

The intramolecular Heck reaction

SUSAN E. GIBSON (née Thomas) and RICHARD J. MIDDLETON

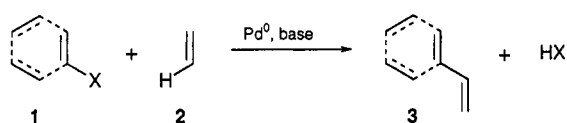
Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London SW7 2AY, UK

Reviewing the literature published up to the end of 1995

1	Introduction
2	Synthesis of heterocycles
2.1	Monocyclisations
2.1.1	Five-membered ring formation
2.1.1.1	Synthesis of indoles and related heterocycles
2.1.1.2	Other nitrogen-containing rings
2.1.1.3	Rings containing other heteroatoms
2.1.2	Six-membered ring formation
2.1.2.1	Nitrogen-containing rings
2.1.2.2	Rings containing other heteroatoms
2.1.3	Synthesis of medium and large rings
2.2	Multiple cyclisations
3	Synthesis of carbocycles
3.1	Monocyclisations
3.1.1	With β -hydride elimination
3.1.2	With anion capture
3.2	Multiple cyclisations
4	Regio- and stereo-control
4.1	Mode of cyclisation — <i>endo</i> or <i>exo</i> ?
4.2	Control of isomerisation and the rôle of additives
4.3	Unexpected products
4.4	Diastereocontrol
4.5	Enantiocontrol
5	Total syntheses
6	Conclusion
7	References

the intramolecular Heck reaction, culminating in the last three years in its widespread application in total synthesis.

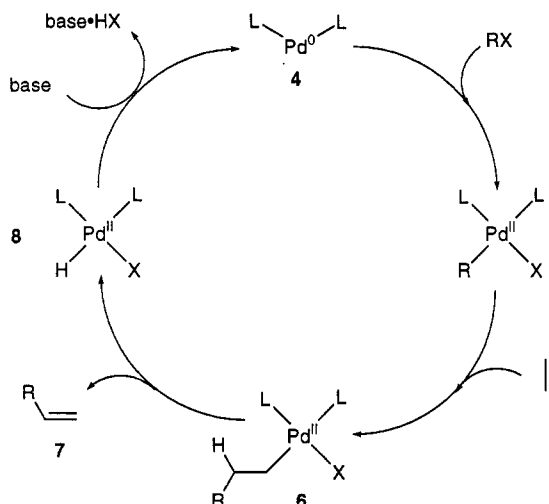
The Heck reaction, defined as the palladium catalysed reaction of a vinyl or aryl halide **1** with an alkene **2** to form a new carbon–carbon bond as in **3** together with the formation of a hydrogen halide as a by-product, was developed as long ago as the early 1970s.¹



The currently accepted mechanism of the reaction was defined in the 1970s² and has remained unmodified in everything but detail since then. The first step is oxidative addition of a 14 electron palladium(0) species **4** to a bond joining a carbon atom to an appropriate group, usually a bromide, iodide or triflate, to form a carbon–palladium σ -bond as in **5**. The carbon atom is usually part of an aryl or vinyl group as any sp^3 hybridised carbon atoms bearing hydrogen atoms β to the palladium atom would lead to facile β -hydride elimination. After coordination of an alkene to the palladium, carbopalladation leads to another carbon–palladium σ -bonded complex **6**. Provided there is now an sp^3 hybridised hydrogen β to the palladium atom, then β -hydride elimination will occur and the product of

1 Introduction

For most of the 1980s the Heck reaction was a well known but little used organometallic reaction. Broadly designated as the palladium catalysed arylation or vinylation of alkenes it had great potential in organic synthesis, but, perhaps due to recognised problems such as lack of regioselectivity and the necessity for harsh reaction conditions, only a few research groups pursued its promise. The intramolecular version of the reaction was almost unheard of until the mid-eighties, when the synthesis of heterocycles by this method started to be properly explored; and the question of whether carbocycles could be synthesised *via* the intramolecular Heck reaction was left virtually unanswered until the late eighties. Since this time, however, there has been an explosion of interest in



the reaction 7 will be released from the cycle. The palladium(II) complex **8** thus formed then undergoes reductive elimination to regenerate the palladium(0) species **4** which can then continue round the catalytic cycle.

If the palladium in a complex similar to **6** is lacking an appropriate β -hydrogen then the complex may be long-lived and thus susceptible to a further cross-coupling reaction. This step may take place with the use of anionic or neutral nucleophiles as well as organometallics but the term 'anion capture' is generally used to avoid confusion with the Heck coupling steps.

The group bonded to the unsaturated carbon atom which undergoes the oxidative addition step is usually iodide, bromide or, more recently, triflate. Chlorides do not give very good results although some success has been achieved with aroyl³ and benzyl chlorides.⁴ The standard Heck conditions of catalytic quantities of palladium (usually palladium acetate) and an amine base in a polar aprotic solvent have been found to be widely applicable. (Phosphine ligands are necessary to aid the oxidative addition step in the case of bromides but not iodides.) The reaction generally requires high temperatures under these conditions. More recently, modification of the conditions by Jeffery *et al.*⁵ through use of an inorganic base together with a phase transfer agent has allowed the Heck reaction to occur at lower temperatures. These have come to be known as the Jeffery conditions and have widened the scope and effectiveness of the Heck reaction still further. Other modifications to conditions have sometimes been found to be advantageous and these will be described later.

Since the real upturn in interest in the Heck reaction in the last few years there have been several reviews of the Heck reaction and related palladium catalysed coupling reactions.⁶ In spite of the number of examples and specific features of the intramolecular reaction, however, there has been no comprehensive review devoted to this area to date, and thus such a review is undertaken herein. Due to the variety of Heck-type couplings that now exist some definition of the scope of the review is necessary. Therefore, for the purposes of this review, an intramolecular Heck reaction is defined as one where: 1) the first step in the catalytic cycle involves oxidative addition of palladium(0) into a carbon–heteroatom σ -bond to form a carbon–palladium(II) σ -bond, and 2) the next step involves coordination to and the carbopalladation of an alkene, alkyne or allene which is part of the same molecule.

In the next two sections, we review all intramolecular Heck reactions falling within the above definition leading to the synthesis of, first, heterocycles (Section 2) and then carbocycles (Section 3). Section 4 deals with several areas of specific interest in the intramolecular Heck reaction and Section 5 provides a few examples of the application of the reaction in the area of total synthesis.

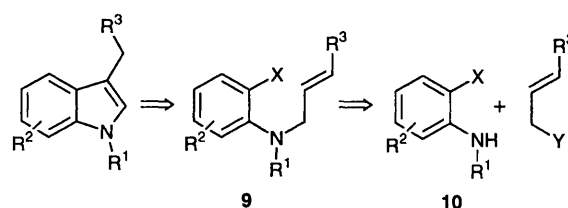
2 Synthesis of heterocycles

2.1 Monocyclisations

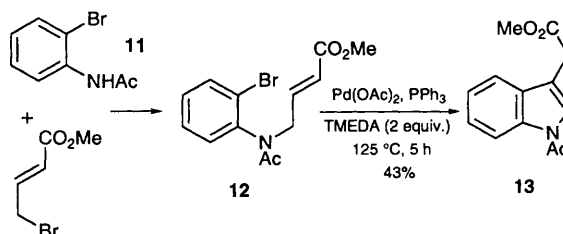
2.1.1 Five-membered ring formation

2.1.1.1 Synthesis of indoles and related heterocycles

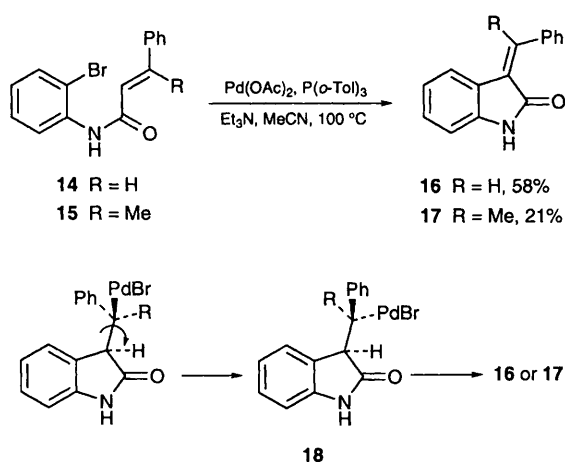
This section deals with the synthesis of indoles and heterocycles containing the indole skeleton. There are more examples of the synthesis of indoles by the intramolecular Heck reaction than of any other group of compounds. This is mainly due to the immense importance of indoles as a species in biologically active compounds. Other, more practical, reasons for their prevalence are the commercial availability of *ortho*-iodo and *ortho*-bromo anilines **10** and the ease of forming carbon–nitrogen bonds, thereby giving rise to a wide variety of possible substrates **9** for the intramolecular Heck reaction. It is in these types of substrates that many of the steric and electronic factors which affect the Heck cyclisation have been explored.



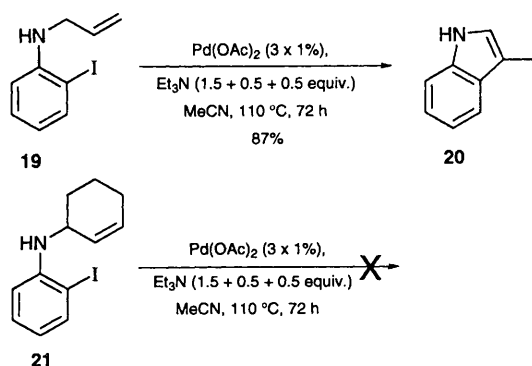
In 1977 Mori *et al.* reported the first intramolecular Heck cyclisations.⁷ They found that aryl bromide **12** could be cyclised to the indole **13** in 43% yield when reacted neat with palladium acetate (2 mol%)/triphenylphosphine (4 mol%) as the catalyst and TMEDA (2 equiv.) as the base. Under these conditions other by-products were also formed (such as the deallylated product **11**), but these could be largely avoided through the use of DMF as a solvent. The aryl chloride was found to give no cyclised product due to the difficulty of the initial oxidative addition step. Also worth noting here is the fact that the initially formed double bond would be exocyclic but this completely isomerises in the reaction mixture to the more stable endocyclic position, probably through the re-addition of the HPdBr species and a second β -hydride elimination. This isomerisation can be prevented by the addition of silver salts which give the exocyclic isomers in good yields;⁸ the use of silver and other salts will be discussed later.



Subsequently, in 1979, Mori *et al.*⁹ and Heck *et al.*¹⁰ published syntheses of indolones using the standard conditions of catalytic palladium, with a phosphine as ligand and an organic base, usually triethylamine. In Heck's paper *N*-cinnamoyl- and *N*-(β -methylcinnamoyl)-*o*-bromoaniline **14** and **15** were cyclised to the benzylideneindolones **16** and **17** with 1 mol% palladium acetate and 4 mol% tri-*o*-tolylphosphine at 100 °C. (Tri-*o*-tolylphosphine is sometimes used in place of triphenylphosphine in order to prevent the formation of phosphonium salts.) Once again, the preference for 5-*exo*-trig cyclisation over 6-*endo*-trig cyclisation is observed and the factors influencing this preference in the Heck cyclisation will be examined later. A reversal of alkene stereochemistry is also seen and this reflects the necessity for palladium to adopt a *syn* relationship to the β -hydrogen as in **18** before β -hydride elimination can occur. Apparent exceptions to this rule will also be discussed later.

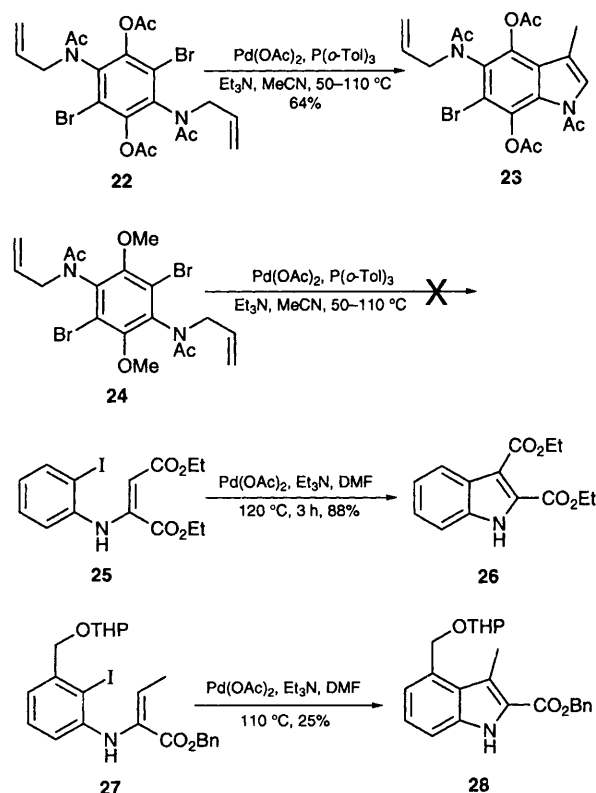


All the examples described so far involve alkenes conjugated to a carbonyl group, which is known to activate alkenes towards Heck insertion. In order to synthesise indoles by the cyclisation of unactivated *N*-allylanilines, Hegedus *et al.* found that sequential addition of the catalyst at various times over the course of the reaction gave much improved yields.¹¹ The catalyst appears to become deactivated as the reaction proceeds, possibly through the formation of colloidal palladium; where the cyclisation occurred, as in, for example, the cyclisation of **19** to **20**, yields



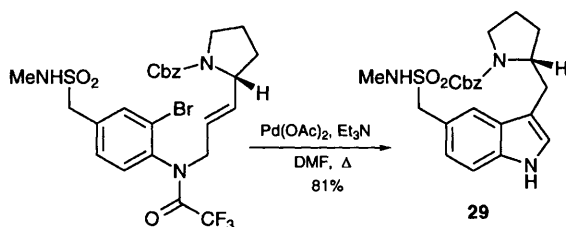
of 50–87% were observed. Several other points were noted. First, use of phosphines was necessary in the case of aryl bromides but not aryl iodides as might be expected from the intermolecular examples;¹² second, the reactions exhibited a clear preference again for the 5-*exo* over the 6-*endo* cyclisation; and third, the complete failure of *N*-cyclohexenylaniline **21** to react suggests a stereoelectronic constraint on the cyclisation.

Although, for some substrates, the Heck cyclisation can tolerate various substituents on the aromatic ring and the alkene and give good yields of indoles under the right conditions,¹³ it can also be very sensitive. Small changes in either the reaction conditions or steric or electronic factors in the substrate can have a huge effect on the yield of indole produced.¹⁴ For example, Hegedus *et al.* reported a case where acetate substituents on the aromatic ring of **22** gave a good yield of the indole **23** but when they were replaced with the more electron donating methoxy substituents as in **24** no cyclised product was obtained.¹⁵ Another good example of this sensitivity is provided by the cyclisation of aryl iodide **25** which gave indole **26** in very good yield,¹⁶ whilst under very similar conditions the similar substrate **27** gave only a poor yield of the desired product **28**.¹⁷

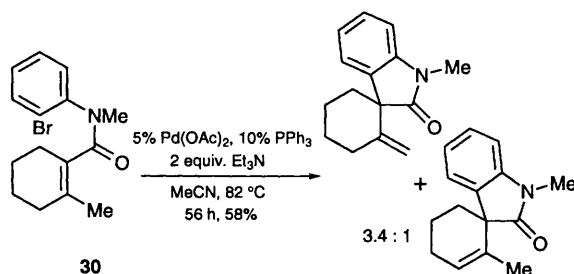


The attractiveness of this method of indole synthesis was improved further by Larock *et al.* who found that the use of Jeffery's phase transfer conditions instead of the standard Heck conditions gave improved yields at lower temperatures.¹⁸ The conditions employed used 2 mol% palladium

acetate, 1 equivalent of tetrabutylammonium chloride, DMF as solvent and 2.5 equivalents of base (either sodium carbonate, triethylamine or sodium acetate). It was also noted that substitution on either nitrogen or the double bond slowed the reaction. Heck conditions and Jeffery conditions have been used several times over the past few years in the synthesis of simply substituted target indoles,¹⁹ one such example being the synthesis of an analogue of sumatriptan **29**.²⁰

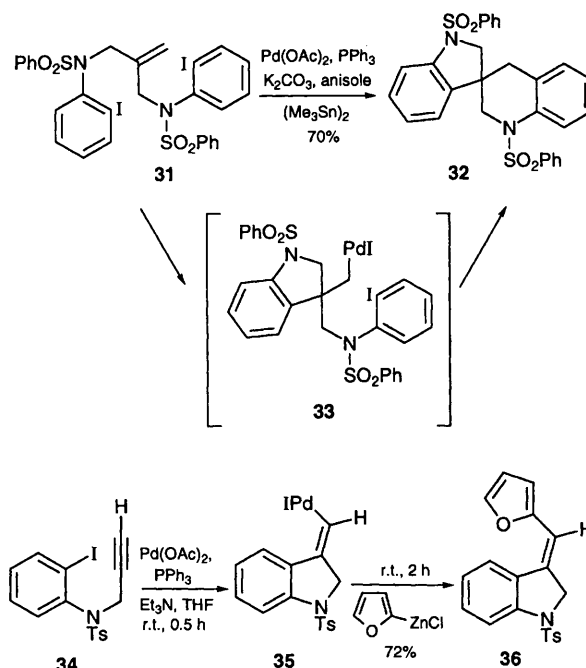


This methodology is not limited only to the formation of simple indoles as polycyclic fused ring and spirocyclic systems related to the indole system have also been synthesised.²¹ The earliest examples were the syntheses of various carbazoles in 1980 by Iida *et al.*²² but only poor yields were obtained. In 1987 Overman *et al.* published details of the synthesis of a number of spirocyclic indolones,²³ one of which was formed by cyclisation onto a tetrasubstituted alkene **30**. Palladium catalysed arylations or vinylations of tetrasubstituted alkenes do not occur when performed intermolecularly and thus the versatility of the intramolecular reaction was again demonstrated. In recent years, Overman has shown that quaternary centres in oxindoles may be formed both diastereoselectively²⁴ and enantioselectively²⁵ as will be discussed later.



