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Beibei Guo, Edwin Otten, and Johannes G. de Vries

Contents

Abstract The nitrile is an extremely useful functional group in organic synthesis: it can be transformed into amides, carboxylic acids, amines and imines; yet it is relatively stable and can be easily carried through several synthetic steps before

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being converted. The conversions of nitriles under mild conditions are thus very important transformations. Great progress has been made in the last decade in the use of metal pincer complexes as catalysts for quite a number of reactions of nitriles and nitrile-containing molecules. The selective hydrogenation of nitriles either to the amines or to the imines usually follows a Noyori-type outer-sphere mechanism. Coordination of aliphatic nitriles to the metal centre renders the α-proton rather acidic allowing deprotonation followed by carbon-carbon coupling reactions. The pyridine-based metal pincer complexes introduced by Milstein allow for novel mechanisms based on metal-ligand cooperativity in which the pyridine undergoes dearomatisation induced by deprotonation of one of the side arms. The nitrile can undergo a cycloaddition to the complex in its dearomatised form, creating a new bond between the nitrogen atom and the metal, whereas the nitrile carbon atom forms a C-C bond with the carbon atom of one of the pincer side-arms. The resulting metalimide undergoes nucleophilic addition more easily than the nitrile. It can also easily rearrange to the enamide, which can undergo C-C bond forming reactions. Also, oxo- and aza-Michael reactions are facilitated on the unsaturated nitriles, such as acrylonitriles or pentenitriles. Most reactions proceed under mild conditions in excellent yields.

1 Introduction

The nitrile functional group is very important from an organic synthetic perspective. It can be transformed into amides, carboxylic acids, amines and imines; yet it is relatively stable and can be easily carried through several synthetic steps before being converted. Thus, activation of the $C \equiv N$ bond under mild conditions can be seen as a very important research area. In this review, we will discuss the recent progress in reactions of nitriles catalysed by transition metal pincer complexes.

In 1976, Moulton and Shaw were the first to report organometallic complexes based on pincer ligands [1]. Since then, pincer complexes have received increasing attention due to their unique stability, selectivity and often unusual reactivity [2–12]. Taking advantage of these properties, efficient methodologies have been developed for the activation of nitriles that are often tolerant of many other functional groups. These pincer complexes may react in the same way as traditional metal complexes [13, 14]: the nitrogen atom of the nitrile may coordinate to the metal centre, which leads to increased acidity of the α-proton enabling the use of the resulting anion as a carbon nucleophile (Scheme 1, left side). In addition, they are
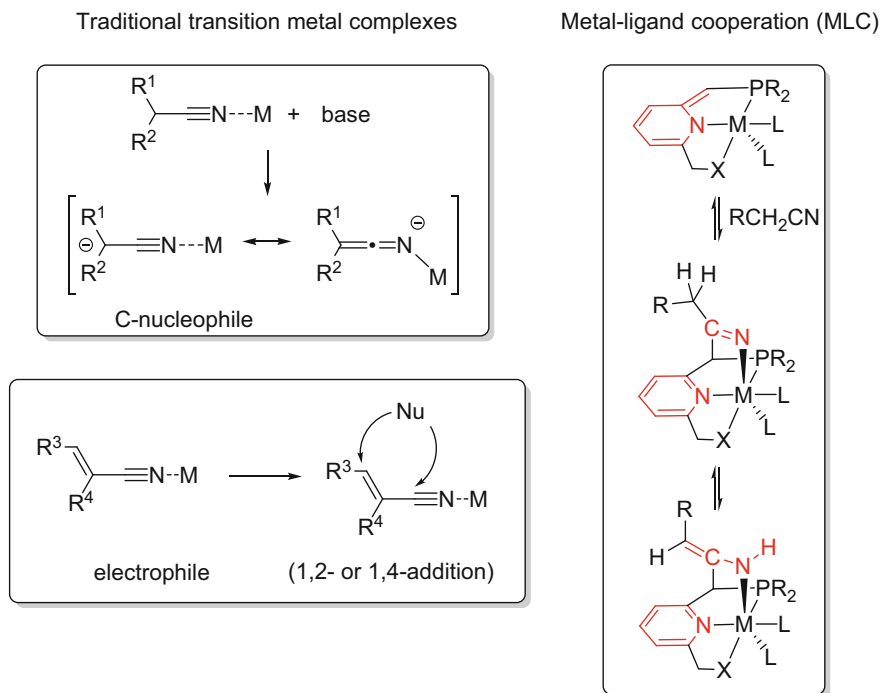
Scheme 1 Activation of nitriles by conventional metal complexes (Lewis acids) and metal-ligand cooperative pincer complexes (X = NR'$_2$ or PR'$_2$)

excellent hydrogenation and dehydrogenation catalysts that, depending on the ligand structure, may operate according to the classic Noyori-type (transfer) hydrogenation mechanism. However, in the PNP and PNN metal complexes based on pyridines, Milstein and co-workers also found novel mechanisms based on metal-ligand cooperativity [15] in which the pyridine undergoes dearomatisation induced by deprotonation of one of the side arms [16]. These mechanisms are also operative on nitriles, which were found to undergo cycloaddition onto these dearomatised complexes, forming a new bond between the nitrogen atom and the metal, whereas the carbon atom forms a C-C bond with the carbon atom of one of the side arms [17, 18]. The initially formed imide form can further tautomerise to the enamide form (Scheme 1, right side). The relative stabilities of these forms depend on the substituent R [18]. The addition as well as the tautomerisation is reversible. This change in bond order of the nitrile significantly reduces the activation barrier for its reaction with nucleophiles and other reactions. In addition, the metalated enamine form is a good nucleophile allowing substitution reactions and aldol condensations.

2 Hydrogenation of Nitriles

2.1 Hydrogenation of Nitriles to Amines

A range of different pincer complexes based on ruthenium, iron, cobalt and manganese have been used for the hydrogenation of nitriles to the primary amines (Scheme 2).
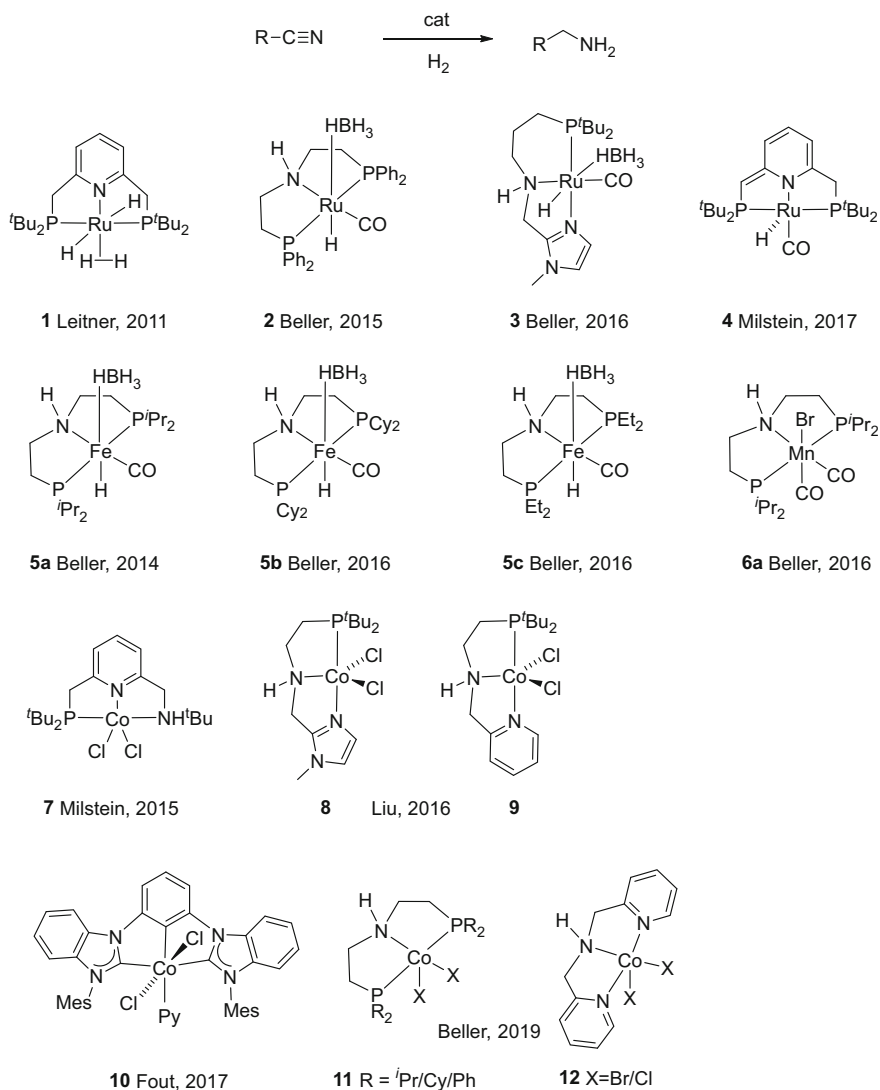
Scheme 2 Pincer complexes used as catalyst for the hydrogenation of nitriles to amines

Table 1 Hydrogenation of nitriles to amines by Ru pincer complex **1**

59 (65)%[a]   95 (36)%   96 (88)%

62%   80 (96)%   95 (90)%

93 (75)%   92 (82) %   90 (74) %
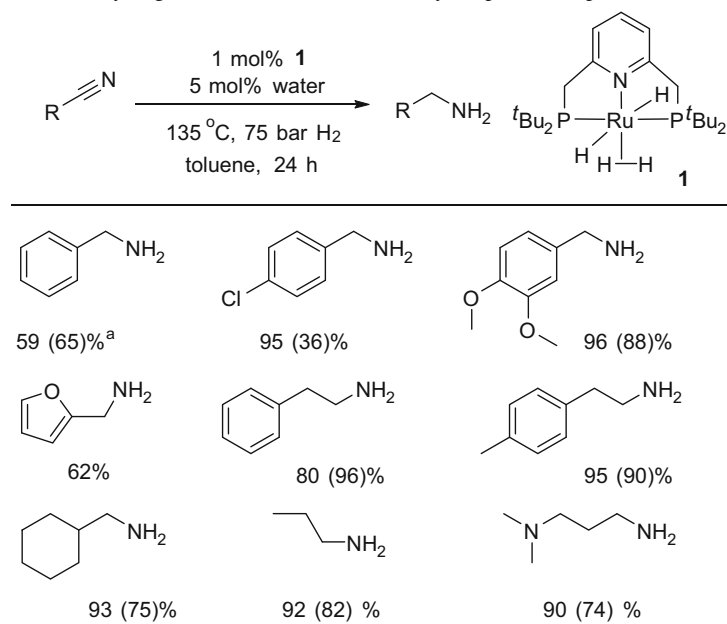
[a]Numbers in bracket are yields without water additive

Leitner's group reported the first pincer complex-catalysed hydrogenation of nitriles to amines [19]. With 0.4 mol% of the non-classical ruthenium hydride complex **1** as catalyst, they successfully reduced eight different nitriles including aliphatic and aromatic nitriles at 135°C (Table 1). In order to reach high selectivity and full conversion, a high H_2 pressure (75 bar) and long reaction times (45 h) were required. Interestingly, they found that addition of 2 mol% of water increased the yields (especially for *p*-chlorobenzonitrile, from 35% to 95%) and significantly shortened the reaction time (from 45 h to 24 h). They proposed water played a key role in the prevention of secondary amine formation, a well-known side reaction in nitrile hydrogenation, via hydrolysis of the secondary imines: the water hydrolyses the secondary imine forming the primary amine and the aldehyde, which can react with the ammonia, released in the secondary imine-forming step (Scheme 3). Although this methodology required relatively harsh condition (135°C and 75 bar H_2), it was the first highly selective and catalytic reduction of nitriles to amines by a pincer complex.

The Beller group used the well-known ruthenium-MACHO-BH complex **2**, which was developed earlier by Takasago chemists [20, 21], for the hydrogenation of nitriles under milder conditions (Scheme 4) [22]. Using 1 mol% of catalyst and 30 bar hydrogen at 100°C, aliphatic nitriles were hydrogenated with isolated yields

R−C≡N

Ru cat

H$_2$
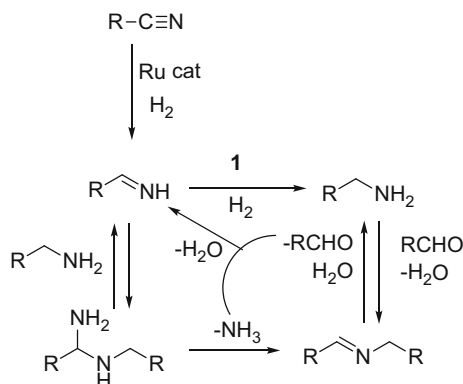
Scheme 3 Role of water in the Ru pincer complex **1** catalysed hydrogenation of nitriles
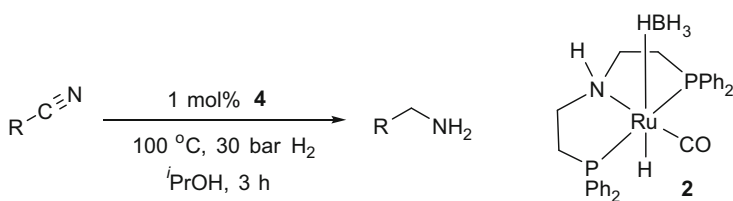
Scheme 4 Hydrogenation of nitriles using Ru-MACHO-BH
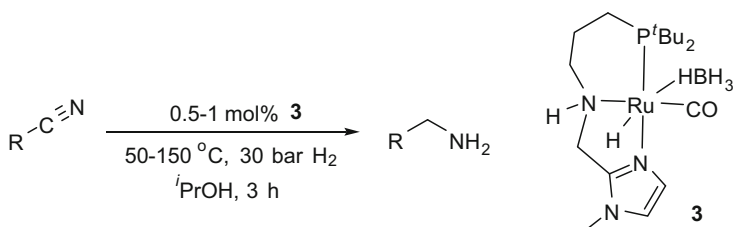
Scheme 5 Hydrogenation of nitriles using Ru PNN complex **3**

from 77 to 98%, whereas aromatic nitriles could be reduced with isolated yields between 68 and 99%. Interestingly, the usually problematic ester-substituted benzonitrile was selectively reduced (94% isolated yield) leaving the ester group intact.

Ru NNP pincer complexes bearing an imidazole moiety were also developed by the same group [23]. Different substituents on the phosphorus atom were investigated, but complex **3** carrying *tert*-butyl substituents gave the best results. A large range of aromatic, heteroaromatic and aliphatic nitriles was hydrogenated at 30 bar hydrogen (Scheme 5). For most substrates, a temperature of 50°C was sufficient, but for more sluggish substrates, temperatures between 70 and 150°C were used. In all cases the nitrile was completely converted, and the primary amines were obtained in GC yields of 75–99%.

Milstein and co-workers developed the low-pressure hydrogenation of nitriles to primary amines catalysed by pyridine-based pincer Ru complex **4** in which the pyridine is dearomatised [24]. With lower catalyst loading (0.3 mol%), lower temperature (110°C) and no extra additives, aromatic nitriles could be reduced with high selectivity and conversions (Scheme 6). The authors assume a ligand-assisted mechanism (Scheme 7), in which the catalyst **4** rapidly reacts with the nitrile to form nitrile complex **I**, which is hydrogenated to the dihydride complex **II** in which the aromaticity is restored and the side arm protonated. Next, in an outer-
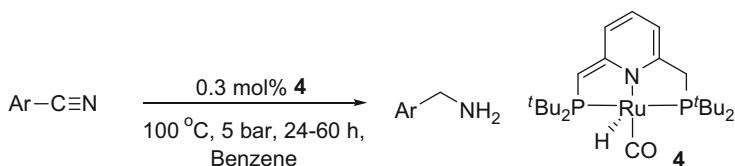
Scheme 6 Hydrogenation of nitriles to amines by Ru pincer complex **9**
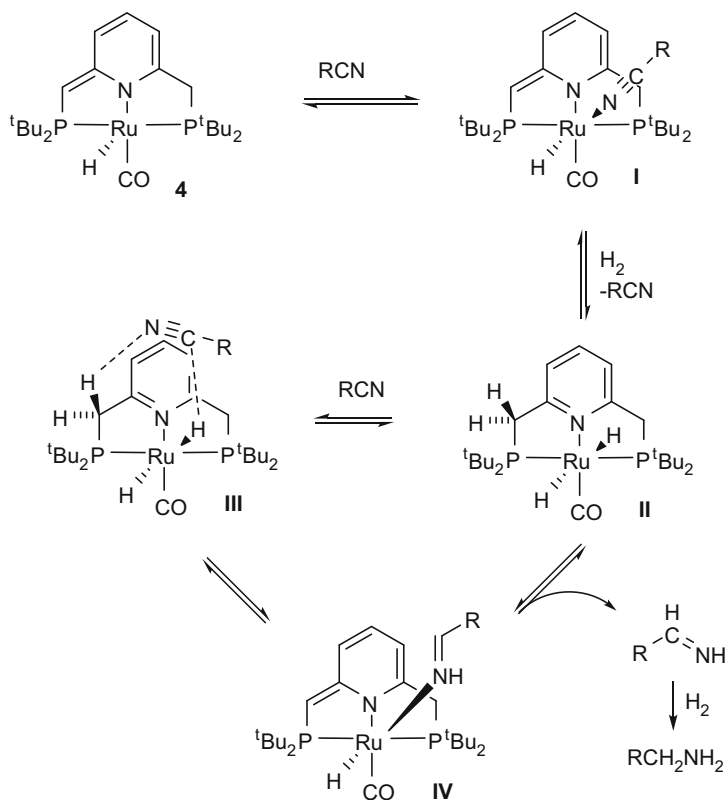
Scheme 7 Proposed mechanism of nitrile hydrogenation using a dearomatised Ru PNP pincer complex

sphere mechanism (intermediate **III**), the hydride is transferred to the carbon atom under simultaneous protonation of the nitrogen atom by the proton on the side arm under dearomatisation of the pyridine resulting in the imine complex **IV**, which releases the imine which is further hydrogenated to the amine by a similar mechanism.

Beller and co-workers reported the first iron-based pincer complex-catalysed hydrogenation of nitriles to the amines [25]. The catalyst **5a** they had developed before [26] showed high reactivity in the hydrogenation reaction and good selectivity (up to >99%) for the primary amines with isopropanol as solvent under 30 bar H_2 atmosphere at 70–130°C. As to the substrate scope investigation, this reaction showed a very broad applicability: (hetero)aromatic nitriles, aliphatic nitriles and dinitriles were all efficiently converted (Table 2). Catalytic hydrogenation of benzonitriles with electron-donating substituents gave the amines good to excellent

Table 2 Nitrile hydrogenation with iron-based pincer complex **5a**

R' = H	97%
R' = Me	96%
R' = ^{t}Bu	82%
R' = Ph	99%
R' = SMe	81%
R' = OMe	88%
R' = CF_3	71%
R' = F	81%
R' = Cl	78%
R' = Br	88%
R' = NH_2	93%
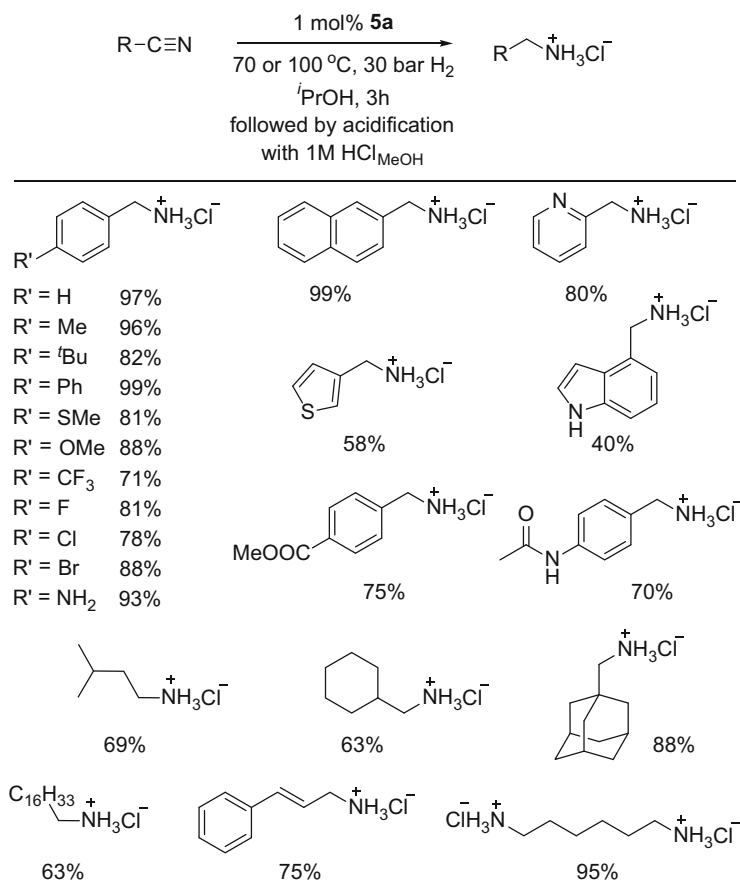
yields (81–99%), whereas benzonitriles with electron-withdrawing substituents as well as heteroaromatic nitriles required slightly higher temperatures (100–130°C). Remarkably, not only common halogens (CF$_3$, F, Cl, Br), amino and methoxy functional groups were tolerated as aromatic substituents (71–93% yields), but ester- and acetamide-substituted nitriles were also reduced in synthetically useful yields (75% and 70%). Primary, secondary as well as tertiary aliphatic nitriles were all converted with good yields (63–95%). Noteworthily, cinnamonitrile could be selectivity hydrogenated without reducing the C=C bond (allylamine: saturated amine >25:1). Adiponitrile was reduced in excellent yield to hexamethylenediamine, a monomer for nylon-6,6, with good selectivity (95% isolated yield) and high rate (TOF of 250 h^{-1}). In addition, this reaction was scaled up to 25 mmol.

