Alternatives to Phosphorus-Containing Pincer Ligands in Catalytic Hydrogenation

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Abstract

This dissertation reports on the development and application of alternatives to phosphine-containing pincer ligands in homogeneously catalysed hydrogenations. Building on the broad spectrum of phosphorus- and nitrogen-containing pincer ligands described in literature, the family of phosphine-free "NNS" ligands was introduced. Ruthenium(II) complexes of the general formula $RuCl_2(NNS)(PPh_3)$ were synthesised, characterised, and applied successfully in the selective hydrogenation of α,β-unsaturated aldehydes and ketones to the corresponding allylic alcohols. Additionally, these complexes were active in the hydrogenation of esters to alcohols, and even α,β-unsaturated esters were hydrogenated to allylic alcohols with unprecedented selectivity.

The flexibility of NNS-type ligands makes it unlikely that these ligands should lead enantioselective hydrogenation, even if an asymmetric variation were to be designed specifically for this purpose. However, application of the commercially available (*S,S*)-DACH-phenyl ligand, also known as the Trost ligand, to an alcoholic solution of $RuCl_3 \cdot xH_2O$, led to the *in situ* formation of a catalytic species which gave good conversions and enantioselectivity in the hydrogenation of a range of aromatic ketones.

Cobalt(II) complexes $CoCl_2(NNS)$ and $Co_2Cl_4(NNS)_2$, were prepared and characterised. Upon investigation of their catalytic activity, the monomeric complex was identified as precursor for cobalt nanoparticles, which selectively hydrogenated olefins in the presence of carbonyl groups. Hence, in the scope of this work, it was shown that the NNS ligand class type enabled contrasting types of reactivity and selectivity depending on metal and activation strategy.

Zusammenfassung

Die vorliegende Dissertation beschreibt die Entwicklung von Alternativen für phosphanhaltige Pincer-Liganden, sowie deren Anwendung in homogenkatalysierten Hydrierungen. Aufbauend auf dem breiten Spektrum literaturbekannter phosphor- und stickstoffhaltiger Pincer-Liganden, wurde die Familie „NNS-Liganden“ eingeführt. Ruthenium(II)-Komplexe der allgemeinen Formel $RuCl_2(NNS)(PPh_3)$ wurden dargestellt, charakterisiert und erfolgreich in der selektiven Hydrierung der C=O Funktionalität von α,β-ungesättigten Aldehyden und Ketonen angewendet. Außerdem waren diese Komplexe höchst aktiv in der Hydrierung von Estern zu Alkoholen. Darüber hinaus konnten α,β-ungesättigte Ester mit bisher unübertroffener Selektivität zu Allylakoholen reduziert werden.

Nach dem bisherigen Erkenntnisstand verhindert die Flexibilität der NNS-Liganden, dass diese Ligandenklasse in asymmetrischen Hydrierungen zu guten Ergebnissen führt, selbst wenn eine asymmetrische Variation speziell für diese Anwendung entworfen werden würde. Jedoch konnte im Rahmen der Arbeit gezeigt werden, dass die Umsetzung des (*S,S*)-DACH-Phenyl Liganden, auch bekannt als „Trost Ligand“ mit einer Ruthenium(III)-Quelle *in situ* zu einer katalytisch-aktiven Spezies führt, die gute Umsätze und Enantioselektivitäten in der Hydrierung von aromatischer Ketone zeigte.

Die Cobalt(II)-Komplexe $CoCl_2(NNS)$ und $Co_2Cl_4(NNS)_2$ wurden synthetisiert und charakterisiert. Untersuchungen der katalytischen Aktivität zeigten, dass der mononukleare Komplex als Vorläufer für Cobalt-Nanopartikel geeignet ist. Diese Nanopartikel ermöglichen die selektive Hydrierung von Olefinen in Anwesenheit von Carbonylgruppen. Damit konnte im Rahmen der Arbeit gezeigt werden, dass die Verbindungsklasse der NNS-Liganden in Abhängigkeit vom Metall und der Aktivierungsstrategie unterschiedliche Reaktivitäten und Selektivitäten ermöglicht.

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Abbreviations

Cat.	catalyst
Conv.	conversion
Subst.	substrate
Sel.	selectivity
Ref.	reference
e.e.	enantiomeric excess
(*R*)	dextrorotatory enantiomer
(*S*)	levorotatory enantiomer
Me	methyl
Et	ethyl
^{i}Pr	isopropyl
^{t}Bu	*tert*-butyl
Cy	cyclohexyl
Ph	phenyl
p-Tol	*para*-tolyl
COD	1,5-cyclooctadiene
DPPB	1,4-bis(diphenylphosphino)butane
DACH-Phenyl	*trans*-1,2-diaminocyclohexane-*N,N'*-bis(2-diphenylphosphinobenzoyl)
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EN	ethylene diamine
MeOH	methanol
MeCN	acetonitrile
NNS	2-(alkylthio)-*N*-((pyridin-2-yl)methyl)ethan-1-amine ligands in general
NN^{Me} S	2-(ethylthio)-*N*-methyl-*N*-(pyridin-2-ylmethyl)ethan-1-amine
NN^{H}S	2-(ethylthio)-*N*-((pyridin-2-yl)methyl)ethan-1-amine
OAc	acetate
^{i}PrOH	isopropanol
HFIP	hexafluoroisopropanol
THF	tetrahydrofuran
TPPTS	3,3',3"-phosphanetriyltris(benzenesulfonic acid) trisodium

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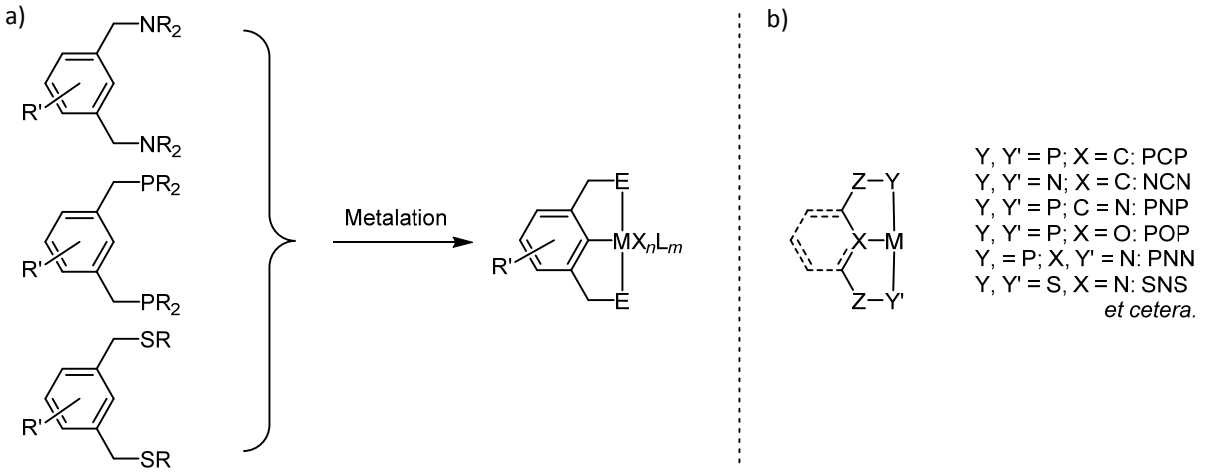
1. Introduction

1.1 Pincer Complexes and their Role in Homogeneous Hydrogenation

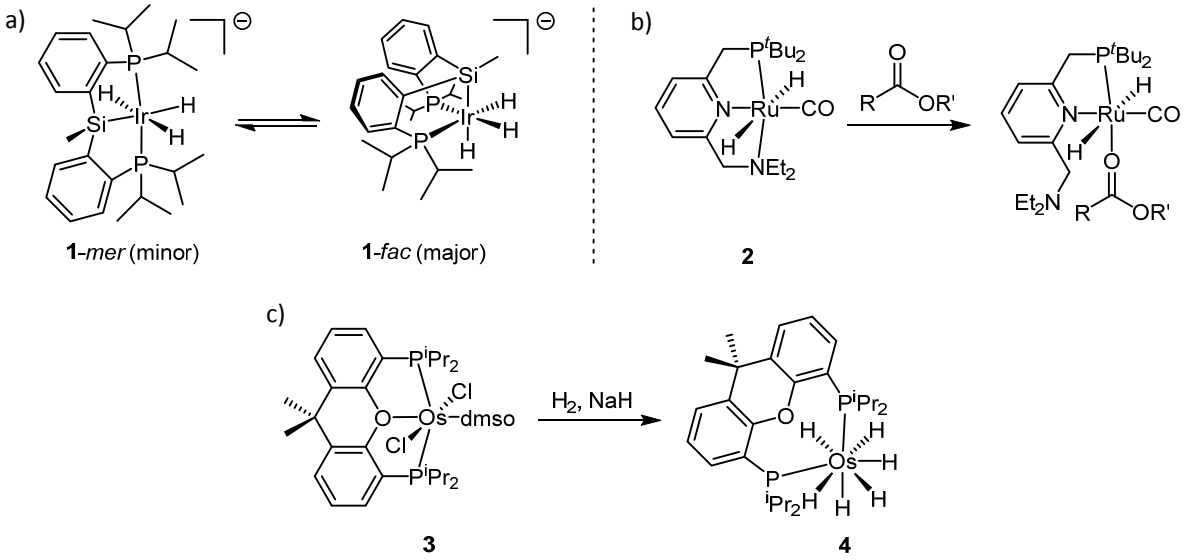
1.1.1 Definition and Structural Features

Within the fields of organometallic chemistry and homogeneous catalysis, pincer ligands have risen to fame as a versatile class of ligands with a broad range of applications.[1] Van Koten originally used the term to refer to tridentate monoanionic ligands consisting of an aryl flanked by two neutral donor side arms such as an amine, phosphine or thioether, which enforce a rigid meridional coordination when metalated (Scheme 1.1a), and such complexes are still the most common pincer complexes to date.[2] Nowadays, however, a broader definition is generally accepted, and any tridentate ligands preferring meridional (*mer*) coordination are usually referred to as pincer ligands, which are typically referred to as YXY' ligands (Scheme 1.1b).[3] Although not always straightforward to prepare, there is no requirement for the ligand to be symmetric, and for instance Milstein's PNN–pincer complexes exhibit some very interesting chemistries.[4]



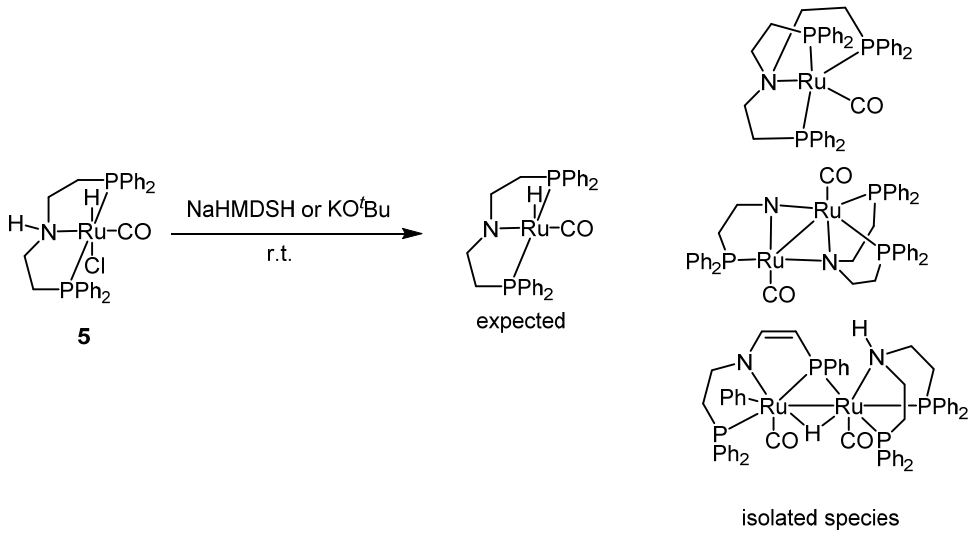
Scheme 1.1: a) NCN, PCP, SCS pincers as dubbed by Van Koten. b) General structure and nomenclature of pincer complexes as the term is used nowadays.

In terms of rigidity, examples are known where a pincer ligand actually coordinates in a facial (*fac*) manner, as in the *fac-mer* equilibrium of complex **1** (Scheme 1.2a). One of the side arms can decoordinate to facilitate coordination of a substrate (Scheme 1.2b), or even the central binding moiety (Scheme 1.2c) decoordinates under certain conditions, such as activation of **3** under hydrogen atmosphere.[4] Indeed, hemilability and flexibility of the pincer ligand have been recognised as a feature that, in certain cases, increases catalytic activity or impacts selectivity.[5]



Scheme 1.2: Selected examples from literature of a) *fac-mer* isomerism in anionic IrH_3(PSiP) (**1**);[4a] b) decoordination of the $–NEt_2$ arm in Milstein's RuH_2(CO)(PNN) complex (**2**);[4b] c) decoordination of the central coordinating moiety in a Xantphos-based OsH_6(POP) (**4**) complex.[4c]

Although pincer complexes are often considered exceptionally robust, a recent study concerning the activation mechanism of the Ru-MACHO complex **5**, which is used in a variety of (de)hydrogenation reactions, shows that this is not necessarily true. The authors found that upon activation, even at room temperature, the precatalyst degraded in a variety of ways, with rather dramatic effects on the ligand (Scheme 1.3).[6]

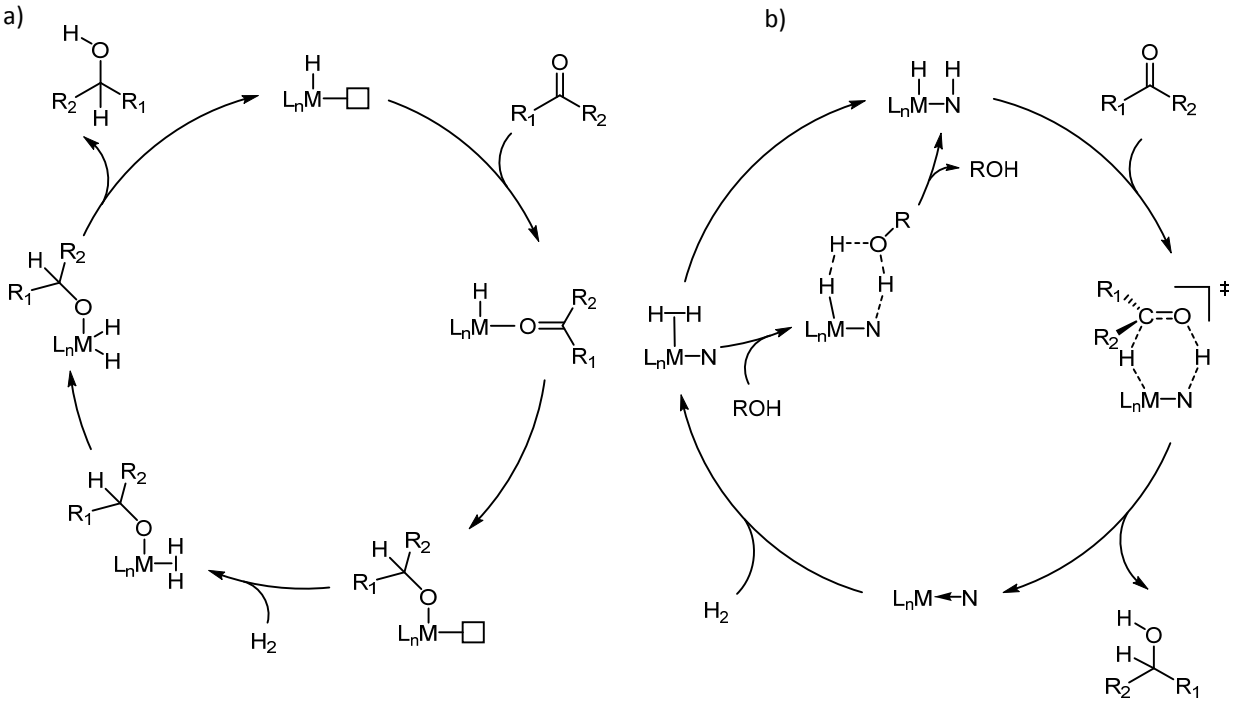


Scheme 1.3: Activation of Ru-MACHO **5** by strong base. In addition to the expected, activated complex, several stable degradation products were isolated, and their solid state structures were determined by X-ray diffraction analysis.[6]

1.1.2 Mechanism of Hydrogenations Catalysed by Pincer Complexes

The main role of pincer complexes in homogeneous hydrogenation reactions revolves around the metal-ligand bifunctional mechanism, *via* which polarised double bonds are reduced.[7] In classical hydrogenations, oxidative addition of H_2 to an active metal centre

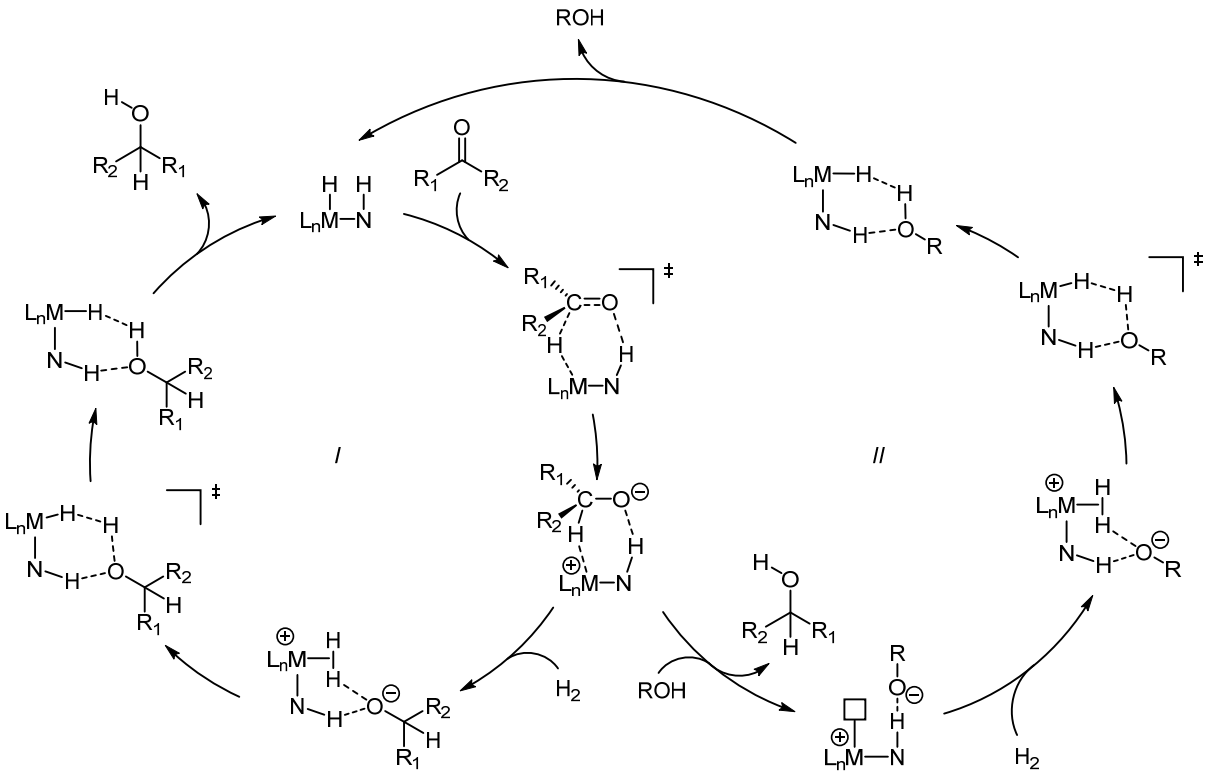
leads to a dihydride complex, which then transfers its hydrides to the double bond to be reduced, which is known as the Schrock-Osborn mechanism (Scheme 1.4a).[8] In contrast, Ikariya, Noyori and co-workers reported greatly improved activities and selectivities in the hydrogenation of carbonyl groups by Ru-diphosphine-diamine type catalysts.[9] Rationalising these findings, it was proposed that the diamine ligand does not merely imparts steric and electronic properties, but rather that the amine proton from the ligand is transferred to the carbonyl oxygen simultaneously with the transfer of the hydride from the metal to the carbonyl carbon in a six-membered transition state. The 16e organometallic species thus generated may then activate a molecule of hydrogen (or, in the case of transfer hydrogenation, dehydrogenate an alcohol, for example) *via* heterolytic splitting (Scheme 1.4b). Importantly, the oxidation state of the metal remains the same throughout the catalytic cycle, which probably works out positively on the lifetime of the catalyst. Although this type of metal-ligand bifunctional outer-sphere mechanism was originally reported for Ru-diphosphine/diamine systems, it has since been accepted for pincer complexes too, in particular those containing the M-N-H motive, which will be discussed in more detail below.[10]



Scheme 1.4: a) Schrock-Osborn (inner-sphere) type hydrogenation of a carbonyl moiety; b) Noyori-Ikariya type (outer-sphere) hydrogenation mechanism.

It is important to note that in recent years, Dub and Gordon observed that use of *N*-methylated analogues of the ligands (thus, those that do not contain an N-H functionality to participate directly in hydrogenation and H_2 activation) often leads to comparable turnovers. This led to the conclusion that the bifunctional mechanism, as was widely accepted, could not be the full explanation. They proposed an updated '$H^{(-)}/H^{(+)}$ outer sphere mechanism' (Scheme 1.5). Although the ligand does strongly influence the reaction, it is argued that it does not do so chemically, but rather cooperates by stabilising rate-determining transition

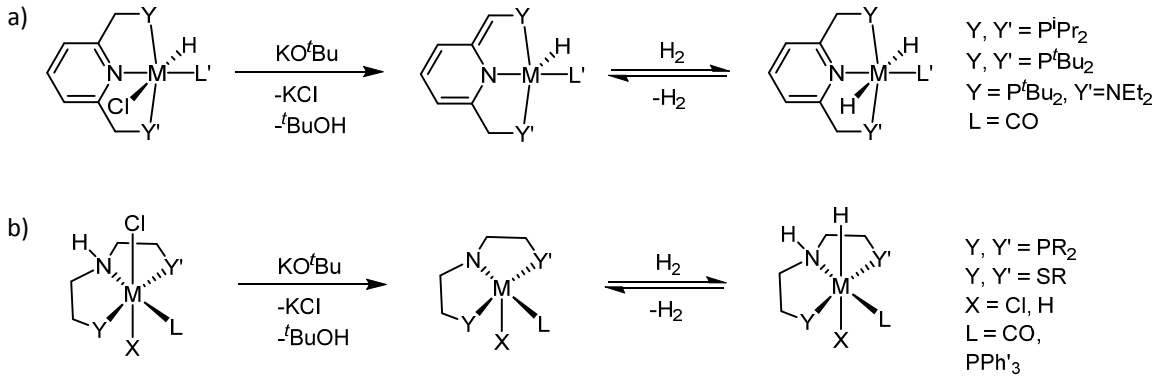
states *via* hydrogen-bonding. This proposed mechanism was subsequently corroborated by DFT calculations concerning a range of catalysts that had been reported earlier.[11]



Scheme 1.5: $H^{(-)}/H^{(+)}$ outer sphere mechanism as proposed by Dub and Gordon. Cycle I describes the hydrogenation reaction in general; cycle II describes the mediating effect of alcohol as solvent. In each case the proton can remain attached to nitrogen throughout the cycle.

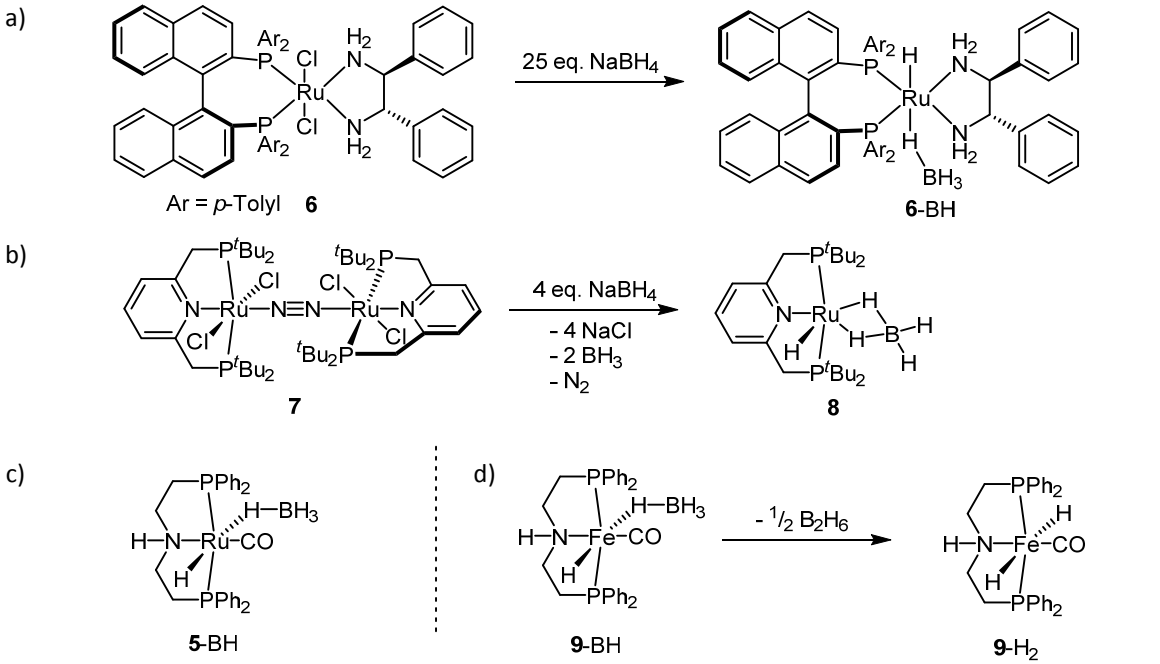
1.1.3 Activation Strategies for Hydrogenation by Pincer Complexes

Based on the actual structure of the pincer complex, several different activation strategies are described in literature.[1] The Milstein-type PNN and PNP complexes, containing a pyridine ring in the ligand backbone, can be deprotonated at the benzylic CH_2 bridge. This leads to dearomatisation of the ligand backbone, which in the presence of H_2 rearomatises, yielding the dihydride complex (Scheme 1.6a). As mentioned in Section 1.1.1, when Y' = NEt_2, the amine moiety can decoordinate, making space for a substrate to be hydrogenated *via* an inner-sphere mechanism.[4b, 12] In contrast, deprotonation of non-aromatic PNP or SNS pincer complexes is usually expected to lead to the corresponding complex with the pincer as anionic amido ligand, which can reversibly activate H_2 (Scheme 1.6b).[1, 2b, 13]



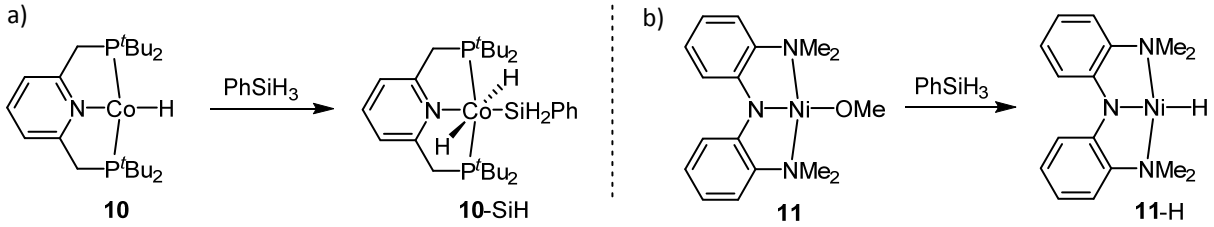
Scheme 1.6: Base activation of two types of pincer complexes commonly applied for hydrogenation.

As an alternative to activation by base, metal-pincer complexes often react with reagents such as borohydrides (or, in fact, $LiBEt_3H$, $LiAlH_4$ and similar reagents), once again based on work from the Noyori lab (Scheme 1.7a).[14] Like base activation, this type of activation is often performed *in situ*.[1, 15] The charm, however, lies in isolation of the activated complex, which opens the way for catalysis with substrates that are unstable or would undergo side reactions in the presence of bases or hydride reagents. Many examples can be found in literature of isolated pincer-borohydride complexes, such as Milstein's RuH(PNP)(η^2-BH_4) (**8**) (Scheme 1.7b),[14b] the **5**-BH analogue of the aforementioned complex **5** (Scheme 1.7c),[14c,d] or the Fe(PNP) borohydride **9**-BH, which was reported by three groups simultaneously.[14e-g] The active species is formed by dissociation of BH_3 (or ½ B_2H_6) under reaction conditions (Scheme 1.7d).[14d,e,g] In other cases, reaction with $NaBH_4$ directly led to formation of hydride complexes instead.[16]



Scheme 1.7: a) Isolated Ru(PP)(NN) borohydride complex first reported by Noyori, opening the way for base-free bifunctional hydrogenations;[14a] b) Preparation of a Ru(PNP) borohydride, as reported by Milstein;[14b] c) commercially available Ru-MACHO-BH;[14c,d] d) Loss of BH_3 leading to active Fe(PNP) dihydride.[14e-g]

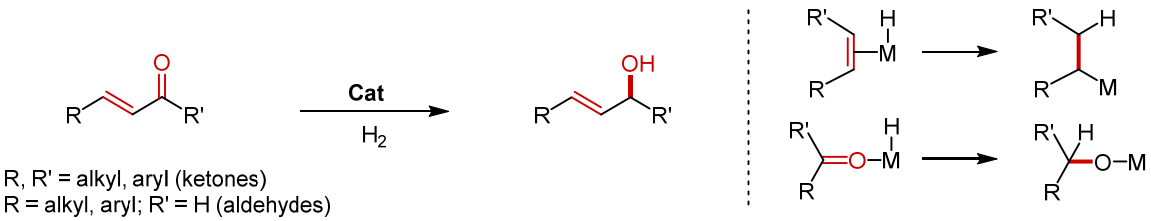
Another catalyst activation strategy suitable for catalytic reductions would be the reaction of the precatalyst with a silane. Unsurprisingly, this strategy finds wide use in hydrosilylation reactions, where the active catalyst is formed *in situ* by oxidative addition of the silane, which is present in large excess w.r.t. catalyst.[17] However, activated complexes such as **10**-SiH and **11**-H have also been isolated and may well be active as hydrogenation catalyst too (Scheme 1.8).[18]



Scheme 1.8: a) Formation of a Co(III) dihydridosilane complex by oxidative addition of a $PhSiH_3$;[18a] b) Preparation of a Ni(PNP) hydride by reaction with $PhSiH_3$.[18b]

1.2 Chemoselective Homogeneous Hydrogenation of α,β-Unsaturated Aldehydes and Ketones to Allylic Alcohols

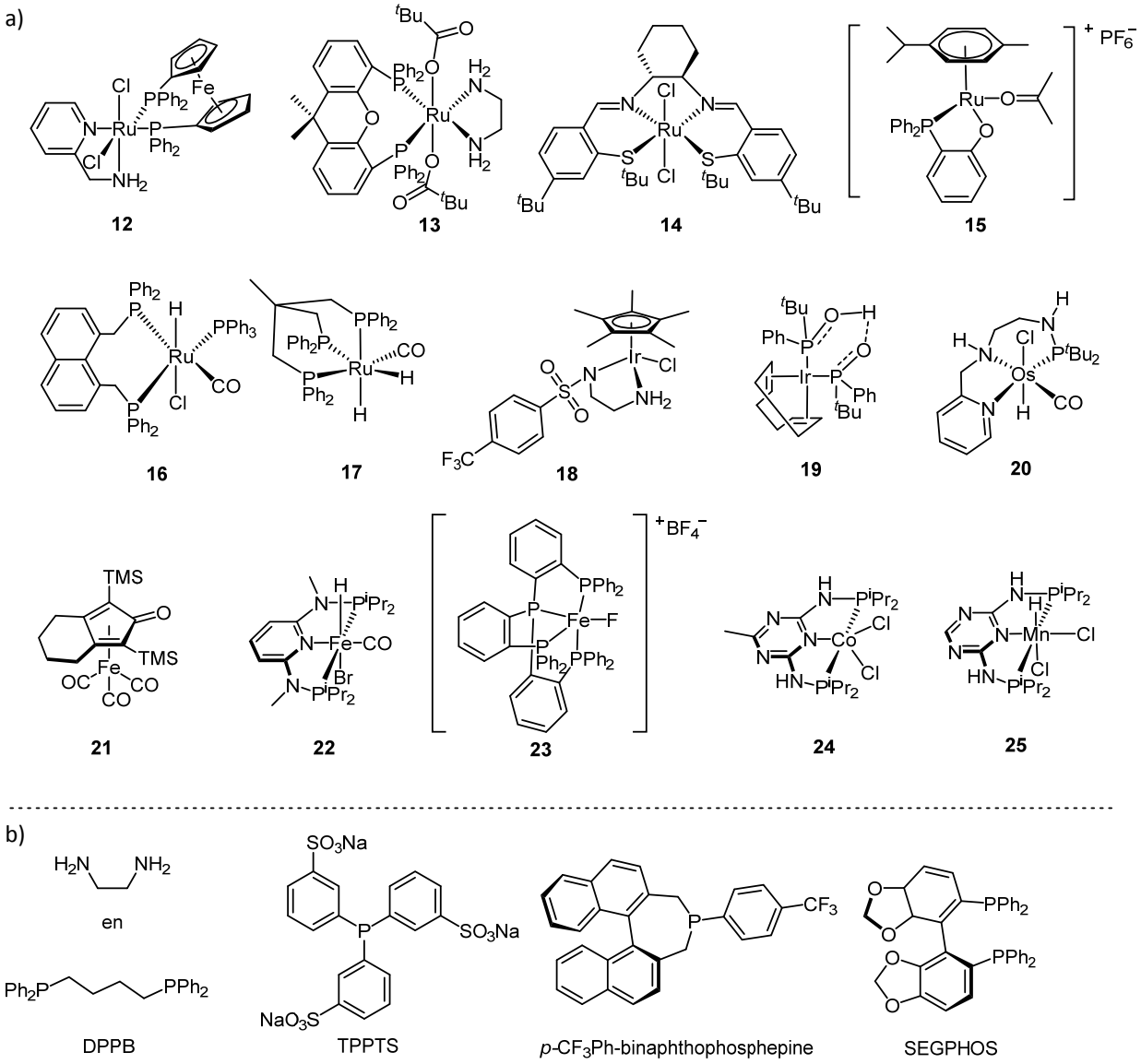
Allylic alcohols are compounds of interest for both the pharmaceutical as well as flavour and fragrance industries, as highlighted by Dupau.[19] An atom-economical approach for their preparation is the selective hydrogenation of α,β-unsaturated aldehydes and ketones, provided high selectivities for the reduction of the carbonyl moiety can be achieved (Scheme 1.9a). The hydrogenation of olefinic C=C bonds is thermodynamically favoured by approximately 35 kJ mol^{-1} when compared to C=O bonds.[20] This means that, in order to obtain the allylic alcohols selectively, catalysts are required that intrinsically favour the reduction of the carbonyl moiety. Heterogeneous catalysts were investigated and reviewed, especially for the hydrogenation of α,β-unsaturated aldehydes, but are left out of consideration here for the sake of brevity.[21]



Scheme 1.9: a) Selective, catalytic hydrogenation of α,β-unsaturated aldehydes and ketones to allylic alcohols; b) coordination of an olefin and carbonyl functionality to a metal hydride, followed by insertion of a hydride.

One important distinction between the two functionalities is the way they coordinate to a metal centre, *i.e.* olefins typically coordinate in an η^2 fashion, whereas carbonyls coordinate end-on with the oxygen atom (Scheme 1.9b). This means that steric interactions can be exploited to allow only the carbonyl moiety to coordinate, after which two equivalents of hydride are transferred, leading to the alcohol *via* the aforementioned Schrock-Osborn type mechanism. Indeed, early work from the group of Graziani reported selectivities of C=O over

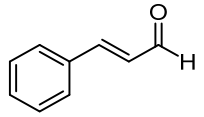
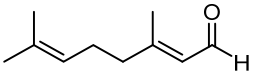
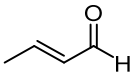
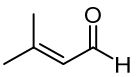
C=C hydrogenation, which were achieved using various metal sources with excess of bulky phosphine ligands.[22] Although the excess of phosphine sterically prevented side-on coordination of the olefin, this blocking of coordination sites also led to significant decrease in conversion and generally low turnovers.



Scheme 1.10: a) Examples of complexes active for selective hydrogenation of α,β-unsaturated aldehydes and/or ketones; b) Ligands added *in situ*.

Tables 1.1 (aldehydes) and 1.2 (ketones) summarise the activities and selectivities reported in literature for several representative catalyst systems. Substrates were selected from the original studies. Newly reported, isolated complexes used as catalysts are represented in Scheme 1.10a and 1.11. Ligands added *in situ*, including abbreviations, are depicted in Scheme 1.10b.

Table 1.1: Selected examples of hydrogenation of α,β-unsaturated aldehydes to primary allylic alcohols.

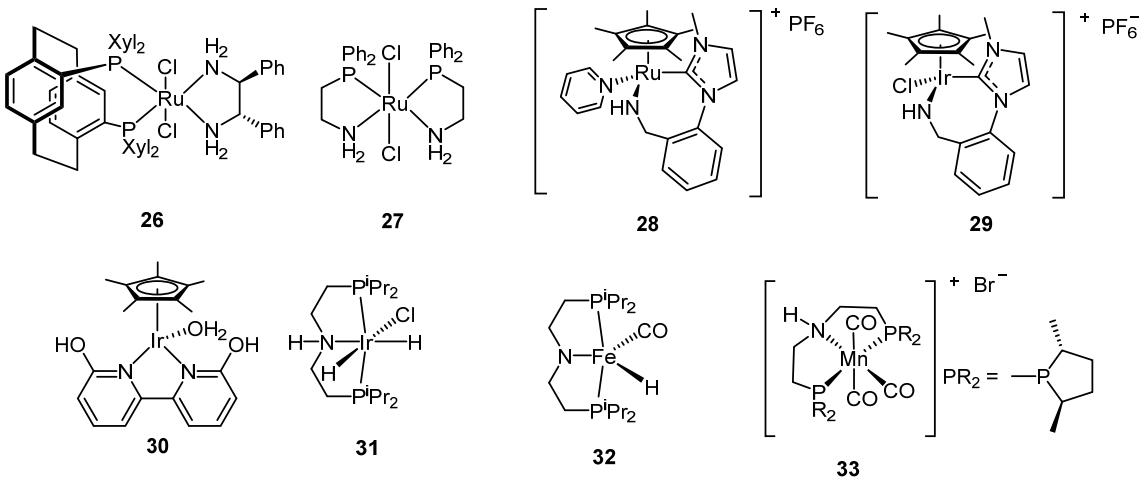





Cinnamaldehyde (**A1**) Citral (**A2**) Crotonaldehyde (**A3**) 3-Methyl-2-butenal (**A4**)

Entry	Cat (S:R)[a]	Add. (eq. w.r.t Cat.)	Conditions	Subst.	Conv. (%) (Yield)	Sel. (%)[b]	Ref.
1	$RuCl_2(PPh_3)_3$ (500)	(en) (1), KOH (2)	4 bar, 28 °C, 0.33 h	**A1**	>99 (88)	100	[23]
	"	"	4 bar, 28 °C, 0.5 h	**A2**	>99 (92)	100	"
2	**12** (2000)	KO^{t}Bu (40)	10 bar, 50 °C, 8 h	**A1**	98	89	[24]
3	**13** (30 000))	Benzoic acid (225)	30 bar, 100 °C, 5 h	**A2**	>99	96	[25]
4	**14** (2000)	KO^{t}Bu (100)	50 bar, 60 °C, 2 h	**A1**	>99	100	[26]
5	**15** (1000)	-	50 bar, 50 °C, 2 h	**A1**	>99	>99	[27]
6	**16** (1600)	-	50 bar, 70 °C, 3h	**A1**	86	94	[28]
	(1200)	-	50 bar, 80 °C, 3h	**A2**	93	96	"
7	**17** (10 000)	-	30 bar, 100 °C, 16 h	**A1**	99	98	[29]
	(5000)	-	30 bar, 100 °C, 16 h	**A2**	>95	92	"
8[c]	$RuCl_3$ (200)	TPPTS (5)	20 bar, 35 °C, 3 h	**A1**	99	98	[30a]
	"	"	20 bar, 35 °C, 4 h	**A3**	95	97	"
	"	"	20 bar, 35 °C, 1 h	**A4**	>99	97	"
	$RuHCl(TPPTS)_3$ (200)	-	20 bar, 40 °C, 1 h	**A1**	73	96	[30b]
	$RuH_2I(TPPTS)_4$ (200)	-	20 bar, 40 °C, 1 h	**A1**	97	95	"
9	**18** (500)	KOH (10)	20 bar, 80 °C, 3.5 h	**A1**	99 (98)	99	[31]
	"	"	20 bar, 80 °C, 5 h	**A2**	98 (93)	95	"
10	**19**	-	5 bar, r.t., 5 h	**A1**	>99	99	[32]
11[d]	$[CuH(PPh_3)]_6$ (20)	$PMePh_2$	5 bar, r.t., 4 h	**A1**	94	97	[33]
	"	"	34 bar, r.t., 4 h	**A2**	90	92	"
12	$Cu(NO_3)(PPh_3)_2$ (500)	DPPB (1), NaOH (10)	50 bar, 50 °C, 3 h	**A1**	>99	68	[34]
	"	"	"	**A4**	>99	72	"
13	**20** (2000)	K_2CO_3 (20)	50 bar, 80 °C, 2.5 h	**A1**	>99	>99	[35]
14	**21** (200)	K_2CO_3 (5)	30 bar, 100 °C, 17 h	**A1**	82	80	[36]
	(1000)	"	"	**A2**	>99	98	"
15	**22** (10 000)	DBU (10)	30 bar, 40 °C, 16 h	**A1**	>99	100	[37]
	"	"	"	**A2**	>99	100	"
16	**23** (250)	TFA (5)	20 bar, 120 °C, 5 h	**A1**	>99 (94)	>99	[38]
	"	"	"	**A2**	99 (97)	>99	"
17	**24** (200)	NaO^{t}Bu (2)	20 bar, 20 °C, 24 h	**A2**	>99	100	[39]
	"	"	"	**A4**	>99	100	"
18	**25** (1000)	-	50 bar, 25 °C, 18 h	**A1**	91	100	[40]

[a]Substrate to catalyst ratio; [b] Selectivity towards allylic alcohol; [c]Biphasic system. [d]Ratio w.r.t. Cu.

The real milestone in carbonyl hydrogenation were the Ru(PP)(NN) based catalysts introduced by the group of Noyori, because metal-ligand bifunctionality represents an inherent selectivity for polarised double bonds.[9a, 23] Similar catalysts were used in various studies, also for the hydrogenation of α,β-unsaturated aldehydes and ketones, often reaching good conversions and selectivities (for example, cat. **12**, Table 1.1, Entry 2, and **26**, Table 1.2, Entry 2).[24, 41] It must be noted that most such ligands used were developed for asymmetric hydrogenation of ketones, meaning that they may well be too expensive when enantioselectivity is not an issue. Noyori's group themselves, however, showed that $RuCl_3(PPh_3)_3$ in combination with ethylene diamine (**en**, Table 1.1, Entry 1, Table 1.2, Entry 1) can already lead to respectable turnovers and excellent selectivities, although the performance was highly substrate-dependent.[23] It was also possible to vary the (PP)(NN) ligand combination to two equivalents of (PN) (**27**, Table 1.2, Entry 3).[42]



Scheme 1.11: Examples of complexes active for selective hydrogenation of α,β-unsaturated ketones.

The requirement of base activation for most bifunctional catalysts presents another challenge, particularly in the case of aldehydes, as this class of substrates is base sensitive. Dupau *et al.* circumvented this issue by using ruthenium carboxylate **13**, which do not require any further activation by base (Table 1, Entry 3).[25] Good selectivities can also be obtained when water-soluble ruthenium complexes were employed in a biphasic system with aldehydes (Entry 8).[30] Importantly, bifunctional pincer complexes were also introduced for this reaction. Overall, high conversions and selectivities are typically reported using ruthenium complexes, which is preferred over other noble metals such as iridium in view of its lower cost.[25-29, 31, 32, 44, 45]

Table 1.2: Selected examples of hydrogenation of α,β-unsaturated ketones to secondary allylic alcohols.

Benzylidene acetone (**K1**) 2-Cyclohexen-1-one (**K2**) 3-Methyl-2-cyclohexen -1-one (**K3**) 1-Acetylcyclohexene (**K4**)

Entry	Cat (S:R)[a]	Add. (eq. w.r.t Cat.)	Cond.	Subst.	Conv. (%) (Yield)	Sel. (%)[b]	Ref.
1	$RuCl_2(PPh_3)_3$ (500)	(en) (1), KOH (2)	4 bar, 28 °C, 3 h	**K1**	>99 (97)	>99.9	[23]
			4 bar, 28 °C, 1 h	**K2**	>99 (92)	100	
			8 bar, 28 °C, 1.5 h	**K3**	9.8	>99.9	
2	**26** (3000)	KO^{t}Bu (50)	8 bar, r.t., 2.5 h	**K1**	>99	100	[41]
				K4	>99	100	
3	**27** (1000)	KO^{t}Bu (1)	10 bar, 25 °C, 2 h	**K1**	>99	100	[42]
4	**28** (600)	KO^{t}Bu (8)	8 bar, 25 °C, 1 h	**K1**	99	100	[43]
5	**29** (200)	KO^{t}Bu (16)	25 bar, 50 °C, 5 h	**K1**	99	88	[43]
6	**30** (50)	-	1 bar, 25°C, 24 h	**K2**	71xxx	>99	[44]
7	**31** (300)	KO^{t}Bu (10)	10 bar, r.t., 1 h	**K1**	>99 (99)	100	[45]
				K2	>99	50	
8	**20** (2000)	K_2CO_3 (20)		**K1**	>99	98	[35]
				K2	>99	92	
9	$[CuH(PPh_3)]_6$ (20)[c]	$PMePh_2$	34 bar, r.t., 18 h	**K1**	>99	92	[33]
10	$Cu(NO_3)(PXy_3)_2$ (200)	*R*-SegPhos (1), NaO^{t}Bu (10)	50 bar, 30 °C, 16 h	**K1**	>99	68	[46]
11	$Cu(OAc)_2$ (300)	*p*-CF_3Ph-binaphthophosp.	50 bar, 10 °C, 16 h	**K1**	65	>99	[47]
				K4	58	>99	
12	**32** (500)	-	10 bar, 70 °C, 24 h	**K1**	95	81	[48]
13	**33** (50) (100)	KO^{t}Bu (5)	30 bar, 40 °C, 4 h	**K2**	>99	>99	[49]
				K3	>99	94	

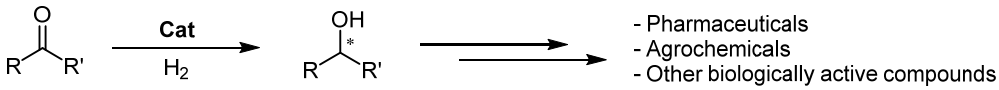
[a]Substrate to catalyst ratio; [b] Selectivity towards allylic alcohol; [c]Ratio w.r.t. Cu.

Over the last decade, the use of base metal complexes in homogeneous catalysis has taken a flight, and several such catalysts have since been reported to give satisfactory selectivities in the hydrogenation of α,β-unsaturated carbonyl compounds. In this context, worth mentioning is Stryker's reagent, which is an early example of a copper catalyst for selective hydrogenation (Table 1, entry 11 and Table 2, Entry 9).[33] Following this promising study, however, only a handful of other copper catalysts were reported (Table 1, Entry 12, Table 2, Entry 10 and 11).[34, 46, 47]

Typically, base-metal catalysts require comparatively high loadings, or bear expensive ligands, which are not cheap and usually air-sensitive, which partially off-sets gains made by using base metals (representative examples are listed in Table 1, Entry 14-18 and Table 2, Entry 12 and 13).[34-38, 45, 46] This sparked our interest in the development of cheap ligands for use in chemoselective carbonyl hydrogenation, which is summarised in Sections 2.1.1 and 2.3.

