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Hydroamination: Direct Addition of Amines to Alkenes and Alkynes

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1. Introduction

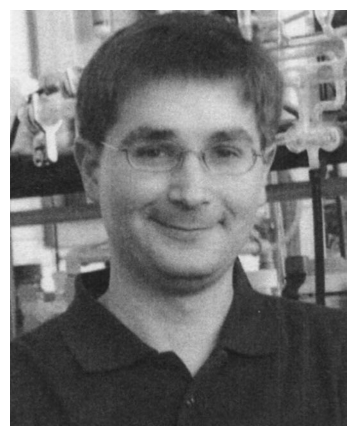
Nitrogen-containing compounds, such as amines, enamines, and imines, are valuable and commercially important bulk chemicals, specialty chemicals, and pharmaceuticals.[1] Among various synthesis routes, hydroamination, the direct formation of a new C−N bond by addition of an amine to an unsaturated CC bond, is of particular significance. The reaction offers an atom-efficient pathway starting from readily accessible alkenes and alkynes. While the reaction is thermodynamically feasible under normal conditions (slightly exothermic but nearly ergoneutral, because hydroamination reactions are entropically negative, in particular in the intermolecular variant),[2,3] there is a high reaction barrier. The 2 + 2 cycloaddition of N−H across the CC bond, which is orbital-forbidden under thermal conditions but can be promoted with light,[4] can be avoided by the use of a catalyst opening other reaction pathways. However, relatively low reaction temperatures (generally ≤200−300 °C) are required, because the conversion is limited by the reaction equilibrium at higher temperatures.[5]

The hydroamination of alkenes is more difficult compared with that of alkynes because of the lower reactivity and electron density of C═C bonds.[6] A particular challenge is the reversal of the regiochemistry to obtain the anti-Markovnikov product.[7] For good reason, the catalytic anti-Markovnikov addition of $H-NR_2$ to olefins was listed as one of the so-called "Ten Challenges for Catalysis".[6] During recent years, hydroamination became a widely explored operation in the synthesis of nitrogen heterocycles and complex molecules. The Markovnikov addition of protected amines to alkynes is now an established synthesis strategy. With the development of a new generation of catalysts, the addition of protected amines to alkenes will quickly become a routine reaction. More challenging and, thus, demanding further development time is the conversion of strongly basic amines, such as ammonia, as well as achieving adequate control of the regioselectivity in anti-Markovnikov fashion.

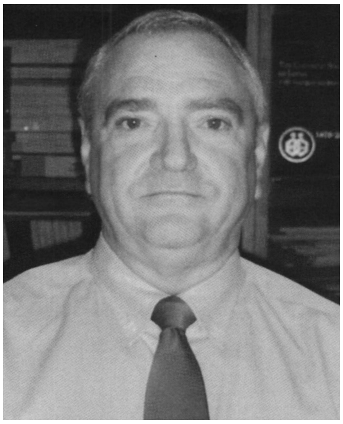
During the last decade, the interest of the scientific community in hydroamination has increased sharply (Figure 1). While mostly alkali and lanthanide metal catalysts were used in early studies, the focus has shifted recently to the use of zirconium, titanium, and late transition metal catalysts. Most catalysts are employed as homogenous catalysts, while the development of heterogeneous catalysts lags behind. In this respect, new strategies for the immobilization of homogeneous catalysts will gain increased importance. Some examples are described below.

Since the last comprehensive review by Müller and Beller in 1998,[8] review articles covering many aspects of hydroamination have been published (see Table 1). The article of Alonso et al. deserves particular attention for its thorough coverage of the hydroamination of alkynes.[9] In the review article presented here, the development of the subject from 1998 until June 2007 is discussed. The first part of this report covers mechanistic aspects of hydroamination with early and late transition metal catalysts. The use of heterogeneous

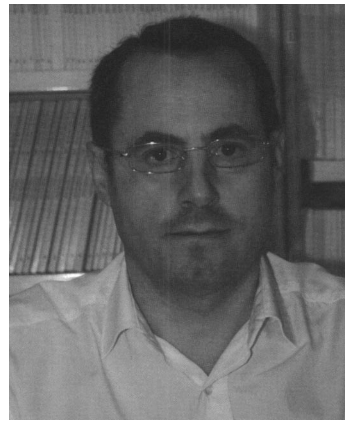
Thomas E. Müller was born in Landshut, Southern Germany, in 1967. He received his undergraduate education at LMU München and ETH Zürich. His Diplomarbeit led him for the first time to the United Kingdom, where he worked with D. M. L. Goodgame, IC London, on coordination polymers. After returning to Switzerland, he received his Diploma in 1991. He joined the research group of D. M. P. Mingos at IC London the following year and received his Ph.D. degree in 1995 for studies on polyaromatic phosphines and their coordination to noble metals. In 1995, he moved to the University of Sussex to pursue postdoctoral research on fullerenes and nanotubes with D. M. Walton and Sir H. K. Kroto. After working for two years as Liebig-Stipendiat in close collaboration with M. Beller and W. A. Herrmann at TU München, he started his habilitation in 1998 in the group of J. A. Lercher. In 2003, he continued at TU München as Privatdozent. After visiting professor positions at NUS Singapore (2005) and University of Tokyo (2005), he accepted the position as head of CAT Catalytic Center, RWTH Aachen, in 2007. He has published more than 50 papers, mainly in the field of amine synthesis, mechanistic studies on hydroamination, reductive amination, hydrogenation of nitriles, and catalyst immobilization. His current research interest is focused on homogeneous catalysis with transition metal complexes, immobilization of homogeneous catalysts, supported ionic liquids and metal nanoparticles, multiphase reactions, and building block systems for heterogeneous catalysis.



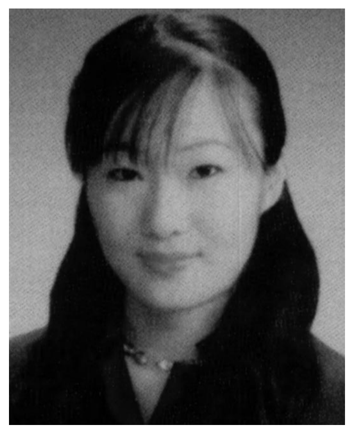
Kai Carsten Hultzsch studied chemistry at the University of Mainz, Germany, and Toronto, Canada, from 1991 to 1996. He finished is Ph.D. in 1999 under the guidance of Jun Okuda in Mainz. After two years as a Feodor Lynen postdoctoral fellow in the group of Richard R. Schrock at MIT, he began his independent research career in 2001 as a DFG Emmy Noether fellow at the University of Erlangen-Nürnberg, Germany. After finishing his habilitation in 2006 and visiting professor positions in Erlangen (2005/2006) and Münster (2007), he accepted his assistant professor position at Rutgers University, Piscataway, NJ, in 2007. He is the recipient of the Wöhler Young Investigator Award, the ADUC Award for Habilitands, the Lieseberg Award from the University of Heidelberg, and the Emmy-Noether-Habilitation-Award from the University of Erlangen-Nürnberg. His main areas of interests are transition metal catalyzed stereoselective olefin heterofunctionalizations and (co)polymerization of nonpolar and polar monomers.



Miguel Yus was born in Zaragoza (Spain) in 1947 and received his B.Sc. (1969), M.Sc. (1971), and Ph.D. (1973) degrees from the University of Zaragoza. After spending two years as a postdoctoral fellow at the Max Planck Institut für Kohlenforschung in Mülheim a.d. Ruhr, he returned to Spain to the University of Oviedo where he became associate professor in 1977, being promoted to full professor in 1987 at the same university. In 1988, he moved to a chair in Organic Chemistry at the University of Alicante where he is currently the head of the Organic Synthesis Institute (ISO). Professor Yus has been visiting professor at different institutions and universities such as ETH-Zentrum, Oxford, Harvard, Uppsala, Tucson, Okayama, Paris, Strasbourg, and Kyoto. He is coauthor of more than 400 papers, mainly in the field of the development of new methodologies involving organometallic intermediates, and three patents. Professor Yus has been a member of the Advisory Board of the journals, among others, *Tetrahedron*, *Tetrahedron Letters*, *Chemistry Letters*, *European Journal of Organic Chemistry*, *Trends in Organic Chemistry*, and *Current Chemical Biology*, being Regional Editor of *Letters in Organic Chemistry* also. He has given more than 100 lectures, most of them abroad, and already supervised 43 Ph.D. students. Among others, he has received twice the Japan Society for the Promotion of Science Prize (Okayama, 1999; Kyoto, 2007), the French-Spanish Prize of the Societé Française de Chimie (Paris, 1999), the C.A. Stiefvater Memorial Lecture Award (Nebraska, 2001), the Nagase Science and Technology Foundation fellowship (Kyoto, 2003), the Cellchem Lectureship (Sheffield, 2005), the Singenta Lectureship (Basel, 2007), and the Fundeun-Iberdrola Prize (Alicante, 2007). His current research interest is focused on the preparation of very reactive functionalized organometallic compounds and their use in synthetic organic chemistry, arene-catalyzed activation of different metals, preparation of new metal-based catalysts, including metallic nanoparticles, for homogeneous and heterogeneous selective reactions, and asymmetric catalysis. In 2002, he and other members of the ISO founded the new chemical company MEDALCHEMY, S.L., to commercialize fine chemicals.



Francisco Foubelo was born in Carreña-Cabrelas (Asturias) in 1961. He studied chemistry at the University of Oviedo from which he received B.S. (1984), M.S. (1986), and Ph.D. (1989) degrees. After a postdoctoral stay (1989−1991) as a Fulbright fellow at Princeton University, he moved to the University of Alicante and joined the research group of Professor M. Yus where he became Associate Professor in 1995 and Full Professor in 2002. Now he is a member of the Department of Organic Chemistry and the Organic Synthesis Institute (ISO) at the same university. He has published more than 80 papers and is cofounder of the new chemical company MEDALCHEMY, S.L., as a spin-off of the University of Alicante. His research interests are focused on the development of new synthetic methodologies for the preparation of functionalized organolithium compounds from different precursors and the application of these organometallic intermediates in organic synthesis. Heterofunctionalization of alkenes and the development of new synthetic methods for asymmetric synthesis related to chiral sulfinimines are recent interests.



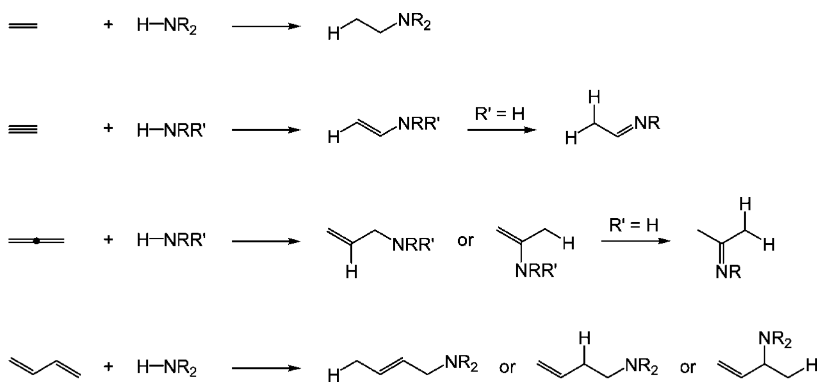
Mizuki Tada was born in 1979 in Tokyo (Japan). She studied and received her B.Sc. (2001) and M.Sc. (2003) from the Department of Chemistry, Graduate School of Science at The University of Tokyo. She obtained her Ph.D. in 2005 from The University of Tokyo under the supervision of Prof. Yasuhiro Iwasawa. She became the assistant professor of chemistry in 2004−2007 and was promoted to associate professor in the Department of Chemistry, Graduate School of Science, at The University of Tokyo in 2008. Her current research focuses on the catalyst surface, advanced surface design of supported metal-complex catalysts, surface molecular-imprinted catalysts and *in situ* time-resolved characterization of catalyst surfaces.

catalysts, base and acid catalyzed hydroamination, and some stoichiometric reactions, such as the mercuration/demercuration protocol are described next. Recently, non-conventional reaction conditions, in particular the use of microwaves and radical chemistry in solution, have been introduced in hydroamination. In the final part of this report, the scope of hydroamination reactions as new and highly exciting access to complex nitrogen-containing molecules is discussed.

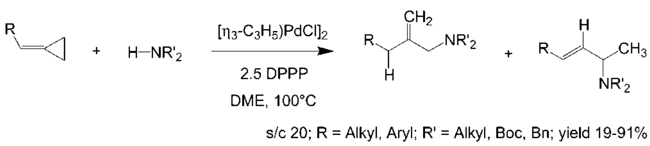
Hydroamination in the context of this review article is defined as the addition of $H-NR_2$ across a nonactivated alkene or alkyne providing a higher substituted amine or enamine, respectively. When ammonia or a primary amine is reacted with an alkyne, the enamine formed isomerizes subsequently to the corresponding imine. The addition of amines to allenes and dienes is closely related and will be covered. For the latter reactions, regioselectivity is an important issue, even when symmetric substrates are used, as 1,2 and 2,1 addition, and for dienes, 1,4 addition provides different products (Scheme 1).

Related reactions, such as the reaction of nitrogen nucleophiles with cyclopropanes[62–67] or cyclopropenes[68] (for an example, see Scheme 2), telomerization of amines with butadiene,[69–74] additions to alkenes activated by a neighboring electron-accepting substituent, such as the aza-Michael reaction[20,75–79] and the addition to acrylic acid or acrylonitrile derivatives,[80–84] oxidative amination using molecular oxygen[85] or styrene[86] as oxidant, and allylic amination of 3-alkenyl-carbonates[87] are generally not considered in this review except for cases where it seems appropriate. The hydroamination of slightly activated substrates, such as

Scheme 1



Scheme 2



norbornene, vinylethers, and, in particular, vinylarenes is, however, included.

2. Hydroamination Reactions Involving Rare-Earth Metals, Actinides and Alkaline Earth Metals

Rare-earth metal complexes are highly efficient catalysts for intramolecular hydroamination of various C−C unsaturations such as alkenes, alkynes, allenes, and dienes, but reduced rates are observed in intermolecular hydroamination processes. Attractive features of rare-earth metal catalysts include very high turnover frequencies and excellent stereoselectivities, rendering this methodology applicable to concise synthesis of naturally occurring alkaloids and other polycyclic azacycles. The general hydroamination mechanism involves rate-limiting C−C multiple bond insertion into the Ln−N bond, followed by rapid protonolysis by other amine substrates. The groundbreaking studies in the groups of T. J. Marks,[30] some of which were summarized in the 1998 review,[8] and later G. A. Molander have utilized predominantly lanthanocene complexes. Since then, sterically less encumbered ligand designs (e.g., constrained-geometry complexes, post-metallocenes) have been developed to improve reaction rates and alter catalyst stereoselectivities. Metallocene and non-metallocene chiral lanthanide complexes have

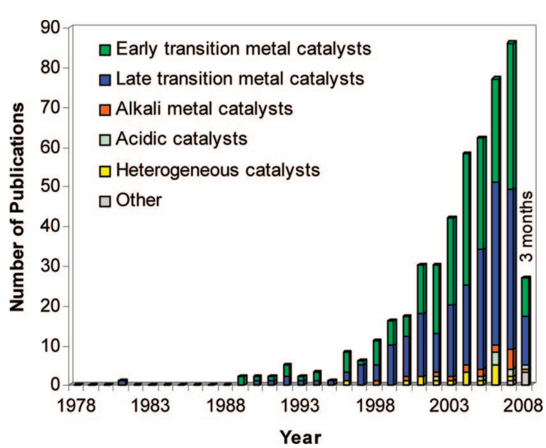
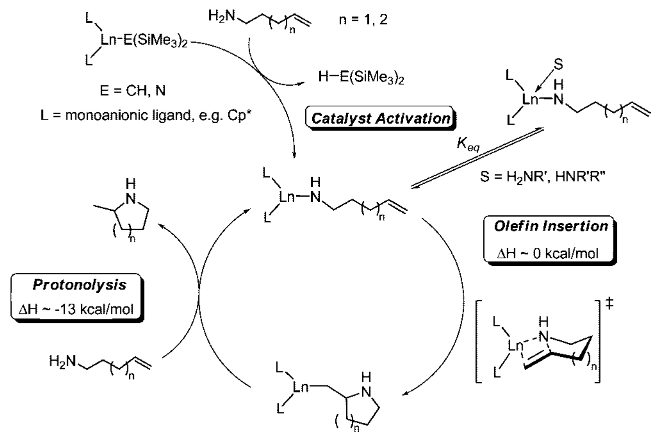


Figure 1. Number of articles published on hydroamination.

Scheme 3. Simplified Mechanism for Rare-Earth Metal Catalyzed Hydroamination/Cyclization of Aminoalkenes



been synthesized for enantioselective hydroamination. While the rare-earth metal catalysts are very efficient catalysts for hydroamination, their sensitivity to oxygen and moisture have limited their use in many applications.

As will be discussed in chapter 3, recent developments in catalytically active group 4 metal complexes have resulted in significant improvements in their reactivity towards aminoalkenes, and the first highly enantioselective examples using chiral catalysts have been reported. Similar to rare-earth metals, group 4 metal complexes are very oxophilic, which reduces their functional group tolerance. Nevertheless, group 4 metal catalysts have been applied to the synthesis of a range of biologically active molecules of relevance to pharmaceutical industry.

2.1. Mechanistic Aspects

The mechanism of the hydroamination/cyclization[30,88,89] 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 3). 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[88] is usually rate-determining, giving rise to a zero-order rate dependence on substrate concentration and first-order rate dependence on catalyst concentration (eq 1).

$$\text{rate} = -\frac{d[\text{subst}]}{dt} = k[\text{subst}]^0[\text{catalyst}]^1 \qquad (1)$$

The resting state of lanthanocene catalysts is an amido amine species of the general form $Cp^*_2Ln(NHR)(NH_2R)$

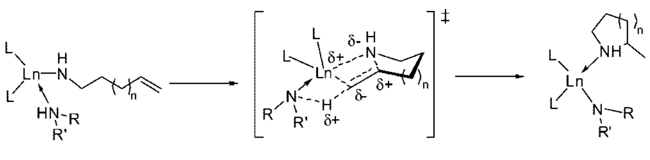
Table 1. Review Articles on Hydroamination Reactions[a]

ref	authors	no. of cited refs	covering until	topics in order of importance	substrates			
					alkenes	alkynes	dienes	allenes
10	Andrea, Eisen	118	09/2007	thorium and uranium catalysts	X	X		
11	**Aillaud, Collin, Hannedouche, Schulz**	**61**	**07/2007**	**asymmetric hydroamination**	**X**	**X**	**X**	**X**
12	Brunet, Chu, Rodriguez-Zubiri	122	04/2007	platinum catalyzed hydroamination promoted with halide anions	X			
13	Lee, Schafer	135	04/2007	group IV amidate complexes	X	X		X
14	Severin, Doye	40	10/2006	recent developments in hydroamination of alkynes		X		
15	**Hunt**	**169**	**01/2007**	**computational aspects of hydroamination with organolanthanides**	**X**	**X**	**X**	**X**
16	Liu, Bender, Han, Widenhoefer	78	10/2006	platinum catalysts	X			
17	Widenhoefer, Han	116	05/2006	gold catalysts	X	X	X	X
18	Mitsudo, Ura, Kondo	94	02/2006	zerovalent ru complexes		X		
19	Rowlands	55	2006	free radical reactions	X			
20	Hii	30	2006	palladium catalysts, enantioselective				
21, 22	Gottfriedsen, Edelmann	308, 285	05/2005	chemistry of organolanthanides and actinides	X	X		
23	**Hultzsch**	**53**	**12/2004**	**rare-earth and group IV metal catalysts**	X			
24	Doye	93	12/2004	titanium metallocene catalysts		X		
25	Hultzsch, Gribkov, Hampel	87	11/2004	non-metallocenes rare-earth catalysts, enantioselective	X			
26	Odom	92	10/2004	titanium diamide complexes		X		
27	Rosenthal, Burlakov, Arndt, Baumann, Spannenberg, Shur	76	09/2004	zirconium and titanium metallocene complexes		X		
28	Arndt, Okuda	94	08/2004	cationic alkyl complexes of rare-earth metals	X			
29	**Hultzsch**	**120**	**08/2004**	**asymmetric hydroamination**	**X**	**X**	**X**	**X**
30	Hong, Marks	24	02/2004	organolanthanide catalysts	X	X	X	X
31	Brunet, Poli	16	2004	selected aspects of Ru, Pd catalysis	X			
32	Beller, Tillack, Seayad	118	2004	green aspects	X	X		
33	Barbaro, Bianchini, Giambastiani, Parisel	148	11/2003	enantioselective hydroamination with iridium and nickel complexes	X			
9	**Alonso, Beletskaya, Yus**	**456**	**10/2003**	comprehensive review on alkynes		**X**		
34	Buffat	148	08/2003	synthesis of piperidines	X	X		
35	Hartwig	40	07/2003	palladium, nickel, and rhodium catalysts	X		X	
36	Leung	57	07/2003	vinyl- and alkynylphosphines	X	X		
37	Beller, Seayad, Tillack, Jiao	34	06/2003	regioselectivity	X	X		
38	Roesky, Müller	24	04/2003	enantioselective hydroamination	X		X	
39	Salzer	55	11/2002	arene(tricarbonyl)chromium complexes	X			
40	Bytschkov, Doye	44	08/2002	group IV metal complexes		X		X
41	Pohlki, Doye	38	07/2002	recent results in 2002		X		
42	Gibson, Ibrahim	67	02/2002	asymmetric catalysis using [(arene)$Cr(CO)_3$] complexes as ligands	X			
43	Duncan, Bergman	55	2002	imidozirconocene complexes				
44	**Seayad, Tillack, Hartung, Beller**	**142**	**2002**	**base catalyzed hydroamination reactions**	**X**	**X**	X	
45	Taube	22	2002	micro review				
46	Molander, Romero	130	09/2001	lanthanocene catalysts	X	X		X
47	Nobis, Drieβen-Hölscher	26	05/2001	recent results in 2002	X	X		X
48, 49	Müller	55, 56	02/2001	homogeneous and heterogeneous catalysts, respectively	X	X		X
50	Siebeneicher, Doye	37	11/2000	chemistry of [Cp_2TiMe_2]		X		
51	Togni, Bieler, Burckhardt, Kollner, Pioda, Schneider, Schnyder	21	07/1999	iridium catalysts, protected amines	X			
52	Haak, Doye	37	1999	micro review	X	X		
53	Yamamoto, Radhakrishnan	36	08/1998	Pd^{II} catalyzed addition of pronucleophiles				X
54	Eisen, Straub, Haskel	46	1998	organoactinide catalyzed telomerisation		X		
55	Johannsen, Jørgensen	165	1998	synthesis of allylic amines			X	
56	Merola	93	1997	iridium catalysts				
8	**Müller, Beller**	**239**	**07/1997**	**comprehensive review, mechanistic aspects**	**X**	**X**	**X**	**X**
57	Brunet	56	1997	rhodium catalyst, hydroamination with lithium phenylamide	X			
58	Simpson, Cole-Hamilton	200	01/1996	reactions catalyzed with rhodium trialkylphosphine complexes	X			
59	Anwander	115	1996	homogeneous lanthanide catalysts				
60	Taube	21	1996	micro review				
61	Marks, Gagne, Nolan, Schock, Seyam, Stern	49	1989	thermodynamic aspects	X			

[a] Important articles with particular focus on hydroamination are marked in bold.

based on spectroscopic and crystallographic evidence.[88] However, lanthanocene catalysts are only slightly inhibited by the presence of external bases, such as *n*-propylamine or THF, but depending on the steric congestion around the metal center and substrate structure, significant deviations from zero-order rate kinetics have been observed, and these have been attributed to substrate self-inhibition and product inhibition. For example, sterically open *ansa*-lanthanocenes and constrained-geometry catalysts have displayed product inhibition (apparent first-order kinetics),[88,90–92] while self-acceleration has been observed in the cyclization of aminohexene derivatives using sterically more encumbered catalysts.[91] Metal centers in non-metallocene-type catalysts are often more accessible to amine bases, as evidenced by

Scheme 4. Proposed Amine Participation in the Olefin Insertion Transition State of the Hydroamination/Cyclization[a]



[a] RR′NH = substrate or hydroamination product.

coordinating solvents (e.g., THF) found in the precatalysts, and kinetic deviations have been observed more frequently.[93–95]

Coordinative saturation of the metal center through strong amine binding results in reduced electrophilicity and therefore reduced catalytic activity. Therefore, if binding of either the substrate (K^{subst}) or the product azacycle (K^{prod}) to the catalyst is substantial, the rate of the reaction is reduced to the same extent as the reservoir of the more reactive, coordinatively unsaturated species is diminished with increasing amine (substrate/product) concentration (eq 2).

$$\text{rate} = -\frac{d[\text{subst}]}{dt} = \frac{k[\text{catalyst}]}{1 + K^{\text{subst}}[\text{subst}] + K^{\text{prod}}[\text{prod}]} \quad (2)$$

In many instances the binding constants of the substrate (e.g., primary aminoalkene) and product azacycle are similar or virtually identically ($K^{subst} \approx K^{prod} \equiv K_{eq}$), resulting in apparent zero-order rate dependence on substrate concentration, because the overall amine concentration remains constant throughout the reaction (eq 3; [L] = [subst] + [prod]).

$$\text{rate} = -\frac{d[\text{subst}]}{dt} = \frac{k[\text{catalyst}]}{1 + K_{\text{eq}}[\text{L}]} \quad (3)$$

The rare-earth metal alkyl species formed in the insertion process is prone to rapid protonolysis with a second amine molecule, regenerating the rare-earth metal amido species and releasing the heterocyclic product. Surprisingly, kinetic studies using N-deuterated aminoalkenes[88b,95] have revealed a large primary kinetic isotope effect with k_H/k_D in the range of 2.3−5.2, although no N−H bond breaking is involved in the rate-determining olefin insertion step. A plausible explanation involves partial proton transfer from a coordinated amine to the α-carbon in the four-membered insertion step (Scheme 4). However, some experimental data, in particular the observation of sequential hydroamination/bicyclization sequences (*vide infra*), is in conflict with these findings, because the latter requires a finite lifetime for the rare-earth metal alkyl intermediate.

From a thermodynamic point of view, rare-earth metal catalyzed hydroamination/cyclization of aminoalkenes differs significantly from reactions involving aminoalkynes, aminoallenes, and conjugated aminodienes. For terminal aminoalkenes, the olefin insertion step of the Ln−amide into the carbon−carbon double bond is approximately thermoneutral, and it is only slightly exothermic for an internal aminoalkene with an 1,2-disubstituted alkene (Scheme 5, step A).[88,92] The following protonolysis of the primary rare-earth metal alkyl species is quite exothermic, to a lesser extent also for the secondary rare-earth metal alkyl species. In marked contrast, insertion of an alkyne, allene, or 1,3-diene into the Ln−amide bond is very exothermic (Scheme 5, steps B−D).[91,96,97] Protonolysis of the resulting vinyl (in case of alkynes and allenes) or η^3-allyl (in case of conjugated dienes) rare-earth metal species is about thermoneutral (for the vinylic species) to slightly endothermic (for the allylic species) due to the significant stabilization of these species. Despite these significant differences, it was proposed that in all these cyclization reactions the insertion step is rate-determining,[89a,b] followed by a rapid protonolysis step. However, recent DFT analyses of the catalytic cycle of the rare-earth metal catalyzed hydroamination of dienes and allenes suggest that protonolysis of the rare-earth metal η^3-

Scheme 5. Thermodynamics of the Elementary Steps in Rare-Earth Metal Catalyzed Hydroamination/Cyclization[88,91,92,96,97]

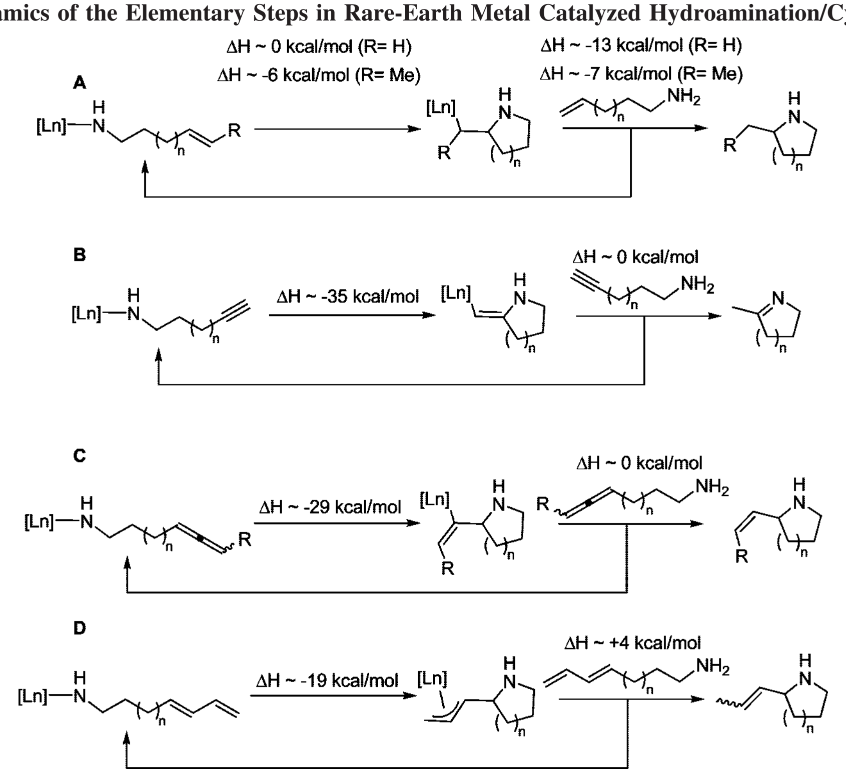
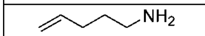
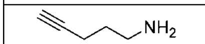
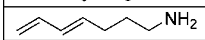
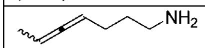
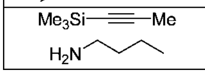
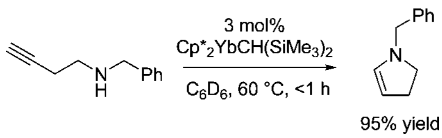


Table 2. Comparison of Activation Parameters for Hydroamination/Cylization Reactions.

Substrate	Catalyst	TOF /h^{-1} (°C)	$\Delta H^{\ddagger}$ /kcal mol^{-1}	$\Delta S^{\ddagger}$ /cal mol^{-1}	E_a /kcal mol^{-1}	Ref.
	$Cp^*_2LaCH(SiMe_3)_2$ (**1a-La**)	13 (25)	12.7(1.4)	-27.0(4.6)	13.4(1.5)	88b
	$Me_2Si(C_5Me_4)_2SmCH(SiMe_3)_2$ (**2a-Sm**)	21.6 (125)	17.7(2.1)	-24.7(5.0)	18.5(2.0)	92
	$Cp^*_2SmCH(SiMe_3)_2$ (**1a-Sm**)	580 (21)	10.7(8)	-27.4(6)	11.3(2.0)	96b
	$Cp^*_2LaCH(SiMe_3)_2$ (**1a-La**)	40 (25)	10.4(0.4)	-32.7(1.2)	10.4(0.4)	91
	$Cp^*_2LuCH(SiMe_3)_2$ (**1a-Lu**)	7 (23)	16.9(1.3)	-16.5(4.3)	17.6(1.4)	98b
	$Me_2Si(C_5Me_4)_2NdCH(SiMe_3)_2$ (**2a-Nd**)	13 (60)	17.2(1.1)	-25.9(9)	17.8(1.8)	99

Scheme 6. 5-*endo-dig*-Hydroamination/Cyclization of a Homopropargylamine.[100]



allyl species (in hydroamination of dienes) or vinylic species (in hydroamination of allenes) is the rate-limiting step.[89c–e]

The activation parameters associated with the rate-determining step of the catalytic cycle indicate that the hydroamination/cyclization involves a highly ordered transition state (Table 2). The highest enthalpic barrier is observed for the cyclization of the internal aminoalkenes, originating from steric and electrostatic repulsion of the 1,2-disubstituted olefin.

Quite generally, rare-earth metal catalyzed cyclizations of aminoalkenes, aminoalkynes, and aminodienes produce exclusively the exocyclic hydroamination products. However, cyclization of homopropargylamines leads to the formation of the endocyclic enamine product via a 5-*endo-dig*-hydroamination/cyclization (Scheme 6),[100] most likely due to steric strain in the four-membered ring exocyclic hydroamination product. Interestingly, the 5-*endo-dig* cyclization is even preferred in the presence of an olefin group that would lead to a 6-*exo* hydroamination product.

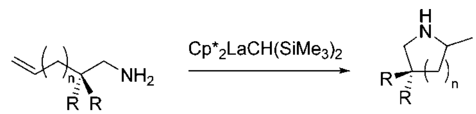
Initial studies on intermolecular hydroamination of alkynes with primary amines[101] suggested for organoactinide catalysts a mechanism closely related to that found for neutral group 4 metal catalysts (*vide infra*), involving a [2 + 2] cycloaddition pathway proceeding via reactive $L_2An{=}NR$ imido species. This proposal was put forth based on kinetic and structural evidence.[101] However, the observation of actinide-catalyzed hydroamination of an alkyne with a secondary amine,[102] as well as hydroamination/cyclization reactions of primary and secondary aminoalkenes,[103] provide strong evidence that a second mechanistic pathway must be operative. The reaction proceeds via insertion of the olefinic double bond into an actinide−amide σ-bond in a polar and highly ordered four-centered insertion transition state, analogous to the lanthanide-mediated reaction.

2.2. Catalysts and Scope of Reaction

As reviewed earlier,[8,30] rare-earth metal catalysts are among the most active and most versatile catalysts for the intramolecular hydroamination of (terminal) aminoalkenes (Scheme 7)[88,104] and aminoalkynes (Scheme 8),[96] producing pyrrolidines, piperidines, indolines, and azepanes. The rate of cyclization generally decreases with increasing ring size (5 > 6 ≫ 7).[88,96]

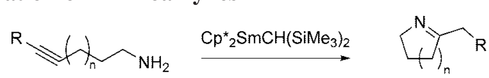
Catalytic activity in rare-earth metal catalyzed hydroamination/cyclization of aminoalkenes generally increases with increasing ionic radius of the rare-earth metal ion (Table 3, entries 1−3 and 7−9).[88] Better accessibility of the metal center also results in increased rates of cyclization, as observable in the tied-back *ansa*-lanthanocene precatalysts $Me_2Si(C_5Me_4)_2LnE(SiMe_3)_2$ (**2a**,**b-Ln**; E = CH (**a**), N (**b**)) in comparison to the sterically more hindered permethyllanthanocenes $Cp^*_2LnE(SiMe_3)_2$ (**1a**,**b-Ln**; E = CH (**a**), N (**b**)) (Figure 2 and Table 3, entries 3−6). A further increase in catalyst activity was observed when sterically more open and less electron-donating constrained-geometry catalysts

Scheme 7. Lanthanocene-Catalyzed Hydroamination/Cyclization of Aminoalkenes[88]



n	R	T /°C	TOF /h
1	H	60	140
1	Me	25	95
2	H	60	5
3	Me	60	0.3

Scheme 8. Lanthanocene-Catalyzed Hydroamination/Cyclization of Aminoalkynes[96]



n	R	T /°C	TOF /h
1	H	21	580
1	Me	21	96
1	$SiMe_3$	21	>7600
1	Ph	60	2830
2	Ph	60	328
3	Ph	60	0.11

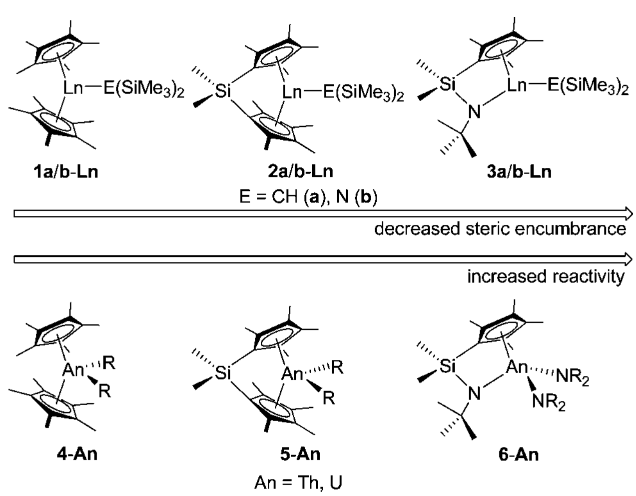
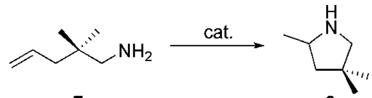


Figure 2. Dependence of catalytic activity in hydroamination/cyclization of aminoalkenes on steric demand of the catalyst ligand framework for rare-earth metal and actinide catalysts.

Table 3. Rate Dependence on Ionic Radius and Steric Demand of the Ancillary Ligand in the Rare-Earth Metal Catalyzed Cyclization of Aminoalkenes

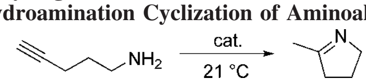


7 **8**

entry	catalyst	ionic radius,[107] Å	T, °C	TOF, h^{-1}	ref
1	$Cp^*_2LaCH(SiMe_3)_2$ (**1a-La**)	1.160	25	95	88
2	$Cp^*_2SmCH(SiMe_3)_2$ (**1a-Sm**)	1.079	60	48	88b
3	$Cp^*_2LuCH(SiMe_3)_2$ (**1a-Lu**)	0.977	80	<1	88b
4	$Me_2Si(C_5Me_4)_2LuCH(SiMe_3)_2$ (**2a-Lu**)	0.977	80	75	88b
5	$Me_2Si(C_5Me_4)(C_5H_4)LuCH(SiMe_3)_2$	0.977	80	200	88b
6	*meso*-[(ebi)YbN(SiMe3)2][a]	0.985	25	0.6[b]	108
7	$Me_2Si(C_5Me_4)(^tBuN)NdN(SiMe_3)_2$ (**3b-Nd**)	1.109	25	200	105
8	$Me_2Si(C_5Me_4)(^tBuN)SmN(SiMe_3)_2$ (**3b-Sm**)	1.079	25	181	105
9	$Me_2Si(C_5Me_4)(^tBuN)LuCH(SiMe_3)_2$ (**3a-Lu**)	0.977	25	90	105
10	$Me_2Si(C_5Me_4)(^tBuN)Th(NMe_2)_2$ (**6-Th**)	1.09	25	15	103a,b
11	$Me_2Si(C_5Me_4)(^tBuN)U(NMe_2)_2$ (**6-U**)	1.05	25	2.5	103a,b

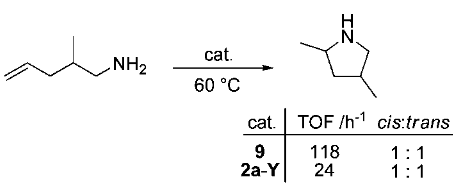
[a] ebi = ethylene-*bis*-(η^5-indenyl). [b] Estimated value (2 mol % catalyst, 70 h, 79% isolated yield).

Table 4. Rate Dependence on Ionic Radius and Steric Demand of the Ancillary Ligand in the Rare-Earth Metal and Actinide Catalyzed Hydroamination Cyclization of Aminoalkynes



entry	catalyst	ionic radius,[107] Å	TOF, h^{-1}	ref
1	$Cp^*_2LaCH(SiMe_3)_2$ (**1a-La**)	1.160	135	96b
2	$Cp^*_2NdCH(SiMe_3)_2$ (**1a-Nd**)	1.109	207	96b
3	$Cp^*_2SmCH(SiMe_3)_2$ (**1a-Nd**)	1.079	580	96b
4	$Cp^*_2LuCH(SiMe_3)_2$ (**1a-Lu**)	0.977	711	96b
5	$Me_2Si(C_5Me_4)_2NdCH(SiMe_3)_2$ (**2a-Nd**)	1.109	78	96b
6	$Cp^*_2UMe_2$ (**4-U**)	1.05	26	103a,b
7	$Me_2Si(C_5Me_4)(^tBuN)Th(NR_2)_2$ (**6-Th**)	1.09	7.8	103a,b
8	$Me_2Si(C_5Me_4)(^tBuN)U(NR_2)_2$ (**6-U**)	1.05	1210	103a,b

Scheme 9



$Me_2Si(C_5Me_4)(^tBuN)LnE(SiMe_3)_2$ (**3a**,**b-Ln**; E = CH (**a**), N (**b**)) were utilized.[105] Electronic effects also play a pivotal role for catalytic activity. Thus, decreased reactivity of a constrained-geometry indenyl lutetium complex containing an electron-donating pyrrolidinyl substituent was observed in comparison to **3a-Lu**.[106]

The stereoelectronic characteristics of the ancillary ligand are significantly more pronounced for organoactinide catalysts. The constrained-geometry complexes $Me_2Si(C_5Me_4)$-$(^tBuN)An(NR_2)_2$ (**6-An**; An = Th, U; NR_2 = NMe_2, NMeEt, NEt_2)[103] are highly active hydroamination catalysts for essentially the same set of substrates as applied to lanthanide catalysts. In contrast, the sterically more encumbered and electronically more saturated *ansa*-actinocenes $Me_2Si(C_5Me_4)_2AnR_2$ (**5-An**; An = Th, U; R = CH_2SiMe_3, CH_2Ph) or the permethylactinocene $Cp^*_2AnR_2$ (**4-An**) react rather sluggishly with aminoalkene substrates.

