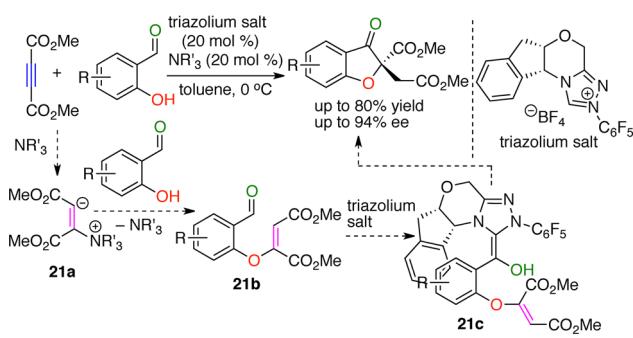
## 2.6. Involving a Michael Reaction

Wang's group reported a sequential oxa-Michael/Michael cascade in 2009.<sup>80</sup> Using a chiral diphenylprolinol TMS ether catalyst, the reaction between 2-hydroxy cinnamaldehydes and nitro-olefins furnishes enantioenriched chromans in high diastereo- and enantioselectivities (Scheme 41). Mechanistic studies indicate that an aminal intermediate is involved in the mechanism, which can arise from cinnamaldehyde by an iminium-related isomerization and cyclization. In addition to diphenylprolinol TMS ether, chiral tertiary amine-thiourea was also shown to be suitable in an analogous reaction.<sup>81</sup>

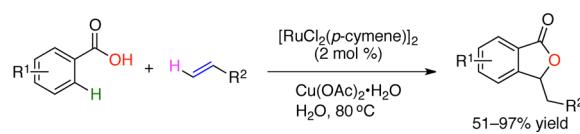
In addition, a variety of 4-amino-substituted chromanes can also be prepared by a consecutive oxa-Michael/aza-Henry reaction (Scheme 42).<sup>82</sup> High stereoselectivity was achieved using a chiral diaminocyclohexane-supported thiourea. The meta-substituents on the aromatic ring of (2-nitrovinyl)-benzenes were found to favor this reaction. Wang described an example of an oxa-Michael/aldol cascade.<sup>83</sup> Enantioenriched 4*H*-chromenes bearing a quaternary stereogenic center were obtained under mild conditions (Scheme 43).

Rovis and co-workers demonstrated an interesting cascade Michael/Stetter reaction using salicylaldehydes and alkynes.<sup>84</sup> A cooperative organocatalytic system was established to produce benzofuranones with high enantioselectivities (Scheme 44). In this case, a tertiary amine is thought to promote the Michael addition reaction, and an NHC catalyst may be responsible for the Stetter transformation. Note that a trace amount of catechol increases the selectivity of the reaction, which may be derived from a Dakin oxidation of salicylaldehyde.

The dehydrogenative cross-coupling/oxa-Michael addition cascade was investigated by Ackermann's group.<sup>85</sup> Using Cu(OAc)<sub>2</sub>·H<sub>2</sub>O as oxidant, a ruthenium complex promotes the reaction between benzoic acids and olefins giving annulated

**Scheme 40.** Synthesis of Complex Trioxadispiroketal Derivative<sup>79</sup>**Scheme 41.** oxa-Michael/Michael Reaction in Enantioselective Synthesis of Chromans<sup>80</sup>**Scheme 42.** Synthesis of 4-Aminochromanes by an oxa-Michael/aza-Henry Cascade<sup>82</sup>**Scheme 43.** Synthesis of Chiral 4*H*-Chromenes by an oxa-Michael/Aldol Reaction<sup>83</sup>**Scheme 44.** Synthesis of Benzofuranones by a Sequential Michael/Stetter Reaction<sup>84</sup>

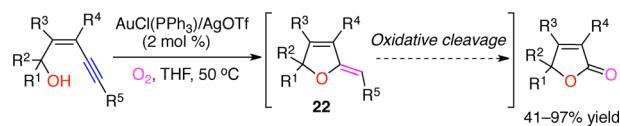
lactones (Scheme 45). Interestingly, starting from *ortho*-iodobenzyl alcohols and acetylenes, a Pd-catalyzed Michael/Heck reaction allows access to alkylidene phthalans.<sup>86</sup> Notably, various natural products, including 3-deoxyisoocochracinic acid,

**Scheme 45.** Ruthenium-Catalyzed Oxidative Alkenylation/Michael Addition Reaction<sup>85</sup>

isoocochracinic acid and isoocochracinol, have been successfully prepared by this protocol.

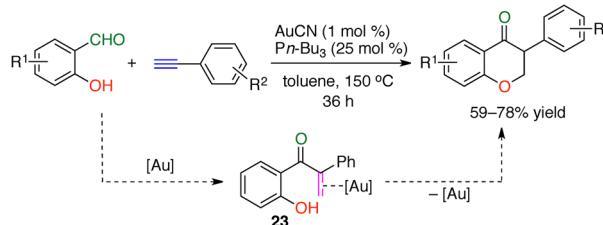
## 2.7. With Other Transformations

Liu's group reported a gold(I)-catalyzed hydroalkoxylation/oxidative cleavage reaction of (*Z*)-enyneols.<sup>87</sup> Using a mixture of (Ph<sub>3</sub>P)AuCl/AgOTf, butenolides were obtained under a dioxygen atmosphere (Scheme 46). Meanwhile, formation of

**Scheme 46.** Synthesis of Butenolides via a Hydroalkoxylation/Oxidative Cleavage Reaction<sup>87</sup>

the corresponding carboxylic acids as side products was observed in this transformation. Notably, radical scavengers, such as 4-hydroxy-TEMPO and 2,6-di-*tert*-butylcresol, shut down the reaction. This result indicates that a radical species may be involved in the catalytic cycle. Furthermore, extension of this protocol to access spirocycles was also successful.<sup>88</sup>

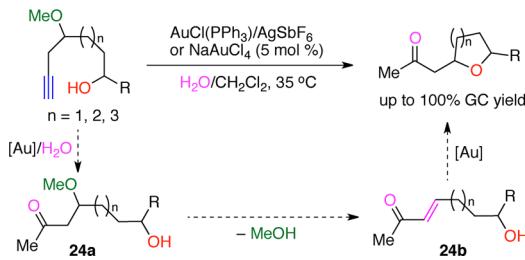
Au(I)-mediated hydroacylation/hydroalkoxylation cascade has been shown by Li's group.<sup>89</sup> The reaction between salicylaldehydes and aryl acetylenes furnishes isoflavanones in good yields (Scheme 47). A phosphane ligand of *Pn*-Bu<sub>3</sub> was found to give the best result. Other phosphanes, including PPh<sub>3</sub>, Pt-Bu<sub>3</sub>, tri-*o*-tolylphosphine and tri-2-furylphosphine do

**Scheme 47.** Au(I)-Catalyzed Annulation of Salicylaldehydes with Aromatic Alkynes<sup>89</sup>

not form the desired products. Electron-withdrawing substituents on the aromatic alkynes facilitate the transformation. However, aliphatic-substituted alkynes cannot be employed in this reaction.

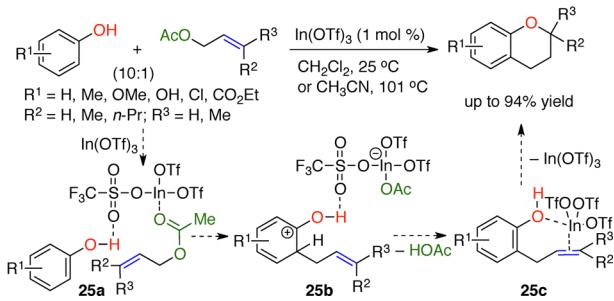
Hashmi demonstrated a cycloisomerization/hydroalkoxylation sequence using the  $\text{AuCl}_3$  salt in MeCN.<sup>90</sup> Floreancig's group found that a mixture of  $(\text{PPh}_3)\text{AuCl}$  and  $\text{AgSbF}_6$  enabled the conversion of methoxy-containing alkynols into ketone-containing tetrahydrofurans (Scheme 48).<sup>91</sup> A gold(I)-promoted hydration of alkynes is thought to proceed initially, followed by a methoxyl group elimination and cyclization leading to the final products.

**Scheme 48. Gold(I)-Catalyzed Hydration/Elimination/Cyclization Protocol<sup>91</sup>**



An interesting  $\text{In}(\text{OTf})_3$ -mediated reaction between phenols and allylic acetates provides facile access to dihydrobenzopyran skeletons (Scheme 49).<sup>92</sup> Multisubstituted allylic partners are

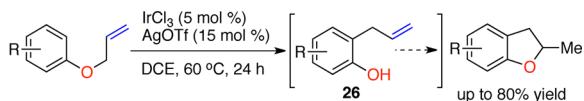
**Scheme 49. Indium(III)-Mediated Annulation of Phenols and Allylic Acetates<sup>92</sup>**



superior to unsubstituted allylic partners in this reaction. The proposed mechanism involves a Friedel–Crafts alylation at the ortho position of the phenols that proceeds smoothly, followed by the processes of rearomatization and  $\text{AcOH}$  elimination leading to 2-allyl phenols (**25c**), which then can undergo a cyclization giving the final products with regeneration of the catalytic species. In addition, using allyl aryl ethers, substituted dihydrobenzofurans can also be prepared via an Ir(III)-catalyzed Claisen rearrangement/hydroalkoxylation cascade (Scheme 50).<sup>93</sup>

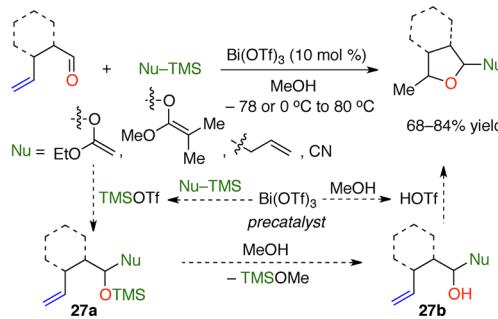
By treatment of unsaturated aldehydes with silylated partners, functionalized tetrahydrofurans can be formed in

**Scheme 50. Iridium(III)-Catalyzed Claisen Rearrangement/Hydroalkoxylation Protocol<sup>93</sup>**



methanol (Scheme 51).<sup>94</sup> In this case, a  $\text{TMSOTf}$  is thought to be the active catalytic species in the silylation step, which may

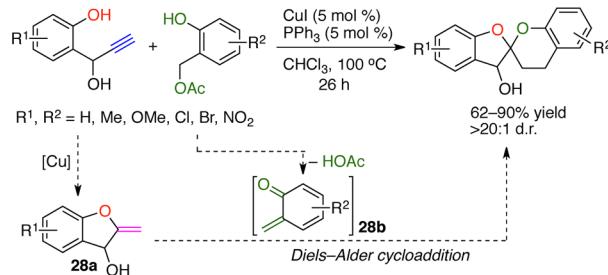
**Scheme 51.  $\text{Bi}(\text{OTf})_3$ -Mediated Multicatalytic Synthesis of Tetrahydrofurans<sup>94</sup>**



be derived from the reaction between  $\text{Bi}(\text{OTf})_3$  and silyl nucleophiles.<sup>95</sup> A triflic acid released from  $\text{Bi}(\text{OTf})_3$  is presumably responsible for the hydroalkoxylation transformation.

Using a combination of  $\text{CuI}$  and  $\text{PPh}_3$ , a hydroalkoxylation/Diels–Alder cycloaddition reaction allows the synthesis of spiroketals (Scheme 52).<sup>96</sup> 2-(1-Hydroxyprop-2-ynyl)phenols

**Scheme 52. Cu(I)-Catalyzed Hydroalkoxylation/Diels–Alder Cycloaddition Sequence<sup>96</sup>**



and *o*-methyleneacetoxymethoxyphenols are suitable reaction partners in this case. High diastereoselectivity was achieved in chloroform media. Chloride, bromide, alkoxy and nitro groups are tolerated by the catalytic system.

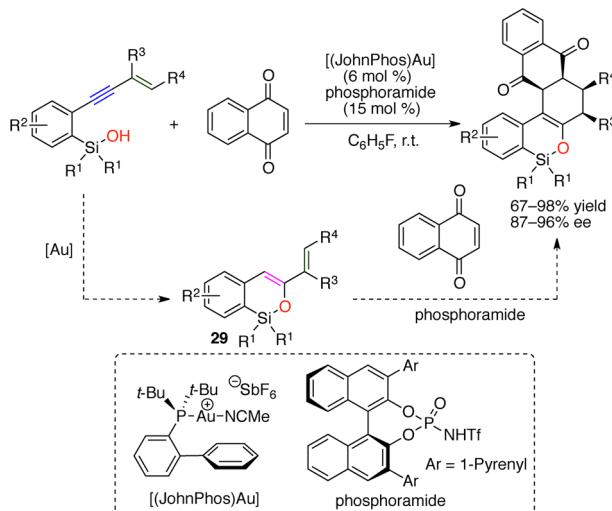
Recently, Gong's group demonstrated an interesting  $\text{Au}(\text{I})/\text{Brønsted acid}$  binary catalytic system.<sup>97</sup> Using enynyl silanols and benzoquinone, optically active fused polycycles were obtained at ambient temperature (Scheme 53). A mixture of (2-biphenyl)-di-*tert*-butylphosphine (JohnPhos)-ligated  $\text{Au}(\text{I})$  complex and chiral binaphthol (BINOL)-based phosphoramidate gives the best result in fluorobenzene. It is noteworthy that an olefin migration takes place after the Diels–Alder cycloaddition of 3-vinyl-1*H*-benzo[*c*][1,2]oxasiline and naphthoquinone, resulting in the formation of a more stable conjugated product.

### 3. THROUGH THE ADDITION OF A N–H BOND TO AN UNSATURATED C–C BOND

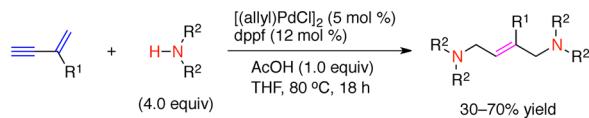
#### 3.1. Double Hydroamination

Yamamoto and co-workers reported a Pd-catalyzed double hydroamination in 1998.<sup>98</sup> In the presence of an  $[(\text{allyl})\text{PdCl}]_2$  complex, the reaction between conjugated enynes and secondary amines gives rise to allylic amines (Scheme 54). An amino allene is thought to be the active intermediate in this transformation.

**Scheme 53.** Asymmetric Synthesis of Polycycles Using a Gold(I)/Chiral Brønsted Acid Binary Catalytic System<sup>97</sup>

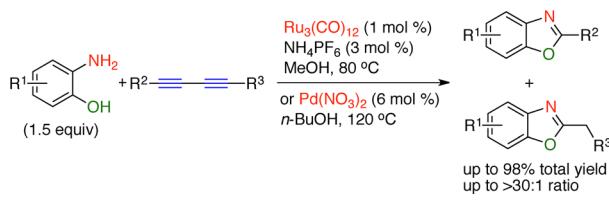


**Scheme 54.** Palladium-Catalyzed Double Hydroamination of Conjugated Enynes<sup>98</sup>



Then, the same group investigated the reaction of diarynes with *ortho*-aminophenols for the synthesis of functionalized benzoxazoles (Scheme 55).<sup>99</sup> Interestingly, a  $\text{Ru}_3(\text{CO})_{12}$

**Scheme 55.** Synthesis of Benzoxazoles from 2-Aminophenols and Diarynes<sup>99</sup>

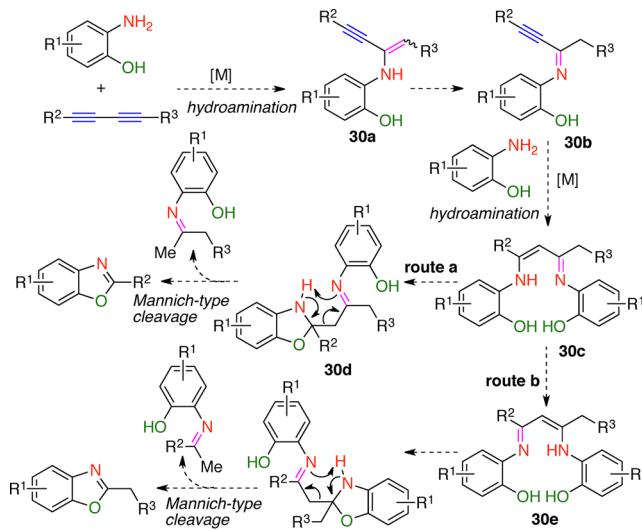


complex was found to favor the transformation of terminal diarynes, while the reaction of internal diarynes was promoted by the  $\text{Pd}(\text{NO}_3)_2$  salt. The authors proposed a mechanism involving the formation of  $\beta$ -aminoimines **30c** by the double hydroamination of diarynes, which then undergo cyclization and a Mannich-type cleavage process, leading to two distinct benzoxazole products via two possible reaction routes (Scheme 56).

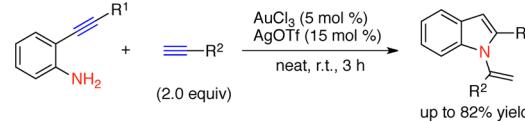
The gold(III)-catalyzed double hydroamination of 2-alkynylanilines and terminal alkynes has been investigated by Li and co-workers.<sup>100</sup> A mixture of  $\text{AuCl}_3$  and  $\text{AgOTf}$  enables the reaction proceeding smoothly with the formation of unusual *N*-alkenylindoles in good yields (Scheme 57). The authors proved that the hydroamination between indole and phenylacetylene do not take place under standard conditions. This result indicates that the intermolecular hydroamination may occur initially, followed by an intramolecular cyclization giving the final products in the transformation.