1.3 Asymmetric Hydrogenation of Ketones

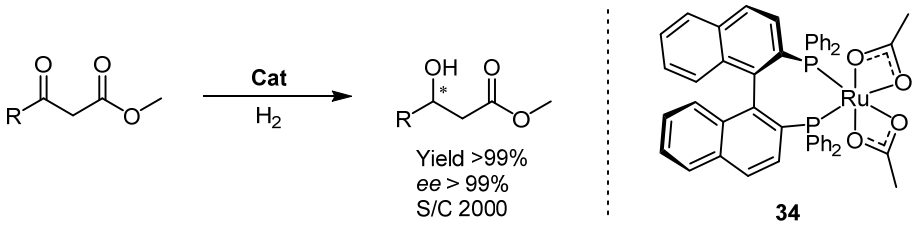
The hydrogenation of non-symmetric (prochiral) substrates can, depending on catalyst and reaction conditions, result in an excess of one of the possible products enantiomers, which is called asymmetric hydrogenation (AH, Scheme 1.12). Indeed, the asymmetric hydrogenation of ketones to chiral secondary alcohols is a widely recognised atom-economical method to introduce chirality in a compound class. The chiral alcohol may either be desired as product itself, or a convenient starting point for further functionalisation. This reaction has been investigated and reviewed extensively.[50]



Scheme 1.12: Asymmetric hydrogenation of prochiral ketones to chiral secondary alcohols.

1.3.1 Ruthenium- and Iridium-Catalysed AH of Ketones

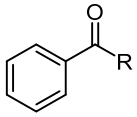
In 1987, the report of Ru(binap)$(OAc)_2$ (**34**)catalysed AH of β-keto esters set a high standard in terms of turnovers, yields, as well as *ee* (enantiomeric excess) values (Scheme 1.13).[51] Chiral diphosphine ligands have since been applied together with various metals, and for different classes of prochiral substrates. In fact, the first Noyori-type Ru(PP)(NN) catalysts, as discussed above, were designed for the AH of aromatic ketones, achieving respectable *ee*'s around 80% with excellent turnover numbers up to 2 400 000.[9a, 50c]



Scheme 1.13: Asymmetric hydrogenation of β-keto esters by a Ru-binap system.

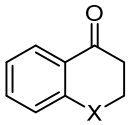
As Yoshimura *et al.* mention in their review, no single catalyst is known that works well for the AH of all ketones, and for different classes of substrates, different catalysts need to be developed.[50b] Most (PP)(NN)-type catalysts are based on ruthenium with a chiral diphosphine as well as a chiral diamine ligand, although in some cases the chiral diphosphine could be replaced by an achiral diphosphine or two equivalents of a bulky monophospine ligand, as recently reviewed by Xie *et al*. (Scheme 1.14). [50c, 52] A downside of this class of catalysts is that they require addition of a strong base, and are prone to lose the diamine ligand, which can get displaced by coordinating substrates or solvents.[50b]

Table 1.3: Selected examples of AH of prochiral ketones **K'** catalysed by Noyori-type $RuCl_2$(PP)(NN) complexes.



K1'

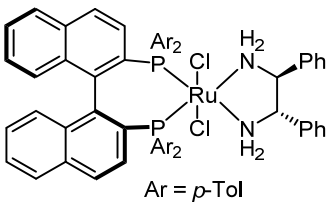
K2'



K3'

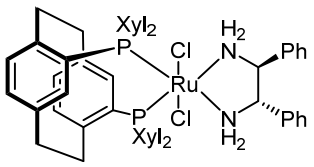
Entry	Cat (S:R)[a]	Add. (eq. w.r.t Cat.)	Cond.	Subst.	Conv. (%) (Yield)[b]	*ee* (%,)[c]	Ref.
1	**6** (500)	KOH (2)	4 bar, r.t., 3 h	**K1'** (R=Me)	>99	87	[9a]
	"	"	"	**K3'** (X=CH_2)	>99	59	"
	(2 400 000)	KO^{t}Bu (24000)	45 bar, r.t., 3 h	**K1'** (R=Me)	>99	80	[9c]
2	**26** (3000)	KO^{t}Bu (50)	8 bar, r.t., 0.5 h	**K1'** (R=Me)	>99	99	[41]
	"	"	"	**K1'** (R=^{i}Pr)	>99	71	"
	"	"	"	**K2'** (R=Cy)	>99	49	"
	(40 000)	KO^{t}Bu (100)	8 bar, r.t., 4 h	**K1'** (R=Me)	(97)	98.5	"
3	**35** (5000)	KO^{t}Bu (70)	50 bar, r.t., 1.5 h	**K1'** (R=Me)	>99	99	[52a]
	(100 000)	KO^{t}Bu (1400)	50 bar, 40 °C, 72 h	**K1'** (R=Me)	98	98	
4	**36** (2500)	KOH (2.5)	15 bar, r.t., 4 h	**K1'** (R=Me)	>99	90	[52b]
5	**37** (1000)	KO^{t}Bu (20)	20 bar, 25 °C, 10 h	**K1'** (R=Me)	>99	96	[52c]
	(10 000)	"	20 bar, 25 °C, 24 h	"	>99	95	

a) Substrate to catalyst ratio; b) Conversions as reported based on GC or NMR, isolated yields between parentheses; c) enantiomeric excess of the product alcohol.



Ar = *p*-Tol

6



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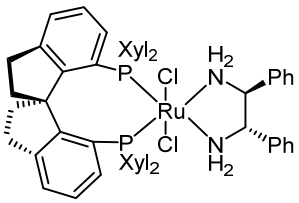

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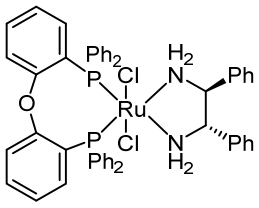

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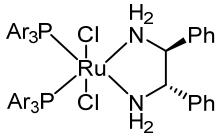


Ar = 3,5-(3,5-dimethylphenyl)phenyl

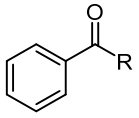
37

Scheme 1.14: Selected examples of $RuCl_2$(PP)(NN) catalysts.

Complexes such as **38** and **39** incorporate the –NH functionality in the pincer ligand, and these can compete well with (PP)(NN) type systems, especially when challenging substrates such as *tert*-butyl ketones are hydrogenated. In order to obtain good *ee*'s for acetophenone

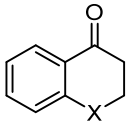
with complex **38**, however, additional steric bulk needed to be installed on the ligand.[65] The Ru-SNNS complex **14**, which was described before in view of its chemoselectivity, exhibits *ee*'s from 80-95%. Although the *ee* dropped to 61%, **14** still gave full conversion at a substrate to catalyst ratio of 10^{-5}.[26] Chiral arene complexes **40**-**41** are of interest as well, as they too are phosphine-free and do not require additives.[54a-b] Another strategy is to use cyclometallated complexes with chiral ancillary ligands, such as complex **42**, which have increased stability when compared to pincer or tetradentate complexes, and indeed improved substrate to catalyst ratios were reported.[54c] Table 1.4 summarises the performance of catalysts **38**-**42**, and **14**, as depicted in Scheme 1.15.

Table 1.4: Selected examples of AH of ketones catalysed by Ru and Ir complexes.



K1'

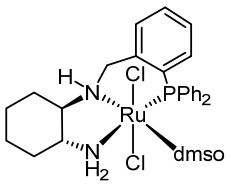
K2'



K3'

Entry	Cat (S:R)[a]	Add. (eq. w.r.t Cat.)	Cond.	Subst.	Conv. (%) (Yield)[b]	*ee* (%,)[c]	Ref.
1	**38** (100)	KO^{t}Bu (2)	50 bar, 50 °C, 24 h	**K1'** (R=^{t}Bu)	>99 (>99)	74	[65a]
	"	"	"	**K1'** (R=Me)	>99	0	[65b]
2	**39** (5000)	KO^{t}Bu (50)	10 bar, r.t., 0.33 h	**K1'** (R=Me)	(99)	98	[65c]
	(1000)	"	10 bar, r.t., 4 h	**K2'** (R=Cy)	(98)	88	"
3	**14** (2000)	KOH (100)	50 bar, r.t., 3 h	**K1'**	99	88	[26]
	"	"	"	**K3'** (X=CH_2)	99	95	"
4	**40** (3000)	-	10 bar, 60 °C, 15 h	**K3'** (X=O)	>99	97	[54a]
5	**41** (500)	-	15 bar, 60 °C, 24 h	**K3'** (X=CH_2)	88 (83)	93	[54b]
	(5000)	"	"	**K3'** (X=O)	>99 (99)	99	"
6	**42** (10 000)	KO^{t}Bu (200)	5 bar, 40 °C, 0.5 h	**K1'** (R=Me)	>99	92	[54c]
	"	"	5 bar, 40 °C, 1 h	**K1'** (R=Et)	97	99	"
	"	"	5 bar, 40 °C, 1 h	**K2'** (R=hexyl)	>99	42	"

a) Substrate to catalyst ratio; b) Conversions as reported based on GC or NMR, isolated yields between parentheses; c) enantiomeric excess of the product alcohol.



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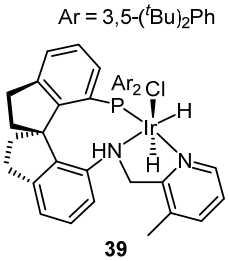

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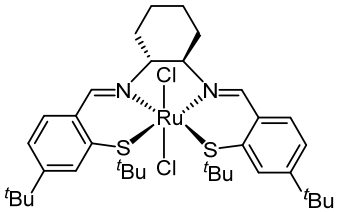
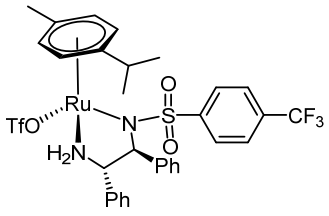


14



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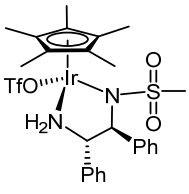

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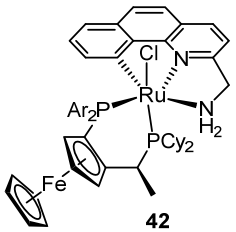


42

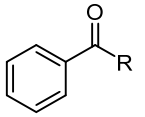
Scheme 1.15: Selected Ru and Ir complexes active in the AH of ketones.

1.3.2 Base Metal-Catalysed AH of Ketones

Copper-catalysed AH of ketones has mainly focused on *in situ* generated species, and has led to decent yields and selectivities, which resulted in a prominent place in the recent review by Yoshimura *et al*.[50b, 47, 55] Morris reported the use of tetradentate Fe-PNNP catalyst **43**, which constitutes the first example of an iron-catalysed asymmetric hydrogenation, although conversion and *ee* were disappointing when hydrogen pressure was used (Entry 1).[56] It must be noted that transfer hydrogenations using this catalyst proceeded with *ee*'s up to 99%. An extensive study subsequently determined that these transfer hydrogenations were actually catalysed by iron nanoparticles.[56b] Gao reported that their macrocyclic ligand, combined with iron carbonyl as metal precursor (**44**) showed good activity and enantioselectivity for a broad range of aromatic ketones (Entry 2), but aliphatic ketones were not investigated.[57] To date, the best-performing base metal catalyst may well be the chiral Fe-PNP complex **45**, which was also reported by the group of Morris, achieving 1000 turnovers with an *ee* of 95%, although this catalyst did not work with the aliphatic substrates they investigated (Entry 3).[58]

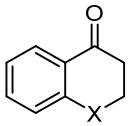
In addition, two examples of manganese-pincer catalysed hydrogenations were recently reported. Interestingly, pincer complex **46**, reported by Clarke, worked very well for a range of bulky aromatic ketones, but gave a poor *ee* for acetophenone (Entry 4).[59] The Beller group reported that Mn-PNP **33** also worked rather poorly for acetophenone in terms of *ee*, but gave good results for a range of aliphatic ketones (Entry 5).[49]

Table 1.5: Selected examples of AH of ketones catalysed by base metal complexes.



K1'

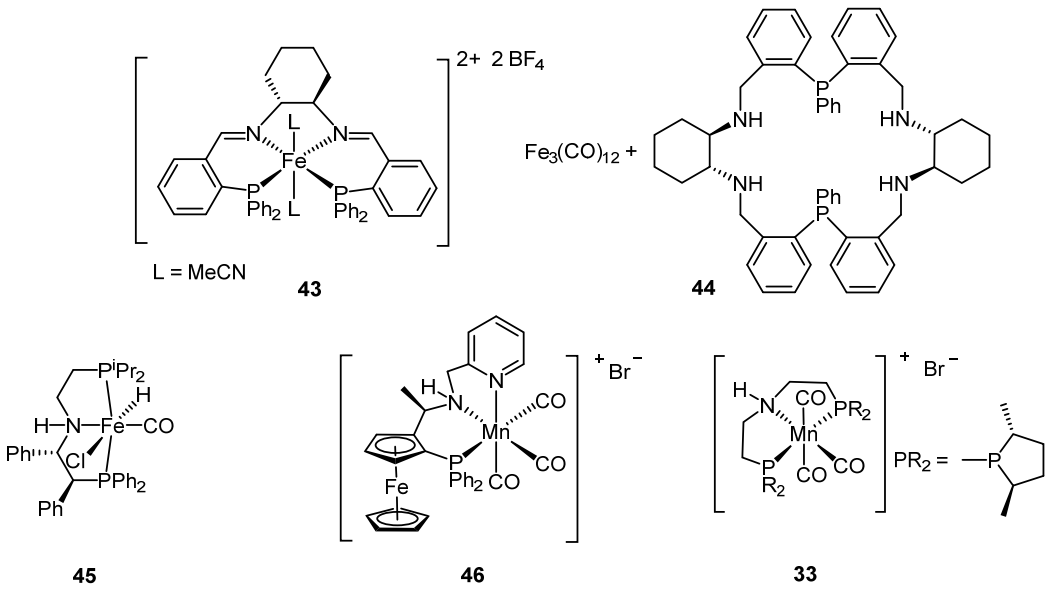
K2'



K3'

Entry	Cat (S:R)[a]	Add. (eq. w.r.t Cat.)	Cond.	Subst.	Conv. (%) (Yield)	*ee* (%,)[b]	Ref.
1	**43** (225)	KO^{t}Bu (15)	25 bar, 50 °C, 18 h	**K1'** (R=Me)	40	27	[56]
2	**44** (200)	KOH (40)	50 bar, 45 °C, 5 h	**K1'** (R=Me)	(97)	97	[57]
	"	"	50 bar, 45 °C, 10 h	R=^{i}Pr	(92)	99	
	"	"	50 bar, 45 °C, 10 h	R=Cy	(63)	99	
3	**45** (1000)	KO^{t}Bu (10)	10 bar, 50 °C, 1.5 h	**K1'** (R=Me)	>99	95	[58]
	"	"	10 bar, 50 °C, 1.5 h	R=Cy	38	62	
4	**46** (100)	KO^{t}Bu (10)	50 bar, 50 °C, 16 h	**K1'** (R=Me)	99 (80)	20	[59]
	"	"	"	R=^{i}Pr	99 (87)	82	
5	**33** (100)	KO^{t}Bu (5)	30 bar, 30 °C, 4 h	**K1'**	99 (88)	2	[45]
	"	"	30 bar, 40 °C, 4 h	**K2'** (R=Cy)	>99	84	
	"	"	30 bar, 60 °C, 4 h	**K3'** (X=CH_2)	99	80	

a) Substrate to catalyst ratio; b) Conversions as reported based on GC or NMR, isolated yields between parentheses; c) enantiomeric excess of the product alcohol.

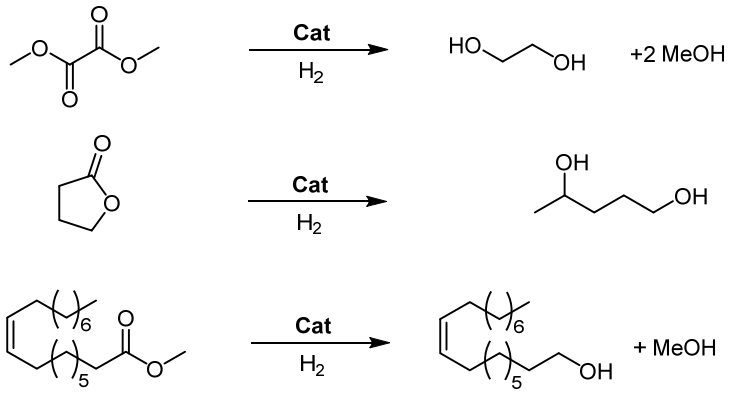


Scheme 1.16: Selected Fe and Mn complexes active in the AH of ketones.

Summarising, despite the vast amount of research already done in the field of AH, most catalysts work for a narrow scope of substrates, as different steric demands are placed on the ligands depending on substrate sterics. Tailor-made ligands, however, can be costly and require extensive screening and optimisation. As such, there is still demand for broadly applicable, robust catalytic systems, which should preferably be cheap, readily available complexes, or generated *in situ* from readily available catalyst precursors.

1.4 Hydrogenation of Esters to Alcohols

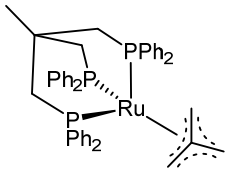
The hydrogenation of esters provides an important route to a range of alcohols, based on the wide variety of ester compounds readily available (Scheme 1.17). A large portion of work in this area focussed on dicarboxylic esters, fatty esters, and lactones, yielding diols or fatty alcohols of industrial interest. On industrial scale, the hydrogenation of fatty esters is performed using chromium-based catalysts, which is of environmental concern.[60]



Scheme 1.17: Hydrogenation of a) dimethyl glycolate to ethylene glycol and methanol; b) *γ*-valerolactone to 1,4-pentanediol; c) methyl oleate to oleyl alcohol and methanol.

1.4.1 Ruthenium- and Osmium-Catalysed Hydrogenation of Esters

In early reports, harsh reaction conditions (120-200 °C, 80-200 bar H_2) were typically reported employing various ruthenium-phosphine complexes, and turnover numbers were low.[61] Notably, the group of Elsevier established a ruthenium-triphos system, with zinc as additive, as preferred catalyst for the hydrogenation of esters to alcohols.[62a-c] This system was recently revisited by Leitner *et al.* when they added acidic co-catalysts, which allowed them to hydrogenate carboxylic acids. It was established that the molecularly defined Ru(Triphos)(TMM) (**47**) hydrogenated esters quantitatively in 16-24 hours in the absence of additives at 1 mol% catalyst loading, under 50 bar H_2 atmosphere at 140 °C.[62d,e]



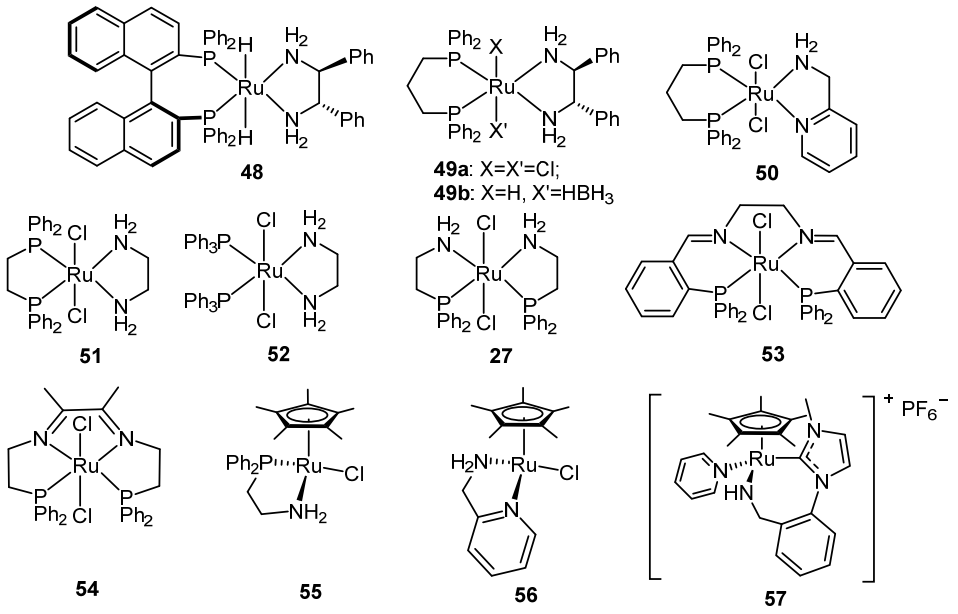
47

Yield >99%
S/C 100
additive-free

Scheme 1.18: Ru(Triphos)(TMM) (**47**).

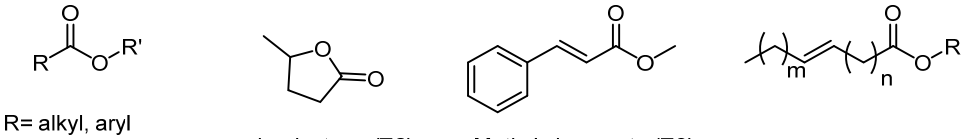
As discussed previously, breakthroughs from the Noyori group led to great excitement about $RuX_2(PP)(NN)$ catalysts such as complexes **48**-**51**, which were applied in the hydrogenation of esters.[63] Reportedly, the $RuH_2(PP)(NN)$ catalyst **48** even reduces esters at -20 °C, and the elementary reaction steps can be observed at temperatures as low as -80 °C, but higher temperatures are required to dissociate the product from the catalyst and recover the hydride species. This study provided an important insight in the bifunctional hydrogenation mechanism of esters with this type of catalyst.[63c] Similarly, ruthenium complexes **50**-**54** bearing PN-type ligands, as reported by Saudan *et al.* from Firmenich, showed good turnovers, whereas a simple $RuCl_2$(dppe)(en) (**48**) or $RuCl_2(Ph_3)_2$(en) (**49**) complex only gave trace amounts of conversion, suggesting that the steric bulk and rigidity of the original Noyori-type catalysts were crucial for the catalyst performance (Table).[64] Ru-Cp* complexes such as **55**-**56** were also applied successfully.[65]

Milstein and co-workers used their pre-activated ruthenium pincer complex **58** for the hydrogenation of esters as well. Reaction conditions were particularly mild in comparison (only 5.4 bar H_2, and additive-free), but catalyst loadings of around 1 mol % were required to obtain good yields.[4b] This sparked the development of similar complexes **59-61**, including those bearing CNN pincers (based on *N*-heterocyclic carbenes instead of phosphine donors) leading to a broader substrate scope and catalyst loadings as low as 0.025 mol%.[14c, 66] Remarkably, the modified Milstein-type catalyst **61** reduced methyl formate and dimethyl carbonate to methanol selectively.[66c]



Scheme 1.19: Ruthenium catalysts based on the Ru(PP)(NN), $(PN)_2$ and Cp*(PN) motive.

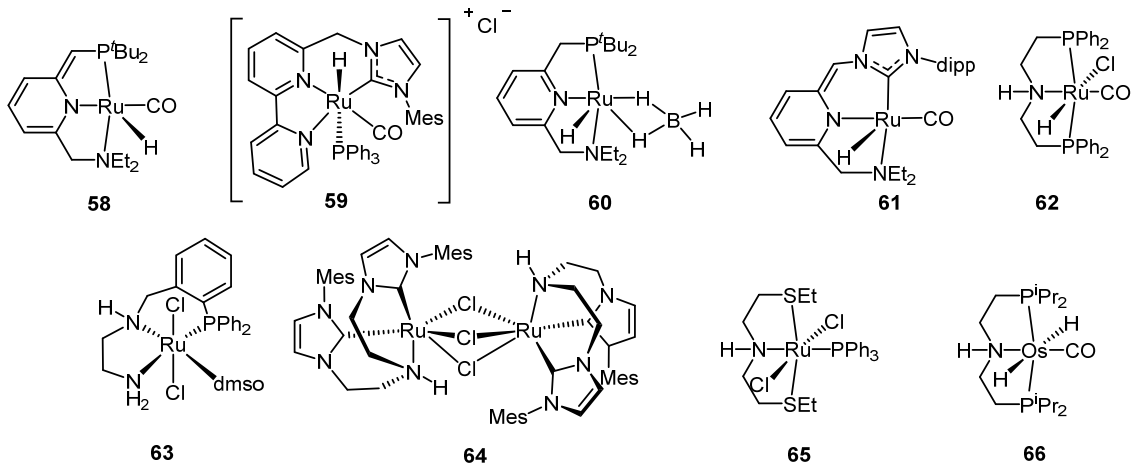
Table 1.6: Selected examples of ester hydrogenation catalysed by Ru(PP)(NN), $(PN)_2$ and Cp*(PN) complexes.



R= alkyl, aryl
R'= alkyl, aryl (**E1**) *y*-valerolactone (**E2**) Methyl cinnamate (**E3**) Unsatd. ester (**E4**)

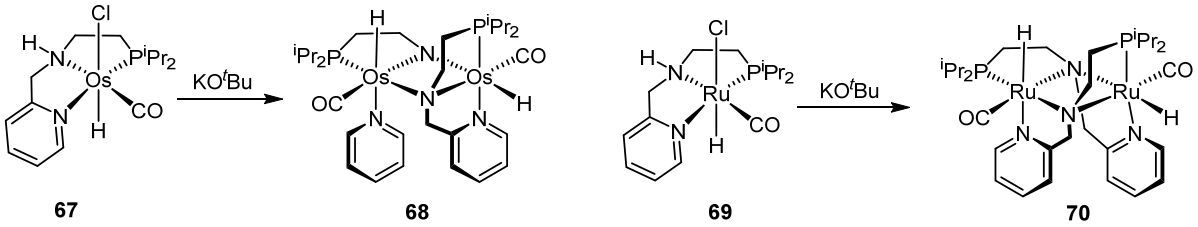
Entry	Cat (S:R)[a]	Add. (eq. w.r.t Cat.)	Cond.	Subst.	Conv. (%) (Yield)	Sel. (%)[b]	Ref.
1	**48** (100)	KO^{t}Bu (9)	4 bar, 50 °C, 3 h	**E1** (R=Ph, R'=Me)	>99	-	[63c]
	(50)	"	4 bar, 30 °C, 3 h	**E3**	>99	0	"
2	**49a** (500)	NaOMe (50)	50 bar, 100 °C, 3 h	**E1** (R=Ph, R'=Me)	>99	97	[63a]
	49b (500)	-	50 bar, 80 °C, 16 h	**E1** (R=Ph, R'=Me)	>99	97	"
3	**50** (200)	KO^{t}Bu (50)	50 bar, 100 °C, 1 h	**E1** (R=*p*-Tol, R'=Me)	>99 (96)	-	[63b]
4	**51** (2000)	NaOMe (100)	50 bar, 100 °C, 1 h	**E1** (R=Ph, R'=Me)	0.5	-	[64]
5	**52** (2000)	NaOMe (100)	50 bar, 100 °C, 1 h	**E1** (R=Ph, R'=Me)	0	-	"
6	**27** (2000)	NaOMe (100)	50 bar, 100 °C, 1 h	**E1** (R=Ph, R'=Me)	>99 (97)	-	"
	"	"	"	**E1** (R=octyl, R'=Me)	(94)	-	"
7	**53** (2000)	NaOMe (100)	50 bar, 100 °C, 1 h	**E1** (R=Ph, R'=Me)	>99	-	"
	"	"	50 bar, 100 °C, 2.5 h	**E3**	(87)	12	"
	"	"	"	**E4** (m=4, n=2, R=Et)	(93)	99	"
8	**54** (2000)	NaOMe (100)	50 bar, 100 °C, 1 h	**E1** (R=Ph, R'=Me)	96	-	"
9	**55** (100)	NaOMe (25)	50 bar, 100 °C, 14 h	**E1** (R=Ph, R'=Et)	(97)	-	[65a]
	"	"	"	**E2**	(98)	-	[65b]
10	**56** (50)	KO^{t}Bu (12.5)	50 bar, 100 °C, 14 h	**E2**	>99 (73)	-	"
11	**57** (1500)	KO^{t}Bu (8)	25 bar, 50 °C, 2 h	**E1** (R=Ph, R'=Me)	78	-	[65c]
	"	"	25 bar, 50 °C, 4 h	**E1** (R=^{t}butyl, R'=Me)	98	-	"

a) Substrate to catalyst ratio; b) Conversions as reported based on GC or NMR, isolated yields between parentheses; c) For **E2**, selectivity towards diol; for **E3** and **E4**, selectivity towards the alcohol with olefinic double bonds intact.



Scheme 1.20: Pincer complexes reported for ester hydrogenation.

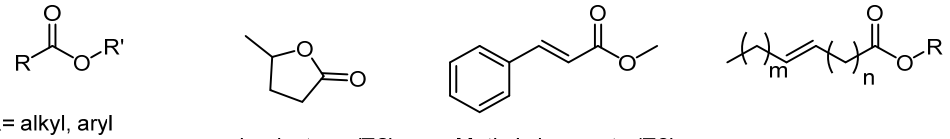
Other notable ruthenium pincers are Clarke's PNN complex **63** and the Ru-MACHO complex **62** used by Kuriyama *et al.* from Takasago.[63b, 14c-d] The latter was used to scale up the hydrogenation of methyl (*R*)-lactate to (*R*)-1,-propanediol to 2200 kg with 96% yield and 99.2% *e.e.* in 12 hours. Gusev and Schlaf reported the Os-PNP complex **66**, which catalysed the hydrogenation of esters under rather harsh conditions, and performed well even for triglycerides. However, this complex was incompatible with olefins, which needed to be prehydrogenated using Pd/C.[67] The group of Gusev reported osmium- and ruthenium-PNN complexes **67** and **69**, as well as the phosphine-free Ru-SNS pincer **65**, all of which were successfully applied in the ester hydrogenation. Interestingly, upon activation by KO^{t}Bu in the absence of H_2, dimeric complexes **68** and **70** could be isolated, which were highly active in the absence of base.[68]



Scheme 1.21: Os- and Ru-PNN complexes and their activated dimeric forms.

Despite tremendous improvements made in terms of turnovers and milder reaction conditions, chemoselectivity with respect to olefinic double bonds remained problematic, especially in the case of α,β-unsaturated esters, of which only one example was reported before. The ruthenium dimer **64**, bearing a bis-*N*-heterocyclic carbene pincer, yielded 72% selectivity towards cinnamyl alcohol in the hydrogenation of methyl cinnamate. In the case of simple esters, remarkable TONs of up to 80 000 were achieved with this catalyst.[69]

Table 1.7: Selected examples ester hydrogenation catalysed by Ru and Os pincer complexes.

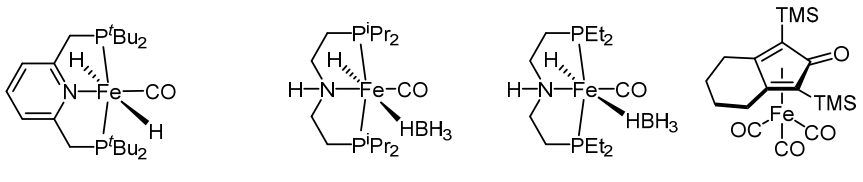


Entry	Cat (S:R)[a]	Add. (eq. w.r.t Cat.)	Cond.	Subst.	Conv. (%) (Yield)	Sel. (%)[b]	Ref.
1	**58** (100)	-	5 bar, 115 °C, 4 h	**E1** (R=Ph, R'=Et)	99	-	[4b]
2	**59** (100)	KO^{t}Bu (1)	5 bar, 135 °C, 2 h	**E1** (R=Ph, R'=Et)	98	-	[66a]
3	**60** (200)	-	10 bar, 110 °C, 12 h	**E1** (R=Ph, R'=Me)	97	-	[14b]
	"	"-	"	**E1** (R=pentyl, R'=hexyl)	94	-	"
4	**61** (100)	KO^{t}Bu (1)	5 bar, 105 °C, 2 h	**E1** (R=Ph, R'=Et)	>99	-	[66c]
5	**62** (1000)	NaOMe (100)	50 bar, 100 °C, 16 h	**E1** (R=Ph, R'=Me)	98 (90)	-	[14c-d]
	"	"	"	**E1** (R=undecyl, R'=Me)	98 (90)	-	"
6	**63** (200)	KO^{t}Bu (50)	50 bar, 50 °C, 16 h	**E1** (R=Ph, R'=Me)	99 (97)	-	[63b]
7	**64** (40 000)	KO^{t}Bu (800)	50 bar, 70 °C, 16 h	**E1** (R=pentyl, R'=Et)	>99	-	[69]
	(4000)	KO^{t}Bu (80)	"	**E1** (R=Ph, R'=Et)	99	-	"
	(2500)	KO^{t}Bu (50)	"	**E3**	82	72	"
8	**65** (4000)	KO^{t}Bu (50)	50 bar, 40 °C, 6 h	**E1** (R=Ph, R'=Me)	95	-	[68c]
	(10 000)	"	50 bar, 100 °C, 2 h	**E1** (R=pentyl, R'=Me)	98	-	"
	(2000)	"	50 bar, 40 °C, 24 h	**E4** (m=4, n=1, R =Me)	>99	73	"
9	**66** (1000)	-	65 bar, 220 °C, 24 h	**E1** (R=octyl, R'=hexyl)	93	88	[67]
10	**67** (2000)	KO^{t}Bu (20)	50 bar, 100 °C, 1.5 h	**E1** (R=Ph, R'=Me)	>99	-	[68]
11	**68** (2000)	-	50 bar, 100 °C, 1.5 h	**E1** (R=Ph, R'=Me)	99	-	"
	"	"	50 bar, 100 °C, 2 h	**E1** (R=pentyl, R'=Me)	>99	-	"
	"	"	50 bar, 100 °C, 6 h	**E4** (m=4, n=1, R=Me)	>99	100	"
12	**69** (2000)	KO^{t}Bu (20)	50 bar, 100 °C, 1.7 h	**E1** (R=Ph, R'=Me)	>99	-	"
13	**70** (10 000)	-	50 bar, 100 °C, 14 h	**E1** (R=Ph, R'=Me)	>99	-	"

a) Substrate to catalyst ratio; b) Conversions as reported based on GC or NMR, isolated yields between parentheses; c) For **E2**, selectivity towards diol; for **E3** and **E4**, selectivity towards the alcohol with olefinic double bonds intact.

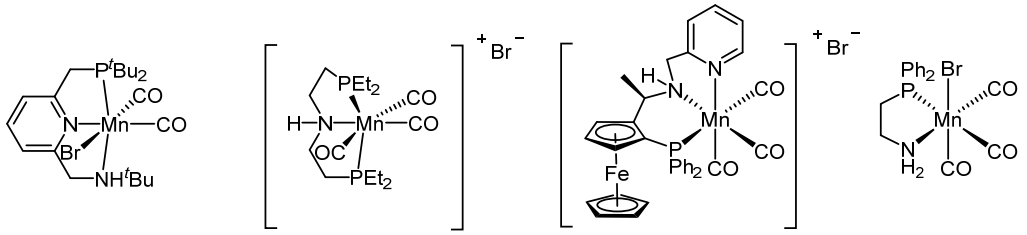
1.4.2 Base Metal-Catalysed Hydrogenation of Esters

A general trend in homogeneous catalysis over the last decade, is the interest in using base metals to catalyse the hydrogenation of esters, but only a couple of examples have been reported (Table 1.8). The groups of Milstein (**71**), Beller (**7**-BH**, 72**-BH) and Guan (**7**-BH) were the first to use iron pincer complexes for this reaction.[70] Complex **71** was only used for hydrogenation of trifluoroacetate esters, like complex **21**, as reported by Pignataro.[71] Although catalyst loadings were relatively high (0.5-3%), mild reaction conditions could be used in some cases. Here, too, did isolation of the borohydride analogue allow for base-free reactions. Selectivity towards allylic alcohols starting from the α,β-unsaturated esters, however, was not achieved.



Scheme 1.22: Iron complexes reported for ester hydrogenation.

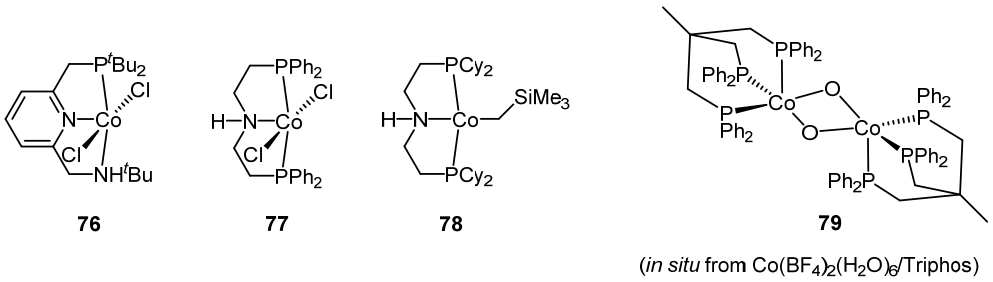
The group of Milstein slightly modified their ligand system, and reported the manganese analogue **73** of their complexes, which performed well, although under slightly harsher reaction conditions and at 2 mol% catalyst loading. Beller reported similar results using their aliphatic pincer **74**. The group of Clarke, based on their earlier experience with asymmetric hydrogenation, developed chiral Mn-PNN complexes like **46**, which was active for ester hydrogenation (as well as for the AH of ketones, as discussed before).[59a] The group of Pidko showed that bidentate PN ligands can outperform pincer complexes in this case, and a series of esters was hydrogenated at only 0.2 mol% **75** loading (although 75 mol% of KO^{t}Bu was required as co-catalyst).[73] Non-conjugated olefinic double bonds in fatty esters remained untouched, but methyl cinnamate was fully reduced to the saturated alcohol.



73 **74** **46** **75**

Scheme 1.23: Manganese complexes reported for ester hydrogenation.

Finally, several examples of cobalt-catalysed ester hydrogenation are known as well (Scheme 1.24). Three pincer complexes **76-78** were reported, including the pre-activated complex **78**.[74] De Bruijn *et al.* introduced the Co-Triphos system **79**, which was generated *in situ*.[75]

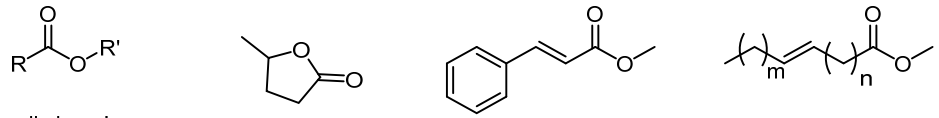


76 **77** **78** **79**

(*in situ* from $Co(BF_4)_2(H_2O)_6$/Triphos)

Scheme 1.24: Cobalt complexes reported for ester hydrogenation.

Table 1.8: Selected examples of hydrogenation of esters catalysed by base metal complexes.



R= alkyl, aryl
R'= alkyl, aryl (**E1**) *y*-valerolactone (**E2**) Methyl cinnamate (**E3**) Unsatd. methyl ester (**E4**)

Entry	Cat (S:R)[a]	Add. (w.r.t. Cat.)	Conditions	Subst.	Conv. (%) (Yield)[b]	Sel. (%)[c]	Ref.
1	**71** (100)	NaOMe (5)	25 bar, 40 °C, 16 h	**E1** (R=CF_3, R'=butyl)	77	-	[70a]
	(33)	"	25 bar, 40 °C, 60 h	**E1** (R=CF_3, R'=^{i}propyl)	77	-	"
2	**7**-BH (33)	-	10 bar, 115 °C, 3 h	**E1** (R=Ph, R'=Me)	(92)	-	[70c]
	"	"	16 bar, 115 °C, 24 h	**E1** (R=octyl, R'=Me)	(72)	-	"
	"	"	16 bar, 115 °C, 24 h	**E3**	(93)	0	"
3	**72** (100)	-	30 bar, 60 °C, 6 h	**E1** (R=Ph, R'=Me)	>99 (99)	-	[70e]
	"	"	"	**E2**	>99 (98)	99	"
	"	"	"	**E3**	>99 (95)	0	"
	"	"	"	**E4** (m=3, n=2)	>99 (98)	99	"
4	**21** (100)	TMAO (2), TEA (20)	70 bar, 90 °C, 17 h	**E1** (R=CF_3, R'=hexyl)	>99	-	[71]

		"	"	**E1** (R=CF_3, R'=^{i}Pr)	>99	-	„
5	**73** (100)	KH (2)	20 bar, 100 °C, 50h	**E1** (R=Ph, R'=Me)	99	99	[72a]
	"	"	20 bar, 100 °C, 28h	**E1** (R=pentyl, R'=Me)	95	99	"
6	**74** (50)	KO^{t}Bu (5)	30 bar, 110 °C, 24h	**E1** (R=Ph, R'=Me)	97	-	[72b]
	"	"	"	**E2**	>99 (95)	-	"
	"	"	"	**E3**	99 (93)	0	"
7	**46** (100)	KO^{t}Bu (10)	50 bar, 75 °C, 18h	**E1** (R=naphthyl, R'=Me)	99 (87)	-	[59a]
	(1000)		"	**E1** (R=propyl, R'=butyl)	82	-	"
8	**75** (500)	KO^{t}Bu (375)	50 bar, 100 °C, 16h	**E1** (R=Ph, R'=Me)	99	98	[73]
	"	"	"	**E3**	99	0	"
	"	"	"	**E4** (m=n=7)	95	100	"
9	**76** (25)	$NaBEt_3H$ (2) KO^{t}Bu (6.25)	50 bar, 130 °C, 48h	**E1** (R=Ph, R'=Me)	0	-	[74a]
	"	"	50 bar, 130 °C, 70h	**E2**	50	100	"
	"	"	50 bar, 130 °C, 48h	**E1** (R=pentyl, R'=butyl)	85	-	"
10	**77** (20)	NaOMe (4)	50 bar, 120 °C, 6 h	**E1** (R=Ph, R'=Me)	>99	100	[74b]
	"	"	"	**E1** (R=napthyl, R'=Me)	99	77	"
	"	"	50 bar, 120 °C, 24 h	**E1** (R=heptyl, R'=Me)	87	75	"
11	**78** (50)	-	55 bar, 120 °C, 20h	**E1** (R=Ph, R'=Me)	24	63	[74c]
	"	-	"	**E1** (R=Ph, R'=Et)	94	96	"
	(1000)	-	55 bar, 120 °C, 5h	**E2**	99.8 (91.6)	98	"
	(50)	-	55 bar, 120 °C, 20h	**E3**	>99	0	"
12	**79** (10)	-	80 bar, 100 °C, 5h	**E1** (R=Ph, R'=Me)	98 (95)	-	[75]
	"	-	80 bar, 100 °C, 22h	**E2**	98 (63)	64	"
	"	-	80 bar, 100 °C, 22h	**E4** (m=n=1)	>99 (90)	0	"

a) Substrate to catalyst ratio; b) Conversions as reported based on GC or NMR, isolated yields between parentheses; c) For **E2**, selectivity towards diol; for **E3** and **E4**, selectivity towards the alcohol with olefinic double bonds intact.

In summary, several well-performing catalytic systems for the hydrogenation of esters are known nowadays, but several issues remain to be solved. As Dub and Ikariya rightly mentioned in their review, ester hydrogenation catalysts often behave differently in the presence of methanol or methyl esters.[60b] Even under mild reaction conditions, chemoselectivity of the ester moiety over (especially conjugated) olefinic double bonds is hard to achieve. The ligands used in the most successful ruthenium catalysts are expensive, sensitive, and not readily accessible, and the same can be said for the handful of base metal catalysts that were reported.

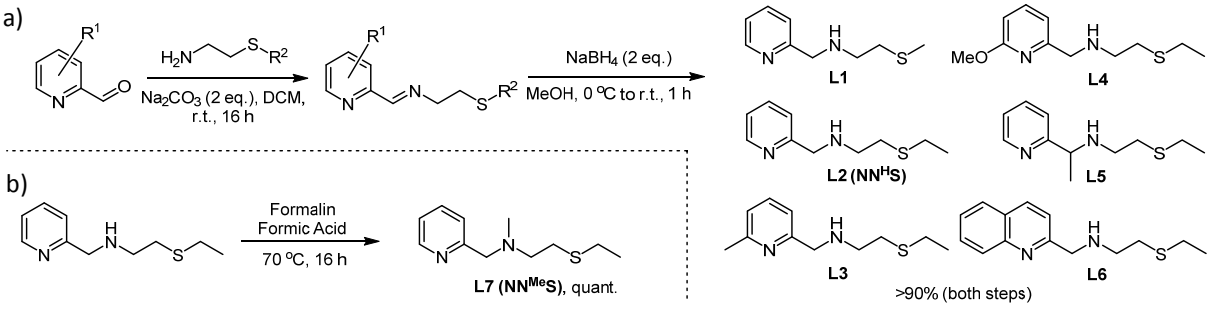
2. Aim and Summary of this Dissertation

2.1 Hydrogenation of Aldehydes and Ketones

As described in sections 1.1 and 1.2, a range of metal complexes are known to catalyse the homogeneous hydrogenation of aldehydes and ketones. Of practical interest are catalysts that exhibit high activities and chemoselectivities, which are typically complexes of precious metals. In recent years, the development of cheaper and often more environmentally friendly catalysts has focussed on complexes of base metals such as Fe, Co, and Mn. However, the environmental impact and cost of phosphorus- and carbene-based ligands can outweigh the gains made by using base metals, especially when comparatively high catalyst loadings are required. We decided instead to design a phosphine-free pincer ligand based on nitrogen and sulphur as donor atoms, and apply its complexes for the hydrogenation of carbonyl functionalities. In addition, we aimed to identify readily accessible chiral ligands for the asymmetric hydrogenation of ketones.

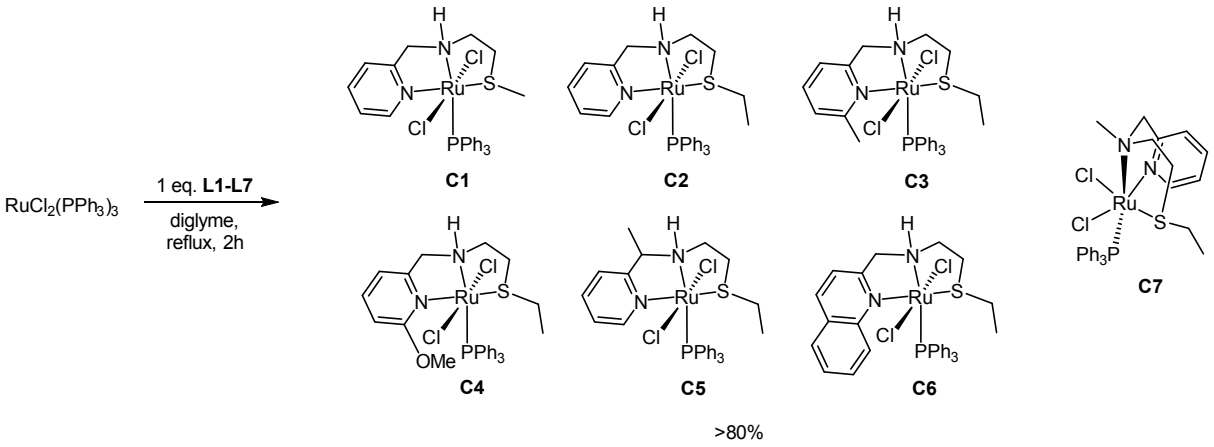
2.1.1 Selective Hydrogenation of α,β-Unsaturated Aldehydes and Ketones Catalysed by Ru-NNS Complexes

Ligands of the $NN^{H}S$ type (where $NN^{H}S$ = 2-(alkylthio)-*N*-(pyridin-2-yl-methyl)ethan-1-amine) were prepared in two steps from the respective pyridine-2-carboxaldehyde and amine precursors according to Scheme 2.1a. The *N*-methylated variety ($NN^{Me}S$) was obtained by Eschweiler-Clarke methylation (Scheme 2.1b). The rationale behind the ligand design is that the N-H functionality could be deprotonated to access a classical Noyori-type bifunctional mechanism. Alternatively, in the case of $NN^{Me}S$, the benzylic CH_2 group could be deprotonated in a Milstein-type activation, although it must be noted here that the mechanism, recently proposed by Dub and Gordon (discussed in more detail in section 1.1.2), provides an alternative explanation.



Scheme 2.1: a) Synthesis of **L1**-**L6** by condensation of (substituted) pyridine carboxaldehydes and *N*-alkylthio ethylamines, followed by sodium borohydride reduction of the resulting imine. b) Eschweiler-Clarke Methylation of **L2** to **L7**.

Addition of the ligands to a suspension of readily available $RuCl_2(PPh_3)_3$ in refluxing diglyme yielded the corresponding $RuCl_2(NNS)(PPh_3)$ complexes in good yields (Scheme 2.2).



Scheme 2.2: Synthesis of **C1**-**C7** by ligand exchange starting from $RuCl_2(NNS)(PPh_3)$.

