Transition Metal-Catalyzed Asymmetric Hydroamination of Alkenes (AHA)

Kai C. Hultzsch

Institut für Organische Chemie, Friedrich-Alexander Universität Erlangen-Nürnberg, Henkestr. 42, 91054 Erlangen, Germany
Fax (+49)-9131-852-6865, e-mail: hultzsch@chemie.uni-erlangen.de

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Dedicated to Dick Schrock on the occasion of his 60th birthday.

Abstract: The hydroamination of unsaturated carbon-carbon linkages allows a facile and highly atom-economical access to industrially relevant nitrogen-containing basic and fine chemicals as well as naturally occurring alkaloid skeletons. Significant research efforts have led to the development of efficient catalyst systems for intra- and intermolecular hydroamination reactions. Of particular interest are hydroaminations promoted by chiral catalysts, in which a new chiral center is generated or chiral substrates are kinetically resolved. This review will give an overview on the current state of the art in this rapidly evolving field of catalysis.

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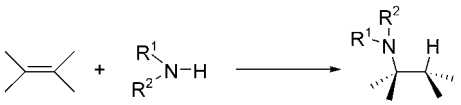
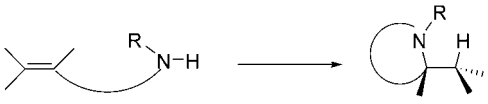
Keywords: amines; asymmetric catalysis; homogeneous catalysis; hydroamination; nitrogen heterocycles

1 Introduction

Amines are undoubtedly an important class of compounds, because many natural occurring compounds and biologically active molecules contain amine functionalities. Industrial applications of amines range from simple use as solvents, additives for pharmaceuticals, bactericides, flotation auxiliaries, anti-foam agents, corrosion inhibitors, detergents or dyes. Classical methods for their synthesis, either on laboratory or industrial scale, include transformations of alcohols or alkyl halides into amines, reductive amination of carbonyl compounds, aminoalkylation, reduction of amides, nitriles, azides or nitro compounds and last but not least the Ritter reaction.[1] All these methods have in common that refined starting materials are required, which are often expensive and which can be difficult to synthesize or dangerous to handle. The hydroamination reaction, on the other hand, is a 100% atom-economical, waste-free process of fundamental simplicity in which an amine is added to an olefin either in an intermolecular [Eq. (1)] or intramolecular [Eq. (2)] fashion.[2,3] Therefore, from an industrial point of view this reaction could be a highly useful and efficient method for the synthesis of a wide variety of industrially relevant basic and fine chemicals, as well as pharmaceuticals, from readily available and inexpensive starting materials.



(1)



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The direct addition of amines to alkenes is thermodynamically feasible ($\Delta G^0 \approx -14.7$ kJ mol^{-1} for the addition of ammonia to ethylene)[2a,b] with a slightly exothermic to thermoneutral reaction enthalpy. However, this seemingly simple reaction is hampered by a high activation barrier caused by an electrostatic repulsion between the nitrogen lone pair of the approaching amine

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Kai Carsten Hultzsch was born in Wiesbaden, Germany in 1971. He studied chemistry at the University of Mainz from 1991–1996. In 1994/1995 he spent one semester in the group of Prof. Ian Manners at the University of Toronto. He finished his PhD in 1999 under the guidance of Prof. Jun Okuda in Mainz working on rare earth metal-based constrained geometry catalysts. He then joined the group of Prof. Richard R. Schrock at the Massachusetts Institute of Technology in Cambridge, MA as a Feodor Lynen postdoctoral fellow developing homogeneous and heterogeneous asymmetric metathesis catalysts. In 2001 he began his independent research career as a DFG Emmy Noether fellow at the University of Erlangen-Nürnberg. His main area of interest is the development of transition metal-based catalysts for enantioselective and stereoselective olefin heterofunctionalization, as well as (co)polymerization of non-polar and polar monomers.

and the π-bond of the electron-rich olefin. A concerted [2+2] addition of the N–H bond to the alkene is an orbital-symmetry forbidden process and is unfavorable due to the large difference in energy between the carbon–carbon π-bond and the N–H σ-bond. The activation barrier cannot be overcome by increasing the reaction temperature because the negative reaction entropy shifts the equilibrium towards the starting materials. Therefore, amines add commonly only to activated, electron-deficient alkenes in the absence of a catalyst.[4]

Over the last two decades many groups have contributed to the area of transition metal-catalyzed hydroamination and various catalyst systems based on early transition metals (groups 3–5, as well as lanthanides and actinides) or late transition metals (groups 8–10) have been developed.[5] Unfortunately, all catalyst systems are more or less confined in their choice of substrates. Most common are hydroaminations of activated C–C multiple bonds, either alkynes, strained olefins (e.g., norbornene), vinylarenes or 1,3-dienes. An important goal in transition metal catalysis is to gain control over diastereoselectivity and regiochemistry (Markovnikov/anti-Markovnikov addition) of the hydroamination product. In this respect, generation of a chiral center in the hydroamination process constitutes a particularly attractive application of this reaction, but the asymmetric hydroamination of alkenes (AHA) has remained a challenging task. This area has drawn much less attention and was briefly reviewed recently.[6] However, significant progress in this area since then prompted us to give a more up to date overview of this rapidly evolving field including results until August 2004. Hydroamination of alkynes will only be covered as long as a new chiral center is generated in that process. Furthermore, hydroamination reactions of enantiomerically pure substrates using achiral catalysts[7] are outside of the scope of this review.

2 Rare Earth Metal-Based Catalysts

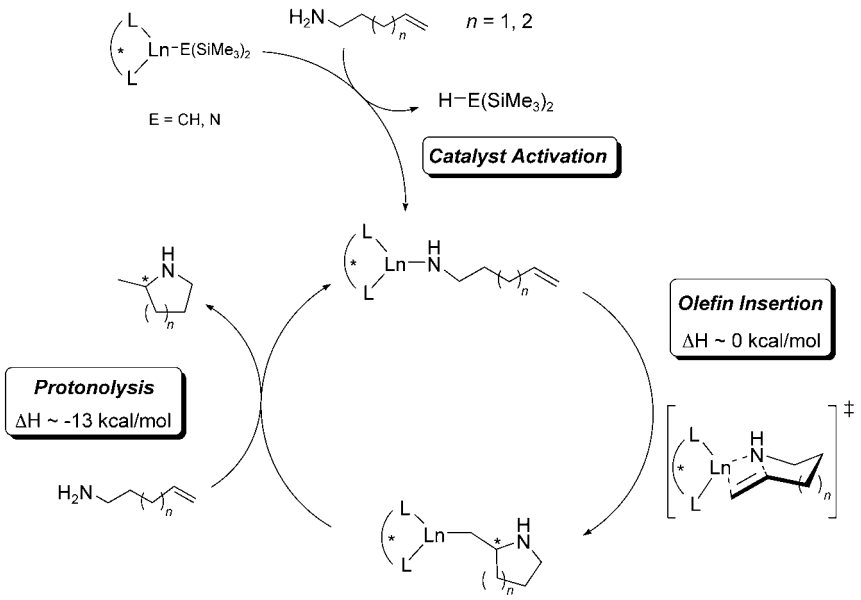
2.1 Hydroamination/Cyclization of Aminoalkenes

The chemistry of organometallic rare earth metal compounds has progressed over the last two decades significantly, in particular because of the unique chemical behavior of these elements facilitating a wide variety of catalytic applications, ranging from polymer to small molecule synthesis.[8] Unfortunately, the high air and moisture sensitivity of these compounds require elaborate Schlenk and glove-box techniques, not commonly found in most synthetic organic laboratories. Furthermore, many functional groups are either not tolerated (e.g., alcohols, acids) or significantly reduce catalytic performance (e.g., ethers).

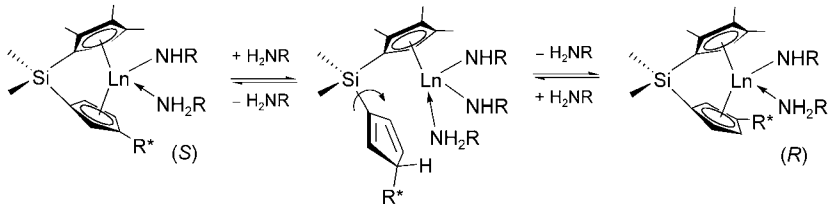
Nevertheless, organo-rare earth metal complexes have been found to be particularly suitable for the hydroamination of alkenes with non-activated double bonds.[21] However, intermolecular hydroamination reactions with these catalysts are problematic. Unfavorable factors are not only the negative reaction entropy, but also the competition between strongly coordinating amines and weakly binding alkenes. Therefore, most rare earth metal-catalyzed reactions have been performed in an intramolecular fashion producing predominantly pyrrolidine and piperidine derivatives. Although rare earth metals have been shown to catalyze the intermolecular hydroamination at elevated temperatures,[9] no example of an asymmetric intermolecular hydroamination has been reported to date.

Early catalyst systems were based solely on the metallocene ligand framework and only very recently have other ligand sets been utilized for rare earth metal hydroamination catalysts.[10]

The mechanism of the hydroamination/cyclization[11,12] proceeds through a rare earth metal-amido species, which is formed upon protonolysis of a rare earth metal-amido or -alkyl bond in the precatalyst (Scheme 1). The first step of the catalytic cycle involves insertion of the olefin into the rare earth metal-amido bond with a seven-membered chair-like transition state (for $n=1$). The roughly thermoneutral insertion step[12] is usually rate-determining, giving rise to a zero order rate dependence on substrate concentration and first order rate dependence on catalyst concentration. The re-



Scheme 1. Simplified mechanism for rare earth metal-catalyzed hydroamination/cyclization.



Scheme 2. Epimerization of chiral lanthanocene complexes during the hydroamination reaction.

sulting rare earth metal-alkyl species undergoes fast protonolysis with a second amine molecule, regenerating the rare earth metal-amido species and releasing the heterocyclic product.

2.1.1 Chiral Lanthanocene Catalysts

The first asymmetric hydroamination catalyst system based on C_1-symmetrical chiral *ansa*-lanthanocene complexes with a (+)-neomenthyl, (−)-menthyl or (−)-phenylmenthyl substituent attached to one of the cyclopentadienyl ligands was reported in 1992 by Marks (Figure 1).[13] The chiral cyclopentadienyl ligands can coordinate with either diastereotopic face giving rise of two diastereomeric complexes. However, one of the two diastereomers usually predominates and most of the catalysts were obtained diastereomerically pure by fractional crystallization.

Catalysts **1**–**3** displayed the same high catalytic activity as their achiral counterparts,[11] with catalytic activity increasing with increasing ionic radius.[14] Catalytic results for the most common substrates, 2,2-dimethylpent-4-enylamine (**4**) and pent-4-enylamine (**6**), are compiled in Tables 1 and 2. Unfortunately, the chiral lanthanocenes underwent facile epimerization under the conditions of catalytic hydroamination *via* reversible protolytic cleavage of the metal cyclopentadienyl bond (Scheme 2).[13,15,16]

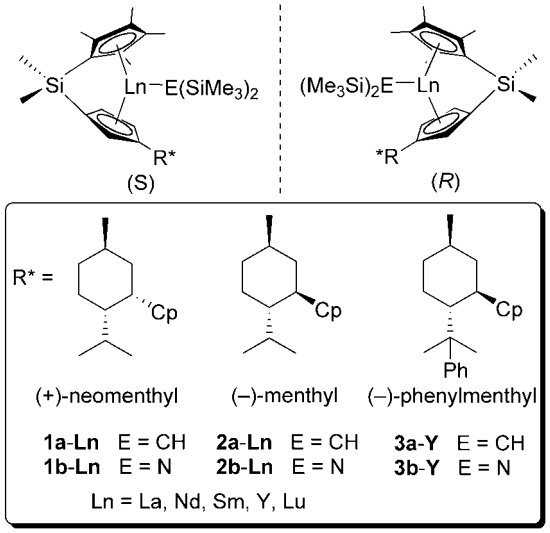
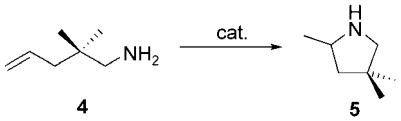


Figure 1. Chiral lanthanocene precatalysts for asymmetric hydroamination.

Table 1. Lanthanocene-catalyzed asymmetric hydroamination/cyclization of 2,2-dimethyl-pent-4-enylamine (**4**).