Using a Pt(II) or Au(I) complex, 2-aminobenzamides react with alkynols, giving rise to substituted tetrahydroquinazolines

**Scheme 56.** Proposed Mechanism

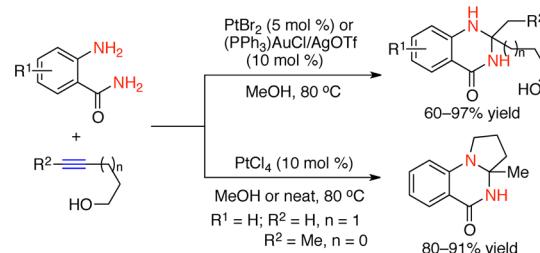


**Scheme 57.** Au(III)-Catalyzed Synthesis of *N*-Alkenylindoles<sup>100</sup>



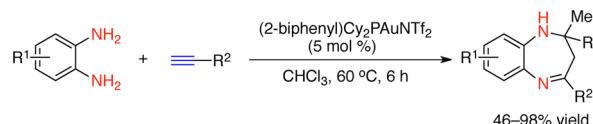
nones (Scheme 58).<sup>101</sup> Interestingly, formation of unusual tricyclic hexahydroprrolo[1,2-*a*]quinazolin-5-one products was observed when using the  $\text{PtCl}_4$  salt.

**Scheme 58.** Reaction of 2-Aminobenzamides with Alkynols<sup>101</sup>

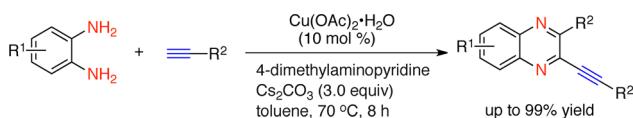


Besides the 2-aminobenzamide substrates, *o*-phenylenediamines can also be utilized to react with terminal alkynes.<sup>102</sup> Using a phosphine-ligated gold(I) complex, the formation of biologically and pharmaceutically important 1,5-benzodiazepines was achieved in chloroform (Scheme 59). In contrast, replacing the Au(I) complex with a copper(II) salt, the reaction provides facile access to unusual quinoxaline compounds (Scheme 60).<sup>103</sup>

**Scheme 59.** Gold(I)-Catalyzed Synthesis of 1,5-Benzodiazepines<sup>102</sup>

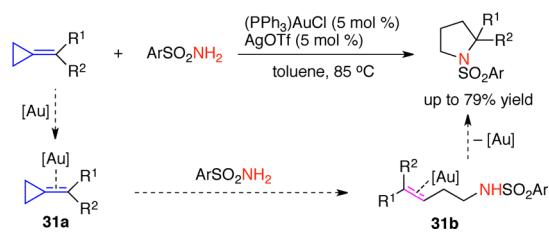


**Scheme 60. Copper(II)-Catalyzed Synthesis of Quinoxalines<sup>103</sup>**



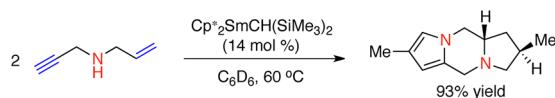
In addition, Shi's group demonstrated a gold(I)-catalyzed domino ring-opening/ring-closing hydroamination reaction.<sup>104</sup> In the presence of  $\text{AuCl}(\text{PPh}_3)$  and  $\text{AgOTf}$ , substituted pyrrolidines were prepared from methylenecyclopropanes and sulfonamides (Scheme 61).

**Scheme 61. Au(I)-Catalyzed Reaction of Methylenecyclopropanes and Sulfonamides<sup>104</sup>**



Interestingly, organolanthanide complexes were proved to be suitable precatalysts in the double hydroamination. Marks and co-workers presented an example of organolanthanide-mediated tandem cyclization of *N*-allylpropargylamine in 1998 (Scheme 62).<sup>105</sup> In this reaction, an activated lanthanide-amido

**Scheme 62. Organolanthanide-Mediated Tricyclization of *N*-allylpropargylamine<sup>105</sup>**



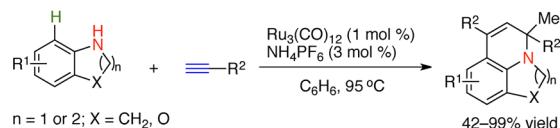
catalytic species (**32a**) is thought to be formed initially from organolanthanide and *N*-allylpropargylamine, which enables the biscyclization to occur with the formation of tricyclic N-heterocyclic compounds and regeneration of the catalyst (Scheme 63). Similarly, synthetically important nitrogen-containing heterocycles, including natural products derived from (+)-xenovenine,<sup>106</sup> tetrahydroisoquinolines,<sup>107</sup> octahy-

droindolizine,<sup>108</sup> and bicyclic[2.2.1]heptanes<sup>109</sup> can be easily prepared by this method.

### 3.2. With Hydroarylation

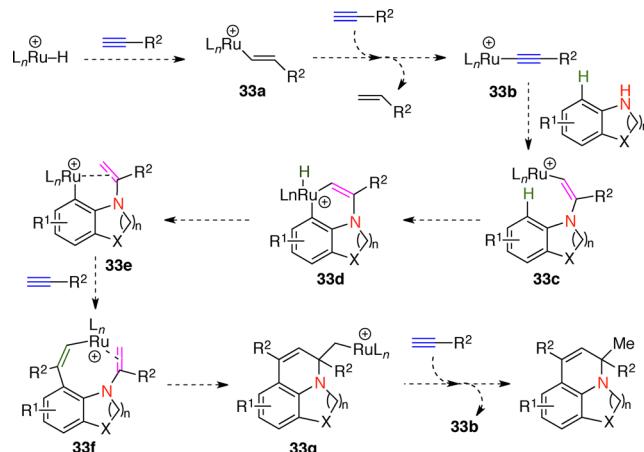
The hydroamination/hydroarylation cascade was reported by Yi's group in 2005.<sup>110</sup> Using a  $\text{Ru}_3(\text{CO})_{12}$  complex, the reaction between benzocyclic amines and alkynes provides tricyclic quinolines in good to excellent yields (Scheme 64). The

**Scheme 64. Synthesis of Tricyclic Quinoline Derivatives<sup>110</sup>**



authors proposed a mechanism involving the formation of a ruthenium acetylide initially, which then inserts into the N–H bond of amines leading to an alkynylruthenium complex **33c** (Scheme 65). Subsequently the ortho-C–H bond of arenes can

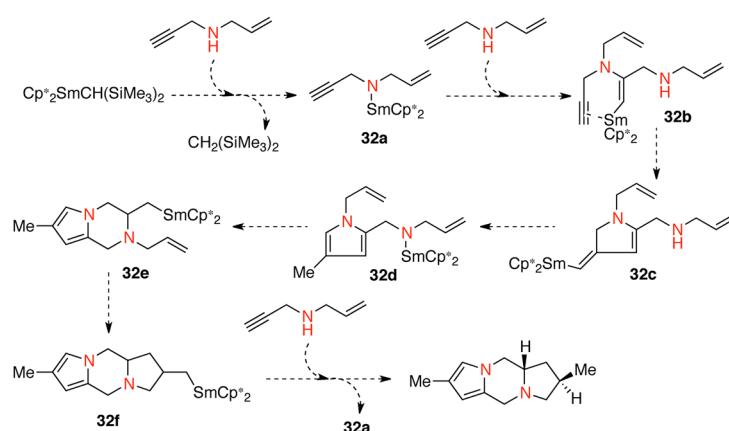
**Scheme 65. Proposed Mechanism**



be activated, followed by the consecutive processes of insertion, cyclization and demetalation, giving the corresponding tricyclic products. In addition, 1,2-dihydroquinoline derivatives can also be prepared from primary arylamines.<sup>111</sup>

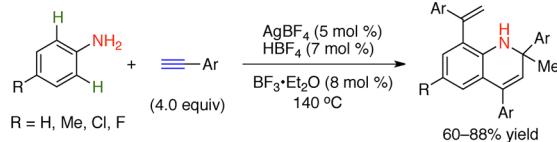
Li and co-workers showed that a mixture of  $\text{AgBF}_4$ ,  $\text{HBF}_4$ , and  $\text{BF}_3\cdot\text{Et}_2\text{O}$  enables the reaction of anilines and alkynes

**Scheme 63. Proposed Mechanism**



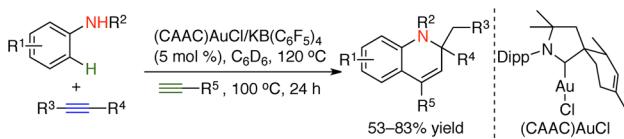
proceeding smoothly with the formation of an unusual 2-olefin-substituted dihydroquinoline (Scheme 66).<sup>112</sup> This result

**Scheme 66.** Synthesis of 1,2-Dihydroquinolines<sup>112</sup>



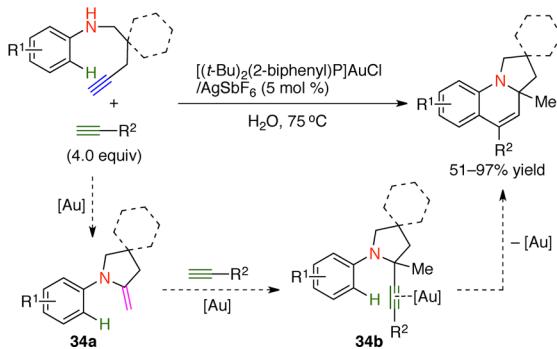
indicates that two ortho-C–H bonds of anilines are simultaneously activated by the catalytic species under harsh conditions. In addition, Che's group found that an NHC-ligated gold(I) complex displays good catalytic activity in a similar reaction.<sup>113</sup> Bertrand greatly expanded the substrate scope using secondary arylamines, as well as internal and terminal alkynes (Scheme 67).<sup>114</sup> A bulky and rigid cyclic(alkyl)-(amino)carbene (CAAC) dramatically promotes the catalytic activity of the ensuing gold(I) complex in this transformation.

**Scheme 67.** Gold(I)-Catalyzed Three-Component Reaction Using a CAAC Ligand<sup>114</sup>



Hydroamination followed by alkynylation and cyclization has been reported by Che's group.<sup>115</sup> Using a JohnPhos-ligated Au(I) complex, 1,4-aminoalkynes react smoothly with terminal alkynes giving [1,2-*a*]quinolines in water (Scheme 68). The

**Scheme 68.** Synthesis of Pyrrolo[1,2-*a*]quinolines<sup>115</sup>



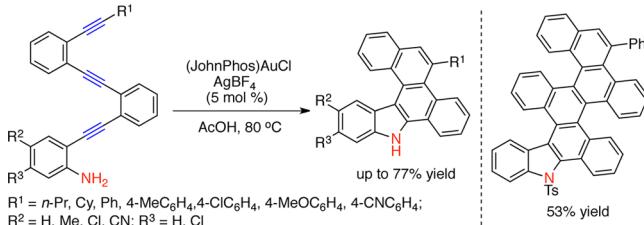
authors successfully isolated a propargylamine intermediate by decreasing the reaction temperature, which is thought to arise from a hydroamination/alkynylation transformation. Furthermore, extension of this method to the gram-scale synthesis of pyrrolo[1,2-*a*]quinolines was achieved.

Using a combination of AuBr<sub>3</sub> and AgSbF<sub>6</sub>, Liu and co-workers demonstrated an analogue for the synthesis of substituted pyrrolo[1,2-*a*]quinolin-1(2*H*)-ones.<sup>116</sup> The syntheses of fused nitrogen-containing polycycles, including pyrrolo[1,2-*a*]quinoxalines, indolo[3,2-*c*]quinolines, and indolo[1,2-*a*]quinoxalines, have been independently reported by Patil<sup>117</sup> and Liu.<sup>118</sup>

Ohno's group showed that a consecutive hydroarylation reaction proceeds smoothly after a hydroamination step.<sup>119</sup>

Using a cationic gold(I) complex, the conversion of aniline trienes to benzo[*a*]naphtho[2,1-*c*]carbazole derivatives was successful (Scheme 69). It is worth mentioning that this method can be applied in the synthesis of highly fused tetra- and pentacyclic conjugated molecules.

**Scheme 69.** Au(I)-Catalyzed Polycyclization<sup>119</sup>



### 3.3. With an Amidation or Amination Reaction

Buchwald's group showed that a copper-catalyzed amidation/hydroamidation reaction between haloenynes and *tert*-butyl carbamate gives rise to pyrroles (Scheme 70).<sup>120</sup> The use of

**Scheme 70.** Cu(I)-Catalyzed Amidation/Hydroamidation Reaction<sup>120</sup>

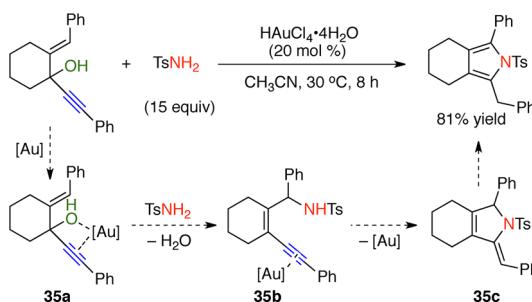


bis(*tert*-butyloxycarbonyl)hydrazine results in the formation of substituted pyrazoles. Langer demonstrated the related Pd-catalyzed version for the synthesis of benzothieno[3,2-*b*]quinolines and thieno[3,2-*b*]pyrroles.<sup>121</sup>

Treatment of 2-halophenylacetylenes with hydrazines produced 2*H*-indazoles via a Pd-catalyzed coupling/cyclization/isomerization transformation.<sup>122</sup> In addition, an alternative alkynylation/amination/hydroamination cascade provided facile access to 2-substituted indoles from 1-chloro-2-iodobenzene, phenylacetylene and amines.<sup>123</sup>

Liang's group found that the gold(I) salt HAuCl<sub>4</sub>·4H<sub>2</sub>O enables the reaction of 1-en-4-yn-3-ols and sulfonamides to proceed under mild conditions (Scheme 71).<sup>124</sup> Substituted pyrrole derivatives were obtained by mechanisms involving an amination/cyclization/isomerization pathway. Then, the groups of Liu<sup>125</sup> and Tu<sup>126</sup> demonstrated analogous catalytic protocols by treatment of enynols with amines.

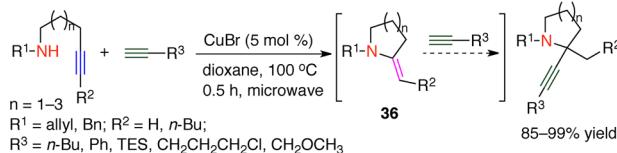
**Scheme 71.** Au(III)-Catalyzed Synthesis of Pyrrole Derivatives<sup>124</sup>



### 3.4. With Alkynylation

Xu and Hammond reported a procedure for hydroamination of secondary amines followed by an alkynylation of the resulting enamines. <sup>127</sup> Using the CuBr salt, formation of five-, six-, and seven-membered N-heterocycles was observed under microwave conditions (Scheme 72). However, highly strained three-

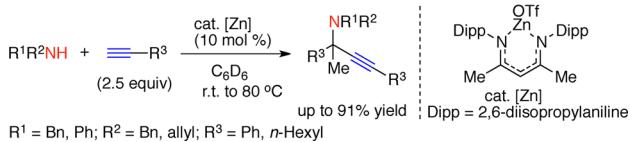
**Scheme 72. Cu(I)-Catalyzed Sequential Hydroamination/Alkynylation Reaction**<sup>127</sup>



or four-membered rings cannot be constructed by this method. It is worth mentioning that a 7-ynamine leads to an unexpected acyclic product rather than the corresponding eight-membered ring compound.

Using a copper(II) salt, the treatment of secondary amines with two different alkynes allows for the synthesis of  $\gamma,\delta$ -alkynyl- $\beta$ -amino acids.<sup>128</sup> In addition, acyclic propargylamine can also be produced from a single alkyne partner.<sup>129</sup> Notably, a zinc complex supported by a bulky  $\beta$ -diiminate ligand gives high performance in an analogous reaction (Scheme 73).<sup>130</sup>

**Scheme 73. Zinc-Promoted Reaction of Secondary Amines with Terminal Alkynes**<sup>130</sup>



A Sonogashira coupling/hydroamination cascade was demonstrated by Kundu's group in 2001.<sup>131</sup> Then, Jiang and Ma expanded the substrate scope using 2-bromobenzamides and terminal alkynes.<sup>132</sup> A combination of CuI and L-proline results in the formation of 3-methyleneisoindolin-1-ones.

Alper and co-workers successfully incorporated a carbonylation reaction into this sequence by using a Pd/Cu dual catalytic system.<sup>133</sup> Functionalized isoindolin-1-ones were obtained from a multicomponent reaction of aromatic dihalides, alkynes, carbon monoxide and amines (Scheme 74). It is worth mentioning that the formation of the Z-isomers as major products was observed in this transformation.

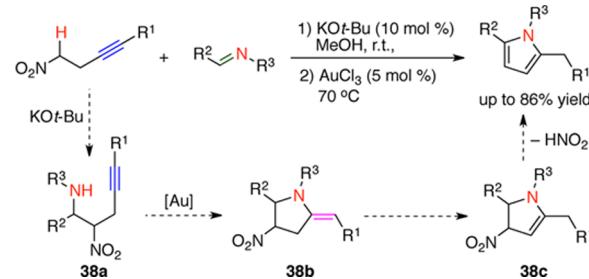
### 3.5. With a Mannich-Type Transformation

The installation of an amino fragment into the terminus of alkynes by a Mannich-type reaction can be combined with a hydroamination into a single sequence. Ohno and Fujii showed that a three-component reaction of ethynylanilines, paraformaldehyde and secondary amines leads to 2-(aminomethyl)indoles (Scheme 75).<sup>134</sup> The copper salt CuBr promotes the transformation with generation of water as a side product. In

addition, aliphatic and aromatic aldehydes can also be employed in this transformation.<sup>135</sup> Extension of this method to the synthesis of diversely functionalized N-heterocycles, including pyrroloindoless,<sup>136</sup> dipyrrrolopyridines,<sup>136</sup> indole-fused 1,4-diazepines,<sup>137</sup> 1,2,3,4-tetrahydro- $\beta$ -carbolines,<sup>138</sup> and dihydropyrazoles,<sup>139</sup> was reported by the same group.

