Catalytic applications of transition metals in organic synthesis

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Reviewing the literature published between 1 November 1995 and 31 October 1996. Continuing the coverage in *Contemporary Organic Synthesis*, 1996, **3**, 259

1 Introduction

This review highlights advances made in transition metal catalysed reactions in the twelve months up to 31 October 1996. There has been steady progress in many areas of transition metal catalysis and spectacular advances have been made in others. Of particular note is the application of transition metal catalysed reactions towards the construction of a library of compounds by a combinatorial approach. Additionally, ligands for transition metal catalysed reactions are now being generated by combinatorial methods, allowing for the possibility of rapid screening of ligand candidates.

There is a high volume of material published in the area of transition metal catalysed reactions, and as a consequence this review cannot be fully comprehensive. Nevertheless, the more novel and exciting aspects of the field are covered herein.

2 Oxidation

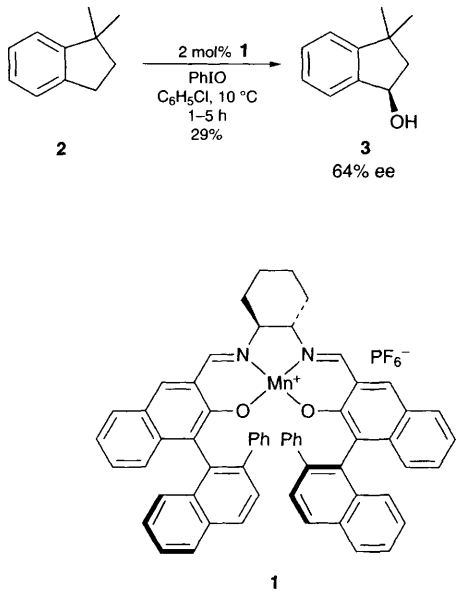
Oxidations are of fundamental importance in organic chemistry. Transition metal catalysed oxidations have been known for many years, although each year new developments are made in the selectivity of such reactions. The development of the catalytic aminohydroxylation by the Sharpless group is a particular highlight this year.

2.1 Oxidation of C–H bonds

The controlled oxidation of simple hydrocarbons is a difficult process, since the initial products are susceptible to further oxidation.[1] The use of a substrate containing especially reactive C–H bonds (*e.g.* benzylic or allylic groups) enables a more selective reaction.

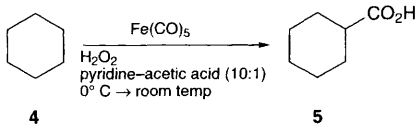
Katsuki and co-workers have employed the Mn(salen) complex **1** as a catalyst for asymmetric benzylic oxidation.[2] 1,1-Dimethylindane **2** was oxidised to the corresponding alcohol **3** with 64% ee, albeit in modest yield, using iodosylbenzene as the stoichiometric oxidant (**Scheme 1**).

As well as direct oxidation of C–H bonds, it is possible to perform these reactions in the presence of carbon monoxide, thereby producing carboxylic acids. Fujiwara and co-workers have published an account of their work in this area, whilst Barton



Scheme 1

and Delanghe have shown that iron pentacarbonyl acts as a source of carbon monoxide, as well as a promoter in the conversion of cyclohexane **4** into cyclohexanecarboxylic acid **5** (**Scheme 2**).[4] Based on



Scheme 2

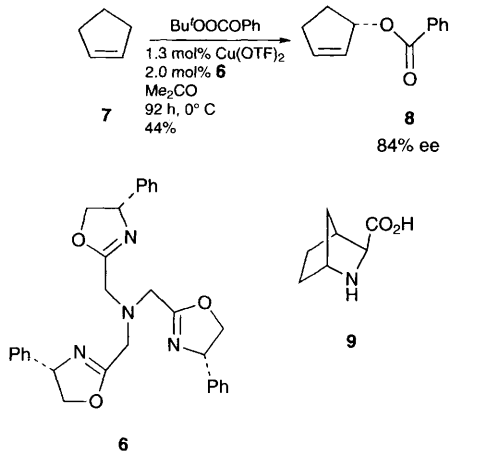
the amount of starting material employed the yield was only 12%, but based on the amount of iron pentacarbonyl used, the yield was 120%! Clearly more than one carbon monoxide can be delivered from each iron pentacarbonyl.

Further examples of enantioselective allylic oxidation reactions have been reported. Katsuki and co-workers employed ligand **6** in the conversion of cyclopentene **7** into the cyclopentenyl ester **8** (**Scheme 3**).[5] Södergren and Andersson used the ligand **9** in a similar reaction.[6]

2.2 Functional group oxidation

Although there are now very many methods for the oxidation of alcohols to aldehydes or ketones, an unusual new addition has been reported by Muzart and co-workers.[7] Tetralol **10** is oxidised into tetralone **11** by treatment with a molybdenum catalyst and sodium percarbonate as the stoichiometric oxidant. The ammonium salt Adogen 464 is also added (**Scheme 4**).

Methylrhenium trioxide has recently been examined as a catalyst for several reactions.[8] Two research groups have demonstrated that methylrhenium trioxide can be used to catalyse the oxidation of organonitrogen compounds.[9,10] For example,



Scheme 3

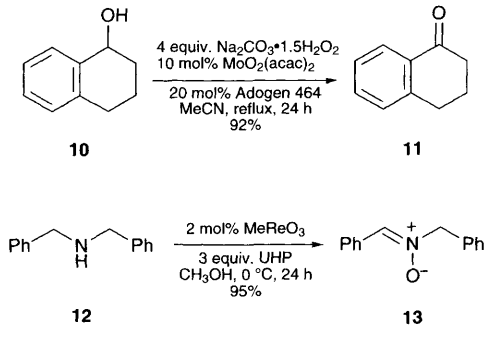
amine **12** is oxidised into the nitrone **13** upon treatment with urea hydrogen peroxide (UHP) and catalytic methylrhenium trioxide (**Scheme 4**).

2.3 Epoxidation

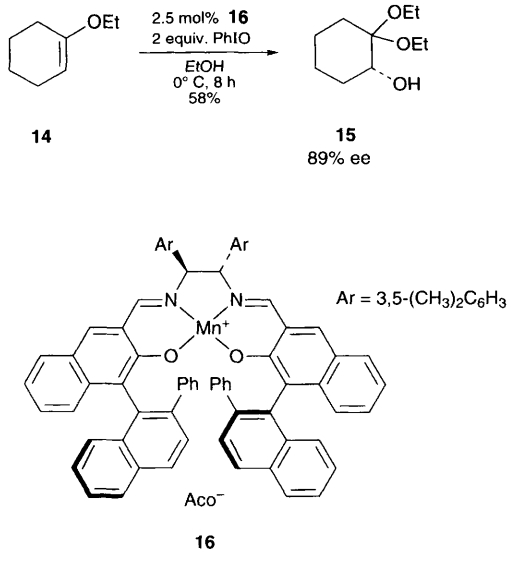
The Jacobsen–Katsuki epoxidation of alkenes using enantiomerically pure (salen)manganese(III) complexes has become a valuable method for the asymmetric epoxidation of alkenes. The reaction is being used in synthetic sequences by other research groups—a testament to the utility of this reaction.

An interesting development has been described by Fukuda and Katsuki in the reaction of enol derivatives where the product formed is a hydroxy acetal.[11] Thus, the enol ether **14** is oxidised to the hydroxy acetal **15** using iodosylbenzene and the catalyst **16** (**Scheme 5**). It is possible that the reaction proceeds *via* the epoxide which is then opened up, although the mechanism has not yet been fully elucidated. Adam and co-workers have reported related results using silyl enol ethers as substrates which afford α-hydroxy ketones on work-up.[12]

Two industrial groups have reported details concerning the addition of *N*-oxides to the standard (salen)manganese(III) catalysed epoxidation reactions using catalyst **17** (**Scheme 6**). The Smith-Kline Beecham group showed the beneficial effect

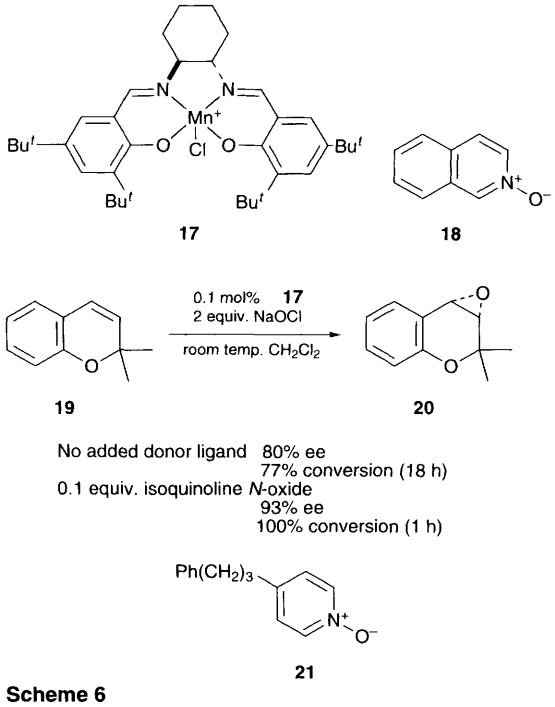


Scheme 4



Scheme 5

of isoquinoline *N*-oxide **18** as a donor ligand.[13] The enantioselectivity was enhanced as well as the rate of reaction in the conversion of chromene **19** into the epoxide **20**. The Merck group reported that the enantioselective epoxidation of indene similarly benefited from the presence of 4-(3-phenylpropyl)pyridine *N*-oxide **21**.[14]