4 **5**

Entry	Catalyst	T [°C]	TOF [h^{-1}]	ee [%] (configuration/sign)[a]	Ref.
1	(*R*)-**1b-La**	25		14 (−)[b]	[13a, c]
2	(*R*,*S*)-**1a-Nd**	−20		61 (−)[b]	[13c]
3	(*R*)-**1a-Sm**/(*R*)-**1b-Sm**	25		51 (−)[b]	[13a, c]
4	(*R*)-**1a-Sm**/(*R*)-**1b-Sm**	−30		64 (−)[b]	[13a, c]
5	(*R*,*S*)-**1a-Y**	25	38	36 (−)[b]	[13c]
6	(*R*)-**1b-Y**	25	21	40 (−)[b]	[13c]
7	(*R*,*S*)-**1a-Lu**	25		36 (+)[b]	[13c]
8	(*R*)-**1b-Lu**	25		40 (+)[b]	[13c]
9	(*S*)-**2b-Sm**	25	84	53 (+)[b]	[13a, c]
10	(*S*)-**2b-Sm**	−30		74 (+)[b]	[13a, c]
11	(*R*)-**2a-Y**/(*R*)-**2b-Y**	25	9	43 (+)[b]	[13c]
12	(*R*)-**2a-Lu**	25		29 (−)[b]	[13c]
13	(*R*)-**3a-Y**	25	8	56 (+)[b]	[13c]
14	(60/40) (*R*,*S*)-**3b-Y**	25		54 (+)[b]	[13c]
15	(*S*)-**10-Sm**	25	33.4	32 (+)[c]	[16a]
16	(*S*)-**10-Y**	25		17 (+)[c]	[16a]
17	(*S*)-**10-Lu**	25		1.5 (+)[c]	[16a]

[a] $[\alpha]_D^{20}$: −24.3° for (*R*)-**5**, see Ref.[13c]
[b] Enantiomeric excess determined by ^{19}F NMR spectroscopy of Mosher amides.
[c] Enantiomeric excess determined by GC of Mosher amides.

Despite this epimerization process, cyclization of aminopentenes yielded pyrrolidine derivatives with up to 74% ee at low temperatures (Table 1, entry 10 and Table 2, entry 13). In fact, the configuration of the planar chiral cyclopentadienyl ligand seems to be of insignificant importance for the stereochemical outcome of the cyclization. Both (*R*) and (*S*) catalysts (or mixtures thereof) gave the products with similar enantiomeric excess and identical sense of optical rotation (Table 1, entries 5 and 6, 7 and 8, 13 and 14, and Table 2, entries 1 and 2, 5–7, 9 and 10, 12 and 14). Hence, access to the opposite enantiomer of the hydroamination product requires a redesign of the chiral lanthanocene catalyst.

Complexes with a (+)-neomenthyl substituent on the cyclopentadienyl ligand generally produced the (*R*)-(−)-pyrrolidines, whereas (−)-menthyl- and (−)-phenylmenthyl-substituted complexes yielded the (*S*)-(+)-pyrrolidines. The only exceptions seem to be complexes based on the smallest rare earth metal investigated, lutetium, which gave the opposite enantiomer (Table 1, entries 7, 8, 12 and Table 2, entry 11). Maximum enantioselectivities were observed with samarocene catalysts. Complexes based on rare earth metals with either larger or smaller ionic radius were less selective (Figure 2). The *gem*-dimethyl-substituted aminopentene **4** was cyclized 3–10 times faster than the unsubstituted aminopentene **6** due to the favorable Thorpe–Ingold effect,[18] but this went along with a diminished selectivity (Δee = 1–26%).

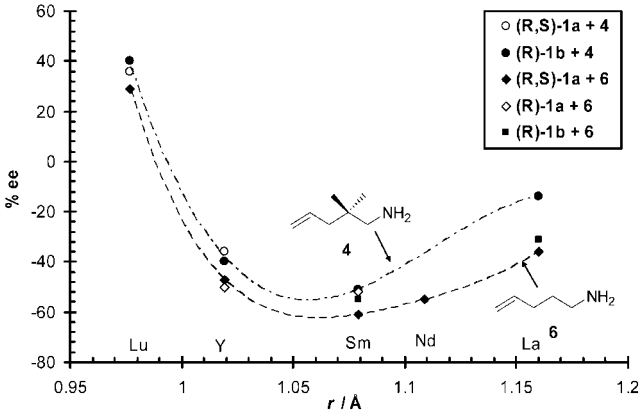
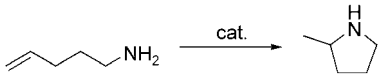


Figure 2. Ionic radius dependence of enantiomeric excess for pyrrolidines obtained from aminopentenes **4** and **6** with neomenthyl-substituted lanthanocene catalysts **1**. The lines are drawn as a guide for the eye.

There is no general trend in which the enantioselectivity of pyrrolidine products depends on the chiral substituent on the cyclopentadienyl ligand for a given rare earth metal. For catalysts **1**–**3** based on yttrium the absolute value of the enantiomeric excess increases in the order neomenthyl < menthyl < phenylmenthyl for aminopentene **4**, but in the order neomenthyl < phenylmenthyl < menthyl for aminopentene **6**.

Table 2. Lanthanocene-catalyzed asymmetric hydroamination/cyclization of pent-4-enylamine (**6**).



6 **7**

Entry	Catalyst	T [°C]	TOF [h^{-1}]	ee [%] (configuration/sign)[a]	Ref.
1	(*R*,*S*)-**1a-La**	25		36 (−)[b]	[13c]
2	(*R*)-**1b-La**	25		31 (−)[b]	[13a, c]
3	(*R*,*S*)-**1a-Nd**	25	93	55 (−)[b]	[13c]
4	(*R*,*S*)-**1a-Nd**	0	11	64 (−)[b]	[13c]
5	(*R*,*S*)-**1a-Sm**	25	42	61 (−)[b]	[13c]
6	(*S*)-**1b-Sm**	25	33	55 (−)[b]	[13c]
7	(*R*)-**1a-Sm**/(*R*)-**1b-Sm**	25	62	52 (−)[b]	[13a, c]
8	(*R*)-**1a-Sm**/(*R*)-**1b-Sm**	0		58 (−)[b]	[13a, c]
9	(*R*,*S*)-**1a-Y**	25	4	47 (−)[b]	[13c]
10	(*R*)-**1b-Y**	25		50 (−)[b]	[13c]
11	(*R*,*S*)-**1a-Lu**	25		29 (+)[b]	[13c]
12	(*S*)-**2b-Sm**	25	33	62 (+)[b]	[13a, c]
13	(*S*)-**2b-Sm**	0		72 (+)[b]	[13a, c]
14	(*R*)-**2b-Sm**	25		60 (+)[b]	[13c]
15	(*R*)-**2a-Y**/(*R*)-**2b-Y**	25		69 (+)[b]	[13c]
16	(*R*)-**3a-Y**	25		64 (+)[b]	[13c]
17	(*S*)-**10-Sm**	25	2.6	46 (+)[c]	[16a]
18	(*S*)-**10-Sm**	60	28.4	37 (+)[c]	[16a]
19	(*S*)-**10-Y**	60	2.9	5 (+)[c]	[16a]
20	(*S*)-**10-Lu**	60		16 (−)[c]	[16a]

[a] $[\alpha]_D^{20}$: −20.0° for (*R*)-**7**, see Ref.[17a]
[b] Enantiomeric excess determined by ^{19}F NMR spectroscopy of Mosher amides.
[c] Enantiomeric excess determined by GC of Mosher amides.

A stereomodel explaining the observed absolute configuration of the pyrroldine product **7** has been proposed (Figure 3).[13c] Preferred formation of the (*S*) pyrrolidine enantiomer was rationalized by unfavorable steric interactions between an axial substituent of the substrate with the substituents on the cyclopentadienyl ligands of the (*S*) lanthanocene diastereomer in the transition state of the cyclization. Therefore, significant enantiomeric excess can only be achieved if either the (*R*) or (*S*) diastereomer predominates in the epimerization equilibrium under catalytic conditions. Indeed, when precatalysts **1**–**3** were treated with a 40–50 fold excess of *n*-propylamine, the resulting amido-amine lanthanocenes equilibrated within 2 h at 25 °C to give predominantly the (*R*) isomer for (+)-neomenthyl complexes **1** in a roughly 80:20 (*R*):(*S*) ratio, whereas (−)-menthyl

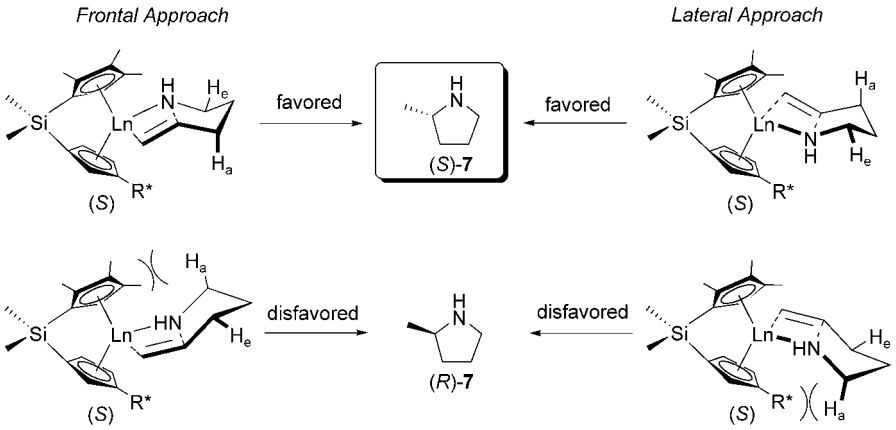
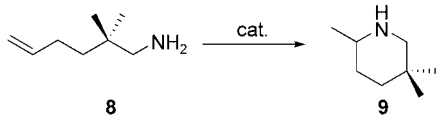


Figure 3. Proposed stereomodels for the observed absolute product configuration of **7**.[13c]

Table 3. Catalytic hydroamination/cyclization of 2,2-dimethyl-hex-5-enylamine (**8**).

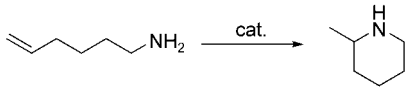


8 **9**

Entry	Catalyst	T [°C]	TOF [h^{-1}]	ee [%] (configuration/sign)	Ref.
1	(*R*)-**1a-Sm**/(*R*)-**1b-Sm**	25		17 (*R*)[a]	[13a, c]
2	(*S*)-**2b-Sm**	25	2	15 (*R*)[a]	[13a, c]
3	(*S*)-**10-Sm**	25	0.6	41 (*S*)[b]	[16a]
4	(*S*)-**10-Sm**	60	89.4	43 (*S*)[b]	[16a]
5	(*S*)-**10-Y**	25	2.1	67 (*S*)[b]	[16a]
6	(*S*)-**10-Y**	60	86	54 (*S*)[b]	[16a]
7	(*S*)-**10-Lu**	60		15 (*S*)[b]	[16a]

[a] Enantiomeric excess determined by ^{19}F NMR of Mosher amides.
[b] Enantiomeric excess determined by GC of Mosher amides.

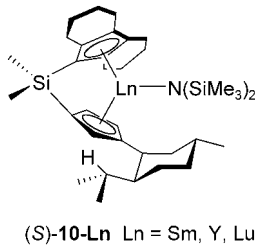
Table 4. Catalytic hydroamination/cyclization of hex-5-enylamine (**11**).[16a]



11 **12**

Entry	Catalyst	T [°C]	TOF [h^{-1}]	ee [%] (sign)[a]
1	(*S*)-**10-Sm**	60	6.6	10 (+)
2	(*S*)-**10-Y**	60	3.6	3.2 (+)

[a] $[\alpha]_D^{20}$: 5.2° for (*S*)-**12**, see Ref.[17b], enantiomeric excess determined by GC of Mosher amides.



(*S*)-**10-Ln** Ln = Sm, Y, Lu

Figure 4. Chiral lanthanocene complexes with extended "wingspan".

and (−)-phenylmenthyl complexes favored the (*S*) isomer [> 95:5 for **2** and ≈ 90:10 (*S*):(*R*) for **3**].[13b, c] Equilibrium ratios were independent of the epimer ratio of the precatalyst. The antipodal epimer equilibrium ratios for (+)-neomenthyl complexes opposed to (−)-menthyl or (−)-phenylmenthyl complexes[19] rationalize the reversion of absolute product configuration observed for products obtained with (−)-menthyl-, respectively, (−)-phenylmenthyl-substituted catalysts in comparison to products obtained with (+)-neomenthyl-substituted catalysts. For the smaller and sterically more congested lutetocenes other steric factors must be considered in order to explain the opposite configuration observed with these catalysts.

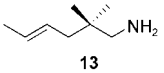
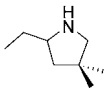
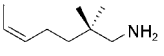
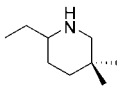
Cyclization of aminohexene **8** generated the six-membered piperidine **9** with disappointingly low enantioselectivity compared to the formation of five-membered ring pyrrolidine products (Table 3, entries 1 and 2).

In 2002 Marks expanded the library of chiral *ansa*-lanthanocene complexes by replacing the tetramethylcyclopentadienyl ligand in **2** with an octahydrofluorenyl ligand (Figure 4).[16a] The extended "wingspan" of this ligand was supposed to provide an increased enantiofacial discrimination for prochiral substrates. Indeed, (*S*)-**10-Sm** and (*S*)-**10-Y** displayed improved enantioselectivity for the cyclization of *gem*-dimethyl-substituted aminohexene **8** (Table 3, entries 3–6). However, the less reactive, unsubstituted aminohexene **11** (Table 4) was cyclized with low enantioselectively and pyrrolidines **5** and **7** were formed less selectively than with the corresponding tetramethylcyclopentadienyl complexes **2** (Table 1, entries 9, 11, 12 *vs.* entries 15–17; Table 2, entries 12, 14, 15 *vs.* entries 17–20).