The versatility of this synthetic method has been extended still further by the use of the 'anion capture' methodology.²⁶ Although there is one earlier example of hydride capture to give a 3,3-dimethylindoline,¹⁸ the true scope of this method was first demonstrated by Grigg *et al.* who synthesised indole-related heterocycles by cyclisation onto geminally disubstituted alkenes with hydride,²⁷ cyanide²⁸ and carbonyl²⁹ capture, and onto alkynes with capture by organotin,³⁰ organozinc and organoboron reagents.³¹ In one such example iodoaniline derivative **31** was cyclised to give the alkyl palladium species **33** which then underwent transmetalation with hexamethylditin, followed by a

Stille type coupling to give **32**.³² Luo *et al.* have recently reported conditions under which intramolecular cyclisations onto terminal alkynes such as **34** provide vinyl palladium intermediates **35** which may be trapped *in situ* with a wide range of organozinc reagents to provide products such as **36** in good yield.³³

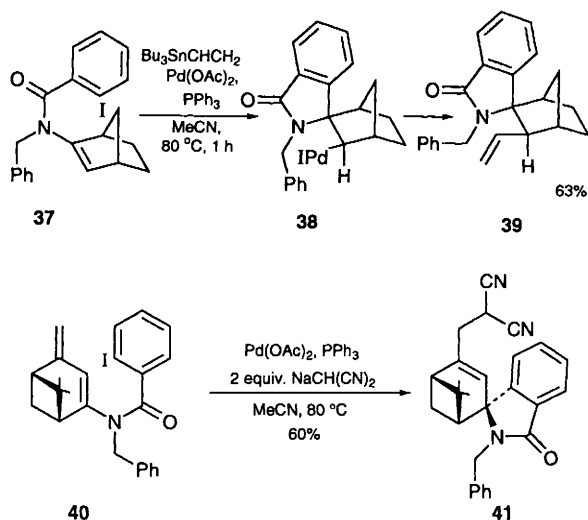


Finally, there have been several other palladium catalysed syntheses of indoles and related heterocycles which fall just outside the scope of this review but may be of interest to the reader.³⁴

2.1.1.2 Other nitrogen-containing rings

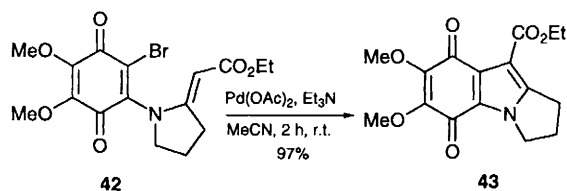
Isoindolones were first synthesised by Grigg *et al.* as part of the work which demonstrated the feasibility of forming fused, spiro and bridged ring compounds by the intramolecular Heck reaction.³⁵ They were formed in good yields from vinyl amides of 2-iodobenzoic acids such as **37**. As such amides are readily synthesised, a wide variety of substrates were thus available upon which a whole host of methodologies could be tested. Such vinyl amides were one of the main ways of testing the 'anion capture' methodology and were thus cyclised with hydride,²⁷ cyanide²⁸ and carbonyl²⁹ capture. Furthermore, as bridgehead double bond formation is disfavoured, cyclisation onto amide substituted norbornenes provided a stable alkylpalladium intermediate which could then undergo organotin³⁰ or organoboron capture.³¹ Hence **37** was cyclised to **39** via **38** in good yield.

Cyclisations onto dienes or allylic acetates gave π -allylpalladium complexes which then underwent capture with organozinc reagents³¹ or carbon, nitrogen or oxygen nucleophiles.³⁶ For example, dienamide **40** was cyclised to **41**. Other syntheses of isoindolones have been described, all occurring *via*



5-*exo*-trig cyclisations.³⁷ Isoindolones have also been synthesised in studies on stereoselectivity³⁸ and control of isomerisation³⁹ and in the synthesis of indoloindoles *via* cyclisation onto an indole ring.⁴⁰

The intramolecular Heck strategy has also been applied to the synthesis of a range of natural products featuring nitrogen-containing five membered rings such as camptothecin,⁴¹ magallan-sine,⁴² lentiginosine⁴³ and the mitocenes.^{15,44} A key step in the synthesis of an example of the latter was the cyclisation of an appropriately substituted *N*-vinyl- or *N*-allyl-bromoquinone. For example, quinone **42** was cyclised to the indolequinone **43** in excellent yield. The Heck cyclisation methodology

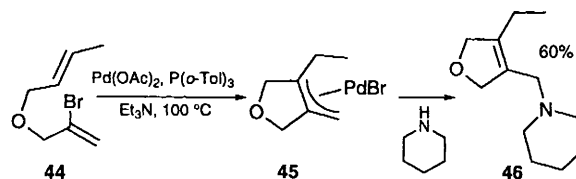


for the formation of indoles has also been applied to the synthesis of indole-type aromatic heterocycles where in place of a benzene ring there is a thiophene or selenophene to give thienopyrroles and selenopyrroles.^{16c} Cyclisations which construct nitrogen-containing heterocycles on pre-formed indole rings as in the synthesis of the indolo[3,2,1-*ij*][1,6]-naphthyridine ring system⁴⁵ and cyclisations onto the 2,3-double bond of indoles⁴⁶ have been reported. Pyrrolidinones have also been formed from the Heck cyclisation of α -haloamides but only in poor to moderate yields.⁴⁷ Lastly, in a recent paper by Shibasaki *et al.*⁴⁸ the enantioselective formation of a five membered ring containing a nitrogen atom from a prochiral substrate was described; this work will be discussed more fully later.

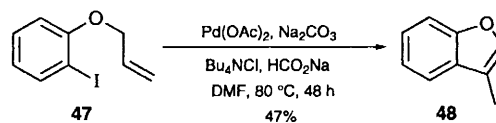
2.1.1.3 Rings containing other heteroatoms

This section is devoted almost exclusively to the formation of oxygen-containing rings. The earliest

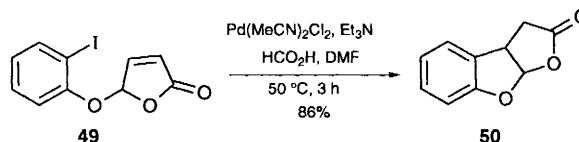
example involved the cyclisation of bromodialkenyl ethers and capture of the stable π -allylpalladium intermediate with a secondary amine, such as piperidine.⁴⁹ By this method, vinyl bromide **44** was cyclised to the 2,3-disubstituted dihydrofuran **46** *via* the π -allylpalladium intermediate **45** in good yield.



Larock *et al.* applied the conditions which had proved to be most successful for their synthesis of indoles¹⁸ to the synthesis of benzofurans.⁵⁰ In this case, however, there is the complication that palladium(0) is known to react with aryl allyl ethers to give π -allylpalladium complexes. Together with one equivalent of sodium formate (whose rôle may be to reduce any stable π -allylpalladium complexes that form thus releasing the palladium back into the catalytic cycle), the mild modified Jeffery conditions provided good yields of the desired benzofurans. In this manner iodoaryl allyl ether **47** gave 3-methylbenzofuran **48**. Negishi *et al.* also described the synthesis of benzofurans from aryl allyl ethers but used the standard Heck conditions. They obtained similar or slightly better yields but also obtained a mixture of isomers.⁵¹

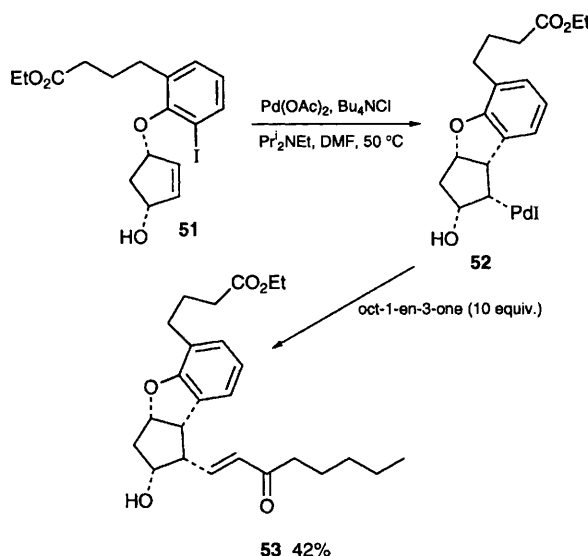


Hoffmann *et al.* described an intramolecular hydroarylation reaction on aryl allyl ether **49** which gives the ABC ring system of the aflatoxins **50**.⁵² In this case there is no *syn*- β -hydrogen for the palladium to eliminate and so a hydride source was provided by preformed triethylammonium hydrogencarbonate.



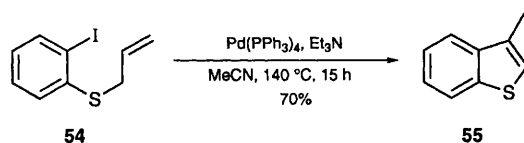
Other benzofurans have been synthesised by cyclisations onto proximate alkynes with hydride capture⁵³ and spiro-fused benzofuran-2(3*H*)-ones have also been synthesised.^{25a,54} Recently an example of a cyclisation onto a carbohydrate template to form a fused five membered ring containing oxygen has also been reported.⁵⁵

The anion capture approach has been used by Larock *et al.* in a synthesis of prostaglandin-type compounds.⁵⁶ Intramolecular cyclisation of **51** leads to alkylpalladium intermediate **52** which lacks an appropriate *syn*- β -hydrogen for elimination and so is



available for anion capture. Both capture with alkenes (an intermolecular Heck) and organotin compounds (a Stille type coupling) have been used with alkenes giving the best results as exemplified by the synthesis of **53**.

There is only one publication, to date, on the synthesis of five-membered rings containing sulfur and this describes the synthesis of benzo-[b]thiophenes by cyclisation of aryl allyl or aryl prop-2-ynyl thioethers.⁵⁷ Although there are possible problems associated with the thiophilicity of palladium, under fairly standard Heck conditions at high temperature the desired benzothiophenes can be formed. For example, in a simple case, aryl allyl thioether **54** was cyclised to 3-methylbenzo[b]thiophene **55** in good yield.



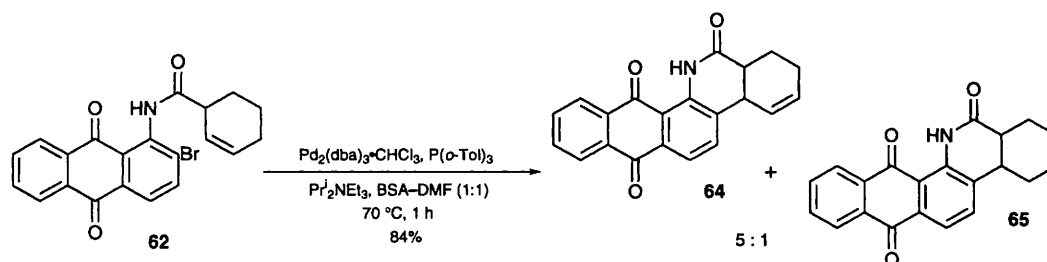
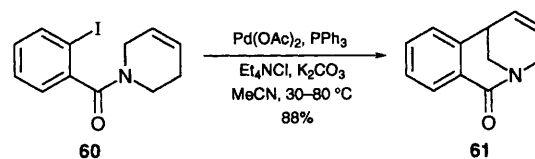
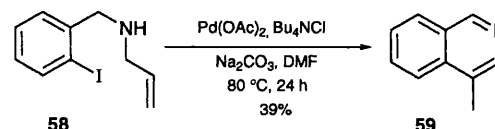
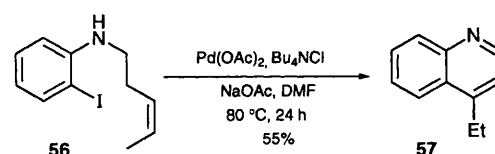
2.1.2 Six-membered ring formation

2.1.2.1 Nitrogen-containing rings

This section deals mainly with the synthesis of quinolines and isoquinolines and their partially saturated analogues. These have been formed by either 6-*endo* or 6-*exo* cyclisations. As 5-*exo* cyclisa-

tion is almost always preferred over 6-*endo* cyclisation^{15,35,58} the 6-*endo* cases must be dominated by other steric, electronic or stereoelectronic factors.^{21,59} This topic will be dealt with more fully later.

6-*Exo* cyclisations of aryl bromides or iodides onto appropriately positioned alkenes can lead to substituted quinolines,¹⁸ as in the cyclisation of **56** to **57**, or isoquinolines and related heterocycles,^{9,18,35,37a} as in the cyclisation of **58** to **59**. Where the alkene is itself part of a ring then spiro, fused²³ or bridged³⁵ rings may be formed as illustrated by the cyclisation of *N*-allyl amide **60** to **61** in excellent yield. Fused ring systems have also been formed when the aryl iodide moiety was attached to the nitrogen atom of an indole ring bearing an alkene.⁴⁵ When this methodology was directed towards the synthesis of dynemicin-A the fused quinolones **64** and **65** were successfully synthesised from **62**.⁶¹ The BSA [*N,O*-bis(trimethylsilyl)acetamide] **63** was found to be crucial to the success of the cyclisation as it temporarily protects the secondary amide, a group which has been known to give problems in intramolecular cyclisations.²³ 6-*Exo* cyclisation to form quinolones has also been employed in the total synthesis of (*R,R*)-crinan,⁶² racemic lycoricidine⁶³ and (+)-lycoridine.⁶⁴ Useful heterocycles can also be formed by 6-*exo* cyclisations onto indoles.^{46,45}



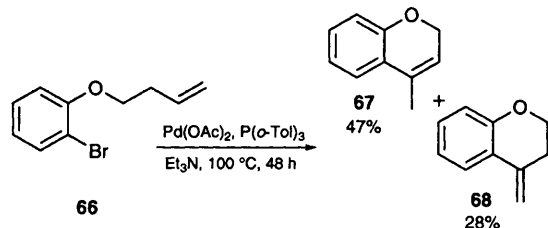
BSA = *N,O*-bis(trimethyl)acetamide **63**

The tandem cyclisation–‘anion capture’ methodology can also be applied to the synthesis of six-membered rings containing nitrogen. This has been demonstrated by cyclisations onto proximate alkynes and capture with either hydride,^{53,66} cyanide²⁸ or organotin reagents.³⁰ 6-*Exo* cyclisations of benzyl halides onto alkenes with either hydride or sodium tetraphenylborate capture have also been used to prepare 3,3-disubstituted tetrahydroisoquinolines in good yield.⁴⁶

Substituted piperidines may be synthesised by cyclisation of bromodialkenyl amines and subsequent trapping of the π -allylpalladium intermediate with an *in situ* nucleophile.⁴⁹ The cyclisation of an *N*-allyl iodide onto a cyclic alkene to form a bridged ring product has also been successfully used in an approach to the *Strychnos* alkaloids.⁶⁷ Fused pyridinequinones have been synthesised as the minor product by a 6-*endo* cyclisation of bromoquinones where the major products were the desired indoloquinones formed *via* the preferred 5-*exo* cyclisation.¹⁵

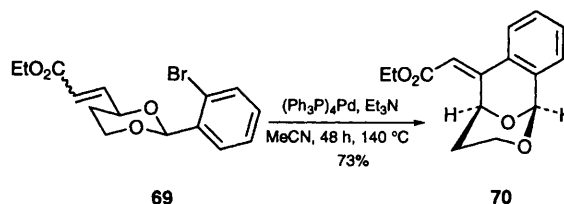
2.1.2.2 Rings containing other heteroatoms

As for the five-membered rings, this section deals almost exclusively with the synthesis of oxygen-containing rings and again there are far fewer examples of this type than their nitrogen analogues. The earliest examples were reported by Heck *et al.*⁴⁹ and included the cyclisation of a *o*-bromoaryl homoallyl ether **66** to give a mixture of isomers **67** and **68**.

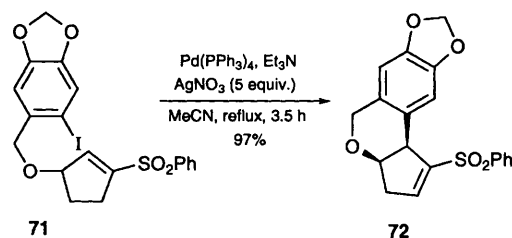


There was only one other publication in this area⁶⁸ until Negishi *et al.* reported the synthesis of fused and spiro tetrahydrobenzopyrans from *o*-iodobenzyl allyl ethers, and dihydropyrans from iododialkenyl ethers under standard Heck conditions.⁵¹ On the whole, however, mixtures of isomers were formed. Overman *et al.* also used this methodology (but with the addition of silver salts to prevent isomerisation) to form a spiro tetrahydrobenzopyran system in their total synthesis of (\pm)-tazettine and (\pm)-6a-epipretazettine.⁶⁹ Also under standard Heck conditions bromoaryl **69** gave tricyclic **70** in good yield.⁷⁰ High temperatures were necessary to isomerise the double bond to the thermodynamically preferred (*Z*) product. Other examples of the formation of oxygen-containing six-membered rings *via* the 6-*exo* cyclisation of aryl halides onto proximate alkenes have been reported.^{28,71}

An iodopyridine derivative was successfully cyclised onto an allyl ether in very good yield as a



key step in the synthesis of 20-(*S*)-camptothecin.⁷² Six-membered cyclic ethers have also been formed by cyclisations of iodoaryls onto vinyl sulfones⁷³ (such as the cyclisation of **71** to **72**) and nitroalkenes.⁷⁴ In both cases the bromoaryl gave no cyclised product, the addition of silver salts gave improved yields and phosphines were necessary. It is worthy of note that a nonpolar solvent was found to give by far the best results for the cyclisation onto the nitroalkene.

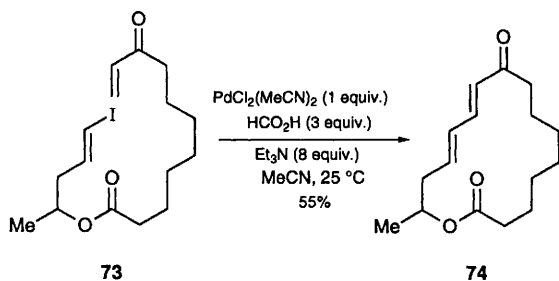


A six-membered ring containing a nitrogen–oxygen bond has been synthesised by the intramolecular Heck reaction in the synthesis of FR 900482 by Danishefsky *et al.*⁷⁵ This proceeded in excellent yield with a large excess of triethylamine but otherwise under standard Heck conditions. Lastly, a cyclisation of a sulfonamide by Grigg *et al.* gave a 1 : 1 mixture of 6-*exo* and 7-*endo* products with the nitrogen–sulfur bond as part of the bridged system.⁷⁶ Thus, together with the other examples, this demonstrates that the intramolecular Heck reaction can be used not only in the presence of carbon–heteroatom bonds but also heteroatom–heteroatom bonds.