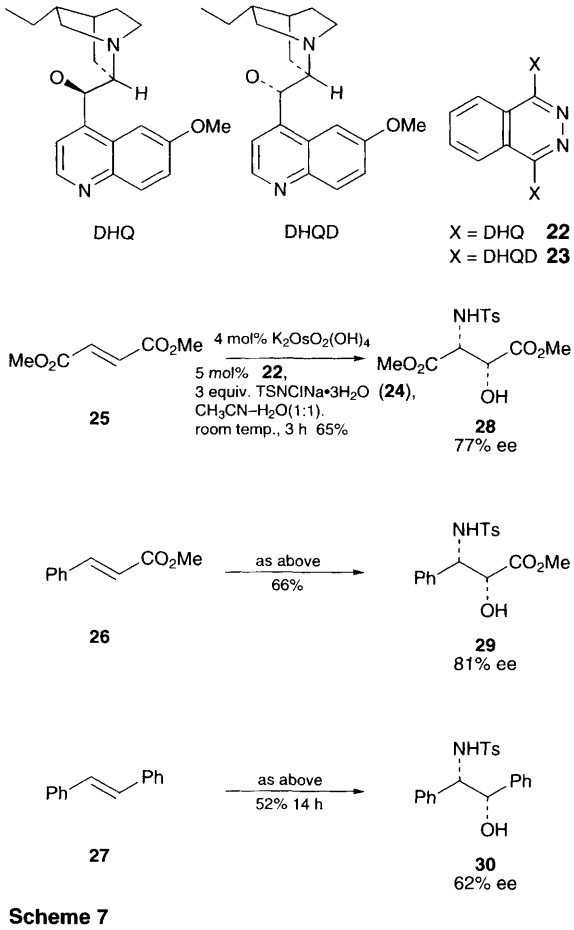


Scheme 6

the Sharpless asymmetric dihydroxylation, but the main advances have been reported in previous years.[16]

The Sharpless group has reported the catalytic asymmetric aminohydroxylation of alkenes.[17] This is a very exciting development in enantioselective transition metal catalysed chemistry.[18]

The Sharpless AA (asymmetric aminohydroxylation) reaction has been described at the beginning of what will no doubt be a long story. The alkene undergoes catalysed asymmetric aminohydroxylation in the presence of the familiar $(DHQ)_2PHAL$ **22** and $(DHQD)_2PHAL$ **23** ligands and an osmium complex (**Scheme 7**). Thus alkenes **25–27** are converted into the addition products **28–30** using chloramine T trihydrate ($TsNClNa \cdot 3H_2O$). As Sharpless points out, it is interesting that alkene **25**, which is a poor substrate in the related asymmetric dihydroxylation reaction, works well here. Further developments of this reaction are certain to provide numerous synthetic possibilities.



Scheme 7

2.4 Dihydroxylation and aminohydroxylation

Further examples of diastereoselective[15] and enantioselective dihydroxylation reactions have been published. There are now many papers appearing on

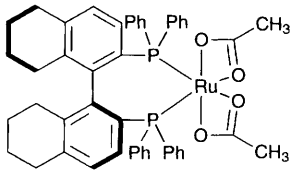
Iqbal and co-workers have described a one-pot epoxidation–ring-opening of alkenes.[19] These methods also lead to derivatives of amino alcohols directly from alkenes.

3 Hydrogenation and related processes

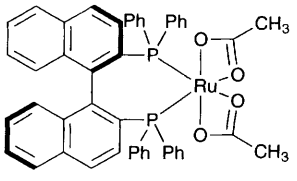
This section discusses some of the recent developments involving the hydrogenation of alkenes, ketones and imines. Hydrosilylation and hydroboration are also included in this section.

3.1 Hydrogenation of alkenes

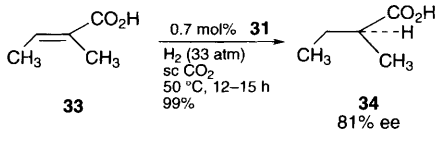
The asymmetric hydrogenation of alkenes using the enantiomerically pure ruthenium catalysts **31** and **32** represents one of the most effective asymmetric transition metal catalysed processes. Noyori and co-workers have shown that the hydrogenation of alkene **33** to the reduced product **34** can be performed in supercritical (sc) carbon dioxide (**Scheme 8**).[20] The enantioselectivity and rate of conversion are further enhanced by the addition of $CF_3(CF_2)_6CH_2OH$.



31 $Ru(OAc)_2[(S)\text{-}H_8\text{-}BINAP]$



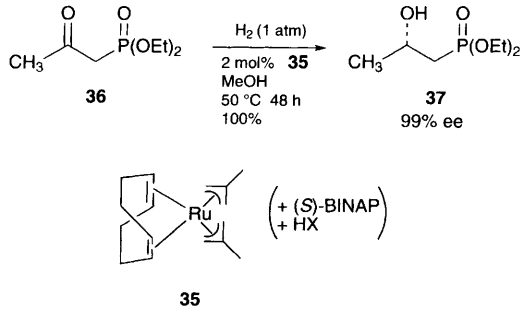
32 $Ru(OAc)_2[(R)\text{-}BINAP]$



33 **34** 81% ee

Scheme 8

and co-workers have reported the hydrogenation of ketones possessing a β-stereocentre.[22]

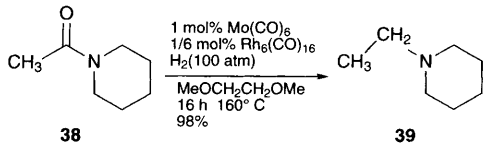


36 **37** 99% ee

35

Scheme 9

The reduction of amides to amines is generally achieved using metal hydride complexes such as $LiAlH_4$. However, Fuchikami and co-workers have shown that the combination of two transition metal complexes can have a synergistic effect.[23] For example, the combination of a rhodium complex and molybdenum complex affords a catalytic system capable of reducing amide **38** to the amine **39** (**Scheme 10**). Other bimetallic systems were also effective.



38 **39**

Scheme 10

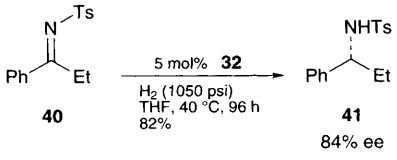
3.2 Hydrogenation of carbonyl compounds

The Noyori-type catalysts **31** and **32** may also be applied to the asymmetric hydrogenation of ketones. Genêt has used the related catalyst **35** in the asymmetric hydrogenation of β-keto phosphonates.[21] The β-keto phosphonate **36** is reduced to the corresponding alcohol **37** in superb yield and enantioselectivity under mild conditions (**Scheme 9**). Noyori

3.3 Hydrogenation of imines

Charette and Giroux have developed an effective asymmetric hydrogenation of *N*-tosylimines using enantiomerically pure ruthenium catalysts.[24] In the presence of the catalyst **32**, the *N*-tosylimine **40** is

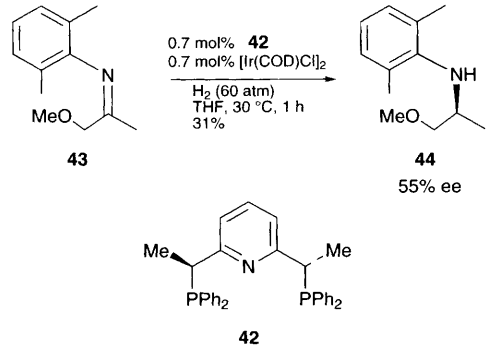
hydrogenated into sulfonamide **41** with good yield and enantioselectivity (**Scheme 11**).



40 **41**
84% ee

Scheme 11

Sablong and Osborn have used iridium complexes of ligand **42** to effect an asymmetric hydrogenation reaction.[25] The highest enantioselectivity was obtained in the conversion of imine **43** into the amine **44** (**Scheme 12**).



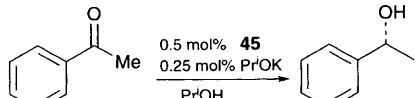
43 **44**
55% ee

42

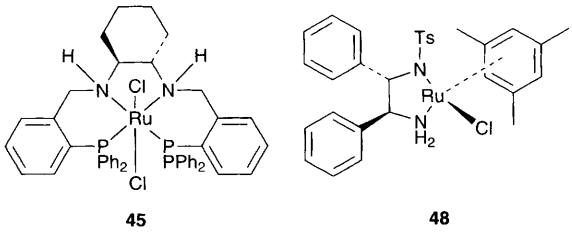
Scheme 12

3.4 Transfer hydrogenation of ketones

The transfer hydrogenation of ketones may be achieved, for example, using aluminium isopropoxide under Meerwein–Ponndorf–Verley conditions with isopropyl alcohol as the hydride donor. Transition metals may also be employed to catalyse the same reaction, and there have recently been advances made in the asymmetric version of this reaction. As with conventional hydrogenation, ruthenium catalysts are highly efficient for transfer hydrogenation reactions. The catalyst **45** has been employed to convert acetophenone **46** into (*R*)-phenethyl alcohol **47** using isopropyl alcohol–isopropoxide as the hydride donor (**Scheme 13**).[26] Knochel and co-workers have reported similar results using a ferrocene-based diamine ligand.[27] The ruthenium catalyst **48**, also reported by Noyori and co-workers, is again highly effective in hydrogen transfer reactions.[28] The conversion of acetophenone **46** into the alcohol **47** occurs with 98% enantiomeric excess and >99% yield using formic acid–triethylamine as the hydride donor.