Based on DFT studies, it was proposed that dissociation of BH$_3$ in the form of B$_2$H$_6$ from **5a** leads to the formation of the dihydride complex **I** (Scheme 5), which is the active catalyst. The calculations also allowed the authors to distinguish between the two possible mechanisms: in an inner-sphere mechanism, the CO needs to dissociate first in order to allow coordination of the nitrile. This is endergonic by 23.78 kcal mol^{-1}. In the outer-sphere mechanism, the iron-bound hydride and proton from the amine are transferred simultaneously, and the activation barrier for this is 15.35 kcal mol^{-1}. Based on this, the outer-sphere mechanism (Scheme 8) is clearly preferred.
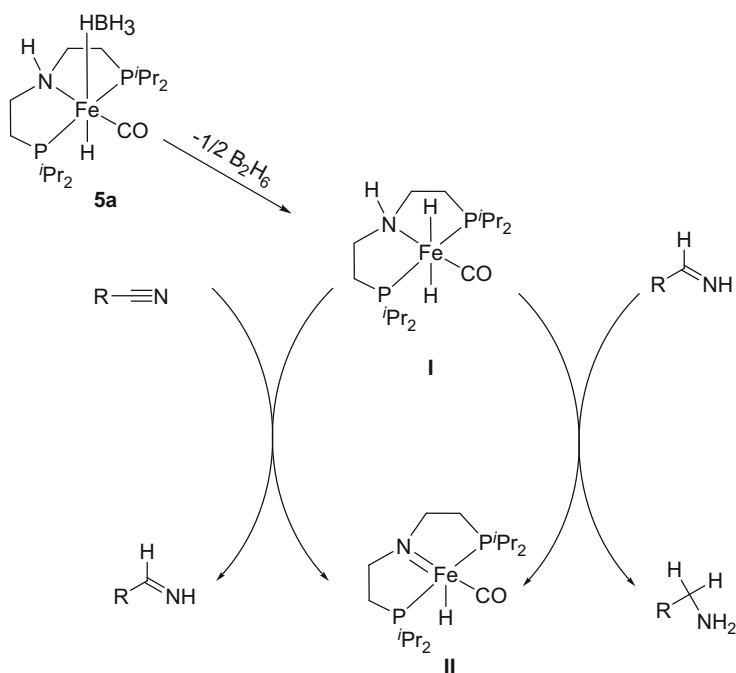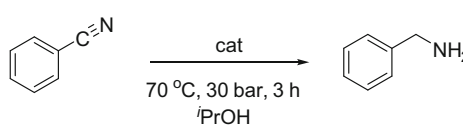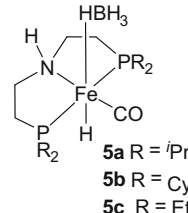
Scheme 8 Outer-sphere mechanism for nitrile hydrogenation with **5a**

To further improve the performance of iron pincer complex **5a**, the Beller group studied the effect of the alkyl substituents at the phosphorus atoms. Thus, a new iron pincer complex was prepared with cyclohexyl substituents at the phosphorus atoms, and the performance of this complex was compared to the complexes **5a** (R = *i*Pr) and **5c** (R = Et) in the hydrogenation of benzonitrile (Table 3) [27]. Although at 1 mol% catalyst loading the performance of the three catalysts was very similar, at catalyst loadings of 0.5 and 0.25 mol%, complex **5c** was totally inactive, whereas **5a** and **5b** were able to convert the nitrile to the amine in good yields.

Using the same ligand, the Beller group also prepared a manganese complex **6a** which contains two additional CO ligands as well as bromide [28]. The presence of the halide necessitates the use of base (NaO*t*Bu) to activate the catalyst; in this step the proton from the amine group is removed, together with the bromide. This activated catalyst is well set up to add hydrogen to form the hydride complex. This catalyst requires higher hydrogen pressure (50 bar) and catalyst loading (3 mol%) than the iron complexes, and yet reaction times of 24–60 h were still required. A range of aromatic and heteroaromatic nitriles were hydrogenated at 120°C during 24 h resulting in good yields (47–99%) of the benzylamines (Scheme 9). Aliphatic nitriles on average reacted more sluggishly and took 24–60 h. The aliphatic amines were obtained in isolated yields of 78–97% as the HCl salts. Cinnamonitrile was reduced to 3-phenyl-prop-2-enyl-1-amine in 54% isolated yield.

Table 3 Effect of the alkyl substituent of **5** on the hydrogenation of benzonitrile

		Yield of benzylamine		
Entry	Catalyst loading (mol%)	**5a**	**5b**	**5c**
1	1.0	92%	89%	85%
2	0.5	90%	90%	0%
3	0.25	88%	87%	0%
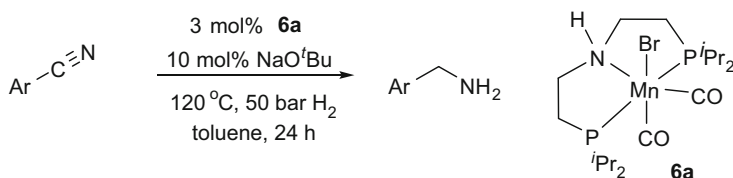
Scheme 9 Use of a manganese PNP pincer complex for the hydrogenation of nitriles

Table 4 Hydrogenation of nitriles to amines by cobalt pincer complex **7**[a]

R' = H   85%
R' = Me   99%
R' = OMe   99%
R' = CF$_3$ 57%
R' = F   83%
R' = Cl   93%
R' = Br   6%
R' = NH$_2$ 86%
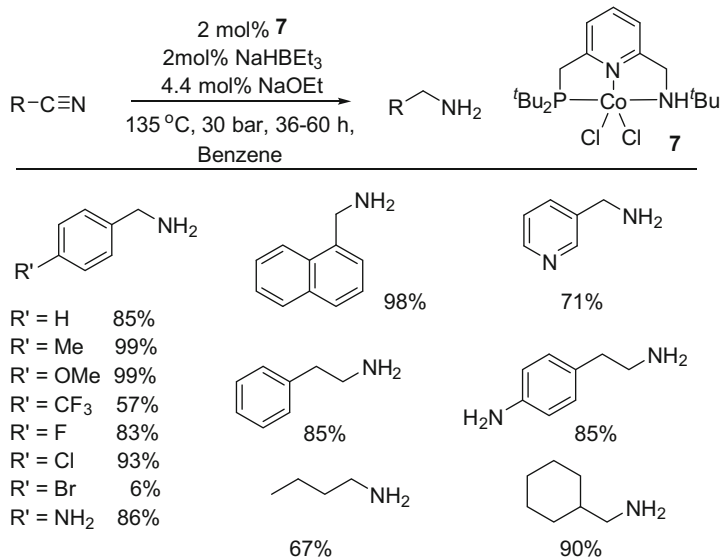
[a] Yields determined by 1H NMR spectroscopy with respect to toluene or dimethylformamide as an internal standard or by GC analysis

Milstein's group reported the first cobalt pincer complex (**7**)-catalysed hydrogenation of nitriles to amines [29]. After activation of the catalyst by base (NaOEt) and a reducing agent (NaEt$_3$BH, presumably to reduce Co(II) to the active Co(I)), aromatic nitriles could be hydrogenated to the primary amines in benzene at 135°C and under 30 bar H$_2$, in up to >99% yield. A broad functional group tolerance including electron-donating groups and electron-withdrawing groups was found, with bromide being the exception (Table 4). In the case of pyridine-based substrates, the catalyst became sluggish (77% conversion, 71% yield after 36 h). Yields of aliphatic amines were somewhat lower, due to base-induced side reactions.

In 2017, Fout and co-workers reported the hydrogenation of nitriles to primary amines by a bis(carbene) pincer cobalt complex **10** with broad scope and excellent yields (Scheme 10) [30]. Interestingly, they found that when **10** is reacted with NaHBEt$_3$, not only does reduction occur to Co (I) complex **10′**, but the Et$_3$B that is formed in this reduction turned out to be an indispensable component in the nitrile reduction process. The authors presume that through coordination of Et$_3$B with the nitrile, a side-on coordination of the nitrile to cobalt becomes possible, which effectively facilitates the insertion of the triple bond into the cobalt-hydride bond. The authors used *para*-hydrogen-induced polarisation transfer NMR studies to gain further mechanistic information. The intermediacy of the dihydride was proven, and the imine intermediate could be observed by NMR spectroscopy. By using 1.04 eq.
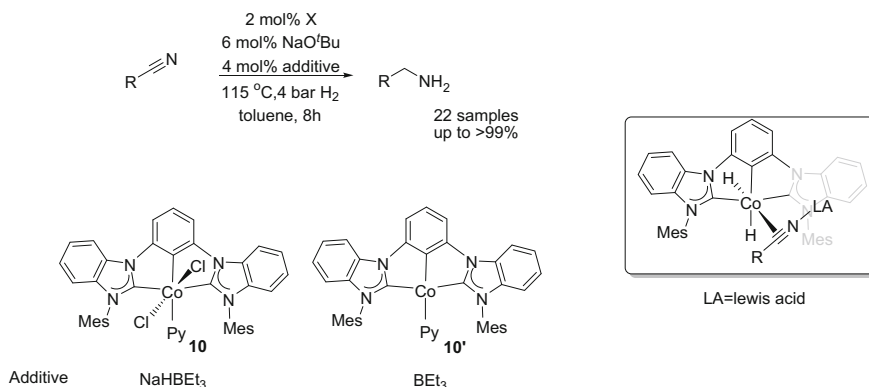
Scheme 10 Use of a CCC-pincer ligand in the Co-catalysed hydrogenation of nitriles to amines
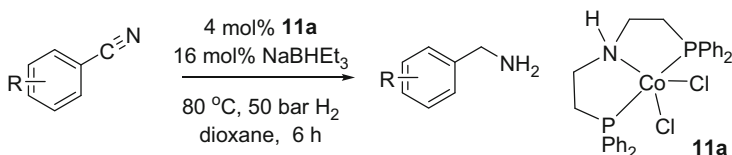
Scheme 11 Hydrogenation of nitriles to amines catalysed by Co(MACHO)Cl$_2$ (**11a**)

of Et$_3$B, it was possible to selectively reduce 4-acetyl-benzonitrile to 4-acetylbenzylamine.

Using the MACHO ligand as well as analogues with different substituents on phosphorus (*i*Pr, Cy), four pincer complexes were made based on cobalt by the Beller group [31]. These cobalt complexes contain halogen ligands; this necessitates the use of base and/or a reductant to activate the catalyst. Compared with iron analogue **5a**, these complexes require higher H$_2$ pressure (50 bar) and a higher catalyst loading (4 mol%) and still need a longer reaction time (6 h) to reach full conversion. The best catalyst was the one based on the MACHO ligand (**11a**). A range of aromatic and aliphatic nitriles were hydrogenated in good yields (Scheme 11).

Thus far, there is only a single report on the transfer hydrogenation of nitriles catalysed by pincer complexes. Zhou, Liu and co-workers reported the Co-NNP pincer complex-catalysed transfer hydrogenation of nitriles to primary, secondary or tertiary amines using NH$_3$BH$_3$ as hydrogen source (Scheme 12) [32]. At 50 °C in hexane, complex **8** bearing an imidazole moiety selectively converted aromatic and aliphatic nitriles to primary amines in good to excellent yields (26 examples). Transfer hydrogenation of aromatic nitriles with pyridine-based PNN cobalt complex **9** in hexafluoroisopropanol (HFIP) at room temperature surprisingly led to the formation of the symmetric secondary amines in good to excellent yields. A few aliphatic nitriles also gave the secondary amines, but in mediocre yields. If the same hydrogenation was performed in the presence of primary or secondary amines, the

Scheme 12 Transfer hydrogenation of nitriles catalysed by cobalt complexes **8** and **9**

$$R-C \equiv N \xrightarrow{NH_3\text{-}BH_3}$$

1 mol% **8**

50°C, hexane

$$\rightarrow R \diagup NH_2$$

0.5 mol% **9**

HFIP, rt

$$\rightarrow R \diagdown N(H) \diagup R$$

0.5 mol% **9**

R^1NHR^2

HFIP, rt

$$\rightarrow R \diagdown N \diagup R^2, R^1$$

8   **9**
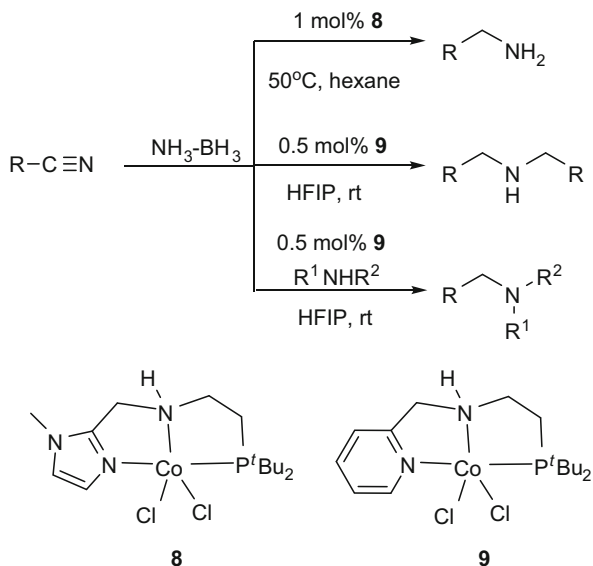
nonsymmetrical secondary and tertiary amines were formed, respectively. The analogous catalysts in which the ligand was N-methylated gave very similar results in the hydrogenation of benzonitrile as the non-methylated catalysts. Based on this observation, the authors assumed that these reactions proceed via an inner-sphere mechanism.

2.2 Hydrogenation of Nitriles to Imines

We have already seen the formation of secondary imines in the previous section, as an unwanted side reaction, which needed to be repressed, here we discuss the on-purpose hydrogenation of nitriles to the imines. A range of metal pincer complexes has been used for the hydrogenation of nitriles to the imines (Scheme 13).

The first selective hydrogenation of nitriles to secondary imines using a pincer complex as catalyst was reported by the Milstein group [33]. In the absence of amines, benzonitriles with electron-donating substituents (H, methyl, methoxy) could be reduced to the corresponding symmetrical secondary imines at 70°C under 4 bar H_2 using the bipyridine-based PNN Ru pincer complex **13** in excellent yields (Table 5). Using the same conditions, addition of (cyclo-)hexylamine led to hydrogenative cross-coupling forming unsymmetrical secondary imines. This reaction was shown to have a broad substrate scope with (hetero)aromatic and aliphatic nitriles forming the unsymmetrical imines in good to excellent yields. Electron-withdrawing substituents are not well-tolerated as *para*-fluoro-benzonitrile formed the imine in only 50% yield.
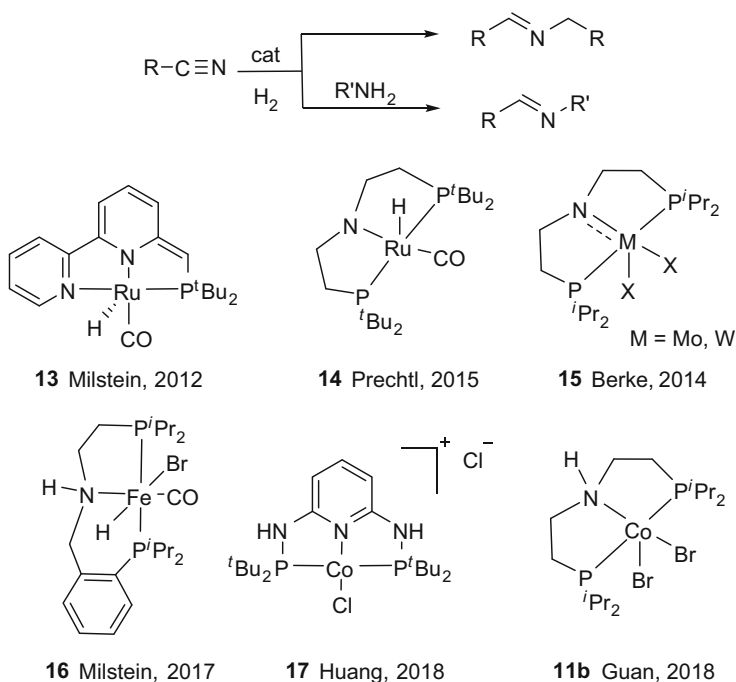
Scheme 13 Hydrogenation of nitriles to imines by pincer complexes

In view of all the possible equilibria between the imines and amines during the hydrogenation (see also Scheme 3), it can be rather challenging to obtain high selectivity to a single product. Interestingly, Choi and Prechtl managed to selectively synthesise either imines or amines by simply tuning solvent and temperature in the hydrogenation of nitriles with complex **14** [34]. At 50°C in toluene under 4 bar H_2, six nitriles could be reduced to the imines with or without addition of amines. However, at 90°C in isopropanol under 4 bar H_2, it was possible to selectively hydrogenate the nitriles to the amines, and five primary amines were obtained in moderate to excellent yields (Scheme 14).

Berke and Chakraborty used non-noble metal pincer complexes based on molybdenum and tungsten as catalyst for the hydrogenation of nitriles to secondary imines [35]. Using the molybdenum PNP^{iPr} complex **15a**, ten substrates, including aromatic, heteroaromatic and aliphatic nitriles, were reduced with up to >99% conversion and >96% selectivity (Table 6). Both electron-donating substituents (methyl and methoxy) and electron-withdrawing substituents (CF_3, F, Br, Cl) are tolerated. The analogous tungsten complex **15b** was much slower, although in some cases more selective towards formation of the desired secondary imine.

