

Chapter 2

***N*-Heterocyclic Carbene Complexes in Additions to Multiple Bonds**

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Abstract The use of *N*-heterocyclic carbene (NHC) complexes as homogeneous catalysts in addition reactions across carbon-carbon double and triple bonds and carbon-heteroatom double bonds is described. The discussion is focused on the description of the catalytic systems, their current mechanistic understanding and occasionally the relevant organometallic chemistry. The reaction types covered include hydrogenation, transfer hydrogenation, hydrosilylation, hydroboration and diboration, hydroamination, hydrothiolation, hydration, hydroarylation, allylic substitution, addition, chloroesterification and chloroacylation.

2.1 Introduction

The first isolation of stable cyclic and acyclic nucleophilic carbenes by Arduengo and Bertrand, and the development of synthetic methods for their introduction to metals, either by direct reactions with metal precursors of the preformed, or *in situ* generated carbenes, or by the silver transmetallation methodology, initiated detailed studies aiming at a better understanding and use of these ligands in homogeneous catalysis. The current refined description of the metal-NHC bonding across the Periodic Table and the factors affecting it, the semi-quantitative parametrisation of the ligand topology and the space it occupies around the metal, the dynamic processes in which *N*-heterocyclic carbene (NHC) ligands are involved, and the invention of ways to introduce ligand chirality, provide the essential tools for further catalyst discovery, tuning and development. In this chapter an overview of the use of NHC complexes as catalysts in addition reactions across C–C and C-heteroatom multiple bonds is presented. The emerging picture is that NHC ligands are unique in some catalytic applications and complementary to the well-established tertiary phosphines, which we initially thought they were mimicking.

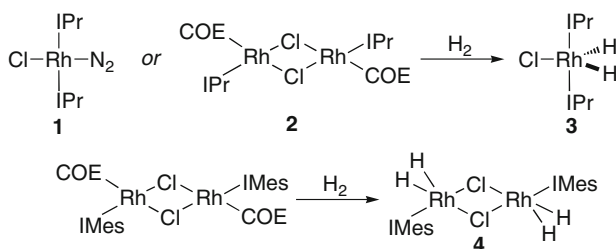
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2.2 Hydrogenation of Alkenes and Alkynes

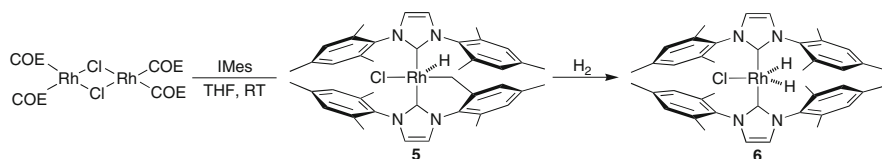
The Rh–NHC complexes, with or without phosphine co-ligands, have been studied as hydrogenation catalysts of alkenes with molecular hydrogen, with the aim to develop more active, selective (and/or enantioselective) and thermally stable catalysts.

Rh(III)(NHC) hydrides have been studied as catalysts for this type of hydrogenation. The products from the reaction of Rh(I) complexes with H_2 are dependent on the nature of the NHC. The reaction of $[RhCl(IPr)_2(N_2)]$ **1** ($IPr = N,N'$ -bis-[2,6-(di-*iso*-propyl)phenyl]imidazol-2-ylidene) with H_2 gave the monomeric complex **3** [1], which was also obtained from the reaction of $[RhCl(COE)(IPr)_2]$ **2** with H_2 and excess IPr , while the reaction of $[RhCl(COE)(IMes)]_2$ with H_2 gave the chloride bridged species **4** (Scheme 2.1) [2].



Scheme 2.1 Reactions of Rh(I) NHC complexes with hydrogen

$[Rh(COE)_2Cl]_2$ in the presence of $IMes$, N,N' -bis-[2,4,6-(trimethyl)phenyl]imidazol-2-ylidene, reacted with H_2 at room temperature to give the trigonal bipyramidal $[Rh(H)_2Cl(IMes)_2]$ **6** (which is analogous to **3**) *via* intermediate formation of the isolable cyclometallated **5** (Scheme 2.2) [3].



Scheme 2.2 The formation of the rhodium dihydride complex *via* a cyclometallated intermediate

The hydrogenation activity of the isolated hydrides **3** and **6** towards cyclooctene or 1-octene was much lower than the Wilkinson's complex, $[RhCl(PPh_3)_3]$, under the same conditions [2]; furthermore, isomerisation of the terminal to internal alkenes competed with the hydrogenation reaction. The reduced activity may be related to the high stability of the Rh(III) hydrides, while displacement of a coordinated NHC by alkene may lead to decomposition and Rh metal formation.

The catalytic hydrogenation of alkenes by mixed NHC/phosphine complexes of rhodium was also studied. Initial results of the hydrogenation of cyclohexene by *trans*- $[RhCl(ICy)(L)_2]$ ($ICy = N,N'$ -(dicyclohexyl)imidazol-2-ylidene, $L = PPh_3$,

$\text{P}(\text{O}^i\text{Ph})_3$) and *trans*- $[\text{RhCl}(\text{ICy})_2\text{PPh}_3]$ showed poor activity compared to Crabtree's catalyst $[\text{Ir}(1,5\text{-COD})(\text{Py})(\text{PCy}_3)][\text{PF}_6]$ or its IMes analogue, $[\text{Ir}(1,5\text{-COD})(\text{Py})(\text{IMes})][\text{PF}_6]$, under the same conditions [4, 5]. Systematic optimisation was conducted by generating the catalysts *in situ* from $[\text{RhCl}(1,5\text{-COD})(\text{ICy})]$ and two or four equivalents of PPh_3 under H_2 [5]. In these studies an induction period was observed, while the phosphine was required to prevent catalyst decomposition. The activities were one fifth to one tenth of the original Wilkinson's catalyst. The reduced activities may be ascribed to reduced phosphine pre-dissociation to form the coordinatively and electronically unsaturated active species. In view of the observation that NHCs dissociate from $[\text{RhCl}(\text{NHC})(\text{L})_2]$ in the presence of L, it may be that the active species of the *in situ* systems contains only phosphine ligands [6].

Chiral monodentate carbene complexes of Rh and Ir of the type $[\text{MCl}(1,5\text{-COD})(\text{NHC})]$ (M = Rh, Ir) with the ligands **7–9** (Fig. 2.1) have been studied as catalysts for the enantioselective hydrogenation of methyl-2-acetamido acrylate. Even though the activities were high, the enantiomeric excesses (*ee*) were poor [7, 8].

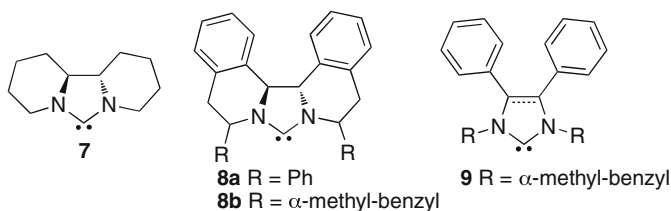


Fig. 2.1 Chiral NHC ligand designs used in the Rh-catalysed enantioselective hydrogenation of methyl-2-acetamido acrylate by dihydrogen

Replacement of one PCy_3 in $[\text{RuCl}(\text{H})(\text{CO})(\text{PCy}_3)_2]$ **10** by IMes gave $[\text{RuCl}(\text{H})(\text{CO})(\text{PCy}_3)(\text{IMes})]$, **11** (Fig. 2.2) which is an active catalyst for the direct hydrogenation of 1-hexene, allylbenzene and cyclooctene. At higher temperatures (*ca.* 100°C) the activity of **11** is superior to **10**. Furthermore, small (1–2 equiv.) quantities of $\text{HBF}_4 \cdot \text{Et}_2\text{O}$ act as co-catalyst, by enhancing the dissociation of PCy_3 (through the formation of $[\text{PCy}_3\text{H}^+][\text{BF}_4^-]$) [9]. Similar behaviour was observed in the hydrogenation of 1-octene by $[\text{Ru}(\text{CO})(\text{Cl})(\text{Ph})(\text{PCy}_3)(\text{SIMes})]$, **12** [10]. $[\text{RuCl}(\text{H})(\text{CO})(\text{PPh}_3)(\text{NHC})]$ (NHC = IMes, SIMes), **13**, is more active for the hydrogenation of cyclooctene or *cis*- and *trans*-cyclododecene [11] due to the increased lability of PPh_3 compared to PCy_3 . In the latter case isomerisation competes with hydrogenation [12].

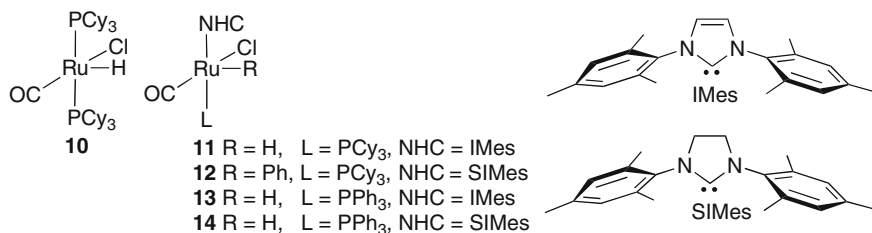


Fig. 2.2 Ruthenium-based hydrogenation catalysts bearing NHC ligands

Reaction of the 18e-species $[\text{Ru}(\text{H})_2(\text{CO})(\text{IMes})(\text{PPh}_3)_2]$ **15** with trimethyl vinylsilane gave the cyclometallated complex **16** and trimethylethylsilane; **16** can be converted to the original dihydride **15** by reaction with H_2 (1 atm, room temperature) or $^i\text{PrOH}$ (50°C) [13]. Catalytically, vinylsilane can be hydrogenated by **16** in $^i\text{PrOH}$ in quantitative yield (Fig. 2.3) [14].

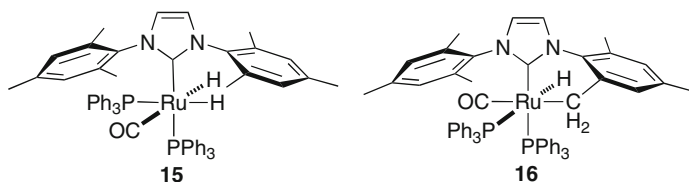


Fig. 2.3 Ru-IMes and cyclometallated Ru-IMes complexes used as catalysts for the hydrogenation of trimethylvinylsilane

Reduction of acetophenone by $^i\text{PrOH}/\text{H}_2$ has been studied with the ruthenium complexes $[\text{Ru}(\text{H})(\eta^2\text{-BH}_4)(\text{CO})\text{L}(\text{NHC})]$, ($\text{L} = \text{NHC}$, PPh_3 , $\text{NHC} = \text{IMes}$, IPr , SIPr). The activity of the system is dependent on the nature of the NHC and requires the presence of both $^i\text{PrOH}$ and H_2 , implying that transfer and direct hydrogenation mechanisms may be operating in parallel [15].

Replacement of the pyridine in Crabtree's complex by NHC ($\text{NHC} = \text{IMes}$, IMe) gave very active catalysts for the hydrogenation by H_2 of various alkenes to alkanes, including hindered tertiary and quaternary alkenes. For terminal 1-alkenes (1-octene), the IMes analogue gives best conversions, while for tertiary and quaternary alkenes (1-methyl-cyclohexene and 2,3-dimethyl-2-butene) the IMe analogue is more suitable [16]. On the other hand, replacement of PCy_3 by NHC ($\text{NHC} = \text{IMes}$, ICy , SIMes) in Crabtree's complex $[\text{Ir}(1,5\text{-COD})(\text{Py})(\text{PCy}_3)]^+$, gave a catalyst for the hydrogen transfer reduction of aryl- and alkyl-ketones to alcohols, cyclic alkenes to alkanes, dienes to alkenes, α,β -unsaturated carbonyl compounds to alcohols, and aromatic nitro compounds to anilines. Best activities were observed with $\text{NHC} = \text{ICy}$ [12].

Initial attempts to develop Pd-NHC complexes as hydrogenation catalysts for alkenes or alkynes focused on the use of $[\text{Pd}(\text{NHC})_2]$ species. However, these did not withstand the reaction conditions decomposing to metallic Pd and imidazolium salts or imidazolidine, presumably after H_2 oxidative addition to form $\text{Pd}(\text{NHC})$ hydrides, followed by imidazolium elimination. Reports by Elsevier on the stability of $\text{Pd}(\text{NHC})$ fragment under hydrogenation conditions opened the way for the development of $\text{Pd}(\text{NHC})$ hydrogenation catalysts [17]. The catalysts proved very selective for the 'semi-hydrogenation' of arylalkynes to Z-alkenes with high chemo- and stereo-selectivity, being far superior than the known $\text{Pd}(\text{bipy})$ and $\text{Pd}(\text{diazabutadiene})$ based complexes. The catalysts were best generated *in situ* from a $\text{Pd}(0)$ source, preferentially **17**, an imidazolium or imidazolidinium salt and KO^tBu , at room temperature, in the presence of the alkyne and H_2 (1 atm). Surprisingly, better activities were observed with the unsaturated imidazol-2-ylidene precursors such as **18**. Preformed $\text{Pd}(\text{NHC})$ complexes, for example **19**, were not as active as the *in situ* generated catalysts (Fig. 2.4).