46 **47**
97% ee



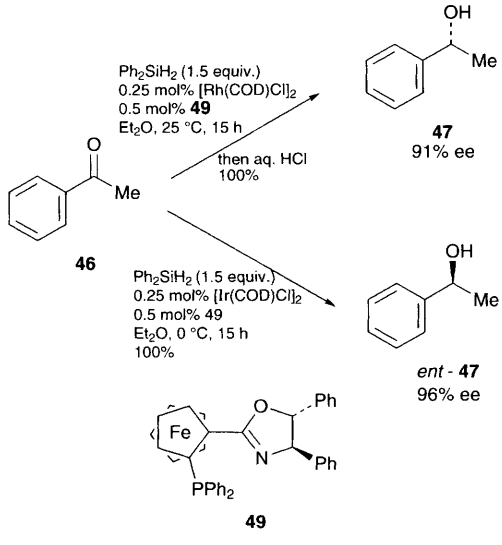
45 **48**

Scheme 13

3.5 Hydrosilylation and hydroboration

Hydrosilylations are mechanistically and synthetically related to hydrogenations.

Uemura and co-workers have found an unusual difference of the rhodium catalysed asymmetric reaction in comparison with the iridium catalysed variant.[29] The rhodium catalysed hydrosilylation of acetophenone **46**, in the presence of the ligand **49**, affords the (*R*)-alcohol **47** (after hydrolysis) (**Scheme 14**). However, the iridium catalysed process affords the (*S*)-alcohol *ent*-**47**!

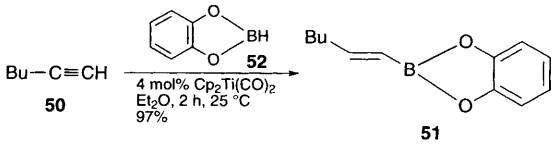


49

Scheme 14

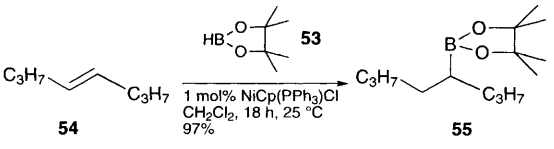
Hydroborations are often catalysed by rhodium complexes, although certain early transition metal complexes are also competent catalysts. He and Hartwig have shown that dicarbonyltitanocene or dimethyltitanocene catalysed the hydroboration of

alkynes and alkanes.[30] For example, hex-1-yne **50** is converted into the vinylborane **51** on treatment with catecholborane **52** and dicarbonyltitanocene catalyst (**Scheme 15**).



Scheme 15

Srebnik and Pereira have continued to examine hydroborations using pinacolborane **53**.[31] Whereas Wilkinson's catalyst affords terminal pinacolboronate products from internal alkynes or alkenes, the nickel catalyst $NiCp(PPh_3)Cl$ is highly selective for direct hydroboration. Thus octene **54** is converted into the hydroboration product **55** with 99:1 selectivity and excellent yield (**Scheme 16**). Diboration of dienes using bis(pinacolato)diboron has also been reported.[32]



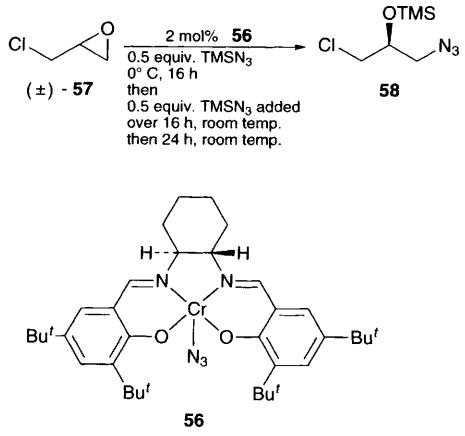
Scheme 16

4 Lewis acid catalysed reactions

Lewis acids catalyse a variety of reactions, including additions to carbonyl groups, Diels–Alder reactions and ring-opening reactions of epoxides. Although some of the transition metals described in this section are, strictly speaking, not functioning as Lewis acids, it is convenient to discuss synthetically related processes together.

4.1 Ring-opening of epoxides

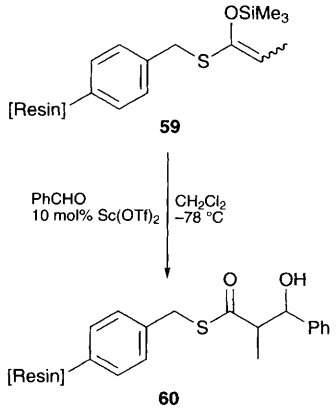
Schaus and Jacobsen have shown that it is possible to effect the ring-opening reaction of epichlorohydrin under dynamic kinetic resolution conditions.[33] Complex **56** catalyses the addition of trimethylsilyl azide to racemic epichlorohydrin **57**, affording the enantiomerically enriched product **58**, along with small amounts of achiral 1,3-dichloro- and 1,3-diazo-derivatives (**Scheme 17**).



Scheme 17

4.2 Aldol reactions

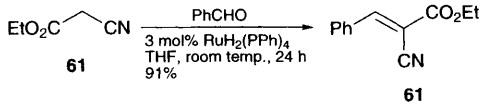
The advent of combinatorial synthesis has encouraged research groups to examine reactions on solid phase supported reactants. The Mukaiyama aldol reaction is no exception—Kobayashi and co-workers have performed aldol reactions on polymer-supported silyl enol ethers using catalytic scandium trifluoromethanesulfonate (triflate).[34] Thus the polymer-supported silyl enol ether **59** undergoes an aldol reation with benzaldehyde to afford the polymer-supported aldol adduct **60** (**Scheme 18**). The authors demonstrate the principle of how a library of aldol adducts can be created using this methodology. This research group has also shown that polymer-supported silyl enol ethers can be coupled to imines, again using catalytic scandium triflate.[35]



Scheme 18

Nitriles with activated α-hydrogens will undergo aldol condensation reactions and Michael reactions catalysed by ruthenium complexes. Extensive results have been published by the Murahashi group on this reaction.[36] For example, the nitrile **61** undergoes an

aldol condensation reaction with benzaldehyde to give the product **62** in good yield (**Scheme 19**). The Michael reaction has also been described by a Spanish group.[37]

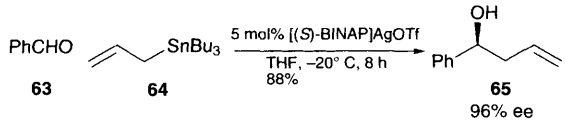


Scheme 19

4.3 Allylation of aldehydes and imines

The titanium catalysed allylation of aldehydes with allyltributyltin is a convenient small scale procedure for the synthesis of homoallylic alcohols, and is rendered enantioselective using a titanium 1,1-bi(2-naphthol) (BINOL) complex. Falck and co-workers have exploited this reaction in the synthesis of the antimitotic curacin A.[38]

Yamamoto and co-workers have reported an interesting use of an enantiomerically pure silver catalyst applied to this reaction.[39] Thus, benzaldehyde **63** reacts with allyltributyltin **64** in the presence of a silver triflate–(*S*)-BINAP complex to give the allylation product **65** in good yield and excellent enantiomeric excess (**Scheme 20**).



Scheme 20

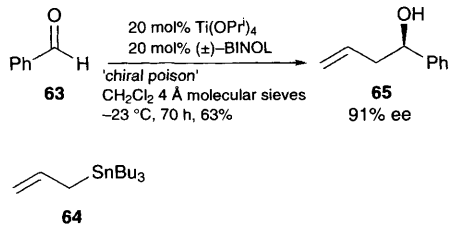
Scandium triflate[40] and enantiomerically pure (salen)titanium complexes[41] have also been reported to catalyse this reaction.

Faller and co-workers have used this reaction to demonstrate their 'chiral poisoning' chemistry.[42] Racemic BINOL–titanium isopropoxide catalyses the allylation reaction of benzaldehyde **63** with allyltributyltin **64** in 65% yield, although the product is, of course, racemic. However, by the addition of an enantiomerically pure poison (diisopropyl D-tartrate–titanium isopropoxide) an enantiomerically enriched product is formed (**65**, **Scheme 21**). The 'poison' has no catalytic activity in its own right, but selectively deactivates the (*R*)-BINOL–Ti catalyst leaving the (*S*)-BINOL–Ti catalyst to effect an enantioselective reaction.

Using palladium or platinum complexes to catalyse the allylation reaction results in a chemoselective allylation of imines in the presence of aldehydes. This can be rationalised mechanistically by the intermediacy of π-allyl complexes.[43]

4.4 Diels–Alder reactions

The Diels–Alder reaction is often catalysed by Lewis acids, typically titanium or boron catalysts.

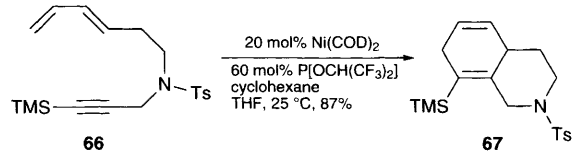


'chiral poison' = 60 mol% D-diisopropyl tartrate
20 mol% $Ti(OPr^i)_4$

Scheme 21

Howarth and Gillespie have used niobium and tantalum complexes as unusual Lewis acids to catalyse Diels–Alder reactions.[44]

Wender and Smith have shown that nickel complexes can catalyse the Diels–Alder reaction between dienes and alkynes.[45] The dienyne **66** undergoes intramolecular Diels–Alder reaction in the presence of a nickel catalyst to give the Diels–Alder adduct **67** (**Scheme 22**). This chemistry was applied to the synthesis of compounds containing the yohimbine skeleton.