Characterisation of the complexes by ^{1}H- and ^{31}P-NMR revealed an equilibrium between two different isomers in solution; the ratio between the isomers was roughly 4:1 at room temperature. VT-NMR experiments for **C2** and **C7** in toluene-*d8* at three different temperatures showed coalescence at 75 °C. As a matter of fact, X-ray diffraction analysis of crystals obtained showed the NNS ligand coordinated in a *mer* or *fac* fashion for **C2** and **C7**, respectively (Figure 2.1).

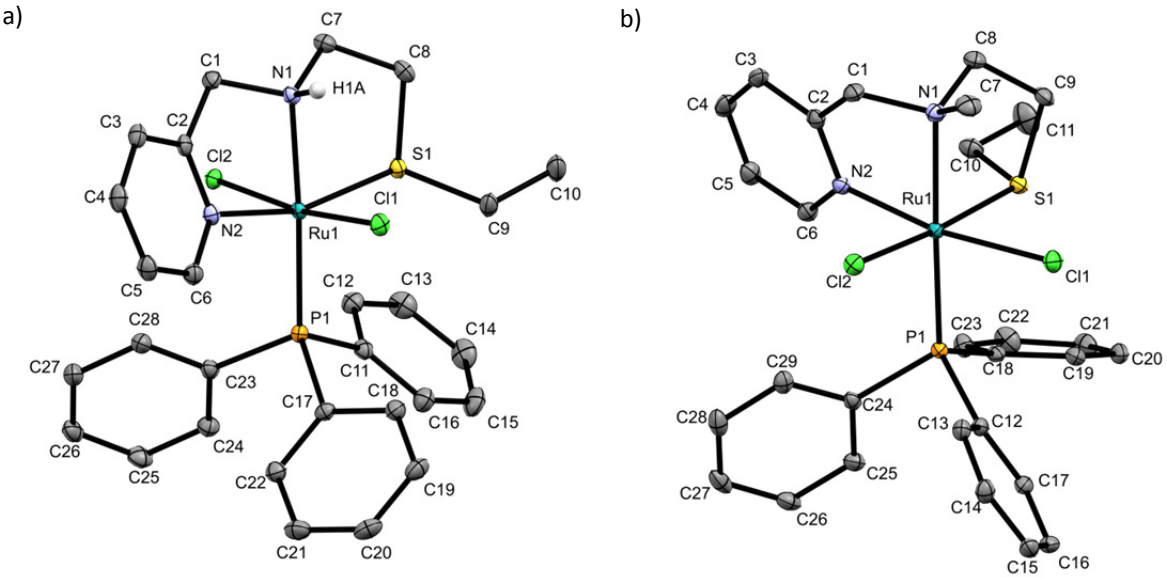
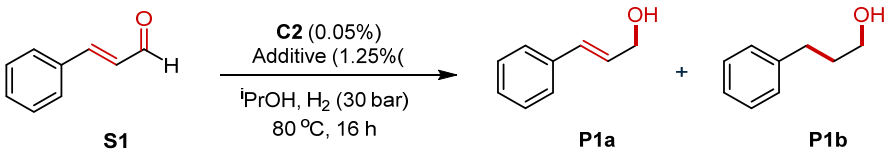


Figure 2.1: ORTEP drawings (30% probability ellipsoids, hydrogen atoms except for NH (H1A) for **C2** were omitted for clarity). Selected bond lengths (Å) and angles (°): for a) **C2**: Ru1-S1 2.3360(5), Ru1-N1 2.1252(17), Ru1-N2 2.0956(16), Ru1-P1 2.2960(5), Ru1-Cl1 2.4199(5), Ru1-Cl2 2.4273(5); S1-Ru1-N1 84.23(5), S1-Ru1-N2 162.42(5), N1-Ru1-N2 78.27(6), N1-Ru1-P1 175.62(5), Cl1-Ru1-Cl2 171.97(2), Cl1-Ru1-N1 84.80(5), Cl1-Ru1-N2 83.65(5), Cl1-Ru1-S1 93.239(18), C1-N1-C7 115.23(16); b) **C7** (b): Ru1-N1 2.215(2), Ru1-N2 2.069(2), Ru1-S1 2.3039(7), Ru1-Cl1 2.4445(7), Ru1-Cl2 2.4535(7), Ru1-P1 2.2827(7); N1-Ru1-N2 78.47(9), N1-Ru1-S1 85.11(6), N2-Ru1-S1 93.72(6), N1-Ru1-P1 177.83(7), S1-Ru1-Cl2 172.07(3), N1-Ru1-Cl2 87.79(6), N2-Ru1-Cl1 170.59(6), Cl1-Ru1-Cl2 94.14(2), C1-N1-C8 108.8(2), Cl1-Ru1-S1 82.65(3), N2-Ru1-Cl2 88.32(6), P1-Ru1-Cl2 94.35(2)

Due to hindered rotation of the PPh_3 ligand, ^{13}C-NMR analysis of the complexes proved inconclusive, and consequently, determination of the structures in solution was unsuccessful. However, it stands to reason that the two isomers observed in solution resemble the two conformations whose structures were determined in the solid state. Addition of base to a solution of **C2** led to a dark green suspension, from which no activated complex could be isolated or identified, even when the experiment was repeated in the presence of hydrogen atmosphere, suggesting that the active species require a certain pressure of hydrogen gas to remain stable.

The activity of $RuCl_2(NNS)(PPh_3)$ complexes was investigated for the hydrogenation of carbonyl functionalities in the presence of conjugated carbon-carbon double bonds; cinnamaldehyde **S1** was selected as benchmark substrate. A screening of different additives for catalyst activation was carried out using **C2** as representative catalyst, the results of which are shown in Table 2.1. *tert*-Butoxide bases activated the catalyst, and the hydrogenation of **S1** to cinnamyl alcohol **P1a** and phenylpropanol **P1b** proceeded with full conversion overnight (Entry 1-3). Considering the sum of the products did not add up to 100%, and selectivity towards **P1a** was not perfect, it was decided to perform the reaction with freshly sublimed potassium *tert*-butoxide instead (Table 2.1, Entry 4). Surprisingly, this led to worse selectivity, but it was subsequently found that the hydrogenation of the aldehyde was typically achieved already after 1 hour reaction time using freshly sublimed KO^tBu (*vide infra*).

Table 2.1: Screening of bases and lewis acids for the hydrogenation of cinnamaldehyde catalysed by **C2**.



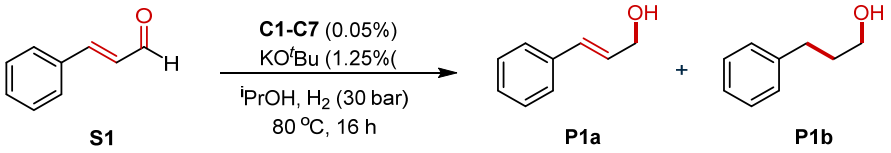
S1 **P1a** **P1b**

Entry[a]	Base/Lewis Acid	Conversion (%)[b]	Yield **P1a** (%)[b]	Yield **P1b** (%)[b]
1	LiO^tBu	>99	75	7
2	NaO^tBu	>99	76	5
3	KO^tBu	>99	88	3
4	KO^tBu[c]	>99	51	43
5	$Al(O^iPr)_3$	7	0	0
6	$Ti(O^iPr)_4$	15	0	0
7	$CaCO_3$	11	0	0
8	Na(PhCOO)	15	0	0
9	K(PhCOO)	22	0	0
10	K_3PO_4	20	0	0
11	2,6-Lutidine	25	0	0

[a] Reaction conditions: *trans*-cinnamaldehyde (1 mmol), dodecane (internal standard, 200 µL), dry iPrOH (2 mL), **C2** (0.05 mol%), additive (1.25 mol%), 80 °C, 30 bar H_2, 16 h. [b] Determined by GC using dodecane as internal standard. [c] KO^tBu sublimed and stored under Ar prior to reaction. KO^tBu stored under ambient conditions decomposed over time, which in turn leads to a lower actual base loading, or side reactions catalysed by KOH or K_2CO_3.

Interestingly enough, all seven complexes, including the *N*-methylated **C7** gave decent to excellent conversions and selectivities (Table 2.2). Screening reactions were initially allowed to react overnight (16 hours), but the selectivities were disappointing. When the reactions were run for 1 hour, **C2** still gave full conversion with better selectivity (Table 2.2, Entry 3). These findings suggested that the allylic alcohol **P1a** is the primary reaction product, which can subsequently be hydrogenated further to **P1b**. Indeed, carefully controlling the duration of the hydrogenation allowed the selective hydrogenation of all tested α,β-unsaturated carbonyl compounds.

Table 2.2: Screening of Ru-NNS complexes **C1-C7** for the hydrogenation of cinnamaldehyde.

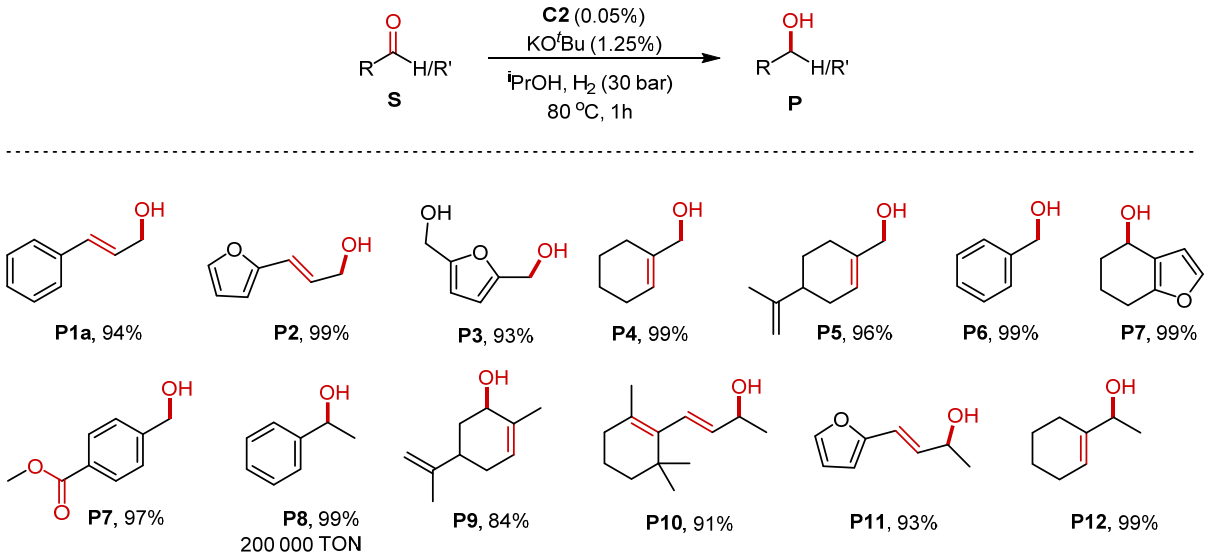


S1 P1a P1b

Entry[a]	Catalyst	Conv. 1h (%)[b]	Yield **P1a:P1b** 1h (%)[b]	Conv. 16h (%)[b]	Yield **P1a:P1b** 16h (%)[b]
1	**C1**	22	7:0	>99	70:12
2	**C2**	>99	90:10	>99	51:43
3	**C2**[c]	52	52:0	n.d.	n.d.
4	**C3**	86	56:2	>99	66:5
5	**C4**	59	36:23	>99	80:14
6	**C5**	21	12:0	98	63:8
7	**C6**	17	11:3	>99	62:32
8	**C7**	56	37:16	>99	76:12
9	-	n.d.	n.d.	15	1:1

[a] Reaction conditions: *trans*-cinnamaldehyde (1 mmol), dodecane (internal standard, 200 µL), dry isopropanol (2 mL), **C1-C7** (0.05 mol %), KO^{t}Bu (1.4 mg, 1.25 mol %), 80 °C, 30 bar H_2. [b] Determined by GC using dodecane as internal standard. [c] 10 eq. base w.r.t. **C2** (0.6 mg KO^{t}Bu, 0.5 mol %).

A range of aromatic and α,β-unsaturated aldehydes and ketones was readily hydrogenated on a 10-25 mmol scale, and the corresponding alcohols were isolated with high yields, as summarised in Scheme 2.3. The hydrogenation of acetophenone gave full conversion to **P8** after 16 hours with a catalyst loading as low as 5 ppm, corresponding to 200 000 turnovers, indicating that the catalytically active species remained stable as long as hydrogen pressure was maintained. It should be noted that the ester moiety of methyl 4-formylbenzoate (**S7**) was not reduced when the reaction was performed in methanol, and **P7** was isolated in excellent yield, which contrasts to results obtained with the same type of catalyst in different solvents (see Sections 2.2 and 3.2).



Scheme 2.3: Substrate scope (isolated yields) for the selective hydrogenation of aromatic and α,β-unsaturated aldehydes and ketones catalysed by Ru-NNS complex **C2**.

In summary, we designed and prepared a new family of ruthenium catalysts based on NNS tridentate ligands. These complexes were not as structurally rigid as typical pincer complexes, but exhibited excellent activity and selectivity in the hydrogenation of a range of aromatic and α,β-unsaturated aldehydes and ketones.

The published article concerning this work is included in section 3.1.

2.1.2 Ruthenium-Catalysed Asymmetric Hydrogenation of Aromatic Ketones using the Trost Ligand

Asymmetric hydrogenation of double bonds is an appealing strategy for introducing chiral centres into molecules, but its application in industrial processes strongly depends on the cost and availability of the chiral ligands required. In line with our work on the hydrogenation of ketones, we were interested in developing a cheap catalytic system for the asymmetric hydrogenation (AH) of ketones to the corresponding chiral alcohols, which are valuable building blocks for the synthesis of active pharmaceutical ingredients. The Trost ligand ((1*S*,2*S*)-1,2-diaminocyclohexane-*N*,*N*'-bis(2'-diphenylphosphinobenzoyl), or (*S*,*S*)-DACH-phenyl, Figure 2.3) is a well-known chiral ligand used in a range of asymmetric reactions, and is readily available from commercial sources. However, prior to this work, it was not reported for asymmetric hydrogenation.

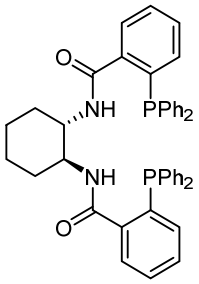
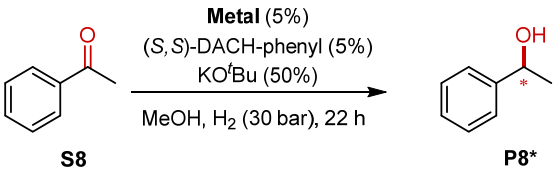


Figure 2.2: (*S,S*)-DACH-phenyl, Trost Ligand.

Taking an *in situ* approach for identifying promising metal precursors for this reaction, a range of metal sources was screened for the asymmetric hydrogenation of acetophenone in methanol in the presence of KO^{t}Bu as activator. The results are summarised in Table 2.3. When base metal precursors were used, only trace amounts of conversion were observed, with the exception of $NiCl_2$ (Table 2.3, Entry 1). However, this reaction yielded racemic product. In contrast, several Ru(II) and Ru(III) sources also led to full conversions, with promising *ee*'s, especially when the reaction temperature was lowered from 80 °C to 60 °C. Surprisingly, the best enantioselectivity was obtained using $RuCl_3$ or $RuCl_3$ hydrate, the latter being significantly cheaper (Table 2.3, Entry 14 and 15).

Table 2.3: Screening of metal sources for the AH of acetophenone with (*S,S*)-DACH-phenyl.



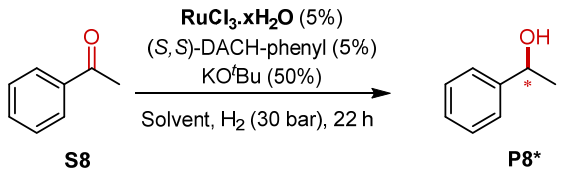
Entry[a]	Metal source	Temperature (°C)	Conversion (%)[b]	*e.e.* (abs. conf.)
1	$NiCl_2$	80	98	0
2	$Ni(NO_3)_2{\cdot}6H_2O$	80	0	-
3	$Ni(cod)_2$	80	0	-
4	$Ni(CO)_2(PPh_3)_2$	80	0	-3
5	$CoCl_2$	80	1	29 (*R*)

6	$FeBr_2$	80	0	-
7	$FeBr_3$	80	0	-
8	$Fe(CO)_5$	80	0	-
9	$FeCl_2{\cdot}4H_2O$	80	1	23 (*S*)
10	$RuCl_2(PPh_3)_3$	80	96	44 (*R*)
11	$RuCl_3$	80	98	32 (*S*)
12	$RuH_2(CO)(PPh_3)_3$	80	69	29 (*R*)
13	$RuCl_2(PPh_3)_3$	60	91	43 (*R*)
14	$RuCl_3$	60	97	56 (*S*)
15	$RuCl_3{\cdot}xH_2O$	60	99	46 (*S*)
16	$RuCl_2(PPh_3)_4$	60	92	40 (*R*)
17	$[RuCl_2(C_6H_6)]_2$	60	98	23 (*S*)
18	$RuHCl(CO)(PPh_3)_3$	60	4	29 (*R*)

[a] Reaction conditions: acetophenone (0.1 mmol), hexadecane (30 µL) metal source (5 mol%), (*S,S*)-DACH-phenyl (6.9 mg, 5 mol%), KO^{t}Bu (5.6 mg, 50 mol%), 30 bar H_2, 22 h; cod=1,5-cyclooctadiene. [b] Determined by GC analysis. [c] Absolute configuration assigned by comparison of the optical rotation with literature.

Using $RuCl_3{\cdot}xH_2O$, an optimisation of solvent and temperature was carried out (Table 2.4). Although good to excellent conversions were obtained in most solvents, the best enantioselectivity was obtained at room temperature in methanol (Table 2.4, Entry 3). Despite the ruthenium(III) chloride hydrate being a suitable catalyst precursor, the addition of extra water to the reaction mixture had a clear detrimental effect on the outcome (Entry 12-15).

Table 2.4: Screening of solvents and temperature for the AH of acetophenone.



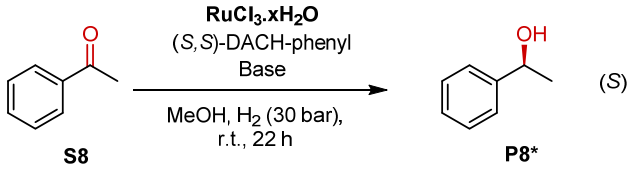
S8 **P8***

Entry[a]	Solvent	Temperature (°C)	Conversion (%)[b]	*e.e.* (abs. conf.)
1	MeOH	60	99	46 (*S*)
2	MeOH	35	98	67 (*S*)
3	MeOH	22	97	69 (*S*)
4	MeOH	0	63	65 (*S*)
5	^{i}PrOH	60	>99	0
6	DMF	60	>99	35 (*S*)
7	Benzene	60	74	17 (*R*)
8	MeCN	60	72	13 (*S*)
9	Toluene	60	>99	22 (*S*)
10	THF	60	>99	28 (*S*)
11	EtOH	60	98	5 (*S*)
12	MeOH/H_2O (1:1)	60	>99	0
13	MeOH/H_2O (4:1)	60	81	0
14	^{i}PrOH/H_2O (1:1)	60	13	6 (*R*)
15	^{i}PrOH/H_2O (4:1)	60	>99	0

[a] Reaction conditions: acetophenone (0.1 mmol), hexadecane (30 µL) metal source (5 mol%), (*S,S*)-DACH-phenyl (6.9 mg, 5 mol%), KO^{t}Bu (5.6 mg, 50 mol%), 30 bar H_2, 22 h. [b] Determined by GC analysis. [c] Absolute configuration assigned by comparison of the optical rotation with literature.

Having established the most suitable metal source, reaction solvent, and temperature, one parameter left requiring optimisation was the base. As such, several readily available bases were screened (Table 2.5). Additionally, the catalyst loading was varied in this table. Decrease of the catalyst loading to 1 mol%, in the presence of 5 mol% of Na_2CO_3 led to the highest *ee* observed, namely 96% (*S*), without detrimental effect on the conversion (Table 2.5, Entry 17).

Table 2.5: Screening of bases for the AH of acetophenone.

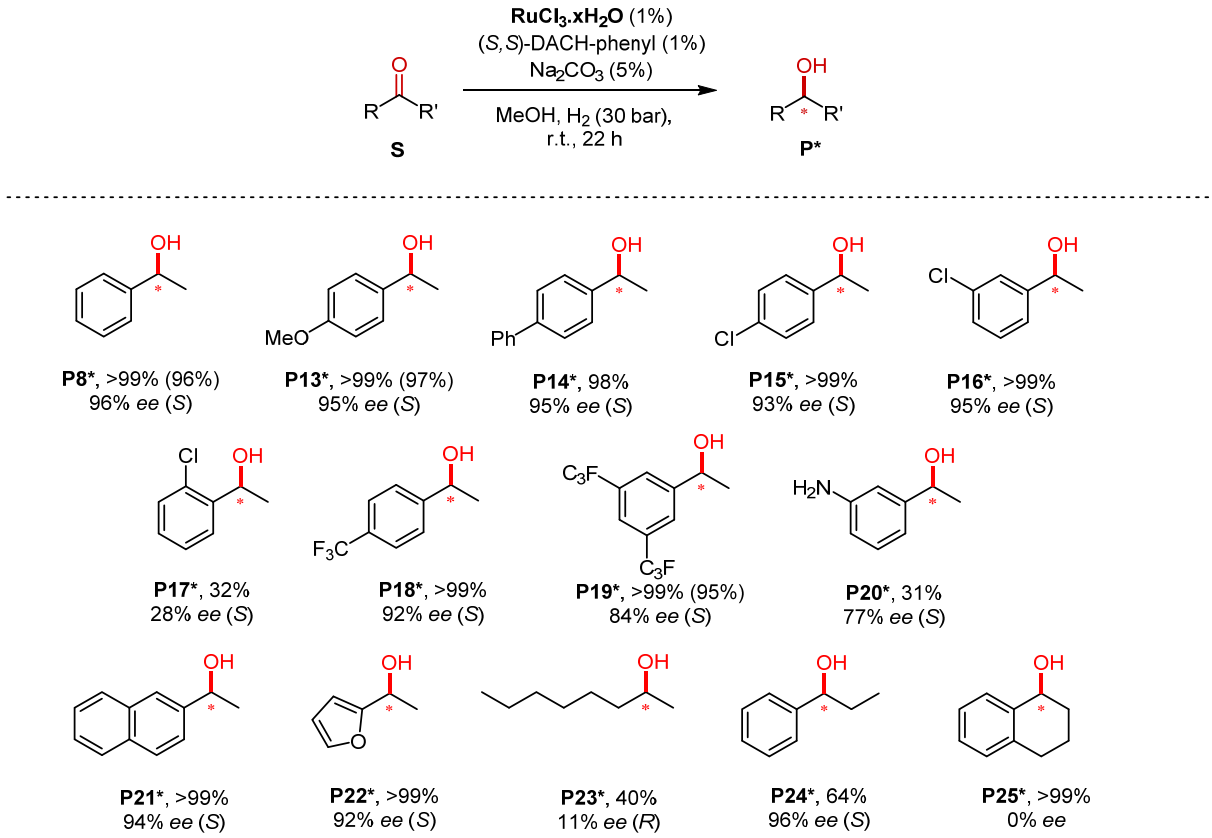


Entry[a]	Base (%)	Catalyst loading (%)	Conversion (%)[b]	*e.e.*(*S*)[c]
1	-	5	0	-
2	KO^{t}Bu (50)	5	93	70
3	KO^{t}Bu (25)	5	97	76
4	KO^{t}Bu (5)	5	0	0
5	KOH (25)	5	>99	71
6	K_2CO_3 (25)	5	98	53
7	Cs_2CO_3 (25)	5	98	69
8	LiO^{t}Bu (25)	5	98	63
9	LiOH·H_2O (25)	5	>99	64
10	NaOMe (25)	5	99	70
11	NaO^{i}Pr (25)	5	31	86
12	NaO^{t}Bu (25)	5	98	66
13	NaOH (25)	5	99	89
14	Na_3PO_4 (25)	5	99	87
15	Na_2CO_3 (25)	5	99	89
16	Na_2CO_3 (12.5)	2.5	>99	93
17	Na_2CO_3 (5)	1	>99 (96)[g]	96
18	Na_2CO_3 (2.5)	0.5	97	94
19[d]	Na_2CO_3 (2.5)	0.5	>99	95
20	Na_2CO_3 (0.5)	0.1	0	-
21[d]	Na_2CO_3 (0.5)	0.1	0	-
22[e]	Na_2CO_3 (5)	1	42	94
23[f]	Na_2CO_3 (5)	1	63	95

[a] Reaction conditions: acetophenone (0.1 mmol), hexadecane (30 µL) metal source (5 mol%), (*S,S*)-DACH-phenyl (6.9 mg, 5 mol%), base, 30 bar H_2, r.t, 22 h. [b] Determined by GC analysis (see the Supporting Information). [c] Absolute configuration assigned by comparison of the optical rotation with literature data. [d] 80 bar H_2. [e] Reaction performed in the presence of 3 Å molecular sieves. [f] Reaction performed in the presence of Hg^0 (10 mmol/100 equiv.). [g] Isolated yield (6 mmol scale).

Under these reaction conditions, a range of ketones was hydrogenated to the corresponding alcohols (Scheme 2.4). Good to decent conversions and *ee*'s were obtained in most cases, with the notable exceptions of **P17**, **P20**, **P23**, **P24**, and **P25**. This suggests the reaction was rather sensitive to steric influences close to the ketone, and coordinating groups in the substrate may poison the catalyst. Kinetic investigations under the optimised reaction conditions showed an induction period, whereas $RuCl_3$·xH_2O pre-treated by reflux in isopropanol overnight did not show such an induction period, suggesting the *in situ*

reduction of Ru(III), presumably to Ru(II) was required to generate the catalytically active species.



Scheme 2.4: Substrate scope for the asymmetric hydrogenation of ketones by an *in situ* generated $RuCl_3$/*S,S*-DACH-phenyl catalyst system. Yields were determined by GC; yields between brackets are isolated yields.

In summary, starting from a cheap ruthenium source, the well-known and readily available Trost ligand was applied for the first time in the asymmetric hydrogenation of aromatic ketones, High yields and enantioselectivities were obtained, at catalyst loadings as low as 1 mol%.

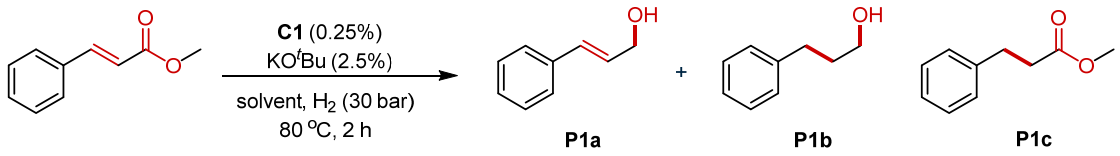
The published article concerning this work is included in section 3.3.

2.2 Hydrogenation of (α,β-Unsaturated) Esters Catalysed by Ru-NNS Complexes

The hydrogenation of carboxylic acid esters is more challenging than that of aldehydes and ketones. As such, comparatively harsh reaction conditions are often reported. Consequently, only one example of good selectivity towards allylic alcohols starting from α,β-unsaturated esters was reported in literature.[69] For this reaction, too, a trend towards base metal complexes can be observed in recent years. Likewise, the costs of the ligands employed may eclipse the costs of the metal.

The Ru-NN^{H}S complex **C1**, which was described above, was also investigated for the hydrogenation of esters, and a strong solvent effect was observed. As reported, the ester moiety of methyl 4-formylbenzoate was not reduced when the reaction was performed in methanol, but in toluene the reaction proceeded smoothly, and the diol **P30** was isolated quantitatively. Interested in the chemoselectivity, we investigated the hydrogenation of the α,β-unsaturated ester methyl cinnamate in various solvents at 80 °C (Table 2.6).

Table 2.6: Solvent screening for the hydrogenation of methyl cinnamate catalysed by **C1**.



Entry[a]	Solvent	Conversion (%)[b]	Yield **P1a:P1b:P1c** (%)[b]
1	heptane	74	41:5:15
2	THF	17	4:0:12:
3	MeOH[j]	99	0:0:95
4	EtOH	98	43:7:1
5	^{i}PrOH	82	45:4:1
6	DMF	10	0:0:5
7	toluene	99	71:18:3

[a] Reaction conditions: methyl cinnamate (1 mmol), dodecane (internal standard, 50 µL), dry solvent (2 mL), **C1** (1.5 mg, 0.5 mol %), KO^{t}Bu (2.5 mol %), 80 °C, 30 bar H_2. [b] Determined by GC using dodecane as internal standard.

Interestingly, the reaction in methanol showed 99% conversion, no alcohol as product, and 95% yield of saturated ester, *i.e.* the carbon-carbon double bond was hydrogenated selectively, leaving the ester intact. In toluene, full conversion was obtained too, with a modest yield of 72% of cinnamyl alcohol before further optimisation. The use of THF led to poor conversion of 11%, yielding only the saturated ester. It is known that some ruthenium complexes dehydrogenate methanol to carbon monoxide, which may then remain coordinated to the metal. Another possible parameter impacting the selectivity is the lability of the thioether moiety of the NN^{H}S ligand. Dissociation of this ligand arm would lead to a different catalytic species, which may well exhibit different reactivity. As we were unable to characterise the catalytically active species, we decided to increase the steric bulk on the thioether by introducing a *tert*-butyl group, and the corresponding complex **C8** was isolated and investigated by X-ray diffraction analysis (Figure 2.4). It was hypothesised that this would lead to increased steric clash with the ancillary PPh_3 ligand, thus promoting the

dissociation of the ligand arm; an elongated Ru-S bond length of 2.3648(5) Å was obtained for **C8**, compared to 2.3369(10) Å for **C1**. Indeed, when this complex was used in the hydrogenation of methyl cinnamate in toluene, a selectivity of 64% for the saturated ester was obtained.

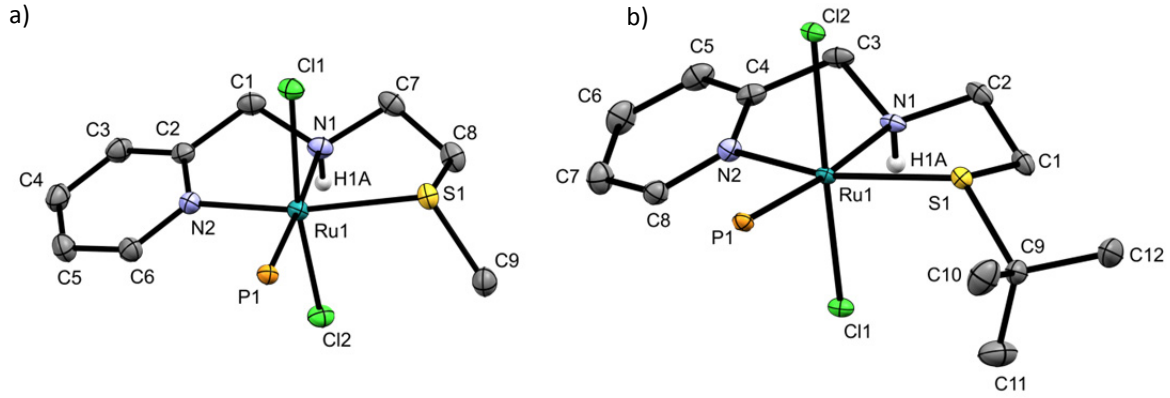
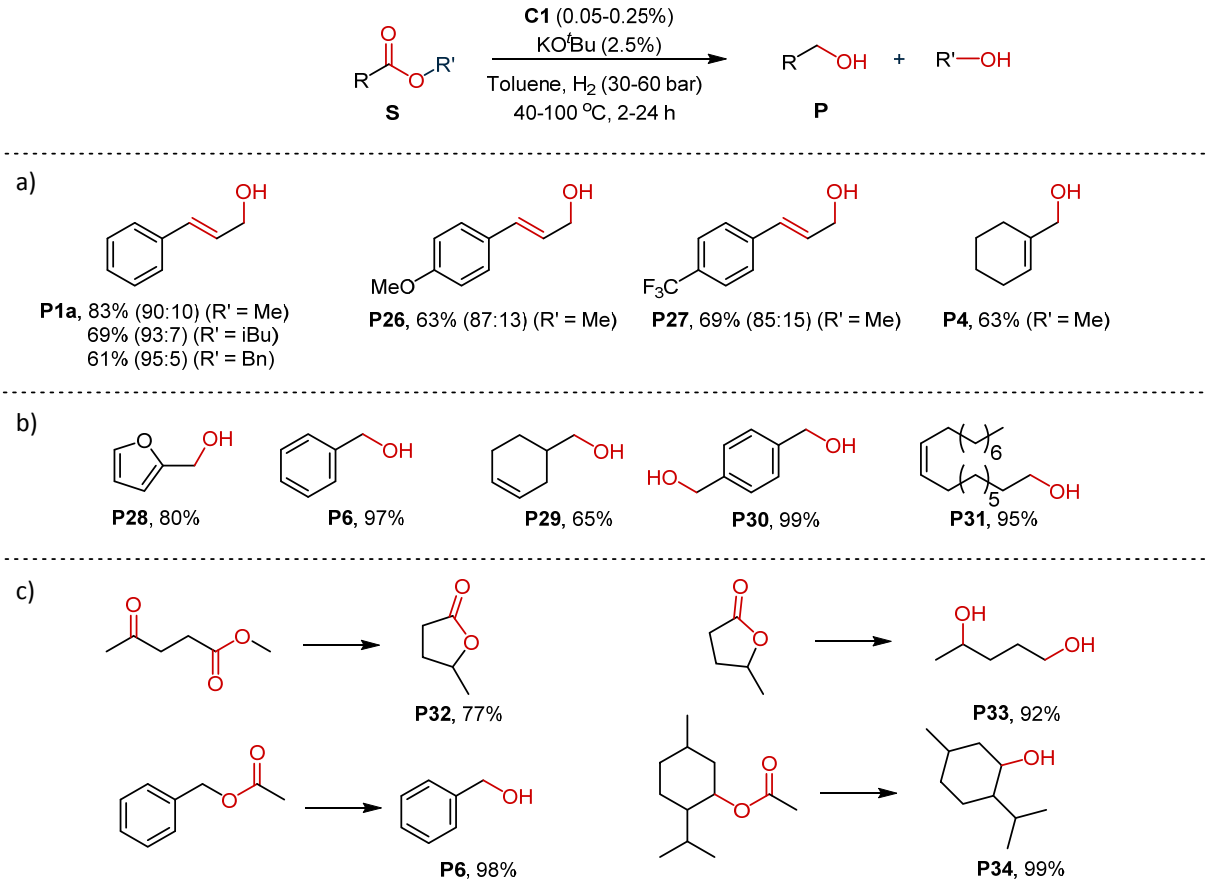


Figure 2.3: ORTEP drawings (30% probability ellipsoids, hydrogen atoms, except for NH, and PPh_3 phenyl rings were omitted for clarity). Selected bond lengths (Å) and angles (°): for a) **C1**: Ru1-S1 2.3369(10), Ru1-N1 2.134(3), Ru1-N2 2.075(3), Ru1-P1 2.2985(9), Ru1-Cl1 2.4219(9), Ru1-Cl2 2.4188(9); S1-Ru1-N1 84.43(10), S1-Ru1-N2 163.28(9), N1-Ru1-N2 78.88(13), N1-Ru1-P1 176.96(10), Cl1-Ru1-Cl2 167.59(3), Cl1-Ru1-N1 87.17(9), Cl1-Ru1-N2 95.04(9), Cl1-Ru1-S1 83.01(3); b) **C8**. Ru1-S1 2.3648(5), Ru1-N1 2.1331(18), Ru1-N2 2.1026(18), Ru1-P1 2.3104(5), Ru1-Cl1 2.4168(5), Ru1-Cl2 2.4197(5); S1-Ru1-N1 83.11(5), S1-Ru1-N2 159.49(5), N1-Ru1-N2 76.56(7), N1-Ru1-P1 174.58(5), Cl1-Ru1-Cl2 170.296(18), Cl1-Ru1-N1 83.47(5), Cl1-Ru1-N2 84.17(5), Cl1-Ru1-S1 96.254(18).

Considering that one equivalent of methanol is formed in the hydrogenation of a methyl ester, and having established the detrimental effect of methanol on the desired selectivity, further optimisation was carried out on the homologous isobutyl cinnamate. For this substrate, 95% selectivity was obtained when the reaction temperature was lowered to 40 °C. Under these conditions, the maximum selectivity was 90% when methyl cinnamate was used, and several other α,β-unsaturated esters were reduced with modest to excellent selectivities (Scheme 2.5a). Several other methyl esters were successfully reduced, and the corresponding alcohols obtained in modest to excellent yields (Scheme 2.5b). The selective hydrogenation of the ketone moiety of methyl levulinate (ML) in methanol afforded *γ*-valerolactone (GVL, **P32**) in good yield, while using toluene as reaction solvent allowed the reduction of GVL to 1,4-pentanediol (**P33**). In addition, two simple acetates were reduced in near-quantitative yields opening up the possibility to use this as a mild deprotection method for alcohols protected as their acetates. (Scheme 2.5c, **P6** and **P34**).

Ru-NN^{H}S catalysts were proven efficient catalysts for the hydrogenation of a range of esters to the corresponding alcohols. Unprecedented selectivity for the allylic alcohol was achieved in the hydrogenation of several α,β-unsaturated esters. The generality of the reaction was shown by the hydrogenation of acetates and various methyl esters. Moreover, the hydrogenation of the biobased *γ*-valerolactone to 1,4-pentanediol (**P33**) was easily scalable to 500 mmol.

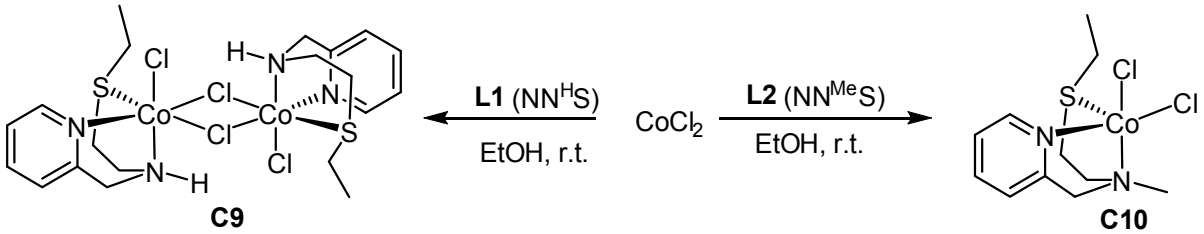


Scheme 2.5: Substrate scope (isolated yields) for a) the selective hydrogenation of α,β-unsaturated esters to allylic alcohols; b) other methyl esters; c) ML, GVL and two examples of acetates, catalysed by **C1**.

The published article concerning this work is included in section 3.2.

2.3 Co-NNS Complexes as Catalyst Precursor for the Selective Hydrogenation of Olefins

Looking to combine the benefits of cheap, readily accessible NNS ligands with those of base metals, two Co-NNS complexes were synthesised according to Scheme 2.6. The structures of these complexes were elucidated by X-ray diffraction analysis (Figure 2.5). Reaction of $NN^{H}S$ with $CoCl_2$ yielded the dimeric **C9**, whereas the methyl group of $NN^{Me}S$ apparently provided enough steric hindrance to prevent the complex from dimerising, and monomeric **C10** was obtained.[76]



Scheme 2.6: Synthesis of Co-NNS complexes **C9** and **C10**.

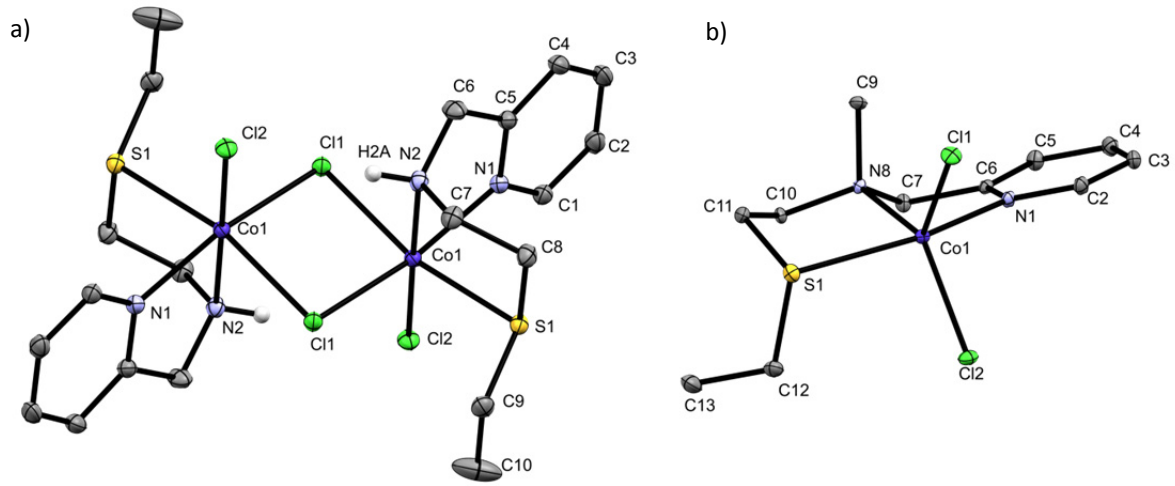
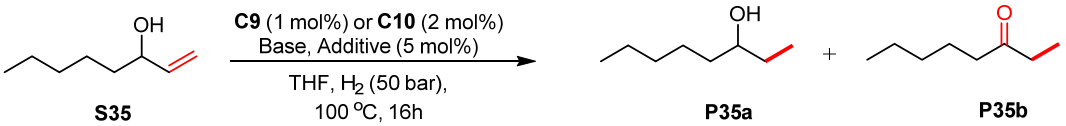


Figure 2.4: ORTEP drawings for (30% probability ellipsoids, hydrogen atoms, except NH for **C9**, were omitted for clarity.) Selected bond lengths (Å) and angles (°) for a) **C9**: Co1-S1 2.5162(4), Co1-N1 2.1159(11), Co1-N2 2.1704(11), Co1-Cl1 2.4186(3), Co1-Cl1A 2.4991(3), Co1-Cl2 2.3633(3); N1-Co-N2 78.41(4), N1-Co1-S1 83.76(3), N2-Co1-S1 83.72(3), Cl1-Co1-Cl1A 91.547(12), Cl2-Co1-Cl1 95.210(13), C6-N2-C7 115.33(11); b) **C10**: Co1-S1 2.5612(8), Co1-N1 2.102(2), Co1-N8 2.122(2), Co1-Cl1 2.2785(8), Co1-Cl2 2.2885(8); N1-Co1-N8 78.14(8), N1-Co1-S1 161.69(6), N8-Co1-S1 84.06(6), Cl1-Co1-Cl2 118.99(3), C7-N8-C10 111.20(2).

In order to determine the catalytic activity of these complexes, a high-throughput screening (HTS) was carried out, screening several solvents, bases and additives for the hydrogenation of 1-octene, acetophenone, and 1-octen-3-ol (details for the HTS can be found in section 5.1). This initial screening showed activity in hydrogenation of olefinic double bonds, and not ketones, and was used as starting point for more careful optimisation. 1-Octen-3-ol was selected as model substrate, because isomerisation of the allylic alcohol to ketone was observed as a side reaction during HTS. The results of the optimisation are summarised in Tables 2.7 (additives) and 2.8 (solvents). The dimeric **C9** gave only trace amounts of hydrogenation. **C10**, in the presence of $NaBH_4$ as reductant, yielded 95% of 3-octanol as the

only product. Trace amounts of isomerisation were observed in the presence of base, and up to 30% of 3-octanone were detected when the reaction was carried out in methanol (Table 2.8, entry 3). However, when the reaction was performed in the absence of hydrogen atmosphere, no isomerisation took place at all, suggesting the formation of a cobalt hydride species is required for the isomerisation to take place.

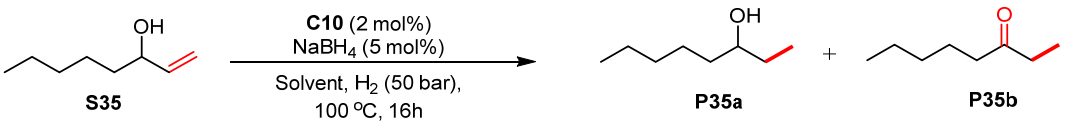
Table 2.7: Screening of additives for the hydrogenation/isomerisation of 1-octen-3-ol catalysed by **C9** or **C10**..



Entry[a]	Catalyst	Base	Additive	Yield **P35a:P35b** (%)[b]
1	**C9**	-	-	0:0
2	**C9**	KO^{t}Bu	-	0:1
3	**C9**	NaOH	PPh_3	0:0
4	**C9**	NaOH	$NaBH_4$	12:0
5	**C9**	NaOH	Zn	3:0
6	**C10**	-	-	0:0
7	**C10**	KO^{t}Bu	-	0:1
8	**C10**	KO^{t}Bu	PPh_3	41:0
9	**C10**	KO^{t}Bu	$NaBH_4$	20:0
10	**C10**	NaOEt	PPh_3	94:3
11	**C10**	NaOEt	$NaBH_4$	94:1
12	**C10**	NaOH	PPh_3	90:5
13	**C10**	NaOH	$NaBH_4$	95:1
14	**C10**	NaOEt	Zn	12:0
15	**C10**[c]	NaOH	PPh_3	41:4
16	**C10**[c]	NaOH	$NaBH_4$	72:2
17	**C10**	NaOH	-	0:0
18	**C10**	-	$NaBH_4$	95:0

[a] Reaction conditions: 0.33 mmol 1-octen-3-ol, 1.0 mL THF, 1 mol% **1** or 2 mol% **2**, 5 mol% of additive and base, 50 bar H_2, 100 °C, 16 h reaction time. [b] Determined by GC using dodecane as internal standard. [c] 1 mol% of **2**.

Table 2.8: Screening of solvents for the hydrogenation/isomerisation of 1-octen-3-ol catalysed by **C10**.

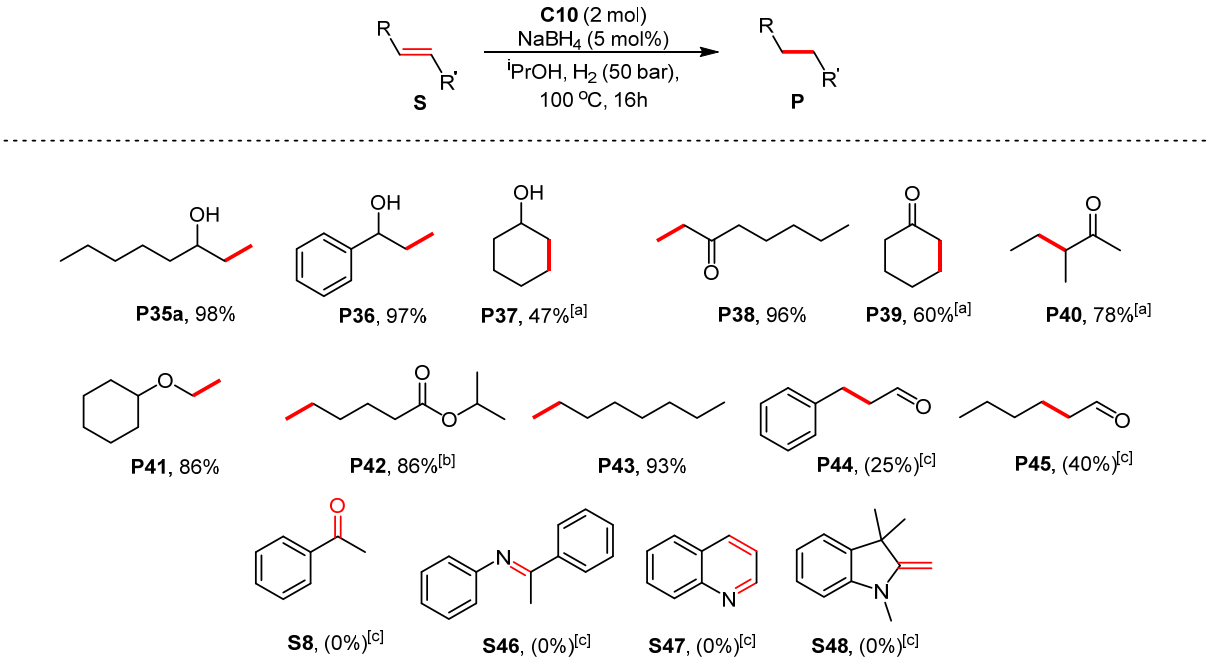


Entry[a]	Catalyst	Solvent	Yield **P35a:P35b** (%)[b]
1	**C9**	THF	95:1
2	**C9**	Toluene	1:2
3	**C9**	MeOH	58:30
4	**C9**	^{i}PrOH	>99:0
5	**C9**	Hexafluoroisopropanol	0:0

[a] Reaction conditions: 0.33 mmol 1-octen-3-ol, 1.0 mL solvent, 2 mol% **2**, 5 mol% of $NaBH_4$, 50 bar H_2, 100 °C, 16 h reaction time. [b] Determined by GC using dodecane as internal standard.