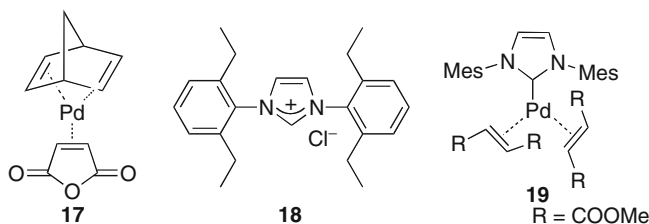


Fig. 2.4 Components of the Pd-based catalytic system for the hydrogenation of arylalkynes. The pre-formed complex **19** shows reduced activity

Recently, the direct hydrogenation of a wide range of alkenes was successfully carried out using $[\text{Pd}(\text{SIPr})(\text{PCy}_3)]$ **20** in alcohols or THF. Complex **20** in the presence of H_2 forms *trans*- $[\text{Pd}(\text{H})_2(\text{SIPr})(\text{PCy}_3)]$. The activity of the catalytic system is very high under mild conditions (1 bar, rt, 0.25 mol%Pd). Reduction of the alkene functionality can be selective in α,β -unsaturated carbonyl compounds, while alkynes can be ‘semi-hydrogenated’ to *Z*-alkenes with good selectivity as seen above [18].

Bidentate NHC-Pd complexes have been tested as hydrogenation catalysts of cyclooctene under mild conditions (room temperature, 1 atm, ethanol). The complex **22** (Fig. 2.5), featuring ‘abnormal’ carbene binding from the C^4 carbon of the imidazole heterocycles, has stronger $\text{Pd}-\text{C}_{\text{NHC}}$ bonds and more nucleophilic metal centre than the C^2 bound ‘normal’ carbene chelate **21**. The different ligand properties are reflected in the superior activity of **22** in the hydrogenation of cyclooctene at 1–2 mol% loadings under mild conditions. The exact reasons for the reactivity difference in terms of elementary reaction steps are not clearly understood [19].

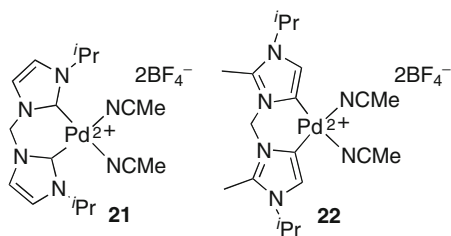


Fig. 2.5 Palladium-based hydrogenation catalysts with bidentate ‘normal’ and ‘abnormal’ NHC ligands

The development of functionalised NHC ligands, bearing NHC functional group(s) tethered to classical donors, provides additional ways of tuning the coordination sphere of the metal both sterically and electronically, and opens new ways for catalyst design. The chiral complexes **23**, **24** and **25** (Fig. 2.6) have been used for the enantioselective hydrogenation of substituted aryl alkenes (**23** and **24**), functionalised alkenes **24** and α,β -unsaturated esters **25** with good *ees*. The oxazoline carbene species (**23** and **24**) operate under milder conditions than analogous complexes where NHC is replaced by phosphine [20–23]. Theoretical calculations on the mechanism of hydrogenation of the arylalkenes with **23** and the origin optical induction, support an Ir(III)/(V) cycle with rate determining metathetical insertion of the hydride to a

coordinated alkene. The face selectivity is determined by the interaction of the 1-adamantyl substituent of the oxazoline with the phenyl group of the substrate [24].

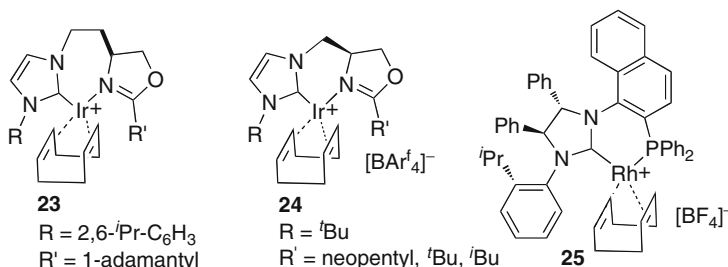
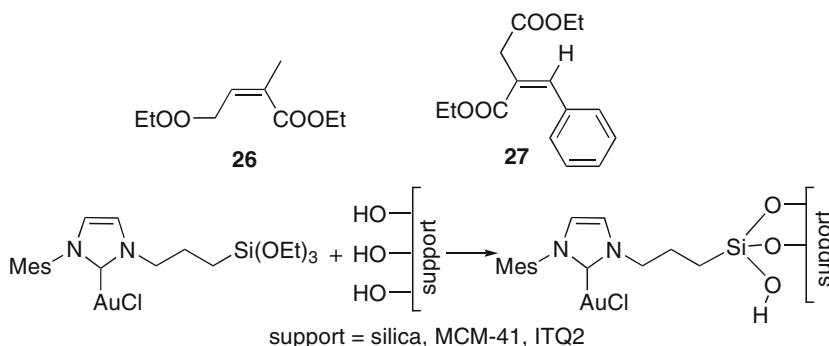


Fig. 2.6 Chiral functionalised NHC complexes as enantioselective hydrogenation catalysts with dihydrogen

The supported Au complexes presented in Scheme 2.3 show increased activity in the hydrogenation by H₂ of diethylcitraconate **26** and diethylbenzylidene succinate **27**, compared to [AuCl(PPh₃)] (40°C, 4 atm, ethanol). The nature of the support has an effect on the TOF (turnover frequency) of the reaction, being highest with ITQ-2 and lowest with silica. The preferred mechanism of hydrogen activation involves heterolytic splitting rather than homolysis or oxidative addition steps [25].



Scheme 2.3 Hydrogenations catalysed by a supported Au-NHC complex

2.3 Transfer Hydrogenation and Related Reactions

The transfer hydrogenations of carbonyl compounds to alcohols catalysed by a variety of NHC complexes have been intensively studied. The strong M-C_{NHC} bond and the excellent σ -donating properties of the NHC ligands are responsible for the stabilisation of hydrides and alkoxides that are intermediates in the postulated catalytic cycles. Rh, Ir, and Ru species, where the metal is coordinated by monodentate NHCs and classical co-ligands (pyridine, phosphines or cyclopentadienyl analogues) [26–28],

‘pincer’ pyridine di-carbenes [29, 30] bidentate di-carbenes [31] and functionalised NHCs [28, 32–35] are particularly successful catalysts. Steric and electronic tuning of the coordinated NHCs is important for the successful catalysts. Less hindered, alkyl substituted NHCs usually give more active catalysts than their analogues with bulky aryl substituents. The influence of the electronic properties of the NHC on activity and selectivity is more subtle. For example, imidazol-based NHC complexes are generally most active for the reduction of ketones, while in specific cases rhodium complexes with ‘abnormal’ C⁴ bound NHCs are more active compared to C² bound analogues [36]; iridium complexes with the weaker σ -donating triazol based NHCs have been developed for the reduction of imines, alkenes and the stepwise one-pot reductive amination of aldehydes [27]. However, the structure and property principles underlying catalyst tuning are still underdeveloped with these ligand systems and the NHC ligands in general. Co-ligands (for example pyridine donors, cyclopentadienyl analogues, etc.) are also important in the catalyst design, presumably by stabilising the metal in the active oxidation state, or providing labile sites for substrate coordination. In addition, in polydentate functionalised NHC complexes, a possible hemilability of the tethered classical donor has been implied during catalysis and supported by spectroscopic studies [34, 37].

In the majority of the known examples, the donor of hydrogen equivalents is isopropanol; HCOO[−] or HCOOH/Et₃N azeotrope are less successful. Aromatic ketones (mainly acetophenone and benzophenone) were the easiest to reduce even under mild conditions and low catalyst loadings.

The required bases for the reaction include KOH, KO^tBu and K₂CO₃, the latter usually added in higher base/substrate ratios than KOH. However, K₂CO₃ is the base of choice for the reduction of aldehydes, where aldehyde decarbonylation and subsequent catalyst deactivation or formation of aldol side products interfere with the reduction [38]. The transfer hydrogenation of imines is more challenging due to competing formation of the catalytically inactive complex involving σ -coordination of the imine, and therefore NHC based catalysts for this purpose are less common [27, 29, 39]. The activity of certain NHC complexes in imine reduction has been exploited for the one-pot sequential reductive amination of aldehydes to amines. In the reported system, the added base K₂CO₃ acts also as a drying agent during the imine formation [27]. Selected complexes that have been studied as transfer hydrogenation catalysts and related catalytic data are shown in Figs. 2.7 and 2.8 and Tables 2.1 and 2.2, respectively.

Two versatile hydrogen auto-transfer processes were catalysed by the iridium complexes **41** and **42** [28, 40]. The first, *N*-alkylation of primary amines using alcohols as electrophiles, involves oxidative hydrogen elimination from the alcohol to form an aldehyde, which, in the presence of amine, is converted to imine and the latter reduced to the secondary amine by transfer hydrogenation. The second system involves oxidative hydrogen elimination from one primary and one secondary alcohol to form an aldehyde and ketone, respectively, which undergo aldol coupling and reduction of the α,β -enone to alkylated alcohols. Both transformations are very attractive compared to conventional alkylations with organic halides, due to their reduced waste [41]. The reactions are carried out in refluxing toluene in the presence of base (KOH, KO^tBu, NaHCO₃) with high conversions at low catalyst loadings (1.0 mol%).

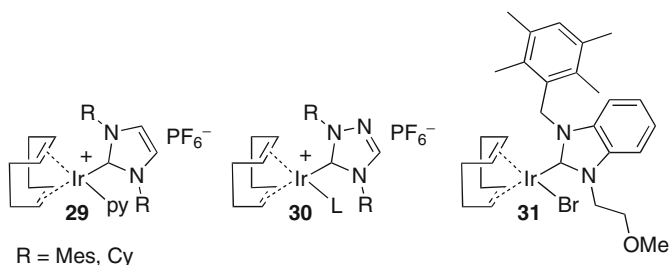


Fig. 2.7 Selected NHC complexes that have been studied as transfer hydrogenation catalysts

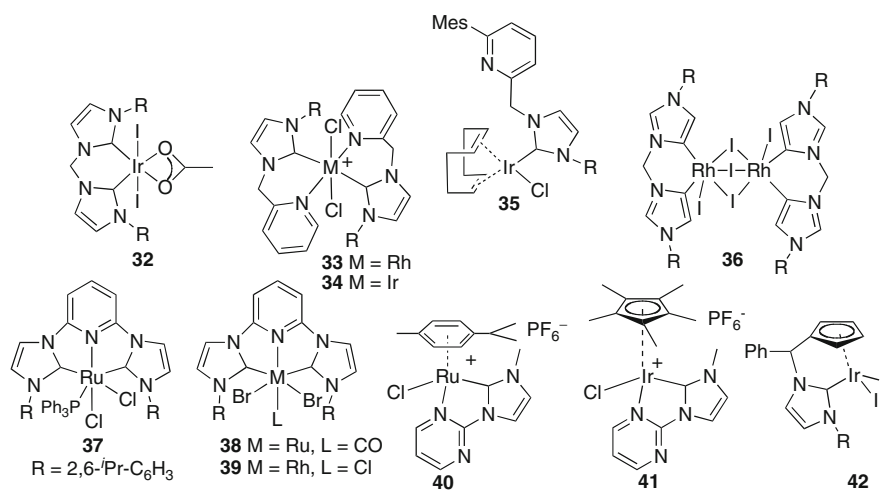


Fig. 2.8 Selected NHC complexes that have been studied as transfer hydrogenation catalysts

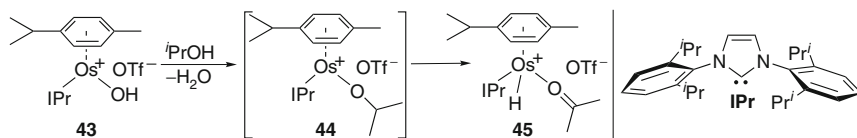
Table 2.1 Selected transfer hydrogenation data of R¹R²C=O, R¹= alkyl, phenyl, R²= alkyl, H or Ph. All reactions were carried out in refluxing *i*PrOH (82°C)

R ¹	R ²	Complex (mol%)	Base (subst./base)	Time (h)	Conv. (%)	Ref
Ph, Ar	Me	32 (0.01)	KOH (2000/1)	2	98	[31]
<i>p</i> -tolyl	H	32 (0.1)	K ₂ CO ₃ (2:1)	0.25	98	[38]
Ph	Me	40/41 (1.0)	KOH (10:1)	3	98	[28]
Ph	Me	37 (0.015)	KO ^t Bu (10:1)	12	80	[29]
Ph	Me	39 (0.006)	KOH (2:1)	6	30	[30]
Ph	Me	31 (0.5)	KOH (20:1)	1.5	98	[35]
Me	Bu ⁿ	32 (0.1)	KOH (200:1)	24	88	[42]
-(CH ₂) ₅ -		38 (0.005)	KOH (2:1)	20	65	[30]
-(CH ₂) ₅ -		41 (0.1)	KOH (1:1)	4.5	99	[28]
-(CH ₂) ₅ -		40 (1.0)	KOH (10:1)	5	99	[28]
-(CH ₂) ₅ -		31 (0.5)	KOH (20:1)	2	98	[28]
Ph	Ph	36 (0.5)	KOH (10:1)	2	97	[36]
Ph	Ph	39 (0.006)	KOH (2:1)	24	98	[30]
Ph	Ph	34 (0.1)	KOH (2:1)	2	99	[32]

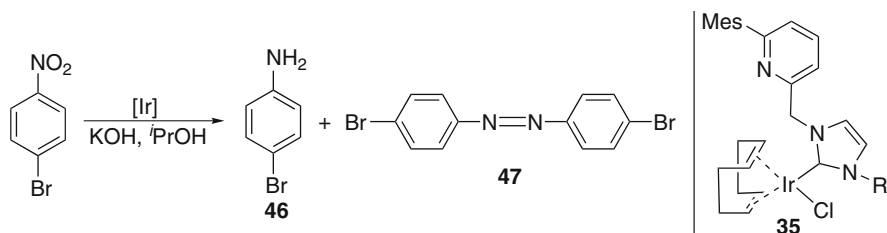
Table 2.2 Transfer hydrogenation of *N*-benzylidene aniline. Solvent is ^tPrOH

Complex (mol%)	Base (base:substr.)	T (°C)	Time (h)	Conv. (%)	Ref
37 (0.015)	K ^t OBu (10:1)	55	20	60–70	[29]
30 (1.0)	K ₂ CO ₃ (2:1)	82	0.5	92–100	[27]
40 (1.0)	KOH (10:1)	82	5	70–80	[28]

Transfer hydrogenation of aldehydes with isopropanol without addition of external base has been achieved using the electronically and coordinatively unsaturated Os complex **43** as catalyst. High turnover frequencies have been observed with aldehyde substrates, however the catalyst was very poor for the hydrogenation of ketones. The stoichiometric conversion of **43** to the spectroscopically identifiable in solution ketone complex **45**, via the non-isolable complex **44** (Scheme 2.4), provides evidence for two steps of the operating mechanism (alkoxide exchange, β-hydride elimination to form ketone hydride complex) of the transfer hydrogenation reaction [43].