Scheme 22

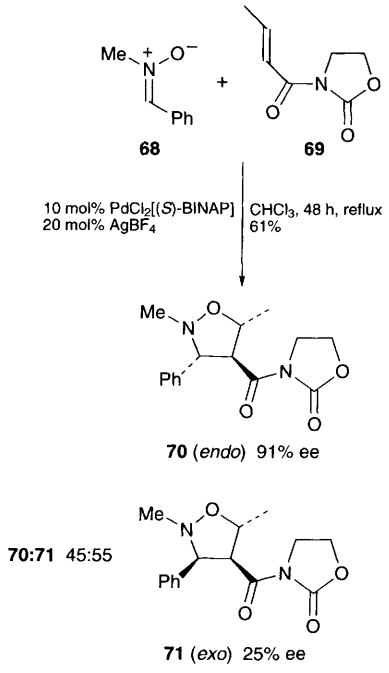
4.5 1,3-Dipolar cycloaddition of nitrones

The asymmetric 1,3-dipolar cycloaddition of nitrones to alkenes has been reported with enantiomerically pure titanium complexes.[46] Enantiomerically pure palladium complexes also catalyse these reactions.[47] Thus, cycloaddition of the nitrone **68** to the achiral alkene **69** afford the *endo*- and *exo*-adducts **70** and **71** in the presence of a palladium–(*S*)-BINAP complex (**Scheme 23**).

4.6 Acylation and related reactions

Scandium triflate is rapidly becoming a useful catalyst for a wide range of reported examples. Yamamoto and co-workers have employed scandium triflate as an active Lewis acid catalyst for the acylation of alcohols with acid anhydrides.[48] The reaction is still effective for tertiary alcohols and hindered phenols. The phenol **72** is acylated under very mild conditions to give the ester **73** (**Scheme 24**). Scandium triflamide has been reported to have even greater catalytic activity than scandium triflate.[49]

Direct acylation of phenol and naphthol derivatives using hafnium triflate as catalyst has been described by Kobayashi and co-workers.[50]



Scheme 23

1-Naphthol **74** is converted into the 2-acetylated derivative **75** using acetyl chloride and the hafnium catalyst (**Scheme 25**). The reaction may proceed *via* direct acetylation and/or *via* *O*-acylation followed by Fries rearrangement.

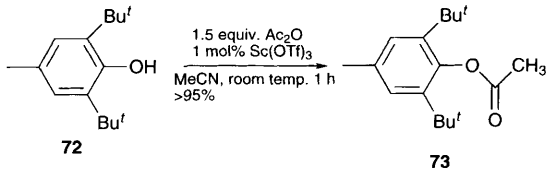
Scandium triflate and copper triflate have both been reported as catalysts in Friedel–Crafts alkylation reactions.[51,52] Both scandium triflate and scandium triflamide are very active catalysts for the acetalisation of ketones with alcohols or diols.[53]

5 Catalytic coupling reactions

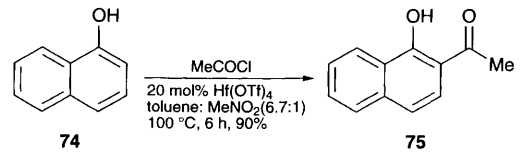
Transition metals are able to catalyse many coupling reactions, especially C–C bond forming processes. There are often no equivalent uncatalysed reactions. Although the majority of work in this area involves palladium catalysed transformations, the role of other metals is becoming more evident.

5.1 Heck reactions

The Heck reaction of allyl alcohols often affords ketones (from the enol) rather than the expected 'Heck' product. Kang and co-workers have shown that iodonium salts undergo Heck reaction to give the substituted alkene product.[54] For example, allylic

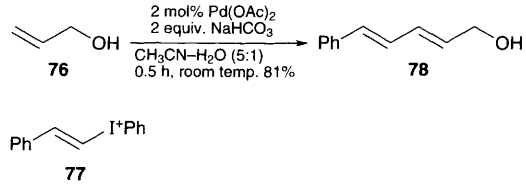


Scheme 24



Scheme 25

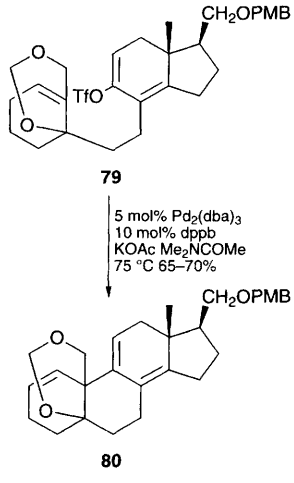
alcohol **76** reacts with the iodonium salt **77** to give the diene **78** (**Scheme 26**).



Scheme 26

Yun and Mohan have demonstrated the feasibility of preparing a library of indole compounds using Heck chemistry on a solid support.[55]

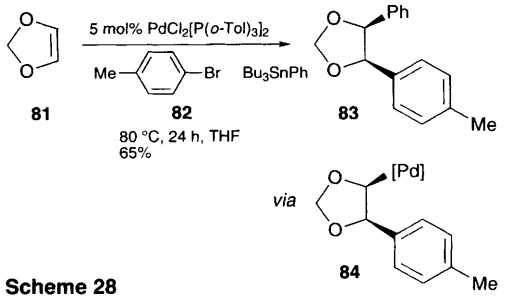
Overman and co-workers have employed a Heck cyclisation strategy in the synthesis of a steroid skeleton.[56] The intramolecular Heck reaction of compound **79** affords the coupled product **80**, where alkene migration has occurred (**Scheme 27**).



Scheme 27

Kosugi and co-workers have combined a Heck reaction with a Stille coupling in the conversion of the alkene **81** and bromotoluene **82** into the *cis*-substituted product **83** (**Scheme 28**).[57] Presumably the reaction proceeds *via* the σ-palladium complex **84**, which, since it is unable to undergo β-elimina-

tion, can be intercepted by phenyltributyltin in a Stille process.



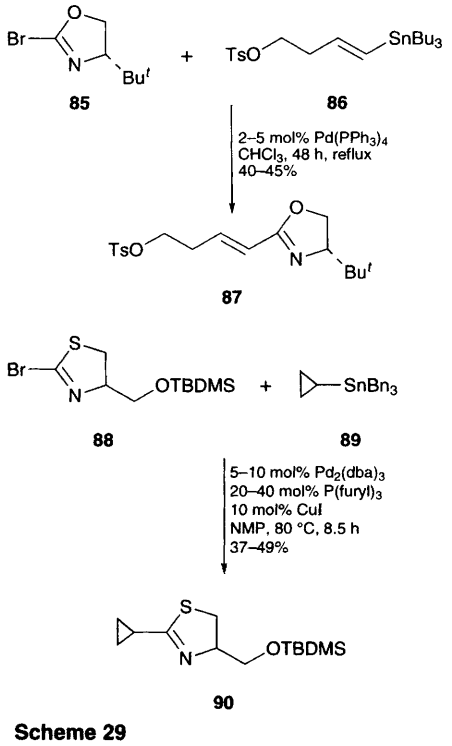
81 82 83 84

80 °C, 24 h, THF
65%

Scheme 28

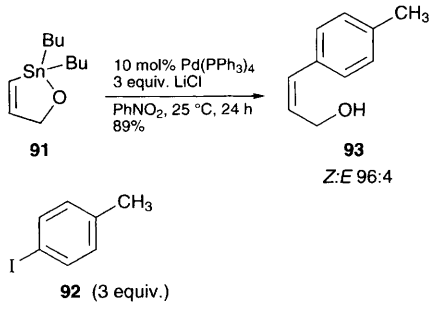
5.2 Stille reaction

Since organostannanes are compatible with many functional groups, their coupling reactions (Stille reactions) are often synthetically useful. Meyers and Novachek have coupled the 2-bromo-2-oxazoline **85** with the organostannane **86** affording product **87** in reasonably good yield considering the sensitivity of the functional groups involved (**Scheme 29**).[58] Schmitz and Romo have reported the Stille reaction between 2-bromo-2- hiazoline **88** and the cyclopropylstannane **89**.[59]



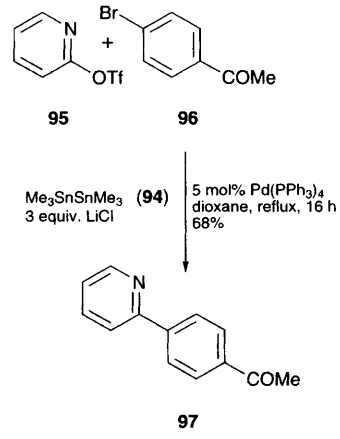
Scheme 29

Kraus and Watson have used the dihydrostannoxole **91** in a Stille coupling process with aryl halides including iodotoluene **92**, affording the alkene **93** with good control over $Z:E$ geometry (**Scheme 30**).[60]



Scheme 30

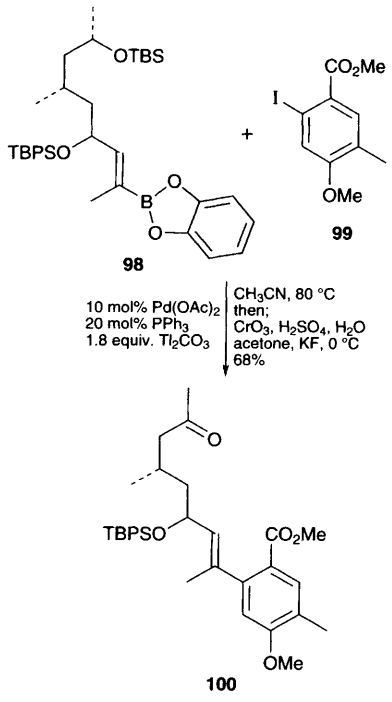
The cross-coupling reaction between two electrophilic partners can be mediated by the addition of hexamethylditin **94**.[64] In the coupling between the pyridyl triflate **95** and bromoacetophenone **96**, the product **97** is obtained in good yield (**Scheme 31**). The pyridyl triflate is quickly converted into the corresponding pyridylstannane (an unstable intermediate) which then undergoes Stille coupling.



