

Catalytic applications of transition metals in organic synthesis

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1 Introduction

This review describes highlights of the literature involving homogeneous transition metal catalysed reactions published during 1999. As with previous reviews in this series,¹ the authors have aimed to discuss emerging areas and new procedures, as well as particularly noteworthy synthetic examples of older methodology.

2 Oxidation reactions

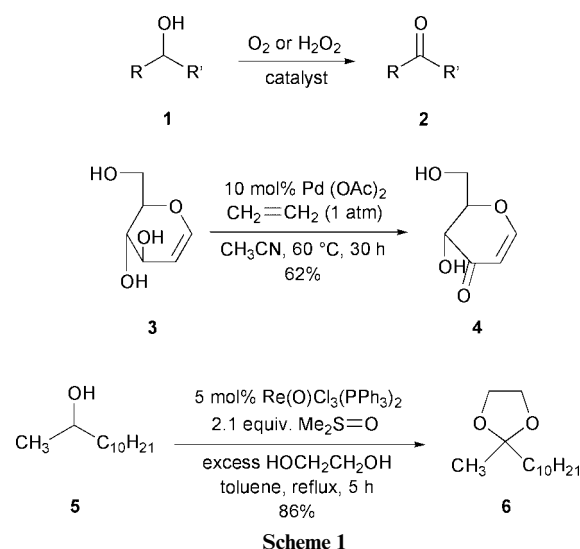
One of the oldest oxidation reactions, the conversion of alcohols **1** into the corresponding carbonyl compounds **2**, has been receiving considerable attention using transition metal catalysts and molecular oxygen. Various catalytic systems have been reported, including the use of copper chloride–phenanthroline,² copper chloride–osmium tetroxide³ and various complexes of palladium(II).⁴ The use of hydrogen peroxide with ruthenium⁵ and rhenium⁶ catalysts has also been shown to provide systems capable of converting alcohols into aldehydes and ketones. Interestingly, the oxidation of alcohol **3** into ketone **4** (Scheme 1) can be achieved using a palladium catalyst and uses ethylene as the stoichiometric oxidant.⁷ In general, the use of a heterogeneous palladium catalyst was found to give better conversion.

The rhenium-catalysed oxidation of secondary alcohols in the presence of ethylene glycol has been shown to provide direct conversion into ketals.⁸ For example, dodecan-2-ol **5** undergoes oxidation–ketal formation with only a small amount (5%) of ketone formation.

Oxidation of alkenes to afford epoxides, diols and amino alcohols are useful processes, which have been achieved successfully using transition metal catalysts with good turnovers, and in appropriate cases with asymmetric induction.

However, there is always scope for improvement, in terms of reaction scope, turnover number, and selectivity. Francis and Jacobsen have employed combinatorial ligand libraries with a range of metal catalysts to investigate alkene epoxidation.⁹ Collman and co-workers have designed enantiomerically pure iron porphyrin catalysts which give high enantiomeric excess (up to 90% ee) and turnover numbers in the epoxidation of terminal alkenes.¹⁰

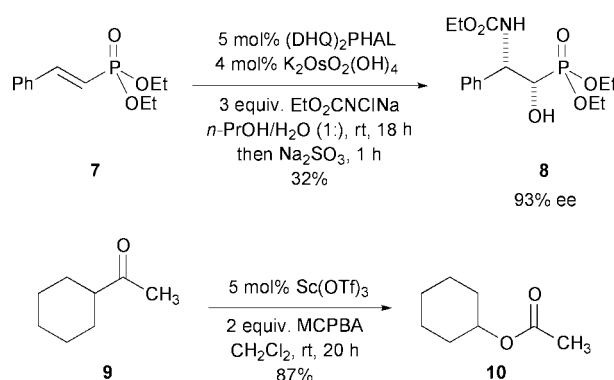
Dihydroxylation reactions continue to attract attention. Donohoe and co-workers have developed dihydroxylation con-



Scheme 1

ditions that favour the formation of *syn*-products from cyclic allylic trichloroacetamide starting materials, although stoichiometric osmium tetroxide is required.¹¹ Kobayashi and co-workers have designed a reusable polymer-supported osmium catalyst which is effective for achiral and for enantioselective dihydroxylation.¹²

Thomas and Sharpless have applied the related amino-hydroxylation reaction to unsaturated phosphonates.¹³ Using the standard (DHQ)₂PHAL catalyst, the unsaturated phosphonate **7** could be derivatised with high enantiomeric excess, but with low chemical yield (Scheme 2).

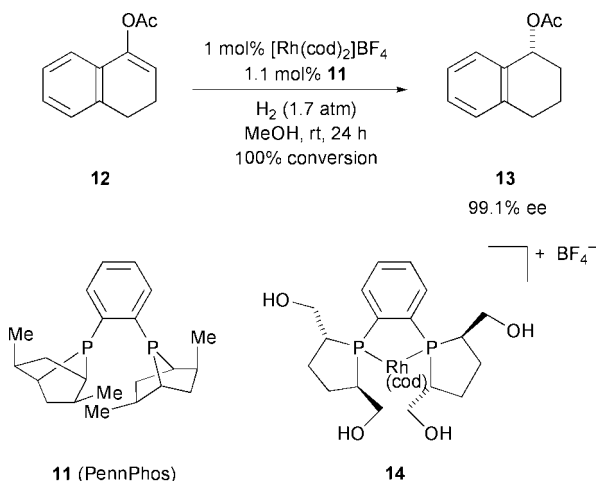


Scheme 2

Over the last few years, scandium triflate has found many applications as a Lewis acid catalyst. Kotsuki and co-workers have demonstrated that scandium triflate accelerates the Baeyer–Villiger oxidation of ketones.¹⁴ For example, ketone **9** is converted into ester **10** using scandium triflate as a catalyst.

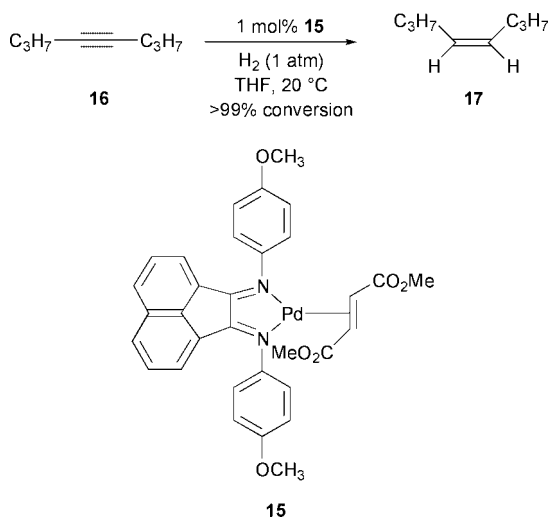
3 Reduction reactions and related processes

Transition metal catalysed reduction of alkenes now has a long history, and there are many examples of highly enantioselective variants of this reaction. The PennPhos ligand **11** is especially effective in the rhodium-catalysed enantioselective reduction of cyclic enol acetates¹⁵ and cyclic enamides.¹⁶ Thus the enol acetate **12** was converted into the acetate **13** with very high enantioselectivity (Scheme 3). Chelating diphosphines such as DuPHOS are still finding application,¹⁷ including the recent preparation of the water-soluble analogue of the rhodium complex **14**.¹⁸



Scheme 3

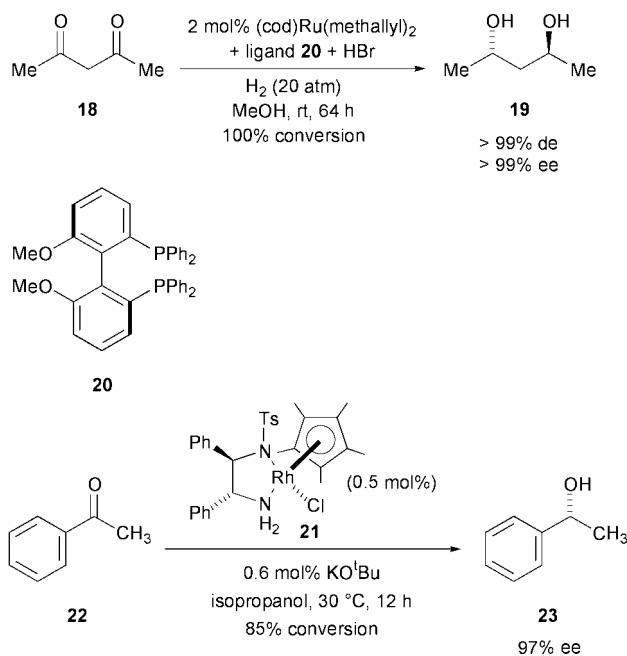
In general, the semi-hydrogenation of alkynes to the corresponding (*Z*)-alkenes is often less selective than would be desirable. van Laren and Elsevier have demonstrated that the palladium complex **15** is a good pre-catalyst for the semi-hydrogenation of a range of alkynes.¹⁹ Thus oct-4-yne **16** is converted into the (*Z*)-alkene **17** with excellent selectivity (Scheme 4).



Scheme 4

The asymmetric reduction of ketones is also a useful transformation, and can be achieved either by direct hydrogenation or transfer hydrogenation. The ruthenium-catalysed direct hydrogenation of diketones has been reported to give very high diastereoselectivity and enantioselectivity.^{20,21} For example, pentane-2,4-dione **18** is converted into pentane-2,4-diol **19** with almost complete stereoselectivity using (*S*)-MeOBIPHEP **20** as the ligand (Scheme 5).

The majority of work involving asymmetric transfer hydrogenation has involved the use of ruthenium complexes.²² The



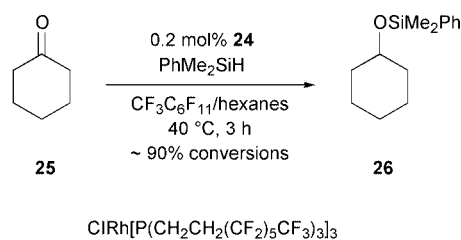
Scheme 5

rhodium complex **21** has now been exploited in transfer hydrogenation, and found to be efficient for these reactions.²³ Acetophenone **22** was reduced to phenethyl alcohol **23** with high enantioselectivity.