Using 2 mol% of **C10** in the presence of 5 mol% of $NaBH_4$ in isopropanol (Table 2.8, Entry 4) led to quantitative yield of 3-octanol. Under these conditions, a variety of terminal and

internal olefins was reduced with full conversions, and the products were isolated in good to excellent yields (Scheme 2.6). Interestingly, ketones (**S38**-**40**) and esters (**S42**) were not reduced even under these harsh conditions, and excellent chemoselectivity was obtained even for α,β-unsaturated ketones. Aldehydes, however, seemed to deactivate the catalyst, as only mediocre conversions were obtained, although even in these cases the saturated aldehyde was the sole product (**P44**-**45**).



Scheme 2.7: Substrate scope (isolated yields) and limitations for the selective hydrogenation of olefins catalysed by **C10**. [a] Only product observed, full conversions. Separating these products from ^{i}PrOH in high yield proved difficult due to their volatility. [b] Starting from the methyl ester. [c] Values between brackets based on GC; these products were not isolated.

It was observed, however, that reactions leading to good conversions invariably contained a black residue after the vials were removed from the autoclave. The hydrogen consumption was monitored over time. After an induction period, the hydrogen consumption took place *via* a roughly sigmoidal curve. These findings suggested the reaction was possibly catalysed by Co nanoparticles. Accordingly, a poisoning experiment was carried out by injecting a sub-stoichiometric amount (0.15 eq. w.r.t. Co) of PMe_3 into the autoclave after the induction period was over and the reaction had started. This effectively stopped hydrogen consumption, leaving the reaction at 65% conversion. This strongly indicated that the reaction was catalysed by nanoparticles, which are deactivated when their surface is saturated with PMe_3. These were selective to the hydrogenation of olefins, and did not reduce aldehydes, ketones, or esters, which is in contrast to other recent reports of Co nanoparticle-catalysed hydrogenations.[77] Hence, it is likely that the NN^{Me}S ligand does not fully dissociate, but rather stabilises and partially deactivates the nanoparticles, rendering them selective to olefinic double bonds.

In summary, Co-NNS complexes were prepared, and the monomeric **C10**, bearing the $NN^{Me}S$ ligand, was identified as a nanoparticle precursor which exhibited excellent chemoselectivity for the hydrogenation of olefins in the presence of carbonyl functionalities. This represents a completely opposite chemoselectivity when compared to the Ru-NNS catalysts described previously.

The submitted manuscript concerning this work is included in section 3.4; supporting information for this manuscript is included in section 5.1.

3. Selected Publications

3.1 Selective Hydrogenation of α,β-Unsaturated Aldehydes and Ketones by Air-Stable Ruthenium NNS Complexes

P. Puylaert, R. van Heck, Y. Fan, A. Spannenberg, W. Baumann, M. Beller, J. Medlock, W. Bonrath, L. Lefort, S. Hinze, and J.G. de Vries

Chemistry - A European Journal **2017**, 23, 8473-8481

DOI: 10.1002/chem.201700806

Electronic Supporting Information (ESI) for this article is available free of charge under https://doi.org/10.1002/chem.201700806.

The own contribution to this work is 75%.

ChemPubSoc Europe

DOI: 10.1002/chem.201700806

CHEMISTRY A European Journal Full Paper

Homogeneous Catalysis

Selective Hydrogenation of α,β-Unsaturated Aldehydes and Ketones by Air-Stable Ruthenium NNS Complexes

Pim Puylaert,[a] Richard van Heck,[a] Yuting Fan,[a] Anke Spannenberg,[a] Wolfgang Baumann,[a] Matthias Beller,[a] Jonathan Medlock,[b] Werner Bonrath,[b] Laurent Lefort,[c] Sandra Hinze,[a] and Johannes G. de Vries*[a]

Abstract: The selective hydrogenation of the carbonyl functionality of α,β-unsaturated aldehydes and ketones is catalysed by ruthenium dichloride complexes bearing a tridentate NNS ligand as well as triphenylphosphine. The tridentate ligand backbone is flexible, as evidenced by the equilibrium observed in solution between the *cis*- and *trans*-isomers of the dichloride precatalysts, as well as crystal structures of several of these complexes. The complexes are activated by base in the presence of hydrogen and readily hydrogenate carbonyl functionalities under mild conditions. Despite the activation by base, side reactions are negligible, even for aldehyde substrates, because of the low amount of base. Thus, the corresponding allylic alcohols can be isolated in very good yields on a 10–25 mmol scale. Turnover numbers up to 200 000 were achieved.

Introduction

Selective catalytic hydrogenation and transfer hydrogenation reactions of the carbonyl functionality in α,β-unsaturated aldehydes and ketones are of great relevance for organic synthesis, as well as industrial application in, for instance, the production of flavours, fragrances or vitamins.[1] Achieving a high selectivity for the reduction of the carbonyl moiety is inherently difficult, because the reduction of the carbon–carbon double bond is thermodynamically favoured by approximately 35 kJ mol^{-1}.[2]

Although many different types of heterogeneous catalysts have been tested,[3] their use has rarely led to more than 90% selectivity to the desired allylic alcohols.[4]

Typical homogeneous hydrogenation catalysts include the complexes of precious metals, such as Ru, Os, Rh and Ir, with diphosphine/diamine ligand pairs or pincer ligands.[1a,5] In industrial application, ruthenium is strongly preferred in view of its lower cost. High selectivities towards the allylic alcohols were obtained with ruthenium complexes based on water-soluble ligands.[6] Later, it was shown that these complexes suffer from product inhibition and the ligand was found to be quaternised by the substrate to some extent.[7] Generally, the reduction of the carbonyl moiety by ruthenium complexes containing amine or picoline functionalities is considered to take place through a bifunctional metal–ligand mechanism.[8]

The development of cheaper and environmentally more benign processes led to recent interest towards analogous Fe-,[9] Co-,[10] Mn-[11] and Cu-based[12] catalysts. One downside of these catalysts is that the catalyst loadings are relatively high in comparison to precious metal catalysts. In addition, alkylphosphine ligands are often required, which are not cheap and usually air-sensitive, thus largely off-setting the gain made by using base metals. A further challenge in the hydrogenation of aldehydes lies in the use of strong bases that are needed to activate the catalyst, as aldehydes themselves are base-sensitive. Dupau et al. showed that side reactions can be prevented by using ruthenium carboxylate rather than chloride complexes as the former does not require addition of base.[13] Despite the vast body of work performed on catalytic hydrogenation, high activity paired with good selectivity towards the carbonyl functionality, especially in the case of α,β-unsaturated aldehydes, remains challenging.

A promising alternative lies in the development of simple ligands containing donor atoms other than phosphorus, such as nitrogen, carbon or sulfur.[5g,14] For the selective hydrogenation of α,β-unsaturated aldehydes and ketones, we developed ruthenium complexes with ligands of the NNS type, as shown in Figure 1. The ligands are obtained in a simple two-step procedure from readily available starting materials; they are air- and moisture-stable, and derivatives are readily prepared by using various substituted pyridines and 2-alkylthioethylamines. These ruthenium complexes are highly active precatalysts in the chemoselective hydrogenation of α,β-unsaturated ketones and aldehydes. Excellent selectivities were obtained even in

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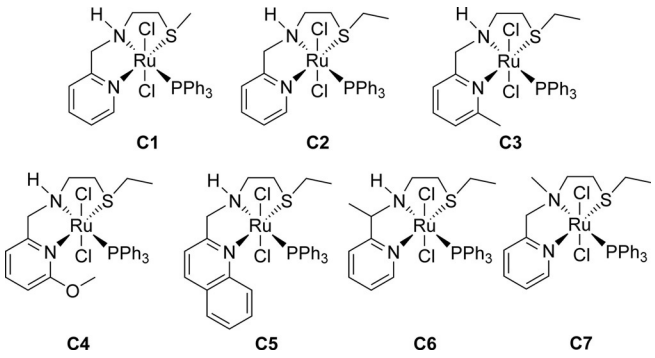


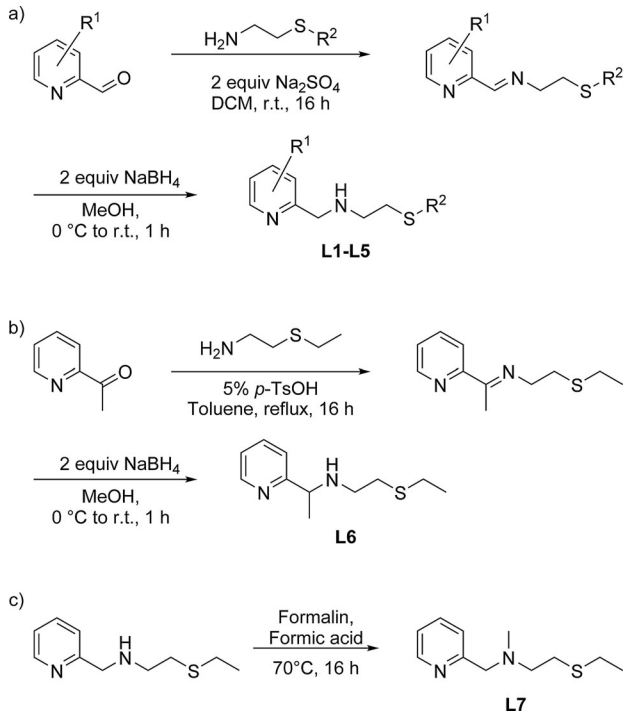
Figure 1. Ru–NNS complexes presented in this work.

presence of base required for the activation of the precatalysts.

Results and Discussion

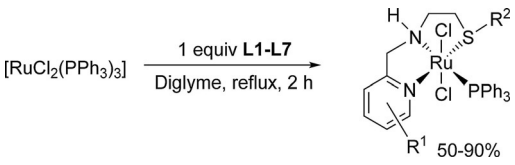
Preparation of ligands and complexes

The ligands were obtained in good yields by reductive amination of the corresponding aldehydes and ketones. Ligands **L1**–**L5** were synthesised at room temperature via the intermediate imine formed from the 2-alkylthio-ethylamines and (substituted) 2-pyridinecarboxaldehydes, followed by $NaBH_4$ reduction (Scheme 1 a). Formation of **L6** (Scheme 1 b) was slow at room temperature, and was therefore performed by overnight reflux in toluene in the presence of 5 mol% of *p*-toluenesulfonic acid. The *N*-methylated amine **L7** was obtained by Eschweiler–Clarke methylation of **L2** (Scheme 1 c).



Scheme 1. Preparation of NNS ligands a) **L1**–**L5**, b) **L6**, and c) **L7**.

The corresponding $[RuCl_2(NNS)(PPh_3)]$ complexes were prepared in good yields from $[RuCl_2(PPh_3)_3]$ by reflux in diglyme in the presence of one equivalent of ligand, according to Scheme 2.



Scheme 2. Preparation of $[RuCl_2(NNS)(PPh_3)]$ complexes.

Structure and properties

^1H- and $^{31}P\{^1H\}$-NMR spectroscopy showed that the complexes **C1**–**C7** exist in solution as an equilibrium mixture of isomers. The ratio between the major and minor isomers is approximately 4:1 at room temperature, based on integration of the ^1H-NMR signals. ^1H- and $^{31}P\{^1H\}$ VT-NMR spectra of **C2** in $[D_8]$ toluene showed coalescence at 75 °C (Figure 2; VT-NMR spectra of **C7** are available in the Supporting Information). Thus the equilibrium is fast at elevated temperatures, and is not expected to influence the catalyst activation. After storing the complexes under ambient conditions for several weeks, the ^1H- and $^{31}P\{^1H\}$-NMR spectra looked identical, showing that the complexes were air- and moisture-stable.

Upon addition of freshly sublimed potassium *tert*-butoxide (2 equiv relative to Ru), the orange solution of **C2** in $[D_8]$toluene, $[D_8]$THF or $[D_6]$benzene turned dark green immediately. The characteristic $^{31}P\{^1H\}$-NMR signals at $\delta = 52.6$ and

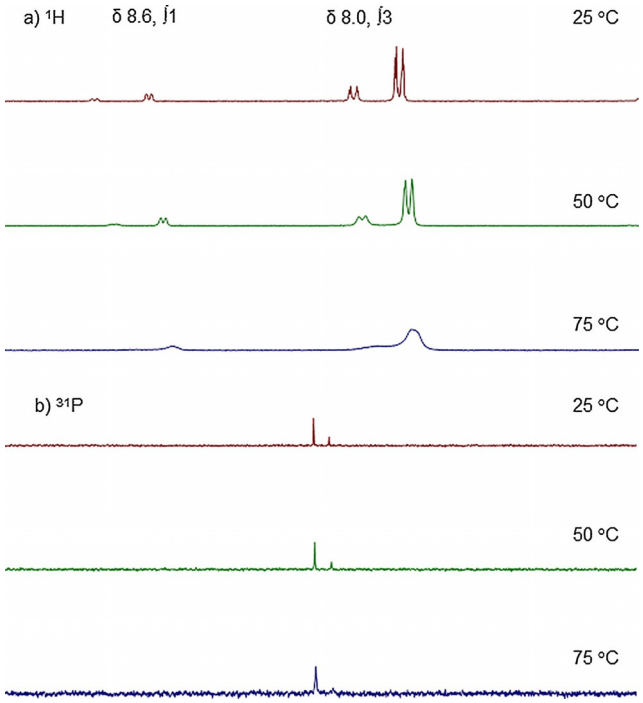


Figure 2. Variable-temperature NMR spectra of **C2** in $[D_8]$toluene a) ^1H-NMR (pyridine signals) and b) $^{31}P\{^1H\}$-NMR of **C2**.

51.6 ppm (major and minor isomer, respectively) disappeared completely. Two doublets at $\delta = 60.7$ and 54.4 ppm appeared, both with a *J* coupling value of 23 Hz, which must arise from coupling with another phosphorus nucleus (Figure 3).

Figure 3. $^{31}P\{^{1}H\}$-NMR spectrum (50–70 ppm) of **C2** in [D_8]toluene after addition of 2 equivalents of KO*t*Bu. Left peak appears at $\delta = 60.7$ and right peak at 54.5 ppm.

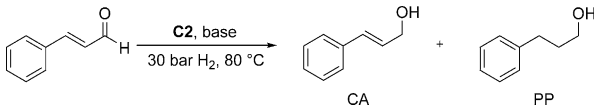
This suggests that upon deprotonation in the absence of a hydride donor, the activated complex dimerises. This hypothesis was supported by the appearance of signals at *m/z* 1117.170 and 1158.183 in the mass spectrum, with isotope patterns corresponding to a complex possessing two ruthenium atoms, although these signals are not readily assigned. So far, we have been unable to isolate this species for further investigation. Addition of 1–5 equivalents of isopropanol to these solutions did not result in any hydride signals, and upon heating the complex degraded, as evidenced by a brown precipitate and the appearance of the signal for uncoordinated PPh_3 around $\delta = -5$ ppm. Hydride signals were not observed when the NMR experiments were repeated under a pressure of up to 10 bar of H_2.

Crystals of **C2**, **C3** and the tertiary amine complex **C7** suitable for X-ray diffraction analysis were obtained. The solid-state structures were determined as the *trans*-(*mer-)* (**C2** and **C3**) and *cis*-(*fac-)* dichloride (**C7**) complexes (Figure 4). Dissolving the crystalline material in deuterated solvent at −18 °C, and subsequent measurement of the $^{31}P\{^{1}H\}$-NMR spectra showed the same signals as before, in the same ratios, indicating that the equilibrium established readily. It is likely that the two equilibrium forms of complexes **C1**–**C7** observed in solution by NMR correspond to the same *fac* and *mer* isomers. Recent theoretical work by Chen et al. on Gusev's Ru–SNS hydrogenation catalysts supports this hypothesis, and showed that the geometry of the isolated complexes does not necessarily resemble the catalytic species. The flexibility of the ligand may actually be an important factor for catalyst activity.[15]

Hydrogenation reactions

Catalytic hydrogenations were performed at 80 °C with 30 bar H_2 in isopropanol. A base screening was performed for the overnight hydrogenation reaction of *trans*-cinnamaldehyde to cinnamyl alcohol at 1 mmol scale with 0.05 mol% **C2** as catalyst. As shown in Table 1, full conversions were obtained with

Table 1. Screening of different bases and Lewis acids for the hydrogenation of *trans*-cinnamaldehyde to cinnamyl alcohol.[a]



Entry	Base[a]	Conversion [%][b]	CA [%][b]	PP [%][b]
1	LiO*t*Bu	100	75	7
2	NaO*t*Bu	100	76	5
3	KO*t*Bu	100	88	3
4	KO*t*Bu[c]	100	51	43
5	[Al(*i*OPr)$_3$]	7	0	0
6	[Ti(*i*OPr)$_4$]	15	0	0
7	$CaCO_3$	11	0	0
8	Na(PhCOO)	15	0	0
9	K(PhCOO)	22	0	0
10	K_3PO_4	20	0	0
11	2,6-lutidine	25	0	0

[a] Reaction conditions: *trans*-cinnamaldehyde (1 mmol), dodecane (internal standard, 200 μL), dry *i*PrOH (2 mL), **C2** (0.05 mol%), base (1.25 mol%), 80 °C, 30 bar H_2, 16 h. [b] Determined by GC using dodecane as internal standard. [c] KO*t*Bu sublimed and stored under Ar prior to reaction. KO*t*Bu stored under ambient conditions decomposes over time, which in turn leads to a lower actual base loading, or side reactions catalysed by KOH or K_2CO_3.

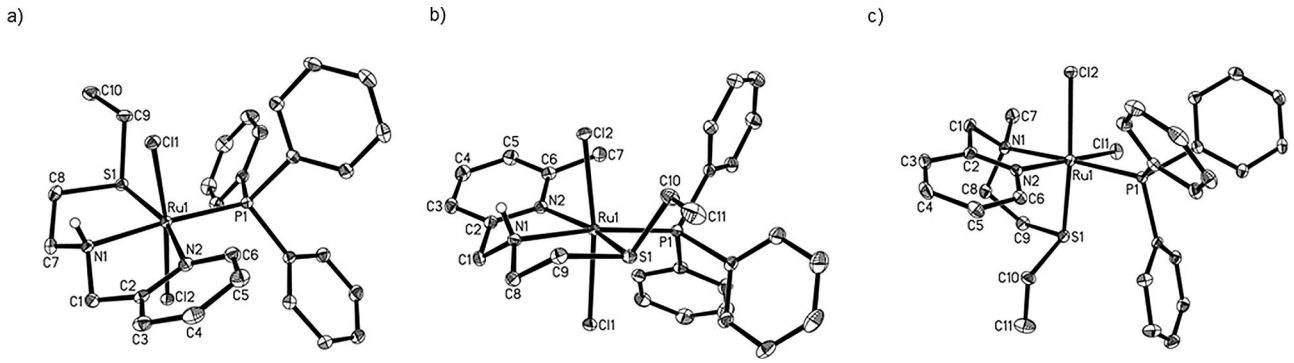
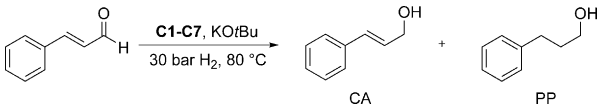


Figure 4. ORTEP drawings (30% probability ellipsoids, hydrogen atoms, except H1A for **C2** and **C3**, are omitted for clarity.) Selected bond lengths (Å) and angles (°) for a) complex **C2**: Ru1–S1 2.3360(5), Ru1–N1 2.1252(17), Ru1–N2 2.0956(16), Ru1–P1 2.2960(5), Ru1–Cl1 2.4199(5), Ru1–Cl2 2.4273(5); S1-Ru1-N1 84.23(5), S1-Ru1-N2 162.42(5), N1-Ru1-N2 78.27(6), N1-Ru1-P1 175.62(5), Cl1-Ru1-Cl2 171.97(2), Cl1-Ru1-N1 84.80(5), Cl1-Ru1-N2 83.65(5), Cl1-Ru1-S1 93.239(18), C1-N1-C7 115.23(16); b) complex **C3**: Ru1–S1 2.3184(4), Ru1–N1 2.1184(14), Ru1–N2 2.1818(14), Ru1–P1 2.3161(4), Ru1–Cl1 2.4327(4), Ru1–Cl2 2.4207(4),; S1-Ru1-N1 84.05(4), S1-Ru1-N2 160.75(4), N1-Ru1-N2 76.94(5), N1-Ru1-P1 172.48(4), Cl1-Ru1-Cl2 171.162(15), Cl1-Ru1-N1 86.67(4), Cl1-Ru1-N2 94.49(4), Cl1-Ru1-S1 87.308(15), C1-N1-C8 113.66(13); c) complex **C7**: Ru1–N1 2.215(2), Ru1–N2 2.069(2), Ru1–S1 2.3039(7), Ru1–Cl1 2.4445(7), Ru1–Cl2 2.4535(7), Ru1–P1 2.2827(7); N1-Ru1-N2 78.47(9), N1-Ru1-S1 85.11(6), N2-Ru1-S1 93.72(6), N1-Ru1-P1 177.83(7), S1-Ru1-Cl2 172.07(3), N1-Ru1-Cl2 87.79(6), N2-Ru1-Cl1 170.59(6), Cl1-Ru1-Cl2 94.14(2), C1-N1-C8 108.8(2), Cl1-Ru1-S1 82.65(3), N2-Ru1-Cl2 88.32(6), P1-Ru1-Cl2 94.35(2).

tert-butoxide bases (entries 1–4). In addition to cinnamyl alcohol (CA), 3-phenylpropanol (PP) was also observed in small amounts. It appears the starting material is first hydrogenated to CA, which then reacts further to PP. Notably, when using freshly sublimed potassium *tert*-butoxide, the reaction is faster and more over hydrogenation is observed in these initial screening reactions that were run overnight (entry 4). The other bases gave disappointing results. The yields of CA and PP did not correspond to the total conversion, suggesting base-catalysed side reactions occurred in these initial screening reactions. Lewis acid activation with $[Al(OiPr)_3]$ and $[Ti(OiPr)_4]$ was also investigated (entries 5 and 6), but none of the expected products (CA and PP) were observed

Under the same reaction conditions, the $[RuCl_2(NNS)(PPh_3)]$ complexes **C1**–**C7** were tested in the catalytic hydrogenation of *trans*-cinnamaldehyde in the presence of freshly sublimed KO*t*Bu (Table 2). In overnight reactions, all complexes achieved

Table 2. Screening of **C1**–**C7** for the hydrogenation of *trans*-cinnamaldehyde to cinnamyl alcohol.[a]



Entry	Complex	Conv. 1 h [%][b]	Yield 1 h (CA:PP) [%][c]	Conv. 16 h [%][b]	Yield 16 h (CA:PP) [%][b]
1	**C1**	22	7:0	100	70:12
2	**C2**	100	90:10	100	51:43
3	**C2**[c]	52	52:0	n.d.	n.d.
4	**C3**	86	65:2	100	66:5
5	**C4**	59	36:23	100	80:14
6	**C5**	21	12:0	98	63:8
7	**C6**	17	11:3	100	62:32
8	**C7**	56	37:16	100	76:12
9	–	n.d.	n.d.	15	1:1

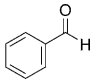
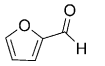
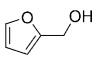
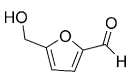
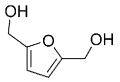
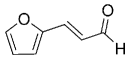
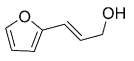
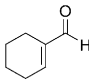
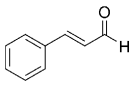
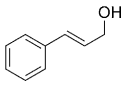
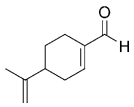
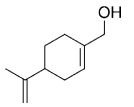
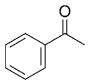
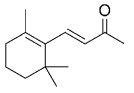
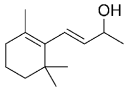
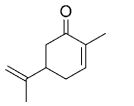
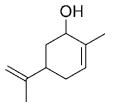
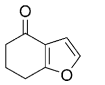
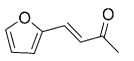
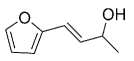
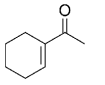
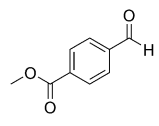
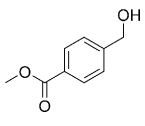
[a] Reaction conditions: *trans*-cinnamaldehyde (1 mmol), dodecane (internal standard, 200 μL), dry isopropanol (2 mL), **C1**–**C7** (0.05 mol%), KO*t*Bu (1.4 mg, 1.25 mol%), 80 °C, 30 bar H_2. [b] Determined by GC using dodecane as internal standard. [c] 10 equiv base w.r.t. **C2** (0.6 mg KO*t*Bu, 0.5 mol%).

full conversion, with CA as the main product together with varying amounts of PP. When the reaction time was shortened to 1 h, only **C2** gave full conversion and a yield of CA of 90%. The fact that the amount of PP is higher after 16 h suggests CA is the primary product of the reaction and PP is a secondary product formed through hydrogenation of CA. Note that only 52% conversion was reached after 1 h if ten equivalents of base were used with respect to the catalyst, instead of the usual 25 equivalents. Again, it was observed that the yields of both alcohols did not always add up to 100%, which suggests that, in the case of slower catalysts, base-catalysed side reactions took place leading to unidentified by-products which were not detected by GC.

The fact that *N*-methylated **C7** also catalysed the hydrogenation indicates that the NH functionality in the ligand is not essential, although this does not rule out involvement of the secondary amine in the reaction mechanism of the first six complexes. This is in accordance with recent reports by Ikariya, Dub, Gordon and co-workers on the mechanism of the asymmetric hydrogenation and transfer hydrogenation of acetophenone.[8b,16]

With these results in hand, it was apparent that the purity of the base and short reaction times are crucial in obtaining both high yields and selectivities. For further reactions, KO*t*Bu was sublimed and stored under argon atmosphere. Precatalyst C2 was then employed in the hydrogenation of a range of aldehydes and ketones at a 10 mmol scale (Table 3).

Table 3. Substrate scope.[a]

Entry	Substrate	Product	Yield [%]
1			99
2			99
3			93[b]
4			99
5			99
6			94[c]
7			96
8			97
9			91
10			84
11			99
12			93
13			99
14			97[d]

[a] Reaction conditions: substrate (10 mmol), dry isopropanol (20 mL), **C2** (3.2 mg, 0.05 mol%), KO*t*Bu (14 mg, 1.25 mol%), 80 °C, 30 bar H_2, 1 h. Listed yields are isolated yields. [b] 0.5 mol% catalyst, 5.0 mol% KO*t*Bu. [c] 25 mmol scale. [d] 2 mmol scale in dry methanol (10 mL); reaction time 3 h.

Next to representative α,β-unsaturated aldehydes and ketones, Table 3 also includes furfural (entry 2) and hydroxymethylfurfural (HMF, entry 3), which are of interest as biomass-derived platform chemicals.[17] In entries 7 and 10, no hydrogenation of the non-conjugated C=C bond was observed. The substrate of entry 14 contains both an aldehyde and an ester functionality. Only the aldehyde was hydrogenated under the reaction conditions. This reaction was performed in methanol instead of isopropanol, to prevent transesterification. The hydrogenation of *trans*-cinnamaldehyde was scaled up to 25 mmol leading to a slightly higher yield of the desired CA. The hydrogenated products were isolated in high yields after one hour reaction time, corresponding to TONs of 2000.

Workup typically consisted of filtration over a plug of silica and distillation in vacuo. In some cases (entries 6, 7, and 10), slight over-hydrogenation already occurred during cooling down of the reaction vessel, and column chromatography was necessary to obtain clean products. For the hydrogenation of HMF (entry 3), 0.5 mol% of pre-catalyst was required. This can be ascribed to impurities and decomposition products in liquid HMF, a known problem in its chemistry.[18]

The hydrogenation of acetophenone was repeated with **C2** loadings of 50 and 5 ppm, using stock solutions, and 25 equivalents base with respect to the precatalyst. Full conversion was reached overnight, corresponding to TONs of $>200\,000$ after 16 h.

Conclusion

New air-stable Ru–NNS(TPP) dichloride complexes based on tridentate, easy to prepare ligands have been synthesised in good yields. The complexes are highly suitable as precatalysts in the fast and selective hydrogenation of a range of aromatic and α,β-unsaturated aldehydes and ketones. The need for in situ catalyst activation by a strong base did not lead to significant side reactions at the short reaction times that were used. Full conversions corresponding to TONs of 2000 were obtained invariably within one hour, and TONs $>200\,000$ were achieved overnight.

Experimental Section

General

Reagents and solvents were obtained from commercial sources and used as received unless noted otherwise. Dry solvents were obtained from a solvent purification system (CH_2Cl_2, toluene, heptane,) purchased water-free in a bottle with septum (isopropanol) or distilled before use (diglyme, deuterated solvents, isopropanol.) GC analysis was carried out on an Agilent 7890B GC system with a HP-5 normal-phase silica column, using He as a carrier gas and dodecane as standard. NMR spectra were recorded on a Bruker AV400, Bruker AV300 or Bruker Fourier300 NMR spectrometer. ^{1}H and ^{13}C-NMR spectra were referenced w.r.t. the solvent signal. NMR experiments under hydrogen pressures larger than 1 bar were carried out in a Wilmad Labglass pressure NMR tube. All chemical shifts are in ppm, coupling constants in Hz. HR-MS measurements were recorded on an Agilent 6210 time-of-flight LC/MS (ESI) or Thermo Electron MAT 95-XP (EI, 70 eV), peaks as listed correspond to the highest abundant peak and are of the expected isotope pattern. X-ray diffraction data were collected on a Bruker Kappa APEX II Duo diffractometer. The structures were solved by direct methods[19] and refined by full-matrix least-squares procedures on F^2.[20] CCDC 1532411–1532413 contain the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

NNS ligand synthesis

2-(Ethylthio)-*N*-[(6-methylpyridin-2-yl)methyl]ethan-1-amine (L3): 6-Methylpyridine-2-carboxaldehyde (3.0 g, 25 mmol) and 2-(ethylthio)ethylamine (2.63 g, 2.8 mL, 1 equiv) were dissolved in CH_2Cl_2 (75 mL), and Na_2SO_4 (7.1 g, 50 mmol) was added. The suspension was stirred at room temperature overnight, and filtered. The filter cake was washed with CH_2Cl_2, and the combined volatiles were removed in vacuo, yielding 5.45 g of imine as a brown oil, which was used directly in the following step without further purification. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 8.34$ (s, 1H, -CCH=*N*-), 7.74 (d, 1H, $J_{H\text{-}H} = 7.5$ Hz, CH_{arom}), 7.59 (t, 1H, $J_{H\text{-}H} = 7.5$ Hz, CH_{arom}), 7.15 (d, 1H, $J_{H\text{-}H} = 7.5$ Hz, CH_{arom}), 3.83 (dt, 2H, $J_{H\text{-}H} = 7.2$ Hz, $J_{H\text{-}H} = 1.3$ Hz), 2.84 (t, 2H, $J_{H\text{-}H} = 7.0$ Hz), 2.56 (s, 3H), 2.56 (q, 2H, $J_{H\text{-}H} = 7.2$ Hz) 1.23 ppm (t, 3H, $J_{H\text{-}H} = 7.4$ Hz); HRMS (ESI+): *m/z* calcd for $C_{11}H_{16}N_2S$: 208.1034; found: 209.1109 $[M+H]^+$. The imine (5.45 g) was dissolved in MeOH (50 mL), and $NaBH_4$ (2.6 g, 2 equiv) was added in portions at 0 °C. The mixture was then stirred at room temperature for another hour, after which the solvent was removed in vacuo. CH_2Cl_2 (20 mL) and water (20 mL) were added, and the aqueous layer was extracted three more times with DCM (20 mL). The combined organic layers were washed with brine (20 mL) and dried over Na_2SO_4. Evaporating the solvent and drying in vacuo yielded 4.95 g (94%) of **L3** as an orange oil, which could be used for complex synthesis directly, or further purified by Kugelrohr distillation. ^{1}H-NMR (300 MHz, $CDCl_3$): $\delta = 7.45$ (t, 1H, $J = 7.6$ Hz, CH_{arom}), 7.07 (d, 1H, $J = 7.8$ Hz, CH_{arom}), 6.96 (d, 1H, $J = 7.5$ Hz, CH_{arom}), 3.84 (s, 2H), 2.80 (dt, 2H, $J = 6.6$, 1.0 Hz), 2.66 (dt, 2H, $J = 6.6$, 1.0 Hz), 2.48 (m, 5H), 1.23 ppm (t, 3H, $J = 7.4$ Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): $\delta =$ 158.9, 157.8, 136.5, 121.3, 118.9, 54.9, 48.2, 31.8, 25.6, 24.4 ppm; HRMS (ESI+): *m/z* calcd for $C_{11}H_{19}N_2S$: 211.1269 $[M+H]^+$; found: 211.1265.

2-(Ethylthio)-*N*-(1-[pyridin-2-yl]ethyl)ethan-1-amine (L6): To a solution of 2-acetylpyridine (3.0 g, 25 mmol) and 2-(ethylthio)ethylamine (2.63 g, 2.8 mL, 1 equiv) in toluene (75 mL), Na_2SO_4 (7.1 g, 50 mmol) and *p*-toluenesulfonic acid (210 mg, 5 mol%) were added, and the mixture was heated to reflux overnight. The imine was then reduced to **L6** analogously to **L3** for an overall yield of 80%. ^{1}H NMR (300 MHz, CD_2Cl_2): $\delta = 8.51$ (ddd, 1H, $J_{H\text{-}H} = 4.8$ Hz, $J_{H\text{-}H} = 1.9$ Hz, $^3J_{H\text{-}H} = 1.0$ Hz, CH_{arom}), 7.64 (td, 1H, $J_{H\text{-}H} = 7.6$ Hz, $J_{H\text{-}H} = 1.8$ Hz, CH_{arom}), 7.32 (dt, 1H, $J_{H\text{-}H} = 7.8$ Hz, $J_{H\text{-}H} = 1.1$ Hz, CH_{arom}), 7.14 (ddt, 1H, $J_{H\text{-}H} = 7.5$ Hz, $J_{H\text{-}H} = 4.8$ Hz, $J_{H\text{-}H} = 1.2$ Hz, CH_{arom}), 3.84 (q, 1H, $J_{H\text{-}H} = 6.9$ Hz, CH), 2.71–2.55 (m, 4H, CH_2), 2.47 (q, 2H, $J_{H\text{-}H} = 7.4$ Hz, CH_2), 2.05 (d, 1H, $J = 39.3$ Hz, NH), 1.34 (d, 3H, $J_{H\text{-}H} = 6.9$ Hz, CH_3), 1.20 ppm (d, 3H, $J_{H\text{-}H} = 7.5$ Hz, CH_3); ^{13}C NMR (75 MHz, CD_2Cl_2): $\delta = 165.4$, 149.7, 136.9, 122.3, 121.4, 59.7, 47.1, 32.7, 26.1, 23.2, 15.2 ppm; HRMS (ESI+): *m/z* calcd for $C_{11}H_{19}N_2S$: 211.1269 $[M+H]^+$; found: 211.1265.

2-(Ethylthio)-*N*-methyl-*N*-(pyridin-2-ylmethyl)ethan-1-amine (L7): 2-(Ethylthio)-*N*-(pyridin-2-ylmethyl)ethan-1-amine (**L2,** 850 mg, 3.75 mmol), formalin (4 mL of 37 wt% formaldehyde in water) and formic acid (4 mL) were heated to 70 °C overnight. All volatiles were removed in vacuo. To the sticky brown residue, CH_2Cl_2 (10 mL) was added and extracted with a saturated $NaHCO_3$ solu-

tion in water (10 mL). The aqueous layer was extracted three more times with CH_2Cl_2 (10 mL). The organic layers were washed with brine and then dried over Na_2SO_4. Removal of the solvent yielded 754 mg (3.59 mmol, 96%) of **L7** as an orange liquid. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.51 (ddd, 1H, J = 4.8 Hz, J = 1.9 Hz, J = 1.0 Hz, CH_{arom}), 7.64 (td, 1H, J = 7.6 Hz, J = 1.8 Hz, CH_{arom}), 7.32 (dt, 1H, J = 7.8 Hz, J = 1.1 Hz, CH_{arom}), 7.14 (ddt, 1H, J = 7.5 Hz, J = 4.8 Hz, J = 1.2 Hz, CH_{arom}), 3.84 (q, 1H, J = 6.9 Hz, CH), 2.71–2.55 (m, 4H, CH_2), 2.47 (q, 2H, J = 7.4 Hz, CH_2), 2.05 (d, 1H, J = 39.3 Hz, NH), 1.34 (d, 3H, J = 6.9 Hz, CH_3), 1.20 ppm (d, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 165.4, 149.7, 136.9, 122.3, 121.4, 59.7, 47.1, 32.7, 26.1, 23.2, 15.2 ppm; HRMS (ESI+): *m/z* calcd for $C_{11}H_{19}N_2S$: 211.1269 $[M+H]^+$; found: 211.1265.

2-(Methylthio)-*N*-[(pyridin-2-yl)methyl]ethan-1-amine (L1): Pyridine-2-carboxaldehyde and 2-(methylthio)ethylamine were converted to **L1** analogously to the procedure given for **L3** in a yield of 92%. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.43 (ddd, 1H, J = 4.9 Hz, J = 1.8 Hz, J = 0.9 Hz, CH_{arom}), 7.57 (td, 1H, J = 7.7 Hz, J = 1.8 Hz, CH_{arom}), 7.24 (d, 1H, J = 7.8 Hz, CH_{arom}), 7.07 (dd, 1H, J = 7.5 Hz, J = 5.0 Hz, CH_{arom}), 3.81 (s, 2H), 2.75 (td, 2H, J = 6.5 Hz, J = 0.8 Hz, CH_2), 2.58 (td, 2H, J = 6.5 Hz, J = 0.6 Hz, CH_2), 1.99 ppm (s, 3H, CH_3); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 160.2, 149.1, 136.2, 121.9, 121.7, 54.8, 47.6, 34.4, 15.0 ppm; HRMS (ESI+): *m/z* calcd for $C_9H_{15}N_2S$: 183.0956 $[M+H]^+$; found: 183.0950.

2-(Ethylthio)-*N*-[(pyridin-2-yl)methyl]ethan-1-amine (L2): Pyridine-2-carboxaldehyde and 2-(ethylthio)ethylamine were converted to **L2** analogously to the procedure given for **L3** in a yield of 94%. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.51 (ddd, 1H, J = 4,8 Hz, J = 1.5 Hz, J = 0.9 Hz, CH_{arom}), 7.64 (td, 1H, J = 7.5 Hz, J = 1.8 Hz, CH_{arom}), 7.32 (d, 1H, J = 7.8 Hz, CH_{arom}), 7.19–7.12 (m, 1H, CH_{arom}), 3.88 (s, 2H, CH_2), 2.85–2.79 (m, 2H, CH_2), 2.72–2.66 (m, 2H, CH_2), 2.52 (q, 2H, J = 7.5 Hz, CH_2), 2.09 (d, 1H, J = 9.6 Hz, NH), 1.23 ppm (t, 3H, J = 7.4 Hz, CH_3); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 161.6, 149.7, 136.8, 122.5, 122.3, 55.4, 48.9, 32.5, 26.2, 15.3 ppm; HRMS (ESI+): *m/z* calcd for $C_{10}H_{17}N_2S$: 197.1112 $[M+H]^+$; found: 197.1108.

2-(Ethylthio)-*N*-[(6-methoxypyridin-2-yl)methyl]ethan-1-amine (L4): 6-Methoxypyridine-2-carboxaldehyde and 2-(ethylthio)ethylamine were converted to **L4** analogously to the procedure given for **L3** in a yield of 95%. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.54 (dd, 1H, J = 8.1 Hz, J = 7.4 Hz, CH_{arom}), 6.87 (d, 1H, J = 7,2), 6.63 (d, 1H, J = 8.1 Hz), 4.55 (s, NH), 3.92 (s, 3H), 3.90 (m, NH), 3.80 (s, 2H), 2.83 (t, 2H, J = 6.5 Hz), 2.66 (t, 2H, J = 6.5 Hz), 2.52 (t, 2H, J = 7.5 Hz), 1.23 ppm (t, 3H, J = 7.2 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 163.8, 157.3, 138.8, 114.5, 108.7, 54.3, 53.2, 48.1, 32.0, 25.8, 14.8 ppm; HRMS (ESI+): *m/z* calcd for $C_{11}H_{19}N_2OS$: 227.1218 $[M+H]^+$; found: 249.1039 $[M+Na]^+$.

2-(Ethylthio)-*N*-[(quinolin-2-yl)methyl]ethan-1-amine (L5): Quinolin-2-carboxaldehyde and 2-(ethylthio)ethylamine were converted to **L5** analogously to the procedure given for **L3** in a yield of 82%. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.13 (d, 1H, J = 8.4 Hz, CH_{arom}), 8.00 (d, 1H, J = 8.7 Hz, CH_{arom}), 7.82 (dd, 1H, J = 8.3 Hz, J = 1.5 Hz, CH_{arom}), 7.69 (ddd, 3H, J = 8.5 Hz, J = 6.9 Hz, J = 1.5 Hz, CH_{arom}), 7.55–7.45 (m, 2H, CH_{arom}), 4.08 (s, 2H, CH_2), 2.89 (td, 2H, J = 6.8 Hz, J = 1.2 Hz, CH_2), 2.73 (td, 2H, J = 6.4 Hz, J = 0.9 Hz, CH_2), 2.55 (q, 2H, J = 7.4 Hz, CH_2), 2.14 (d, 1H, J = 11.4 Hz, NH), 1.24 ppm (t, 3H, J = 7.4 Hz, CH_3); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 161.5, 136.7, 129.8, 129.5, 128.1, 127.9, 126.5, 121.0, 56.0, 49.1, 32.6, 26.2, 15.3 ppm; HRMS (ESI+): *m/z* calcd for $C_{14}H_{19}N_2S$: 247.1269 $[M+H]^+$; found: 247.1267.

Synthesis of $[Ru(NNS)(PPh_3)Cl_2]$ complexes

$[Ru(6\text{-}MeNNS^{Et})(PPh_3)Cl_2]$ (C3): $[RuCl_2(PPh_3)_2]$ (1 g, 1.04 mmol) and ligand (1 equiv) were placed in a 25 mL Schlenk tube under an argon atmosphere, and dissolved in dry diglyme (2 mL). The reaction mixture was heated to 162 °C for 2 h, allowed to cool down to room temperature, and then stored at −18 °C overnight to precipitate further. While cooling on a dry ice/isopropanol bath, cold Et_2O (2 mL) was added, the precipitate was filtered by cannula, and washed with Et_2O (5×2 mL). The orange powder was dried in vacuo, affording 530 mg (79%) of **C3** as an orange powder. Note that the complex exists as an equilibrium mixture of two conformations in solution. Crystals suitable for X-ray diffraction analysis were grown by slow diffusion of pentane into a concentrated solution of **C3** in CH_2Cl_2. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 7.67–7.16 (m, 17H, CH_{arom}), 7.01 (d, 1H, J = 7.8 Hz, CH_{arom}), 5.65 (m, 2H), 4.47 (m, 1H), 3.5 (m, 1H), 3.34 (m, 1H), 3.22 (d, 1H, J = 11.1 Hz), 2.98 (m, 1H), 2.59 (m, 1H), 1.53 (m, 2H), 0.87 ppm (t, 3H, J = 7.5 Hz); ^{31}P-NMR (122 MHz, CD_2Cl_2): δ = 48.8, 45.8 ppm; HRMS (ESI+): *m/z* calcd for $C_{29}H_{33}Cl_2N_2PRuS$: 644.0523 $[M]^+$; found: 644.0518; elemental analysis calcd (%) for $C_{29}H_{33}Cl_2N_2PRuS$: C 54.04, H 5.16, N 4.35, S 4.97; found: C 53.72, H 5.09, N 4.17, S 5.27. Crystal data for **C3**: $C_{29.5}H_{34}Cl_3N_2PRuS$, M = 687.03, triclinic, space group $P1$, a = 9.8567(3), b = 10.0175(3), c = 15.9263(5) Å, α = 100.0358(7), β = 97.5261(7), γ = 99.4249(7)° V = 1506.85(8) Å^3, T = 150(2) K, Z = 2, 57859 reflections measured, 7259 independent reflections (R_{int} = 0.0303), final R values [$I > 2\sigma(I)$]: $R1$ = 0.0226, $wR2$ = 0.0526, final R values (all data): $R1$ = 0.0290, $wR2$ = 0.0564, 358 parameters.

$[Ru(NNS^{Me})(PPh_3)Cl_2]$ (C1): $[RuCl_2(PPh_3)_2]$ and **L1** (1 equiv) were converted to **C1** analogously to the procedure given for **C3**. Complex **C1** was obtained in 80% yield as an orange powder. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.47 (d, 1H, $J_{H\text{-}H}$ = 5.7 Hz), 7.72 (m, 1H), 7.56 (m, 6H), 7.32 (m, 10H), 6.86 (t, 1H, $J_{H\text{-}H}$ = 6.3 Hz), 5.45 (br s, 1H, NH), 5.20 (t, 1H, $J_{H\text{-}H}$ = 12.6 Hz), 4.38 (m, 1H), 3.41 (m, 3H), 3.26 (d, 1H, $J_{H\text{-}H}$ = 11.1 Hz), 2.55 (m, 1H), 1.14 ppm (m, 2H); ^{31}P-NMR (122 MHz, CD_2Cl_2): δ = 51.8, 50.7 ppm; HRMS (ESI+): *m/z* calcd for $C_{27}H_{29}Cl_2N_2PRuS$: 616.0210 $[M]^+$; found: 616.0197; elemental analysis calcd (%) for $C_{27}H_{29}Cl_2N_2PRuS$: C 52.60, H 4.74, N 4.54, S 5.20; found: C 52.92, H 4.77, N 4.68, S 5.58.

$[Ru(NNS^{Et})(PPh_3)Cl_2]$ (C2): $[RuCl_2(PPh_3)_2]$ and **L2** (1 equiv) were converted to **C2** analogously to the procedure given for **C3**. Complex **C2** was obtained in in 84% yield as an orange powder. Crystals suitable for X-ray diffraction analysis were grown by recrystallisation of **C2** from hot toluene. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.45 (d, 1H, $J_{H\text{-}H}$ = 5.7 Hz), 7.72 (m, 1H), 7.57 (m, 6H), 7.34 (m, 10H), 6.86 (t, 1H, $J_{H\text{-}H}$ = 6.3 Hz), 5.49 (br s, 1H, NH), 5.22 (t, 1H, $J_{H\text{-}H}$ = 13.5 Hz), 4.40 (m, 1H), 3.47 (m, 2H), 3.36 (m, 1H), 2.80 (m, 1H), 2.52 (m, 1H), 1.27 (m, 2H), 1.19 (m, 1H), 0.95 ppm (t, 3H, $J_{H\text{-}H}$ = 7.5 Hz); ^{31}P-NMR (122 MHz, CD_2Cl_2): δ = 51.8, 50.7 ppm. HRMS (ESI+): *m/z* calcd for $C_{28}H_{31}Cl_2N_2PRuS$: 630.0366 $[M]^+$; found: 630.0388,; elemental analysis calcd (%) for $C_{28}H_{31}Cl_2N_2PRuS$: C 53.33; H 4.96, N 4.44, S 5.08; found: C 53.12, H 4.80, N 4.52, S 5.47. Crystal data for **C2**: $C_{35}H_{39}Cl_2N_2PRuS$, M = 722.68, monoclinic, space group $P2_1/c$, a = 17.6874(11), b = 12.4773(7), c = 15.0717(9) Å, β = 92.4695(11)°, V = 3323.1(3) Å^3, T = 150(2) K, Z = 4, 43978 reflections measured, 7633 independent reflections (R_{int} = 0.0419), final R values [$I > 2\sigma(I)$]: $R1$ = 0.0280, $wR2$ = 0.0594, final R values (all data): $R1$ = 0.0409, $wR2$ = 0.0651, 373 parameters.