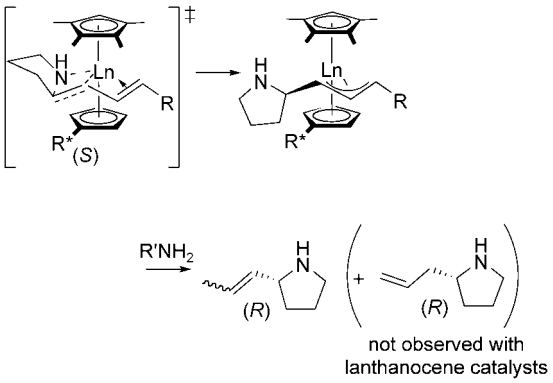
Hydroamination/cyclization of terminal olefins always generates α-methyl-substituted azacycles. It would be highly desirable to create longer side-chains, but internal olefins are much less reactive for hydroamination. The hydroamination of 1,1- or 1,2-disubstituted olefins requires significantly harsher reaction conditions.[20] Internal alkenes **13** and **15** react only sluggishly at 80–100 °C (Table 5).[16b] Piperidine **16** was formed with comparable rates as pyrrolidine **14**, which is in contrast to the general trend of significant faster five-membered ring formation observed with other aminoalkenes. Enantioselectivities were rather moderate, but (*S*)-**10-Y** afforded piperidine **16** with an astonishing 58% ee at 100 °C.

The hydroamination of 1,3-dienes on the other hand proceeds with relative ease, because of the formation of a rather stable η^3-allyl intermediate during the cata-

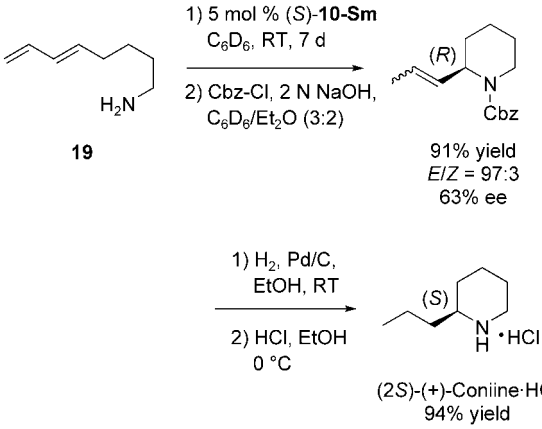
Table 5. Catalytic asymmetric hydroamination/cyclization of sterically encumbered aminoalkenes.[16b]

Entry	Substrate	Product	Catalyst[a]	T [°C]	TOF [h^{-1}]	ee [%] (sign)
1			(*S*)-**2b-Sm**	80	0.26	28 (+)
2	**13**	**14**	(*S*)-**10-Sm**	80	0.18	24 (+)
3			(*S*)-**10-Y**[b]	100	0.07	26 (+)
4			(*S*)-**2b-Sm**	80	0.16	16 (+)
5	**15**	**16**	(*S*)-**10-Sm**	80	0.11	16 (+)
6			(*S*)-**10-Y**[b]	100	0.30	58 (−)
7			(*S*)-**10-Y**[c]	60	0.03	68 (−)

[a] Reaction conditions: 5 mol % catalyst, C_6D_6.
[b] Reaction performed in *o*-xylene-d_{10}.
[c] 20 mol % catalyst.



Scheme 3. Stereomodel for the hydroamination/cyclization of aminodienes. The silicon linker bridging the two cyclopentadienyl ligands is omitted for the sake of clarity.



Scheme 4. Synthesis of (+)-coniine·HCl *via* enantioselective aminodiene hydroamination/cyclization.[21b] Cbz = benzyloxycarbonyl.

lytic cycle. Protonation of this η^3-allyl species can yield *E*/*Z* vinylpyrrolidines and vinylpiperidines and in certain cases also the allyl isomers (Scheme 3). Cyclizations with lanthanocenes (*S*)-**2b-Sm**, (*S*)-**2-Y** or (*S*)-**10-Sm** (Table 6) generated the *E* olefins with high selectivity ($E/Z \geq 93:7$).[21] The reaction rates are higher for the aminodienes compared to the corresponding aminoalkenes, despite increased steric encumbrance of the cyclization transition state (Scheme 3). The increased rates go at the expense of enantioselectivities (compare Table 2, entries 12, 15 and 17 with Table 6, entries 1–3, respectively Table 3, entry 3 with Table 6, entry 6). The aminooctadiene **19** is the only exception with 63% ee observed in benzene solution at 25 °C (71% ee in methylcyclohexane at 0 °C) using (*S*)-**10-Sm**, which represents a significant improvement in comparison to 10% ee observed for **11** at 60 °C (Table 4, entry 1 and Table 6, entry 5).

The enantiomeric excess of **20** was indifferent in various aromatic and aliphatic solvents.[21b] Addition of exogeneous chiral phosphine or pyBox ligands had little or no positive influence on enantioselectivity and *E*/*Z* ratio, but reaction rates were depressed.

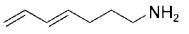
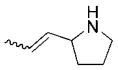
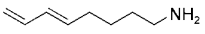
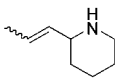
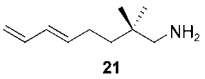
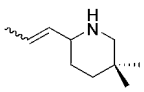
The intramolecular hydroamination allows access to a wide range of alkaloid skeletons[7a–c,9b,10b,22,23] and pharmaceutically relevant targets.[20b] Marks utilized the chiral octahydrofluorenylsamarocene complex (*S*)-**10-Sm** for the synthesis of (+)-coniine in a few steps starting from aminodiene **19** (Scheme 4).[21b]

2.1.2 Chiral Catalysts Based on Non-Cyclopentadienyl Ligands

In the second half of 2003 several groups reported almost simultaneously new chiral hydroamination catalyst systems based on non-metallocene ligand frameworks (Figures 5 – 7 and 9).[24–27] Livinghouse reported similar chiral catalyst systems, however no results on asymmetric hydroamination were reported.[10d]

Scott applied enantiopure biaryldiamido complexes (*R*)-**23** and (*R*)-**24a–d** as catalysts for the asymmetric

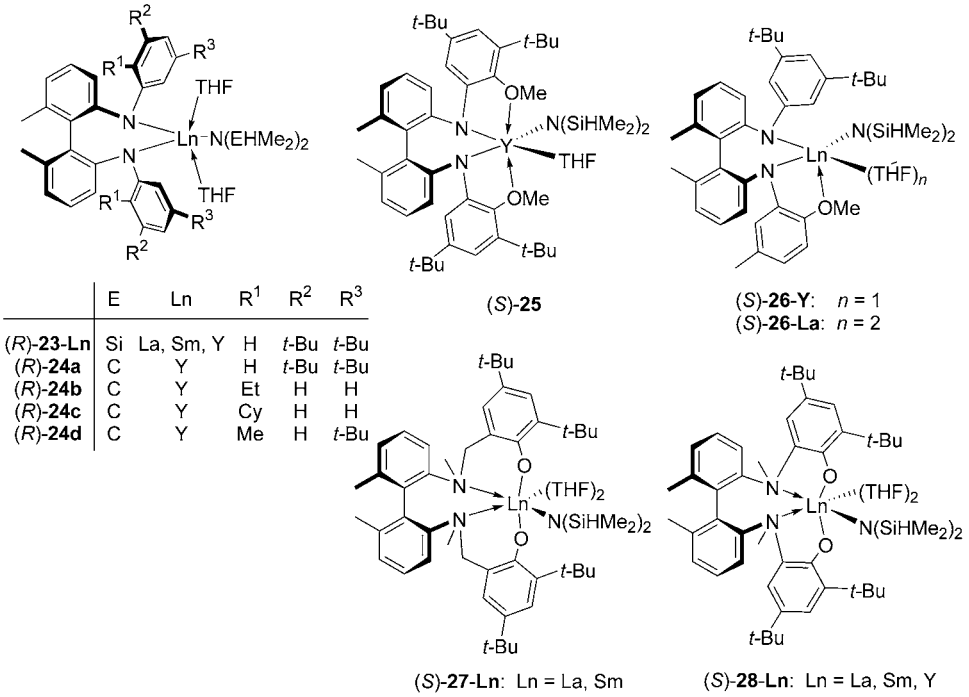
Table 6. Catalytic asymmetric hydroamination/cyclization of aminodienes.

Entry	Substrate	Product	Catalyst	[cat.]/[s] [%]	T [°C]	TOF [h^{-1}]	ee [%] (configuration)	E:Z:allyl	Ref.
1			(*S*)-**2-Sm**		23	74	25 (*R*)[a]	98:2:0	[21b]
2	**17**	**18**	(*S*)-**2-Y**		25	0.09	41 (*R*)[b]	98:2:0	[21b]
3			(*S*)-**10-Sm**	7	25	12	23 (*R*)[b]	93:7:0	[21]
4			(*S*)-**2-Sm**		25	0.1	37 (*R*)[b]	98:2:0	[21b]
5	**19**	**20**	(*S*)-**10-Sm**	7	25	0.11	63 (*R*)[b]	97:3:0	[21]
6			(*S*)-**10-Sm**		25	1.7	19 (*R*)[b]	96:4:0	[21b]
	21	**22**							

[a] Enantiomeric excess determined by chiral HPLC analysis of 1-naphthoyl amides of the hydrogenated product. Note that the apparent change of absolute configuration in comparison to aminoalkenes is caused by an inversion of the Cahn–Ingold–Prelog priority sequence.
[b] Enantiomeric excess determined by optical rotation of the HCl salt of the hydrogenated product.

hydroamination/cyclization (Figure 5).[24a] The catalysts were generated *in situ* from *N*-arylated-biaryldiamine ligands and a trisamide [$Ln(NR_2)_3(THF)_2$] (R = $SiHMe_2$, *i*-Pr) precursor.[28] The bis(dimethylsilyl)amido complexes (*R*)-**23-Ln** (Ln = La, Sm, Y) showed only very low catalytic activity for aminopentene **4** even at 60 °C. The rather low to moderate enantioselectivities were increasing with decreasing ionic radius of the metal (Table 7, entries 1–3).

Although tris{bis(dimethylsilyl)amido}-rare earth metal complexes have proven to be the most convenient and most selective precursors for complex syntheses,[29] the resulting bis(dimethylsilyl)amido precatalysts react only sluggishly with aminoalkenes, because of the low



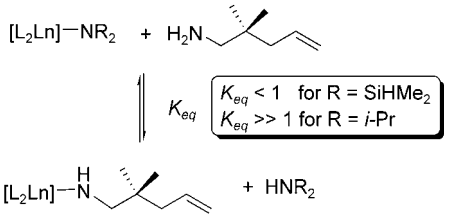
	E	Ln	R^1	R^2	R^3
(*R*)-**23-Ln**	Si	La, Sm, Y	H	*t*-Bu	*t*-Bu
(*R*)-**24a**	C	Y	H	*t*-Bu	*t*-Bu
(*R*)-**24b**	C	Y	Et	H	H
(*R*)-**24c**	C	Y	Cy	H	H
(*R*)-**24d**	C	Y	Me	H	*t*-Bu

Figure 5. Chiral bisarylamido and aminophenolate catalysts for asymmetric hydroamination.

basicity of the bis(dimethylsilyl)amido ligand {pK_a [HN(SiHMe$_2$)$_2$] = 22.8}.[30] Therefore, the equilibrium of the initiation step (Scheme 5) lies on the side of the precatalyst.[31] Substitution of the bis(dimethylsilyl)amido ligand by the significantly more basic and hence more reactive diisopropylamido ligand {pK_a [HN(*i*-Pr)$_2$] = 35.7}[32] led to more active catalyst systems (*R*)-**24a**–**d**, which could operate at 35 °C, but no increase in enantioselectivity for pyrrolidine **5** was observed (Table 7, entries 4–7). Increasing the denticity of the ligand by introduction of *ortho*-anisole substituents on nitrogen [complexes (*S*)-**25** and (*S*)-**26**] did not improve the enantioselectivity (Table 7, entries 8–10), potentially as a result from fluxional coordination of the anisole oxygen.[33]

Scott observed a better enantioselectivity of 61% ee using the lanthanum catalyst (*S*)-**27-La** having a reduced *N*-methylated Schiff base ligand, but catalytic activity remained relatively low (Table 7, entry 12).[24b] Interestingly, in this system the enantioselectivity decreased with decreasing ionic radius. Complexes of the parent Schiff base ligand were significantly less active, supposedly due to migratory insertion reactions at the imine unit of the ligand. Furthermore, decreasing the bite angle of the aminophenolate ligand by removing the methylene linker between the phenol unit and the biarylamine in complex (*S*)-**28-Y** gave almost racemic pyrrolidine **5**.