The asymmetric hydrogenation of imines has been reported by Brintzinger and co-workers using titanocene and zirconocene complexes.²⁴ Iridium catalysed enantioselective hydrogenation of imines in supercritical carbon dioxide has also been reported.²⁵

As well as the catalysed addition of H–H across multiple bonds, it is possible to catalyse the addition of B–H, Si–H and similar non-oxidative additions. These reactions are discussed in this section.

The rhodium-catalysed hydrosilylation of ketones is a well-known reaction. Dinh and Gladysz have developed a fluorous biphasic variant of this process using the fluorous-soluble catalyst **24** (Scheme 6).²⁶ At temperatures above 0 °C, the fluorous solvent and hexanes are miscible. Thus, during the course of the reaction, monophasic conditions are present. However, at the end of the reaction, cooling and separation of the phases allows the fluorous phase (with the Rh complex) to be recycled. The chemistry was applied to the reduction of ketone **25**, as well as to the reduction of enones.

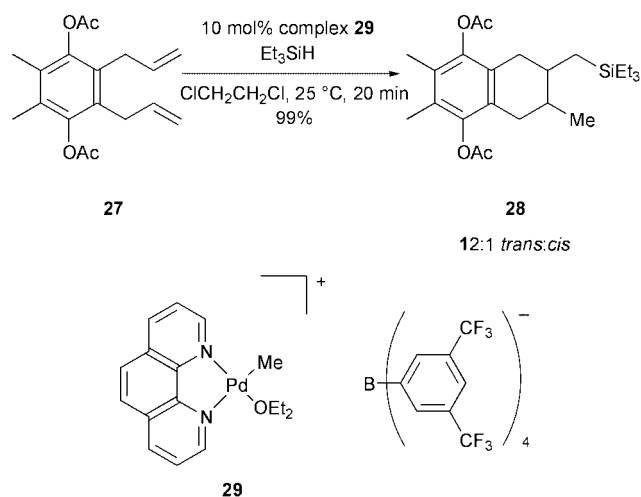


Scheme 6

Enantioselective hydrosilylations of ketones were reported using titanium–bisoxazoline complexes²⁷ as well as with rhodium diphosphine complexes.^{28,29} Enantioselectivities in excess of 90% were recorded in the latter examples.

Hydrosilylation of alkenes can also be catalysed by transition metal complexes. Stengone and Widenhoefer have reported unusual examples of hydrosilylation of suitable dienes to give

cyclisation products.^{30,31} Examples include the cyclisation-hydrosilylation of diene **27** into the silane **28** using the cationic palladium complex **29** (Scheme 7).

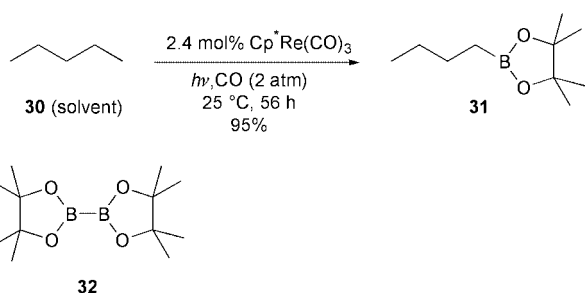


Scheme 7

Hydroboration of alkenes can be accelerated by transition metal catalysts, most notably rhodium complexes. The regiochemistry of the transition-metal catalysed process does not reflect the uncatalysed reaction, and can be dependent upon the ligands and borane being employed.³²

Fluorous biphasic catalysis has been applied to rhodium-catalysed hydroboration employing complex **24**.³³ This procedure allows the initial hydroboration product to be separated from the catalyst prior to oxidative work-up. The catalyst may then be re-used.

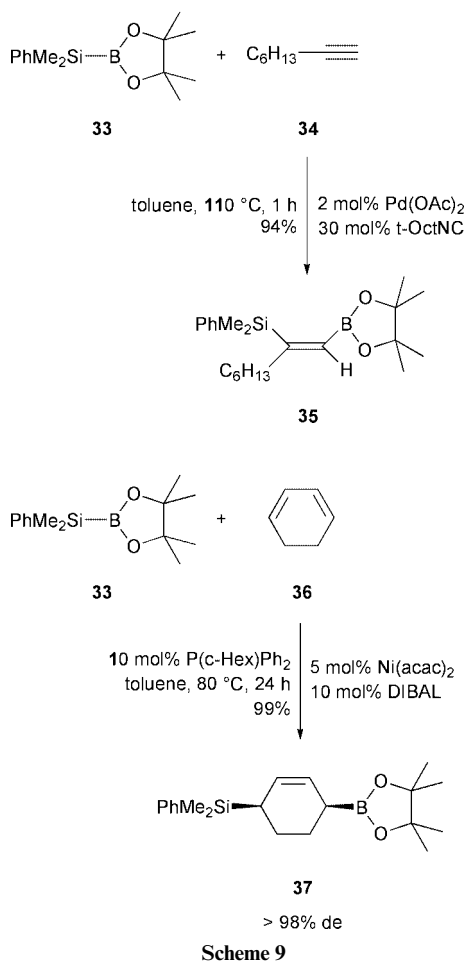
The catalysed transformation of alkanes into alkylboron derivatives has been achieved by Chen and Hartwig.³⁴ Simple alkanes including *n*-pentane **30** can be converted into primary alkylboronate ester **31** using a rhenium catalyst and the diboronate **32**, under photochemical conditions (Scheme 8). Such selective alkane activation is remarkable.



Scheme 8

The addition of Si–B across multiple bonds can be catalysed by transition metals. Ito and co-workers have shown that the addition of the silylborane **33** across alkynes, including octyne **34**, takes place to give the (*Z*)-alkene **35** with excellent regio-control (Scheme 9).³⁵ The addition of the same silylborane to dienes affords 1,4-addition, using a nickel catalysed variant of the reaction. In the presence of a suitable phosphine, good diastereocontrol is also observed. Thus cyclohexadiene **36** is converted into the addition product **37** with high *cis*-selectivity.³⁶

A fairly wide range of heteroatoms may be added across multiple bonds with the use of transition metal catalysts. For example, Tanaka has recently shown that compounds containing P–S bonds can be added across alkynes with excellent regio- and stereoselectivity.³⁷



Scheme 9

4 Lewis acid catalysed reactions

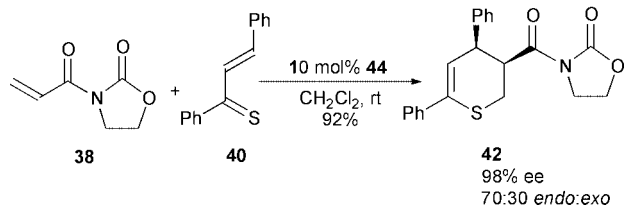
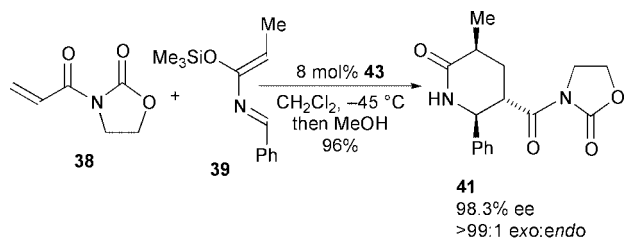
This section considers various transition metal catalysed reactions, including nucleophilic attack on carbonyl compounds, epoxide opening and Diels–Alder reactions. Some of the specific reactions can only be marginally identified as Lewis acid catalysed processes, but seem to find a better home in this section than in the others.

Diels–Alder reactions are well known to be accelerated by Lewis acid catalysis. The dienophile **38** is often employed in such reactions since it is capable of two-point binding to the Lewis acid, which imparts conformational rigidity in the transition state. The reaction of dienophile **38** with cyclopentadiene has been achieved in high enantioselectivity using many transition metal catalysts, including recent examples describing the use of enantiomerically pure platinum(II) or palladium(II) BINAP complex.³⁸ Evans and co-workers have discussed the enantiomeric outcome in terms of the geometry of the metal, the counterion and structure of the ligand.³⁹

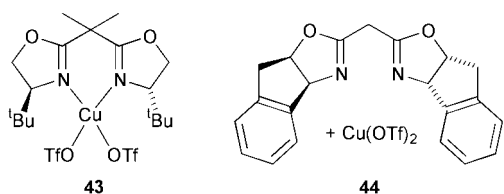
As well as conventional all-carbon dienes, heterodienes including the azadiene **39**⁴⁰ and the thiadiene **40**⁴¹ have been successfully employed in enantioselective Diels–Alder reactions, using the copper(II) catalysts **43** and **44** (Scheme 10). Evans and co-workers have used copper(II)–bisoxazoline complexes for the hetero-Diels–Alder reaction between oxygen-containing heterodienes and electron rich dienophiles.⁴²

Enantioselective hetero-Diels–Alder reactions between dienes with aldehydes as the hetero-dienophile have been a popular route for the construction of various pyran derivatives. Recent additions to the list of successful asymmetric catalysts for this reaction include palladium and platinum BINAP complexes⁴³ and enantiomerically pure chromium(III) complexes.⁴⁴

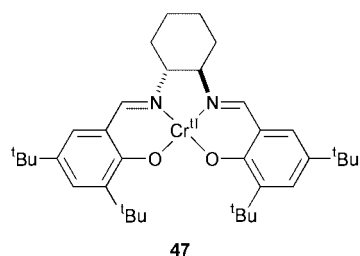
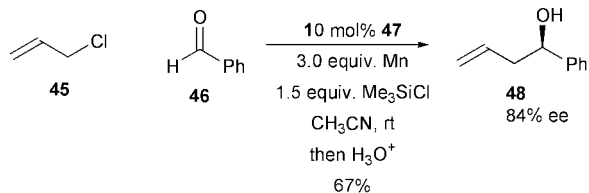
Direct nucleophilic addition to carbonyl groups and related functions can also be considered as Lewis acid catalysed reactions. As well as the addition of cyanide to aldehydes,^{45,46} the



Scheme 10



allylation of carbonyl groups has been of interest over the last few years. Attention has mainly been directed towards enantioselective variants of this process. For example, the first catalytic enantioselective Nozaki–Hiyama reaction has been reported.⁴⁷ Allyl chloride **45** can be added to benzaldehyde **46** in the presence of a chromium salen complex **47** (Scheme 11). Manganese is used as a stoichiometric reduction agent in order to regenerate the chromium(II) catalyst.