**Scheme 2.4** Experimental evidence in support of the mechanism for the base-free transfer hydrogenation of carbonyl compounds catalysed by complex **43**

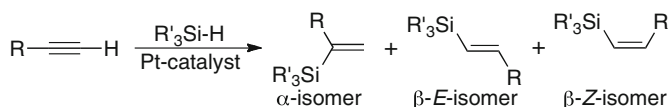
The iridium complex **35** has been also used as catalyst for the transfer hydrogenation of substituted nitroarenes [34]. Good to very good conversions were observed (2.5 mol%, in refluxing isopropanol, 12 h). A mixture of two products was obtained, the relative ratio of which depends on the concentration of added base (KOH) and catalyst. (Scheme 2.5)

**Scheme 2.5** Products formed in the transfer hydrogenation reduction of nitroarenes by complex **35**

This behaviour was rationalised by a stepwise reduction mechanism, in which a high catalyst or KOH concentration gives a high hydride concentration and leads to the aniline formation and suppression of intermolecular reactions to the dimeric azo-compound.

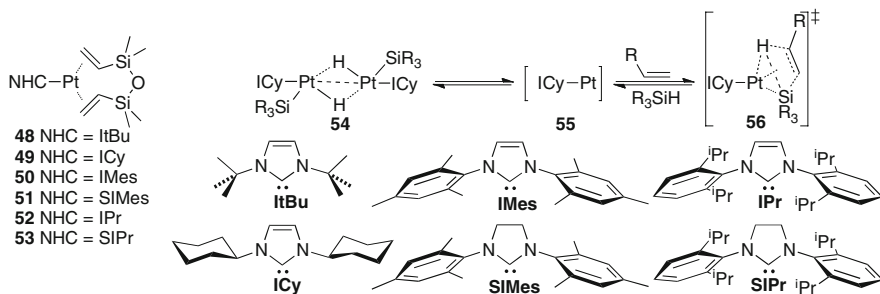
2.4 Hydrosilylation Reactions

The hydrosi(ly)lations of alkenes and alkynes are very important catalytic processes for the synthesis of alkyl- and alkenyl-silanes, respectively, which can be further transformed into aldehydes, ketones or alcohols by established stoichiometric organic transformations, or used as nucleophiles in cross-coupling reactions. Hydrosilylation is also used for the derivatisation of Si containing polymers. The drawbacks of the most widespread hydrosilylation catalysts [the Speier's system, $\text{H}_2\text{PtCl}_6/\text{PrOH}$, and Karstedt's complex $[\text{Pt}_2(\text{divinyl-disiloxane})_3]$ include the formation of side-products, in addition to the desired *anti*-Markovnikov Si-H addition product. In the hydrosilylation of alkynes, formation of di-silanes (by competing further reaction of the product alkenyl-silane) and of geometrical isomers (α -isomer from the Markovnikov addition and *Z*- β and *E*- β from the *anti*-Markovnikov addition, Scheme 2.6) are also possible.



Scheme 2.6 Possible isomeric products in the hydrosilylation of alkynes (disilanes from further hydrosilylation of the alkenyl silanes are excluded)

Therefore, improved chemo- and stereo-selectivities of the catalysts are challenging goals of current research in the area. The reduced chemoselectivity and the formation of side-products with the Speier and Karstedt catalysts is attributed to poor catalyst stability under the reaction conditions, and efforts to improve it have focused on the use of NHC ligand designs, taking advantage of the high strength of the $\text{Pt}-\text{C}_{\text{NHC}}$ bond.



Scheme 2.7 Platinum-NHC complexes as hydrosilylation catalysts

Complexes of the type **48–53** (Scheme 2.7) have been targeted as pre-catalysts for the hydrosilylation of alkenes [44]. For example, in the hydrosilylation of 1-octene with $(\text{Me}_3\text{SiO})_2\text{Si}(\text{Me})\text{H}$, which was studied in detail as a model reaction, the activity of complexes **48–49** with alkyl substituted NHC ligands, is inferior to that of the Karstedt's system. However, selectivity and conversions are dramatically improved due to the suppression of side-product formation. In this reaction

only the *anti*-Markovnikov addition product is observed. The complexes **50–52** with bulky aryl substituted NHCs, show activity comparable to that of the Karstedt's complex with excellent chemo- and regio-selectivity, even though they exhibit variable induction periods. The higher activity is attributed to electronic factors and the steric organisation around the Pt imposed by the ligand; the induction period is possibly due to slow diene dissociation from the pre-catalysts to form the 'underligated' 'Pt-NHC' active species. Further insight into the nature of the catalytic species was obtained by the reaction of **49** with excess silane, leading to the isolation of **54**, which was fully characterised; **54** converts to the active monomeric catalyst **55** by cleavage of the weakly bound dimer and loss of silane. Based on kinetic data, the reaction of **54** with alkene and silane is more likely to proceed *via* the concerted transition state **56** rather than two distinct oxidative addition and insertion elementary steps. Hydrosilylation of styrene with Et₃SiH catalysed by **51** (formed *in situ* from Pt(norbornene)₃ and SiMes-HCl/KO^tBu) also gave excellent conversions (~99%) with high selectivity (*ca.* 82%) to the *anti*-Markovnikov product [45].

The hydrosilylation of alkynes has also been studied using as catalysts Pt, Rh, Ir and Ni complexes. The improvement of the regioselectivity of the catalyst and the understanding of stereoelectronic factors that control it have been major incentives for the ongoing research. From numerous studies involving non-NHC catalysts, it has been established that there is a complex dependence of the product ratio on the type of metal, the alkyne, the metal coordination sphere, the charge (cationic *versus* neutral) of the catalytic complex and the reaction conditions. In the Speier's and Karstedt's systems, mixtures of the thermodynamically more stable α - and β -*E*-isomers are observed. Bulky phosphine ligands have been used on many occasions in order to obtain selectively β -*E*-isomers.

The Pt complexes **48–53** mentioned previously are pre-catalysts for the hydrosilylation of 1-octyne with bis-(trimethylsilyloxy)methylsilane and other silanes [46]. Complexes **52** and **53** provide good conversions at very low loading (0.005 mol%) with high selectivity (10:1) for the β -*E*-isomer. Further studies have pointed to the steric influence of the *o*-groups of the aryl substituents of the NHC as being responsible for the high stereoselectivity. The linear correlation of the A_H angle (see Chapter 1, Fig. 1.16) of the NHC with the observed β -*E*/ α - ratio (larger A_H angles in more selective catalysts) was explained by the steric interactions between the out-of-the-coordination-plane aryl substituents of the NHC with the alkyne substituents prior to the insertion step. In addition to steric interactions, electronic factors are also responsible for the improved stereoselectivity.

The Rh and Ir complexes **57–62** (Fig. 2.9) with functionalised *N*-heterocyclic carbene ligands are also catalyst precursors for the hydrosilylation of alkynes. For example, terminal alkynes were hydrosilylated with HSi(Me)₂Ph in the presence of **57** or **58**, yielding very good conversions to mixtures of the three possible stereoisomers, with preference for the β -*E*-isomer. A more detailed study of the catalytic reaction profile using **58** showed that the β -*Z*-isomer was formed during the initial stages of the reaction, and later isomerised to the thermodynamically more stable *E*-isomer. Interestingly, hydrosilylations with HSi(OEt)₃ showed preference for the β -*Z*-isomer, without any tendency for isomerisation. Rationalisation of these data is further complicated by the ambiguous nuclearity of the active catalysts originating

from **58** and the exact coordination sphere of the active species [47]. On the other hand, reactions catalysed by the cationic **57** gave from the outset the β -*E*-isomer.

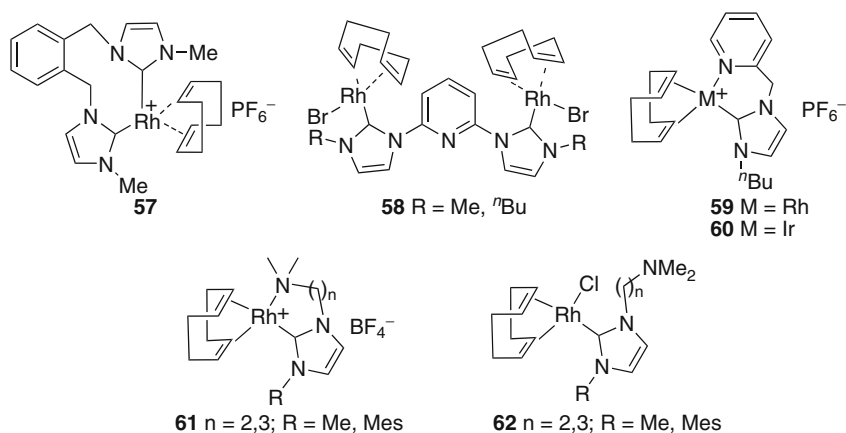
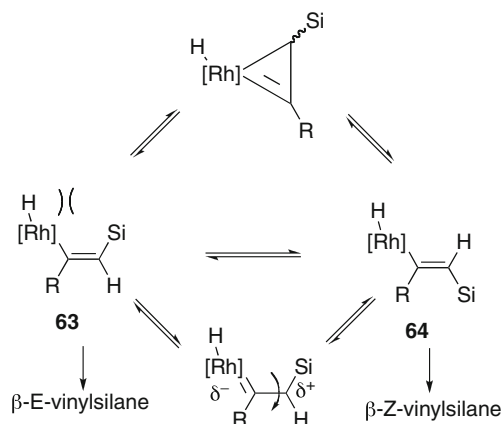


Fig. 2.9 Hydrosilylation catalysts based on Rh- and Ir-NHC complexes

Complexes **59** and **60** catalyse the hydrosilylation of phenylacetylene (but not other terminal alkyl alkynes) with $\text{HSi}(\text{Me})_2\text{Ph}$. Generally, the Rh analogue is more active than the relative Ir. Both catalysts gave mixtures of all regioisomers, with a preference for the β -*Z*-isomer, in contrast to what has been reported with other non-NHC cationic complexes of Rh, where the β -*E* isomers are predominating. Here also the exact nature of the catalytic species is unclear [48].

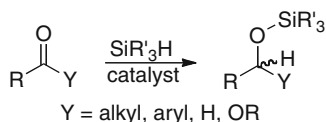
Complexes **61** and **62** have been used for the hydrosilylation of a range of terminal alkynes with $\text{HSi}(\text{Me})_2\text{Ph}$. The product distribution is strongly dependent on the nature of the alkyne and the catalyst. In general, catalysts with less bulky NHC ligands are more active. With terminal alkynes substituted with small linear alkyls (e.g. 1-hexyne), high conversions under mild conditions were obtained, and in some cases very good selectivities for the β -*Z*-vinylsilane. In contrast, the hydrosilylations of $\text{Et}_3\text{SiC}\equiv\text{CH}$ gave predominantly the β -*E*-vinylsilane. These data have been rationalised by postulating the classical Chalk-Harrod hydrosilylation mechanism (Si-H oxidative addition followed by alkyne insertion into the M-Si bond to give intermediate **63** and reductive elimination to the product β -*E*-vinylsilane). Isomerisation of **63**–**64** followed by reductive elimination leads to the β -*Z*-isomer. With small alkyls on the alkyne-C (for example in 1-hexyne), intermediate **64** is favoured due to reduced Rh–SiR₃ interaction leading to product β -*Z*. Larger alkyls on the alkyne-C result in reduced selectivities due to the establishment of an equilibrium between **63** and **64**. On the other hand, in the hydrosilylation of $\text{Et}_3\text{SiC}\equiv\text{CH}$, electronic factors are more important in determining the stability of **63** relative to **64** leading to substantial amounts of β -*E*-vinylsilane (Scheme 2.8) [49].



Scheme 2.8 Rationalisation of the selectivity observed in the hydrosilylation of alkynes by the complexes **61** and **62**

Nickel complexes formed *in situ* by the reaction of $\text{Ni}(\text{1,5-COD})_2$ with the imidazolium salts $\text{IMes}\cdot\text{HCl}$ or $\text{IPr}\cdot\text{HCl}$ in the presence KO^tBu catalyse the hydrosilylation of internal or terminal alkynes with Et_3SiH . Interestingly, Ni tri-butylphosphine complexes are inactive in this hydrosilylation reaction. The monosilylated addition products were obtained with slow addition rates of the alkyne in the reaction mixture and were formed with variable degree of stereoselectivity, depending on the type of the alkyne, the silane and the ligand on Ni [50].

The catalytic hydrosilylation of other $\text{C}=\text{X}$ functional groups ($\text{X} = \text{O}, \text{NR}$) constitute alternative routes to the reduction of aldehydes, ketones, imines and other carbonyl compounds (Scheme 2.9), circumventing the use of molecular hydrogen or occasionally harsh transfer hydrogenation conditions.



