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The uses of pincer complexes in organic synthesis

John T. Singleton*

AstraZeneca R&D Charnwood, Process Research and Development department, Bakewell Road, Loughborough, Leicestershire LE11 5RH, UK

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* Tel.: +44-1509-644-438; fax: +44-1509-645-588; e-mail: john.singleton@astrazeneca.com

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1. Scope of the review

This report is a summary of the many uses that chemists have found for pincer complexes in organic synthesis. Although pincer complexes have been synthesized since the early 1970s, they have only recently been used as catalysts in organic reactions. This review aims to concentrate on only pincer complexes that have, or are currently emerging with, specific uses for a synthetic organic chemist.

The syntheses and properties of NCN pincer complexes were reviewed by Rietveld et al.[1] in 1997, while an alternative review by van Koten,[2] only recently published, focuses on the synthesis of many pincer complexes and the possible applications of some, as crystalline switches or sensors for SO_2. With many types of pincer complexes using PCP, CNC and SCS ligands amongst others in existence, it is beyond the scope of any review to examine the synthesis of every pincer complex. It is hoped, therefore, that a review of how the unique properties of these complexes have been exploited, to advance specific reactions, will prove useful.

2. Introduction

Pincer complexes consist of a metal centre and a pincer skeleton. The pincer skeleton is a tridentate ligand which is connected to the metal via at least one metal–carbon σ bond. The most common type of pincer skeleton is an aryl anion, which is connected to the metal via only one metal–carbon σ bond; substituents *ortho*- to this σ bond are held in a fixed position and can co-ordinate to the metal site via O, S, N or P donor atoms (Fig. 1).

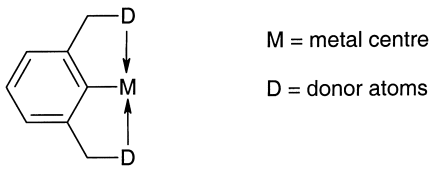


Figure 1.

Transition metal pincer complexes using phosphorus as the donor atoms (PCP pincer complexes) were reported in the early 1970s.[3] The term PCP refers to the three atoms directly attached to the metal, phosphorus, carbon and phosphorus. Other common pincer complexes contain the NCN, SCS and CNC skeletons. The CNC skeleton or ligand is slightly different to the other pincer ligands because, whilst being tridentate, it bonds to the metal by two metal–carbon σ bonds.

It is the presence of at least one metal–carbon σ bond in a pincer complex that is responsible for many of the desirable properties of these compounds. This linking of the metal to a ligand prevents, at least to a large extent, the metal disassociating from the ligand (leaching) and gives the complexes a high degree of thermal stability.

The donor atoms and their substituents can control the accessibility of the metal to potential substrates and the electron density around the metal. This allows potential fine tuning of the reactivity of the complex. It is also possible that stereochemical information can be introduced, for example, at the benzylic carbons in the generic pincer complex (Fig. 1) or by the donor atom substituents, creating potential stereoselective catalysts.

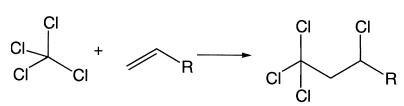
A realisation that pincer ligands offer a unique, highly-protective environment for the resident metal and opportunities to fine tune the metal properties has spawned extensive research into the use of these complexes as catalysts. The following sections review the use of pincer complexes in Kharasch additions, Heck reactions, Suzuki couplings, dehydrogenation reactions, hydrogen transfer reactions, aldol reactions, Michael reactions, cyclopropanation reactions, allylation of alcohols and allylic alkylation.

3. Uses

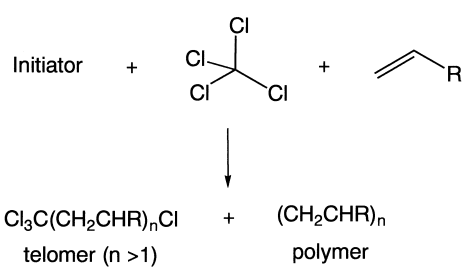
3.1. Kharasch additions

In 1945, Kharasch discovered that carbon tetrachloride underwent direct addition to olefinic double bonds (Scheme 1).[4] It is widely accepted that this addition occurs via a free radical process[5] and is a classic example of anti-Markovnikov addition.

Research has shown that a wide variety of polyhalogenated compounds will add across virtually any olefin. The Kharasch addition, however, is often overlooked in organic



Scheme 1.



Scheme 2.

synthesis, mainly because of competing telomerisation and polymerisation reactions (Scheme 2).

3.1.1. Nickel-catalysed Kharasch additions. To minimise competing reactions in the Kharasch addition, transition metal complexes have been used as initiators. Work by Matsumoto[6] and Davis[7] indicates that the radical generated (e.g. $^{\cdot}CCl_3$) is held within the coordination sphere of the transition metal initiator, facilitating the conversion of the alkene to the 1:1 CCl_4 adduct.

In the late 1980s van Koten et al.[8] began investigating the use of bidentate ligands based on the 1,3-[(dimethylamino)methyl]benzene moiety and found that lithiation at the 2-position allowed oxidative addition of almost any transition metal, creating the first NCN pincer complexes. The NCN pincer ligands were found to stabilise a variety of metal oxidation states and the discovery of the very low redox potential (Ni^{II}/Ni^{III}) for nickel NCN pincer complexes was thought to make them ideal catalysts for Kharasch additions.

The nickel NCN pincer complex **1** (Fig. 2) was found to be an excellent catalyst for the reaction of methyl methacrylate with CCl_4, producing the 1:1 adduct in 90% yield after 15 min at room temperature.[9]

Traditional transition metal-catalysed Kharasch additions usually require more forcing conditions.[10] The $NiCl_2(PR_3)_2$ catalyst usually requires temperatures of 140°C, whilst one of the most active compounds[11] for promoting Kharasch additions, $RuCl_2(PPh_3)_3$, is inactive at <40°C.

Substitution at the *p*-position (R) of the nickel NCN pincer complex (Fig. 2) has been shown to have a significant effect on its catalytic activity.[12] Electron-donating groups (R=NMe_2 or OMe) have been shown to increase catalytic activity, while electron withdrawing groups (R=Cl or MeC(O)) decrease the activity. It is believed that electron-donating groups stabilise the nickel(III) intermediate produced during radical initiation within the catalytic cycle of the Kharasch addition (Scheme 3).

3.1.2. Supported nickel catalysts. Recent advances in the field of nickel NCN pincer complexes include their binding to inert supports. The nickel catalyst **1** has been incorporated into a polysiloxane polymer.[13] The resulting macromolecule is easier to recover from reaction mixtures and has been shown to be equally as effective as the unbound catalyst. The same research group has also used this nickel pincer complex to create the first dendrimer catalysts.

Dendrimer molecules are tree-like species, which are built up from a small molecule by a series of stepwise repeated reactions. As such, the size, weight, shape and number of end groups can be readily controlled.

van Koten et al. have shown that the nickel NCN pincer complex can be attached to both non-polar carbosilane dendrimers[12] and very polar amino acid-based dendrimers.[14] These soluble compounds show catalyst activity for the reaction of methyl methacrylate with CCl_4, similar to that of the original nickel NCN pincer catalyst. There is no possibility of the metal leaching, as it is covalently bound to the macromolecule. Once the reaction is complete, these soluble dendrimer catalysts can be readily recovered by membrane filtration.[14]

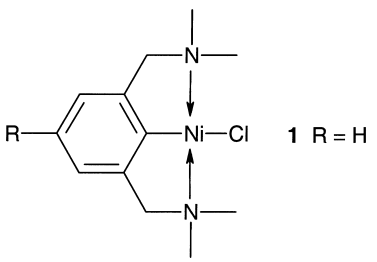
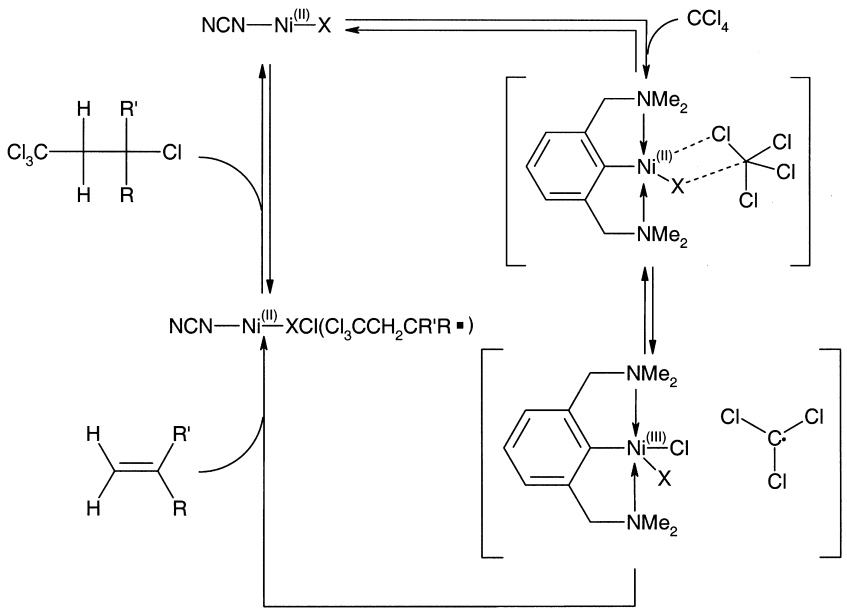
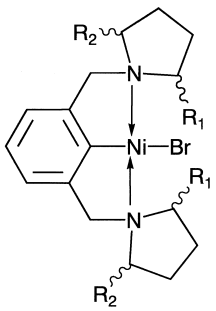


Figure 2.



Scheme 3.



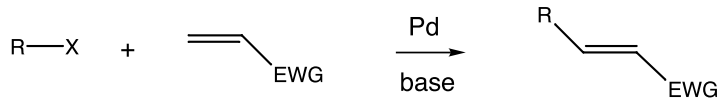
2 R1 = Me (racemic), R2 = H
3 R1 = Me (S), R2 = H
4 R1 = Me (R), R2 = Me (R)
5 R1 = C(O)OPr^{i} (S), R2 = H

Figure 3.

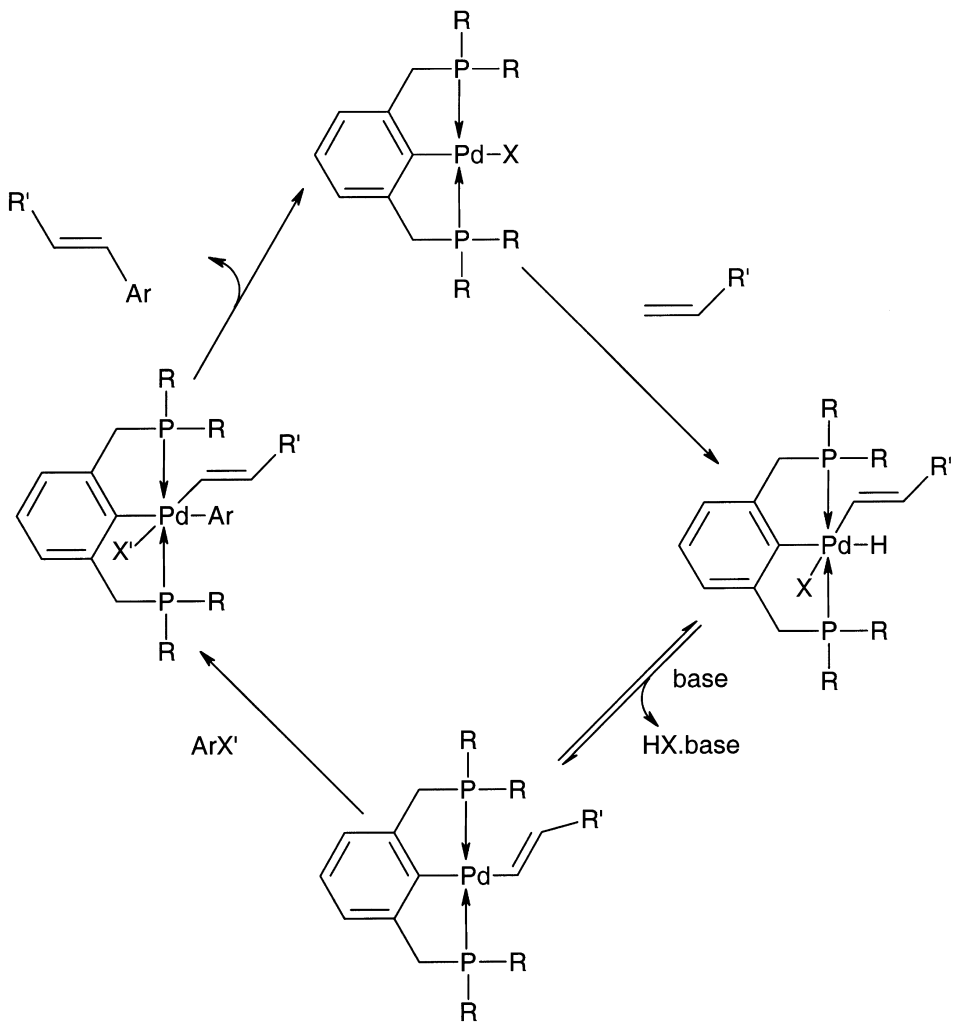
3.1.3. Enantioselective Kharasch additions. The need for more enantioselective syntheses has prompted L. van de Kuil et al.[15] to investigate the use of chiral nickel NCN pincer complexes to promote an enantioselective variant of the Kharasch addition. By replacing the two *N*-methyl substituents with substituted pyrrolidine ring systems, three chiral and one achiral pyrrolidine NCN pincer complexes **2**–**5** were created (Fig. 3).