Our own development of chiral rare earth metal hydroamination catalysts began with 3,3′-disubstituted biphenolate and binaphtholate bis(dimethylsilyl)amido complexes (*R*)-**29a** and (*R*)-**31** (Figure 6), which were found to possess moderate catalytic activity and enantioselectivities in the cyclization of **4** at elevated temperature.[25] The highest enantioselectivity of 57% ee was observed in the cyclization of the unsubstituted aminopentene **6** using the sterically more hindered (*R*)-**31**. The catalytic activity of (*R*)-**29a** and (*R*)-**31** suffered from the low basicity of the bis(dimethylsilyl)amido ligand, similar to catalysts (*R*)-**23**, resulting in a sluggish initiation and non-zero order rate dependencies on substrate concentration. However, both complexes displayed high thermal stability and no significant loss in enantioselectivity was observed even at 100 °C. This suggests that the biphenolate and binaphtholate complexes are configurational stable under the conditions of catalytic hydroamination and that intermolecular ligand redistribution reactions leading to achiral catalytically active species were insignificant.



Scheme 5. Equilibrium for catalyst activation.

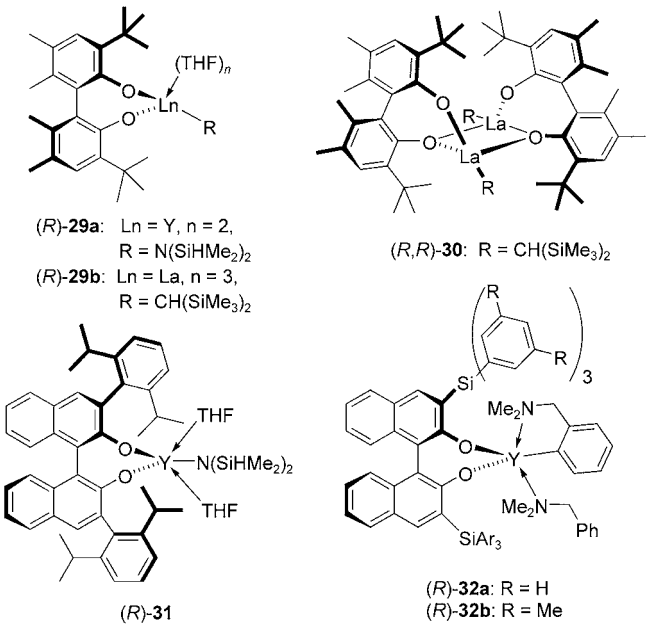
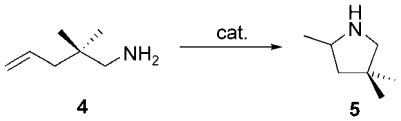


Figure 6. Chiral biphenolate and binaphtholate catalysts for asymmetric hydroamination.

The problem of low catalytic activity was solved by utilizing the homoleptic trisalkyl species [La{CH(SiMe$_3$)$_2$}$_3$] as metal source for catalyst synthesis.[34,35] The homochiral phenolate-bridged biphenolate alkyllanthanum dimer (*R*,*R*)-**30** and its monomeric tris(THF) adduct (*R*)-**29b** showed high catalytic activity at room temperature (Table 7, entries 15 and 16), comparable in magnitude to lanthanocene catalysts. Furthermore, both catalysts showed the expected zero order rate dependence on substrate concentration. It is noteworthy that the catalytic activity of the monomeric tris(THF) adduct (*R*)-**29b** is almost twice that of the homochiral dimer (*R*,*R*)-**30**, suggesting that the dimeric structure of the precatalyst (*R*,*R*)-**30** remains intact under the catalytic conditions in the absence of THF. Although highly catalytically active, (*R*)-**29b** and (*R*,*R*)-**30** produced essentially racemic products. Obviously, the relatively small *tert*-butyl substituents are insufficient to transmit effectively the chirality of the biphenolate ligand onto the substrate during the cyclization.

Consequently, binaphtholate yttrium-aryl complexes (*R*)-**32a** and (*R*)-**32b**, with sterically more demanding tris(aryl)silyl substituents in the 3 and 3′ positions, showed not only good catalytic activity at room temperature, but also achieved better enantioselectivities compared to other biphenolate and binaphtholate complexes (Table 7, entries 19 and 20; Table 8, entries 5 and 6).[36] The highest catalytic activity and highest enantioselectivity of up to 83% ee were observed for the most hindered catalyst (*R*)-**32b**. The large tris(aryl)silyl not only enhances the stereodirecting effect of the ligand,

Table 7. Non-metallocene-catalyzed asymmetric hydroamination/cyclization of 2,2-dimethyl-pent-4-enylamine (**4**).



4 **5**

Entry	Catalyst	[cat.]/[s] [%]	T [°C]	t [h]	Conversion [%]	TOF [h^{-1}]	ee [%] (configuration/sign)[a]	Ref.
1	(*R*)-**23-Y**[c]	3	60	336	100		50[b]	[24a]
2	(*R*)-**23-Sm**[c]	3	60	168	100		33[b]	[24a]
3	(*R*)-**23-La**[c]	3	60	168	100		18[b]	[24a]
4	(*R*)-**24a**[c]	3	35	120	100		45[b]	[24a]
5	(*R*)-**24b**[c]	3	35	120	100		20[b]	[24a]
6	(*R*)-**24c**[c]	3	35	120	100		21[b]	[24a]
7	(*R*)-**24d**[c]	3	35	120	100		23[b]	[24a]
8	(*S*)-**25**[c]	3	60	192	100		21[b]	[33]
9	(*S*)-**26-Y**[c]	3	60	168	100		40[b]	[33]
10	(*S*)-**26-La**[c]	3	60	120	100		34[b]	[33]
11	(*S*)-**27-Sm**	1	70	30	100		27[b]	[24b]
12	(*S*)-**27-La**	1	70	40	100		61[b]	[24b]
13	(*S*)-**28-Y**	1	70	24	100		11[b]	[24b]
14	(*R*)-**29a**	4	70	22	77	2.5	36[b]	[25]
15	(*R*)-**29b**[d]	2	25	1	98	61	8[b]	[34]
16	(*R*,*R*)-**30**	2	25	1.5	95	35	8[b]	[34]
17	(*R*)-**31**	4	60	7	92	13.5	28.3[b]	[25]
18	(*R*)-**31**	4	100	0.75	>99		28.0[b]	[25]
19	(*R*)-**32a**	4	22	3	>98	8	43[b]	[36]
20	(*R*)-**32b**	4	22	2	>98	14	53[b]	[36]
21	**35a-La**[e]	5	23		>98	25	67 (*R*)[f]	[26]
22	**35a-Nd**[e]	5	23		>98	~10	61 (*R*)[f]	[26]
23	**35a-Sm**[e]	5	23		>98	13	55 (*R*)[f]	[26]
24	**35b-La**[e]	5	23		>98	3.2	6 (*R*)[f]	[26]
25	**35c-La**[e]	5	23		>98	1.3	39 (*R*)[f]	[26]
26	**35d-La**[e]	5	23		>98	7.1	56 (*S*)[f]	[26]
27	**35e-La**[e]	5	23		>98	1.8	25 (*R*)[f]	[26]
28	**35f-La**[e]	5	23		>98	21	61 (*S*)[f]	[26]
29	**35g-La**[e]	5	23		>98	17	55 (*S*)[f]	[26]
30	**35h-La**[e]	5	23		>98	17	59 (*S*)[f]	[26]
31	**36**[g]	5	23		>98	10	63 (*R*)[f]	[26]

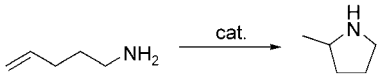
[a] $[\alpha]_D^{20}$: −24.3° for (*R*)-**5**, see Ref.[13c]
[b] Enantiomeric excess determined by ^{19}F NMR spectroscopy of Mosher amides.
[c] Catalyst prepared in situ from $[Ln\{N(EHMe_2)_2\}_3(THF)_2]$ (E = Si, C) and 1.1–1.25 equivs. of ligand.
[d] Generated *in situ* from (*R*,*R*)-**30** by addition of 3.5 equivs. of THF.
[e] Catalyst prepared *in situ* from 5 mol % $[Ln\{N(SiMe_3)_2\}_3]$ (Ln = La, Nd, Sm) and 6 mol % of ligand.
[f] Enantiomeric excess determined by chiral HPLC analysis of 1-naphthoyl amides.
[g] Catalyst prepared *in situ* from 5 mol % $[La\{N(SiMe_3)_2\}_3]$ and 11.5 mol % of (4*R*,5*S*)-Ph_2BoxH.

but also prevents undesired formation of phenolate-bridged dimeric species. Addition of a few equivalents of THF diminishes the catalytic activity only slightly, but can have a positive effect on the enantiomeric excess.[37]

Desymmetrization of the two allyl groups in aminodiene **33** was inefficient using our biphenolate or binaphtholate catalysts and pyrrolidine **34** was formed with low diastereoselectivity (up to 1.8:1, Table 9). The sterically demanding second allyl group significantly increased turnover rates by a factor of five compared to *gem*-dimethyl-substituted **4**. Interestingly, the biphenolate lanthanum catalysts (*R*)-**29b** and (*R*,*R*)-**30** generated the minor diastereomer with significantly higher enantioselectivity, whereas other catalysts usually gave both diastereomers with comparable enantiomeric excesses.

Marks reported the application of the highly modular catalyst system **35a–h** and **36** based on readily available bisoxazoline ligands.[26,38] The catalysts were usually prepared *in situ* from $\{Ln[N(SiMe_3)_2]_3\}$ (Ln = La, Nd, Sm, Y, Lu) and the corresponding bisoxazoline ligand (Figure 7). The hydroamination reactions with these catalyst

Table 8. Non-metallocene-catalyzed asymmetric hydroamination/cyclization of pent-4-enylamine (**6**).

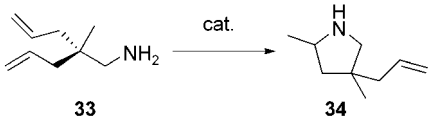


6 **7**

Entry	Catalyst	[cat.]/[s] [%]	T [°C]	t [h]	Conversion [%]	TOF [h^{-1}]	ee [%] (configuration)	Ref.
1	(*R*)-**29b**	2	60	25	98	5.3	0[a]	[34]
2	(*R*,*R*)-**30**	2	60	19	>99	5	2[a]	[34]
3	(*R*)-**31**	4	70	43	91		57[a]	[25]
4	(*R*)-**31**	4	100	16	>99		52[a]	[25]
5	(*R*)-**32a**	4	22	24	>98	1.2	69[a]	[36]
6	(*R*)-**32b**	4	22	20	>98	2.2	83[a]	[36]
7	**35a-La**	5	23			0.09	40 (*R*)[b]	[26]

[a] Enantiomeric excess determined by ^{19}F NMR spectroscopy of Mosher amides.
[b] Enantiomeric excess determined by chiral HPLC analysis of 1-naphthoyl amides.

Table 9. Catalytic hydroamination/cyclization of 2-allyl-2-methylpent-4-enylamine (**33**).



33 **34**

Entry	Catalyst	[cat.]/[s] [%]	T [°C]	t [h]	Conversion [%]	TOF [h^{-1}]	ee [%]	dr	Ref.
1	(*R*)-**29b**	2	25	0.15	>99	≥330	1/28	1.4:1	[34]
2	(*R*,*R*)-**30**	2	29	0.4	>99	≥120	5/18	1.15:1	[34]
3	(*R*)-**31**	10	90	6.5	>99	1.5	32/34	1.1:1	[25]
4	(*R*)-**32a**	2	22	1	>98	75	63/53	1.8:1	[36]
5	(*R*)-**32b**	2	22	1.2	>98	70	65/65	1.4:1	[36]

systems are ligand accelerated[39,40] with a maximum rate observed for a 1:1 ligand to metal ratio (Table 7, entry 21). A higher 2:1 ligand to metal ratio did not significantly alter the enantioselectivity, but resulted in a reduced catalytic activity (Table 7, entry 31). Reactions performed with isolated catalysts showed higher rates, but similar enantioselectivities.

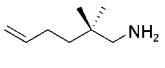
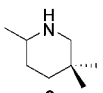
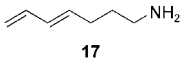
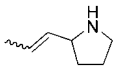
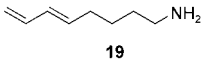
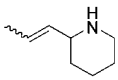
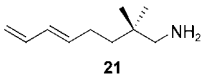
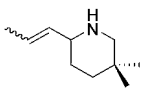
A survey of the different bisoxazoline ligands revealed that an aromatic group in the 4 position and an alkyl or aryl substitution in the 5 position of the bisoxazoline ligand are crucial for high enantioselectivities and good catalytic activity (Table 7, entries 21–30). The highest turnover frequency (25 h^{-1}) and highest enantioselectivity (67% ee) in the cyclization of **4** was observed for **35a-La**, the complex with the largest rare earth metal, lanthanum, and (4*R*,5*S*)-Ph_2Box as ligand. Higher steric hindrance in the 4 position of the ligand, e.g., by a 1-naphthyl group (complex **35h**), did not improve the enantioselectivity and was slightly detrimental to catalyst activity (Table 7, entry 30). Catalysts with aryl groups in the 4 position yield pyrrolidine **5** with the opposite absolute configuration than catalysts having alkyl substituents.