Scheme 2.9 Hydrosilylation of carbonyl compounds to silyl ethers

The hydrosilylation of carbonyl compounds by Et_3SiH catalysed by the copper NHC complexes **65** and **66–67** constitutes a convenient method for the direct synthesis of silyl-protected alcohols (silyl ethers). The catalysts can be generated *in situ* from the corresponding imidazolium salts, base and CuCl or $[\text{Cu}(\text{MeCN})_4]\text{X}^-$, respectively. The catalytic reactions usually occur at room temperature in THF with very good conversions and exhibit good functional group tolerance. Complex **66**, which is more active than **65**, allows the reactions to be run under lower silane loadings and is preferred for the hydrosilylation of hindered ketones. The wide scope of application of the copper catalyst [dialkyl-, arylalkyl-ketones, aldehydes (even enolisable) and esters] is evident from some examples compiled in Table 2.3 [51–53].

Table 2.3 Selected data for the hydrosilylation of $R^1YC=O$, R^1 = alkyl, phenyl, Y = alkyl, H or OEt

R^1	Y	Catalyst (3 mol%)	Silane (Si:substrate)	Base (mol%)	T ($^{\circ}C$)	t (h)	Conv. (%)	Ref
$-(CH_2)_5-$		IPr-HBF ₄ /CuCl	HSiEt ₃ (5:1)	NaO ^t Bu (20%)	rt	2	99	[33]
$-(CH_2)_5-$		65	HSiEt ₃ (3:1)	NaO ^t Bu (6–12%)	rt	0.75	100	[33]
$-(CH_2)_5-$		66	HSiEt ₃ (2:1)	NaO ^t Bu (12%)	rt	0.5	95	[32]
Me	Et	IPr-HBF ₄ /CuCl	HSiEt ₃ (5:1)	NaO ^t Bu (20%)	rt	4	96	[33]
Ph	Me	IPr-HBF ₄ /CuCl	HSiEt ₃ (5:1)	NaO ^t Bu (20%)	rt	3	99	[33]
Ph	Me	65	HSiEt ₃ (3:1)	NaO ^t Bu (6–12%)	rt	3	98	[33]
Ph	Me	66	HSiEt ₃ (2:1)	NaO ^t Bu (12%)	rt	4	98	[32]
ⁱ Pr	ⁱ Pr	66	HSiEt ₃ (2:1)	NaO ^t Bu (12%)	rt	0.3	94	[32]
<i>p</i> -tolyl	H	66	HSiEt ₃ (2:1)	NaO ^t Bu (12%)	rt	0.3	92	[32]
C ₆ H ₁₁	H	66	HSiEt ₃ (2:1)	NaO ^t Bu (12%)	rt	0.6	70	[32]
Benzyl	OEt	66	HSiEt ₃ (2:1)	NaO ^t Bu (12%)	55	6	69	[32]

The proposed mechanism of the catalytic reaction involves the formation of the Cu(I) alkoxide **68** by displacement of either the chloride or the NHC from **65–67**, followed by conversion to the hydride **69** by metathetical exchange of the *tert*-butoxide by the H of the silane (Fig. 2.10).

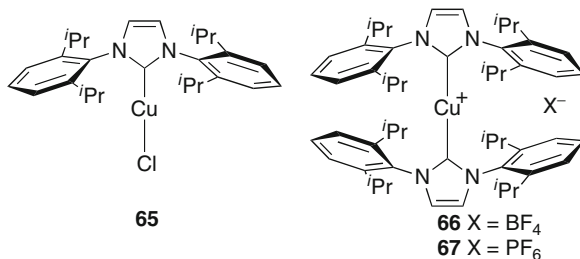
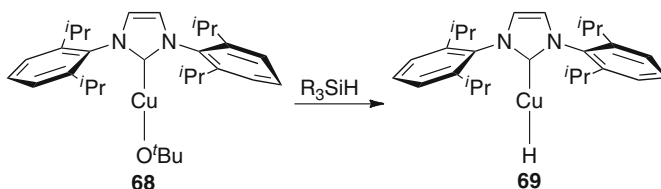


Fig. 2.10 Hydrosilylation catalysts of carbonyl compounds based on Cu-NHC complexes

Transfer of the hydride from the Cu to the electrophilic carbon and cleavage of the copper alkoxide by the silane regenerates **69**. Recent reports point to the influence of the type of the counter ion X[−] of the homoleptic **66–67** on the activity, the BF₄[−] being superior to the PF₆[−] analogue; this effect has been attributed to differences in the rate of active catalyst generation from the homoleptic [Cu(NHC)₂]⁺X[−] and NaO^tBu due to solubility differences of the inorganic salts formed during the displacement of the NHC by ^tBuO[−] [54] (Scheme 2.10).



Scheme 2.10 Intermediates in the Cu-catalysed hydrosilylation of carbonyl compounds

The Rh-catalysed asymmetric hydrosilylation of prochiral ketones has been studied with complexes bearing monodentate or heteroatom functionalised NHC ligands. For example, complexes of the type [RhCl(1,5-cod)(NHC)] and [RhL(1,5-cod)(NHC)][SbF₆[−]], **70**, where L = isoquinoline, 3,5-lutidine and NHC are the chiral monodentate ligands **71** (Fig. 2.11).

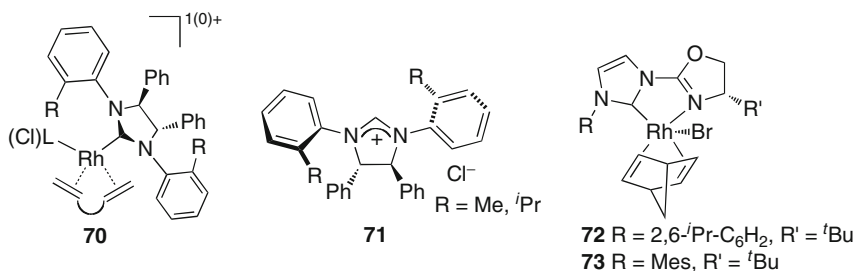


Fig. 2.11 Chiral ligand designs in Rh catalysts for the enantioselective hydrosilylation of carbonyl compounds

X-ray crystallography and variable temperature ^1H NMR studies show that the conformation of the coordinated imidazolidin-2-ylidene, in both the neutral and cationic complexes **70**, is *anti, anti* with respect to the Ph of the backbone of the NHC, exclusively in the solid state and predominantly in solution at lower temperatures (-75°C). At room temperature in solution, possible conformer interconversion by the rotation around the phenyl-N bond of the NHC substituent is apparent from the broadness of the peaks in the NMR spectra. Hydrosilylation of acetophenone by Ph_2SiH_2 catalysed by **70** at room temperature or at -20°C results in maximum *ee* of 58%. However, at lower temperatures the reaction rates are much slower [55].

NHC complexes of Rh functionalised with chiral oxazoline ligands, for example **72** and **73**, have been developed as pre-catalysts for the enantioselective hydrosilylation of ketones. After abstraction of the Br from **72–73** with silver reagents, the cationic complexes obtained were employed for the hydrosilylation of prochiral ketones with various silanes. The conversions and enantioselectivities observed were dependent on the nature of the R and R' groups of the ligand, the silane and reaction conditions. Higher enantioselectivities for the hydrosilylation of acetophenone to 1-phenyl-ethanol were observed with bulky silanes [Ph_2SiH_2 , (*p*-tolyl) $_2\text{SiH}_2$] at the optimum temperature (-60°C); both higher or lower temperatures had a detrimental effect on the *ee* observed. This nonlinear temperature dependence of the *ee* has been interpreted by assuming two enantioselectivity determining steps in the catalytic reaction, one possibly involving the reversible coordination of the prochiral ketone onto Rh and the other the migratory insertion of the coordinated ketone into the Rh–Si bond, that can become rate-determining. Under optimised conditions acetophenone was reduced at 92% yield, with very good *ee* (90%), while other methyl-*n*-alkyl ketones were reduced at good asymmetric induction (65–80% *ee*) depending on the ketone [56]. Interestingly, introduction of a methylene spacer between the NHC and the chiral oxazoline in **72–73** results in catalysts that show disappointing chiral induction [57].

2.5 Hydroboration and Diboration Reactions

The metal catalysed hydroboration and diboration of alkenes and alkynes (addition of H–B and B–B bonds, respectively) gives rise to alkyl- or alkenyl-boronate or diboronate esters, which are important intermediates for further catalytic transformations, or can be converted to useful organic compounds by established stoichiometric methodologies. The *syn*-diboration of alkynes catalysed by Pt phosphine complexes is well-established [58]. However, in alkene diborations, challenging problems of chemo- and stereo-selectivity control still need to be solved, with the most successful current systems being based on Pt, Rh and Au complexes [59–61]. There have been some recent advances in the area by using NHC complexes of Ir, Pd, Pt, Cu, Ag and Au as catalysts under mild conditions, which present important advantages in terms of activity and selectivity over the established catalysts.

The Ag complex **74** catalyses the diboration of internal and terminal alkenes to 1,2-bis-diboronate esters by bis(catecholato)diboron, (Bcat)₂, in THF at room temperature. Variable conversions (30–90%) were obtained at 5 mol% loading after 60 h.

Terminal alkenes with electron-rich substituents (Ph, Cy) gave the highest conversions. This reaction represents the first example of a Ag-NHC complex catalysed reaction. The choice of silver was rationalised based on the mechanism of diboration, which involves the insertion of the electron rich metal centre into the B–B bond, followed by the alkene insertion and the release of the mono- or di-boronated organic products. The electron rich Ag^I with low energy d orbitals minimises π -alkene bonding and, therefore, β -H elimination is suppressed, resulting in inhibition of vinyl boronates formation. It is interesting to note that although **74** is chiral, it does not induce any enantioselectivity in the diboration reactions of prochiral substrates [62].

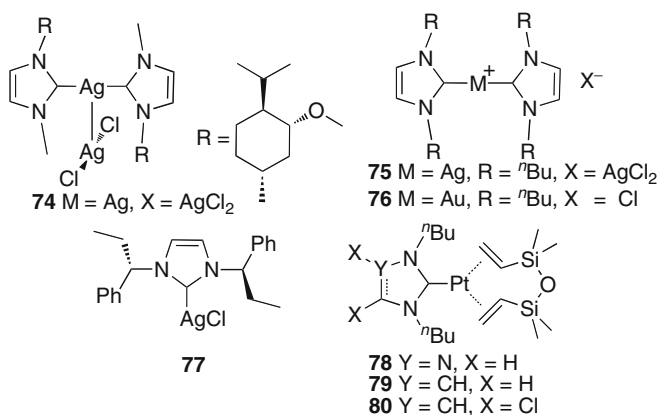


Fig. 2.12 Silver, gold and platinum complexes with monodentate NHC ligands as catalysts for the diboration of alkenes and alkynes

Diboration of terminal alkenes has also been studied with other d¹⁰ metals (Fig. 2.12) including the Ag^I and Au^I complexes **75–77** and the Pt⁰ complexes **78–79**. Styrene is diborylated with 100% selectivity and good conversions in THF (46% for **75** and 94% for **77** at 5 mol%, 60 h) using equimolecular amounts of (Bcat)₂. The difference in activity between the Ag and Au complexes has been ascribed to the increased lability of the Ag–NHC bond, which may lead to catalyst decomposition under the reaction conditions. In both catalytic systems it is believed that the active species involves only one coordinated NHC ligand. Complex **77** is less active than **74** and **75**, possibly due to steric reasons. The enantioselectivity of **77** in the diboration of prochiral alkenes is very low [63].

Diboration of terminal and internal alkynes by (Bcat)₂ [B(cat)₂:alkyne = 1:1] was also achieved by using complexes **78** and **79** at room temperature in THF. Best activity was observed with **78** containing the less electron donating triazolylidene carbene ligand. Terminal alkenes can also be diborylated under the same conditions, however the selectivity for the diborylated product was much lower (up to 65%) [64].

The palladium (II) NHC complexes **81** and **82** (Fig. 2.13) have also been used as catalysts in the diboration of styrene. In the presence of NaOOCCH₃ (1 equiv.,

5 mol% catalyst, in THF at rt), excellent conversions were obtained when $(\text{Bcat})_2$ was the boron source. Selectivities were also high for the diborylated product when excess of $(\text{Bcat})_2$ was used [$(\text{Bcat})_2$:styrene 3:1]. Other terminal and internal alkenes were also diborylated in high yields and selectivities under the same conditions. A mechanism involving metathetical Pd–B bond formation (without change of the oxidation state) may be operating. However, an involvement of $\text{Pd}^{\text{II}}/\text{Pd}^{\text{IV}}$ species, formed by oxidative addition of B–B to a cationic Pd^{II} and formation of an NHC stabilised Pd^{IV} -boryl complex, is also plausible. In the presence of base (NaOAc), the mechanism could involve transmetalation, and in this case interaction of the boron entering group with the base giving borate species may increase its nucleophilicity and facilitate the Pd–B(cat) bond formation. DFT and *in situ* ^{11}B NMR experiments support these mechanistic models [65].

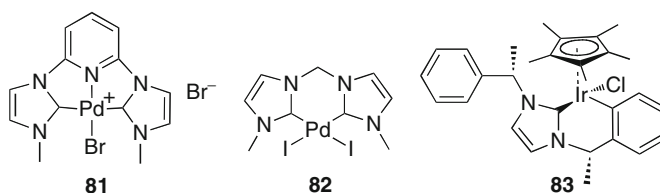


Fig. 2.13 Diboration catalysts based on palladium and iridium NHC complexes

The Ir complexes **83** or $[\text{Ir}(\text{IMes})\text{Cl}_2\text{Cp}^*]$, in the presence of NaOAc and excess of $(\text{Bcat})_2$, catalyse the diboration of styrene, at high conversions and selectivities for the diborated species, under mild conditions. Other terminal alkenes react similarly. The base is believed to assist the heterolytic cleavage of the $(\text{cat})\text{B}-\text{B}(\text{cat})$ bond and the formation of $\text{Ir}-\text{B}(\text{cat})$ species, without the need of B–B oxidative addition [66].