2.1.3 Synthesis of medium and large rings

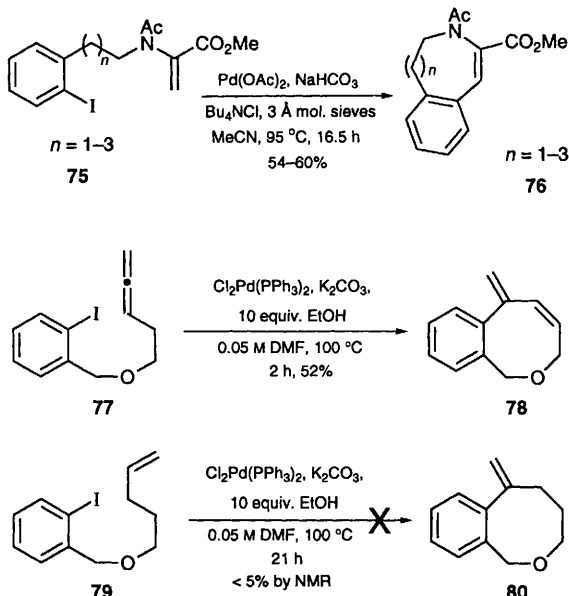
Due to there being relatively few examples, the synthesis of medium and large ring heterocycles *via* the intramolecular Heck reaction will be dealt with together in this section. (Some of the factors governing these cyclisations will be dealt with in more detail in Section 4.) The first example of the synthesis of a large ring by the intramolecular Heck reaction was reported in 1981 when the 16-membered lactone **74** was prepared from **73** in 55% yield.⁷⁷ This reaction used one equivalent of palladium and a slow addition of the substrate **73** to the reaction mixture in order to prevent the formation of dimers and oligomers by the intermolecular reaction.

A seven-membered cyclic ether was formed by a 7-*endo* cyclisation with piperidine capture of a π -allylpalladium intermediate in the same manner as the capture of **45** to give **46**.⁴⁹ The 7-*exo* cyclisation



has been used to provide benzazepines^{40a} and cyclic ethers,⁵¹ amides^{23,53,78} and sulfonamides.⁵³

In the last year, two reports of the synthesis of seven-, eight- and nine-membered rings using the Heck reaction have appeared. Gibson (née Thomas) *et al.* cyclised aryl iodides tethered to dehydroalanine units by two to four methylene groups **75** under anhydrous Jeffery conditions to give seven-, eight- and nine-membered rings **76** by *endo* ring closure.⁷⁹ Negishi *et al.* have synthesised seven-, eight- and nine-membered cyclic ethers by cyclisation onto allenes in reasonable yields but have found that the corresponding cyclisations onto alkenes only proceed in very poor yield.⁸⁰ Thus allene **77** cyclised to the eight-membered ring **78** in good yield but alkene **79** gave no isolated yield of **80**. The reported results seem to indicate that allenes are more reactive than either alkenes or alkynes towards intramolecular carbopalladation and thus the versatility of the Heck reaction is increased still further.



Sundberg *et al.* have formed an eight-membered ring via an 8-*endo* cyclisation of a 3-iodo-(*N*)-methylindole onto a pendant alkene under Jeffery conditions.⁸¹ Following this, in the last year, Rigby *et al.* have reported that, in the cyclisations of aryl iodides onto enamides to form medium sized rings, Jeffery conditions gave the product of *endo* cyclisation and standard Heck conditions gave the product of *exo* cyclisation.^{58b} During the course of their investiga-

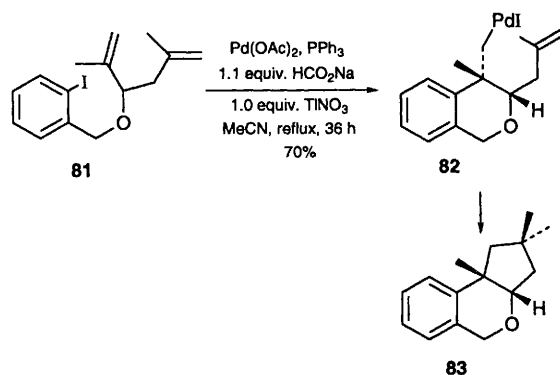
tion, they formed both seven- and eight-membered rings containing nitrogen in good yield. Lastly, the synthesis of 16- to 22-membered lactones (also containing amide functionality) in 24 to 42% yield has been recently reported by Stocks *et al.*⁸² They cyclised aryl iodides onto alkenes under standard Heck conditions; the tendency for large rings to form by exclusively *endo* cyclisations was noted.

2.2 Multiple cyclisations

The development of multiple Heck cyclisations in the synthesis of heterocycles has been carried out largely by the groups of Grigg and Overman. Biscyclisations were first reported by Overman *et al.* in 1988⁸³ in the synthesis of spiro and fused ring systems. The importance of silver salts in promoting the desired reaction was also shown. The next several papers on the subject were by Grigg *et al.* who demonstrated the powerful nature of the methodology by combining a bis-cyclisation with an 'anion capture' step.^{27b,29,84}

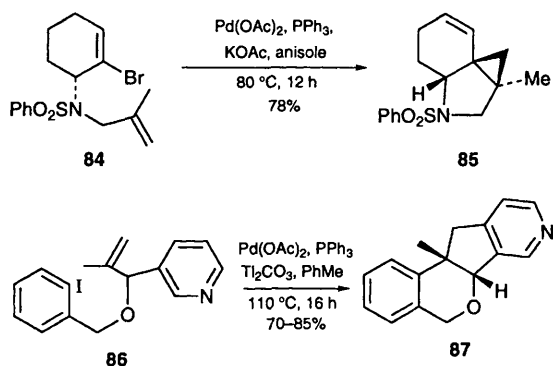
Grigg has coined several terms to describe the various species that must be present in a multiple Heck cyclisation. The 'starter species' is that into which palladium undergoes initial oxidative addition (*e.g.* an aryl or vinyl halide or triflate); the 'relay species', of which there may be more than one, is that which undergoes carbopalladation in a ring forming step (*e.g.* an alkene or alkyne) to give a carbopalladated intermediate; the 'terminating species' is that part of the substrate from which the palladium can return to the catalytic cycle by either β -hydride elimination or anion capture. There are two obvious but important restrictions that must be noted. Firstly, the relay species must be such that after carbopalladation, β -hydride elimination cannot occur (*e.g.* an alkene must be appropriately substituted). Secondly, anion capture must take place at a slower rate than the various cyclisation steps and thus alkynes are more likely to be successful as relay species due to their higher reactivity toward carbopalladation than alkenes.

This methodology has been successfully employed in the synthesis of many varied ring structures. For example **81** was cyclised via **82** to **83** in good yield with hydride capture.^{27b} The importance of using either silver or thallium salts was again demonstrated and the use of tetraethylammonium chloride

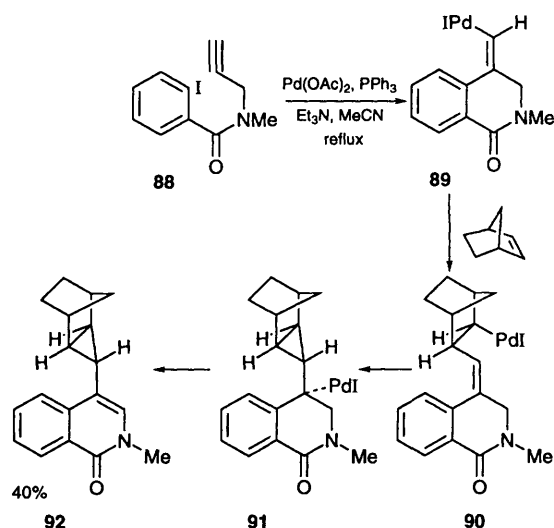


led to faster reaction times but also to an increased amount of premature capture product.

The reactivity of certain alkylpalladium intermediates has also been demonstrated.^{84,85} For example, after vinyl bromide **84** cyclised onto the proximal alkene to give a 'neopentyl'-palladium species, this then underwent another cyclisation to give the cyclopropane **85**.⁸⁵ Alkylpalladium intermediates will even undergo cyclisations onto aromatic rings, a process which has been termed 'Friedel-Crafts alkylation'. Spiroindolines have been synthesised by this method,⁸⁶ as have bridged-ring⁷⁶ and angularly fused-ring systems, as in the synthesis of **87** from **86**.⁸⁷

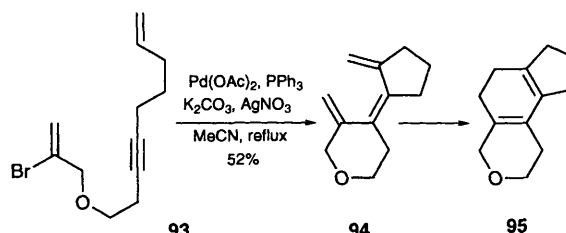


The powerful nature of this methodology has been demonstrated further in a cascade cyclisation incorporating an intermolecular step.⁸⁸ A 6-*exo* cyclisation onto an appropriately positioned alkyne **88** provides the vinyl palladium intermediate **89** which can then undergo an intermolecular Heck reaction with norbornene to give **90**. The alkylpalladium intermediate so formed cannot undergo β -hydride elimination and so cyclises to form a cyclopropane and another alkylpalladium intermediate **91** which can β -eliminate to form the final product **92**. An alkyne is necessary as the first relay species as it will undergo carbopalladation much more rapidly than an alkene, thus diminishing the importance of the

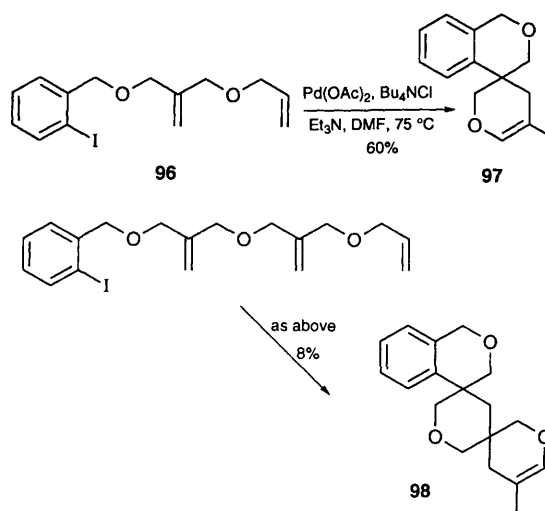


straightforward intermolecular Heck reaction with norbornene as a competing reaction.

De Meijere *et al.* have shown that in the palladium catalysed cyclisation cascade of certain diene-yne an electrocyclic ring closure can follow the β -hydride elimination step.⁸⁹ Thus diyne **93** underwent palladium catalysed cyclisation to give **94** which then underwent electrocyclic ring closure to **95**.



Overman *et al.* have applied the palladium catalysed cascade cyclisation approach to the synthesis of spirocyclic polyethers.⁹⁰ They found that the Jeffery conditions were the best for the synthesis of tricyclic diether **97** but gave only a poor yield when applied to the synthesis of tetracyclic triether **98**. An important competing side reaction appears to be the palladium catalysed isomerisation of the allylic ether to the more stable enol ether moiety.



3 Synthesis of carbocycles

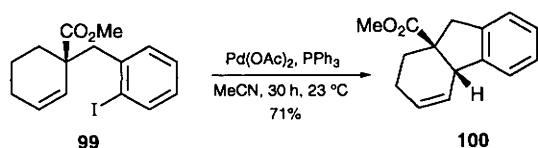
3.1 Monocyclisations

3.1.1 With β -hydride elimination

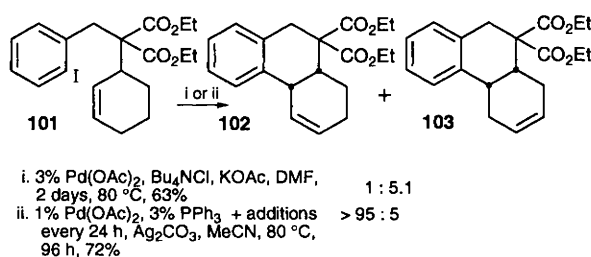
The intramolecular Heck reaction has been exploited far less in the synthesis of carbocycles than the synthesis of heterocycles. This was especially so in the earlier years of the 1980s. The imbalance is fast being remedied, however, as the reaction is applied not only to the synthesis of biologically interesting molecules, natural products, substituted aromatics *etc.*, but also to cascade cyclisations. There is no synthetic reason why carbocycles may

not be as easily prepared by this reaction as heterocycles but it was not until the late 1980s that the area really started to flourish.

In 1984 and then later in 1988 Grigg *et al.* reported the cyclisations of several substituted 2-bromo- α,ω -dienes.⁹¹ In 1987, as part of their paper on the synthesis of polycyclic systems containing quaternary centres, Overman *et al.* reported the formation of the fused ring carbocycle **100** from iodoarene **99**.²³ In 1988, Negishi *et al.* published their research on the formation of carbocycles by the cyclisation of iododienes.⁹² They found that the best conditions used triphenylphosphine as the ligand and a mixture of acetonitrile and THF as the solvent. Using dibenzylideneacetone as the ligand gave a much slower reaction, again underlining the sensitive nature of this reaction to the conditions used.

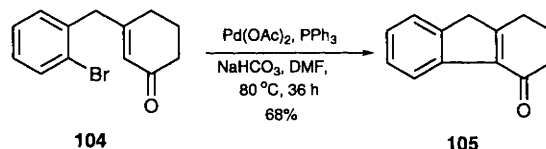


Concurrently, Larock *et al.* reported their study on the effect of different conditions on the formation of carbocycles from iodoarene substituted alkenes.⁹³ They found that in the cyclisation of iodoarene **101** to tricyclic **102** and **103**, modified Jeffery conditions gave the desired product in good yield but as a mixture of the two double bond regioisomers in a 1:5.1 ratio. Overman's conditions,²³ which had proved successful in the synthesis of spiro and fused ring systems, and controlled isomerisation with silver salts were found to slow the reaction down but at the same time gave a > 95:5 ratio of the two regioisomers. Standard Heck conditions do, however, give good yields of carbocycles with certain substrates^{40a,94} although sometimes care in the choice of phosphine is necessary.⁹⁵

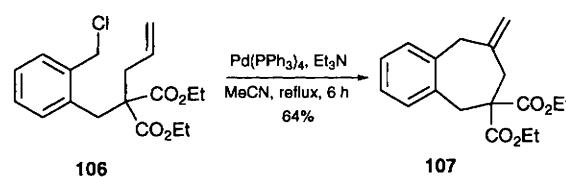


A further paper by Negishi *et al.* in 1988 reported that the position of the double bond in the cyclisation product could sometimes be controlled by cyclising onto alkenes bearing carbonyl groups.⁹⁶ For example, vinyl bromide **104** was cyclised to **105** in good yield under standard Heck conditions.

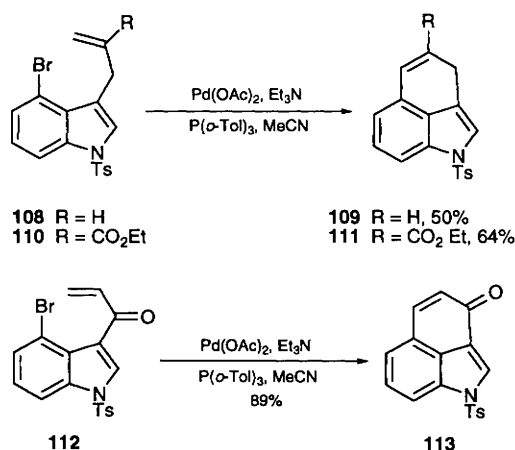
Negishi *et al.* also examined the use of benzyl halides for the initial oxidative insertion step.⁴⁰ They found that benzyl chlorides gave the best results as iodides and bromides gave a greater amount of



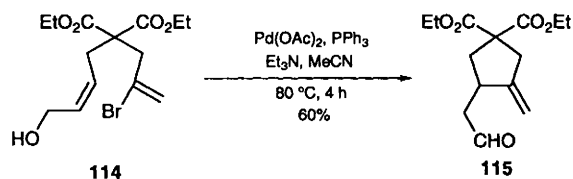
double bond regioisomers. The formation of five- and seven-membered ring carbocyclic products as well as a bis-cyclisation under standard Heck conditions were reported. For example, benzyl chloride **106** underwent 7-*exo* cyclisation to give **107** in good yield. Negishi *et al.* have also found that cyclisation of vinyl halides onto alkenes can sometimes lead to a cyclopropylcarbonyl-homoallyl rearrangement *via* a second cyclisation of an alkyl-palladium species and so an initial 6-*exo* cyclisation can lead to a seven-membered ring and a 5-*exo* cyclisation to a six-membered ring. This rearrangement will be dealt with in more detail in Section 4.3.



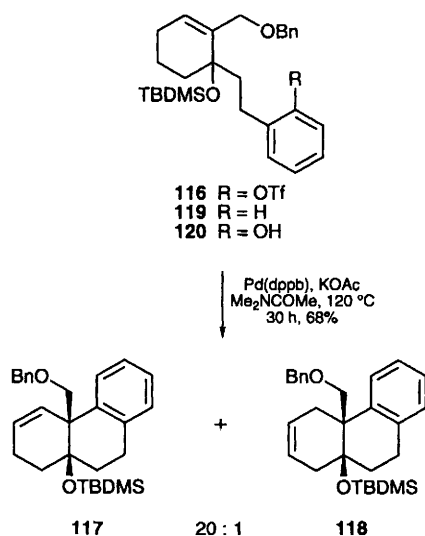
The intramolecular Heck reaction was applied to the synthesis of bioactive molecules in an approach to the ergot alkaloids by Hegedus *et al.*⁹⁸ Bromoindoline **108** containing a monosubstituted alkene underwent 6-*endo* cyclisation to **109** in 50% yield under standard Heck conditions. This yield was increased to 64% in the case of the geminally disubstituted alkene **110** which cyclised to **111**. It appears to be the conjugation of the alkene in **110** to an electron withdrawing group rather than its disubstitution which leads to the increase in yield, as cyclisation of α,β -unsaturated ketone **112** to **113** also proceeded smoothly.



Cyclisation onto allylic alcohols has also been reported.⁹⁹ When *exo* cyclisation onto an allylic alcohol occurs the alkylpalladium intermediate can undergo β -hydride elimination to form an enol. This enol can then tautomerise to the aldehyde as in the cyclisation of vinyl bromide **114** to cyclopentane **115**.