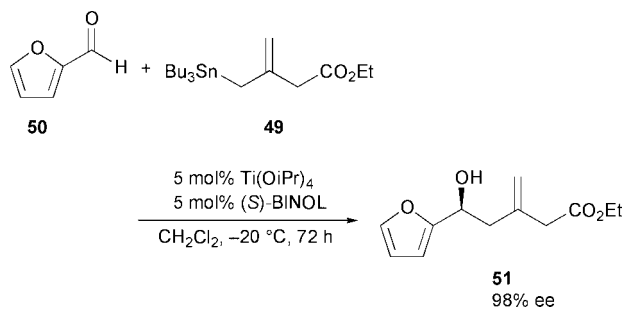


Scheme 11

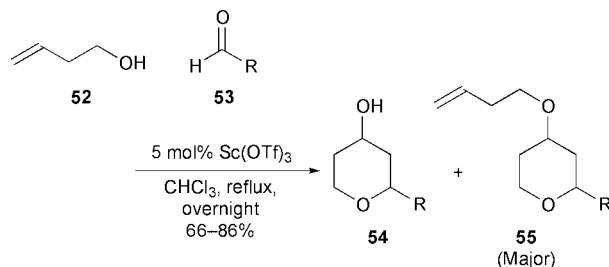
The titanium catalysed addition of allylstannanes to aldehydes has been extended by Keck and Yu to include the use of the functionalised allylstannane **49**.⁴⁸ The reaction with furfuraldehyde **50** affords the product **51** with high enantioselectivity and yield (Scheme 12).

The use of allylsilanes as the nucleophilic component has been reported in the addition to aldehydes and imines using allyl palladium complexes.⁴⁹

Interestingly, the use of homoallyl alcohol **52** in the addition to aldehydes **53** affords a Prins-type cyclisation, when scandium triflate is employed as the catalyst.⁵⁰ It is suggested that the reaction proceeds *via* a cationic ring closure and trap to afford the alcohol **54** and the ether **55** as the reaction products (Scheme 13).

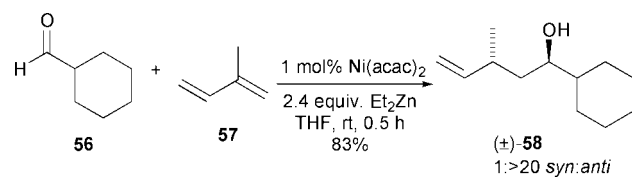


Scheme 12



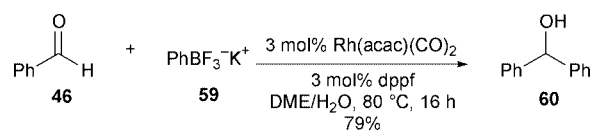
Scheme 13

A rather unusual addition of 1,3-dienes to aldehydes has been reported by Tamaru and co-workers.⁵¹ The process relies on the use of a nickel catalyst in conjunction with either diethylzinc or triethylborane as the promoter. For example allyl alcohol **56** reacts with isoprene **57** to give the homoallylic alcohol **58** with good diastereoselectivity (Scheme 14). The reaction was also successful on other aldehydes and ketones, although in the case of the latter, regiocontrol in addition of the unsymmetrical diene was a problem.



Scheme 14

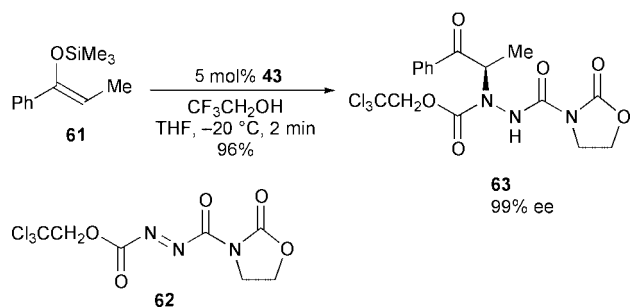
Batey and co-workers have reported a fairly general procedure for the rhodium catalysed delivery of aryl and alkenyl groups on to aldehydes (as well as enones).⁵² Trifluoroborate salts including compound **59** were found to be effective for the addition to aldehydes (Scheme 15).



Scheme 15

The aldol reaction can be considered as a special case of nucleophilic addition to carbonyl compounds. Evans and co-workers have published detailed studies of the Mukaiyama aldol reaction catalysed by copper(II)–bisoxazoline complexes.⁵³ Related copper catalysts,⁵⁴ and even enantiomerically pure silver complexes have also been used in enantioselective catalytic aldol reactions.⁵⁵

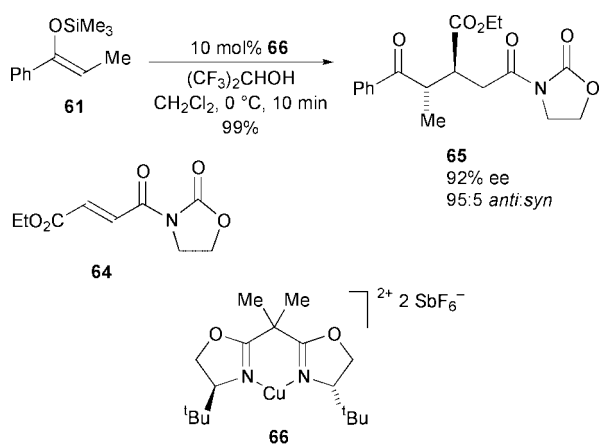
Evans and Johnson have also shown how the ubiquitous copper(II)–bisoxazoline complexes can also be employed in the amination of silyl enol ethers.⁵⁶ For example, the silyl enol ether **61** reacts with the designed aminating reagent **62** to give very high enantioselectivity in just two minutes using copper(II) complex **43** (Scheme 16).



Scheme 16

An interesting alternative approach to the generation of enolates has been described by Motherwell and co-workers.⁵⁷ Their approach has been to isomerise allylic alkoxides into enolates, and then trap the enolates *in situ*.

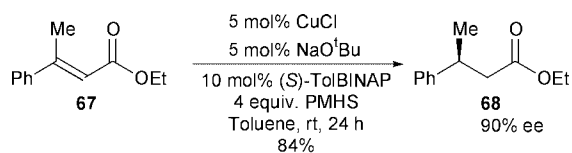
Changing the counterion in copper(II) complex **43** from triflate to hexafluoroantimonate has allowed Evans and co-workers to achieve the conjugate addition of silyl enol ethers to Michael acceptors.⁵⁸ Thus, silyl enol ether **61** reacts with the electron-deficient alkene **64** to provide the conjugate addition product **65** with good stereocontrol using the enantiomerically pure copper complex **66** (Scheme 17).



Scheme 17

Feringa and co-workers have published further research details about the use of their copper(II)–phosphine complexes for the conjugate addition of dialkyl zinc reagents to enones.^{59,60}

Buchwald and co-workers have used copper(II)–Tol-BINAP complexes in the enantioselective conjugate reduction of enoate esters.⁶¹ For example, substrate **67** is reduced in good yield to provide the ester **68** with good enantioselectivity (Scheme 18).

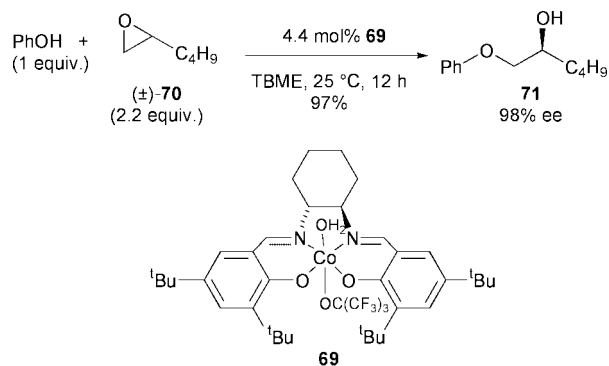


PMHS = Polymethylhydrosiloxane

Scheme 18

Hayashi and co-workers have further developed the use of rhodium catalysts in conjugate addition reactions of arylboron compounds to electron deficient alkenes, including vinyl phosphonates.⁶²

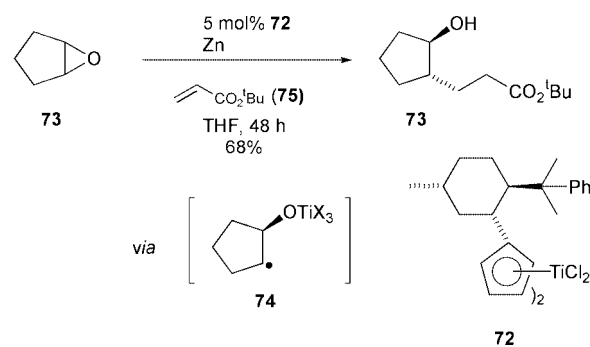
The ring-opening reactions of epoxides can be considered as Lewis acid catalysed reactions under appropriate conditions. Jacobsen's group has developed efficient kinetic resolution in the ring-opening of racemic epoxides. For example, the cobalt salen complex **69** catalyses the conversion of epoxide **70** into the alcohol **71** with very high selectivity (Scheme 19).



Scheme 19

Kinetic resolution reactions of epoxides have also been achieved with ruthenium(salen) complexes⁶⁴ and chromium(salen) complexes.⁶⁵ The enantioselective ring-opening of *meso*-aziridines has been achieved using chromium complexes with up to 94% ee.⁶⁶

Gansäuer and co-workers have demonstrated a reductive opening of *meso*-epoxides that undergo trapping to form a new C–C bond.⁶⁷ Thus, the titanocene-based catalyst **72** was employed in the conversion of cyclopentene oxide **73** into the presumed intermediate **74** which adds to *tert*-butyl acrylate **75** affording the alcohol **76** with good selectivity (Scheme 20).