Dixon's group described a nitro-Mannich/hydroamination cascade to produce substituted pyrroles.<sup>140</sup> In this case, the base KOt-Bu was proposed to promote the addition of nitrobut-1-ynes to imines, followed by a gold(III)-catalyzed hydroamination and isomerization yielding pyrroles through the elimination of the nitro group (Scheme 76). Fluoride, alkoxy, alkoxycarbonyl, nitro, and thienyl are well tolerated.

**Scheme 76. Synthesis of Substituted Pyrroles**<sup>140</sup>



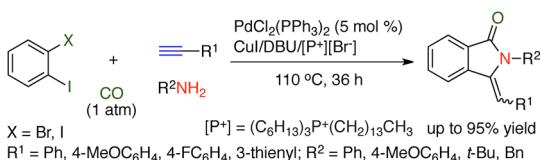
Jørgensen and co-workers demonstrated an interesting binary catalytic system using chiral thiourea–amine and an achiral gold complex.<sup>141</sup> Enantioenriched 2,3-dihydro-1*H*-pyrroles can be easily formed from propargylated malononitriles and N-Boc-protected imines.

### 3.6. Involving a Michael Addition Reaction

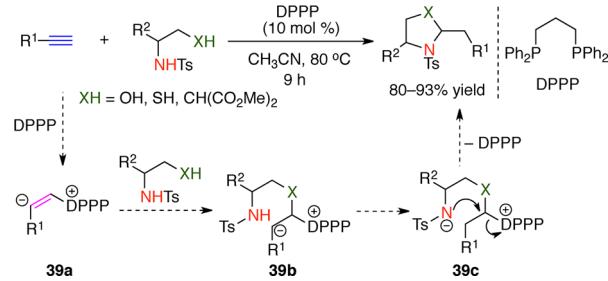
Kwon's group found that a diphenylphosphinopropane (DPPP) organocatalyst facilitates a double Michael reaction with the formation of oxazolidines, thiazolidines, and pyrrolidines (Scheme 77).<sup>142</sup> Amino-acid-derived pronucleophiles are suitable Michael donors to add across terminal alkynes. The mechanism proposes that a vinyl anion (39a) may be formed initially, followed by a consecutive proton transfer/conjugate addition/SN2 displacement process leading to the cyclic product. Using dinucleophile partners, a wide range of benzannulated N-heterocycles can be prepared by this method.<sup>143</sup> In addition to the terminal alkyne substrates, allenes can also be used to yield the related five-membered heterocycles.<sup>144</sup>

Recently, Hamada described a primary amine-mediatedaza-Michael/Michael cascade.<sup>145</sup> Synthesis of optically active  $\gamma$ -

**Scheme 74. Synthesis of 3-Methyleneisoindolin-1-ones**<sup>133</sup>

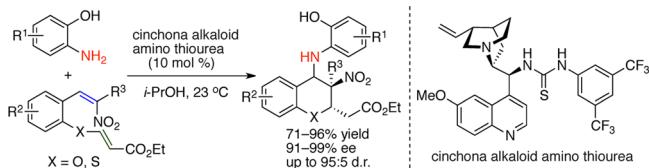


**Scheme 77. Bisphosphine-Promoted Double-Michael Addition Reaction<sup>142</sup>**



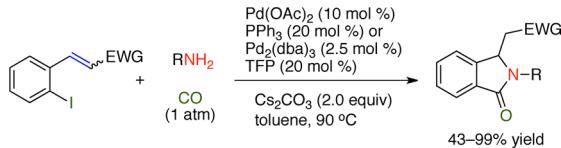
lactams bearing three contiguous stereocenters was achieved. In addition, Chen and Xiao found that a bifunctional thiourea catalyst could be employed in the same sequence.<sup>146</sup> Using anilines and nitro-olefin enoates, substituted 4-aminobenzopyrans were obtained in excellent enantio- and diastereoselectivities (Scheme 78).

**Scheme 78. Chiral Bifunctional Thiourea-Catalyzed aza-Michael/Michael Reaction<sup>146</sup>**



In 2003, Grigg and co-workers published a Pd-catalyzed three-component carbonylation/amination/Michael addition reaction.<sup>147</sup> 3-Substituted isoindolin-1-ones were generated from electron-deficient 2-iodostyrenes, carbon monoxide, and amines (Scheme 79). Then, the same group extended this

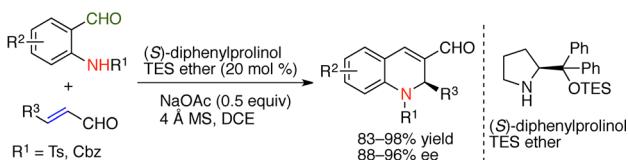
**Scheme 79. Palladium-Catalyzed Carbonylation/Amination/Michael Addition Cascade<sup>147</sup>**



method to the production of *N*-aminoisoindolones and phthalazones using hydrazines as nucleophiles.<sup>148</sup> In addition, replacement of CO by allenes resulted in the formation of six-membered cyclic products.<sup>149</sup>

Wang and co-workers showed a Michael addition/aldol/dehydration cascade between N-protected amino benzaldehydes and  $\alpha,\beta$ -unsaturated aldehydes (Scheme 80).<sup>150</sup> A chiral diphenylprolinol TES ether gives optically active 1,2-dihydroquinolines in high enantioselectivities. Using pyruvalde-

**Scheme 80. Diphenylprolinol TES Ether-Catalyzed Synthesis of 1,2-Dihydroquinolines<sup>150</sup>**

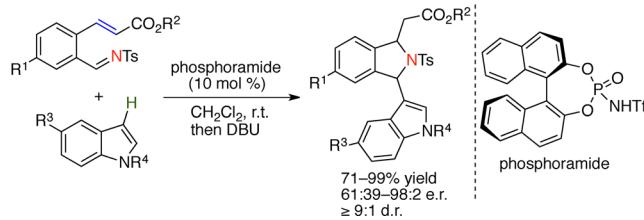


hyde 2-tosyl hydrazone as substrate, functionalized 2,3-dihydropyridazines can be prepared by a similar protocol.<sup>151</sup>

Li found that the  $\text{FeCl}_3\text{-H}_2\text{O}$  salt enables a Michael addition/cyclization reaction to proceed, resulting in the formation of 3-carbonyl-substituted quinolines.<sup>152</sup> Vicario demonstrated the aza-Michael/hemiaminal formation cascade.<sup>153</sup> Enantiopure *N*-heterocycles, including pyrazolidines, pyrazolines and pyrazolidinones, can be produced by this method. In addition, a combination of Hoveyda–Grubbs catalyst and  $\text{BF}_3\text{-OEt}_2$  provides facile access to cyclic  $\beta$ -amino carbonyl derivatives via a cross-metathesis/aza-Michael transformation.<sup>154</sup>

Enders' group described a Friedel–Crafts/aza-Michael addition sequence.<sup>155</sup> Functionalized isoindoline derivatives were produced with high selectivities (Scheme 81). In this

**Scheme 81. Brønsted Acid-Promoted Synthesis of Chiral Isoindolines<sup>155</sup>**

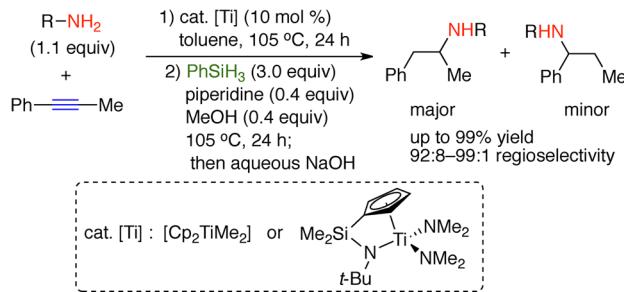


reaction, a BINOL-derived *N*-triflyl phosphoramido is proposed to promote the addition of indoles to iminoenoates, and the 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) base may be responsible for the cyclization step.

### 3.7. With Hydrosilylation

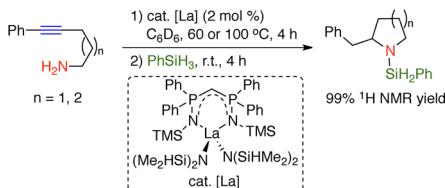
Doye's group demonstrated an interesting hydroamination/hydrosilylation sequence in 2005.<sup>156</sup> Titanium(IV) precatalysts enable the reaction between primary amines and alkynes to proceed effectively, and then the resulting imines can be treated with a mixture of phenylsilane, piperidine and MeOH, giving rise to secondary amines after an aqueous workup (Scheme 82). Anilines are superior to aliphatic amines in this

**Scheme 82. Ti(IV)-Catalyzed Hydroamination/Hydrosilylation Reaction<sup>156</sup>**



transformation, while the steric hindrance on anilines was found to strongly influence the conversion. Notably, using chiral Ti(IV) precatalysts, optically active cyclic amines can also be prepared by this method. Recently, Djukic reported an analogous synthetic protocol using a tricarbonylchromium-bound iridacycle.<sup>157</sup>

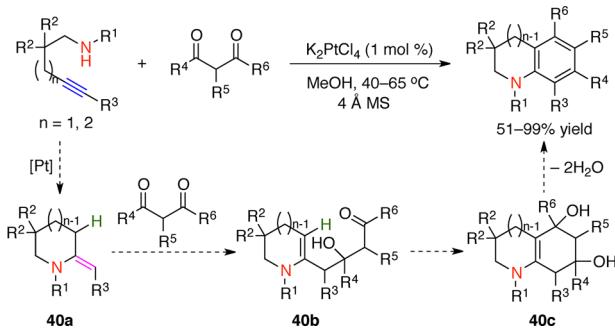
Without the hydrolysis process, formation of silylamides was observed using a bis(phosphinimino)methanide lanthanum amide (Scheme 83).<sup>158</sup> In addition, the related yttrium complex also display high catalytic activity in this transformation.<sup>159</sup>

**Scheme 83. Synthesis of Silylamides from Aminoalkynes<sup>158</sup>**

Messerle demonstrated that a cationic iridium(I) complex allows access to *N*-triethylsilylpyrrolidine as major product.<sup>160</sup>

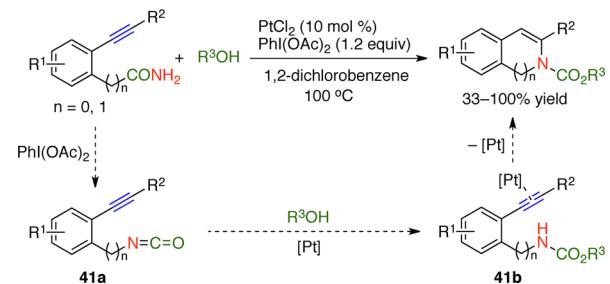
### 3.8. With Other Transformations

An interesting tandem strategy to access to substituted indolines and tetrahydroquinolines was established by Che's group.<sup>161</sup> Using the K<sub>2</sub>PtCl<sub>4</sub> salt, aminoalkynes react smoothly with 1,3-diketones giving the corresponding heterocycles with high regioselectivities (Scheme 84). A sequential hydro-

**Scheme 84. Synthesis of Substituted Indolines or Tetrahydroquinolines<sup>161</sup>**

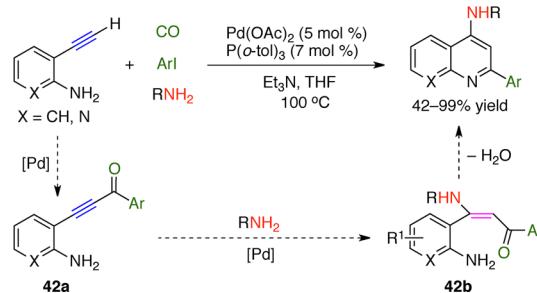
amination/nucleophilic addition/cyclization/elimination transformation may be involved in the reaction pathway. Notably, mechanistic studies indicate that the platinum salt is responsible for the enamine formation rather than the last cyclization step.

By treatment of 2-alkynylbenzamides with PhI(OAc)<sub>2</sub>, the related isocyanates 41a can be formed via a Hofmann-type rearrangement, which may be attacked by nucleophilic alcohols, followed by a cyclization leading to indoles or isoquinolines (Scheme 85).<sup>162</sup> Extension of this method to the formation of

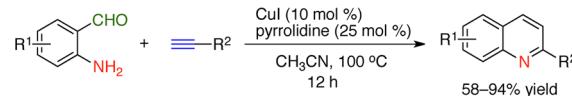
**Scheme 85. Synthesis of Indoles or Isoquinolines<sup>162</sup>**

macrocyclic bis(indole) and bis(yne carbamate) was also successful. Saito and Hanzawa demonstrated a Ru-catalyzed amino-Claisen rearrangement/hydroamination cascade.<sup>163</sup> Using a combination of a rhodium complex and a phosphane ligand, *N*-propargylanilines can be converted to substituted indoles in hexafluoroisopropyl alcohol.

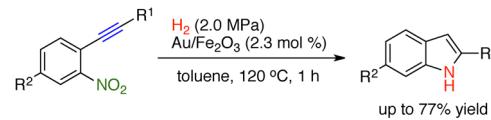
An interesting multicomponent reaction of 2-ethynylanilines, carbon monoxide, aryl iodides and amines furnishes 2-aryl-4-aminoquinolines with high chemoselectivities (Scheme 86).<sup>164</sup>

**Scheme 86. Synthesis of 2-Aryl-4-aminoquinolines<sup>164</sup>**

A Pd(OAc)<sub>2</sub>/tri(*o*-tolyl)phosphine mixture displays good catalytic activity in the transformation. A domino carbonylative coupling/cyclization/dehydration process is thought to be involved in the reaction pathway. In the presence of CuI and pyrrolidine, 2-substituted quinolines can be obtained from 2-aminobenzaldehydes and alkynes (Scheme 87).<sup>165</sup>

**Scheme 87. Synthesis of 2-Substituted Quinolines<sup>165</sup>**

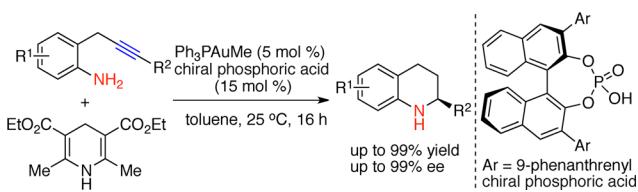
The hydrogenation/hydroamination sequence was reported by Corma and co-workers in 2009.<sup>166</sup> In the presence of a Au/TiO<sub>2</sub> catalyst, nitroaromatics were reacted smoothly with terminal alkynes, leading to substituted imines under H<sub>2</sub> pressure. Replacing alkynes with  $\alpha,\beta$ -unsaturated ketones, formation of secondary amines was observed by a hydrogenation/Michael addition reaction pathway. In addition, gold nanoparticles supported on Fe<sub>2</sub>O<sub>3</sub> also display high catalytic activity in an analogous transformation.<sup>167</sup> Substituted indoles were prepared from (2-nitroaryl)alkynes (Scheme 88).

**Scheme 88. Au/Fe<sub>2</sub>O<sub>3</sub>-Catalyzed Hydrogenation/Hydroamination Reaction<sup>167</sup>**

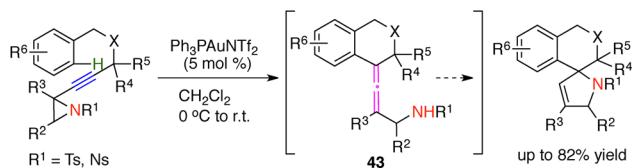
Gong's group developed a hydroamination/asymmetric hydrogenation cascade using an achiral gold complex/chiral Brønsted acid binary catalytic system.<sup>168</sup> The reaction between 2-(2-propynyl)anilines with Hantzsch ester gives rise to enantioenriched tetrahydroquinolines (Scheme 89). The use of aldehydes and enamides as reactants provides facile access to structurally complicated tricyclic N-heterocycles with high enantioselectivities.<sup>169</sup> Extending this method to the formation of optically active secondary amines was achieved.<sup>170</sup> In addition, analogous binary catalysis has also been reported by Patil's group.<sup>171</sup> 2,3-Disubstituted indoles were obtained via a hydrohydrazination/Fischer indolization reaction pathway.