Contrary to the general trend, cyclization of unsubstituted aminopentene **6** using **35a-La** proceeded with lower enantioselectivity compared to dimethyl-substituted aminopentene **4** (Table 7, entry 21 *vs.* Table 8, entry 7). Turnover frequencies for **6** are always lower than for **4**, due to the Thorpe–Ingold effect.[18] However, this difference in activity is significantly more pronounced for **35a-La** (25 h^{-1} *vs.* 0.09 h^{-1}) than observed for lanthanocenes [e.g., 84 h^{-1} *vs.* 33 h^{-1} for (*S*)-**2b-Sm**] or binaphtholate complexes [e.g., 14 h^{-1} *vs.* 2.2 h^{-1} for (*R*)-**32b**].

The bisoxazolinato complex **35a-La** was also tested in the cyclization of aminodienes (Table 10, entries 2–4).[41] Enantioselectivities were comparable to, or even greater than, those observed for lanthanocene catalysts. However, *E*/*Z* ratios of vinylpyrrolidine **18** and vinylpiperidines **20** and **22** were close to 1:1 along with traces of allylpiperidine for **21**. Again, the reaction rates were higher and the observed enantioselectivities lower than for the corresponding aminoalkenes (Table 8, entry 7 *vs.* Table 10, entry 2, respectively, Table 10, entry 1 *vs.* entry 4).

Overall the bisoxazolinato complex **35a-La** gave a more consistent level of enantioselectivity for a wider range of substrates as compared to lanthanocene catalysts.

Table 10. Asymmetric hydroamination/cyclizations catalyzed by **35a-La**.[a]

Entry	Substrate	Product	T [°C]	TOF [h^{-1}]	ee [%] (configuration)[b]	*E:Z*:allyl
1	 **8**	 **9**	60	4.0	56 (*S*)	
2	 **17**	 **18**	23	3.0	17 (*S*)	63:37:0
3	 **19**	 **20**	60	0.6	54 (*R*)	41:59:0
4	 **21**	 **22**	23	1.4	45 (*R*)	39:57:4

[a] Catalyst prepared *in situ* from 5 mol % {La[N(SiMe$_3$)$_2$]$_3$} and 6 mol % of (4*R*,5*S*)-Ph$_2$BoxH.
[b] Enantiomeric excess determined by chiral HPLC analysis of 1-naphthoyl amides of the hydrogenated product. Note that the apparent change of absolute configuration for aminodiene substrates in comparison to aminoalkenes is caused by an inversion of the Cahn–Ingold–Prelog priority sequence.

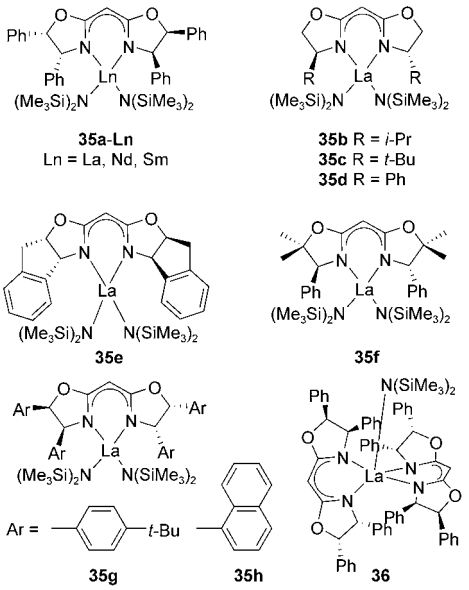
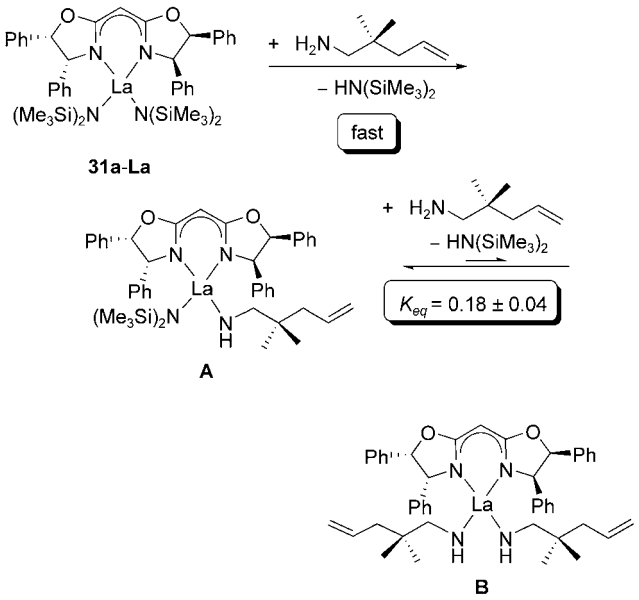


Figure 7. Bisoxazolinato complexes for asymmetric hydroamination.



Scheme 6. Initiation equilibrium for bisoxazolinato catalysts.

Protonolysis of the first bis(trimethylsilyl)amido ligand in **35a-La** is immediate and quantitative, but substitution of the second bis(trimethylsilyl)amido is incomplete (Scheme 6). In principle, the two species **A** and **B** could have different propagation rates and selectivities. In spite of that, the reactions were shown to be zero order in substrate concentration, and first order in catalyst concentration. A dependence of enantioselectivities on substrate to catalyst ratio has not been reported.

Molecular modeling studies indicate that for **35a-La** an equatorial approach of the olefin to the apical

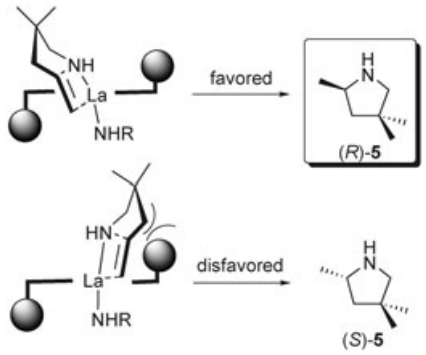


Figure 8. Stereomodel for enantioselective hydroamination/cyclization of aminopentene **4** by **35a-La** with an equatorial approach of the olefin.[26]

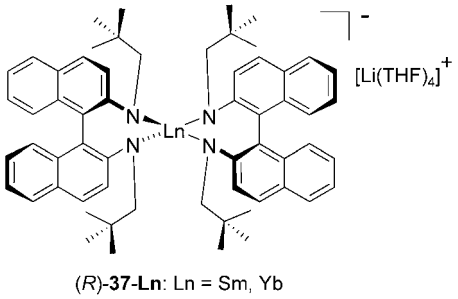


Figure 9. Anionic diamidobinaphthylate complexes for asymmetric hydroamination.

La–N bond is more likely than an apical approach of the olefin to an equatorial La–N bond, because the equatorial approach would favor the correct (*R*) pyrrolidine product (Figure 8), whereas in an apical approach the minor (*S*) product would be slightly favored. It was proposed that the reversion of absolute configuration of the hydroamination product when exchanging alkyl substituents for aryl substituents in the bisoxazoline ligands may be caused by a change in the mode of approach of the olefin.

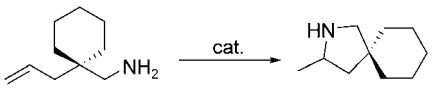
The ate complex $[Li(THF)_4](Ln\{(R)\text{-}1,1'\text{-}[C_{10}H_6N(CH_2\text{-}t\text{-}Bu)]_2\}_2)$ [(*R*)-**37**, Figure 9],[27] from the Collin and Trifonov group is a rather unusual hydroamination catalyst system. It is the only ate complex reported to catalyze hydroamination and lacks an obvious leaving amido or alkyl group, which would be replaced during the initiation step by the substrate. It seems feasible that at least one of the amido groups is protonated during the catalytic cycle, analogous to the mechanism proposed for Michael and aldol reactions catalyzed by rare earth metal-alkali metal-BINOL heterobimetallic complexes.[42] Ultimately, this protonation could result in a complete loss of one of the two diamidobinaphtyl ligands.

Cyclization of *C*-(1-allylcyclohexyl)-methylamine (**38**) to the spirocyclic pyrrolidine **39** proceeded with good activity but rather low enantioselectivity at 25 °C using the samarium catalyst (*R*)-**37-Sm** (Table 11, entry 1). A better enantioselectivity of 40% ee as well as higher catalytic activity was achieved using the complex having the smaller ytterbium ion, (*R*)-**37-Yb**. Lowering the reaction temperature to −20 °C increased the enantiomeric excess to 53% ee, albeit with significant loss in activity. The influence of the counter cation on the enantioselectivity and catalytic activity was not reported. Other aminoalkenes have not been cyclized, making a comparison with other chiral catalysts difficult. However, the reactivity of **38** in comparison to **4** or **6** should be significantly higher due to the Thorpe–Ingold effect.[18]

2.2 Kinetic Resolution of Chiral Aminoalkenes

Most intramolecular AHAs have been performed by differentiation of enantiotopic faces of the alkene in achiral aminoalkene substrates. Chiral aminoalkenes on the other hand can be resolved *via* kinetic resolution if the two enantiomers of the substrate have different rates of cyclization. Early attempts to perform kinetic resolution of **40a** with chiral lanthanocene complexes were frustrated by low enantiomeric excess (<20% ee) at various extents of conversion.[13c] However, bi-

Table 11. Catalytic asymmetric hydroamination/cyclization of *C*-(1-allylcyclohexyl)-methylamine (**38**).[27]

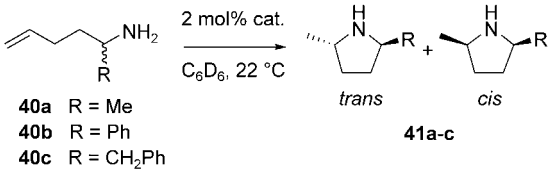


38 **39**

Entry	Catalyst	[cat.]/[s] [%]	*T* [°C]	*t* [h]	Conversion [%]	ee [%] (sign)[a]
1	(*R*)-**37-Sm**	5	25	2	78	24
2	(*R*)-**37-Yb**	6	25	0.5	94	40 (+)
3	(*R*)-**37-Yb**	6	0	17	81	47
4	(*R*)-**37-Yb**	6	−20	24	13	53

[a] Enantiomeric excess determined by GC of Mosher amides.

Table 12. Catalytic kinetic resolution of chiral aminopentenes.



Entry	Substrate	Catalyst[a]	t [h]	Conversion [%]	*trans*:*cis*	ee of recovered starting material [%]	ee of *trans* product [%] (sign)	k_{rel}[b]	Ref.
1	**40a**	(*R*)-**31**[c]	1.5	61	6.4:1	43	35	2.6	[25]
2	**40a**	(*R*)-**32a**	25.5	53	11:1	72	68	9.5	[36]
3	**40a**	(*R*)-**32b**	26	52	13:1	80	78 (−)[d]	16	[36]
4	**40b**	(*R*)-**32a**	95	50	≥50:1	74	(+)	15	[36]
5	**40b**	(*R*)-**32b**	18[e]	52	≥50:1	63		7	[36]
6	**40c**	(*R*)-**32a**	9	50	20:1	42	40 (−)	3.6	[36]
7	**40c**	(*R*)-**32b**	27	52	20:1	38	34	2.9	[36]

[a] Reaction conditions: 2 mol % catalyst, C_6D_6, Ar atm, 22 °C.
[b] Based on starting material
[c] 5 mol % catalyst, 90 °C.
[d] A (−) optical rotation corresponds to a (2*S*,5*S*) absolute configuration, see Ref.[17c]
[e] At 40 °C.

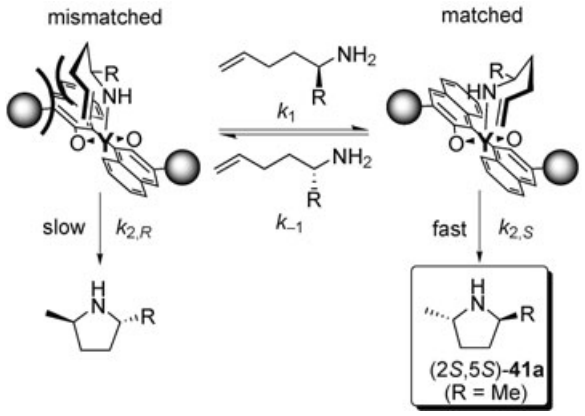


Figure 10. Proposed stereomodel for kinetic resolution of chiral aminoalkenes with an equatorial approach of the olefin.

naphtholate complexes (*R*)-**31**, (*R*)-**32a** and (*R*)-**32b** were found to be significantly more effective in kinetic resolution of various chiral aminopentenes (Table 12) with k_{rel} values[43] as high as 16 and enantiomeric excess for recovered starting material reaching 80% ee at conversions close to 50% (Table 12, entry 3).[25,36] The 2,5-disubstituted pyrrolidines were obtained in good to excellent *trans* diastereoselectivity, depending on the steric hindrance of the α-substituent. The sterically more hindered binaphtholate catalyst (*R*)-**32b** was more effective in the kinetic resolution process of the sterically less demanding **40a**, whereas the sterically more encumbered **40b** was more efficiently kinetically resolved using (*R*)-**32a**.