$[Ru(6\text{-}MeONNS^{Et})(PPh_3)Cl_2]$ (C4): $[RuCl_2(PPh_3)_2]$ and **L4** (1 equiv) were converted to **C4** analogously to the procedure given for **C3**. Complex **C4** was obtained in 88% yield as an orange powder. ^{1}H-NMR (400 MHz, CD_2Cl_2): δ = 7.94 (m, 2H), 7.65 (m, 2H), 7.42–7.14 (m, 12H), 7.07 (d, 1H, $J_{H\text{-}H}$ = 7.6 Hz), 6.56 (d, 1H, $J_{H\text{-}H}$ = 8.4 Hz), 5.56–

5.36 (m, 2H), 4.46 (m, 1H), 3.50–3.19 (m, 2H), 3.21 (dd, 1H, $J_{H\text{-}H}$ = 11.0 Hz, $J_{H\text{-}H}$ = 2.2 Hz), 2. 87 (m, 1H), 2.83 (s, 3H,), 2.50 (m, 1H), 1.33 (m, 1H), 0.87 ppm (t, 3H, $J_{H\text{-}H}$ = 5.5 Hz); ^{31}P-NMR (122 MHz, CD_2Cl_2): δ = 47.2, 45.9 ppm; HRMS (ESI+): *m/z* calcd for $C_{29}H_{33}Cl_2N_2OPRuS$: 660.0468 $[M]^+$; found: 660.0469 ; elemental analysis calcd (%) for $C_{29}H_{33}Cl_2N_2OPRuS$: C 52.73, H 5.04, N 4.24, S 4.85; found: C 52.45, H 5.01, N 4.35, S 5.16.

[Ru(QuinNS^{Et})(PPh$_3$)Cl$_2$] (C5): [$RuCl_2(PPh_3)_2$] and **L5** (1 equiv) were converted to **C5** analogously to the procedure given for **C3**. Complex **C5** was obtained in 58% yield as a red powder. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.12 (d, 2H $J_{H\text{-}H}$ = 8.4 Hz), 7.74–6.66 (m, 19H), 5.90 (br s, NH), 5.74 (t, 1H, $J_{H\text{-}H}$ = 13.3 Hz), 4.72 (m, 1H), 3.58–3.40 (m, 3H), 3.05 (m, 1H), 2.72 (m, 1H), 1.66 (m, 1H), 0.95 ppm (t, 3H, $J_{H\text{-}H}$ = 7.5 Hz); ^{31}P NMR (122 MHz, CD_2Cl_2): δ = 48.9, 45.9 ppm; HRMS (ESI+): *m/z* calcd for $C_{32}H_{33}Cl_2N_2PRuS$: 680.0519 $[M]^+$; found: 680.0500.

[Ru(*N*-Me-NS^{Et})(PPh$_3$)Cl$_2$] (C6): [$RuCl_2(PPh_3)_2$] and **L6** (1 equiv) were converted to **C6** analogously to the procedure given for **C3**. Complex **C6** was obtained in 62% yield as a pale yellow powder. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.53 (d, 1H, $J_{H\text{-}H}$ = 5.7 Hz), 7.72 (m, 1H), 7.57 (m, 6H), 7.33 (m, 10H), 6.85 (t, 1H, $J_{H\text{-}H}$ = 6.6 Hz), 5.35 (m, 1H), 4.93 (br s, NH), 3.68–3.31 (m, 3H), 2.81 (m, 1H), 2.53 (m, 1H), 1.80 (d, 3H, $J_{H\text{-}H}$ = 6.9 Hz), 1.25 (m, 1H), 0.97 ppm (t, 3H, $J_{H\text{-}H}$ = 7.2 Hz). ^{31}P NMR (122 MHz, CD_2Cl_2): δ = 51.5, 50.3 ppm; HRMS (ESI+): *m/z* calcd for $C_{29}H_{33}Cl_2N_2PRuS$: 644.0518 $[M]^+$; found: 644.0513; elemental analysis calcd (%) for $C_{29}H_{33}Cl_2N_2OPRuS$: C 54.04, H 5.16, N 4.35, S 4.97; found: C 54.19, H 5.19, N 4.35, S 5.30.

[Ru(NN^{Me}S^{Et})(PPh$_3$)Cl$_2$] (C7): [$RuCl_2(PPh_3)_2$] and **L7** (1 equiv) were converted to **C7** analogously to the procedure given for **C3**, but with a reaction time of 14 h, yielding 54% of **C7** as an orange powder. Crystals suitable for X-ray diffraction analysis were grown by slow diffusion of pentane into a concentrated solution of C7 in dichloromethane. ^{1}H-NMR (300 MHz, CD_2Cl_2): δ = 8.11 (d, 1H, $J_{H\text{-}H}$ = 5.7 Hz), 7.92 (m, 6H), 7.47 (dt, 1H, $J_{H\text{-}H}$ = 7.5, $J_{H\text{-}H}$ = 1.5 Hz), 7.30 (m, 10H), 6.56 (t, 1H, $J_{H\text{-}H}$ = 7.5 Hz), 5.67 (d, 1H, $J_{H\text{-}H}$ = 14.4 Hz), 3.87 (d, 1H, $J_{H\text{-}H}$ = 14.4 Hz), 3.15 (s, 3H), 2.86 (m, 1H), 2.70 (m, 1H), 2.30 (m, 2H), 0.74 (m, 1H), 0.67 (t, 3H, $^1J_{H\text{-}H}$ = 6.9 Hz), 0.42 ppm (m, 1H); ^{31}P-NMR (122 MHz, CD_2Cl_2): δ = 51.4, 50.4 ppm; HRMS (ESI+): *m/z* calcd for $C_{29}H_{33}Cl_2N_2PRuS$: 644.0518 $[M]^+$; found: 644.0505. Crystal data for **C7**: $C_{29}H_{33}Cl_2N_2PRuS$, M = 644.57, monoclinic, space group $P2_1$, a = 8.8469(3), b = 15.1574(5), c = 10.3199(3) Å, β = 102.3524(9)°, V = 1351.82(8) Å^3, T = 150(2) K, Z = 2, 22735 reflections measured, 6528 independent reflections (R_{int} = 0.0206), final R values [$I > 2\sigma(I)$]: $R1$ = 0.0188, $wR2$ = 0.0433, final R values (all data): $R1$ = 0.0199, $wR2$ = 0.0438, 327 parameters.

Hydrogenation screening reactions (1 mmol scale)

In a typical reaction, 4 mL glass reaction vials and stirring bars were dried in the oven at 110 °C. The reaction vessels were charged with base (0.0125 mmol), closed with PTFE/rubber septa, placed in a multiple reactor inlet suitable for a pressure vessel, and brought under argon atmosphere by three vacuum-argon cycles. With a syringe the reaction vessels were charged with **C2** as a stock solution in dry isopropanol (1 mL, 0.5 M, 0.05 mol%), followed by dodecane (200 μL), and a solution of cinnamaldehyde in dry isopropanol (1 mL, 1 M). The reaction vessels were transferred to an argon-filled pressure vessel, which was flushed with three nitrogen and three hydrogen cycles, then pressurised to 30 bar hydrogen, heated to 80 °C and stirred for 16 h.

For the screening of the different precatalysts **C1**–**C7**, appropriate amounts of complex and base were added to the reaction vials in the glovebox, and dry isopropanol (2 mL), cinnamaldehyde (1 mmol) and dodecane (200 μL) were added by syringe.

Substrate scope

Aldehydes and ketones, except for HMF, were distilled in vacuo from PPh_3 prior to use. Reactions were performed in a 100 mL hastelloy autoclave vessel, to which substrate (usually 10 mmol), dry isopropanol (20 mL), **C2** (0.05 mol%), and KO*t*Bu (1.25 mol%), were added under a flow of argon. For the hydrogenation of HMF 0.5 mol% of **C2** and 5.0 mol% of KO*t*Bu were employed. The vessel was flushed three times with 30 bar of N_2, and then pressurised with 30 bar of H_2, and heated to 80 °C for 1 h. After cooling to room temperature and depressurising, the orange solutions were filtered over SiO_2, and concentrated in vacuo. Unless otherwise noted, the product was then obtained by vacuum distillation in a Kugelrohr apparatus. Analytical data of the isolated alcohols correspond to those found in literature.

Benzyl alcohol (Table 3, entry 1): Benzaldehyde (1.06 g, 10 mmol, 1.01 mL) was hydrogenated to give benzyl alcohol (1.08 g, 99% yield) as a colourless liquid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.19 (m, 5H), 4.58 (s, 2H), 1.80 ppm (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 140.9, 128.6, 127.7, 127.0, 54.3 ppm; HRMS (EI): *m/z* calcd for C_7H_8O: 108.0570 $[M]^+$; found: 108.0565.[21]

Furfuryl alcohol (Table 3, entry 2): Furfural (960 mg, 10 mmol, 0.83 mL) was hydrogenated to give furfuryl alcohol (950 mg, 99% yield) as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 1H), 6.27 (m, 1H), 6.22 (d, 1H, $J_{H\text{-}H}$ = 3.2 Hz), 4.53 (d, 2H, $J_{H\text{-}H}$ = 5.2 Hz), 1.90 ppm (t, 1H, $J_{H\text{-}H}$ = 5.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 154.0, 142.6, 110.4, 107.8, 57.5 ppm; HRMS (ESI+): *m/z* calcd for $C_5H_6O_2Na$: 121.0265 $[M+Na]^+$; found: 121.0255.[22]

2,5-Di(hydroxymethyl)furan (Table 3, entry 3): 5-(Hydroxymethyl)-furfural (1.26 g, 10 mmol) was hydrogenated to give 2,5-di(hydroxymethyl)furan (1.20 g, 93% yield), which was isolated as a white crystalline solid. Note that the catalyst loading was increased to 0.5% (31 mg), and the KO*t*Bu loading to 5% (70 mg). ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 6.21 (s, 2H), 5.19 (t, 2H, $J_{H\text{-}H}$ = 5.7 Hz), 4.38 ppm (d, 1H, $J_{H\text{-}H}$ = 5.7 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 155.1, 107.9, 56.2 ppm; HRMS (ESI+): *m/z* calcd for $C_6H_8O_3Na$: 151.03657 $[M+Na]^+$; found: 151.0361.[11b]

3-(2-Furyl)-2-propen-1-ol (Table 3, entry 4): 3-(2-Furyl)acrolein (1.22 g, 10 mmol) was hydrogenated to give 3-(2-furyl)-2-propen-1-ol (1.23 g, 99% yield), which was isolated as a colourless oil (mixture of isomers). Note that the allylic alcohol obtained turns bright orange over time when exposed to air. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 8.42 (d, 1H, $J_{H\text{-}H}$ = 2.1 Hz), 7.47 (t, 1H, $J_{H\text{-}H}$ = 1.5 Hz) 7.44 (dd, 1H, $J_{H\text{-}H}$ = 1.8 Hz, $J_{H\text{-}H}$ = 1.5 Hz), 7.30 (m, 2H), 4.03 ppm (t, 2H, $J_{H\text{-}H}$ = 4.8 Hz); ^{13}C NMR (75 MHz, CD_2Cl_2): δ = 153.0, 142.4, 128.1, 119.1, 111.7, 108.2, 63.1 ppm; HRMS (ESI+): *m/z* calcd for $C_7H_8O_2Na$: 147.04165 $[M+Na]^+$; found: 147.04175.[23]

1-Cyclohexene-1-methanol (Table 3, entry 5): 1-Cyclohexene-1-carboxaldehyde (1.10 g, 10 mmol, 1.2 mL) was hydrogenated to give 1-cyclohexenemethanol (1.10 g, 99% yield) as a colourless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 5.62 (m, 1H), 3.91 (d, 2H, $J_{H\text{-}H}$ = 4.8 Hz), 1.95 (m, 4H), 1.56 (m, 4H), 1.21 ppm (br m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.6, 123.1, 67.8, 25.6, 24.9, 22.6, 22.5 ppm; HRMS (ESI+): *m/z* calcd for $C_7H_{12}ONa$: 135.0780 $[M+Na]^+$; found: 135.0779.[24]

Cinnamyl alcohol (Table 3, entry 6): Cinnamalydehyde (3.30 g, 25 mmol, 3.3 mL) was hydrogenated in isopropanol (50 mL), with **C2** (7.8 mg) and KO*t*Bu (35 mg). The resulting yellow oil was purified by column chromatography (SiO_2; pentane:ethyl acetate 4:1), yielding cinnamyl alcohol (3.16 g, 94% yield) as white crystals.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.22 (m, 5H), 6.62 (d, 1H), 6.37 (m, 1H), 4.33 (m, 2H), 1.49 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.7, 131.1, 128.6, 128.6, 127.7, 126.5, 63.7 ppm; HRMS (EI): *m/z* calcd for $C_9H_{10}O$: 134.0726 $[M]^+$; found: 134.0727.[22]

Perrilyl alcohol (Table 3, entry 7): Perillaldehyde (1.50 g, 10 mmol, 1.58 mL) was hydrogenated to give perillyl alcohol (1.48 g, 96% yield) as a colourless liquid. The product was isolated by column chromatography (SiO_2; heptane:ethyl acetate 5:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.63 (br, 1H), 4.65 (m, 2H), 3.93 (s, 2H), 2.10–1.70 (m, 5H), 1.67 (s, 3H), 1.50 (brs, 1H), 1.43 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.8, 137.2, 122.4, 108.6, 67.2, 41.1, 30.4, 27.5, 26.1, 20.8 ppm; HRMS (ESI+): *m/z* calcd for $C_{10}H_{17}O$ $[M+H]^+$: 153.1274; found: 153.1276.[11b]

1-Phenylethanol (Table 3, entry 8): Acetophenone (1.20 g, 10 mmol, 1.17 mL) was hydrogenated to give benzyl alcohol (1.18 g, 97% yield) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (m, 5H), 4.78 (m, 1H), 1.88 (d, 1H, $J_{H\text{-}H}$ = 3.3 Hz), 1.38 (d, 3H, $J_{H\text{-}H}$ = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.8, 128.5, 127.5, 125.4, 70.4, 25.2 ppm; HRMS (EI): *m/z* calcd for $C_8H_{10}O$: 122.0726 $[M]^+$; found: 122.0727.[21]

β-Ionol (Table 3, entry 9): β-Ionone (1.92 g, 10 mmol, 2.0 mL) was hydrogenated to give β-ionol (1.76 g, 91% yield) as a colourless oil. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 6.09 (d, 1H, $J_{H\text{-}H}$ = 14.7 Hz), 5.53 (dd, 1H, $J_{H\text{-}H}$ = 15.9; $J_{H\text{-}H}$ = 6.8 Hz), 4.41 (quint, 1H, $J_{H\text{-}H}$ = 6.3 Hz), 2.02 (t, 1H, $J_{H\text{-}H}$ = 6.3 Hz), 1.71 (d, 3H, $J_{H\text{-}H}$ = 0.9 Hz), 1.63 (m, 2H), 1.53 (brs, 1H), 1.49 (m, sH), 1.36 (d, 3H, $J_{H\text{-}H}$ = 6.3 Hz), 1.03 (s, 6H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 137.8, 136.8, 128.9, 127.7, 69.7, 39.5, 34.1, 32.8, 28.8, 23.7, 21.5, 19.4 ppm; HRMS (EI): *m/z* calcd for $C_{13}H_{22}O$: 194.1665 $[M]^+$; found: 194.1666.[25]

Carveol (Table 3, entry 10): L-Carvone (1.56 g, 10 mmol) was hydrogenated to carveol, which was isolated as a mixture of two diastereomers. After 1 h reaction time, some hydrogenation of the C=C double bond had already occurred. Thus, the product was isolated by column chromatography (SiO_2; heptane:ethyl acetate 20:1), yielding the product (1.28 g, 84% yield) of a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, major diastereomer): δ = 5.52 (m, 1H), 4.66 (m, 2H), 4.12 (brs, 1H), 3.95, 2.30–1.38 ppm (m, 14H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.2, 149.0, 136.2, 134.3, 125.4, 123.9, 109.2, 109.0, 70.9, 68.6, 40.5, 38.0, 36.8, 35.2, 31.1, 31.0, 21.0, 20.9, 20.7, 19.0 ppm; HRMS (EI): *m/z* calcd for $C_{10}H_{16}O$: 152.1196 $[M]^+$; found: 152.1198.[26]

4,5,6,7-Tetrahydro-4-benzofuranol (Table 3, entry 11): 4,5,6,7-Tetrahydro-4-benzofuranone (1.36 g, 10 mmol, 1.2 mL) was hydrogenated to give 4,5,6,7-tetrahydro-4-benzofuranol (1.37 g, 99% yield) as a colourless liquid. ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.31 (m, 1H), 6.44 (d, 1H, $J_{H\text{-}H}$ = 2.0 Hz), 4.77 (t, 1H, $J_{H\text{-}H}$ = 4.4 Hz), 2.60 (m, 2H), 2.09–1.81 ppm (m, 5H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 152.6, 141.1, 120.0, 109.1, 64.1, 32.7, 23.0, 19.0 ppm; HRMS (ESI+): *m/z* calcd for $C_8H_{11}O_2$: 139.0754 $[M+H]^+$; found: 139.0755.[27]

4-(2-Furanyl)-3-buten-2-ol (Table 3, entry 12): 4-(2-Furanyl)-3-buten-2-one (1.36 g, 10 mmol) was hydrogenated to give 4-(2-furanyl)-3-buten-2-ol (1.28 g, 93%yield). Note that the allylic alcohol obtained turns bright orange over time when exposed to air. ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 7.38 (d, 1H, $J_{H\text{-}H}$ = 1.8), 6.41 (m, 2H), 6.26 (m, 2H), 4.49 (qd, 1H, $J_{H\text{-}H}$ = 6.3), 2.06 (brs, 1H), 1.38 (d, 3H, $J_{H\text{-}H}$ = 6.6). ^{13}C NMR (75 MHz, CD_2Cl2): δ = 152.4, 141.9, 132.3, 117.7, 111.3, 108.0, 68.4, 23.4. HRMS (ESI+): *m/z* calcd for $C_8H_{10}O_2Na$: 161.0573 $[M+Na]^+$; found: 161.0577.[28]

1-(Cyclohex-1-en-1-yl)ethan-1-ol (Table 3, entry 13): 1-(1-Cyclohexen-1-yl)-ethanone (1.24 g, 10 mmol) was hydrogenated to give 1-(cyclohex-1-en-1-yl)ethan-1-ol (1.25 g, 99%) as a colourless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.57 (brs, 1H), 4.06 (q, 1H, $J_{H\text{-}H}$ = 6.3 Hz), 2.15 (s, 1H), 1.93 (m, 4H), 1.53 (m, 4H), 1.16 ppm (d, 3H, $J_{H\text{-}H}$ = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.3, 121.3, 72.0, 24.9, 23.6, 22.6, 22.6, 21.5 ppm; HRMS (ESI+): *m/z* calcd for $C_8H_{14}ONa$: 149.0937 $[M+Na]^+$; found: 149.0936 .[29]

Methyl 4-(hydroxymethyl)benzoate (Table 3, entry 14): Methyl 4-formylbenzoate (0.33 g, 2 mmol) was dissolved in methanol (10 mL) to give methyl 4-(hydroxymethyl)benzoate (0.32 g, 97% yield) as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, 2H, $J_{H\text{-}H}$ = 8.1 Hz), 7.37 (d, 2H, $J_{H\text{-}H}$ = 8.1 Hz), 4.68 (d, 2H, $J_{H\text{-}H}$ = 4.2 Hz), 3.88 (s, 3H), 3.52 ppm (t, 1H, $J_{H\text{-}H}$ = 4.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.2, 146.3, 129.7, 128.9, 126.4, 64.3, 52.1 ppm; HRMS (EI): *m/z* calcd for $C_9H_{10}O$ $[M]^+$: 166.0625; found: 166.0630.[30]

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Conflict of interest

The authors declare no conflict of interest.

Keywords: alcohols · homogeneous catalysis · hydrogenation · ligand · ruthenium

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3.2 Inexpensive Ruthenium NNS-Complexes as Efficient Ester Hydrogenation Catalysts with High C=O vs. C=C Selectivities

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Inexpensive Ruthenium NNS-Complexes as Efficient Ester Hydrogenation Catalysts with High C=O vs. C=C Selectivities

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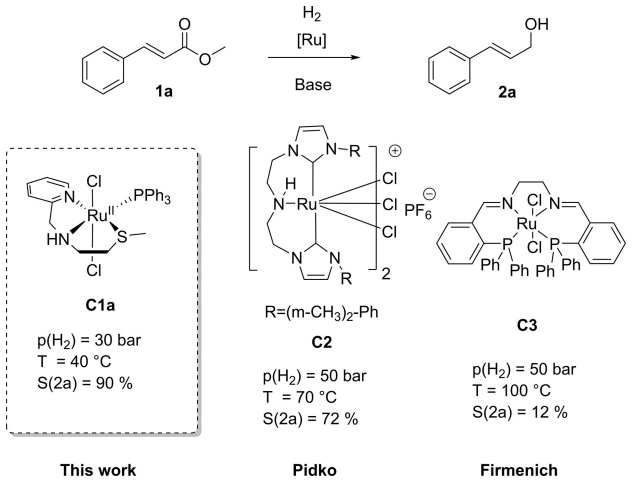
Abstract: $Ru(NNS)(PPh_3)Cl_2$ (NNS = 2-(methylthio)-N-(pyridin-2-yl-methyl)ethan-1-amine) was employed in the hydrogenation of α,β-unsaturated esters, reaching selectivities for the allylic alcohol up to 95% in the hydrogenation of iso-butylcinnamate. In addition, several ester substrates were hydrogenated with catalyst loadings as low as 0.05 mol%. Surprisingly, selectivity of the hydrogenation of the C=O *vs* the C=C bonds strongly depends on the solvent.

Keywords: ester hydrogenation; ruthenium; S-ligands; allylic compounds; chemoselectivity

1 Introduction

Interest in the homogeneous hydrogenation of carboxylic acid esters has grown vastly in the past decade.[1] Most of the reported catalysts are sophisticated complexes based on ruthenium,[1a,2] and more recently also based on iron,[3] cobalt[4] or manganese.[5] These catalysts now reach rates which vastly exceed those obtained by heterogeneous catalysts at much lower temperatures. Although manganese and iron are more earth-abundant transition metals than ruthenium, these catalysts have the drawback that, most of the existing catalysts rely on non-symmetrical phosphine ligands, which can make the ligand more expensive than the metal employed.[2a–c,3,5a,6] This cost aspect was recently addressed by the development of sulfur containing SNS-[7] and NNS-pincer[8] ligands. Although thus far these ligands have proven effective only with ruthenium and iridium, the resulting complexes are air stable and the ligands easily obtained by simple nucleophilic substitution or condensation reactions. However, despite the huge development of the field of homogenous hydrogenation, selective hydrogenation of the carbonyl group in α,β-unsaturated esters still represents a challenge.[9]

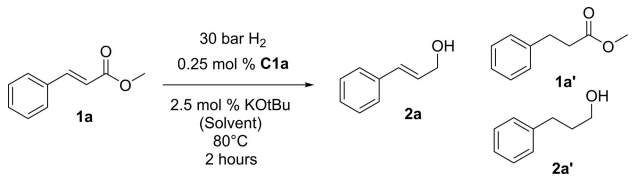
To the best of our knowledge, only two complexes have been reported which enable this transformation, however, with only moderate selectivity towards the unsaturated alcohol, utilizing methyl cinnamate (**1a**) as substrate (Scheme 1).[10]



Scheme 1. Selectivities in the hydrogenation of methyl cinnamate (**1a**) towards cinnamyl alcohol (**2a**) with different ruthenium complexes.

2 Results and Discussion

Recently, we reported on the development of a class of ruthenium NNS-pincer complexes which showed high selectivity in the hydrogenation of unsaturated aldehydes and ketones to the corresponding unsaturated alcohols.[11] These findings encouraged us to employ complex **C1a** (Scheme 1) in the hydrogenation of methyl cinnamate (**1a**). As it is well known that the solvent polarity has a major effect on olefin hydrogenation,[12] we decided to perform a careful solvent screening. In addition to the desired product **2a** we also monitored formation of the alkene hydrogenation product **1a**′ as well as the saturated alcohol **2a**′ using GC. The reaction conditions as well as the products monitored with GC are shown in Scheme 2. The results of this screening are shown in Figure 1.



Scheme 2. Reaction conditions in the solvent screening and the products monitored by GC. c(**1a**) = 0.5 mol L^{-1}.

Toluene, THF, MeOH and *n*-heptane were investigated first, as they represent typical π-polarizable, aprotic-polar protic, and apolar solvents. The reaction in THF resulted in only 11% conversion, mainly towards the undesired saturated ester **1a**′. In methanol, 95% conversion with high selectivity to **1a**′ (92% yield) was observed. This is in line with studies about the solvent effect in homogenous hydrogenation of olefins, in which methanol or THF/methanol mixtures are considered the most effective solvents. Fortunately, the application of toluene or n-heptane shifted the selectivity towards the desired allyl alcohol **2a**. In toluene, maximum conversion and yield were observed under the given reaction conditions (X = 99%, Y(**2a**) = 72%). The reproducibility in heptane was compromised by the low solubility of **C1a** in the solvent at room temperature. Since methanol had the effect of switching the selectivity from carbonyl to olefin hydrogenation, other alcohols were investigated as solvents (Figure 1). Inevitably, trans-esterification of the starting material **1a** with the alcoholic solvent occurred in all cases, and was most dominant in the presence of the linear alcohols EtOH and 1-hexanol. Transesterification of methyl cinnamate **1c** with the product alcohol **2c** was also observed. In the case of cyclohexanol and *t*-BuOH, only poor conversion of the starting material **1a** and no formation of the unsaturated alcohol **2a** was observed. It was suspected that a different catalytic species formed in methanol, which exhibits a higher activity towards olefin hydro-

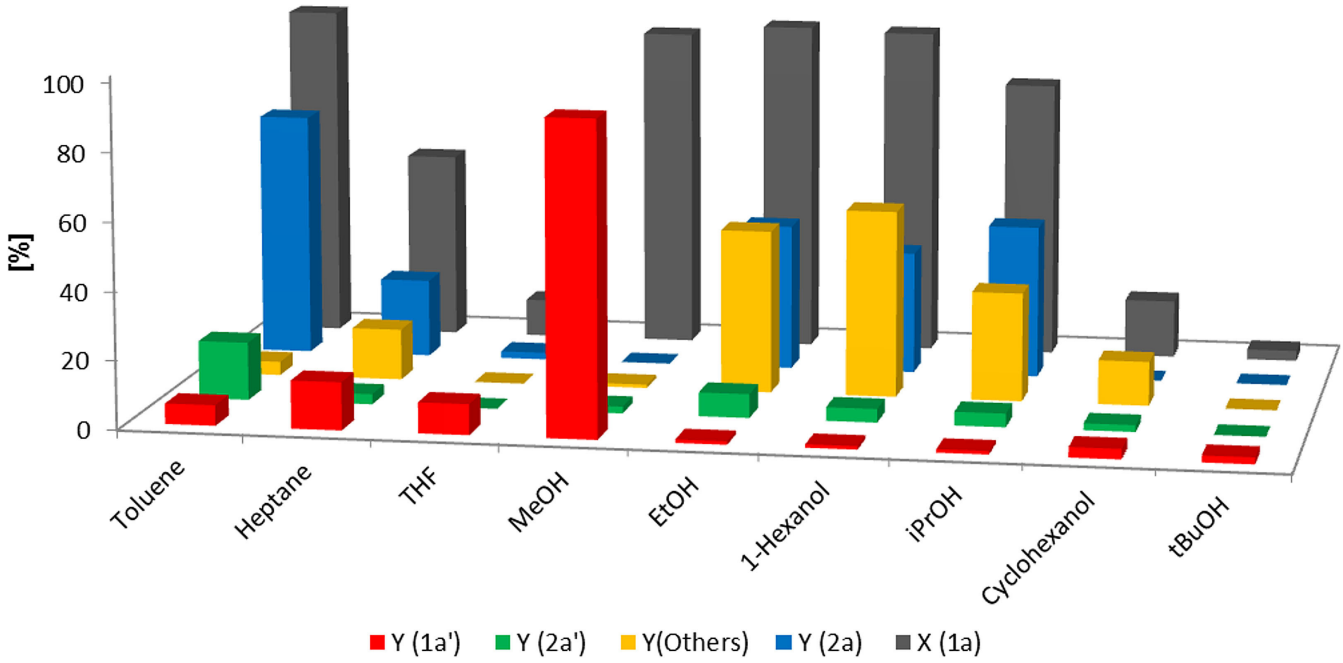


Figure 1. Effect of different solvents on product distribution in the hydrogenation of **1a**. Conversion (X) and Yields (Y) were determined by GC with *n*-dodecane as internal standard. Reaction conditions: 30 bar H_2, 0.25 mol% **C1a**, 2.5 mol% KO*t*Bu, T = 80 °C, *c*(**1a**) = 0.5 mol L^{-1}, t = 2 h.

genation. It is well known that ruthenium pincer complexes can dehydrogenate methanol to carbon monoxide under basic conditions.[13] The generated CO remains bound to the ruthenium centre and can lower the activity of the complex for ester hydrogenation, as Gusev *et al.* demonstrated by exchanging triphenyl phosphine ligands with CO in their SNS complexes.[7a] To test this hypothesis, **C1a** was dissolved in methanol together with 2.0 eq. KO*t*Bu, which led to the formation of various ruthenium hydride species. (See ESI). Unfortunately, the number of different species, and their labile nature made it impossible to further characterize them. Another reason for the altered reactivity in methanol could be the lability of the sulfur moiety which might be exchanged by small nucleophiles like methanolate. To get insight into this, complex **C1b** was synthesized, bearing a *tert*-butyl group on the sulfur atom. Single crystals of both **C1a** and **C1b** were grown, and their structures determined by single crystal X-ray diffraction analysis (Figure 2). In both complexes the coordination geometry at the Ru atom is distorted octahedral. In **C1b** the Ru–S distance is slightly elongated in comparison to **C1a** (**C1a**: 2.3333(9), 2.3369(10) **C1b**: 2.3648(5) Å.

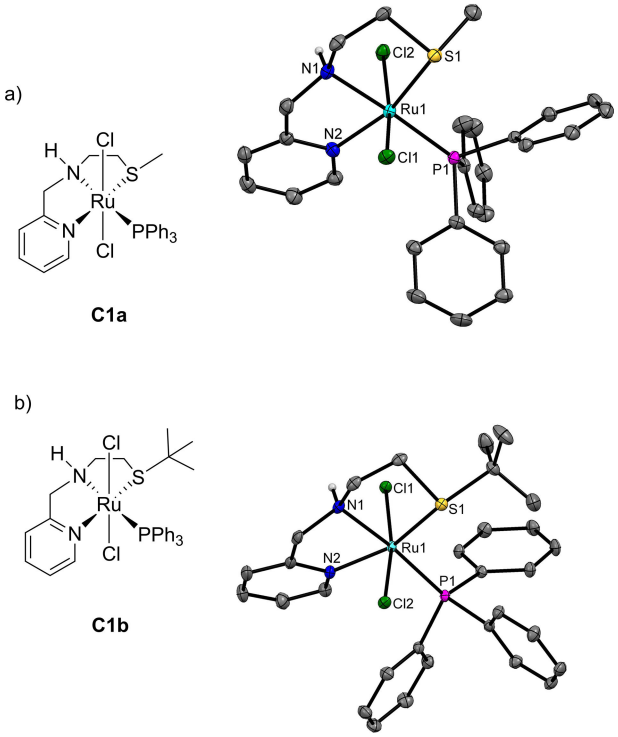
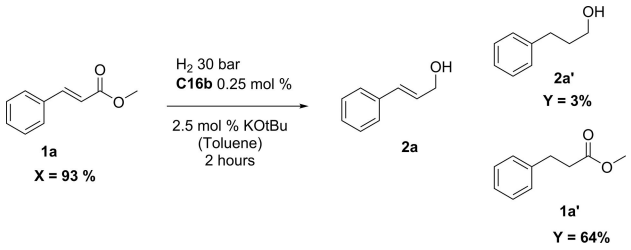


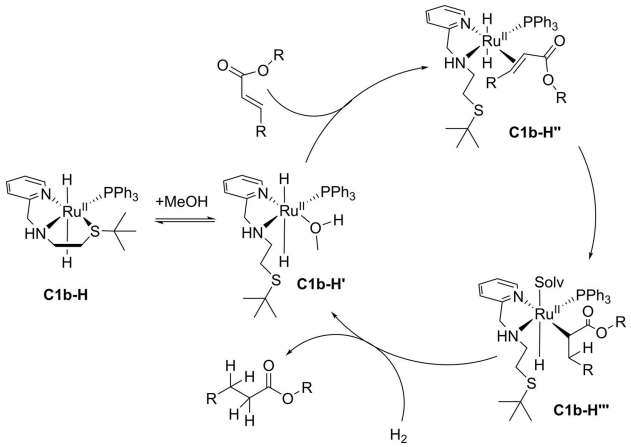
Figure 2. ORTEP diagrams of a) RuNNSMe (**C1a**), b) RuNNSt–Bu (**C1b**), with displacement ellipsoids drawn at 30% probability level, hydrogen atoms, except those attached to nitrogen, are omitted for clarity.[14]

We then applied the two complexes **C1a** and **C1b** to the hydrogenation of methyl cinnamate (**1a**) in toluene under otherwise similar conditions.Indeed, in contrast to **C1a**, which delivered the unsaturated alcohol **2a** as main product (X = 99%, Y(**2a**) = 72%, see Figure 1), **C1b** showed a high selectivity towards the saturated ester **1a′** (X = 93%, Y(**1a′**) = 64%, Scheme 3).



Scheme 3. Results of the hydrogenation of **1a** with **C1b**.

Presumably, complex **C1b** is activated through metal-ligand-cooperation, which is typical for pincer complexes bearing an amine functionality[1b,15] and/or a benzylic position which can be deprotonated.[2b] This could lead to the ruthenium diyhdride species **C1b-H** (Scheme 4). Methanol, either formed by transesterification of KO*t*Bu with the substrate, or generated during hydrogenation of methyl esters, might then replace the sulfur moiety yielding species **C1b-H′**. This hemilabile behaviour is also known in other pincer complexes.[16] Now, the methanol ligand can be replaced by the substrate coordinating to the metal centre in an η^2-binding mode (**C1b-H″**). This allows migratory insertion into the Ru–H bond (**C1b-H‴**). Reductive elimination of the product and subsequent oxidative addition of H_2 can form **C1b-H′**, closing the



Scheme 4. Proposed mechanism for the hydrogenation of methyl cinnamate (**1a**) with complex **C1b** and the role of methanol in the catalytic cycle.

catalytic cycle. This resembles the mechanism reported for olefin hydrogenation with Wilkinson's catalyst.[17]

Since it is clear that the presence of methanol leads to poor selectivity, we decided to perform further optimization experiments, with the homologous isobutyl cinnamate (**1b**) at 100 °C, 80 °C and 40 °C (See ESI). It should be noted that, especially at 100 °C formation of the saturated ester **1b′** was observed as a side product (up to 12% area percentage). At this temperature, a decrease in selectivity was observed. Still, this experiment underlines the remarkable activity of RuNNS^{Me} (**C1a**) in ester hydrogenation reactions, since 94% of the starting material had been converted in 10 minutes to a total yield of alcohols of 68%. Further, by lowering the temperature to 40 °C, formation of product **2a** was delayed, which might be due to a higher accumulation of transesterification products, which then lowers the TOF of the substrate **1b** via competition for the active catalytic species (Figure 3). After 205 minutes, the saturated alcohol **2a′** had formed in only 5% yield, whereas a yield of 95% of cinnamyl alcohol (**2a**) was measured via GC. Unfortunately, we were not able to further suppress the formation of the byproduct **2a′** by further lowering the temperature as the catalyst was not activated, and thus no conversion was observed at all. Lowering the catalyst concentration only increased reaction time but did not increase selectivity (see ESI for details). At 40 °C, it was also possible to convert substrate **1a** to the alcohol **2a** (Table 1).The ratio between the unsaturated alcohol and the saturated by-product was 90:10. The best selectivity so far was achieved with the aforementioned isobutyl cinnamate **1b**. The mixture of alcohols was isolated in 70% yield. Unfortunately, we were not able to separate the unsaturated product **2a** due to its similar properties with **2a′**. The hydrogenation of linear aliphatic α,β-unsaturated esters unfortunately led to the formation of the saturated alcohol, which might indicate an electronic effect on product selectivity. Varying the substituents of the aromatic ring however, had only a minor effect on the selectivity, as 4-methoxy-methyl-cinnamate (**1c**) showed similar reactivity to **1a**. Exchanging the methoxy group with trifluoromethyl led to a slightly higher formation of the saturated alcohol. When the double bond was located in a ring, as in substrate **1f**, it was possible to isolate 63% of the pure allylic alcohol, although conversion was only 77%. In practice, it is quite easy to separate the allyl alcohol in good yield by distillation from the unsaturated ester if conversion is kept below 100%. The unconverted unsaturated ester could be returned to the hydrogenation reaction in a continuous process.

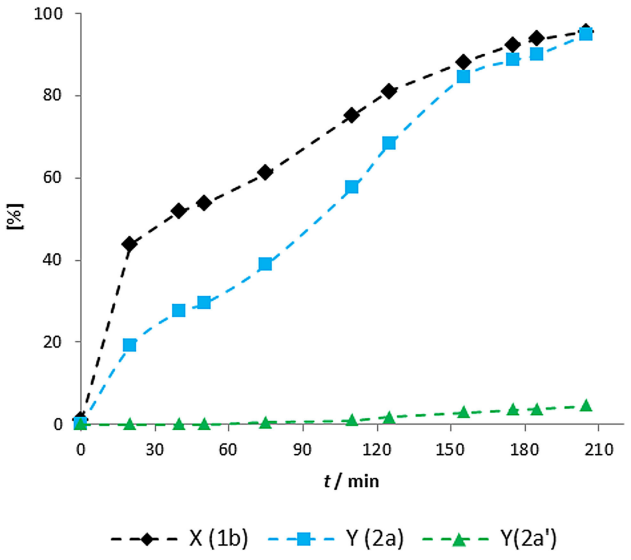
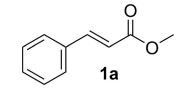
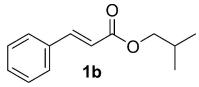
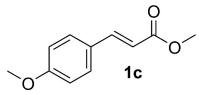
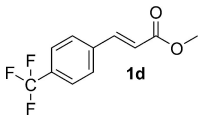
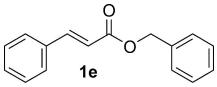
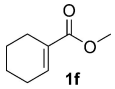


Figure 3. Reaction profile of the hydrogenation of isobutyl cinnamate (**1b**). Conditions: c(**1b**) = 0.5 mol l^{-1}; initial pressure 30 bar Hydrogen, 0.25 mol% **C1a**, 2.5 mol% KO*t*Bu in Toluene at 40 °C. Dashed lines serve only as guide for the eye and do not represent actual data points.

Table 1. Hydrogenation of various α,β-unsaturated esters.

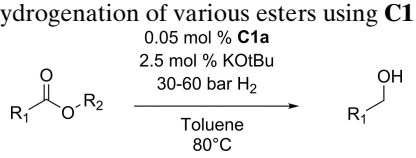
Entry	Substrate	X [%]	Y [%]	(UA/SA)[e]
1	 1a	99%[a]	99%[a] 83%[b]	90:10[a] 90:10[c]
2	 1b	99%[a]	96%[a] 69%[b]	95:5[a] 93:7[c]
3	 1c	n.d.	63%[b]	87:13[c]
4	 1d	n.d.	60%[b,f]	85:15[c]
5	 1e	92%[a]	61%[a]	95:5[a]
6	 1f	77%[d]	63%[b]	100[c]

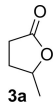
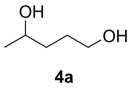
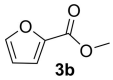
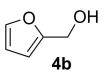
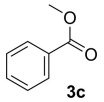
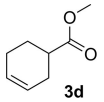
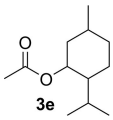
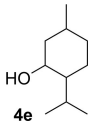
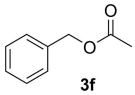
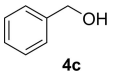
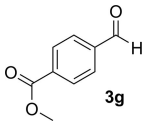
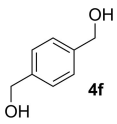
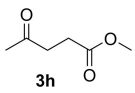
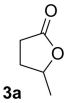
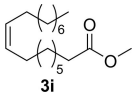
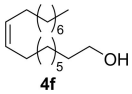
Reaction conditions: 40 °C, 30 bar H_2. 15 mmol substrate in 30 ml toluene, 0.25 mol % **C1a,** 2.5 mol % KOtBu, reaction time 4 h, despite entry 1 (16 h),
[a] Determined by GC,
[b] Isolated yield of the combined product alcohols,
[c] Determined with NMR spectroscopy,
[d] Based on recovered starting material,
[e] Ratio unsaturated (UA) saturated alcohol (SA),
[f] 10 mmol in 20 ml toluene.

Since one of the major research areas in our group is the formation of platform chemicals from renewable resources,[18] we were also in interested in the applicability of this catalyst to the hydrogenation of γ-valerolactone (**3a**) to 1,4-pentanediol (**4a**, Table 2, entry 1). 1,4-Pentanediol (**4a**) is a potential renewable building block in polymer chemistry, replacing petrochemical derived diols.[18b,19] Initially, we utilized a catalyst loading of 0.25 mol% and isolated **4a** in 92% yield after 2 hours reaction time. It was also possible to perform the reaction at a 500 mmol scale in only 2 mL of toluene at a catalyst loading as low as 0.05 mol%, yielding 91% of **4a**.

The acetate group is commonly used as protecting group in organic synthesis.[20] Entries 5 and 6 show that this hydrogenation is an efficient method for the deprotection of acetylated alcohols. This can be useful in cases where conventional hydrolysis is not feasible. We previously reported that the RuNNS catalyst selectively hydrogenates the aldehyde functionality in methyl 4-formylbenzoate in methanol.[11] Indeed, when this reaction was performed in toluene, both aldehyde and ester were reduced (entry 7). Interestingly, when the solvent was changed to methanol, the ketone functionality in methyl levulinate (**3h**, Entry 8) was hydrogenated selectively; subsequent ring-closing delivered γ-valerolactone (**3a**). Demonstrating once more the control of selectivity via simple exchange of the solvent. Although already known in literature for other catalyst systems, it is notworthy that it is also possible to hydrogenate unsaturated fatty acid esters such as methyl oleate (**3if**) (Table 2, entry 9) without affecting the olefinic bond.

Table 2. Hydrogenation of various esters using **C1a**.



Entry	Substrate	Product	Yield [%][a]	Time [h]	$p(H_2)$ [bar]
1	 **3a**	 **4a**	92[b] 91[c]	2	60
2	 **3b**	 **4b**	80	10	50
3	 **3c**	 **4c**	97	24	40
4	 **3d**	 **4d**	65	3	30
5	 **3e**	 **4e**	99	3	40
6	 **3f**	 **4c**	98	3	40
7	 **3g**	 **4f**	99	3	40
8	 **3h**	 **3a**	77[d]	2	50
9	 **3i**	 **4f**	95	3	30

Reaction conditions: 15 mmol ester substrate 30 ml of Toluene;
[a] Isolated yields.
[b] 0.25 mol% of **C1a**.
[c] 500 mmol substrate, 2 mL toluene.
[d] Reaction was run in methanol with 0.25 mol% **C1a**.

3 Conclusion

In summary, we have shown that RuNNS-complex **C1a** is a highly active ester hydrogenation catalyst. We observed high selectivities towards allylic alcohols in the hydrogenation of α,β-unsaturated esters, which demonstrates that the NNS ligand class is an efficient and in expensive alternative to the established phosphorous based ligands. Further, there is a remarkable influence of both alkyl rest as well as of the solvent on this selectivity It was possible to change the selectivity from ester hydrogenation towards olefin or ketone hydrogenation by simply modifying the ligand or by solvent exchange. This, thoughtfully applied, can be a useful tool in organic synthesis or fine chemical industry. However further experiments are needed and studies to increase the catalysts selectivity and to understand the effect of methanol on the system are continued in our laboratory.

Experimental Section

Preparation of NNS-Ru-Complexes

C1a was prepared according to previously published work of our group;[11] the preparation of **C1b** is given below.

2-(Methylthio)-N-(pyridin-2-ylmethyl)ethanamine (NNS^{Me})(Standard procedure SP1):

A dry 50 ml Schlenk round bottom flask equipped with a magnetic stirring bar was charged with 20 ml dichloromethane, followed by 1.07 g (10 mmol, 1.0 eq.) of pyridinecarboxaldehyde, 0.91 g (10 mmol, 1.0 eq.) of 2-(methylthio) ethanamine and 3.0 g (20 mmol, 2.0 eq) of anhydrous sodium sulfate. The resulting suspension was then stirred over night

at ambient temperature. Afterwards, the inorganic salts were filtered off and washed with dichloromethane (2×10 ml) and the solvent was removed in vacuo. The resulting red oil was then dissolved in 20 ml of methanol in a 50 ml round bottom flask and subsequently 0.8 g (20 mmol, 2.0 eq.) of sodium borohydride were added portion wise at 0 °C. Afterwards, the reaction mixture was allowed to warm up to room temperature and stirred for 2 hours. Then the reaction was quenched by adding 20 ml of dichloromethane and 20 ml of a saturated $NaHCO_3$ solution. When gas evolution ceased, the mixture was poured in a seperatory funnel, and the organic layer was separated. The aqueous layer was extracted with DCM (3×10 ml). The combined organic layers were dried over sodium sulfate. Evaporation of the solvent yielded a dark yellow oil from which 0.96 g (52% of theory) of the title compound was isolated via kugelrohr distillation (200 °C, 0.5 mbar) as a clear slightly yellowish oil.

^{1}H NMR (300 MHz,$CDCl_3$) δ 8.53 (d, J = 4.0 Hz, 1H, Pyr*H*), 7.62 (td, J = 7.6, 1.8 Hz, 1H, Pyr*H*), 7.30 (d, J = 7.8 Hz, 1H, Pyr*H*) 7.13 (dd, J = 7.3, 5.0 Hz, 1H, Pyr*H*), 3.91 (s, 2H, PyrCH_2N), 2.85 (d, J = 6.5 Hz, 2H, NCH_2CH_2S), 2.67 (t, J = 6.4 Hz, 2H, NCH_2CH_2S), 2.15 (s, br, 1H, N*H*), 2.06 (s, 3H, SCH3); ^{13}C NMR (75 MHz, CDCl3) δ 159.70, 149.35, 136.49, 122.21, 121.98, 54.93, 47.61, 34.44, 15.31; HRMS (EI) calculated for $C_9H_{14}N_2S$: 182.08722 (M+); found 182.08617 (M+).

2-(*tert*-Butylthio)-N-(pyridin-2-ylmethyl)ethan-1-amine (NNS^{tBu}):

This ligand was prepared like NNS^{Me} reacting 0.51 g (5 mmol, 1.0 eq.) of pyridine carboxaldehyde (17), 0.72 g (5 mmol, 1.0 eq.) of 2-(tert-butylthio)ethanamine and 1.5 g (10 mmol, 2.0 eq) of anhydrous sodium sulfate. Kugelrohr distillation was performed at 230 °C and 0.5 mbar, yielding 0.88 g (80%) of **20b**.

^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.54 (d, J = 4.9 Hz, 1H, Pyr*H*), 7.64 (td, J = 7.6, 1.8 Hz, 1H, Pyr*H*), 7.34 (d, J = 7.7 Hz, 1H, Pyr*H*), 7.17 (dd, J = 7.1, 5.2 Hz, 1H, Pyr*H*), 3.90 (s, 2H, PyrCH_2N), 2.85 (t, J = 6.5 Hz, 2H, NCH_2CH_2S), 2.73 (t, J = 6.9 Hz, 2H, NCH_2CH_2S), 2.02 (s, br, 1H, N*H*), 1.31 (s, 9H, C(CH_3)$_3$); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 163.18, 152.07, 139.13, 124.85, 124.65, 57.83, 52.22, 44.75, 33.80, 31.84; HRMS (ESI+) calculated for $C_{12}H_{20}N_2S$: 225.1420 (M+H) found: 225.14239.