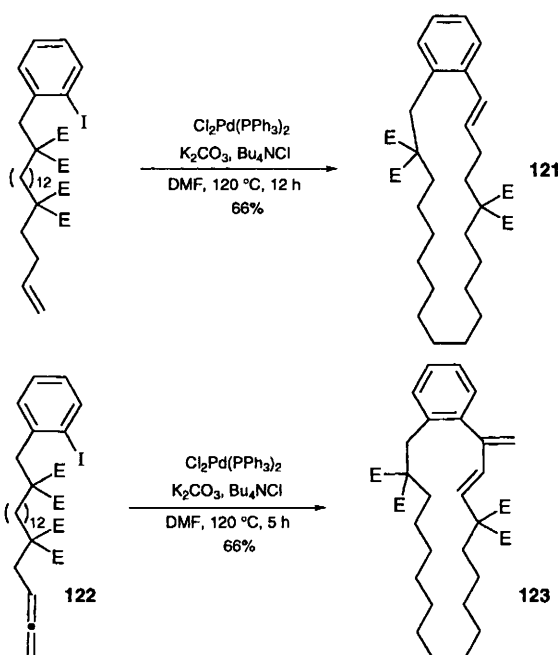


Overman *et al.* have more recently used vinyl and aryl triflates for the synthesis of cis angularly fused ring products.¹⁰⁰ Although, for example, aryl triflate **116** cyclised in a 6-*exo* manner to give a mixture of regioisomers **117** and **118** in good yield, the conditions of the reaction required careful development. Bidentate phosphines were found to be necessary as monodentate phosphines gave only partial conversion and amine bases were found to have a deleterious effect in giving less selectivity in the formation of the two isomers and also leading to the reduced product **119**. (Amine bases are thought to be hydride donors in palladium catalysed reactions.¹⁰¹) Other bases also gave problems: silver salts led to decomposition of the starting material and bases such as sodium hydrogen carbonate gave side reactions such as the formation of **120**. Lastly none of the desired product was observed at temperatures below 100 °C. With respect to tuning conditions, it has recently been shown that by varying the phosphine used, both the regio- and stereo-selectivity of an intramolecular Heck reaction can be altered.¹⁰² It is also worthy of mention that although almost none of the reactions indicated so far for the synthesis of carbocycles have used the Jeffery conditions, these can, in certain circumstances, give excellent yields of carbocyclic products.¹⁰³



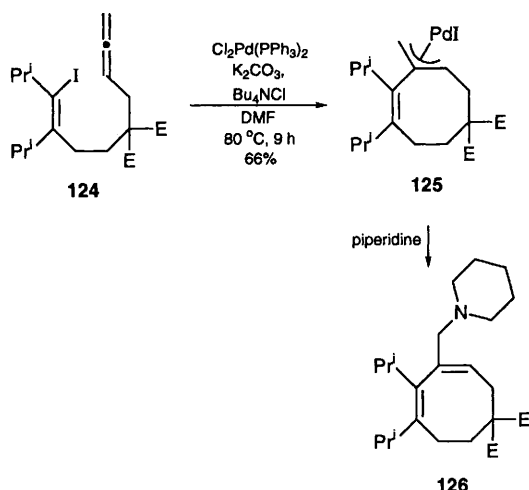
Both medium and large ring carbocyclic products have been formed by the intramolecular Heck reaction. Although Roberts *et al.* had difficulty in controlling the regioselectivity of the reaction, they cyclised a bromindole onto a monosubstituted alkene to form, in a 2:1 ratio, the 8-*endo* and 7-*exo* products respectively in an 88% yield under standard Heck conditions.¹⁰⁴

Negishi *et al.* have synthesised both medium and large ring carbocyclic products *via* cyclisation onto both alkenes and allenes under high dilution Jeffery conditions.⁸⁰ They found that they could only synthesise medium sized rings in very low yield with alkenes but that large rings, such as the 21-membered **121**, could be prepared in good yield by this method. The large rings were formed almost exclusively in an *endo* fashion. The cyclisations with allenes proved to be very successful and 7- through 20-membered rings were formed, on the whole, in good to very good yields under high dilution Jeffery conditions. For example, the 20-membered ring **123** was formed in 86% yield from allene **122**. It was shown that carbon-carbon bond formation takes place at the central carbon atom of an allene to form a π -allylpalladium intermediate which can be trapped with a variety of nucleophiles. Indeed intra-



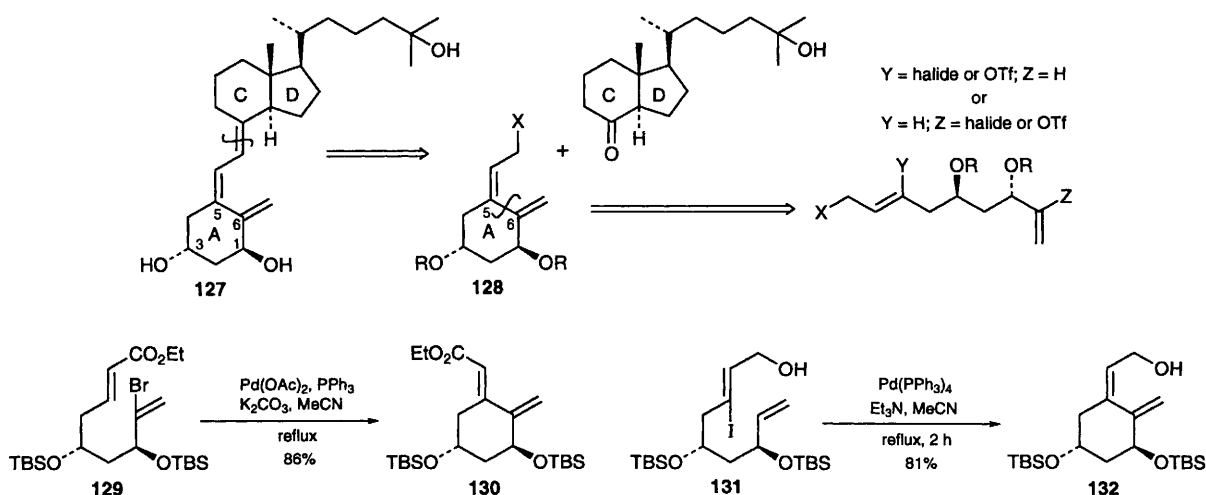
molecular nucleophilic capture can take place to afford another cyclisation. This is exemplified in the cyclisation of allene **124** to π -allylpalladium intermediate **125** which is then trapped with piperidine to form eight-membered ring **126**. The rate of allene cyclisation was shown to be much faster than alkene cyclisation and it was proposed that it was due to this factor, rather than the lack of competing side reactions, that such good yields of large rings could be obtained. Lastly the geometry of the endocyclic double bond in the newly formed ring was shown to be (*Z*) in eight- and less-membered rings, (*E*) in 11- and more membered rings and to depend on other factors in nine- and ten-membered rings. Thus, the combination of allenes and the intramolecular Heck reaction appears to be a potentially excellent strategy for macrocyclic synthesis.

The majority of the work on the development of the intramolecular asymmetric Heck reaction has involved the synthesis of carbocycles.^{43,105} These will



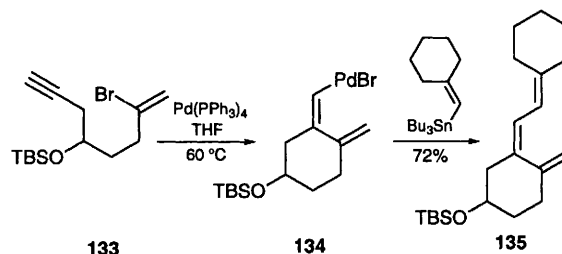
be discussed in detail later. Several total syntheses have employed the intramolecular Heck mediated formation of carbocycles as a key step: the synthesis of (\pm) - γ -apopicropodyphyllin,¹⁰⁶ formed by a 6-*endo* cyclisation; the synthesis of optically pure opioids,¹⁰⁷ via 6-*exo* cyclisations; (\pm) -duocarmycin,¹⁰⁸ via a 6-*exo* cyclisation; (\pm) -aphidicolin,¹⁰⁹ via a 5-*exo* cyclisation; (\pm) -*cis*-trikentrin A,¹¹⁰ via a 5-*exo* cyclisation; taxol,¹¹¹ via an 8-*exo* cyclisation and (\pm) -dehydrotubifoline,¹¹² via a 6-*exo* cyclisation.

Several groups have synthesised variously substituted and protected forms of the vitamin D₃ A-ring via an intramolecular Heck 6-*exo* cyclisation.¹¹³ The A-ring synthon **128** can be obtained by disconnection of 1 α ,25-dihydroxyvitamin D₃ **127** and the synthesis of **127** from **128** has been described.¹¹⁴ The synthon **128** can itself be disconnected at the bond joining the two double bonds to reveal a substrate for the intramolecular Heck reaction where either C(5) or C(6) can bear the halide or triflate. Both approaches have been taken: for example, Shimizu *et al.*^{113a,b} cyclised **129** to **130** in very good yield under standard conditions with potassium acetate as base, whilst Hatakeyama *et al.* cyclised vinyl iodide **131** to **132** under similar conditions with triethylamine as base.^{113f}



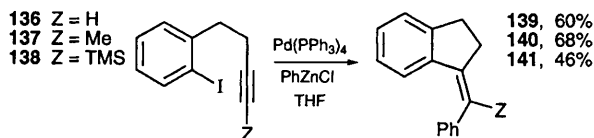
3.1.2 With anion capture

Nuss *et al.* have described an approach to the skeleton of vitamin D₃ which combines the intramolecular Heck cyclisation to form the A-ring with an anion capture that introduces the rest of the molecule.¹¹⁵ Cyclisation of the alkyne **133** leads to the vinylpalladium intermediate **134** which can then undergo capture by the vinyltin reagent to give the product **135**.



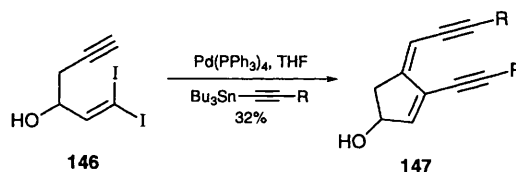
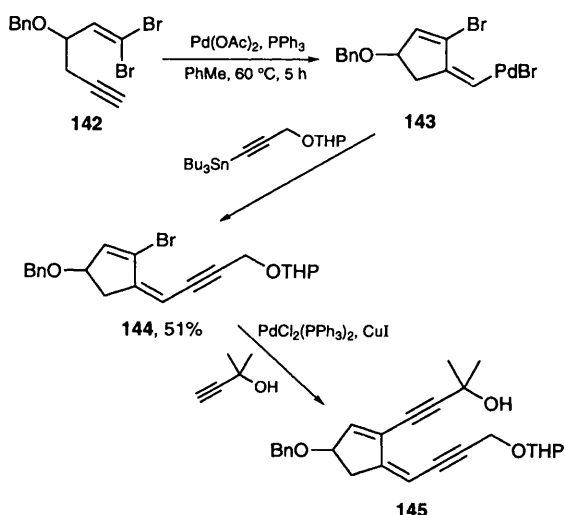
The earliest example of an intramolecular Heck carbocycle synthesis followed by anion capture was reported in 1983 by Heck *et al.* They cyclised bromodienes and captured the moderately stable π -allyl palladium intermediate with piperidine thus forming five-membered rings.¹¹⁶ Several years later Grigg *et al.* exploited the tandem cyclisation-anion capture approach not only in the synthesis of heterocycles but also carbocycles. This was initially via 5-*exo* cyclisation onto 1,3-dienes followed by capture of the intermediate π -allylpalladium intermediate with either organotin reagents³⁰ or carbon nucleophiles.³⁶ Hydride capture has also been shown to be useful in the synthesis of carbocycles containing quaternary carbon centres.¹¹⁷

Wang *et al.* described the Heck cyclisation of aryl halides onto a range of terminally substituted alkynes followed by capture with phenylzinc chloride.¹¹⁸ They found that aryl iodides invariably gave better results than aryl bromides and that substitution on the alkyne can have a significant effect on the yield with the trimethylsilylated substrate giving only moderate yields. Thus **136–138** were cyclised to **139–141** in the yields indicated.



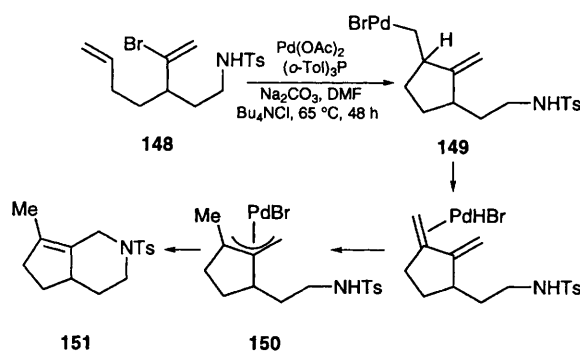
Negishi *et al.* studied the efficiency of various metals for the introduction of a range of organic functional groups in the anion capture process.¹¹⁹ As has been noted before, the main competing reaction in this process is anion capture of the initial intermediate formed by oxidative addition of palladium(0). The cyclisation reaction needs to occur significantly faster than this competing reaction for high yields of the desired product to be obtained. Alkynes (or even allenes) are therefore a better substrate for carbopalladation than alkenes and the vinylpalladium species thus formed is always stable enough to undergo anion capture. Negishi *et al.* therefore captured the product of an intramolecular 5-*exo* cyclisation of an aryl iodide onto an alkyne with alkenyl-, alkynyl- and aryl-metals. They found that tin was good for introducing either alkenyl or alkynyl groups but that zirconocene chlorides were the best for alkenyls. They also found that the best metal for the introduction of aryl groups was aluminium and that organozincs reacted too fast and therefore gave too high a yield of the competing premature capture product.

This methodology has been used in the construction of the ene-yne system found in the neocarzinostatin chromophore. Torii *et al.* reported that cyclisation of the geminally dibrominated alkene **142** onto the proximate alkyne gave the vinylpalladium intermediate **143** which then underwent anion capture with the alkynylstannane to give **144** in reasonable yield.¹²⁰ Palladium catalysed cross-coupling of **144** with another alkyne gave conjugated ene-yne **145**. Thus two different acetylenic appendages may be introduced by this technique. Nuss *et al.* found that with 1,1-diiodoalkenes the two possible organostannane coupling steps may occur in a one-pot reaction.¹²¹ For example when diiodoalkene **146** was reacted in THF with 5 equiva-

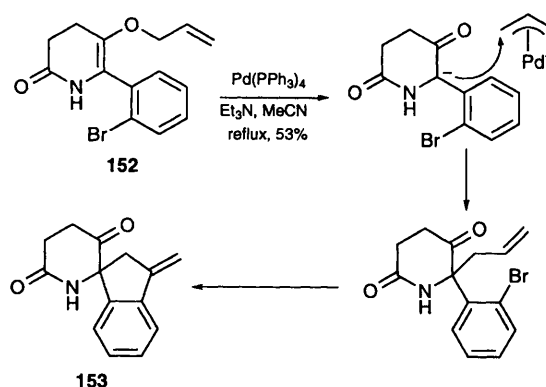


lents of the alkynylstannane then **147** could be formed in 32% yield.

The earliest examples of the anion capture process involved, as mentioned previously, the trapping of a π -allyl intermediate by a secondary amine. In the last few years it has been shown that the formation of the intermediate π -allyl complex is regioselective and thus the product may be formed regioselectively.¹²² Thus vinyl bromide **148** cyclises to **149** which then rearranges to **150**. Intramolecular nucleophilic attack by the sulfonamide then generates **151** in good yield. Spirocyclic products may also be formed by this method. It is not only sulfonamides that can be used as nucleophiles. Carbon-centred nucleophiles derived from alkyl sulfones¹²³ and α -substituted malonates have also been successfully used.¹²⁴ Overman *et al.* have used intramolecular capture of π -allylpalladium intermediates formed by the intramolecular Heck reaction in their synthesis of morphine.¹²⁵ In this case the internal nucleophile was a hydroxy group.

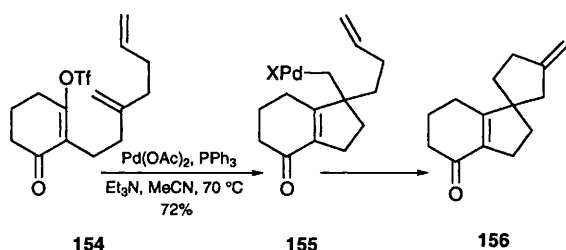


Lastly, a palladium catalysed rearrangement followed by an intramolecular Heck reaction has been reported by Watson *et al.*¹²⁶ The palladium catalysed reaction of alkenyl allyl ether **152** was expected to provide the product of a 7-*exo* cyclisation, but in fact a palladium(0) catalysed 1,3-allyl shift occurred followed by a 5-*exo* cyclisation to give the spirocyclic product **153**.

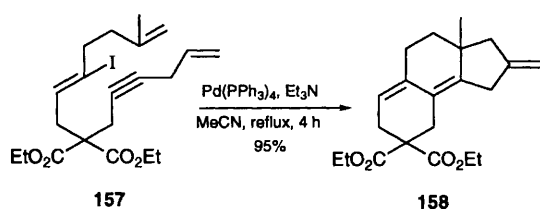


3.2 Multiple cyclisations

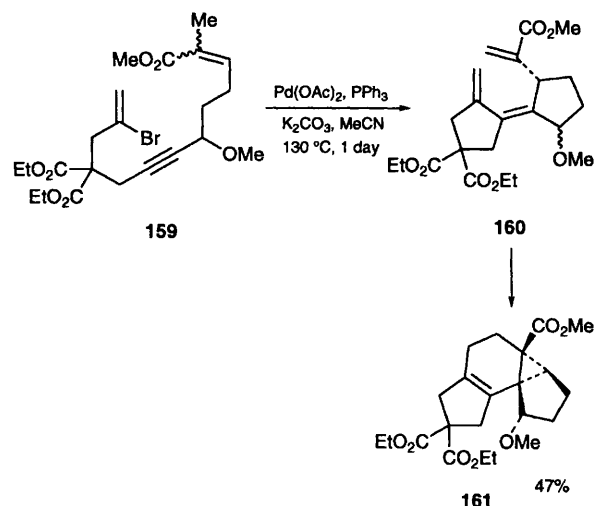
The area of palladium catalysed cascade cyclisations is a relatively new and exciting one whereby, with the correctly tailored substrate, several rings may be formed in one reaction under diastereo- and, potentially, enantio-control.¹²⁷ Much of the initial work on multiple Heck cyclisations was performed in the area of heterocycle synthesis. In 1988, however, Overman *et al.* reported a series of bis-cyclisations from aryl iodides which formed spiro, fused and bridged ring compounds in good yields using silver carbonate as the base.¹²⁸ This was followed, in the next year, by a report of the use of vinyl triflates under standard Heck conditions in bis-cyclisations to form spiro carbocycles.¹²⁹ For example, vinyl triflate **154** was cyclised *via* alkylpalladium intermediate **155** to the tricyclic product **156** in good yield. Investigations into performing the cyclisation enantioselectively were also made.