Au(I)-catalyzed Friedel–Crafts-type cyclization/hydroamination produces 1-azaspiro[4.5]decanes (Scheme 90).<sup>172</sup> This

**Scheme 89.** Achiral Gold Complex/Chiral Brønsted Acid Binary Catalysis<sup>168</sup>

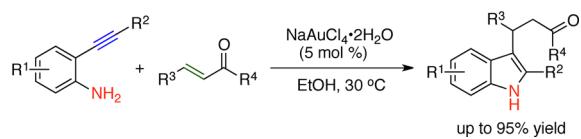


**Scheme 90.** Au(I)-Catalyzed Friedel–Crafts Type Cyclization/Hydroamination Reaction<sup>172</sup>



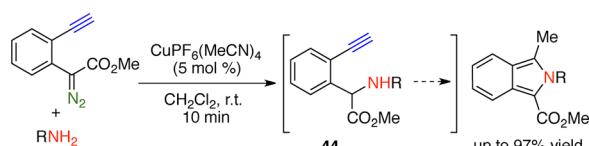
reaction presumably takes place by the formation of an aminoallene intermediate **43** via an anti- $S_N2'$ -type cyclic pathway. Using 2-alkynylanilines and  $\alpha,\beta$ -enones, a gold(III) salt enables a cyclization/conjugated addition reaction to proceed effectively with the formation of substituted indoles (Scheme 91).<sup>173</sup> Interestingly, starting from 2-ethynylphenyl-

**Scheme 91.** Synthesis of C3-Alkyl-Substituted Indoles<sup>173</sup>



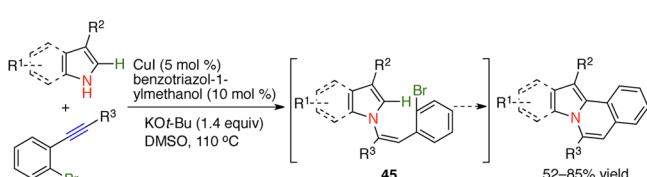
diazoacetates and amines, isoindoles can be easily formed via a copper–carbene-mediated N–H insertion and cyclization process (Scheme 92).<sup>174</sup>

**Scheme 92.** Cu(I)-Catalyzed N–H Insertion/Cyclization Reaction<sup>174</sup>



Verma and Larock reported a copper(I)-promoted hydroamination/coupling reaction for the formation of synthetically important indolo- and pyrrolo[2,1-*a*]isoquinolines (Scheme 93).<sup>175</sup> Using a benzotriazol-1-ylmethanol ligand, CuI gives higher performance than CuCl, CuBr, Cu<sub>2</sub>O, and Cu(OAc)<sub>2</sub>. Electron-donating substituents on the C5 position of the indole

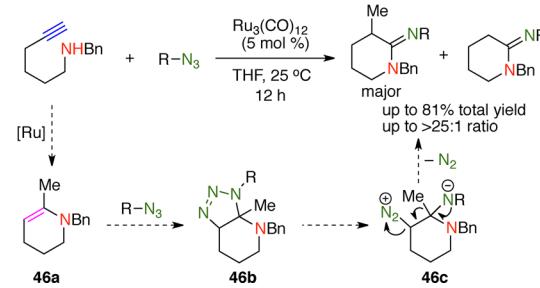
**Scheme 93.** Synthesis of Indolo- or Pyrrolo[2,1-*a*]isoquinolines<sup>175</sup>



ring favor the transformation. Alkoxy, amino, cyano, and thienyl groups are well tolerated.

Chang's group developed an interesting one-pot synthetic protocol for the synthesis of cyclic amidines.<sup>176</sup> A Ru<sub>3</sub>(CO)<sub>12</sub> complex promotes the reaction between 1,5-aminoalkynes and azides at ambient temperature (Scheme 94). Various groups,

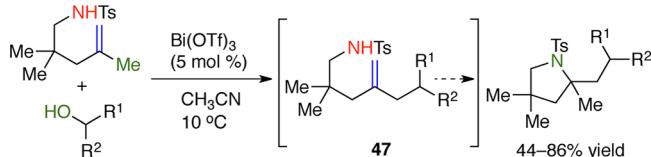
**Scheme 94.** Synthesis of Cyclic Amidines<sup>176</sup>



including sulfonyl, benzoyl, phosphoryl, and benzyloxycarbonyl, can be introduced into the scaffold of the amidines. Mechanistic studies indicate that a methyl migration may occur with the release of nitrogen, resulting in  $\alpha$ -methyl amidines as major products.

The Bi(OTf)<sub>3</sub>-mediated ene-reaction/hydroamination cascade has been achieved by Takaki and Komeyama.<sup>177</sup> Using amino-olefins and enophiles, five-membered N-heterocycles can be prepared in acetonitrile (Scheme 95). Diver investigated

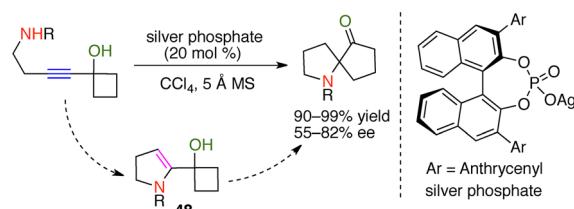
**Scheme 95.** Bi(OTf)<sub>3</sub>-Mediated Tandem Ene-Reaction/Hydroamination Reaction<sup>177</sup>



an enyne metathesis/cyclization one-pot procedure using Grubbs' catalyst and a Brønsted acid.<sup>178</sup> High diastereoselective formation of dehydropiperidine heterocycles was achieved from chiral propargyl amino acid.

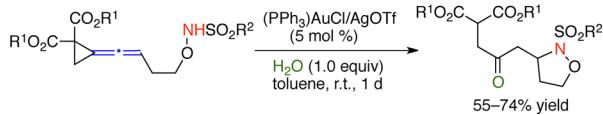
Tu's group showed that a silver phosphate allows the conversion of cyclobutanols to 1-azaspirocycles (Scheme 96).<sup>179</sup> A tandem hydroamination/semipinacol rearrangement process is thought to be involved in the mechanism. Notably, extending this method to the total synthesis of (–)-cephalotaxine was successful. Shi reported a Lewis acid-catalyzed domino hydroamination/ring-opening reaction.<sup>180</sup> Using a Yb(OTf)<sub>3</sub> or Au(I) complex, five-membered N,O-heterocycles

**Scheme 96.** Synthesis of 1-Azaspirocycles from Cyclobutanols<sup>179</sup>



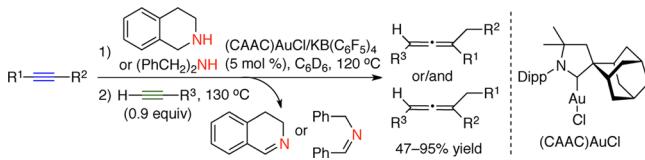
bearing an alkynyl or carbonyl scaffold can be easily formed (Scheme 97).

**Scheme 97. Au(I)-Catalyzed Domino Hydroamination/Ring-Opening Reaction<sup>180</sup>**



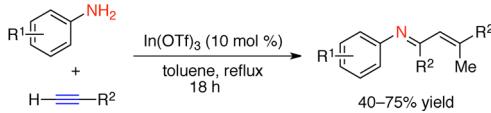
Bertrand's group reported an interesting gold(I)-catalyzed homo- and cross-coupling of alkynes for the construction of multisubstituted allenes.<sup>181</sup> In this case, a secondary amine such as tetrahydroisoquinoline or dibenzylamine serves as a hydrogen donor with generation of the corresponding imine as a side product (Scheme 98). Unsurprisingly, formation of

**Scheme 98. Cross-Coupling of Two Distinct Alkynes in the Synthesis of Allenes<sup>181</sup>**



two regioisomeric allenes was observed when using unsymmetric internal alkynes. Starting from anilines and terminal alkynes, the  $\text{In}(\text{OTf})_3$  salt enables rapid access to conjugated ketamines by mechanisms involving a hydroamination/hydroalkylation reaction pathway (Scheme 99).<sup>182</sup>

**Scheme 99. Indium-Catalyzed Hydroamination/Hydroalkylation Reaction<sup>182</sup>**

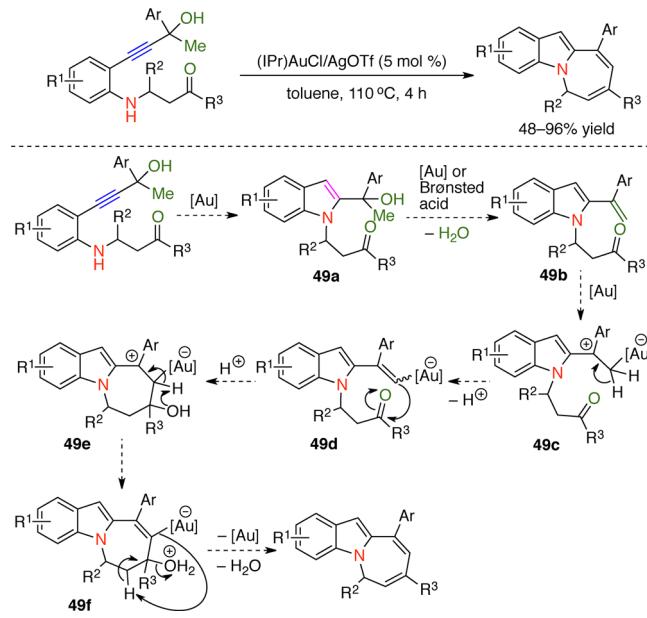


Recently, Bandini found that an NHC-ligated gold(I)/AgOTf mixture promotes the conversion of 2-alkynylanilines to seven-membered azepino[1,2-*a*]indoles (Scheme 100).<sup>183</sup> This reaction is proposed to proceed via a hydroamination/dehydration/cyclization pathway. Mechanistic studies show that a nucleophilic alkynylgold species **49d** would be involved in the transformation, which can be formed by insertion of the cationic gold(I) into the electron-rich double bond of 2-vinyl indole with loss of a proton.

Looper demonstrated a concise synthetic route to form complex (+)-saxitoxin in a total of 14 steps,<sup>184</sup> in which a silver(I)-mediated hydroamination cascade reaction acts as a key step in the efficient synthesis of an important bicyclic guanidinium ion core from alkynyl bisguanidine.

Interestingly, using allylbenzene and primary or secondary amines as the starting materials, a catalytic amount of *n*-BuLi and tetramethylethylenediamine (TMEDA) promotes the reaction with the formation of pharmacologically important amphetamines by mechanisms involving an isomerization/hydroamination cascade.<sup>185</sup> In addition, the use of *n*-BuLi as the sole catalytic species enables a hydroamination/aryne cyclization to proceed effectively, leading to N-substituted indole-

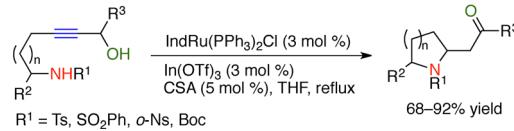
**Scheme 100. Au(I)-Promoted Hydroamination/Dehydration/Cyclization Cascade<sup>183</sup>**



lines.<sup>186</sup> Using the same base, high regio- and diastereoselective conversion of cyclohexa-2,5-dienes to bicyclic allylic amines was achieved.<sup>187</sup>

Trost's group found that tethered propargyl alcohols can be easily converted to carbonyl-substituted pyrrolidines by a redox isomerization/Michael addition reaction (Scheme 101).<sup>188</sup> A

**Scheme 101. Synthesis of Pyrrolidines from Propargyl Alcohols<sup>188</sup>**



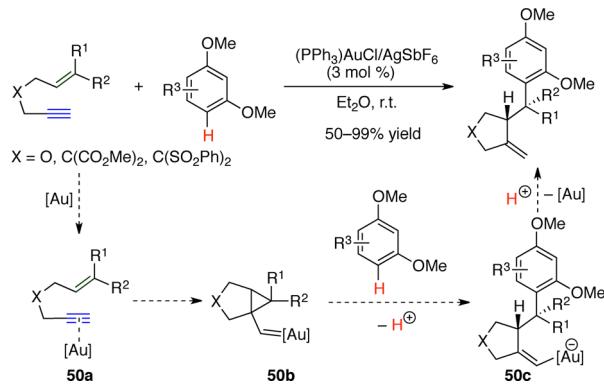
ruthenium complex, indium triflate, and camphorsulfonic acid mixture gives the best result in this transformation. A combination of  $\text{AuCl}(\text{PPh}_3)$  and  $\text{Zn}(\text{ClO}_4)_2$  results in the formation of 2-aminopyrroles from 4-yne-nitriles and amine nucleophiles.<sup>189</sup>

## 4. THROUGH THE ADDITION OF A C–H BOND TO AN UNSATURATED C–C BOND

### 4.1. Adding an $sp^2$ -C–H Bond to an Unsaturated C–C Bond

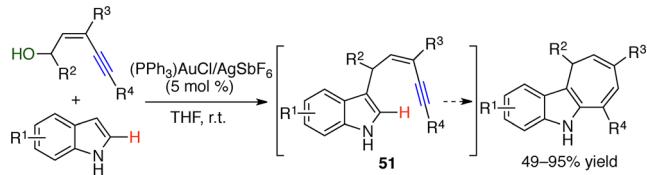
**4.1.1. With Hydroarylation.** Genêt and Michelet achieved the synthesis of carbo- and heterocycles using a gold(I)-catalyzed reaction of enynes and electron-rich arenes (Scheme 102).<sup>190</sup> It is worthwhile mentioning that the solvent strongly influences the chemoselectivity of this reaction. Diethyl ether was found to give the best result with the generation of the products as single stereoisomers. A Friedel–Crafts-type addition/carbocyclization may be involved in the reaction pathway via the formation of a carbenic gold species (**50b**). An asymmetric variant using chiral phosphanes was achieved with good enantiocontrol.<sup>191</sup> Gandon's group found that the  $\text{GaCl}_3$  salt efficiently promotes the conversion of arenynes to fused polycycles through a cycloisomerization/Friedel–Crafts cascade.<sup>192</sup>

**Scheme 102. Au(I)-Catalyzed Reaction of Enynes with Electron-Rich Arenes<sup>190</sup>**



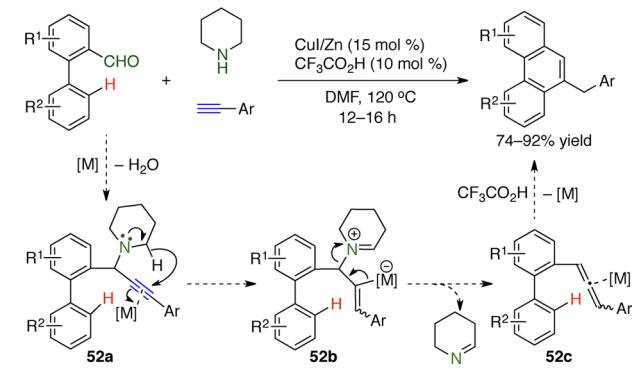
A tandem Friedel–Crafts alkylation/hydroarylation approach to form substituted indenols was reported by Chan.<sup>193</sup> The Yb(OTf)<sub>3</sub> salt enables the reaction of propargylic alcohols and phenols to proceed effectively with the generation of water as a byproduct. Liu illustrated the same sequence by treatment of (*Z*)-enynols with indoles (Scheme 103).<sup>194</sup> A phosphine-ligated gold(I) complex allows facile access to indole-fused macrocycles.

**Scheme 103. Au(I)-Catalyzed Friedel–Crafts Alkylation/Hydroarylation Reaction<sup>194</sup>**



Interestingly, using a mixture of zinc dust, CuI, and CF<sub>3</sub>CO<sub>2</sub>H, functionalized phenanthrenes can be obtained from a three-component reaction of biphenyl-2-carbaldehydes, terminal alkynes, and piperidine (Scheme 104).<sup>195</sup> The

**Scheme 104. Synthesis of Phenanthrenes by a Three-Component Reaction<sup>195</sup>**

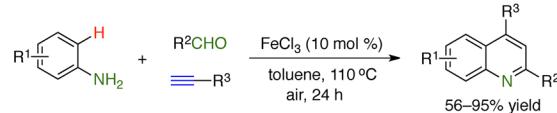


mechanism involves a sequential coupling/allene formation/carbocyclization/isomerization transformation. Other acids, such as triflic acid, trichloroacetic acid, and methanesulfonic acid, cannot be employed in this case.

Tu's group described the iron(III)-catalyzed procedure for the formation of quinoline derivatives.<sup>196</sup> The simple FeCl<sub>3</sub> salt

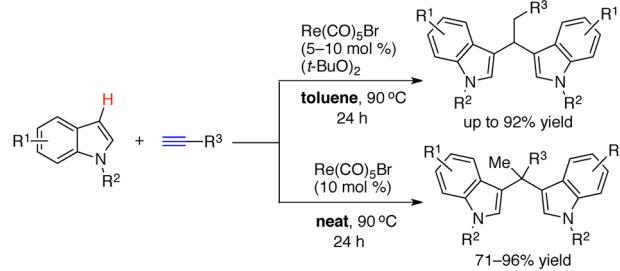
allows the reaction of aromatic primary amines, benzaldehydes and alkynes to occur under air (Scheme 105). Functional groups, including chloride, bromide, alkoxy, and thienyl, can be tolerated by the catalytic system.

**Scheme 105. Iron(III)-Catalyzed Synthesis of Quinoline Derivatives<sup>196</sup>**



Wang showed that a Re(CO)<sub>5</sub>Br complex promotes the reaction between indoles and terminal alkynes with the formation of bisindolylalkanes (Scheme 106).<sup>197</sup> It is worth

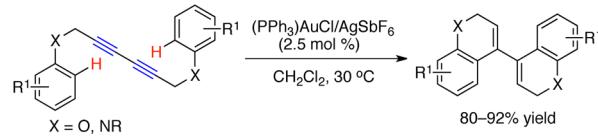
**Scheme 106. Rhodium-Catalyzed Site-Switchable Double Hydroarylation<sup>197</sup>**



mentioning that the regioselectivity of this reaction was strongly influenced by the reaction conditions. With toluene as the solvent, formation of the related anti-Markovnikov adducts as major products was observed, whereas neat conditions were found to facilitate the Markovnikov addition.

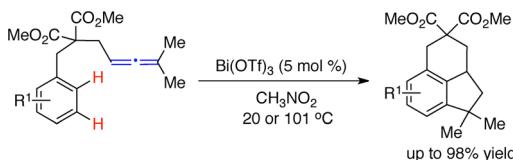
Lee used a gold(I)-catalyzed double hydroarylation of dialkynyl diethers to achieve bicyclic 2*H*-chromenes and 2*H*-quinolines (Scheme 107).<sup>198</sup> Using a gold(I)/Brønsted acid

**Scheme 107. Au(I)-Catalyzed Synthesis of Bicyclic 2*H*-Chromenes and 2*H*-Quinolines<sup>198</sup>**



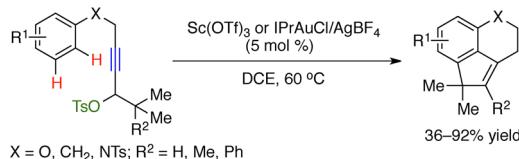
relay catalytic system, this method was successfully extended to the one-pot synthesis of fused dioxofluoranthenes. Besides the gold complex, the simple Bi(OTf)<sub>3</sub> salt also gave high performance in a bishydroarylation of aryl allenes.<sup>199</sup> Functionalized tricyclic compounds were prepared under mild conditions (Scheme 108).