Because the rate of Ni–N bond dissociation is very slow in these types of complex, it was hoped that chiral information could be transferred from the complex to the substrate. Unfortunately, when used as catalysts in the standard reaction of CCl_4 with methyl methacrylate, both compounds **4** and **5** were completely inactive. Compound **5** under the reaction conditions appeared to form a stable nickel(III) complex. It is surmised that compound **4** was inactive due to the steric bulk of the substituents on the pyrrolidines. Steric bulk also appears to account for the poor catalytic activity of **2** and **3** in comparison with the NCN nickel pincer complex **1**. Similar compounds with ethyl or isopropyl substituents at the donor nitrogens have also demonstrated poor catalytic activity in Kharasch additions.[10]

Compounds **2** (achiral) and **3** (chiral) were tested for chiral induction in the Kharasch addition of CCl_4 to prochiral



Scheme 4.



Scheme 5.

styrene. No optical rotations were however observed. A small diastereomeric excess was observed in the reaction of L-menthyl methacrylate with CCl_4 (16%), using catalyst **3**, but similar diastereomeric excesses were also observed using achiral catalysts **1** and **2**.

3.1.4. Summary. While substitution at the donor nitrogens of nickel pincer complexes has yet to produce a highly enantioselective catalysts for the Kharasch addition, work still continues in this area. The binding of pincer complexes to novel supports producing efficient, soluble catalysts for a wide variety of Kharasch additions, which can easily be separated at the end of the reaction, is currently proving particularly successful.

3.2. Heck reactions

The vinylation of aryl halides catalysed by palladium compounds, the Heck reaction (Scheme 4) has been widely exploited by synthetic chemists since it's introduction in the 1960s.[16]

A conventional Heck coupling is based on an aryl iodide or bromide (R–X) and a terminal alkene.[17] The most efficient carbon–carbon bond formations arise when the alkene possesses an electron-withdrawing group (EWG) such as CO_2R or CN. Most frequently, the Heck reaction is performed with palladium tetrakistriphenylphosphine, made from $Pd(OAc)_2$ and 4 equiv. of PPh_3. Unfortunately, like the majority of catalysts for the Heck reaction, palladium tetrakistriphenylphosphine is not air or particularly thermally stable. With a view to finding the most stable, robust and efficient catalysts, several groups have investigated palladium pincer complexes as potential catalysts.

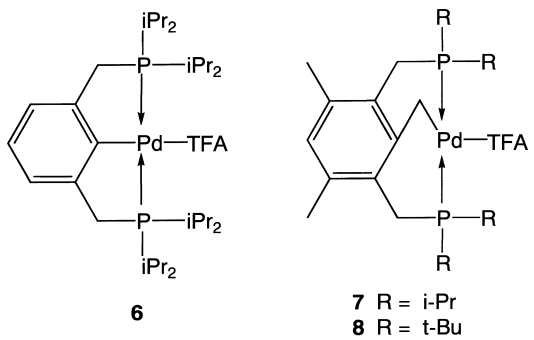


Figure 4.

3.2.1. Mechanism using palladium(II) pincer complexes.

The mechanism for Heck coupling reactions involving palladium pincer complexes is currently under debate, as the palladium in the pincer complexes is Pd(II) and it is unlikely to be reduced to Pd(0). This means that the conventional Pd(0)/Pd(II) mechanism[17] for Heck couplings is unlikely to apply. The current theory is that the reaction proceeds via a mechanism involving Pd(II)/Pd(IV) oxidation states (Scheme 5).

It seems unlikely that the sequence could be initiated by oxidative addition of the aryl halide to the metal, as this would produce a stable 18-electron complex, which would not be expected to undergo further reaction. The reaction is therefore initiated by the alkene co-ordinating to the complex, followed by the loss of HCl. Oxidative addition of the aryl halide would lead to formation by subsequent reductive elimination, regenerating the catalyst. The high probability that the Heck reactions catalysed by pincer complexes proceed via different mechanisms to the other palladium-catalysed Heck couplings gives rise to potentially different constraints and opportunities.

3.2.2. Phosphino-palladium PCP pincer complexes.

Milstein et al.[18] were the first to report on the use of palladium pincer complexes as catalysts for the Heck reaction. These phosphino-palladium PCP pincer complexes **6**, **7** and **8** (Fig. 4) are readily prepared by treating Pd(TFA)2 with the corresponding diphosphine in THF at 80°C. The high stability that the tridentate PCP pincer ligands infer means that these complexes show no degradation in solution at 140°C for up to 300 h. The compounds are also not sensitive to oxygen or moisture.

All three pincer complexes show very high catalytic activity. Table 1 shows selected results for several Heck reactions catalysed by these complexes.

Quantitative yields for the reaction of iodobenzene with methyl acrylate, using *N*-methylpyrrolidinone (NMP) as the solvent and sodium carbonate (1 equiv.) as base, have been achieved on stirring at 140°C with two of the three catalysts. In reactions where catalyst loadings of $<10^{-4}$ mol% were used, the number of moles of product formed/mole of catalyst, or turnover number (TON), can be as high as 500,000. These catalysts have also been tested on the less reactive aryl bromides. Catalyst **7** has been shown to catalyse the reaction of bromobenzene with methyl acrylate, giving a 93% yield and an observed TON of 132,900.

Table 1. Selected Heck reactions using phosphino PCP palladium pincer complexes **6**–**8**

Aryl halide	Alkene	Catalyst	Time/temperature (h/°C)	TON[a]	Yield (%)
PhI	CH_2=CHCOOMe	**6**	60/40	142,900	100
PhI	CH_2=CHCOOMe	**7**	40/140	528,700	95
PhI	CH_2=CHCOOMe	**8**	40/140	142,900	100
PhI	CH_2=CHCOOBu	**7**	14/160	142,900	100
PhI	CH_2=CHPh	**7**	60/140	133,000	93
p-MeOPhI	CH_2=CHCOOMe	**7**	16/140	142,900	100
PhBr	CH_2=CHCOOMe	**7**	63/140	132,900	93
p-OCHPhBr	CH_2=CHCOOMe	**7**	63/140	113,300	79

[a] TON (turnover number)=mol product/mol catalyst.

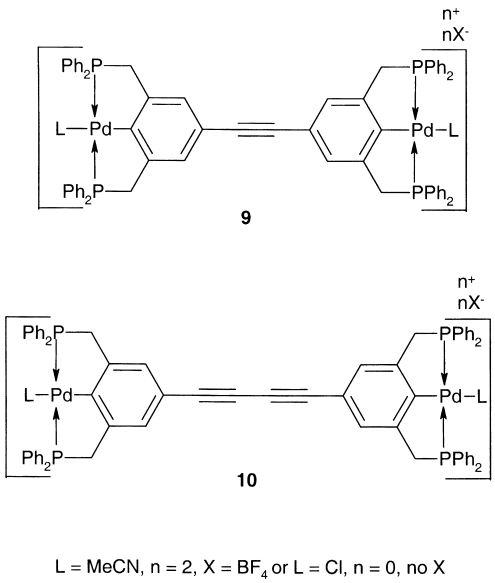


Figure 5.

Acetylene-bridged variations of these phosphino PCP palladium pincer complexes have been investigated by Beletskaya et al.[19] (Fig. 5).

These binuclear palladium complexes in which two pincer groups are connected by an ethynediyl-**9** or a butadiynediyl-bridge **10**, have possible applications as building blocks for conjugated organometallic oligomer and polymer type catalysts. Polymer catalysts are considerably easier to isolate and recycle than convention homogenous monomers. Both types of acetylene-bridged catalyst **9** and **10** have shown good preliminary catalytic activity in the Heck reaction of iodobenzene with styrene or methyl acrylate, but have yet to be tested on a wider range of Heck reactions.

3.2.3. Phosphinito-palladium PCP pincer complexes. While the phosphino PCP pincer complexes **6**–**10** have shown good catalytic activity in Heck reactions involving aryl iodides and some activity in reactions with aryl bromides, they are completely inactive in reactions of the more practical aryl chlorides with alkenes. Complex **11**, however, developed by Jensen et al.[20] (Fig. 6) has been found to be a highly active catalyst in Heck reactions involving aryl chlorides.

Work by Beller and Zapf[21] has demonstrated that the activity of palladium catalysts in the Heck reaction can be enhanced by substitution of phosphine ligands with phosphorus ligands bearing EWGs. Jensen et al.[22] extended

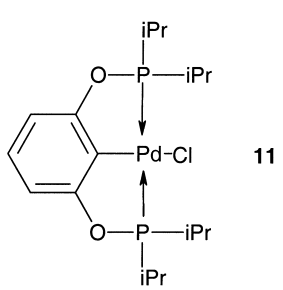


Figure 6.

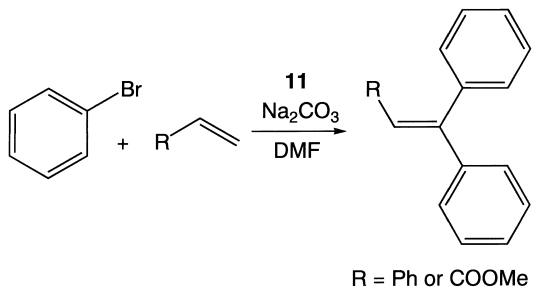
Table 2. Selected Heck reactions of aryl chlorides with styrene in the presence of a phosphinito-palladium PCP pincer complex

Aryl chloride	Base	Yield (%)
PhCl	CsOAc	>99
4-MeC(O)PhCl	CsOAc	>99
4-MeOPhCl	CsOAc	86
4-HC(O)PhCl	CsOAc	81
2-MePhCl	CsOAc	83

this work and used 1,3-bis(phosphinito)benzene to produce phosphinito-palladium pincer complexes. Their catalytic activity in the reaction of styrene with various aryl chlorides was then examined (Table 2).

Heck reactions with aryl chlorides generally require a higher catalyst loading than the corresponding aryl bromide reactions. The Jensen group used 0.67 mol% of their phosphinito catalyst **11** in dioxane at 120°C and 1.1 equiv. of base. The system almost exclusively produces the corresponding *trans* stilbene and is one of the few to show reactivity with electron-rich and sterically-hindered aryl chlorides.

The phosphinito complex **11** displays a similar catalytic activity in the Heck reaction of aryl iodides and alkenes as the phosphine catalysts **6**, **7** and **8**, in regard to both yield and TONs. The Heck reactions of bromobenzene, and styrene or methyl acrylate, however, catalysed by complex **11**, surprisingly produced the trisubstituted olefins[22] (Scheme 6). These trisubstituted olefins are not produced when Milstein's phosphino PCP palladium complexes were used.