Negishi *et al.* used alkynes as the relay species with β -hydride elimination to form an alkene as the terminating step in a cascade cyclisation.¹³⁰ For example, the tricyclisation of vinyl iodide **157** to **158** was performed in excellent yield under standard Heck conditions.¹³¹ As had been shown earlier in the synthesis of heterocycles, the 'neopentyl'-palladate intermediate is highly reactive and so, if the palladium is γ to a double bond then a cyclopropane ring can be formed. Grigg *et al.* have demonstrated that this is the case in carbocyclic synthesis as well.⁸⁵

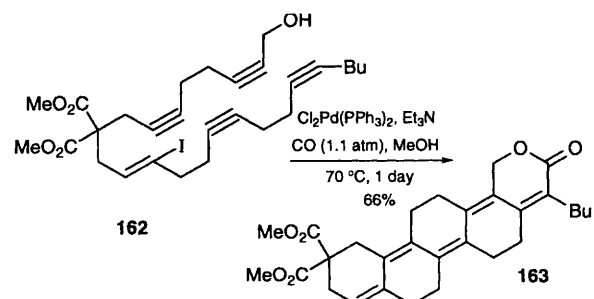


De Meijere *et al.* have shown that palladium catalysed multiple cyclisations followed by a pericyclic reaction can be used in the construction of fused heterocyclic systems.⁸⁹ Only moderate yields were obtained, however, and they propose that this was due to the presence of the oxygen atom as, in purely carbocyclic systems, very clean reactions may be obtained.¹³² The pericyclic reaction can take the form of either a 6π electrocyclic rearrangement to form a cyclohexadiene, or an intramolecular Diels–Alder to form a strained ring system. In a typical example, **159** underwent

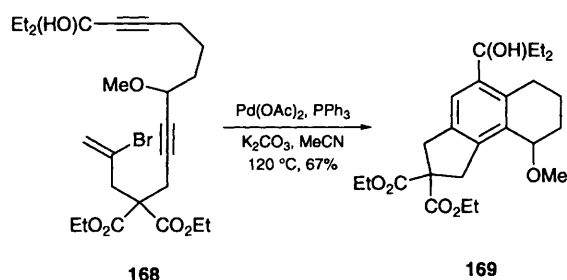
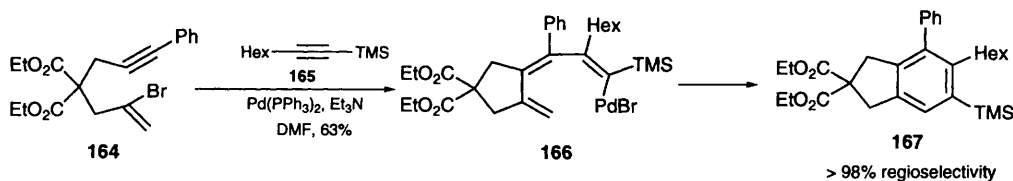


palladium catalysed cyclisation to *cis/trans* **160** and at the higher temperature of 130°C *trans* **160** underwent a Diels–Alder cyclisation to give tetracyclic product **161**.¹³³

Negishi *et al.* have extended the area of multiple cyclisations to the formation of pentacycles with carbonylative esterification as the termination step.¹³⁴ As carbon monoxide insertion into a carbon–palladium σ bond and subsequent acyl palladation is a possibility in the presence of carbon monoxide then the relay species must be alkynes. This is because carbopalladation of alkynes occurs more quickly than insertion of carbon monoxide which occurs more quickly than carbopalladation of alkenes. Nucleophilic capture of the terminating acylpalladium species can be either intermolecular with, for instance, methanol or intramolecular with the use of a pendant hydroxy function to form a lactone. For example, vinyl iodide **162** was cyclised in good yield to the pentacyclic lactone **163**.



It is also possible to form benzene rings through the use of multiple Heck cross-couplings. This can be done by either a mix of inter- and intra-molecular steps^{130,135} or in a completely intra-molecular fashion.¹³⁶ For example, vinyl bromide **164** undergoes a Heck cyclisation to form a vinyl-palladium intermediate which then undergoes an intermolecular cross coupling with an alkyne **165** to form another vinyl palladium intermediate **166**. This intermediate then undergoes either electrocyclic ring closure and palladium hydride elimination or 6-*endo* carbopalladation to give the benzene deriva-



tive **167**. This occurs with high regioselectivity.^{135c} In an intramolecular version enediyne **168** is cyclised to bisannulated benzene derivative **169** in good yield.¹³⁶

Finally, Overman's group have shown that the palladium catalysed cyclisation approach to the formation of carbocycles can be used successfully in the synthesis of natural products such as the synthesis of the scopadulcic acids.¹³⁷

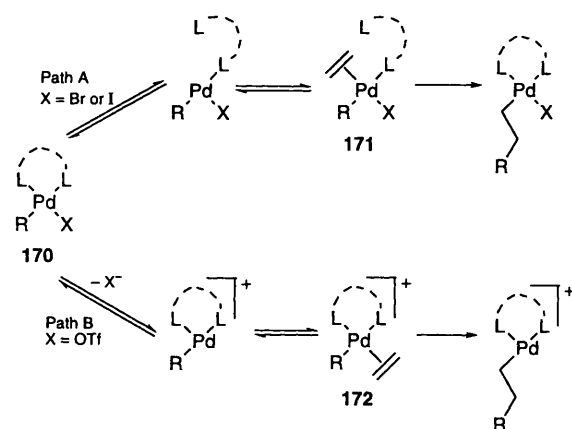
4 Regio- and stereocontrol

4.1 Mode of cyclisation — *endo* or *exo*?

There are several problems commonly associated with the Heck reaction, many of which have been at least partially overcome in the past few years. For example, reaction substrates were originally limited to aryl or vinyl bromides or iodides but more recently it was discovered that the often more accessible aryl or vinyl triflates may also be used.¹³⁸ Also, the previous general necessity for high reaction temperatures is now sometimes avoidable through the use of the Jeffery conditions. The problem of regioselectivity in the carbopalladation step is another area to which much attention has been paid as this is one of the most fundamentally important aspects of the Heck reaction.

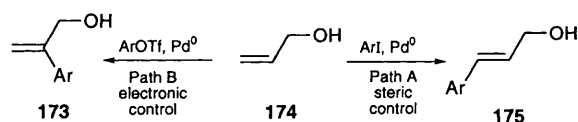
Before discussing the intramolecular reaction it is important to establish the factors influencing regioselectivity in the intermolecular version. The Cabri–Hayashi model^{6d,101c,139} for the coordination and carbopalladation steps will be very helpful to these discussions. (It is of note that the carbopalladation step is presented as irreversible in the Cabri–Hayashi model and that kinetic studies seem to provide some support for this hypothesis.¹⁴⁰)

After oxidative addition to give complex **170** the reaction may take either Path A or B and the factor determining which occurs is the nature of 'X' in complex **170**. If palladium undergoes oxidative addition into an aryl or vinyl halide bond then 'X' is a halide (usually either bromide or iodide) and the reaction proceeds down Path A. In order for the reacting alkene to coordinate to the palladium, then, due to the strong nature of the palladium–



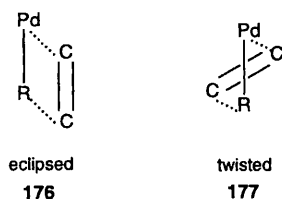
halide bond, another ligand must dissociate as in **171**. This may be a phosphine or a solvent molecule or if a chelating bisphosphine is present then one of its phosphorus atoms must dissociate before alkene coordination can take place. If 'X' is a triflate then Path B is followed. As the triflate group is only weakly coordinated to the palladium, it can dissociate to form the cationic complex **172** to which the alkene can then coordinate.

In a simple reaction like that of an aryl iodide with an α -substituted alkene such as **174** then the reaction follows Path A and the alkene coordinates to give the neutral complex **171**. In this case steric considerations dominate and the new carbon–carbon bond tends to be formed at the least substituted end of the alkene to give disubstituted alkene **175**. In the reaction of an aryl triflate with **174** the reaction follows path B to give cationic complex **172**. The cationic nature of the palladium increases the polarisation of the double bond and so electronic factors dominate the carbopalladation step and the aryl group is transferred to the end of the alkene with the lowest electron density to give product **173**. Thus it can be seen that the regioselectivity of the intermolecular Heck reaction may be influenced by the choice of substrate for the reaction.



In the intramolecular version conformational constraints also exist, as well as the steric and electronic constraints already considered. The alkene should ideally be coplanar with the palladium and the carbon atom of the aryl or vinyl species, *i.e.* in an eclipsed conformation as

illustrated by **176** as opposed to a twisted conformation **177**. This is borne out by observation of intermolecular reactions¹⁴¹ and Overman *et al.* have also provided evidence to support this theory in their synthesis of the *Amaryllidaceae* alkaloids where the eclipsed and twisted conformations would lead to different diastereomers of the product.^{69,137c}

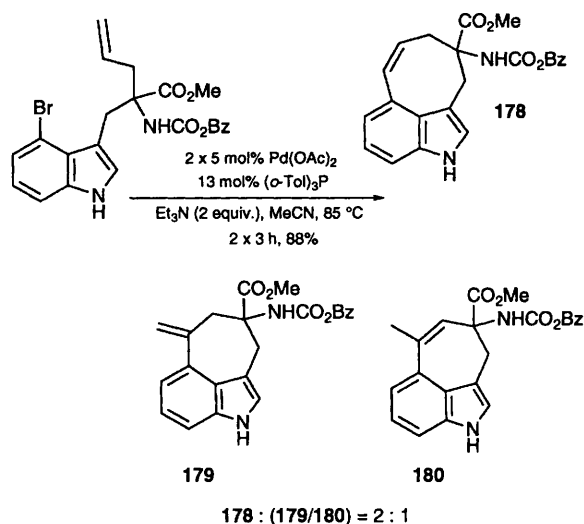


Accessing an eclipsed conformation in an intermolecular reaction is not normally a problem and it is thus only the orientation of the alkene, which is governed by steric and/or electronic considerations, that determines the regioselectivity of the carbopalladation step. In an intramolecular reaction, however, the alkene may be limited to only one eclipsed conformation due to the size and/or shape of the substrate. In this case only one of the possible regioisomers will be formed.

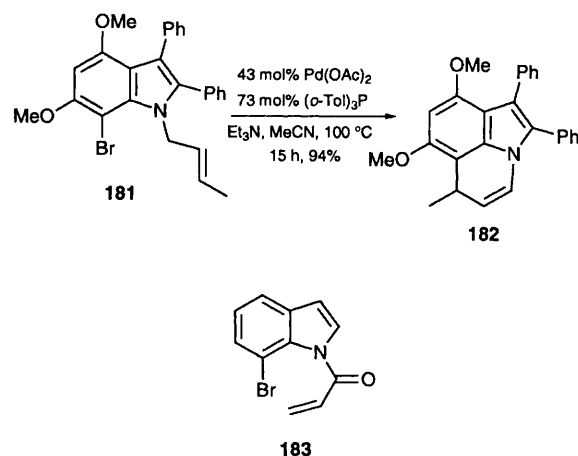
In the formation of large rings *via* the intramolecular Heck reaction, only *endo* selectivity has been observed to date.^{77,80,82} Due to the large and flexible nature of the substrate very little conformational constraint is present and so both possible eclipsed conformations of the alkene are accessible. The reaction therefore behaves in a manner similar to an intermolecular reaction. As all cases reported to date have employed Path A conditions, steric factors have dominated and *endo* cyclised products have been formed.

As we move into the area of medium sized rings, there may still be a degree of flexibility in the substrate chain but now the conformational constraints become more important than they were for the larger rings and therefore it may prove energetically more difficult to adopt the alkene conformation favoured on steric or electronic grounds alone. A fine balance of steric, electronic and conformational influences may in fact lead to mixture of products. For example, in their synthesis of the conformationally constrained tryptophan derivatives,¹⁰⁴ Roberts *et al.* isolated a 2:1 mixture of the products **178** and **179/180** derived from 8-*endo* and 7-*exo* cyclisations respectively.

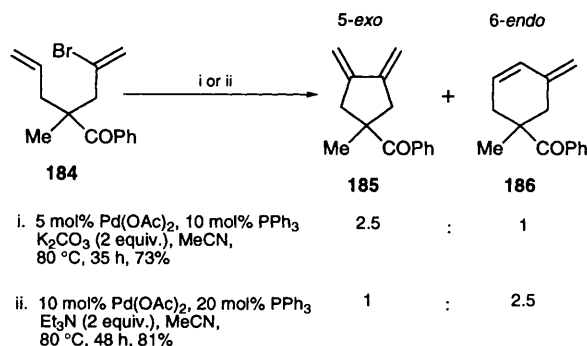
For the synthesis of five-, six- and seven-membered rings, the reaction almost always occurs *via* the *exo* mode of cyclisation as conformational considerations now outweigh any steric or electronic factors in the system. It is possible, however, to construct substrates for the Heck reaction which give only the 6-*endo* cyclisation. For example, Hegedus *et al.* observed exclusive 6-*endo* cyclisation of substrates such as **112** in their approach to the synthesis of ergot alkaloids.⁹⁸ Other similar examples were reported by Black *et al.*⁵⁹ in their cyclisations of 7-bromo-*N*-allylindoles. For example,



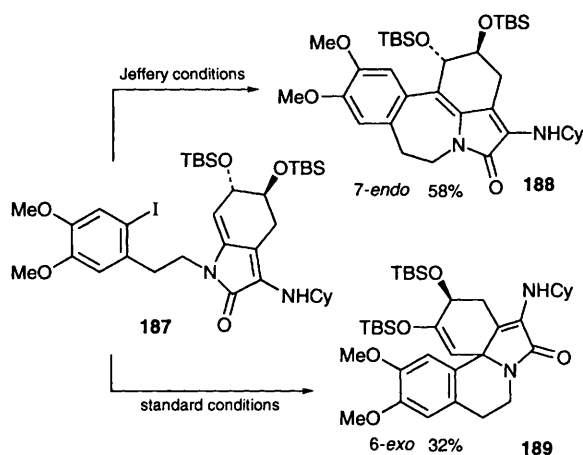
cyclisation of the *N*-crotyl derivative **181** gave the tricyclic compound **182** in 94% yield. This particular preference for the *endo* cyclisation has been investigated more fully by Dankwardt *et al.*²¹ who have shown that this selectivity occurs when the alkene component is an allyl substituent on a ring fused to the aromatic ring bearing the halide and where the halide and the alkene are peri to each other as in **183**. They have also shown that this high selectivity exists only when the ring fused to the aromatic ring is five-membered; with six-membered systems a mixture of *exo* and *endo* cyclised products is obtained.



Although the structure of the substrate frequently dictates the regioselectivity of the intramolecular Heck reaction, it appears that sometimes the reaction conditions can be used to favour one mode of cyclisation or the other. For example, a study of the conversion of **184** to **185** and **186** suggests that small changes in catalyst concentration and base can lead to a reversal of regioselectivity.^{35,91a} In one reaction (i), a 2:1:20 ratio of triphenylphosphine to palladium acetate to substrate with 2 equivalents of potassium carbonate gave a 2.5:1 ratio of *exo*:*endo* cyclised products, whilst, in a second reaction (ii), a



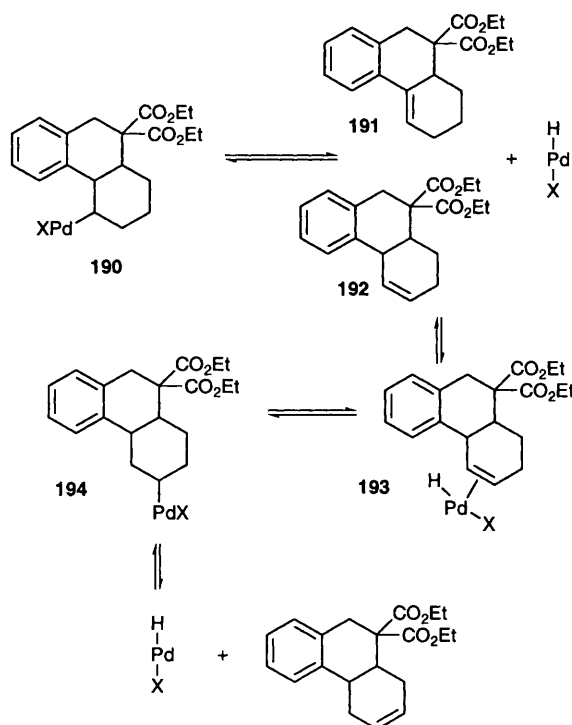
2:1:10 ratio of phosphine to palladium to substrate with 2 equivalents of triethylamine gave a 1:2.5 ratio of *exo:endo* products. Similarly, it has recently been shown that, for certain substrates, the use of the Jeffery conditions can lead to the formation of *endo* cyclised products whereas standard conditions yield *exo* cyclised products.^{58b} Thus aryl iodide **187** forms the seven-membered ring **188** under Jeffery conditions and the six-membered ring **189** under standard Heck conditions.



The regioselectivity of the intramolecular Heck reaction is thus still an area with many uncertainties. Although the structure of the substrate frequently dictates the regioselectivity, it is evident that when two competing pathways are energetically similar then the conditions may be altered to favour one mode of cyclisation over the other. Further rigorous studies are required before a clear understanding of the effects of any given variable will emerge.

4.2 Control of isomerisation and the rôle of additives

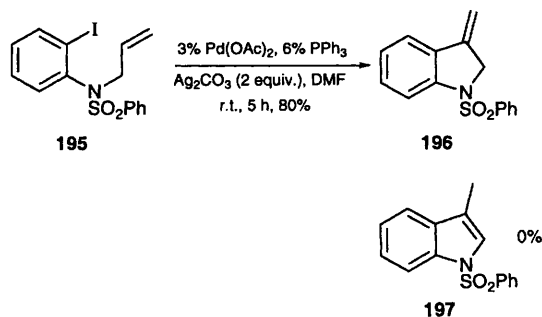
The question of regioselectivity arises not only in the carbopalladation step, as discussed above, but also in the β -hydride elimination step. Here the direction of elimination may be a problem as illustrated by the potential conversion of intermediate **190** to either **191** or **192**. Moreover, the palladium hydride formed from β -elimination may subsequently coordinate to the newly-formed double



bond to give **193**, add again to give another alkyl-palladium intermediate **194**, and re-eliminate with the formation of a different double bond. Repetition of this process may lead to a variety of different products. The first problem is not as serious as the second as there is generally a preferred direction of elimination.

It has been found, however, that both problems can be dealt with to a greater or lesser extent through the use of either silver¹⁴² or thallium¹⁴³ salts. They are used to sequester halide ions from the palladium complex **170** formed in the initial oxidative addition step, thus forming a series of cationic palladium complexes. Due to its cationic nature the palladium not only coordinates the alkene more rapidly, hence partly explaining the rate enhancing effect of these salts, but it also effectively undergoes more selective β -hydride elimination. This may be explained by faster β -elimination and/or a shorter lifetime of the hydridopalladium species thus formed.