Scheme 31

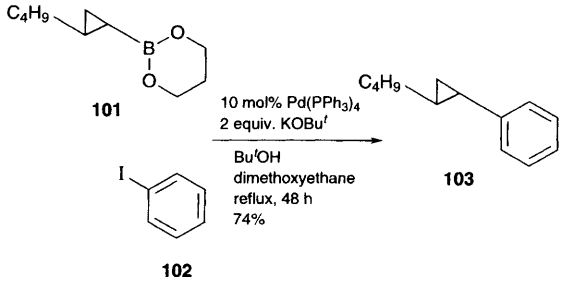
5.3 Suzuki reaction

The Suzuki coupling reaction of organoboranes also tolerates the presence of other functional groups. For example, Markó and co-workers have coupled the vinylborane **98** with the iodoarene **99** to afford the product **100**, which represents a synthesis of the left hand subunit of milbemycin $\beta 3$ (**Scheme 32**).[62] Thallium carbonate greatly improved this coupling process.



Scheme 32

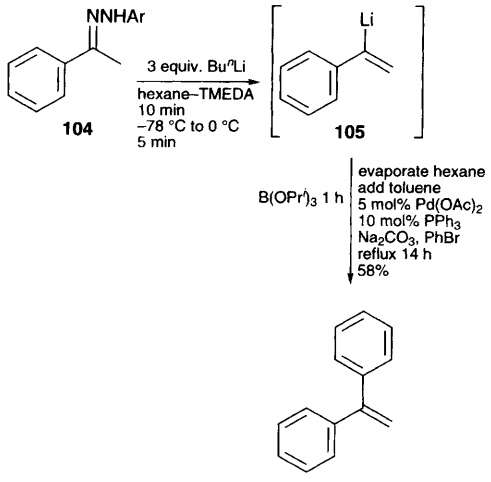
Hildebrand and Marsden have reported that cyclopropylboronate esters can be employed in the Suzuki coupling reaction.[63] Compound **101** (obtained by cyclopropanation of a vinylboronate) underwent coupling with iodobenzene **102** to give the *trans*-substituted cyclopropane **103** (**Scheme 33**).



Scheme 33

Reports of aryldiazonium salts[64] and iodonium salts[65] as electrophilic coupling partners in the Suzuki coupling have been published. Hallberg and co-workers have shown the benefit of microwave irradiation for Suzuki coupling reactions on solid phase supported reactants.[66]

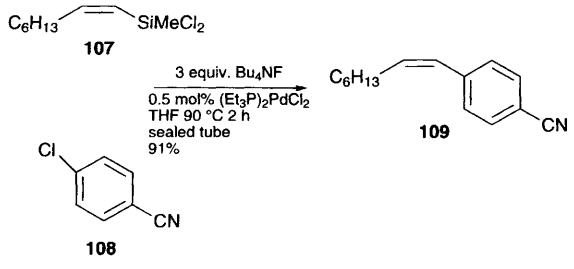
Passafaro and Keay have combined a Shapiro reaction with a Suzuki coupling in a useful one-pot process.[67] The hydrazone **104** was treated with butyllithium, which is expected to generate vinyl anion **105**. Addition of triisopropyl borate affords an intermediate vinylboronate which then undergoes Suzuki coupling with bromobenzene to give 1,1-diphenylethene **106** (**Scheme 34**).



Scheme 34

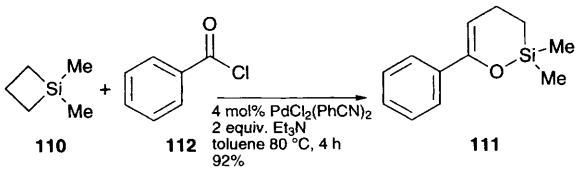
5.4 Organosilanes in coupling reactions

Organosilanes are competent partners in transition metal catalysed coupling reactions, using chlorinated silanes in the presence of fluoride. Hatanaka and co-workers have published many examples of such coupling reactions with chloroarenes (which themselves are usually unreactive coupling partners). The vinylsilane **107** is coupled to *p*-chlorobenzonitrile **108** to afford the *Z*-substituted alkene **109** (**Scheme 35**).[68]



Scheme 35

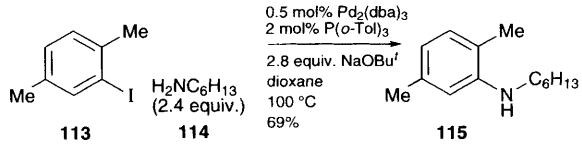
Due to ring strain, silacyclobutanes are relatively reactive. Compound **110** has been employed in a coupling reaction to give the cyclic silyl enol ether **111** on treatment with benzoyl chloride **112** and a palladium catalyst (**Scheme 36**).[69,70]



Scheme 36

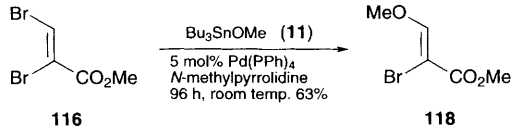
5.5 Catalytic synthesis of carbon–heteroatom bonds

The palladium catalysed amination of aryl iodides continues to attract interest. Wolfe and Buchwald have shown the importance of dioxane as the solvent in the reaction of aryl iodide **113** with the simple amine **114** (**Scheme 37**). The aryl amine product **115**, as well as many related analogues, has been isolated in good yield.[71] The beneficial effect of employing chelating diphosphine ligands in these aryl amination reactions has been independently reported by two research groups.[72,73] The reaction has already been applied to the amination of polymer-bound aryl bromides.[74,75]



Scheme 37

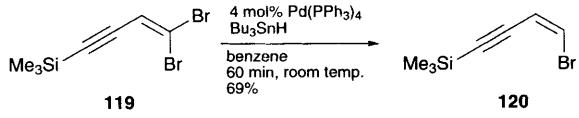
Rossi and co-workers have used alkoxystannane and thioalkoxystannone derivatives to effect palladium catalysed carbon–oxygen and carbon–sulfur bond formation.[76] Thus the dibromoalkene **116** undergoes regioselective coupling with the alkoxystannane **117** to give the enol ether **118** (**Scheme 38**). Arylboronic esters can be prepared using coupling reactions between aryl halides and bis(pinacolato)diboron.[77a] The same reagent undergoes coupling with alkynes to give alkenes with 1,2-boron substituents.[77b]



Scheme 38

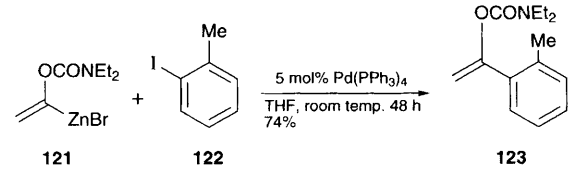
5.6 Other coupling reactions

A wide range of organic fragments may be coupled using transition metal catalysts, which is one of the main attractions of these processes. The reduction of carbon–halogen bonds may be thought of as a coupling between an organic fragment and hydride. Uenishi and co-workers have reported a selective palladium catalysed hydrogenolysis of 1,1-dibromoalk-1-enes.[78] This process is illustrated by the conversion of dibromide **119** into the *Z*-bromoalkene **120** (**Scheme 39**). The palladium catalysed reduction of alkyl halides using triethylsilane as solvent has also been reported.[79]

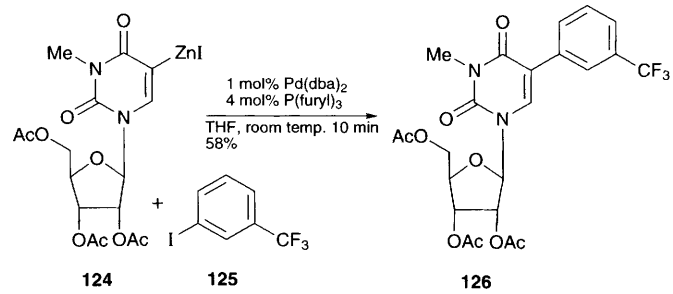


Scheme 39

Zinc reagents have a long history in catalytic coupling chemistry. Snieckus and co-workers have recently reported the coupling between the zinc reagent **121** and aryl halides, such as iodotoluene **122**.[80] The coupled product **123** could be converted into an acetyl group, which represents an overall anionic equivalent of the Friedel–Crafts reaction (**Scheme 40**). The tolerance of other functional groups is clearly demonstrated in the coupling of the organozinc reagent **124** with the iodoarene **125** to give the product **126** in good yield (**Scheme 41**).[81]

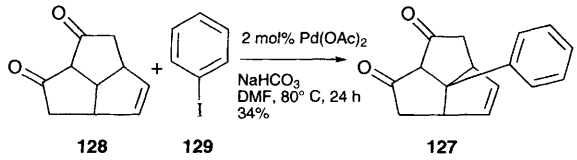


Scheme 40



Scheme 41

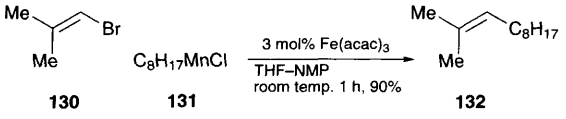
De Meijere and co-workers have reported the unexpected formation of the centro-substituted triquinane **127** in the coupling of diketone **128** and iodobenzene **129** (**Scheme 42**).[82] The reaction may proceed *via* oxidation to an α,β-unsaturated diketone, followed by a reductive Heck hydroarylation.