The stoichiometric insertion of terminal alkenes into the Cu–B bond of the $(\text{NHC})\text{Cu}-\text{B}(\text{cat})$ complex, and the isolation and full characterisation of the β -boryl-alkyl-copper (I) complex has been reported. The alkyl complex decomposes at higher temperatures by β -H elimination to vinylboronate ester [67]. These data provide experimental evidence for a mechanism involving insertion of alkenes into Cu–boryl bonds, and establish a versatile and inexpensive catalytic system of wide scope for the diboration of alkenes and alkynes based on copper.

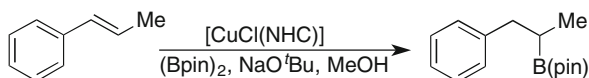
The complexes $[\text{Cu}(\text{NHC})(\text{MeCN})][\text{BF}_4]$, $\text{NHC} = \text{IPr}$, SIPr , IMes , catalyse the diboration of styrene with $(\text{Bcat})_2$ in high conversions (5 mol%, THF, rt or reflux). The $(\text{Bcat})_2$ /styrene ratio has also an important effect on chemoselectivity (mono-*versus* di-substituted borylated species). Use of equimolecular ratios or excess of $\text{B}(\text{cat})_2$ results in the diborylated product, while higher alkene: $\text{B}(\text{cat})_2$ ratios lead selectively to mono-borylated species. Alkynes (phenylacetylene, diphenylacetylene) are converted selectively (90–95%) to the *cis*-di-borylated products under the same conditions. The mechanism of the reaction possibly involves σ -bond metathetical reactions, but no oxidative addition at the copper. This mechanistic model was supported by DFT calculations [68].

Platinum mediated regioselective H–B addition of $\text{H}-\text{B}(\text{cat})$ to vinyl arenes and alkynes has been realised using the complexes **79** and **80** (Fig. 2.12). The reactions

with vinyl arenes proceed at rt in THF (0.05 mol%) giving high conversions (80–100%) of mixtures of alkyl or alkenyl boranes, with predominantly branched product (70–90%). Interestingly, the activity of the catalytic system is maintained days after the completion of the reaction, while addition of PPh_3 into the catalytically active system retards or deactivates it. Aryl alkynes are hydroborated selectively to the mono-borylated product, with higher selectivity to the linear alkenyl borane. The addition of aryl iodides into the catalytic system results in the cross coupling of the *in situ* formed alkenyl boranes with the aryl iodide in one pot, giving alkenyl arenes [69].

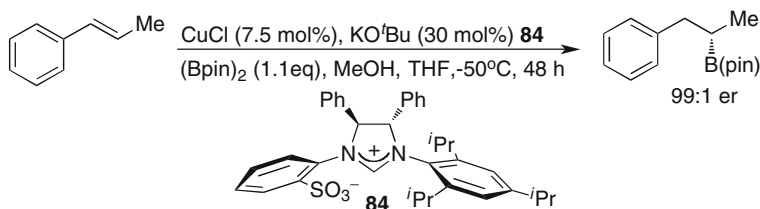
In an attempt to study the electronic effects of the substituents in the four- and five-positions of the coordinated imidazol-2-ylidene on the $\text{M}-\text{C}_{\text{NHC}}$ bonding, and the related catalytic reactivity, the complexes $[\text{RhCl}(1,5\text{-COD})(\text{NHC})]$, where NHC is imidazol-2-ylidene substituted in the four- or five-positions with the σ - or π -electron withdrawing groups $-\text{CF}_3$, $-\text{Cl}$, $-\text{NO}_2$ and $-\text{CN}$, were used as catalysts in the hydroboration of alkynes with $\text{HB}(\text{pin})$. In the hydroboration of phenylacetylene, it was found that complexes with ligands bearing π -electron withdrawing groups in the four- and/or five-position of the imidazolylidene, were affording lower yields of products than the ones with σ -electron withdrawing groups. These data have been interpreted as an indication that π -interactions between the coordinated NHC with a metal exist, a fact that was disputed in the early era of the NHC ligand development, and may have important implications in catalyst design [70]. However, in the hydroboration of 1-octyne no effect was observed.

Hydroboration of acyclic and cyclic aryl alkenes with $(\text{Bpin})_2$ (1.1 equiv.) in the presence of NaO^tBu (1–100 mol%) and MeOH (2 equiv.) is catalysed by $[\text{CuCl}(\text{NHC})]$, (0.5–5 mol%) $\text{NHC} = \text{IMes}$, SIMes and ICy , and proceeds with very good conversions and regioselectivity (Scheme 2.11).



Scheme 2.11 Hydroboration of arylalkenes catalysed by copper NHC complexes

This regioselectivity is opposite to the one observed by the non-catalysed additions of $\text{BH}_3 \cdot \text{THF}$ or 9-BBN to the same alkene, or those catalysed by Rh and Ir catalysts. Chiral NHC ligands (generated from **84**) on Cu under the same conditions proceed with high enantioselectivity (enantiomeric ratio 99:1) [71] (Scheme 2.12).



Scheme 2.12 Enantioselective hydroboration of arylalkenes catalysed by copper NHC complexes

2.6 Hydroamination Reactions

Intermolecular and intramolecular hydroamination of alkenes and alkynes is an atom economical method for the synthesis of a range of acyclic and cyclic alk(en)ylamines from simpler amine precursors. The reaction can be catalysed by either electropositive (main group metals, early transition metals and lanthanides-actinides) or late transition metals, under different mechanistic regimes. The relatively facile intramolecular hydroamination of alkynes and allenes is more ubiquitous and commonly studied. Intermolecular hydroamination of alkenes is more challenging and examples with activated, electron-deficient alkenes have recently appeared. Control of regioselectivity (Markovnikov, *anti*-Markovnikov) and suppression of competing side-reactions (alkene isomerisation, oligomerisation, etc.) in addition to high activity, especially when expensive late transition metals are used as catalysts, are important features of the catalyst development [72, 73]. NHC complexes with both electropositive and late transition metals have been studied as alkene and alkyne hydroamination catalysts.

A catalytic system comprising $\text{Ti}(\text{NMe}_2)_4$, $\text{LiN}(\text{SiMe}_3)_2$ and IMes has been developed for the intermolecular hydroamination of terminal aliphatic alkynes (1-hexyne, 1-octyne, etc.) with anilines [toluene, 100°C , 10 mol% $\text{Ti}(\text{NMe}_2)_4$]. Markovnikov products were dominant. Substituted anilines reacted similarly. High conversions (85–95%) were observed with specific anilines. The optimum $\text{Ti}/\text{IMes}/\text{LiN}(\text{SiMe}_3)_2$ ratio was 1:2:1. However, the nature of the active species and especially the role of $\text{LiN}(\text{SiMe}_3)_2$ are unclear [74].

The Rh and Ir complexes **85–88** (Fig. 2.14) have been tested for the intramolecular hydroamination/cyclisation of 4-pentyn-1-amine to 2-methyl-1-pyrroline ($n = 1$). The reactions were carried out at 60°C (1–1.5 mol%) in THF or CDCl_3 . The analogous rhodium systems were more active. Furthermore, the activity of **87** is higher than **85** under the same conditions, which was attributed to the hemilability of the P donor in the former complex, or to differences in the *trans*-effects of the phosphine and NHC ligands, which may increase the lability of the coordinated CO in the pre-catalyst [75, 76].

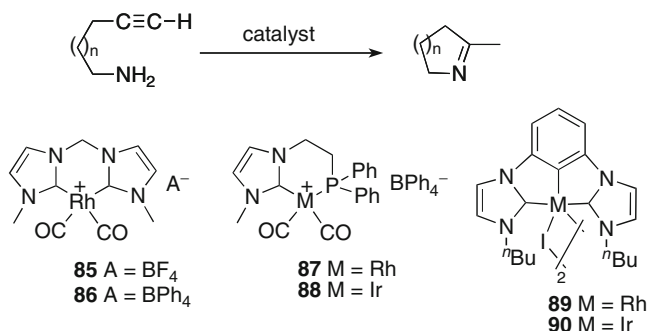


Fig. 2.14 Rhodium and iridium catalysts for the intramolecular hydroamination of alkynes

The ‘pincer’ complexes **89–90** (Fig. 2.14) catalyse the intramolecular hydroamination/cyclisation of unactivated alkenes, yielding pyrrolidines and piperidines ($n = 1, 2$, respectively). The reactions can be carried out in benzene or water with high

conversions (>95% at 2.5 mol% at 110°C, overnight). Rh and Ir catalysts show very similar activity without competing alkene isomerisation. Interestingly, no reaction was observed with primary amines. The reaction mechanism may involve metal-amido bond formation followed by alkene insertion and reductive elimination, or π -coordination of the alkene followed by nucleophilic attack on the activated coordinated alkene [77, 78].

Hydroamination of activated alkenes has been reported with complexes **91–93** (Fig. 2.15). For example, **91** catalyses the hydroamination of methacrylonitrile (X = CN in Scheme 2.13) by a range of secondary amines (morpholine, thiomorpholine, piperidine, *N*-methylpiperazine or aniline) in good to excellent conversions (67–99%) and *anti*-Markovnikov regioselectivity (5 mol%, –80°C or rt, 24–72 h). Low enantioselectivities were induced (*ee* 30–50%) depending on the amine used and the reaction temperature [79].

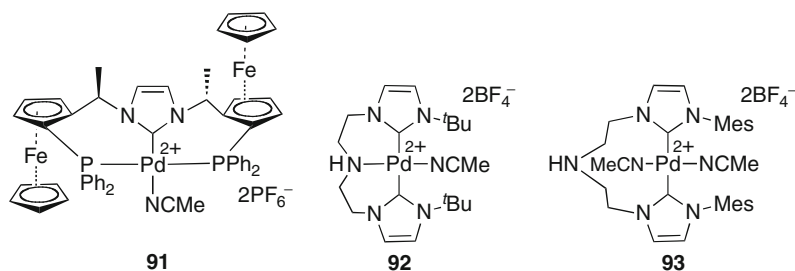
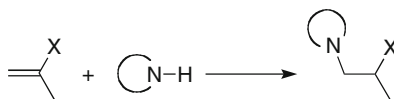


Fig. 2.15 Hydroamination catalysts based on palladium NHC complexes

Complexes **92** and **93** also show good activity for the hydroamination of methacrylonitrile with morpholine, piperidine or *N*-methylpiperazine (70–93% conversion at 2.5 mol%, 90°C in 24 h) [80].



Scheme 2.13 Intermolecular hydroamination of activated alkenes

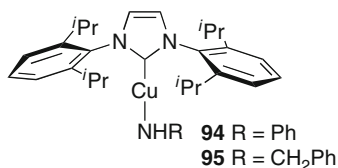
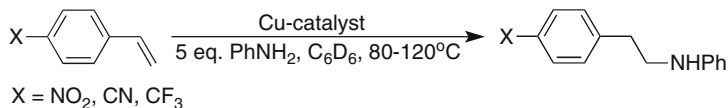


Fig. 2.16 Copper-amido complexes as catalysts for the intermolecular hydroamination of electron-deficient alkenes

The well-defined copper complexes **94** and **95** (Fig. 2.16) have been used as catalysts for the intermolecular hydroamination of electron-deficient alkenes [Michael acceptors, X = CN, C(=O)Me, C(=O)(OMe)] and vinyl arenes substituted

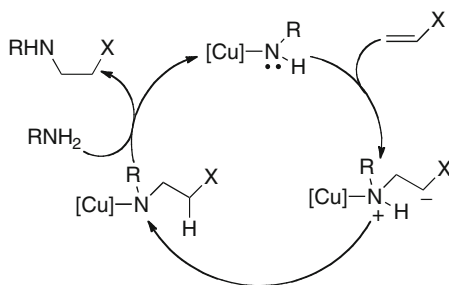
by the electron-withdrawing groups NO_2 , CN , CF_3 but not Cl , Br or H (Schemes 2.13 and 2.14).



Scheme 2.14 Copper-catalysed intermolecular hydroamination of electron-deficient aryl alkenes

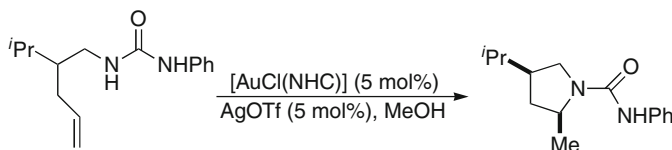
The hydroaminations of electron-deficient alkenes with aniline or small primary alkylamines proceed at high conversions (85–95%, under mild conditions, 5 mol%, rt), giving exclusively the *anti*-Markovnikov addition product. Secondary dialkyl or bulky primary amines require longer reaction times. With amines containing β -hydrogens, no imine side-products were observed.

The proposed reaction mechanism involves intermolecular nucleophilic addition of the amido ligand to the olefin to produce a zwitterionic intermediate, followed by proton transfer to form a new copper amido complex. Reaction with additional amine (presumably *via* coordination to Cu) yields the hydroamination product and regenerates the original copper catalyst (Scheme 2.15). In addition to the NHC complexes **94** and **95**, copper amido complexes with the chelating diphosphine 1,2-bis-(di-*tert*-butylphosphino)-ethane also catalyse the reaction [81, 82].