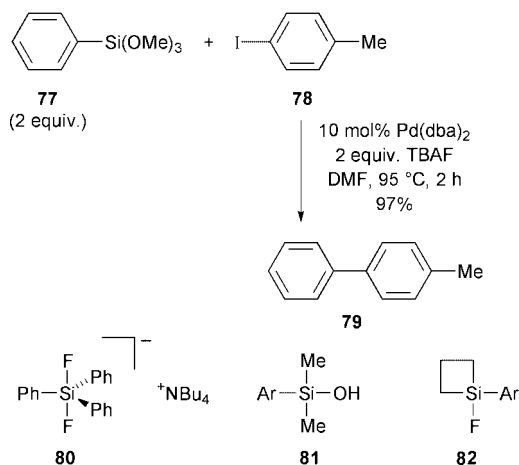
Scheme 20

5 C–C coupling reactions

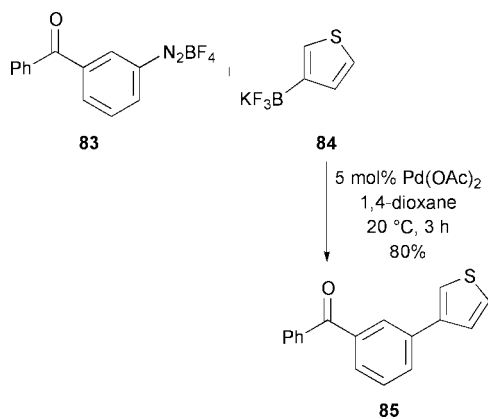
Transition metal catalysed C–C bond forming reactions are now routine transformations in synthetic organic chemistry, with palladium complexes being exploited more than other catalysts. Traditional 'nucleophilic' coupling reagents include organotin, organoboron and organozinc reagents. There have been several recent reports on the use of various organosilicon reagents in coupling reactions. Mowery and DeShong have employed siloxane derivatives in the presence of fluoride.⁶⁸ Siloxane **77** was coupled with aryl iodide **78** to give the hetero-coupled product **79** in excellent yield (Scheme 21). Other organosilicon reagents employed in coupling reactions include triphenyldifluorosilicate **80**,⁶⁹ silanols **81**⁷⁰ and arylsilylcyclobutanes **82**.⁷¹ Genêt and co-workers have employed organotrifluoroborates in coupling reactions with diazonium salts.⁷² One example is provided by the coupling of the partners **83** and **84** affording the product **85** in good yield (Scheme 22).

Cyclobutanols have been used by Nishimura and Uemura as unusual reagents in coupling reactions.⁷³ The bicyclic alcohol **86** undergoes palladium catalysed coupling with bromobenzene **87** to give the ring-opened compound **88** with the formation of a new C–C bond (Scheme 23).

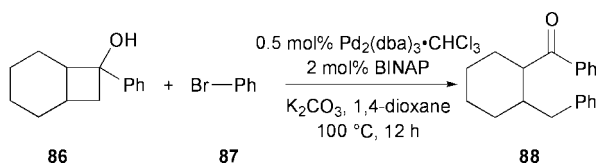
The Suzuki cross-coupling reaction is a widely used reaction and has seen many synthetic applications. Recent examples include the coupling of borane **89** (formed *in situ* by addition of 9-BBN to the alkene precursor) with the cyclic ketene acetal phosphate **90** affording the highly functionalised product **91** with excellent chemical yield (Scheme 24).⁷⁴



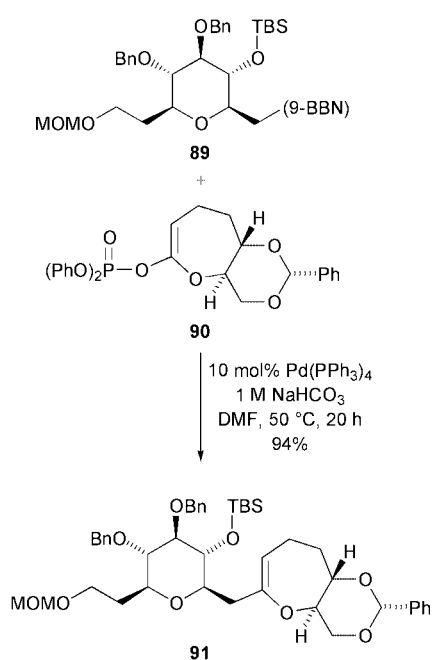
Scheme 21



Scheme 22

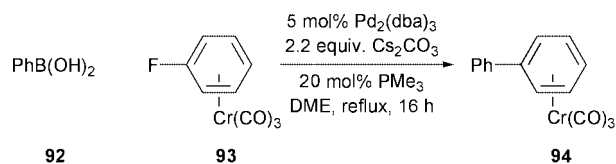


Scheme 23



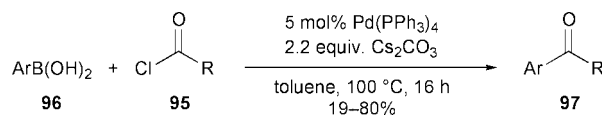
Scheme 24

Widdowson and Wilhelm have used an aryl fluoride **93** as the coupling partner in a Suzuki reaction (Scheme 25).⁷⁵ The replacement of the C–F bond may either occur *via* unprecedented oxidative addition or *via* an addition–elimination sequence to the aryl unit, which is facilitated by the electron-withdrawing chromium tricarbonyl group.



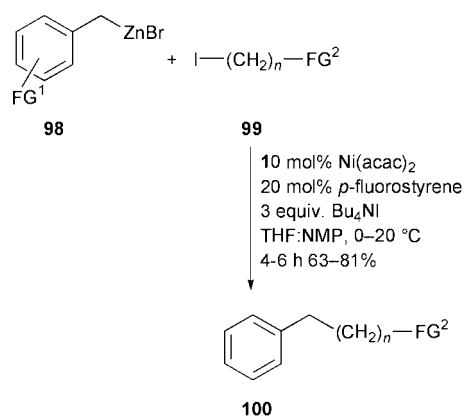
Scheme 25

Haddach and McCarthy have reported conditions for the first examples of Suzuki reactions involving acid chlorides **95**.⁷⁶ The reaction required the use of anhydrous conditions due to the reactivity of the acid chloride. A range of ketones **97** was prepared in reasonable yield (Scheme 26).



Scheme 26

The transition metal catalysed coupling of two sp³ carbon atoms is not straightforward. Complicating factors include slow C–X oxidative addition as well as the possibility for β-hydride elimination.⁷⁷ Knochel and co-workers have demonstrated that benzylic zinc reagents **98** undergo nickel catalysed coupling reactions with functionalised and non-functionalised primary alkyl halides **99** (Scheme 27).⁷⁸ The alkene additive is one of several reagents which was shown to accelerate similar reactions.⁷⁹

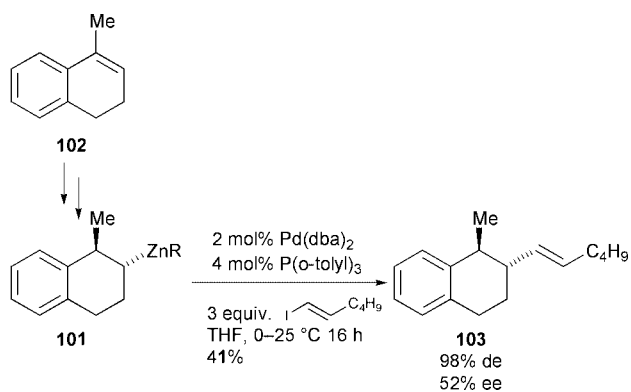


Scheme 27

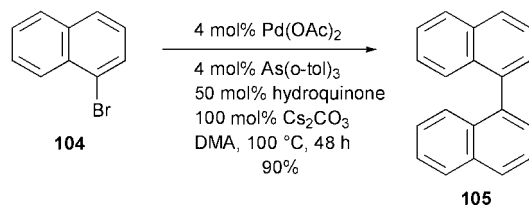
Boudier and Knochel have also shown that chiral zinc reagents can undergo coupling reactions with retention of stereochemistry.⁸⁰ The zinc reagent **101** can be derived from alkene **102** by hydroboration with an enantiomerically pure borane followed by a transmetalation procedure. The product **103** was isolated with excellent diastereocontrol and reasonable enantioselectivity (Scheme 28).

For some coupling reactions, small amounts of homocoupling are observed. Often this is a nuisance, but when homocoupling is required, Rawal and co-workers have reported a useful method for achieving this transformation.⁸¹ Hydroquinone is used as the stoichiometric reductant. For example bromonaphthalene **104** undergoes homocoupling to give the binaphthyl **105** (Scheme 29).

The Heck reaction provides a useful preparation of alkenes and has found many uses in organic synthesis. There has been



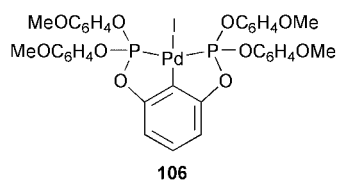
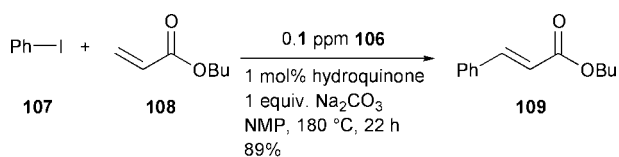
Scheme 28



Scheme 29

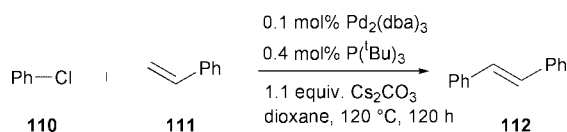
considerable interest in achieving Heck reactions in non-organic solvents, including perfluorinated solvents,⁸² supercritical carbon dioxide,⁸³ and water.⁸⁴ The use of supported palladium catalysts is also of interest, including a recent report of the use of palladium chloride and tetraphenylphosphonium bromide intercalated clay.⁸⁵

With appropriate catalysts, the turnover number of Heck reactions can be very high. Shibasaki and co-workers have found that the palladium complex **106** is able to catalyse the Heck reaction of iodobenzene **107** with butyl acrylate **108** to give the product **109** (Scheme 30) with an extraordinarily high turnover number of 8.9 million!⁸⁶