128 129 127

Scheme 42

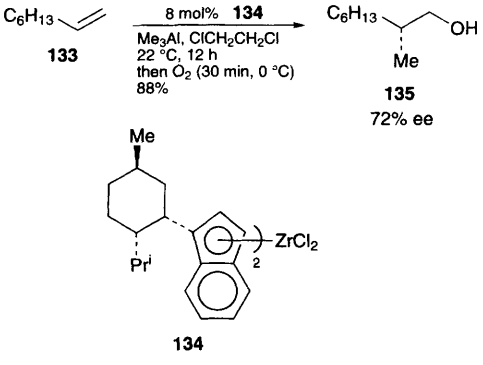
Cahiez and Marquais have employed an iron catalyst to effect the cross-coupling reaction of vinyl halides and organomanganese reagents.[83] Thus, vinyl bromide **130** and octylmanganese chloride **131** are coupled to form alkene **132** (**Scheme 43**).



130 131 132

Scheme 43

The zirconium catalysed enantioselective methylalumination of monosubstituted alkenes has been described by Kondakov and Negishi.[84,85] After oxidation, the alcohol is isolated as the product. Thus oct-1-ene **133** undergoes enantioselective methylalumination catalysed by complex **134** to afford the alcohol **135** in good yield and enantioselectivity (**Scheme 44**).

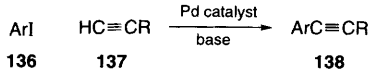


133 135 134

Scheme 44

5.7 Reactions involving alkynes

The coupling reaction between an aryl halide **136** and a terminal alkyne **137** can be effected by a palladium catalyst to give the product **138** (**Scheme 45**). Copper salts[86] or silver salts[87] have been shown to have a beneficial effect on such reactions, although good yields can be obtained without these additives.[88]

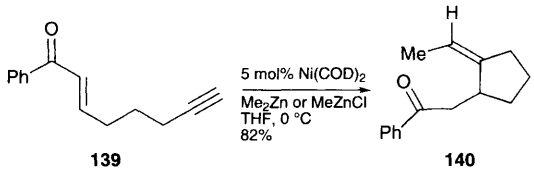


136 137 138

Scheme 45

The stereoselective addition across an alkyne can be a synthetically useful process. For example, the *trans*-addition of allylstannanes across alkynes catalysed by zirconium tetrachloride has been demonstrated.[89]

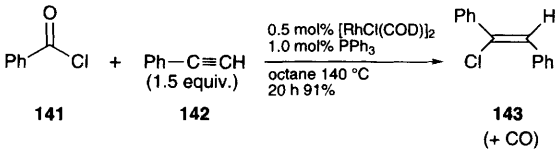
Nickel catalysts activate alkynes towards nucleophilic addition. Thus, the alkyne **139** undergoes an addition–cyclisation reaction initiated by the nickel catalysed addition of an alkylzinc reagent to an alkyne (**Scheme 46**).[90] It is noteworthy that direct conjugate addition to the enone moiety was not observed. A related three component coupling of alkyne, α,β-unsaturated aldehyde and bromide has also been reported.[91]



139 140

Scheme 46

An unusual decarbonylative addition of aroyl chlorides to alkynes is catalysed by rhodium complexes.[92] Benzoyl chloride **141** adds regio- and stereo-selectivity to alkyne **142** to give vinyl chloride **143** (**Scheme 47**).



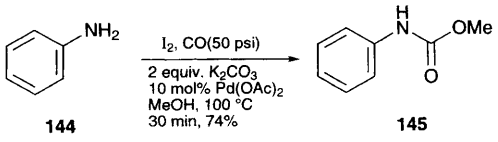
141 142 143 (+ CO)

Scheme 47

Intramolecular additions of methylenecyclopropanes to alkynes have been reported,[93] as well as an unusual palladium catalysed *cis*-selenophosphonylation of alkynes.[94]

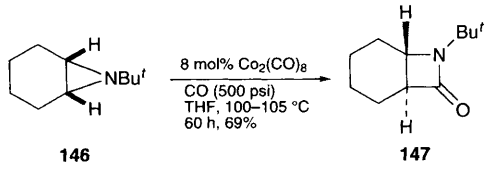
5.8 Carbonylation

Many transition metal catalysed reactions which proceed under carbon monoxide pressure result in the formation of organic carbonyl compounds. Pri-Bar and Schwartz describe the conversion of aniline **144** into the urethane **145** by an iodine promoted, palladium catalysed reaction in the presence of methanol (**Scheme 48**).[95]



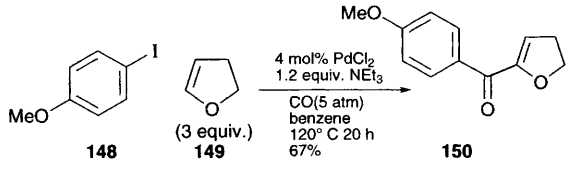
Scheme 48

The research group of Alper has had a long standing interest in catalysed carbonylative ring-expansion reactions.[96] The cobalt catalysed ring-expansion of bicyclic aziridine **146** is noteworthy since the bicyclic β-lactam **147** is strained, due to the inversion mechanism which is operative during the carbonylation process (**Scheme 49**).[97]



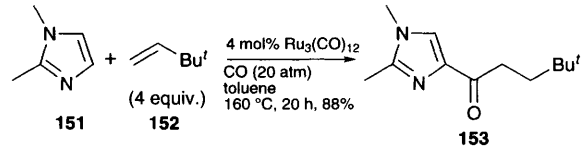
Scheme 49

Miura and co-workers have reported a hybrid Heck reaction–carbonylation. Aryl iodide **148** is coupled with dihydrofuran **149** to give the 2-substituted dihydrofuran product **150** with no detectable amounts of other isomers (**Scheme 50**).[98]



Scheme 50

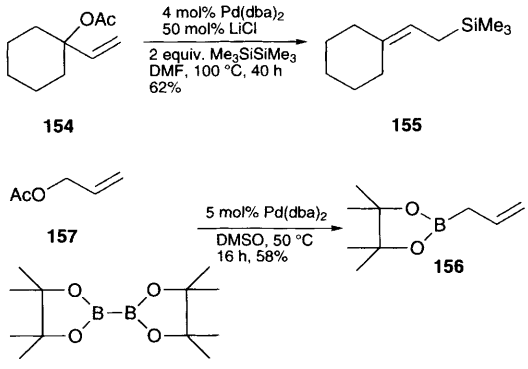
Another alkene coupling–carbonylation reaction using a ruthenium catalyst has been published.[99] Imidazole **151** is coupled to alkene **152** to give the ketone **153** with good regioselective addition across the alkene (**Scheme 51**).



Scheme 51

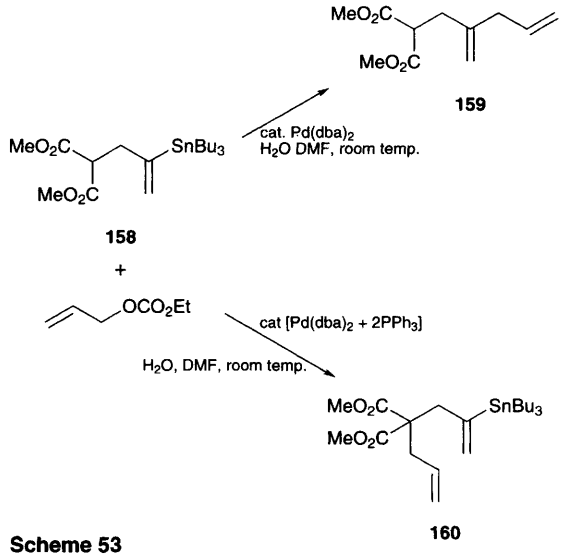
An account of work from the Murai group describing catalytic reactions using silanes and carbon monoxide has also appeared.[100]

The silylation of allyl acetates using disilanes has been reported.[101] Thus, allyl acetate **154** is converted into the allylsilane **155** in good yield. Allylboronate **156** can be prepared by the palladium catalysed reaction of allyl acetate **157** with bis(pinacolato)diboron (**Scheme 52**).[102]



Scheme 52

Echavarren and co-workers have reported that compound **158** can undergo allylic substitution *via* two possible pathways.[103] Using no phosphine, the 'tin-free' product **159** is formed whilst, in the presence of phosphine, a more conventional allylic substitution occurs (**Scheme 53**). These workers have used the phrase 'palladium-switchable bis-nucleophiles' to describe their work.