Cyclization of aminoalkynes commonly proceeds significantly faster than cyclization of aminoalkenes.[96] Furthermore, terminal as well as internal alkynes react with comparable rates, while internal double bonds in aminoalkenes react

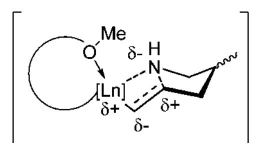
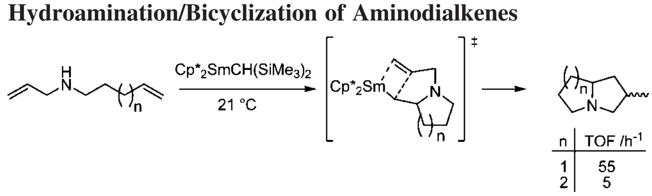


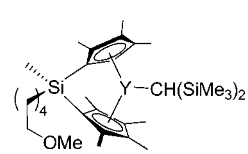
Figure 3. Proposed stabilization of the olefin insertion transition state through intramolecular chelation.

Scheme 10. Lanthanocene Catalyzed Intramolecular Hydroamination/Bicyclization of Aminodialkenes



significantly slower and under much more forcing reaction conditions (*vide infra*). Interestingly, the reactivity pattern in rare-earth metal catalyzed hydroamination/cyclization reactions of aminoalkynes with respect to ionic radius size and steric demand of the ancillary ligand follows the opposite trend to that observed for aminoalkenes, for example, generally *decreasing* rates of cyclization with *increasing* ionic radius of the rare-earth metal and more open coordination sphere around the metal (Table 4).[96]

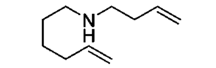
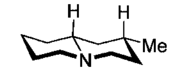
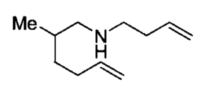
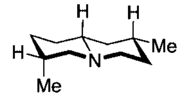
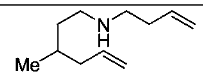
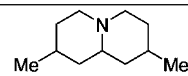
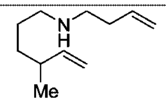
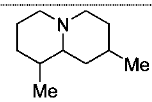
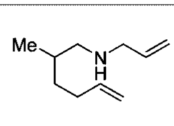
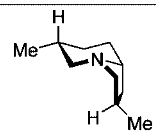
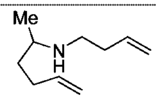
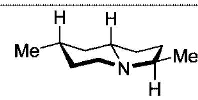
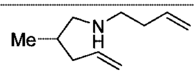
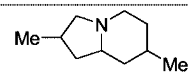
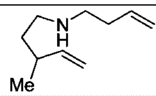
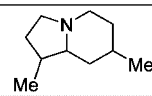
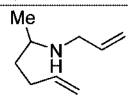
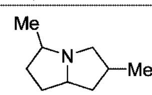
The hydroamination reactions using oxophilic lanthanide catalysts are best performed in non-polar aliphatic or aromatic solvents, whereas slight rate depressions are noticeable in polar solvents, such as THF ($k_{toluene}/k_{THF} \approx 5$).[88b] Interestingly, the *ansa*-yttrocene **9**,



9

with an ether functionality tethered to the silicon bridge, was shown to display increased reactivity (up to 5-fold) in the cyclization of aminoalkenes relative to the nonfunctionalized *ansa*-yttrocene $Me_2Si(C_5Me_4)_2YCH(SiMe_3)_2$ (**2a-Y**), though the effect on diastereoselectivity was minimal to negligible (Scheme 9).[109] It was suggested that this effect results from a stabilization of the polar olefin insertion transition state

Table 5. Stereoselective Rare-Earth Metal Catalyzed Hydroamination/Bicyclization of Aminodialkenes Using $Cp^*_2LnCH(SiMe_3)_2$ (Ln = Nd (1a-Nd), Sm (1a-Sm)[111]

Entry	Aminodialkene	Product	Catalyst [a]	T / °C	dr	Yield / %
1			**1a-Nd**	rt	>50:1	85
2			**1a-Nd**	50	>20:1	90
3			**1a-Nd**	rt	1:1.3[b]	86
4			**1a-Nd**	rt	1:1.9[b]	89
5			**1a-Nd**	40	27:1	80
6			**1a-Sm**	rt	25:1	91
7			**1a-Sm**	rt	1:1[b]	84
8			**1a-Sm**	rt	6:1[b]	91
9			**1a-Sm**	50	2:1[b]	83

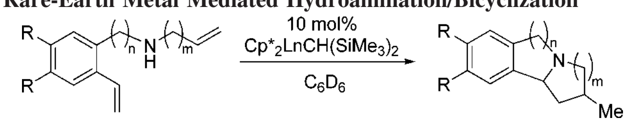
[a] General conditions: 10 mol % catalyst in C_6D_6, 4 d. Substrates were generated *in situ* from their corresponding hydrochloride salts. [b] The stereochemistry of these products has not been reported.

through an intramolecular chelation of the tethered donor group (Figure 3).

Hydroamination/bicyclization of aminodialkenes, aminodialkynes, and aminoalkeneynes allows facile access to pyrrolizidines and indolizidines in a tandem C−N and C−C bond-forming process (Scheme 10).[110] This process has significant synthetic potential in the synthesis of complex naturally occurring alkaloidal skeletons. An important prerequisite for the success of this reaction sequence is a sufficient lifetime of the rare-earth metal alkyl intermediate formed in the initial insertion process of the alkene/alkyne in the Ln−amide bond to permit the carbocyclization step. However, this sequence is in conflict with the large primary kinetic isotope effect observed for primary aminoalkenes, which suggests partial N−H bond breaking in the course of the olefin insertion step (*vide supra*).

A more detailed study extended the hydroamination/bicyclization methodology also to quinolizidines and probed the influence of alkyl substituents in various positions of the substrate backbone on the sense and magnitude of diastereoselection.[111] While methyl substitution in the β-position to the secondary amine nitrogen effected high stereoselection (Table 5, entries 2, 5, and 6), more remote positions closer to the olefinic group (Table 5, entries 3, 4, 7, and 8) gave poor selectivities. Possibly because of stereoelectronic reasons, the larger neodymium catalyst performed better in the formation of quinolizidines and indolizidines involving six-membered ring formation in the initial hydroamination step, whereas the smaller samarium ion was more effective when the initial hydroamination step involved formation of a five-membered ring.

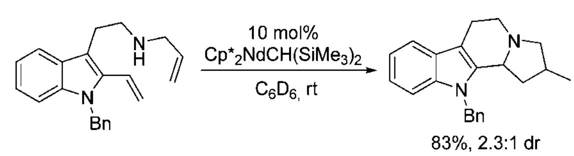
Table 6. Preparation of Tricyclic Aromatic Azacycles through Rare-Earth Metal Mediated Hydroamination/Bicyclization[112]



entry	R	*n*	*m*	Ln	*T*, °C	dr	yield, %
1	H	1	1	Sm	rt	<5.5:1[b]	79
2	OMe	1	1	Sm	45−50	4.7:1[b]	84
3	OMe	1	2	Sm	45−50	>50:1[b]	59[a]
4	H	2	1	Nd	9−rt	1.7:1[b]	76
5	OMe	2	1	Nd	9−rt	1.4:1[b]	82
6	H	2	2	Nd	rt	26:1[c]	>73
7	OMe	2	2	Nd	45−50	16:1[c]	69

[a] Isolated as HCl salt in the presence of BHT, but readily oxidized in solution. [b] Stereochemistry not established. [c] The major isomer has a 1,3-*cis* relationship of the two stereocenters according to an X-ray crystallographic analysis.

A further extension of this methodology gave access to tricyclic (Table 6) and tetracyclic (eq 4) alkaloidal skel-



(4)

Scheme 11. Proposed Mechanism of Lanthanocene-Catalyzed Inter- and Intramolecular Hydroamination/Tricyclization.[110b]

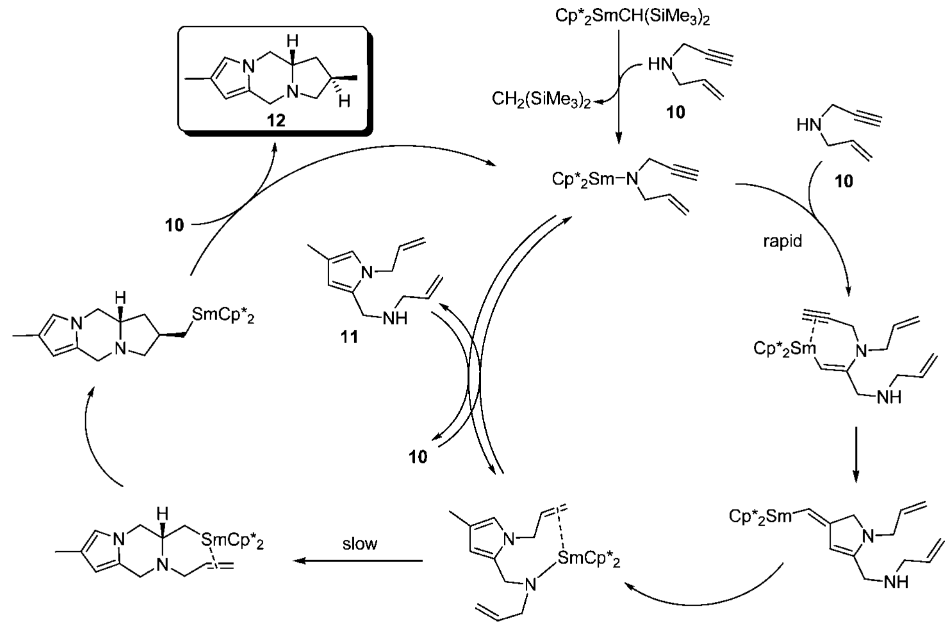
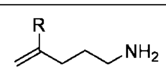
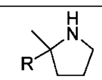
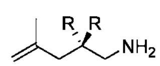
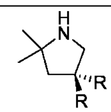
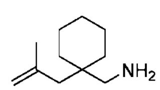
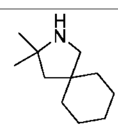
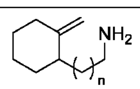
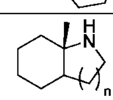
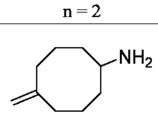
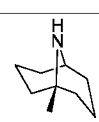
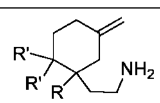
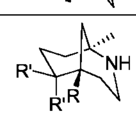
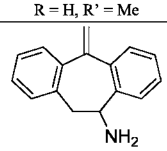
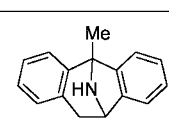


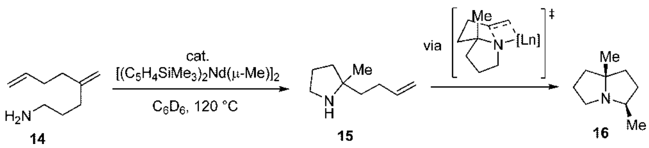
Table 7. Rare-Earth Metal Catalyzed Hydroamination/Cyclization of Hindered *Gem*-Disubstituted Aminoalkenes Using $[(C_5H_4SiMe_3)_2Ln(\mu\text{-}Me)]_2$ (Ln = Nd, Sm)

Entry	Aminoalkene	Product	Ln	[cat.]/[s] /%	Solvent	*T* / °C	*t* / h	Yield / %	Ref.
									
1	R = Me		Nd	3.9	--[a]	120	12	95	113a
2	R = Ph		Nd	4.5	C_6D_6	120	168	90	113a
									
3	R = Me		Sm	5.6	--[a]	70	2	93	113a
4	R = Ph		Sm	4	C_6D_6	25	1	98	113a
5			Sm	3.8	C_6D_6	25	1	92	113a
									
6	n = 1		Nd	4.8	C_6D_6	120	48	80	113a
7	n = 2		Nd	4.9	C_6D_6	140	168	90	113a
8			Nd	10.5	C_6D_6	120	0.08	94	113a
									
9	R = Me, R' = H		Nd	8	C_6D_6	120	48	97	113a
10	R = H, R' = Me		Nd	14	C_6D_6	120	72	91	113a
11	 13	 MK-801	Nd	1	C_6D_6	40	2	98	113b

[a] Reaction in neat solution.

etons.[112] Particularly high diastereoselectivities were achieved in the formation of the pyrido[2,1-*a*]isoindolizine (Table 6, entry 3) and benzo[*a*]quinolizine (Table 6, entry 6) ring systems. Remarkably, electron-donating methoxy substitution of the aromatic ring did not sequester catalyst activity and selectivity to a significant extent.

Scheme 12



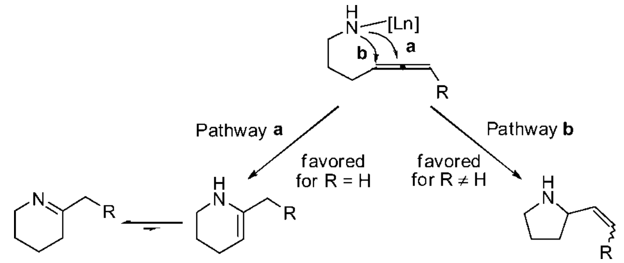
More intriguingly, a sequence of inter- and intramolecular hydroaminations and carbocyclizations were utilized to assemble the tricyclic polyheterocycle **12** with exclusive trans diastereoselectivity (Scheme 11).[110b] Initial intermolecular alkyne hydroamination and intramolecular carbocyclization of the aminoalkeneyne **10** is rapid (TOF = 236 h^{-1} at 60 °C), followed by a slow intramolecular alkene hydroamination/carbocyclization sequence (TOF = 1 h^{-1} at 60 °C) that allows isolation of the pyrrole intermediate **11**.

Cyclization of aminoalkenes with sterically demanding 1,1-disubstituted alkenes generally requires harsher reaction conditions than cyclization of aminoalkenes containing terminal olefinic groups, unless the substrate is significantly activated by *gem*-dialkyl substitution (Table 7).[113,114] Remarkably, facile cyclization of the sterically hindered aminodibenzocycloheptane **13** at 40 °C with only 1 mol % catalyst loading produced the anticonvulsant drug dizocilpine (MK-801; Table 7, entry 11),[113b] which is a noncompetitive antagonist of the NMDA receptor.[115]

Interestingly, cyclization of the aminodialkene **14** yields initially the pyrrolidine **15** (Scheme 12).[113a] Obviously, formation of the five-membered pyrrolidine ring is kinetically favored over formation of an azocane, despite the fact that the sterically more encumbered 1,1-disubstituted olefin has to react first. A subsequent second hydroamination/cyclization results in the formation of the pyrrolizidine **16** through a highly organized chair-like transition state.

Aminoalkenes with 1,2-disubstituted alkenes are less reactive than 1,1-disubstituted alkenes, and cyclization generally requires stringent reaction temperatures (≥100 °C, Table 8).[92,116] The rate dependency on ring size (5 > 6) is less prevalent for these substrates and can be even reversed in some cases (Table 8, entries 1 and 7). Although one might

Scheme 13



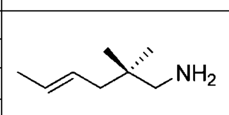
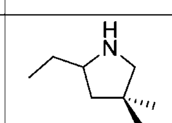
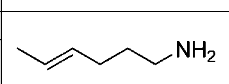
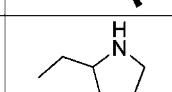
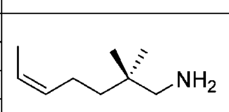
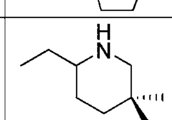
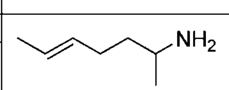
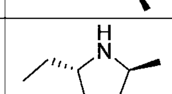
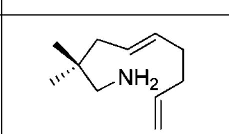
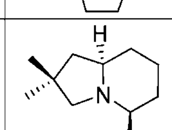
expect that the higher steric demand of the internal olefins favors cyclization using sterically open catalysts, the rate of cyclization of aminoalkenes with 1,2-disubstituted alkenes decreases in the order $Me_2Si(C_5Me_4)_2LnR$ > Cp^*_2LnR ≫ $Me_2Si(C_5Me_4)(^tBuN)LnR$, in marked contrast to results obtained for aminoalkenes with terminal double bonds. This effect on reactivity was attributed to the reduced electron-donating ability of the amido substituent in the constrained-geometry catalysts in comparison to the cyclopentadienyl ligand in the lanthanocenes.

Cyclization of an aminodialkene produces indolizidines through two consecutive hydroamination/cyclization steps (Table 8, entry 13).

To avoid such harsh reaction conditions associated with the cyclization of aminoalkenes containing 1,2-disubstituted carbon−carbon double bonds, more reactive unsaturated moieties, such as aminoallenes or aminodienes can be employed.

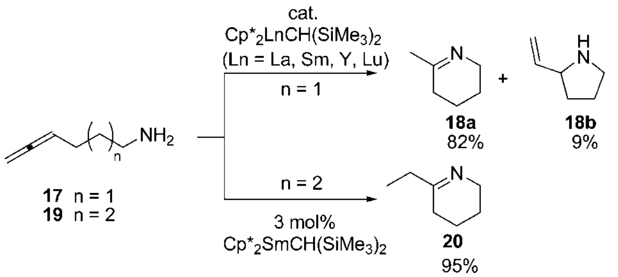
Hydroamination/cyclization of aminoallenes is generally faster than the reaction of (terminal) aminoalkenes, but slower (by a factor of 5−20) than aminoalkynes.[98] The cyclization can follow two different pathways leading to two possible regioisomers (Scheme 13). Monosubstituted, terminal allenes often form a mixture of products; however formation of the cyclic imine through the endocyclic pathway a (R = H, Scheme 13) is generally favored. However, while this is true for the hexadienylamine **17** (Scheme 14), cyclization of the homologous heptadienylamine **19** produced exclusively the tetrahydropyridine **20**. The mode of formation of **20** is

Table 8. Rare-Earth Metal Catalyzed Hydroamination/Cyclization of Aminoalkenes with 1,2-Disubstituted Alkenes

Entry	Aminoalkene	Product	Catalyst[a]	T / °C	TOF / h^{-1}	Conv. / %	Ref.
1			$Cp^*_2LaCH(SiMe_3)_2$ **(1a-La)**	125	8.54	>95	92
2			$Me_2Si(C_5Me_4)_2SmCH(SiMe_3)_2$ **(2a-Sm)**	125	21.6	>95	92
3			$Me_2Si(C_5Me_4)(^tBuN)SmN(SiMe_3)_2$ **(3b-Sm)**	125	3.59	>95	92
4			$Me_2Si(C_5Me_4)(^tBuN)Th(NMe_2)_2$ **(6-Th)**	100	0.6	≥90	103b
5			$Cp^*_2LaCH(SiMe_3)_2$ **(1a-La)**	125	1.12	>95	92
6			$Me_2Si(C_5Me_4)(^tBuN)SmN(SiMe_3)_2$ **(3b-Sm)**	125	0.03	42	92
7			$Cp^*_2LaCH(SiMe_3)_2$ **(1a-La)**	125	11.5	>95	92
8			$Me_2Si(C_5Me_4)_2SmCH(SiMe_3)_2$ **(2a-Sm)**	125	14.4	>95	92
9			$Me_2Si(C_5Me_4)(^tBuN)SmN(SiMe_3)_2$ **(3b-Sm)**	125	0.35	>95	92
10			$Me_2Si(C_5Me_4)(^tBuN)U(NMe_2)_2$ **(6-U)**	100	2.2	≥90	103b
11			$Me_2Si(C_5Me_4)(^tBuN)SmN(SiMe_3)_2$ **(3b-Sm)**	120	0.41	95[b]	92
12			$Me_2Si(C_5Me_4)(^tBuN)YN(SiMe_3)_2$ **(3b-Y)**	120	0.23	90[c]	92
13			$Me_2Si(C_5Me_4)(^tBuN)SmN(SiMe_3)_2$ **(3b-Sm)**	125	0.3	85[d]	92

[a] Reactions with 5 mol % catalyst in *o*-xylene-d_{10}. [b] trans/cis = 11:1. [c] trans/cis = 16:1. [d] cis/trans = 81:19.

Scheme 14. Rare-Earth Metal Catalyzed Hydroamination/Cyclization of Monosubstituted Aminoallenes



currently not known, because it might involve either cyclization of **19** through exocyclic pathway b (Scheme 13), followed by an isomerization of the allylamine, or it might involve an allene to alkyne isomerization of the aminoallene starting material prior to the hydroamination/cyclization step.

Cyclization of 1,3-disubstituted allenes on the other hand proceeds exclusively through the exocyclic pathway b to generate an allylamine (R ≠ H, Scheme 13). Nonbranched aminoallenes are cyclized with high *Z* stereoselectivity irrespective of the size of the rare-earth metal ion (Table 9, entry 1; Table 10). Branched, α-substituted aminoallenes form exclusively 2,5-*trans*-pyrrolidines and 2,6-*cis*-piperidines with rare-earth metal catalysts (Table 9, entries 3, 5, and 7), albeit with no stereoregularity of the double bond geometry (*E*/*Z* ratio close to 1:1). Furthermore, the rate of cyclization of these α-substituted aminoallenes with the amino group attached to a secondary carbon significantly exceed the rates of cyclization of the corresponding nonbranched aminoallenes with an amino group attached to a primary carbon (compare Table 9, entries 3 and 5, with Table 9, entry 1, and Table 10, entry 2).

The rate dependence on the ionic radius of the rare-earth metal in hydroamination/cyclization of aminoallenes differs from that observed for aminoalkenes (increasing rates with increasing ionic radius) and aminoalkynes (decreasing rates with increasing ionic radius) and results in highest rates for the yttrocene Cp*$_2$YCH(SiMe$_3$)$_2$ (**1a-Y**), whereas larger and smaller rare-earth metals are less effective (Table 10).

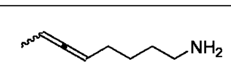
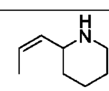
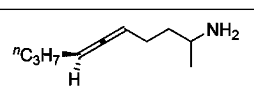
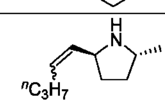
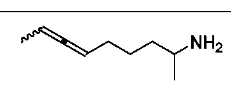
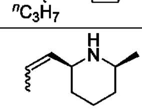
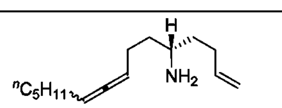
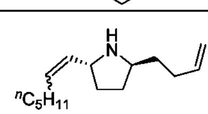
Hydroamination/cyclization of aminoallenes has found synthetic application in the synthesis of pyrrolidine- and pyrrolizidine-based alkaloids.[117] The pyrrolidine alkaloid (+)-197B and the indolizidine alkaloid (+)-xenovenine were prepared using a hydroamination/cylization reaction as a key step (Scheme 15). Reaction of the aminoallene−alkene **21** containing an allene and a terminal alkene moiety positioned in equal distance to the amino group requires the constrained-geometry catalyst Me$_2$Si(C$_5$Me$_4$)(^{t}BuN)SmN(SiMe$_3$)$_2$ (**3b-Sm**) to achieve facile and stereospecific bicyclization (Scheme 15). In contrast, sterically more encumbered lanthanocene catalysts react selectively at the allene moiety and leave the alkene moiety untouched (Table 9, entry 7).

A second method to circumvent limitations in the cyclization of 1,2-disubstituted aminoalkenes are hydroamination/cyclization reactions of conjugated aminodienes.[91,97] These substrates react with relative ease because of the formation of a rather stable η^3-allyl intermediate during the catalytic cycle. Note however, that the transition state leading to this η^3-allyl intermediate is sterically more demanding than the corresponding transition state in the cyclization of aminoalkenes. Protonation of this η^3-allyl species leads predominantly to *E*/*Z* vinyl *N*-heterocycles (Scheme 16). Formation of the corresponding allyl isomers has been observed in certain cases, although the protonation step leading to the allyl isomer is more endothermic. In contrast to cyclization of aminoallenes, cyclization of conjugated aminodienes yields exclusively the exocyclic products and no evidence for endocyclization was observed.

Following the general trends observed for aminoalkenes, increasing rare-earth metal ionic radii as well as more open ligation results in increased rates of aminodiene cyclization. Although the reactions predominantly exhibit zero-order rate dependence on substrate concentration, deviations from this ideal kinetic have been observed, namely, competitive product inhibition (leading to *decreased* rates at higher conversions) when sterically open constrained-geometry catalysts were employed and substrate self-inhibition (leading to *increased* rates at higher conversions) when sterically encumbered lanthanocene catalysts were used.

In contrast to the cyclization of aminoallenes, which generally yield predominantly the *Z* vinyl azacycle, lanthanocene-catalyzed transformations of terminal monosubstituted aminodienes favor the *E* vinyl isomer. The product ratio is shifted in favor of the *Z* vinyl azacycle and the allyl product with decreasing ionic radius of the rare-earth metal (Table 11, entries 1−3). However, cyclization of 1,4-disubstituted substrates yields predominantly (Table 11, entry

Table 9. Rare-Earth Metal and Actinide Catalyzed Hydroamination/Cyclization of 1,3-Disubstituted Aminoallenes Using Cp*$_2$LnCH(SiMe$_3$)$_2$ (1a-Ln, Ln = La, Sm)[98] and Me$_2$Si(C$_5$Me$_4$)(^{t}BuN)U(NMe$_2$)$_2$ (6-U)[103b]

Entry	Aminoallene	Product	Cat.	*T* / °C	Product *Z*/*E* ratio	TOF / h^{-1}	Yield / %
1			**1a-Sm**	60	95:5[a]	0.15	95
2			**6-U**	60	n.d.	0.1	≥95
3			**1a-Sm**	23	67:33[b]	>630	>95[c]
4			**6-U**	25	n.d.[d]	29	≥95
5			**1a-Sm**	23	55:45[e]	0.23	>95[c]
6			**6-U**	60	n.d.[f]	1.3	≥95
7	 **21**		**1a-La**	23	72:28	n.d.	85

[a] Selectivity reported for Cp*$_2$YCH(SiMe$_3$)$_2$ (**1a-Y**); selectivity for **1a-Sm** was not reported. [b] A ratio of 58:42 was reported in ref 98b. [c] Conversion. [d] trans/cis = 4:1. *Z*/*E* ratio was not determined. [e] Selectivity reported for Cp*$_2$LuCH(SiMe$_3$)$_2$ (**1a-Lu**); selectivity for **1a-Sm** was not reported. [f] cis/trans = 3:1. *Z*/*E* ratio was not determined.

Scheme 15. Synthesis of Naturally Occurring Alkaloids through Rare-Earth Metal Catalyzed Hydroamination/Cylization of Aminoallenes[117]

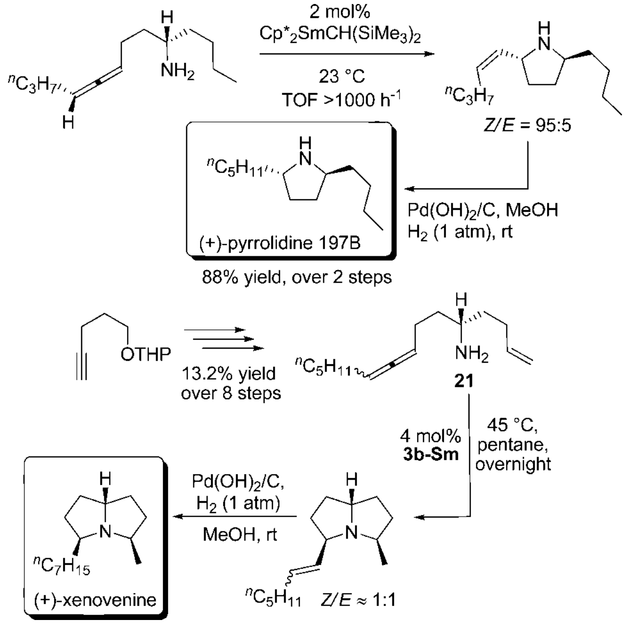
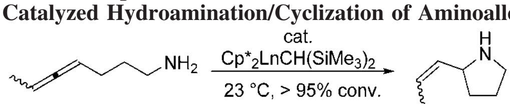


Table 10. Rate Dependence on Ionic Radius in the Rare-Earth Metal Catalyzed Hydroamination/Cyclization of Aminoallenes[98]

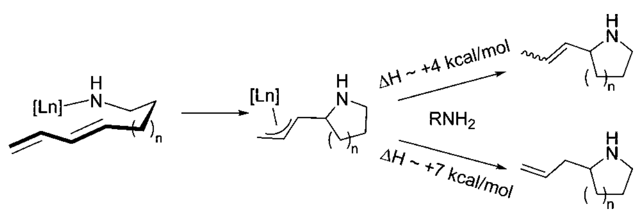


entry	Ln	ionic radius,[107] Å	product *Z*/*E* ratio	TOF, h^{-1}
1	La	1.160	79:21	4.1
2	Sm	1.079	88:12	13.0
3	Y	1.019	86:14	31.4
4	Lu	0.977	81:19	7.3

8) or exclusively (Table 11, entry 9) the allyl product, presumably as a result of double bond isomerization following the hydroamination process.[91]

Cyclization of the α-methyl substituted aminoheptadiene **22** proceeded with low to good trans diastereoselectivity for the pyrrolidine product (Table 12, entries 1 and 2). However, using a sterically encumbered lanthanocene catalyst, cyclization of the aminodiene **23** produced the piperidine alkaloid

Scheme 16



(±)-pinidine with excellent 2,6-*cis* and high *E* double bond diastereoselectivity (Table 12, entry 3).

2.3. Intermolecular Hydroamination Using Rare-Earth Metal Catalysts

While intramolecular hydroamination reactions are catalyzed very efficiently by rare-earth metal catalysts, intermolecular hydroamination reactions are significantly more challenging and only a limited number of reports, utilizing either lanthanocene[99] or binaphtholate[95] catalysts, have been documented in

Table 11. Catalytic Hydroamination/Cyclization of Conjugated Aminodienes Using $Cp^*_2LnCH(SiMe_3)_2$ (1a-Ln), $Me_2Si(C_5Me_4)(^tBuN)SmN(SiMe_3)_2$ (3b-Sm),[91,97] **and $Me_2Si(C_5Me_4)(^tBuN)U(NMe_2)_2$ (6-U)**[103b]

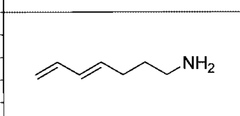
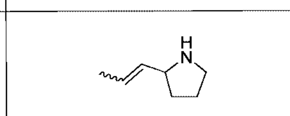
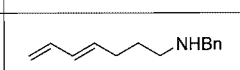
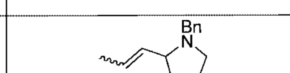
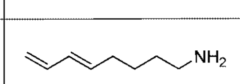
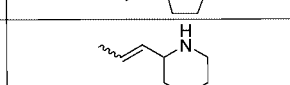
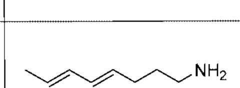
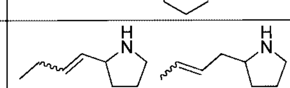
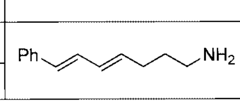
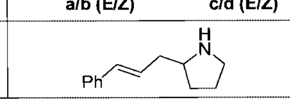
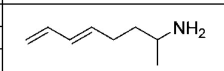
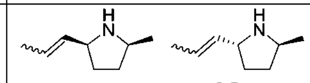
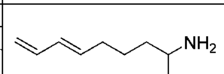
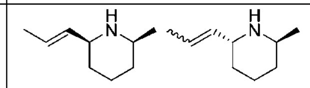
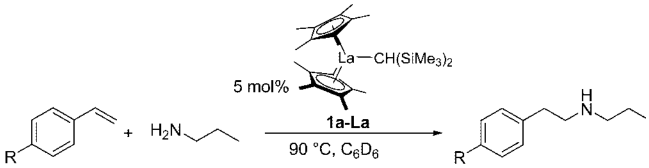
Entry	Aminodiene	Product	Cat.	*T* / °C	Product *E*/*Z*:allyl ratio	TOF / h^{-1}	Conv. / %
1			1a-La	25	84:16:0	40	>95
2			1a-Sm	60	72:11:17	0.79	>95
3			1a-Y	60	30:19:51	0.05	93
4			3b-Sm	25	59:41:0	3.1	90
5			6-U	60	93% allyl	5.5	≥95
6			3b-Sm	60	87:7:6	5.8	80
7			1a-La	25	98:2:0	3.0	>95
8		 a/b (E/Z) c/d (E/Z)	1a-La	60	a:b:c:d 38:0:47:15	1.8	94
9			1a-La	60	>94% *E* allyl	89	92
10			6-U	60	79% allyl	0.3	≥95

Table 12. Rare-Earth Metal Catalyzed Hydroamination/Cyclization of α-Methyl Aminodienes[97]

Entry	Aminodiene	Product	Cat.[a]	T / °C	ratio	TOF / h^{-1}
	 22	 2,5-*cis* 2,5-*trans*			2,5-*cis*:2,5-*trans*	
1			1a-La	25	42:58[b]	1.0
2			3b-Sm	25	10:90	78
	 23	 2,6-*cis* (±)-pinidine 2,6-*trans*			2,6-*cis*:2,6-*trans*	
3			1a-La	25	178:1[c]	3.7
4			3b-Sm	60	78:22	4.0

[a] Using 5 mol % catalyst in C_6D_6, reaction until >95% conversion. [b] Approximately 10% of allyl product formed. [c] *E*/*Z*/allyl isomer ratio 94:1:5.

Table 13. Lanthanocene-Catalyzed Anti-Markovnikov Hydroamination of Vinyl Arenes[99b]



entry	R	TOF,[a] h^{-1}	yield, %
1	H	2.0	90
2	CH_3	1.5	93
3	F	0.94[b]	88
4	CF_3	3.4	83[c]
5	OMe	0.2	89
6	NMe_2	0.05	30
7	SMe	3.6	85

[a] Turnover rates were determined using 10 mol % catalyst and 10-fold excess vinyl arene in toluene-d_8. [b] At 120 °C. [c] Containing 5% of the Markovnikov regioisomer.

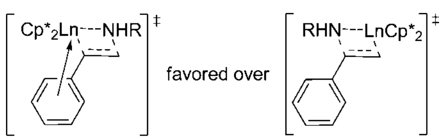
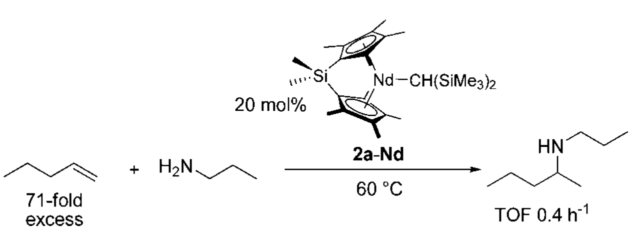


Figure 4. Aryl directing effect leads to preferred 2,1-insertion.

the literature. Difficulties in intermolecular hydroamination reactions originate primarily from inefficient competition between strongly binding amines and weakly binding alkenes for vacant coordination sites at the catalytically active metal center. The rate dependence of the reaction is first-order in olefin concentration, but zero-order in amine concentration (eq 5).

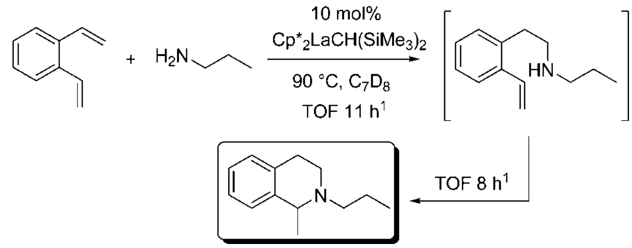
$$\text{rate} = k[\text{amine}]^0[\text{alkene}]^1[\text{catalyst}]^1 \qquad (5)$$

Consequently, better catalyst performance is achieved using an excess of olefinic starting material, although this contradicts atom-economical aspects of the hydroamination reaction. Since the previous review in 1998,[8] little progress has been made and the Markovnikov addition of *n*-propylamine to 1-pentene (eq 6) catalyzed by $Me_2Si(C_5Me_4)_2NdCH(SiMe_3)_2$ (**2a-Nd**) remains the state of the art in this field.[99]

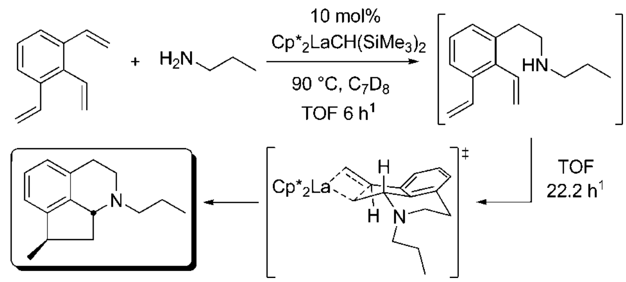


(6)

Scheme 17. Rare-Earth Metal Catalyzed Tetrahydroisoquinoline Synthesis via Two Subsequent Hydroaminations[99b]



Scheme 18. Rare-Earth Metal Catalyzed Tetrahydrosioquinoline Synthesis via Two Subsequent Hydroaminations[99b]



However, the rare-earth metal catalyzed hydroamination of more activated olefinic substrates, for example, vinyl arenes, has been been studied more intensively, in particular with respect to functional group tolerance (Table 13).[99b] A variety of polar functional groups, such as fluoride, trifluoromethyl, (thio)ethers, and amines are tolerated. Electron-donating substituents decreased the rate of amine addition due to electrostatic repulsion between the nitrogen lone pair and

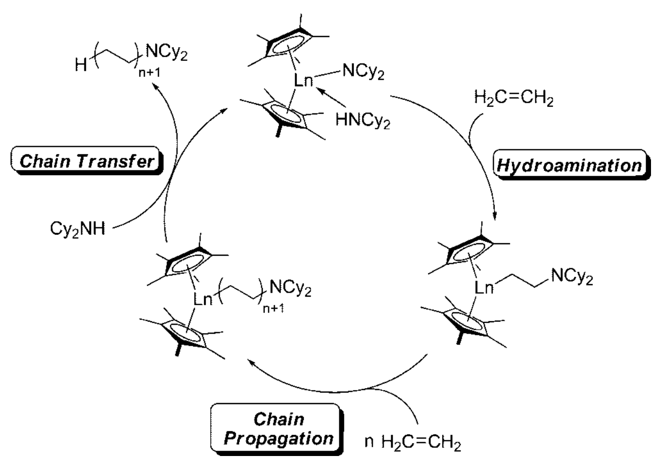


Figure 5. Mechanism of rare-earth metal-catalyzed synthesis of amine-capped polyethylene.