Chakraborty, Milstein and co-workers synthesised iron PNP pincer complex **16** in 47% yield in three steps [36]; this catalyst needs to be activated by treatment with an equivalent of ^{t}BuOK. It was used for the hydrogenative cross-coupling of

Table 5 Hydrogenation of nitriles to imines by **13**[a]

$$R-C\equiv N + R'NH_2 \xrightarrow[\substack{THF, 70^oC \\ -NH_3}]{\substack{0.6 \text{ mol% } \mathbf{13} \\ 4 \text{ bar } H_2}} R\diagup N \diagdown R'$$

[b]R1 = H 88%	R1=H 85%
R1 = Me 81%	R1=Me 84%
R1 = OMe 92%	R1=OMe 90%
	R1=F 50%
R1 = H 91%	81% [c]
R1 = OMe 85%	
80%	74%
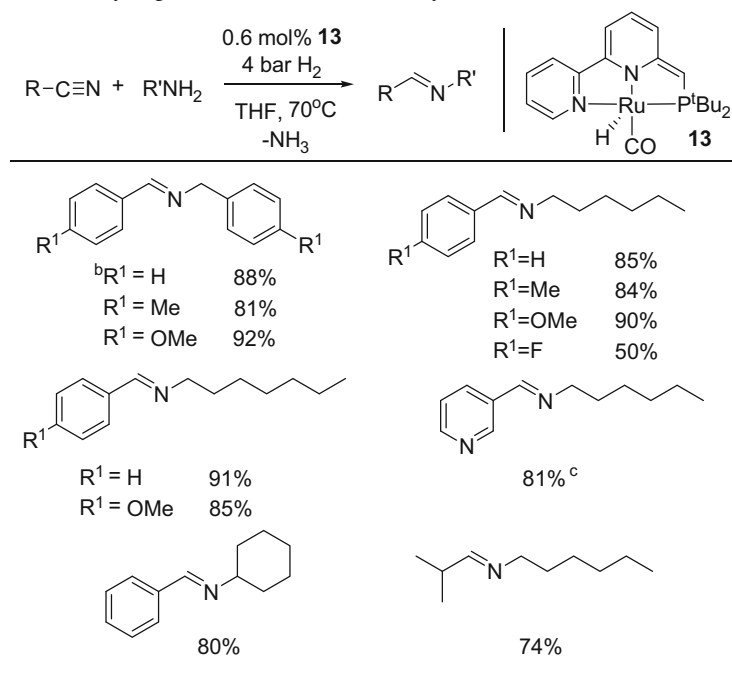
[a]Yields of the products and conversion of nitriles were determined by gas chromatography (GC) using toluene as an internal standard
[b]no amines added; [c]0.8 mol% catalyst was used

$$R\diagup N \diagdown R \text{ or } R\diagup N{\diagdown}R' \xleftarrow[\substack{90\ ^oC, 4 \text{ bar } H_2 \\ toluene}]{\substack{\text{Optionally:}RNH_2 \\ 1 \text{ mol% } \mathbf{14}}} R{-}C\equiv N \xrightarrow[\substack{50\ ^oC, 4 \text{ bar } H_2 \\ {^i}PrOH}]{0.5 \text{ mol% } \mathbf{14}} R\diagup NH_2$$
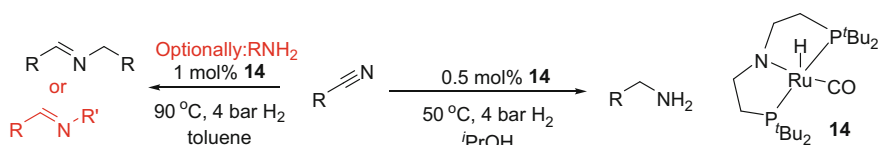
Scheme 14 Tunable hydrogenation of nitriles to imines or amines by **14**

(hetero)aromatic nitriles with amines and anilines at 60°C and 20 bar H_2 with benzene as the solvent, which resulted in good to excellent yields of the imines (Table 7). The more challenging aliphatic nitriles were still sluggishly reduced (5–58% yields) even at higher temperatures and/or higher catalyst/base loading.

This catalyst was also used for the hydrogenation of nitriles to symmetrical secondary imines at higher temperature and pressure (90°C and 30 bar) (Scheme 15) [37]. With low catalyst loadings (1–2 mol%), benzonitriles with electron-donating (Me, MeO, NMe$_2$) substituents and *p*-fluorobenzonitrile were hydrogenated to the imines in moderate to excellent yields. Heteroaromatic nitriles required 2 mol%

Table 6 Hydrogenation of nitriles by **15a,b**[a]

R−C≡N $\xrightarrow[\text{THF, 140}^{o}\text{C, 60 bar H}_2]{\text{5 mol\% \textbf{15a} or \textbf{15b}}}$ R—CH=NH + R—CH₂—NH₂ + R—CH=N—CH₂—R
(a)   (b)   (c)

15a (Mo complex): N—Mo(—P^{i}Pr₂)(—NO)(—CO)(—P^{i}Pr₂)

15b (W complex): N—W(—P^{i}Pr₂)(—NO)(—CO)(—P^{i}Pr₂)
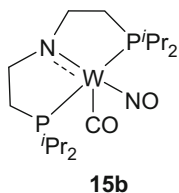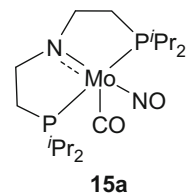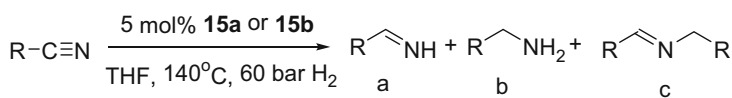
Entry	Substrates	Cat	Time (h)	Conversion (%)	Sel(%) (a:b:c)
1-2	(phenyl)—CN	15a 15b	<4 14	>99 91	10 : 0 : 90 26 : 0 : 74
3-4	(methyl-phenyl)—CN	15a 15b	<6 16	>99 3	0 : 10 : 90 0 : 0 : 100
5	MeO—(phenyl)—CN	15a	<6	>99	0 : 7 : 93
6-7	CF₃-(phenyl)—CN	15a 15b	<6 14	>99 0	0 : 22 : 78 0
8	Br—(phenyl)—CN	15a	16	98	4 : 0 : 96
9-10	(cyclohexyl)—CN	15a 15b	<4 16	>99 14	0 : 22 : 78 0 : 0 : 100
11	(benzyl)—CN	15a	14	40	0 : 0 : 100
12-13	(thiophene)—CN	15a 15b	<8 14	>99 0	43 : 8 : 49 0
14	F,F-(phenyl)—CN	15a	6	>99	4 : 0 : 96
15	F,Cl-(phenyl)—CN	15a	14	22	54 : 0 : 46

[a]Conversions and selectivity were determined by GC/MS on the basis of substrate consumption [b]Sel = selectivity

Table 7 Hydrogenation of nitriles to imines by **16**[a]

$$R-C\equiv N \ + \ R'-NH_2 \xrightarrow[\substack{C_6H_6,\ 60^\circ C,\ 10\text{-}20\ bar\ H_2 \\ -NH_3}]{\substack{1\ mol\%\ \mathbf{16} \\ 1mol\%\ {}^tBuOK}} R\diagup\!\!\!{}^N\diagdown^{R'}$$

16

R^1 = H 96%	96%	88%
R^1 = o-Me 98%		
R^1 = p-OMe 96%		
R^1 = p-Cl 97%	64%	89%
R^1 = p-Br 66%		
10%[b]	37%[b]	58%[b]
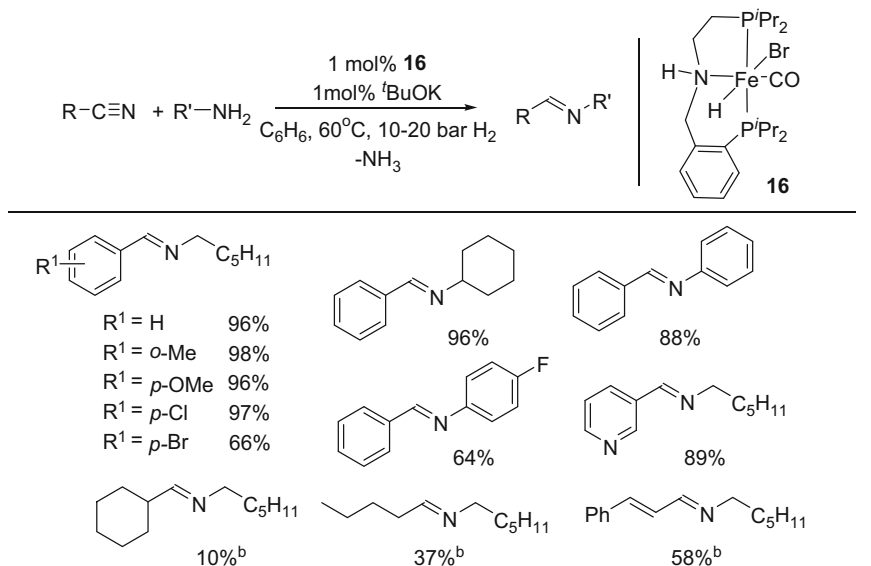
[a]Yields and conversions determined by GC-MS and NMR analysis using m-xylene or toluene as internal standards   [b]8 mol% Catalyst used

$$R-C\equiv N \xrightarrow[\substack{C_6H_6,\ 90^\circ C,\ 30\ bar\ H_2 \\ -NH_3}]{1\text{-}8\ mol\%\ cat\ and\ {}^tBuOK} R\diagup\!\!\!{}^N\diagdown R$$

16
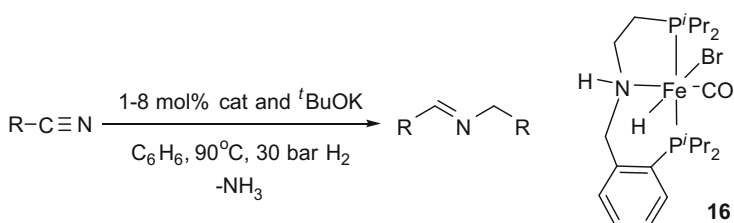
Scheme 15 Hydrogenation of nitriles to symmetrical imines by **16**

catalyst loading to reach high conversions and yields. For the more challenging aliphatic nitriles, a decrease in conversion and yields (11–69%) was observed, even when using 8 mol% catalyst loading.

The Milstein group proposed the same mechanism for this reaction as the one they had published earlier (Scheme 16) [36]. The bromide complex is deprotonated by base forming the amido complex **I**, which reacts with hydrogen to the *cis*-dihydride complex **II**, which they assume will isomerise to the (unobserved) *trans*-complex **III**. The *trans*-dihydride complex, which they assume to be the active species, reduces the nitriles (or primary imines) to primary imines (or amines) regenerating the amido complex via hydride and proton transfer. Then the
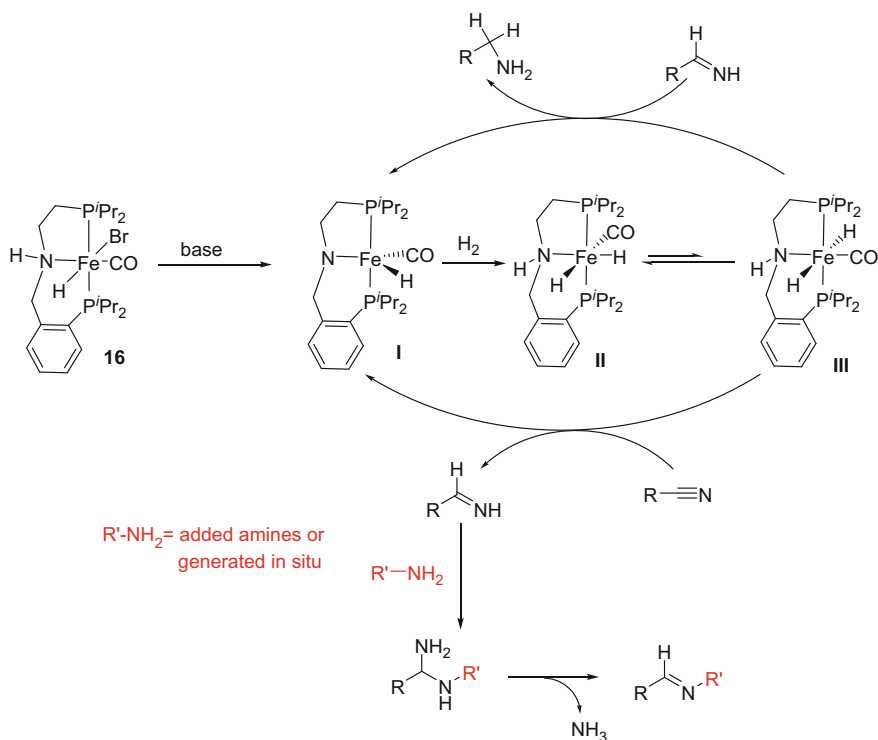
Scheme 16 Hydrogenation of nitriles to imines by **16**
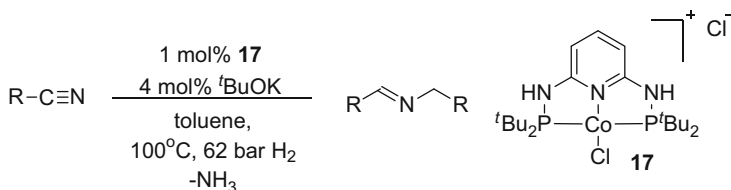
Scheme 17 Hydrogenation of nitriles to imines by **17**

intermediary primary imines may react with the added or produced amines giving a *gem*-diamine. After liberation of ammonia, the desired imine is produced.

Huang and co-workers reported the synthesis of Co-PN^{3}P pincer complexes and their application in the hydrogenation of nitriles to secondary imines [38]. At 62 bar of H$_2$, 100°C and using toluene as solvent, high selectivity and excellent yields of the imines could be achieved with only 1 mol% of catalyst **17** and 4 mol% base (Scheme 17). Under the same catalytic conditions, more challenging substrates (heterocyclic and aliphatic nitriles) were also converted to the corresponding imines with moderate to good yields.
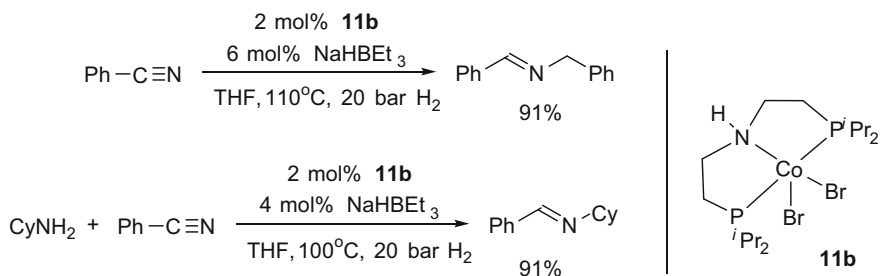
Scheme 18 Hydrogenation of benzonitrile to imines by **11b**

Guan and his co-worker used the Co-PN^{H}P complex **11b** to catalyse the selective hydrogenation of benzonitrile to secondary imines with or without an added amine (Scheme 18) [39]. Both reactions proceeded in excellent yields.

3   α-Functionalisation of Nitriles

3.1   *α-Alkylation with Alcohols*

The first ruthenium-catalysed α-alkylation of nitriles by alcohols was reported by Grigg almost 40 years ago [40]. This is a borrowing hydrogen-type reaction, in which the alcohol is dehydrogenated to the aldehyde, which undergoes a Knoevenagel reaction with the nitrile. After dehydration, the formed double bond is reduced with the hydrogen equivalents that were obtained in the first dehydrogenation step, leading to a net alkylation. Many transition metal complexes, mostly based on noble metals, were developed in this field. Esteruelas and co-workers successfully synthesised a series of Ru and Os pincer complexes based on xantphos [41]. They reported the alkylation of phenylacetonitrile with benzyl alcohol and 1-octanol, catalysed by Ru pincer complex **18** with 20 mol% base at 110°C using toluene as solvent (Scheme 19). The alkylation products were obtained in 79% yield with TOF$_{50\%}$ = 18 h^{-1} (benzyl alcohol) and 68% yield with TOF$_{50\%}$ = 1.4 h^{-1} (1-octanol).

R = Ph   79%; TOF$_{50\%}$ = 18 h^{-1}
R = (CH$_2$)$_6$CH$_3$ 68%; TOF$_{50\%}$ = 1.4 h^{-1}
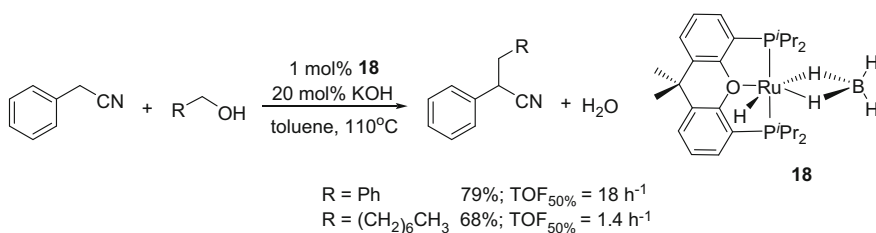
Scheme 19 Alkylation of benzyl nitrile with alcohols by **18**

Table 8 Alkylation of nitriles with alcohols by **19**[a]

$$R^1 \diagdown CN + R^2 \diagdown OH \xrightarrow[\substack{\text{toluene} \\ 135^\circ C, 4 \text{ h}}]{\substack{0.5 \text{ mol\% } \mathbf{19} \\ 1 \text{ mol\% KO}^t\text{Bu}}} \underset{R^1}{\overset{CN}{\diagdown}} R^2 + H_2O$$

[structure of catalyst **19**: Ru-MACHO complex]

91%	95%	61%
93%	96%	97%
90%	96%	83%[b]
66%[b]	61%[c]	83%[c]
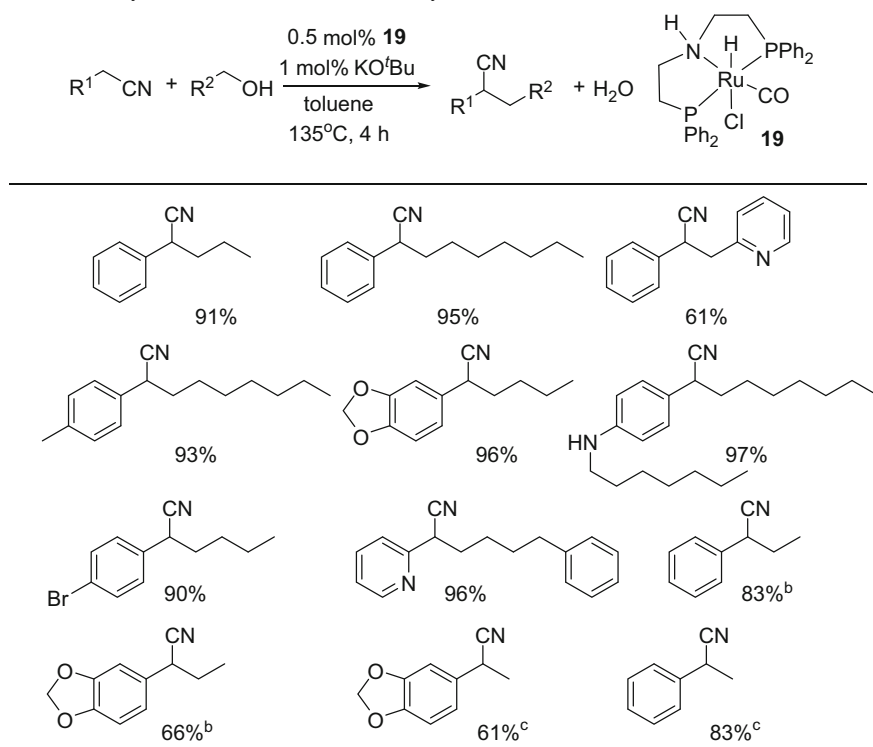
[a]Isolated yield of products after column chromatography [b]Catalyst (2 mol %), and KO^{t}Bu (4 mol %) [c]Catalyst (2.5 mol %), and KO^{t}Bu (5 mol %), 40 h

Gunanathan investigated the same reaction using the ruthenium-MACHO catalyst **19** [42]. The reaction was performed at an oil-bath temperature of 135°C in toluene with 0.5–2.5 mol% catalyst and 2 eq. ^{t}BuOK (relative to catalyst). In this way, the α-alkylation of arylmethyl nitriles with primary alcohols was achieved with moderate to excellent yields and a broad substrate scope, including amino, halogen, methyl and methoxy substituents, on the aromatic nitrile (Table 8). 2-Pyridyl-substituted alcohols could also be used. Notably, the more challenging low-boiling alcohols (methanol and ethanol) could also be applied in this reaction, omitting the toluene as solvent at an oil-bath temperature of 135°C, resulting in synthetically useful yields (42–83%).