**Scheme 108. Bi(OTf)3-Promoted Bishydroarylation of Aryl Allenes<sup>199</sup>**



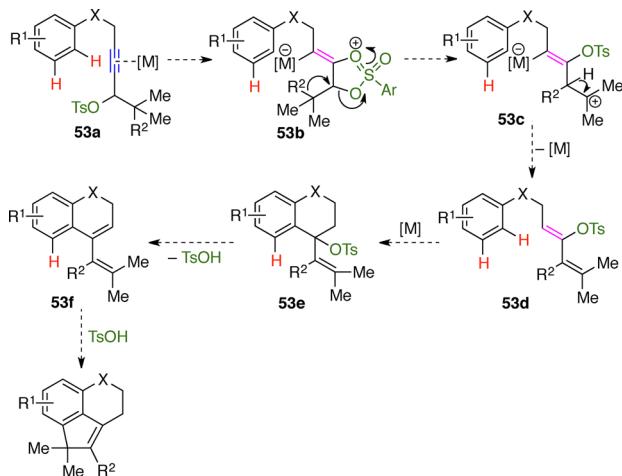
The double hydroarylation of  $\omega$ -aryl propargyl tosylates was reported by González's group.<sup>200</sup> The  $\text{Sc}(\text{OTf})_3$  salt or cationic gold(I) complex facilitates the reaction with the formation of carbo- and heteropolycyclic products (Scheme 109). Functional

**Scheme 109. Synthesis of Tricycles via Double C–H Functionalization<sup>200</sup>**



groups, including fluoride, bromide, iodide, cyano, and nitro, are well tolerated. In this transformation, a migration of the tosylate group to the triple bond may initially occur, followed by a 1,2-shift of  $\text{R}^2$  and protodemetalation leading to dienes **53d**, which then can convert to the corresponding tricycles via a consecutive nucleophilic addition/elimination/cycloisomerization process (Scheme 110). A Brønsted acid of  $\text{TsOH}$  derived from the elimination reaction is thought to promote the final cycloisomerization step.

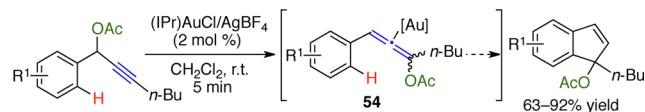
**Scheme 110. Proposed Reaction Pathway**



Nolan's group demonstrated a gold(I)-catalyzed rearrangement/hydroarylation cascade for the synthesis of indenes.<sup>201</sup> An NHC-ligated cationic gold complex of  $(\text{iPr})\text{AuCl}/\text{AgBF}_4$  [ $\text{iPr} = \text{N,N}'\text{-bis}(2,6\text{-diisopropylphenyl})\text{imidazol-2-ylidene}$ ] enables the reaction of aryl propargylic acetates to occur at room temperature (Scheme 111). In this case, an allene intermediate (**54**) may be formed by two consecutive 1,2-migrations of the acetate group. However, a direct 1,3-OAc-migration in this process cannot be ruled out.

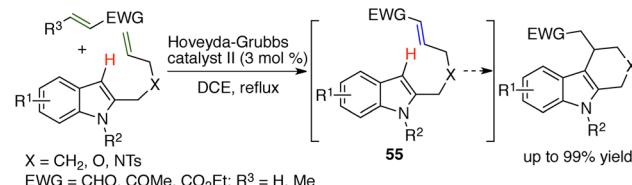
A Ru-mediated cross-metathesis (CM)/hydroarylation cascade was investigated by Xiao.<sup>202</sup> Using the Hoveyda–Grubbs second-generation catalyst,  $\omega$ -indolyl alkenes react smoothly

**Scheme 111. Synthesis of Indenes via Au(I)-Catalyzed Rearrangement/Hydroarylation<sup>201</sup>**



with electron-deficient olefins giving rise to tricyclic indoles (Scheme 112). An active ruthenium methylene complex,

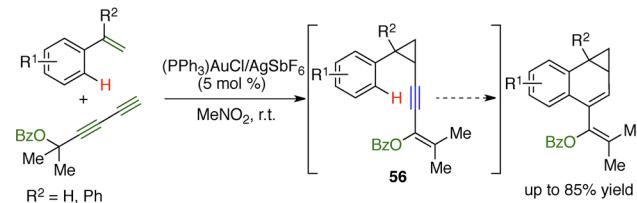
**Scheme 112. Ruthenium-Catalyzed Cross-Metathesis/Hydroarylation Reaction<sup>202</sup>**



derived from a CM reaction, may serve as a Lewis acid in promoting the final hydroarylation. An alternative asymmetric version was reported by the same group.<sup>203</sup> High enantiomeric excess (84–91% ee) was achieved.

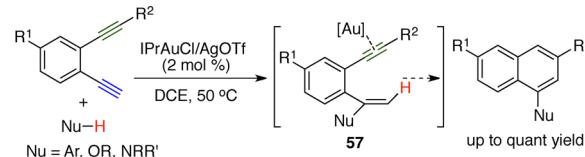
Toste's group reported a gold(I)-catalyzed cyclopropanation/hydroarylation cascade.<sup>204</sup> Using a mixture of  $\text{AuCl}(\text{PPh}_3)$  and  $\text{AgSbF}_6$ , the annulation between diynyl esters and styrenes furnishes benzonorcaradienes under mild conditions (Scheme 113). Other Lewis acids, including  $\text{AuCl}$ ,  $\text{AuCl}_3$ , and  $\text{PtCl}_2$ , only give the corresponding alkynyl cyclopropanes.

**Scheme 113. Au(I)-Promoted Cyclopropanation/Hydroarylation Reaction<sup>204</sup>**



Hashmi and co-workers achieved the synthesis of functionalized naphthalenes by a gold(I)-promoted hydroarylation/aromatization transformation.<sup>205</sup> For insight into the mechanism, the authors successfully prepared and characterized the first gem-diaurated aryl gold complex by treatment of gold acetylides with  $(\text{iPr})\text{AuNTf}_2$  in benzene. Fujii and Ohno demonstrated an analogous catalytic system.<sup>206</sup> In this case, heteroarenes, alcohols and amines can be employed as external nucleophiles to react with diynes (Scheme 114).

**Scheme 114. Gold(I)-Catalyzed Synthesis of Naphthalenes<sup>206</sup>**

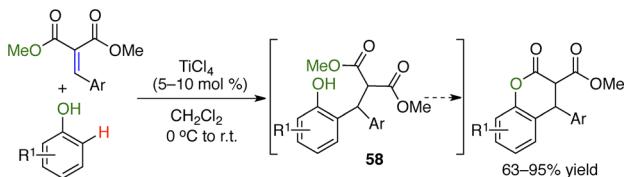


An alternative Au(I)-mediated hydroarylation/cycloisomerization cascade was described by Hashmi's group.<sup>207</sup> Starting from furans and ethynyl vinyl ketones, substituted indanones bearing a phenol scaffold can be constructed by this method, even though the yields are lower.

The treatment of benzylidene malonates with phenols provides access to dihydrocoumarins by mechanisms involving a hydroarylation/lactonization pathway (Scheme 115).<sup>208</sup>  $\text{TiCl}_4$  was found to be superior to  $\text{Cu}(\text{OTf})_2$  and  $\text{Sc}(\text{OTf})_3$  in this

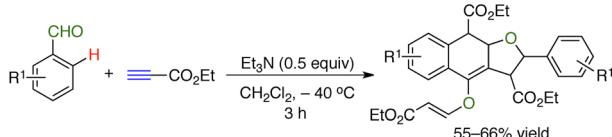
reaction. Fluoride, bromide, alkoxy, alkoxycarbonyl, and nitro groups are tolerated by the catalytic system.

**Scheme 115. Synthesis of Dihydrocoumarins via a Hydroarylation/Lactonization Pathway<sup>208</sup>**



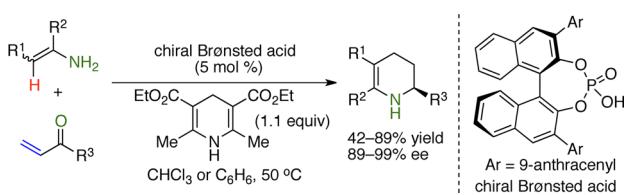
Replacement of benzylidene malonates with dienes, benzopyrans and benzofurans can be achieved using a silver-promoted hydroarylation/hydroalkoxylation cascade.<sup>209</sup> A Ru(III)-catalyzed tandem oxidation/hydroarylation procedure was reported by Darses for the synthesis of 2-alkyl aromatic ketones.<sup>210</sup> Besides transition metal complexes, triethylamine can also be used as a catalyst in efficiently promoting a reaction of aromatic aldehydes with terminal acetylenes (Scheme 116).<sup>211</sup> Fused O-heterocycles were constructed through several chemical bond formations.

**Scheme 116. Et<sub>3</sub>N-Promoted Cascade Reaction in the Synthesis of Fused Polycycles<sup>211</sup>**



**4.1.2. With a Michael Reaction.** Using a Hantzsch ester as a hydrogen donor, the reaction between enamines and  $\alpha,\beta$ -unsaturated ketones allows the synthesis of substituted tetrahydropyridines (Scheme 117).<sup>212</sup> High enantioselectivity

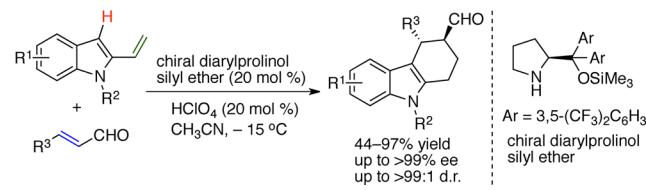
**Scheme 117. Enantioselective Synthesis of Substituted Tetrahydropyridines<sup>212</sup>**



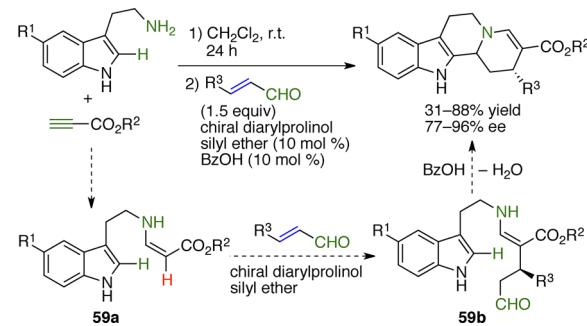
was achieved using a chiral BINOL phosphoric acid catalyst. A wide range of functional groups, including fluoride, bromide, cyano, alkoxy, alkoxycarbonyl, thienyl, and ketone, are tolerated. A mechanism involving a Michael addition/cyclization/isomerization/transfer hydrogenation pathway can be considered in this transformation.

Replacing enamines with 2-vinylindoles, enantioenriched tetrahydrocarbazoles can be easily formed through a Friedel–Crafts alkylation/Michael addition/aromatization cascade (Scheme 118).<sup>213</sup> A mixture of chiral diarylprolinol ether and perchloric acid gives high performance in this case. Using benzoic acid, tryptamines react smoothly with ethyl propionates and then  $\alpha,\beta$ -enals, leading to optically active indoloquinolizidines by mechanisms involving a Michael addition/Pictet–Spengler cyclization transformation (Scheme 119).<sup>214</sup>

**Scheme 118. Treatment of 2-Vinylindoles with  $\alpha,\beta$ -Unsaturated Aldehydes<sup>213</sup>**

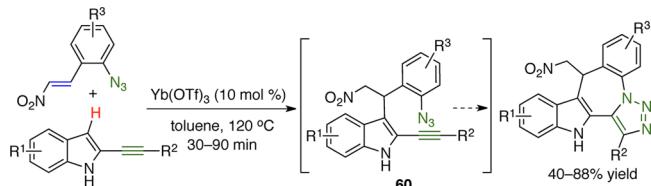


**Scheme 119. Synthesis of Enantioenriched Indoloquinolizidines<sup>214</sup>**



The Michael addition/1,3-dipolar cycloaddition sequence was reported by Kundu's group.<sup>215</sup> Starting from 2-alkynyl indoles and 1-azido-2-(2-nitrovinyl)benzenes, the Yb(OTf)<sub>3</sub> salt enables the reaction occurring smoothly with the formation of polycyclic benzazepines in good yields (Scheme 120). In

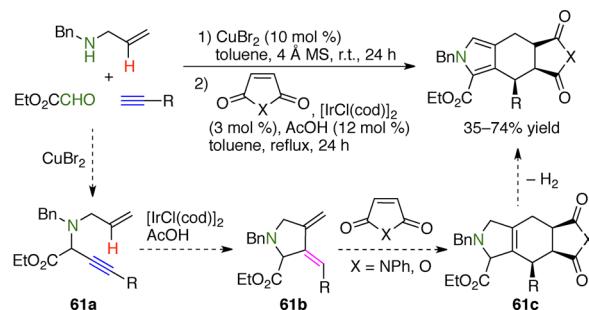
**Scheme 120. Yb(OTf)<sub>3</sub>-Catalyzed Michael Addition/Cycloaddition Reaction<sup>215</sup>**



addition, Sc(OTf)<sub>3</sub> also displays catalytic activity in this reaction. Other Lewis acids, including Zn(OTf)<sub>2</sub>, Cu(OTf)<sub>2</sub>, AgOTf, and Hg(OAc)<sub>2</sub>, fail to give the desired products.

**4.1.3. With Other Transformations.** Yamamoto and co-workers showed that a multicomponent reaction allows easy access to fused pyrrole-2-carboxylates (Scheme 121).<sup>216</sup> Using the CuBr<sub>2</sub> salt, a Mannich condensation of N-benzylallylamines, ethyl glyoxalate, and alkynes leads to 1,6-enynes 61a, which

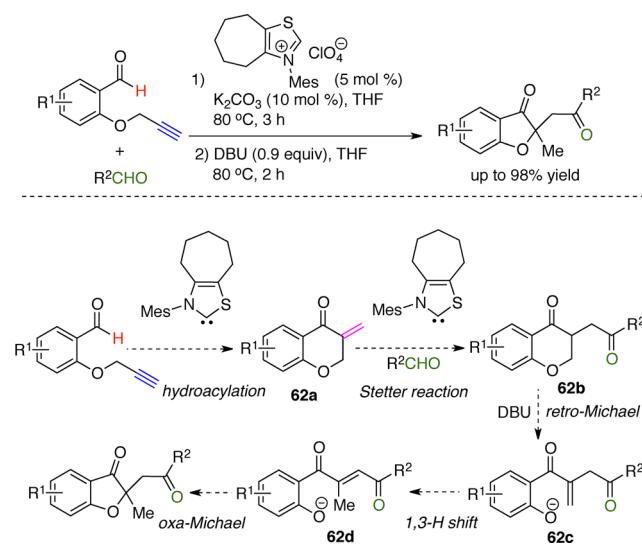
**Scheme 121. Synthesis of Polycyclic Pyrrole-2-carboxylates<sup>216</sup>**



then can convert to the corresponding dienes (**61b**) by treatment with a mixture of  $[\text{IrCl}(\text{cod})_2]$  and AcOH. Subsequently, a cycloaddition reaction may occur with the formation of the Diels–Alder adducts, followed by a dehydrogenation giving the final products. Dienophiles, including *N*-phenylmaleimide, maleic anhydride, and 1,4-naphthoquinone, can be employed in the transformation.

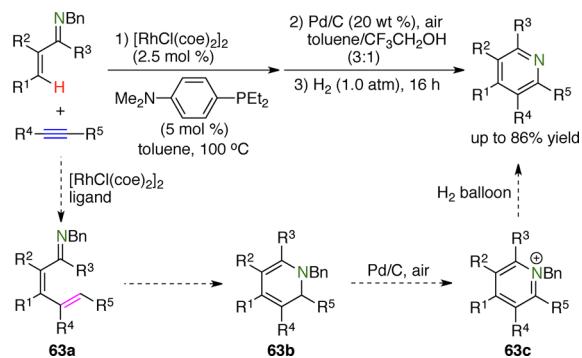
Using an NHC/Brønsted base binary catalyst, the formation of benzofuran-3-(2*H*)-ones was demonstrated by Zeitler and co-workers.<sup>217</sup> A thiazol-2-ylidene is thought to promote the hydroacylation/Stetter reaction, and the base DBU may be responsible for the consecutive retro-Michael/1,3-proton shift/oxa-Michael transformation (Scheme 122). Both aromatic and aliphatic aldehydes are suitable partners to react with salicylaldehydes.