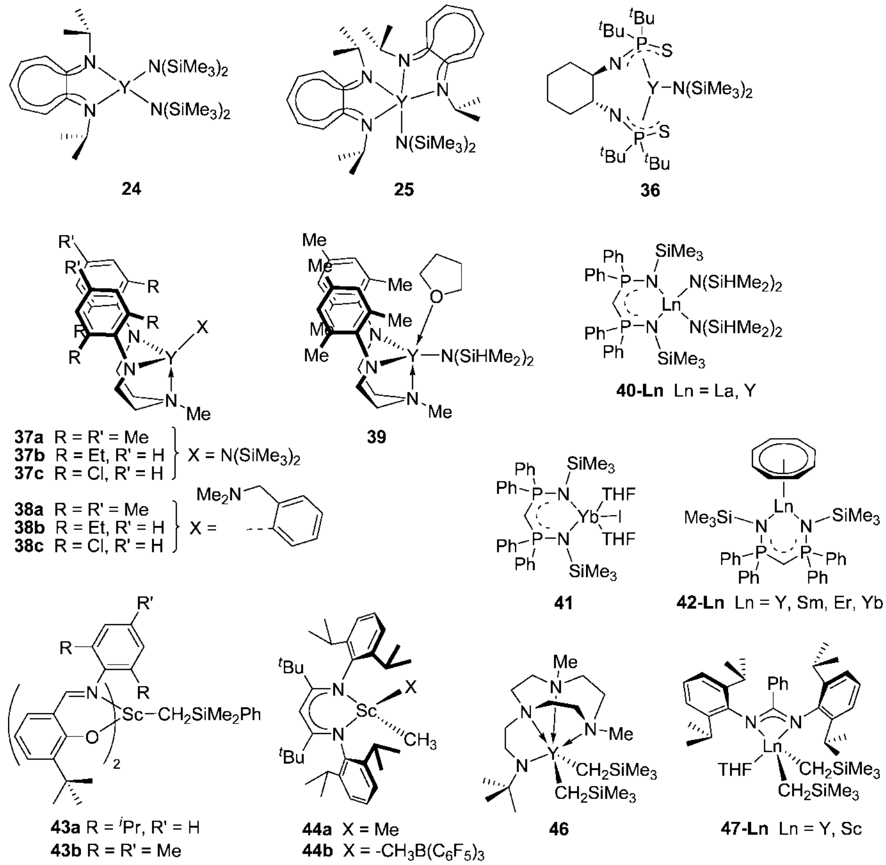
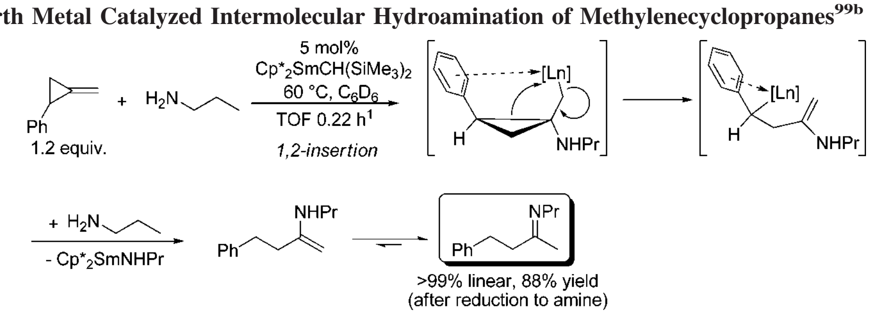


Figure 6. Non-metallocene rare-earth metal based hydroamination catalysts.

Scheme 19. Rare-Earth Metal Catalyzed Intermolecular Hydroamination of Methylenecyclopropanes[99b]



the π electrons of the vinyl arene. The strict anti-Markovnikov regiochemistry (except for the strong electron-deficient trifluoromethylstyrene; Table 13, entry 4) results from an aryl directing effect leading to a preferred 2,1-insertion[118] of the vinyl arene into the Ln−N bond (Figure 4), placing the metal adjacent to the weakly coordinating aromatic π system.

Intermolecular hydroamination of divinylarenes allows facile access to tetrahydroisoquinolines in two consecutive hydroamination steps (Scheme 17).[99b] The initial intermolecular hydroamination reaction generates exclusively the anti-Markovnikov regiosiomer, while the subsequent intramolecular hydroamination regiospecifically forms the Markovnikov tetrahydroisoquinoline product.

Starting from trivinylbenzene, this reaction sequence can be combined with a bicyclization step leading to the tricyclic hexahydrocyclopenta[*ij*]isoquinoline framework with high regiospecificity and exclusive trans diastereoselectivity (Scheme 18). The high trans diastereoselectivity can be explained with similar arguments as discussed for diastereoselective hydroamination/cyclization of α-substituted aminoalkenes (*vide infra*, Figure 7).

An application of an amine as chain transfer reagent in the lanthanide-catalyzed ethene polymerization was disclosed recently,[119] which allows the preparation of amine-capped polyolefins via intermolecular hydroamination as chain transfer reaction (Figure 5). The finely balanced steric demands of the dicyclohexylamine used in the polymerization decreases the rate of protonolysis relative to the rate of propagation to produce narrow monomodal polyethylene with high molecular weight (M_n = (53−1100) × 10^3 g mol^{-1},

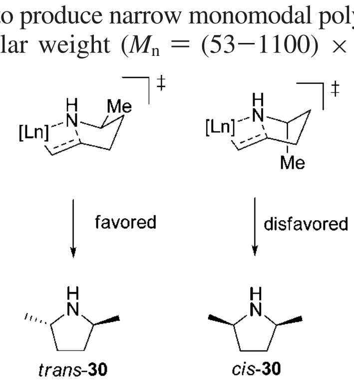
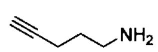
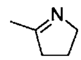
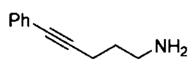
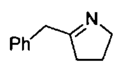
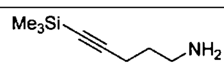
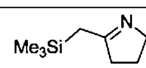
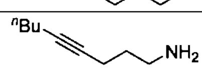
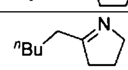
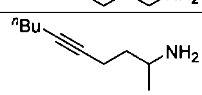
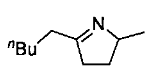
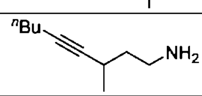
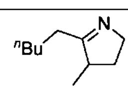
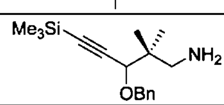
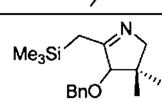
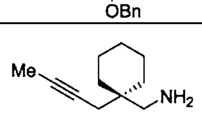
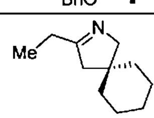
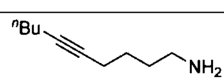
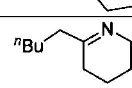
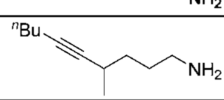
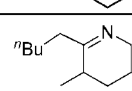
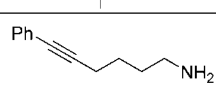
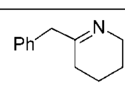
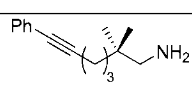
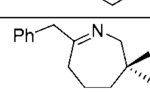


Figure 7. Proposed cyclization transition states for the preferred formation of *trans*-2,5-dimethyl-pyrrolidine (**30**).

Table 14. Comparison of Various Rare-Earth Metal and Actinide Catalysts in Hydroamination/Cyclization Reactions of Aminoalkynes

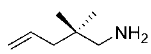
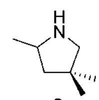
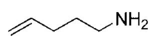
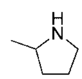
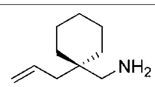
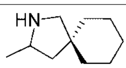
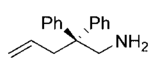
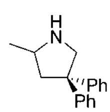
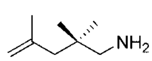
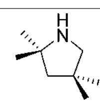
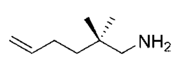
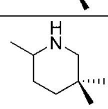
Entry	Aminoalkyne	Product	Catalyst	[cat.]/[s] /%	T /°C	t /h	Conv. /%	TOF /h^{-1}	Ref.
1			**1a-Lu**		21			711	96b
2			**6-U**		25		≥95	1210	103
3			**24**	2	21		quant.	0.4	124
4			**25**	2	21	164	quant.	0.6	124
5			**26-Y**	3-5	60		71	0.3	126
6			**41**	2.8	60	56	>95	0.63	137
7			**42-Sm**	2	120		quant.	1.54	138
8			**1a-Sm**		21			77	96
9			**6-U**		25			51	103
10			**24**	2	21	100	quant.	0.5	124
11			**25**	2	21		quant.	1.5	124
12			**26-Y**	3-5	60		75	0.1	126
13			**26-Y**	3	60	23	91	1.3	93
14			**26-La**	3-5	60		quant.	0.09	126
15			**34b / 26-Y**	5	60	9	94		131
16			**35a / 26-Y**	5	60	1.5	96		131
17			**38a**	3	60	7.5	70		93
18			**38c**	3	60	0.25	93		93
19			**39**	3	60	20	97	2.2	93
20			**40-La**	1	60	1	quant.		136
21			**41**	5.3	90	18	>95	1.05	137
22			**42-Sm**	2	120		quant.	0.60	138
23			**42-Y**	2	120		quant.	0.36	138b
24			**42-Er**	2	120		quant.	2.26	138b
25			**42-Yb**	2	120		87	0.40	138b
26			**43a**	10	25	2	>95		139
27			**43b**	10	25	0.75	>95		139
28			**44a**	10	65	2	>90		139
29			**44b**	10	25	0.75	>90		139
30			**6-U**		25		≥95	300 0	103b
31			**40-La**	2	60	4	99		136
32			**34b / 26-Y**	5	25	1.5	95		131
33			**34b / 26-Y**	5	120	13	81		131
34			**34b / 26-Y**	5	25	0.2	98		131
35			**40-La**	2	rt	30	99		136
36			**34b / 26-Y**	5	150	71	93		131
37			**34b / 26-Y**	5	150	18	92		131
38			1a-Sm		21			4	96
39			6-U		60		≥95	5.0	103b
40			**40-La**	2	100	4	95		136
41			**34b / 26-Y**	5	120	158	48		131

M_w/M_n = 1.6−2.7) with moderate catalyst activity (up to 2.5×10^4 g PE/(mol Ln·atm$_{ethene}$·h).

Another versatile olefinic substrate for intermolecular hydroaminations is methylenecyclopropane (Scheme 19),[99b] utilizing the ring strain of the cyclopropane ring as the driving force for the reaction.

Ring opening of the unsymmetrical phenylmethylenecyclopropane (PhMCP) proceeds with high regioselectivity to

Table 15. Comparison of Various Rare-Earth Metal and Actinide Catalysts in Hydroamination/Cyclization Reactions of Aminoalkenes

Entry	Aminoalkene	Product	Catalyst	[cat.]/[s] /%	*T* /°C	*t* / h	Conv. / %	TOF /h^{-1}	Ref.
1	 7	 8	**1a-La**		25			95	88
2			[Sc{N(SiMe$_3$)$_2$}$_3$] (**26-Sc**)	5	120	3	>98		130b
3			[Y{N(SiMe$_3$)$_2$}$_3$] (**26-Y**)	2.7	24	6	>95		127
4			[Y{N(SiMe$_3$)$_2$}$_3$] (**26-Y**)	3	25	3	89	11.6	93
5			[Nd{N(SiMe$_3$)$_2$}$_3$] (**26-Nd**)	2.7	24	4	>95		127
6			**33a** / **26-Y**	2.7	45	30	>95		127
7			**34b** / **26-Sc**	5	120	2.5	>95		130b
8			**35d** / **26-Sc**	5	120	36	>98		130b
9			**37a**	3	25	3.5	96	8.4	93
10			**37b**	3	25	4	98	8.9	93
11			**37c**	2	25	41	92	1.2	93
12			**38a**	3	25	3.65	95	10	93
13			**38a**[a]	5	25	4	96	5.5	93
14			**38b**	3	25	5	97	7.6	93
15			**38c**	3	25	25	96	1.2	93
16			**39**	4	40	13	41	1.3	93
17			**40-La**	1.3	60	6	quant.		136
18			**44b**	5	65	24	>90		139
19			**46**	1	50	24	25		140
20			**46** / [PhNMe$_2$H][B(C$_6$F$_5$)$_4$]	1	50	12	>99		140
21			**47-Sc**	1	50	6	>90		140
22			**47-Y**	1	50	0.8	>99		140
23			**47-Y** / [PhNMe$_2$H][B(C$_6$F$_5$)$_4$]	1	50	24	13		140
24	 27	 28	**1a-La**		60			140	88
25			**6-An** (An = Th, U)		60		≥95	0.3	103b
26			[La{N(SiMe$_3$)$_2$}$_3$] (**26-La**)	3	80	168	80		93
27			**38a**	3	90	30	4		93
28			**38c**	3	60	60	97		93
29			**40-La**	1.1	60	3	quant.		136
30			**41**	5.1	120	96	92	0.19	137
31			**42-Er**	2	120		56	0.20	138b
32			**4-Th**		60		≥95	2.8	103b
33			**5-Th**		25		≥95	120	103b
34			**6-U**		25		≥95	430	103
35			**6-Th**		25		≥95	1460	103
36			**40-La**	2	60	1.5	quant.		136
37			**42-Sm**	2	120		75	0.19	138b
38			**43b**	10	65	2	>95		139
39			**44a**	10	25	135	>80		139
40			**44b**	5	25	2	>95		139
41			[Y{N(SiMe$_3$)$_2$}$_3$] (**26-Y**)	3	70	8	94		127
42			**6-U**		25		≥95	15	103b
43			**40-La**	2.2	60	22	quant.		136

[a] In the presence of 5 equiv of THF.

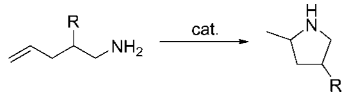
generate the linear product predominantly. The primary 1,2-insertion product is stabilized by π−arene interaction, thus orienting the Ln−C bond *syn* to the appropriate cyclopropane C−C bond that leads upon ring cleavage to the favored linear product.

2.4. Post-Metallocene Rare-Earth Metal Based Hydroamination Catalysts

The application of organometallic rare-earth metal complexes in hydroamination catalysis[30] has significantly advanced over the last two decades with catalyst development depending heavily on cyclopentadienyl ligands.[120] However, cyclopentadienyl-free catalysts can be expected to show deviating reactivity and selectivity from their metallocene counterparts and therefore expand the spectrum of available catalysts. Further advantages of these so-called post-metallocenes[121,122] originate from the larger variety of preparative easily accessible non-cyclopentadienyl ligand sets,[123] with significantly more diverse steric and electronic properties.

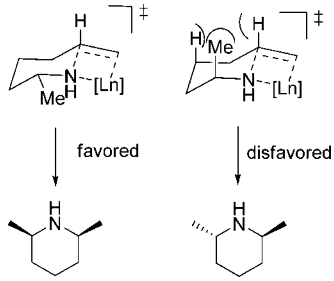
The first cyclopentadienyl-free rare-earth metal based hydroamination catalyst system using (aminotroponiminato)yttrium complexes **24** and **25** (Figure 6) was reported in 1998,[124,125] though catalytic activity was relatively low in comparison to lanthanocene catalysts, and only more reactive aminoalkyne substrates were cyclized (Table 14, entries 3, 4, 10, and 11). In 2001, it was realized that even simple rare-earth metal trisamides [Ln{N(SiMe$_3$)$_2$}$_3$] (**26-Ln**, Ln = La, Nd, Y) serve as efficient hydroamination catalysts for the hydroamination of aminoalkynes (Table 14, entries 5, 12−14)[126] and aminoalkenes (Table 15, entries 2−5, 41; Table 16, entries 2, 3, 6, and 7).[127] However, only aminoalkene substrates activated by the *gem*-dialkyl effect[114] could be cyclized efficiently, whereas in the absence of *gem*-

Table 16. Diastereoselective Rare-Earth Metal Catalyzed Hydroamination/Cyclization of β-Substituted Aminoalkenes



entry	R	catalyst	[catal]/[subst], %	*T*, °C	*t*, h	cis/trans	conv, %	ref
1	Me	**1a-La**		25		1.5:1	[a]	88
2	Me	[Y{N(SiMe$_3$)$_2$}$_3$] (**26-Y**)	2.7	90	240	2:1[b]	>95	127
3	Me	[Nd{N(SiMe$_3$)$_2$}$_3$] (**26-Nd**)	2.7	90	168	2:1[b]	>95	127
4	Me	**34b/26-Sc**	5	120	84	1.6:1	>95	130b
5	Me	**34c/26-Y**	5	60	61	1.5:1	99[c]	129
6	Ph	[Y{N(SiMe$_3$)$_2$}$_3$] (**26-Y**)	2.7	90	1.5	1.7:1[b]	95	127
7	Ph	[Nd{N(SiMe$_3$)$_2$}$_3$] (**26-Nd**)	2.7	90	1.5	2.2:1[b]	95	127
8	Ph	**34b/26-Sc**	5	120	72	2.1:1	>95	130b
9	Ph	**40-La**	1.7	60	36	79:21[b]	82	136

[a] TOF 36 h^{-1}. [b] The cis/trans assignment has been corrected from that reported, based on the stereomodel predicting preference for the cis diastereomer. [c] Isolated yield of the phosphonamide derivative.



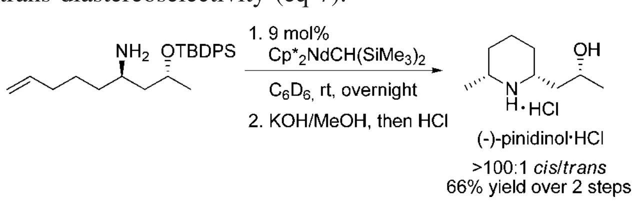
cis-**32** *trans*-**32**

Figure 8. Proposed cyclization transition states for the preferred formation of *cis*-2,6-dimethyl-piperidine (**32**).

dialkyl substitution, for example, in pent-4-enylamine (**27**), no or only low activity was observed (Table 15, entry 26).[93]

Since then a number of non-metallocene rare-earth metal-based catalysts have been developed. The cyclization of chiral aminoalkenes, such as 1-methyl-pent-4-enylamine (**29**) or 1-methyl-hex-5-enylamine (**31**), can serve as a good test for the versatility of non-metallocene catalysts to quantify their catalytic activity as well as diastereoselectivity. The preferred formation of *trans*-**30** can be explained with minimal 1,3-diaxial interactions in the chair-like cyclization transition state (Figure 7),[88b,116] and analogous arguments for the homologous aminohexene derivative **31** account for the preferred formation of the *cis*-2,6-disubstituted piperidine **32** (Figure 8).[128]

The lanthanocene catalyst Cp*$_2$LaCH(SiMe$_3$)$_2$ (**1a-La**) showed good catalytic activity in the cyclization of **29** but low diastereoselectivity (Table 17, entry 1), which could be improved when the reaction was carried out in the presence of a 3-fold excess of *n*-propylamine relative to the aminoalkene substrate (Table 17, entry 2). Also, sterically more open *ansa*-lanthanocenes Me$_2$Si(C$_5$Me$_4$)$_2$LnE(SiMe$_3$)$_2$ (**2a-Nd**) displayed higher diastereoselectivities (Table 17, entry 3). The synthetic validity of this approach has been demonstrated in the synthesis of pinidinol with excellent cis/trans diastereoselectivity (eq 7).[128]

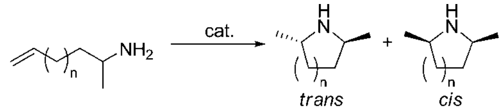


(7)

Initial attempts to utilize non-metallocene catalysts, such as the homoleptic trisamides [Ln{N(SiMe$_3$)$_2$}$_3$] (**26-Ln**, Ln = La, Nd, Y) were frustrated by low activity and poor diastereoselectivities for this particular substrate (Table 17, entries 5−8).[93,127,129] Significantly enhanced rates and improved diastereoselectivities of up to 49:1 (trans/cis) were achieved using catalyst systems generated *in situ* from chelating diamines **33** and **34** or bis(thiophosphinic amides) **35** (Figure 9) and Ln{N(SiMe$_3$)$_2$}$_3$] (**26-Ln**, Ln = Nd, Dy, Y, Sc).[129,130] These catalyst systems were also effective in the cyclization of the six-membered ring substrate **31** with moderate cis diastereoselectivity (Table 17, entries 32−37) and most notably even 1,2-disubstituted aminoalkenes (Table 18). Smooth cyclization of aminoalkynes led to five- to seven-membered rings (Table 14),[131] even in the presence of ether groups in the substrate. Unfortunately, except for the crystallographic analysis of the less active and less selective catalyst **36** (Figure 6),[130a] generated from **35c** and **26-Y**, no structural information of the other catalyst systems is known. Because different steric demand of the other ligands could result in higher aggregated species, a common phenomenon in rare-earth metal chemistry, it is difficult to extract well-grounded structure−reactivity/selectivity relationships.

Reasonable structure−reactivity/selectivity relationships could be obtained from well-defined diamidoamine complexes **37a−c** and **38a−c**, which displayed not only good catalytic activity at room temperature but also high trans/cis diastereoselectivities of up to 23:1 in the cyclization of **29** (Table 17, entries 25−30).[93] Clearly, the sterically least demanding 2,6-dichlorophenyl-substituted diamidoamine complexes gave the lowest trans/cis ratio of 14:1. The diamidoamine complexes were also very efficient in the cyclization/hydroamination of a variety of aminoalkenes and aminoalkynes, but unexpectedly failed in some cases (Table 14, entry 18 vs entry 17; Table 15, entry 28 vs entry 27). In those cases, the electron-withdrawing 2,6-dichlorophenyl groups in complexes **37c** and **38c** effectively prevented protolytic cleavage of the diamidoamine ligand from the catalytically active species, which was the apparent cause of catalyst deactivation when more electron-donating groups were present; hence more basic diamidoamine ligands were employed. Another important finding was that less basic[132] bis(dimethylsilyl) amido ligands (for example, in complex **39**) can result in reduced rates of hydroamination in comparison to more basic and more reactive bis(trimethylsilyl)amido or aryl complexes (e.g., **37** and **38**) due to hampered and incomplete initiation (Table 15, entries 9−16, Figure 10). The bis(dimethylsilyl)amido ligand is most likely also responsible for reduced rates of cyclization observed with phenylene-bridged binuclear mono(cyclopentadienyl) rare-earth metal com-

Table 17. Diastereoselective Hydroamination/Cyclization of 1-Methyl Aminoalkenes Using Rare-Earth Metal Catalysts



29 n = 1
31 n = 2
30 n = 1
32 n = 2

entry	catalyst	Substrate	[catal]/[subst], %	*T*, °C	*t*, h	conv, %	trans/cis	TOF, h^{-1}	ref
1	**1a-La**	**29**		25			8:1	45	88b
2	**1a-La**	**29**		25			≥50:1[a]		88b
3	**2a-Nd**	**29**		25			20:1		88b
4	*meso*-[(ebi)YbN(SiMe$_3$)$_2$][b]	**29**	2	70	48	86[c]	10:1		108
5	**26-La**	**29**	3	90	13	>99	4:1		93
6	**26-Nd**	**29**	2.7	90	48	94	4:1		127
7	**26-Y**	**29**	2.7	90	144	94	7:1		127
8	**26-Y**	**29**	5	60	744	>95	9:1		129
9	**33a/26-Y**	**29**	5	60	51	>95	11:1		129
10	**33b/26-Y**	**29**	5	60	84	>95	19:1		129
11	**34a/26-Y**	**29**	5	60	1.2	>95	19:1		129
12	**34b/26-Sc**	**29**	5	60	1.5	>95	49:1		130b
13	**34b/26-Y**	**29**	5	60	0.25	>95	19:1		129
14	**34d/26-Y**	**29**	5	60	42	>95	11:1		129
15	**34e/26-Y**	**29**	5	60	11	>95	19:1		129
16	**34f/26-Y**	**29**	5	60	2	>95	16:1		129
17	**35a/26-Y**	**29**	5	60	0.25	>95	13:1		130a
18	**35a/26-Nd**	**29**	5	60	0.75	>95	6:1		130a
19	**35b/26-Y**	**29**	5	60	1	>95	13:1		130a
20	**36**	**29**	5	60	15	>95	8:1		130a
21	**35d/26-Y**	**29**	5	60	1	>95	7:1		130a
22	**35e/26-Y**	**29**	5	60	3	>95	9:1		130a
23	**35f/26-Y**	**29**	5	60	2	>95	16:1		130a
24	**35g/26-Y**	**29**	5	30	5	>95	33:1		130a
25	**37a**	**29**	3	25	5.3	83	22:1	5.2	93
26	**37b**	**29**	3	25	4.4	91	19:1	6.2	93
27	**37c**	**29**	1.6	25	7.9	92	14:1	9.1	93
28	**38a**	**29**	3	25	5	98	22:1	7.8	93
29	**38b**	**29**	3	25	8	89	23:1	4.3	93
30	**38c**	**29**	3	25	6	91	13.5:1	6.8	93
31	**40-La**	**29**	3	100	35	81	4:1		136
32	**33a/26-Y**	**31**	5	120	10	>95	1:4		129
33	**34a/26-Y**	**31**	5	120	0.75	>95	1:4		129
34	**34b/26-Y**	**31**	5	120	1.6	>95	1:5		129
35	**34c/26-Y**	**31**	5	120	<0.25	>95	1:4		129
36	**35a/26-Y**	**31**	5	120	1	>95	1:4		130a
37	**35a/26-Nd**	**31**	5	120	2	>95	1:6		130a

[a] Reaction in presence of 3-fold excess of *n*-propylamine relative to **29**. [b] ebi = ethylenebis(η^5-indenyl). [c] Isolated yield of acetyl amide.

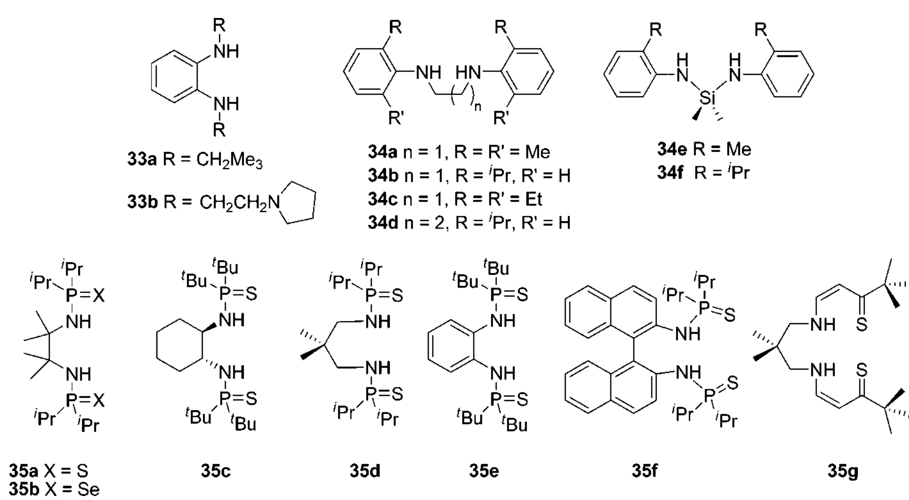
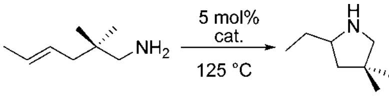


Figure 9. Chelating diamines used as ligands for non-metallocene rare-earth metal hydroamination catalysts.

plexes.[133] Apparently, for the same reason anilido rare-earth metal complexes are catalytically inactive in hydroamination/cyclization.[134]

A variety of non-metallocene hydroamination catalysts based on the bis(phosphinimino)methanide ligand CH-(PPh$_2$NSiMe$_3$)$_2^-$ have been introduced.[135,136] Although the catalytic activity of the bis(phosphinimino)methanide bis(dimethylsilylamide) complexes **40-La** was rather moderate (Tables 14, 15, and 17), it could be utilized in sequential hydroamination/hydrosilylation reactions of aminoalkynes

Table 18. Application of Non-metallocene Catalysts in the Hydroamination/Cyclization of 1,2-Disubstituted Aminoalkenes



entry	catalyst	*t*, h	conv, %	ref
1	**34b/26-Y**	12	>95	129
2	**34b/26-Nd**	11	>95	129
3	**34c/26-Nd**	6.5	>95	129
4	**35a/26-Y**	14	>95	130a
5	**35a/26-Nd**	15	>95	130a

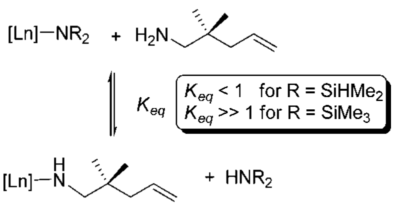


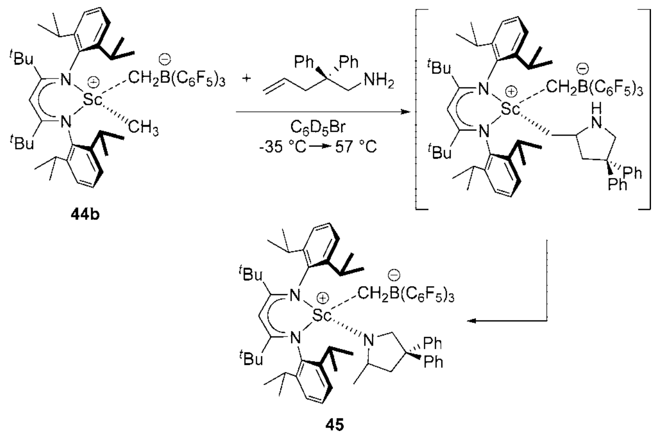
Figure 10. Equilibrium of catalyst activation.

(*vide infra*). The divalent bis(phosphinimino)methanide ytterbium complex **41** was also shown to catalyze cyclization of aminoalkynes with low activity, but aminoalkenes reacted very sluggishly even when activated by *gem*-dialkyl substitution (Table 15, entry 30).[137] As observed earlier with divalent samarocene,[104] the actual catalytically active species is presumably trivalent based on the observed color change upon substrate addition. Curiously, also the bis(phosphinimino)methanide cyclooctatetraene complexes **42-Ln** (Ln = Y, Sm, Er, Yb)[138] displayed some catalytic activity towards aminoalkynes and *gem*-dialkyl activated aminoalkenes, despite lacking a reactive amido or alkyl group that can be protolytically cleaved from the precatalyst during the catalyst activation step. The mode of operation of this catalyst system is unclear at present.

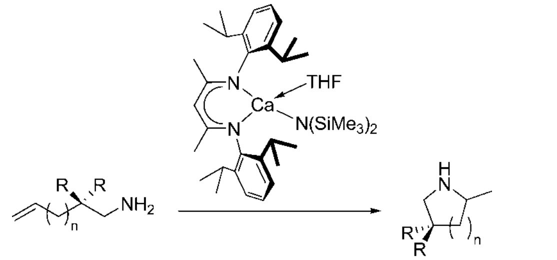
The smallest rare-earth metal, scandium, has been used rarely in hydroamination because the catalytic activity usually decreases with decreasing ionic radius of the metal. Nevertheless, if the access of the substrate to the metal center is well controlled, the higher Lewis acidity of scandium can compensate for this handicap. The scandium complexes based on salicylaldiminato (**43**) or β-diketiminato (**44a**) ligands showed good activity in the transformation of aminoalkynes (Table 14, entries 26 and 27), but only moderate activity when reacted with *gem*-dialkyl-activated aminoalkenes (Table 15, entries 38 and 39).[139] However, the catalytic activity of the neutral β-diketiminato dialkyl complex **44a** could be significantly improved upon activation with $B(C_6F_5)_3$, generating the highly reactive scandium alkyl cation methyltriarylborate adduct **44b**. Steric shielding of the metal center by sterically demanding 2,6-diisopropylphenyl groups prohibits excess amine binding, and no significant product inhibition was observed. Stoichiometric reaction of **44b** with 2,2-diphenylpent-4-en-1-amine led to the spectroscopically characterized cationic amide species **45** (Scheme 20).

A similar rate enhancement was observed for the triazacyclononane−amide dialkyl complex **46** (Figure 6).[140] Activation of **46** with $[PhNMe_2H][B(C_6F_5)_4]$ generated a cationic species that displayed a 10-fold higher rate than the neutral complex (Table 15, entries 19 and 20). However, this trend is not general but more likely the exception. In case of the benzamidinate complex **47**, the neutral complex exhibited fairly good activity (Table 15, entries 21 and 22),

Scheme 20. Stoichiometric Reaction of a Scandium Alkyl Cation with an Aminoalkene Substrate



Scheme 21. A β-diketiminato calcium catalyst for hydroamination/cyclization of aminoalkenes[142]



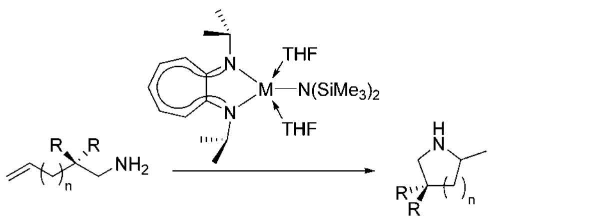
R	n	[cat.]/[s] /%	*T* /°C	*t* /h	Conv. /%
H	1	10	25	21	>99
Me	1	10	25	0.25	>99
Ph	1	10	25	0.25	>99
Me	2	20	60	6	86

but the rate of the reaction dropped by more than 2 orders of magnitude when the corresponding cationic species was used. Quite generally, it is expected that the Ln−amide bond is stronger for the more electron-deficient species, thus impeding the insertion process of the olefin into the Ln−amide bond. However, in case of **44** and **46**, the relief of steric strain around the metal center upon formation of the cationic species could compensate for this impediment and result in an overall net rate increase in comparison to the neutral, sterically more congested analogues.

2.5. Alkaline-Earth Metal Based Hydroamination Catalysts

The chemistry of organometallic alkaline earth metal complexes is closely related to that of the rare-earth elements.[141] Therefore, it is not too astounding that alkaline-earth metal complexes are active in the hydroamination/cyclization of aminoalkenes and aminoalkynes, as demonstrated recently by Hill using a β-diketiminato calcium amide complex (Scheme 21).[142] The catalyst activity is quite comparable to rare-earth metal-based catalysts for the formation of pyrrolidines and piperidines. NMR spectroscopic investigations suggest that the mechanism follows the general mechanism proposed for rare-earth metals. A limiting factor was the observation of a facile Schlenk-type ligand redistribution reaction under the catalytic conditions, resulting in catalyst deactivation and formation of the homoleptic bis(β-diketiminato) and diamido species. An initial attempt to perform asymmetric hydroamination using a chiral bisoxazolinato calcium complex gave only low enantiomeric

Scheme 22. Aminotroponiminato Calcium and Strontium Catalysts for Hydroamination/Cyclization of Aminoalkenes[144]



R	n	M	[cat.]/[s] /%	T /°C	t /h	Conv. /%
H	1	Ca	10	25	40	>90
H	1	Sr	10	25	72	70
Me	1	Ca	2	25	3.5	>95
Me	1	Sr	3	25	72	90
Ph	1	Ca	2	25	1	99
Ph	1	Sr	3	25	1.5	99
Me	2	Ca	8	60	15	>90
Me	2	Sr	15	60	15	>80

excess (up to 10% ee) as a result of a facile Schlenk equilibrium.[143]

Roesky et al. investigated the catalytic activity of aminotroponiminato calcium and strontium complexes, which could be applied in catalyst loadings as low as 2 mol % (Scheme 22).[144] The catalytic activity of the alkaline-earth metal catalysts seems to decrease with increasing ionic radius of the metal, which stands in contrast to the general trends observed for alkali and rare-earth metal based catalysts.

2.6. Asymmetric Synthesis of Amines Using Rare-Earth Metal Catalysts

Marks reported in 1992 the first asymmetric hydroamination catalyst system based on C_1-symmetric chiral *ansa*-lanthanocene complexes with a (+)-neomenthyl, (−)-menthyl, or (−)-phenylmenthyl substituent attached to one of the cyclopentadienyl ligands (Figure 11).[90,145] The chiral cyclopentadienyl ligands can coordinate with either diastereotopic face giving rise to two diastereomeric complexes. However, one of the two diastereomers usually predominates, and most of the catalysts were obtained diastereomerically pure by fractional crystallization.

Catalysts **48**−**50** displayed the same high catalytic activity as their achiral counterparts,[88] with catalytic activity increasing with increasing ionic radius (*vide supra*). Catalytic results

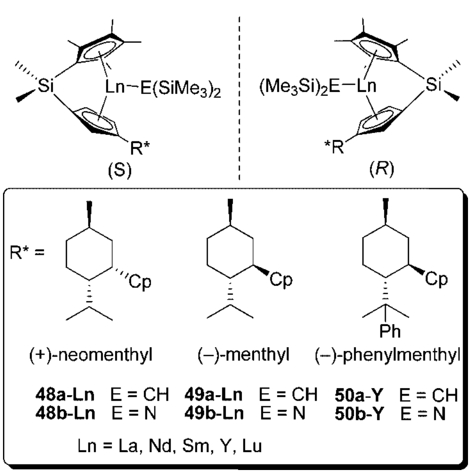
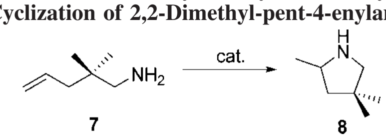


Figure 11. Chiral lanthanocene precatalysts for asymmetric hydroamination.

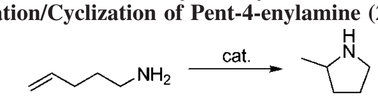
Table 19. Lanthanocene-Catalyzed Asymmetric Hydroamination/Cyclization of 2,2-Dimethyl-pent-4-enylamine (7)



entry	catalyst	*T*, °C	TOF, h^{-1}	% ee (config)[a]	ref
1	(*R*)-**48b-La**	25		14 (*R*)	90,145a
2	(*R,S*)-**48a-Nd**	−20		61 (*R*)	90
3	(*R*)-**48a-Sm**/(*R*)-**48b-Sm**	25		51 (*R*)	90,145a
4	(*R*)-**48a-Sm**/(*R*)-**48b-Sm**	−30		64 (*R*)	90,145a
5	(*R,S*)-**48a-Y**	25	38	36 (*R*)	90
6	(*R*)-**48b-Y**	25	21	40 (*R*)	90
7	(*R,S*)-**48a-Lu**	25		36 (*S*)	90
8	(*R*)-**48b-Lu**	25		40 (*S*)	90
9	(*S*)-**49b-Sm**	25	84	53 (*S*)	90,145a
10	(*S*)-**49b-Sm**	−30		74 (*S*)	90,145a
11	(*R*)-**49a-Y**/(*R*)-**49b-Y**	25	9	43 (*S*)	90
12	(*R*)-**49a-Lu**	25		29 (*R*)	90
13	(*R*)-**50a-Y**	25	8	56 (*S*)	90
14	(60/40) (*R,S*)-**50b-Y**	25		54 (*S*)	90
15	(*S*)-**53-Sm**	25	33.4	32 (*S*)	147
16	(*S*)-**53-Y**	25		17 (*S*)	147
17	(*S*)-**53-Lu**	25		1.5 (*S*)	147
18	**56**	60	48	26 (*S*)	150
19	**57**	25		11 (*S*)	150

[a] $[\alpha]_D^{20} = -24.3°$ for (*R*)-**8**, see ref.[90]

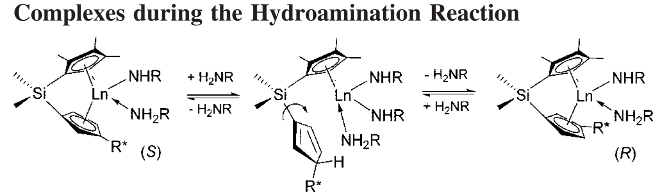
Table 20. Lanthanocene-Catalyzed Asymmetric Hydroamination/Cyclization of Pent-4-enylamine (27)



entry	catalyst	*T*, °C	TOF, h^{-1}	% ee (config)[a]	ref
1	(*R,S*)-**48a-La**	25		36 (*R*)	90
2	(*R*)-**48b-La**	25		31 (*R*)	90,145a
3	(*R,S*)-**48a-Nd**	25	93	55 (*R*)	90
4	(*R,S*)-**48a-Nd**	0	11	64 (*R*)	90
5	(*R,S*)-**48a-Sm**	25	42	61 (*R*)	90
6	(*S*)-**48b-Sm**	25	33	55 (*R*)	90
7	(*R*)-**48a-Sm**/(*R*)-**48b-Sm**	25	62	52 (*R*)	90,145a
8	(*R*)-**48a-Sm**/(*R*)-**48b-Sm**	0		58 (*R*)	90,145a
9	(*R,S*)-**48a-Y**	25	4	47 (*R*)	90
10	(*R*)-**48b-Y**	25		50 (*R*)	90
11	(*R,S*)-**48a-Lu**	25		29 (*S*)	90
12	(*S*)-**49b-Sm**	25	33	62 (*S*)	90,145a
13	(*S*)-**49b-Sm**	0		72 (*S*)	90,145a
14	(*R*)-**49b-Sm**	25		60 (*S*)	90
15	(*R*)-**49a-Y**/(*R*)-**49b-Y**	25		69 (*S*)	90
16	(*R*)-**50a-Y**	25		64 (*S*)	90
17	(*S*)-**53-Sm**	25	2.6	46 (*S*)	147
18	(*S*)-**53-Sm**	60	28.4	37 (*S*)	147
19	(*S*)-**53-Y**	60	2.9	5 (*S*)	147
20	(*S*)-**53-Lu**	60		16 (*R*)	147
21	**56**	100	0.8	35 (*S*)	150

[a] $[\alpha]_D^{20} = -20.0°$ for (*R*)-**28**.[148a]

Scheme 23. Epimerization of Chiral Lanthanocene Complexes during the Hydroamination Reaction



for the most common substrates, 2,2-dimethyl-pent-4-enylamine (**7**) and pent-4-enylamine (**27**), are compiled in Tables 19 and 20. Unfortunately, the chiral lanthanocenes underwent

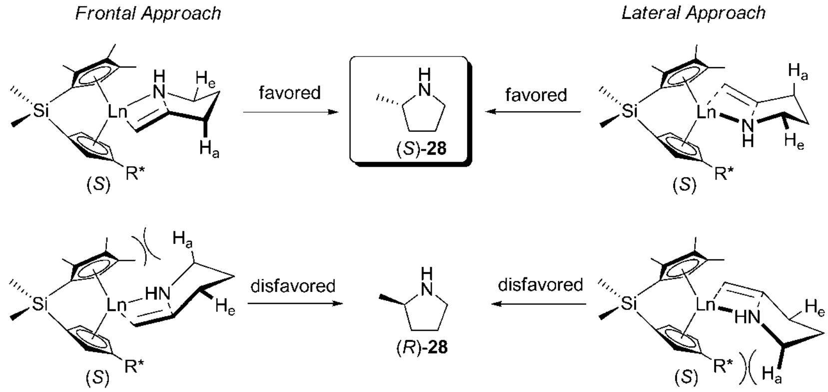


Figure 12. Proposed stereomodels for the observed absolute product configuration of **27**.[90]

facile epimerization under the conditions of catalytic hydroamination via reversible protolytic cleavage of the metal cyclopentadienyl bond (Scheme 23).[90,92,145–147]

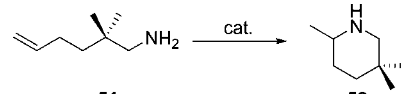
Despite this epimerization process, cyclization of aminopentenes yielded pyrrolidine derivatives with up to 74% ee at low temperatures (Table 19, entry 10, and Table 20, entry 13). In fact, the configuration of the planar chiral cyclopentadienyl ligand seems to be of insignificant importance for the stereochemical outcome of the cyclization. Both (*R*) and (*S*) catalysts (or mixtures thereof) gave products with similar enantiomeric excess and identical sense of optical rotation (Table 19, entries 5 and 6, 7 and 8, 13 and 14, and Table 20, entries 1 and 2, 5−7, 9 and 10, 12 and 14). Hence, only introduction of a different chiral auxiliary to the cyclopentadienyl ligand permits access to the opposite enantiomer of the hydroamination product.