The mechanism they proposed contains the following steps (Scheme 20): the catalyst is activated with base to form the amido complex **I**. This complex undergoes two separate reactions: on the one hand, it dehydrogenates the alcohol to the aldehyde via alkoxy species **IV**, which undergoes β-hydrogen elimination to form the aldehyde and the dihydride complex **V**. **I** also reacts with the alkyl nitrile to form
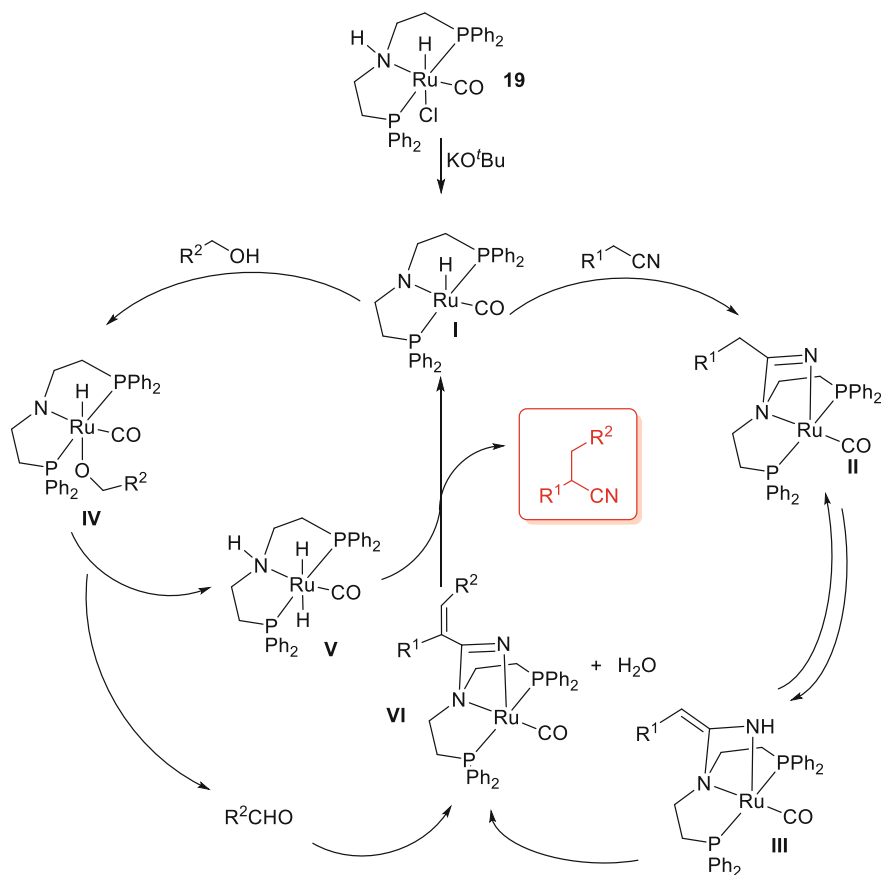
Scheme 20 Mechanism proposed by Gunanathan for the alkylation of nitriles with alcohols catalysed by **19**

the imine species **II** via metal-ligand cooperation, which isomerises to the enamine form **III**. The complex **III** then reacts with the aldehyde and loses water to form species **VI**. This species releases the α,β-unsaturated nitrile, which is reduced by complex **V** to the α-alkylated nitrile. It should be stated, though, that four-membered unsaturated metalla-aminals such as **II**, **III** and **VI** are unprecedented and no proof for their existence was offered by the authors. An alternative mechanism via base-catalysed aldol condensation of the alkyl nitrile on the aldehyde seems more likely. More recently, calculations were performed by Zhang and co-workers, showing that the mechanism of Scheme 20 is unlikely in view of the high barriers involved [43]. Instead, their calculations favour the end-on mechanism as shown in Scheme 22 (bottom part).

Zhu, Hao and co-workers synthesised a series of Ru NNN complexes based on bipyridyl imidazoline ligands and investigated the use of these complexes as
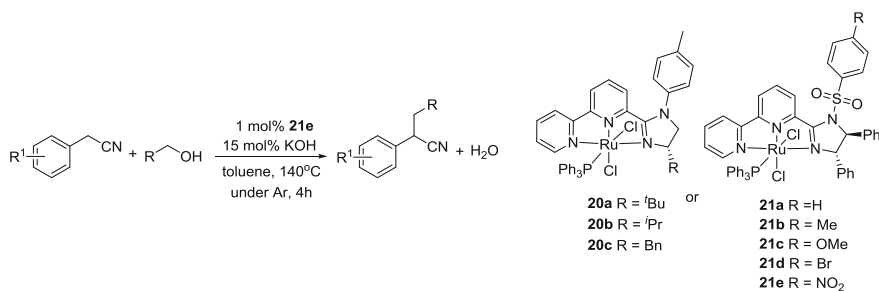
**Scheme 21** Alkylation of benzyl nitriles with alcohols by Ru NNN pincer complexes

catalysts for the α-alkylation of arylmethyl nitriles with primary alcohols (Scheme 21) [44]. With complex **21e,** which showed the highest rates, a variety of alkylated nitriles could be successfully synthesised with 20–97% isolated yields at 140°C in toluene using 1.5 mol% catalyst loading and 0.15 eq. base additive. In most reactions benzyl alcohol or substituted benzyl alcohols were used as alkylating agents.

3.2 α-Olefination of Benzyl Cyanide and Aliphatic Nitriles with Alcohols

Milstein reported the α-olefination of nitriles with primary alcohols using Mn pincer complex **22** as catalyst [45]. This complex catalysed the dehydrogenative coupling of benzylic alcohols or purely aliphatic alcohols with (substituted) arylmethyl nitriles without any additives, resulting in moderate to excellent yields of the α,-β-unsaturated nitriles. Notably, the α-olefination of benzyl cyanide with cinnamyl alcohol resulted in the diene in a very good yield (81%) (Table 9).

Gunanathan and co-workers used the ruthenium-MACHO catalyst **19** for the olefination of (substituted) benzyl cyanide or aliphatic nitriles with secondary alcohols (Table 10) [46]. The reaction needs 2 eq. of base relative to **19**; it not only serves to activate the catalyst but is also needed as catalyst for the Knoevenagel reaction. The reaction was performed in toluene at an oil-bath temperature of 135°C leading to the formation of the desired products in 20–93% yield. A broad substrate scope was achieved with methyl, methoxy, vinyl and halogen substituents on the aryl rings of the benzyl cyanide part. 2-Pyridin-2-ylacetonitrile was also used as substrate as were aliphatic nitriles and dinitriles. Most of the alkylations were performed with symmetrical secondary alcohols, such as cyclohexanol as this leads to a single product. Unsymmetrical secondary alcohols were also used in a number of cases, but their use leads to the formation of a mixture of *E*- and *Z*-isomers.
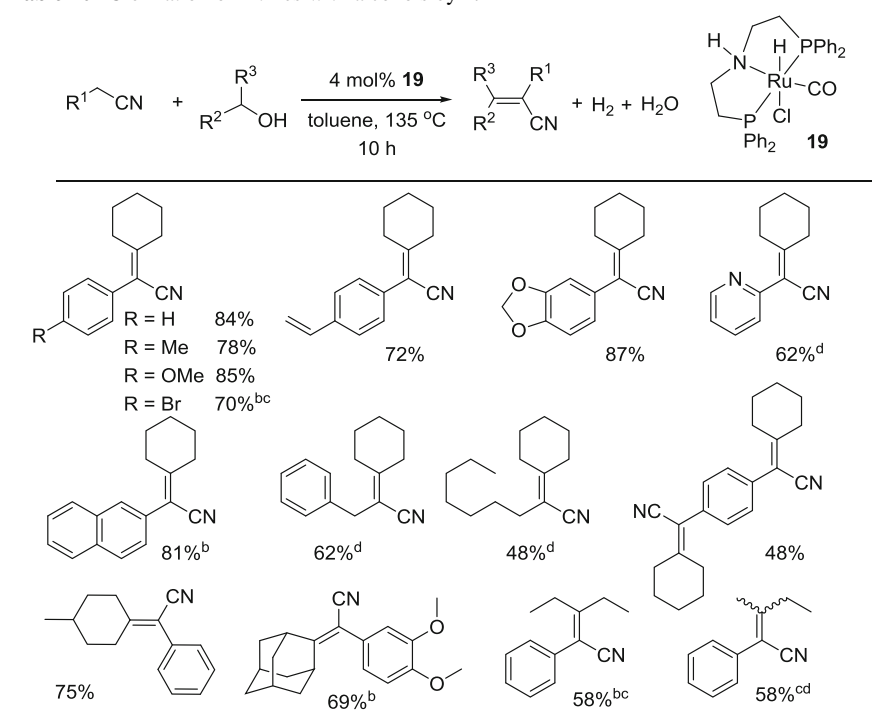
The proposed mechanism (Scheme 22, top) starts with the dehydrogenation of the alcohol by activated catalyst **II** via alkoxide complex **III** forming the corresponding

Table 9 Olefination of nitriles with primary alcohols catalysed by **22**[a]
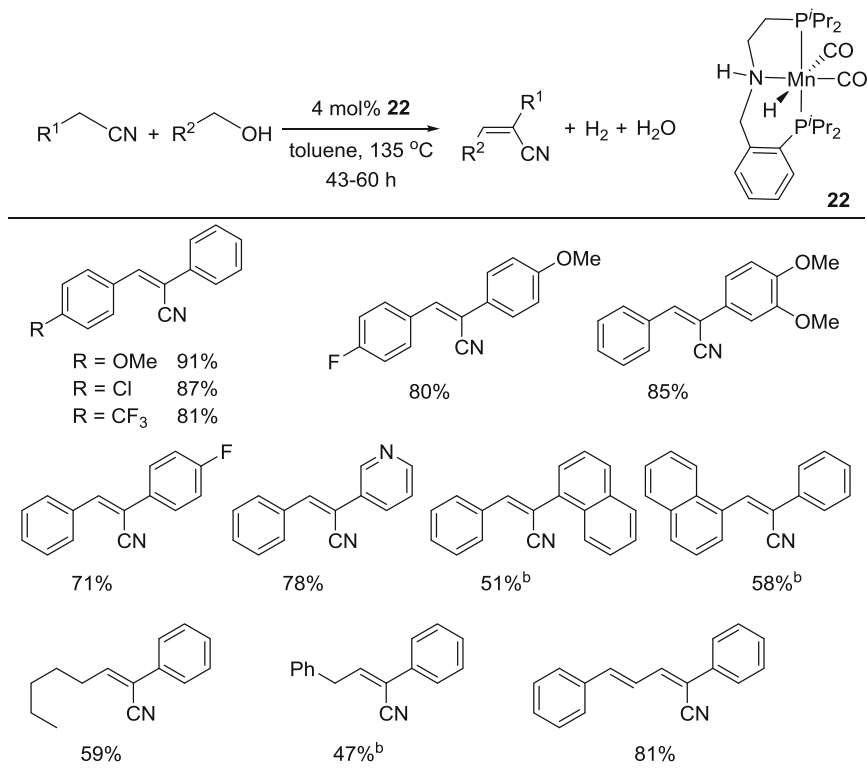
[a]Isolated yields [b]Yield by GC or NMR analysis using N,N-dimethylaniline internal standard

aldehydes or ketones by β-hydride elimination leading to the dihydride complex **IV**, which can lose hydrogen to reform **II**. Next, a Knoevenagel reaction between the nitriles and the in situ-formed aldehydes or ketones takes place catalysed by the extra base or by the Mn catalyst, which occurs via proton abstraction by the amide group in the activated complex. This latter mechanism, proposed by Milstein, was put in doubt by Sola, Poater and co-workers, who published an alternative version, based on DFT calculations, in which the activated complex **II** reacts with benzyl cyanide to form a (2-phenylvinylidene)amide manganese complex **V**, which is the nucleophile in the aldol condensation reaction leading to complex **VI**, which eliminates the nitrile (Scheme 22, bottom) [47].

Balaraman used manganese catalyst (**6b**) based on the MACHO ligand for the olefination of substituted and unsubstituted benzyl cyanides using mostly cyclic secondary alcohols such as cyclohexanol (Scheme 23) [48]. A total of 36 α, β-unsaturated nitriles were synthesised in this way with yields ranging from 20 to 88%.
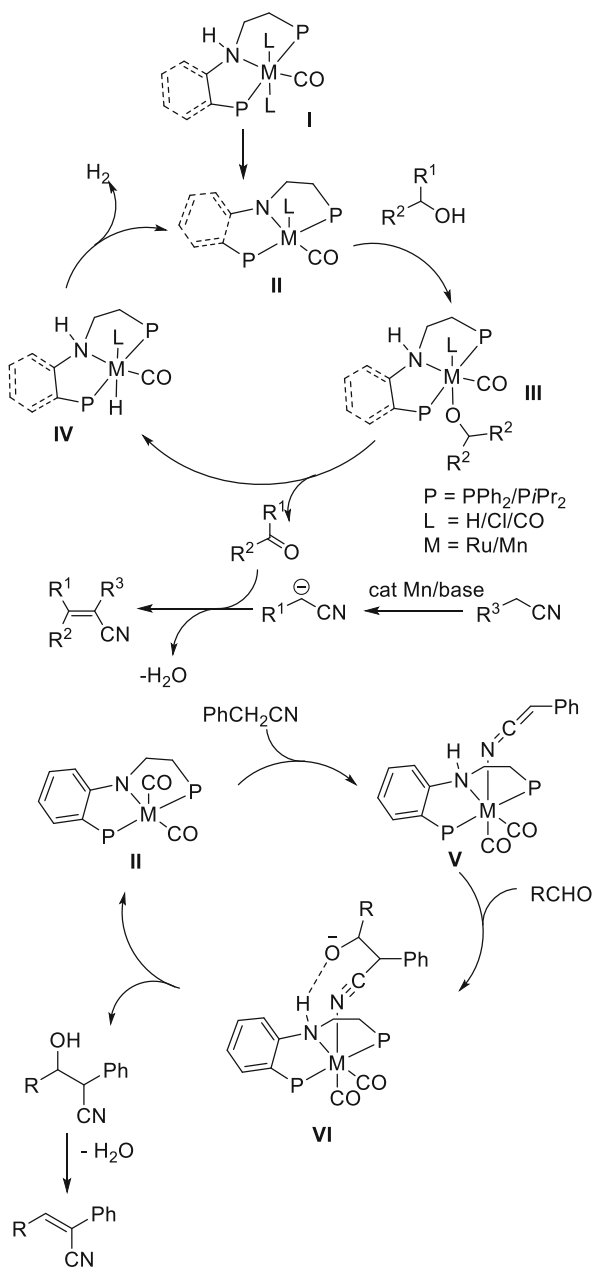
Table 10 Olefination of nitriles with alcohols by **19**[a]

$$R^1 \smile CN \; + \; \underset{R^2}{\overset{R^3}{\diagup}}\!\!\!\diagdown OH \xrightarrow[\text{toluene, 135 }^{\circ}\text{C}]{\text{4 mol\% }\mathbf{19}} \; \underset{R^2}{\overset{R^3 \quad R^1}{\diagdown}}\!\!\!=\!\!\!\underset{CN}{\diagup} \; + \; H_2 + H_2O$$

R = H	84%
R = Me	78%
R = OMe	85%
R = Br	70%[bc]

72%   87%   62%[d]

81%[b]   62%[d]   48%[d]   48%

75%   69%[b]   58%[bc]   58%[cd]

[a]Isolated yields [b]Using 2 mol % catalyst and 4 mol % base [c]Reaction time of 24 h
[d]Using 5 mol % catalyst 1 and 10 mol % base

3.3 α-Alkylation of Aliphatic and Benzylic Nitriles via Michael Addition on Unsaturated Ketones or Esters

Milstein and co-workers studied the reactivity of a Re complex based on a pyridine-containing PNP[tBu] pincer with nitriles and found novel pathways for the activation of the C≡N bond [17]. Based on the aromatisation and dearomatisation of the pyridine in the ligand backbone, the stoichiometric reaction of nitriles with the pincer complex **24** resulted in ketimido or enamino adducts, with remarkably low energy barriers. In addition, these processes are highly reversible (Scheme 24), opening the way to a lot of interesting reactivities. Taking advantage of these, they successfully demonstrated the Michael addition of benzyl nitriles to α,β-unsaturated esters and ketones with moderate to excellent yields (Table 11).

Based on the stoichiometric studies, they proposed the following mechanism: reaction of **24** with benzyl cyanide leads to the enamido complex **I**. This complex reacts as a nucleophile in a Michael reaction on methyl acrylate to form the

Scheme 22 Proposed mechanisms for olefination of nitriles with alcohols by pincer complexes

P = PPh$_2$/PiPr$_2$
L = H/Cl/CO
M = Ru/Mn
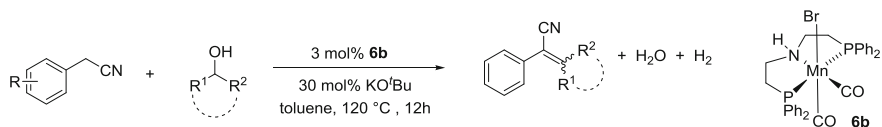
Scheme 23 Manganese-catalysed olefination of benzyl cyanides with secondary alcohols
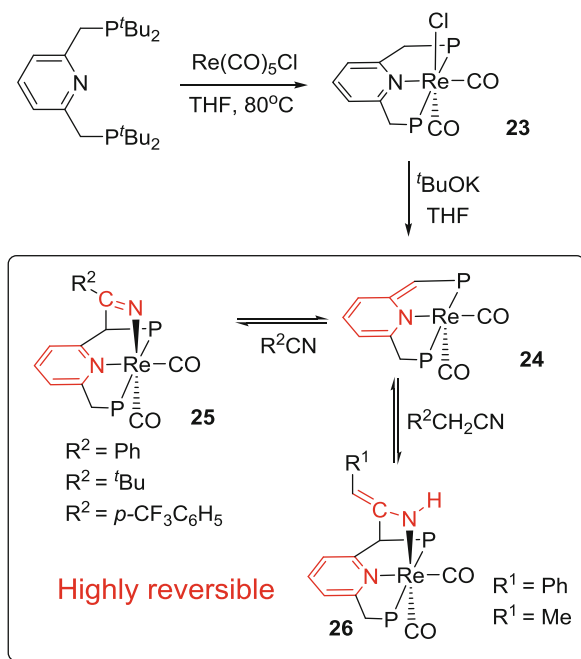

Scheme 24 Activation of nitriles via metal-ligand cooperation (MLC) by Re-pincer complex **24** (^{t}Bu groups on P atoms omitted for clarity)

zwitterionic intermediate **II**. Proton transfer leads to ketimido intermediate **III**, which undergoes elimination to form starting complex **24** and the alkylated benzyl cyanide (Scheme 25).

The same group also reported the synthesis of the manganese pincer complex **25** based on the same ligand [49]. Interestingly, this catalyst was able to catalyse the same Michael reaction with lower catalyst loading and at a lower temperature. This paper mainly focused on fully aliphatic nitriles (Table 12). The effect of α- or β-substituents on the acrylate substrate was also investigated. Whereas the presence of an α-methyl group had no deleterious effect, the presence of a β-methyl group led to formation of the alkylated product in only 18% yield.