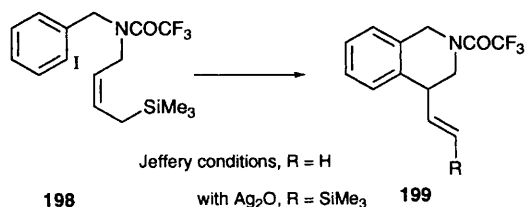
The first reported use of silver salts to control isomerisation in the intramolecular Heck reaction was by Overman *et al.*²³ Since then their use has become more widespread in the synthesis of both hetero- and carbo-cycles in mono-^{69,73,93} and poly-cyclisations.^{89,132,136,137} A good example of their use is in the control of isomerisation in the synthesis of 3-methyleneindolines.⁸ Without silver salts the cyclisation of **195** would form substituted indole **197** via initial elimination followed by re-addition of the hydridopalladium species and re-elimination to bring the double bond into conjugation with the aromatic ring. With the addition of silver carbonate, however, exclusive formation of the desired *exo*-methyleneindoline **196** was achieved.



Denmark *et al.* found that not only were silver salts necessary for good yields of the desired products from intramolecular Heck arylations of nitroalkenes, but also that the nature of the anion was very important.⁷⁴ For instance, silver carbonate worked well but silver nitrate gave none of the desired product. The importance of the anion has also been noted in asymmetric cyclisations but, as yet, there is little understanding of its rôle. The use of silver salts with vinyl triflates has led to decomposition of the starting material.¹⁰⁰ (However, silver salts should not be necessary in such cases, as when triflate is used as the leaving group then the reaction should follow Path B of the Cabri–Hayashi model to form a cationic palladium complex anyway.)

Thallium salts have been found to have a similar effect to silver salts and have been exploited in the intramolecular Heck reaction, predominantly by Grigg, in monocyclisations,^{39,42,63,64,66b} and polycyclisations.^{29,87,88}

Tietze *et al.* have found that allyl silanes may be used to control isomerisation.⁵³ Under Jeffery conditions the silyl group eliminates, but with the addition of silver oxide β -hydride elimination occurs to yield vinyl silanes as in the cyclisation of **198** to **199**.

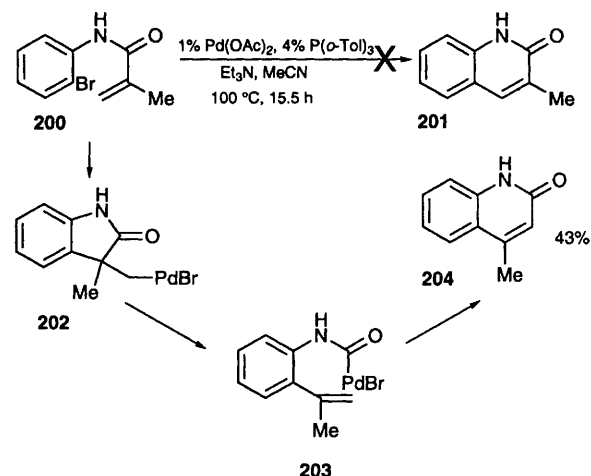


Finally, the addition of water to the reaction mixture when a phase transfer agent is present¹⁴⁴ has been found to accelerate the reaction⁵⁵ and in one case its presence was essential for the reaction to proceed.¹¹⁰

4.3 Unexpected products

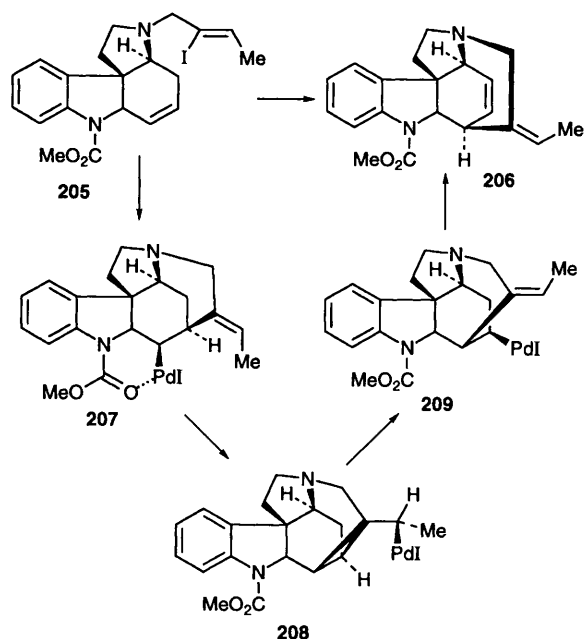
Occasionally, the products formed from a Heck reaction do not fit the accepted mechanism. Often there is a reasonably obvious explanation but sometimes the proposed explanation raises as many questions as it answers.

One of the very earliest examples of an unexpected product involved an attempted cyclisation of anilide **200** to quinolone **201** by Heck *et al.*¹⁰ The isomeric quinolone actually formed, **204**, was clearly not produced *via* the usual mechanism and so an alternative mechanism was proposed. This relied on the preferential formation of the 5-*exo* intermediate **202**. Lacking β -hydrogen atoms, the palladium undergoes a β -carbonyl elimination to form an acylpalladium intermediate **203** which then cyclises *via* a 6-*endo* process to form **204**.

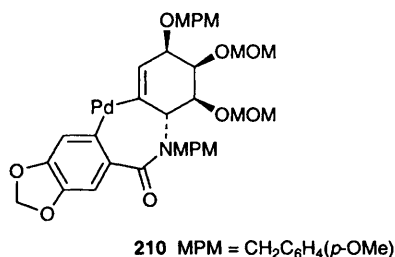


An interesting rearrangement was discovered by Rawal *et al.* in their efforts directed towards the synthesis of *Strychnos* alkaloids.¹⁴⁵ At first sight, the cyclisation of **205** appeared to have proceeded *via* a 7-*endo* route to give **206** in preference to the 6-*exo* product, but on further inspection, the geometry of the exocyclic double bond is seen to be incorrect for such a cyclisation. It was therefore proposed that the cyclisation had occurred *via* the 6-*exo* mode but that the alkylpalladium intermediate thus formed had not undergone the expected β -hydride elimination but instead formed a six-membered palladocycle with the neighbouring carbamate group¹⁴⁶ to give **207**. This intermediate could then rearrange with the aid of the pendant exocyclic double bond *via* the cyclopropylcarbinyllpalladate intermediate **208** to form the alkylpalladium intermediate **209** and the observed product **206**. Examples of homoallylpalladate–cyclopropylcarbinyllpalladate rearrangements¹⁴⁷ have also been observed by Negishi *et al.* during the course of studies on the cyclisations of vinyl halides onto geminally disubstituted terminal alkenes.⁹⁷

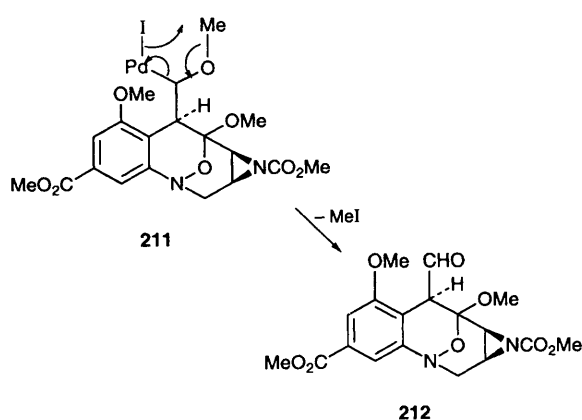
In several other cases the apparent mode of cyclisation should result in an alkylpalladium intermediate lacking a syn β -hydrogen atom for elimination and yet elimination still occurs. The reasons for this are varied. In cyclisations onto alkenes coordinated to carbonyl groups then oxo- π -allylpalladium intermediates have been invoked^{105g,71b,94a} through which the palladium can orient itself *syn* to a β -hydrogen. Where the alkylpalladium intermediate has palladium bound to a



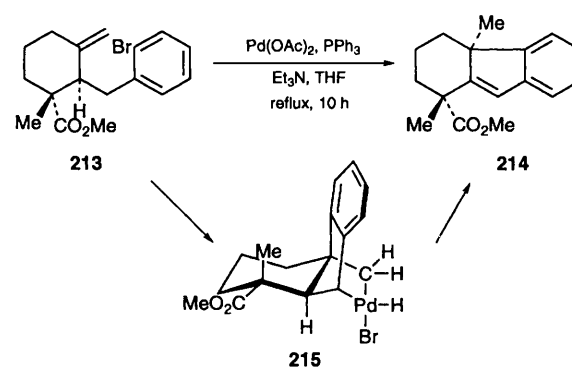
benzylic carbon then 'stereomutation' has been proposed to allow *syn* β -hydride elimination.^{37b,68} In syntheses of lycoricidine^{63,64} 6-*exo* cyclisation is apparently followed by *anti* β -hydride elimination to give the desired product and so an intermediate such as **210** is proposed which would lead to the product *via* a reductive elimination step.



Danishefsky *et al.* have reported the formation of an aldehyde *via* cyclisation onto an enol ether.^{75b} They propose that the elimination of palladium from **211** occurs *via* an 'Arbuzov-like unravelling' to give aldehyde **212**.



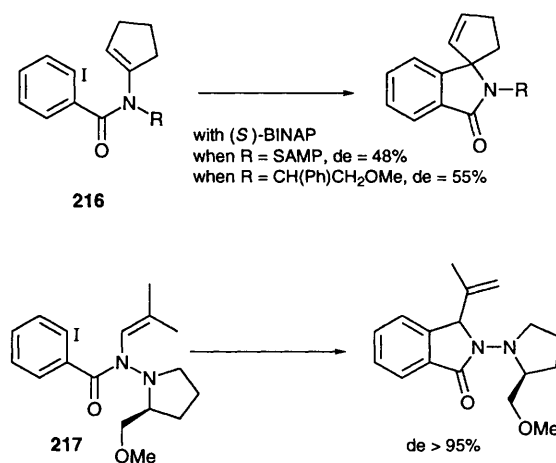
In a recent example, 5-*exo* cyclisation of **213** gave **214** when stoichiometric amounts of palladium acetate and triphenylphosphine were used with a large excess of triethylamine in refluxing THF.¹¹⁷ It was proposed that the alkylpalladium intermediate underwent intramolecular oxidative addition into the benzylic carbon–hydrogen bond to form **215** which then underwent sequential reductive elimination and β -hydride elimination of the palladium.



Lastly an example of what appears to be *syn* dealkoxypalladation has been reported.⁵⁵ Although for palladium(II) this is unprecedented, an example of *syn* elimination of palladium(0) from a β -hydroxy organopalladium intermediate is known.¹⁴⁸

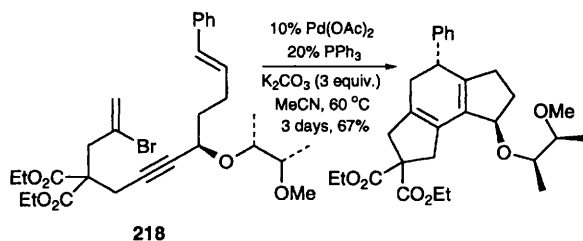
4.4 Diastereocontrol

The intramolecular Heck reaction is often highly diastereoselective as has been shown in Overman's elegant synthesis of scopadulcic acid A.¹³⁷ The use of chiral auxiliaries in providing stereocontrol, however, has not received much attention. Grigg *et al.* have shown that amino ethers may be effective chiral auxiliaries for the Heck reaction.³⁸ Thus, in the cyclisation of iodoarene **216** onto the pendant cycloalkene, no diastereoselectivity was observed for the two chiral auxiliaries indicated when achiral phosphines were used, but when (*S*)-BINAP was used diastereoselectivities of between 48 and 55% were achieved. When the acyclic alkene **217** bearing SAMP (or RAMP) as the chiral auxiliary was

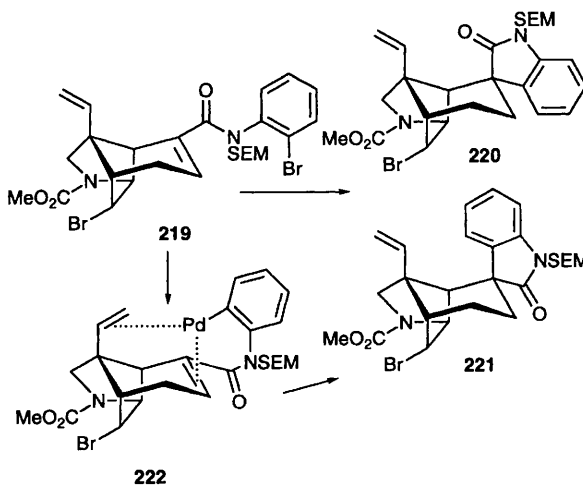


subjected to standard cyclisation conditions, diastereoselectivities of 95% were achieved with achiral phosphines.

In the cyclisation of dienyne **218** carried out by de Meijere *et al.*¹³³ the stereoselectivity of the final electrocyclisation step is controlled by the pendant chiral ether to give a diastereomeric excess of >95%.



Overman *et al.* have reported an example where the diastereoselectivity of an intramolecular Heck reaction was controlled by the conditions used.^{24b} Thus, when triethylamine was used as the base in the cyclisation of aryl bromide **219**, an 89:11 ratio of **220** to **221** was formed in very good yield. With silver phosphate as the base, however, a 3:97 ratio of **220** to **221** was formed in good yield. Their proposal to account for this reversal in stereoselectivity was that the cationic palladium intermediate formed by the action of the silver salts can coordinate to both alkenes present in the substrate to form intermediate **222** and therefore carbopalladation is directed in this case onto the upper face of the alkene.

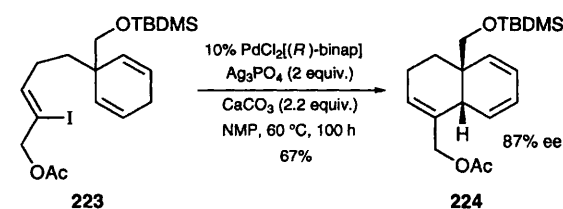


4.5 Enantiocontrol

The area of the asymmetric intramolecular Heck reaction has been explored mainly by the Shibasaki group. They have shown that prochiral vinyl iodides and vinyl triflates can be cyclised to products with high optical purity in the presence of enantiopure phosphines. For vinyl iodides the addition of silver salts is important to obtain a good ee^{105a} as would be expected from the Cabri–Hayashi model. When a

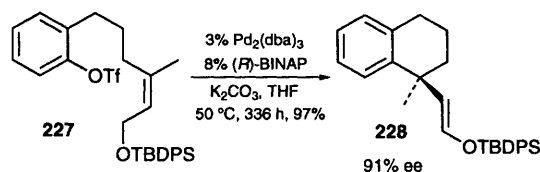
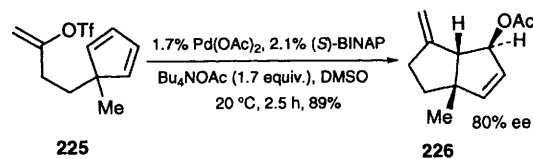
chiral bisphosphine is used, obviously the highest degree of influence over the enantioselectivity of the reaction is exerted when both phosphorus atoms are bound to the palladium atom. For this to be the case when the palladium coordinates to the alkene, the reaction must proceed along Path B. It was also found that the nature of the silver anion was very important and that silver phosphate gave the best results.

The best phosphine for this reaction has been found to be the BINAP ligand and better ees were obtained when the preformed palladium dichloride-BINAP catalyst was used.^{105b} The best solvents were polar and aprotic and *N*-methylpyrrolidinone was found to give consistently good results. The use of calcium carbonate as an additional base was also beneficial.^{105c} Under these conditions vinyl iodide **223** was cyclised to **224** in good yield and with a good ee.^{105d} Tris(dibenzylideneacetone)bispalladium has also been found to be a good catalyst for asymmetric Heck reactions of vinyl iodides. Experimentation with various ligands and salts often proves beneficial as in the synthesis of indolizidines⁴⁸ where BPPFOF {1-[1',2-bis(diphenylphosphino)ferrocenyl]ethanol} was found to be the best chiral ligand and silver-zeolite the best source of silver ions.



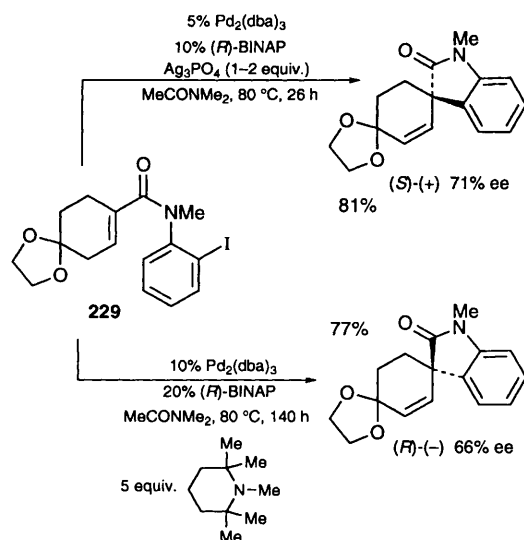
It has also been found that the use of vinyl triflates, which obviates the need for silver salts, gives good enantioselectivities with BINAP as the ligand.^{105e} When used with a phase transfer agent such as tetrabutylammonium acetate then the cyclisation can be followed by anion capture with the acetate anion as in the conversion of **225** to **226**.^{105c,f}

It has been found that nonpolar solvents give the best results when triflates are used^{105g} and under such conditions, with THF as the solvent and potassium carbonate as the base, asymmetric quaternary centres can be formed as in the cyclisation of aryl triflate **227** to tetrahydronaphthalene **228**.^{105h,j,k}



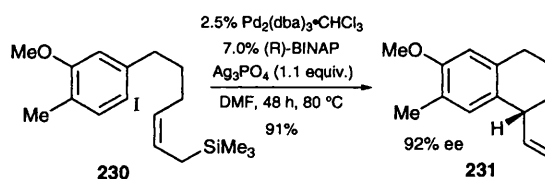
The solvent that gave the highest ees with triflates was 1,2-dichloroethane but under the standard range of conditions only a poor conversion of starting material was possible. This conversion was improved, however, upon the addition of alcohols, the most effective being pinacol or the acetate anion.^{105f} It appears that Pd⁰ is oxidised readily in 1,2-dichloroethane to Pd^{II}Cl₂L_n and that the addition of pinacol or potassium acetate prevents this process. Thus a new set of conditions have been developed for the intramolecular asymmetric Heck reaction of triflates: namely, palladium acetate as the catalyst, BINAP as the chiral ligand, two equivalents of potassium carbonate as the base together with either 15 equivalents of pinacol or one equivalent of potassium acetate in 1,2-dichloroethane.