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 19, entries 7, 8, 12, and Table 20, entry 11). Maximum enantioselectivities were observed with samarocene catalysts, while lanthanocenes based on either larger or smaller rare-earth metals were less selective. The *gem*-dimethyl-substituted aminopentene **7** was cyclized 3−10 times faster than the unsubstituted aminopentene **27** due to the favorable *gem*-dialkyl effect,[114] but this went alongside a diminished selectivity (Δee = 1−26%).

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 **48**−**50** based on yttrium the absolute value of enantiomeric excess increases in the order neomenthyl < menthyl < phenylmenthyl for aminopentene **7**, but in the order neomenthyl < phenylmenthyl < menthyl for aminopentene **27**.

A stereomodel that could explain the observed absolute configuration of the pyrroldine product **28** has been proposed (Figure 12).[90] Preferred formation of the (*S*)-pyrrolidine enantiomer was rationalized by unfavorable steric interactions between an axial substituent of the substrate and 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 **48**−**50** 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 **48** in a roughly 80:20 (*R*)/(*S*) ratio, whereas (−)-menthyl and (−)-phenylmenthyl complexes favored the (*S*) isomer (>95:5 for **49** and ~90:10 (*S*)/(*R*) for **50**).[90,145b] Equilibrium ratios were independent of the epimer ratio of the precatalyst. The antipodal epimer equilibrium ratios for (+)-neomenthyl complexes versus (−)-menthyl or (−)-phenylmenthyl complexes[149] rationalize the reversion of absolute product configuration observed for products obtained with (−)-menthyl- or (−)-phenylmenthyl-substituted catalysts in comparison to products obtained with (+)-neomenthyl-substituted catalysts. Other steric factors must be considered for the smaller and sterically more congested lutetocenes to explain the opposite configuration observed with these catalysts.

Table 21. Catalytic Hydroamination/Cyclization of 2,2-Dimethyl-hex-5-enylamine (8)

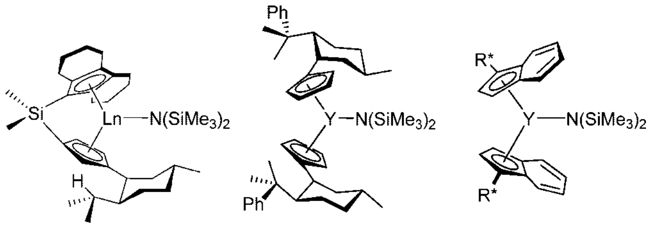


51 52

entry	catalyst	*T*, °C	TOF, h^{-1}	% ee (config)	ref
1	(*R*)-**48a-Sm**/(*R*)-**48b-Sm**	25		17 (*R*)	90,145a
2	(*S*)-**49b-Sm**	25	2	15 (*R*)	90,145a
3	(*S*)-**53-Sm**	25	0.6	41 (*S*)	147
4	(*S*)-**53-Sm**	60	89.4	43 (*S*)	147
5	(*S*)-**53-Y**	25	2.1	67 (*S*)	147
6	(*S*)-**53-Y**	60	86	54 (*S*)	147
7	(*S*)-**53-Lu**	60		15 (*S*)	147

Cyclization of aminohexene **51** generated six-membered piperidine **52** with disappointingly low enantioselectivity compared with formation of five-membered ring pyrrolidine products (Table 21, entries 1 and 2). Better selectivities were obtained however, when chiral octahydrofluorenyl complexes (*S*)-**53-Sm** and (*S*)-**53-Y** (Figure 13)[147] were applied to the *gem*-dimethyl-substituted aminohexene **51** (Table 21, entries 3−6). It was proposed that the extended "wingspan" of the octahydrofluorenyl ligand should increase enantiofacial discrimination for prochiral substrates. However, inferior selectivities for the less reactive, unsubstituted aminohexene **54** (Table 22) and pyrrolidines **8** and **28** disagree with this argument (compare Table 19, entries 9, 11, and 12 with entries 15−17 and Table 20, entries 12, 14, and 15 with entries 17−20).

More recent attempts to circumvent the problem of catalyst epimerization by using two nonlinked chiral cyclopentadienyl



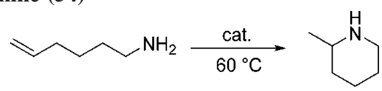
(*S*)-**53-Ln**
Ln = Sm, Y, Lu

56

57
R* = (+)-neomenthyl

Figure 13. Chiral lanthanocene complexes with extended "wingspan" (left) and nonlinked chiral yttrocenes (middle and right).[147,150]

Table 22. Catalytic Hydroamination/Cyclization of Hex-5-enylamine (54)[147]

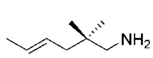
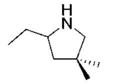
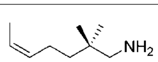
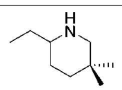


54 **55**

entry	catalyst	TOF, h^{-1}	% ee (config)[a]
1	(*S*)-**53-Sm**	6.6	10 (*S*)
2	(*S*)-**53-Y**	3.6	3.2 (*S*)

[a] $[\alpha]_D^{20}$ = 5.2° for (*S*)-**55**.[148b]

Table 23. Catalytic Asymmetric Hydroamination/Cyclization of Sterically Encumbered Aminoalkenes[92]

Entry	Substrate	Product	Cat.[a]	*T* / °C	TOF / h^{-1}	% *ee* (sign)
1	 **58**	 **59**	(*S*)-**49b-Sm**	80	0.26	28 (+)
2			(*S*)-**53-Sm**	80	0.18	24 (+)
3			(*S*)-**53-Y**[b]	100	0.07	26 (+)
4	 **60**	 **61**	(*S*)-**49b-Sm**	80	0.16	16 (+)
5			(*S*)-**53-Sm**	80	0.11	16 (+)
6			(*S*)-**53-Y**[b]	100	0.30	58 (−)
7			(*S*)-**53-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.

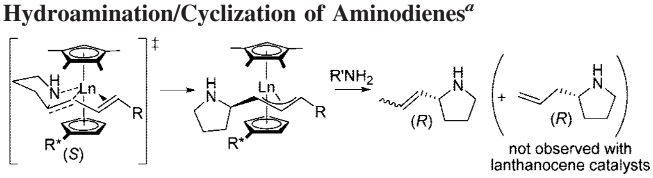
ligands, for example, the bis((−)-phenylmenthylcyclopentadienyl) complex **56**, thus avoiding formation of diastereomeric complexes, resulted in no improvement (Table 19, entry 18, and Table 20, entry 21).[150] The sterically more encumbered bis(neomenthylindenyl) yttrocene **57** formed predominantly the p-*S*,p-*S* diastereomer, but the catalyst was prone to protolytic loss of an indenyl ligand.

As noted earlier, internal olefins are much less reactive for hydroamination of 1,1- or 1,2-disubstituted olefins and require significantly harsher reaction conditions.[92,113,116,130a] Internal alkenes **58** and **60** react only sluggishly at 80−100 °C (Table 23).[92] Piperidine **61** was formed with rates comparable to pyrrolidine **59**, which is in contrast to the general trend of significantly faster five-membered ring formation observed with other aminoalkenes. Enantioselectivities were rather moderate, but (*S*)-**53-Y** delivered piperidine **61** with astonishing 58% ee at 100 °C.

Hydroamination of 1,3-dienes is quite facile due to the transient formation of an η^3-allyl intermediate, which forms *E*/*Z* vinylpyrrolidines and vinylpiperidines upon protonation and, under certain conditions, also allyl isomers (Scheme 24). Cyclizations with lanthanocenes (*S*)-**49b-Sm**, (*S*)-**49-Y**, or (*S*)-**53-Sm** (Table 24) generated the *E* olefins with high selectivity (*E*/*Z* ≥ 93:7).[91,97] The reaction rates are higher for the aminodienes compared with the corresponding aminoalkenes, despite increased steric encumbrance of the cyclization transition state (Scheme 24). The increased rates go at the expense of enantioselectivities (compare Table 20, entries 12, 15, and 17, with Table 24, entries 1−3, and Table 21, entry 3, with Table 24, entry 6). The aminooctadiene **64** is the only exception with 63% ee observed in benzene solution at 25 °C (71% ee in methylcyclohexane at 0 °C) using (*S*)-**53-Sm**, which represents a significant improvement in comparison to 10% ee observed for **54** at 60 °C (Table 22, entry 1, and Table 24, entry 5).

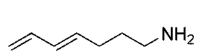
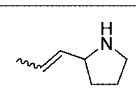
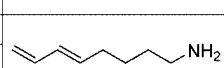
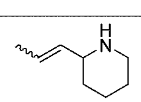
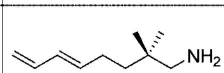
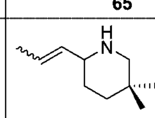
The enantiomeric excess of **65** was indifferent to various aromatic and aliphatic solvents.[91] Addition of exogenous

Scheme 24. Stereomodel for the Hydroamination/Cyclization of Aminodienes[a]



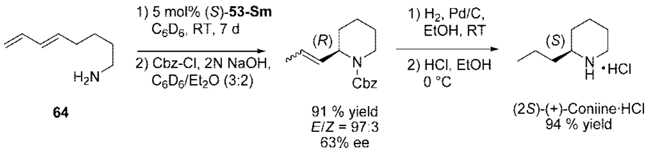
[a] The silicon linker bridging the two cyclopentadienyl ligands was omitted for the sake of clarity.

Table 24. Catalytic Asymmetric Hydroamination/Cyclization of Aminodienes

Entry	Substrate	Product	Cat.	[cat.]/[s] /%	*T* /°C	TOF /h^{-1}	% *ee* (config)	*E*:*Z*:*allyl*	Ref.
1	 **62**	 **63**	(*S*)-**49b-Sm**		23	74	25 (*R*)[a]	98:2:0	91
2			(*S*)-**49-Y**		25	0.09	41 (*R*)[b]	98:2:0	91
3			(*S*)-**53-Sm**	7	25	12	23 (*R*)[b]	93:7:0	91,97
4	 **64**	 **65**	(*S*)-**49b-Sm**		25	0.1	37 (*R*)[b]	98:2:0	91
5			(*S*)-**53-Sm**	7	25	0.11	63 (*R*)[b]	97:3:0	91,97
6	 **66**	 **67**	(*S*)-**53-Sm**		25	1.7	19 (*R*)[b]	96:4:0	91

[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.

Scheme 25. Synthesis of (+)-Coniine·HCl via Enantioselective Aminodiene Hydroamination/Cyclization[91]



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[110–113,117,127,128,151,152] and pharmaceutically relevant targets.[113b] Marks utilized the chiral octahydrofluorenyl samarocene complex (*S*)-**53-Sm** for the synthesis of (+)-coniine in a few steps starting from aminodiene **64** (Scheme 25).[91]

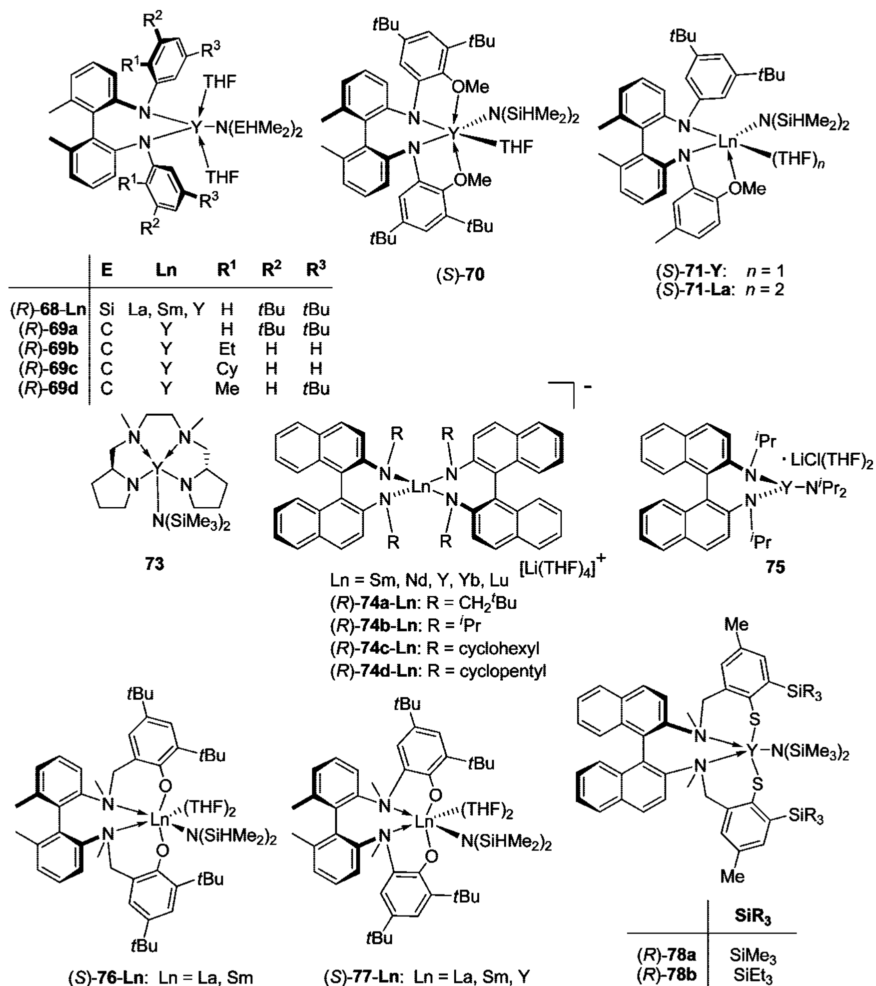
2.7. Chiral Rare-Earth Metal Catalysts Based on Non-Cyclopentadienyl Ligands

Intensified research efforts in the area of rare-earth metal hydroamination catalysts have led recently to significant progress in the field of chiral non-metallocene hydroamination catalyst systems.[94,95,153–164]

One of the first studies involved the application of enantiopure biaryl diamido precatalysts (*R*)-**68** and (*R*)-**69a−d** (Figure 14),[153a] generated *in situ* from N-arylated biaryl diamine ligands and a trisamido [Ln(NR$_2$)$_3$(THF)$_2$] (R = SiHMe$_2$, *i*Pr) precursor,[165] with moderate success in asymmetric hydroamination/cyclization reactions. The bis(dimethylsilyl)amido complexes (*R*)-**68-Ln** (Ln = La, Sm, Y) showed only very low catalytic activity for aminopentene **7** even at 60 °C as a result of hampered initiation caused by the low basicity of the bis(dimethylsilyl)amido ligand (Figure 10).[132] The rather low to moderate enantioselectivities were increasing with decreasing ionic radius of the metal (Table 25, entries 1−3).

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)[166] led to more active catalyst systems (*R*)-**69a−d**,[153a] allowing reactions to be performed at 35 °C, but no increase in enantioselectivity for pyrrolidine **8** was observed (Table 25, entries 4−7). Increasing the denticity of the ligand by introduction of *ortho*-anisole substituents on nitrogen (complexes (*S*)-**70** and (*S*)-**71**) did not improve enantioselectivity (Table 25, entries 8−10), potentially as a result from fluxional coordination of the anisole oxygen.[153b]

More reactive and in some cases more enantioselective catalysts (up to 66% ee) were generated by treatment of various chelating chiral diamines, such as **35f** (Figure 9) or **72** (Figure 15), with [Y{N(SiMe$_3$)$_2$}$_3$] (**26-Y**) (Table 25, entries 11 and 12).[154] The related complex **73** (Figure 14) with a proline derived chiral diamido diamine ligand

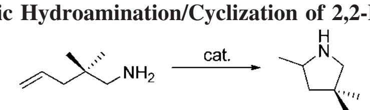


	E	Ln	R¹	R²	R³
(*R*)-**68-Ln**	Si	La, Sm, Y	H	*t*Bu	*t*Bu
(*R*)-**69a**	C	Y	H	*t*Bu	*t*Bu
(*R*)-**69b**	C	Y	Et	H	H
(*R*)-**69c**	C	Y	Cy	H	H
(*R*)-**69d**	C	Y	Me	H	*t*Bu

	SiR$_3$
(*R*)-**78a**	SiMe$_3$
(*R*)-**78b**	SiEt$_3$
(*R*)-**78c**	SiMe$_2$Ph

Figure 14. Chiral bisarylamido and amino(thio)phenolate catalysts for asymmetric hydroamination.[153–158]

Table 25. Non-metallocene-Catalyzed Asymmetric Hydroamination/Cyclization of 2,2-Dimethyl-Pent-4-Enylamine (7)



7 8

entry	catalyst	[catal]/[subst], %	*T*, °C	*t*, h	conv, %	TOF, h^{-1}	% ee (config)[a]	ref
1	(*R*)-**68-Y**	3	60	336	100		50	153a
2	(*R*)-**68-Sm**	3	60	168	100		33	153a
3	(*R*)-**68-La**	3	60	168	100		18	153a
4	(*R*)-**69a**	3	35	120	100		45	153a
5	(*R*)-**69b**	3	35	120	100		20	153a
6	(*R*)-**69c**	3	35	120	100		21	153a
7	(*R*)-**69d**	3	35	120	100		23	153a
8	(*S*)-**70**	3	60	192	100		21	153b
9	(*S*)-**71-Y**	3	60	168	100		40	153b
10	(*S*)-**71-La**	3	60	120	100		34	153b
11	**35f/26-Y**	5	25	15	95		61	154
12	**72/26-Y**	5	10	168	95		66	154
13	**73**	7	25	8	95		11	155
14	(*R*)-**74b-Yb**	10	25	168	49		69	156c
15	(*R*)-**74c-Yb**	10	25	168	77		73	156c
16	**75**	11	25	23	77		68	156d
17	(*S*)-**76-Sm**	1	70	30	100		27	154
18	(*S*)-**76-La**	1	70	40	100		61	157
19	(*S*)-**77-Y**	1	70	24	100		11	157
20	(*R*)-**78a**	5	30	552	>95		89 (*S*)	158
21	(*R*)-**78a**	5	60	15	>95		78 (*S*)	158
22	(*R*)-**78b**	5	60	12	>95		83 (*S*)	158
23	(*R*)-**78c**	5	60	9	>95		87 (*S*)	158
24	(*R*)-**79a**	4	70	22	77	2.5	36 (*S*)	94
25	(*R*)-**79b**	2	25	1	98	61	8 (*S*)	159
26	(*R*,*R*)-**80**	2	25	1.5	95	35	8 (*S*)	159
27	(*R*)-**81**	4	60	7	92	13.5	28.3 (*S*)	94
28	(*R*)-**81**	4	100	0.75	>99		28.0 (*S*)	94
29	(*R*)-**82a-Sc**	2	60	5.5	93	13	73 (*S*)	95
30	(*R*)-**82a-Y**	4	22	3	95	8	43 (*S*)	95, 160
31	(*R*)-**82a-Y**	3	60	0.07	92	480	65 (*S*)	95
32	(*R*)-**82b-Y**	4	22	2	95	14	53 (*S*)	95, 160
33	(*R*)-**83a**	3.5	22	0.45	95	94	31 (*S*)	95
34	(*R*)-**90a-Sc**	5	120			0.28	58 (*R*)	162
35	(*R*)-**90a-Lu**	5	60			0.16	61 (*S*)	162
36	(*R*)-**90b-Nd**	5	23			0.053	65 (*S*)	162
37	(*R*)-**90c-Nd**	5	23			3.0	37 (*S*)	162
38	(*R*)-**90d-Y**	5	60			2.8	42 (*S*)	162
39	(*R*)-**90e-La**	5	23			0.16	40 (*S*)	162
40	(*R*)-**90f-Y**	5	60			0.82	7.4 (*S*)	162
41	**91a-La**	5	23		>98	25	67 (*R*)	161
42	**91a-Nd**	5	23		>98	∼10	61 (*R*)	161
43	**91a-Sm**	5	23		>98	13	55 (*R*)	161
44	**91b-La**	5	23		>98	3.2	6 (*R*)	161
45	**91c-La**	5	23		>98	1.3	39 (*R*)	161
46	**91d-La**	5	23		>98	7.1	56 (*S*)	161
47	**91e-La**	5	23		>98	1.8	25 (*R*)	161
48	**91f-La**	5	23		>98	21	61 (*S*)	161
49	**91g-La**	5	23		>98	17	55 (*S*)	161
50	**91h-La**	5	23		>98	17	59 (*S*)	161
51	**92**	5	23		>98	10	63 (*R*)	161
52	**93**	5	100	80	99		10	163

[a] $[\alpha]_D^{20} = -24.3°$ for (*R*)-**8**.[90]

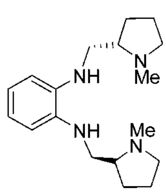


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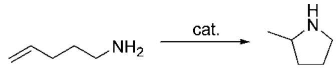
Figure 15. A chelating diamine with proline-derived chirality.

displayed good catalytic activities, but only very low enantioselectivities (Table 25, entry 13).[155]

The ate-complexes $[Li(THF)_4][Ln\{(R)\text{-}1,1'\text{-}\{C_{10}H_6N(R)\}_2\}_2]$ ((*R*)-**74a**−**d**; Ln = Sm, Yb, Y; R = CH_2tBu (**a**), iPr (**b**), cyclohexyl (**c**), cyclopentyl (**d**); Figure 14),[156] are unusual hydroamination catalysts and the only ate complexes reported to catalyze hydroamination. They lack an obvious leaving amido or alkyl group, which could be replaced during the initiation step by the substrate, similar to the achiral cyclooctatetraene bis(phosphinimino)methanide complexes **42-Ln** (Figure 6).[138] However, in case of the diamidobinaphthyl complexes (*R*)-**74a-Ln**, it is very likely that at least one of the amido groups is protonated during the catalytic cycle, analogous to the mechanism proposed for Michael additions and aldol reactions catalyzed by rare-earth-metal−alkali-metal−BINOL heterobimetallic complexes.[167] Although the exact role of the alkali metal

Table 26. Non-metallocene-Catalyzed Asymmetric Hydroamination/Cyclization of Pent-4-Enylamine (27)

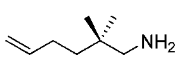
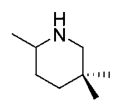
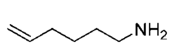
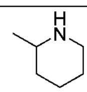
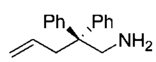
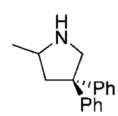
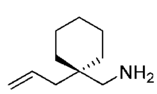
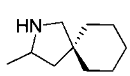
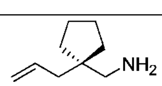
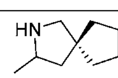
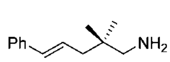
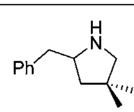
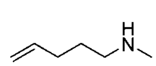
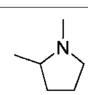


27 28

entry	catalyst	[catal]/[subst], %	T, °C	t, h	conv, %	TOF, h^{-1}	% ee (config)[a]	ref
1	(*R*)-**78a**	5	60	10	>95		69 (*S*)	158
2	(*R*)-**78b**	5	60	5	>95		73 (*S*)	158
3	(*R*)-**78c**	5	60	8	>95		81 (*S*)	158
4	(*R*)-**79b**	2	60	25	98	5.3	0	159
5	(*R*,*R*)-**80**	2	60	19	>99	5	2	159
6	(*R*)-**81**	4	70	43	91		57	94
7	(*R*)-**81**	4	100	16	>99		52	94
8	(*R*)-**82b-Lu**	5	22	16.5	93	1.7	90 (*S*)	95
9	(*R*)-**82b-Lu**	4	0	190	92	0.13	92 (*S*)	95
10	(*R*)-**82a-Y**	2	25	24	95	2.6	70 (*S*)	95
11	(*R*)-**82a-Y**	2	60	0.8	95	93	66 (*S*)	95
12	(*R*)-**82b-Y**	4	22	20	>98	2.2	83 (*S*)	95, 160
13	(*R*)-**83a**	3	22	1.4	89	37	72 (*S*)	95
14	**91a-La**	5	23			0.09	40 (*R*)	161

[a] $[\alpha]_D^{20} = -20.0°$ for (*R*)-28.[148a]

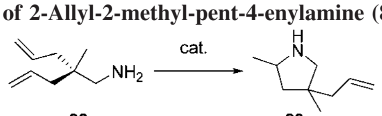
Table 27. Non-metallocene-Catalyzed Asymmetric Hydroamination/Cyclization of Aminoalkenes

Entry	Aminoalkene	Product	Catalyst	[cat.]/[s] /%	Temp. / °C	t / h	Conv. / %	TOF /h^{-1}	% *ee* (config)	Ref.
1			(*R*)-**78a**	5	60	18	>95		65	158
2			(*R*)-**78b**	5	60	10	>95		75	158
3			(*R*)-**78c**	5	75	3	>95		80	158
4			(*R*)-**82a-Lu**	2	60	7.5	96	6.4	42	95
5			(*R*)-**82b-Sc**	2	60	64	97	0.9	61	95
6			(*R*)-**90a-Y**	5	120		25	0.039	13 (*S*)	162
7			**91a-La**	3	60			4.0	56 (*S*)	161
8			(*R*)-**82a-Lu**	2	80	14	95	4.0	40	95
9			(*R*)-**82b-Lu**	2	80	21	94	2.1	55	95
10			(*R*)-**90c-Lu**	5	60		30	0.074	24 (*S*)	162
11	 **84**	 **85**	(*R*)-**74c-Yb**	10	25	144	100		66	156c
12			**75**	6	25	12	100		65	156d
13			(*R*)-**82a-Sc**	2	25	0.6	94	110	95	95
14			(*R*)-**82b-Sc**	2	25	3	96	20	74 (*S*)	95
15			(*R*)-**82a-Lu**	2	25	0.25	96	≥180	93 (*S*)	95
16			(*R*)-**82a-Y**	2	25	0.06	96	≥840	84 (*S*)	95
17			(*R*)-**90a-Y**	5	60		98	2.1	26 (*S*)	162
18			**91a-La**	1.3	23			660	34 (*R*)	161
19			**93**	5	25	2	99		9	163
20	 **86**	 **87**	**73**	10	25	0.5	100		11	155
21			(*R*)-**74a-Yb**	6	0	17	81		47	156a
22			(*R*)-**74b-Yb**	5	25	48	67		70	156b,c
23			(*R*)-**74c-Yb**	10	0	96	88		76	156c
24			(*R*)-**74d-Yb**	6	25	20	90		87	156f
25			**75**	4	25	4	100		68	156d
26			(*R*)-**82a-Sc**	2	25	6	97	11	85 (*S*)	95
27			(*R*)-**82b-Sc**	2	25	13	96	5.0	61 (*S*)	95
28			(*R*)-**82a-Lu**	2	25	0.11	95	460	83 (*S*)	95
29			**93**	5	60	12	99		14	163
30			(*R*)-**74c-Yb**	10	0	144	36		78	156c
31			(*R*)-**78a**	5	60	8	>95		73	158
32			(*R*)-**78b**	5	60	9	>95		80	158
33			(*R*)-**78c**	5	30	72	>95		86	158
34			(*R*)-**82a-Sc**	2	100	72	91	0.6	72	95
35			(*R*)-**82a-Lu**	2	60	10	98	4.0	67	95
36			(*R*)-**78a**	5	60	36	>95		60	158
37			(*R*)-**78b**	5	60	38	>95		63	158
38			(*R*)-**78c**	5	60	30	>95		69	158
39			(*R*)-**82b-Sc**	2	60	44	93	0.9	53	95

cation in the catalytic cycle is unclear at present, it has been noted that exchange of lithium in **74** against potassium is detrimental for catalytic activity and enantioselectivity.[156f]

Cyclization of *gem*-dialkyl activated substrates[114] proceded with (*R*)-**74-Ln** in moderate activity, but enantioselectivities as high as 87% ee were achieved (Table 25, entries 14 and 15; Table 27, entries 11, 21−24, and 30). The enantiomeric excess was optimized by lowering the reaction temperature to 0 °C, at the expense of catalytic activity. The diamidobinaphthyl diisopropylamido complex **75** (formed as LiCl adduct) exhibited significantly better activity with enanti-

Table 28. Catalytic Hydroamination/Cyclization of 2-Allyl-2-methyl-pent-4-enylamine (88)



88 89

entry	catalyst	[catal]/[subst], %	*T*, °C	*t*, h	conv, %	TOF, h^{-1}	% ee	dr	ref
1	(*R*)-**79b**	2	25	0.15	>99	≥330	1/28	1.4:1	159
2	(*R*,*R*)-**80**	2	29	0.4	>99	≥120	5/18	1.15:1	159
3	(*R*)-**81**	10	90	6.5	>99	1.5	32/34	1.1:1	94
4	(*R*)-**82a-Sc**	2	22	23	93	3	88/78	2.7:1	95
5	(*R*)-**82a-Lu**	2	22	0.8	94	80	86/76	2.3:1	95
6	(*R*)-**82b-Lu**	2	22	1.6	95	67	77/74	1.6:1	95

oselectivities very similar to those observed for (*R*)-**74c-Ln** at 25 °C.[156d]

The aminophenolate complexes (*S*)-**76** were designed to improve the reach around of the chiral chelating ligand framework. Indeed, enantioselectivities of up to 61% ee were observed using the lanthanum catalyst (*S*)-**76-La**, but catalytic activity was rather low (Table 25, entry 18).[157] 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; however, pyrrolyl salicylaldimine rare-earth metal catalysts were shown recently to be viable hydroamination/cyclization catalysts with low to moderate enantioselectivities of up to 71% ee.[164] The influence of the reach around of the ligand was probed by removing the methylene linker between the phenol unit and the biaryl amine in complex (*S*)-**77-Y**, thereby decreasing the aminophenolate ligand bite angle, which gave almost racemic pyrrolidine **8**.[157]

The aminothiophenolate catalyst system (*R*)-**78**, with structural resemblance to the aminophenolate complexes (*S*)-**76**, was reported to exhibit significantly higher enantioselectivities, though catalytic activity remained low.[158] The highest selectivity of 89% ee (Table 25, entry 20) was observed in the cyclization of **7** at 30 °C, but the reaction required 23 d with 5 mol % catalyst to reach >95% conversion. Reactions at elevated temperatures proceeded within significantly shorter times at the expense of selectivity. However, the catalyst system was quite general and a range of substrates, including internal olefins or secondary amines, generating five- and six-membered ring products with good to high enantioselectivities (Table 25, entries 20−23; Table 26, entries 1−3; Table 27, entries 1−3, 31−33 and 36−38). Variation of the steric demand of the silyl substituent attached to the thiophenolate moiety allowed facile fine-tuning of the enantiomeric excess, resulting in increasing selectivity with increasing steric hindrance. Although no kinetic data was reported, the catalytic activity seemed also to increase with increasing steric demand of the ligand, possibly because of weaker binding of exogenous amine bases.

3,3′-Disubstituted biphenolate and binaphtholate bis(dimethylsilyl)amido complexes (*R*)-**79a** and (*R*)-**81** (Figure 16) were found to possess moderate catalytic activity and enantioselectivities in the cyclization of **7** at elevated temperature.[94] The highest enantioselectivity of 57% ee was observed in the cyclization of the unsubstituted aminopentene **27** using the sterically more hindered (*R*)-**81**. The catalytic activity of (*R*)-**79a** and (*R*)-**81** suffered from the low basicity of the bis(dimethylsilyl)amido ligand, similar to catalysts (*R*)-**68** and **39**, resulting in a sluggish initiation (Figure 10) and non-zero-order rate dependencies on substrate concentration. However, the biphenolate and binaphtholate complexes displayed high thermal stability, and no significant loss in enantioselectivity was observed even at 100 °C, suggesting high configurational integrity under the conditions of catalytic hydroamination and insignificant intermolecular ligand redistribution reactions that could lead to achiral catalytically active species.

Significantly higher rates were observed using more reactive alkyl complexes, such as the homochiral phenolate-bridged biphenolate alkyllanthanum dimer (*R*,*R*)-**80** and its monomeric tris(THF) adduct (*R*)-**79b** (Table 25, entries 25 and 26).[159] Both catalysts showed the expected zero-order rate dependence on substrate concentration, and the twofold higher rate of the monomeric tris(THF)-adduct (*R*)-**79b** indicated that the dimeric structure of (*R*,*R*)-**80** remains intact under the catalytic conditions in the absence of THF. Unfortunately, the lack of significant steric hindrance from the relatively small *tert*-butyl substituents impedes efficient transfer of chirality from the biphenolate ligand on the substrate in the cyclization transition state, and the hydroamination products were essentially racemic.

Consequently, binaphtholate aryl complexes (*R*)-**82a-Ln**, (*R*)-**82b-Ln** (Ln = Sc, Y, Lu), and (*R*)-**83** with sterically more demanding tris(aryl)silyl substituents in 3 and 3′ positions not only showed superior catalytic activity at room temperature, comparable in magnitude to lanthanocene catalysts, but also achieved up to 95% ee, among the highest enantioselectivities observed so far (Table 25, entries 29 and 31; Table 26, entries 8−13; Table 27, entries 13−16, 26−28).[95,160] Catalytic activity increased with increasing ionic radius, and the smallest rare-earth metal, scandium, generally required higher reaction temperatures. The lanthanum catalyst (*R*)-**83a** displayed the highest turnover rates for the *gem*-dimethyl-substituted **7** (94 h^{-1} at 22 °C) and the unactivated aminopentene **27** (37 h^{-1} at 22 °C). Cyclization of highly activated *gem*-diphenyl-substituted[114] **84** proceeded with rates as high as 840 h^{-1} at 25 °C using (*R*)-**82a-Y**. Sterically less hindered substrates, such as **7** and **27**, were cyclized more efficiently (with respect to rate and enantioselectivity) using the sterically more hindered tris(3,5-xylyl)silyl-substituted binaphtholate complexes (*R*)-**82b-Ln**. The opposite trend was observed for the sterically more demanding substrates **84** and **86**. Steric overcrowding of the coordination sphere around scandium resulted in generally lower selectivity and slower rates for (*R*)-**82b-Sc** in comparison to the sterically less crowded (*R*)-**82a-Sc** and (*R*)-**82b-Lu**, containing the larger lutetium ion. Based on kinetic and mechanistic evidence an equilibrium between a highly reactive catalytically active species and its significantly less active and less enantioselective amine adduct (as indicated in Scheme 3) was proposed.[95] Key evidence for this proposal was the observation of substrate self-inhibition and rate depression at high substrate concentrations. Most interest-

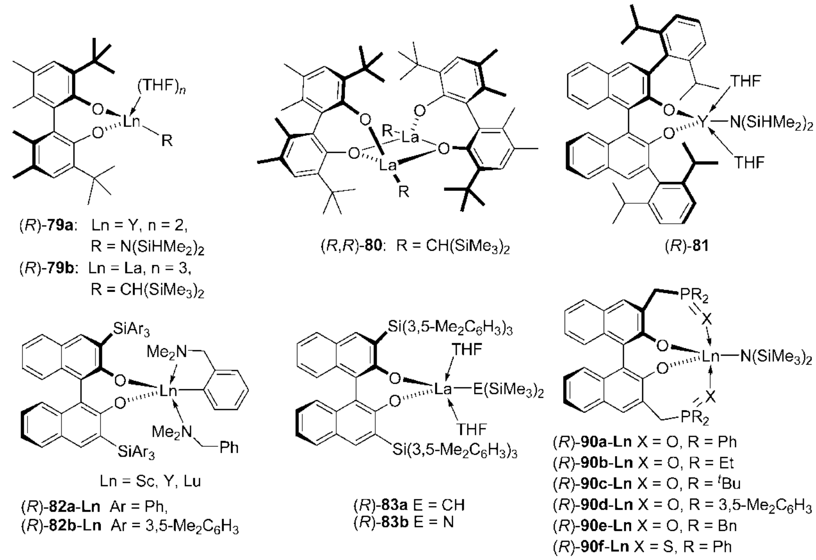


Figure 16. Chiral biphenolate and binaphtholate catalysts for asymmetric hydroamination.

ingly, while generally the enantiomeric excess degraded slightly with increasing temperature in most cases (e.g., Δee $\approx$ 1.5% ee/10 °C for substrate **27**), it was found that the enantiomeric excess of pyrrolidine **8** increased with increasing temperature when using (*R*)-**82a-Y** (Table 25, entries 30 and 31), which can be explained by a shift of the equilibrium in favor of the more reactive, more selective, and entropically favored catalytic species at elevated temperatures.

Desymmetrization of the two allyl groups in aminodiene **88** was rather inefficient with all biphenolate or binaphtholate catalysts resulting in low diastereoselectivities (up to 2.7:1, Table 28) for pyrrolidine **89**. The sterically demanding second allyl group significantly increased turnover rates up to 40-fold compared with *gem*-dimethyl-substituted **7**. Interestingly, the minor diastereomer of pyrrolidine **89** exhibited a significantly lower enantiomeric excess than the major diastereomer for all triphenylsilyl-substituted binaphtholate complexes (*R*)-**82a-Ln**, while both diastereomers were obtained with essentially identical enantiomeric excess using tris(3,5-xylyl)silyl-substituted binaphtholate complexes (*R*)-**82b-Ln**.

In an attempt to improve the stereodirecting effect of binaphtholate ligands, various organophosphine oxide- and sulfide-substituted binaphtholate complexes **90a**−**f** (Figure 16) have been introduced recently.[162] However, the binding of the organophosphine oxide resulted in significant reduced rates and low to moderate enantiomeric excess (up to 65% ee). The influence of the ionic radius on the enantiomeric excess depended significantly on the steric demand of the organophosphine oxide (or sulfide). For example, the moderately encumbered complex **90a** displayed increasing enantiomeric excess with decreasing ionic radius of the metal to a maximum of 61% ee (*S*) for substrate **7** using the lutetium complex **90a-Lu**. However, the smaller scandium complex produced the pyrrolidine with opposite absolute configuration in 58% ee (*R*). The reason for this inversion in product configuration is unclear at present.