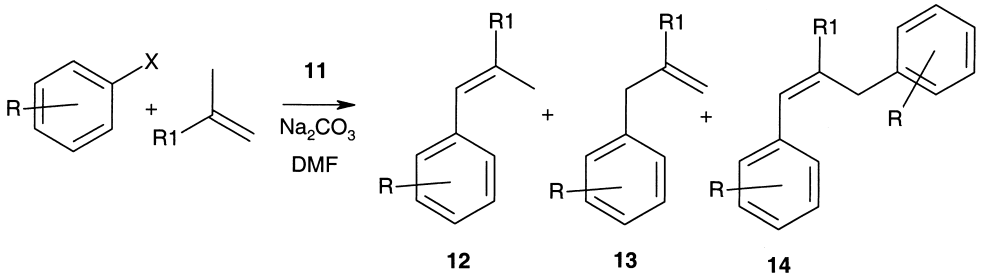
Scheme 6.

The synthetic importance of trisubstituted olefins led Jensen et al. to investigate the activity of the pincer complex **11** in Heck couplings of iodo- and bromobenzene with the disubstituted alkenes, butyl methyl acrylate and α-methyl-styrene (Table 3).

The phosphinito-palladium PCP pincer complex **11** catalyses the reaction of all the substrates studied, producing high yields of the intended products. The ratio of products favours the trisubstituted alkene **12** by >80% and, by using sodium bicarbonate as the base, the ratio of *E*/*Z* isomers in the desired compound is ≥9:1.

Similar yields and TONs for Heck reactions forming trisubstituted alkenes have been achieved using the palladacycle complex **15** (Fig. 7), although the best ratio of *E*/*Z* isomers of the desired product is only 4:1.

Table 3. Heck couplings of disubstituted alkenes with halobenzenes in DMF



R1 = Ph or COOBu

R, X, R1	Base	Yield (%)	**12** (%)	**13** (%)	**14** (%)	*E*/*Z*	TON
H, I, COOBu	KOAc	>99	98	2	0	1.5/1	1208
H, I, COOBu	Na_2CO_3	>99	90	2	8	19/1	1196
H, I, COOBu	DIPEA	>99	98	2	0	12/1	1202
H, Br, COOBu	Na_2CO_3	>99	80.5	2.5	17.0	13/1	1200
Cl, Br, COOBu	Na_2CO_3	>99	92	8	0	9/1	1204
H, Br, Ph	Na_2CO_3	95	92	4	4	14/1	950
Cl, Br, Ph	KOAc	94	95	5	0	20/1	940

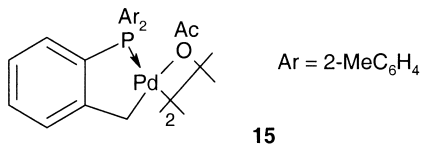


Figure 7.

Shibasaki et al.[23] have continued the search for even more active Heck catalysts and have reported a modified PCP palladium pincer complex **16** (Fig. 8). Again, the use of EWGs on the phosphorus donor atoms in the form of a phosphinito-ligand produces good results.

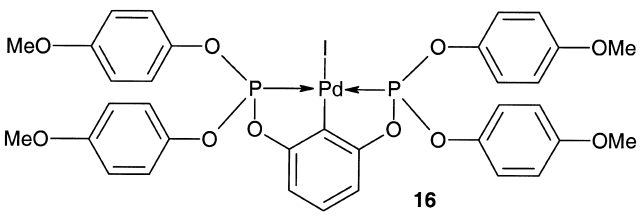


Figure 8.

While no results on the formation of trisubstituted alkenes have been reported using the catalyst **16**, it has been compared with Jenson's catalysts in the reaction of iodobenzene with butyl acrylate in NMP using sodium bicarbonate (1 equiv.) as the base (Table 4).

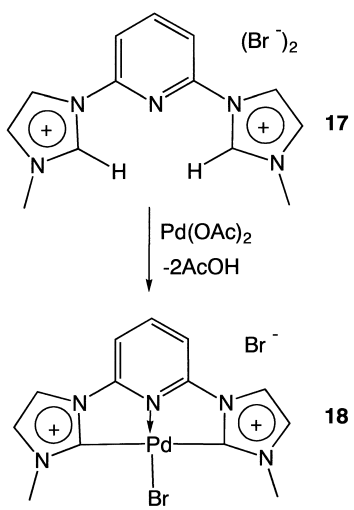
Shibasaki's catalyst **16** is capable of producing higher TONs than any of Jensen's catalyst, but the yields obtained using this catalyst were not as impressive until the temperature of the reaction was increased to 180°C. The use of hydroquinone (1 mol%) as an additive at low catalyst concentrations has produced the highest TON of all Heck reactions to date, with iodobenzene as the substrate. The reaction of *p*-iodoanisole with butyl acrylate using catalyst **16** and hydroquinone as an additive produced a yield of 98%, and TON of 980,000.

Table 4. Heck reactions of iodobenzene and butyl acrylate

Catalyst (ppm)	Additive	Time/temperature (h/°C)	Yield (%)	TON
6 (7.0)	None	40/140	4	5650
7 (7.0)	None	64/140	100	142,900
16 (1.0)	None	40/140	65	650,000
16 (1.0)	None	40/140	68	680,000
16 (1.0)	None	18/180	95	950,000
16 (0.1)	Hydroquinone	22/180	95	8,900,000

Hydroquinone has also been used to improve the yield of the coupling of alkenes to aryl halides possessing EWGs. Traditionally, high TONs for Heck reactions with these deactivated aryl halides have been difficult to achieve. The true role of hydroquinone in these reactions, however, has not been fully determined.

3.2.4. Phosphine-free palladium pincer complexes. Phosphine-free palladium pincer complexes have been investigated as potential Heck catalysts. Crabtree et al.[24] recently



Scheme 7.

reported that the carbene precursor **17** could be added to palladium acetate to form the tridentate CNC palladium pincer complex **18** (Scheme 7).

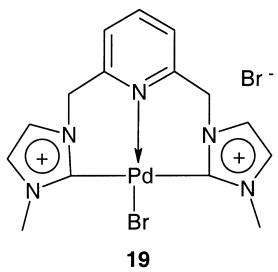
As before, the pincer skeleton protects the metal centre efficiently, giving these complexes excellent air and thermal stability. The complex **18** can be heated to 165°C in dimethylacetamide (DMA) for 24 h without any signs of decomposition. The compound shows good catalytic activity in the reaction of aryl halides with styrene carried out in DMA and excellent rates of reaction (Table 5).

Table 5. Heck reactions using the CNC palladium pincer complex **18**

Aryl halide	Atm	Catalyst (mol%)	Reaction time (h)	Stilbene yield (%)	TON
PhBr	Argon	5	1	>99	20
PhBr	Air	5	1	>99	20
PhI	Air	5	1	>99	20
PhI	Air	1	1	89	89
PhI	Air	0.0001	20	33	3300
p-(CHO)PhCl	Argon	5	20	75	15

The pincer complex **18** is reported to be so stable towards air that several of these Heck reactions could be carried out in the absence of an inert atmosphere without any detrimental effect on yield. The catalyst has been shown to be effective in the reactions of iodo- and bromobenzene as well as in that of an aryl chloride with styrene.

Recently, Crabtree et al.[25] have inserted a CH_2 spacer unit between the rings of the pincer complex **18** to create a more soluble catalyst **19** (Fig. 9).



19

Figure 9.

Crabtree's modified catalyst **19** is able to olefinate aryl bromides and activated aryl chlorides more efficiently (Table 6), resulting in higher TONs.

The overall performance of the catalysts **18** and **19** is significantly better than the results published by Danopoulos

Table 6. Olefination of aryl halides using catalyst **19**

Aryl halide	Catalyst (mol%)	Reaction time (h)	Stilbene yield (%)	TON
p-(CHO)PhCl	0.2	0.5	90	450
p-($CH_3C(O)$)PhCl	0.2	0.25	97	485
p (CH_3O)PhBr	0.2	1	97	485
p-$CH_3C(O)$PhBr	0.2	0.25	98	485

Reaction conditions: 1.4 mol equiv. styrene, 1.1 equiv. sodium acetate, refluxing DMA.

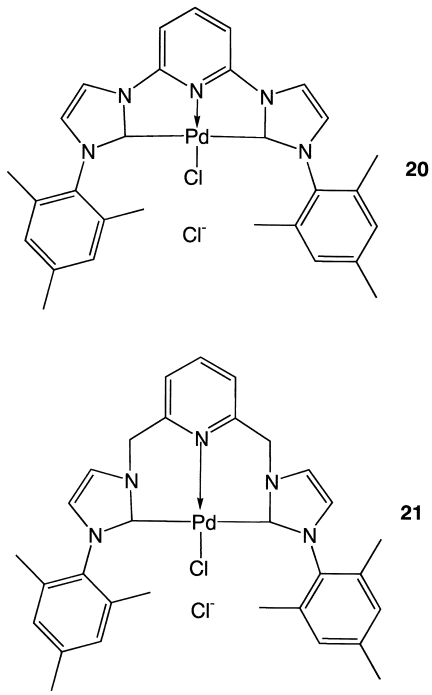


Figure 10.

et al.[26] whose related catalysts **20** and **21** contain aryl substituents at the imidazole units (Fig. 10).

Higher catalyst loadings for all CNC pincer complexes have been required (low TONs) in comparison with many of the phosphine-based pincer complexes, and the results are therefore more of an indication that there are alternatives to phosphine ligands, rather than an advance of the Heck chemistry itself.

Another alternative to the phosphine pincer complexes are the tridentate SCS palladium pincer complexes developed by Bergbreiter et al.[27] (Fig. 11).

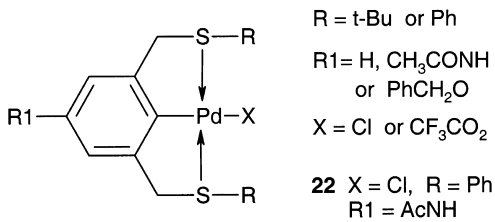
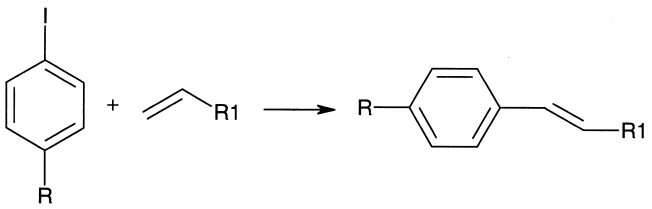


Figure 11.

The most stable of these catalysts is **22**. Catalytic reactions of **22** using various aryl iodides and alkenes have been conducted in DMF or NMP at 105–110°C using 1 equiv. of triethylamine or sodium carbonate as the base, without the need for an inert atmosphere (Table 7).

The catalyst **22** does not appear to be as active as the phosphine-based pincer complexes (lower TONs of around 1000 versus 100,000s), but the yields obtained are still very good, all >90%. Catalysts of this type offer a useful alternative, particularly as the 5-amido-SCS–Pd complex can be bonded to a poly(ethylene glycol) (PEG) support (Fig. 12).

Table 7. Heck reactions using 0.1 mol% SCS–Pd catalyst **22**



R	R1	Yield (%)
H	CO_2Me	92
H	CO_2t-Bu	93
H	C_5H_4N	94
H	Ph	92
NHAc	CO_2Me	95
OMe	CO_2Me	94
COOH	CO_2Me	95

The-PEG supported SCS–Pd complex **23** is a highly stable catalyst that, after each reaction, can be isolated by precipitation with diethyl ether and reused with little or no loss in performance for at least three cycles (Fig. 13).

3.2.5. Summary. Palladium pincer complexes have already become useful catalysts in Heck reactions. The original phosphino donor ligands have been modified by the addition of EWGs and the resulting phospinito pincer complexes have shown some of the highest TONs reported for the Heck reaction. These complexes are also able to catalyse the traditionally difficult Heck couplings of aryl chlorides or electron-rich aryl compounds. This is probably a result of the alternative Pd(II)/Pd(IV) mechanism operating as opposed to the traditional Pd(0)/Pd(II) mechanism.