More recently, Milstein and co-workers prepared pyridine-based PCP-ruthenium complexes in which the pyridine is bound via the carbon atom in the 4-position to
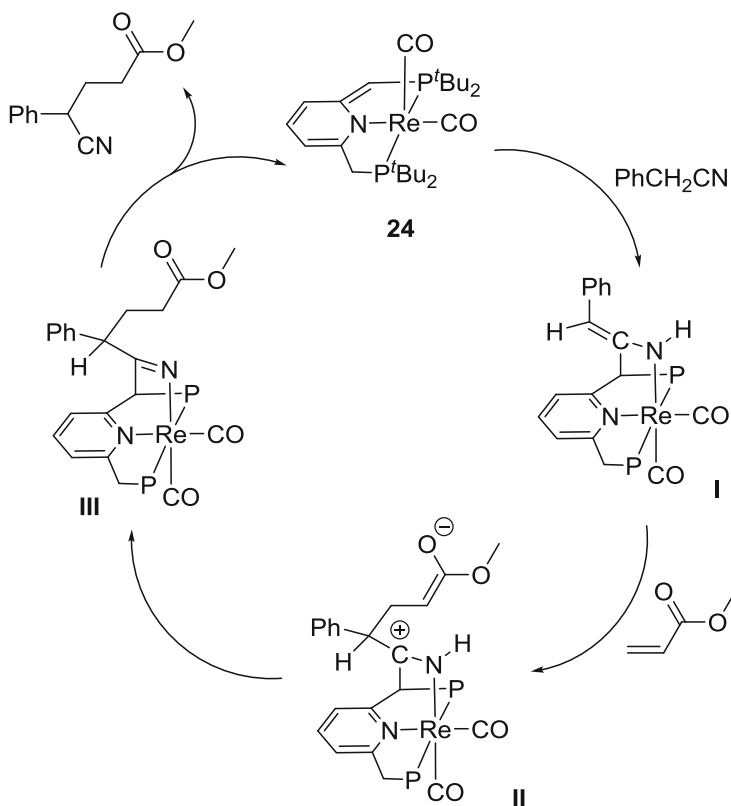
Table 11 Michael addition of benzyl nitriles to α,β-unsaturated esters and ketones by **24**[a]
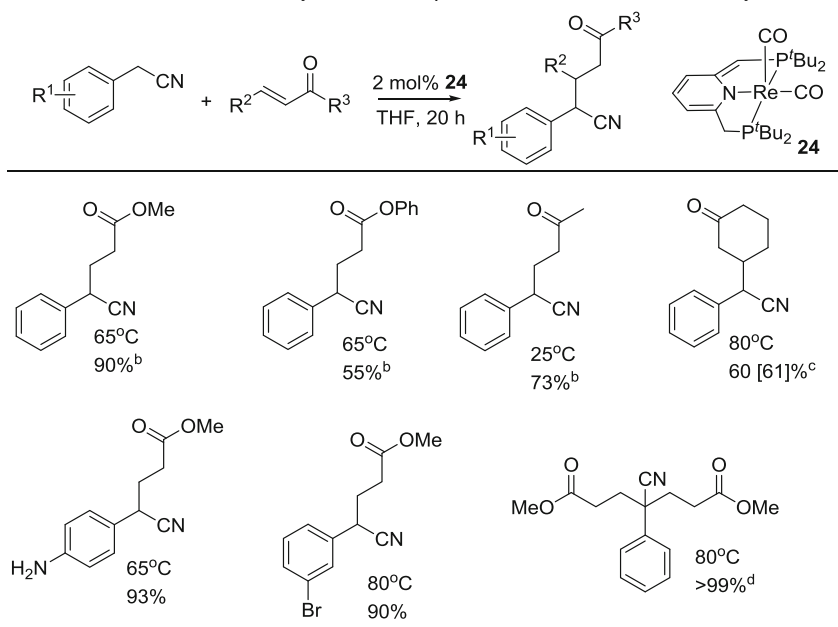
[a] Conversion with respect to the Michael acceptor (determined by GC); yield determined by NMR [b] 2 mol% catalyst [Re(PNP^{t}Bu-HNC=CHPh)(CO)$_2$] [c] Michael addition product obtained as a 1:1 mixture of diastereomers; number in bracket is conversion [d] 1 mol% catalyst loading, reaction time 12 h

ruthenium [50]. This unusual structure is still capable of activating the C≡N bond via metal-ligand cooperation. Under the influence of base, the methylene group in the side arm is deprotonated, and the ensuing negative charge is delocalised across the pyridine ring. This negatively charged species can react with nitriles as before leading to ketimido adduct **27** (Scheme 26). This adduct was used as catalyst for the double Michael reaction of benzyl cyanide on ethyl acrylate (2 eq.). If only one equivalent of ethyl acrylate was used, a mixture of mono- and dialkylated benzyl cyanide was obtained.

3.4 α-Deuteration of Nitriles

Gunanathan reported the selective deuterium labelling of aliphatic nitriles at the α-position using D$_2$O as deuterium source [51]. With 2 eq. of base relative to catalyst and D$_2$O as solvent, ruthenium-MACHO complex **19** catalysed the α-deuteration of nitriles resulting in 50–96.5% labelling (Scheme 27). Remarkably, a broad range of

Scheme 25 Proposed mechanism for the Michael addition of benzyl nitriles to α,β-unsaturated esters and ketones catalysed by **24** (^{t}Bu groups omitted for clarity)

functional groups including amide, ester, thiol, amine, indole and heterocycles were tolerated. The authors propose a mechanism in which the nitrile adds across the ruthenium-nitrogen bond of the activated catalyst **I** to form a four-membered metallacycle **II** containing an imine group (Scheme 27). This complex can isomerise to the enamide form **III** in which the NH is exchanged for deuterium to form **IV**; isomerisation back to the imine form **V** and elimination of the nitrile complete the first deuteration step. The authors observe a species at m/z 669 which they propose as the protonated form of the fully deuterated adduct **V′**.

However, as discussed in Sect. 3.1 (Scheme 20), Zhang and co-workers performed DFT calculations on a similar mechanism involving structures **II** and **III** and concluded that the occurrence of such intermediates is highly unlikely in view of the high barriers that need to be overcome [52]. The species at m/z 669 is more easily explained by the end-on nitrile adduct **VI** or by the ketenimide adduct **VIII** (Scheme 28; see also structure **V** in Scheme 22). Deuterium exchange with D$_2$O can either occur by deprotonation at the carbon centre α to the nitrile, the acidity

Table 12 Michael addition of nitriles to α,β-unsaturated esters and ketones catalysed by **25**[a]
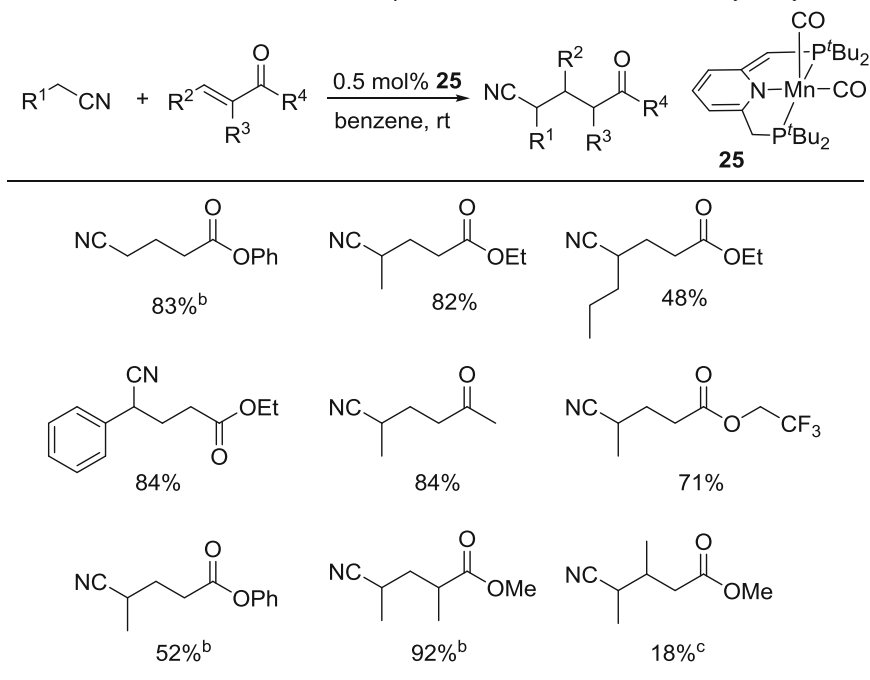
[a]Isolated yields [b]nitriles were used as solvent [c]The yields were determined by 1H NMR spectroscopic analysis using an internal standard
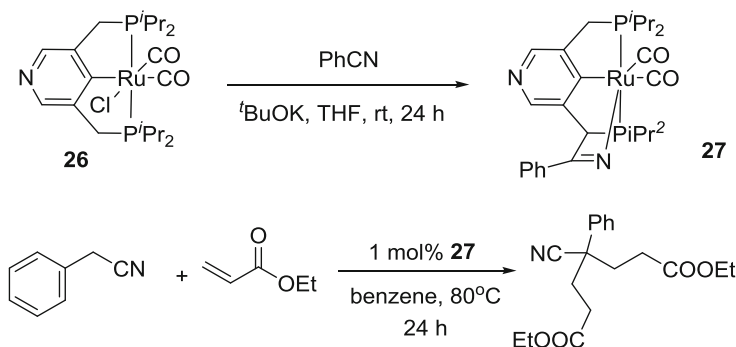
Scheme 26 Michael addition of benzonitrile to α,β-unsaturated ester catalysed by **26**

of which is increased by coordination to the Lewis acidic metal centre. Alternatively, deprotonation/deuterium exchange can be facilitated by the basicity of the amido-N atom in the ligand backbone (Scheme 28).
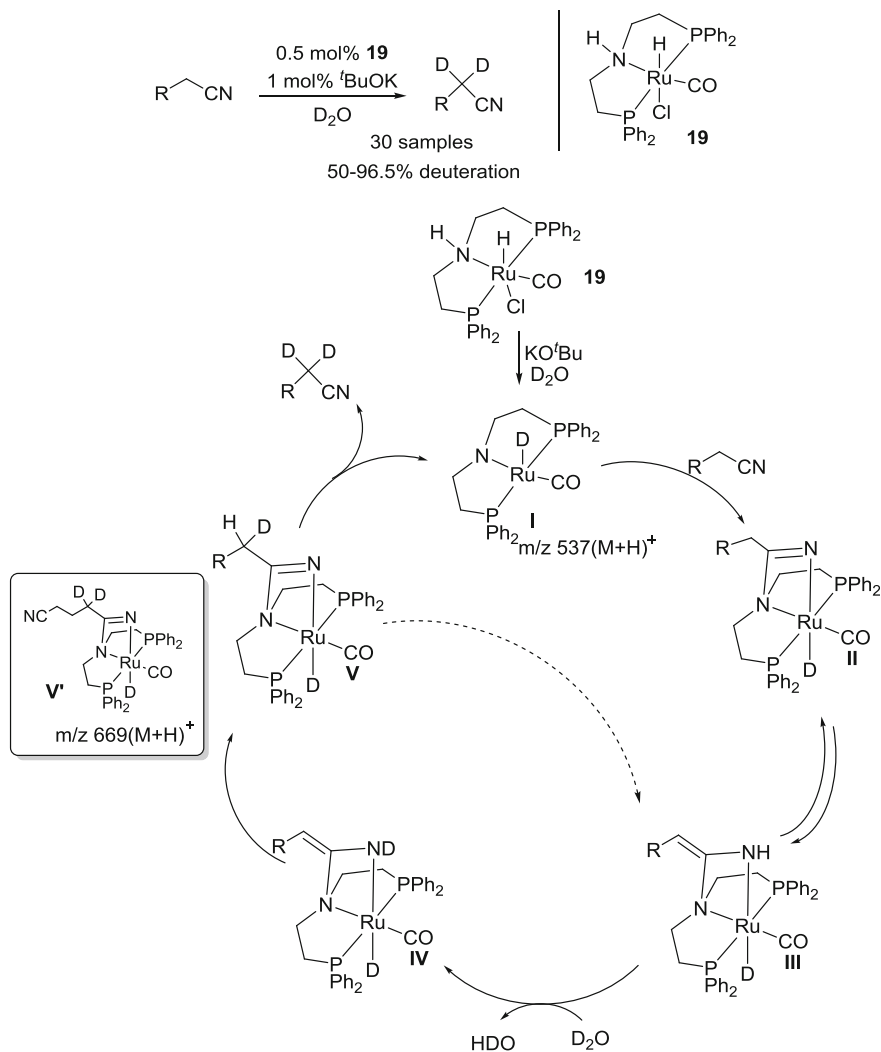
Scheme 27 Proposed mechanism for the α-deuteration of aliphatic nitriles catalysed by **19**

3.5 α-Acylation of Unsaturated Nitriles

Szymczak and co-workers reported the hydrogenative acylation of α,β-unsaturated nitriles catalysed by a ruthenium pincer complex [53]. The reaction, which was performed with 4 eq. of the anhydride, complex **28** as catalyst at 100°C and 7 bar H_2, using toluene as solvent and DBU as base, resulted in the desired products in good to excellent yields (Table 13). The reaction worked well on aliphatic as well as benzylic nitriles, and electron-donating as well as electron-withdrawing substituents on the
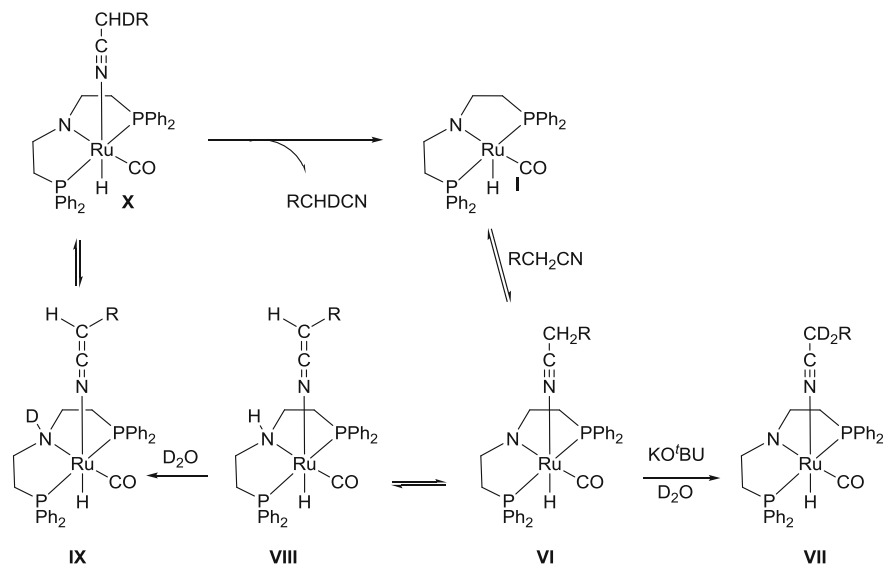
Scheme 28 Alternative mechanisms for the α-deuteration of aliphatic nitriles catalysed by **19**

Table 13 Hydrogenative acylation of α,β-unsaturated nitriles by **28**[a]

95%

R = OMe 83%
R = CF$_3$ 74%

R = OMe 78%
R = CF$_3$ 85%

84%[b]

79%[b]

81%
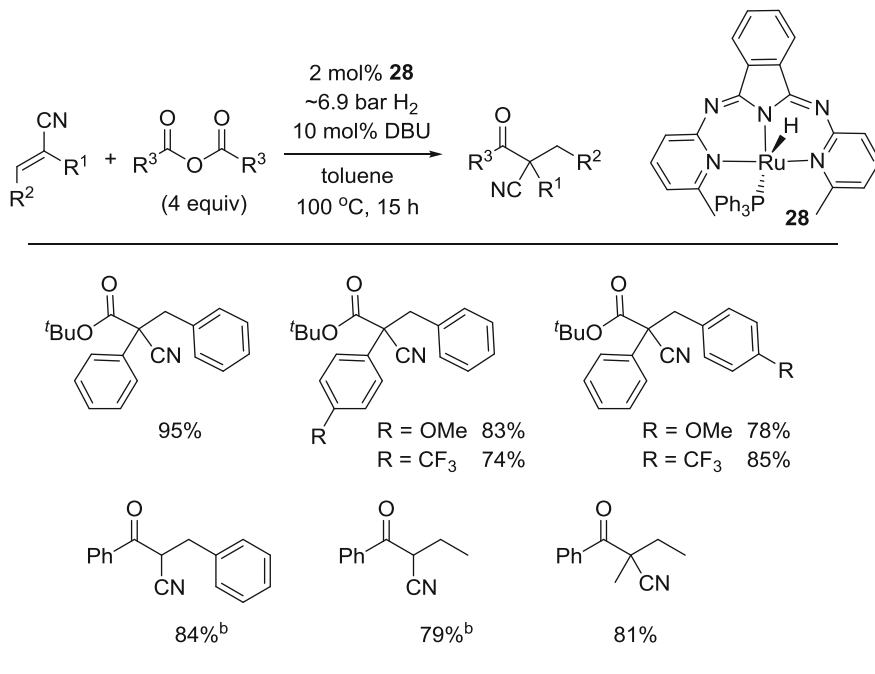
[a] Isolated yields [b] Reaction performed at 150°C in mesitylene
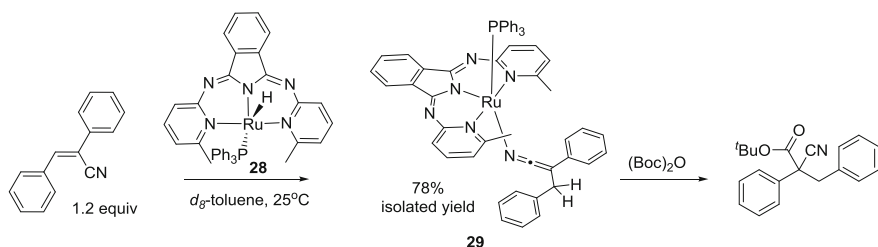
Scheme 29 Synthesis of keteniminate adduct from **28** and 2,3-diphenylacrylonitrile and its reaction with Boc anhydride

aromatic rings were well-tolerated. Since acylation of saturated nitriles under the reaction conditions failed, the authors proposed that the role of DBU is solely to activate the anhydrides, but it does not promote the base-assisted acylation of the reduced nitriles. Stoichiometric reaction between **28** and 1,2-diphenylacrylonitrile allowed the successful isolation and characterisation of complex **29** (Scheme 29). Since **29** reacted stoichiometrically with (Boc)$_2$O to form the acylated product, their hypothesis that the reaction proceeds via the intermediacy of keteniminates like **29** seems highly likely.

## 3.6 Aldol and Mannich Reactions with Aldehydes or Protected Imines

The combination of a transition metal complex with a base can function as an efficient catalyst for the α-alkylation of nitriles with aldehydes (aldol reaction) or imines (Mannich reaction).

Ozerov and co-workers reported the coupling of acetonitrile with aldehydes using Ni(II)(PNP)OTf pincer complex **30a** as catalyst [54]. At rt. or 45°C with an equivalent amount of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base and excess acetonitrile as solvent (9.6–48 equivalents), aldehydes were converted, catalysed by 5 mol% of **30a**, forming β-hydroxy nitriles in good to excellent yields (Scheme 30). The authors propose a mechanism in which the nitrile coordinates to the cationic nickel complex and is thus activated for deprotonation by DBU. The thus formed anion reacts with the aldehyde in an aldol condensation reaction. NMR investigation only showed the presence of the cationic complex formed from **30a** and DBU. The reactions with the analogous palladium and platinum complexes led to the formation of the product in much lower yields under the same conditions.

Szabó and co-workers reported the α-alkylation of nitriles with tosylimines catalysed by the Pd pincer complex **31a** [55, 56]. This Mannich reaction, which required the addition of a weak base such as NaHCO$_3$, allowed the high-yield synthesis of the tosylated β-aminonitriles from allyl or benzyl nitriles and tosylimines (Scheme 31, top). The authors assume that the nitrile binds to the
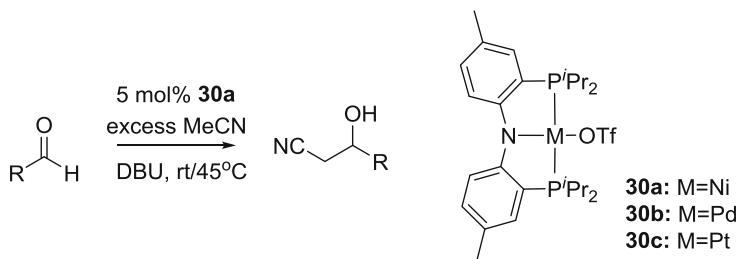
Scheme 30 Coupling of aldehydes with acetonitrile catalysed by **30a**
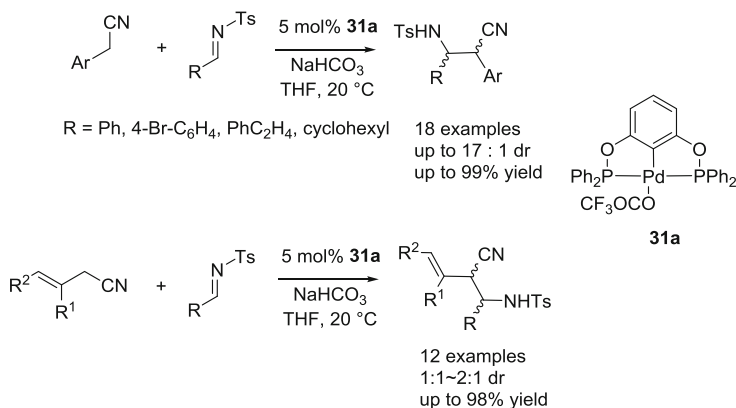
Scheme 31 Mannich reaction of nitriles with tosylimines catalysed by **31a**

cationic palladium complex, allowing facile deprotonation at the α-position even with a weak base. The anion then reacts with the tosylated imine to form the desired product.