Scheme 30

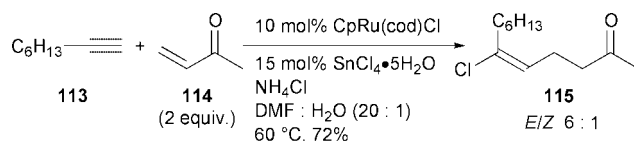
Littke and Fu have demonstrated that the Heck reaction of aryl chlorides is favoured using tri-*tert*-butylphosphine and dioxane as solvent. The reaction of chlorobenzene **110** with styrene **111** affords stilbene **112** under reasonably mild conditions (Scheme 31).⁸⁷



Scheme 31

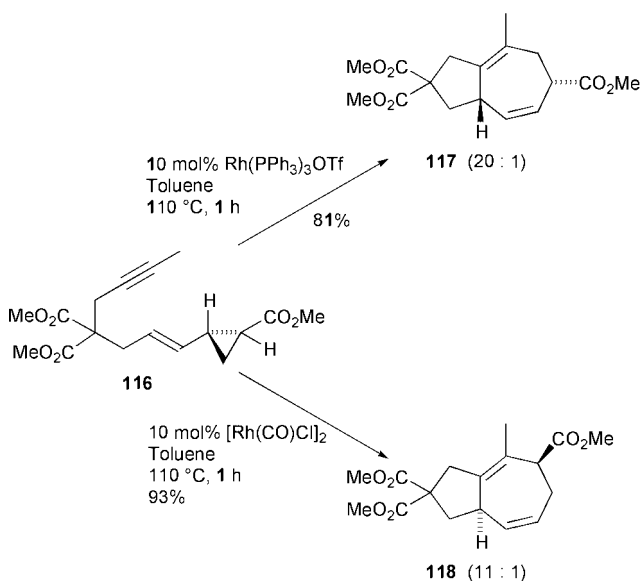
Coupling reactions between alkenes and alkynes have been catalysed by palladium⁸⁸ and ruthenium complexes.⁸⁹ Trost and Pinkerton have observed a three component coupling between

ammonium chloride, an alkyne **113** and an alkene **114** (Scheme 32).⁹⁰ They demonstrated that the reaction could be applied to many other alkynes.

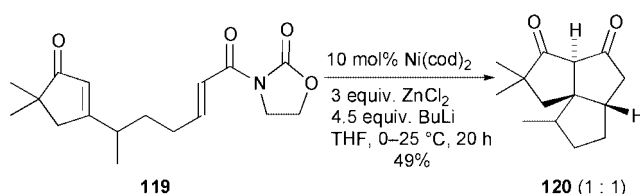


Scheme 32

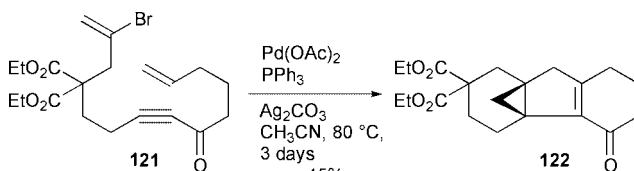
A cyclisation reaction involving the [5 + 2]-cycloaddition of a vinylcyclopropane group with an alkyne has been reported by Wender and Dyckman.⁹¹ The regioselectivity of the cyclisation of compound **116** could be chosen by selection of an appropriate catalyst, leading to either regioisomer **117** or **118** (Scheme 33). Other transition metal catalysed cyclisation reactions are well known. Montgomery and co-workers have reported an interesting bicyclisation reaction of the cyclopentenone **119** into the angular triquinane structure **120** (Scheme 34).⁹² A complex tetracyclisation of precursor **121** affords the tetracycle **122** as a single product (Scheme 35).⁹³



Scheme 33

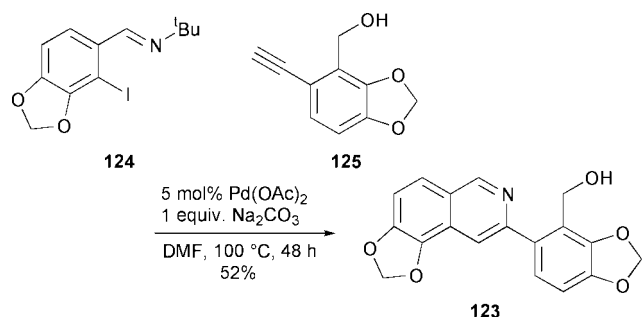


Scheme 34



Scheme 35

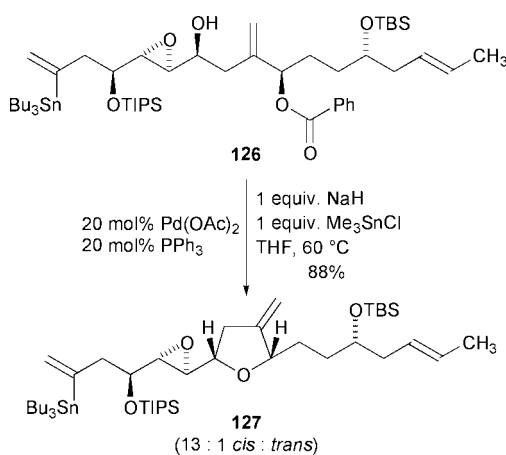
Transition metal catalysed reactions that generate aromatic compounds and heteroaromatic compounds are also fairly well documented.⁹⁴ Roesch and Larock have employed a palladium catalysed annulation reaction in the synthesis of the isoquinoline decumbenine **B** **123** from the *o*-iodoaryl imine **124** and alkyne **125** (Scheme 36).⁹⁵



Scheme 36

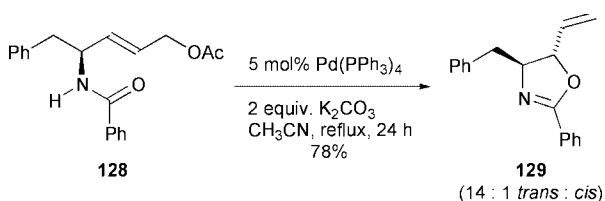
6 Allylic substitution reactions

Palladium catalysed allylic substitution reactions offer mild reaction conditions and the opportunity to control regio- and stereoselectivity with appropriate ligand tuning. Williams and Meyer have reported an example of an intramolecular allylic substitution reaction on the highly functionalised substrate **126**.⁹⁶ The reaction proceeds with complete regiocontrol and good selectivity for the *cis*-substituted product **127** (Scheme 37).



Scheme 37

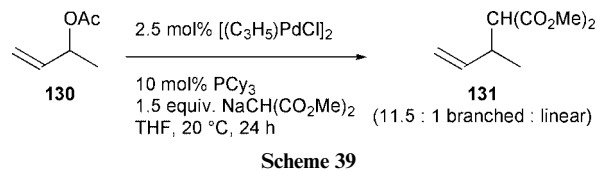
An example of induced diastereocontrol is provided by the cyclisation of the benzamide **128** under palladium catalysed allylic substitution conditions to provide the oxazoline **129** with good *trans*-selectivity (Scheme 38).⁹⁷ Other workers have shown that similar 5-vinyloxazolines are able to epimerise.⁹⁸



Scheme 38

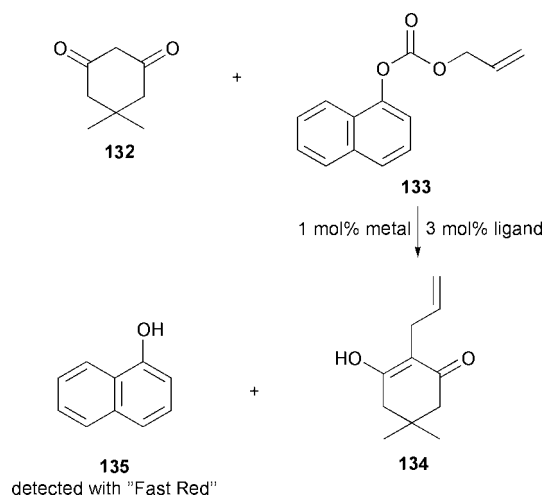
For many palladium catalysed allylic substitution reactions of allyl acetates, the regiochemistry of the starting allyl acetate is unimportant, since both regioisomers proceed *via* a common π -allyl intermediate. However, Williams and co-workers have shown that using tricyclohexylphosphine as the ligand, a branched acetate **130** preferentially affords a branched product **131** (Scheme 39).⁹⁹

Allylic substitution reactions are catalysed by metals other than palladium. Lavastre and Morken have devised a simple system for screening the viability of particular metal–ligand combinations.¹⁰⁰ Thus, the reaction between dimedone **132** and the allyl carbonate **133** affords product **134** and 1-naphthol **135**,



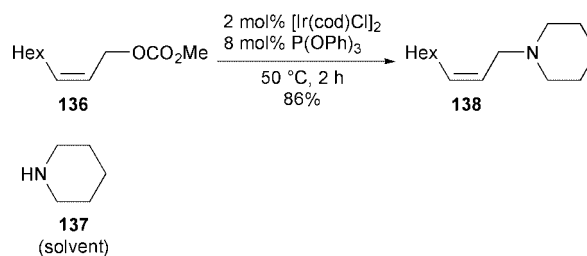
Scheme 39

which is readily detected on treatment with Fast Red diazonium salt (Scheme 40). A visual inspection of a 96-well plate clearly reveals the successful combinations.



Scheme 40

One interesting use of an iridium catalyst is the preservation of the (*Z*)-geometry of an allyl carbonate during the substitution reaction.¹⁰¹ The (*Z*)-allyl carbonate **136** is converted into the (*Z*)-allylamine **138** with no formation of the (*E*)-isomer and only small amounts of the branched product (2%) (Scheme 41).



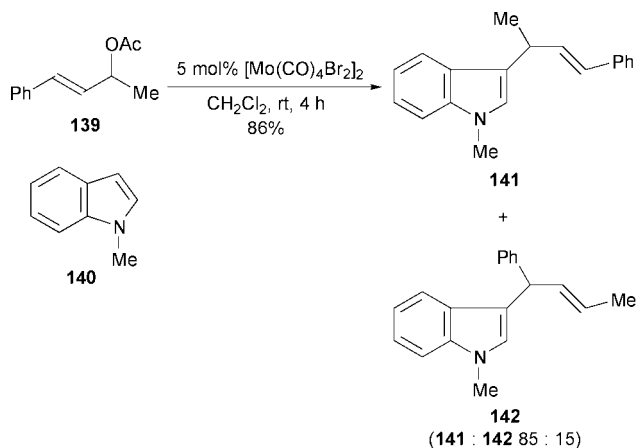
Scheme 41

Kocovsky and co-workers have employed molybdenum catalysts for allylic substitution reactions involving silyl enol ethers derived from simple aldehydes, ketones and esters.¹⁰² Further examples have employed electron-rich aromatic and heteroaromatic compounds as the nucleophilic component.¹⁰³ Thus *N*-methylindole **140** undergoes allylation with a molybdenum catalyst to give the 3-substituted products **141** and **142** (Scheme 42).