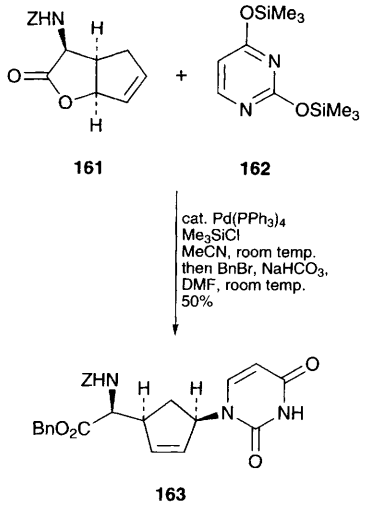


Scheme 53

5.9 Allylic substitution

Allylic electrophiles undergo transition metal catalysed coupling reactions with many nucleophiles. The palladium catalysed nucleophilic substitution of lactone **161** with uracil derivaive **162** affords the

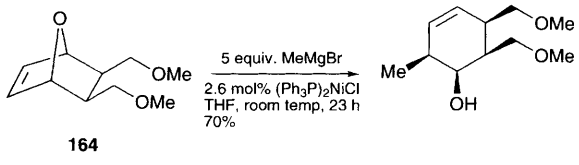
substitution product **163**, which was used in the preparation of carboxylic polyoxins (**Scheme 54**).[104]



Scheme 54

Asymmetric variants of the palladium catalysed allylic substitution reaction were discussed at length in the previous article, as well as in a comprehensive review.[105]

Lautens and Ma have ring opened the oxabicyclic compound **164** with Grignard reagents, using nickel catalysts (**Scheme 55**).[106]

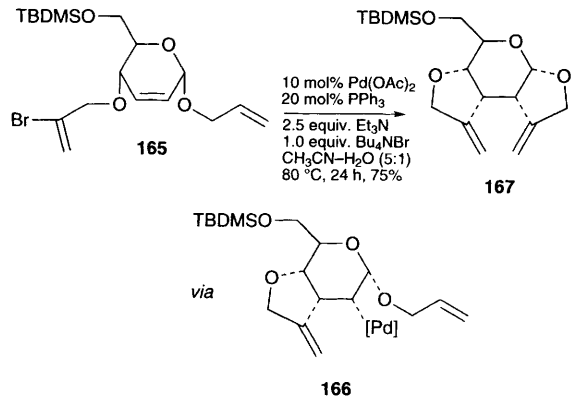


Scheme 55

5.10 Cyclisation

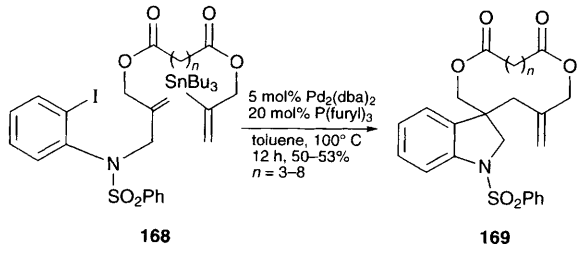
Cyclisations cover many aspects of transition metal catalysed processes. This section deals with catalysed processes where the main theme is cyclisation, and where several events take place consecutively. However, there are also cyclisation reactions detailed elsewhere in this review.

A palladium catalysed cascade cyclisation on the carbohydrate template **165** has been reported by Sinou and co-workers.[107] The process is essentially two sequential Heck reactions, where the intermediate **166** cannot undergo β-elimination and hence undergoes a second Heck cyclisation to give the product **167** (**Scheme 56**).



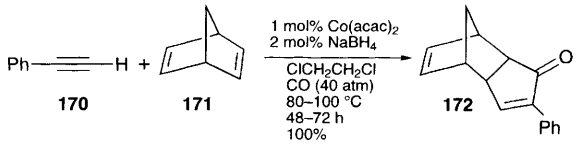
Scheme 56

Grigg and co-workers have shown that the vinylstannane **168**, which is formed *in situ* from an alkyne undergoes a palladium catalysed bicyclisation to form the macrocycle **169** (**Scheme 57**).[108] The reaction proceeds *via* Heck reaction of the aryl iodide onto the alkene and then trapping by the vinylstannane.



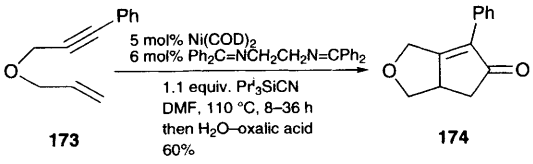
Scheme 57

Pauson–Khand cyclisation provides a useful synthesis of cyclopentenones. Lee and Chung have employed a catalytic system under fairly mild conditions in the reaction between phenylacetylene **170** and norbornadiene **171** (**Scheme 58**). The use of sodium borohydride was required for the excellent yield.[109]



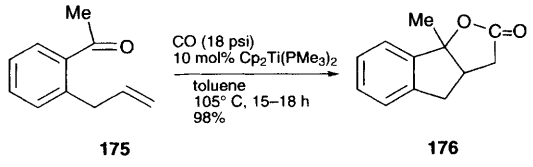
Scheme 58

Buchwald and co-workers have continued their research into a related titanium catalysed bicyclisation using nitriles instead of carbon monoxide.[100] This group has also reported a nickel catalysed variant of the reaction.[111] Enyne **173** undergoes bicyclisation with triisopropylsilyl cyanide, which after hydrolysis of the silyl imine affords the ketone **174** (**Scheme 59**).



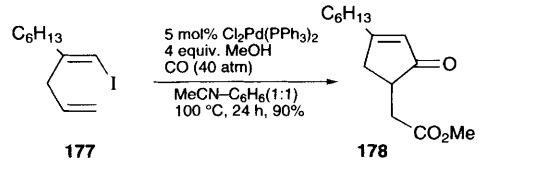
Scheme 59

Replacing the alkyne function in a Pauson–Khand cyclisation with a ketone function provides the opportunity for a hetero-Pauson–Khand reaction.[112] For example, using the Buchwald titanium catalyst, the unsaturated ketone **175** is converted into the lactone **176** (**Scheme 60**). Using similar substrates and the same catalyst, but using diphenylsilane in place of carbon monoxide, provides a reductive cyclisation procedure.[113]



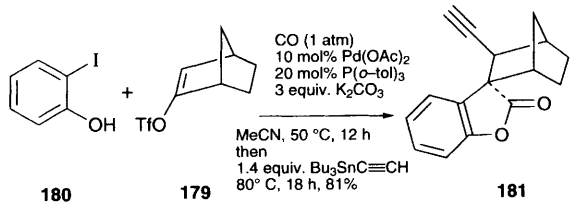
Scheme 60

Cascade cyclisation reactions in the presence of carbon monoxide can lead to the incorporation of one or more C=O units. Such a process is exemplified by the conversion of vinyl iodide **177** into the keto ester **178**, where two C=O units have been incorporated (**Scheme 61**).[114] Negishi and co-workers have also reported an example where four C=O units are installed in one tricyclisation cascade![115]



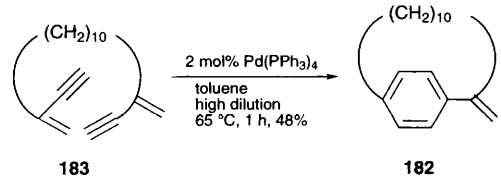
Scheme 61

Grigg and co-workers have designed 'tetramolecular queuing processes'.[116] Vinyl triflate **179** undergoes an initial palladium catalysed carbonylation with phenol **180**, and then the CO atmosphere is removed, and the temperature raised such that a Heck–anion capture process affords the product **181** with four new bonds (**Scheme 62**).



Scheme 62

The preparation of aromatic rings *via* metal catalysed cyclisation of suitable precursors can afford very rapid construction of arenes. Yamamoto and co-workers have reported a remarkable synthesis of paracyclophane **182** from the acyclic precursor **183** (**Scheme 63**).[117] The synthesis of furans by a palladium catalysed cyclisation of keto alkynes has also been reported.[118]

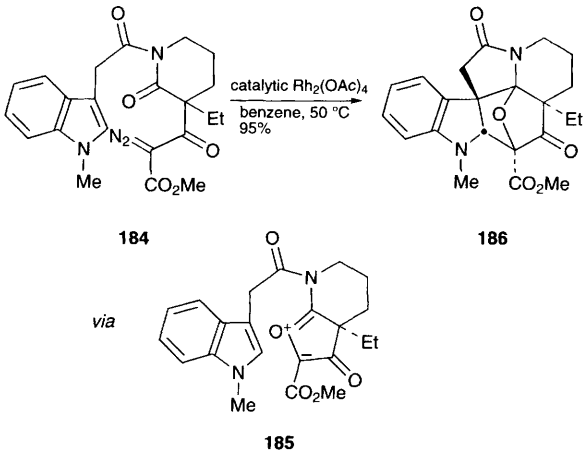


Scheme 63

6 Reactions involving metal carbenoids

Transition metal catalysed cyclopropanations as well as their asymmetric and intramolecular variants are synthetically useful processes, although many of the major developments have been reported in previous reviews in this journal.

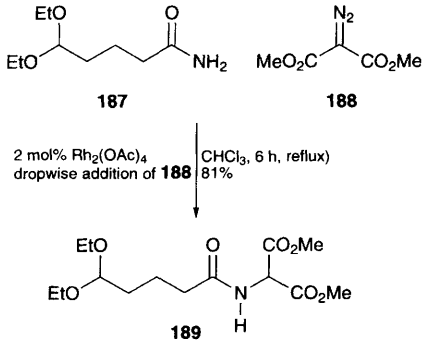
Tandem reactions have an ability to generate significant complexity in a one-pot process and Davies and Doan have published a tandem rhodium catalysed cyclopropanation–Cope rearrangement strategy as a route to the tremulane skeleton.[119] Padwa and Price have reported a rhodium catalysed cyclisation–dipolar addition reaction, where diazo precursor **184** undergoes a rhodium catalysed conversion into the intermediate dipolar compound **185** (**Scheme 64**).[120] Subsequent *in situ* cycloaddition with the indole moiety, providing the product **186**, which possesses the *Aspidosperma* skeleton.