However, the authors propose a different mechanism for the Mannich reaction of allyl cyanides (Scheme 31, bottom) as this reaction does not proceed with other palladium salts or complexes, which seems to exclude a role as Lewis acid for the catalyst. They propose a mechanism that starts with formation of the *cis*-η^1-allylpalladium complex, rather than the trans-complex, the α-bound η^1-allylpalladium complex or the N-bound complex, all of which were found to be higher in energy by DFT calculations. This complex then reacts with the tosylimine in an S$_N$2'-type reaction leading to selective alkylation in the α-position of the nitrile (Scheme 32).

More recently, Butcher developed a series of bis-benzimidazole-based pincer complexes and applied **31b** in the coupling of nitriles with sulfonimines with yields from 50 to 99% (Scheme 33) [57]. The catalyst was activated by reaction with AgOAc; in addition, 1.5 eq. of base (K$_2$CO$_3$) and molecular sieves (4 Å) were used as additives.
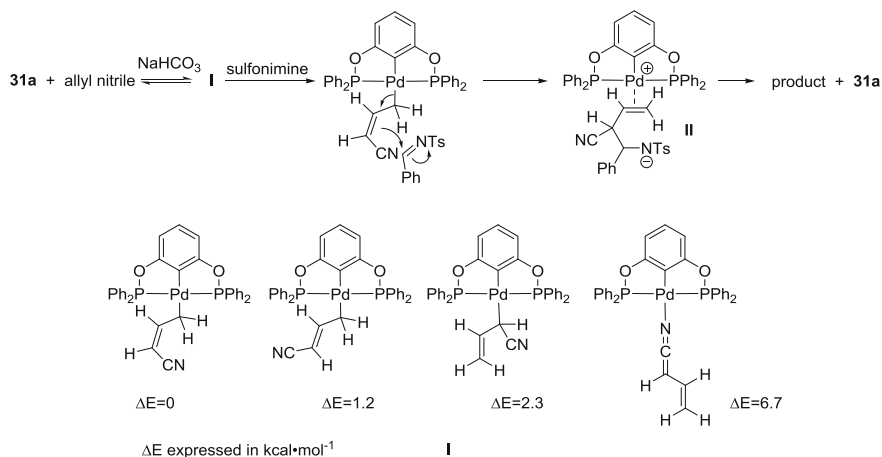
Scheme 32 Stability of palladium-crotononitrile complexes calculated by DFT and proposed mechanism of the Mannich reaction between nitriles and sulfonimines by **31a**
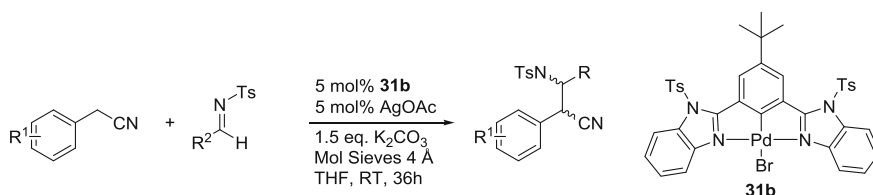
Scheme 33 Mannich reaction between benzyl cyanides and tosylimines catalysed by **31b**

3.7 Enantioselective α-Functionalisation of Nitriles

Quite some effort has gone into developing enantioselective versions of the reactions described above. Richards and co-workers did pioneering work on the synthesis of cationic NCN Pd pincer complexes **32a–e** bearing two chiral oxazoline ligands on the central benzene ring (Scheme 34) [58, 59]. They reported the asymmetric Michael addition of 2-methyl-cyanoacetate to α,β-unsaturated ketones/nitriles catalysed by these complexes. Unfortunately, the enantioselectivity of these reactions remained low and did not exceed 34%. Motoyoma and co-workers found that simply replacing the Pd metal by Rh (carrying additional chloride and Me$_3$Sn ligands) but using similar ligands gave complexes **33a–f** that led to a significant improvement of the enantioselectivity of this type of reaction, reaching values above 80% [60]. Uozumi [61] and co-workers used their unique Pd pincer complex **34a** bearing two chiral hexahydro-1H-pyrrolo[1,2-c]imidazol-1-one moieties on the central benzene ring. In the Michael reaction on ethyl acrylate catalysed by this complex, an ee of 83% was obtained.
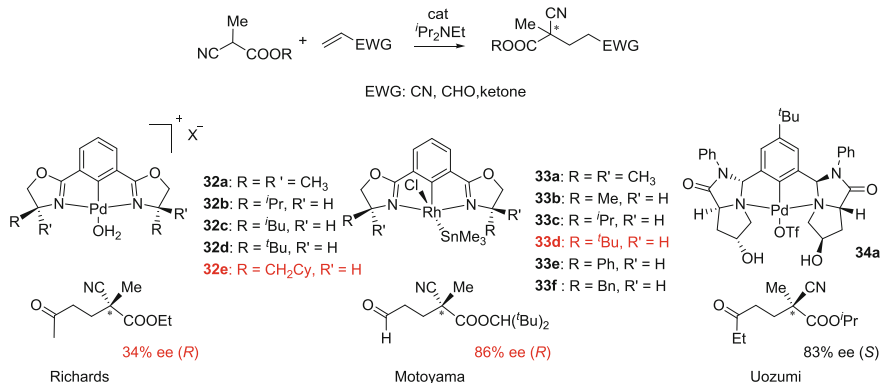
Scheme 34 Enantioselective Michael addition of 2-methyl-cyanoacetate catalysed by chiral pincer complexes
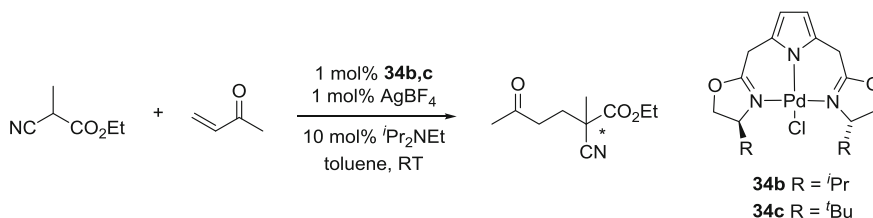
Scheme 35 Enantioselective Michael reaction of 2-methyl-cyanoacetate and MVK catalysed by a chiral palladium pincer complex

Mazet and Gade [62] developed an interesting ligand class based on the 2,5-bis-oxazolinemethylpyrrole structure. These ligands were used in combination with palladium for the asymmetric Michael reaction of ethyl 2-methyl-cyanoacetate and methyl vinyl ketone (MVK) (Scheme 35). Unfortunately, these catalysts (**34b,c**) were very slow and conversions were as low as 14–29%; the product was obtained with ee values of 21 and 43%.

Arai and co-workers developed a series of NCN pincer complexes bearing two imidazolidine moieties on the central benzene ring [63, 64]. The corresponding Pd complexes **35a,b** were successfully applied in the conjugate addition of malononitrile to β-substituted nitroethylenes with good to excellent yields and ee's (Scheme 36) [63]. Both aliphatic and (hetero)aromatic β-substituents were well-tolerated. Using 3 mol% of the analogous Rh pincer complex **36a,b** in toluene resulted in high yields and enantioselectivities in the asymmetric Mannich reaction of malononitrile with N-Boc imines [64].

Nakamura, Shibata and co-workers investigated the use in catalysis of bis (imidazoline) pincer ligands, which are easily synthesised and highly tunable. Using 1,3-bis(imidazoline)-benzene palladium pincer complexes as catalyst, they have successfully reacted many very challenging nitriles with imines (Scheme 37). Substrates included benzyl nitriles (up to 99% yield, 93:7 dr, 92% ee) [65],
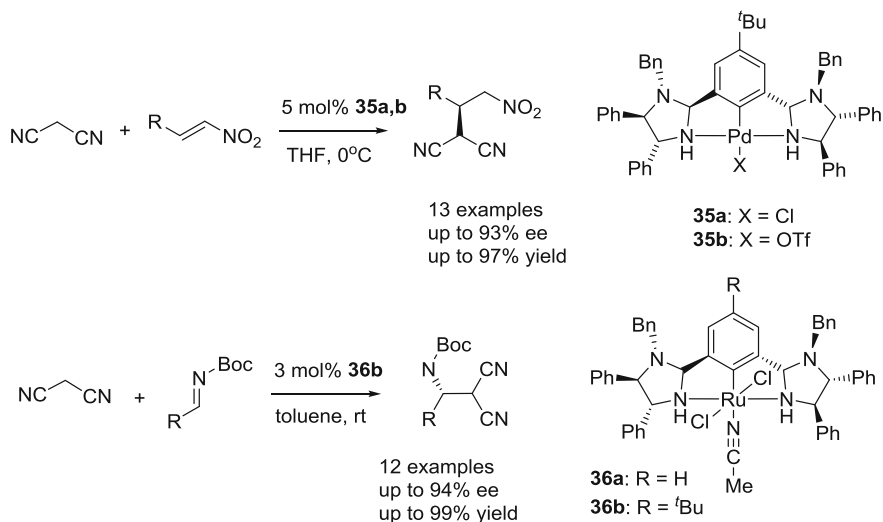
Scheme 36 Pincer complexes bearing two imidazolidine moieties as catalyst in enantioselective reactions: (**a**) Michael addition (top); (**b**) Mannich reaction (bottom)
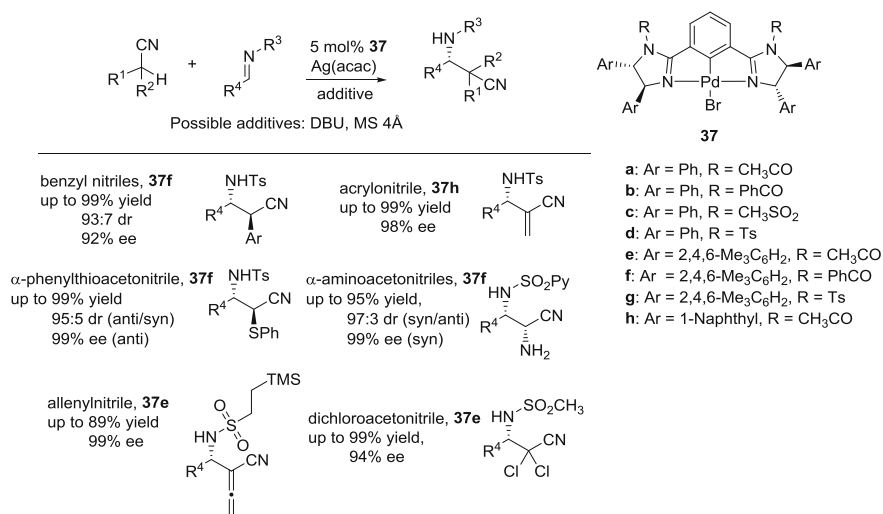
Scheme 37 Pincer complexes based on bis(imidazoline) ligands as catalyst in enantioselective reactions

cyanoacetic acid (up to 82% yield, 90% ee) [66], α-phenylthioacetonitriles [up to 99% yield, 95:5 dr (anti/syn), 99% ee (anti)] [67], α-aminoacetonitriles [up to 95% yield, 97:3 dr (syn/anti), 99% ee (syn)] [68], dichloroacetonitrile (up to 99% yield, 94% ee) [69] and allenylnitriles (up to 89% yield, 99% ee) [70]. Whereas these
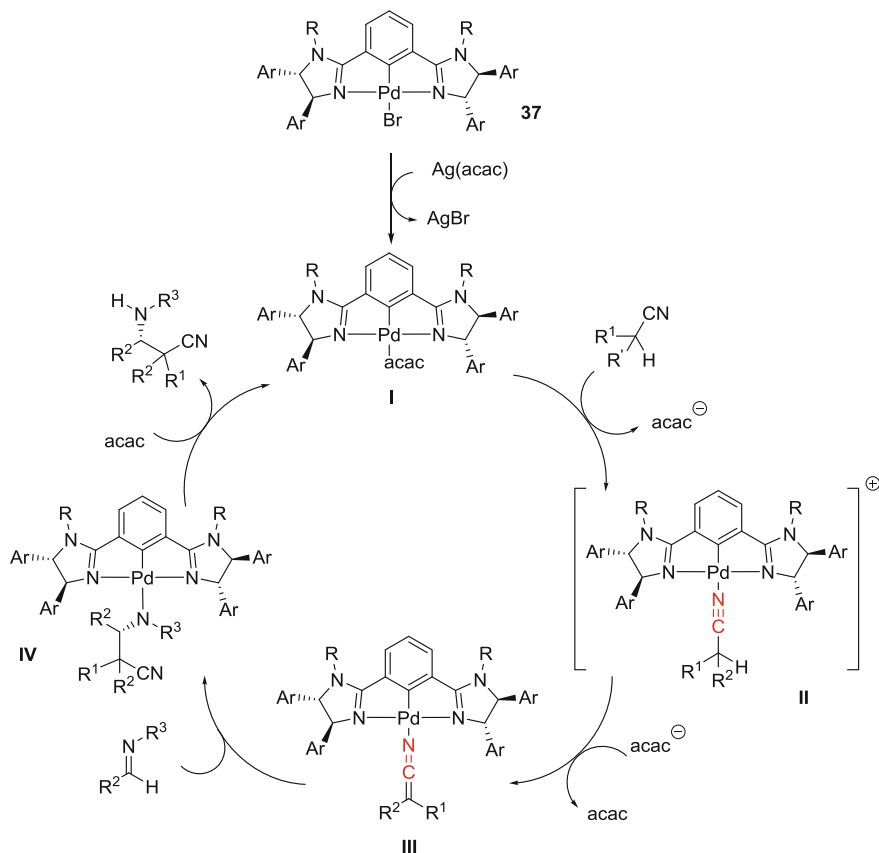
Scheme 38 Proposed mechanism for enantioselective Mannich reactions catalysed by **37**

transformations are all Mannich-type reactions, the same catalyst has also been used for an aza-Morita-Baylis-Hillman reaction between acrylonitrile and tosylated imines (for the product, see Scheme 37, upper right). Here, the products were also isolated in excellent yields and ee's (up to 99% yield, 98% ee) [71].

The authors proposed a general mechanism for the Mannich reactions (Scheme 38): first, the Pd-Br pincer complex is activated by the silver salt, leading to the formation of the cationic complex **II** in which the nitrile is end-on coordinated to the palladium. A loss of a proton, aided by the presence of basic acac anion, leads to the formation of the neutral keteneimido adduct **III**. This adduct reacts with the tosylated imine to form **IV**; the formed tosylated amine anion now binds to the palladium in preference to the neutral nitrile. Protonation of **IV** generates the product and regenerates **I**.

When cyanoacetic acid is used in the Mannich reaction with sulfonylated imines, decarboxylation occurs leading to the formation of sulfonylated β-amino nitriles [66]. The authors claim that no decarboxylation was observed in the absence of
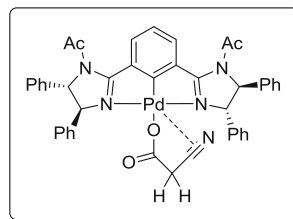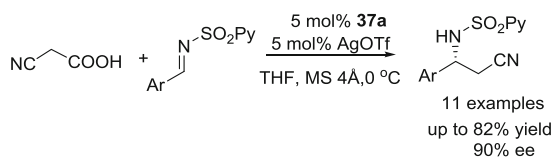
Scheme 39 Asymmetric Mannich reaction of cyanoacetic acid catalysed by **37a** followed by decarboxylation

imines or with α,α-disubstituted α-cyanoacetic acid. Using atmospheric pressure chemical ionisation (APCI) mass spectroscopic analysis, they established the presence of the sulfonylated α-cyano-β-aminopropionic acid intermediate in the reaction mixture at the end of the reaction (cationic mode, m/z calcd. for $C_{15}H_{14}N_3O_4S$, 332.1; found, 332.2), which suggests that the CO_2 is extruded after the C-C bond formation event. They assume that the catalytic cycle starts by the binding of the acetoacetic acid via the carboxylate. They observe a complex in the APCI that has the correct mass for $[M + H]^+$ (Scheme 39); however, the complex in which the cyanoacetate binds via the nitrile would give exactly the same MS and thus cannot be excluded.

Recently, the same group used complex **37e** as catalyst for the asymmetric conjugate addition of α,α-dithioacetonitriles to nitroalkenes. The reactions proceeded in excellent yield and the products were obtained with excellent ee's [72].

4 Hetero-Michael Addition to α,β-Unsaturated Nitriles

4.1 Lewis Acid Catalysis

The hetero-Michael reaction on α,β-unsaturated nitriles gives access to a large number of interesting structures. Apart from the β-substituted hydroxy-, alkoxy-, amino-, phosphino- or (alkyl)thio-propionitriles, one can of course easily convert the nitrile group in these products by hydrogenation to the analogous amines, by hydration to the amides and by hydrolysis to the carboxylic acids. These reactions become even more interesting when they are enantioselective. The synthesis of chiral pharma intermediates is often quoted as a reason to develop these reactions.

Trogler reported the first palladium pincer complex (**38**)-catalysed aza-Michael addition (Scheme 40) [73]. However, this reaction was limited to acrylonitrile as substrate. Nevertheless, up to 44 turnovers were achieved by this catalyst in the reaction between aniline and acrylonitrile at room temperature. Inspired by this work, Hartwig used in situ prepared PCP as well as PNP palladium pincer complexes and achieved good to excellent yields (76–99%) in the addition of primary and

Scheme 40 Aza-Michael addition on α,β-unsaturated nitriles catalysed by palladium pincer complexes

R^1 = H, Me
R^2 = H, Me

R^3 = R^4 = -(CH$_2$)$_5$-
R^3 = Ph, R^4 = H
R^3 = n-Bu, R^4 = H

38

39a   **39b**

Y = OAc, TFA

Trogler, 1992   Hartwig, 2001

R^1 = H, Me
R^2 = H, Me

5 mol% **40**
solvent
24 h, rt

40 Ni(Pigiphos)(ClO$_4$)$_2$

THF	ionic liquids
91% yield 22% ee	higher TON (up to 300) reusable after 5 recycles catalyst air stable lower ee
99% yield 69% ee	
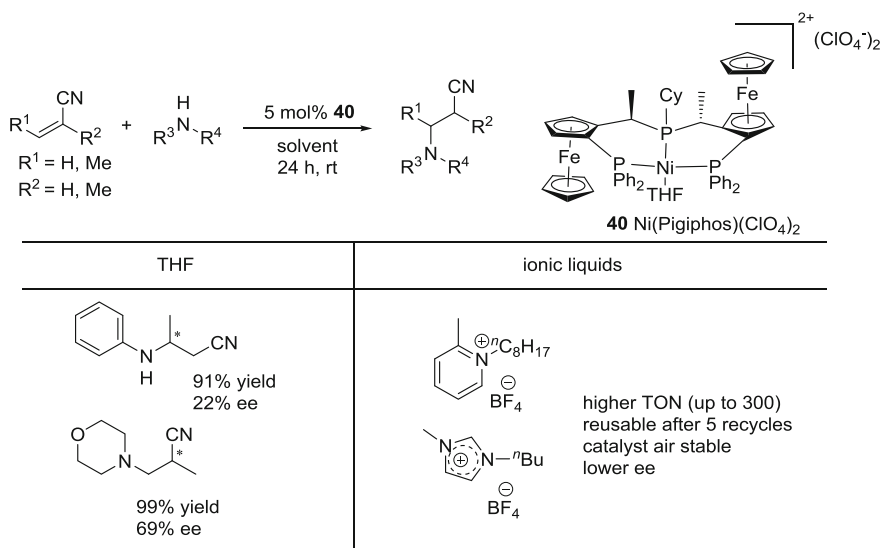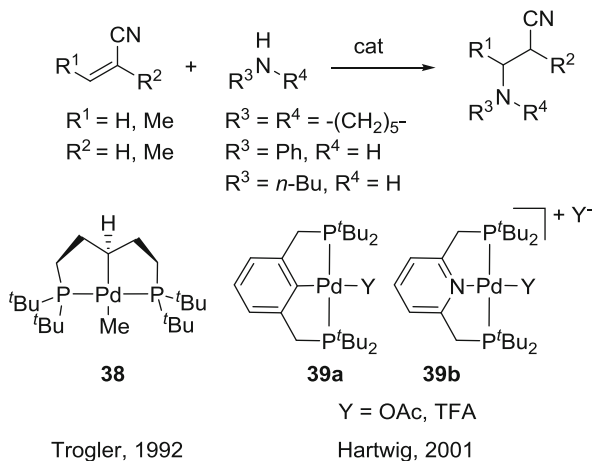
Scheme 41 Asymmetric aza-Michael addition catalysed by a Ni Pigiphos complex

secondary amines as well as aniline to methacrylonitrile and crotonitrile (Scheme 40) [74].