**Scheme 122. Synthesis of Substituted Benzofuran-3-(2*H*)-ones<sup>217</sup>**



Bergman and Ellman described an interesting C–H alkenylation/cyclization/aromatization cascade.<sup>218</sup> Using  $\alpha,\beta$ -unsaturated imines and alkynes, formation of substituted pyridines was achieved via a one-pot protocol (Scheme 123). A mixture of rhodium complex and phosphane enables the C–H alkenylation and cyclization to proceed with the formation of dihydropyridines **63b**. To probe the mechanism, a C–H-activated rhodium complex was successfully synthesized and

**Scheme 123. The Construction of Pyridine Core from  $\alpha,\beta$ -Unsaturated Imines and Alkynes<sup>218</sup>**

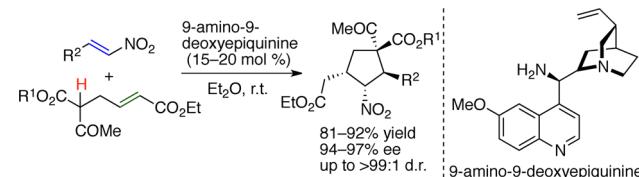


characterized by treatment of Rh with phosphane and imine. Kinetic simulations indicate that the reductive elimination would be the rate-limiting step in this transformation. In addition to  $\alpha,\beta$ -unsaturated imines, the use of ketoximes as partners in similar reactions was also reported by Ellman<sup>219</sup> and Cheng.<sup>220</sup>

## 4.2. Adding an sp<sup>3</sup>-C–H Bond to an Unsaturated C–C Bond

**4.2.1. Involving Double Michael Reaction.** sp<sup>3</sup>-C–H bonds, such as  $\alpha$ -C–H bonds of acetoacetates and nitroalkanes, can serve as Michael donors to undergo a consecutive double addition reaction leading to carbocycles. Two types of organocatalysts derived from cinchona alkaloids and prolinyl TMS ethers offer high performance in this transformation. Chen and Deng achieved a chiral primary amine-promoted double Michael reaction in 2007.<sup>221</sup> Then, Zhong's group broadened the substrate scope using nitro-olefins and acetoacetate esters (Scheme 124).<sup>222</sup> Formation of cyclo-

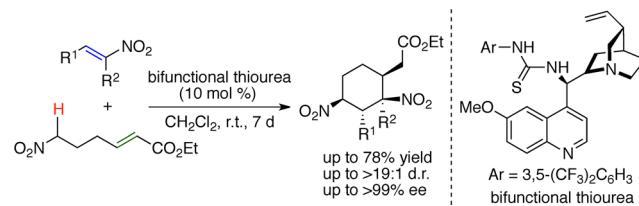
**Scheme 124. Enantioselective Synthesis of Multisubstituted Cyclopentanes<sup>222</sup>**



pentanes with high diastereo- and enantioselectivities was obtained under mild conditions. In combination with a *N*-Boc-D-phenylglycine, the same organocatalyst allows easy access to enantioenriched spirocyclohexanone-oxindoles and spirocyclohexanone-pyrazolones, through a formal [5 + 1] double Michael addition process.<sup>223</sup>

Using a chiral bifunctional thiourea catalyst, the double Michael addition between nitrohex-4-enoates and nitro-olefins furnishes optically active nitrocyclohexanes (Scheme 125).<sup>224</sup> A

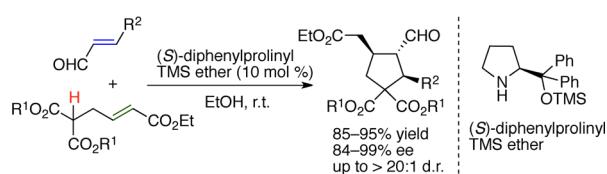
**Scheme 125. Bifunctional Thiourea-Catalyzed Synthesis of Nitrocyclohexanes<sup>224</sup>**



concerted coordination of thiourea with both nitronate and ester moieties may play a crucial role in promoting this reaction. An analogous catalytic protocol to form chiral pyranochromenes was demonstrated to have a mechanism involving a Michael/oxa-Michael/tautomerization reaction pathway.<sup>225</sup>

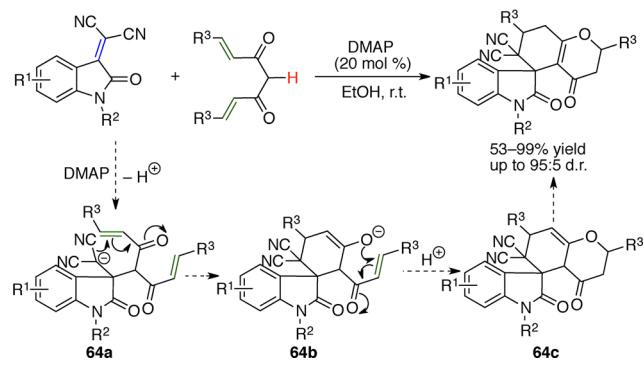
On the other hand, chiral diphenylprolinol TMS ether facilitates the formation of enantioenriched cyclopentanes (Scheme 126).<sup>226</sup> It is worth mentioning that the solvent strongly affects the conversion and selectivity of the reaction. Ethanol is superior to  $\text{CH}_2\text{Cl}_2$ , toluene, THF, and DMSO in this transformation. Extending this procedure to the formation of fused carbocycles<sup>227</sup> and cyclohexenes<sup>228</sup> was also successful.

**Scheme 126. Using Chiral Diphenylprolinol TMS Ether Organocatalyst<sup>226</sup>**



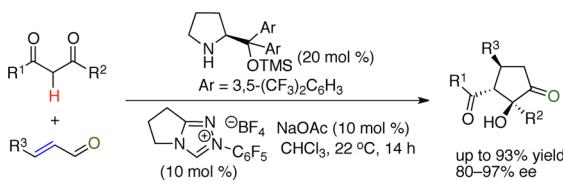
The organic-base-mediated Michael/Michael/oxa-Michael cascade was reported by Yan's group.<sup>229</sup> Starting from curcumins and isatylidene malononitriles, a catalytic amount of 4-dimethylaminopyridine (DMAP) enables the reaction proceeding smoothly with the formation of polycyclic spirooxindoles in good yields with high diastereoselectivities (Scheme 127).

**Scheme 127. DMAP-Promoted Cascade Michael/Michael/oxa-Michael Reaction<sup>229</sup>**



**4.2.2. With Michael/Cyclization Reactions.** Rovis and co-workers reported a chiral secondary amine/NHC dual catalyst system for the synthesis of chiral cyclopentanones (Scheme 128).<sup>230</sup> In this case, a diarylprolinol TMS ether is

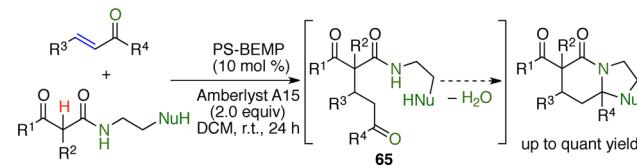
**Scheme 128. Cascade Michael Addition/Cross-Benzoin Reaction Using a Secondary Amine/NHC Dual Catalytic System<sup>230</sup>**



thought to promote the Michael addition, and an NHC derived from a triazolium salt may be responsible for the cross-benzoin cyclization. The authors showed that a synergistic effect between these two catalytic species would be involved in the mechanism. In addition to 1,3-diketones, aliphatic aldehydes,<sup>231</sup> and  $\beta$ -oxo sulfones<sup>232</sup> can also be employed as Michael donors in similar reactions.

Dixon achieved a base- and acid-promoted cascade between amide pronucleophiles and  $\alpha,\beta$ -unsaturated ketones (Scheme 129).<sup>233</sup> Fused polycyclic N-heterocycles were prepared at ambient temperature. The proposed mechanism involves a base-catalyzed Michael addition followed by an acid-promoted iminium ion formation and cyclization. Analogous basicity and acidity binary catalytic systems have been demonstrated by

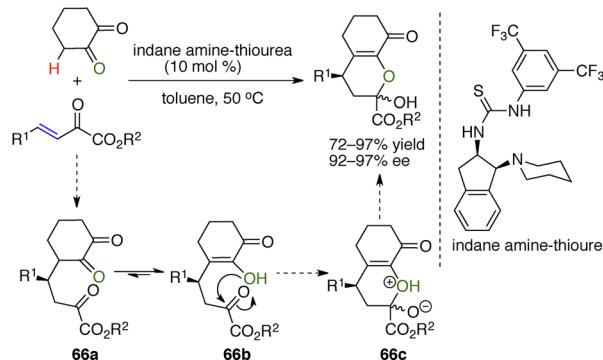
**Scheme 129. Michael Addition/Iminium Ion Formation/Cyclization Cascade<sup>233</sup>**



Franzén,<sup>234</sup> Ye,<sup>235</sup> and Rios<sup>236</sup> for the construction of quinolizidine, oxazolidine, and piperidine derivatives, respectively.

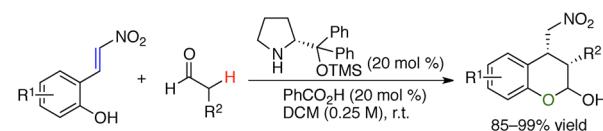
A combined Michael addition, enolation, and cyclization cascade allows for the synthesis of dihydro-2H-pyrans.<sup>237</sup> Using cyclic 1,2-diones and  $\alpha$ -keto esters, a chiral Indane-substituted thiourea results in high enantioselectivity in toluene (Scheme 130). Notably, this method is compatible with common functional groups, including fluoride, chloride, bromide, nitro, alkoxy, thienyl, and naphthyl.

**Scheme 130. Synthesis of Dihydro-2H-pyrans by a Michael/Enolation/Cyclization Protocol<sup>237</sup>**



Ramachary's group demonstrated a chiral secondary amine/benzoic acid cocatalyzed Barbas–Michael/acetalization cascade.<sup>238</sup> Substituted 3-alkyl-4-nitromethylchroman-2-ols were obtained from 2-(2-nitrovinyl)phenols and aldehydes (Scheme 131). Kim and co-workers greatly expanded the substrate scope using 2-hydroxycinnamaldehydes and nitroalkanes.<sup>239</sup>

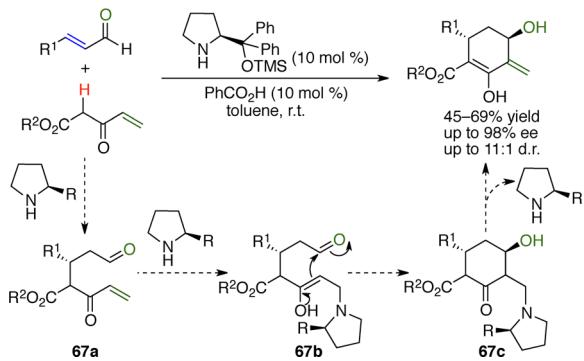
**Scheme 131. Synthesis of 3-Alkyl-4-nitromethylchroman-2-ols<sup>238</sup>**



A tandem Michael/Morita–Baylis–Hillman reaction between  $\alpha,\beta$ -unsaturated aldehydes and Nazarov reagents provides straightforward access to optically active cyclohexenones (Scheme 132).<sup>240</sup> High enantio- and diastereoselectivities were obtained using a catalytic amount of chiral diarylprolinol silyl ether and benzoic acid in toluene. With *para*-nitrobenzoic acid, this method has been successfully extended to prepare enantioenriched 3,4-dihydropyranols.<sup>241</sup>

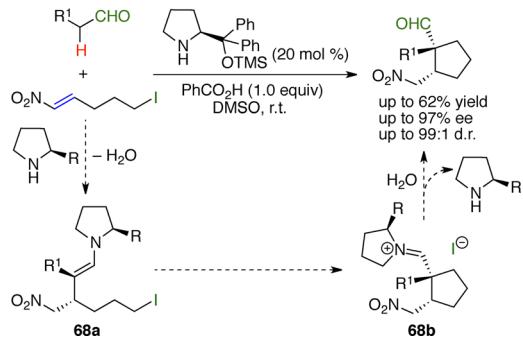
On the other hand, in the presence of a stoichiometric amount of benzoic acid, a Michael addition/ $\alpha$ -alkylation reaction proceeds smoothly with the formation of cyclo-

**Scheme 132. Synthesis of Cyclohexenones by a Michael/Morita–Baylis–Hillman Reaction<sup>240</sup>**



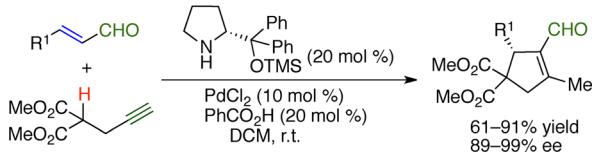
pentanes with high selectivities (Scheme 133).<sup>242</sup> Interestingly, the resulting compound can be easily functionalized through a Pinnick oxidation and reduction, leading to a novel cyclic  $\gamma$ -amino acid derivative.

**Scheme 133. Synthesis of Cyclopentanes via a Michael Addition/Alkylation Cascade<sup>242</sup>**



It is worthwhile to mention that a chiral secondary amine/PdCl<sub>2</sub>/benzoic acid multiple catalyst allows facilitate access to enantioenriched cyclopentenes (Scheme 134).<sup>243</sup> In this

**Scheme 134. Asymmetric Synthesis of Cyclopentenes<sup>243</sup>**

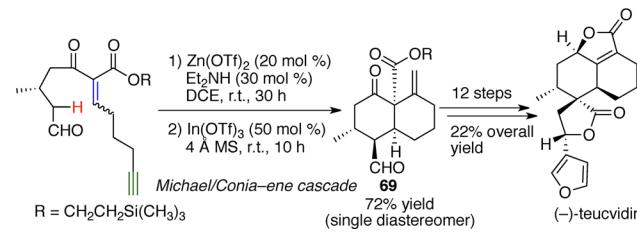


reaction, the PdCl<sub>2</sub> salt may play a crucial role as a Lewis acid to activate the triple bond of propargyl malonate. Dixon investigated the related intramolecular transformation for the synthesis of fused carbocycles.<sup>244</sup>

Importantly, using a sequential Michael/Conia–ene reaction as a key step, Lee and co-workers achieved the total synthesis of (–)-teucvidin (Scheme 135).<sup>245</sup> A *cis*-decalin framework (**69**) bearing three new stereogenic centers was constructed as a single diastereomer.

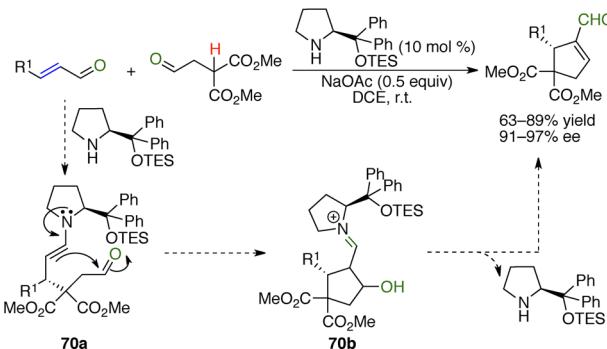
Recently Wu's group demonstrated a Michael addition/Pictet–Spengler cyclization cascade for the synthesis of optically active indoloquinolizidines.<sup>246</sup> Using  $\beta$ -keto esters,  $\alpha,\beta$ -unsaturated aldehydes, and tryptamines, a chiral secondary amine organocatalyst gives high enantioselectivity in this transformation.

**Scheme 135. Total Synthesis of (–)-Teucvidin via a Sequential Michael/Conia–ene Reaction<sup>245</sup>**



**4.2.3. With Michael/Aldol Reactions.** Using two different aldehydes in a single catalytic system, the more bulky 2-oxoethyl malonate may serve as a Michael donor to react with less sterically hindered  $\alpha,\beta$ -unsaturated ones, giving rise to cyclopentenes by mechanisms involving a Michael addition/aldol condensation cascade (Scheme 136).<sup>247</sup> Notably,

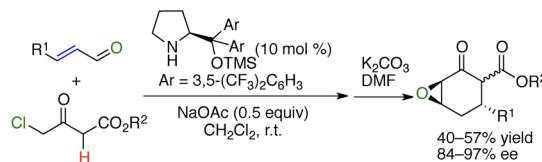
**Scheme 136. Synthesis of Cyclopentenes by a Michael/Aldol Condensation Reaction<sup>247</sup>**



extension of this method to the synthesis of optically active cyclohexenes,<sup>248</sup> cyclohexanones,<sup>249</sup> 2-hydroxy-9-oxobicyclo[3.3.1]nonanes,<sup>250</sup> and imidazole-containing bicycles<sup>251</sup> was also successful using chiral amine organocatalysts.

In addition, a  $\gamma$ -chloro- $\beta$ -keto ester Michael donor leads to epoxycyclohexanones with high enantioselectivities (Scheme 137).<sup>252</sup> NaOAc was found to be superior to KHCO<sub>3</sub> and

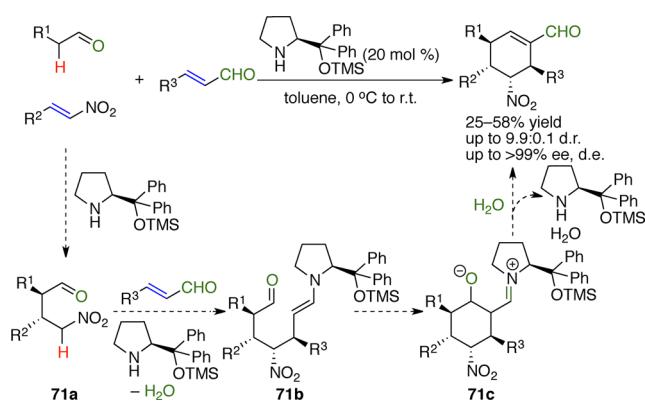
**Scheme 137. Michael/Aldol/S<sub>N</sub>2 Cyclization Cascade to Access Epoxycyclohexanones<sup>252</sup>**



K<sub>2</sub>HPO<sub>4</sub>, which is thought to promote the aldol transformation, while another inorganic base, K<sub>2</sub>CO<sub>3</sub>, may facilitate the deprotonation of the resulting alcohols, followed by an S<sub>N</sub>2-type cyclization giving the epoxy products.

Enders demonstrated an interesting double Michael addition/aldol cascade for the synthesis of enantioenriched cyclohexenes.<sup>253</sup> A chiral secondary amine was proved to be suitable catalyst with the formation of four stereogenic centers with complete enantioselectivity (Scheme 138). Jørgensen<sup>254</sup> and Rueping<sup>255</sup> broadened the substrate scope in the efficient synthesis of optically active carbocyclic aldehydes. Then, Enders and co-workers successfully introduced a Diels–Alder

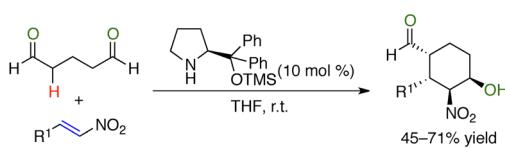
**Scheme 138. Sequential Double Michael Addition/Aldol Reaction<sup>253</sup>**



transformation into this triple-cascade sequence.<sup>256</sup> Enantioenriched tricyclic carbon scaffolds were constructed at ambient temperature.