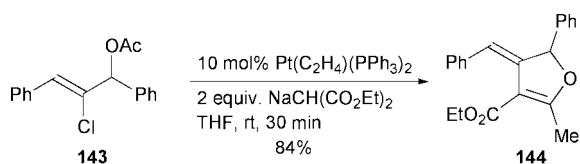
Platinum complexes have been used to give allylic substitution reactions where a nucleophilic attack at the central carbon is also involved.¹⁰⁴ The chlorinated allylic acetate **143** is converted into the heterocycle **144** in good yield by this process (Scheme 43).

There are now many good ligands reported each year that are capable of providing high enantioselectivity in allylic substitution reactions. A selection of these ligands is given by structures **145**,¹⁰⁵ **146**,¹⁰⁶ **147**,¹⁰⁷ **148**,¹⁰⁸ **149**,¹⁰⁹ **150**,¹¹⁰ **151**,¹¹¹ and **152**.¹¹²

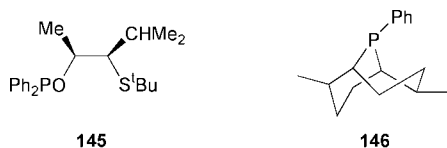
Evans and co-workers have employed ligand **145** in the enantioselective allylic substitution of the racemic heterocycle **153**.¹⁰⁵ Amination with benzylamine affords the substitution



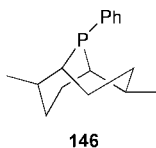
Scheme 42



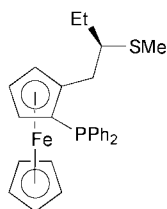
Scheme 43



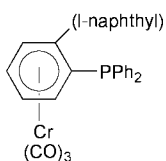
145



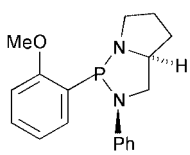
146



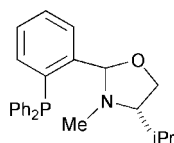
147



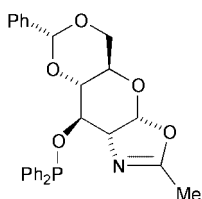
148



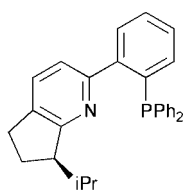
149



150



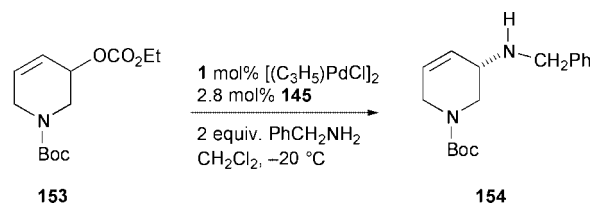
151



152

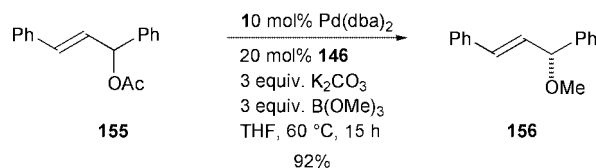
product **154** in high enantioselectivity (Scheme 44). Schleich and Helmchen have used the acetate analogue of compound **153** in enantioselective alkylation reactions achieving up to 98% enantiomeric excess.¹¹³

Hamada and co-workers used the monodentate ligand **146** in an unusual asymmetric etherification reaction.¹⁰⁶ The bench-



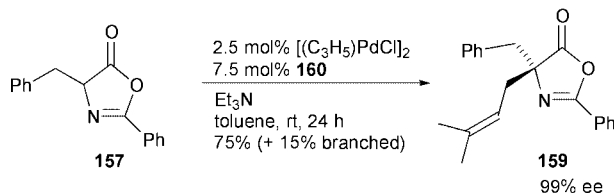
Scheme 44

mark substrate **155** was converted into the methyl ether **156** using trimethyl borate with potassium carbonate, catalysed by a palladium complex (Scheme 45).



Scheme 45

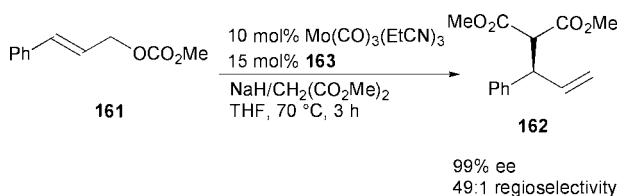
Trost and Hembre have applied palladium catalysed allylic substitution to the kinetic resolution of conduritols.¹¹⁴ Enantioselective allylation reactions with prochiral nucleophiles are less well studied, but a few successful examples have been reported recently.^{115,116} The azalactone **157** has been exploited as a prochiral nucleophile by Trost and Ariza to give exceptionally high enantioselectivity upon palladium catalysed prenylation with allyl acetate **158** (Scheme 46).¹¹⁷ Ligand **160** has been successful in many other enantioselective palladium catalysed allylic substitution reactions.



Scheme 46

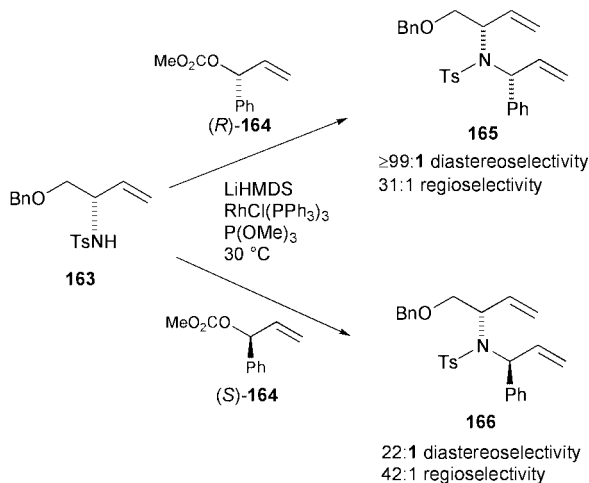
The use of other transition metals in enantioselective allylic substitution reactions is receiving more attention. High enantioselectivities have been reported for ruthenium,¹¹⁸ iridium,^{119,120} and platinum¹²¹ catalysed variants of the reaction. The copper catalysed substitution of allyl chlorides with diorganozinc compounds under the control of an enantiomerically pure amino ferrocene has also been reported.¹²² Of particular note is the enantioselective molybdenum-catalysed allylic substitution reported by Glorius and Pfaltz.¹²³ In one of the best examples, cinnamyl carbonate **161** was converted into the branched substitution product **162** with excellent control of regiochemistry and enantioselectivity (Scheme 47).

Evans and Robinson have reported further examples of the use of rhodium-catalysed allylic substitution.¹²⁴ The reactions typically occur with retention of both stereochemistry and regiochemistry. The allylamine derivative **163** (itself prepared by rhodium-catalysed allylic substitution) underwent substitution with either enantiomer of carbonate



Scheme 47

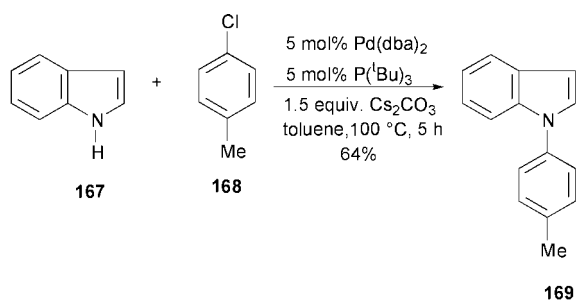
164 to give the diastereomeric products **165** or **166** with good preservation of stereochemistry (Scheme 48). These substrates were subsequently subjected to a ring-closing metathesis reaction.



Scheme 48

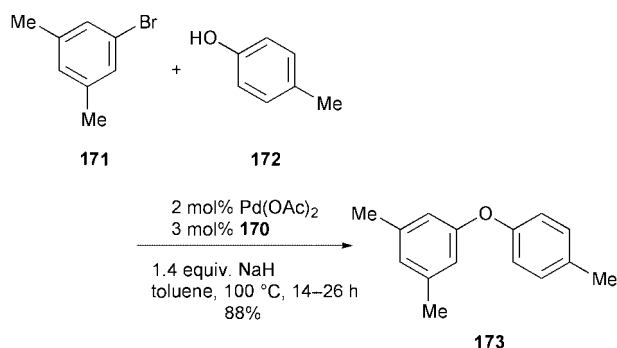
7 Heteroatom coupling reactions

The amination of aryl halides has rapidly become established as a useful tool in organic synthesis. As well as simple amines, other nitrogen-containing functional groups have been used in palladium catalysed “amination” reactions including hydrazones,¹²⁵ lactams,¹²⁶ carbamates and indoles.¹²⁷ For example indole **167** has been arylated using aryl chloride **168** in reasonable yield using a palladium–tri-*tert*-butylphosphine combination (Scheme 49).



Scheme 49

Buchwald and co-workers have demonstrated that ligand **170** and related compounds are effective in palladium catalysed diaryl ether formation.¹²⁸ Aryl bromide **171** and phenol **172** were effectively coupled to give the ether **173** in good yield (Scheme 50).