Bisoxazoline ligands are also very versatile and modular ligands in asymmetric catalysis.[168] Complexes **91a**−**h** and **92** could be conveniently generated *in situ* from [Ln{N(SiMe$_3$)$_2$}$_3$] (Ln = La, Nd, Sm, Y, Lu) and the corresponding bisoxazoline ligand (Figure 17).[161] Hydroamination reactions with these catalysts are ligand accelerated[169] with a maximum rate observed for a 1:1 ligand to metal ratio (Table 25, entry 41). A higher 2:1 ligand to metal ratio did

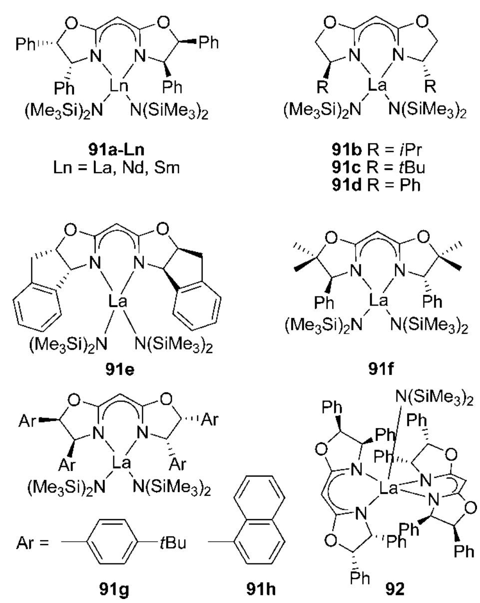
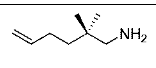
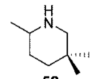
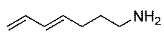
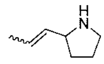
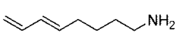
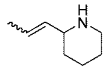
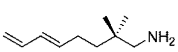
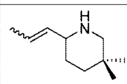


Figure 17. Bisoxazolinato complexes for asymmetric hydroamination.

Table 29. Asymmetric Hydroamination/Cyclizations Catalyzed by 91a-La[a]

Entry	Substrate	Product	*T* /°C	TOF /h^{-1}	% *ee* (config)[b]	*E:Z:allyl*
1	 51	 52	60	4.0	56 (*S*)	
2	 62	 63	23	3.0	17 (*S*)	63:37:0
3	 64	 65	60	0.6	54 (*R*)	41:59:0
4	 66	 67	23	1.4	45 (*R*)	39:57:4

[a] Catalyst prepared in situ from 5 mol % $[La\{N(SiMe_3)_2\}_3]$ (**26**) and 6 mol % of (4*R*,5*S*)-Ph_2BoxH. [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.

not significantly alter enantioselectivity but resulted in reduced catalytic activity (Table 25, entry 51). Reactions performed with isolated catalysts showed higher rates but similar enantioselectivities.

A survey over 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 is crucial for high enantioselectivities and good catalytic activity (Table 25, entries 41−50). The highest turnover frequency (25 h^{-1}) and highest enantioselectivity (67% ee) in the cyclization of **7** was observed for **91a-La**, the complex with the largest rare-earth metal, lanthanum, and (4*R*,5*S*)-Ph_2Box as ligand. This complex gave a consistent level of enantioselectivity for a wide range of substrates compared. Higher steric hindrance in the 4 position of the ligand, for example, by a 1-naphthyl group (complex **91h**), did not improve enantioselectivity and was slightly detrimental to catalyst activity (Table 25, entry 50). Catalysts with aryl groups in the 4 position yield pyrrolidine **8** with opposite absolute configuration than that obtained with catalysts having alkyl substituents.

Contrary to the general trend, cyclization of unsubstituted aminopentene **27** using **91a-La** proceeded with lower enantioselectivity compared with dimethyl-substituted aminopentene **7** (Table 25, entry 41, vs Table 26, entry 14). Turnover frequencies for **27** are always lower than for **7**, due to the *gem*-dialkyl effect.[114] However, this difference in activity is significantly more pronounced for **91a-La** (25 h^{-1} vs 0.09 h^{-1}) than that observed for lanthanocenes (e.g., 84 h^{-1} vs 33 h^{-1} for (*S*)-**49b-Sm**) or binaphtholate complexes (e.g., 14 h^{-1} vs 2.2 h^{-1} for (*R*)-**82b-Y**).

The bisoxazolinato complex **91a-La** was also tested in cyclization of aminodienes (Table 29, entries 2−4).[170] Enantioselectivities were comparable to or even greater than those observed for lanthanocene catalysts. However, *E*/*Z* ratios of vinylpyrrolidine **63** and vinylpiperidines **65** and **67** were close to 1:1 along traces of allylpiperidine for **66**. Again, the reaction rates were higher and the observed enantioselectivities lower than for the corresponding aminoalkenes (Table 26, entry 14, vs Table 29, entry 2; Table 29, entry 1 vs entry 4).

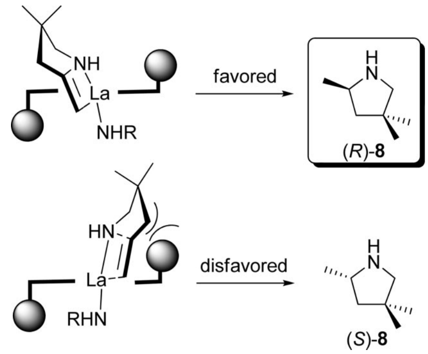
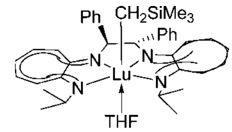


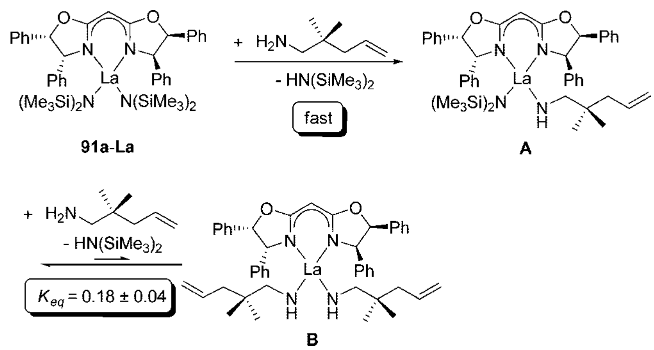
Figure 18. Stereomodel for enantioselective hydroamination/cyclization of aminopentene **7** by **91a-La** with an equatorial approach of the olefin.[161]



93

Figure 19. A chiral bridged bis(aminotroponiminate) complex for asymmetric hydroamination.[163]

Scheme 26. Initiation Equilibrium for Bisoxazolinato Catalysts[161]

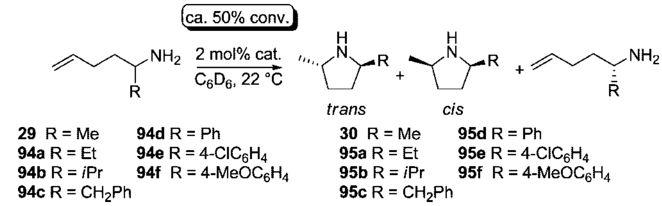


Protonolysis of the first bis(trimethylsilyl)amido ligand in **91a-La** is immediate and quantitative, but substitution of the second bis(trimethylsilyl)amido is incomplete (Scheme 26). In principle, the two species **A** and **B** could have different propagation rates and selectivities. Despite that, the reactions were zero-order in substrate concentration and first-order in catalyst concentration. A dependence of enantioselectivities on substrate to catalyst ratio was not reported.

Molecular modeling studies indicate that for **91a-La** an equatorial approach of the olefin to the apical La−N bond is more likely than an apical approach of the olefin to an equatorial La−N bond, because the equatorial approach favors the correct (*R*) pyrrolidine product (Figure 18), 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 alkyl substituents are exchanged for aryl substituents in the bisoxazoline ligands is caused by a change in the mode of olefin approach.

The chiral bis(aminotroponiminate) complex **93** (Figure 19), analogous to **25** (Figure 6), can be obtained by introduction of a chiral 1,2-diaminodiphenylethane linker.[163] Unfortunately, the lutetium complex **93** showed only low to moderate enantioselectivities, possibly as a result of the flat arrangement of the two aminotroponiminate moieties and the remote disposition of the two phenyl groups causing only

Table 30. Catalytic Kinetic Resolution of Chiral Aminopentenes



entry	substrate	catalyst[a]	*t*, h	conv, %	trans/cis	% ee of recov. start. mater.	% ee of trans product (sign)	f^b	ref
1	**29**	(*R*)-**81**[c]	1.5	61	6.4:1	43	35	2.6	94
2	**29**	(*R*)-**82b-Y**	26	52	13:1	80	78 (−)[d]	16	95, 160
3	**94a**	(*R*)-**82b-Y**	6	51	20:1	57		5.9	95
4	**94b**	(*R*)-**82a-Y**	6	50.5	18:1	37		3.0	95
5	**94c**	(*R*)-**82a-Y**	9	50	20:1	42	40 (−)	3.6	95, 160
6	**94d**	(*R*)-**82a-Lu**	15[e]	52	≥ 50:1	83		19	95
7	**94d**	(*R*)-**82a-Y**	95	50	≥ 50:1	74	(+)	15	95, 160
8	**94e**	(*R*)-**82a-Y**	18[e]	50	≥ 50:1	71		12	95
9	**94f**	(*R*)-**82a-Y**	8[e]	50	≥ 50:1	78		19	95

[a] Reaction conditions: 2 mol % catalst, C_6D_6, Ar atm, 22 °C. [b] Resolution factor based on starting material; $f = K^{dias} \times k_{fast}/k_{slow}$. [c] 5 mol % catalyst, 90 °C. [d] A (−) optical rotation corresponds to a (2*S*,5*S*) absolute configuration. [e] At 40 °C.

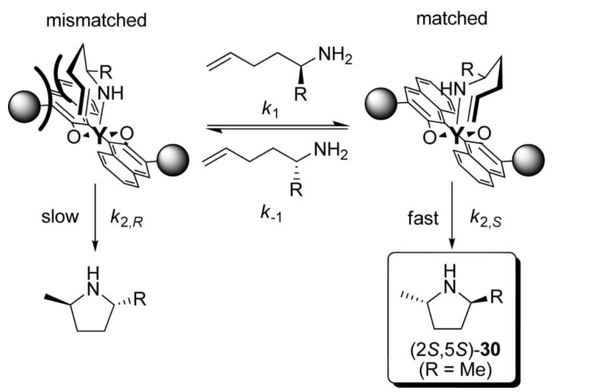


Figure 20. Proposed stereomodel for kinetic resolution of chiral aminoalkenes with an equatorial approach of the olefin.

little stereodifferentiation in the cyclization transition step. However, the modular design of the ligand set might allow improved selectivity by applying other chiral linker units.[171]

2.8. Kinetic Resolution of Chiral Aminoalkenes

Most intramolecular asymmetric hydroaminations have been performed by desymmetrization of a prochiral aminoalkene, while efficient kinetic resolution of chiral aminoalkenes has been reported only recently.[95,160] Early attempts to perform kinetic resolution of **29** with chiral lanthanocene complexes were frustrated by low enantiomeric excess (<20% ee) at various extents of conversion.[90] However, binaphtholate complexes (*R*)-**81**, (*R*)-**82a-Ln** and (*R*)-**82b-Ln** were found to be significantly more effective in kinetic resolution of various chiral aminopentenes (Table 30) with resolution factors *f*[172] as high as 19 and enantiomeric excess for recovered starting material reaching 83% ee at conversions close to 50% (Table 30, entry 6).[94,95,160] The 2,5-disubstituted pyrrolidines were obtained in good to excellent trans diastereoselectivity, depending on the steric hindrance of the α-substituent. Kinetic resolution of **94d** using 1 mol % (*R*)-**82a-Lu** gave enantiopure (*S*)-**95d** (≥ 99% ee) in 33% re-isolated yield at 64% conversion.

A stereomodel was proposed for the observed preferred formation of (2*S*,5*S*)-**30** using (*R*)-**82b** as catalyst (Figure 20). Fast exchange between matching and mismatching aminoalkene is imperative prior to cyclization for an effective kinetic resolution process. Cyclization of (*R*)-**29** is impeded by a sterically unfavorable interaction of the vinylic methylene protons with a trisarylsilyl substituent in the chair-like transition state.

3. Group 4/5 Metal Based Catalysts

3.1. Mechanistic Aspects

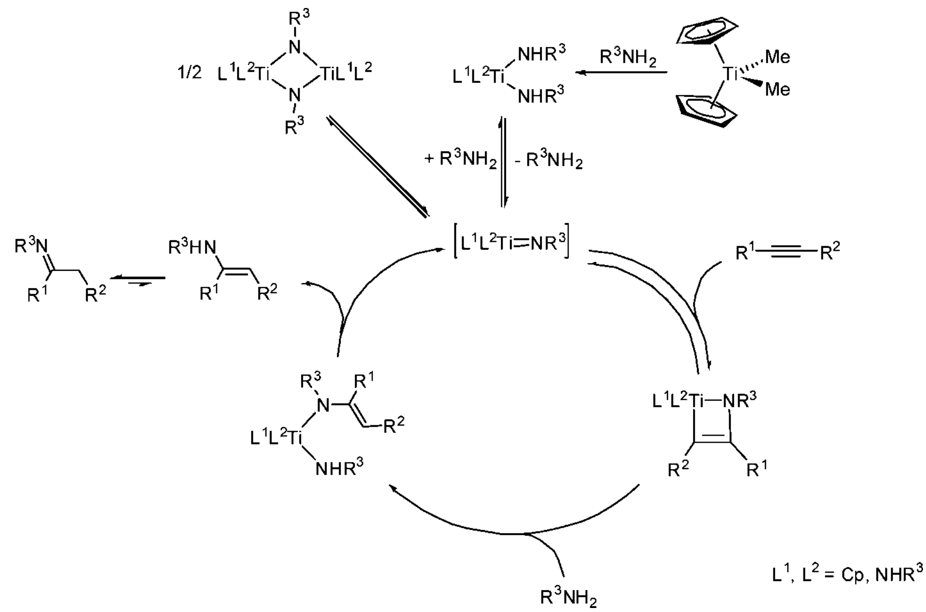
The mechanism of the group 4 metal catalyzed hydroamination of alkynes and allenes has been thouroughly investigated in detailed kinetic and mechanistic,[173,174] as well as computational, studies.[175,176]

The catalytically active species is believed to be a metal imido complex, which undergoes a reversible, rate-determining [2 + 2]-cycloaddition with an alkyne or allene to yield an azametallacyclobutene species (Scheme 27).[173,177,178] The metal imido species is generated via reversible α-elimination of an amine from a bis(amido) precursor. Depending on the steric demand of the imido ligand and the ancillary ligands, the imido species is also in equilibrium with an imido-bridged dimer, favoring the dimeric species with decreasing demand of the ancillary and imido ligands. Hence, many stercially less encumbered catalyst systems perform better with sterically demanding amines, and the rate of the reaction generally does not correlate linearly with the concentration of the catalyst.

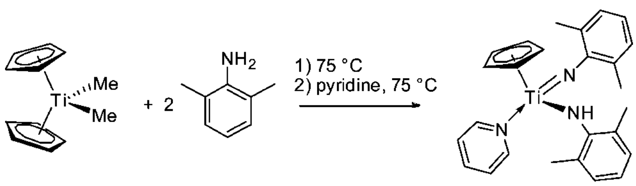
The kinetic[174] and theoretical[175] analysis of the titanocene-catalyzed hydroamination of alkynes is in agreement with slow protonation of the azametallacyclobutene in comparison to cycloreversion. The resulting enamide amido complex then undergoes α-elimination of the enamine, regenerating the catalytically active imido species. These findings are in contrast with the previously studied zirconocene catalyst system $Cp_2Zr(NHAr)_2$,[173a] in which the first-order rate dependence on the concentration of the alkyne and metal bisamide catalyst precursor, as well as inverse first-order rate dependence on amine concentration, suggested that the α-elimination of the amine to form the imido species is rate-determining and protonation of the azametallacycle is rapid.

Although it has been postulated that the mechanism of titanocene-catalyzed hydroamination involves the formation of a titanium imido species (Scheme 27), this species was never observed directly under catalytic conditions in the reaction mixture. However, it was noted that in some

Scheme 27. Proposed Reaction Mechanism for the Titanium-Catalyzed Addition of Amines to Alkynes



reactions free cyclopentadiene was formed and that the reaction required a certain induction period until the catalytically active species is generated from the precatalyst. A closer investigation of this initiation period revealed formation of a half-sandwich titanium imido amido complex starting from Cp_2TiMe_2 (**96**) and 2,6-dimethylaniline, which could be isolated as its pyridine adduct **97** (eq 8).[179] The imido complex is a highly effective hydroamination catalyst for alkynes and allenes and does not show the induction period observed for **96**(Scheme 28).



96 **97**
62 % yield

(8)

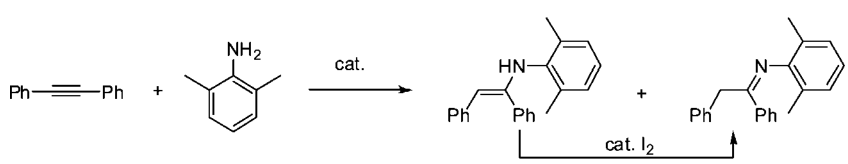
Cationic group 4 metal complexes catalyze hydroamination/cyclization reactions of secondary aminoalkenes.[180,181] The mechanism is believed to be similar to that proposed for rare-earth metals with a catalytically active cationic zirconium amido species (Scheme 29). The catalyst systems investigated in these studies displayed no catalytic hydroamination reactivity with primary aminoalkenes, which was attributed to a facile deprotonation of the cationic zirconium amido species to yield a less reactive zirconium imido species.

However, more recent studies indicate that titanium and in particular zirconium imido species are indeed capable of productive hydroamination/cyclization reactions involving primary aminoalkenes.[182–190] Based on some preliminary mechanistic data, in particular the general inability of these catalyst systems to effect cyclization of secondary aminoalkenes, it was suggested that the reaction involves a [2 + 2] cycloaddition of metal imido species to the olefin, followed by subsequent protonation of the azametallacyclobutane by the aminoalkene substrate (Scheme 30). Such [2 + 2]-cycloadditions of imido species with alkenes have been observed previously,[173c,e] but the formation of the azametallacyclobutane is generally reversible, and the cycloaddition product is unstable in the absence of excess olefin.[173e]

Considering the lack of steric hindrance in the aminoalkenes, it can be anticipated that the catalytically active metal imido species is in equilibrium with a dimeric species, as well as the corresponding bis(amido) species, analogous to the species involved in alkyne hydroamination.

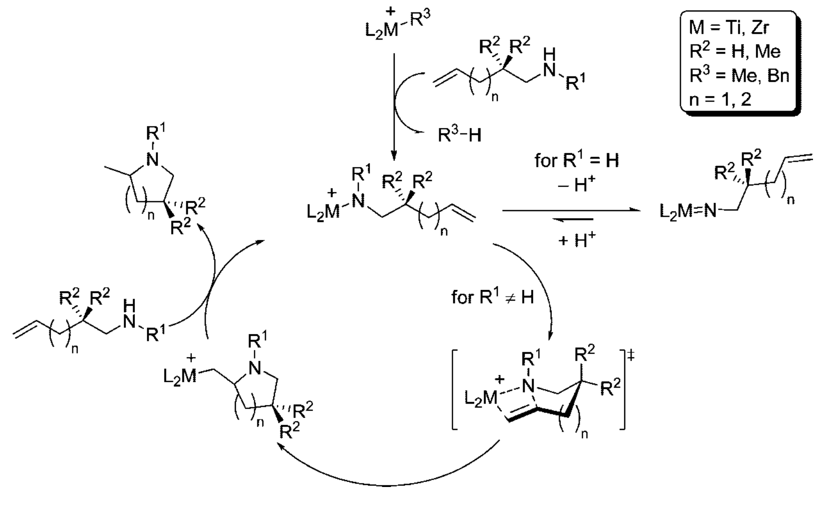
The two mechanisms for hydroamination/cylization of aminoalkenes using either neutral or cationic group 4 metal catalysts seem to be complementary to each other with regard to substrate scope (primary vs secondary aminoalkenes). However, this mechanistic borderline does not hold up for all neutral group 4 metal catalyst systems, as indicated by the observation of secondary aminoalkene cyclizations catalyzed by neutral constrained geometry zirconium catalysts[103c] and $Zr(NMe_2)_4$.[191]

Scheme 28



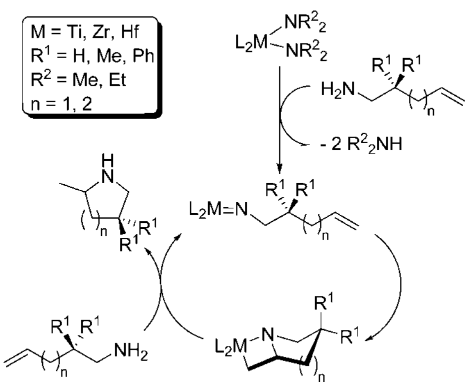
cat.	*T* / °C	*t*	yield / %
97	75	$t_{1/2}$ < 15 min	> 95
96	105	72 h	89 (after hydrolysis)
$Cp_2Zr(NHAr)_2$	120	13 d	60

Scheme 29. Proposed Mechanism for Hydroamination/Cyclization of Secondary Aminoalkenes Using Cationic Group 4 Metal Catalysts[a]



[a] The anion, $B(C_6F_5)_4^-$ or $CH_3B(C_6F_5)_3^-$, is omitted for clarity.

Scheme 30. Proposed Simplified Mechanism for the Hydroamination/Cyclization of Primary Aminoalkenes Using Neutral Group 4 Metal Catalysts



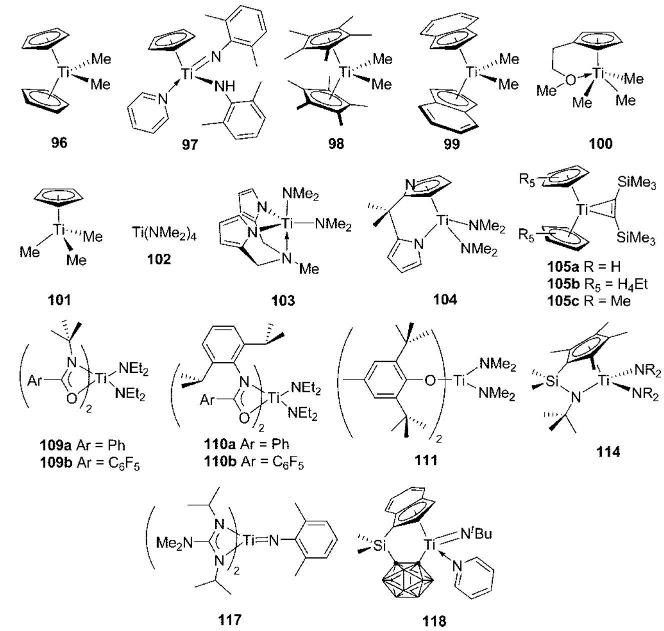


Figure 21. Group 4 metal hydroamination (pre-)catalysts.

3.2. Catalysts and Scope of Reaction

Following the initial reports from Bergman[173] and Livinghouse,[151,192] which have been the subject of a previous review in 1998,[8] a large number of titanium-based hydroamination catalyst systems have been developed (some of which are depicted in Figure 21). Titanium catalysts are particular useful in the inter- and intramolecular hydroamination of alkynes and allenes. Important issues, such as the (Markovnikov/anti-Markovnikov) regioselectivity in the hydroamination of internal and terminal alkynes, have been addressed successfully. Although there is a preconception of low functional group tolerance for early transition metal catalysts, the examples presented in this section will show that an astounding variety of functional groups of key importance for further functionalization and transformations are tolerated after all. The utility of these catalyst systems has been documented well in the synthesis of various highly industrially and biologically relevant acyclic and cyclic nitrogen-containing motifs. The development of catalysts for the hydroamination of alkenes is a very recent and very promising advancement. Interestingly, zirconium seems to be superior to titanium for the latter transformations.

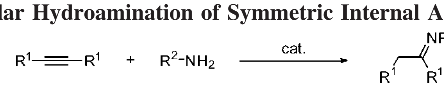
The readily available titanocene Cp_2TiMe_2 (**96**) reacted efficiently with sterically demanding amines (anilines, *tert*-butyl amine, cyclohexyl amine) with good yields (Table 31), but sterically less demanding amines, such as *n*-hexyl amine or benzyl amine, reacted very sluggishly, supposedly due to facile formation of bridging imido dimers.[193] 1-Phenylpropyne reacted with aniline exlusively to the anti-Markovnikov isomer (Table 32, entry 1). The rather long reaction times could be significantly shortend using microwave irradiation (*vide infra*).

The sterically more encumbered permethyltitanocene catalyst $Cp^*_2TiMe_2$ (**98**) was superior to Cp_2TiMe_2 (**96**) in the hydroamination of alkynes using sterically less demanding amines, for example, *n*-alkyl amines or benzyl amines (Table 31, entries 9, 10, and 12−15).[194] However, hydroamination of unsymmetric alkynes gave a mixture of regioisomers for such sterically nondemanding amines (Table 32, entries 3−5), and only *p*-toluidine formed the anti-Markovnikov product with high selectivity (Table 32, entries 6). The regioselectivity is determined by the steric properties of the amine rather than steric influence of the ancillary cyclopentadienyl ligand. A broader catalyst screening of a range of cyclopentadienyl titanium complexes revealed that Ind_2TiMe_2 (**99**) is one of the most general catalysts,[195−197] which catalyzes hydroaminations of internal and terminal alkynes with primary aryl-, *tert*-alkyl-, *sec*-alkyl-, and *n*-alkylamines. Unsymmetrical 1-phenyl-2-alkylalkynes and terminal arylalkynes react with modest to excellent anti-Markovnikov regioselectivity, while terminal alkylalkynes form predominantly the Markovnikov adducts with anilines. The regioselectivity generally increased with increasing size of the amine (Table 32, entries 7−9) and decreasing size of the alkyl substituent (Table 32, entries 8 and 10). Slow addition of sterically undemanding amines, such as *n*-alkyl or benzylamines, is required to achieve efficient rates (Scheme 31), because the reaction is inverse first-order in amine concentration. The marked higher reactivity of *n*-propylamine in comparison to other higher *n*-alkylamines can be attributed to its low boiling point (78 °C), thus reducing its actual concentration in the liquid phase under the reaction conditions (105 °C, sealed Schlenk flask). This was further exploited by applying gaseous methyl- and ethylamine in the hydroamination of 2-alkyl-1-phenylalkynes to generate *N*-methyl- and *N*-ethyl-β-phenethylamine derivatives (Scheme 32).[198] In agreement with general trends,[196,199,200] the lack of steric hindrance in methyl- and ethylamine diminishes drastically the observed regioselectivity in hydroaminations of terminal alkynes (anti-Markovnikov/Markovnikov = 1:1).

Mechanistic investigations have suggested that the catalytically active species in some titanocene-catalyzed hydroamination reactions is actually a mono(cyclopentadienyl) titanium imido amido species.[179] A comparison of donor-functionalized mono(cyclopentadienyl) titanium precatalysts, for example, **100** (Figure 21), with the corresponding nonfunctionalized mono(cyclopentadienyl) complex **101** revealed superior activity of the former in alkyne hydroamination reactions (Table 31, entries 19 and 20; Table 32, entries 13 and 14; Table 33, entries 6 and 7).[201] This increase in activity was attributed to a protection of the catalytically active mono(cyclopentadienyl) imido amido species [(Cp′)Ti(=NR)(NHR)] by the pendant ether/amine-donor against formation of a mono(cyclopentadienyl) trisamido species [(Cp′)Ti(NHR)$_3$] or aggregation to give an imido-bridged dimer of the form [(Cp′)Ti(μ-NR)(NHR)]$_2$. Notable exceptions to these observations were only reactions involving sterically highly demanding amines, such as *tert*-butyl amine or 2,6-diisopropylaniline (Table 31, entries 21−24; Table 32, entries 15−18).

The commercially available titanium tetraamide Ti(NMe$_2$)$_4$ (**102**) is also a viable hydroamination catalyst for internal and terminal alkynes, with moderate to excellent Markovnikov selectivity (Table 31, entry 25; Table 33, entries 8, 10, 11, 13, 15, and 17).[204] However, the di(pyrrolyl) amine complex **103** (Figure 21) was a more generally applicable catalyst than **102**, with excellent Markovnikov selectivities for the hydroamination of terminal alkynes (Table 33, entries 9, 12, 14, 16, 18, and 19).[205] The substrate scope included sterically less demanding amines, such as benzyl amine, and even the electron-deficient $C_6F_5NH_2$ reacted, though at a significantly reduced rate. However, the isopropylidene-linked di(pyrrolyl) complex **104** showed far superior reactivity, catalyzing the rapid and exothermic addition of aniline and cyclohexylamine to terminal alkynes with Markovnikov

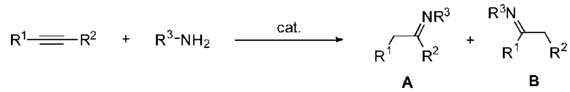
Table 31. Group 4/5 Catalyzed Intermolecular Hydroamination of Symmetric Internal Alkynes



entry	R^1	R^2	catalyst	[catal]/[subst], %	*T*, °C	*t*, h	yield, %	ref
1	Ph	Ph	**96**	3	100	72	62^a	193
2	Ph	Ph	**104**	5	75	24	84^a	206
3	Ph	2,6-Me$_2$C$_6$H$_3$	**96**	3	100	72	68^a	193
4	Ph	2,6-Me$_2$C$_6$H$_3$	**117**	5	105	120	55	202
5	Ph	^{t}Bu	**96**	3	100	72	86^b	193
6	Ph	^{t}Bu	**99**	5	105	5	84^c	195
7	Ph	Cy	**96**	3	100	72	86^b	193
8	Ph	Cy	**104**	10	100	48	72^a	206
9	Ph	^{n}Pr	**96**	6	114	48	10^c	194
10	Ph	^{n}Pr	**98**	2	114	12	89^c	194
11	Ph	^{n}Pr	**99**	5	105	3	89^c	196
12	Ph	^{n}Hex	**98**	6	114	5	89^c	194
13	Ph	PMB	**98**	6	114	6	97^c	194
14	Et	PMB	**98**	6	114	24	91^c	194
15	^{n}Pr	PhCH$_2$	**98**	6	114	24	82^c	194
16	Ph	*p*-Tol	**99**	5	105	24	98^c	196
17	Ph	Ph$_2$CH	**99**	5	105	5	90^c	196
18	^{n}Pr	2,6-Me$_2$C$_6$H$_3$	**99**	5	105	24	92^c	196
19	Ph	Cy	**100**	5	100	1	100	201b
20	Ph	Cy	**101**	5	100	8	92.5	201b
21	Ph	^{t}Bu	**100**	5	100	3.5	98	201b
22	Ph	^{t}Bu	**101**	5	100	2	100	201b
23	Ph	2,6-^{i}PrC$_6$H$_3$	**100**	5	100	8	60	201b
24	Ph	2,6-^{i}PrC$_6$H$_3$	**101**	5	100	0.5	100	201b
25	Et	Ph	**102**	10	75	17	87^d	204a
26	Et	Ph	**103**	10	75	72	63	205a
27	Et	Ph	**104**	5	50	24	94	206
28	Et	Cy	**104**	10	75	48	73	206
29	Ph	Ph	TiCl$_4$/^{t}BuNH$_2$^{e}	10	105	18	95^d	203
30	^{n}Pr	*p*-Tol	TiCl$_4$/^{t}BuNH$_2$^{e}	10	105	6	94^d	203
31	Ph	4-Br-2-MeC$_6$H$_3$	TiCl$_4$/^{t}BuNH$_2$^{e}	10	105	18	83^d	203
32	Ph	Ph	**120**	5	135	12	>95	218a
33	Ph	Ph	**121**	5	135	8	>95	218a
34	Et	Ph	**120**	5	135	24	83^a	218a

^{a} After reduction with LiAlH$_4$. ^{b} After reduction with Pd/C/H$_2$. ^{c} After reduction with NaBH$_3$CN/ZnCl$_2$. ^{d} After hydrolysis. ^{e} TiCl$_4$/^{t}BuNH$_2$ ratio 1:6.

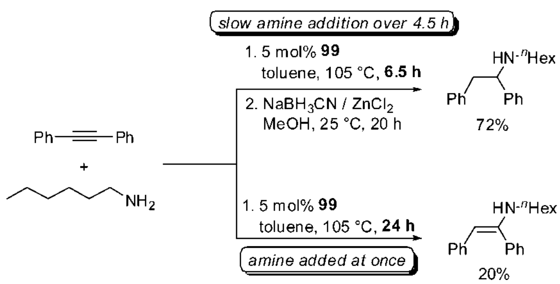
Table 32. Group 4/5 Catalyzed Intermolecular Hydroamination of Unsymmetric Internal Alkynes



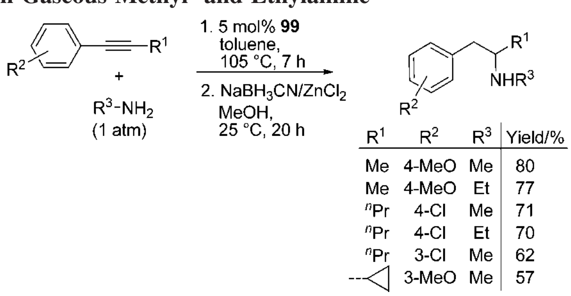
entry	R^1	R^2	R^3	catalyst	[catal]/[subst], %	T, °C	t, h	yield, %	A/B	ref
1	Ph	Me	Ph	**96**	1	100	40	99[a]	100:0	193
2	Ph	Et	Ph	**96**	3	100	40	73[a]	100:0	193
3	Ph	Me	PMB	**98**	3	114	24	82[b]	56:44	194
4	Ph	Me	$PhCH_2$	**98**	6	114	24	94[b]	74:26	194
5	Ph	Me	^{n}Hex	**98**	6	114	24	93[b]	56:44	194
6	Ph	Me	*p*-Tol	**98**	6	114	24	95[b]	97:3	194
7	Ph	Me	*p*-Tol	**99**	5	105	24	99[b]	98:2	196
8	Ph	Me	^{t}Bu	**99**	5	105	24	80[b]	>99:1	196
9	Ph	Me	cyclopentyl	**99**	5	105	24	89[b]	18:1	196
10	Ph	cyclopropyl	^{t}Bu	**99**	5	105	24	76[b]	6:1	196
11	Ph	Me	$PhCH_2$[c]	**99**	5	105	2	76[b]	28:1	196
12	Ph	Me	^{n}Hex[c]	**99**	5	105	2	83[b]	16:1	196
13	Ph	Me	Cy	**100**	5	100	0.83	100	100:0	201b
14	Ph	Me	Cy	**101**	5	100	8	37	100:0	201b
15	Ph	Me	^{t}Bu	**100**	5	100	0.75	100	100:0	201b
16	Ph	Me	^{t}Bu	**101**	5	100	0.25	100	100:0	201b
17	Ph	Me	2,6-^{i}PrC_6H_3	**100**	5	100	2	100	100:0	201b
18	Ph	Me	2,6-^{i}PrC_6H_3	**101**	5	100	0.16	100	100:0	201b
19	Ph	Me	Ph	**104**	5	50	6	83	1:50	206
20	Ph	Me	Cy	**104**	5	75	24	93	1:11	206
21	Ph	Me	Ph	$TiCl_4$/^{t}BuNH_2[d]	10	105	11	75[d]		203
22	Ph	Me	2,6-$Me_2C_6H_3$	**110a**	5	110	24	16	>99:1	213
23	Ph	Me	2,6-$Me_2C_6H_3$	**110b**	5	110	24	97	>99:1	213
24	Ph	Me	Ph	**119**	5	80	24	41	0:100	217
25	^{n}Pr	Me	Ph	**121**	5	135	24	71	1:1	218a

[a] After hydrolysis with SiO_2 to the ketone. [b] After reduction with $NaBH_3CN/ZnCl_2$. [c] Slow addition of amine by syringe pump. [d] $TiCl_4$/^{t}BuNH_2 ratio 1:6.

Scheme 31. Effect of Slow Amine Addition in the Titanium-Catalyzed Hydroamination of Alkynes with *n*-Alkylamines[196]



Scheme 32. Titanium-Catalyzed Alkyne Hydroamination with Gaseous Methyl- and Ethylamine[198]



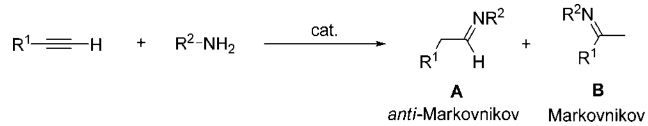
selectivity (except Table 33, entries 21 and 22), and only internal alkynes required heating of the reaction mixture.[206] Recent studies involving a variety of bis(2-arylpyrrolyl) complexes revealed that complexes comprising of two nonlinked 2-arylpyrrolyl ligands and electron-defficient aromatic substituents in the pyrrolyl unit showed superior activity to their linked counterparts.[207]

An important challenge in particular for industrial applications remains the anti-Markovnikov functionalization of compounds with unsaturation in the terminal position.[37] The anti-Markovnikov hydroamination of terminal alkynes has been studied intensively and a range of catalysts particular suitable for this task have been developed. The η^2-alkyne titanocene $Cp_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CSiMe_3)$ (**105a**) was found to efficiently catalyze the anti-Markovnikov addition of the sterically demanding *tert*-butyl amine to terminal aliphatic alkynes with high (>98%) regioselectivity (Table 33, entries 24−26).[200] Sterically less demanding aliphatic amines produced also anti-Markovnikov adducts, albeit with reduced regioselectivity (Table 33, entries 27 and 28), while aromatic amines led predominantly to the Markovnikov product in which the regioselectivity correlated with the steric demand of the aniline derivative (Table 33, entries 29−34). This reversal of regioselectivity in hydroamination of aliphatic terminal alkynes with aniline derivatives seems to be universal for a number of titanium based hydroamination catalysts, such as Ind_2TiMe_2 (**99**),[196] the di(pyrrolyl) amine complex **103**,[205] and the di(pyrrolyl)methane complex **104**.[206]

The sterically more hindered η^2-alkyne titanocenes $(C_5R_5)_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CSiMe_3)$ (**105b**,**c**; $C_5R_5 = C_5H_4Et$ (**b**), C_5Me_5 (**c**)) were more effective in the hydroamination with simple nonhindered amines, such as *n*-butyl amine or benzylamine,[200b] but increasingly ineffective for the hydroamination of sterically demanding amines to the point where no hydroamination reactivity was observed for the permethyltitanocene **105c** when *tert*-butyl amine was used. These trends in reactivity are in agreement with observations made with $Cp^*_2TiMe_2$ (**98**) and Cp_2TiMe_2 (**96**).[194] The increasing steric demand of the cyclopentadienyl ligand resulted in a shifting of the regioselectivity from predominantly anti-Markovnikov (**105a**) to predominantly Markovnikov (**105c**) (Table 33, entries 35−40). A computational study revealed that the regioselectivity is determined by the relative stability of the imido alkyne complex that preceeds the [2 + 2] cycloaddition step (Scheme 33).[200b] The preference for anti-Markovnikov addition for *tert*-butyl amine can be based on a repulsive steric interaction of the *tert*-butyl substituent with the aliphatic substituent of the alkyne in the imido alkyne intermediate **M** leading to the Markovnikov product. The Markovnikov regioselectivity for aromatic amines on the other hand is based on the favorable alternating positive and negative charges in the Markovnikov imido alkyne intermediate **M′**.