[Ru(NNS^{Me})(PPh_3)Cl_2] (**C1 a**)

In a dry 25 ml Schlenk tube equipped with a magnetic stir bar, 962 mg (1 mmol, 1.0 eq.) of tris(triphenylphosphine) ruthenium(II)dichloride were dissolved in 2 ml of anhydrous diglyme. To this solution 219 mg (1.2 mmol, 1.2 eq) of 2-(methylthio)-N-(pyridin-2-ylmethyl)ethan-1-amine were added. The resulting reaction mixture was refluxed for 2 hours. Afterwards, the mixture was stored overnight at −20 °C. The next day an orange-yellow precipitate could be filtered off. This was washed with diethylether (5×2 ml). The remaining solid was then dissolved in dichloromethane and subsequently transferred to another Schlenk tube where the solvent was evaporated, yielding 515 mg (84% of theory) of an orange crystalline solid. The obtained complex consisted of two coordination isomers.

Major isomer:

^{1}H-NMR (300 MHz, CD_2Cl_2) δ 8.47 (d, *J* = 5.0 Hz, 1H, Pyr*H*), 7,72 (m, 1H, Pyr*H*), 7.64–7.49 (m, 6 H, 6×Ar*H*), 7.40–7.24 (m, 10 H, Ar*H*), 6.87 (t, *J* = 6.7 Hz, 1H, Pyr*H*), 5.47 (s, br, 1H, N*H*), 5.24 (t, $J_{H\text{-}H}$ = 6.3 Hz, 1H, PyrCH_2N), 4.38 (m, 1H, Pyr-CH2-N), 3.43 (m, 2H), 3.29 (d, *J*(H–H) = 11.0, 1H), 2.57 (m, 1H), 1.50 (s, 3H, SCH_3); ^{31}P-NMR (122 MHz, CD_2Cl_2) δ 51.75 (s, 1 P, *P*Ph_3); Minor isomer: ^{1}H-NMR (300 MHz, CD_2Cl_2) δ 8.69 (d, 3 J = 5.0 Hz, 1H, Pyr*H*), 7,72 (m, 1H, Pyr*H*), 7.64–7.49 (m, 6H, 6×Ar*H*), 7.40–7.24 (m, 10H, 10×Ar*H*), 6.87 (t, J = 6.7 Hz, 1H, Pyr*H*), 5.47 (s, br, 1H, N*H*), 5.24 (t, J(H–H) = 6.3 Hz, 1H, PyrCH_2N), 4.38 (m, 1H, PyrCH_2N), 3.43 (m, 2H), 3.29 (d, *J*(H–H) = 11.0, 1H), 2.57 (m, 1H), 1.53 (s, 3H, SCH_3); ^{31}P-NMR (122 MHz, CD_2Cl_2) δ 50.70 (s, 1 P, *P*Ph_3); HRMS (ESI+) calculated for $C_{27}H_{29}Cl_2N_2PRuS$: 616.0210 (M+) found: 616.0202 (M+).

[Ru(NNS^{t-Bu})(PPh_3)Cl_2] (**C 1b**)

In a dry 25 ml Schlenk tube equipped with a magnetic stir bar, 962 mg (1 mmol, 1.0 eq.) of tris(triphenylphosphine) ruthenium(II)dichloride were dissolved in 2 ml of anhydrous diglyme. To this solution 270 mg (1.2 mmol, 1.2 eq) of 2-(*tert*-butylthio)-*N*-(pyridin-2-ylmethyl)ethanamine was added. The resulting reaction mixture was refluxed for 4 hours. Afterwards, the mixture was stored overnight at −20 °C. The next day a yellow precipitate could be filtered off. This was washed with diethylether (5×2 ml). The remaining solid was then dissolved in toluene and subsequently transferred to another Schlenk tube where the solvent was evaporated, yielding 200 mg (30% of theory) of a yellow crystalline solid.

Major isomer:

^{1}H-NMR (300 MHz, CD_2Cl_2) δ 8.11 (d, J = 5.8 Hz, 1H, Pyr*H*), 7.70–7.49 (m, 5H, 5×Ar*H*), 7.40–7.24 (m, 11H, Ar*H*), 6.57 (t, *J* = 6.7 Hz, 1H, Pyr*H*), 5.75 (s, br, 1H, N*H*), 5.26 (t, J_{H-H} = 6.3 Hz, 1H, PyrCH_2N), 4.40 (m, 1H, Pyr-CH_2-N), 3.53 (m, 2H), 3.21 (d, *J*(H–H) = 11.0, 1H), 3.08 (m, 1H), 1.0 (s, 9H, SC(CH_3)$_3$). ^{31}P NMR (122 MHz, CD_2Cl_2) δ 49.3 (s, 1 P, *P*Ph_3); Minor isomer: ^{31}P NMR (122 MHz, CD_2Cl_2) δ 38.6 (s, 1 P, *P*Ph_3);

HRMS (ESI+) calculated for $C_{30}H_{35}ClN_2PRuS$: 623.09906 (M–Cl), $C_{30}H_{35}Cl_2N_2PRuS$: 658.06791 (M+), $C_{30}H_{35}ClN_2PRuS$: 664.12561 (M–Cl+MeCN); found: 623.09034 (M–Cl), 658.07430 (M+), 664.12426 (M–Cl+MeCN).

Hydrogenation Reactions

Screening reactions:

In a typical screening reaction, oven dried 4 ml glass vials equipped with magnetic stirring bars were used. To each vial 1.5 mg (2 µmol; 0.25 mol%) of **C1a** or **C1b** and 1 mmol of methyl cinnamate **1a** were added, and the exact weight of the substrate noted. The vials were placed in an aluminum inlet suitable for high pressure reactions and closed with PTFE/rubber septa pierced with a needle. Afterwards, 2 ml of the desired solvent, 50 µl (2.5 mol%) of a freshly prepared solution of potassium *tert*-butoxide in THF (c = 1.0 mol/l) and 50 µl of *n*-dodecane were added via syringe. Then the

vessels were put in an argon flushed 300 ml stainless steel autoclave which was pressured two times with 10 bars of N_2, followed by two times 10 bars with H_2 and finally pressurized with 30 bars of H_2. The autoclave was then put in an aluminum block which was preheated to 80 °C. After 2 hours the reactor was carefully depressurized and 100 µl samples of each vial where taken. Subsequently the samples were filtered through celite, diluted with 1 ml of acetone, and analyzed by gas chromatography.

Reaction monitoring

A 100 ml hastelloy autoclave with mechanical stirrer and a high pressure sample outlet was charged with [Ru(N-NS^{Me})(PPh_3)Cl_2] **C1a** (23 mg, 0.038 mmol, 0.25 mol%), ester substrate **1b** (15 mmol), 30 ml of toluene, KO*t*Bu (41 mg, 0.38 mmol, 2.5 mol%), and 1000 µl of anhydrous *n*-dodecane under an argon atmosphere. The autoclave vessel was flushed with 20 bar of N_2 three times, with 10 bar of H_2 two times, then pressurized to 30 bar H_2 and heated to the desired temperature and stirred. During the reaction, samples in the size of approximately 100 µl were taken, filtered over celite and diluted with 1 ml of acetone. Results for 40 °C are shown in Figure 3. For exoperiments at 80 °C and 100 °C please refer to the supporting information.

Hydrogenations:

A 100 ml hastelloy autoclave with mechanical stirrer was charged with the desired amount of Ru(NNS^{Me})(PPh_3)Cl_2, KO*t*Bu (41 mg, 0.38 mmol, 2.5 mol%), ester substrate (15 mmol) and 30 ml of toluene under an argon atmosphere. If lower amounts of substrates were used solvent and catalyst/base were adjusted accordingly. The autoclave vessel was flushed with 20 bar of N_2 three times, with 10 bar of H_2 two times, then filled with H_2 to a desired pressure, heated to the desired temperature and stirred for the indicated time. During the reaction time the vessel was repressurized to keep the pressure over 20 bars. The pressure vessel was cooled down to room temperature and then carefully depressurized. Then 0.1 ml of the reaction mixture was filtered through celite and rinsed with acetone (1 ml), and analyzed by gas chromatography and/or the alcohol fraction isolated.

Conflict of Interest

The authors declare no conflict of interest.

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3.3 Use of the Trost Ligand in Ruthenium-Catalyzed Asymmetric Hydrogenation of Ketones

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Use of the Trost Ligand in the Ruthenium-Catalyzed Asymmetric Hydrogenation of Ketones

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The Trost ligand, (1*S*,2*S*)-1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl) (**L**), is reported for the first time as a ligand for the asymmetric hydrogenation (AH) of ketones. Ligand (*S*,*S*)-**L** was screened in the presence of several metal salts and was found to form active catalysts if combined with ruthenium sources in the presence of hydrogen and a base. Reaction optimization was performed by screening different Ru sources, solvents, and bases. Under the optimized conditions, the complex formed by the combination of (*S*,*S*)-**L** with $RuCl_3(H_2O)_x$ in the presence of Na_2CO_3 was able to promote the AH of several ketones at room temperature in good yields with up to 96% *ee*. The reaction kinetics measured under the optimized conditions revealed the presence of a long induction period, during which the initially formed Ru species was transformed into the catalytically active complex by reaction with hydrogen. Remarkably, a ketone that is a precursor of the antiemetic drug aprepitant was hydrogenated in excellent yield with a good *ee* value.

In spite of the enormous advancements in the development of asymmetric catalysis over the past half a century, its industrial application is still in its early stages.[1] Indeed, at present the classical resolution of diastereoisomeric salts is still the method that is most widely exploited to obtain enantiomerically pure compounds, despite its intrinsically poor atom economy. Among enantioselective catalytic methodologies, asymmetric hydrogenation (AH) is probably the most appealing one from an industrial point of view owing to its practicality and the use of cheap and clean reducing agents such as H_2.[2] Despite this, the number of industrially implemented AH processes is still fairly limited.[1,2] One of the main reasons for this paradox is the high cost of the catalysts, which often contain expensive metals and/or ligands. For this reason, replacement of the precious metals traditionally used in AH (e.g., Rh, Ir, Ru) with cheap base metals (e.g., Fe, Co, Ni) has recently become an important research goal.[3,4] However, much less attention has been paid to the cost of the chiral ligand, which is often comparable or even higher than that of the metal. For a successful industrial application of AH, the availability on short notice of gram and kilogram amounts of chiral ligands is often a key issue.[5] Actually, noble metals can still be an economically viable option, provided that the chiral ligand is sufficiently cheap, readily available, and robust. The "Trost ligand", (1*S*,2*S*)-1,2-diaminocyclohexane-*N*,*N*′-bis(2′-diphenylphosphinobenzoyl) (**L**) (Figure 1), meets these requirements to a large extent, as it is commercially available at a reasonable price or, alternatively, can by synthesized in one step from *trans*-1,2-diaminocyclohexane, readily available in both enantiomeric forms. Ligand **L** was developed in 1992 by Trost and Van Vranken for Pd-catalyzed asymmetric allylic alkylations (AAAs),[6] and it was soon recognized as one of the most effective ligands for this kind of transformation.[7] Quite surprisingly, despite this success, the use of the Trost ligand has remained mostly restricted to Pd-catalyzed AAAs,[8] and—to the best of our knowledge—no successful application in AH has so far been reported.[9] The AH of ketones is an important transformation providing access to chiral alcohols, which are valuable building blocks for the synthesis of fine chemicals and active pharmaceutical ingredients. Over the past decade, the AH of ketones has been predominantly investigated with chiral ruthenium complexes containing various ligand combinations of mono- or bidentate phos-

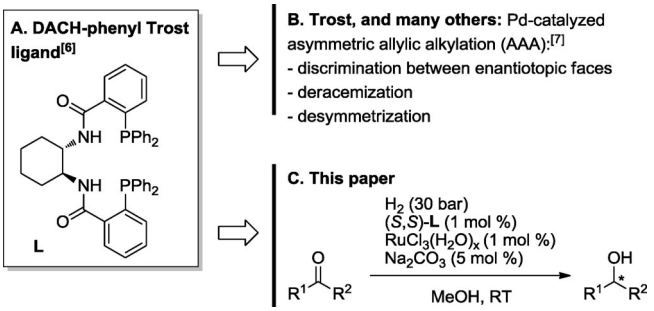

Figure 1. A) *trans*-1,2-Diaminocyclohexane-*N*,*N*′-bis(2-diphenylphosphinobenzoyl), better known as the Trost ligand,[6] B) its best-known applications,[7] and C) its new application described in this paper.

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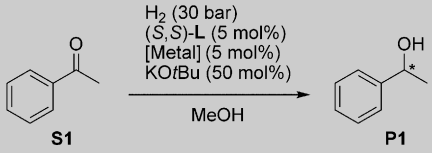
phines and diamines, analogous to the original Noyori's 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP)–Ru–diamine complexes.[10–12] Ruthenium catalysts based on PNNP ligands (in which N = imine or amine) have also been reported in the AH and transfer hydrogenation of ketones.[13]

We thus set out to investigate the potential of Trost's diphosphine ligand (**L**) for the AH of ketones. Using acetophenone (**S1**) as a model substrate and KO*t*Bu as the base, we screened different metal precursors in the presence of the Trost ligand under 30 bar (1 bar = 0.1 MPa) of H_2 at 80 °C (Table 1, entries 1–12). No or trace conversions were obtained upon using Ni, Co, and Fe salts (Table 1, entries 2–9), with the exception of $NiCl_2$ (Table 1, entry 1; conversion = 98%), which, however, led to racemic product **P1**. In sharp contrast, several Ru sources showed good activity and led to promising enantioselectivity (Table 1, entries 10–18). Lowering the reaction temperature from 80 to 60 °C led to a significant improvement in the enantioselectivity without erosion of the yield (Table 1, entry 14 vs. 11), and for this reason, additional Ru sources were screened at 60 °C (Table 1, entries 15–18). As a general trend, the Ru complexes containing PPh_3 gave the product with absolute configuration opposite to that obtained with the others (Table 1, entries 10, 12, 13, 16, 18 vs. 11, 14, 15, 17). In absolute terms, the best *ee* values were obtained with anhydrous or hydrated $RuCl_3$ (Table 1, entries 11, 14, and 15).[14] As $RuCl_3(H_2O)_x$ is remarkably cheaper than anhydrous $RuCl_3$, the hydrated salt was selected as the Ru source for further reaction optimization.

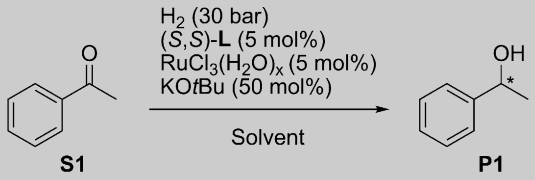
Table 1. Screening of different metal sources in the AH of acetophenone (**S1**) in the presence of the Trost ligand, (*S,S*)-**L**.[a]



Entry	Metal source	*T* [°C]	Conv. [%][b]	*ee* [%],[b] abs. conf.[c]
1	$NiCl_2$	80	98	0
2	$Ni(NO_3)_2{\cdot}6H_2O$	80	0	–
3	$Ni(cod)_2$	80	0	–
4	$Ni(CO)_2(PPh_3)_2$	80	0	–
5	$CoCl_2$	80	1	29, *R*
6	$FeBr_2$	80	0	–
7	$FeBr_3$	80	0	–
8	$Fe(CO)_5$	80	0	–
9	$FeCl_2{\cdot}4H_2O$	80	1	23, *S*
10	$(PPh_3)_3RuCl_2$	80	96	44, *R*
11	$RuCl_3$	80	98	32, *S*
12	$(PPh_3)_3Ru(CO)H_2$	80	69	29, *R*
13	$(PPh_3)_3RuCl_2$	60	91	43, *R*
14	$RuCl_3$	60	97	56, *S*
15	$RuCl_3(H_2O)_x$	60	99	46, *S*
16	$(PPh_3)_4RuCl_2$	60	92	40, *R*
17	$[(C_6H_6)RuCl_2]_2$	60	98	23, *S*
18	$(PPh_3)_3Ru(CO)(Cl)H$	60	4	29, *R*

[a] Reaction conditions: **S1**/metal/(*S,S*)-**L**/KO*t*Bu = 100:5:5:50, P_{H_2} = 30 bar, solvent: MeOH, c_0(**S1**) = 0.2 M, reaction time: 22 h; cod = 1,5-cyclooctadiene. [b] Determined by GC analysis (see the Supporting Information). [c] Absolute configuration assigned by comparison of the optical rotation sign with literature data.[3b]

Table 2. Solvent and temperature screening in the AH of acetophenone (**S1**) with $RuCl_3(H_2O)_x$/(*S,S*)-**L**.[a]



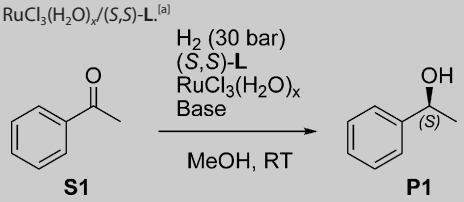
Entry	Solvent	*T* [°C]	Conv. [%][b]	*ee* [%],[b] abs. conf.[c]
1	MeOH	60	99	46, *S*
2	MeOH	35	98	67, *S*
3	MeOH	22	97	69, *S*
4	MeOH	0	63	65, *S*
5	*i*PrOH	60	> 99	0
6	DMF	60	> 99	35, *S*
7	benzene	60	74	17, *R*
8	MeCN	60	72	13, *S*
9	toluene	60	> 99	22, *S*
10	THF	60	> 99	28, *S*
11	EtOH	60	98	5, *S*
12	MeOH/H_2O (1:1)	60	> 99	0
13	MeOH/H_2O (4:1)	60	81	0
14	*i*PrOH/H_2O (1:1)	60	13	6, *R*
15	*i*PrOH/H_2O (4:1)	60	> 99	0

[a] Reaction conditions: **S1**/$RuCl_3(H_2O)_x$/(*S,S*)-**L**/KO*t*Bu = 100:5:5:50, P_{H_2} = 30 bar, c_0(**S1**) = 0.2 M, reaction time: 22 h. [b] Determined by GC analysis (see the Supporting Information). [c] Absolute configuration assigned by comparison of the optical rotation sign with literature data.[3b]

A solvent screening was then performed, the results of which are shown in Table 2. Although full conversions were achieved with several different solvents (Table 2, entries 1, 5, 6, and 9–11), the best *ee* value was obtained in MeOH (Table 2, entry 1). Decreasing the temperature led to a higher *ee* value without a substantial effect on the yield (Table 2, entries 2 and 3), although no improvements could be obtained below room temperature (Table 2, entry 4). Notably, the presence of water was found to affect the enantioselectivity dramatically: upon using MeOH/H_2O mixtures, the *ee* dropped to zero (Table 2, entries 12 and 13). Furthermore, running the reaction in *i*PrOH yielded racemic **P1** owing to background base-promoted transfer hydrogenation (Table 2, entries 5, 14, and 15). On the basis of these results, we decided to perform further optimization in MeOH at room temperature (Table 3).

The role of base was investigated, and it was found that without KO*t*Bu the reaction did not proceed (Table 3, entry 1).[10a,15] By varying the base/catalyst ratio (Table 3, entries 2–4), 5:1 turned out to be optimal (Table 3, entry 3). From a base screening (Table 3, entries 5–15), it emerged that the base employed had a strong influence on the enantioselectivity. Remarkably, simple inorganic bases such as alkaline hydrox-

Table 3. Investigation of the role of the base in the AH of acetophenone (**S1**) with $RuCl_3(H_2O)_x$/(*S*,*S*)-**L**.[a]

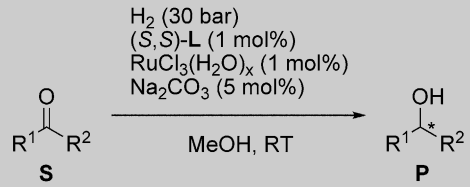


Entry	Base	Base/ catalyst	Catalyst loading [mol%]	Conv. [%][b]	*ee* [%][b,c]
1	none	–	5	0	0
2	KO*t*Bu	10	5	93	70
3	KO*t*Bu	5	5	97	76
4	KO*t*Bu	1	5	0	0
5	KOH	5	5	>99	71
6	K_2CO_3	5	5	98	53
7	Cs_2CO_3	5	5	98	69
8	LiO*t*Bu	5	5	98	63
9	LiOH·H_2O	5	5	>99	64
10	NaOMe	5	5	99	70
11	NaO*i*Pr	5	5	31	86
12	NaO*t*Bu	5	5	98	66
13	NaOH	5	5	99	89
14	Na_3PO_4	5	5	99	87
15	Na_2CO_3	5	5	99	89
16	Na_2CO_3	5	2.5	>99	93
17	Na_2CO_3	5	1	>99 (96)[g]	96
18	Na_2CO_3	5	0.5	97	94
19[d]	Na_2CO_3	5	0.5	>99	95
20	Na_2CO_3	5	0.1	0	–
21[d]	Na_2CO_3	5	0.1	0	–
22[e]	Na_2CO_3	5	1	42	94
23[f]	Na_2CO_3	5	1	63	95

[a] Reaction conditions: P_{H_2} = 30 bar, c_0(**S1**) = 0.2 M, reaction time: 22 h. [b] Determined by GC analysis (see the Supporting Information). [c] Absolute configuration assigned by comparison of the optical rotation sign with literature data.[3b] [d] P_{H_2} = 80 bar. [e] Reaction performed in the presence of 3 Å molecular sieves. [f] Reaction performed in the presence of Hg^0 (10 mmol/100 equiv.). [g] Yield of isolated product (reaction performed on a 6 mmol scale).

ides and carbonates were found to promote the reaction efficiently (Table 3, entries 5–7, 9, and 13–15). Among them, those bearing sodium as the counterion led to *ee* values that were higher than those obtained in the presence of other counterions. Decreasing the catalyst loading to 1 mol% in the presence of Na_2CO_3 led to a remarkable increase in the enantioselectivity (up to 96% *ee*) without affecting the conversion (Table 3, entries 16 and 17 vs. entry 15). No further improvement in terms of the *ee* could be obtained below a catalyst loading of 1 mol% (Table 3, entries 18–21). However, full conversion was still obtained at a 0.5 mol% catalyst loading, which corresponded to a turnover number (TON) of 200. A similar effect was also observed upon using NaOH and Na_3PO_4 as the bases (see the Supporting Information). Increasing the hydrogen pressure had a modest or no influence on the enantioselectivity (Table 3, entry 19), whereas decreasing it to 10 bar led to a drop in the conversion and a decrease in the *ee* value (see the Supporting Information). Given that the presence of H_2O was found to be harmful to the enantioselectivity (see Table 2), a reaction was run in the presence of 3 Å molecular sieves (to scavenge any trace amount of H_2O), but the only observed effect was a drop in the conversion (Table 3, entry 22). Finally, running the hydrogenation in the presence of an excess amount of Hg^0 led only to a slight decrease in the con-

Table 4. Substrate screening in the AH of ketones catalyzed by $RuCl_3(H_2O)_x$/(*S*,*S*)-**L**.[a]



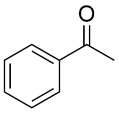
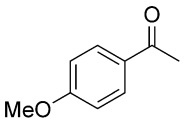
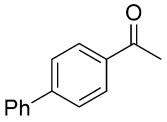
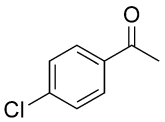
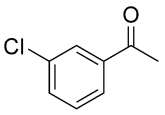
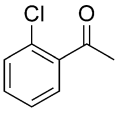
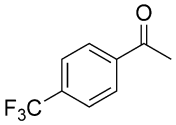
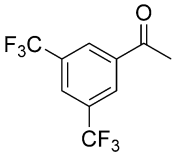
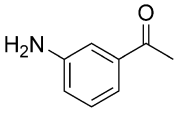
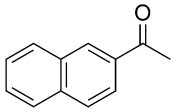
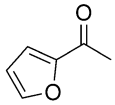
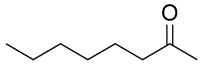
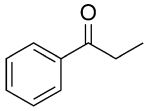
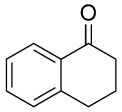
Entry	Substrate		Conv. [%][b]	*ee* [%],[c] abs. conf.[d]
1		**S1**	>99 (96)[e]	96, *S*
2		**S2**	>99 (97)[e]	95, *S*
3		**S3**	98	95, *S*
4		**S4**	>99	93, *S*
5		**S5**	>99	95, *S*
6		**S6**	32	28, *S*
7		**S7**	>99	92, *S*
8		**S8**	>99 (95)[e]	84, *S*
9		**S9**	31	77, *S*

Table 4. (Continued)

Entry	Substrate		Conv. [%][b]	*ee* [%],[c] abs. conf.[d]
10		**S10**	>99	94, *S*
11		**S11**	>99	92, *S*
12		**S12**	40	11, *R*
13		**S13**	64	96, *S*
14		**S14**	>99	0

[a] Reaction conditions: P_{H_2} = 30 bar, c_0(substrate) = 0.2 M, reaction time: 22 h. [b] Determined by GC analysis in the presence of an internal standard (hexadecane). GC traces showed only the presence of the reaction products (secondary alcohols) and, if the reaction was not complete, the starting ketones (see the Supporting Information). Given the high chemoselectivity, percent conversions and percent yields are practically coincident. [c] Determined by GC or HPLC on a chiral stationary phase (see the Supporting Information). [d] Absolute configuration assigned by comparison of the optical rotation sign with literature data (see the Supporting Information). [e] Yield of isolated product (reaction performed on a 6 mmol scale).

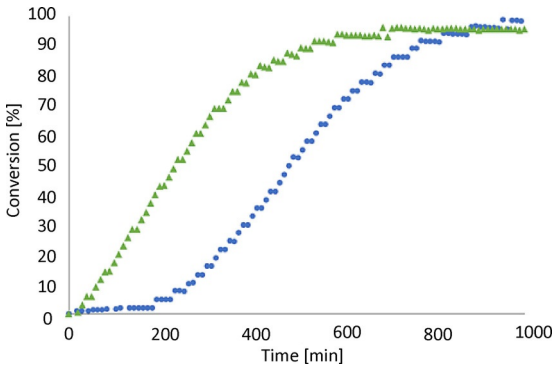


Figure 2. Kinetics of the AH of acetophenone catalyzed by [Ru]/(*S*,*S*)-**L** under the optimized reaction conditions (●) and after overnight pretreatment (see the Supporting Information) of $RuCl_3(H_2O)_x$ with refluxing *i*PrOH (▲). Hydrogenation conditions: **S1**/[Ru]/(*S*,*S*)-**L**/Na_2CO_3 = 100:1:1:5; solvent: MeOH; c_0(**S1**) = 0.95 M; P_{H_2} = 30 bar; T = 19 °C; $c_{catalyst}$ = 9.5 mM. Measured kinetic parameters (for trace ▲): $k = 3.03 \times 10^{-4}$ mol min^{-1} L^{-1}; $t_{1/2}$ = 229 min.

version, which allowed us to conclude that the active catalyst was probably homogeneous.[3c,16]

Under the optimized reaction conditions, the substrate scope of the $RuCl_3(H_2O)_x$/(*S*,*S*)-**L** catalytic system was investigated (Table 4). In general, 3- and 4-substituted acetophenones were hydrogenated in good yields with high *ee* values (92–95%) irrespective of the electron-withdrawing or electron-donating properties of the substituent (Table 4, entries 2–5 and 7). The only exception was 1-(3-aminophenyl)ethanone (**S9**) (Table 4, entry 9), which—possibly as a result of catalyst poisoning by coordination of the amino group to ruthenium—gave a low conversion and a diminished *ee* value (77%). Remarkably, 3,5-disubstituted acetophenone **S8**, precursor of the antiemetic drug aprepitant,[17] was hydrogenated in excellent yield with a good *ee* value (Table 4, entry 8). On the contrary, a low conversion and a low *ee* value were obtained with 1-(2-chlorophenyl)ethanone (**S6**), most certainly because of the steric bulk created by its *ortho* substituent (Table 4, entry 6 vs. entries 4 and 5). Other aryl- and heteroaryl methyl ketones such as **S10** and **S11** were hydrogenated with full conversions and high *ee* values (Table 4, entries 10 and 11), whereas fully aliphatic methyl ketone **S12** gave a low conversion and a low *ee* value (Table 4, entry 12). Propiophenone (**S13**) was reduced with the same *ee* value as acetophenone (96%), albeit with a lower conversion (Table 4, entry 12 vs. 1), which thus confirmed that the catalyst was rather sensitive to steric factors. Finally, cyclic ketone **S14** was transformed into the corresponding alcohol with full conversion but with no enantioselectivity at all (Table 4, entry 14).

To get some information about the $RuCl_3(H_2O)_x$/(*S*,*S*)-**L** catalytic system, we determined the kinetics of the hydrogenation of acetophenone (**S1**) under the optimized catalytic conditions. The conversions were calculated from the hydrogen uptake.

In the plot of conversion versus time shown in Figure 2 (●) it can be noted that the reaction has a long induction time (≈3 h). Notably, this induction period remains the same independent of the complexation time of (*S*,*S*)-**L** with $RuCl_3(H_2O)_x$ under an argon atmosphere preceding the introduction of H_2 into the reaction vessel. However, the induction time disappears if $RuCl_3(H_2O)_x$ is pretreated with refluxing *i*PrOH (i.e., a reducing agent), before the hydrogenation is performed under the optimized conditions (Figure 2,▲). This finding suggests that the formation of the hydrogenation catalyst occurs after reduction of $RuCl_3(H_2O)_x$ to a lower-valent species, probably Ru^{II}. The conversion plot appears to obey a zero-order kinetics law in the 0–75% conversion range. Unfortunately, our attempts to isolate and/or characterize the active complex were unsuccessful owing to its high sensitivity.

In summary, we described a new method for the ruthenium-catalyzed asymmetric hydrogenation of ketones based on the use of the Trost ligand, (*S*,*S*)-**L**, which had so far never found application in metal-catalyzed reductions. The new $RuCl_3(H_2O)_x$/(*S*,*S*)-**L** catalytic system could be readily prepared in situ and provided access to a range of chiral alcohols with good conversions and high enantioselectivities (up to 96% *ee*). Kinetic studies demonstrated that the formation of the catalytically active species took place slowly in the presence of H_2. Compared to numerous other known methods for the asymmetric hydrogenation of ketones,[10] the one described in this

paper has the advantage of employing a commercially available chiral ligand (i.e., **L**) and a Ru source [i.e., $RuCl_3(H_2O)_x$] that is the cheapest available on the market. Therefore, our new method represents a step forward to address the catalyst cost issues that often discourage the industrial use of asymmetric catalysis.

Experimental Section

General procedure for hydrogenation

In a Schlenk vessel under an argon atmosphere, a stock solution of the catalyst was prepared by dissolving $RuCl_3(H_2O)_x$ (2.7 mg, 0.01 mmol), ligand (*S*,*S*)-**L** (6.9 mg, 0.01 mmol), and Na_2CO_3 (5.3 mg 0.05 mmol) in dry methanol (5 mL). The solution was stirred at room temperature for 45 min, and then aliquots (0.5 mL, each corresponding to 0.001 mmol/0.01 equiv. of [Ru]) were dispensed into vials containing the freshly distilled substrate(s) (0.1 mmol, 1 equiv.), placed into an argon-filled vessel. The vials were transferred into an autoclave, which was purged with H_2 (3×) and then pressurized to 30 bar, and the mixtures were magnetically stirred at room temperature for 22 h. After venting H_2, hexadecane (0.1 mmol) was added to each vial and GC analysis was performed. The *ee* values were determined by chiral-phase GC or HPLC (see the Supporting Information for details).

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · hydrogenation · ketones · ruthenium · Trost ligand

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3.4 Phosphine-free Pincer Cobalt Catalyst Precursors for the Selective Hydrogenation of Olefins

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The own contribution to this work is 40%.

Supporting information for this work is included in the appendix (Section 5.1)

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Phosphine-free Pincer Cobalt Catalyst Precursors for the Selective Hydrogenation of Olefins

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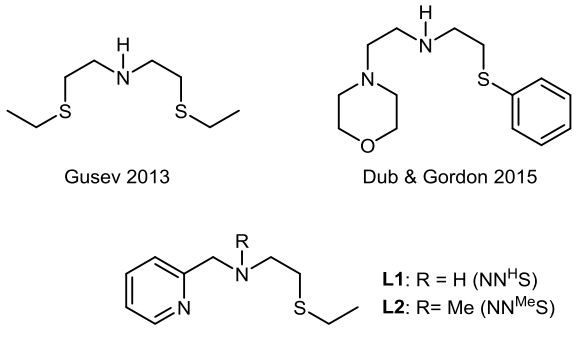
Abstract. Cobalt(II) complexes bearing phosphine-free tridentate NNS ligands were prepared. The secondary amine ligand **L1** yielded a dimeric complex, whereas *N*-methylation on the central nitrogen atom (**L2**) led to the formation of the monomeric complex **2**. Upon activation with reducing agent, complex **2** selectively catalysed the hydrogenation of olefins in the presence of (conjugated) reducible moieties such as ketones. After investigation of the reaction kinetics and poisoning experiments, it was concluded that **2** is actually a nanoparticle precursor rather than an active homogeneous catalyst itself under the reaction conditions.

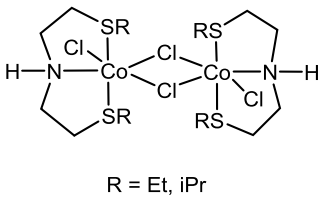
Keywords: Hydrogenation; Cobalt; Alkenes; N ligands; S ligands; Tridentate ligands, Nanoparticles

The field of homogeneous hydrogenation has, over the last decade, undergone a major shift away from noble metals such as Rh, Ir, and Ru towards base metals like Fe, Co, and Mn.[1] Strongly electron-donating, stabilising pincer ligands have played a key role in the development of such catalysts, to the point where pincer complexes of most base metals have now been applied for hydrogenation reactions.[2,3]



Scheme 1. Previously reported N,S-based pincer ligands.

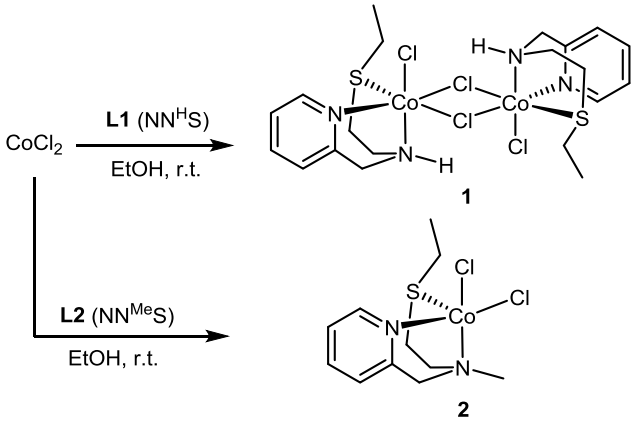
The impact on the environment and the costs of phosphine- or carbene-based ligands, however, should not be underestimated and can even outweigh the advantages of using base metals. Phosphine-based ligands also suffer from shorter shelf-lives and can be hard to prepare on a large scale, due to their sensitivity. In this light, we recently reported the application of flexible alkylthio-*N*-(pyridine-2-yl)methyl-1-ethanamine (NNS) tridentate ligands and their ruthenium complexes in the selective hydrogenations of α,β-unsaturated aldehydes, ketones, and even esters to the corresponding allylic alcohols.[4] Notable examples of similar ligands were published earlier by Gusev, Dub and Gordon in recent years (Scheme 1).[5,6] There is a clear incentive for combining such cheap, readily accessible ligands with base metals in order to reap the benefits provided by both. Midya, Balaraman and co-workers recently reported the acceptorless dehydrogenative coupling of aminoalcohols and alcohols to obtain heterocycles, which was catalysed by a dimeric cobalt(II) complex bearing Gusev's SNS ligand (Scheme 2).[7] At the time, we were evaluating the use of our NNS ligands with cobalt for catalytic hydrogenations, the results of which we report here.



Scheme 2. Co-SNS dimers reported by Balaraman.[7]

The addition of 1 equivalent of ligand to a solution of $CoCl_2$ in ethanol afforded a clean reaction to the Co(II)NNS complexes **1** and **2** depicted in Scheme 3.

Interestingly, the secondary amine ligand **L1** yielded the dimeric, chloride-bridged complex **1**, with the tridentate ligand coordinated in a *fac* manner, while monomeric complex **2** was obtained with the *N*-methylated ligand **L2**. Crystals suitable for X-ray diffraction analysis were obtained for both complexes, and their solid-state molecular structures are shown in Figure 1. Interestingly, it appears that *N*-methylation of the ligand provided sufficient steric hindrance to prevent complex **2** from dimerising.



Scheme 3. Synthesis of Co(NNS) complexes **1** and **2**.

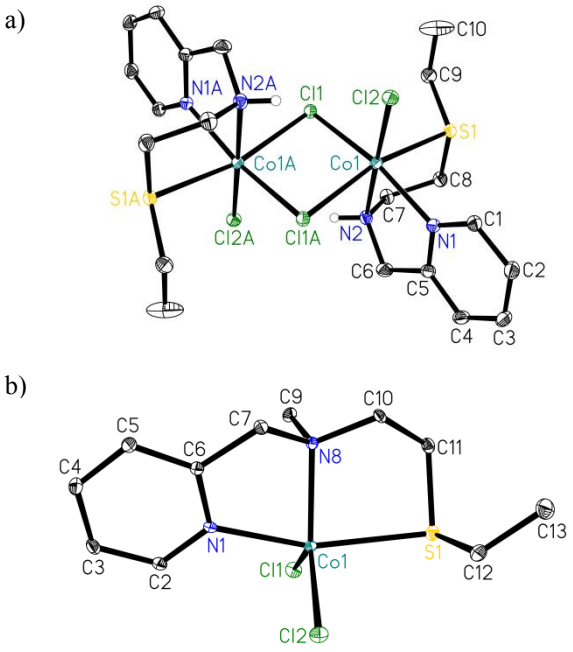


Figure 1. ORTEP drawings (30% probability ellipsoids, hydrogen atoms, except the N-H hydrogen for **1**, were omitted for clarity.) Selected bond lengths (Å) and angles (°) for a) complex **1**: Co1-S1 2.5162(4), Co1-N1 2.1159(11), Co1-N2 2.1704(11), Co1-Cl1 2.4186(3), Co1-Cl1A 2.4991(3), Co1-Cl2 2.3633(3); N1-Co-N2 78.41(4), N1-Co1-S1 83.76(3), N2-Co1-S1 83.72(3), Cl1-Co1-Cl1A 91.547(12), Cl2-Co1-Cl1 95.210(13), C6-N2-C7 115.33(11) and b) complex **2**: Co1-S1 2.5612(8), Co1-N1 2.102(2), Co1-N8 2.122(2), Co1-Cl1 2.2785(8), Co1-Cl2 2.2885(8); N1-Co1-N8 78.14(8), N1-Co1-S1 161.69(6), N8-Co1-S1 84.06(6), Cl1-Co1-Cl2 118.99(3), C7-N8-C10 111.20(2).

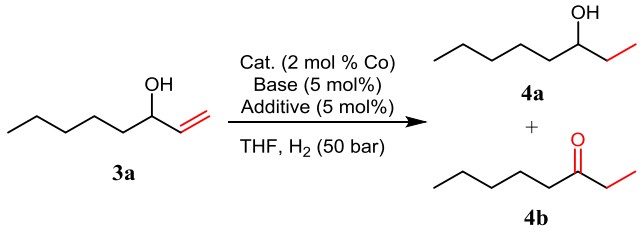
We investigated the obtained complexes in the catalytic hydrogenation of olefins. Several activation pathways were envisioned. Firstly, the addition of a base could deprotonate the ligand NH or the benzylic CH_2, which would then allow the complex to activate hydrogen *via* a bifunctional mechanism. This activation pathway should enable the hydrogenation of polarised unsaturated moieties such as carbonyl groups.[8] Another strategy to activate Co(II) complexes is their reduction, be it *in situ* or *ex situ*, to the corresponding Co(I) complex, which has recently been reported to lead to increased activities.[9] The reaction conditions reported by Balaraman *et al.* for their dehydrogenative coupling (reflux in *m*-xylene) made us suspect that the dimeric complex may well be very stable in solution, and therefore would require elevated temperatures to dissociate into an active, monomeric form.[7] In order to test if the dimer could be dissociated at lower temperatures, we included the addition of monodentate ligand into the screening of activating additives. In an initial high-throughput screening (HTS), the hydrogenation of 1-octene, acetophenone and 1-octen-3-ol were investigated (see Supporting Information). After these initial experiments, 1-octen-3-ol (**3a**) was selected as a model substrate since its isomerisation to the corresponding ketone (**4b**) was observed during the HTS. Consequently, we used this substrate to explore the activity of the Co catalysts in both hydrogenation and isomerisation. The results of the study of the activation of the Co precatalyst by different additives are summarised in Table 1. Interestingly, the best results were obtained using **2** together with a reductant ($NaBH_4$, entry 18). Subsequently, several reaction solvents were investigated, showing that isopropanol gave the highest yields and selectivities (Table 2).

Overall, only traces of the isomerisation product octan-3-one **4b** were observed, except when methanol was used as the reaction solvent (Table 2, Entry 3). The fact that the isomerisation competed with the hydrogenation at 50 bar of hydrogen pressure prompted us to investigate further the isomerization activity of our cobalt NNS complexes. The isomerisation of allylic alcohols to ketones is indeed an interesting reaction. There is only a single report describing the use of cobalt catalysts for this transformation, although our group reported on the use of another base metal (Fe) pincer complex for this reaction.[10] When the reaction was performed in the absence of hydrogen atmosphere, however, no reaction took place at all, suggesting that a cobalt hydride species needs to be generated before any isomerisation can take place. For this reason we decided to only pursue the hydrogenation activity of **1** and **2**.

For all reactions where full conversion with **2** was obtained, a black residue was observed in the reaction mixture at the end of the experiment. This suggested the formation of cobalt nanoparticles, either after

consumption of the substrate or at the start of/during the reaction. In the latter case, the hydrogenation could have possibly been catalysed by cobalt nanoparticles formed *in situ*.[11] In order to investigate this possibility, we measured the reaction kinetics by monitoring the hydrogen uptake at two different catalyst loadings, and performed two types of poisoning experiments.

Table 1. Activation studies for catalysts **1** and **2** in the hydrogenation of 1-octen-3-ol.



#[a]	Cat.	Base	Additive	Yield **4a**:**4b** (%)[b]
1	**1**	-	-	0:0
2	**1**	KO^{t}Bu	-	0:1
3	**1**	NaOH	PPh_3	0:0
4	**1**	NaOH	$NaBH_4$	12:0
5	**1**	NaOH	Zn	3:0
6	**2**	-	-	0:0
7	**2**	KO^{t}Bu		0:1
8	**2**	KO^{t}Bu	PPh_3	41:0
9	**2**	KO^{t}Bu	$NaBH_4$	20:0
10	**2**	NaOEt	PPh_3	94:3
11	**2**	NaOEt	$NaBH_4$	94:1
12	**2**	NaOH	PPh_3	90:5
13	**2**	NaOH	$NaBH_4$	95:1
14	**2**	NaOEt	Zn	12:0
15[c]	**2**	NaOH	PPh_3	41:4
16[c]	**2**	NaOH	$NaBH_4$	72:2
17	**2**	NaOH	-	0:0
18	**2**	-	$NaBH_4$	95:0

[a] Reaction conditions: 0.33 mmol 1-octen-3-ol, 1.0 mL THF, 1 mol% **1** or 2 mol% **2**, 5 mol% of additive and base, 50 bar H_2, 100 °C, 16 h reaction time. [b] Determined by GC using dodecane as internal standard. [c]) 1 mol% of **2**.

Table 2. Solvent screening for the hydrogenation of 1-octen-3-ol by catalyst **2**.

#[a]	Cat.	Solvent	Yield **4a**:**4b** (%)[b]
1	**2**	THF	95:1
2	**2**	Toluene	1:2
3	**2**	MeOH	58:30
4	**2**	iPrOH	>99:0
5	**2**	HFIP[c]	0:0

[a] Reaction conditions: 0.33 mmol 1-octen-3-ol, 1.0 mL solvent, 2 mol% **2**, 5 mol% of additive, 50 bar H_2, 100 °C, 16 h reaction time. [b] Determined by GC using dodecane as internal standard. [c] HFIP = hexafluoroisopropanol.

The hydrogen uptake curve at 1 mol% catalyst loading (shown in Figure 2a) shows an induction period of around 30 minutes, during which no hydrogen was consumed. After this time, the reaction proceeded to full conversion and >99% yield through a roughly sigmoidal curve, which is often indicative for nanoparticle-catalysed reactions.[12] Mercury poisoning experiments provided no conclusive evidence (details can be found in the Supporting Information). The hydrogenation reaction proceeded to a certain extent, suggesting that nanoparticles were not the active catalyst. However, it has been reported that Co nanoparticles do not readily form an amalgam with mercury.[12,13] Consequently, we decided to perform a second poisoning experiment with PMe_3 instead, the results of which are shown in Figure 2b.[14] When hydrogen started being consumed after the induction period, a sub-stoichiometric amount of PMe_3 (0.15 eq. w.r.t. **2**) was injected into the autoclave using excess of H_2 pressure, leading to an immediate stop of the hydrogen consumption. This is a strong indication that the reaction is catalysed by cobalt nanoparticles, which are poisoned when their surface gets saturated with PMe_3.

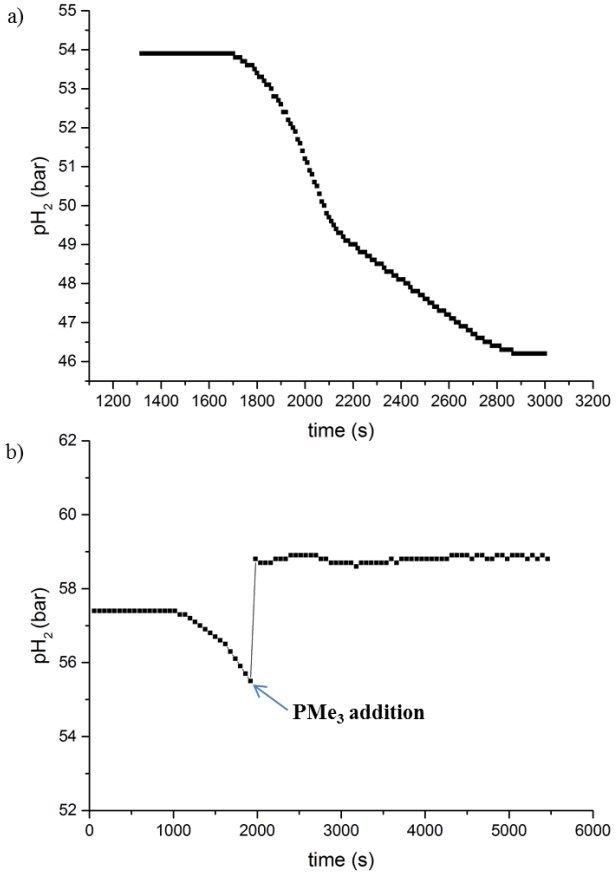


Figure 2. a) Hydrogen uptake curve at 1 mol% catalyst loading under normal reaction conditions (corrected for heating to 100 °C). b) Hydrogen uptake under the same conditions, where a PMe_3 solution was injected after the induction period, which initially increased the total pressure, but then remained stable. At this point a conversion of 65% had been achieved (determined by GC, dodecane as internal standard.)

A variety of terminal and internal olefins were reduced with full conversions, and the corresponding products were isolated in good to excellent yields, as illustrated in Figure 3. During our initial HTS experiment, we observed that our Co complexes were not active in the hydrogenation of acetophenone.