Scheme 50

Lipshutz and co-workers have used diphenylphosphine–borane in palladium catalysed coupling reactions with aryl nonaflates.¹²⁹ For example, the aryl nonaflate **174** is converted into the phosphine–borane adduct **175** in good yield (Scheme 51). The coupling of diphenylphosphine with aryl triflates with subsequent isolation of the vinylphosphine–borane adducts has also been reported.¹³⁰

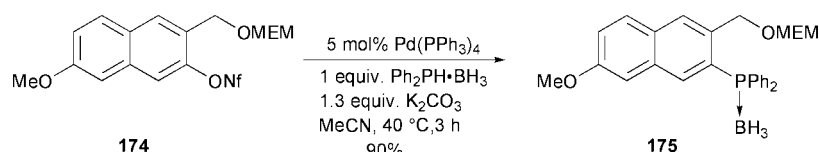
8 Carbonylation reactions

This section considers transition-metal catalysed reactions that involve the use of carbon monoxide. However, an unusual decarbonylation reaction is given as the first example. Murai and co-workers have shown that the ketone group in compound **176** is removed by a ruthenium catalyst (Scheme 52).¹³¹ The neighbouring oxazoline moiety is required in order for the reaction to proceed.

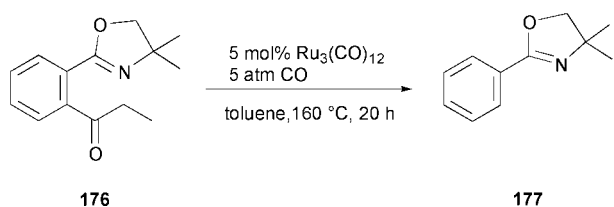
The Pauson–Khand reaction normally involves the cyclisation of an alkene, an alkyne and carbon monoxide to provide a cyclopentenone. Originally, the reaction was performed using stoichiometric amounts of cobalt reagent, but catalytic variants are known.^{132,133} Under catalytic Pauson–Khand conditions, the diyne **178** undergoes cyclisation to give a dienone which subsequently reacts with more diyne to give product **179** by a [2 + 2 + 2] cycloaddition (Scheme 53).¹³⁴

The titanocene-catalysed Pauson–Khand reaction has been developed by the Buchwald group.¹³⁵ Recent applications have involved the asymmetric variant of this reaction using the enantiomerically pure titanocene complex **180**.¹³⁶ Enyne **181** is converted into cyclopentenone **182** in good yield and with good enantioselectivity (Scheme 54). The asymmetric variant of the titanocene-catalysed reaction has been extended to substrates where the alkene and alkyne groups are tethered by a nitrogen-containing bridge.¹³⁷

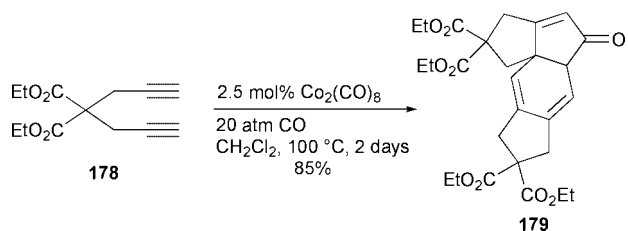
Hydroformylation reactions involve the addition of H_2 and CO across an alkene. However, under suitable reaction conditions, subsequent functional group transformations can take place to give alternative products. Rische and Eilbracht have developed a method for the conversion of methallyl chloride **183** into diamines, such as compound **184** (Scheme 55).¹³⁸ The



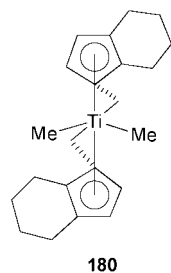
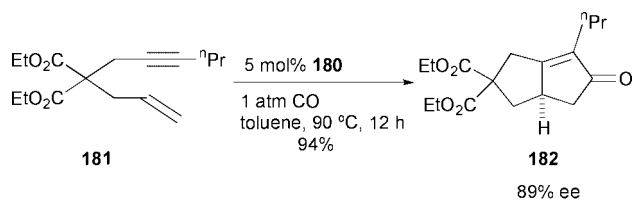
Scheme 51



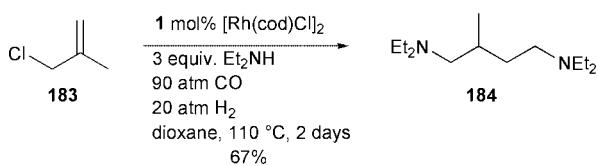
Scheme 52



Scheme 53



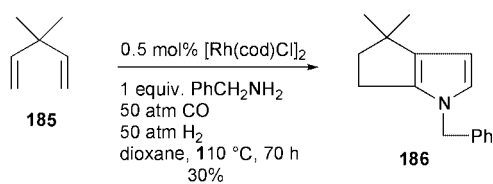
Scheme 54



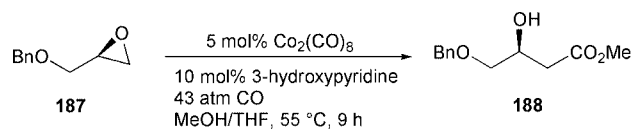
Scheme 55

reaction proceeds *via* allylic amination of the allyl chloride, hydroformylation of the alkene followed by reductive amination of the intermediate aldehyde.

The combination of a primary amine with 1,4-dienes under hydroformylation conditions provides an unusual synthesis of pyrroles.¹³⁹ Diene **185** reacts with benzylamine under rhodium catalysed hydroformylation conditions to give the pyrrole **186** in moderate yield (Scheme 56). Carbonylation reactions have been performed on many substrates, typically aryl halides. Hinterding and Jacobsen have used enantiomerically pure epoxides as the substrate for a methoxycarbonylation reaction using a cobalt catalyst.¹⁴⁰ Epoxide **187** is converted into the ring-opened product **188** with inclusion of carbon monoxide (Scheme 57).

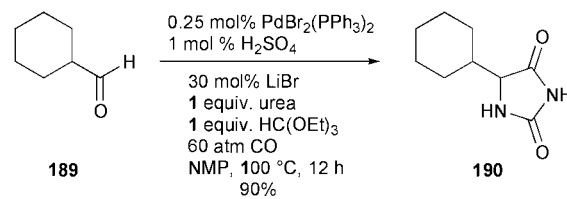


Scheme 56



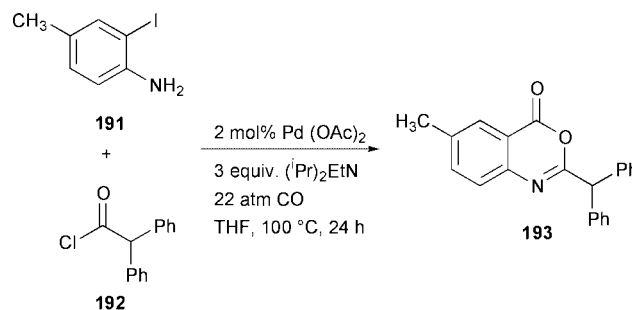
Scheme 57

Beller and co-workers have extended their unusual amido-carbonylation reaction of aldehydes to the formation of hydantoin.¹⁴¹ Cyclohexanecarbaldehyde **189** was converted into hydantoin **190** in good yield by reaction with urea and carbon monoxide, catalysed by palladium, bromide, and acid (Scheme 58). The role of the bromide is to convert the aldehyde into a suitable intermediate which is capable of undergoing reaction with the palladium catalysis.



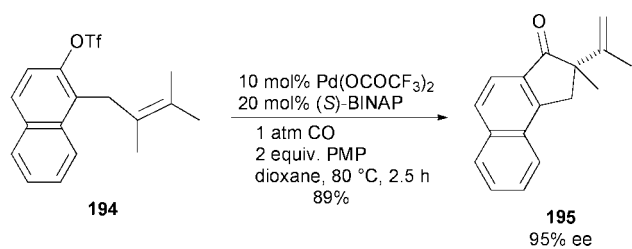
Scheme 58

Another interesting example of a cyclisation reaction has been reported by Larksarp and Alper.¹⁴² The combination of an *o*-iodoaniline, an acid chloride and carbon monoxide affords benzoxazinones. The reaction is assumed to proceed *via in situ* amide formation, carbonylation of the aryl iodide and cyclisation. The reaction is represented by the reaction of iodoaniline **191** with acid chloride **192**, which provides the heterocyclic product **193** in good yield (Scheme 59).



Scheme 59

Enantioselective reactions involving carbonylation are known and a recent example involves the carbonylation–Heck cyclisation of the aryl triflate **194** (Scheme 60).¹⁴³ After initial carbonylation of the C–O bond, the reaction pathway is assumed to proceed *via* addition of Pd–C across the alkene and subsequent β -hydride elimination to liberate the terminal alkene.

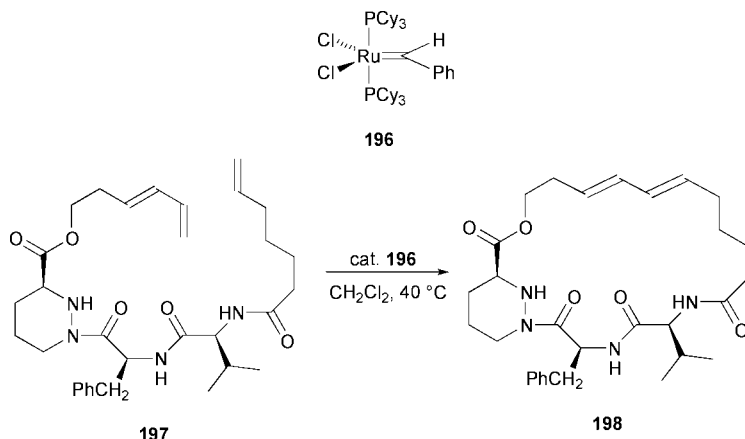


PMP = 1,2,2,6,6-pentamethylpiperidine

Scheme 60

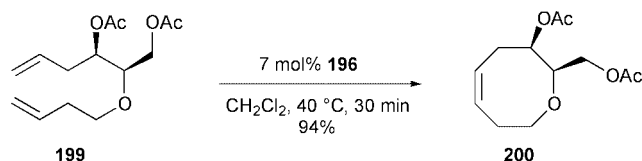
9 Alkene metathesis reactions

Alkene metathesis reactions, and in particular ring-closing alkene metathesis reactions catalysed by the Grubbs ruthenium



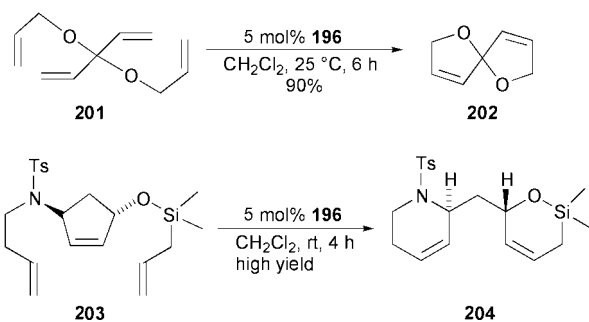
Scheme 61

complex **196** have been widely used by organic chemists in the last few years. Substrates of increasing complexity,¹⁴⁴ often with very large ring sizes have been subjected to the ring-closing metathesis reaction.¹⁴⁵ Some specific examples include the ring-closing metathesis reactions of compound **197** to give diene **198** (Scheme 61),¹⁴⁶ and closure of diene **199** to give the eight-membered cyclic ether **200** (Scheme 62).¹⁴⁷



Scheme 62

Tandem ring-closing–metathesis reactions are also known, illustrated by the conversion of tetraene **201** into the spiro-cycle **202** in good yield (Scheme 63).¹⁴⁸ An interesting ring rearrangement of triene **203** has been reported.¹⁴⁹ The cyclopentene ring in **203** has been sacrificed for the benefit of the two six-membered rings in the product **204** (Scheme 63).