Non-phosphine-based pincer complexes have also shown activity in Heck couplings of aryl iodides with alkenes. While not as active as the phosphine-based compounds, CNC or SCS palladium pincer complexes do offer potential alternatives and have been combined with inert supports to give efficient, easily isolated, reusable catalysts.

3.3. Suzuki couplings

The palladium-catalysed coupling of an aryl halide with an organoboron compound, the Suzuki reaction[28] (Scheme 8), is regarded as one of the most efficient ways of forming a carbon–carbon bond. Unfortunately, fairly high catalyst concentrations and the difficulties and costs associated with the removal of palladium from the product have limited its commercial use.

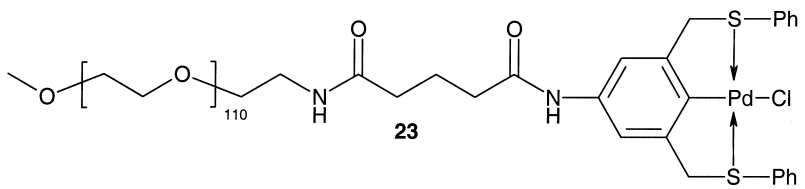


Figure 12.

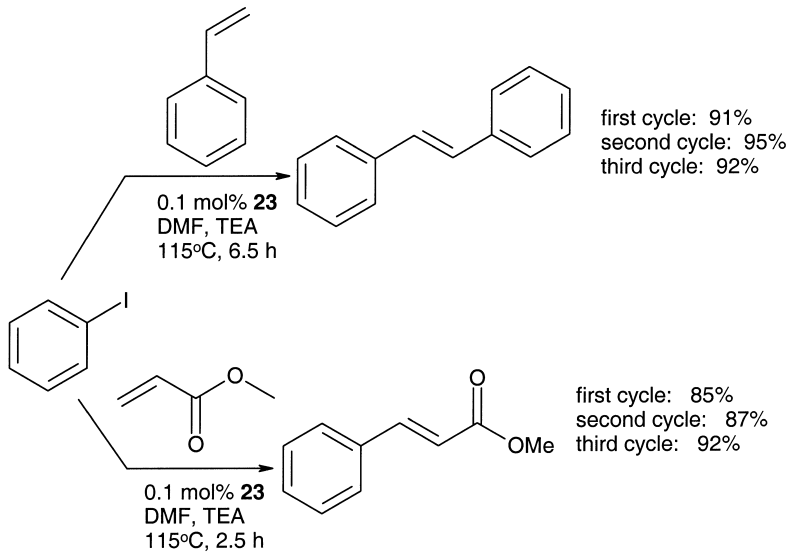
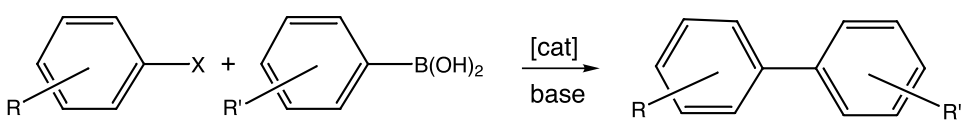
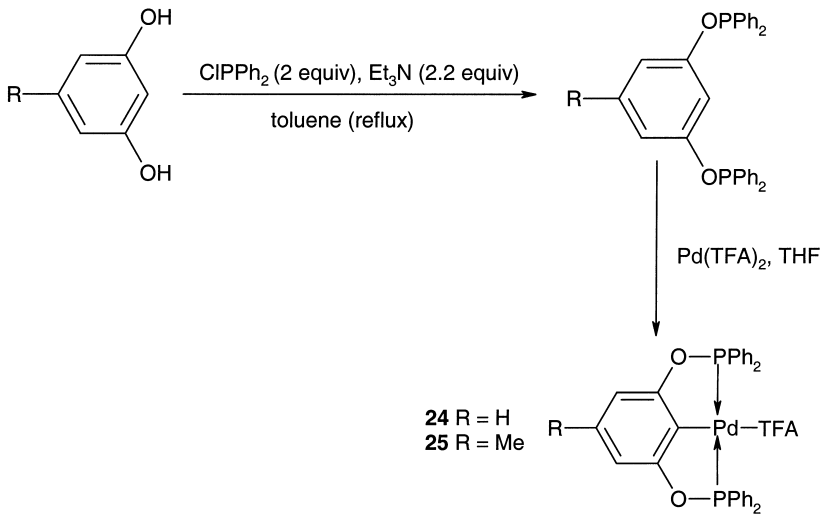


Figure 13.



Scheme 8.



Scheme 9.

3.3.1. Palladium PCP pincer complexes. Many palladium catalysts have been used to promote the Suzuki coupling and, whilst they are very efficient, many suffer from poor thermal stability, as well as poor stability towards air and moisture. Following the successful application of pincer complexes as catalysts in the Heck reactions, several groups have investigated their use in Suzuki couplings. These pincer complexes are not only more stable than the traditional catalysts but, also, by virtue of the palladium–carbon σ bond, they are far less likely to contaminate the product with stubborn palladium residues.

Two palladium pincer complexes **24** and **25** have been synthesized and evaluated by Bedford et al.[29] in the Suzuki coupling of various aryl halides and phenylboronic acid. These catalysts can be easily synthesized from the corresponding diol in good yields (Scheme 9) and show no degradation in solutions open to air and in the presence of moisture for up to 10 days.

The PCP–palladium complexes **24** and **25** show good catalytic activity in the Suzuki coupling of phenylboronic acid with standard substrates such as 4-bromoacetophenone. The complexes also have good catalytic activity in the reactions of phenylboronic acid with deactivated or sterically-hindered aryl bromides (Table 8).

While other catalysts for Suzuki reactions appear to be more active than the palladium pincer complexes **24** and **25**, e.g.

Table 8. Suzuki coupling of aryl halides with phenylboronic acid

Aryl halide (1 equiv.)	Catalyst (mol%)	Yield by GC (%)	TON
4-Bromoacetophenone	**24** (0.001)	59	59,000
4-Bromoacetophenone	**25** (0.001)	92	92,000
4-Bromoanisole	**24** (0.01)	61	6100
4-Bromoanisole	**25** (0.01)	72	7200
2-Bromotoluene	**24** (0.01)	87	8700
2-Bromo-*p*-xylene	**24** (0.01)	67	6700
2-Bromo-*p*-xylene	**25** (0.01)	63	6300
4-Chloronitrobenzene	**24** (0.01)	43	4300
4-Chloronitrobenzene	**24** (0.1)	67	670

Reaction conditions: 1.5 equiv. phenylboronic acid, 130°C, toluene, 18 h.

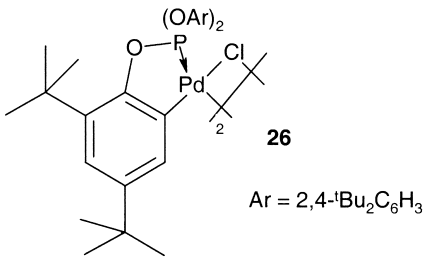


Figure 14.

the palladacycle **26** (Fig. 14), these are often much more difficult and expensive to synthesise and are far less stable.

3.3.2. Palladium SCS pincer complexes. As with the Heck reaction, the use of phosphine-free palladium complexes has also been investigated. The SCS palladium pincer complex **27** (Fig. 15) has been found to catalyse the Suzuki coupling of *p*-bromotoluene and benzeneboronic acid. The catalyst loadings (typically, 1 mol%) are again higher than the phosphine-based pincer complexes, but a respectable 69% yield of phenyltoluene has been achieved.[30]

3.3.3. Summary. While the investigation into the use of PCP and SCS pincer complexes in Suzuki reactions is still in its infancy, their exceptional stability and ease of synthesis offer potential advantages over the traditional catalysts for Suzuki couplings. The strength with which the ligand is bound (covalently) to the metal also means that the amount of palladium able to dissociate from the complex and contaminate the intended product should be minimal.

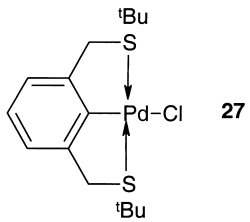


Figure 15.

3.4. Dehydrogenation reactions

The selective functionalisation of aliphatic compounds is a highly-desirable goal within organic chemistry. Many research groups are currently examining the production of important organic building blocks such as terminal alkenes through the dehydrogenation of readily-available alkanes.

Two decades ago, Crabtree et al.[31] reported the use of soluble transition metal complexes in the stoichiometric conversion of alkanes to alkenes. In the following years, many groups have joined this area using transition metal complexes such as rhodium or iridium as catalysts. The most recent and successful of these systems use dihydro-bisphosphosphine iridium complexes[32] $[H_2Ir(PR_3)_2]$ and a sacrificial alkene such as *tert*-butylethylene (tbe). Unfortunately, these systems have generally suffered from very slow reaction rates and rapid catalyst decomposition.

3.4.1. Iridium and ruthenium PCP pincer complexes. Mono-hydrido iridium and ruthenium complexes containing phosphine-based pincer ligands $MClH[2,6\text{-}(CH_2P^tBu_2)_2\text{-}C_6H_3]$ had been reported as early as the mid 1970s by Moulton and Shaw.[33] These complexes have high thermal stabilities, subliming at a temperature >180°C without any decomposition. The possibility that the complexes could be adapted to create dehydrogenation catalysts led to work by the groups of Jensen et al.,[34] Goldman et al.[35] and Leitner et al.[36] All three groups began separate investigations into the synthesis and use of dihydro-PCP pincer complexes (Fig. 16) as potential catalysts for aliphatic dehydrogenations.

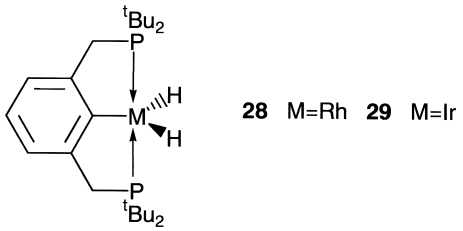


Figure 16.

The standard reaction for the study of new dehydrogenation catalysts is the dehydrogenation of cyclooctane in the presence of tbe. GC is used to monitor the production of cyclooctene.

At 150°C, the dehydrogenation of cyclooctane by the rhodium complex **28** proceeds at a rate of 0.8 turnovers h^{-1}. The catalyst showed no signs of decomposition after 1 week under these conditions, which is in contrast to the typical half-life of about 12 h for conventional dehydrogenation catalysts. At 200°C, the turnover h^{-1} was increased to 1.8, although decomposition of the catalyst was observed after 24 h.[37]

A strikingly higher activity was observed using the iridium complex **29**. At 150°C, dehydrogenation of cyclooctane preceded at 82 turnovers h^{-1}, while a rate of 720 turnovers h^{-1} was observed at 200°C. The iridium complex also shows no decomposition for >1 week at both temperatures. Comparable activities have only been achieved using the pre-catalyst $[RhCl(PMe_3)_2(CO)]$ under 68 atm H_2. The high hydrogen pressure is required to form the active dihydro ruthenium complex and 6–8 equiv. of the hydrogen acceptor, norborene, are also required.

3.4.2. Catalyst inhibition. The catalytic activity of the pincer complex **29** is suppressed by nitrogen. Maximum catalytic rates can only be achieved if the reaction is freeze–pump–thaw degassed and argon used as the inert atmosphere. This unusual nitrogen inhibition is due to the formation of the surprisingly stable dinitrogen complex **30** (Fig. 17). This dinitrogen complex can be isolated in quantitative yield if a solution of the complex **29** is exposed to a nitrogen atmosphere.[37]

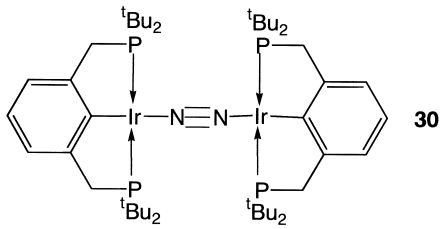


Figure 17.