Scheme 2.15 Postulated mechanism for the copper-catalysed hydroamination of electron-deficient alkenes

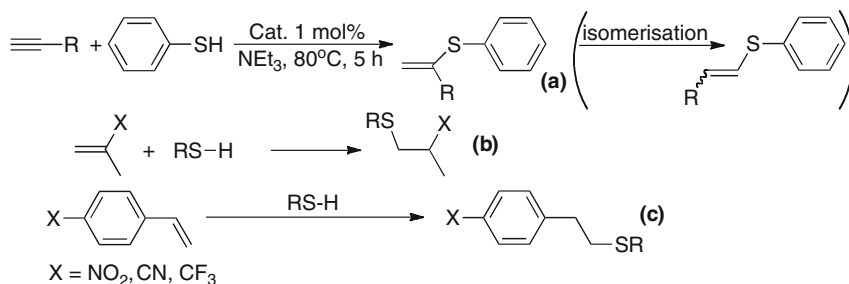
Finally, intramolecular hydroamination/cyclisation of *N*-alkenyl ureas was catalysed by the well-defined $[\text{AuCl}(\text{IPr})]$ complex (Scheme 2.16), in the presence of AgOTf (5 mol%, rt, methanol, 22 h). The cationic $\text{Au}(\text{IPr})^+$ is presumably the active species [83].



Scheme 2.16 Gold-catalysed intramolecular hydroamination of alkenes

2.7 Hydrothiolation, Hydroalkoxylation and Hydroaryloxylation Reactions

Hydrothiolations (addition of H–SR across the CC multiple bond) of alkynes, electron-deficient alkenes and electron-deficient vinyl arenes have been catalysed by NHC complexes of Ni and Cu, respectively [Scheme 2.17a–c].



Scheme 2.17 Product formation in the hydrothiolation of alkynes and alkenes

The hydrothiolation of terminal alkyl alkynes with **96** (Fig. 2.17) proceeds with good degree of regio- and chemo-selectivity, especially with thiophenol and *p*-methoxy-thiophenol as substrates. Isomerisation to the internal alkenyl thiolates accounts for less than 9% of the thiolated products under the reaction conditions. In addition, further hydrothiolation of the vinyl thioether product is not observed. Typical conversions of 70–85% at 1 mol% loading at 80°C within 5 h are observed. Arylthiols substituted with electron-withdrawing groups afford lower conversions.

The thiolato complex **97** that was postulated as the active catalytic species in the reaction was prepared from **96** and the thiol in the presence of NEt₃. Certain analogues of **97** (NHC = IMes, SIMes, IPr, SIPr; R = Ph) have also been independently synthesised, isolated and fully characterised. A plausible mechanism for the hydrothiolation involves insertion of the alkyne into the Ni–SR bond forming the (non-isolable) β-thioalkenyl complex, from which the product can be released *via* alkanolysis of the Ni–C bond by the thiol and regeneration of the active catalyst **97** [84].

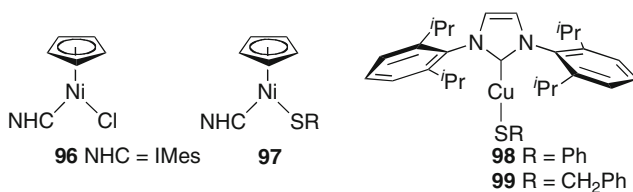


Fig. 2.17 Nickel and copper complexes as catalysts for the hydrothiolation of alkynes and activated alkenes

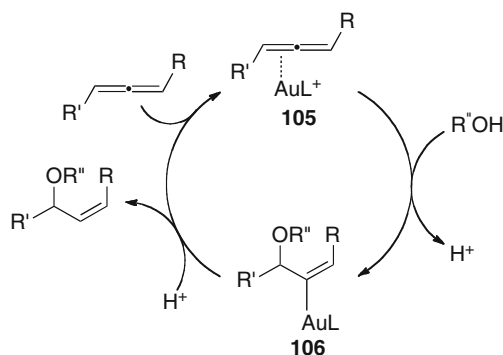
The hydrothiolation of electron-deficient alkenes [X = CN, C(=O)(OMe)] and *p*-nitro-styrene was catalysed by the Cu^I complexes **98** and **99**. The reactions with phenyl- or benzyl-thiol proceed with high conversions (>90%, rt, 5 mol%).

Anti-Markovnikov products are only observed. The postulated mechanism for these reactions is analogous to the previously discussed for the copper-catalysed hydroamination (Scheme 2.15) with the coordinated thiolate (rather than the amide) acting as nucleophile [82, 85].

Hydroalkoxylation and hydroaryloxylation (addition of H–OR and H–OAr, respectively, across the CC multiple bonds) of electron-deficient alkenes, by alcohols or phenols was studied in the presence of [Cu(OR)(NHC)], NHC = IPr, R = OEt, **100**; NHC = IPr, R = OPh, **101**; NHC = SIPr, R = OEt, **102**; NHC = SIPr, R = OPh, **103**; NHC = IMes, R = OPh, **104**], as well-defined catalysts. In general, the addition of alcohols to the alkenes is slower than the addition of amines. For the addition of ethanol, highest activities are observed with **100** (conversion of acrylonitrile or methyl vinyl ketone with ethanol >95% after 12 h and 5 min, respectively, at rt, 5 mol%). For the addition of phenol to acrylonitrile the most efficient catalyst is **104**.

In attempted hydroalkoxylation of methylacrylate with ethanol catalysed by the copper ethoxides **100** or **102**, copper-catalysed transesterification to the ethylacrylate was observed instead of the addition reaction [81].

Intermolecular hydroalkoxylation of 1,1- and 1,3-di-substituted, tri-substituted and tetra-substituted allenes with a range of primary and secondary alcohols, methanol, phenol and propionic acid was catalysed by the system [AuCl(IPr)]/AgOTf (1:1, 5 mol% each component) at room temperature in toluene, giving excellent conversions to the allylic ethers. Hydroalkoxylation of monosubstituted or trisubstituted allenes led to the selective addition of the alcohol to the less hindered allene terminus and the formation of allylic ethers. A plausible mechanism involves the reaction of the *in situ* formed cationic (IPr)Au⁺ with the substituted allene to form the π -allenyl complex **105**, which after nucleophilic attack of the alcohol gives the σ -allenyl complex **106**, which, in turn, is converted to the product by protonolysis and concomitant regeneration of the cationic active species (IPr)-Au⁺ (Scheme 2.18) [86].



Scheme 2.18 Postulated mechanism for the Au-NHC catalysed hydroalkoxylation of allenes

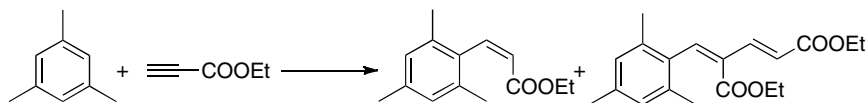
2.8 Hydration Reactions

The hydration of alkynes to ketones, catalysed by $[\text{AuCl}(\text{IPr})]/\text{AgSbF}_6$ in 1,4-dioxane/ H_2O (2:1) or methanol has been studied in detail. The reaction proceeds at surprisingly low catalyst loadings (50–1,000 ppm), especially, for terminal alkynes in methanol, and is extremely sensitive to the nature of the catalyst, the silver activator and the reaction conditions. The best activity is obtained with the IPr ligand on Au, while silver salts with anions other than $[\text{SbF}_6]^-$, either reduce the conversion or result in catalytically inactive species. Interestingly, diphenylacetylene is hydrated faster in 1,4-dioxane than methanol, the reverse behaviour being observed for the terminal phenylacetylene. This feature may imply that two different reaction mechanisms may be operating in dioxane and methanol, with methanol being a non-innocent solvent. This proposition is also supported by the detection of vinyl methylether intermediates, resulting from the direct addition of methanol to the alkyne, which in turn converts to the final ketone product. The nature of the catalytic species involved in this reaction is not known, but may involve solvated, hydroxo- or alkoxo-gold complexes $(\text{NHC})\text{Au}(\text{solvent})^+$, $(\text{NHC})\text{Au}(\text{OH})$, $(\text{NHC})\text{Au}(\text{OR})$. The Au–NHC based catalytic system described here is much more active than the previously known phosphine analogue, $[\text{AuMe}(\text{PPh}_3)]$ which requires the use of strong acids (H_2SO_4 , $\text{CF}_3\text{SO}_3\text{H}$, etc.) for catalyst activation [87, 88].

The intermolecular hydration of allenes catalysed by $[\text{AuCl}(\text{IPr})]/\text{AgOTf}$ (1:1, 5 mol%) in dioxane/water at room temperature, has also been studied. In most cases, low to modest yields (25–65%) of *E*-allylic alcohols were obtained by selective addition of the water to the terminal C atom of the allene group [89].

2.9 Hydroarylation Reactions

Hydroarylation, (addition of H-Ar , $\text{Ar} = \text{aryl}$), of alkynes, catalysed by $\text{Pd}(\text{OOCCH}_3)_2$ or $\text{Pd}(\text{OOCF}_3)_2$ in acetic acid, is an atom-economic reaction, giving rise to substituted *cis*-stilbenes (Fujiwara reaction). Catalytic conversions and improved chemoselectivity to the mono-coupled product under mild conditions can be achieved by modification of the metal coordination sphere with NHC ligands. Hydroarylation of mesitylene by ethylpropiolate (Scheme 2.19) catalysed by complex **107** (Fig. 2.18) proceeds in good conversions (80–99%, 1 mol%) under mild conditions at room temperature.



Scheme 2.19 Products from the hydroarylation reactions of activated alkynes

Surprisingly, the organometallic catalyst shows good stability under the reaction conditions ($\text{CF}_3\text{COOH}/\text{CH}_2\text{Cl}_2$). In the absence of **107** (Fig. 2.18), $\text{Pd}(\text{OAc})_2$ under the same conditions catalyses the same reaction with reduced activity (*ca.* 50% conversion in 24 h) and different chemoselectivity. Arenes, substituted by electron-withdrawing substituents react slower. Both internal and terminal alkynes undergo the reaction, however, the former require more forcing conditions [90].

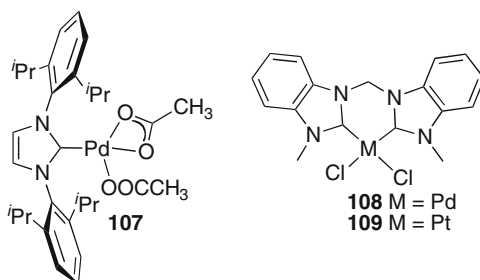
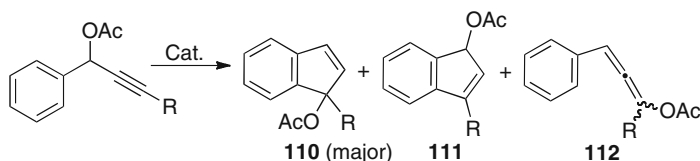


Fig. 2.18 Palladium and platinum NHC complexes as catalysts in hydroarylations of alkynes

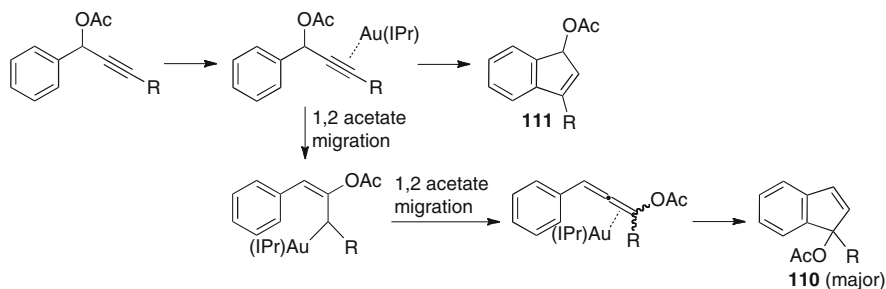
High activities and selectivities for the *Z*-monoarylated stilbene were also obtained by the intermolecular hydroarylation of pentamethylbenzene by ethylpropiolate in $\text{CF}_3\text{COOH}/1,2\text{-C}_2\text{H}_4\text{Cl}_2$ (1:4) catalysed by **108** (0.1 mol%, 80°C, 95% in 7 h). NHC ligands with bulkier substituents on the NHC show higher activity. The mechanism operating in this transformation has not been fully elucidated, but there are indications that during the reaction the NHC ligand of **108** remains bidentate. Encouraging results were also obtained when using the Pt analogue **109** as catalyst in hydroarylation reactions [91].

The intramolecular hydroarylation/cyclisation of aryl propargylic acetates catalysed by the system $[\text{AuCl}(\text{IPr})]/\text{AgBF}_4$ (1:1, 2 mol%, 72–92%, rt, 5 min) was developed as a versatile and efficient method leading to indene derivatives **110** (Scheme 2.20). Analogous catalytic systems, where the IPr was substituted by PPh_3 , gave lower conversions and chemo-/regio-selectivity.



Scheme 2.20 The synthesis of substituted indenenes by intramolecular hydroarylation of aryl propargylic acetates

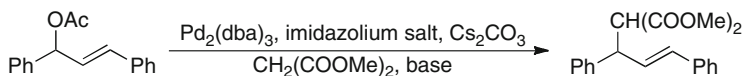
The postulated mechanism for the reaction involves activation of the alkyne by π -coordination to the cationic $(\text{IPr})\text{Au}^+$, followed by direct nucleophilic attack by the electron-rich aromatic ring to form product **111**. Alternatively, two 1, 2-acetate migrations give the activated allene complex, which can be cyclised to product **110** by nucleophilic attack of the aromatic ring on the activated allene (Scheme 2.21) [92].