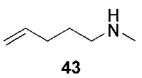
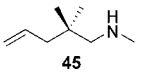
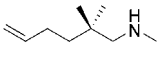
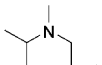
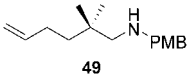
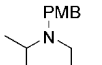
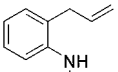
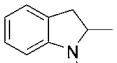
A stereomodel was proposed for the observed preferred formation of (2*S*,5*S*)-**41a** using (*R*)-**32b** as catalyst (Figure 10). Fast exchange between matching and mismatching aminoalkene is imperative prior to cyclization for an effective kinetic resolution process. Cyclization of (*R*)-**40a** is impeded by a sterically unfavorable interaction of the vinylic methylene protons with a trisarylsilyl substituent in the chair-like transition state.

3 Group 4 Metal-Based Catalysts

The application of group 4 metal catalysts in asymmetric hydroamination reactions would be highly desirable. The chemistry of group 4 organometallic compounds has flourished over the last two decades and is well developed thanks to their high importance in polyolefin synthesis. They are commonly significantly less sensitive and easier to prepare than rare earth metal complexes. Most important of all, many potential precatalysts or catalyst precursors are commercially available.

However, the first asymmetric hydroamination by a chiral group 4 metal catalyst was reported by Scott using the aminophenolate complex (*S*)-**42** (Figure 11) only recently.[44,45] The cationic zirconium complex (*S*)-**42** readily cyclized secondary aminoalkenes with up to 82% ee (Table 13). Reactions were commonly performed at 100 °C in bromobenzene using 10 mol % of catalyst. Cyclization of **45** at 70 °C led to a significant amount of double bond isomerization of the substrate and only 70% conversion to the pyrrolidine in low enantiomeric excess was observed (Ta-

Table 13. Zr-catalyzed asymmetric hydroamination/cyclization of secondary aminoalkenes using (*S*)-**42** in C_6D_5Br.[44]

Entry	Substrate	Product	[cat.]/[s] [%]	*T* [°C]	*t*[a] [h]	*ee* [%]
1	 **43**	 **44**	10	100	4	64
2	 **45**	 **46**	5	70	48[b]	14
3	 **47**	 **48**	10	100	3	82
4	 **49**	 **50**	10	100	192	nd
5	 **51**	 **52**	10	100	3	20

[a] Time to 100% conversion of substrate.
[b] 70% conversion to hydroamination product and 30% double bond isomerized aminoalkene. PMB = *para*-methoxybenzyl; nd = not determined.

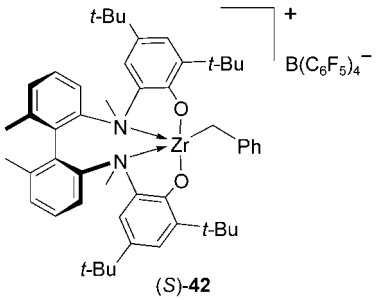
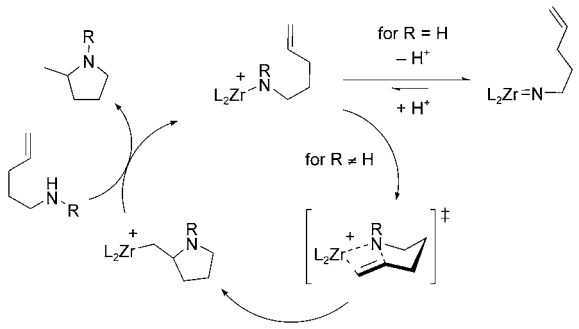


Figure 11. Cationc zirconium aminophenolate complex for asymmetric hydroamination.

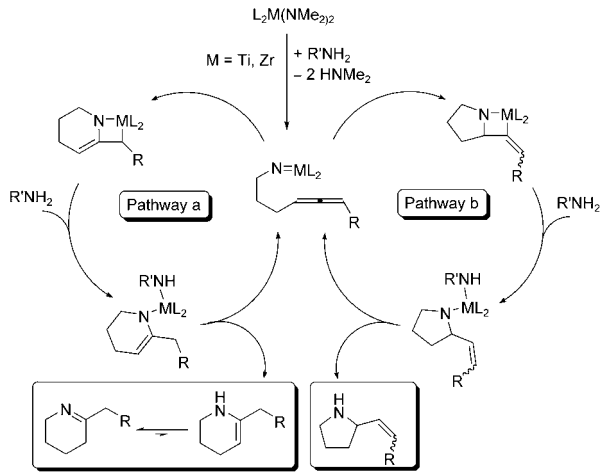


Scheme 7. Proposed mechanism for zirconium-catalyzed hydroamination of aminoalkenes.

ble 13, entry 2). The *N-para*-methoxybenzyl-protected aminoalkene **49** was cyclized very slowly, either because of increased steric demand of the benzyl substituent or due to coordinative sequestering of the catalyst by the methoxy functionality.

The mechanism is believed to be similar to that proposed for rare earth metals with a catalytically active cationic zirconium amido species (Scheme 7). No reaction was observed with primary aminoalkenes, because cationic zirconium amido species are readily deprotonated to yield catalytically inactive zirconium imido species (*vide infra*).

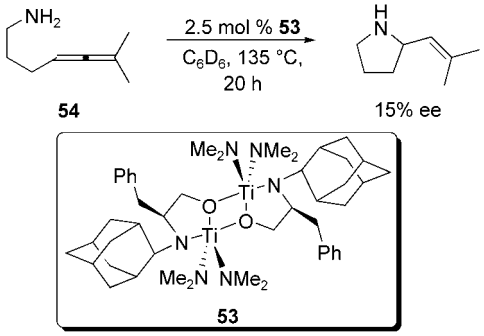
The hydroamination catalyzed by neutral titanium and zirconium complexes operates by a completely different mechanism (Scheme 8),[2j,k,n] involving a [2+2] cycloaddition of a metal imido species and an alkyne or allene to give an azametallacyclobutene or, respectively, an azametallacyclobutane intermediate. The reaction is restricted to alkynes and allenes because the metal imido intermediates are unreactive towards non-activated alkenes.[46] Cyclization of aminoallenes can proceed *via* two pathways generating two regioisomeric products. Formation of imines (pathway a) usually predominates for monosubstituted aminoallenes, whereas



Scheme 8. Two pathway mechanism for the hydroamination/cyclization of aminoallenes catalyzed by neutral group 4 metal complexes.

vinylpyrroldines (pathway b) are generated preferentially if 1,3-disubstituted or trisubstitued aminoallenes are employed.[7b,47] Therefore asymmetric ring closing of di- or trisubstituted aminoallenes should be feasible using chiral titanium or zirconium catalysts.

Indeed, Johnson very recently utilized chiral amino alcohol-titanium complexes, e.g., the presumed dimeric complex **53**, in the cyclization of aminoallene **54** [Eq. (3)],[48,49] but enantioselectivities were low.



(3)

4 Late Transition Metal-Catalyzed Hydroamination

In contrast to early transition metals, late transition metals are significantly more functional group tolerant as well as air and moisture insensitive. Therefore, catalytic processes involving late transition metals have been used more routinely in synthetic organic laboratories. Unfortunately, late transition metal hydroamination catalysts have been restricted to activated carbon-carbon multiple bonds, such as norbornene, styrene, conjugated dienes, alkynes and α,β-unsaturated carbonyl compounds. Although late transition metal-olefin complexes are readily attacked by an amine nucleophile, the resulting (2-aminoalkyl)metal complexes are often resistant to protolytic cleavage, except under highly acidic conditions, which are incompatible with the presence of free amines.[2c, i] Therefore, hydroamination of unactivated alkenes has only been realized using stoichiometric amounts of transition metals.

4.1 Iridium-Based Catalysts

Following a report by Milstein on the iridium-catalyzed hydroamination of norbornene with aniline,[50] Togni investigated various iridium complexes with chiral chelating diphosphines (Figure 12, Table 14).[51] The low activity and moderate enantioselectivity of the iridium chloro complexes could be significantly improved by addition of Schwesinger's "naked" fluoride $\{N[P(NMe_2)_3]_2\}^+F^-$. Catalysts **55a–c** based on Josiphos-type ligands showed the best turnover rates, but the optimal enantiomeric excess of up to 95% ee was achieved with the BINAP- and Biphemp-based catalysts **57** and **58**. The reason for the strong fluoride effect is not clear, especially as addition of fluoride led to a reversal of absolute product configuration (Table 14, entries 1 and 2), but hydrogen bridging of the fluoride could play a role.

The hydroamination proceeded with high *exo*-selectivity. Trace amounts of the *endo*-adduct were only formed in the absence of fluoride ions. Complexes **56a**,**b** based on planar chiral arene-chromium tricarbonyl ligands, though very similar to ferrocene-based Josiphos catalysts, were unsuitable for catalytic hydroaminations.[51b] They produced only trace amounts of aminonorbornane (**59**), possibly due to thermal instability of the chromo arene complexes.

The mechanism of iridium-catalyzed hydroamination was investigated in detail for the achiral catalyst system (Scheme 9).[50] In the first step aniline adds oxidatively to the catalytically active species which is believed to

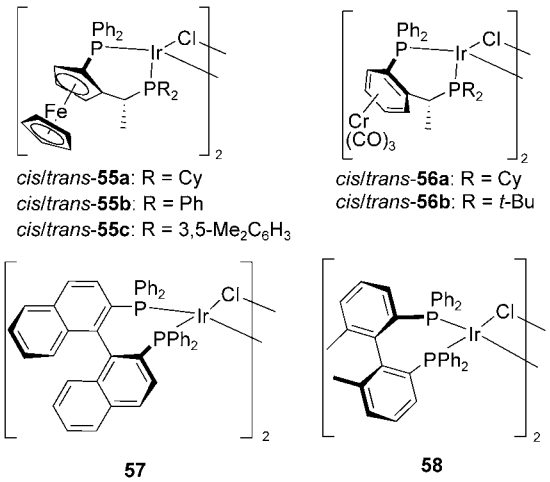
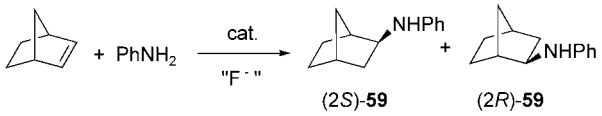


Figure 12. Chiral iridium-based hydroamination catalysts.

Table 14. Iridium-catalyzed intermolecular hydroamination of norbornene with aniline.

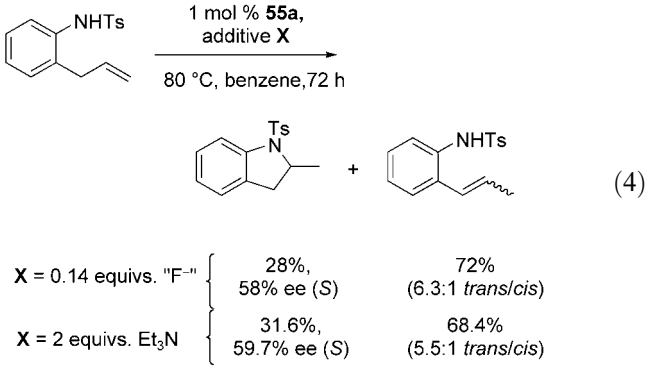


Entry	Catalyst	$[F^-]/[Ir]$	T [°C]	Yield [%]	TOF [h^{-1}]	*ee* [%] (configuration)	Ref.
1	**55a**[a]	0	50	12	0.17	51 (2*S*)	[51a]
2	**55a**[a]	1	50	81	1.11	50 (2*R*)	[51a]
3	**55b**[a]	1	50	27	0.38	9 (2*R*)	[51a]
4	**55c**[a]	1	50	36	0.50	26 (2*R*)	[51a]
5	**56a**[b]	40	60	trace		51.1 (2*S*)	[51b]
6	**56b**[b]	40	60	trace		70.3 (2*S*)	[51b]
7	**57**[a]	0	50	12	0.08	57 (2*R*)	[51a]
8	**57**[a]	4	75	22	0.15	95 (2*R*)	[51a]
9	**58**[a]	1	75	37	0.26	43 (2*S*)	[51a]
10	**58**[a]	4	75	24	0.17	92 (2*S*)	[51a]

[a] Reaction conditions: 1 mol % cat. + $\{N[P(NMe_2)_3]_2\}^+F^-$, no solvent, 72 h.
[b] Reaction conditions: 0.1 mol % cat. + $\{N[P(NMe_2)_3]_2\}^+F^-$, no solvent, 96 h.

be $[L_2IrCl]$. The resulting irdium-anilido-hydrido species reacts then with norbornene by insertion of the olefin into the iridium-anilido bond. The addition takes place across the sterically better accessible *exo* face. The catalytic cycle is then completed by the reductive elimination of aminonorbornane **57** from the azametallacyclobutane intermediate.