The high regioselectivity of the titanocene catalyst **105a** was also utilized in the double hydroamination of 1,7-octadiyne **106** with *tert*-butyl amine to form exclusively the 1,8-bisimine **107** (eq 9).[200] However, the hydroamination of 1,4- and 1,5-diynes with shorter aliphatic chains linking the two alkyne moieties catalyzed by **103**, **104**,[209] and $TiCl_4$/${}^tBuNH_2$[210] lead selectively to substituted pyrroles in moderate to good yield via 5-*endo*-dig or 5-*exo*-dig cyclizations, respectively (Scheme 34). The first hydroamination step produces a 4- or 5-iminoalkyne, which undergoes thermal cyclization. A possible second hydroamination step is generally slower than the thermal cyclization, if at least one internal (i.e., less reactive) alkyne moiety is present in the substrate. Successful competition between the second hy-

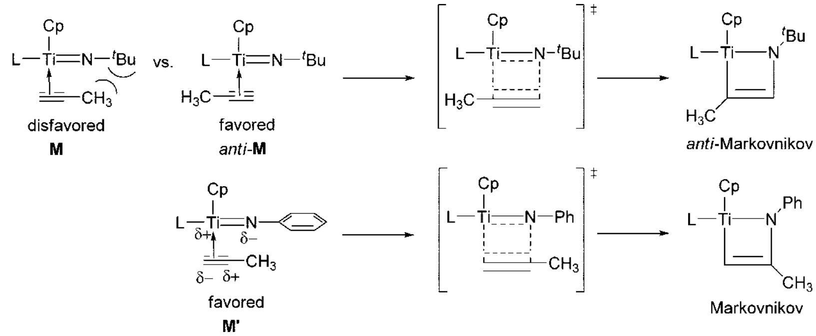
Table 33. Group 4/5 Catalyzed Intermolecular Hydroamination of Terminal Alkynes



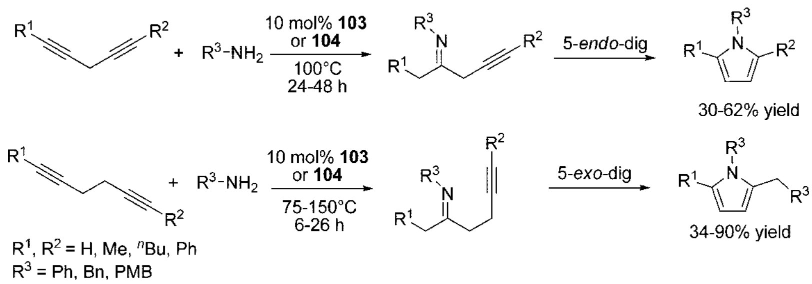
entry	R^1	R^2	catalyst	[catal]/[subst], %	*T*, °C	*t*, h	yield, %	**A/B**	ref
1	Ph	*p*-Tol	**99**	5	75	6	77[a]	4.5:1	196
2	*p*-$MeOC_6H_4$	^{t}Bu	**99**	5	75	8	77[a]	>99:1	196
3	^{n}Hex	*p*-Tol	**99**	5	105	1	95[a]	1:4	196
4	${}^nC_{10}H_{21}$	*p*-Tol	**99**	5	105	2	87[a]	1:2.5[b]	196
5	${}^nC_{10}H_{21}$	^{t}Bu	**99**	5	105	2	75[a]	>99:1	196
6	Ph	2,6-$Me_2C_6H_3$	**100**	5	100	2.5	100	100:0	201b
7	Ph	2,6-$Me_2C_6H_3$	**101**	5	100	8	73	100:0	201b
8	Ph	Ph	**102**	10	75	2	49[c]	1:2	204b
9	Ph	Ph	**103**	10	75	8	38[c]	1:2	205b
10	Ph	^{t}Bu	**102**	10	75	10	53	50:1	204b
11	^{n}Bu	*p*-Tol	**102**	10	75	2	87[d]	1:4	204b
12	^{n}Bu	*p*-Tol	**103**	10	75	6	94	1:>50	205a
13	^{n}Bu	4-$MeOC_6H_4$	**102**	10	75	2	93[d]	1:6	204a
14	^{n}Bu	4-$MeOC_6H_4$	**103**	10	75	6	99	1:<50	205a
15	^{n}Bu	3-$MeOC_6H_4$	**102**	10	75	2	82[d]	1:40	204a
16	^{n}Bu	3-$MeOC_6H_4$	**103**	10	75	6	83	1:>50	205a
17	^{n}Bu	3,5-$Cl_2C_6H_3$	**102**	10	75	2	72[d]	1:23	204a
18	^{n}Bu	3,5-$Cl_2C_6H_3$	**103**	10	75	6	78	1:>50	205a
19	^{n}Bu	C_6F_5	**103**	10	75	72	51	1:>50	205a
20	^{n}Bu	Ph	**104**	5	25	0.08	57	1:40	206
21	Ph	Ph	**104**	5	25	0.08	41[c]	1.2:1	206
22	Ph	Cy	**104**	5	25	0.17	54	20:1	206
23	Ph	Mes	$TiCl_4$/${}^tBuNH_2$[e]	10	75	4	62[a]	0:100	203
24	^{n}Bu	^{t}Bu[e]	**105a**	2.5	85	2	90	>99:1	200a
25	^{n}Octyl	^{t}Bu[e]	**105a**	2.5	85	24	93	63:1	200a
26	$PhCH_2$	^{t}Bu[e]	**105a**	2.5	85	24	88	100:0	200a
27	^{n}Bu	^{s}Bu[e]	**105a**	5	85	24	86	3:1	200a
28	^{n}Bu	CH(Me)Ph[f]	**105a**	5	100	24	79	2:1	200a
29	^{n}Bu	Ph[f]	**105a**	5	85	24	94	1:3	200b
30	^{n}Hex	4-$MeOC_6H_4$[f]	**105a**	2.5	85	24	61[d]	50:50	200b
31	^{n}Hex	2-$EtOC_6H_4$[f]	**105a**	5	100	24	80[d]	9:91	200b
32	^{n}Hex	2-MeC_6H_4[f]	**105a**	5	85	24	93[d]	12:88	200b
33	^{n}Hex	2,6-$Me_2C_6H_3$[e]	**105a**	5	85	24	68[d]	2:98	200b
34	^{n}Hex	2,6-$Me_2C_6H_3$[e]	**105b**	5	100	24	80[d]	1:>99	200b
35	^{n}Hex	^{n}Bu[f]	**105a**	10	120	24	48	72:28	200b
36	^{n}Hex	^{n}Bu[f]	**105b**	10	100	24	62	44:56	200b
37	^{n}Hex	^{n}Bu[f]	**105c**	10	120	24	51	22:78	200b
38	^{n}Hex	$PhCH_2$[f]	**105a**	10	120	24	46	82:18	200b
39	^{n}Hex	$PhCH_2$[f]	**105b**	10	100	24	66	57:43	200b
40	^{n}Hex	$PhCH_2$[f]	**105c**	10	120	24	51	19:81	200b
41	^{n}Hex	^{n}Bu[f]	**111**	10	100	24	81		200a
42	^{n}Bu	^{t}Bu	**109b**	10	65	24	93	99:1	211
43	^{n}Bu	$PhCH_2$	**109b**	10	65	24	50	12:1	211
44	^{n}Bu	2,6-$Me_2C_6H_3$	**109b**	10	65	24	79	1:99	211
45	^{n}Bu	2,6-$Me_2C_6H_3$	**110a**	5	65	24	72[c]	<1:49	213
46	^{n}Bu	2,6-$Me_2C_6H_3$	**110b**	5	65	24	84[c]	<1:49	213
47	^{n}Bu	$PhCH_2$	**110a**	5	65	24	88[c]	>49:1	213
48	^{n}Bu	$PhCH_2$	**110b**	5	65	24	45[c]	2:1	213
49	Ph	2,6-$Me_2C_6H_3$	**110a**	5	65	24	62[c]	>49:1	213
50	Ph	2,6-$Me_2C_6H_3$	**110b**	5	65	24	69[c]	3:1	213
51	Ph	2,6-$Me_2C_6H_3$	**117**	5	105	18	94	73:27	202
52	^{n}Bu	2,6-$Me_2C_6H_3$	**117**	5	105	48	88	14:86	202
53	Ph	2,6-$Me_2C_6H_3$	**118**	5	95	20	100[d]	4:1	208
54	Ph	^{t}Bu	**118**	5	95	20	100[d]	55:45	208
55	^{n}Bu	Ph	**119**	5	80	20	85	1:99	217
56	Ph	Ph	**120**	5	135	2	65[c]	0:100	218a
57	^{n}Pr	Ph	**120**	5	135	2	70	0:100	218a

[a] After reduction with $NaBH_3CN/ZnCl_2$. [b] **A/B** ratio 1:3.8 at 75 °C. [c] After reduction with $LiAlH_4$. [d] After hydrolysis. [e] Amine/alkyne = 1.5:1. [f] Amine/alkyne = 1.2:1.

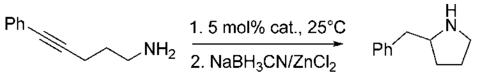
Scheme 33. Reaction Pathway of [2 + 2] Cycloaddition Leading to Predominantly Anti-Markovnikov Addition for Sterically Demanding Amines and Markovnikov Addition for Aromatic Amines



Scheme 34. Pyrrole Synthesis via Diyne Hydroaminatio/Cyclization[209]

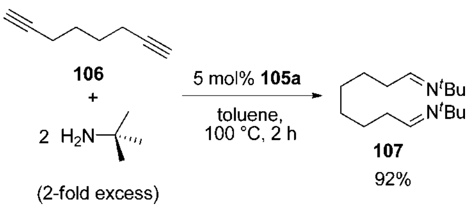


Scheme 35. Mild Hydroamination/Cyclization of Aminoalkynes Catalyzed by Bis(Amidate) Titanium Complexes[211]

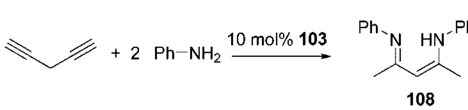


cat.	t / h	Yield / %
109a	3.5	98
109b	0.25	97

droamination and the cyclization was only observed in case of the highly reactive 1,4-pentadiyne, generating predominantly the β-diketiminate **108** (eq 10).[209]



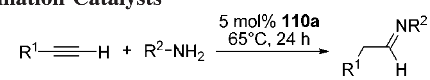
(9)

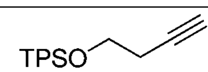
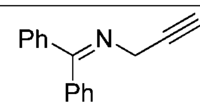
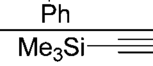
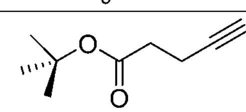
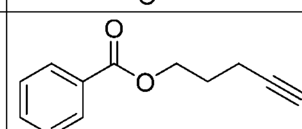
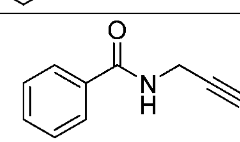
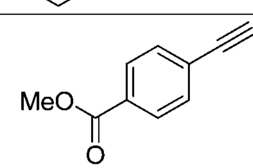


(10)

The bis(amidate) titanium complexes **109a,b**[211] and **110a**[212] (Figure 21) exhibit increased catalytic activity under milder reaction conditions (e.g., room-temperature hydroamination/cyclization of aminoalkynes, Scheme 35) in comparison to cyclopentadienyl-based catalyst systems. This has been attributed to the electron-withdrawing nature of the amidate ligand, resulting in a more electropositive metal center. These catalyst systems were efficient in the anti-Markovnikov hydroamination of terminal alkynes with aliphatic amines, while aromatic amines add to terminal aliphatic alkynes with the usual Markovnikov selectivity (Table 33, entries 42−47 and 49). In particular **110a** with the sterically demanding 2,6-diisopropylphenyl substituents combines high catalytic activity with high anti-Markovnikov regioselectivity. Although the strong electron-withdrawing perfluorophenyl substituent in **110b** resulted in enhanced reaction rates for internal alkynes (Table 32, entries 22 and 23), this catalyst showed also diminished regioselectivity (Table 33, entries 48 and 50) and the perfluorophenyl substituent was prone

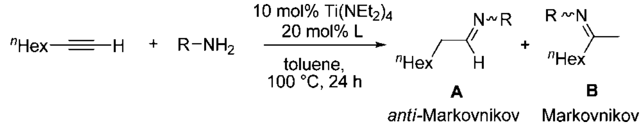
Table 34. Functional Group Tolerance of Bis(amidate) Titanium Hydroamination Catalysts[212]

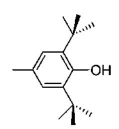
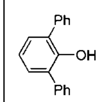
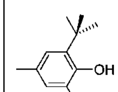
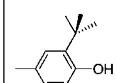
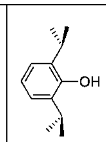
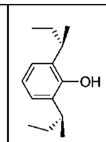
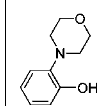
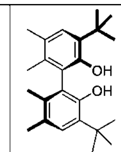
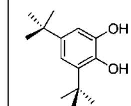


Entry	Alkyne	R^2	Yield /%
1		^{i}Pr	92[a]
2		^{t}Bu	99
3		^{i}Pr	90
4		^{i}Pr	85[b]
5		^{i}Pr	86[a]
6		^{t}Bu	80[b]
7		^{t}Bu	91[b]

[a] After hydrolysis with SiO_2. [b] After reduction with $NaBH_4$.

Table 35. Control of Regioselectivity in Titanium-Catalyzed Hydroamination of Terminal Alkynes[214b]



L									
	112a	**112b**	**112c**	**112d**	**112e**	**112f**	**112g**	**113a**	**113b**
					Bn-NH$_2$				
A:B	20:80	43:57	70:30	84:16	86:14	88:12	93:7	30:70	28:72
Yield/%	99	86	44	52	72	70	40	30	48
					^{s}Bu-NH$_2$				
A:B	10:90	49:51	72:28	94:6	94:6	94:6	95:5	56:44	76:24
Yield/%	98	97	88	94	97	98	90	88	91
					^{t}Bu-NH$_2$				
A:B	74:26[a]	74:26	92:8	99:1	99:1	99:1	98:2	97:3	99:1
Yield/%	50	18	20	66	44	30	49	86	74

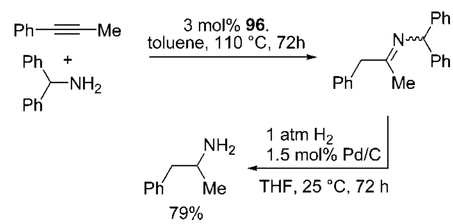
[a] **A/B** = 88:12 and 58% yield for Ti(NEt$_2$)$_4$/**112a** = 1:1.

to nucleophilic aromatic substitution with sterically undemanding aliphatic amines (or aminoalkenes) resulting in catalyst deactivation.[213]

The bis(amidate) complex **110a** tolerated a variety of functional groups, inlcuding homopropargyllic silylethers, imine-protected amines, carboxylic esters, and amides (Table 34).[212] The addition to trimethylsilylacetylene proceeded without silyl migration, in contrast to the rare-earth metal catalyzed reaction.[99]

The stercially demanding bis(aryloxide) catalyst system **111** (Figure 21) was found to be a highly efficient catalyst for the Markovnikov addition of sterically nonhindered amines, such as benzyl amine, *n*-alkylamines, *sec*-butyl amine, cyclooctyl amine or aniline derivatives.[199,214] A broad ligand screening with catalysts prepared in situ from Ti(NEt$_2$)$_4$ and 2 equiv of the aryloxides revealed that the regioselectivity can be reversed from high Markovnikov selectivity to high anti-Markovnikov selectivity by decreasing the steric demand of the aryloxide ligand (Table 35). Substitution of the *tert*-butyl groups in **112a** with phenyl groups in **112b** produced a regioirregular hydroamination product (anti-Markovnikov/Markovnikov ≈ 1:1).[214b] Further steric relief, for example, in the aryloxide **112c**, shifted the ratio in favor of the anti-Markovnikov product and the aryloxides **112d−g** exhibit high anti-Markovnikov selectivity. Based on a computational study, this unprecedented change of regioselectivity is caused by steric factors that govern the relative stability of the Markovnikov and anti-Markovnikov π−alkyne imido complex that precedes the azametallacyclobutene intermediate.[214b] Sterically less hindered phenols (e.g., pentafluorophenol, phenol) and simple alkoxide ligands exhibited significantly reduced activity. The steric demand of the amine also influences the observed regioselectivity and turnover rates of the bis(aryloxide) titanium catalyst systems. *tert*-Butyl amine gave good to excellent anti-Markovnikov selectivity with all catalysts, though at significantly reduced rates. Here, the rate of the reaction could be improved by reducing the metal to ligand ratio to 1:1 (using **112a** as ligand). Bidentate alkoxo and aryloxide ligands, for example, **113a** and **113b**, generally possessed modest activity and low Markovnikov selectivity in the hydroamination of sterically undemanding amines, for example, benzyl amine. Increasingly demanding amines, for example, *sec*- or *tert*-butyl amine, resulted in increasing preference for the anti-Markovnikov product in good yields, if bulky *ortho*-substituents were present in the bisaryloxide.

Scheme 36. Benzhydrylamine as Ammonia Equivalent in Hydroamination Reactions[215]

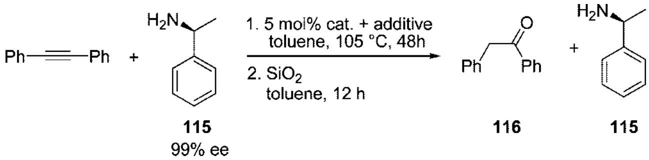


While most hydroamination processes utilize primary or secondary aliphatic and aromatic amines to generate secondary or tertiary hydroamination products, the access to primary amine hydroamination products via direct addition of ammonia to alkenes or alkynes has been unsuccessful with early transition metal based catalysts. However, benzhydrylamine constitutes an ammonia equivalent in hydroamination reactions that allows access to primary amines after hydrogenolytic deprotection of the benzhydrylamine hydroamination product (Scheme 36).[215]

Hydroamination reactions involving enantiomerically pure chiral amines, such as 1-phenethylamine or 1-cyclohexylethylamine, can result in partial racemization of the amine with many titanium-based hydroamination catalysts, even in the absence of an alkyne substrate.[216] However, no racemization was observed when sterically hindered Cp*$_2$TiMe$_2$ (**98**) or the constrained geometry catalyst Me$_2$Si(C$_5$Me$_4$)(^{t}BuN)-Ti(NMe$_2$)$_2$ (**114**) was applied (Table 36). Apparently, addition of pyridine mostly suppresses racemization.

Several group 5 metal based catalyst systems, such as the imido-bridged dimer [V(μ^2-NPh)(NMe$_2$)$_2$]$_2$ (**119**),[217] the tantalum alkyl imido complex [(Me$_3$CCH$_2$)$_3$Ta=NCMe$_3$] (**120**),[218] or the more potent cationic complex [(PhCH$_2$)$_2$Ta=NCMe$_3$]$^+$[B(C$_6$F$_5$)$_4$]$^-$ (**121**),[218] have been shown to be viable precatalysts for the hydroamination of terminal and internal alkynes, as well as allenes, though catalytic activity is inferior to group 4 metal catalysts (Tables

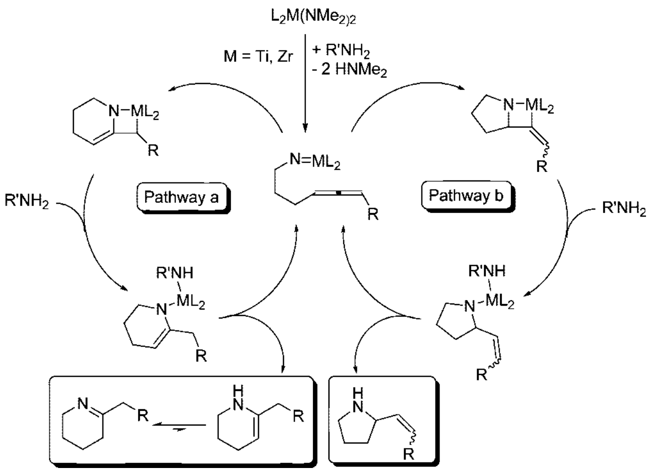
Table 36. Partial Racemization of Chiral Amines during Titanium Catalyzed Hydroamination[216]



entry	catalyst	additive	yield of **116**, %	% ee of re-isolated **115**
1	**96**		≥95	80
2	**98**		≥95	99
3	**99**		≥95	64
4	**99**	5 mol % pyridine	*a*	95
5	**102**		50	24
6	**114**		≥95	99

[a] Not reported

Scheme 37. Two-Pathway Mechanism for the Hydroamination/Cyclization of Aminoallenes Catalyzed by Neutral Group 4 Metal Complexes



31–33). The mechanism originally proposed to operate via [2 + 2]-cycloadditions of metal imido species analogous to group 4 metal catalysts[217,218a] has come under some scrutiny.[218b,219]

The hydroamination of allenes is generally more challenging than the hydroamination of alkynes due to the larger number of possible regioisomers, in particular in intramolecular reactions that can lead either to imines (Scheme 37, pathway a) or allylamines (Scheme 37, pathway b).

The half-sandwich titanium imido complex **97** (Figure 21) is an efficient catalyst for intermolecular reactions involving

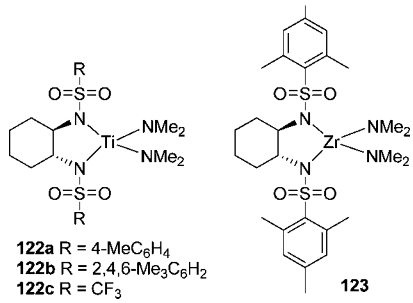


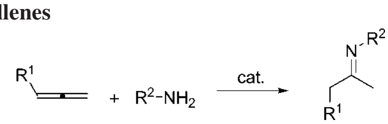
Figure 22. Group 4 metal bissulfonamide hydroamination precatalysts.

the sterically demanding 2,6-dimethylaniline and monosubstituted allenes (Table 37, entries 1, 3, and 5) or cyclo-1,2-dienes,[179] while the scope of the reaction extended also to sterically less demanding aliphatic amines using the bis(amidate) titanium complex **110a** (Table 37, entries 8–10).[220] The cationic tantalum alkyl imido complex $[(PhCH_2)_2Ta{=}NCMe_3]^+[B(C_6F_5)_4]^-$ (**121**)[218] required significantly harsher reaction conditions, which is in agreement with observations made in alkyne hydroaminations.

Intramolecular hydroamination of mono- and 1,3-disubstituted aminoallenes is conveniently achieved using $Ti(NMe_2)_4$ (**102**) or the more reactive bissulfonamide complexes **122a–c** (Figure 22, Table 38).[221] The reactivity of the bissulfonamide complexes is enhanced by either sterically demanding substituents (**122b**) or electron-withdrawing substituents (**122c**). Formation of the cyclic imine was generally favored over the allylamine with good (**102**) to exclusive regioselectivity (**122c**, except in case of the formation of a tetrahydro-2*H*-azepine, Table 38, entry 15). Interestingly, the corresponding bissulfonamide zirconium complex **123** displayed an inverted regioselectivity for 1,3-disubstituted (as well as trisubstituted) aminoallenes in favor of the allylamine products with high *Z* selectivity (Table 38, entry 17).[221b] It was also noted that the cationic zirconocene $[Cp_2ZrMe]^+$-$[MeB(C_6F_5)_3]^-$ (**124a**) exhibits superior catalytic activity in comparison to the neutral zirconocene Cp_2ZrMe_2,[221b] which has been attributed to a lanthanide-like insertion mechanism,[176a] as opposed to a metal imido [2 + 2]-cycloaddition mechanism predicted for neutral zirconium complexes.[176b]

Similar to rare-earth metal catalysts, group 4 metal based complexes, such as $Ti(NMe_2)_4$ (**102**), $Zr(NMe_2)_4$ (**127**), and the bis(aminopyridinato) complex **128** (Figure 23), were shown to catalyze the intermolecular ring-opening hydroami-

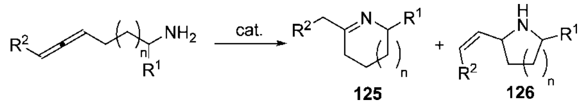
Table 37. Intermolecular Hydroamination of Allenes



entry	R¹	R²	catalyst	[catal]/[subst], %	*T*, °C	*t*, h	yield, %	ref
1	H	$2,6-Me_2C_6H_3$	**97**	10	45	*a*	>95	179
2	H	$2,6-Me_2C_6H_3$	**121**	2	135	24	>95	218
3	Ph	$2,6-Me_2C_6H_3$	**97**	7	90	24	96[b]	179
4	Ph	$2,6-Me_2C_6H_3$	**110a**	5	90	7	76[c]	220
5	^{n}Hex	$2,6-Me_2C_6H_3$	**97**	10	90	48	85[d]	179
6	$PhCH_2$	$2,6-Me_2C_6H_3$	**110a**	5	85	24	93[c]	220
7	$PhCH_2$	Ph	**110a**	5	85	24	83[c]	220
8	$PhCH_2$	^{t}Bu	**110a**	10	120	24	71[e]	220
9	$PhCH_2$	^{i}Pr	**110a**	10	120	24	91[e]	220
10	$PhCH_2$	$PhCH_2$	**110a**	10	120	24	85[e]	220

[a] $t_{1/2}$ < 30 min. [b] *E*/*Z* = 4.5:1. [c] Isolated yield of secondary amine after reduction with $LiAlH_4$. [d] *E*/*Z* = 5.2:1. [e] Isolated yield of ketone after hydrolysis with SiO_2.

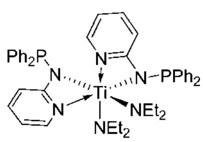
Table 38. Intramolecular Group 4/5 Metal Catalyzed Hydroamination of Aminoallenes



125 126

entry	R^1	R^2	*n*	catalyst	[catal]/[subst], %	*T*, °C	*t*, h	**125/126**	yield **125**, %	ref
1	H	H	1	**102**	5	75	3	100:0	quant.	221
2	H	H	1	**97**	5	135	2	72:10	72	221b
3	H	H	1	$TiCl_4/^tBuNH_2$[a]	5	75	15	100:0	97	203
4	H	H	1	**122a**	5	25	5	100:0	quant.	221
5	H	H	1	**122b**	5	25	3	100:0	quant.	221b
6	H	H	1	**122c**	5	25	6.5	100:0	92	221b
7	H	H	1	**123**	5	75	4	94:6	94	221b
8	H	H	1	**124a**	5	135	18	34:66	34	221b
9	4-MeC_6H_4	H	1	**102**	5	75	9	90:10	90	221
10	4-MeC_6H_4	H	1	**122a**	5	75	5	100:0	79	221
11	4-MeC_6H_4	H	1	**122b**	5	75	0.5	100:0	88	221
12	4-$MeOC_6H_4$	H	1	**122a**	5	75	1.5	100:0	95	221
13	4-FC_6H_4	H	1	**122a**	5	75	10	100:0	93	221
14	2,4-$Cl_2C_6H_3$	H	1	**122a**	5	75	2	100:0	88	221
15	4-MeC_6H_4	H	2	**122a**	10	75	3	93:7	90	221b
16	H	Et	1	**122b**	5	75	2	100:0	96	221b
17	H	Et	1	**123**	5	75		1:4	62[b]	221b
18	4-MeC_6H_4	Et	1	**122b**	5	105	2	100:0	93	221b
19	4-MeC_6H_4	Et	1	**122c**	5	75	20	100:0	87	221b

[a] $TiCl_4/^tBuNH_2$ ratio 1:2. [b] *Z*/*E* > 20:1.



128

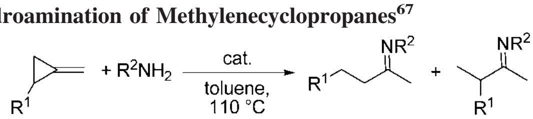
Figure 23. Titanium precatalyst for hydroamination of methylenecyclopropanes[67]

nation of methylenecyclopropanes (Table 39).[67] Analogous to those with lanthanide-based catalysts,[99b] hydroamination reactions involving the unsymmetrical phenylmethylenecyclopropane (PhMCP) led to the linear regioisomer **129** (R^1 = Ph) when titanium-based catalysts were applied. Generally, **128** exhibited superior activity in the case of sterically undemanding aliphatic and aromatic amines, while **102** outperformed **128** when bulky 2,6-disubstituted anilines were applied, as a result of unfavorable steric interactions with the aminopyridinato ancillary ligand in **128**. The high regioselectivity was proposed to result from a preference of the stabilized benzylic titanium intermediate **131** (Scheme 38, pathway **a**) as opposed to a primary alkyl species **132**.

The rate of the reaction was found to be first-order in catalyst and PhMCP but inverse first-order in amine, which is in agreement with the proposed mechanism and a rate-determining [2 + 2]-cycloaddition step between the titanium imido species and PhMCP.

The tetraamido zirconium complex $Zr(NMe_2)_4$ (**127**) showed significant reduced catalytic activity in comparison to titanium-based catalysts, but it is interesting to note, that the branched imine **130** (R^1 = Ph) becomes the prevailing hydroamination product. This switch in regioselectivity upon exchanging titanium for zirconium is reminiscent of an analogous reversed regioselectivity observed in aminoallene cyclizations when the group 4 metal catalyst is varied.[221b] The difference in regiochemistry was proposed to result from an alternative protonation mechanism for the azametallacyclobutane intermediate, followed by subsequent ring-opening of the cyclopropane via proton transfer from a metal-bound amido ligand to the sterically more accessible methylene ring carbon atom (Scheme 39).

Table 39. Group 4 Metal Catalyzed Hydroamination of Methylenecyclopropanes[67]

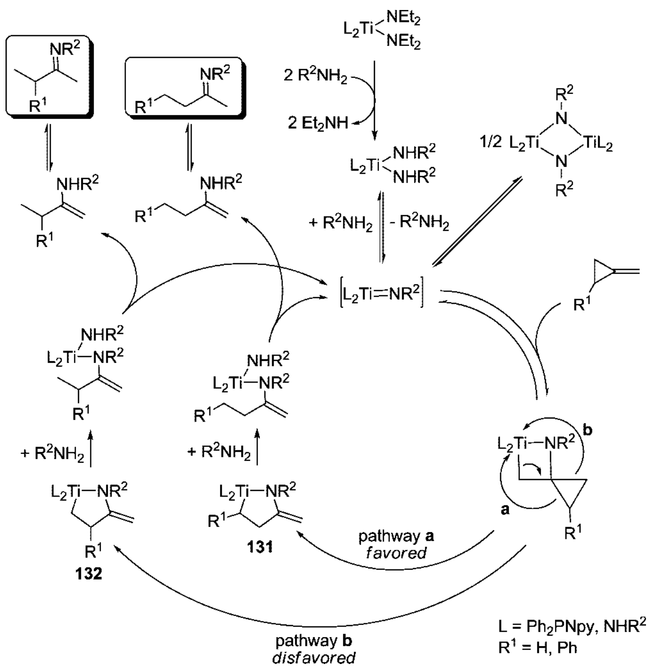


129 130

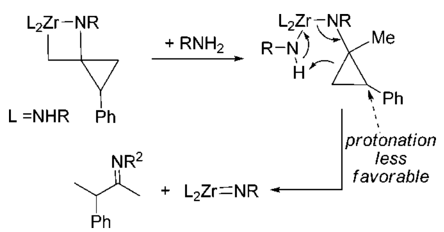
entry	R^1	R^2	catalyst	[catal]/[subst], %	*t*, h	**129/130**	TOF, h^{-1}	yield **129**, %
1	H	Et	**128**	2	36	*a*	1.29	90
2	H	Ph	**102**	2	100	*a*	2.5	100[b]
3	H	Ph	**128**	2	45	*a*	1.05	90
4	Ph	^nBu	**102**	2	100	90:10	0.05	19[b]
5	Ph	^nBu	**128**	5	20	100:0	6.25	90
6	Ph	Ph	**102**	2	24	83:17	5.0	100[b]
7	Ph	Ph	**128**	5	17	87:13	1.15	83
8	Ph	2,6-$Me_2C_6H_3$	**102**	2	23	84:16	6.9	100[b]
9	Ph	2,6-$Me_2C_6H_3$	**127**	2	145	10:90	0.48	92[b]
10	Ph	2,6-$^iPr_2C_6H_3$	**102**	2	22	80:20	7.8	100[b]
11	Ph	2,6-$^iPr_2C_6H_3$	**127**	2	215	29:71	0.42	100[b]
12	Ph	2,6-$^iPr_2C_6H_3$	**128**	5	120	100:0	0.04	24[b]

[a] For R^1 = H **129** and **130** are identical. [b] Overall conversion.

Scheme 38. Proposed Mechanism of Titanium Catalyzed Intermolecular Hydroamination of Methylenecyclopropanes[67]



Scheme 39. Proposed Azametallacyclobutane Protonation/ Ring-Opening in Zirconium Catalyzed Hydroamination of PhMCP[67]



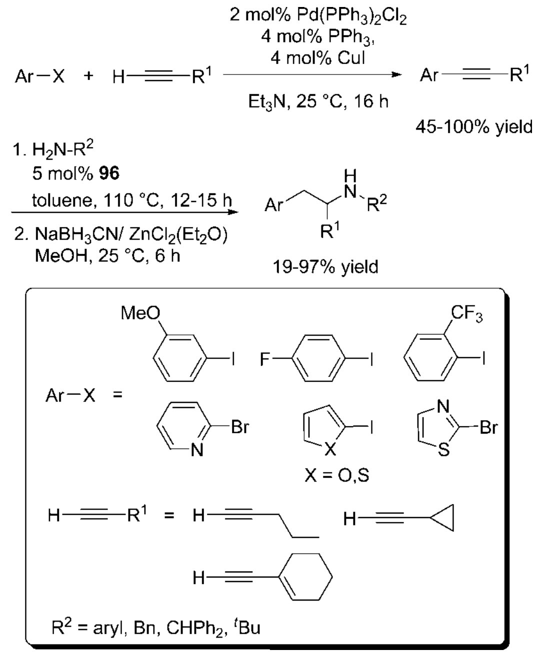
3.3. Applications of Hydroamination Reactions in Multistep Reaction Sequences

Titanium-catalyzed hydroaminations have become a powerful tool for the assembly of bi- and tricyclic nitrogen-containing skeletons in conjunction with palladium-catalyzed cross-coupling reactions.

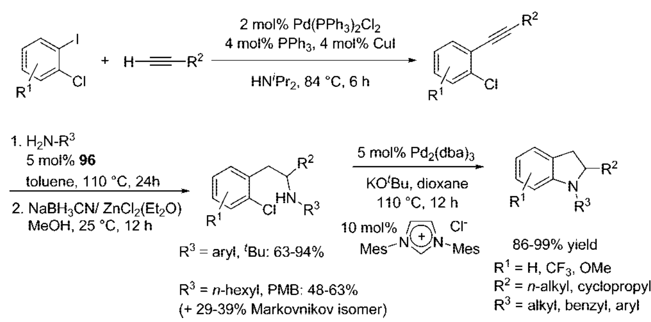
A diverse array of biologically active β-arylethylamines can be prepared in three steps via a flexible Sonogashira cross-coupling/hydroamination/reduction sequence (Scheme 40).[222] As noted above, 2-alkyl-1-arylalkynes undergo efficient anti-Markovnikov hydroamination (generally <2% Markovnikov product observed) using the titanocene catalyst **96**. Remarkably, a range of heterocycles, such as furan, pyridine, thiophene, and thiazole, were tolerated as well.

The tolerance of aryl halides in the titanium-catalyzed hydroamination step allowed further extension of the reaction sequence to the synthesis of the indoline, pyrrolizidine, and indolizidine framework (Schemes 41 and 42).[152a] Intermolecular hydroamination of *ortho*-chloro-substituted 2-alkyl-1-arylalkynes, which are readily prepared through Sonogashira coupling reactions of 1-chloro-2-iodoarenes, produces β-arylethylamines (after reduction with $NaBH_3CN/ZnCl_2$) with high anti-Markovnikov regioselectivity in the case of sterically demanding amines but diminished regioselectivity for *n*-alkylamines and benzylamines (Scheme 41). Subsequent Buchwald−Hartwig coupling furnished the indolines in high yield. A variation of this methodology is the intramolecular hydroamination of *ortho*-halide-substituted aminoalkyl(phenyl)alkynes to cyclic β-arylethylamines (after reduction) that can be readily cyclized via palladium-catalyzed cross-coupling to pyrrolizidine (Scheme 42, $n = 1$) and indolizidine derivatives (Scheme 42, $n = 2$). The intramolecular hydroamination readily proceeded with high regioselectivity without the need for sterically demanding amines.[223]

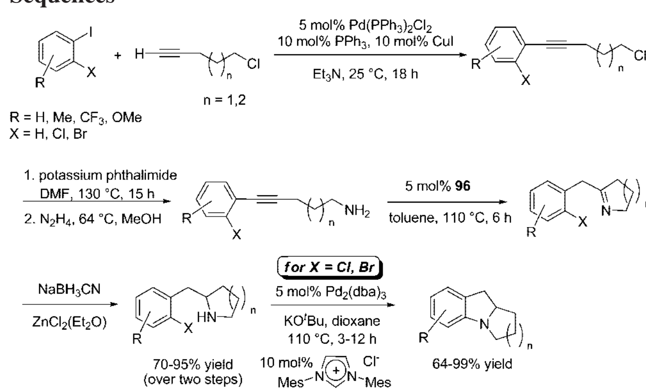
Scheme 40. Synthesis of β-Arylethylamines via Sequential Sonogashira Cross-Coupling, Titanium-Catalyzed Hydroamination and Subsequent Reduction[222]



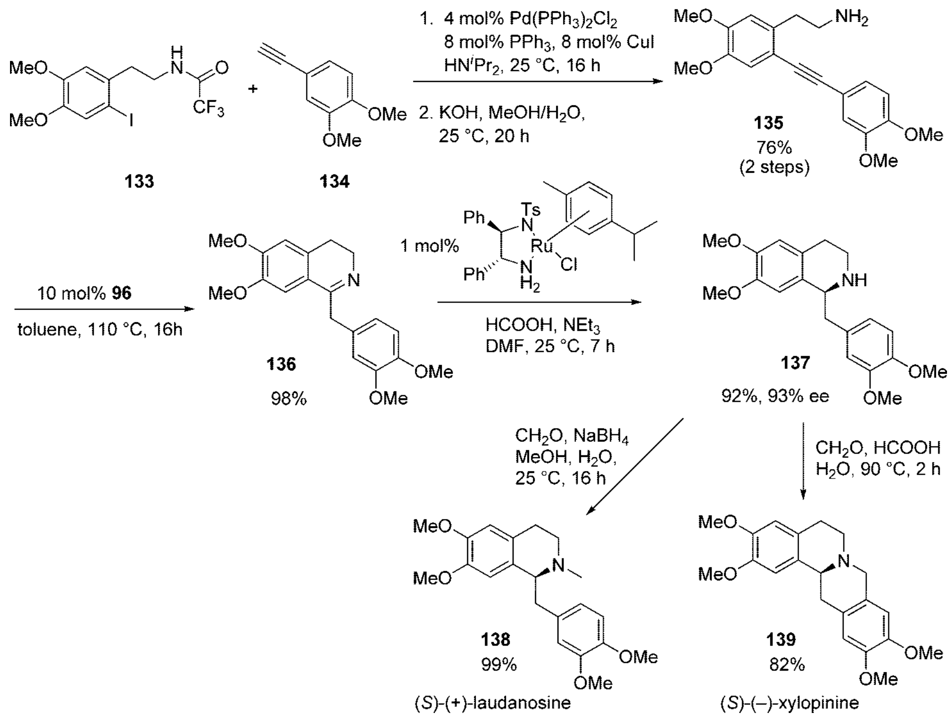
Scheme 41. Indoline Synthesis via Intermolecular Hydroamination/Cross-Coupling Sequences[152a]



Scheme 42. Pyrrolizidine and Indolizidine Synthesis via Intramolecular Hydroamination/Cross-Coupling Sequences[152a]



Scheme 43. Synthesis of Opium Alkaloids Involving Titanium-Catalyzed Hydroamination/Cyclization[152c]

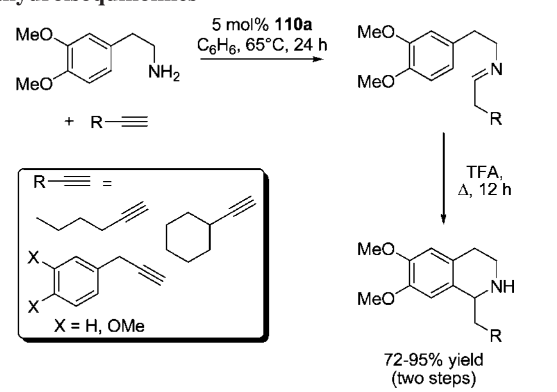


An extension of this methodology represents the application of the hydroamination/cyclization to the synthesis of the opium alkaloids (*S*)-(+)-laudanosine (**138**) and (*S*)-(−)-xylopinine (**139**) (Scheme 43).[152c] Sonogashira coupling of the aryl iodide **133** and the phenyl acetylene **134** furnished the aminoalkyne **135** after deprotection of the amide. Highly regioselective titanium-catalyzed hydroamination/cyclization of **135** led to the 3,4-dihydroisoquinoline **136**, which could be reduced by asymmetric transfer hydrogenation using Noyori's chiral ruthenium catalyst[224] with high enantioselectivity. Reductive amination of the 1,2,3,4-tetrahydroisoquinoline **137** led then directly to (*S*)-(+)-laudanosine (**138**), while Pictet−Spengler cyclization of **137** produced (*S*)-(−)-xylopinine (**139**).