The Togni group developed a new nickel pincer complex **40** based on the Pigiphos ligand [75]. This complex showed good activity in the hydroamination of α,β-unsaturated nitriles (Scheme 41). Even the challenging substrate aniline did react with crotonitrile catalysed by **40** at rt. giving the aminated product in up to 91% yield with 22% ee. Aliphatic amines (morpholine and piperidine) were also evaluated in reactions with methacrylonitrile/crotonitrile leading to the products in excellent yields. The highest ee (69%) was obtained in the hydroamination of
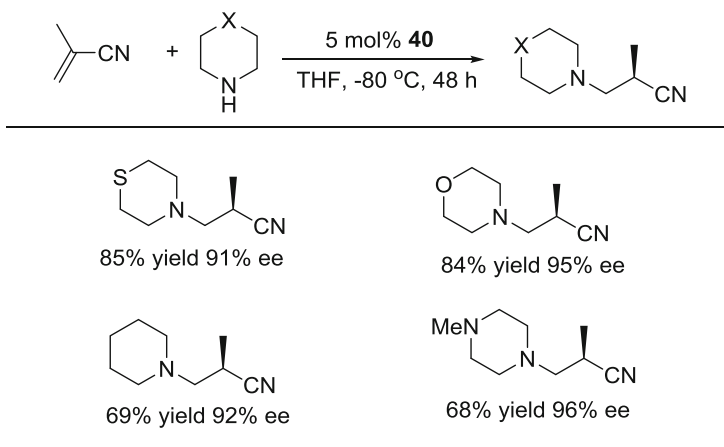
Scheme 42 Asymmetric aza-Michael addition of aliphatic cyclic amines to methacrylonitrile at −80°C catalysed by **40**

methacrylonitrile with morpholine. To further increase the enantioselectivity of this reaction, ionic liquids were explored as solvent [76]. Unfortunately, no improvement w.r.t. the enantioselectivity resulted from this. Nevertheless, the catalytic activity was significantly enhanced by the ionic liquids: higher TON (up to 300, compared with 71 in THF), reusable after five recycles and air stable.

Eventually, excellent enantioselectivity could be obtained in this reaction by lowering the temperature [77]. At −80°C, addition of aliphatic cyclic amines to methacrylonitrile still resulted in excellent yields of the products and >90% ee after 48 h using 5% [Ni(Pigiphos)(THF)](ClO$_4$)$_2$ as catalyst (Scheme 42). However, this high enantioselectivity could not be achieved in the conversion of other substrates, such as crotonitrile or cinnamonitrile.

Based on DFT calculations, the authors proposed a mechanism involving a Lewis acid (metal) activation of the nitrile, which enables the 1,4-addition of the amine to the α,β-unsaturated nitrile forming the ammonium substituted alkyl nitrile (Scheme 43). An asymmetric proton transfer is followed by dissociation of the nitrile [78].

The same catalyst (**40**) was also investigated for the hydrophosphination of methacrylonitrile by the Togni group [79, 80]. One aromatic and five aliphatic secondary phosphines were reacted, and moderate to excellent yields of the tri-substituted phosphines were obtained at −20°C with acetone as solvent (Table 14). Enantioselectivities ranged from 32 to 94%. The authors proposed the same mechanism as for the amine addition.

The Zargarian group extensively investigated the synthesis and use of nickel complexes based on PCP ligands using bisphosphines as well as bisphosphinites with aliphatic or aromatic backbones. These cationic nickel complexes were used as catalysts in the aza-Michael addition of amines such as morpholine and cyclohexylamine as well as aniline to acrylonitrile, crotonitrile and methacrylonitrile. The
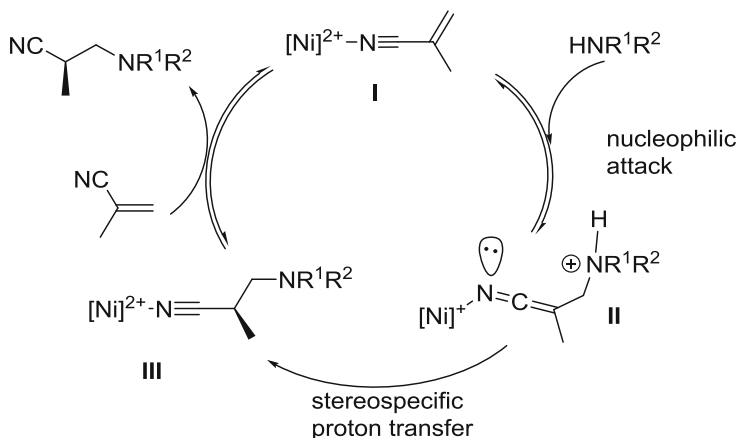
Scheme 43 Proposed mechanism for the asymmetric aza-Michael addition catalysed by **40**

Table 14 Asymmetric Michael addition of phosphines to methacrylonitrile by **40**[a]

Entry	R_2PH	TON	Solvent	Yield (%)	ee (%)
1	Cy_2PH	10	Methacrylonitrile	71	70
2	Ph_2PH	15	Methacrylonitrile	10	32
3	$^iPr_2PH$	45	Acetone	Not isolated	78
4	$^tBu_2PH$	100	Acetone	95	94
5	Ad_2PH	100	Acetone	97	89
6	$(EtMe_2C)_2PH$	116	Acetone	86	90

[a]Isolated yields, Ad = 1-adamantyl

products were obtained in excellent yields and turnover numbers up to 2000 were achieved (Scheme 44) [81, 82].

The same group reported a dimeric nickel-PCN complex **44** which showed good activity in the oxa-Michael addition of aliphatic alcohols and phenols to acrylonitrile [83]. During the substrate scope investigation, the author found that the reaction rate is depending on the alcohol acidity (m-cresol > BnOH > aliphatic alcohols) and very sensitive to the steric hindrance (crotonitrile and methacrylonitrile <5% yields and reaction rate: MeOH > EtOH > n-PrOH > ^iPrOH) (Table 15).

In later research, the same group found that the reactivity of the Ni pincer complex **42** (X = O) in the oxa/aza-Michael additions could be significantly increased by adding Et_3N [84, 85]. This was particularly true for reactions with phenols and anilines. To some extent, water had the same effect.

Liu, Imamoto, Zhang and co-workers prepared a series of chiral PXP Ni pincer complexes. Complex **45** was successfully applied in the hydroamination of methacrylonitrile, crotonitrile and other α- and β-substituted acrylonitriles
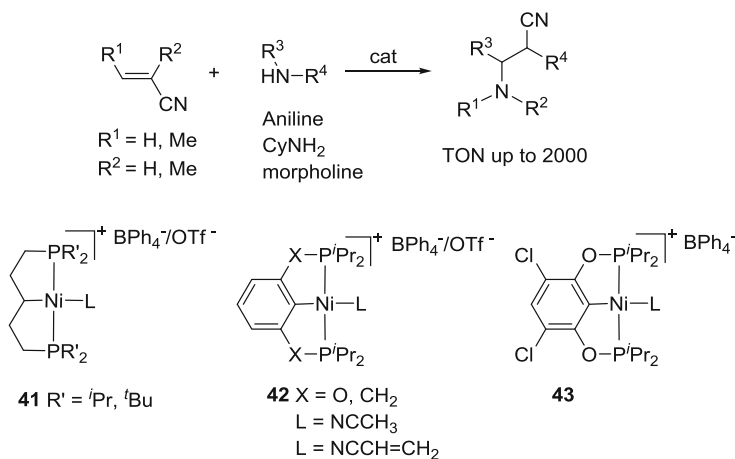
Scheme 44 Ni PCP pincer complexes as catalysts for the aza-Michael addition

Table 15 Oxa-Michael addition of alcohols to acrylonitrile by **44**[a]
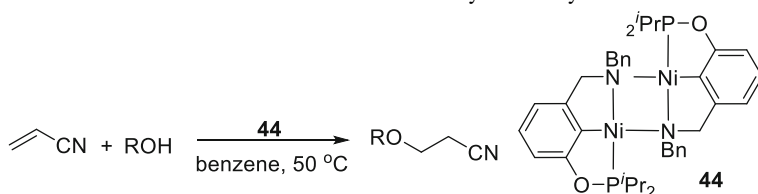
Entry	ROH	X:nitrile:ROH	Time (h)	Yield (%)	TON
1	*m*-Cresol	1:2000:4000	36	99	~2000
2	MeOH	1:200:2000	1.0	100	200
3	EtOH	1:200:2000	1.0	87	174
4	CF_3CH_2OH	1:200:2000	0.5	90	180
5	*n*-PrOH	1:200:2000	8	64	128
6	^{i}PrOH	1:200:2000	24	23	46
7	BnOH	1:200:2000	1.0	100	200

[a]Reaction yields were determined by 1H NMR spectroscopy or GC/MS

[86]. However, the reactions were rather slow and the enantioselectivity did not surpass 46% (Scheme 45).

4.2   Catalysis via Metal-Ligand Cooperation

Thus far, in all hetero-Michael addition reactions, the catalyst has functioned as a Lewis acid activating the α,β-unsaturated nitrile for 1,4-addition and stabilising the developing negative charge on the nitrogen atom. An entirely different mode of
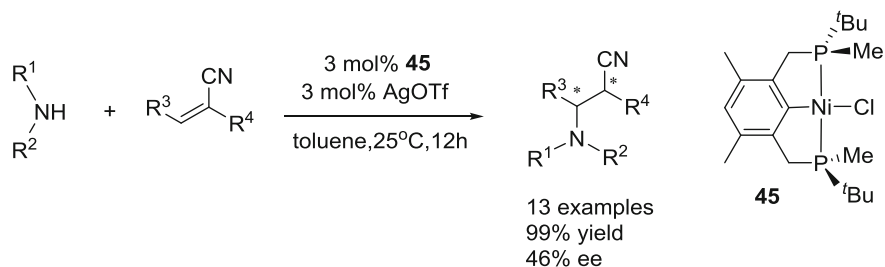
Scheme 45 Chiral nickel PCP pincer complex as catalyst for the aza-Michael addition

reactivity based on metal-ligand cooperativity (MLC) was reported by de Vries, Otten and co-workers [87]. Using the dearomatised Ru PNN pincer complex **46,** which was developed by Milstein and co-workers, they examined the oxa-Michael reaction of α,β-unsaturated nitriles at room temperature in THF. A broad substrate range was investigated, and the product β-alkoxy-nitriles were obtained in moderate to excellent yields. Nitriles investigated included acrylonitrile, crotonitrile, 2- and 3-pentenenitrile and the ester containing 10-cyanodec-9-en-1-yl acetate. No transesterification occurred in the latter substrate. As nucleophiles, primary and secondary aliphatic alcohols, benzyl alcohols and thiols were used. In a later publication, the nitrile scope was further extended to more challenging structures containing β-substituents such as CF_3, p-$CF_3C_6H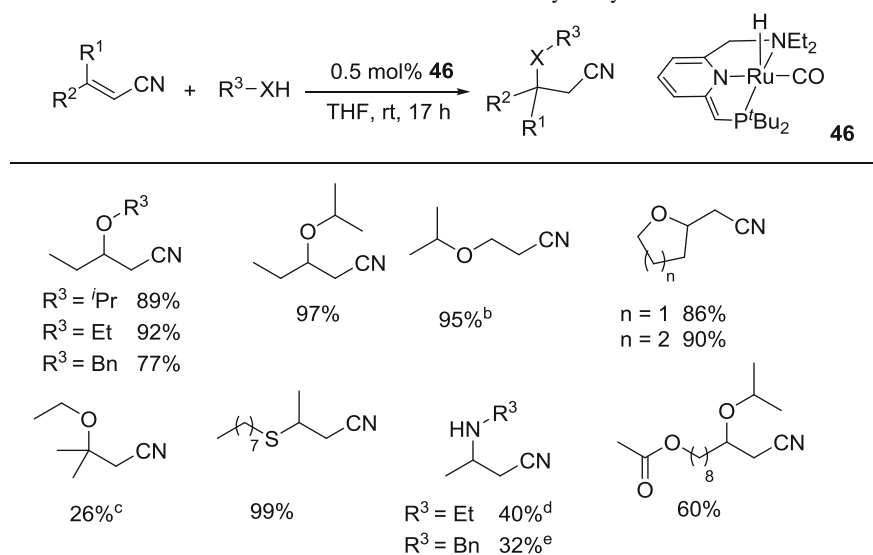_4$ and cyclopentyl. Here the products were obtained in moderate to good yields [88]. Unfortunately, phenols deactivated the catalyst by strongly binding to the ruthenium. Aza-Michael reactions were extremely slow and yields below 50% of the products were obtained (Table 16).

Based on the crystal structure of the dieneamido complex formed from 3-pentenenitrile and **46** (Scheme 46, complex **II**) as well as on DFT calculations, they proposed a mechanism (shown here for 2-pentenenitrile) involving (i) the activation of the C ≡ N bond via metal-ligand cooperation resulting in addition of the nitrile across the ruthenium metal and the carbon atom of the deprotonated side arm leading to the formation of **I** in fast equilibrium with **II**; (b) hydrogen bond-assisted 1,4-addition (**III → IV**); (c) proton transfer (**IV→V**); and (d) release of the product and regeneration of the catalyst (it is the tautomeric form **46-taut** that is the active catalyst).

Milstein and co-workers used manganese PNN pincer complex **47** for the oxa- and aza-Michael reaction for which they assumed the same mechanism as proposed by Otten and de Vries [89]. This catalyst is rather active, which allowed the use of a low catalyst loading of 0.1 mol% (compared to 0.5 mol% of the ruthenium catalyst **46**) to achieve a similar rate in the oxa-Michael reaction. Interestingly, in contrast to the ruthenium catalyst, the aza-Michael addition also worked very well under the same conditions, with an even higher rate than the oxa-Michael reaction. Thus, in the presence of ^{n}BuOH (1 mL) and ^{n}BuNH$_2$ (1 mL), catalyst **47** selectively promoted the aza-Michael addition (Scheme 47).

Table 16 Oxa-Michael addition of alcohols to nitriles catalysed by **46**[a]

R³ = *i*Pr 89%	97%	95%[b]	n = 1 86%
R³ = Et 92%			n = 2 90%
R³ = Bn 77%			
26%[c]	99%	R³ = Et 40%[d]	60%
		R³ = Bn 32%[e]	

[a]Isolated yields [b]Reaction with 0.07 mol%catalyst [c]GC yield [d]5 days at 40°C [e]3 days at 60°C

Scheme 46 Oxa-Michael addition via a MLC mechanism catalysed by **46**
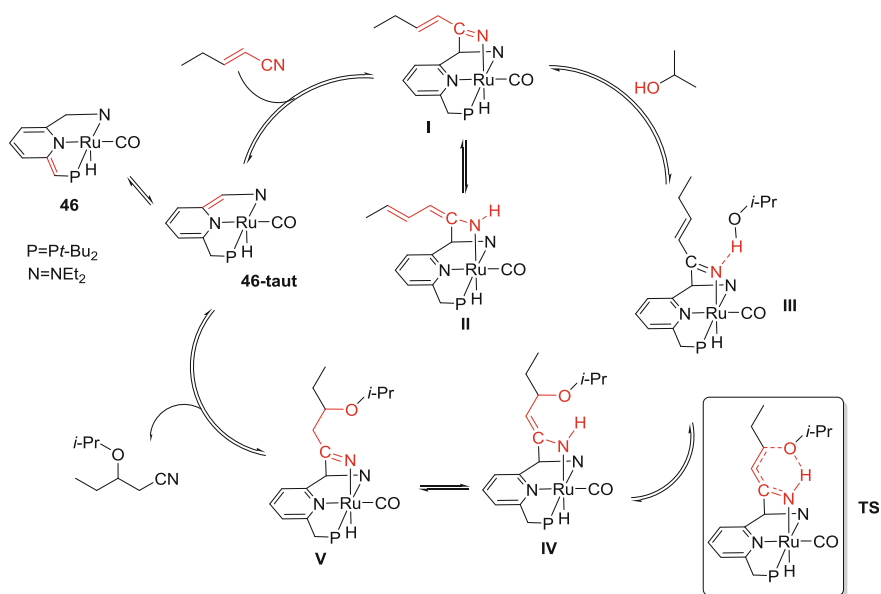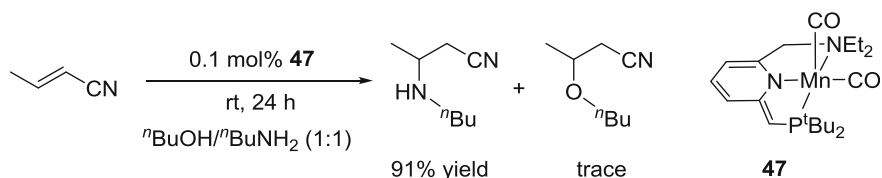
Scheme 47 Aza-Michael addition of amines to nitriles catalysed by **47**

4.3 Hydration of Nitriles

As amides are important structural motifs both in pharmaceuticals and bulk chemicals, their synthesis via hydration of nitriles has attracted considerable attention from the organic synthesis community. Several groups have used metal pincer complexes to catalyse this reaction (Scheme 48).

In 2015, the Piers group reported the use of pincer complex **48** as catalyst for the hydration of nitriles to the analogous amides [90]. With low catalyst loadings (0.05–0.5 mol%) and without additives, excellent yields were achieved at 80°C using (hetero)aromatic and aliphatic nitriles as substrates. Substrates containing acidic groups such as phenols or acetone cyanohydrin did not react. Acrylonitrile did react, but the oxa-Michael addition with isopropanol (used as a solvent) was a major side reaction. The crystal structure of complex **48** showed an unusually long
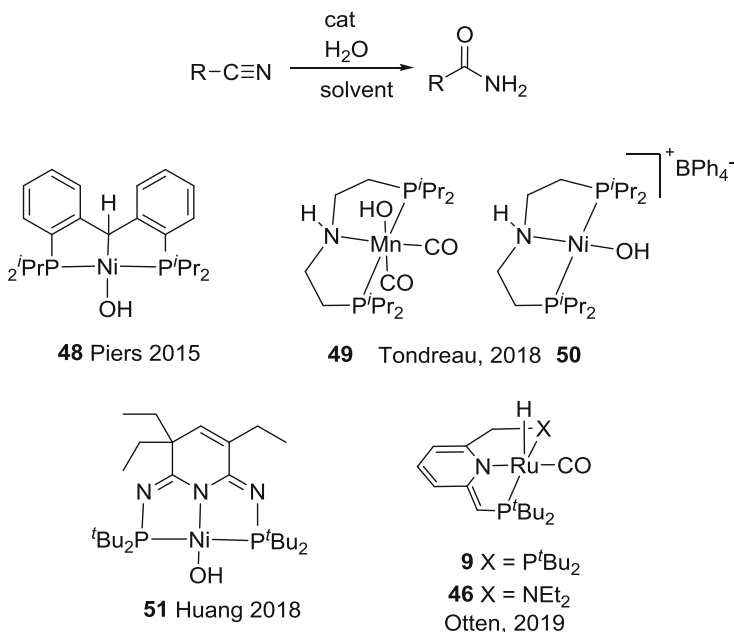
Scheme 48 Hydration of nitriles catalysed by pincer complexes
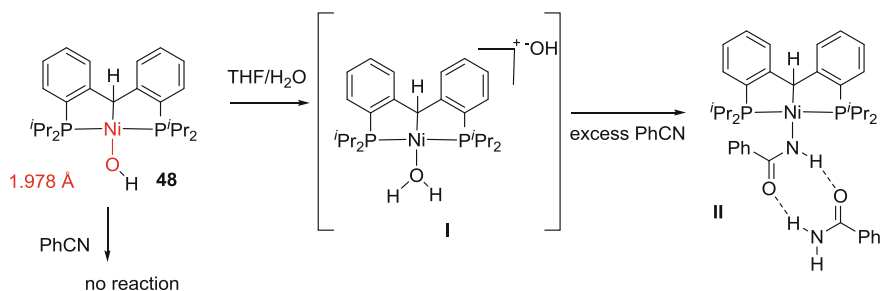
Scheme 49 Mechanism of the hydration of nitriles catalysed by **48**

Ni-O bond (1.978 Å). In addition, they observed ^{17}O exchange in a labelling experiment. This led the authors to propose that **48** reacts with water to form cationic aqua complex **I** (Scheme 49). Surprisingly, complex **48** did not react with benzonitrile. However, upon addition of water, benzonitrile was converted leading to the formation of benzamide. The authors found that several nickel species were present in solution during the reaction but were able to crystallise complex **II** from this mixture. It is assumed that benzonitrile displaces the water ligand in **I** after which attack of the hydroxide on the nitrile occurs leading to the formation of the benzamidyl species.