Overman *et al.* have obtained extremely interesting results in their syntheses of indolones with asymmetric induction.²⁵ With the same enantiomer of a chiral ligand (BINAP) they have obtained either enantiomer of the cyclic product derived from **229** by varying the conditions used. With silver phosphate as the base and dimethylacetamide as solvent both significant ee's and yields of the (*S*)-indolone can be obtained, whilst with 1,2,2,6,6-pentamethylpiperidine and no silver salt present the (*R*)-indolone can also be formed in significant ee. Overman *et al.* have also carried out a bis-cyclisation with moderate enantioselectivity,¹²⁹ but although enantioselective polycyclisations are in principle a very powerful technique, this area is still largely unexplored.



Tietze *et al.* have combined asymmetric conditions with their use of allyl silanes for controlling the regioselectivity of the elimination step to create an asymmetric intramolecular Heck reaction of use in their total synthesis of a norsesquiterpene.^{60a,105f} In the key step, aryl iodide **230** was cyclised to **231** in excellent yield and enantioselectivity.

The asymmetric intramolecular Heck reaction is thus fast becoming a very useful and reliable

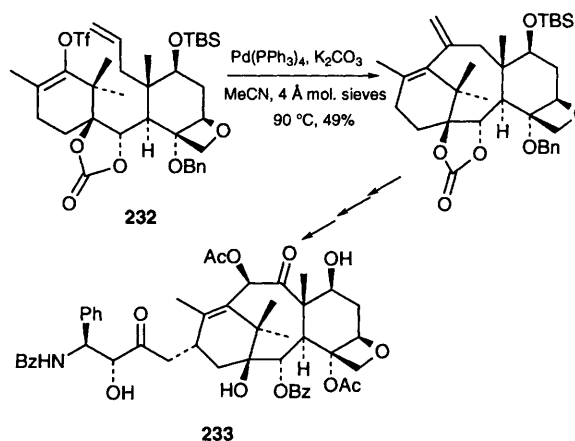


catalytic asymmetric carbon–carbon bond forming reaction.

5 Total syntheses

In the last three years the intramolecular Heck reaction has been widely used in the total synthesis of natural products with the ring generated being both heterocyclic^{41,42,72–74,75a} and carbocyclic.^{43,105,112,125,127b,137} In this section, four examples are described which demonstrate the versatility of the intramolecular Heck reaction.

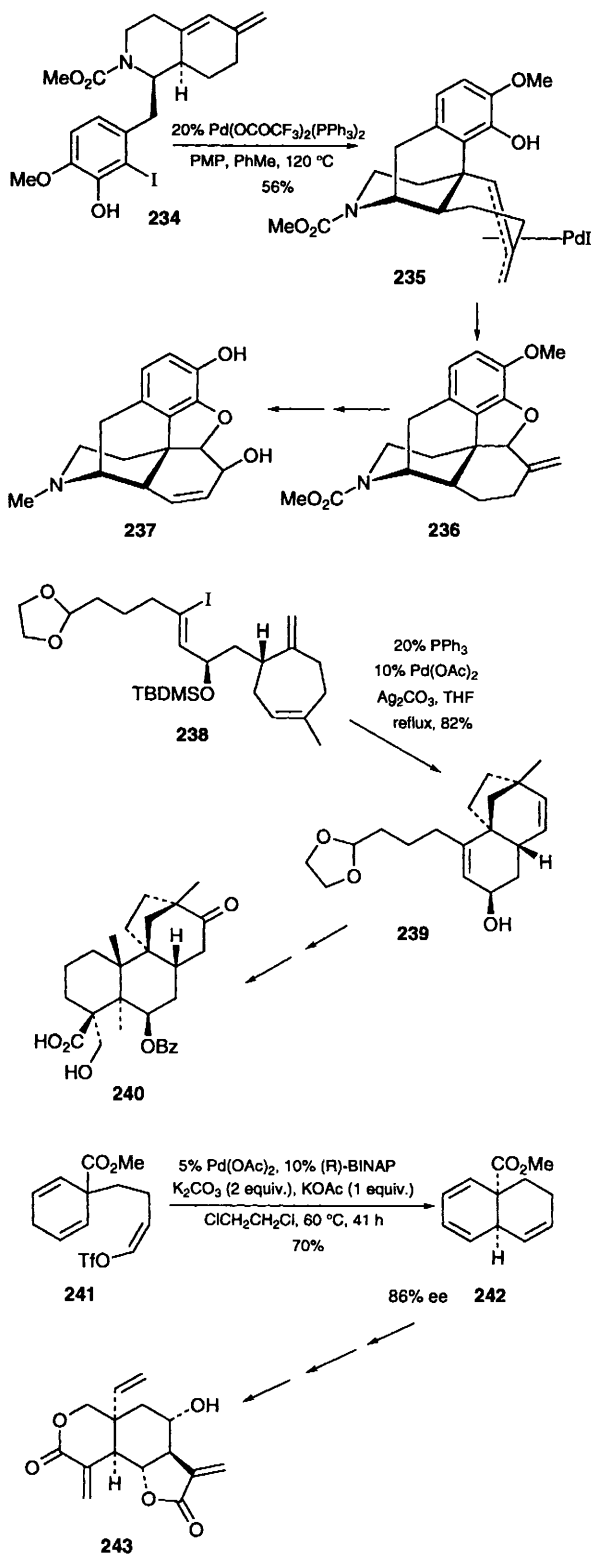
The total synthesis of taxol **233** has been described by Danishefsky *et al.* in a series of papers.¹¹¹ The key step in this synthesis was the closure of the eight-membered ring *via* an intramolecular Heck reaction of the vinyl triflate **232**. The closure was achieved in 49% yield under fairly standard conditions and clearly demonstrated the utility of the reaction for the cyclisations of highly functionalised substrates.



The synthesis of morphine **237** by Overman *et al.* has as its key step an intramolecular Heck reaction followed by an intramolecular anion capture process.¹²⁵ Thus, aryl iodide **234** undergoes a stereoselective Heck cyclisation onto a 1,3-diene to form the π -allylpalladium intermediate **235** which is then captured by an appropriately positioned hydroxy group to give the pentacyclic product **236**.

The usefulness of the polycyclisation methodology has been demonstrated by the synthesis of scopadulcic acid A **240** by Overman *et al.*¹³⁷ In this synthesis vinyl iodide **238** undergoes regioselective bis-cyclisation to give tricyclic **239**.

The synthesis of (+)-vernolepin **243** by Shibasaki *et al.*¹⁰⁵ⁱ corresponds to the first asymmetric total synthesis of this molecule and demonstrates the usefulness of the asymmetric intramolecular Heck reaction. Using the conditions described earlier



(potassium acetate as the additive and 1,2-dichloroethane as the solvent) vinyltriflate **241** was cyclised to bicyclic product **242** in 70% yield and 86% ee.

6 Conclusion

In the past few years, the intramolecular Heck reaction has started to reveal its full potential as a

powerful tool for the synthetic chemist interested in constructing heterocyclic and carbocyclic compounds. Together with its modifications which promote anion capture processes, multiple cyclisations and asymmetric syntheses, and its tolerance of a wide range of functional groups, this reaction is surely now one of the most powerful available to the synthetic organic chemist.

7 References

- (a) T. Mizoroki, K. Mori and A. Ozaki, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 581; (b) R. F. Heck and J. P. Nolley, Jr., *J. Org. Chem.*, 1972, **37**, 2320.
- (a) R. F. Heck, *Acc. Chem. Res.*, 1979, **12**, 146; (b) R. F. Heck, *Org. React.*, 1982, **27**, 345; (c) J. Tsuji, *Organic Synthesis with Palladium Compounds*, Springer, Berlin, 1980; (d) B. M. Trost and T. R. Verhoeven, in *Comprehensive Organometallic Chemistry*, Pergamon, Oxford, 1982, vol. 8, p. 799.
- (a) G. P. Chiusoli, *Pure Appl. Chem.*, 1980, **52**, 635; (b) C.-M. Andersson and A. Hallberg, *Tetrahedron Lett.*, 1987, **28**, 4215.
- (a) G.-Z. Wu, F. Lamaty and E. Negishi, *J. Org. Chem.*, 1989, **54**, 2507; (b) R. Grigg, S. Sukirthalingam and V. Sridharan, *Tetrahedron Lett.*, 1991, **32**, 2545.
- (a) T. Jeffery, *J. Chem. Soc., Chem. Commun.*, 1984, 1287; (b) T. Jeffery, *Tetrahedron Lett.*, 1985, **26**, 2667; (c) T. Jeffery, *Synthesis*, 1987, 70.
- (a) G. D. Daves, Jr. and A. Hallberg, *Chem. Rev.*, 1989, **89**, 1433; (b) R. F. Heck, in *Comprehensive Organic Synthesis*, Pergamon, Oxford, 1991, vol. 4, p. 833; (c) A. de Meijere and F. E. Meyer, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2379; (d) W. Cabri and I. Candiani, *Acc. Chem. Res.*, 1995, **28**, 2; (e) B. C. Soderberg in *Comprehensive Organometallic Chemistry II*, Pergamon, Oxford, 1995, vol. 12, p. 259.
- M. Mori, K. Chiba and Y. Ban, *Tetrahedron Lett.*, 1977, 1037.
- T. Sakamoto, Y. Kondo, M. Uchiyama and H. Yamana, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1941.
- M. Mori and Y. Ban, *Tetrahedron Lett.*, 1979, 1133.
- M. O. Terpko and R. F. Heck, *J. Am. Chem. Soc.*, 1979, **101**, 5281.
- R. Odle, B. Blevins, M. Ratcliff and L. S. Hegedus, *J. Org. Chem.*, 1980, **45**, 2709.
- H. A. Dieck and R. F. Heck, *J. Am. Chem. Soc.*, 1974, **96**, 1133.
- A. Kasahara, T. Izumi, S. Murakami, H. Yanai and M. Takatori, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 927.
- J. P. Michael, S.-F. Chang and C. Wilson, *Tetrahedron Lett.*, 1993, **34**, 8365.
- L. S. Hegedus, T. A. Mulhern and A. Mori, *J. Org. Chem.*, 1985, **50**, 4282.
- T. Sakamoto, T. Nagano, Y. Kondo and H. Yamanaka, *Synthesis*, 1990, 215.
- K. Koerber-Plé and G. Massiot, *Synlett*, 1994, 759.
- R. C. Larock and S. Babu, *Tetrahedron Lett.*, 1987, **28**, 5291.
- (a) P. Martin, *Helv. Chim. Acta*, 1989, **72**, 1554; (b) R. J. Sundberg and W. J. Pitts, *J. Org. Chem.*, 1991, **56**, 3048; (c) A. Arcadi, S. Cacchi, F. Marinelli and P. Pace, *Synlett*, 1993, 743; (d) L. F. Tietze and T. Grote, *J. Org. Chem.*, 1994, **59**, 192; (e) D. Wensbro, U. Annby and S. Gronowitz, *Tetrahedron*, 1995, **51**, 10323.

- 20 J. E. Macor, D. H. Blank, R. J. Pos and K. Ryan, *Tetrahedron Lett.*, 1992, **33**, 8011.
- 21 J. W. Dankwardt and L. A. Flippin, *J. Org. Chem.*, 1995, **60**, 2312.
- 22 H. Iida, Y. Yuasa and C. Kibayashi, *J. Org. Chem.*, 1980, **45**, 2938.
- 23 M. M. Ableman, T. Oh and L. E. Overman, *J. Org. Chem.*, 1987, **52**, 4130.
- 24 (a) W. G. Earley, T. Oh and L. E. Overman, *Tetrahedron Lett.*, 1988, **29**, 3785; (b) A. Madin and L. E. Overman, *Tetrahedron Lett.*, 1992, **33**, 4859.
- 25 (a) A. Ashimori and L. E. Overman, *J. Org. Chem.*, 1992, **57**, 4571; (b) A. Ashimori, T. Matsuura, L. E. Overman and D. J. Poon, *J. Org. Chem.*, 1993, **58**, 6949.
- 26 R. Grigg, *J. Heterocycl. Chem.*, 1994, **24**, 2139.
- 27 (a) B. Burns, R. Grigg, V. Sridharan, P. Stevenson and T. Worakun, *Tetrahedron Lett.*, 1988, **29**, 4329; (b) B. Burns, R. Grigg, V. Santhakumar, V. Sridharan, P. Stevenson and T. Worakun, *Tetrahedron*, 1992, **48**, 7297.
- 28 R. Grigg, V. Santhakumar and V. Sridharan, *Tetrahedron Lett.*, 1993, **34**, 3163.
- 29 R. Grigg, P. Kennewell and A. J. Teasdale, *Tetrahedron Lett.*, 1992, **33**, 7789.
- 30 B. Burns, R. Grigg, P. Ratananukul, V. Sridharan, P. Stevenson, S. Sukirthalingam and T. Worakun, *Tetrahedron Lett.*, 1988, **29**, 5565.
- 31 B. Burns, R. Grigg, P. Ratananukul, V. Sridharan, P. Stevenson, S. Sukirthalingam and T. Worakun, *Tetrahedron Lett.*, 1989, **30**, 1135.
- 32 R. Grigg, A. Teasdale and V. Sridharan, *Tetrahedron Lett.*, 1991, **32**, 3859.
- 33 F.-T. Luo and R.-T. Wang, *Heterocycles*, 1991, **32**, 2365.
- 34 (a) J. M. O'Connor, B. J. Stallman, W. G. Clark, A. Y. L. Shu, R. E. Spada, T. M. Stevenson and H. A. Dieck, *J. Org. Chem.*, 1983, **48**, 807; (b) E. C. Taylor, A. H. Katz, H. Saldora-Zamora and A. McKillop, *Tetrahedron Lett.*, 1985, **26**, 5963; (c) R. C. Larock, N. Berrios-Pena and K. Narayanan, *J. Org. Chem.*, 1990, **55**, 3447; (d) R. C. Larock, *Pure Appl. Chem.*, 1992, **62**, 653; (e) L. S. Hegedus, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1113.
- 35 R. Grigg, V. Sridharan, P. Stevenson and T. Worakun, *J. Chem. Soc., Chem. Commun.*, 1986, 1697.
- 36 R. Grigg, V. Sridharan, S. Sukirthalingam and T. Worakun, *Tetrahedron Lett.*, 1989, **30**, 1139.
- 37 (a) R. Grigg, V. Sridharan, P. Stevenson and S. Sukirthalingam, *Tetrahedron*, 1989, **45**, 3557; (b) R. Grigg, V. Sridharan, P. Stevenson and S. Sukirthalingam and T. Worakun, *Tetrahedron*, 1990, **46**, 4003.
- 38 R. Grigg, M. J. R. Dorrity, J. F. Malone, T. Mongkolassavaratana, W. D. J. A. Norbert and V. Sridharan, *Tetrahedron Lett.*, 1990, **31**, 3075.
- 39 R. Grigg, V. Loganathan, V. Santhakumar, V. Sridharan and A. Teasdale, *Tetrahedron Lett.*, 1991, **32**, 687.
- 40 (a) A. P. Kozikowski and D. Ma, *Tetrahedron Lett.*, 1991, **32**, 3317; (b) G. A. Kraus and H. Kim, *Synth. Commun.*, 1993, **23**, 55.
- 41 D. L. Comins, M. F. Baevsky and H. Hong, *J. Am. Chem. Soc.*, 1992, **114**, 10971.
- 42 R. Yoneda, Y. Sakamoto, Y. Oketo, K. Minami, S. Harusawa and T. Kurihara, *Tetrahedron Lett.*, 1994, **35**, 3749.
- 43 M. Shibasaki and M. Sodeoka, *J. Synth. Org. Chem. Jpn.*, 1994, **52**, 596.
- 44 J. R. Luly and H. Rapoport, *J. Org. Chem.*, 1984, **49**, 1671.
- 45 A. L. Germain, T. L. Gilchrist and P. D. Kemmitt, *Heterocycles*, 1994, **37**, 697.
- 46 E. Desarbres and J.-Y. Méroux, *Heterocycles*, 1995, **41**, 1987.
- 47 (a) M. Mori, N. Kanda, I. Oda and Y. Ban, *Tetrahedron*, 1985, **41**, 5465; (b) M. Mori, I. Oda and Y. Ban, *Tetrahedron Lett.*, 1982, **23**, 5315.
- 48 Y. Sato, S. Nukui, M. Sodeoka and M. Shibasaki, *Tetrahedron*, 1994, **50**, 371.
- 49 L. Shi, C. K. Narula, K. J. Mak, L. Kao, Y. Xu and R. F. Heck, *J. Org. Chem.*, 1983, **48**, 3894.
- 50 R. C. Larock and D. E. Stinn, *Tetrahedron Lett.*, 1988, **29**, 4687.
- 51 E. Negishi, T. Nguyen and B. O'Connor, *Heterocycles*, 1989, **28**, 55.
- 52 S. Wolff and H. M. R. Hoffmann, *Synthesis*, 1988, 760.
- 53 L. F. Tietze and R. Schimpf, *Chem. Ber.*, 1994, **127**, 2235.
- 54 R. Anacardio, A. Arcadi, G. Danniballe and F. Marinelli, *Synthesis*, 1995, 831.
- 55 J.-F. Nguefack, V. Bolitt and D. Sinou, *J. Chem. Soc., Chem. Commun.*, 1995, 1893.
- 56 R. C. Larock and N. H. Lee, *J. Org. Chem.*, 1991, **56**, 6253.
- 57 N. Arnau, M. Moreno-Manas and R. Pleixats, *Tetrahedron*, 1993, **49**, 11019.
- 58 (a) B. Burns, R. Grigg, P. Ratananukul, V. Sridharan, P. Stevenson and T. Worakun, *Tetrahedron Lett.*, 1988, **29**, 4329; (b) J. H. Rigby, R. C. Hughes and M. J. Heeg, *J. Am. Chem. Soc.*, 1995, **117**, 7834.
- 59 D. St. C. Black, P. A. Keller and N. Kumar, *Tetrahedron*, 1992, **48**, 7601.
- 60 (a) L. F. Tietze and R. Schimpf, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1089; (b) L. F. Tietze and O. Burkhardt, *Synthesis*, 1994, 1331; (c) L. F. Tietze and O. Burkhardt, *Liebigs Ann. Chem.*, 1995, 1153.
- 61 T. Okita and M. Isobe, *Tetrahedron*, 1994, **50**, 11143.
- 62 R. Grigg, V. Santhakumar, V. Sridharan, M. Thornton-Pett and A. W. Bridge, *Tetrahedron*, 1993, **49**, 5177.
- 63 S. F. Martin and H.-H. Tso, *Heterocycles*, 1993, **35**, 85.
- 64 (a) N. Chida, N. Ohtsuka and S. Ogawa, *Tetrahedron Lett.*, 1991, **32**, 4525; (b) N. Chida, M. Ohtsuka and S. Ogawa, *J. Org. Chem.*, 1993, **58**, 4441; (c) T. Hudlicky and H. F. Olivo, *J. Am. Chem. Soc.*, 1992, **114**, 9694; (d) M. C. McIntosh and S. M. Weinreb, *J. Org. Chem.*, 1993, **58**, 4823.
- 65 (a) P. Melnyk, J. Gasche and C. Thal, *Tetrahedron Lett.*, 1993, **34**, 5449; (b) P. Melnyk, B. Legrand, J. Gasche, P. Ducrot and C. Thal, *Tetrahedron*, 1995, **51**, 1941.
- 66 (a) B. Burns, R. Grigg, V. Sridharan and T. Worakun, *Tetrahedron Lett.*, 1988, **29**, 4325; (b) R. Grigg, V. Loganathan, S. Sukirthalingam and V. Sridharan, *Tetrahedron Lett.*, 1990, **31**, 6573.
- 67 V. H. Rawal and C. Michoud, *Tetrahedron Lett.*, 1991, **32**, 1695.
- 68 (a) P. C. Amos and D. A. Whiting, *J. Chem. Soc., Chem. Commun.*, 1987, 510; (b) S. A. Ahmad-Junan, P. C. Amos and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1992, 539.
- 69 M. M. Ableman, L. E. Overman and V. D. Tran, *J. Am. Chem. Soc.*, 1990, **112**, 6959.
- 70 B. Wunsch, H. Diekmann and G. Höfner, *Tetrahedron: Asymmetry*, 1995, **6**, 1527.
- 71 (a) M. Catellani, G. P. Chiusoli, M. C. Fagnola and G. Solari, *Tetrahedron Lett.*, 1994, **35**, 5919; (b) G. K.