**4.2.4. With Michael/Henry Reactions.** Hayashi's group studied the tandem Michael addition/Henry reaction for the synthesis of optically active cyclohexanes.<sup>257</sup> Notably, four consecutive stereocenters were constructed simultaneously by treatment of pentane-1,5-dial with nitroalkenes (Scheme 139). A synthetic analogue using 2-cyanocinnamic acid esters as Michael acceptors was reported by Córdova and co-workers.<sup>258</sup>

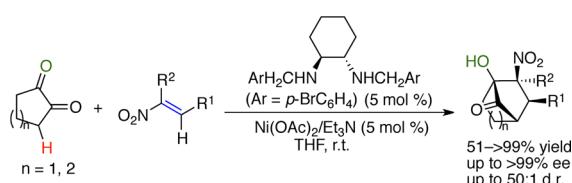
**Scheme 139. Asymmetric Synthesis of Cyclohexanes via a Michael/Henry Reaction<sup>257</sup>**



Besides chiral diarylprolinol silyl ethers, Zhong showed that cinchona alkaloid-derived 9-amino-9-deoxyepiquinines also enable this reaction to proceed effectively.<sup>259</sup> The attainment of optically active five-membered cyclopentanes was also demonstrated by the same group.<sup>260</sup> In addition, using rationally designed N-protected  $\alpha$ -cyanoglycine esters and oxindole Michael donors, enantioenriched 5-hydroxyprolines,<sup>261</sup> and spirooxindoles<sup>262</sup> can be prepared.

In comparison to organocatalysts, transition metal complexes are much less used in these reactions. In combination with Et<sub>3</sub>N and chiral diaminocyclohexane, the Ni(OAc)<sub>2</sub> salt enables the reaction occurring with the formation of enantioenriched bicyclo[3.2.1]octanes (Scheme 140).<sup>263</sup> High diastereo- and enantioselectivities were achieved under mild conditions.

**Scheme 140. Synthesis of Optically Active Bicyclo[3.2.1]octanes Using a Transition Metal Catalytic System<sup>263</sup>**



The three-component double Michael addition/Henry reaction was demonstrated by He's group.<sup>264</sup> Multiply substituted cyclohexanes were prepared from nitromethane, alkenes, and  $\alpha,\beta$ -unsaturated ketones (Scheme 141). It is worth

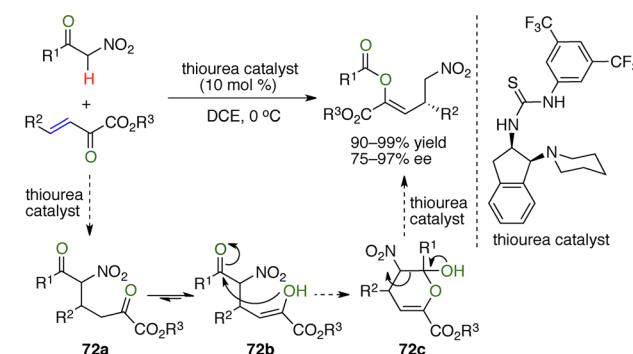
**Scheme 141. Et<sub>3</sub>N-Promoted Double Michael Addition/Henry Reaction<sup>264</sup>**



mentioning that the nucleophilic tertiary amine Et<sub>3</sub>N gives the best result. Interestingly, a combination of diphenylprolinol silyl ether and quinine thiourea offers high performance in a similar reaction.<sup>265</sup> Formation of optically active cyclohexanes with six contiguous stereocenters was observed. In addition to carbon- and heterocycles, the formation of linear nitroamides was also achieved by this strategy.<sup>266</sup>

The Michael addition/hemiketalization/retro-Henry cascade was shown by Wang and co-workers.<sup>267</sup> By treatment of  $\beta,\gamma$ -unsaturated keto esters with  $\alpha$ -nitroketones, an Indane-mediated amine-thiourea allows the formation of enantioenriched 5-nitropent-2-enotes in good yields (Scheme 142). The variation of electronic properties on keto esters does not affect the selectivity of the reaction.

**Scheme 142. Asymmetric Synthesis of 5-Nitro-pent-2-enoates<sup>267</sup>**

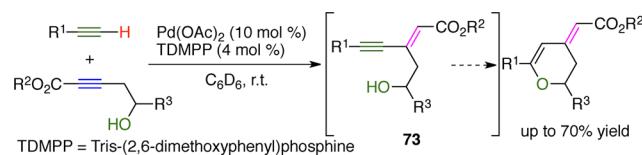


### 4.3. Adding an sp-C–H Bond to an Unsaturated C–C Bond

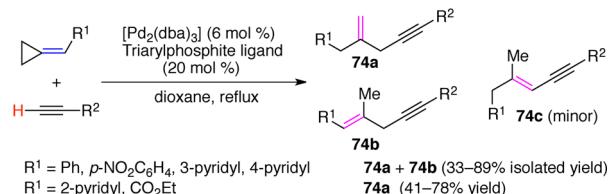
Although numerous reports are available on sequential reactions involving sp<sup>2</sup>- or sp<sup>3</sup>-C–H bond addition to unsaturated C–C bonds, related examples via an sp-C–H transformation remain rare. Trost and co-workers reported a Pd-catalyzed tandem hydroalkylation/cyclization reaction for the synthesis of furans and butenolides.<sup>268</sup> Then, the authors broadened the substrate scope using hydroxyalkynoates and terminal alkynes.<sup>269</sup> A mixture of Pd(OAc)<sub>2</sub> and phosphane ligand provides facile access to functionalized dihydropyrans at room temperature (Scheme 143). Functional groups, including chloride, alkoxy, alkoxy carbonyl, cyano, and hydroxyl, are all tolerated. Seven-membered macrocycles can also be prepared by this method.

Mascareñas' group showed that the treatment of alkylidene-cyclopropanes (ACPs) with terminal alkynes gives rise to substituted 1,4-enynes (Scheme 144).<sup>270</sup> Notably, the substituents on ACPs were found to affect strongly the regioselectivity of the reaction. Formation of a mixture of

**Scheme 143. Palladium-Catalyzed Tandem Hydroalkynylation/Cyclization Reaction<sup>269</sup>**

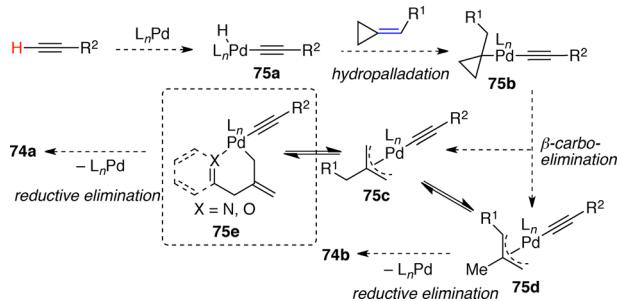


**Scheme 144. Addition of Terminal Alkynes to Alkylidenecyclopropanes<sup>270</sup>**



isomers (**74a**, **74b**, and **74c**) was observed when using aryl, 3- or 4-pyridyl-containing ACPs, while 2-pyridyl- or carboxylate-substituted reactants led to a single regioisomeric product (**74a**). This may be attributed to the directing effect of 2-pyridyl or alkoxy carbonyl (forming a stable intermediate **75e**) in the transformation (Scheme 145). The mechanism proposes

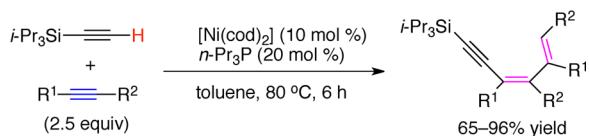
**Scheme 145. Proposed Mechanism**



that a Pd–hydride complex may be generated by insertion of a terminal alkyne into Pd(0), followed by a hydropalladation/β-carbon elimination giving two possible π-allyl-Pd-species (**75c** and **75d**), which can then undergo a reductive elimination yielding the final products.

A nickel-catalyzed cross-trimerization protocol for alkynes was investigated by Ogata and co-workers.<sup>271</sup> A combination of  $[\text{Ni}(\text{cod})_2]$  and  $n\text{-Pr}_3\text{P}$  ligand results in the formation of 1,3-diene-5-yne s from triisopropylsilylacetylene and internal alkynes (Scheme 146). It is noteworthy that three distinct alkynes, including two internal alkynes, can be employed in this reaction, leading to similar products with high chemoselectivities.<sup>272</sup> Following these accounts, an analogous synthetic procedure using two different terminal alkynes and diarylacetylenes was demonstrated by the same group.<sup>273</sup> In

**Scheme 146. Nickel-Catalyzed Cross-Trimerization in the Synthesis of 1,3-Diene-5-yne<sup>271</sup>**



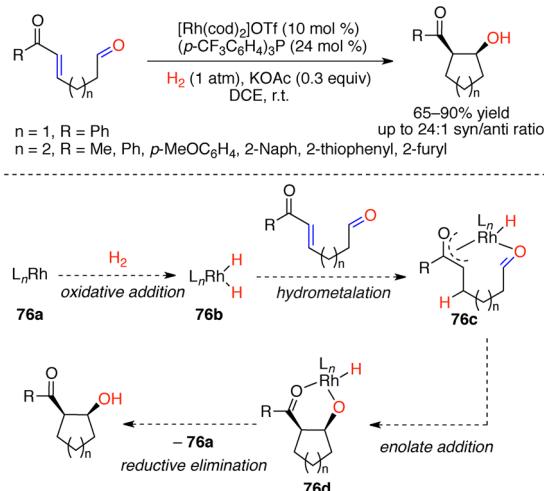
addition, the corresponding 1,5-enyne compounds can also be easily formed by replacement of one alkyne with norbornene.<sup>274</sup>

## 5. THROUGH THE ADDITION OF A H–H BOND TO AN UNSATURATED C–C BOND

### 5.1. Hydrogenative Coupling Reactions

Krische's group reported an interesting reductive aldol coupling of monoenoic monoaldehydes using elemental hydrogen as terminal reductant.<sup>275</sup> A combinative rhodium salt and phosphane allows access to five- and six-membered enolates with high diastereoselectivities (Scheme 147). Formation of the

**Scheme 147. Rh-Catalyzed Reductive Aldol Coupling Using Elemental Hydrogen as Reductant<sup>275</sup>**

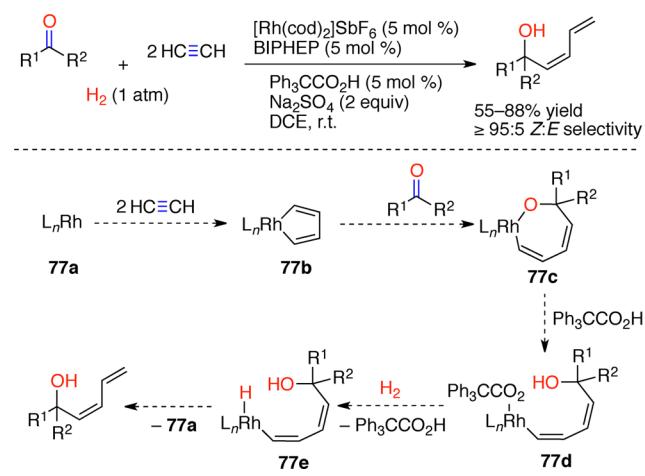


corresponding 1,4-reduction products was also observed in this reaction. The proposed mechanism involves the formation of  $\text{Rh}(\text{H})_2$  complex (**76b**) via an oxidative addition of rhodium to hydrogen, followed by alkene hydrometalation giving  $\text{Rh}(\text{H})$ -alkyl intermediates. Subsequent an enolate addition and reductive elimination may occur leading to the final products. Then, the same group investigated the intermolecular reductive coupling reactions between vinyl ketones and aldehydes.<sup>276</sup> Notably, extending the method to highly enantioselective synthesis of *syn*-aldols was achieved using chiral monodentate phosphonite ligands.<sup>277</sup>

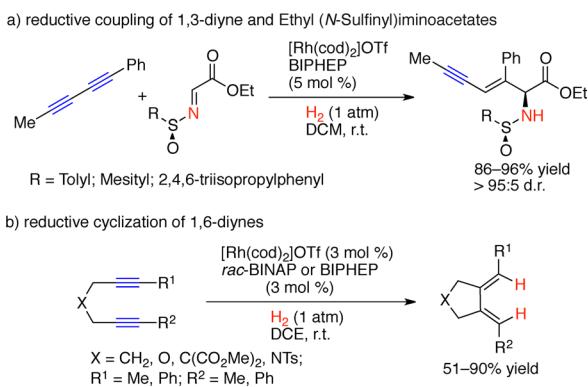
On the other hand, the use of acetylenic aldehydes in a similar reaction results in the formation of cyclic allylic alcohols with high enantioselectivities.<sup>278</sup> Interestingly, Z-butadienylation products can be formed by treatment of carbonyls with acetylene under hydrogen atmosphere (Scheme 148).<sup>279</sup> A mechanism involving the rhodacyclopentadiene (**77b**) formation can be considered, which easily undergo carbonyl insertion giving the related oxarhodacycloheptadiene **77c**. In the presence of triphenylacetic acid, the Rh–O bond cleavage may take place, followed by σ-bond metathesis and reductive elimination forming the Z-dienylation products. Additionally, 1,3-diyne<sup>280</sup> and enynes<sup>281</sup> were proved to be suitable to react with carbonyl partners.

Without triphenylacetic acid, the reaction between conjugated alkynes and electrophilic ethyl (*N*-sulfinyl)-iminoacetates furnishes unsaturated α-amino acid esters under ambient conditions (Scheme 149a).<sup>282</sup> Notably, a mixed rhodium salt and tri-2-furylphosphine enables the reductive

**Scheme 148. Cationic Rh-Catalyzed Carbonyl Z-Dienylation<sup>279</sup>**



**Scheme 149. Catalytic Hydrogenative Coupling of Diynes<sup>282,284</sup>**



coupling of 2-vinyl pyridines and imines occurring with high syn-diastereoselectivity.<sup>283</sup> Starting from 1,6-dynes, 1,2-dialkylidene cyclopentanes can be formed as single stereoisomers (Scheme 149b).<sup>284</sup> Besides rhodium catalysts, cationic iridium complexes also display high catalytic activity in hydrogenative coupling reactions.<sup>285</sup>

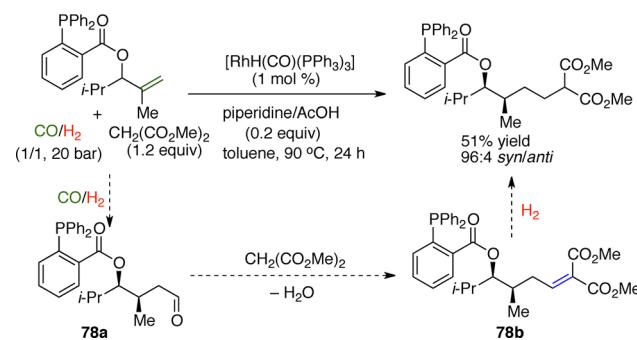
### 5.2. With a Hydroformylation Reaction

The hydroformylation/Knoevenagel/hydrogenation cascade was reported by Breit's group.<sup>286</sup> Under a CO/H<sub>2</sub> atmosphere, a mixture of rhodium complex, piperidine and AcOH allows easy access to the malonate derivative with generation of a new stereogenic center with high regio- and diastereoselectivity (Scheme 150). An alternative method using Wittig reagents leads to their analogues by mechanisms involving a hydroformylation/Wittig olefination/hydrogenation reaction pathway.<sup>287</sup> Robinson and co-workers demonstrated a Rh(I)-catalyzed sequential hydrogenation/hydroformylation/cyclization protocol.<sup>288</sup> Prochiral dienamide esters can be converted to optically active cyclic α-amino acids by this method.

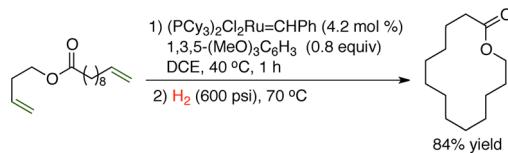
### 5.3. With an Olefin Metathesis Reaction

The olefin metathesis transformation followed by hydrogenation provides facile access to saturated cyclic compounds, including synthetically important macrocycles via a one-pot operation (Scheme 151).<sup>289</sup> A ruthenium alkylidene complex can act as a single catalytic species making the reaction to proceed effectively. It is worthwhile mentioning that this

**Scheme 150. Hydroformylation/Knoevenagel/Hydrogenation Cascade<sup>286</sup>**



**Scheme 151. Synthesis of Macrocycles via an Olefin Metathesis/Hydrogenation Sequence<sup>289</sup>**



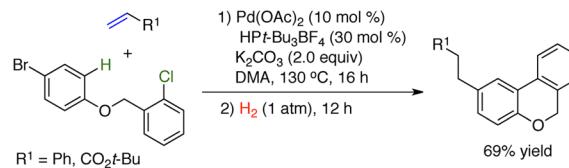
method was successfully applied in the synthesis of the natural product (*R*)-(−)-muscone. Independently, the groups of Cossy<sup>290</sup> and Piva<sup>291</sup> reported that acyclic molecules could be prepared by the same strategy.