The dehydrogenation activity of **29** is also inhibited by high concentrations of alkene. Incremental additions of the hydrogen acceptor tbe maximise the turnover, but only 10% of the cyclooctane used can be effectively dehydrogenated before the catalyst can no longer function. Overcoming the problem of product inhibition is currently the biggest obstacle in the development of dehydrogenation reactions.

3.4.3. Production of terminal alkenes. The kinetic preference of iridium and rhodium complexes for the activation of the terminal C–H bonds is well known. Studies by Felkin et al.[38] found that $IrH_5(P^iPr_3)_2$ catalyses the dehydrogenation of *n*-hexane to hex-1-ene with >90% selectivity. Unfortunately, only 0.3 catalytic turnovers were achieved due to the low activity and low stability of the catalyst.

An investigation by Jensen et al.[39] initially indicated that the pincer complex **29** was highly selective for the dehydrogenation of *n*-octane to internal octenes over oct-1-ene. A more detailed kinetic study, however, later revealed that the complex **29** is kinetically selective towards the production of oct-1-ene. Unfortunately, the catalyst also catalyses alkene isomerisation, at a slower rate. This results in a maximum yield of only 20% of the terminal alkene. Further modifications to the system to reduce the rate of alkene isomerisation could increase the amount of the terminal alkene present.

Goldman et al.[40] have shown that the steric bulk of the hydrogen acceptor can have an effect on the rate of secondary alkene isomerisation. The use of dec-1-ene instead of tbe with catalyst **29**, for example, can effectively dehydrogenate *n*-octane with a selectivity of up to 68% for oct-1-ene after 143 total turnovers, after which the yield of oct-1-ene decreases due to secondary isomerisation. Further

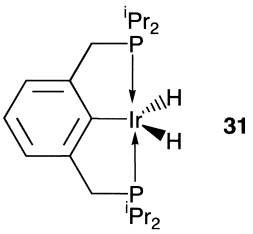


Figure 18.

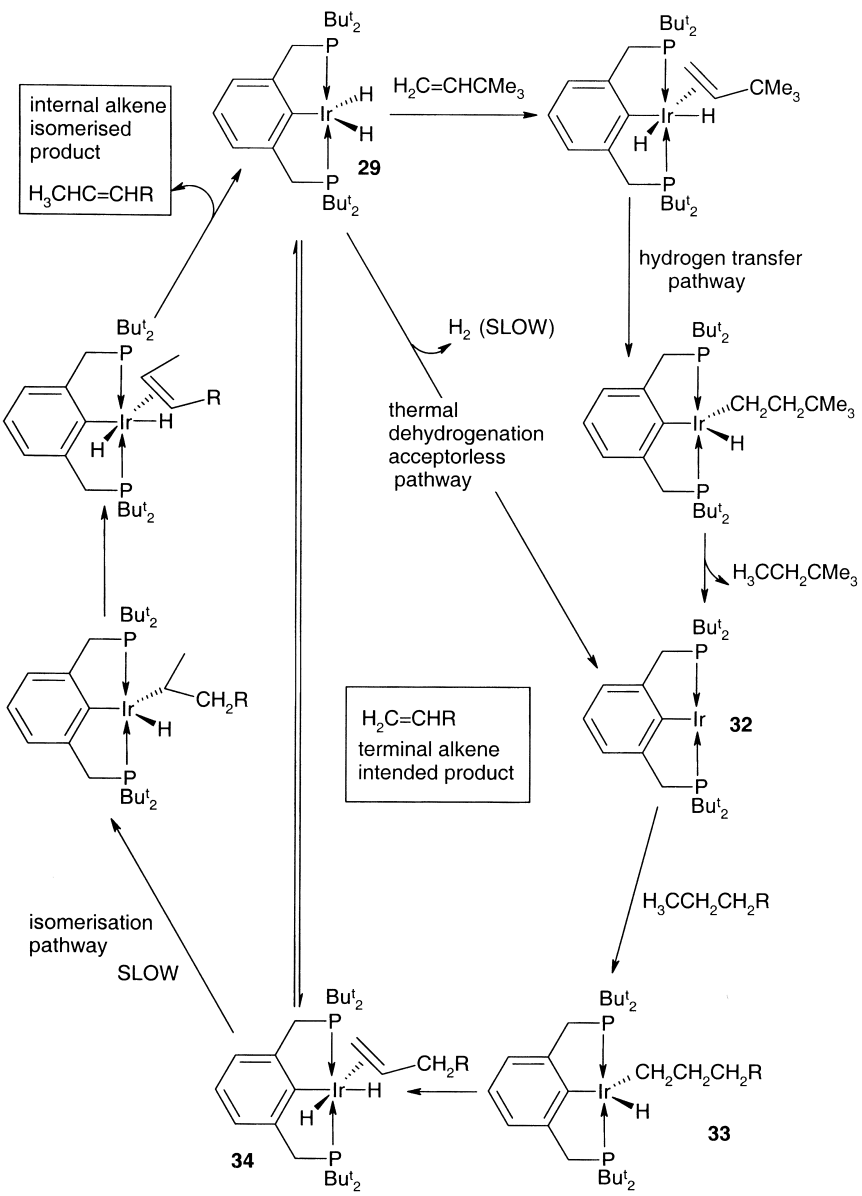
modifications to both catalyst and hydrogen acceptor may therefore soon lead to highly selective terminal alkene formation.

3.4.4. Acceptorless dehydrogenation of alkanes. The economic and environmental advantages in systems not requiring a hydrogen acceptor are clear and many groups have investigated systems for acceptorless dehydrogenation in which the only by-product is hydrogen. Iridium PCP pincer complexes are currently the most efficient catalysts for acceptorless dehydrogenations.[41]

The high activity and long-term stability of these complexes at very high temperatures mean that the TONs that are achieved, in continuously purged, open systems, are at least an order of magnitude better than the TONs for acceptorless dehydrogenation catalysts such as $IrH_2(O_2CR)(PCy_3)_2$. Goldman et al.,[40] for example, have observed TONs of around 1000 for the acceptorless dehydrogenation of cyclodecane using the complex **31** (Fig. 18).

Other acceptorless dehydrogenation catalysts such as $IrH_2(O_2CR)(PCy_3)_2$ are currently only capable of TONs in the 20 s for the dehydrogenation of cyclodecane.

3.4.5. Mechanistic studies of dehydrogenation reactions. The overall mechanism of the dehydrogenation of alkanes by the iridium pincer complex **29** has not yet been thoroughly investigated; Scheme 10 is the current proposed



Scheme 10.

mechanism[42] incorporating both the hydrogen acceptor and acceptorless pathways to dehydrogenation.

The initial process is the dehydrogenation of the dihydride **29** to the key intermediate Ir{2,6-$C_6H_3(CH_2PBu^t_2)_2$} **32**, via either thermal dehydrogenation or hydrogen acceptance. The alkane substrate then undergoes oxidative addition through a C–H bond, forming **33**, and β-hydride elimination from the resulting alkyl group follows, producing **34**, before dissociation of the product regenerates the catalyst and produces the alkene. The mechanism is complicated by the secondary catalytic isomerisation pathway. The kinetic preference is for the formation of terminal alkenes due to the steric constraints around the pincer ligand. Thermodynamically, however, Goldman et al.[39] have indicated the preference for dehydrogenation or isomerisation may be viewed simply as a competition between the terminal alkene product and the hydrogen acceptor for co-ordination to the catalyst. This would explain the preference for a terminal alkene product when the bulky hydrogen acceptor, tbe, is replaced by dec-1-ene, and the formation of internal alkenes as the concentration of terminal alkene product rises. In the case of acceptorless reactions, the high temperatures required for catalyst dehydrogenation result in the domination of the isomerisation pathway, leading to isolation of only the internal alkene products.

3.4.6. Dehydrogenation of cycloalkanes to arenes. Platinum on alumina catalysts have traditionally been employed in the dehydrogenation of cycloalkenes to arenes, the process often requiring temperatures of 450–550°C.[43] Crabtree et al. were the first group to discover an oxidative-addition type system in which an iridium dihydride complex $IrH_2\{OC(O)CF_3\}(PPr^i_3)_2$ could dehydrogenate an alkane to an arene at 150°C in the presence of a hydrogen acceptor (tbe). The system, however, was not catalytic as cleavage of phosphorous–carbon bonds in the complex could occur at this temperature.[44] Jensen et al. found that the high thermal stability of the pincer dihydroiridium complexes **29** made such a catalyst ideally suited for the conversion of a variety of cycloalkanes to arenes.[45]

The catalyst **29** could catalyse the transfer dehydrogenation of six-membered rings, such as cyclohexane or methylcyclohexane, and decalin at temperatures as low as 150°C. The reactions were, however, found to be sensitive to the steric constraints around the iridium centre. The production of naphthalene from decalane required up to 72 h at 200°C. Ethylbenzene and THF could also be dehydrogenated to styrene and furan, respectively, after 1 h at 200°C using 0.005 mol% of catalyst. Such dehydrogenations had not been previously achieved via homogeneous catalysts[46] and, while the catalyst suffers from both nitrogen and product inhibition, modified catalysts of this type could soon provide efficient chemical processes to products such as styrene.

3.4.7. Aliphatic dehydrogenation in the presence of functional groups. The previous discussion indicates that the catalyst **29** still operates in the presence of benzene rings and ethers. Jensen et al. have tried to expand the utility of **29** to other functionalised molecules. Preliminary data[47] indicate that secondary amines can undergo dehydrogenation across the C–N bond and not the C–C bond. Unusually, the system produces imines, which contrasts with standard dehydrogenations, which generally produce nitriles. The same catalytic system can also produce aldehydes and ketones from alcohols[48] this process appearing to occur via activation of the O–H bond rather than by dehydrogenation.[49]

3.4.8. Summary. Dihydroiridium PCP pincer complexes are highly active, robust catalysts for aliphatic dehydrogenation reactions. The unique nature of the pincer ligand allows the metal centre to react with C–H bonds of the substrate, while remaining unreactive towards the C–C and P–C bonds of the ligand. The high thermal stability of these complexes makes them highly-efficient catalysts for acceptorless dehydrogenations and their high activity provides the opportunity to selectively produce α-olefins from linear alkanes. The tolerability of other functional groups present during dehydrogenation is still under investigation.

Unfortunately the complexes described are currently of limited practical value due to problems of product inhibition and/or the requirement of a sacrificial hydrogen acceptor. Modified PCP pincer complexes may provide a possibility for the commercial production of organic feedstocks through catalytic aliphatic dehydrogenation, if these problems can be overcome.

3.5. Transfer hydrogenation reactions

3.5.1. Hydrogenation of ketones to alcohols. Considering the large amount of work on the dehydrogenation of alkanes with pincer complexes and sacrificial hydrogen acceptors such as tbe, which is essentially the transfer hydrogenation of *tert*-butylethene, it is quite surprising that pincer complexes have only just begun to be investigated as potential transfer hydrogenation catalysts, for the reduction of ketones.

van Koten et al.[49] have investigated the use of three ruthenium pincer complexes (Fig. 19) as catalysts in the transfer hydrogenation of several ketones.

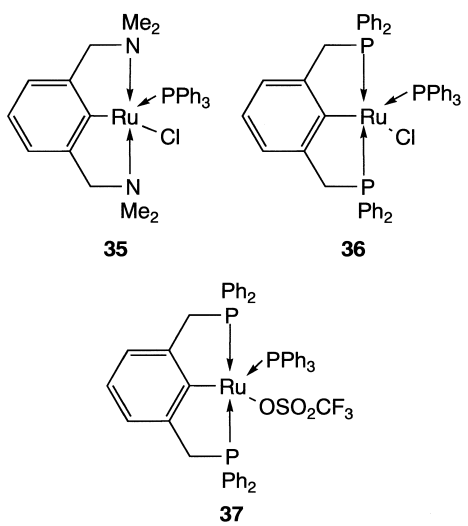
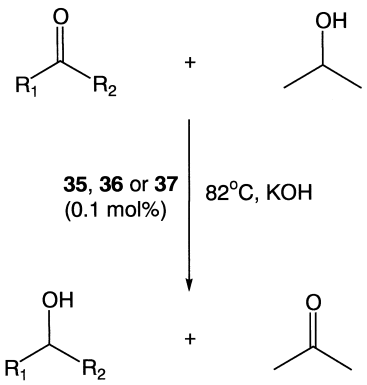
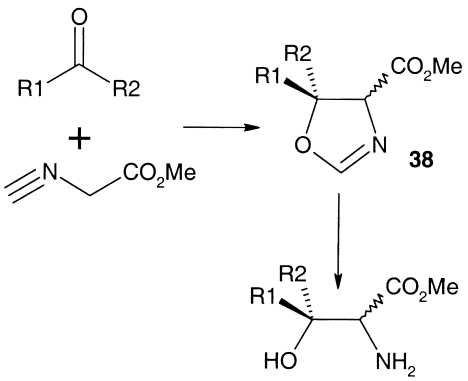


Figure 19.