Scheme 2.21 Postulated mechanism for the synthesis of substituted indenenes by intramolecular hydroarylation of propargylic acetates

2.10 Allylic Alkylations and Other Substitution Reactions

Allylic substitutions catalysed by palladium NHC complexes have been studied and the activity and selectivity of the catalysts compared to analogous Pd phosphine complexes. A simple catalytic system involves the generation of a $\text{Pd}(\text{NHC})$ catalyst *in situ* in THF, from $\text{Pd}_2(\text{dba})_3$, imidazolium salt and Cs_2CO_3 . This system showed very good activities for the substitution of the allylic acetates by the soft nucleophilic sodium dimethyl malonate (2.5 mol% $\text{Pd}_2(\text{dba})_3$, 5 mol% $\text{IPr}\cdot\text{HCl}$, 0.1 equiv. $\text{Cs}_2(\text{CO}_3)_2$, THF, 50°C) (Scheme 2.22). Generation of the malonate nucleophile can also be carried out *in situ* from the dimethylmalonate pro-nucleophile, in which case excess (2.1 equivalents) of Cs_2CO_3 was used. The nature of the catalytic species, especially the number of IPr ligands on the metal is not clear.



Scheme 2.22 Palladium-NHC complex catalysed substitution of allylic acetate by malonate

The substitution proceeds with retention of configuration at the substituted C atom as confirmed by the reaction of suitable isomeric acetates. Retention of configuration has also been observed in analogous Pd-phosphine catalysed reactions [93].

Compared to the Pd phosphine catalysts, the Pd/IPr system showed reduced reactivity, operating at higher reaction temperatures. Allylic carbonates, as well as harder nitrogen nucleophiles, such as amine or sulfonamides, were unreactive [94].

A detailed comparative study of the allylic substitution in allylacetates by amines has been carried out for the two related mixed donor ligand systems **113** and **114** shown in Fig. 2.19. The P-C system shows dramatically lower activity than N-P, which has been attributed to the decreased electrophilicity of the coordinated allyl group, originating from the strongly σ -donating NHC and P donors, compared to N and P donors.

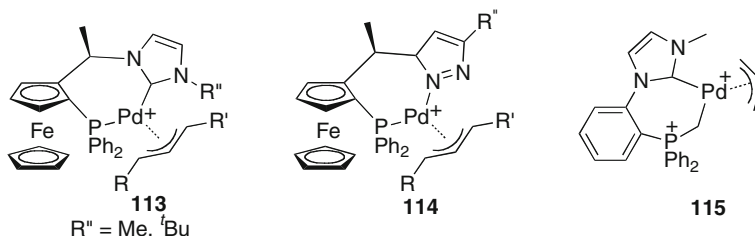


Fig. 2.19 Allylic substitutions with mixed donor Pd complexes

Enantioselectivity (which is linked to the regioselectivity of the attack of the nucleophile to the coordinated allyl) in the allylic amination of 1,3-diphenyl-allyl ethyl carbonate was also very low compared to the P–N system. This was attributed to the comparable *trans*-influence of P and NHC functionalities, leading to poor regioselection of the two allyl termini *trans* to the P and NHC ligands by the nucleophile [95].

Allylic alkylation of 3-acetoxy-1,3-diphenylpropene by sodium dimethylmalonate, catalysed by the Pd-allyl complex **115**, bearing the non-symmetric phosphonium ylide NHC ligand (5 mol%), proceeds to completion with 100% regioselectivity.

Asymmetric allylic alkylation (AAA) has been studied using a variety of novel ligand designs containing one NHC functionality and, usually, a classical heteroatom donor. In addition to the work mentioned earlier with ferrocenylphosphine-functionalised NHC complexes of Pd (**113**), the complexes **116–119** (Fig. 2.20) promote enantioselectivity in AAA reactions. A family of complexes **116** was found to induce up to 90% enantioselectivity in AAA, especially with the more rigid analogues. The nature of the NHC group has an important influence on the stereochemical outcome of the reaction [96]. The AAA of *E*-1,3-diphenylprop-3-en-1-yl acetate by sodium malonate catalysed by a class of imine functionalised NHC complexes **117** gave excellent conversions and enantioselectivities, with *ee* up to 92% in one case. The synthesis of the chiral bidentate ligand uses commercially available chiral *trans*-1,2-diamino-cyclohexane [97].

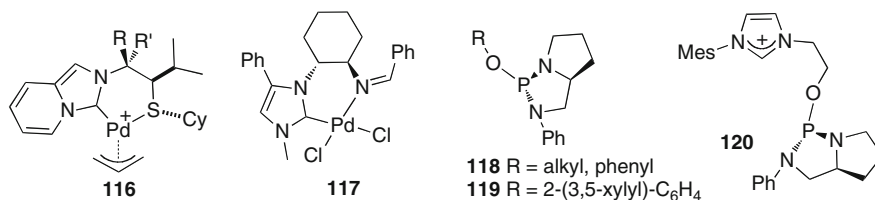
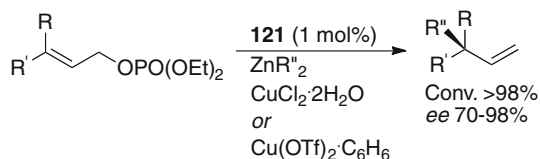


Fig. 2.20 Chiral Pd-NHC catalysts and ligands used for the asymmetric allylic alkylation

A comparative study of the AAA of *E*-1,3-diphenylprop-3-en-1-yl acetate by sodium malonate using the chiral phosphine ligands **118–119** showed that better *ee* were observed if the phosphine ligands were combined with a monodentate NHC. Best enantioselectivities were obtained in a catalytic system generated from [Pd(allyl)](μ-Cl)₂ and **119**/IMes, indicating a synergistic effect of the NHC and phosphine on the enantioselectivity of the reaction. The bidentate **120** showed also this synergism but not as pronounced as the combination of the two monodentate ligands [98].

The Ag complex **121** in the presence of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ or $\text{Cu}(\text{OTf})_2 \cdot \text{C}_6\text{H}_6$ catalyses the allylic alkylations of allyl phosphates by dialkylzinc reagents with high enantioselectivity (Scheme 2.23). A copper complex **122** which is the precursor to the catalytic species was also isolated and structurally characterised (Figs. 2.21 and 2.22) [99].



Scheme 2.23 Copper-catalysed enantioselective allylic alkylation of allyl phosphates

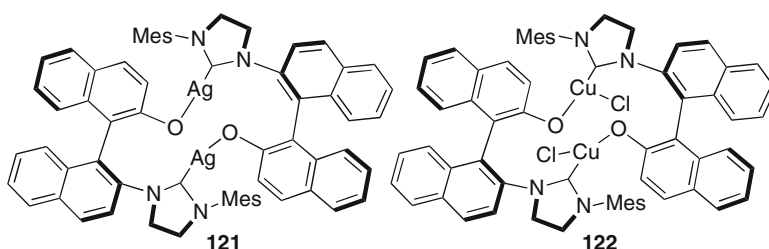


Fig. 2.21 Chiral binap-based catalysts or catalyst precursors for the enantioselective allylic alkylation of allyl phosphates

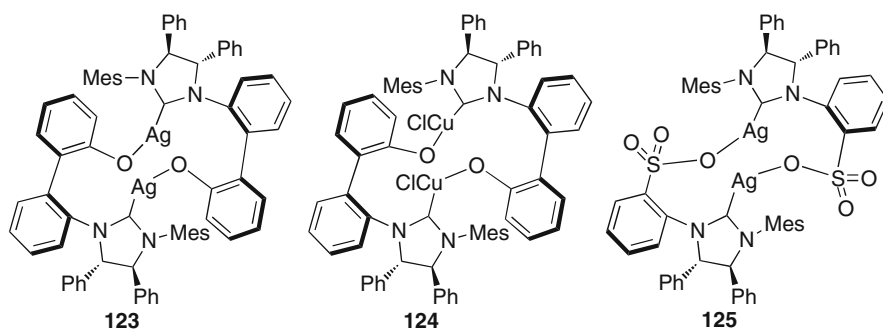
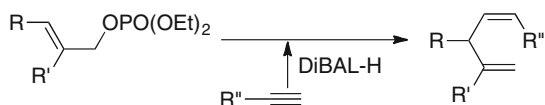


Fig. 2.22 Combination of chiral imidazolidin-2-ylidenes and biphenyl linkers in the chiral catalysts or catalyst precursors for the asymmetric allylic alkylations

The disadvantage of using optically pure binaphthyl building blocks for the synthesis of the NHC ligands in **121** and **122** was addressed by introducing on the imidazolidin-2-ylidene backbone chirality originating from the easily available in optically pure forms 1,2-diphenyl-1,2-diamino-ethane, in combination with racemic biphenyl- rather than optically pure binaphthyl-NHC wingtips. The analogous silver and copper complexes **123** and **124** (Fig. 2.22) were formed as single atropoisomers, and catalysed the alkylation of allyl phosphates by dialkylzincs giving excellent chemical yields and enantioselectivities [100].

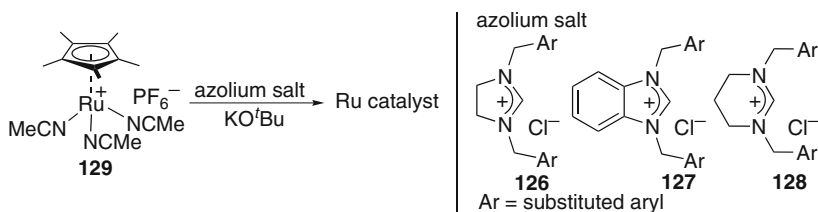
The AAA of allylphosphates by vinyl aluminium reagents generated *in situ* by hydroalumination of terminal alkynes with DIBAL-H *in situ* has recently been reported (Scheme 2.24).



Scheme 2.24 Asymmetric allylic alkylation of allylphosphates by *in situ* generated vinyl Al reagents

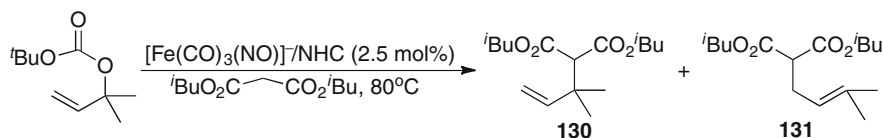
The most active catalyst for this reaction is formed *in situ* from **125** (fig. 2.22), in the presence of copper salts. Interestingly, high conversions and *ee* are only observed with the precursor **125** but not **123** or **121** [101].

Allylic alkylations of cinnamyl carbonate by sodium malonate have been studied with a series of ruthenium catalysts, obtained from the azolium salts **126–128** and the ruthenium complex **129** (Scheme 2.25) in MeCN or THF to give moderate yields of mixtures of alkylated products in the allylic and *ipso*-carbons (90:10 to 65:35). The observed regioselectivity is inferior to similar ruthenium systems with non-NHC co-ligands. The stereoelectronic factors which govern the observed regioselectivity were not apparent [102].



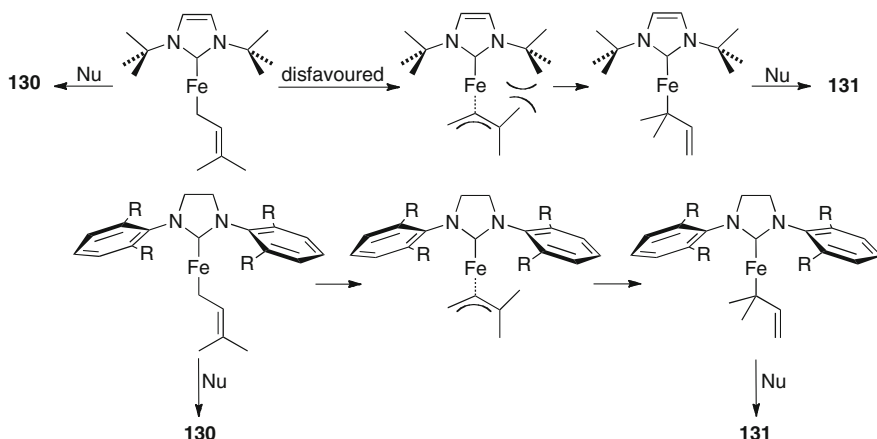
Scheme 2.25 Generation of ruthenium catalysts for the allylic alkylation of cinnamyl carbonate

A regioselective catalytic system for the allylic substitution of non-symmetric allyl carbonates by carbon and nitrogen nucleophiles based on $[\text{nBu}_4\text{N}][\text{Fe}(\text{NO})(\text{CO})_3]$ and PPh_3 was developed (Scheme 2.26). The high regioselectivity was ascribed to the slow σ -allyl- to π -allyl-isomerisation relative to the rate of substitution. However, the use of high excess of the pro-nucleophile and DMF solvent are drawbacks on the atom efficiency and functional group tolerance of the system.



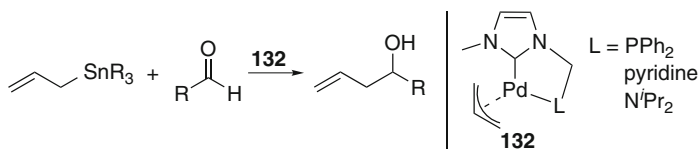
Scheme 2.26 Regioselective iron-catalysed allylic substitution of nonsymmetric allyl carbonates

Replacement of PPh_3 by various NHC ligands, generated *in situ*, resulted in higher conversions by using stoichiometric quantities of the C nucleophile. However, a dependence of the ratio of the isomeric products **130** and **131** on the nature of the NHC ligand was noticed. In general, the bulky SI^tBu favoured the formation of **130**, while with SI^iPr variable ratios of both **130** and **131** were obtained, depending on the substituents of the allyl source and the nucleophilicity of the nucleophile; stronger nucleophiles favoured the formation of **130**. The experimental results were rationalised by the assumption that substitution from the initially formed σ -allyl complex (leading to **130**) is possible, either when bulky SI^tBu is present, which disfavors σ -allyl isomerisation *via* a π -allyl intermediate, and/or when the high nucleophilicity entering group is present, resulting in a fast substitution reaction. When SI^iPr ligands are used, a relatively fast isomerisation process (σ -, π -, σ -allyl) competes with the direct substitution giving rise to substantial amounts of **131** (Scheme 2.27) [103].