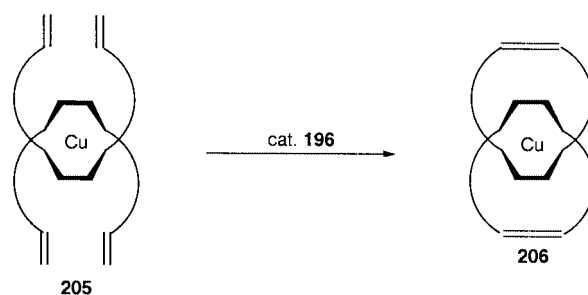


Scheme 63

Sauvage, Grubbs and co-workers have carried out an efficient preparation of catenanes by tandem ring-closing–metathesis of a copper complex **205** with pendant alkene groups.¹⁵⁰ The copper could be removed from the complex **206** to give the free catenane (Scheme 64).

There has been a report of a method for removing ruthenium impurities at the end of the reaction,¹⁵¹ as well as a caveat over the use of chloroform as a solvent—which has been shown to undergo a catalysed Kharasch addition to alkenes.¹⁵²

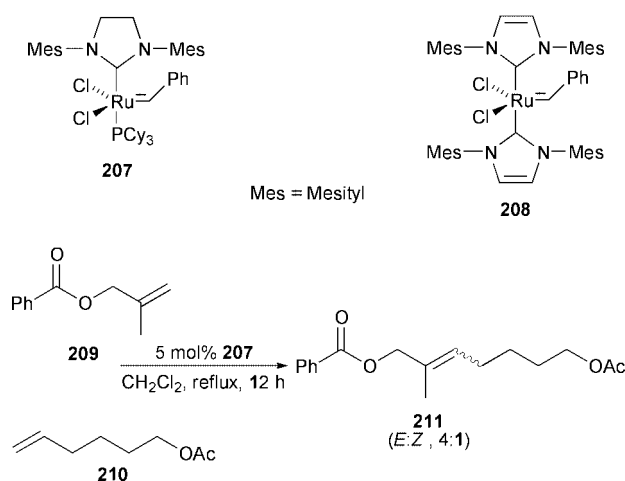
Modified ruthenium catalysts have been reported to have benefits,¹⁵³ as well as polymer-supported catalysts which afford lower levels of ruthenium contamination.¹⁵⁴ Fürstner and Ackermann have used (cymene)RuCl₂(PCy₃) and a combination of [(cymene)RuCl]₂ with PCy₃ as catalyst precursors that



Scheme 64

are activated under neon light.¹⁵⁵ These catalyst combinations are more user-friendly than the Grubbs catalyst **196**.

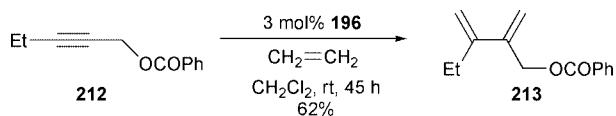
The use of ruthenium complexes where at least one of the tricyclohexylphosphine ligands has been replaced by a carbene have been reported.^{156–158} For example, Grubbs and co-workers have employed complexes **207** and **208**, which exhibit enhanced reactivity as catalysts for ring-closing metathesis reactions.¹⁵⁸ Complex **207** was active for the preparation of tri-substituted alkenes in cross-metathesis reactions, including the coupling of alkenes **209** and **210** to provide the tri-substituted alkene **211** in good yield (Scheme 65). Whilst enantiomerically pure ruthenium complexes have only met with limited success in asymmetric ring-closing metathesis reactions, Hoveyda, Schrock and co-workers have reported further details of highly enantioselective molybdenum catalysed ring-closing metathesis reactions of suitable dienes and trienes.¹⁵⁹



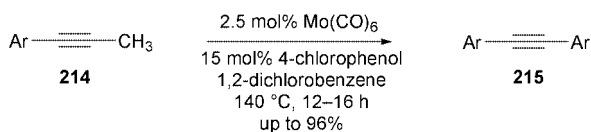
Scheme 65

The use of Grubbs catalyst **196** for an intramolecular enyne metathesis has been shown to be a good method for the synthesis of dienes.¹⁶⁰ One example of this reaction is provided by

the reaction of alkyne **212** with ethylene gas which affords the diene **213** (Scheme 66). Ring-closing metathesis of dialkynes was discussed in the previous review, and usually molybdenum and tungsten catalysts appear to be the most appropriate for this reaction.¹⁶¹ Pschirer and Bunz have reported that a simple molybdenum catalytic system can be employed for alkyne metathesis.¹⁶² Arylalkynes **214** are converted into the 'dimers' **215** using a combination of molybdenum hexacarbonyl and 4-chlorophenol (Scheme 67).



Scheme 66

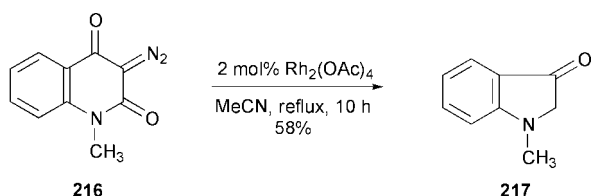


Scheme 67

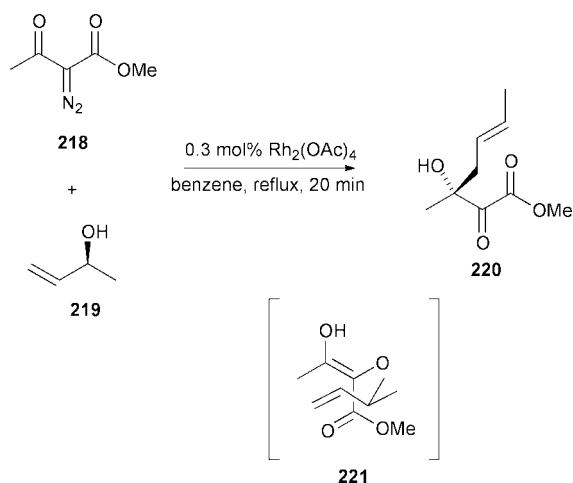
10 Reactions involving metal carbenoids

Decomposition of diazo-compounds and their subsequent reactions are typically achieved with copper or rhodium catalysed reactions. A recent report has demonstrated that scandium triflate can be employed to catalyse the diazocarbonyl insertion reaction into O–H, S–H and N–H bonds.¹⁶³

However, research into applications of dirhodium tetraacetate catalysed reactions is still very topical. The Wolff rearrangement of the diazo-compound **216** to give oxindole **217** has been reported (Scheme 68).¹⁶⁴ Wood and co-workers have reported an interesting rhodium catalysed reaction between diazo-compound **218** and allyl alcohol **219** which affords the product **220**.¹⁶⁵ The reaction is believed to proceed *via* Claisen rearrangement of the intermediate enol **221** (Scheme 69).



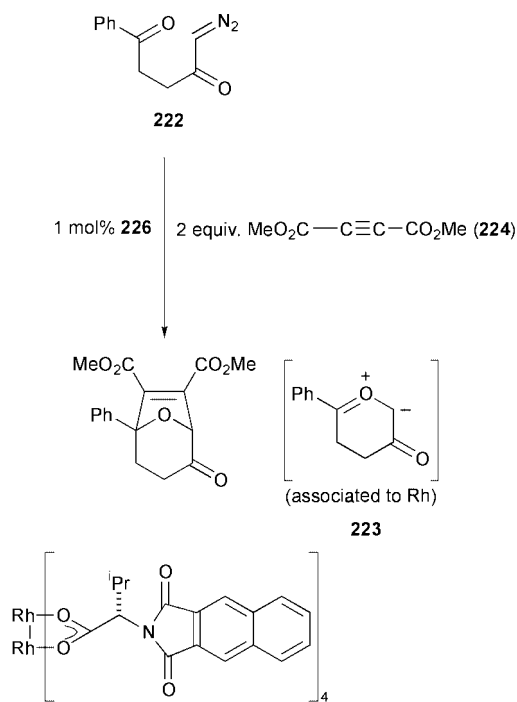
Scheme 68



Scheme 69

Enantioselective rhodium catalysed reactions have been widely exploited. An asymmetric catalytic reaction involving carbonyl ylide formation and subsequent 1,3-dipolar cyclo-

addition has been achieved with high yields and enantioselectivities.¹⁶⁶ One example involves the reaction of diazo-compound **222** which presumably proceeds *via* the formation of the carbonyl ylide **223** or its rhodium complex. This then reacts with dimethyl acetylenedicarboxylate **224** to give the bicyclic product **225** (Scheme 70). The enantiomerically pure rhodium catalyst **226** was employed in this reaction.



Scheme 70

There have also been reports of asymmetric cobalt(salen) catalysed S-ylide formation from allyl aryl sulfides and their subsequent rearrangement.¹⁶⁷ Finally, Davies and co-workers have reported enantioselective C–H insertion reactions of cyclohexa-1,3-diene with diazo-compounds catalysed by enantiomerically pure rhodium(II) complexes.¹⁶⁸

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