Scheme 11.

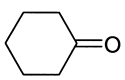
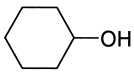
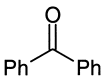
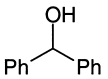
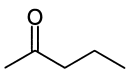
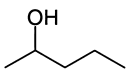


Scheme 12.

Dialkyl, alkyl aryl and diaryl ketones were all successfully reduced in the presence of the pincer catalysts with isopropyl alcohol and KOH as the stoichiometric reductant (Scheme 11).

Table 9 shows that all three catalysts result in highly efficient hydrogenations of ketones, with excellent conversions and high turnover frequencies (TOF=mol of alcohol produced/mol of catalyst/h at 50% conversion).

Table 9. Reductions of ketones catalysed by ruthenium pincer complexes **35**–**37**

Substrate	Product	Complex (mol%)	Conversion (%)	TOF (h^{-1})
		**35** (0.1) **36** (0.01) **37** (0.01)	>98 >98 >98	1100 10,000 27,000
		**35** (0.1) **37** (0.1)	70 90	36 9000
		**35** (0.1) **37** (0.1)	90 >98	83 100
		**35** (0.1) **37** (0.1)	90 90	1000 2000

3.5.2. Summary. In summary, the ruthenium(II) complexes **35**, **36** and **37** form active catalysts in the reduction of ketones by hydrogen transfer from ^{i}PrOH. Currently, van Koten et al. are studying the use of chiral ruthenium pincer complexes in stereoselective reductions.

3.6. Aldol reactions

The synthesis of optically active oxazolines **38** via a gold-catalysed aldol reaction of an aldehyde or ketone with an isocyanoacetate is well known.[50] The resulting oxazolinones can be hydrolysed by treatment with acid, and the ester hydrolysed providing an excellent route to many β-hydroxyamino acids (Scheme 12).

Several platinum and palladium pincer complexes have been found to catalyse the aldol reactions of carbonyl compounds with isocyanates by providing a vacant co-ordination site for the isocyanoacetate. Before the aldol condensation can occur, the preco-ordinated isocyanate must be enolised by the addition of a base (Fig. 20) and this enolate can then react with the carbonyl compound.

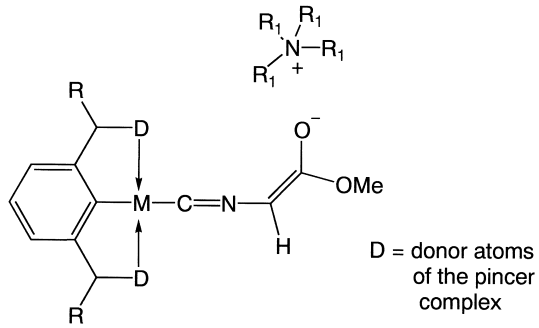


Figure 20.

3.6.1. Asymmetric aldol reactions catalysed by PCP pincer complexes. Venanzi et al.[51] were the first to report the use of a chiral PCP platinum pincer complex (Fig. 21) in the aldol condensations of various aldehydes with methyl isocyanate.

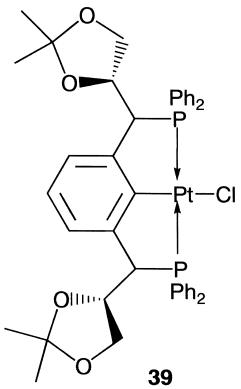
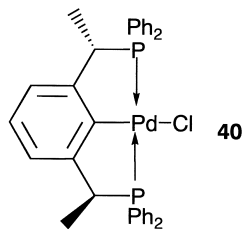


Figure 21.

The synthetic route to this platinum pincer complex **39** is long and difficult, which detracts from this system's utility. A simpler palladium pincer complex **40** was developed by Longmire et al.[52] (Fig. 22) for the same aldol condensations.

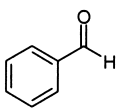
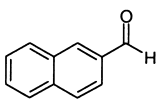
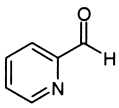
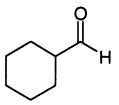
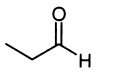
Reasonable enantioselectivities for the formation of oxazolines **38** have been achieved using both catalysts (Table 10),



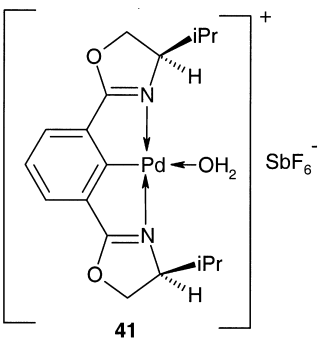
40

Figure 22.

Table 10. Aldol addition of methyl isocyanoacetate to aldehydes

Aldehyde	Catalyst	Yield (%)	% ee (*trans*)	% ee (*cis*)	*trans*/*cis* ratio
	**39**	85[a]	24	67	78/22
	40	96[b]	65	3	70/30
	**39**	81[a]	23	66	81/19
	40	95[b]	52	6	69/31
	**39**	82[a]	0	53	74/26
	40	90[b]	13	29	66/34
	**39**	97[a]	11	74	72/28
	40	95[b]	39	0	93/7
	**39**	91[a]	30	70	91/9
	40	92[b]	18	32	75/25

[a] *Reaction conditions*: DCM, 12% diisopropylamine (DIEA), room temperature.
[b] *Reaction conditions*: THF, AgOTf (1 equiv.) and DIEA (1 equiv), room temperature.



41

Figure 23.

although they are lower than those reported for the gold/ferrocenylphosphine system. The results published indicate that the palladium catalyst **40** produces a higher enantioselectivity for *cis* oxazolines, but a lower enantioselectivity for *trans* oxazolines, when compared with the platinum catalyst **39**.

Although both complexes share a similar pincer skeleton, the subtle differences in ligand structure appear to have a significant influence on the stereochemical outcome of the aldol reactions.

3.6.2. NCN pincer complex-catalysed aldol reactions. Other pincer complexes have also shown catalytic activity in aldol reactions.

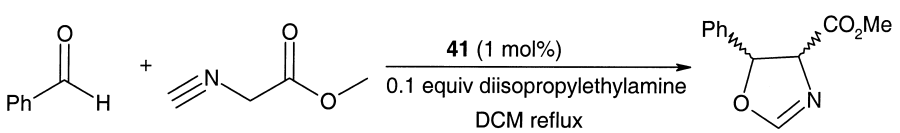
The NCN palladium pincer complex **41** (Fig. 23) has been shown to catalyse the aldol reaction of benzaldehyde and methyl isocyanoacetate[53] (Scheme 13).

The increase in the rate of reaction is small and results in a 4:1 *trans*/*cis* mixture of oxazolines being produced.

3.6.3. SCS pincer complex-catalysed aldol reactions. Following the versatility of the SCS palladium pincer complexes as catalysts in the Heck reaction and the ease with which these complexes can be attached to solid supports, Swager et al.[54] have investigated the use of SCS palladium pincer complexes as both homogeneous and heterogeneous catalysts in various aldol reactions. Three homogeneous catalysts **42**, **43** and **44** (Fig. 24) were synthesized; **42** and **43** are binuclear complexes containing a chiral spacer derived from *O*-isopropylidiene-L-threitol and it was hoped that such complexes could act as effective asymmetric catalysts in aldol reactions.

The reactions of methyl isocyanoacetate and aldehydes (isobutyraldehyde and benzaldehyde) proceed in almost quantitative yield utilising only 1.5 mol% of catalyst. All catalysts achieve the reaction in <4 h using 12 mol% of *N*,*N*-diisopropylethylamine and DCM at room temperature. The absence of only the catalyst results in longer reaction times and lower conversions (60%). The *cis*/*trans* ratio of the products obtained (Scheme 14) is not affected by the structure of the catalyst, but depends on the structure of the aldehyde.

Unfortunately, no enantioselectivity was observed. It is thought that the remoteness of the chiral centres in **42** and **43** means that they are ineffective at inducing chirality in the product. The catalyst **42** has been supported on silica to create an effective heterogeneous catalyst. This catalyst appears to remain fully intact and can be recovered by simple filtration at the end of the reaction. Further development, particularly of the supported catalysts with



Scheme 13.

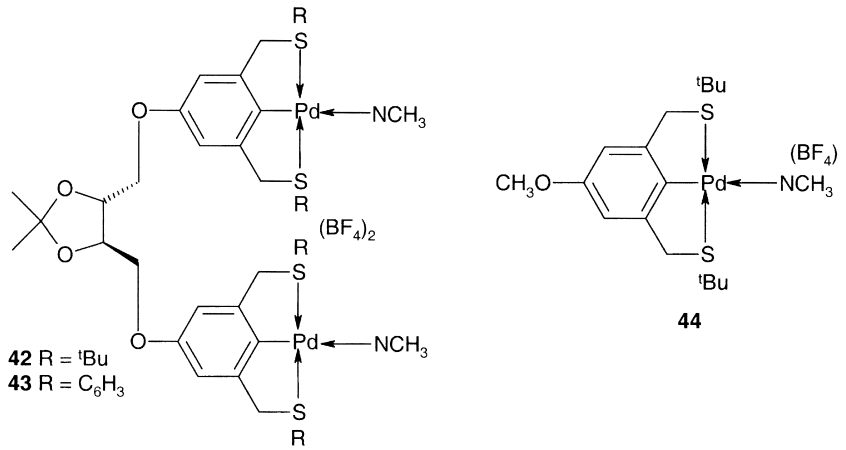
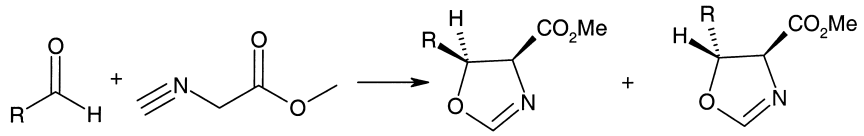


Figure 24.



Scheme 14.

less remote chiral centres may produce catalysts capable of enantioselective aldol reactions.

3.6.4. Summary. The asymmetric aldol reactions of isocyanates are predominately catalysed by gold/ferrocene systems; both platinum and palladium PCP pincer complexes have been shown to be quite efficient catalysts, although they have yet to be sufficiently developed to compete with the gold systems. Palladium NCN and SCS pincer complexes have been shown to catalyse certain aldol reactions, although not stereoselectivity. SCS pincer complexes can be attached to inert supports, creating efficient reusable catalysts; developments towards asymmetric supported catalysts have yet to achieve ees >3%.

3.7. Michael reactions

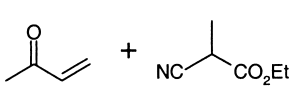
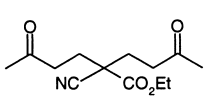
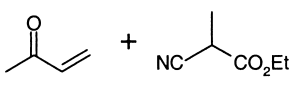
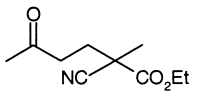
Following the investigation of pincer complexes as catalysts in aldol reactions, Richards et al.[53] have examined the use of the palladium NCN pincer complex **41** as a potential catalyst in other reactions. Catalyst **41** was shown, for example, to increase the rate of the Diels–Alder reaction of cyclopentadiene with methacrolein, but, as the increase was very marginal and with no change in the *exo*/*endo* ratio of the products, this area of research was curtailed.