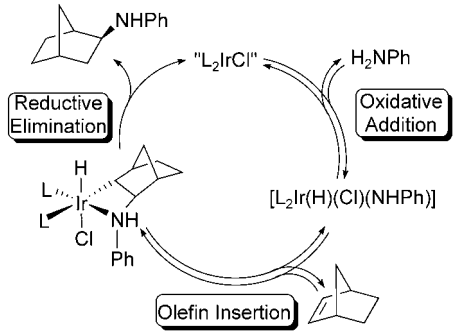
The iridium catalysts have not been tapped for their full potential and the scope is not limited to the hydroamination of norbornene with aniline. Further studies have shown that also simple *N*-tosylated aminoalkenes could be cyclized in moderate yield and enantiomeric excess [Eq. (4)], but double bond isomerization was a major side reaction.[52] The Schwesinger fluoride could be substituted for triethylamine with comparable results.



(4)

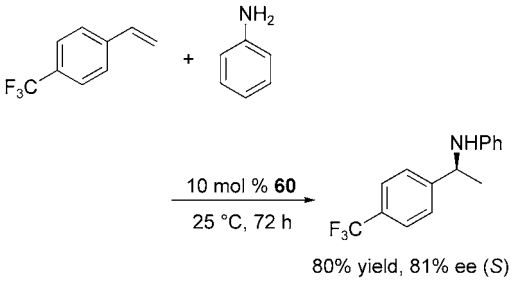
4.2 Palladium-Catalyzed Hydroamination of Vinylarenes and 1,3-Dienes

Significant progress in the asymmetric hydroamination of styrenes[53] and 1,3-dienes[54] using palladium catalysts

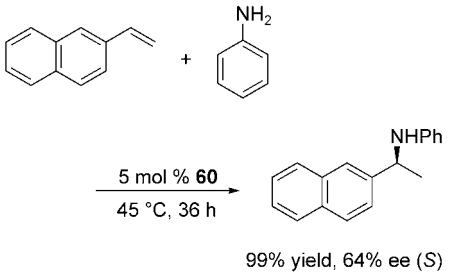


Scheme 9. Mechanism for the iridium-catalyzed hydroamination of norbornene.

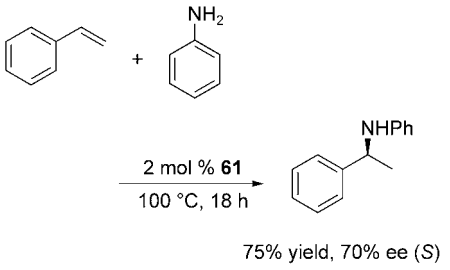
was reported by Hartwig. The Markovnikov addition of aniline to *p*-trifluromethylstyrene and vinylnaphthalene was achieved under mild conditions with up to 81% ee using catalytic amounts of $[\{(R)\text{-BINAP}\}Pd(OTf)_2]$ (**60**) [Eqs. (5) and (6)]. High reaction temperatures are not necessarily detrimental to catalyst selectivity, as demonstrated by Hii for the addition of aniline to styrene at 100 °C in 70% ee using $[\{(R)\text{-BINAP}\}Pd(OH_2)(NCMe)]^{2+}[(OTf)^-]_2$ (**61**) [Eq. (7)].[55]



(5)

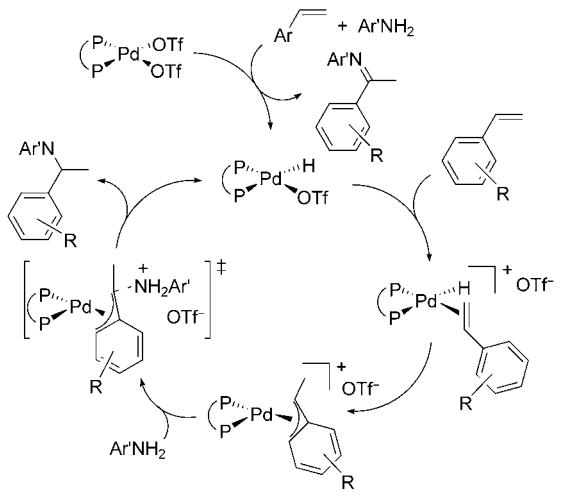


(6)



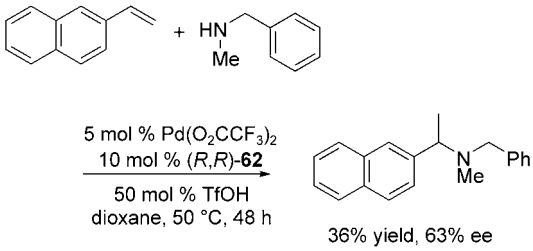
(7)

Mechanistic investigations[56] using stoichiometric amounts of catalyst revealed that the catalytic cycle involves an insertion of the vinylarene into a palladium hydride species (Scheme 10). The secondary insertion of the vinylarene is favored electronically, which explains the highly selective Markovnikov regiochemistry. The resulting η^3-benzyl complex (which could be isolated) then undergoes nucleophilic attack by an external amine with inversion of configuration. It was noted that the isolated η^3-benzyl complex representing the major diastereomer in solution generated the minor enantiomer of the hydroamination product of the catalytic reaction. Therefore it was concluded that, in analogy to asymmetric Rh-catalyzed hydrogenation,[57] the minor diastereomer is more reactive towards nucleophilic attack of the amine.



Scheme 10. Mechanism for the palladium-catalyzed hydroamination of vinylarenes.

The scope of the palladium-catalyzed hydroamination of vinylarenes has been recently extended to secondary alkylamines, e.g., *N*-benzylmethylamine [Eq. (8)].[58] The Markovnikov adduct was obtained in 63% ee, albeit in only 36% yield. A limiting factor for these more basic alkylamines is the competition between nucleophilic attack of the amine at the benzylic carbon leading to the hydroamination product and reversible elimination of styrene from the η^3-benzyl intermediate.



(8)

The optimal chiral ligand for the asymmetric 1,4-addition of aniline to 1,3-cyclohexadiene was found to be (*R*,*R*)-**63b**, a naphthyl version of Trost's ligand (*R*,*R*)-**63a** (Figure 13). The parent ligand (*R*,*R*)-**63a** and other chiral bidentate phosphine ligands, such as (*R*)-BINAP, (*S*,*S*)-DIOP or (*S*,*S*)-BDPP gave only inferior enantioselectivities (Table 15). The catalyst system comprising of $[Pd(\pi\text{-allyl})Cl]_2$ and (*R*,*R*)-**63b** could be applied to a broader range of anilines with consistently high enantioselectivities under neutral conditions at room temperature, but rather moderate activity.[54] Rates could be increased by addition of TFA, but this was accompanied by a loss of stereoselectivity, because a fast exchange of the allylic amine in the presence of acids led to racemization of the hydroamination product.[59] Catalyst deactivation thwarted attempts to increase turnover frequencies by increasing the reaction temperature, resulting in lower overall conversions.

Based on results with achiral catalyst systems,[54] asymmetric hydroamination of other cyclic or acyclic 1,3-dienes is conceivable, but so far only the 1,4-addition of aniline to cycloheptadiene in 66% ee but only 22% yield was reported.

4.3 Palladium-Catalyzed Asymmetric Intramolecular Hydroamination of Aminoalkynes

Hydroamination of aminoalkynes usually generates achiral imine or enamine products. However, Yamamoto recently reported the asymmetric hydroamination of *N*-protected aminoalkynes yielding vinylpyrrolidines and vinylpiperidines using a chiral palladium catalyst and benzoic acid as cocatalyst (Table 16).[60] A survey over different mono- and bidentate phosphine ligands and different *N*-protecting groups revealed that RENORPHOS is the optimal ligand and nonafluorobutanesulfonyl (Nf) the best protecting group.

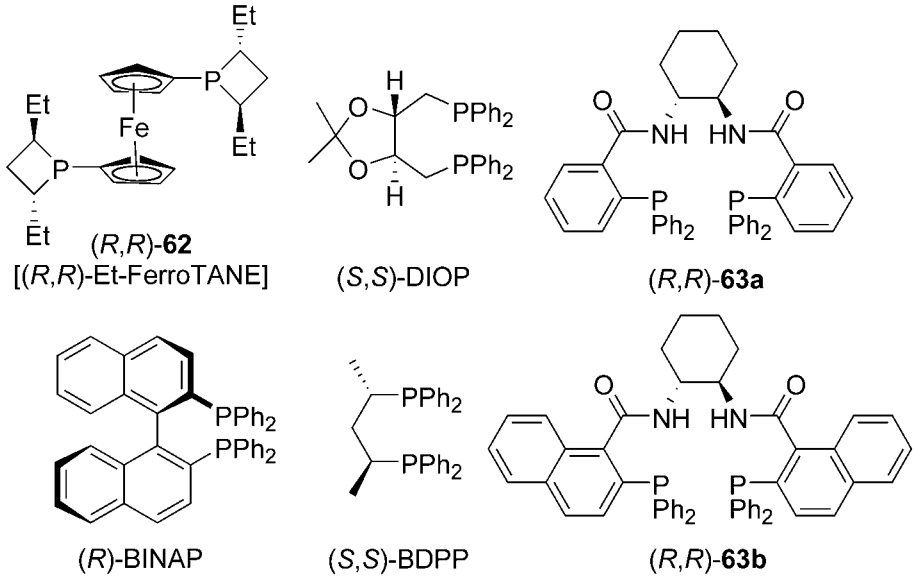
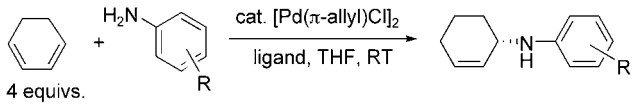


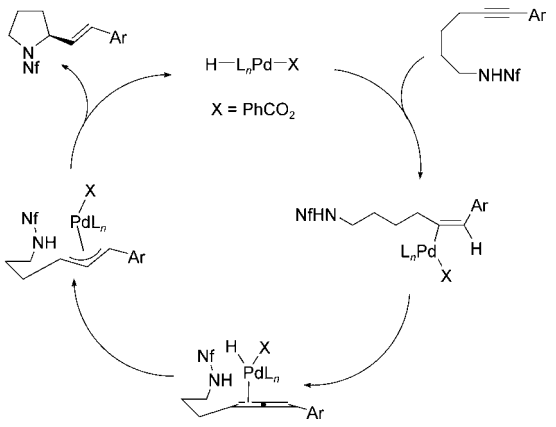
Figure 13. Chiral bidentate ligands for palladium-catalyzed asymmetric hydroaminations.

Table 15. Asymmetric hydroamination of cyclohexadiene with anilines.[54]



Entry	R	Ligand	*t* [h]	Yield [%]	ee [%] (configuration)
1	H	(*R*,*R*)-**63a**[a]	72	65	11 (*S*)
2	H	(*R*,*R*)-**63b**[a]	72	61	91 (*S*)
3	H	(*R*)-BINAP[a]	72	99	7 (*R*)
4	H	(*S*,*S*)-DIOP[a]	72	84	4 (*R*)
5	H	(*S*,*S*)-BDPP[a]	72	31	34 (*R*)
6	*p*-Me	(*R*,*R*)-**63b**[b]	120	78	86 (*S*)
7	*o*-Me	(*R*,*R*)-**63b**[b]	120	59	90 (*S*)
8	*p*-COOEt	(*R*,*R*)-**63b**[b]	120	83	95 (*S*)
9	*p*-CF_3	(*R*,*R*)-**63b**[b]	120	73	95 (*S*)

[a] Reaction conditions: 2.5 mol % $[Pd(\pi\text{-allyl})Cl]_2$, 5 mol % ligand, THF, RT.
[b] Reaction conditions: 5 mol% $[Pd(\pi\text{-allyl})Cl]_2$, 11 mol % ligand.

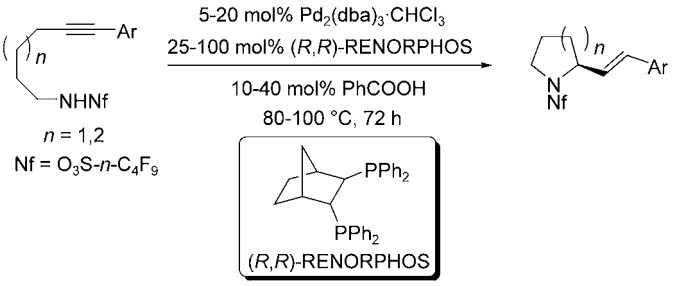


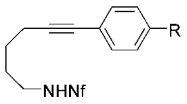
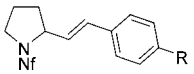
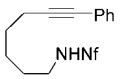
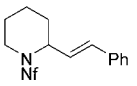
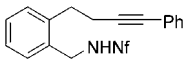
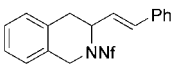
Scheme 11. Plausible mechanism for the palladium catalyzed asymmetric intramolecular hydroamination of aminoalkynes.