Scheme 64

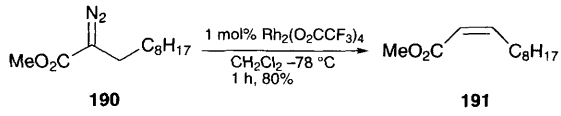
Intramolecular aziridination reactions have been achieved by the rhodium catalysed reaction of a diazo moiety tethered to an oxime.[121]

Catalytic reactions involving carbenes can also undergo insertion reactions into single bonds. Moody and co-workers have employed amides as the insertion substrates.[122] Thus, amide **187** reacts with the diazo compound **188** in the presence of dirhodium tetraacetate to give the insertion product **189**, which was cyclised to oxazoles in a separate step (**Scheme 65**). Using enantiomertically pure rhodium complexes, further examples of enantioselective C–H[123] and Si–H[124] insertion reactions have been reported.



Scheme 65

Diazo esters and diazo ketones undergo an elimination reaction in the presence of a rhodium(II) trifluoroacetate catalyst.[125] The reactions are highly selective for the (*Z*)-alkene, as indicated by the conversion of diazo ester **190** into the (*Z*)-α,β-unsaturated ester **191** (**Scheme 66**).

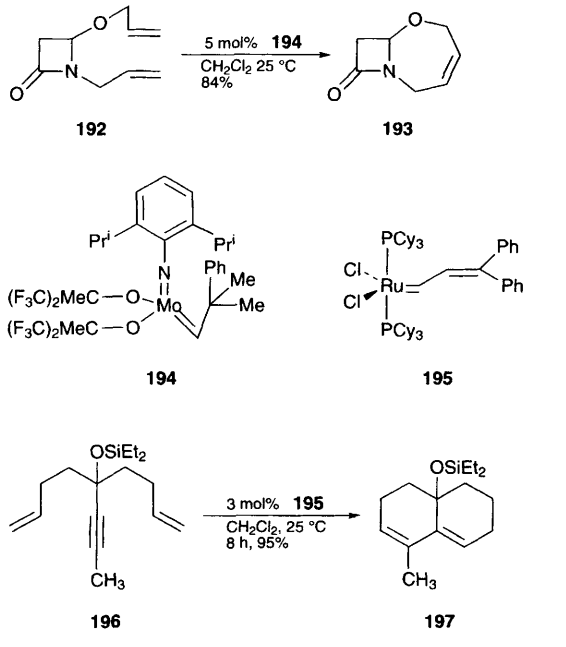


Scheme 66

7 Miscellaneous catalysed reactions

7.1 Ring-closing metathesis

Ring-closing metathesis has rapidly become established as a useful synthetic method in the synthesis of cyclic alkenes. One example is given by the conversion of the diene **192** into the novel β-lactam **193**, using the molybdenum catalyst **194** (**Scheme 67**).[126] Grubbs and co-workers have investigated the ring-closing metathesis of dienynes using the ruthenium catalyst **195**.[127a] The dienyne **196** is converted into the bicyclic compound **197**. The first report of an enantiomerically pure catalyst for ring-closing metathesis has also appeared.[127b]

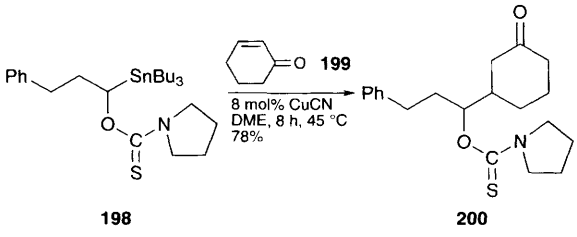


Scheme 67

7.2 Conjugate addition

Copper salts have a long history in catalysing conjugate addition to α,β-unsaturated carbonyl compounds. Falck and co-workers have used copper cyanide to catalyse the conjugate addition of the

α-alkoxystannane **198** to cyclohexenone **199** (**Scheme 68**).[128] Linderman and Siedlecki have used copper catalysts to react α-alkoxystannanes with acid chlorides.[129] Noyori and co-workers have shown that a copper(I)–sulfonamide combined system catalyses the conjugate addition of diorganozincs to α,β-unsaturated ketones.[130] The sulfonamide provides an example of dramatic ligand acceleration.

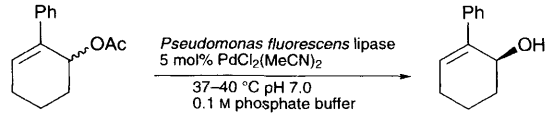


198 **200**

Scheme 68

7.3 Enzyme and palladium combinations

The dynamic resolution of allylic acetates has been achieved using a combination of conventional lipase catalysed enantioselective hydrolysis and *in situ* palladium catalysed racemisation of substrate.[131] Thus, the racemic allylic acetate **201** is converted into the enantiomerically enriched allylic alcohol **202** under dynamic kinetic resolution conditions (**Scheme 69**).

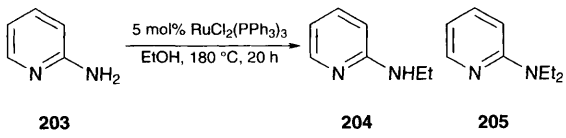


(±)–**201** (+)–**202**

Scheme 69

7.4 Reactions of amines

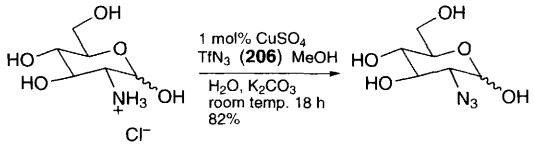
An unusual alkylation of heteroaromatic amines with alcohols has been published by a Japanese group.[132] Thus, 2-aminopyridine **203** affords the monosubstituted product **204** and disubstituted product **205** (**Scheme 70**). The reaction proceeds *via* oxidation of the alcohol to an aldehyde, and then reduction of the so-formed imine or iminium species.



203 **204** **205**

Scheme 70

Whilst the conversion of amines into azides using triflyl azide **206** is a known procedure, Wong and co-workers have discovered that the reaction takes place more efficiently in the presence of copper sulfate as catalyst.[133] The amino sugar **207** is efficiently converted into the azido sugar **208** (**Scheme 71**).

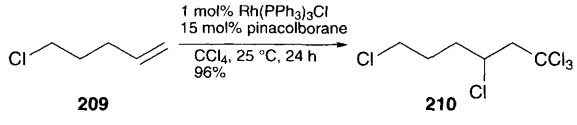


207 **208**

Scheme 71

7.5 Kharasch reaction

The Kharasch reaction between alkenes and carbon tetrachloride has been catalysed by zirconium complexes and by Wilkinson's catalyst.[134] Although neither catalyst was effective by itself, in the presence of catalytic amounts of pinacolborane, alkene **209** was converted into the addition product **210** (**Scheme 72**).



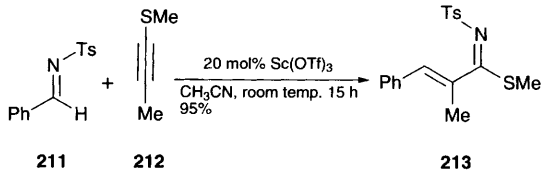
209 **210**

Scheme 72

7.6 α,β-Unsaturated thioimidates

Kobayashi and co-workers have reported an unusual reaction between imines and alkynyl sulfides, which in the presence of scandium triflate catalyst affords α,β-unsaturated thioimidates.[135] The reaction is illustrated by the conversion of imine **211** and alkynyl

sulfide **212** into the product **213** in excellent yield, *via* an initial [2+2] cycloaddition (**Scheme 73**).



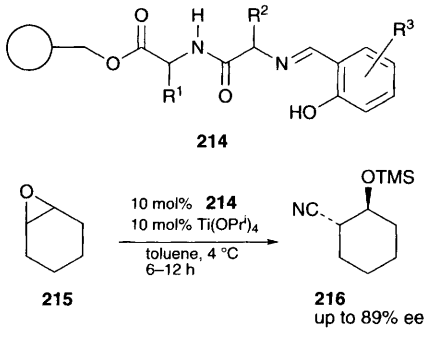
211 **212** **213**

Scheme 73

7.7 Combinatorial synthesis in catalysis

The development of a successful ligand for asymmetric catalysis often requires the preparation of many ligands in order to maximise enantioselectivity. Several research groups have reported the use of a combinatorial approach to ligand synthesis, thereby generating many ligand candidates and screening them quickly. This represents an exciting advance in asymmetric catalysis.

Gilbertson and Wang have prepared a 63-member library of phosphine-containing peptides which were screened in rhodium catalysed asymmetric hydrogenation.[136] Snapper, Hoveyda and co-workers have generated a series of support-bound dipeptide Schiff bases **214** and examined their efficiency in the titanium catalysed addition of TMSCN to *meso*-epoxides, including the conversion of epoxide **215** into the product **216 (Scheme 74)**.[137] The stepwise variation in the modular ligand structure provides a means for identifying a system which gives high enantioselectivity.



Scheme 74

Jacobsen and co-workers have applied combinatorial chemistry to the discovery of metal–ligand complexes, an approach which is also likely to provide dividends in asymmetric catalysis.[138]

Burgess and co-workers have undertaken a solution-phase high-throughput catalyst screening for C–H insertion reactions.[139] Five ligands were screened in combination with different metal salts and solvents to provide 96 different systems. This 'one catalyst per well' strategy certainly allows for rapid screening of reactivity/selectivity.

There can be no doubt that the next few years will see many more examples of combinatorial and high-throughput methods in catalysis.

Acknowledgement

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