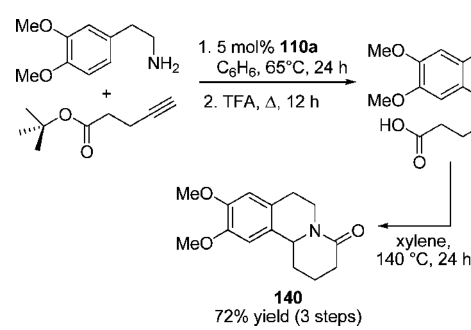
The high anti-Markovnikov regioselectivity of the bis(amidate) titanium catalyst **110a** in the hydroamination of terminal alkynes has been exploited in an alternative route for the efficient one-pot synthesis of 1-substituted tetrahydroisoquinolines via intermolecular hydroamination of phenylethylamines with terminal alkynes, followed by trifluoracetic acid-catalyzed Pictet-Spengler cyclization (Scheme 44).[212] The potential of this reaction sequence was further expanded to the highly atom-economical synthesis of the tricyclic benzo[*a*]quinolizine derivative **140** in 72% overall yield (Scheme 45), generating *tert*-butanol and water as the sole byproducts.

Several reaction sequences for the synthesis of indol derivatives have been reported since the previous review.[8] A one-pot reaction sequence very similar to the aforementioned indoline synthesis (Scheme 41) utilizes β-arylethylimines, generated via anti-Markovnikov hydroamination of *ortho*-chloro-substituted 2-alkyl-1-arylalkynes. Direct Buchwald−Hartwig coupling of the imine under basic conditions via the tautomeric enamine intermediate led to 1,2-disubstituted indoles (Scheme 46).[152b] An analogous approach using *ortho*-halide-substituted aminoalkyl(phenyl)-alkynes produced tricyclic 6,7,8,9-tetrahydropyrido[1,2-*a*]indoles (Scheme 47, $n = 2$) in an intramolecular hydroamination/

Scheme 44. Synthesis of 1-Substituted Tetrahydroisoquinolines[212]

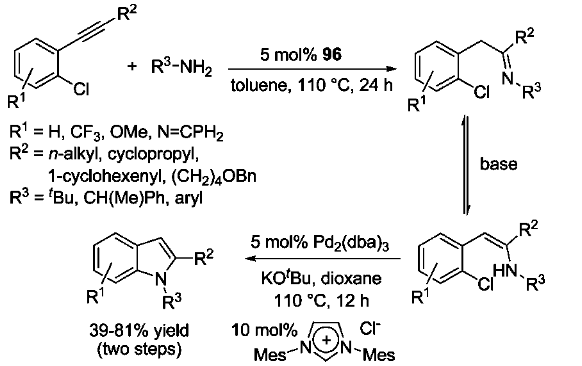


Scheme 45

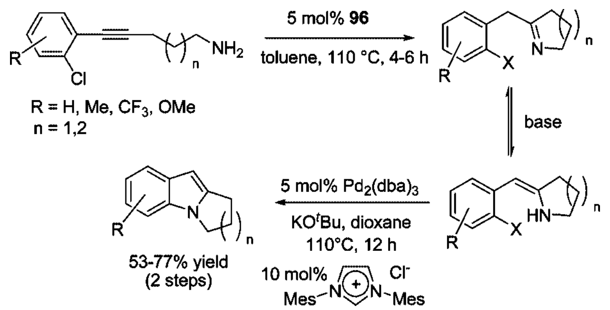


Buchwald−Hartwig sequence in moderate to good yield. Unfortunately, the synthesis of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indoles (Scheme 47, $n = 1$) was limited and gave the lowest yields as a result of unfavorable ring-strain build-up in the two annelated five-membered rings. Further applications of β-(2-haloaryl)ethylimines include the synthesis of substituted benzo[*b*]furans via copper-catalyzed O-arylation of ketones generated via hydrolysis of the β-arylethylimines.[225]

Scheme 46. Synthesis of Indoles via an Intramolecular Hydroamination/Cross-Coupling Sequence[152b]



Scheme 47. Synthesis of Tricyclic Indoles via an Intramolecular Hydroamination/Cross-Coupling Sequence[152b]



The Fischer indole synthesis[226] represents one of the most common approaches for the synthesis of indoles. The phenylhydrazone intermediates are also accessible via addition of arylhydrazines to alkynes, the so-called hydrohydrazination.[227] However, the electron-donating ability of the free lone-pair of the β-nitrogen atom in the titanium hydrazido species significantly alters the reactivity of the Ti=N double bond and can result in increased stability of dimeric, hydrazido bridged species.[228] The 2-((dimethylamino)methyl)pyrrolyl titanium complex **141** and the bis(pentafluorthiophenolate) complex **142** (Figure 24) were specifically designed to accomodate this different electronic and chelating behavior.[227]

Various test reactions showed that **141** and **142** were efficient in the Markovnikov addition of 1,1-dimethylhydrazine to terminal aliphatic alkynes and formed predominantly anti-Markovnikov adducts with phenylacetylene (Table 40).[227] However, only **142** was effective in the addition to 2-alkyl-1-arylalkynes. The observed *E*/*Z* ratio was similar to hydrazones prepared via carbonyl condensation. A further extension of this study using a tetradentate dipyrrolyl diamine titanium complex has been reported recently.[229]

Acetylene was a very reactive substrate, reacting with various aliphatic and aromatic hydrazines at room temperature in the presence of the bis(thiophenolate) titanium catalyst **142** to the corresponding hydrazones in excellent yields (eq 11). As expected, hydrohydrazination of terminal and internal alkynes with aryl-substituted hydrazines produced the desired indoles with the regiochemistry determined by the hydroamination step in moderate to good yield after $ZnCl_2$-induced [3,3]-sigmatropic rearrangement and cyclization of the ene-hydrazine (Table 41, eq 12). The application of the inexpensive catalyst system $TiCl_4$/^{t}BuNH$_2$ bears the advantage that no additional Lewis acid is required to

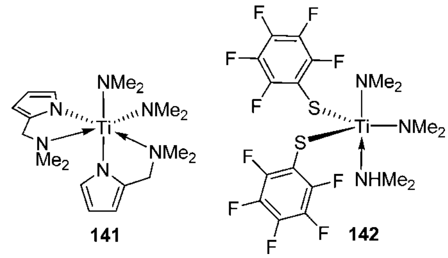
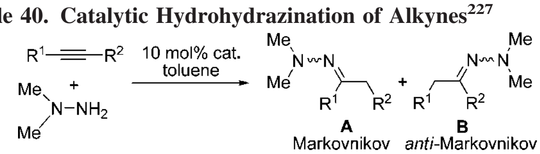


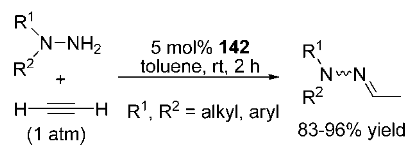
Figure 24. Titanium precatalysts for hydrohydrazination[227]

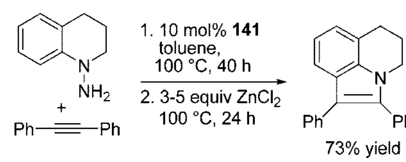
Table 40. Catalytic Hydrohydrazination of Alkynes[227]



R^1	R^2	catalyst	*T*, °C	*t*, h	A/B	*E*/*Z*	yield, %
^{n}Bu	H	**141**	75	24	50:1	3:2	79
^{n}Bu	H	**142**	75	24	10:1	7:3	72
Ph	H	**141**	100	2	1:3	50:1	85
Ph	H	**142**	100	2	1:30	50:1	88
Ph	Me	**141**	100	75	0:100	4:1	13
Ph	Me	**142**	100	10	0:100	4:1	92

facilitate the cyclization, though catalyst loadings were generally quite high.[210]

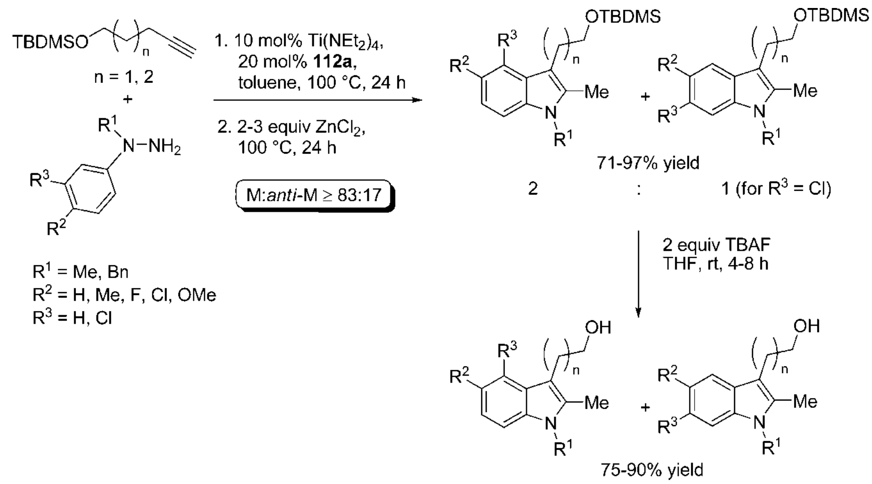

(11)


(12)

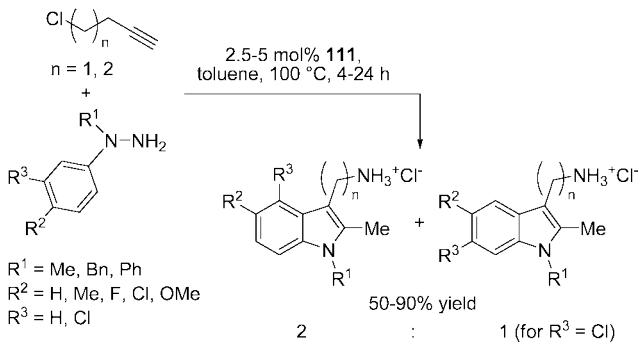
The application of silyl-protected ω-(hydroxylakyl)alkynes allowed facile one-pot access to various tryptophols (Scheme 48, $n = 1$) and homotryptophols (Scheme 48, $n = 2$), which are relevant to pharmaceutical applications as intermediates in the synthesis of a range of potent analgesics and anti-inflammatory drugs.[230] Hydrohydrazination of ω-(chloroalkyl)alkynes with various aryl hydrazines (Scheme 49) on the other hand led directly to the hydrochloride salts of the corresponding tryptamines and its homologues, due to nucleophilic substitution reaction of the chloride with the ammonia liberated during the indole synthesis.[231] The latter reaction is autocatalytic due to formation of the hydrochloride salt and no Lewis acid was required to facilitate the Fischer indole reaction.

An alternative approach for the synthesis of indole derivatives comprises a sequential hydroamination/Heck reaction of 2-chloroaniline with 2-alkyl-1-arylalkynes (Scheme 50).[232] The desired 3-aryl-1*H*-indoles are produced with high regioselectivity in moderate to high yield after 5-*endo* Heck reaction of the intermediate enamine. A significant advantage of this methodology over the Fischer indole approach constitutes the better control of regiochemistry when substituted 2-chloroanilines are applied, giving access to 7-substituted indoles.[232b]

Scheme 48. Synthesis of Tryptophols and Homotryptophols via a Modified Fischer Indole Synthesis[230]



Scheme 49. Synthesis of Tryptamines via Hydroamination/ Fischer Indole Synthesis of ω-(Chloroalkyl)Alkynes with Aryl Hydrazines[231]



3.4. Hydroamination of Alkenes

Earlier studies of group 4 metal hydroamination catalysts have suggested that the scope of these systems is restricted

Scheme 50. Indole Synthesis via Sequential Hydroamination/ Heck Reaction[232]

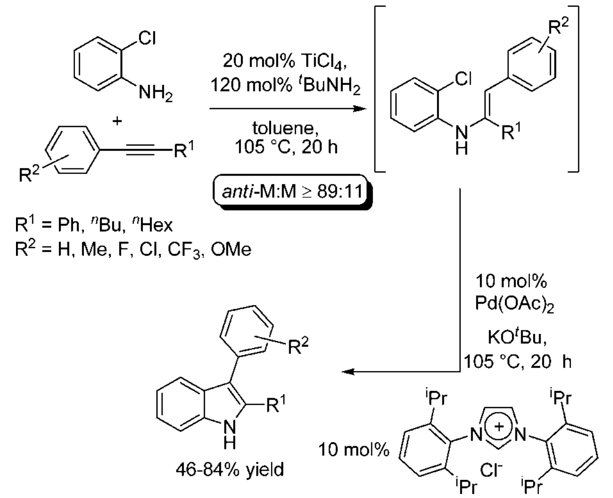
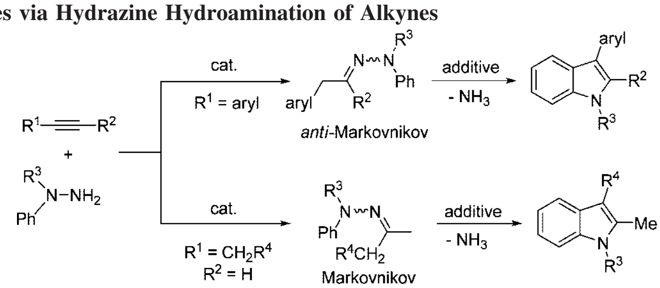


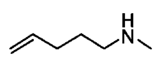
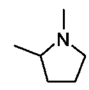
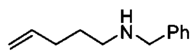
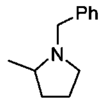
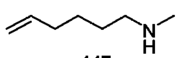
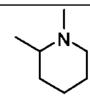
Table 41. Fischer Indole Syntheses via Hydrazine Hydroamination of Alkynes



R^1	R^2	R^3	catalyst	[catalyst]/[s] /%	T, °C	t, h	additive (conditions)	yield, %	ref
				Anti-Markovnikov Product (R^1 = Aryl)					
Ph	H	Me	**142**	2	100	18	3−5 equiv $ZnCl_2$ (100 °C)	95	227
Ph	Me	Me	**142**	10	100	20	3−5 equiv $ZnCl_2$ (100 °C)	90	227
Ph	Ph	Me	**141**	2	100	48	3−5 equiv $ZnCl_2$ (100 °C, 24 h)	69	227
Ph	Ph	Ph	**141**	10	100	48		42	227
Ph	Ph	Ph	$TiCl_4/{}^tBuNH_2$[a]	30	105	24−48		55	210
Ph	Et	Me	$TiCl_4/{}^tBuNH_2$[a]	30	105	24−48		73	210
4-$CF_3C_6H_4$	^{n}Hex	Ph	$TiCl_4/{}^tBuNH_2$[a]	40−50	105	24−48		76	210
4-$MeOC_6H_4$	^{n}Hex	Ph	$TiCl_4/{}^tBuNH_2$[a]	40−50	105	24−48		70	210
4-BrC_6H_4	^{n}Hex	Me	$TiCl_4/{}^tBuNH_2$[a]	100	105	24−48		66	210
Ph	$(CH_2)_4Cl$	Me	$TiCl_4/{}^tBuNH_2$[a]	100	105	24−48		52	210
Ph	H	Me	**105a**	5	100	24	3−4 equiv $ZnCl_2$ (100 °C, 24 h)	52[b]	200b
				Markovnikov Product (R^1 = Alkyl)					
$CH_2{}^n$Pr	H	Me	**142**	2	100	5	3−5 equiv $ZnCl_2$ (100 °C)	56	227
$CH_2{}^n$Pent	H	Me	**105a**	2.5	100	2	3−4 equiv $ZnCl_2$ (100 °C, 24 h)	88	200b
CH_2Ph	H	Me	**105a**	5	100	24	3−4 equiv $ZnCl_2$ (100 °C, 24 h)	84	200b

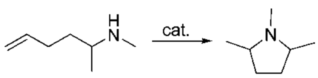
[a] $TiCl_4/{}^tBuNH_2$ ratio 1:6. [b] Mixture of anti-Markovnikov and Markovnikov product (anti-M/M = 42:10).

Table 42. Catalytic Hydroamination/Cyclization Reactions of Secondary Aminoalkenes with Cationic Group 4 Metallocenes[181]

Entry	Substrate	Product	cat.[a]	[cat.]/[s] / mol%	T / °C	*t* / h	Conv. / %	TOF / h^{-1}
1	 **143**	 **144**	**124a**	2	80	7	98	12
2			**124a**[b]	2	80	10	97	6
3			**124a**	2	100	1	97	>50
4			**124b**	2	80	5	91	12
5			**150**	2	100	218	76	
6			**151**	10	100	74	11	
7	 **145**	 **146**	**124b**	2	100	4	95	24
8	 **147**	 **148**	**124b**	2	100	12	98	

[a] Reaction conditions: 2 mol % catalyst, C_6D_5Br, Ar atm. [b] In C_6D_6.

Table 43. Diastereoselective Hydroamination/Cyclization with Cationic Group 4 Metallocenes[181]



152 **153**

catalyst	[catalyst]/[subst], mol %	*T*, °C	*t*, h	conv, %	cis/trans
124a	2	80	15	97	3.3:1
150	5	80	14.5	97	8.6:1
151	5	100	107	97	1:2

to alkynes and allene substrates. However, a first breakthrough was made with the realization that cationic group 4 metal complexes are isoelectronic to lanthanocene complexes. While the lanthanocenes have been studied as homogeneous Ziegler–Natta polymerization model systems,[233] cationic group 4 metal complexes have gained tremendous importance as homogeneous single-site polymerization catalysts over the last three decades.[234] Based on the close relationship between these two classes of complexes, it was anticipated that cationic group 4 complexes also possess hydroamination activity for simple, nonactivated olefins.[180,181]

The cationic alkylzirconocene complexes $[Cp_2ZrMe]^+[X]^-$ (**124a**,**b**; $X^- = MeB(C_6F_5)_3^-$ (**a**), $B(C_6F_5)_4^-$ (**b**)) readily cyclized secondary aminoalkene substrates in aromatic solvents with catalyst loadings as low as 1 mol % (Table 42), notably even in the absence of *gem*-dialkyl substituents.[181] Cyclization of *N*-methyl-pent-4-enyl-amine (**143**) proceeded with a rate of >50 h^{-1} in C_6D_5Br at 100 °C. The rate of the reaction depends slightly on the polarity of the solvent, due to lower solubility of the cationic catalyst species in less polar benzene solution. The rates of cyclization decline in the order 5 > 6 in agreement with classical, stereoelectronically controlled cyclization processes. The cationic titanocene $[Cp_2Ti(CH_2Ph)]^+[B(C_6F_5)_4]^-$ (**150**) and permethylzirconocene $[Cp^*{}_2ZrMe]^+[B(C_6F_5)_4]^-$ (**151**) displayed significantly reduced activity, while no catalytic activity was observed with neutral complexes.

Interestingly, cyclization of the α-substituted aminoalkene **152** produced preferentially the *cis* diastereomer (except for **151**, Table 43), which contrasts with the opposite diastereoselectivity observed in the lanthanide cyclization of the corresponding primary aminoalkene analogue **29** (Figure 7, Table 17). The preferred formation of *cis*-**153** was rationalized with unfavorable

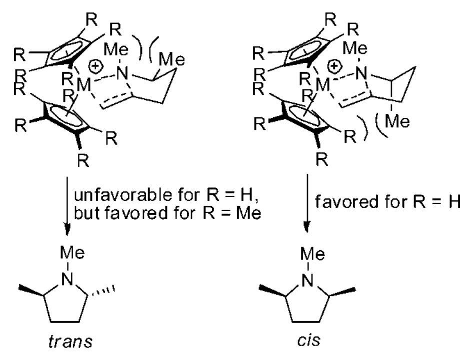


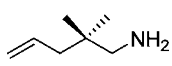
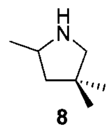
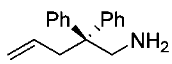
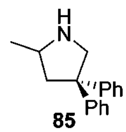
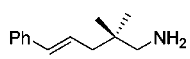
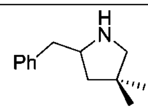
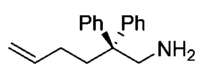
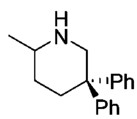
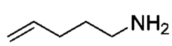
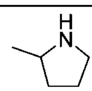
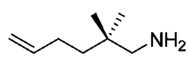
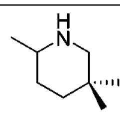
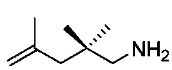
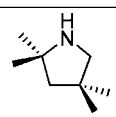
Figure 25. Plausible transition states in the diastereoselective hydroamination/cyclization of **152** with cationic group 4 metallocenes (R = H, M = Ti, Zr; R = Me, M = Zr).

gauche interactions of the *N*-methyl group with the equatorial α-methyl group in the seven-membered chair-like transition state of the cyclization step leading to the trans isomer (Figure 25). However, in case of **151** the steric interactions of the axial α-alkyl substituent with the cyclopentadienyl methyl groups in the cyclization transition state disfavored this reaction path leading to the cis isomer.

The discovery in 2005 that $Ti(NMe_2)_4$ (**102**)[182] catalyzes the hydroamination of *gem*-dialkyl-activated[114] primary aminoalkenes at elevated temperatures (Tables 44 and 45) resulted in bustling research activity and significant progress since then.[183–190] Secondary aminoalkenes did not react, suggesting that the mechanism involves a metal imido species (Scheme 30), which cannot form with a secondary amino group. A survey of a range of cyclopentadienyl titanium complexes (Table 44, entries 9–11, 19–21) identified the bis(indenyl) complex Ind_2TiMe_2 (**99**) as the most versatile titanium-based catalyst next to $Ti(NMe_2)_4$ (**102**).[183] The helical chiral dithiaalkanediyl-bridged bisphenolato titanium and zirconium complexes **154a**,**b** (Figure 26) were not only efficient catalysts for the intermolecular anti-Markovnikov hydroamination of alkynes but showed also activity in the hydroamination/cyclizaton of the *gem*-diphenyl-substituted aminoalkene **84** (Table 44, entries 12 and 13),[184] which might allow asymmetric hydroamination reactions using the enantiopure version of the catalysts.

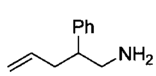
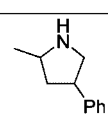
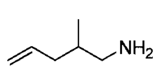
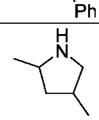
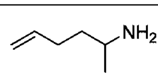
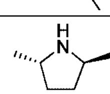
Contrary to general reactivity patterns observed in alkyne hydroamination, zirconium catalysts are commonly slightly more active in the hydroamination of aminoalkenes, as documented in the comparison of the catalytic activity of

Table 44. Titanium- and Zirconium-Catalyzed Hydroamination/Cyclization of Primary Aminoalkenes

Entry	Aminoalkene	Product	Catalyst	[cat.]/[s] /%	T / °C	t / h	Yield / %	Ref.
1	 7	 8	$Ti(NMe_2)_4$ (**102**)	5	110	96	52	182
2			**99**	5	105	96	74	183
3			**110a**	5	110	120	25	186
4			**155**	5	110	120	73	186
5			**156**	5	120	12	94	185
6			**(CGC)ZrMe$_2$**[a]		100		>95[b]	103c
7			**(CGC)ZrMeCl**[a]		100		>95[c]	103c
8	 84	 85	$Ti(NMe_2)_4$ (**102**)	5	110	24	92	182
9			**96**	5	105	24	86	183
10			**99**	5	105	15	97	183
11			**114**	5	105	24	74	183
12			**154a**	5	105	24	76	184
13			**154b**	5	105	24	82	184
14			**110a**	5	110	10	90	186
15			**155**	5	110	4	98	186
16			**155**	5	110	96	38	186
17			**156**	10	150	39	91	185
18			$Ti(NMe_2)_4$ (**102**)	5	110	24	80	182
19			**96**	5	105	24	78	183
20			**99**	5	105	24	89	183
21			**114**	5	105	24	75	183
22			**155**	5	110	24	82	186
23	 27	 28	**156**	10	120	41	89	185
24	 51	 52	**156**	5	120	9	99	185
25			**156**	10	150	45	94	185

[a] CGC = $Me_2Si(C_5Me_4)(^tBuN)^{2-}$. [b] TOF = 0.07 h^{-1} at 100 °C. [c] TOF = 0.14 h^{-1} at 100 °C.

Table 45. Diastereoselective Titanium- and Zirconium-Catalyzed Hydroamination/Cyclization of Aminoalkenes

Entry	Aminoalkene	Product	Cat.	[cat.]/[s] /%	T / °C	t / h	*cis/trans*	Yield / %	Ref.
1			**102**	5	110	168	1.4:1	26	182
2			**102**	5	110	96		38	182
3	 29	 30	**155**	10	110	96	1:11.3	72	186
4			**156**	5	150	22	1.0:1.3	96	185

the bis(amidate) titanium complex **110a** (Figure 21) with the bis(amidate) zirconium imido complex **155** (Figure 26, Table 44, entries 3, 4, 14, and 15).[186] Interestingly, contrary to general trends for classical, stereoelectronically controlled cyclization processes the rate differences for the formation of five- and six-membered rings were not significant in general or were even reversed in some cases.

Most neutral group 4 metal catalyst systems were inactive in the absence of *gem*-dialkyl substituents in the aminoalkene substrate, except for the bis(thiophosphinic amidate) zirconium complex **156**, which catalyzed the cyclization of the simple aminopentene **27**.[154,185,235] Furthermore, also aminoalkenes with 1,1- and 1,2-disubstituted olefinic groups were cyclized in high yield.

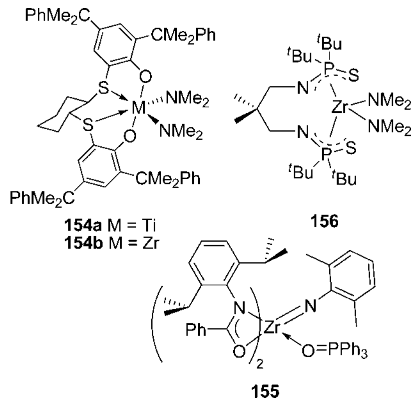
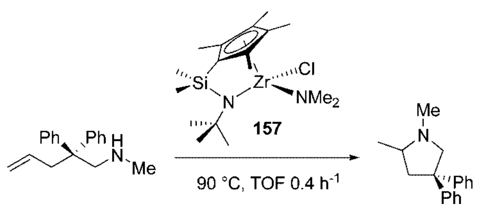


Figure 26. Titanium and zirconium catalysts for hydroamination/cyclization of primary aminoalkenes.

None of the neutral group 4 metal catalysts mentioned above has been observed to catalyze the hydroamination of secondary aminoalkenes, which supports the proposal that the neutral group 4 metal hydroamination catalysts involve a metal imido species that cannot form with secondary amines. However, it has been report recently that the constrained geometry zirconium catalyst **157**(eq 13),

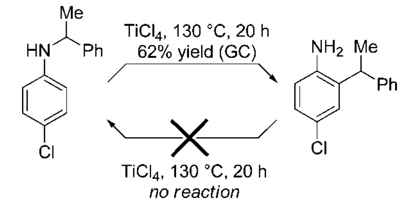


(13)

$Zr(NMe_2)_4$ (**127**), and dipyrrolylmethane zirconium complexes are capable of cyclizing secondary aminoalkenes, and it has been argued that a lanthanide-like mechanism, involving insertion of the olefin in a metal−amide σ-bond, is operational.[103c,191]

Several reports have emerged indicating that $TiCl_4$[236] and the cationic tantalum imido complex $[(PhCH_2)_2Ta{=}NCMe_3]^+[B(C_6F_5)_4]^-$ (**121**)[218] catalyze the hydroamination of norbornene (Table 46) and vinyl arenes (Table 47) with aromatic amines. Prominent byproducts in these reactions result from electrophilic aromatic substitution of the aniline. The amount of these Friedel−Crafts alkylation products decreases with decreasing electron density at the aromatic ring. The $TiCl_4$-catalyzed hydroamination of vinyl arenes proceeded with Markovnikov regioselectivity,[236b] which contrasts with the generally exclusive anti-Markovnikov regioselectivity found with rare-earth metal based catalyst systems.[99b] It was noticed that the hydroamination product

Scheme 51. Irreversible Product Rearrangement in $TiCl_4$-Catalyzed Vinyl Arene Hydroamination



can rearrange irreversibly to the hydroarylation product (Scheme 51). Despite some mechanistic information,[218b,219] the mode of operation of these (pre-)catalyst systems is not fully understood. It is interesting to note that certain Lewis and Brønsted acid catalyzed hydroamination reactions[237–239] show similar Friedel−Crafts alkylation byproducts as those observed in some of the reactions involving $TiCl_4$ or **121**.

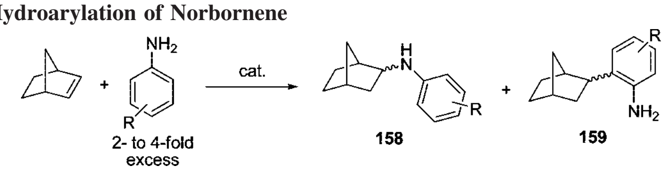
3.5. Asymmetric Hydroamination Using Group 4 Metal Catalysts

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

The first asymmetric hydroamination by a chiral group 4 metal catalyst using the aminophenolate complex (*S*)-**162** (Figure 27) was reported only recently.[180] The cationic zirconium complex (*S*)-**162** readily reacted with secondary aminoalkenes with up to 82% ee (Table 48). Reactions were commonly performed at 100 °C in bromobenzene using 10 mol % of catalyst. Cyclization of **163** 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 (Table 48, entry 2). The *N-para*-methoxybenzyl-protected aminoalkene **167** was cyclized very slowly, because of either increased steric demand of the benzyl substituent or coordinative sequestering of the catalyst by the methoxy functionality.

As noted above, cyclization of aminoallenes can proceed via two pathways generating two regioisomeric products (Scheme 37). Formation of imines (pathway a) usually predominates for monosubstituted aminoallenes, whereas vinylpyrroldines (pathway b) are generated preferentially when 1,3-disubstituted or trisubstitued aminoallenes are employed.[98,117,221] Therefore, asymmetric ring-closing of di-

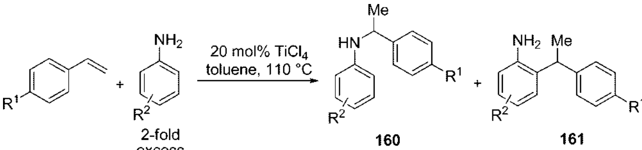
Table 46. Hydroamination and Hydroarylation of Norbornene



aniline	catalyst	[catalyst]/[subst], %	*T*, °C	*t*, h	**158/159**	yield **159**, %	ref
$PhNH_2$	**121**	5	135	24	10:22	10	218a
$PhNH_2$	$TiCl_4$	100	169	2	65:35	48	236a
$2\text{-}BrC_6H_4NH_2$	$TiCl_4$	10	110	18	91:9[a]	88	236a
$2,4\text{-}Br_2C_6H_3NH_2$	$TiCl_4$	10	110	20	96:4[a]	95	236a
$3,5\text{-}(CF_3)_2C_6H_3NH_2$	$TiCl_4$	5	110	21	98:2[a]	83	236a

[a] Ratio for reaction with 100 mol % $TiCl_4$ at 169 °C.

Table 47. $TiCl_4$-Catalyzed Hydroamination and Hydroarylation of Vinyl Arenes[236b]



R^1	aniline	*t*, h	**160**/**161**	yield **160**, %	yield **161**, %
H	$4\text{-}ClC_6H_4NH_2$	22	61:39[a]	30	32
H	$4\text{-}FC_6H_4NH_2$	3	32:68[b]	21	47
H	$3,5\text{-}(CF_3)_2C_6H_3NH_2$	30	>99:1	87	
F	$3,5\text{-}(CF_3)_2C_6H_3NH_2$	30	>99:1	81	
H	$3,5\text{-}(CH_3)_2C_6H_3NH_2$	20	8:92[c]		50
H	$2,4\text{-}Br_2C_6H_3NH_2$	20	7:93[a]		65

[a] At 130 °C. [b] At 170 °C under microwave radiation. [c] At 170 °C using 100 mol % $TiCl_4$.

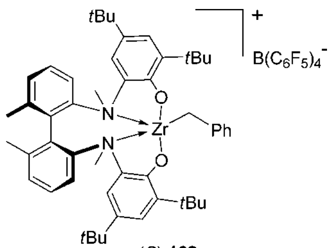
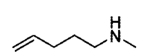
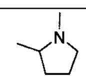
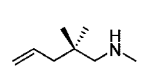
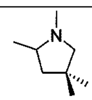
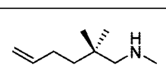
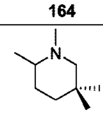
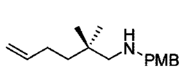
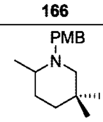
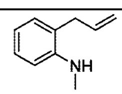
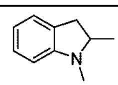


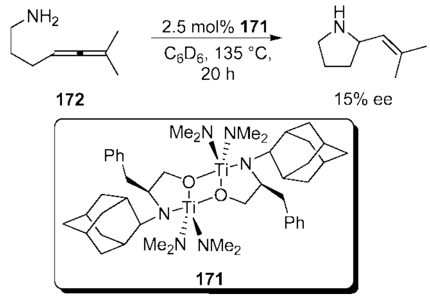
Figure 27. Cationic zirconium aminophenolate complex for asymmetric hydroamination.

Table 48. Zirconium-Catalyzed Asymmetric Hydroamination/Cyclization of Secondary Aminoalkenes Using (*S*)-162 in C_6D_5Br[180c]

Entry	Substrate	Product	[cat.]/[s] /%	*T* /°C	*t*[a] /h	% *ee*
1	 **143**	 **144**	10	100	4	64
2	 **163**	 **164**	5	70	48[b]	14
3	 **165**	 **166**	10	100	3	82
4	 **167**	 **168**	10	100	192	nd
5	 **169**	 **170**	10	100	3	20

[a] Time to 100% conversion of substrate. [b] 70% conversion to hydroamination product and 30% double bond isomerized aminoalkene. [c] nd = not determined.

or trisubstituted aminoallenes should be feasible using chiral titanium or zirconium catalysts. Indeed, chiral amino alcohol titanium complexes, for example, the presumed dimeric complex **171**, have been utilized in the cyclization of aminoallene **172** (eq 14),[240,241] but enantioselectivities were low.



(14)

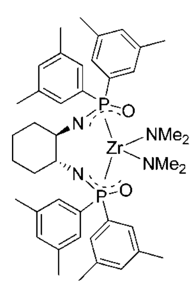
Stimulated by the initial discovery of neutral group 4 metal catalysts for the hydroamination of aminoalkenes, several groups have reported chiral catalyst systems. After screening a wide range of diamido, diolate, and amino alcoholate ligands, the chiral bis(phosphinic amido) zirconium complex (*R*,*R*)-**173** (Figure 28) was found to be superior in reactivity and enantioselectivity for the cyclization of primary aminoalkenes, also in comparison to the corresponding titanium and hafnium complexes.[187] Cyclization of aminopentenes proceeded with enantioselectivities as high as 80% ee, but formation of six-membered rings was somewhat less selective. Unfortunately, preliminary mechanistic studies indicate that this catalyst system undergoes slow ligand redistribution reactions, leading to chiral catalytically inactive, as well as achiral catalytically active, species.

Selectivities of up to 93% ee were observed with the chiral bis(amidate) zirconium complex **174** (Table 49), first introduced by Schafer[188] and soon after also by Scott.[189] Again, selectivities for the formation of six-membered rings were significantly lower than those for five-membered rings, which can be attributed to a larger, less organized eight-membered cyclization transition state.

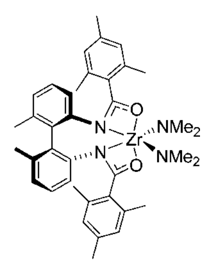
3.6. One-Pot Reaction Sequences Involving Hydroamination Products

One-pot multistep reaction sequences[242,243] are an efficient method to introduce additional complexity and versatility to the hydroamination reaction. Imines, the products of alkyne hydroamination, are a good target for further functionalization, in particular, because they tend to be prone to hydrolysis. In fact, the imines are often isolated and characterized after hydrolysis with SiO_2 or HCl. Synthetically more useful are reductions using $LiAlH_4$, H_2/Pd/C, or $NaBH_3CN/ZnCl_2$. A little bit more elegant are sequential hydroamination/hydrosilylation processes because the metals serve as catalysts in both transformations. This reaction sequence has been accomplished using iridium[244] (eq 15), titanium,[245] and rare-earth metal[136] catalysts.

The titanium catalysts Cp_2TiMe_2 (**96**) and $Me_2Si(C_5Me_4)(^tBuN)Ti(NMe_2)_2$ (**114**) effectively catalyzed the intermolecular hydroamination of alkynes with sterically

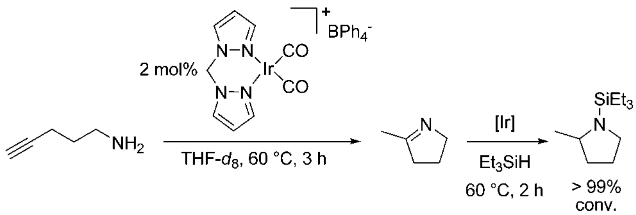


(*R*,*R*)-**173**



(*R*)-**174**

Figure 28. Chiral zirconium catalysts for asymmetric hydroamination of primary aminoalkenes.

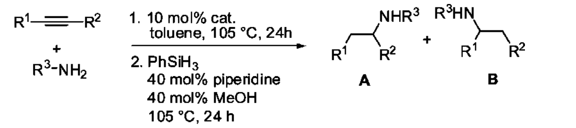


(15)

undemanding anilines and subsequent hydrosilylation with $PhSiH_3$. Aqueous workup produced the free amines due to hydrolysis of the silylamine bond (Table 50, entries 1−4).[245] However, hydrosilylation activity suffered with increasing steric hindrance of the imine. Decreasing yields were observed with increasing number of ortho substituents in the anilines or secondary and tertiary aliphatic amines (Table 50, entries 4−8) or steric demand of the alkyne (Table 50, entry 14). The observed regioselectivity follows the pattern previously observed in hydroamination reactions (*vide supra*).

While the hydroamination of alkynes does not generate a new chiral center, the hydrosilylation of the imine moiety

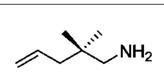
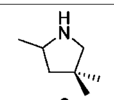
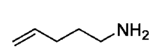
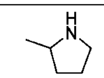
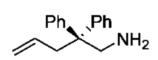
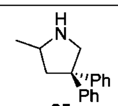
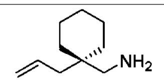
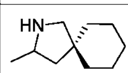
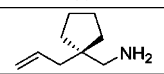
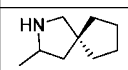
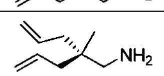
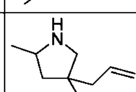
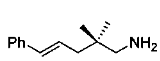
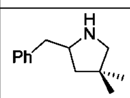
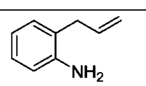
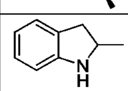
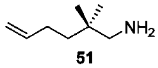
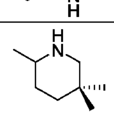
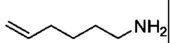
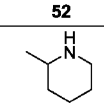
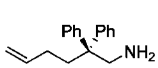
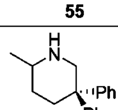
Table 50. Sequential Hydroamination/Hydrosilylation Catalyzed by Cp_2TiMe_2 (96) and $Me_2Si(C_5Me_4)(^tBuN)Ti(NMe_2)_2$ (114)[245]



entry	R^1	R^2	R^3	catalyst	yield, %	A/B
1	Ph	Me	Ph	**96**	85	99:1
2	Ph	Me	4-$MeOC_6H_4$	**96**	86	99:1
3	Ph	Me	4-MeC_6H_4	**114**	99	99:1
4	Ph	Me	4-MeC_6H_4	**96**	85	99:1
5	Ph	Me	3-MeC_6H_4	**96**	71	99:1
6	Ph	Me	2-MeC_6H_4	**96**	57[a]	99:1
7	Ph	Me	2,6-$Me_2C_6H_3$	**96**	nr[a]	
8	Ph	Me	cyclopentyl	**96**	39[a]	95:5
9	4-ClC_6H_4	Me	4-MeC_6H_4	**96**	86	98:2
10	^{n}Hex	H	4-MeC_6H_4	**96**	88[b,c]	31:69
11	Ph	H	4-MeC_6H_4	**96**	65[b]	57:43
12	Ph	H	4-MeC_6H_4	**114**	50[b]	76:24
13	$PhCH_2$	H	4-MeC_6H_4	**96**	76[b,c]	39:61
14	Ph	Ph	4-MeC_6H_4	**96**	31	

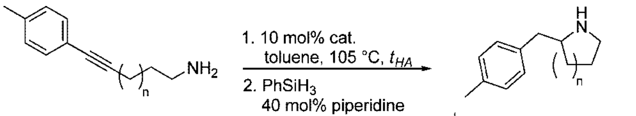
[a] After 48 h hydrosilylation; nr = no reaction. [b] 3 h hydroamination. [c] 5 mol % **96**, 20 mol % piperidine, 20 mol % MeOH.