High enantioselectivities of up to 91% ee were achieved, both for pyrrolidine and piperidine products, though high catalyst loadings (up to 40 mol % Pd and 100 mol % phosphine) were required. Lower catalyst loadings (10 mol % Pd, 25 mol % ligand) resulted in reduced yields and enantioselectivities. Electron-rich alkynes were transformed faster, but gave lower enantiomeric excess.

A plausible mechanism was postulated (Scheme 11).[60] Hydropalladation of the alkyne is thought to generate a vinylpalladium intermediate, which rearranges to a π-allylpalladium species *via* a consecutive β-H-elimination/hydropalladation process. Nucleophilic attack of the amine on this π-allylpalladium species releases the heterocyclic product and regenerates the hydridopalladium catalyst.

Table 16. Catalytic asymmetric intramolecular hydroamination of aminoalkynes.[60]



Entry	Substrate	Product	R	Conditions[a]	Yield [%]	ee [%]
1			H	A	68	83
2			H	B	93	91
3			OMe	A	90	47
4			OMe	B	90	81
5			CF_3	B	85	88
6				A	63	77
7				B	92	90
8				A	70	72
9				B	90	87

[a] Conditions A: 5 mol % $Pd_2(dba)_3 \cdot CHCl_3$, 25 mol % (*R*,*R*)-RENORPHOS, 10 mol % PhCOOH, benzene, 100 °C, 72 h; conditions B: 20 mol % $Pd_2(dba)_3 \cdot CHCl_3$, 100 mol % (*R*,*R*)-RENORPHOS, 40 mol % PhCOOH, benzene/hexane (2:1), 80 °C, 72 h.

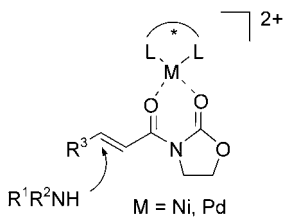


Figure 14. Postulated intermediate for Lewis-acid catalyzed nucleophilic addition of amines to alkenoyl-*N*-oxazolidinones.

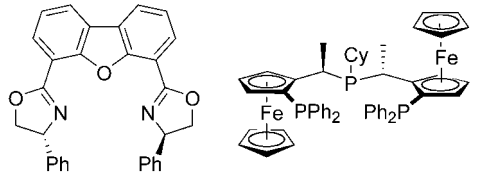


Figure 15. Ligands for nickel- and palladium-catalyzed aza-Michael additions to α,β-unsaturated carbonyl compounds.

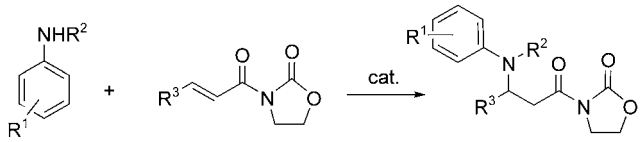
4.4 Asymmetric Aza-Michael Addition of Amines to α,β-Unsaturated Amides and Nitriles

The nucleophilic addition of amines to alkenes with electron-withdrawing groups (e.g., esters, nitriles), the so-called aza-Michael reaction, is known to proceed also in the absence of catalyst, but transition metal-catalyzed additions are of particular interest for enantioselective syntheses.[61]

Several catalyst systems, commonly based on nickel(II) or palladium(II) complexes, have been reported to catalyze the hydroamination of α,β-unsaturated carbonyl compounds. However, in most cases the role of the catalyst is limited to activate the olefinic substrate through Lewis acid coordination for nucleophilic attack of the amine (Figure 14). The chiral Lewis acid blocks one enantiotopic face of the olefin, forcing the amine to approach from the opposite enantiotopic face.

Jørgensen reported that nickel(II) perchlorate, complexed by the dibenzofurandiyl-bis(phenyloxazoline) ligand (*R*)-DBFOX/Ph (**64**, Figure 15), catalyzed the addition of *N*-methylanilines to alkenoyl-*N*-oxazolidinones, allowing a fast access to optically active β-amino acids with up to 96% ee (Table 17, entries 1, 4–11).[62] Anilines with electron-donating substituents gave improved yields, whereas an electron-withdrawing sub-

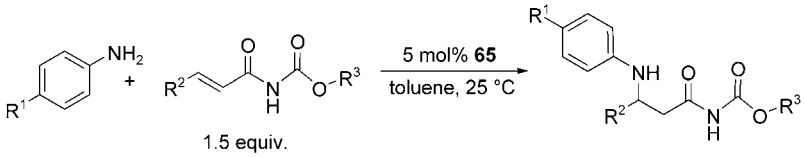
Table 17. Nickel- and palladium-catalyzed asymmetric aza-Michael addition of anilines to alkenoyl-*N*-oxazolidinones.



Entry	Catalyst[a]	R^1	R^2	R^3	Yield [%]	ee [%]	Ref.
1	$Ni(ClO_4)_2 \cdot 6H_2O$/**64**	H	Me	Me	62	90[b]	[62]
2	$Mg(ClO_4)_2 \cdot 6H_2O$/**64**	H	Me	Me	63	39	[62]
3	$Zn(ClO_4)_2 \cdot 6H_2O$/**64**	H	Me	Me	15	64	[62]
4	$Ni(ClO_4)_2 \cdot 6H_2O$/**64**	H	CH_2Ph	Me	6	34	[62]
5	$Ni(ClO_4)_2 \cdot 6H_2O$/**64**	*p*-MeO	Me	Me	75	76	[62]
6	$Ni(ClO_4)_2 \cdot 6H_2O$/**64**	*m*-MeO	Me	Me	73	89	[62]
7	$Ni(ClO_4)_2 \cdot 6H_2O$/**64**	*p*-Me	Me	Me	87	48	[62]
8	$Ni(ClO_4)_2 \cdot 6H_2O$/**64**	*p*-Cl	Me	Me	23	96	[62]
9	$Ni(ClO_4)_2 \cdot 6H_2O$/**64**	*p*-Cl	Me	Me	53[c]	60	[62]
10	$Ni(ClO_4)_2 \cdot 6H_2O$/**64**	H	Me	Pr	25	95	[62]
11	$Ni(ClO_4)_2 \cdot 6H_2O$/**64**	H	Me	Pr	52[d]	69	[62]
12	**61**	H	H	Me	93	93	[63]
13	**61**	*p*-Cl	H	Me	96	90	[63]
14	**61**	*p*-Me	H	Me	85	73	[63]
15	**61**	*p*-MeO	H	Me	89	37	[63]
16	**61**	H	Me	Me	75	87	[63]
17	**61**	H	H	Et	66[e]	41	[63]
18	**61**	H	H	Pr	72[e]	27	[63]

[a] Reaction conditions for entries 1–11: 5 mol % catalyst, 5-fold excess of aniline, CH_2Cl_2, RT, 40 h; for entries 12–18: 10 mol % catalyst, 1.5-fold excess of alkenoyl-*N*-oxazolidinone, toluene, 25 °C, 18 h.
[b] (*S*) absolute configuration determined by X-ray analysis.
[c] Performed at 40 °C.
[d] Performed at 60 °C in dichloroethane.
[e] Performed at 60 °C.

Table 18. Addition of anilines to *N*-alkenoylcarbamates.[64]

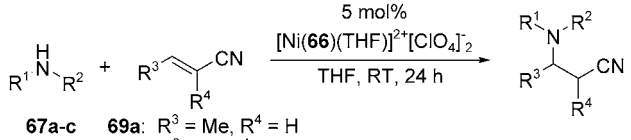


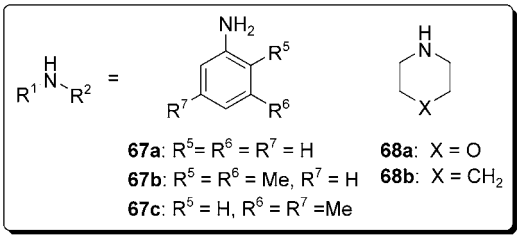
Entry	R^1	R^2	R^3	*t* [h]	Yield [%]	ee [%]
1	H	Me	*t*-Bu	18	>99	97
2[a]	Cl	Me	*t*-Bu	18	>99	>99
3	Me	Me	*t*-Bu	18	93	92
4	OMe	Me	*t*-Bu	40	99	73
5	H	Et	*t*-Bu	72	98	90
6	Cl	Et	*t*-Bu	72	92	85
7	OMe	Et	*t*-Bu	72	>99	16
8	H	*n*-Pr	*t*-Bu	120	98	89
9	H	Me	Me	18	95	92

[a] 2 mol % cat.

stituent lowered the yield. Attempts to improve yields by increasing the reaction temperature were detrimental to product enantioselectivities (Table 17, entries 9 and 11). Furthermore, *N*-benzylaniline showed low conversion and reduced enantioselectivity (Table 17, entry 4). The corresponding magnesium and zinc complexes were inferior in catalytic activity and enantioselectivity in comparison to the nickel catalyst (Table 17, entries 2 and 3).

Table 19. Nickel-catalyzed asymmetric hydroamination of crotonitrile and methacrylonitrile with anilines and secondary cyclic amines.[65]





Entry	Amine	Olefin	Yield [%]	ee [%]
1	**67a**	**69a**	91	22
2	**67a**	**69b**	85	18
3	**67b**	**69a**	35	18
4	**67b**	**69b**	26	24
5	**67c**	**69a**	69	18
6	**67c**	**69b**	52	8
7	**68a**	**69a**	99	*rac*
8	**68a**	**69b**	99	69
9	**68b**	**69a**	85	7
10	**68b**	**69b**	99	20

The cationic palladium complex [{(*R*)-BINAP}Pd(OH_2)(NCMe)]$^{2+}$[OTf^-]$_2$ (**61**) displayed comparable catalytic activity to the nickel system, but was also suitable for primary aniline derivatives (Table 17, entries 12–18).[63] Aniline or *N*-methylaniline added with high enantioselectivity of up to 93% ee to crotonyloxazolidinone. An electron-withdrawing *p*-chloro substituent on the aniline did not significantly alter yield or enantioselectivity, but an electron-donating *p*-methyl or *p*-methoxy group led to reduced enantioselectivities. The system was also susceptible to the increased steric hindrance in pentenoyl- and hexenoyl-*N*-oxazolidinones, resulting in reduced rates at room temperature and moderate enantioselectivity at elevated temperature (Table 17, entries 17 and 18).

Recent work by Hii has shown that [{(*R*)-BINAP}Pd(NCMe)$_2$]$^{2+}$[$OTf]^-_2$ (**65**) also catalyzes enantioselective addition of anilines to *N*-Boc-protected alkenoylamides with good activity and excellent enantioseletivities at room temperature, reaching >99% ee (Table 18).[64] Sterically less demanding carbamates react with comparable rates and selectivity as the bulky *N*-Boc protected substrates (Table 18, entry 9). Interestingly, the least nucleophilic *p*-chloroaniline is the most reactive substrate, whereas electron-rich *p*-methoxy substitution was detrimental for turnover rates as well as enantiomeric excess. This reaction rate dependence on aniline nucleophilicity contradicts a simple Lewis-acid catalyzed mechanism.

Togni described the addition of anilines to crotonitrile and methacrylonitrile with moderate to good yields, but only low enantiomeric excess (Table 19, entries 1–6), using the nickel catalyst [Ni(**66**)(THF)]$^{2+}$[$(ClO_4)^-$]$_2$ containing the tridentate Pigiphos ligand **66** (Figure 15).[65] Secondary cyclic amines, such as morpholine and piperidine were more reactive. An enantioselectivity greater than 25% ee was only observed for the addition of morpholine (**68a**) to methacrylonitrile (**69b**) (Table 19, entry 8). Other tridentate phosphine ligands showed comparable activity, but inferior selectivity.[66] The reaction could be transferred with comparable results to the ionic liquid phase, allowing the recycling of the catalyst without strict exclusion of air and moisture.

5 Outlook

Extensive research effort has gone into the development of hydroamination catalysts and significant progress has been made in recent years. However, many problems have not been solved and no general catalyst has been described combining high catalytic activity and a consistent high level of enantioselectivity for a wide range of substrates, high functional group tolerance and user-friendliness. Challenges for the future include intermolecular asymmetric hydroamination reactions of terminal and internal non-activated carbon-carbon double bonds. Although primary amines are accessible *via* hydroamination using ammonia equivalents,[67] the direct addition of ammonia under mild conditions has remained elusive.[68] AHA using ammonia would be highly desirable from atom-economical and cost-efficiency points of view.

Significantly more effort seems to be necessary before the hydroamination reaction will become a day-to-day tool in every synthetic organic laboratory. However, the high value of the target compounds and the economical benefit will be the pay-off for these endeavors.

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