In addition, incorporation of a cyclization reaction into this sequence was achieved by Cossy.<sup>292</sup> Cyclic lactones and lactols were obtained based on a compatible Ru/PtO<sub>2</sub> catalytic system. Fogg's group found that the third-generation Grubbs catalyst enables a tandem ring-opening metathesis polymerization (ROMP)/hydrogenation reaction to occur, leading to saturated polynorbornanes.<sup>293</sup>

### 5.4. With Other Transformations

Chuah's group described a cyclization/hydrogenation sequence using a Ni/Zr catalytic system.<sup>294</sup> High diastereoselective conversion of (±)-citronellal to menthol was achieved. Fagnou developed a Pd-catalyzed Heck/direct arylation/hydrogenation cascade protocol.<sup>295</sup> A combination of Pd(OAc)<sub>2</sub>/t-Bu<sub>3</sub>P-HBF<sub>4</sub> results in the formation of alkyl-substituted tricyclic biaryls (Scheme 152). Interestingly, Frustrated Lewis Pairs (FLPs), consisting of bisphosphines and B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub>, display good catalytic activity in a hydrosilylation/hydrogenation reaction.<sup>296</sup>

**Scheme 152. Pd-Catalyzed Sequential Heck/Direct Arylation/Hydrogenation Reaction<sup>295</sup>**



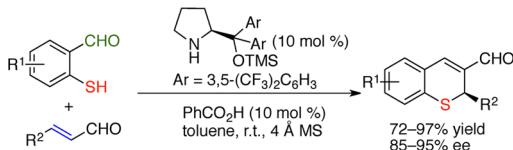
## 6. THROUGH THE ADDITION OF A S–H BOND TO AN UNSATURATED C–C BOND

### 6.1. Involving a Michael/Aldol Process

Wang developed a Michael/aldol/dehydration cascade to achieve optically active thiochromenes.<sup>297</sup> Using a mixture of (S)-pyrrolidine silyl ether and benzoic acid, nucleophilic

thiophenol aldehydes react smoothly with  $\alpha,\beta$ -unsaturated aldehyde partners (Scheme 153). Good yields with high enantioselectivities were obtained in toluene.

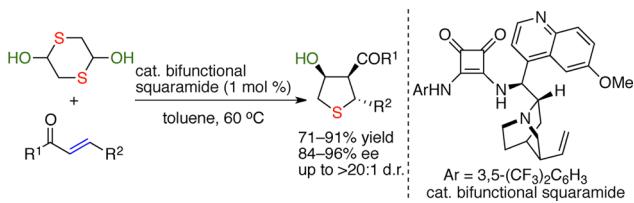
**Scheme 153. (S)-Pyrrolidine Silyl Ether-Promoted Michael/Aldol/Dehydration Reaction<sup>297</sup>**



Without benzoic acid, Jørgensen<sup>298</sup> and Wang<sup>299</sup> found that the related tandem Michael/aldol reactions could occur when using nucleophilic thiols as Michael donors. Highly enantioselective formation of substituted tetrahydrothiophenes was achieved. In addition, chiral bifunctional amine thioureas also give high performance in such reactions. Enantioenriched thiochromananes were obtained from  $\alpha,\beta$ -unsaturated oxazolidinones<sup>300</sup> and *N*-acylpyrazoles.<sup>301</sup>

On the other hand, using 1,4-dithiane-2,5-diol as sulfaf-Michael donor results in the formation of tetrahydrothiophenes (Scheme 154).<sup>302</sup> A chiral squaramide with lower loadings (1 mol %) gives high diastereo- and enantioselectivity in the reaction. Extending this method to the gram-scale synthesis was successful. Xiao's group demonstrated an analogue for the construction of optically active spirocyclic oxindoles.<sup>303</sup>

**Scheme 154. Reaction of 1,4-Dithiane-2,5-diol with Chalcones<sup>302</sup>**



mol %) gives high diastereo- and enantioselectivity in the reaction. Extending this method to the gram-scale synthesis was successful. Xiao's group demonstrated an analogue for the construction of optically active spirocyclic oxindoles.<sup>303</sup>

## 6.2. Double Michael Addition Reaction

A double Michael addition involving the S-H bond transformation was studied by Wang and co-workers.<sup>304</sup> Using a chiral amine thiourea, enantioenriched thiochromananes were obtained from nitroalkenes and 2-propenoic acid ethyl esters (Scheme 155). Mechanistic studies showed that a dynamic

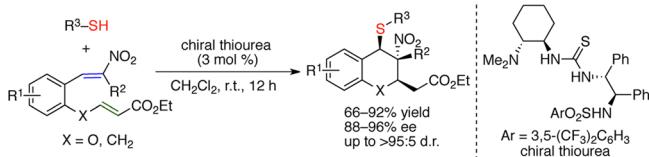
**Scheme 155. Enantioselective Synthesis of Thiochromananes<sup>304</sup>**



kinetic resolution may be involved in the second Michael addition step. A chiral cinchona alkaloid-derived alcohol also gives high performance in a similar reaction.<sup>305</sup> It is worth mentioning that, as compared with a previous report, formation of the desired products with distinct diastereoselectivity was observed. In addition, optically active five-membered tetrahydrothiophenes can also be prepared by this method.<sup>306</sup>

On the other hand, the treatment of nitro-olefin enoates with thiols allows the synthesis of polyfunctionalized chromans (Scheme 156).<sup>307</sup> The variation of substituents on arenethiols

**Scheme 156. Asymmetric Reaction of Thiols and Nitroolefin Enoates<sup>307</sup>**

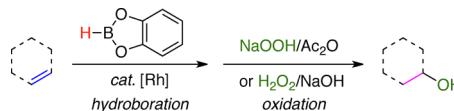


had no significant influence on the selectivity of this reaction. Interestingly, the resulting chroman can be further oxidized by a mixture of H2O2 and NaWO4·2H2O, leading to the related core structure of the gamma secretase inhibitor.

## 7. THROUGH THE ADDITION OF A B–H BOND TO AN UNSATURATED C–C BOND

Sequential transformations involving a hydroboration followed by an oxidation were reported by Evans,<sup>308</sup> Burgess,<sup>309</sup> and Hayashi<sup>310</sup> at the end of the 1980s. In these cases, rhodium(I) complexes, such as Wilkinson's catalyst Rh(PPh3)3Cl, [RhCl-(cod)]2, and [Rh(cod)]2BF4 were employed to promote the reactions of olefins and catecholborane, resulting in the formation of functionalized alcohols (Scheme 157).

**Scheme 157. Synthesis of Alcohols by Rh-Promoted Hydroboration/Oxidation Reactions**

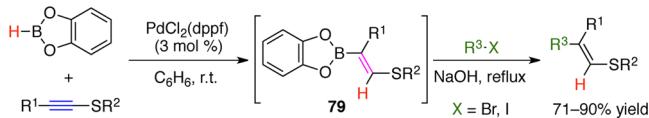


For recovery and reuse of Rh catalysts, Horváth and Gladysz demonstrated an interesting “fluorous biphasic catalysis” protocol.<sup>311</sup> Using lower rhodium loadings, alcohols were formed with high turnover number values. The groups of Burgess<sup>312</sup> and Hartwig<sup>313</sup> achieved the related titanium-catalyzed procedures. In addition, an NHC-ligated platinum complex also offers good performance in a similar reaction.<sup>314</sup>

Given that the borane moiety can couple with electrophiles, Suzuki and Miyaura described a general synthetic procedure for highly regioselective preparation of vinylic sulfides.<sup>315</sup> Using PdCl2(dppf), the reaction between thioacetylenes and catecholborane gives the corresponding boron derivatives (79), which then react with organic halides leading to sulfides (Scheme 158).

Johnson demonstrated that a Pd(PPh3)4 complex allows access to boranes by treatment of vinyloxazolidines with 9-borabicyclo[3.3.1]nonane (9-BBN), which then can undergo a Suzuki cross-coupling with halides leading to unnatural amino

**Scheme 158. Pd-Catalyzed Hydroboration/Coupling Reaction<sup>315</sup>**



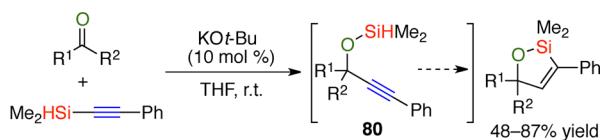
acid products.<sup>316</sup> Following their initial study on a Rh-catalyzed methylenation/hydroboration reaction,<sup>317</sup> Lebel's group achieved the synthesis of substituted olefins by incorporating the Suzuki coupling reaction into this cascade.<sup>318</sup>

On the other hand, using 1,3-diene substrates, the resulting allylic borons can be quenched by benzaldehyde, giving the corresponding erythro alcohols.<sup>319</sup> Interestingly, 1,3-enynes result in the formation of homopropargyl alcohols via an allenylidic intermediate.<sup>319,320</sup> Weller's group described a Rh-mediated hydroboration/dehydrogenation sequence.<sup>321</sup> By treatment of *tert*-butylethene with H<sub>3</sub>B-NMe<sub>2</sub>H, formation of a mixture of amino-borane products was observed.

## 8. THROUGH THE ADDITION OF A Si—H BOND TO AN UNSATURATED C—C BOND

Sequential transformations involving a hydrosilylation process provide a valuable strategy to construct functionalized silicon-containing targets. Lee's group showed that the base KOt-Bu allows access to substituted oxasilacyclopentenes from carbonyls and alkynylsilanes (Scheme 159).<sup>322</sup> The proposed mechanism involves a tandem alkynylation/hydrosilylation reaction pathway via the formation of an activated hydridosilyl ether intermediate 80.

**Scheme 159. KOt-Bu-Promoted Alkynylation/Hydrosilylation Reaction<sup>322</sup>**



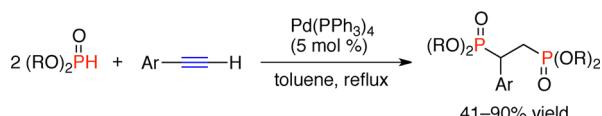
Dussault and co-workers achieved a silylation/hydrosilylation sequence for the synthesis of cyclic oxasilinanes and oxasilepanes.<sup>323</sup> The Lewis acid B(C<sub>6</sub>F<sub>5</sub>)<sub>3</sub> enables the reaction of silanes and alkenes to proceed with high diastereoselectivity. Diethyl and diphenyl-substituted silanes can be employed in this transformation.

## 9. THROUGH THE ADDITION OF A P—H BOND TO AN UNSATURATED C—C BOND

To date, examples of sequential transformations involving the addition of a P—H bond to an unsaturated C—C bond are relatively rare. Lin's group reported a palladium-catalyzed double hydrophosphorylation between phosphites and electron-deficient alkynes in 2000.<sup>324</sup> A Pd(PPh<sub>3</sub>)<sub>4</sub> complex allows access to bisphosphonates with high regioselectivities (Scheme 160). However, only formation of the corresponding monoadduct was observed when using dimethyl phosphite.

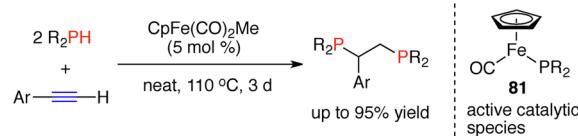
Given the strong electron-donating properties of phosphanes as unique ancillary ligands, the development of an efficient strategy for rapid construction of such scaffolds is especially important. Clearly, the addition of a P(III)—H bond to a multiple bond provides a straightforward method to access

**Scheme 160. Palladium-Catalyzed Double Hydrophosphorylation<sup>324</sup>**



functionalized phosphanes. Recently, Nakazawa achieved an iron-catalyzed double hydrophosphination of arylacetylenes.<sup>325</sup> A CpFe(CO)Me complex enables practical one-pot access to 1,2-bisphosphinoethane derivatives with high regioselectivities (Scheme 161). Other iron salts, including FeCl<sub>2</sub>, FeCl<sub>3</sub>, and

**Scheme 161. Iron-Catalyzed Double Hydrophosphination<sup>325</sup>**



Fe(CO)<sub>5</sub>, do not form the desired products. In this reaction, a CpFe(CO)PR<sub>2</sub> complex **81** is thought to be the active catalytic species, which may be generated from the coordination of phosphane with iron by the elimination of HCOMe.

## 10. CONCLUSIONS

As is clearly outlined in this review, over the past decades, sequential reactions involving hydroelement addition to carbon–carbon multiple bonds expanded rapidly, as witnessed by numerous applications in the construction of sophisticated molecular targets. Although significant advances have been achieved with new synthetic sequences continuously developed, this field still retains some challenges. First, examples of sequential transformations via a hydrohalogenation<sup>326</sup> or hydrocyanation<sup>327</sup> process are scarce. Given that halides and cyanides are versatile building blocks and can be functionalized by various synthetic strategies, considerable efforts may be addressed in the incorporation of such transformations into a compatible sequence, in a more economic and practical manner to achieve synthetically useful molecules. Second, in terms of catalysts, whether from the view of industry or academia, the exploration of readily available, ecologically benign nonrare metals, such as iron, cobalt, and copper, in these reactions is highly desirable toward developing sustainable organic synthesis. Finally, for the concise, rapid, and efficient construction of structurally complicated and biologically important natural products, the application of these methods in total synthesis will become increasingly prominent in the future.

## AUTHOR INFORMATION

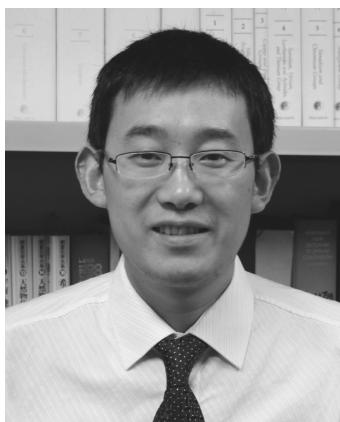
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### Notes

The authors declare no competing financial interest.

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Xiaoming Zeng received his B.Sc. degree at Sichuan Normal University, 2002, and his Ph.D. degree at Sichuan University, 2009 (with Professor Meiming Luo). He spent two years as a visiting scholar in Professor Guy Bertrand's laboratory at the University of California at Riverside, funded by the China Scholarship Council (2007–2009). As a JSPS postdoctoral fellow, he pursued synthetic chemistry with Professor Eiichi Nakamura at the University of Tokyo. He started his independent research group at Xi'an Jiaotong University as a Principal Investigator in January 2012. His research interests focus on developing new synthetic methodologies based on transition metal catalysis, stable carbene synthesis and applications.

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## ABBREVIATIONS

Ac	acetyl	DMF	<i>N,N</i> -dimethylformamide
Ar	aryl	DMSO	dimethylsulfoxide
Bn	benzyl	d	days
BINOL	1,1'-bi-2-naphthol	dppf	1,1'-bis(diphenylphosphino)ferrocene
BIPHEP	(6,6'-dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine)	DPPP	1,3-bis(diphenylphosphino)propane
Boc	tert-butyloxycarbonyl	d.r	diastereomeric ratio
Bz	benzoyl	ee	enantiomeric excess
CAAC	cyclic(alkyl)(amino)carbene	equiv	equivalents
CM	cross-metathesis	er	enantiomeric ratio
cod	1,5-cyclooctadiene	Et	ethyl
Cp	cyclopentadiene	EWG	electron-withdrawing group
Cp*	1,2,3,4,5-pentamethylcyclopentadiene	h	hours
CSA	camphorsulphonic acid	Ind	indenyl
Cy	cyclohexyl	<i>i</i> -Pr	<i>iso</i> -propyl
dba	dibenzylideneacetone	IPr	<i>N,N'</i> -bis(2,6-diisopropylphenyl)imidazol-2-ylidene
DBU	1,8-diazabicyclo-[5.4.0]undec-7-ene	JohnPhos	(2-biphenyl)di- <i>tert</i> -butylphosphine
DCE	1,2-dichloroethane	L <sub>n</sub>	ligand
DCM	dichloromethane	Naph	naphthyl
Dipp	2,6-di- <i>iso</i> -propylphenyl	m	meta
DMA	<i>N,N</i> -dimethylacetamide	Me	methyl
DMAP	4-dimethylaminopyridine	MS	molecular sieves
DME	1,2-dimethoxyethane	MW	microwaves
DMEDA	tetramethylethylenediamine	n-Bu	<i>n</i> -butyl
		n-Hex	<i>n</i> -hexyl
		NHC	<i>N</i> -heterocyclic carbene
		NMR	nuclear magnetic resonance
		n-Oct	<i>n</i> -octyl
		n-Pent	<i>n</i> -pentyl
		NPMoV	molybdoanadophosphate
		n-Pr	<i>n</i> -Propyl
		Ns	4-nitrophenylsulfonyl
		NTf <sub>2</sub>	bis(trifluoromethylsulfonyl)amide
		OMOM	methoxymethoxy
		OTf	trifluoromethanesulfonate
		<i>o</i> -tol	2-methylphenyl
		p	para
		p-cymene	1-methyl-4-(1-isopropyl)benzene
		Ph	phenyl
		PMB	<i>para</i> -methoxybenzyl
		PPTS	pyridinium <i>para</i> -toluenesulfonate
		PS-BEMP	polymer-supported 2- <i>tert</i> -butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine
		p-Tol	4-methylphenyl
		p-Ts	<i>para</i> -toluenesulfonyl
		rac-BINAP	( $\pm$ )-2,2'-bis(diphenylphosphino)-1,1'-binaphthylene
		rt	room temperature
		TBDMS	<i>tert</i> -butyldimethylsilyl (TBS)
		TBDPS	<i>tert</i> -butyldiphenylsilyl
		<i>t</i> -Bu	<i>tert</i> -butyl
		TDMPP	tris(2,6-dimethoxyphenyl)phosphine
		TEMPO	2,2,6,6-tetramethylpiperidine-1-oxyl
		TES	triethylsilyl
		TFA	trifluoroacetate, trifluoroacetic acid
		TFP	tris(2-furanyl)phosphine
		THF	tetrahydrofuran
		TMS	trimethylsilyl
		Ts	tosyl

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