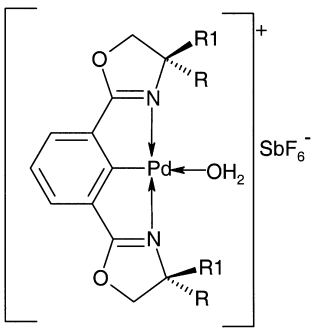
The Michael reactions of methyl vinyl ketone with ethyl cyanoacetate and ethyl α-cyanopropionate in dichloromethane with 10 mol% Hunig's base did, however, show dramatic differences when 1 mol% of the pincer complex **41** was employed as a catalyst (Table 11).

In the case of ethyl cyanoacetate, the double Michael addition adduct was formed exclusively when catalyst **41** was used. For the Michael reaction of methyl vinyl ketone and ethyl α-cyanopropionate, a 6% enantiomeric excess in favour of the *R* conformer was observed using catalyst **41**, in addition to a significant reaction rate increase. It is believed that these reactions proceed via the addition of an enolate bound to the palladium via the nitrile to the Michael acceptor in an analogous manner to the aldol reactions of isocyanates (Fig. 20).

The desire to increase both the reaction rates and the

Table 11. Michael reactions catalysed by palladium pincer complex **41**

Substrates	Product	With **41**		Without **41**	
		Time (h)	Conc (%)	Time (h)	Conc (%)
		3 20	88 100	6 23	0 <5
		<5	100	4 25 95	3 32 76



41 R = ^{i}Pr, R1 = H
45 R = ^{t}Bu, R1 = H
46 R = CH_2Cy, R1 = H

Figure 25.

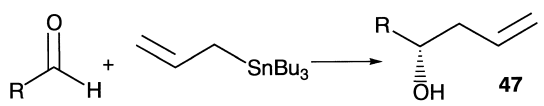
stereoselectivity of such Michael reactions has spawned a family of NCN palladium pincer complexes (Fig. 25).[55] It appears that increasing the size of the substituent on the oxazoline rings (**45** and **46**) increases the enantioselectivity of the reaction, while changing the counter-ions in the complex has little effect.

Modification of the reaction conditions, most significantly replacing dichloromethane with toluene as the solvent, as well as catalyst optimisation has produced ees of up to 34% for the reaction of methyl vinyl ketone with ethyl α-cyanopropionate, using the bulkiest oxazoline catalyst **46**.

In summary, while only modest enantioselectivity has been achieved in pincer complex-catalysed Michael reactions, their efficiency, stability and potential for solid support attachment means that work is directed towards the development of better catalysts and to obtain greater stereoselectivity.

3.8. Enantioselective allylations of aldehydes

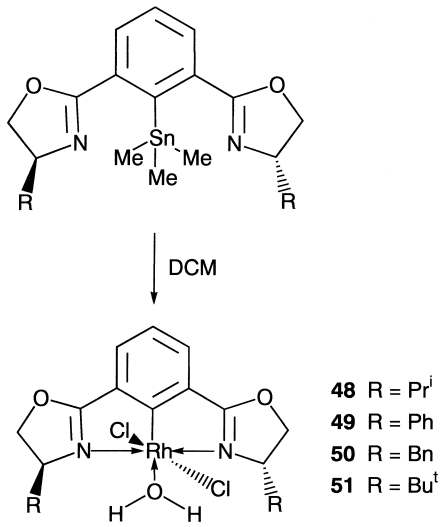
The asymmetric allylation of carbonyl compounds (Scheme 15) is a useful method for the construction of optically pure homoallylic alcohols **47** and, as a result, numerous reactions involving stochiometric amounts of chiral allylmetal reagents have been reported.[56] There are, however, far fewer reactions reported using catalytic chiral Lewis acids. The aim of Nishiyama et al.[57] was to produce a chiral Lewis acid catalyst that, unlike the majority of Lewis acid catalysts, was stable to air and moisture tolerant.



Scheme 15.

The catalysts studied (**48**–**51**) were based on the 2,6-bis-(oxazolinyl)phenyl (Phebox)[53,58] backbone, due to the ease with which chiral derivatives could be produced. Rhodium was utilised as the metal centre to provide air and moisture stability. The pincer complexes were formed by mixing (Phebox)-$SnMe_3$ and a rhodium chloride complex in dichloromethane (Scheme 16). The resulting complexes were stable enough to be purified by silica chromatography.

The allylation of various aldehydes with allyltributyl-stannane proceeded smoothly in dichloromethane at room



48 R = Pr^{i}
49 R = Ph
50 R = Bn
51 R = Bu^{t}

Scheme 16.

temperature using 5 mol% of the pincer complex catalyst. Lowering the reaction temperature, or changing the solvent, only appeared to retard the reactions. The enantioselectivity was unaffected. Increasing the steric bulk on the oxazoline ring of the catalyst does, however, affect the enantioselectivity of the reaction. The use of the catalyst **50** consistently produced alcohols with the highest enantioselectivity for any given aldehyde. Table 12 summarises the results obtained.

Table 12. Asymmetric allylations of aldehydes catalysed with **50**

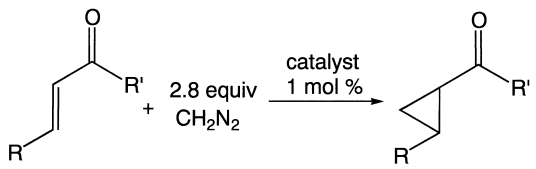
Aldehyde	Yield (%)	ee (%)	Configuration
4-BrC_6H_4CHO	94	43	*S*
PhCHO	88	61	*S*
4-$MeOC_6H_4CHO$	99	80	*S*
2-MeC_6H_4CHO	98	53	*S*
2-furyl-CHO	94	58	*S*
$PhCH_2CH_2CHO$	84	63	*R*[a]
(*E*)-PhCH=CHCHO	98	77	*S*

[a] *R* configuration due to nomenclature.

In summary, the easily prepared, relatively stable, Phebox NCN ruthenium pincer complexes are effective chiral Lewis acid catalysts, for the enantioselective addition of allyltributylstannanes to aldehydes. As with many pincer complex applications, research in this area is still in its infancy. The goal of higher selectivities to complete against other chiral Lewis acid such as the BINAP-derived titanium[59] or silver[60] complexes means that the development of these catalysts, and their applications to other asymmetric reactions, is ongoing.

3.9. Cyclopropanation reactions

The realm of intermolecular asymmetric cyclopropanation currently belongs to the methylenebis(oxazoline)copper(I) (and semicorrin) catalysts of Pfaltz[61] and the pyridine-bis(oxazoline)ruthenium(II) complex of Nishiyama.[62] These compounds catalyse the reaction of diazoacetate esters and styrene, with good *trans*-selectivity and very high enantioselectivity. The use of a diazoester is problematic, however, since further transformation of these esters is



Scheme 17.

difficult and the formation of *cis*-cyclopropanes in high ee almost impossible. The replacement of diazoesters with diazomethane (Scheme 17) has been investigated by Denmark et al.[58]

The Denmark group chose to investigate the use of bis(oxazoline)palladium complexes as potential cyclopropanation catalysts. Initially, η^2-complexes (Fig. 26) were synthesised and these were found to be quite effective catalysts. The cyclopropanation reactions were carried out in a dichloromethane/diethyl ether mixture at 0°C using 0.01 mol% of catalyst and 2.8 equiv. of diazomethane in ether. Unfortunately, the products obtained were practically racemic (enantioselectivity <2%). Prolonged or harsh reaction conditions also highlighted stability problems with some of the catalysts.

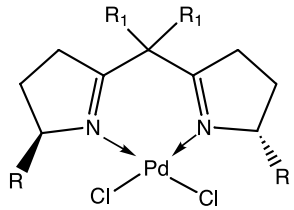


Figure 26.

Believing ligand dissociation and catalysis via the free metal to be responsible for the lack of enantioselectivity, the Denmark group began to investigate the related NCN palladium pincer complexes (Fig. 27).

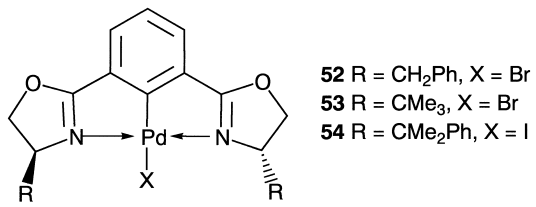


Figure 27.

Despite the greater stability of such pincer complexes and the presence of a metal–carbon σ bond, preventing dissociation, the corresponding cyclopropanation reactions failed to produce any significant stereoselectivity. The yields of cyclopropanes for the reaction of ethyl (*E*)-cinnamate with diazomethane using these catalysts were, however, impressive. The catalysts **52** or **5**, afforded 92 and 98% yields of the resulting cyclopropane, respectively, but with observed ees of <2%. The catalyst **54** was found to be completely inactive.

While none of the bis(oxazoline)palladium catalysts investigated by Denmark et al. are effective asymmetric cyclopropanation catalysts, their ability to form cyclopropanes using diazomethane rather than the more common diazoester is of value. The lack of stereoselectivity achieved by the pincer class of catalysts in these cyclopropanation reactions is not fully understood, and requires further investigation before the value of pincer-complex catalysed cyclopropanation can be determined.

3.10. Asymmetric allylic alkylation

Over 1000 chiral diphosphines have been synthesised for use as asymmetric catalysts. Only a few, e.g. BINAP[63] and Duphos,[64] have the efficiency and selectivity required for commercial applications. In the search for more active and efficient catalysts, Longmire et al.[65] have investigated the use of their chiral ligand **55** (Fig. 28) for asymmetric allylic alkylations.

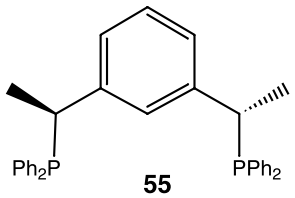
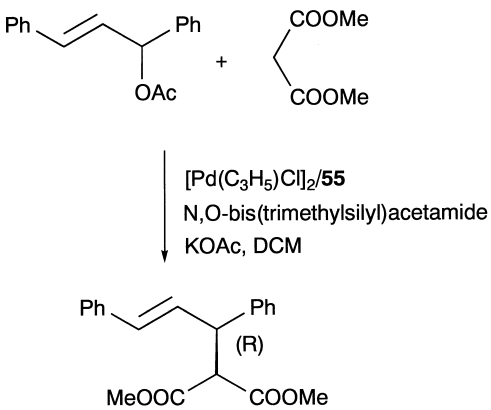


Figure 28.

The ligand **55** had originally been used to form the chiral pincer complex **40** (Fig. 22) which could be used as a catalyst in asymmetric aldol reactions (Section 3.6).

Throughout their investigation into the allylic alkylations of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate (Scheme 18), Longmire et al.[65] chose to add the ligand and a source of palladium(II) separately.



Scheme 18.

A 94% yield was obtained when the reaction was carried out at −20°C over 24 h and an enantiomeric excess of 79% in favour of the (*R*) enantiomer was reported.

Higher enantioselectivities are required for the catalyst to compete with BINAP and Duphos for commercial applications. The modified catalysts also need to be tested in a variety of different allylic alkylations. The reported ease of synthesis of the ligand **55**, and the promising asymmetric alkylation, is, however, encouraging for the further application of palladium PCP pincer complexes as catalysts for asymmetric synthesis in the future.

4. Conclusions

Considering pincer complexes were first discovered 30 years ago, it is surprising that their potential as catalysts is only just being explored.

The metal–carbon σ bond is the key to the high stability of the pincer complexes. The stability of these complexes to air and moisture, as well their thermal stability, means that they offer considerable advantages over the other catalysts commonly employed in Heck reactions and the dehydrogenation of alkanes to alkenes. Some Suzuki reactions have also been carried out without the need for an inert atmosphere.

The metal within the pincer complex is shielded and the electron density around it can be fine tuned by varying the substituents on the pincer skeleton, as in the case of the pincer complexes used to catalyse Kharasch additions. The result has been the production of one of the most active and selective catalysts for Kharasch additions, which practically eliminates the side reactions of telomerisation and polymerisation.