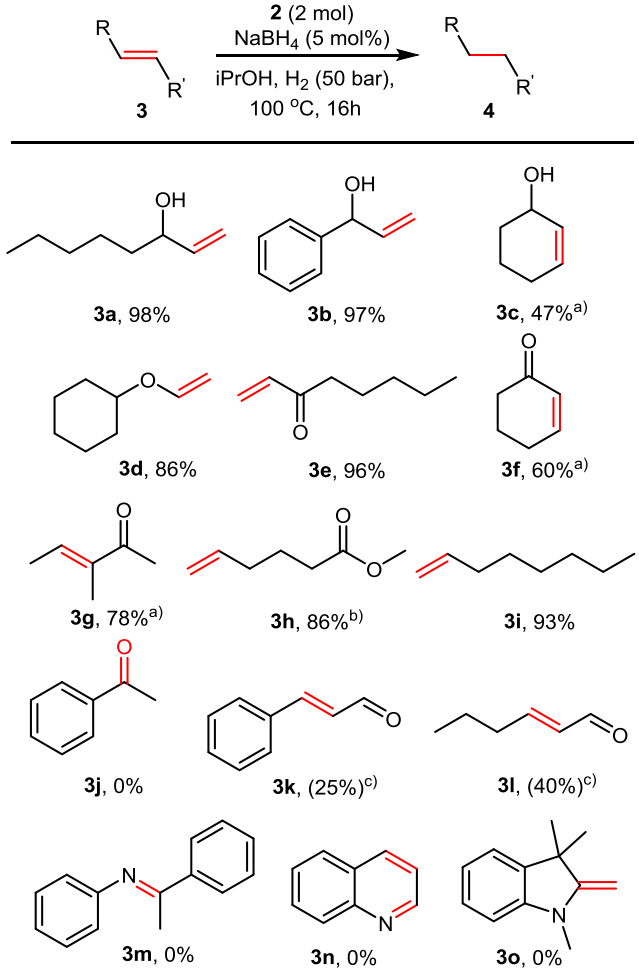


Figure 3. Substrate scope and limitations of the hydrogenation of olefins catalysed by **2**. Reaction conditions: substrate (5 mmol), iPrOH (15 mL), **2** (33.9 mg, 2 mol%), $NaBH_4$ (9.5 mg, 5 mol%), 50 bar H2, 100 °C, 16 h reaction time. a) Isolated yields are low due to volatility of the products compared to IPrOH. b) The isolated product is the isopropyl ester. c) The reactions never reached full conversions, and as such the products were not isolated.

Therefore, we decided to explore the selectivity of the Co nanoparticles in the hydrogenation of olefins in the presence of carbonyl functionalities (Figure 3). Ketones (**3j**) and esters (**3h**) were not reduced even under the harsh conditions employed here. Excellent chemoselectivities were observed with α,β-unsaturated ketones (**3f-3g**), which did not show any reduction of the carbonyl group even after 16 hours. However, aldehydes appear to inhibit the reaction, as conversions of only 25 and 40% were observed in the hydrogenation of cinnamaldehyde (**3k**) and hexen-2-al (**3l**), although even in these cases, the sole product observed was the saturated aldehyde. No conversion was observed for the hydrogenation of an imine (**3m**), quinoline (**3n**) or enamine (**3o**).
These findings contrast not only with our previously reported RuNNS catalysts, but also with the activity of cobalt pincer complexes containing strongly donating phosphine ligands such as those recently described by Junge *et al.*, which hydrogenated esters readily.[9b] Additionally, the cobalt nanoparticles recently reported by the Jacobi von Wangelin group reduced carbonyl groups efficiently, and under far milder reaction conditions.[11a,b] In our case, it is likely that **L2** stabilises the nanoparticles and partially deactivates them, rendering them selective towards olefinic double bonds.

In conclusion, two new cobalt(II) complexes bearing non-phosphorus pincer ligands were synthesised, characterised and their reactivities in catalytic hydrogenation were investigated. The dimeric complex **1** was nearly inactive for hydrogenation, but complex **2**, bearing the *N*-methyl group on its central nitrogen atom, proved useful as catalyst precursor for the selective hydrogenation of C=C bonds in the presence of other reducible moieties. Investigations into the application of such complexes for other types of reactions are currently ongoing.

Experimental Section

Complex synthesis

L1 and **L2** were synthesised according to procedures reported previously.[4a]

$Co_2Cl_4(NN^HS)_2$ (1): In a schlenk flask, $CoCl_2$ (300 mg, 2.3 mmol) was dissolved in ethanol (40 mL). Upon addition of **L1** (420 µL, 450 mg, 1 eq.) the colour of the reaction mixture changed from blue to indigo, and the mixture was stirred overnight under an atmosphere of argon. The solvent was removed *in vacuo*, after which the resulting dark blue oil was redissolved in dichloromethane (1 mL). Et_2O (10 mL) was added, crashing out the majority of the material as a dark blue powder. While cooling on a dry ice/isopropanol bath, The Et_2O/DCM mixture was filtered off via a cannula, and the product was washed twice more with Et_2O, and dried *in vacuo*, yielding **1** (645 mg, 95%) as a dark blue crystalline material.

$CoCl_2(NN^{Me}S)$ (2): **2** (400 mg, 94%) was obtained as an ultramarine powder from $CoCl_2$ (160 mg, 1.25 mmol) and **L2** (240 µL, 260 mg, 1 eq.), analogously to the synthesis of **1**.

Characterisation of **1** and **2** is reported in the Supporting Information

Typical procedure for olefin hydrogenation

4 mL glass vials with stirring bars were dried in the oven and closed with PTFE septa. In the glovebox, **2** (2.2 mg, 0.006 mmol) and $NaBH_4$ (0.6 mg, 0.016 mmol) were weighed off. Solvent (1 mL), dodecane (150 µL), and 1-octen-3-ol were added (50 µL, 0.33 mmol), and the septum pierced with a needle. The vial was transferred to an autoclave, which was flushed with inert gas and then

pressurised twith H_2 to 50 bar, and heated to 100 °C overnight. Full experimental details and characterisation for isolated products can be found in the Supporting Information.

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COMMUNICATION

Phosphine-free Pincer Cobalt Catalyst Precursors for Selective Hydrogenation of Olefins

Adv. Synth. Catal. **2018**

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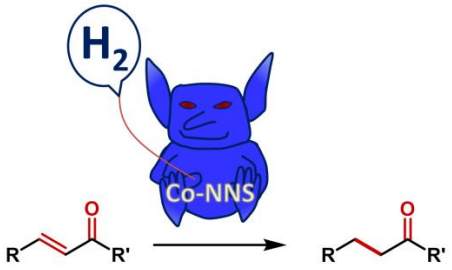

4. Thesis Summary

This work aimed to develop cheaper and more environmentally friendly ligands for catalysts used in homogeneous hydrogenations. The family of "NNS"-type ligands was introduced as a promising alternative to phosphorus-containing pincer ligands, which are used in a wide range of homogeneously catalysed reactions. These NNS ligands, however, did not stabilise transition metal complexes in the same way classical pincer ligands do. It was observed by ^{1}H- and ^{31}P-NMR spectroscopies that $RuCl_2(NNS)(PPh_3)$ complexes may adopt two conformations in solution, which are in equilibrium. Depending on the nature of ligand used, either the *fac* or *mer* complex was isolated in the solid state, and both conformations were elucidated by X-ray diffraction analysis. Upon activation with base, the complexes proved active for the selective hydrogenation of the carbonyl moiety α,β-unsaturated aldehydes and ketones, allowing the corresponding allylic alcohols to be isolated in good to excellent yields. The active catalytic species were not stable in the absence of hydrogen pressure, which prevented their characterisation. (Section 3.1; *Chemistry - A European Journal* **2017**)

The same class of catalysts was active in the hydrogenation of esters, which is a reaction that typically requires strongly electron-donating ligands and/or harsh reaction conditions. An unprecedented selectivity in the hydrogenation of α,β-unsaturated esters was observed for several substrates, and the corresponding allylic alcohols were isolated in good yields. This selectivity exhibited a strong solvent effect. Coordinating, or possibly reactive, solvents reduced the selectivity, presumably *via* decoordination of the ligand's sulphur-containing arm. As the catalytically active species were elusive, this effect was instead probed by introducing a bulky *tert*-butyl group at sulphur. The increased steric bulk on this position had an effect very similar to that of using coordinating solvents, namely suppressing the hydrogenation of the ester functionality, while promoting the hydrogenation of the conjugated olefin. In addition to α,β-unsaturated esters, several biomass-derived esters were hydrogenated with high turnovers. (Section 3.2; *Advanced Synthesis and Catalysis* **2018**)

With the aim of combining cost-efficient ligands with a metal of lower cost than ruthenium, cobalt(II)-NNS complexes were synthesised as well. Depending on the ligand used, either monomeric $CoCl_2(NNS)$ or dimeric $Co_2Cl_4(NNS)_2$ was isolated, both of which are paramagnetic. The structures were determined by X-ray diffraction analysis. The activity of these complexes in hydrogenation reactions was investigated, and it was found that the monomeric complex hydrogenates olefins in the presence of ketone and ester functionalities, hence, it exhibited opposite selectivity when compared to the ruthenium(II) analogues discussed above. Based on kinetics, as well as poisoning experiments using Hg and PMe_3, it was concluded that the monomeric $CoCl_2(NNS)$ actually forms nanoparticles after activation by reducing agent. That these nanoparticles are fully selective to carbon-carbon double bonds contrasts to what has been reported in literature, and suggests that the NNS ligand stabilises the nanoparticles in a way that does not fully deactivate them, but does prevent them from reacting with carbonyl moieties. (Section 3.4; *Manuscript submitted*)

The aforementioned equilibrium between *fac* and *mer* coordination of the NNS ligands, as well as the presumed decoordination of the ligand's sulphur-containing arm, make these ligands unlikely candidates for application in asymmetric hydrogenation. However, the commercially available (*S,S*)-DACH-phenyl, or Trost's ligand, was used in combination with the simple ruthenium precursor $RuCl_3 \cdot xH_2O$ in methanol to generate a catalyst which was active in the asymmetric hydrogenation of a series of aromatic ketones. Of special interest is that this catalytic system only gave the desired results when methanol was used as a solvent, and a significant induction period was observed. It is likely that a catalytically active ruthenium(II) species is generated *in situ*, either before or after coordination to the asymmetric ligand. (Section 3.3; *ChemCatChem* **2017**)

In conclusion, four distinctive hydrogenation reactions are reported, employing ligands and complexes which were either designed specifically for the purpose or had not been applied in hydrogenation chemistry before. These examples showcase that reactivity and selectivity do not necessarily depend on the stability and rigidity of organometallic complexes, but may actually arise from conformational flexibility of the catalytically active complex, and *in situ* generation of the actual catalytically active species.

5. Appendices

5.1 Supporting Information for section 3.4

At the time of writing, the manuscript presented in section 3.4 is not yet available online. The supporting information for this manuscript is included here.

Phosphine-free Pincer Cobalt Catalyst Precursors for Selective Hydrogenation of Olefins

Supporting Information

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1. General Information

Reagents and solvents were obtained from commercial sources and used as received unless noted otherwise. Dry solvents were obtained from a solvent purification system, or purchased water-free in a bottle with septum (isopropanol). Complexes were prepared using standard Schlenk techniques. Stock solutions for high-throughput screening were prepared and distributed using a Zinsser Lissy liquid handling robot equipped with 4 probes inside a glove box (see Figure **S1a**). High-throughput screening was carried out in a Premex 96-Multi Reactor that can accommodate 96 reactions vessels at the same temperature and hydrogen pressure (see Figure **S1b**). This reactor was developed by Premex in cooperation with DSM.[1]

Figure S1: Hardware available at InnoSyn for high throughput screening: a) Liquid handling robot (Zinsser Lissy) and b) Premex 96-Multi Reactor.[1]

GC analysis was carried out on an Agilent 7890B GC system with a HP-5 normal-phase silica column, using He as a carrier gas and dodecane as internal standard. NMR spectra were recorded on a Bruker AV400, Bruker AV300 or Bruker Fourier300 NMR spectrometer. ^{1}H and ^{13}C-NMR spectra were referenced w.r.t. the solvent signal. All chemical shifts are in ppm, coupling constants in Hz. HR-MS measurements were recorded on an Agilent 6210 Time-of-Flight LC/MS (ESI) instrument; peaks as listed correspond to the highest abundant peak and are of the expected isotope pattern.

X-ray diffraction data for **1** and **2** were collected on a Bruker Kappa APEX II Duo and a Bruker D8 VENTURE diffractometer, respectively. The structures were solved by direct methods (SHELXS-97[2] and SHELXT[3], resp.) and refined by full-matrix least-squares procedures on F^2 (SHELXL-2014 and SHELXL-2018, resp[3]). XP (Bruker AXS) was used for molecular graphics. CCDC 1864013-1864014 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

2. Results and Discussion

2.1 High-throughput screening

An initial screening was carried out at 0.2 mmol scale, with 2 mol% catalyst and 4 mol% of additives. Complexes **1** and **2** were initially screened for activity in the hydrogenation of 1-octene, acetophenone and 1-octen-3-one in toluene and THF. Three bases (KO^{t}Bu, NaOMe, and NaOH), and four reductants (Zn, $NaBEt_3H$, $NaBH_4$ and $AlEt_3$) were screened for activation. Additionally, two monodentate ligands (pyridine and PMe_3) were screened based on the assumption that these ligands expedite the dissociation of the dimeric complex **1**. The results of this screening are summarised in Table **S1** (1-octene and acetophenone, which were dissolved in the same stock solution) and Table **S2** (1-octen-3-

ol). In several cases, the results were not interpretable due to broad or overlapping peaks in the GC trace, or other experimental artefacts (listed as 'n.a.').

Table S1. High throughput screening of **1** and **2** in the hydrogenation of 1-octene and acetophenone.

#[a]	Cat	Solvent	Additive 1	Additive 2	% octane[b]	% 1-phenylethanol
1	**1**	THF	KO^{t}Bu		n.a.	0%
2	**1**	THF	KO^{t}Bu	PMe_3	Isomerisation	0%
3	**1**	THF	NaOMe		n.a.	0%
4	**1**	THF	NaOMe	PMe_3	Isomerisation	0%
5	**1**	THF	NaOH		Isomerisation	0%
6	**1**	THF	NaOH	PMe_3	n.a.	0%
7	**1**	THF	KO^{t}Bu	$NaBEt_3H$	n.a.	0%
8	**1**	THF	KO^{t}Bu	Pyridine	n.a.	0%
9	**1**	THF	NaOMe	$NaBEt_3H$	n.a.	0%
10	**1**	THF	NaOMe	Pyridine	n.a.	0%
11	**1**	THF	NaOH	$NaBEt_3H$	n.a.	0%
12	**1**	THF	NaOH	Pyridine	n.a.	0%
13	**1**	toluene	KO^{t}Bu		0%	0%
14	**1**	toluene	KO^{t}Bu	PMe_3	0%	0%
15	**1**	toluene	NaOMe		0%	0%
16	**1**	toluene	NaOMe	PMe_3	Isomerisation	0%
17	**1**	toluene	NaOH		0%	0%
18	**1**	toluene	NaOH	PMe_3	Isomerisation	0%
19	**1**	toluene	KO^{t}Bu	$NaBEt_3H$	0%	0%
20	**1**	toluene	KO^{t}Bu	Pyridine	0%	0%
21	**1**	toluene	NaOMe	$NaBEt_3H$	0%	0%
22	**1**	toluene	NaOMe	Pyridine	0%	0%
23	**1**	toluene	NaOH	$NaBEt_3H$	0%	0%
24	**1**	toluene	NaOH	Pyridine	0%	0%
25	**1**	THF		$AlEt_3$	95%	0%
26	**1**	THF	KO^{t}Bu	$AlEt_3$	90%	0%
27	**1**	Toluene		$AlEt_3$	0%	0%
28	**1**	Toluene	KO^{t}Bu	$AlEt_3$	0%	0%
29	**2**	THF	KO^{t}Bu		n.a.	0%
30	**2**	THF	KO^{t}Bu	$NaBEt_3H$	Isomerisation	0%
31	**2**	toluene	KO^{t}Bu		0%	0%
32	**2**	toluene	KO^{t}Bu	$NaBEt_3H$	Isomerisation	0%
33	**2**	THF	KO^{t}Bu		n.a.	0%
34	**2**	THF	NaOMe	$NaBEt_3H$	Isomerisation	0%
35	**2**	toluene	NaOMe		n.a.	0%
36	**2**	toluene	NaOMe	$NaBEt_3H$	n.a.	0%
37	**2**	THF			n.a.	0%
38	**2**	THF	KO^{t}Bu		n.a.	0%
39	**2**	Toluene			0%	0%
40	**2**	Toluene	KO^{t}Bu		0%	0%
41	**2**	THF		$NaBEt_3H$	50% + isomerisation	0%
42	**2**	THF	KO^{t}Bu	$NaBEt_3H$	30% + isomerisation	0%
43	**2**	Toluene		$NaBEt_3H$	80% + isomerisation	0%
44	**2**	Toluene	KO^{t}Bu	$NaBEt_3H$	80% + isomerisation	0%
45	**2**	THF		$NaBH_4$	80% + isomerisation	0%
46	**2**	THF	KO^{t}Bu	$NaBH_4$	40% + isomerisation	0%
47	**2**	Toluene		$NaBH_4$	0%	0%
48	**2**	Toluene	KO^{t}Bu	$NaBH_4$	0%	0%
49	**2**	THF		Zn^0	80%	0%
50	**2**	THF	KO^{t}Bu	Zn^0	100%	0%
51	**2**	Toluene		Zn^0	0%	0%
52	**2**	Toluene	KO^{t}Bu	Zn^0	0%	0%

[a]Reaction conditions: 1-octene (0.2 mmol), acetophenone (0.2 mmol), solvent (2.5 mL), catalyst (1 mol% **1** or 2 mol% **2**), additives (5 mol%), 50 bar H_2, 100 °C, 16 h reaction time. [b]Area percentages; n.a. indicates the results were not interpretable.

Table S2. High throughput screening of **1** and **2** in the hydrogenation of 1-octen-3-ol.

#	Cat	Solvent	Additive 1	Additive 2	% 3-octanol[b]
1	**1**	THF	KO^{t}Bu		0%
2	**1**	THF	KO^{t}Bu	PMe_3	n.a.
3	**1**	THF	NaOMe		n.a.
4	**1**	THF	NaOMe	PMe_3	n.a.
5	**1**	THF	NaOH		40%
6	**1**	THF	NaOH	PMe_3	60%
7	**1**	THF	KO^{t}Bu	$NaBEt_3H$	20%
8	**1**	THF	KO^{t}Bu	Pyridine	0%
9	**1**	THF	NaOMe	$NaBEt_3H$	10%
10	**1**	THF	NaOMe	Pyridine	0%
11	**1**	THF	NaOH	$NaBEt_3H$	90%
12	**1**	THF	NaOH	Pyridine	5%
13	**1**	toluene	KO^{t}Bu		0%
14	**1**	toluene	KO^{t}Bu	PMe_3	40%
15	**1**	toluene	NaOMe		0%
16	**1**	toluene	NaOMe	PMe_3	n.a.
17	**1**	toluene	NaOH		50%
18	**1**	toluene	NaOH	PMe_3	full conversion
19	**1**	toluene	KO^{t}Bu	$NaBEt_3H$	50%
20	**1**	toluene	KO^{t}Bu	Pyridine	0%
21	**1**	toluene	NaOMe	$NaBEt_3H$	20%
22	**1**	toluene	NaOMe	Pyridine	0%
23	**1**	toluene	NaOH	$NaBEt_3H$	95%
24	**1**	toluene	NaOH	Pyridine	95%
25	**1**	THF		$AlEt_3$	full conversion
26	**1**	THF	KO^{t}Bu	$AlEt_3$	full conversion
27	**1**	Toluene		$AlEt_3$	full conversion
28	**1**	Toluene	KO^{t}Bu	$AlEt_3$	full conversion
29	**2**	THF	KO^{t}Bu		0%
30	**2**	THF	KO^{t}Bu	$NaBEt_3H$	60%
31	**2**	toluene	KO^{t}Bu		0%
32	**2**	toluene	KO^{t}Bu	$NaBEt_3H$	full conversion
33	**2**	THF	NaOMe		0%
34	**2**	THF	NaOMe	NaBet3H	60%
35	**2**	toluene	NaOMe		0%
36	**2**	toluene	NaOMe	NaBet3H	50%
37	**2**	THF			broad
38	**2**	THF	KOtBu		broad
39	**2**	Toluene			broad
40	**2**	Toluene	KOtBu		broad
41	**2**	THF		$NaBEt_3H$	60%
42	**2**	THF	KO^{t}Bu	$NaBEt_3H$	50%
43	**2**	Toluene		$NaBEt_3H$	60%
44	**2**	Toluene	KO^{t}Bu	$NaBEt_3H$	95%
45	**2**	THF		$NaBH_4$	30%
46	**2**	THF	KO^{t}Bu	$NaBH_4$	100%
47	**2**	Toluene		$NaBH_4$	n.a.
48	**2**	Toluene	KO^{t}Bu	$NaBH_4$	n.a.
49	**2**	THF		Zn^0	10%
50	**2**	THF	KO^{t}Bu	Zn^0	n.a.
51	**2**	Toluene		Zn^0	n.a.
52	**2**	Toluene	KO^{t}Bu	Zn^0	n.a.

[a]Reaction conditions: 1-octen-3-ol (0.2 mmol), solvent (2.5 mL), catalyst (1 mol% **1** or 2 mol% **2**), additives (5 mol%), 50 bar H_2, 100 °C, 16 h reaction time. [b]Area percentages; 'n.a.' indicates the results were not interpretable, whereas 'full conversion' indicates no starting material was observed after the reaction, but the products could not be determined.

It was concluded from this preliminary screening that **2**, in combination with base and borohydride reducing agent was active in the hydrogenation of 1-octene as well as 1-octen-3-ol, although isomerisation was observed as side reaction. Reactions where **1** was employed as catalyst typically gave no appreciable quantities of octane, with the notable exception where Et_3Al was used as a reductant in THF. In no single case was 1-phenylethanol observed from the reduction of acetophenone.

2.2 Kinetics and Poisoning Experiments

After a typical experiment, a black residue was observed in the reaction vials (example in Figure **S2**), which prompted us to investigate the formation of nanoparticles.

Figure S2: Black residue after the reaction.

The reaction was followed by monitoring the hydrogen consumption over time, at 5 mmol scale (15 mL solvent), with 1 mol % of catalyst loading (Figure **S3**). The hydrogen uptake curve is sigmoidal, which is often indicative of nanoparticle-catalysed reactions.

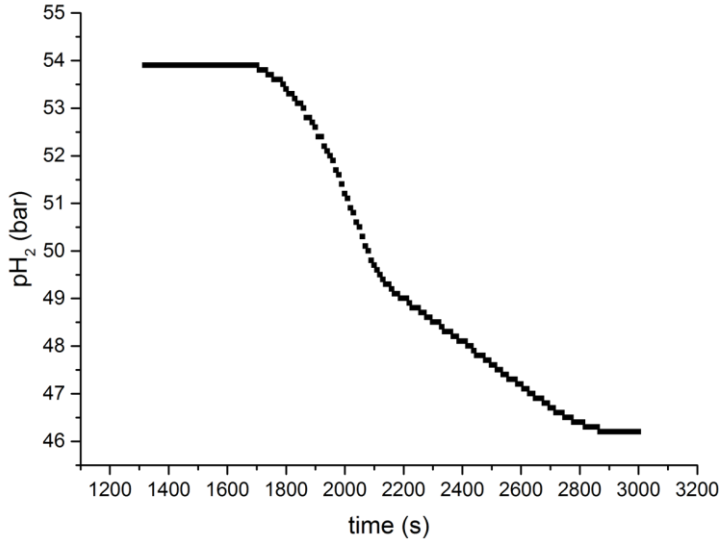


Figure S3: H_2 uptake for the reduction of 1-octen-3-ol with 1 mol % of **2**.

In order to assess whether the reaction was catalysed by nanoparticles, two types of poisoning experiments were performed. Firstly, the reactions were repeated in the presence of mercury on the optimisation scale (section 3.3). This led to lower conversions, but did not quench the reactivity completely (Table **S3**).

Table S3. Mercury poisoning experiments

#[a]	Cat	Hg loading (%)	Conversion (%)
1	**2**	10	57
2	**2**	30	44

[a])Reaction conditions: 0.33 mmol 1-octen-3-ol, 1.0 mL ^{i}PrOH, 2 mol% **2**, 5 mol% of $NaBH_4$, 50 bar H_2, 100 °C, 16 h reaction time.

Based on the reportedly low solubility of cobalt in mercury, it was decided that another poisoning experiment using trimethylphosphine was in order.[4] The reaction was repeated on a 10 mmol scale (30 mL of iPrOH, 1 mol% **2**, 5 mol% $NaBH_4$), and after the induction period was over and the reaction had started, trimethylphosphine (300 µL,0.05 M in toluene, 15% w.r.t. cobalt) was injected under pressure. The hydrogen uptake curves are depicted in Figure **S6** and clearly show after injection of trimethylphosphine, the reaction stopped at 65% conversion (determined by GC with dodecane as internal standard).

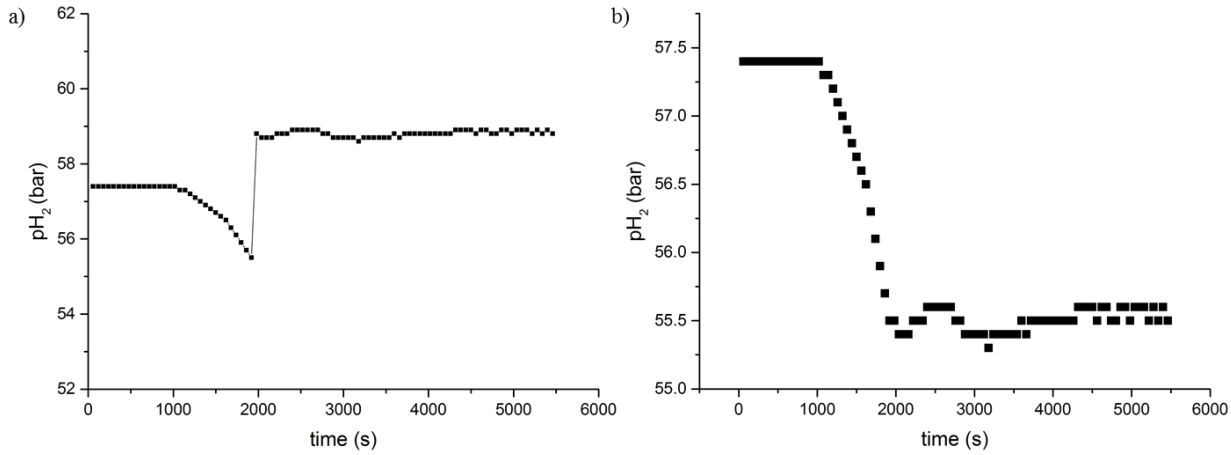


Figure S6: H_2 uptake curve with injection of trimethylphosphine solution after an induction period. Graph a) shows the pressure values as measured; b) is corrected for the pressure spike that resulted from the addition of the solution under additional pressure.

3. Experimental procedures

3.1 Complex synthesis

L1 ($NN^{H}S$) and **L2 ($NN^{Me}S$)** were synthesised according to previously reported procedures.[5]

$Co_2Cl_4(NN^{H}S)_2$ (1): In a schlenk flask, $CoCl_2$ (300 mg, 2.3 mmol) was dissolved in ethanol (40 mL). Upon addition of **L1** (420 µL, 450 mg, 1 eq.) the colour of the reaction mixture changed from blue to indigo, and the mixture was stirred overnight. The solvent was removed *in vacuo*, after which the resulting dark blue oil was redissolved in dichloromethane (1.0 mL). Et_2O (10 mL) was added, crashing out the majority of the material as a dark blue powder. While cooling on a dry ice/isopropanol bath, the Et_2O/DCM mixture was filtered off. The product was washed with Et_2O (2 x 10 mL) and dried *in vacuo*, yielding **1** (645 mg, 95%) as a dark blue crystalline material. Crystals suitable for X-ray diffraction analysis were obtained by slow diffusion of heptane into a solution of **1** in dichloromethane.

HRMS (ESI+): m/z calcd. for $C_{10}H_{16}ClCoN_2S$: 290.0049 $[M\text{-}Cl]^+$; found: 290.0046. *N.b.* $[M]^+$ or $[M\text{-}Cl]^+$ for the dimeric complex were not observed. The complex supposedly dissociated on ionisation.

Elemental analysis calcd. (%) for $C_{20}H_{32}Cl_4Co_2N_4S_2$: C 36.83, H 4.95, N 8.59; found: C 36.96, H 4.89 N 8.43.

ATR-IR (cm^{-1}): ν(NH) 3203, ν(CH) 2967, ν(CH) 2925, ν(CH) 2867, 1604 (m), 1442 (m), 1051 (m), 1017 (m), 940 (m), 764 (s), 418 (m)

Crystal data for complex **1**: $C_{20}H_{32}Cl_4Co_2N_4S_2$, M = 652.27, triclinic, space group $P\bar{1}$, a = 7.6862(3), b = 11.1085(4), c = 17.7851(6) Å, α = 72.8236(10), β = 88.0499(11), γ = 70.2746(10)°, V = 1362.03(9) Å^3, T = 150(2) K, Z = 2, 54839 reflections measured, 6586 independent reflections (R_{int} = 0.0219), final R values ($I > 2\sigma(I)$): R_1 = 0.0214, wR_2 = 0.0537, final R values (all data): R_1 = 0.0236, wR_2 = 0.0554, 299 parameters. The asymmetric unit contains two molecules; in the main text, only one is depicted.

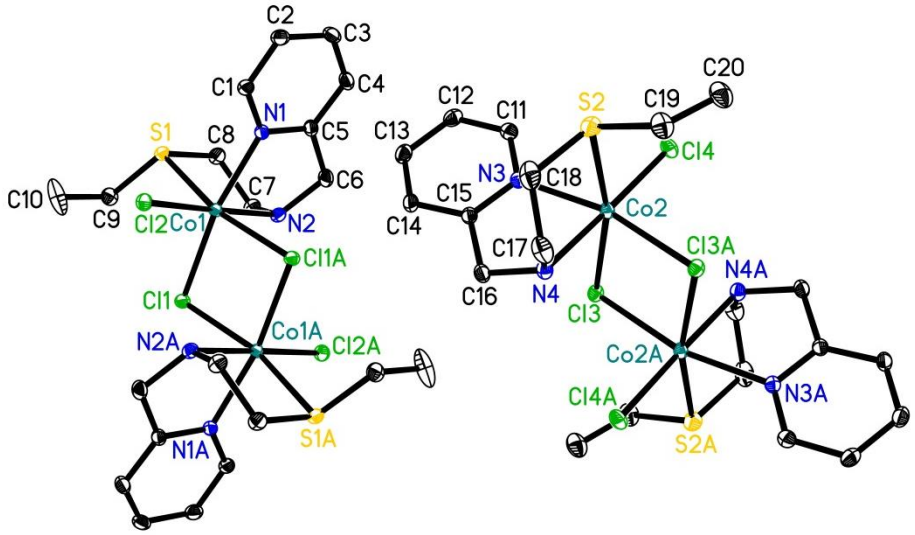


Figure S2: Molecular structure of **1** in the crystal. Displacement ellipsoids correspond to 30% probability. Hydrogen atoms are omitted for clarity. Operators for generating equivalent atoms are -x, -y+1, -z+1 and -x+1, -y+1, -z+2, respectively.

$CoCl_2$(NN^{Me}S) (2): 2 (400 mg, 94%) was obtained as an ultramarine powder from $CoCl_2$ (160 mg, 1.25 mmol) and **L2** (240 µL, 260 mg, 1 eq.), analogously to the synthesis of **1**. Crystals suitable for X-ray diffraction analysis were obtained by slow diffusion of heptane into a solution of **2** in dichloroethane.

HRMS (ESI+): m/z calcd. for $C_{11}H_{18}Cl_2CoN_2S$: 304.0206 $[M\text{-}Cl]^+$; found: 304.0204.

Elemental analysis calcd. (%) for $C_{11}H_{18}Cl_2CoN_2S$: C 38.84, H 5.33, N 8.24; found: C 37.95 H 4.90 N 7.19. *N.b.* These values are outside of the commonly accepted margin of 0.4%. A contamination of $CoCl_2$ is likely present in the obtained powder - when excess of ligand was used to prevent this, it was observed that two equivalents of ligand may coordinate to cobalt.

ATR-IR (cm^{-1}): ν(CH) 2972, ν(CH) 2928, ν(CH) 2853, 1603(m), 1447(m), 1436(m), 1298(m), 1000 (m), 980 (m), 762 (s), 732(m), 473(m), 420(m)

Crystal data for complex **2**: $C_{11}H_{18}Cl_2CoN_2S$, M = 340.16, triclinic, space group $P\bar{1}$, a = 7.0681(9), b = 9.0140(12), c = 12.2372(15) Å, α = 108.210(4), β = 98.899(4), γ = 99.291(5)°, V = 713.18(16) Å^3, T = 150(2) K, Z = 2, 14675 reflections measured, 3215 independent reflections (R_{int} = 0.029), final R

values ($I > 2\sigma(I)$): $R_1 = 0.0336$, $wR_2 = 0.0838$, final R values (all data): $R_1 = 0.0364$, $wR_2 = 0.0852$, 156 parameters.

3.2 Hydrogenation reactions (high-throughput screening, 0.2 mmol scale)

In oven-dried 5 mL headspace vials with crimp neck, **1** or **2** (1.3 mg, 2 mol% Co w.r.t. substrate) was weighed off in the glovebox, and the vials were capped. Stock solutions of the substrates (0.1 M) and additives (0.08 M) were prepared, and injected to the reaction vials by robot. These were then transferred to a parallel reactor, pressurised with H_2 (50 bar) and heated to 100 °C overnight. The results were analysed by GC based on area percentages and used as a starting point for identifying the desired reaction conditions.

3.3 Hydrogenation reactions (optimisation, 0.33 mmol scale)

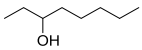
In a typical reaction, 4 mL glass vials were dried in the oven and closed with PTFE septa and screw caps. In the glovebox, catalyst, base, and additive were weighed off. Solvent (1.0 mL), dodecane (150 µL) and 1-octen-3-ol (50 µL, 0.33 mmol) were added, and the septum pierced with a needle. The vial was transferred to an autoclave, which was flushed with inert gas and then pressurised with H_2 (50 bar), and stirred at 100 °C overnight. Yields were determined by GC using dodecane as an internal standard.

3.4 Hydrogenation reactions (substrate scope, 5 mmol scale)

Small-scale reactions were performed in vials as described under **2.2**. Reactions performed at a 5 mmol scale were carried out in a 100 mL hastelloy autoclave vessel, to which **2** (31 mg, 2 mol%) and $NaBH_4$ (9.5 mg, 5 mol%) were added. Under a flow of argon, isopropanol (15 mL) and substrate (5 mmol) were added, the vessel was closed, purged with N_2 and pressurised with H_2 (50 bar). After cooling down, the autoclave was depressurised, and the reaction mixture filtered over a short column of silica. The solvent was evaporated, yielding the product directly unless stated otherwise. Yields refer to isolated yields, the products were analysed by ^{1}H- and ^{13}C-NMR spectroscopy, as well as GC-MS. Analytical data correspond to those reported in literature, where reported. (See section 4 for analytical data, yields and spectra.)

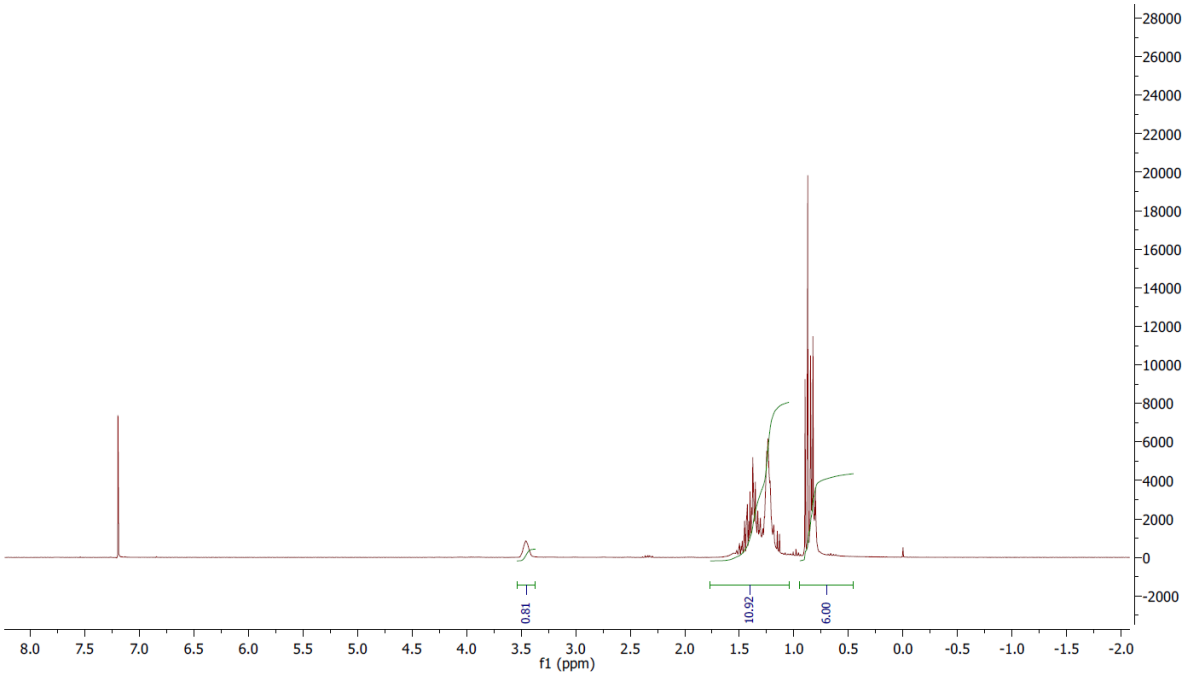
4 Characterisation of isolated products

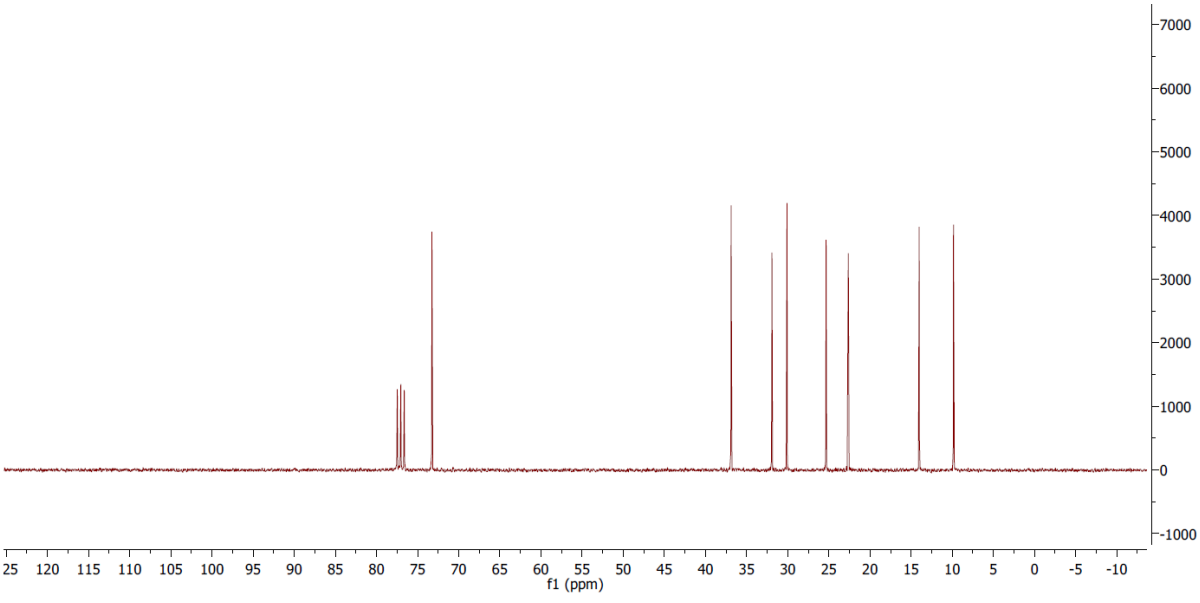
3-Octanol (4a)



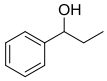
1-Octen-3-ol (**3a**, 0.76 mL, 5.00 mmol) was converted to 635 mg (4.88 mmol, 98 %) of 3-octanol (**4a**).[6]

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.45 (broad, 1H, **H**C-OH), 1.62 – 1.10 (m, 11H, CH_2, CH, OH), 0.87 (t, J = 7.4 Hz, 3H, CH_3), 0.83 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 73.3, 36.9, 31.9, 31.9, 30.1, 25.3, 22.6, 14.0, 9.9. GC-MS: m/z calcd. for $C_8H_{18}O$: 130 $[M]^+$; found: 130.



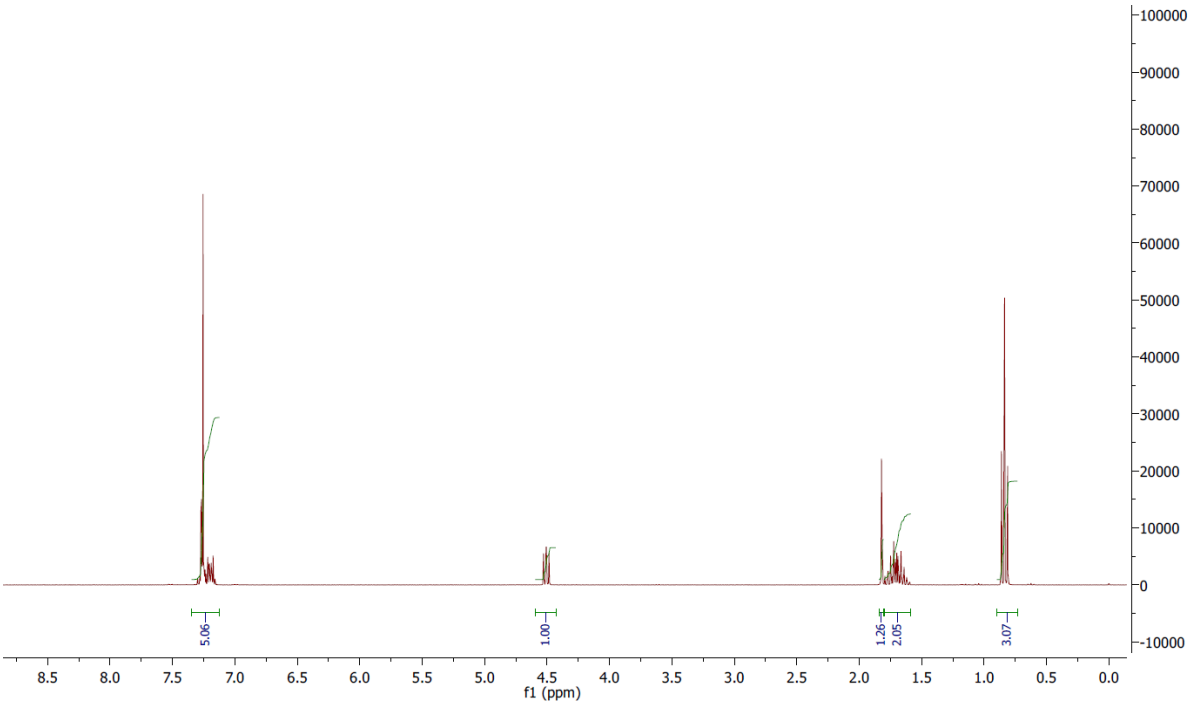


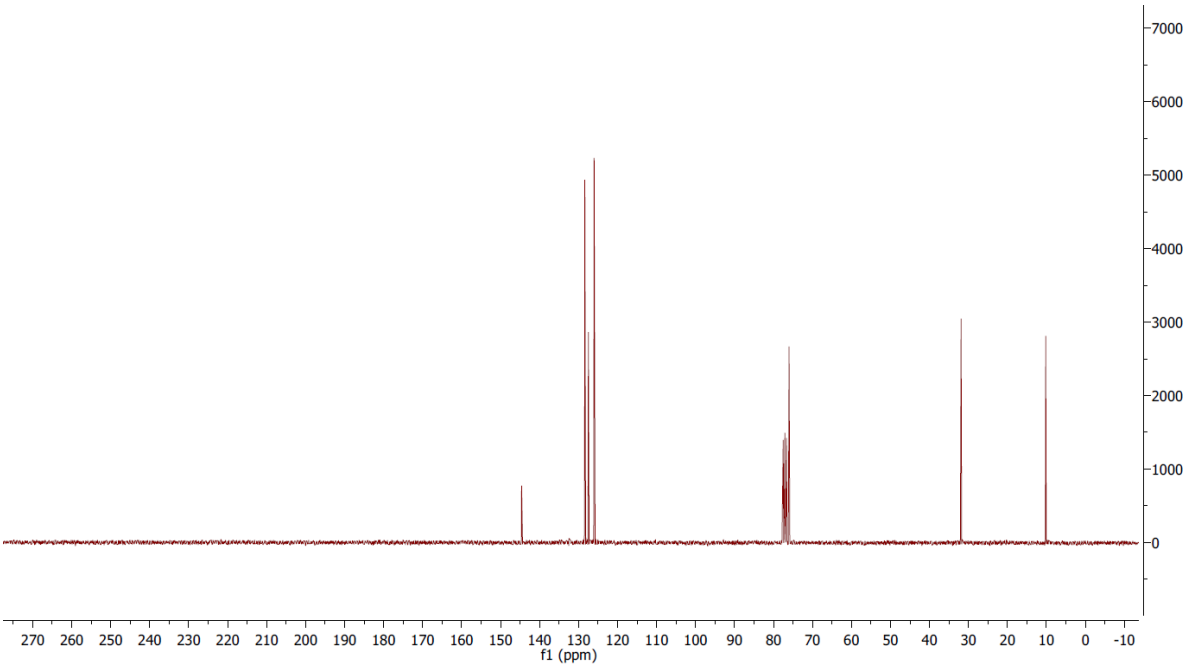
1-phenyl-1-propanol (4b)



α-Vinylbenzyl alcohol (**3b**, 0.66 mL, 5.00 mmol) was converted to 641 mg (4.85 mmol, 97 %) of 1-phenyl-1-propanol (**4b**).[6]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 – 7.13 (m, 5H, CH_{arom}), 4.51 (t, J = 6.6 Hz, 1H, CH), 1.82 (d, J = 0.8 Hz, 1H, OH), 1.80 – 1.59 (m, 2H, CH_2), 0.84 (t, J = 7.4 Hz, 3H, CH_3).^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 128.4, 127.5, 126.0, 76.0, 31.9, 10.2. GC-MS: m/z calcd. for $C_9H_{12}O$: 136 $[M]^+$; found: 136.