Scheme 2.27 Proposed mechanism to account for the observed regioselectivity in the allylic alkylations catalysed by Fe-NHC complexes. Other co-ligands on Fe are omitted for clarity

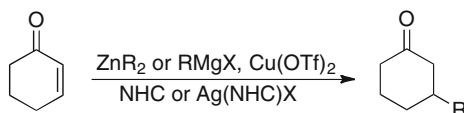
In an interesting system, the reduced electrophilicity of the Pd-allyl complexes with NHC ligands, mentioned previously, was exploited in order to promote stoichiometric and catalytic ‘*umpolung*’ allylation reactions of benzaldehyde, by nucleophilic attack of the coordinated allyl group (Scheme 2.28). The best results were obtained with the family of phosphine- or amine-functionalised NHC complexes [104]. Interestingly, $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}(\text{IMes})]$ complex does not react with aldehydes. It is plausible that the nucleophilic η^1 -allyl Pd intermediate attacks the carbonyl carbon.



Scheme 2.28 Allylation of benzaldehyde mediated by Pd-NHC complexes

2.11 Additions to Conjugated Enones and Related Reactions

The Cu^{II} (for example Cu(OTf)₂) catalysed addition of dialkylzincs or Grignards to α,β -unsaturated carbonyl compounds was found to be accelerated in the presence of *N*-heterocyclic carbenes, generated *in situ* (especially the strongly σ -donating SIMes), or formed by transmetalation from Ag-carbene complexes to copper (Scheme 2.29). For the addition to cyclohex-2-enone, high conversions (>90%) at low catalyst loading (2–5 mol%) were obtained at temperatures –20°C to rt within 5–10 min [105]. The ligand acceleration was attributed to the stabilisation of a putative Cu^{III} transition state by the strongly σ -donating NHC.



Scheme 2.29 Addition to α,β -unsaturated carbonyls mediated by Cu-NHC complexes

Asymmetric versions of this transformation were also developed by using chiral imidazolium pro-ligands as NHC precursors, or silver transmetalation methodology with chiral NHC ligands (Fig. 2.23) [106]. Imidazolium salts with chiral *N*-substituents (**132**) or imidazolidinium salts with chirality at the backbone of the heterocycle (**133**) gave quantitative conversions at –78°C with good *ee* (58% and 70% respectively).

Improvement in the catalyst activities and enantioselectivities was realised by the development of the chiral, bidentate alkoxy-functionalised imidazolium and imidazolidinium pro-ligands (**134** and **136**). **134**, after deprotonation, was used to prepare the well-defined complex **135**. Both **136** in the presence of BuLi and Cu(OTf)₂ or **135** without any additional co-reagents were efficient catalysts in the asymmetric 1,4 addition of dialkylzincs and Grignards to cyclohexen-2-one giving higher *ee* (83% at rt and 51% at –30°C, respectively) [107, 108].

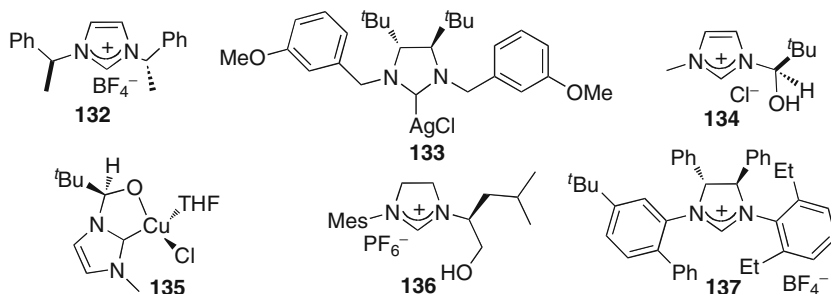
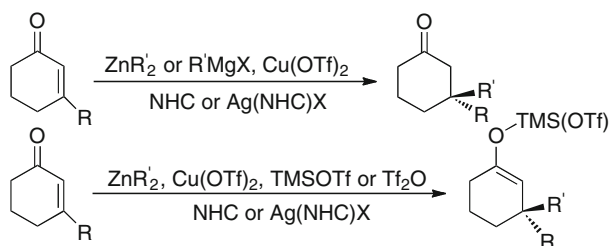


Fig. 2.23 Chiral NHC ligand precursors and complexes used in the asymmetric alkylation of conjugated enones

Recently, attempts were made to replace the air- and moisture-sensitive zinc and magnesium reagents in the copper-catalysed asymmetric conjugate addition, with

easier to handle air-stable carbosilanes. Aryl- or alkenyl-trifluorosilanes, in the presence of the fluoride source tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF, generating *in situ* the nucleophilic aryl- or alkenyl-tetrafluorosilicates) gave good to excellent yields (63–97%) and *ee* (47–97%) of the 1,4 addition products to cyclic enones. The catalysts were generated *in situ* from the imidazolium salt, NaO*t*Bu and CuBr at rt. In this study, evaluation of the efficiency of various chiral (*C*2 and non-*C*2 symmetric) NHC-pro-ligands showed that the non-*C*2 analogue **137** gave the best yields and *ee* [109].

Asymmetric conjugate addition of dialkyl or diaryl zincs for the formation of all carbon quaternary chiral centres was demonstrated by the combination of the chiral **123** and Cu(OTf)₂·C₆H₆ (2.5 mol% each component). Yields of 94–98% and *ee* of up to 93% were observed in some cases. Interestingly, the reactions with dialkyl zincs proceed in the opposite enantioselective sense to the ones with diaryl zincs, which has been rationalised by coordination of the opposite enantiofaces of the prochiral enone in the alkyl- and aryl-cuprate intermediates, which precedes the C–C bond formation, and determines the configuration of the product. The copper enolate intermediates can also be trapped by TMS triflate or triflic anhydride giving directly the versatile chiral enolsilanes or enoltriflates that can be used in further transformations (Scheme 2.30) [110].



Scheme 2.30 Copper-catalysed asymmetric conjugate addition of organozincs to enones

Similarly, highly enantioselective transformations were reported by using other chiral functionalised non-symmetric (**138**) or *C*2 symmetric NHC pro-ligands (**139**–**140**) (Fig. 2.24) in the presence of organometallic bases and copper salts [111, 112].

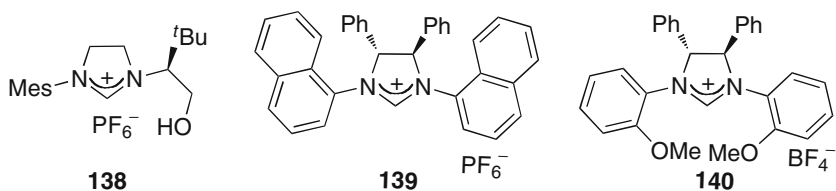


Fig. 2.24 Chiral NHC pro-ligands used in copper-catalysed asymmetric conjugate additions

The asymmetric 1,4-conjugate addition of phenyl boronic acids to cyclohex-2-enone was catalysed by the Pd complex **141** (Fig. 2.25). Good to excellent yields and high *ee* (90–97%) were obtained under mild conditions and low catalyst loadings (rt, 3 mol%)

in THF/H₂O in the presence of base (KOH or K₂CO₃). The labile acetates in **141** are crucial for the success of the reaction as demonstrated by the inactivity of the corresponding iodide complexes. Interestingly, the configuration of the isolated addition product is the opposite to that obtained by the analogous Rh-(binap) catalysed reaction with ligand of the same configuration [113]. Other cyclic enones gave similar results. A plausible catalytic cycle involves reaction of the catalyst with base to form the corresponding hydroxo palladium complex which undergoes transmetalation with the phenyl boronic acids. Insertion of the C=C bond of the enone into the Pd–C bond gives the oxa-allyl species **142** or the enolate **143** which are releasing the product after hydrolysis.

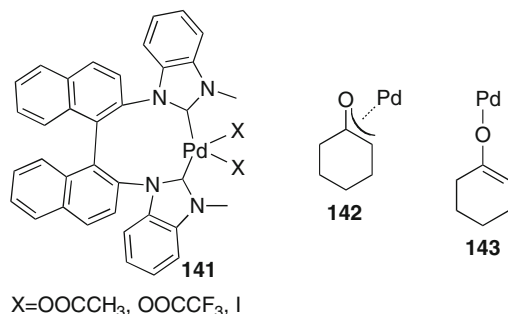
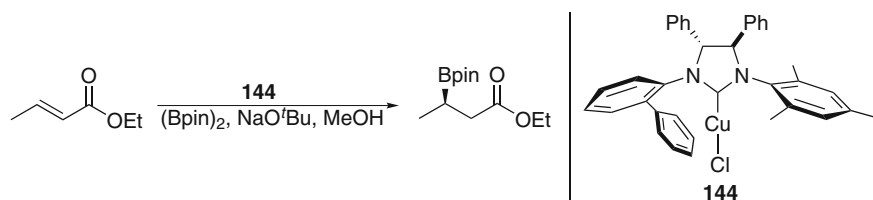


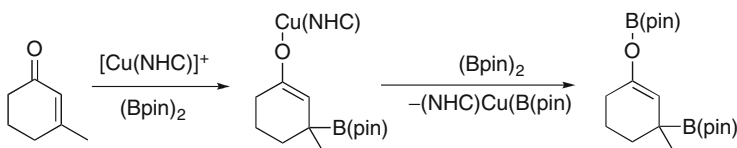
Fig. 2.25 Palladium catalysts and postulated intermediates in the asymmetric conjugate addition of phenyl boronic acids to cyclohex-2-enone

The enantioselective β -borylation of α,β -unsaturated esters with (Bpin)₂ was studied in the presence of various [CuCl(NHC)] or [Cu(MeCN)(NHC)]⁺ (NHC = chiral imidazol-2-ylidene or imidazolidin-2-ylidene) complexes. The reaction proceeds by heterolytic cleavage of the B–B bond of the (Bpin)₂, followed by formation of Cu-boryl complexes which insert across the C=C bond of the unsaturated ester. Best yields and *ee* were observed with complex **144**, featuring a non-C₂ symmetric NHC ligand (Scheme 2.31) [114].



Scheme 2.31 Copper-catalysed asymmetric borylation of conjugated enones

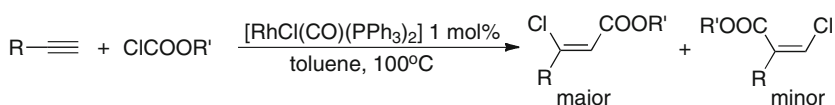
Further insight into the β -borylation reaction of α,β -enones (Scheme 2.32) showed that the reaction can be carried out in THF, and the catalyst generated *in situ* from CuCl (5 mol%), the imidazolium salt (5 mol%), and NaO^tBu (10 mol%), to form the [Cu(O^tBu)(NHC)] as the catalysis initiating species. In this case, stable boron enolate products are formed which need to be hydrolysed by methanol to the ketone products [114].



Scheme 2.32 Borylation of enone mediated by Cu-NHC complexes

2.12 Chloroesterification and Chloroacetylation Reactions

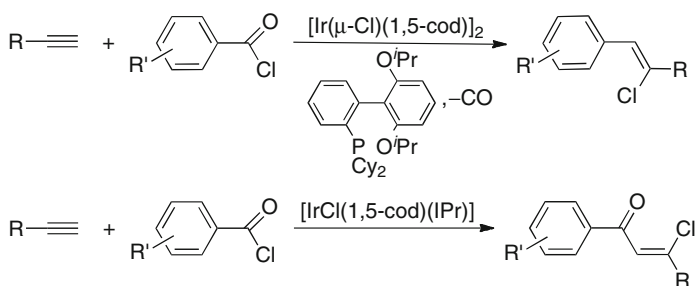
The rare chloroesterification of terminal alkynes (*i.e.* the addition of Cl–COOR across the CC triple bond) catalysed by $[\text{RhCl}(\text{CO})(\text{PPh}_3)_2]$ gave *Z*- β -chloro- α,β -unsaturated esters (Scheme 2.33) [115].



Scheme 2.33 Products in the rhodium catalysed-chloroesterification of alkynes

The chloroesterification of terminal alkynes or conjugated enynes by ClCOOMe was catalysed by complex $[\text{RhCl}(\text{IPr})(1,5\text{-cod})]$ (1 mol%) under similar conditions as the $[\text{RhCl}(\text{CO})(\text{PPh}_3)_2]$. High conversions (70–80%) were obtained with high regio- and stereo-selectivity. Here too, Markovnikov, *Z*-additions products were dominant. Under similar conditions the complex $[\text{RhCl}(1,5\text{-cod})(\text{PPh}_3)]$ gave lower conversions (*ca.* 20%) [116].

Chloroacylation of terminal aryl, alkyl or alkenyl alkynes [*i.e.* the addition of $\text{RC}(=\text{O})\text{--Cl}$ across the CC triple bond] with aromatic acyl chlorides was catalysed by $[\text{IrCl}(\text{cod})(\text{IPr})]$ (5 mol%) in good conversions (70–94%) in toluene (90°C, 20 h). *Z*-addition products were observed only. Internal alkynes were unreactive. Surprisingly, a phosphine/ $[\text{Ir}(\mu\text{-Cl})(1,5\text{-cod})]_2$ system under the same conditions provides decarbonylation products (Scheme 2.34) [117].



Scheme 2.34 Chloroacylation of alkynes catalysed by iridium NHC complexes

2.13 Conclusion

Since the isolation of relatively stable nucleophilic carbenes, their use as ligands for almost all metals of the Periodic Table and their applications in homogeneous catalysis have risen exponentially. This is attested by the increasing number of researchers from diverse backgrounds that are entering this area of study. The deeper understanding of the steric and electronic characteristics of the carbene ligands, and the way they interact with the metal in a catalytic species promise new developments in the rational design of more active, selective and stable catalysts for numerous applications [118]. We believe that exciting developments in this area will appear in the near future.

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