- Friestad and B. P. Branchaud, *Tetrahedron Lett.*, 1995, **36**, 7047.
- 72 F. G. Fang, S. Xie and M. W. Lowery, *J. Org. Chem.*, 1994, **59**, 6142.
- 73 Z. Jin and P. L. Fuchs, *Tetrahedron Lett.*, 1993, **34**, 5205.
- 74 S. E. Denmark and M. E. Schnute, *J. Org. Chem.*, 1995, **60**, 1013.
- 75 (a) K. F. McClure and S. Danishefsky, *J. Am. Chem. Soc.*, 1993, **115**, 6094; (b) K. McClure, S. Danishefsky and G. K. Schulte, *J. Org. Chem.*, 1994, **59**, 355.
- 76 R. Grigg, V. Sridharan, P. Stevenson, P. Teasdale, M. Thornton-Pett and T. Worakun, *Tetrahedron*, 1991, **47**, 9703.
- 77 F. E. Ziegler, U. R. Chakraborty and R. B. Weisenfeld, *Tetrahedron*, 1981, **37**, 4035.
- 78 L. F. Tietze and R. Schimpf, *Synthesis*, 1993, 876.
- 79 S. E. Gibson (née Thomas) and R. J. Middleton, *J. Chem. Soc., Chem. Commun.*, 1995, 1743.
- 80 (a) S. Ma and E. Negishi, *J. Org. Chem.*, 1994, **59**, 4730; (b) S. Ma and E. Negishi, *J. Am. Chem. Soc.*, 1995, **117**, 6345.
- 81 R. J. Sundberg and R. J. Cherney, *J. Org. Chem.*, 1990, **55**, 6028.
- 82 M. J. Stocks, R. P. Harrison and S. J. Teague, *Tetrahedron Lett.*, 1995, **36**, 6555.
- 83 M. M. Abelman and L. E. Overman, *J. Am. Chem. Soc.*, 1988, **110**, 2328.
- 84 R. Grigg, M. J. Dorrity, J. F. Malone, V. Sridharan and S. Sukirthalingam, *Tetrahedron Lett.*, 1990, **31**, 1343.
- 85 R. Grigg, V. Sridharan and S. Sukirthalingam, *Tetrahedron Lett.*, 1991, **32**, 3855.
- 86 R. Grigg, P. Fretwell, C. Meerholtz and V. Sridharan, *Tetrahedron*, 1994, **50**, 359.
- 87 D. Brown, R. Grigg, V. Sridharan and V. Tambyrajah, *Tetrahedron Lett.*, 1995, **36**, 8137.
- 88 R. Grigg and V. Sridharan, *Tetrahedron Lett.*, 1992, **32**, 7965.
- 89 F. E. Meyer, P. J. Parsons and A. de Meijere, *J. Org. Chem.*, 1991, **56**, 6487.
- 90 S. D. Knight and L. E. Overman, *Heterocycles*, 1994, **39**, 497.
- 91 (a) R. Grigg, P. Stevenson and T. Worakun, *J. Chem. Soc., Chem. Commun.*, 1984, 1073; (b) R. Grigg, P. Stevenson and T. Worakun, *Tetrahedron*, 1988, **44**, 2033.
- 92 (a) E. Negishi, Y. Zhang and B. O'Connor, *Tetrahedron Lett.*, 1988, **29**, 2915; (b) Y. Zhang, B. O'Connor and E. Negishi, *J. Org. Chem.*, 1988, **53**, 5588.
- 93 R. C. Larock, H. Song, B. E. Baker and W. H. Gong, *Tetrahedron Lett.*, 1988, **29**, 2919.
- 94 (a) H. Ishibashi, K. Ito, T. Hirano, M. Tabuchi and M. Ikeda, *Tetrahedron*, 1993, **49**, 5471; (b) A. J. Davies, R. J. K. Taylor, D. J. Scopes and A. H. Wadsworth, *Bioorg. Med. Chem. Lett.*, 1992, **2**, 481.
- 95 O. Cornec, B. Joseph and J.-Y. Mérou, *Tetrahedron Lett.*, 1995, **36**, 8587.
- 96 B. O'Connor, Y. Zhang, E. Negishi, F. T. Luo and J. W. Chang, *Tetrahedron Lett.*, 1988, **29**, 3903.
- 97 Z. Owczarczk, F. Lamaty, E. J. Vawter and E. Negishi, *J. Am. Chem. Soc.*, 1992, **114**, 10 091.
- 98 L. S. Hegedus, M. R. Sestrick, E. J. Michaelson and P. J. Harrington, *J. Org. Chem.*, 1989, **54**, 4141.
- 99 J. M. Gaudin, *Tetrahedron Lett.*, 1991, **32**, 6113.
- 100 S. Laschat, F. Narjes and L. E. Overman, *Tetrahedron*, 1994, **50**, 347.
- 101 (a) G. E. Stokker, *Tetrahedron Lett.*, 1987, **28**, 3179; (b) J. P. Konopolski, K. S. Chu and G. R. Negrete, *J. Org. Chem.*, 1991, **56**, 1355; (c) W. Cabri, I. Candiani, S. De Bernardianis, F. Francalanci, S. Penco and R. Santi, *J. Org. Chem.*, 1991, **56**, 5796.
- 102 C. Liljebris, B. Resul and U. Hacksell, *Tetrahedron*, 1995, **51**, 9139.
- 103 D. Sperandio and H. J. Hansen, *Helv. Chim. Acta*, 1995, **78**, 765.
- 104 (a) D. C. Horwell, P. D. Nichols and E. Roberts, *Tetrahedron Lett.*, 1994, **35**, 939; (b) D. C. Horwell, P. D. Nichols, G. S. Ratcliffe and E. Roberts, *J. Org. Chem.*, 1994, **59**, 4418.
- 105 (a) Y. Sato, M. Sodeoka and M. Shibasaki, *J. Org. Chem.*, 1989, **54**, 4738; (b) Y. Sato, M. Sodeoka and M. Shibasaki, *Chem. Lett.*, 1990, 1953; (c) K. Kagechika and M. Shibasaki, *J. Org. Chem.*, 1991, **56**, 4093; (d) Y. Sato, S. Watanabe and M. Shibasaki, *Tetrahedron Lett.*, 1992, **33**, 2589; (e) Y. Sato, T. Honda and M. Shibasaki, *Tetrahedron Lett.*, 1992, **33**, 2593; (f) K. Kagechika, T. Oshima and M. Shibasaki, *Tetrahedron*, 1993, **49**, 1773; (g) K. Kondo, M. Sodeoka, M. Mori and M. Shibasaki, *Synthesis*, 1993, 920; (h) T. Takemoto, M. Sodeoka, H. Sasai and M. Shibasaki, *J. Am. Chem. Soc.*, 1993, **115**, 8477; (i) K. Ohrai, K. Kondo, M. Sodeoka and M. Shibasaki, *J. Am. Chem. Soc.*, 1994, **116**, 11 737; (j) K. Kondo, M. Sodeoka and M. Shibasaki, *J. Org. Chem.*, 1995, **60**, 4322; (k) K. Kondo, M. Sodeoka and M. Shibasaki, *Tetrahedron: Asymmetry*, 1995, **6**, 2453; (l) L. F. Tietze and T. Raschke, *Synlett*, 1995, 597.
- 106 H. Ishibashi, K. Ito, M. Tahuchi and M. Ikeda, *Heterocycles*, 1991, **32**, 1279.
- 107 C. Y. Hong, N. Kado and L. E. Overman, *J. Am. Chem. Soc.*, 1993, **115**, 11 028.
- 108 H. Muratake, I. Abe and M. Natsume, *Tetrahedron Lett.*, 1994, **35**, 2573.
- 109 (a) M. Toyota, Y. Nishikawa and K. Fukumoto, *Tetrahedron Lett.*, 1994, **35**, 6495; (b) M. Toyota, Y. Nishikawa and K. Fukumoto, *Tetrahedron*, 1994, **38**, 11 153.
- 110 P. Wiedenau, B. Monse and S. Blechert, *Tetrahedron*, 1995, **51**, 1167.
- 111 (a) J. J. Masters, D. K. Jung, W. G. Bornmann, S. J. Danishefsky and S. Degala, *Tetrahedron Lett.*, 1993, **34**, 7253; (b) J. J. Masters, D. K. Jung, S. J. Danishefsky, L. B. Snyder, J. K. Park, R. C. Isaacs, C. A. Alaimo and W. B. Young, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 452; (c) J. J. Masters, J. T. Link, L. B. Snyder, W. B. Young and S. J. Danishefsky, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1723; (d) W. B. Young, J. J. Masters and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1995, **117**, 5228.
- 112 V. H. Rawal, C. Michoud and R. Monestel, *J. Am. Chem. Soc.*, 1993, **115**, 3030.
- 113 (a) K. Nagasawa, Y. Zako, H. Ishihara and I. Shimizu, *Tetrahedron Lett.*, 1991, **32**, 4937; (b) K. Nagasawa, H. Ishihara, Y. Zako and I. Shimizu, *J. Org. Chem.*, 1993, **58**, 2523; (c) C. Chen and D. Crich, *Tetrahedron Lett.*, 1992, **33**, 1945; (d) J. L. Mascarenas, A. M. Garcia, L. Castedo and A. Mourino, *Tetrahedron Lett.*, 1992, **33**, 4365; (e) T. Takahashi and M. Nakazawa, *Synlett*, 1993, 37; (f) S. Hatakeyama, H. Irie, T. Shintani, Y. Noguchi, H. Yamada and M. Nishizawa, *Tetrahedron*, 1994, **50**, 13369.
- 114 E. G. Baggiolini, J. A. Iacobelli, B. M. Hennesy and M. R. Uskokovic, *J. Am. Chem. Soc.*, 1982, **104**, 2945.
- 115 J. M. Nuss, M. M. Murphy, R. A. Rennels, M. H. Heravi and B. J. Mohr, *Tetrahedron Lett.*, 1993, **34**, 3079.

- 116 C. K. Narula, K. J. Mak and R. F. Heck, *J. Org. Chem.*, 1983, **48**, 2792.
- 117 J. K. Mukopadhyaya, S. Pal and U. R. Ghatak, *Synth. Commun.*, 1995, **25**, 1641.
- 118 R.-T. Wang, F.-L. Chou and F.-L. Luo, *J. Org. Chem.*, 1990, **55**, 4846.
- 119 E. Negishi, Y. Noda, F. Lamaty and E.J. Vawter, *Tetrahedron Lett.*, 1990, **31**, 4393.
- 120 S. Torii, H. Okumoto, T. Tadokoro, A. Nishimura and M. A. Rashid, *Tetrahedron Lett.*, 1993, **34**, 2139.
- 121 (a) J. M. Nuss, B. H. Levine, R. A. Rennels and M. M. Heravi, *Tetrahedron Lett.*, 1991, **32**, 5243; (b) J. M. Nuss, R. A. Rennels and B. H. Levine, *J. Am. Chem. Soc.*, 1993, **115**, 6991.
- 122 G. D. Harris, R. J. Herr and S. M. Weinreb, *J. Org. Chem.*, 1993, **58**, 5452.
- 123 C. S. Nylund, J. M. Klopp and S. M. Weinreb, *Tetrahedron Lett.*, 1994, **35**, 4287.
- 124 C. S. Nylund, D. T. Smith, J. M. Klopp and S. M. Weinreb, *Tetrahedron*, 1995, **51**, 9301.
- 125 C.Y. Hong and L. E. Overman, *Tetrahedron Lett.*, 1994, **35**, 3453.
- 126 S. P. Watson, G. R. Knox and N. M. Heron, *Tetrahedron Lett.*, 1994, **35**, 9763.
- 127 (a) E. Negishi, *Pure Appl. Chem.*, 1992, **64**, 323; (b) L. E. Overman, M. M. Ableman, D. J. Kucera, V. D. Tran and D. J. Ricca, *Pure Appl. Chem.*, 1992, **64**, 1813.
- 128 M. M. Abelman and L. E. Overman, *J. Am. Chem. Soc.*, 1988, **110**, 2328.
- 129 N. E. Carpenter, D. J. Kucera and L. E. Overman, *J. Org. Chem.*, 1989, **54**, 5846.
- 130 Y. Zhang and E. Negishi, *J. Am. Chem. Soc.*, 1989, **111**, 3454.
- 131 Y. Zhang, G. Wu, G. Agnel and E. Negishi, *J. Am. Chem. Soc.*, 1990, **112**, 8590.
- 132 F. E. Meyer, J. Brandenburg, P. J. Parsons and A. de Meijere, *J. Chem. Soc., Chem. Commun.*, 1992, 390.
- 133 F. E. Meyer, H. Henniges and A. de Meijere, *Tetrahedron Lett.*, 1992, **33**, 8039.
- 134 T. Sigihara, C. Copéret, Z. Owczarczyk, L. S. Harring and E. Negishi, *J. Am. Chem. Soc.*, 1994, **116**, 7923.
- 135 (a) S. Torii, H. Okumoto and A. Nishimura, *Tetrahedron Lett.*, 1991, **32**, 4167; (b) E. Negishi, L. S. Harring, Z. Owczarczyk, M. M. Mohamud and M. Ay, *Tetrahedron Lett.*, 1992, **33**, 3253; (c) E. Negishi, M. Ay and T. Sugihara, *Tetrahedron*, 1993, **49**, 5471.
- 136 F. E. Meyer and A. de Meijere, *Synlett*, 1991, 777.
- 137 (a) D. J. Kucera, S. J. O'Connor and L. E. Overman, *J. Org. Chem.*, 1993, **58**, 5304; (b) L. E. Overman, D. J. Ricca and V. D. Tran, *J. Am. Chem. Soc.*, 1993, **115**, 2042; (c) L. E. Overman, *Pure Appl. Chem.*, 1994, **66**, 1423.
- 138 (a) S. Cacchi, E. Morera and G. Ortari, *Tetrahedron Lett.*, 1984, **25**, 2271; (b) W. J. Scott, M. R. Pena, K. Sward, S. J. Stoessel and J. K. Stille, *J. Org. Chem.*, 1985, **50**, 2302; (c) S. Cacchi and A. Lupi, *Tetrahedron Lett.*, 1992, **33**, 3939.
- 139 (a) W. Cabri, I. Candiani, A. Bedeschi, S. Penco and R. Santi, *J. Org. Chem.*, 1992, **57**, 1481; (b) W. Cabri, I. Candiani, A. Bedeschi and R. Santi, *J. Org. Chem.*, 1992, **57**, 3558; (c) F. Ozawa, A. Kubo and T. Hayashi, *J. Am. Chem. Soc.*, 1991, **113**, 1417.
- 140 E. G. Samsel and J. R. Norton, *J. Am. Chem. Soc.*, 1984, **106**, 5505.
- 141 (a) R. F. Heck, *J. Am. Chem. Soc.*, 1969, **91**, 6707; (b) D. L. Thorn and R. Hoffmann, *J. Am. Chem. Soc.*, 1978, **100**, 2079.
- 142 (a) K. Karabelas and A. Hallberg, *Tetrahedron Lett.*, 1985, **26**, 3131; (b) K. Karabelas, C. Westerlund and A. Hallberg, *J. Org. Chem.*, 1985, **50**, 3896; (c) K. Karabelas and A. Hallberg, *J. Org. Chem.*, 1986, **51**, 5286; (d) K. Karabelas and A. Hallberg, *J. Org. Chem.*, 1988, **53**, 4909; (e) K. Karabelas and A. Hallberg, *J. Org. Chem.*, 1989, **54**, 1773; (f) R. C. Larock and W. H. Gong, *J. Org. Chem.*, 1989, **54**, 2047; (g) K. Nilsson and A. Hallberg, *J. Org. Chem.*, 1990, **55**, 2464; (h) K. Nilsson and A. Hallberg, *J. Org. Chem.*, 1992, **57**, 4015.
- 143 (a) C. Carfagna, A. Musco, G. Sallese, R. Santi and G. Fiorani, *J. Org. Chem.*, 1991, **56**, 261; (b) W. Cabri, I. Candiani, A. Bedeschi and R. Santi, *Tetrahedron Lett.*, 1991, **32**, 1753.
- 144 T. Jeffery, *Tetrahedron Lett.*, 1994, **35**, 3051.
- 145 V. H. Rawal and C. Michoud, *J. Org. Chem.*, 1993, **58**, 5583.
- 146 J. J. Masters and L. S. Hegedus, *J. Org. Chem.*, 1993, **58**, 4547.
- 147 (a) M. Green and R. P. Hughes, *J. Chem. Soc., Dalton Trans.*, 1976, 1880; (b) W. A. Donaldson and C. A. Brodt, *J. Organomet. Chem.*, 1987, **330**, C33.
- 148 U. Hacksell and G. D. Daves Jr, *Organometallics*, 1983, **2**, 772.