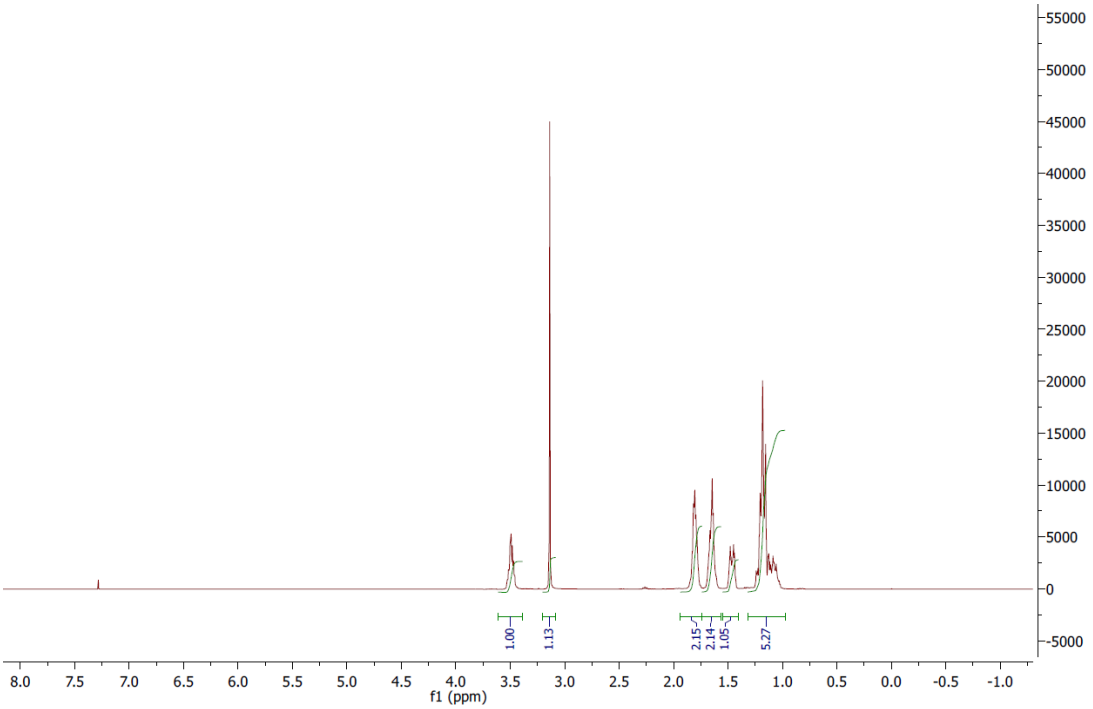


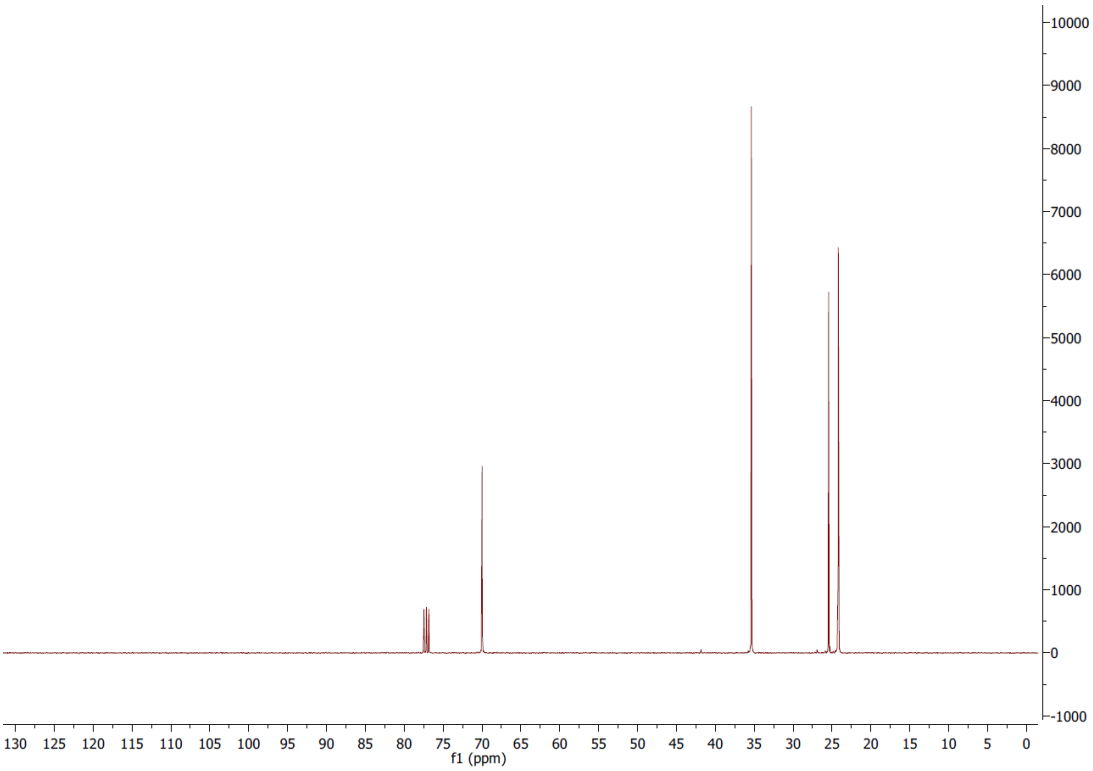


Cyclohexanol (4c)

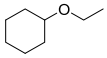
2-Cyclohexen-1-ol (**3c**, 0.49 mL, 5.00 mmol) was converted to 236 mg (2.35 mmol, 47 %) of cyclohexanol (**4c**).[6]

^{1}H NMR (400 MHz, $CDCl_3$): δ 3.49 (tt, J = 9.2, 4.1 Hz, 1H, CH), 3.14 (s, 1H, OH), 1.88 – 1.75 (m, 2H, CH_2), 1.65 (m, 2H, CH_2), 1.46 (m, 1H, CH_2), 1.32 – 0.98 (m, 5H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 70.0, 35.4 (2C), 25.4, 24.2 (2C). GC-MS: m/z calcd. for $C_6H_{12}O$: 100 $[M]^+$; found: 100.



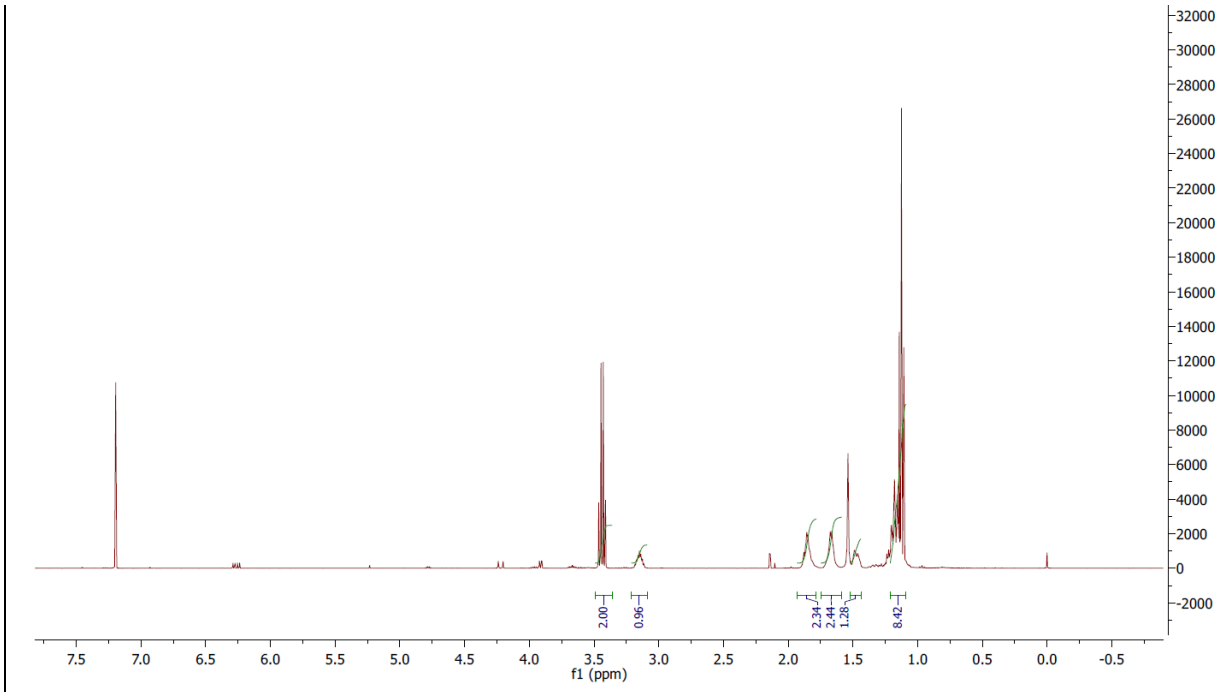


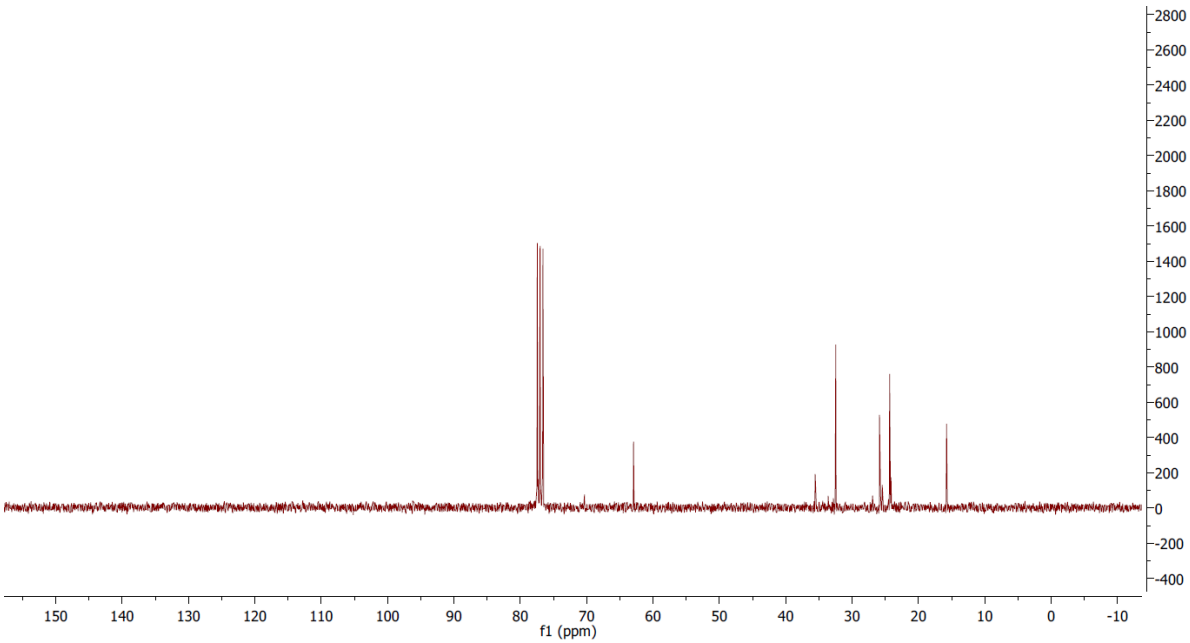
Cyclohexylethylether (4d)



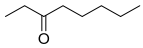
Cyclohexylvinylether (**3d**, 0.71 mL, 5.00 mmol) was converted to 542 mg (4.30 mmol, 86 %) of cyclohexylethylether (**4d**).[10]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (q, J = 7.0 Hz, 2H, O-CH_2), 3.15 (m, 1H, CH), 1.85 (m, 2H), 1.67 (m, 2H), 1.52 – 1.43 (m, 1H), 1.21 – 1.10 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 77.3, 62.9, 32.4 (2C), 25.7, 24.3 (2C), 15.7. GC-MS: m/z calcd. for $C_6H_{12}O$: 128 $[M]^+$; found: 128.



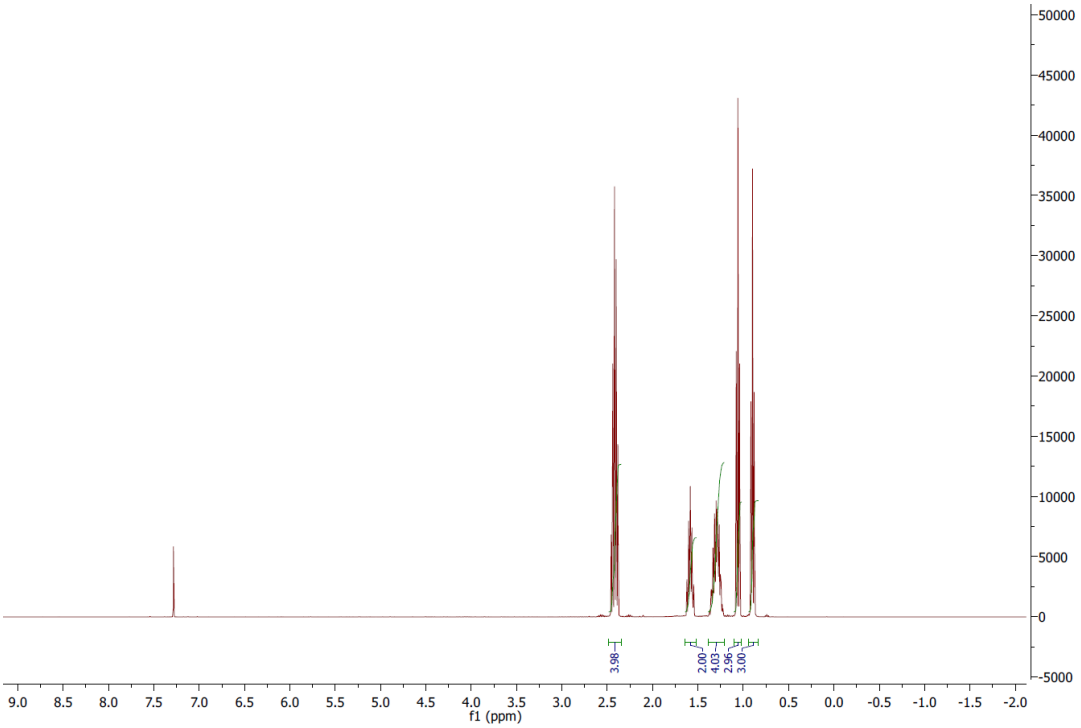


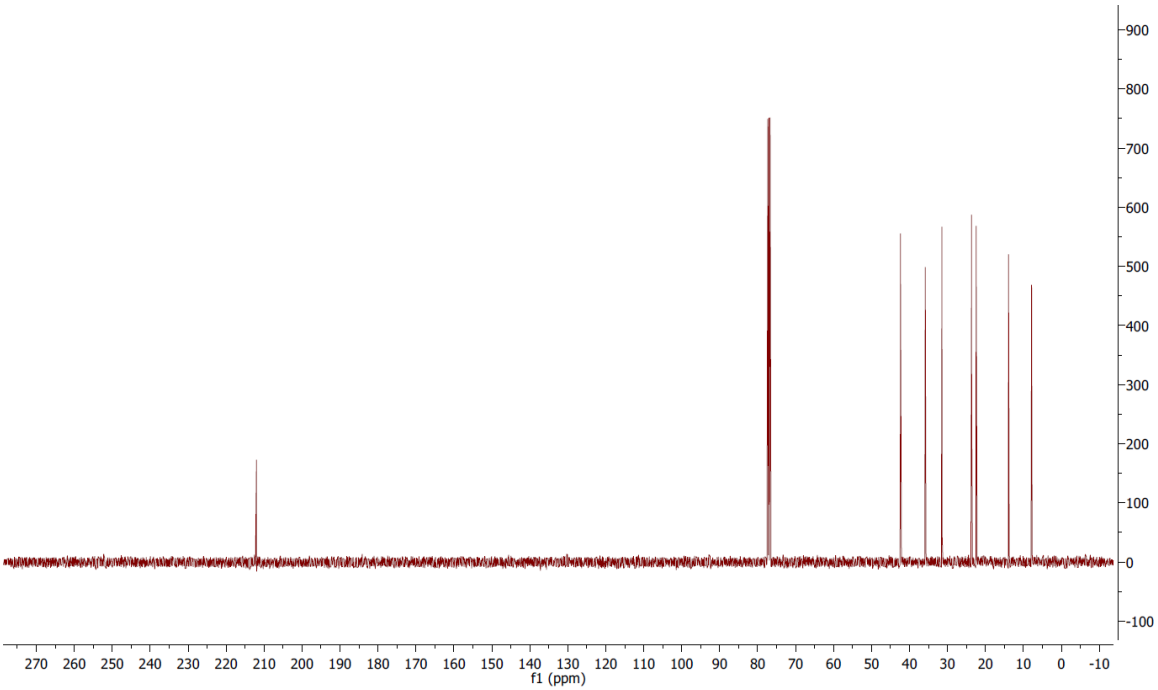
3-Octanone (4e)



1-Octen-3-one (**3e**, 0.76 mL, 5.00 mmol) was converted to 606 mg (4.80 mmol, 96 %) of 3-octanone (**4e**).[8]

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.45 (bs, 1H, OH), 1.62 – 1.10 (m, 11H, CH_2 and CH), 0.87 (t, J = 7.4 Hz, 3H, CH_3), 0.83 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 73.3, 36.9, 31.9, 31.9, 30.1, 25.3, 22.6, 14.0, 9.9. GC-MS: m/z calcd. for $C_8H_{16}O$: 128 $[M]^+$; found: 128.

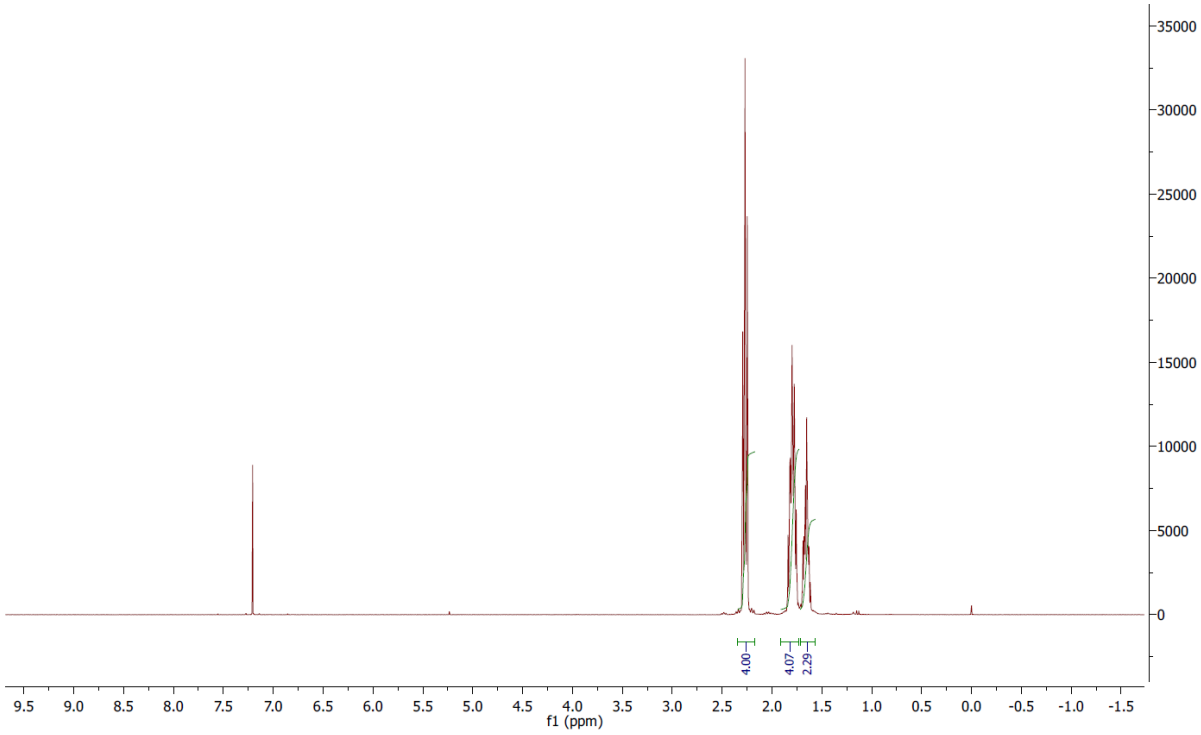


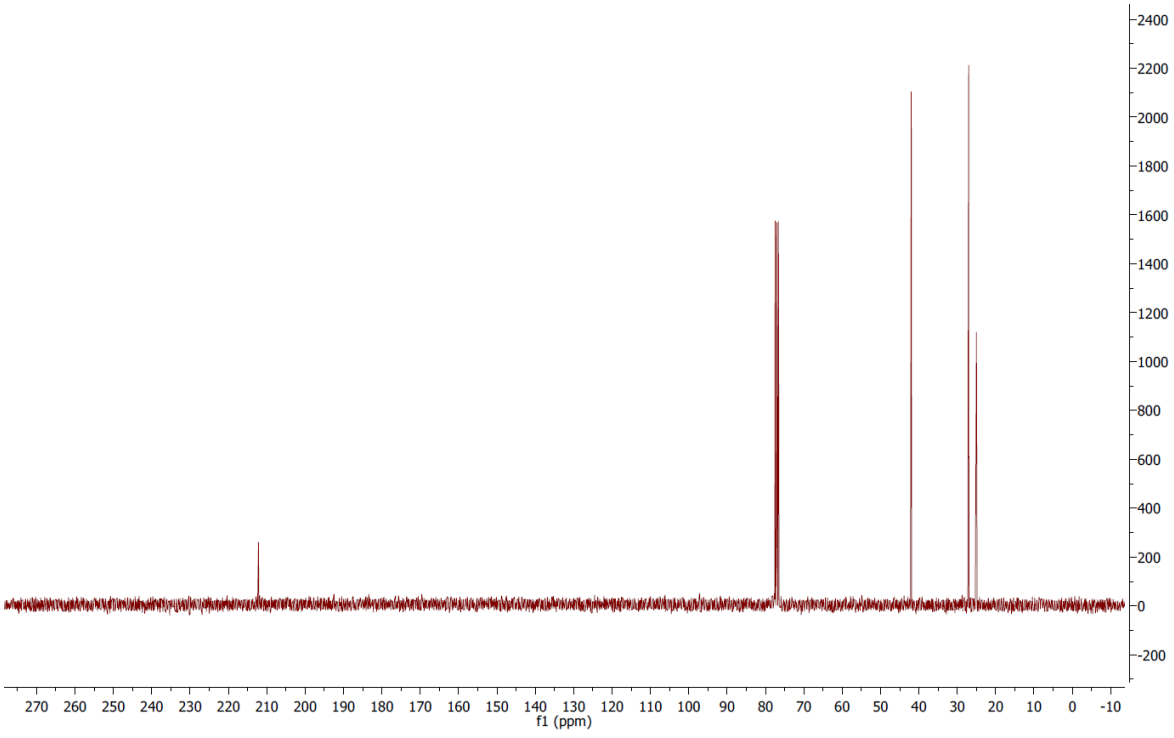


Cyclohexanone (4f)

2-Cyclohexen-1-one (**3f**, 0.48 mL, 5.00 mmol) was converted to 275 mg (2.80 mmol, 56 %) of cyclohexanone (**4f**).[7]

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.27 (t, J = 6.7, 6.1 Hz, 4H, CH_2), 1.90 – 1.73 (m, 4H, CH_2), 1.72 – 1.56 (m, 2H, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.2, 42.0 (2C), 27.0 (2C), 25.0. GC-MS: m/z calcd. for $C_6H_{10}O$: 98 $[M]^+$; found: 98.

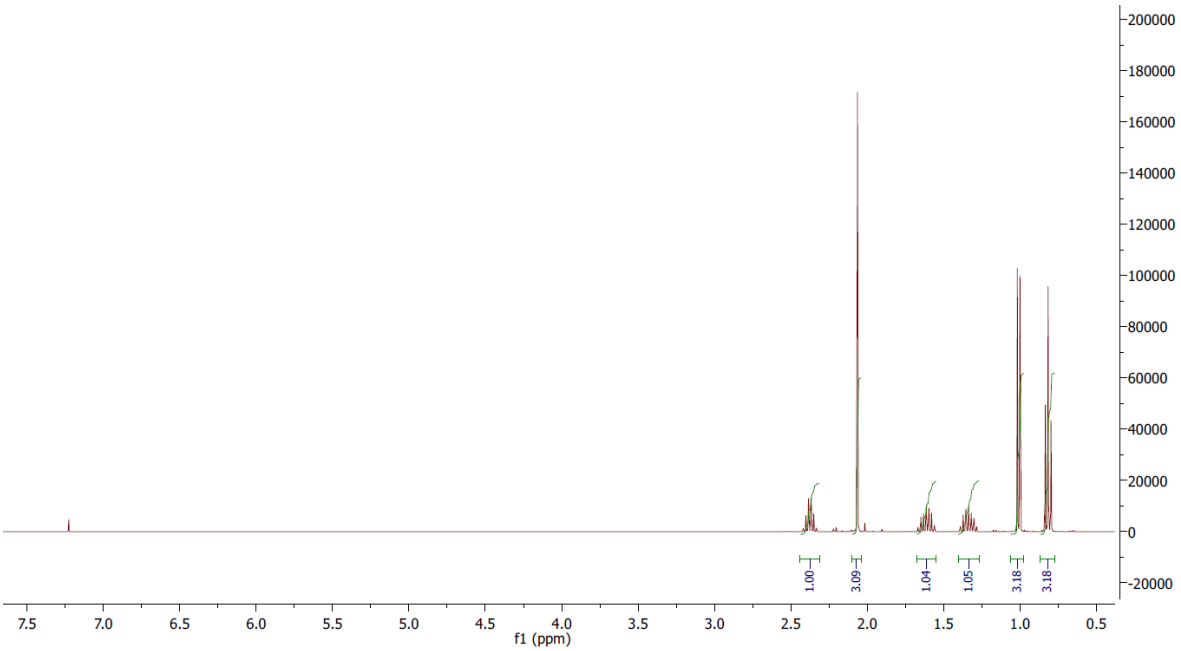


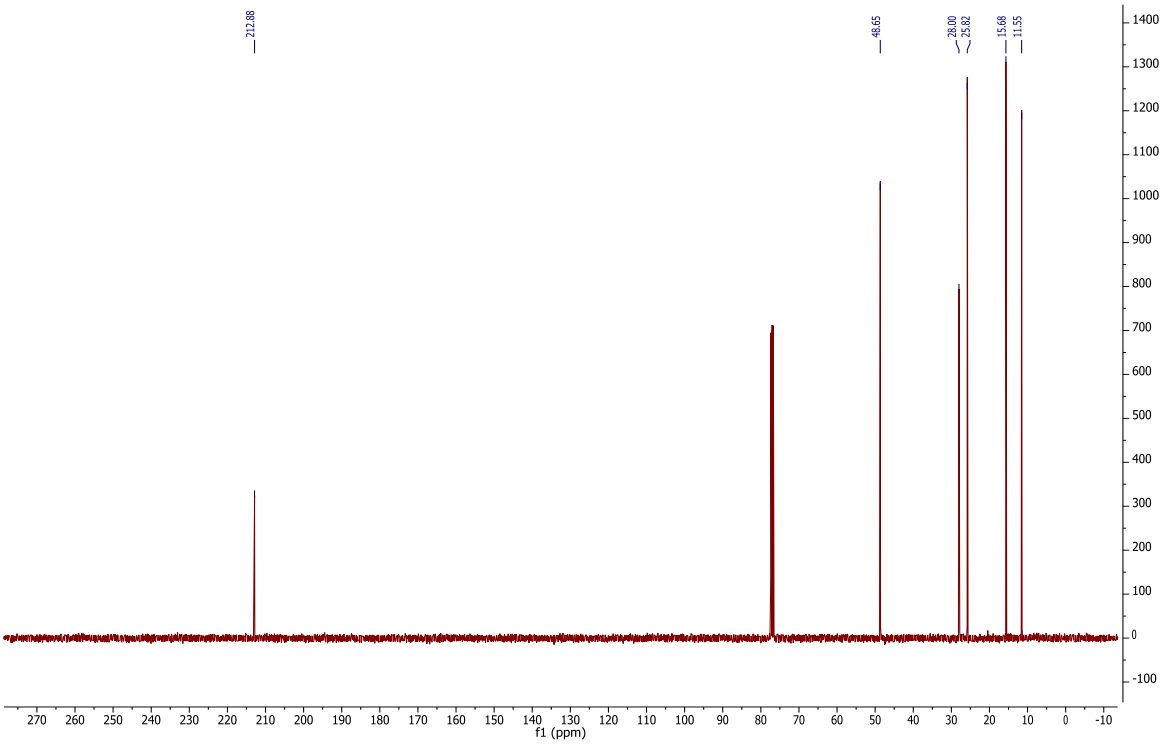


3-Methyl-2-pentanone (4g)

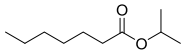
3-Methyl-2-penten-2-one (**3g**, 0.56 mL, 5.00 mmol) was converted to 391 mg (3,90 mmol, 78 %) of 1-phenyl-1-propanol (**4g**).[9]

^{1}H NMR (400 MHz, $CDCl_3$): 2.38 (h, J = 6.9 Hz, 1H, CH), 2.06 (s, 3H, CH_3), 1.68 – 1.55 (m, 1H, CH_2), 1.40 – 1.28 (m, 1H, CH_2), 1.01 (d, J = 7.0 Hz, 3H, CH_3), 0.82 (t, J = 7.4 Hz, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 212.9, 48.7, 28.0, 25.8, 15.7, 11.6. GC-MS: m/z calcd. for $C_6H_{12}O$: 100 $[M]^+$; found: 100.



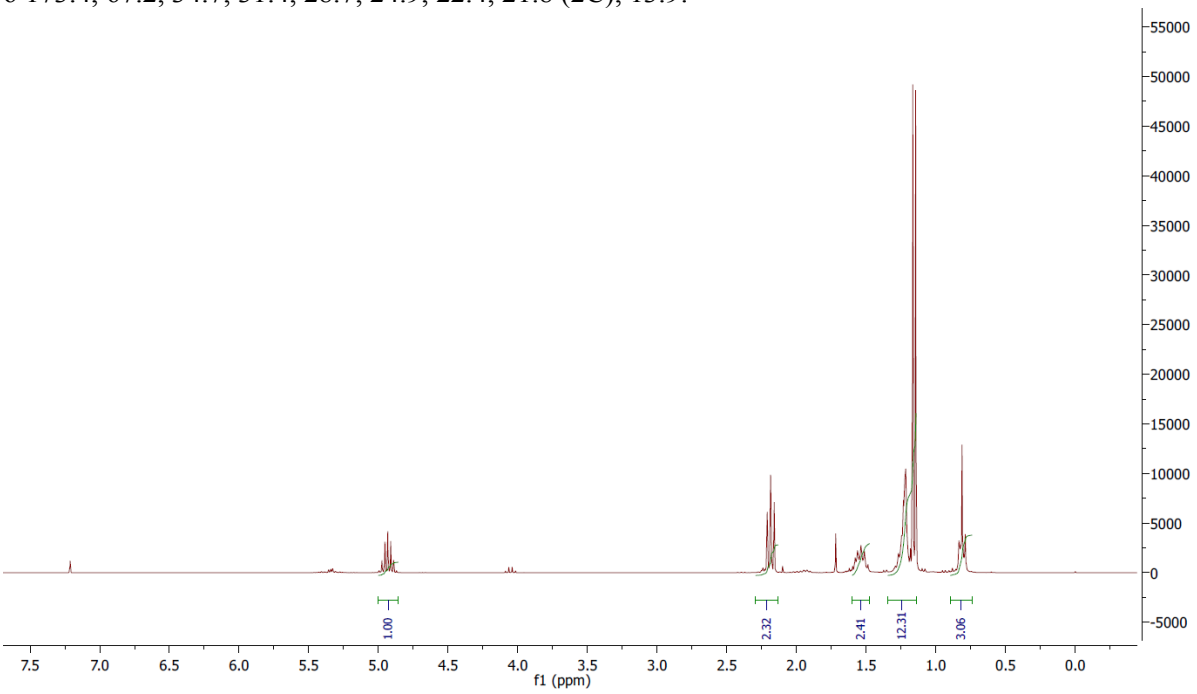


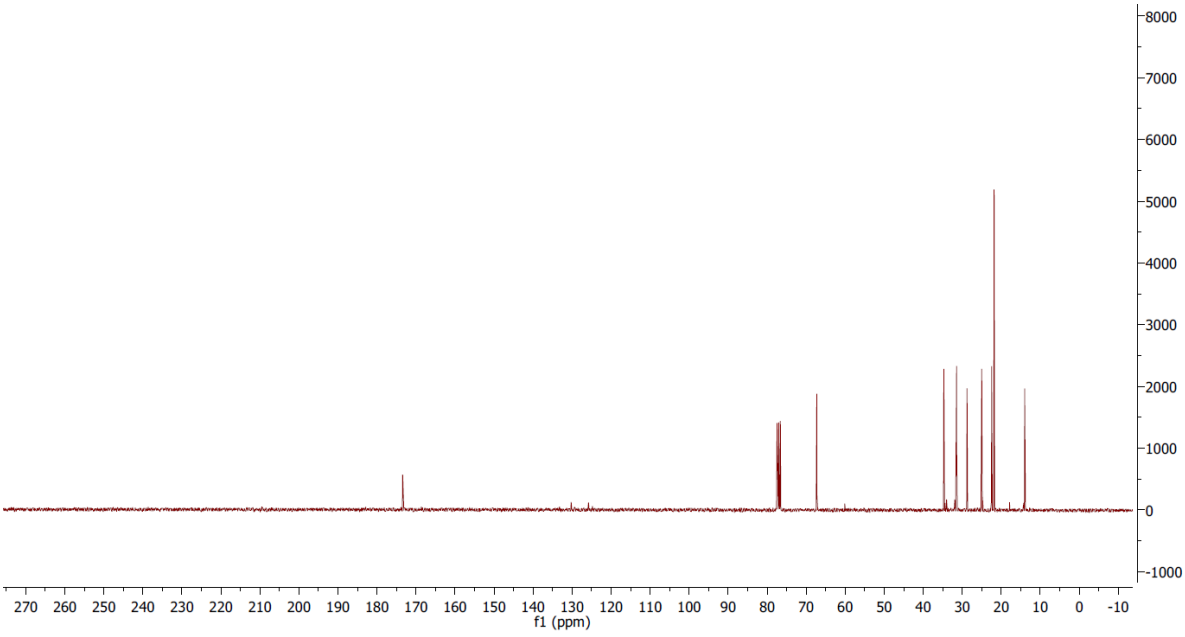
Isopropyl heptanoate (4h)



Methyl 6-heptenoate (**3h**, 0.78 mL, 5.00 mmol) was converted to 740 mg (4.30 mmol, 86 %) of isopropyl heptanoate (**4h**).

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.93 (hept, J = 6.3 Hz, 1H, CH), 2.29 – 2.13 (m, 2H, CH_2), 1.60 – 1.47 (m, 2H, CH_2), 1.35 – 1.14 (m, 12H, CH_2, CH_3), 0.90 – 0.74 (m, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 67.2, 34.7, 31.4, 28.7, 24.9, 22.4, 21.8 (2C), 13.9.

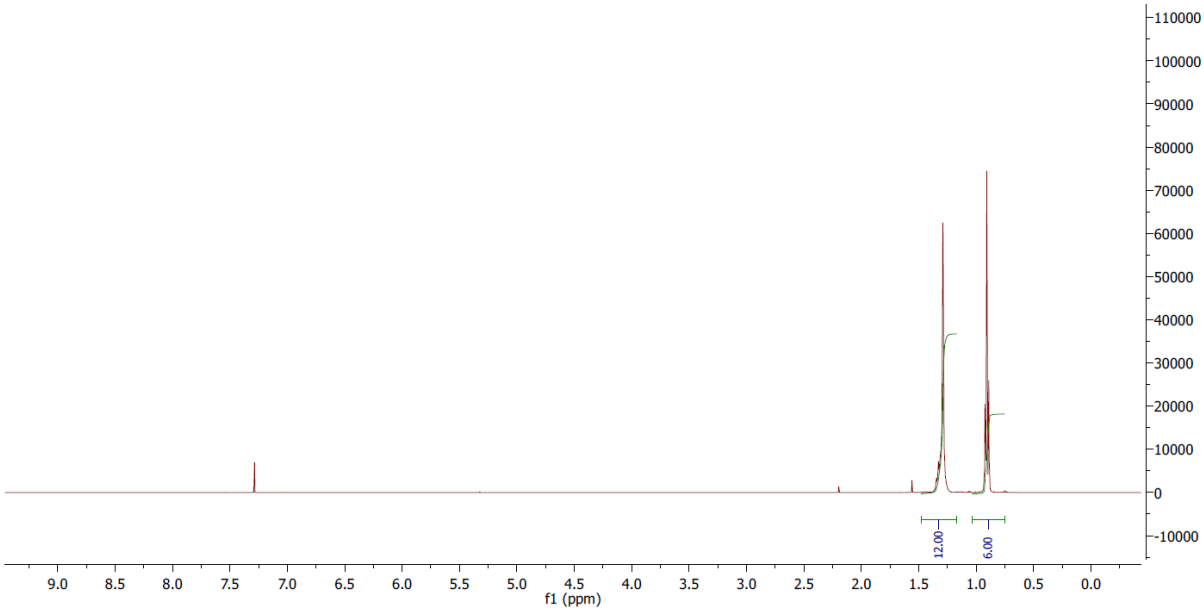


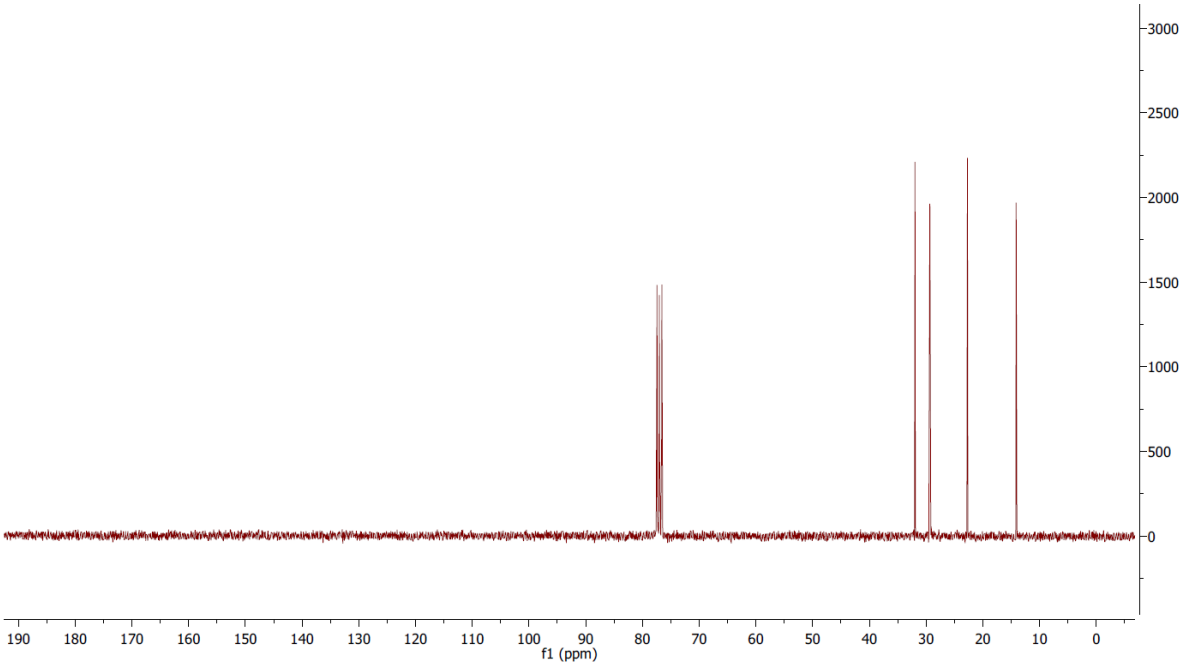


***n*-Octane (4i)**

1-Octene (**3i**, 0.67 mL, 5.00 mmol) was converted to 531 mg (4.65 mmol, 93 %) of *n*-octane (**4i**).[7]

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 – 1.22 (m, 12H, CH_2), 0.91 (t, J = 6.8 Hz, 6H, CH_3). ^{13}C NMR (75 MHz, CDCl3): δ 31.9 (2C), 29.3 (2C), 22.7 (2C), 14.1 (2C). GC-MS: m/z calcd. for C_8H_{18}: 114 $[M]^+$; found: 114.





4. References

[1] See: http://www.premex-reactorag.ch/index.php?page=464

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5.2 Statement: Scientific Independence

Universität Rostock
Dezernat 1
Referat 1.2

Doktorandinnen/Doktoranden-Erklärung gemäß § 4 Absatz 1 Buchstaben g und h der Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock

Name Puylaert, Pim
(Name, Vorname)

Anschrift Amberg 3, 18055, Rostock
(Straße, PLZ, Wohnort)

Ich habe eine Dissertation zum Thema

Alternatives to Phosphorus-Containing Pincer Ligands in Catalytic Hydrogenation

an der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock angefertigt. Dabei wurde ich von Frau/Herrn

Prof. Dr. Johannes G. de Vries

betreut.

Ich gebe folgende Erklärung ab:

1. Die Gelegenheit zum vorliegenden Promotionsvorhaben ist mir nicht kommerziell vermittelt worden. Insbesondere habe ich keine Organisation eingeschaltet, die gegen Entgelt Betreuerinnen/Betreuer für die Anfertigung von Dissertationen sucht oder die mir obliegenden Pflichten hinsichtlich der Prüfungsleistungen für mich ganz oder teilweise erledigt.

2. Ich versichere hiermit an Eides statt, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe. Dazu habe ich keine außer den von mir angegebenen Hilfsmitteln und Quellen verwendet und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen habe ich als solche kenntlich gemacht.

5.3 Statement: Contributions to Published Manuscripts

3.1: Selective Hydrogenation of α,β-Unsaturated Aldehydes and Ketones by Air-Stable Ruthenium NNS Complexes

P. Puylaert, R. van Heck, Y. Fan, A. Spannenberg, W. Baumann, M. Beller, J. Medlock, W. Bonrath, L. Lefort, S. Hinze, and J.G. de Vries, *Chemistry - A European Journal* **2017**, 23, 8473-8481, DOI: 10.1002/chem.201700806

In this project, I synthesised, purified, and crystallised the reported ruthenium complexes, performed most of the reaction optimisation, and assessed the substrate scope, including isolation of all products. I prepared samples for characterisations carried out by the Likat analytical department, and wrote the manuscript. These results led to a patent as well as this publication. My own contribution to this paper is around 75%.

3.2: Inexpensive Ruthenium NNS-Complexes as Efficient Ester Hydrogenation Catalysts with High C=O vs. C=C Selectivities

B.M. Stadler[†], P. Puylaert[†], J. Diekamp, R. van Heck, Y. Fan, A. Spannenberg, S. Hinze, and J.G. de Vries ([†]equal contributions), *Advanced Synthesis and Catalysis* **2018**, 260, 1151-1158, DOI: 10.1002/adsc.201701607

During the course of the first project, we noticed the catalysts were also active for the hydrogenation of esters, which resulted in a second patent. Based on the preliminary results, I wrote a proposal for a master project for Mr. Stadler, who did most of the investigations on the solvent effects on selectivity, and carried out half of the substrate scope reactions. I carried out the rest of the experimental work, including optimisation, substrate scope, as well as synthesising and crystallising the two reported complexes. The manuscript was written together, both main authors contributing around 40% overall.

3.3: Use of the Trost Ligand in Ruthenium-Catalyzed Asymmetric Hydrogenation of Ketones

M. Cettolin, P. Puylaert, L. Pignataro, S. Hinze, C. Gennari, and J.G. de Vries, *ChemCatChem* **2017**, 9, 3125-3130, DOI: 10.1002/cctc.201700545

During this project, I was involved in studying the formation of the active catalytic species. Additionally, I prepared and analysed samples and reference samples to determine the substrate scope yields and *e.e.*'s. My contribution totals around 30%.

3.4: Phosphine-free Pincer Cobalt Catalyst Precursors for the Selective Hydrogenation of Olefins

P. Puylaert, A. Dell'Acqua, F. El Ouahabi, A. Spannenberg, T. Roisnel, L. Lefort, S. Tin, and J.G. de Vries, *Manuscript submitted*

I synthesised, isolated and crystallised several cobalt complexes based on the NNS ligands we reported previously. In order to assess their catalytic activity, I then carried out a high-throughput screening with Dr. Lefort at InnoSyn B.V. in the Netherlands. Based on these results, I wrote a proposal for an Erasmus+ project for Mr. Dell'Acqua, who repeated the most promising reactions and performed further optimisation. We carried out the substrate scope together. I performed the poisoning experiment which identified the active catalyst as cobalt nanoparticles, and finally wrote the communication which has since been submitted. My contribution to this work is around 40%.

5.4 Curriculum Vitae

Personal

Name	Pim Puylaert
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Born	04-09-1988 in Meppel, the Netherlands
E-mail	p.puylaert@gmail.com

Education

From 11/2014 Ph.D. Homogeneous Catalysis, Leibniz Institute for Catalysis/Univ. of Rostock, Germany, with Prof. Johannes G. de Vries
Main topics: Phosphine-free alternatives for pincer ligands in homogeneous catalytic reduction; decarbonylation and carbonylation of biomass-derived platform chemicals.

02/2018-05/2018 Visiting PhD researcher, Institute des Sciences Chimiques de Rennes, France, with Prof. Christophe Darcel and Prof. Christian Bruneau

09/2011-08/2014 M.Sc. Molecular Chemistry, Univ. of Groningen, the Netherlands
1st Thesis "G-Quadruplex Systems for Artificial Photosynthesis" with Prof. Gerard Roelfes, Univ. of Groningen, the Netherlands
2nd Thesis "C-H Activation Reactions by the POP-pincer Osmium-Tetrahydride $OsH_4(xant(P^iPr_2)_2)$ with Prof. Miguel Ángel Esteruelas, Univ. of Zaragoza, Spain

09/2006-06/2011 B.Sc. Chemistry, Univ. of Groningen, the Netherlands
Bachelor thesis "Influence of different Substituents on Carboxylato-bridged Dinuclear Mn-tmtacn Complexes and a Labelling study of Imidazole in $(PPh_4)_2[Fe(CN)_5(im)]\cdot 2H_2O$" with Prof. Wesley R. Browne, Univ. of Groningen, the Netherlands

09/1999-05/2006 Gymnasium, RSG Stad en Esch, Meppel, the Netherlands
Natural Sciences and Engineering, elective courses Latin and Philosophy

Publications

[5] P.Puylaert, A. Dell'Acqua, F. El Ouahabi, A. Spannenberg, T. Roisnel, L. Lefort, S. Tin, J.G. de Vries, *Submitted*

[4] B.M. Stadler[†], P. Puylaert[†], J. Diekamp, R. van Heck, Y. Fan, A. Spannenberg, S. Hinze, J.G. de Vries, *Advanced Synthesis and Catalysis* **2018**; DOI: 10.1002/adsc.201701607 ([†]equal contributions)

[3] M. Cettolin, P. Puylaert, L. Pignataro, S. Hinze, C. Gennari, J.G. de Vries, "Use of the Trost Ligand in the Ruthenium-Catalyzed Asymmetric Hydrogenation of Ketones", *ChemCatChem* **2017**, 9, 3125-3130, *DOI*: 10.1002/cctc.201700545

[2] P. Puylaert, R. van Heck, Y. Fan, A. Spannenberg, W. Baumann, M. Beller, J. Medlock, W. Bonrath, L. Lefort, S. Hinze, J.G. de Vries, "Selective Hydrogenation of α,β-Unsaturated Aldehydes and Ketones by Air-Stable Ruthenium NNS Complexes", *Chemistry - A European Journal* **2017**, 23, 8473-8481, *DOI*: 10.1002/chem.201700806

[1] J. Alos, P. Puylaert, M. Olivan, E. Oñate, M.A. Esteruelas, "C-H Bond Activation Reactions in Ketones and Aldehydes Promoted by POP-Pincer Osmium and Ruthenium Complexes", *Organometallics,* **2015**, 34, 4908-4921, *DOI*: 10.1021/acs.organomet.5b00416

Book chapters and reviews

[2] P. Puylaert, A. Savini, S. Hinze, "Reduction of Nitro Compounds", in *Science of Synthesis: Catalytic Reduction in Organic Synthesis 2*, J.G. de Vries, Ed. **2018**, Georg Thieme Verlag, Stuttgart, *DOI: 10.1055/sos-SD-227-00139*

[1] M. Cettolin, P. Puylaert, J.G. de Vries, "Rhodium-Catalysed Hydrogenations Using Monodentate Ligands", in *Topics in Organometallic Chemistry,* Vol. 61*,* C. Claver, Ed. **2017**, Springer Verlag, Cham, *DOI*: 10.1007/3418_2017_174

Patents

[2] M. Beller, W. Bonrath, J.G. de Vries, Y. Fan, S. Hübner, L. Lefort, J.A. Medlock, P. Puylaert, R. van Heck, **2017,** "Selective hydrogenation of esters to alcohols catalyzed by ruthenium NNS complexes", WO 2017194663 A1 20171116

[1] M. Beller, W. Bonrath, J.G. de Vries, Y. Fan, S. Hübner, L. Lefort, J.A. Medlock, P. Puylaert, R. van Heck, **2017,** "Selective hydrogenation of aldehydes and ketones by ruthenium NNS complexes", WO 2017194662 A1 20171116

Conference participation

[4] 21st International Symposium on Homogeneous Catalysis (ISHC XXI) 2018, Amsterdam, The Netherlands: oral presentation "Selective Hydrogenation of α,β-Unsaturated Aldehydes, Ketones, and Esters by Phosphine-free Pincer-Ruthenium Complexes"

[3] International Symposium on Green Chemistry (ISGC) 2017, La Rochelle, France: oral presentation "Ru-NNS catalysts for selective hydrogenation of α,β-unsaturated Aldehydes, Ketones, and Esters"

[2] 50th Jahrestreffen deutscher Katalytiker 2017, Weimar, Germany (poster presentation)

[1] 20th International Symposium on Homogeneous Catalysis (ISHC XX) 2016, Kyoto, Japan (poster presentation)

Languages

CEFR (Common European Framework of Reference for Languages) levels, where applicable.

Dutch – Native
English – Fluent (C2)
German – Fluent (>C1)
Spanish – Intermediate (B1)
French – Basic (A2)

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