The donor atoms within the pincer complex can bear substituents allowing for greater catalyst tuning. The substitution of EWGs on the phosphorus donor atoms in palladium PCP pincer complexes has therefore produced some of the most highly active Heck reaction catalysts. These improved catalysts allow the use of aryl chlorides in Heck reactions and, in the case of Heck reactions with aryl bromides, the trisubstituted alkenes can be produced.

The donor atoms can be substituted with chiral-containing fragments, producing chiral catalysts. The results obtained using chiral catalysts in Michael reactions and the allylation of aldehydes are very encouraging, with ees of up to 36 and 80%, respectively, being obtained. The discovery of highly enantioselective pincer catalysts, however, particularly for cyclopropanations reactions, appears to be some way off.

The attachment of pincer complexes to solid supports has produced a range of active, easily isolated and reusable catalysts for the Kharasch addition reaction and Heck reactions. Soluble macromolecular and dendrimer catalysts (soluble catalysts that can be recovered by membrane filtration) have been produced for use in both polar and non-polar solvents.

While the synthesis of pincer complexes has not been the focus of this review, several examples showing just how easy some of these catalysts can be synthesised have been included. The realm of pincer complexes is now such a rapidly-expanding area that even during the completion and submission of this review, potential new uses for these complexes in organic synthesis are being reported. The palladium PCP pincer complex **11** has recently been shown to catalyse the cross coupling of phenylacetylene with several aryl chlorides[66] while Morales et al.[67] continue to develop pincer complexes as catalysts for the Heck reactions.

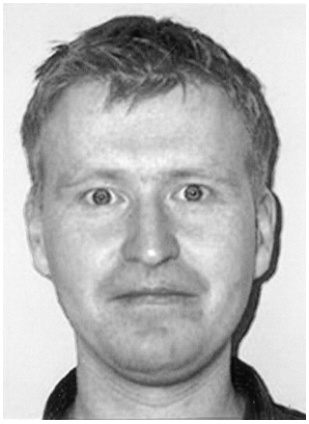
As the number of pincer complexes synthesised continues to increase, the number of synthetic uses will only grow.

References

1. Rietveld, M. H. P.; Grove, D. M.; van Koten, G. *New J. Chem.* **1997**, *21*, 751–771.
2. van Koten, G.; Albrecht, M. *Angew. Chem. Int. Ed.* **2001**, *40*, 3750–3781.
3. Moulton, C. J.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1976**, 1020–1024.
4. Kharasch, M. S.; Jenesen, E. V.; Urry, W. H. *J. Am. Chem. Soc.* **1945**, *67*, 1626–1627.
5. Kharasch, M. S.; Engelmann, H.; Mayo, F. R. *J. Org. Chem.* **1938**, *2*, 288–302.
6. Matsumoto, H.; Motegi, T.; Nakano, T.; Nagai, Y. *J. Organomet. Chem.* **1979**, *174*, 157–161.
7. Bland, W. J.; Davis, R.; Durrant, J. L. A. *J. Organomet. Chem.* **1985**, *280*, 397–406.
8. Gossage, R. A.; van der Kuil, L. A.; van Koten, G. *Acc. Chem. Res.* **1998**, *31*, 423–431.
9. Van de Kuil, L. A.; Grove, D.; Gossage, R. A.; Zwikker, J. W.; Jenneskens, L. W.; Drenth, W.; van Koten, G. *Organometallics* **1997**, *16*, 4985–4994.
10. Grove, D. M.; Verschuren, A. H. M.; van Koten, G.; van Beck, J. A. M. *J. Organomet. Chem.* **1989**, *372*, C1–C6.
11. Nagashima, U.; Tsuji, J.; Sato, K. *Tetrahedron* **1985**, *4*, 393–397.
12. van Koten, G.; Jastrzebski, J. T. B. H. *J. Mol. Catal. A: Chem.* **1999**, *146*, 317–323.
13. Van de Kuil, L. A.; Grove, D. M.; Zwikker, J. W.; Jenneskens, L. W.; Drenth, W.; van Koten, G. *Chem. Mater.* **1994**, *6*, 1675–1683.
14. Gossage, R. A.; Jastrzebski, J. T. B. H.; van Ameijde, J.; Mulders, S. J. E.; Brouwer, A. J.; Liskamp, R. M. J.; van Koten, G. *Tetrahedron Lett.* **1999**, *40*, 1413–1416.
15. van der Kuil, L.; Veldhuizen, Y. S. J.; Grove, D.; Zwikker, J. W.; Jenneskens, L. W.; Drenth, W.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *Recl. Trav. Chim. Pays-Bas.* **1994**, *113*, 267–277.
16. Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518–5526.
17. (a) Heck, R. F. *Org. React.* **1982**, *27*, 345–390. (b) Heck, R. F. *Comprehensive organic synthesis: selectivity, strategy and efficiency in modern organic chemistry*; Trost, B. M.; Fleming, I., Eds.; 1991; Vol. 4. p 833, Chapter 4.3. (c) Cabri, W. *Acc. Chem. Res.* **1995**, *28*, 2–27.
18. Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687–11688.
19. Beletskaya, I. P.; Chuchurjukin, A. V.; Dijkstra, H. P.; van Klink, G. P. M.; van Koten, G. *Tetrahedron Lett.* **2000**, 411075–411079.
20. Morales-Morales, D.; Redón, R.; Yung, C.; Jensen, C. M. *Chem. Commun.* **2000**, 1619–1620.
21. Beller, M.; Zapf, A. *Synlett* **1998**, 792–794.
22. Morales-Morales, D.; Grause, C.; Kasaoka, K.; Redón, R.; Crammer, R. E.; Jensen, C. M. *Inorg. Chim. Acta* **2000**, *300-302*, 958–963.
23. Miyazaki, F.; Yamaguchi, K.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 7379–7383.
24. Peris, E.; Loch, J. A.; Mata, J.; Crabtree, R. H. *Chem. Commun.* **2001**, 201–202.
25. Grundemann, S.; Albrecht, M.; Loch, J. A.; Faller, J. W.; Crabtree, R. H. *Organometallics* **2001**, *20*, 5485–5488.
26. Tulloch, A. A. D.; Danopoulos, A. A.; Tizzard, G. J.; Coles, S. J.; Hursthouse, M. B.; Hay-Motherwell, R. S.; Motherwell, W. B. *Chem. Commun.* **2001**, 1270–1271.

27. Bergbreiter, D. E.; Osburn, P. L.; Liu, Y.-S. *J. Am. Chem. Soc.* **1999**, *121*, 9531–9538.
28. (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147–168. (b) Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
29. Bedford, R. B.; Draper, S. M.; Scully, P. N.; Welch, S. L. *New J. Chem.* **2000**, *24*, 745–747.
30. Zim, D.; Gruber, A. S.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2000**, *2*, 2881–2884.
31. Crabtree, R. H.; Michelcic, J. M.; Quirk, J. M. *J. Am. Chem. Soc.* **1979**, *101*, 7738–7740.
32. Crabtree, R. H.; Parnell, C. P.; Uriarte, R. J. *Organometallics* **1987**, *6*, 696–699.
33. Moulton, C. J.; Shaw, B. L. *J. Chem. Soc., Dalton Trans.* **1976**, 1020–1024.
34. Gupta, M.; Hagen, C.; Flesher, R. J.; Kaska, W. C.; Jensen, C. M. *Chem. Commun.* **1996**, 2083–2084.
35. Wang, K.; Goldman, M. E.; Emge, T. J.; Goldman, A. S. *J. Organomet. Chem.* **1996**, *518*, 55–68.
36. Leitner, W.; Six, C. *Chem. Ber./Recueil.* **1997**, *130*, 555–558.
37. Lee, D. W.; Kaska, W. C.; Jensen, C. M. *Organometallics* **1998**, *17*, 1–3.
38. Felkin, H.; Fillebeen-Khan, T.; Holmes-Smith, R.; Zakrzewski, J. *Tetrahedron Lett.* **1984**, *25*, 1279–1282.
39. Liu, F.; Pak, E. B.; Singh, B.; Jensen, C. M.; Goldman, A. S. *J. Am. Chem. Soc.* **1999**, *121*, 4086–4087.
40. Liu, F.; Goldman, A. S. *Chem. Commun.* **1999**, 655–656.
41. Xu, W.; Rosini, G. P.; Gupta, M.; Jensen, C. M.; Kaska, W. C.; Krogh-Jespersen, K.; Goldman, A. S. *Chem. Commun.* **1997**, 2273–2274.
42. Jensen, C. M. *Chem. Commun.* **1999**, 2443–2449.
43. Wiseman, P. *Petrochemicals*; Ellis Horwood: Chichester, England, 1986; pp 90–91.
44. Crabtree, R. H.; Parnell, C. P.; Uriarte, R. J. *Organometallics* **1987**, *6*, 696–699.
45. Gupta, M.; Hagen, C.; Kaska, W. C.; Crammer, R. E.; Jensen, C. M. *J. Am. Chem. Soc.* **1997**, *119*, 840–841.
46. Gupta, M.; Kaska, W. C.; Jensen, C. M. *Chem. Commun.* **1997**, 461–462.
47. Morales-Morales, D.; Chen, W.; Jensen, C. M. *Book of Abstracts*, 218th ACS National Meeting, 1999; INORG 272.
48. Morales-Morales, D.; Redon, R.; Chen, W.; Yung, C.; Jensen, C. M. *Book of Abstracts*, 220th ACS National meeting, 2000; INORG 274.
49. Dani, P.; Karlen, T.; Gossage, R. A.; Gladiali, S.; van Koten, G. *Angew. Chem. Int. Ed.* **2000**, *39*, 743–745.
50. Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc* **1986**, *108*, 6405–6406.
51. Gorla, F.; Togni, A.; Venanzi, L. *Organometallics* **1994**, *13*, 1607–1616.
52. Zhang, X.; Longmire, J. M.; Shang, M. *Organometallics* **1998**, *17*, 4374–4379.
53. Stark, M. A.; Richards, C. J. *Tetrahedron. Lett.* **1997**, *38*, 5881–5884.
54. Gimenez, R.; Swager, T. *J. Mol. Catal. A: Chem.* **2001**, *166*, 265–273.
55. Stark, M. A.; Richards, C. J. *Organometallics* **2000**, *19*, 1282–1291.
56. Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262–1284.
57. Motoyama, Y.; Narusawa, H.; Nishiyama, H. *Chem. Commun.* **1999**, 131–132.
58. Denmark, S.; Stavenger, R. A.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem.* **1997**, *62*, 3375–3389.
59. Weigend, S.; Ruckner, R. *Chem. Eur. J.* **1996**, *2*, 1077–1081.
60. Yangisaura, A.; Ishiba, A.; Nakashima, H.; Yamamoto, K. *Synlett* **1997**, 88–91.
61. Pfaltz, A. *Chima* **1990**, *44*, 202–213.
62. Nishiyama, H.; Itoh, Y.; Sugawara, Y.; Matsumoto, H.; Aoki, K.; Itoh, K. *Bull. Chem. Soc. Jpn* **1995**, *68*, 1247–1262.
63. Takaya, H.; Mahima, K.; Koyano, K.; Yagi, M.; Kumobayashi, H.; Takemomi, T.; Akugawa, S.; Noyori, R. *J. Org. Chem.* **1986**, *51*, 629–635.
64. Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518–8519.
65. Longmire, J. M.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 1725–1728.
66. Jensen, C. M.; Eberhard, M. R.; Wang, Z. *Chem. Commun.* **2002**, 818–819.
67. Morales-Morales, D.; Redón, R.; Zheng, Y. F.; Dilworth, J. R. *Inorg. Chim. Acta* **2002**, *328*, 39–44.

Biographical sketch



John Singleton was born in 1973. He received his BSc in Chemistry from the University of Leicester in 1994. He then joined Fisons Pharmaceuticals (later AstraZeneca) where he remains as a senior research chemist in the Process Research and Development Department. In 2002, he was awarded an MSc in Organic Synthesis from the University of Sussex.