Huang and co-workers developed PN^{3}P pincer-based Ni-OH complex **51** (Scheme 48) [91]. Stoichiometric reactions between this complex and nitriles were successful, forming the amide adduct. The catalytic hydration of nitriles was achieved at 100°C, albeit with limited substrate scope (six examples); the amides were isolated in moderate to high yields.

Boncella, Tondreau and co-worker described another approach for the hydration of nitriles using non-innocent ligand-based pincer complexes [92]. They synthesised and characterised 5 Ni PNP pincer complexes of which **50** was studied extensively together with the known Mn-OH pincer complex **49**. They managed to obtain Ni and Mn carboxamide complexes from stoichiometric reactions between these complexes and acetonitrile or benzonitrile. However, catalytic conversions failed with the Ni complexes, and very low turnover numbers (1.7–3.9) were achieved with the Mn complex at 50°C using THF (10 wt% water) as solvent. During the mechanistic study, the authors found that nitriles coordinate to the Mn centre by replacing bromide; phenolate or benzyloxide could not be displaced (Scheme 50). Based on this, the authors propose that nucleophilic attack occurs from Mn-OH to the nitrile, which is activated by hydrogen bonding to the NH of the ligand (**I** in Scheme 50). However, the high stability of the metal amide products (**III**) inhibits the catalytic hydration of nitriles.

Otten and co-workers successfully applied the concept of metal-ligand cooperation (MLC) to the hydration of nitriles [93]. Catalysed by the dearomatised Ru PNP and PNN pincer complexes with 5 equiv. water at room temperature, 33 substrates including (hetero)aromatic and aliphatic nitriles were converted in excellent yields to
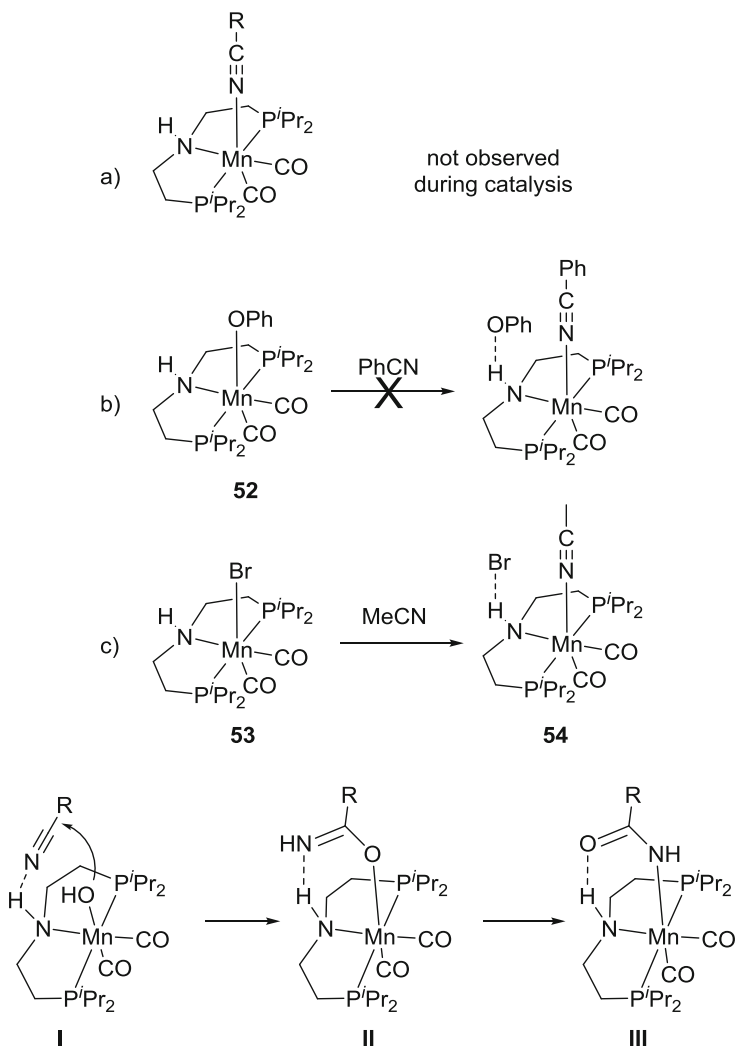
Scheme 50 Proposed mechanism for hydration of nitriles by **49**

the primary amides. Using either more or less water resulted in lower yields of the amides. Based on the stoichiometric reactions between on the one hand the catalyst and nitrile and on the other hand the catalyst with amide, they proposed the following mechanism (Scheme 51): (a) activation of the C $\equiv$ N bond via MLC leading to addition of the nitrile to form the ketimido complex **I** in which the nitrogen is bound to the ruthenium and the carbon atom to the carbon atom of one of the side arms; (b) nucleophilic attack at the carbon atom of the ketimido adduct by water, likely assisted by hydrogen bonding with a second molecule of water (**TS**);
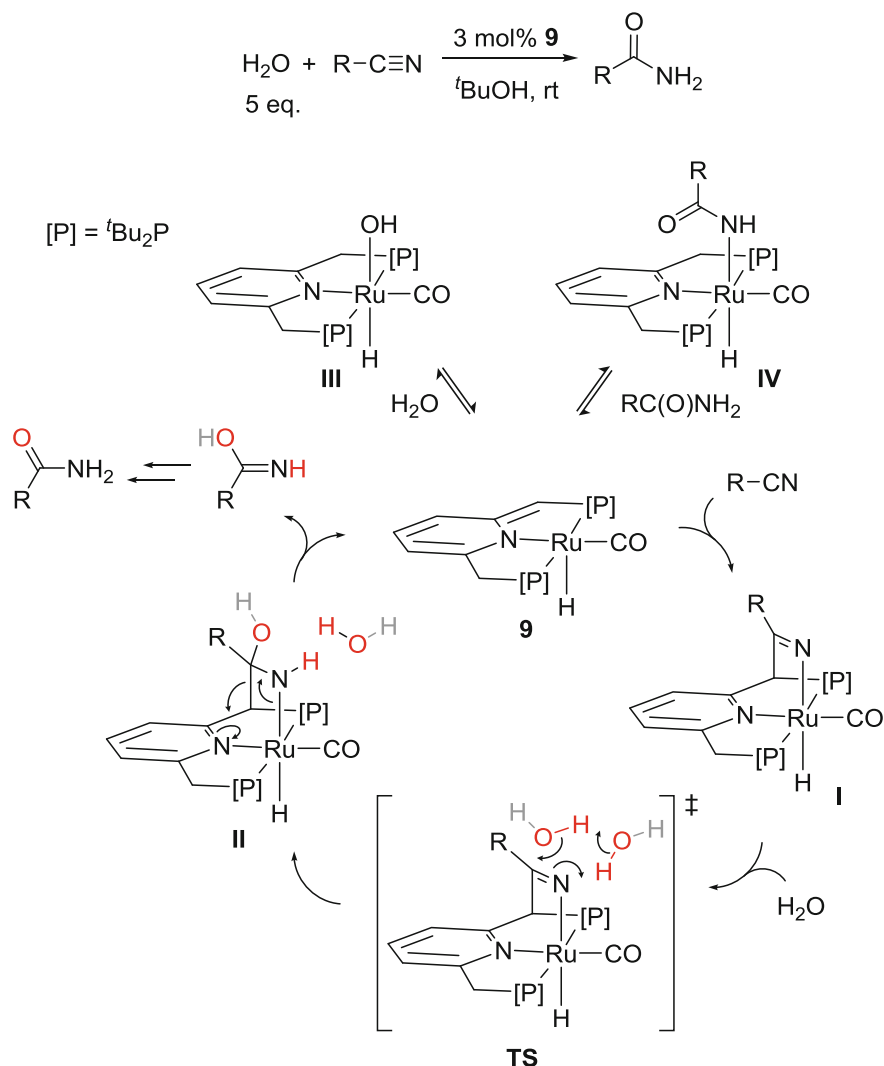
Scheme 51 MLC hydration of nitriles catalysed by **9**

and (c) release of the initially formed iminol, which rapidly tautomerises to the amide product in solution, to regenerate the catalyst. Studies of catalyst speciation suggest that during turnover, the active catalyst **9** is in equilibrium with the aqua complex **III** and the carboxamide complex **IV**; thus, the product amide and water are competitive inhibitors. Nevertheless, the ligand exchange processes are rather fast enabling efficient catalysis, in spite of these inhibitors.

4.4 Amination of Nitriles

Zargarian and co-workers reported the amination of nitriles with primary or secondary amines to the amidines, catalysed by nickel pincer complexes. The reaction was initially discovered as an unwanted side reaction in the Michael addition of amines to cinnamonitrile [84]. More recently, together with French colleagues, they developed a new series of PCP ligands having an imidazolium group as part of the ligand backbone [94]. Bis-cationic complex **55** catalysed the addition of piperidine, morpholine or hexylamine to acetonitrile or benzonitrile with moderate to good yields (Table 17). Use of primary amines led to the formation of mixtures of the N-mono-substituted and the N,N′-disubstituted amidines. Use of a 4:1 mixture of primary amine and nitrile led to the sole production of the disubstituted product. Arnold had previously shown that the Ni PNP complex **56** catalysed the addition of piperidine to acetonitrile with 5 mol% of catalyst at room temperature to give 68% yield of the amidine (Scheme 52) [95].

Table 17 PCP pincer complex-catalysed amination of nitriles
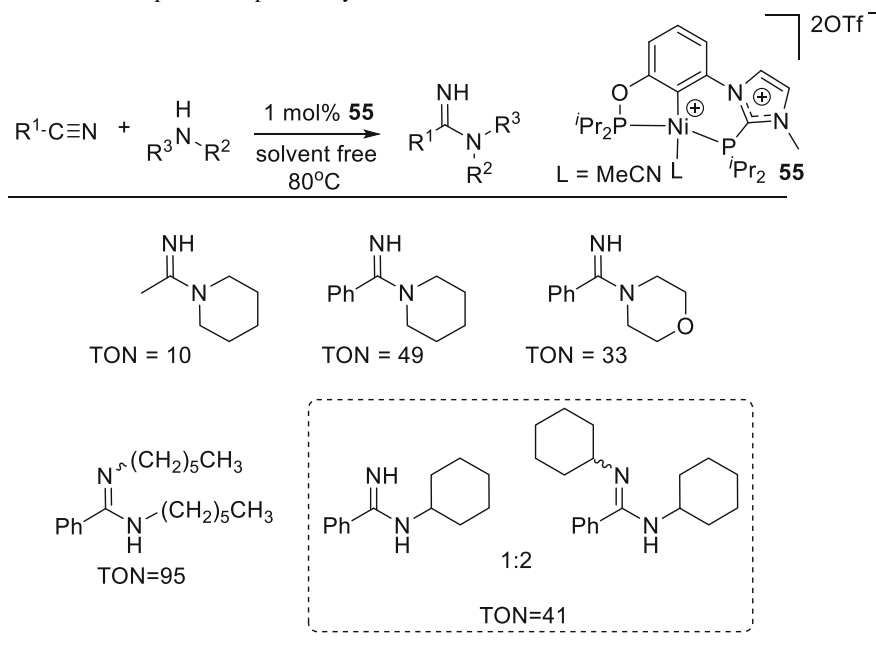
a) Reactions carried out for 21 h (with PhCN) or 5d (with acetonitrile) in
an amine/RCN ratio of 1:1 (for piperidine and morpholine) or
4:1(for cyclohexylamine and n-hexylamine).Yields were determined
by GC-MS with $n\text{-}C_{12}H_{26}$ as internal standard.
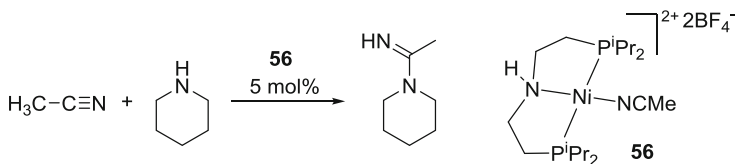
Scheme 52 Nickel PNP pincer complex-catalysed amidine formation

Table 18 Synthesis of 2-alkylaminoquinolines from o-aminobenzyl alcohol, benzyl nitriles and primary alcohols catalysed by Ru pincer complex **57**[a]

[a]Isolated yields
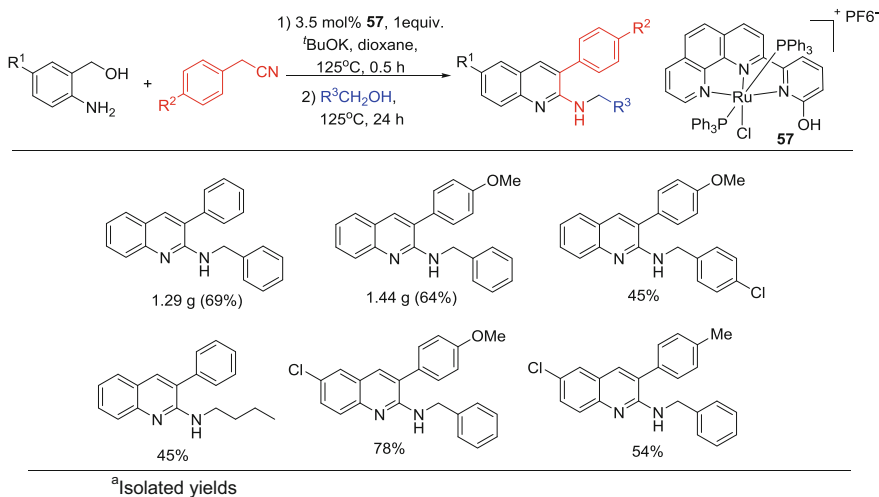
4.5 Synthesis of Heterocycles

Since nitrogen-containing heterocycles are omnipresent in natural products and bioactive molecules, their synthesis under mild conditions, using efficient and green methodologies, is an important topic. A novel route towards heterocycles from alcohols using an acceptorless dehydrogenative coupling (ADC) fits well with such sustainability demands [96]. Kundu reported the synthesis of 2-alkylaminoquinolines from o-amino-benzyl alcohol, benzyl nitriles and primary alcohols, catalysed by 3.5 mol% ruthenium pincer complex **57** [97]. This procedure is a one-pot two-step synthesis, which first step required Ru catalyst, nitrile, o-aminobenzyl alcohol and base in dioxane for 0.5 h at 125°C for the formation of the 2-aminoquinoline, followed by the addition of 2 equivalents of primary alcohol for the borrowing hydrogen-type alkylation of the 2-amino group. The methodology was demonstrated on six examples, two of which were performed on gram scale; yields ranged from 45 to 78% (Table 18). Kundu also used a new cobalt pincer complex **58** bearing an NNN ligand as catalyst for this reaction (Scheme 53)

Scheme 53 Synthesis of 2-alkylaminoquinolines catalysed by Co pincer complex **58**
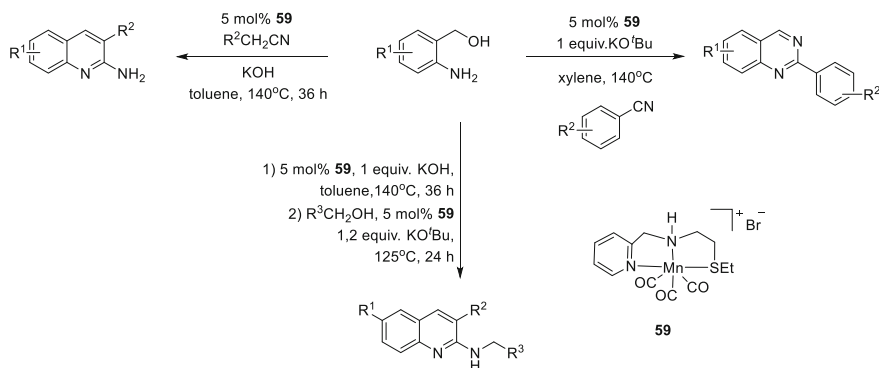
Scheme 54 Tunable synthesis of heterocycles catalysed by Mn pincer complex **59**

[98]. The substrates were similar to the ones used in the previous publication; however, a higher catalyst loading (5 mol% for each step), more base (1 equivalent for each step) and a higher temperature (150°C) were necessary. The reaction was demonstrated with eight examples which included substrates with heteroaromatic and aliphatic substituents, and the products were isolated in moderate to excellent yields.

Srimani showed that the dehydrogenative coupling of *o*-aminobenzyl alcohol and nitriles catalysed by manganese NNS pincer complex **59** as catalyst can lead to two different products [99]. Either quinazoline or 2-aminoquinoline can be selectively obtained by simply tuning the solvent (xylene to toluene) and the base (KO^{t}Bu to KOH). Both pathways could be applied with high functional group tolerance. In addition, the one-pot synthesis of 2-alkylaminoquinolines was also achieved and demonstrated with nine examples in moderate yields (Scheme 54).

The Togni group reported the enantioselective 1,3-dipolar cycloaddition of C, N-cyclic azomethine imines to acrylonitrile and crotonitrile catalysed by [Ni (PigiPhos)](ClO$_4$) (**40**) [100]. Using acrylonitrile as substrate, a range of substituted C,N-cyclic azomethine imines based on (substituted) 3,4-dihydro-isoquinoline reacted at room temperature in CH$_2$Cl$_2$ resulting in excellent yields and ee's of the products (Scheme 55). Using the same conditions, crotonitrile reacted much slower (4 days) and the product was obtained with lower ee (62%). More challenging nitriles reacted very sluggishly (methacrylonitrile, 52% conversion after 48 h at 40°C) or not at all (trans-cinnamonitrile and cis-2-pentenenitrile).
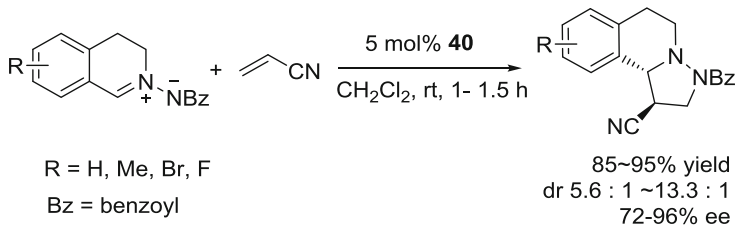
Scheme 55 Enantioselective 1,3-dipolar cycloaddition catalysed by **40**

5 Conclusions

The use of pincer ligands in metal complexes allows a large number of different reactivities, many of which were previously unknown. This is particularly true for nitriles and α,β-unsaturated nitriles that can react in different ways with these complexes. Pincer complexes have been used extensively for hydrogenation reactions of nitriles to the amines, but also to the imines. Here, the classical Noyori-type metal-ligand cooperativity mechanism is often operative. Many catalysts, particularly cationic complexes, can activate the nitriles by functioning as Lewis acid, which makes the α-proton quite acidic leading to the formation of a metal ketenimide complex allowing C-C bond-forming reactions. Quite unusual reactivity was found in the dearomatised pyridine-containing PNN and PNP complexes that were developed by Milstein and co-workers. Here the nitrile can add to the dearomatised pincer complex via metal-ligand cooperation to form a metal nitrogen bond, whereas the carbon atom of the nitrile is bound to the carbon atom of one of the side arms in a fully reversible reaction. The initially formed metal ketimido complex can isomerise further to an enamide structure. In all cases the reactivity of the metal imide is much higher than that of the nitrile allowing a range of reactions such as its hydration. But also oxo- and aza-Michael reactions are facilitated on the unsaturated nitriles, such acrylonitriles or pentenitriles.

It is clear that this interesting reversible reactivity will enable also other transformations, and we can expect more findings in this or similar fields in the near future. Particularly in the field of enantioselective transformations, more developments are expected.

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