Table 49. Zirconium-Catalyzed Asymmetric Hydroamination/Cyclization of Primary Aminoalkenes

Entry	Aminoalkene	Product	Catalyst	[cat.]/[s] /%	*T* /°C	*t* /h	Yield /%	% *ee* (config)	Ref.
1	 **7**	 **8**	(*R*,*R*)-**173**	10	115	48	91[a]	80 (*S*)	187
2			(*R*)-**174**	10	110	3	80[b]	93 (*R*)	188
3			(*S*)-**174**	10	110	18	(>95)[c]	91	189
4	 **27**	 **28**	(*R*,*R*)-**173**	20	135	72	33[a]	62	187
5	 **84**	 **85**	(*R*)-**174**	10	110	1.25	93	74 (*R*)	188
6	 **86**	 **87**	(*R*)-**174**	10	110	3	96	82 (*R*)	188
7			(*R*)-**174**	10	110	5	91[b]	88 (*R*)	188
8	 **88**	 **89**	(*R*)-**174**	10	110	2	82	92 /88[d]	188
9			(*R*,*R*)-**173**	20	135	24	93[a]	62	187
10			(*R*,*R*)-**173**	20	115	48	85[a]	70	187
11	 **51**	 **52**	(*R*,*R*)-**173**	10	85	48	91[a]	51	187
12			(*S*)-**174**	10	110	3	(>95)[c]	38	189
13	 **54**	 **55**	(*R*,*R*)-**173**	10	135	24	79[a]	33	187
14			(*R*)-**174**	--[e]	--[e]	--[e]	--[e]	29 (*R*)	188

[a] Isolated as trifluoracetic amide. [b] Isolated as benzoyl amide. [c] Conversion. [d] Diastereomeric ratio (2*R*/4*S*)/(2*R*/4*R*) = 2.3:1. [e] Data not reported.

Scheme 52. Sequential Titanium-Catalyzed Intramolecular Hydroamination/Asymmetric Hydrosilylation[245]



cat.	n	t_{HA}/h	Yield/%	% *ee*
175	1	15	46	66
175	2	15	50	60
122a	2	6	68	55

can yield a chiral amine. An intramolecular hydroamination/asymmetric hydrosilylation sequence was accomplished using the chiral catalysts (*S*,*S*)-(ebthi)$TiMe_2$ (**175**) and (*R*,*R*)-**122a** (Scheme 52). The aminoalkynes **176a**,**b** underwent efficient hydroamination (> 95% conversion) followed by enantioselective hydrosilylation in up to 66% ee and moderate overall yields.

Rare-earth metal based catalysts, such as the bis(phosphinimino)methanide bis(dimethylsilylamide) complexes **40-Y** and **40-La** catalyzed the sequential intramolecular hydroamination/hydrosilylation under milder conditions and lower catalyst loadings than titanium catalysts (Scheme 53), but no asymmetric variant has been reported to date.[136]

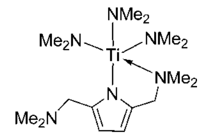
The addition of organometallic reagents to aldimines is a convenient method for the preparation of secondary amines. Aldimines can be prepared efficiently via anti-Markovnikov addition of sterically demanding aliphatic amines to terminal alkynes catalyzed by the titanocene complexes $Cp_2Ti(\eta^2\text{-}Me_3SiC{\equiv}CSiMe_3)$ (**105a**).[200] Subsequent nucleophilic addition of *n*-BuLi or PhLi generated the desired secondary amines in moderate to good yield (Table 51),[246] while MeLi reacted only sluggishly (<20% yield). Although reduced regioselectivity results in overall diminished yields, the separation of the undesired Markovnikov hydroamination byproducts is rather simple because of significantly reduced rates of nucleophilic addition to the ketimines. Secondary amines are generally also available directly through hydroamination of the corresponding internal alkynes, followed by reduction to the amine. However, the regioselectivity in these reactions is more difficult to control, potentially producing the wrong regiosiomer.

Imines can be utilized as precursors for α-amino phosphonates that can serve as building blocks for phosphorous-containing peptide mimetics. Nucleophilic additions of dialkyl phosphites to imines, generated via inter- or intramolecular alkyne hydroamination, were performed in a one-pot procedure using catalytic amounts of Me_2AlCl (Scheme 54).[247] Hydroamination reactions with *p*-anisidine or benzhydryl amine gave access to the primary α-amino phosphonates via oxidative deprotection with ceric ammonium nitrate (CAN) or hydrogenolysis with H_2/Pd/C (Scheme 55).

Aldimines can react as electrophiles with Me_3SiCN in a modified Strecker reaction that begins with the anti-Markovnikov hydroamination of terminal aliphatic or aromatic alkynes with benzylamine or isopropyl amine using the bis(amidate) titanium catalyst **110a** (Figure 21).[248] The trimethylsilyl-protected α-cyanoamines were obtained in high yield (Table 52) and were subsequently hydrolyzed to the corresponding α-amino acids and α-amino methyl esters.

Multicomponent coupling reactions have been utilized to add significant complexity to the hydroamination process. Intermediates of the hydroamination catalytic cycle can be scavenged by other reactants, which has been demonstrated in rare-earth metal catalyzed hydroamination/carbocyclization reactions (*vide supra*).[110–112] In a similar approach, azametallacyclobutene intermediates of the titanium-catalyzed hydroamination of alkynes can be scavenged by isonitriles to generate α,β-unsaturated β-iminoamines (Table 53).[249] The proposed mechanism involves reversible 1,1-insertion of the isonitrile in the azatitanacyclobutene, generating a five-membered iminoacyl-amido species (Scheme 56). Subsequent amine protonolysis releases the β-iminoamine.

The scope of this multicomponent reaction was extended to the iminohydrazination of alkynes with 1,1-disubstituted hydrazines (Table 54) using catalysts **141** (Figure 24) and **177**.[250]



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The generated β-aminohydrazones are valuable intermediates in organic synthesis. Mechanistic studies revealed that in the course of the reaction one of the ancillary 2-((dimethylamino)methyl)pyrrolyl ligands of the precatalyst **141** is lost protolytically to give the β-diketiminato hydrazido intermediate **178** (Scheme 57).[251] Formation of **178** from **141** was readily observed at room temperature, but protonation of **178** became only apparent at 90 °C, suggesting that the protonation step is the rate-limiting step of the catalytic cycle.

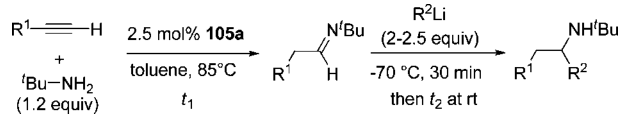
The titanium-catalyzed enyne hydroamination leads to α,β-unsaturated imines, which can be further functionalized using a rhodium-catalyzed C,H-activation/alkyne insertion process to generate dihydropyridines after electrocyclic ring closure (Scheme 58).[252] The rhodium catalyst requires quenching of the titanium species to avoid interference between the two. The scope of this process has been extended to olefinic substrates, which undergo similar insertion reactions to generate alkylated α,β-unsaturated imines.

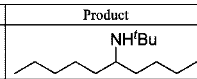
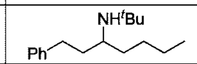
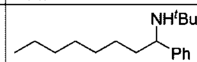
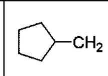
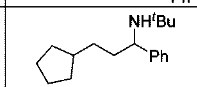
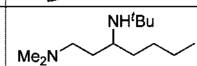
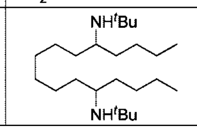
4. Late Transition Metal Complexes as Homogeneous Hydroamination Catalysts

A variety of late transition metal complexes have been tested as homogeneous catalysts (Table 55). Lewis acidic metal complexes with d^8 or d^{10} electron configuration appear to have particular high activity in hydroamination.[253] Thus, Ru^0, Rh^I and Ir^I, Pd^{II} and Pt^{II}, Cu^I, and Zn^{II} catalysts display high activity. Promising but somewhat neglected is catalysis of hydroamination reactions with Ni^0 and Ag^I complexes. Note that some catalysts were identified by rapid screening (Figure 29).[254,255] Gold precatalysts with oxidation state Au^I and Au^{III} were employed; the active oxidation state appears to be Au^I.[336] Pd^0 catalyzes the reaction in the presence of acid and is probably oxidized to Pd^{II} prior to the reaction.[323] For Cu^{II} catalysts, an induction period is usually observed, whereas catalysis with Cu^I follows an approximate first-order kinetics without an induction period.[256] *In situ* EPR spectroscopic measurements confirmed that Cu^{II} is slowly reduced to Cu^I in the presence of substrate.[256] Further, Re^I, Fe^{III}, and Bi^{III} in combination with Cu^I display some activity in hydroamination.

In early studies, Cd^{II} and Hg^{II} were employed as catalysts, but their use conflicts with the move toward green chemistry. However, the mercuriation/demercuriation approach enables some particularly interesting transformations and will be discussed in detail (*vide infra*). In nearly all transition metal

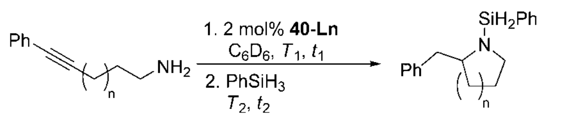
Table 51. One-Pot Sequential Anti-Markovnikov Hydroamination of Terminal Alkynes/Nucleophilic Alkyllithium Addition[246]



Entry	R^1	R^2Li	Product	t_1 / h	t_2 / h	Yield / %
1	^nBu	^nBuLi		2	3	63
2	$PhCH_2$	^nBuLi		24	15	66
3	^nHex	PhLi		2	24	78
4		PhLi		24	24	70
5	Me_2NCH_2	^nBuLi		2	3	49
6	$HC{\equiv}C(CH_2)_4$[a]	^nBuLi		2	3	50

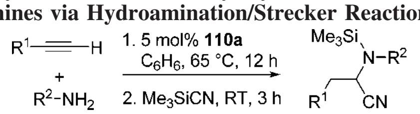
[a] Ratio amine/alkyne = 4:1 and *n*-BuLi/alkyne = 4:1.

Scheme 53. Rare-Earth Metal Catalyzed Intramolecular Hydroamination/Hydrosilylation[136]



Ln	n	T_1/T_2	t_1/t_2	Yield/%
Y	1	60/60	4h/4h	99
La	1	60/RT	4h/4h	70
Y	2	100/RT	16h/4h	99
La	2	60/RT	4h/4h	99

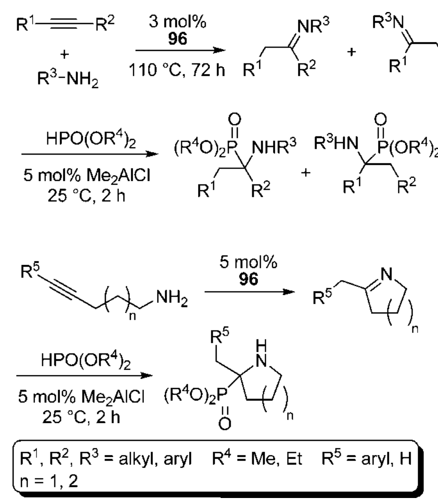
Table 52. Synthesis of *N*-Trimethylsilyl-Protected α-Cyanoamines via Hydroamination/Strecker Reaction[248]



entry	R^1	R^2	yield, %
1	^nBu	Bn	(quant.)[a]
2	Ph	Bn	90
3	Bn	Bn	98
4	Bn	^iPr	86

[a] Conversion.

Scheme 54. One-Pot Sequential Hydroamination/ Hydrophosphonylation[247]



catalyzed hydroaminations, the addition of $H{-}NR_2$ to alkenes and alkynes proceeds with Markovnikov regioselectivity. Redox couples, such as the Rh^I/Rh^{III}, Ir^I/Ir^{III}, and Pd^0/Pd^{II} pairs might be important for reactions that proceed with anti-Markovnikov regioselectivity although pathways via allyl complexes or metal hydrides appear also feasible (*vide infra*). Generally, most late transition metal catalysts for hydroamination provide good functional group tolerance and low oxygen and moisture sensitivity.[257]

4.1. Mechanistic Aspects

Various mechanistic models have been suggested for hydroamination with late transition metals. These can be classified into four categories according to the step, in which the regioselectivity is determined: (i) nucleophilic attack on a coordinated alkene or alkyne, (ii) nucleophilic attack on allylic complexes, (iii) insertion of the alkene/alkyne into a metal−hydride bond, and (iv) oxidative addition of the amine, followed by insertion into the metal−amide bond. While categories i, ii, and iii involve activation of the CC multiple bond, pathway iv entails activation of the amine.

4.1.1. Nucleophilic Attack on Coordinated Alkene/Alkyne

There is overwhelming evidence that the reaction pathway via nucleophilic attack on a coordinated alkene or alkyne might be accurate for many transition metal catalyzed hydroamination reactions. The mechanism was initially proposed by Müller et al. for the palladium-catalyzed cyclization of 6-aminohex-1-yne (Scheme 59)[370] based on preceding suggestions by Venanzi et al. for the cyclization of aminoalkenes using stoichiometric amounts of PtX_4^{2-}, $X^- = Cl^-, Br^-$,[372] and by Trogler et al. for the addition of aniline to the activated alkene bond of acrylonitrile using $[Pd(PR_3)_2(alkyl)_2]$ as precatalyst.[373]

The reaction pathway appears equally feasible for alkenes and alkynes. The key step of this mechanistic model is the activation of the alkene/alkyne by coordination to a Lewis acidic metal center (Scheme 59, step A), which renders it

Scheme 55. Oxidative and Reductive Deprotection of *N*-(4-Methoxyphenyl)- and *N*-Benzhydryl-Substituted α-Amino Phosphonates[247]

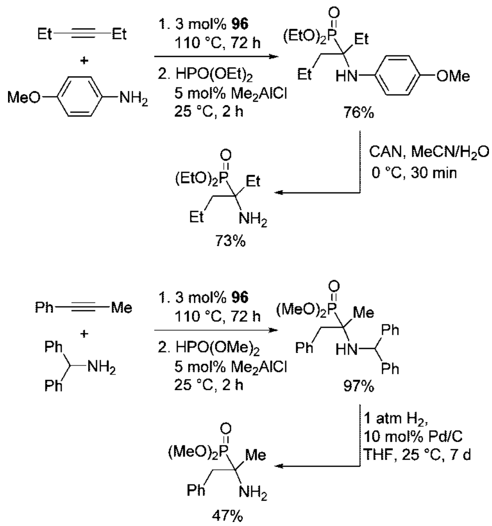
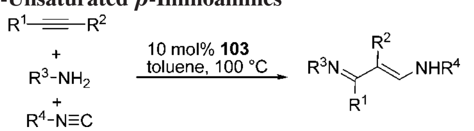


Table 53. Titanium-Catalyzed Three-Component Coupling To Give α,β-Unsaturated β-Iminoamines[249]



R^1	R^2	R^3	R^4	*t*, h	yield, %
^{n}Bu	H	Ph	$CMe_2CH_2CMe_3$	48	83
Me	Ph	Ph	^{t}Bu	48	72
H	Ph	Cy	^{t}Bu	24	78

Scheme 56. Proposed Mechanism for Three-Component Coupling

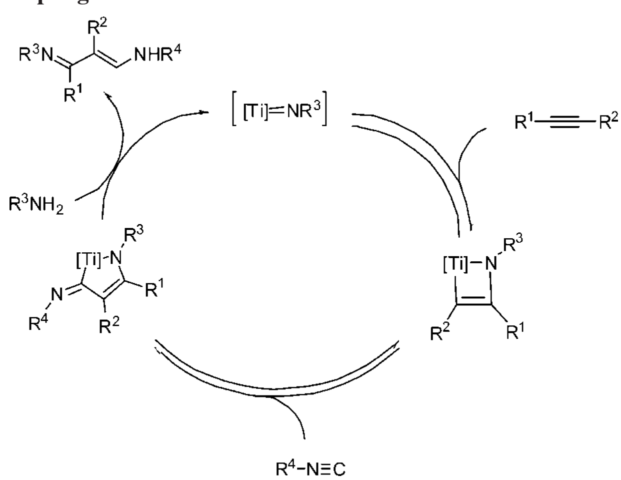
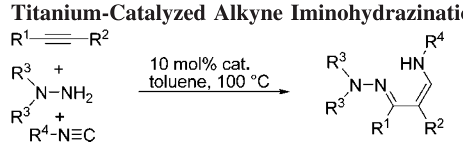


Table 54. Titanium-Catalyzed Alkyne Iminohydrazination[250]



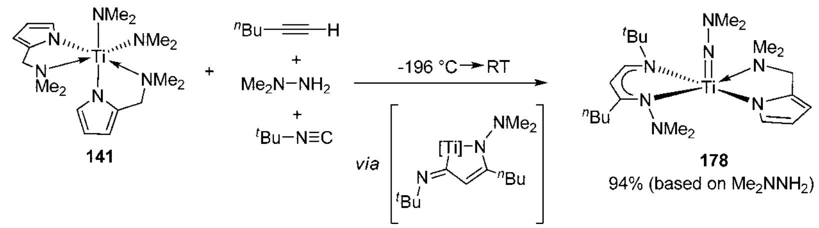
R^1	R^2	R^3	R^4	catalyst	*t*, h	yield, %
^{n}Bu	H	Me	^{t}Bu	**141**	16	63
^{n}Bu	H	Me	Cy	**141**	16	73
H	Ph	Me	^{t}Bu	**177**	16	43

susceptible to nucleophilic attack of the lone electron pair of the amine nitrogen atom (step B). Subsequent protolytic cleavage of the metal−carbon bond in the zwitterionic 2-ammonio-alkyl/alkenyl complex provides the product amine/enamine (step C), which desorbs from the coordination sphere of the metal. In the case that ammonia or a primary amine was added to an alkyne, the resulting enamine isomerizes subsequently to the corresponding imine (step D). As suggested by ab initio DFT studies[374] and experimental evidence,[315,320] the rate-determining step of such a catalytic cycle would be the cleavage of the metal−carbon bond. Thus, the ammonioalkenyl palladium complex **179** (Scheme 60) was identified as the most abundant species during the cyclization of 6-aminohex-1-yne indicating that this complex is either a resting state of the catalyst or, more likely, that the subsequent step, protolytic cleavage of the Pd−C bond is the rate-determining step in the catalytic cycle.[366] Several groups have reported on experimental findings supporting this mechanism for iridium,[277] palladium,[323,320] platinum,[302,310,315] copper,[256] and gold[347] catalysts.

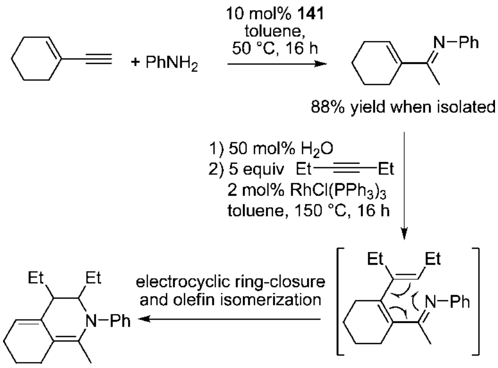
A striking feature of hydroamination with late transition metals is that the reaction is performed frequently in the presence of a Brønsted acid as cocatalyst (see Table 55). In the presence of the amine substrate, the actual acidity in the reaction mixture is determined by the acid strength of the ammonium salt. The Brønsted acid might be involved in three steps of the catalytic cycle:[365,367] (i) As consequence of formation of the ammonium salt in the reaction mixture, the probability of initial coordination of the amine group is reduced, and the alkene/alkyne is more likely to coordinate (*vide infra*). (ii) Protolytic cleavage of the metal−carbon bond probably requires an external source of protons, because intramolecular 1,3-proton shifts are orbitally forbidden. In this respect, the rate of the forward reaction critically depends on the pK_a of the ammonium salt.[315] Currently, it is not clear whether protonolysis of the metal−alkyl/alkenyl bond proceeds via direct protonation of the α-carbon atom or C−H elimination preceded by protonation of the electron-rich metal center (path A and B, respectively; compare Scheme 61 for the platinum-catalyzed hydroamination of ethene). DFT calculations indicate that group 10 catalysts preferentially react via path A, while group 9 catalysts are inclined to path B.[374] Both pathways require that the aminoalkyl/alkenyl complex undergoes protonolysis faster than β-hydrogen elimination, which occurs in the related Wacker oxidation. (iii) In case of alkyne hydroamination, isomerization of the enamine to the corresponding imine[321] has a similar rate as the hydroamination reaction.[369] Accelerated isomerization in acidic media might avoid product inhibition by the enamine.

The choice of the amine is a critical feature of hydroamination with late transition metal complexes. Strongly nucleophilic amines coordinate tightly to the metal center, thus preventing competitive binding of the alkene/alkyne. The N-bound metal−amine complex is a well-characterized example of unproductive substrate binding (catalyst resting state, substrate poisoning).[269,277,375] Reaction rates are generally higher, the lower the basicity of the amine nucleophile is.[302] An example is the correlation between the rate of reaction and the pK_a of para-substituted anilines.[376] For iridium-catalyzed intramolecular hydroamination (Scheme 62), a switch in the kinetic regime from zero-order kinetics to first-order kinetics was observed when 1-amino-2-pent-1-ylbenzene (**180**) was replaced by 1-phenylamino-2-pent-1-ylbenzene (**181**).[277] This is consistent with saturation behavior and rate-determining reaction of **181** with steady-state concentration of the reactive complex. In competitive

Scheme 57



Scheme 58. Tandem Hydroamination/C,H-Activation/Alkyne Insertion Catalysis[252]



hydroamination, **181** was consumed four times faster than **180**, which can be explained by the lower basicity of **181**. The more facile conversion of weakly basic amines is reflected by the widespread use of anilines, carboxamides, sulfonamides, and other protected amines in hydroamination (see remarks in Table 55).

The key step of the reaction cycle is the nucleophilic attack of the amine lone electron pair on the coordinated alkene/alkyne. The regioselectivity of the reaction is determined in this step,[377] which is kinetically controlled at usual reaction temperatures.[5] Nucleophilic attack typically occurs at the α-carbon of the coordinated alkene/alkyne. This selectivity contrasts with that of rhodium-catalyzed, anti-Markovnikov oxidative amination,[378] which may occur by attack of the amine at the β-carbon atom, although in this case amine activation via oxidative addition appears more likely (*vide infra*). In the case of vinylarene hydroamination, significant positive charge on the benzylic carbon atom accounts for the high Markovnikov selectivity.[303] For palladium[377] and platinum,[303] the nucleophilic attack proceeds as an outer-sphere attack. Likewise, sulfonamide attacks from the opposite face of a gold(I)-bound olefin to give the trans addition product after protonolysis of the resulting $Au^{I}-C$ bond, as proven in a deuterium labeling study (Scheme 63).[347] In some instances, the zwitterionic metal complex was isolated[315] or identified *in situ*.[320]

The counterion associated with the mostly cationic catalysts has a significant effect on the rate of reaction. It is striking that cationic complexes with TfO^- as counteranion are by far most frequently employed. In general, increased catalytic activity of the late transition metal complexes is observed with bulkier and less coordinating anions, for example, $TfO^- > Tfa^-$ (Pd-catalysts),[323] $Ts^- \approx TfO^- \gg ClO_4^- \approx BF_4^- \approx Tfa^- \approx PF_6^- \approx NO_3^- \gg Bz^- > Ac^-$ (Ag and Pd catalysts),[370] $BPh_4^- > PF_6^- > BF_4^-$ (Rh-catalysts),[279] $ClO_4^- \approx TfO^- > BF_4^- > PF_6^- > NTf_2^- > SbF_6^- \gg CF_3CO_2^-$, NO_3^- (hydroamination of dienes with Au catalysts).[345] Two explanations for the strong anion effect appear likely: (i) anion and alkene/alkyne compete for binding to the free coordination site; (ii) strong anion/cation interactions and long-lived association between cations and anions (ion pairing) direct free anions to a remote site close to the bidentate N−N[279] or P−P ligand.[379] Polarization of the delocalized electron system of the ligand might lead to reduced positive charge at the metal center destabilizing the ammonioalkyl/alkenyl metal complex and facilitating protolytic cleavage of the metal−carbon bond.

Note that a single coordination site is required for the reaction sequence. Thus, complexes with strongly bound tridentate ligands (see Table 55 and ref 80 for acrylic acid derivatives) are highly efficient catalysts for hydroamination. These tridentate ligands prevent the ammonioalkyl/alkenyl metal complex from undergoing β-hydride elimination as an alternative reaction pathway.[299] A ligand with strong trans effect opposite of the coordination site for substrate binding appears beneficial.[320] Further, well-known Lewis acids, such as Zn^{2+},[353−357] are very active catalysts. In this case, a mechanism involving change in oxidation state (*vide infra*) can be ruled out.

The actual mechanism depends on the choice of the metal complex, the substrate, and the reaction conditions. In consequence, several variants of the reaction mechanism via nucleophilic attack have been described. For a dimeric ruthenium complex, the proposed reaction sequence is initiated by protonation of a μ-coordinated alkyne, followed by nucleophilic attack of the amine, deprotonation of the ammonioalkene complex and dissociation of the product enamine from the coordination sphere.[380]

4.1.2. Nucleophilic Attack on Allylic Complexes

A mechanism based on nucleophilic attack on allylic complexes of late transition metals was proposed for the hydroamination of allenes (Pd catalysts [326,328,329]), dienes (Pd[255,257,319] and Ni catalysts[254]), and trienes (Pd catalysts[296]). For alkynes with a CH group in the α-position, preceding metal-catalyzed isomerization to the corresponding allenes has been suggested (Pd catalysts [311,325]). Note that this mechanism has been proposed also for the Markovnikov addition of amines to vinylarenes using Pd catalysts.[257,308,312,318] A similar mechanism has been suggested for the anti-Markovnikov addition with Ru catalysts,[265,267] while for the anti-Markovnikov addition with Rh catalysts, a reaction sequence involving oxidative addition of the amine was proposed (*vide infra*).[276,282,286,287]

The mechanistic model (Scheme 64) involves initial formation of a metal hydride, which can hydrometallate the allene or diene giving a π-allyl complex. Nucleophilic attack of the amine on the carbon at the 1- or 3-position provides an ammonia alkenyl complex. The later step is endothermic[79,381] but is followed by deprotonation of the ammonium, which renders the overall process exothermic. The last step in the reaction cycle is the displacement of the allylic amine by the next allene or diene. Note that in the absence of acid, a

Table 55. Survey of Late Transition Metal Complexes Known as Homogeneous Catalysts for Hydroamination Reactions (According to Metal, in Chronological Order)

ref	catalyst	inter molecular	intra molecular	substrates: alkenes	alkynes	dienes	allenes	comment
				Ruthenium				
258	$[Ru(CO)_2(PPh_3)(PPh_2C_6H_5C_2H_3)]/NH_4PF_6$	X			X			
259	$[Ru_3(CO)_{12}]/NH_4PF_6$		X		X			one-pot indole synthesis
260	$[Ru_3(CO)_{12}]$ or CuI		X		X			one-pot synthesis of amidines
261	$[Ru_3(CO)_{12}]/NH_4PF_6$	X			X			indene derivatives
262,263	$[Ru_3(CO)_{12}]/HBF_4\ OEt_2$ or $[RuH(PCy_3)_2(CO)(CH_3CN)_2]BF_4$	X			X			hydroamination and C−H bond activation/cyclization protocol of arylamines and alkynes
264	$[Ru{=}CHCH{=}C(CH_3)_2(Cl)(PCy_3)_2(CO)]BF_4$	X		X		X		reaction of aromatic amines with ethene or dienes
265	$[Ru(2\text{-methylallyl})_2(P{-}P)]/TfOH$	X		X				anti-Markovnikov addition
266	$[Ru(H)Cl(CO)(PPh_3)_3]$	X		X				
267	$[Ru(P{-}P)(2\text{-methylallyl})_2]$	X		X				anti-Markovnikov addition
268	$[Ru(\eta^6\text{-cot})(dmfm)_2]$ or $[Ru_3(CO)_{12}]$		X		X			
269	$[RuCp(C_2H_4)(PPh_3)_2]BF_4$	X		X				Ru promoted addition; mechanistic study
270	$[Ru_3(CO)_{12}]/NH_4PF_6$	X			X			
271	$[Ru_3(CO)_{12}]$	X			X			
				Rhodium and Iridium				
272	$[Rh(COD)2]BF4/P{-}P$, P−N or PR_3		X	X				
273	$[Ir(P{-}N)(cod)]BPh_4$		X		X			
274	$[Ir(P{-}N)(CO)HCl]/NaBAr_4$	X	X		X			synthesis of indoles
275	$[Ir(pta)_3(cod)]Cl$		X		X			in water
276	$[Rh(P{-}P)(cod)]BF_4$		X	X				anti-Markovnikov addition
277	$[IrH(PPh_3)_2(CH_3COCH_3)(C_6H_4COCH_3]$		X		X			synthesis of indoles
278	$[M(P{-}NHC)(cod)]BPh_4$, M = Rh, Ir		X		X			
279-281	$[M(N{-}N)(CO)_2]X$, M = Rh, Ir		X		X			
244	$[Ir(N{-}N)(CO)_2]BPh_4$		X		X			tandem hydroamination/hydrosilylation
282	$[Rh(cod)(P{-}P)]BF_4$	X		X				anti-Markovnikov addition
283	$[Rh(cod)_2]BF_4/3\ PCy_3$	X			X			
284	$[IrCp(P{-}P)]$; P−P = MeO-biphep	X		X				enantioselective
86	$[Rh(cod)_2]BF_4/4\ PPh_3$	X		X				hydroamination as side reaction
285	$[Rh(N{-}N)(CO)_2]BPh_4$,		X		X			
286,287	$[Rh(cod)_2]BF_4/2\ PPh_3$	X		X				hydroamination and oxidative amination as parallel reactions, anti-Markovnikov addition
288	$[IrCl(P{-}P)]_2/(N(P(NMe_2)_3)_2)F$; P−P = Josiphos	X		X				use of planar-chiral diphosphines
289,290	$[RhCl(PEt_3)_2]_2/LiNHPh$	X		X				hydroamination and hydroarylation as parallel reactions
291	$[RhCl(PEt_3)_2]_2/LiNHPh$	X		X				hydroamination and oxidative amination as parallel reactions
292	$[IrCl(P{-}P)]$/phosphazenium fluoride	X		X				fluoride effect
				Palladium and Platinum				
293	$[(Cp^*Mo)_3(\mu\text{-}S)_4Pd(dba)]^+PF_6^-$		X		X			
294	$[Pd(P{-}P)(CH_3CN)_2](TfO)_2$; P−P = BINAP, SEGPHOS	X		X				
295	$[Pd(NHC)(NCCH_3)](PF_6)_2$			X				hydroamination of cyanoalkenes
3	$[Pd(P{-}P)](TfO)_2/TfOH$; P−P = ^{t}BuXantphos	X		X				thermodynamic data
296	$[Pd(P{-}P)](Tfa)_2/PhCOOH$; P−P = Xantphos	X				X		synthesis of azabicyclic tropenes
297	$[Pd(P{-}P)(dba)]/PhCOOH$; P−P = RENORPHOS		X		X			enantioselective allylic amination of alkynes
298	$PtBr_2/(PhNH_3)_2SO_4$	X			X			
299	$[Pd(P{-}N{-}P)](BF_4)_2/Cu(TfO)_2$		X	X				protected aminoalkenes
257	$[Pd(P{-}P)](TfO)_2$; P−P = Xantphos	X		X		X		phosphine with large bite angle, added acid unfavorable
300,301	*cis*-$[MX_2(pta)_2]$; M = Pd, Pt; X = Cl, Br, I		X		X			highest rate in polar solvents (D_2O, CD_3OD)
302	$[Pt(cod)](TfO)_2$	X		X	X			sulfonamides and anilines
303	$[PtCl_2(PAr_3)_2]$	X		X				reaction of carboxamides with vinylarenes
304	$PtBr_2/Bu_4PBr/TfOH$	X		X				reaction of aniline with 1-hexene
305	$[Pd(PPh_3)_4]$/benzoic acid		X		X			diastereoselective cyclization
306	$[Pd(dppe)(H_2O)_2](TfO)_2$	X			X			anilines
307	$[PtCl_2(PPh_3)_2]$		X	X				
308	$[Pd(dppf)](CF_3CO_2)_2/TfOH$	X		X				kinetic isotope effect determined
309	$[PtCl_2(PAr_3)_2]$	X		X				carboxamides
310	$PtBr_2/^nBuN_4Br/TfOH$	X		X				biphasic system
311	$[Pd(H)(PhCO_2)(P{-}P)]$; P−P = Renorphos		X		X			enantioselective allylic amination of alkynes
312	$[Pd(CF_3CO_2)_2(dppf)]/TfOH$	X		X				
82	$[Pd(P{-}P)(CH_3CN)(H_2O)](TfO)_2$	X		X				air- and moisture-stable complexes
313	$[Pd(PPh_3)_4]/C_6H_5CO_2H$	X	X		X			
314	$Pd(NO_3)_2$/*o*-aminophenol	X			X			rate enhancement in presence of *o*-aminophenol
315	$[Pt(P{-}C{-}P)]TfO$	X		X				mechanistic study
316,317	$[PdCl_2(CH_3CN)_2]$	X			X			Pd promoted CP-heterocyclization
318	$[Pd(P{-}P)](TfO)_2/TfOH$	X		X				mechanistic study
319	$[Pd(\eta^3\text{-allyl})(P{-}P)]$; P−P = diphosphinidenecyclobutene	X				X		1,2- and 1,4-addition
320	$[Pd(triphos)](TfO)_2/TfOH$		X		X			mechanistic study
321	$K_2[Pd(SCN)_4]$	X		X				
255	$[Pd(PPh_3)_4]/CF_3CO_2H$	X				X		colorimetric assay for rapid catalyst screening
322	PdI_2		X	X				
323	$Pd(CF_3CO_2)_2/dppf/TfOH$	X		X				
324	*trans*-$[PtCl_2(coe)_2]$		X	X				Pt mediated reaction
325	$[Pd(PPh_3)_4]/C_6H_5CO_2H$	X	X		X			
326	$[PdCl(\eta^3\text{-}C_3H_5)]_2/dppf/AcOH$		X				X	
327	$[PdCl(\eta^3\text{-}C_3H_5)]_2/dppf/AcOH$	X			X		X	stereoselective double hydroamination of conjugated enynes
328	$[Pd_2(dba)_3]\cdot CHCl_3/dppf/AcOH$	X					X	
329	$Pd(OAc)_2/2\ PPh_3/Et_3NH^+I^-$	X					X	hydroamination and telomerization as parallel reactions

Table 55. Continued

ref	catalyst	inter-molecular	intra-molecular	substrates: alkenes	alkynes	dienes	allenes	comment
				Copper				
330	[Cu(NHC)(NHPh)]	X		X				electron-deficient alkenes
331	[Cu(P−P)](TfO)$_2$; P−P = BINAP	X		X		X		protected amine (sulfonamide)
				Gold				
332	Au^{III} supported on MCM-41	X		X	X			bifunctional Au−Sn catalyst
333	[Au$_2$(P−P)(nb)]; nb, nitrobenzoate		X				X	
334	Au(TfO)$_3$	X	X		X			catalyst generated *in situ*
335	AuCl$_3$		X		X			synthesis of oxazoles
336	AuCl		X				X	synthesis of 3-pyrrolines
337	[Au(NHC)]TfO		X	X				cyclization of *N*-alkenyl ureas
338	[Au(P(^{t}Bu)$_2$(*o*-biphenyl))]TfO		X	X				
339	[Au(PR$_3$)]X, X = NTf$_2^-$, BF$_4^-$, SbF$_6^-$		X		X			cyclization of imidates
340	[Au(PR$_3$)]TfO, PR$_3$, P(*t*Bu)$_2$(*o*-biphenyl)		X				X	cyclization of *N*-allenyl carbamates
341	[Au(PR$_3$)]TfO		X	X				sulfonamides and benzamides
342	AuCl		X				X	chirality transfer
343	AuBr$_3$	X					X	chirality transfer
344	[Au(PR$_3$)]TfO, PR$_3$, P(*t*Bu)$_2$(*o*-biphenyl)		X	X				alkenyl carbamates
345	[Au(PPh$_3$)]X, X = TfO$^-$, ClO$_4^-$	X				X		anion effect
346	AuCl$_3$		X		X			synthesis of isoindoles
347	[Au(PPh$_3$)]TfO	X	X	X				hydroamination of tosylated aminoalkenes
348	[Au(tpp)Cl]; tpp, porphyrin	X			X			
349	[Au(CH$_3$)(PPh$_3$)]/heteropoly acid or TfOH	X			X			
				Zinc				
350	ZnCl$_2$ or Zn(OTf)$_2$	X			X			hydrohydrazination for domino synthesis of indoles
351	[Zn((^{i}Pr)$_2$ATI)Me]		X	X	X			
352	[Zn((Cy)$_2$ATI)Me]		X	X				synthesis of pyrrolidines
353	[Zn((R)$_2$ATI)Me], [Zn((R)$_2$ATI)$_2$]		X	X				exploratory study with aminotroponiminate zinc complexes
354	[Zn(^{i}PrAt)Alkyl]$_2$		X	X	X			terminal aminoalkenes and alkynes
355	Zn(TfO)$_2$		X		X			continuous operation of process
356	Zn(TfO)$_2$/TfOH		X		X			
357	Zn(TfO)$_2$		X		X			comparison of homogeneous and heterogeneous catalysts
				Multiple or Other Metals				
358	Ph(CH$_3$)$_2$PAuCl/Ag-(*R*)-phosphate		X				X	counterion-mediated enantioselective hydroamination
359	AgX, Zn(TfO)$_2$ X = TfO$^-$, SbF$_6^-$, NO$_3^-$	X			X			comparison of Lewis acids, hydroamination with pyrazole
360	Pd(Ac)$_2$/imidazolium chloride, CuI/KO^{t}Bu		X		X			
361	FeCl$_3$		X		X			cyclization of tosylamides
362	Bi(TfO)$_3$/[Cu(CH$_3$CN)$_4$]PF$_6$	X				X		
363	*fac*-[ReBr(CO)$_3$py$_2$]		X		X			
364	AgNO$_3$	X			X			synthesis of pyrroles
365	[Pd(triphos)](TfO)$_2$, Zn(TfO)$_2$ or [Cu(CH$_3$CN)$_4$]PF$_6$		X		X			kinetic study
366,367	[Pd(triphos)](TfO)$_2$, Zn(TfO)$_2$, [Cu(CH$_3$CN)$_4$]PF$_6$ or [Rh(nor)$_2$]ClO$_4$		X	X	X			TfOH as cocatalyst, exploration of the role of protons
254	[Ni(cod)$_2$]/dppf/TfOH or [PdCl(*π*-allyl)]$_2$/dppf/TfOH	X				X		mostly 1,2-addition providing 3-amino-alkenes; colorimetric assay for rapid catalyst screening
368	Zn(TfO)$_2$, [Cu(CH$_3$CN)$_4$]PF$_6$, [Rh(nor)$_2$]ClO$_4$		X		X			comparison of homogeneous and heterogeneous catalysts
369	[Pd(CH$_3$CN)$_4$](BF$_4$)$_2$, [Cu(CH$_3$CN)$_4$]PF$_6$, [Pd(triphos)](TfO)$_2$, Zn(TfO)$_2$ *		X		X			kinetic study, comparison of homogeneous and heterogeneous catalysts
253,370	[Re(CO)$_5$(H$_2$O)], [Pd(triphos)](TfO)$_2$, Zn(TfO)$_2$, or [Cu(CH$_3$CN)$_4$]PF$_6$		X		X			screening of various complexes, mechanistic study, description of anion effect
371	[Rh(cod)(P−P)]BF$_4$, [Pd(CH$_3$CN)$_4$](BF$_4$)$_2$, AgBF$_4$, AuCl$_3$, [Ir(cod)(PCy$_3$)(py)]PF$_6$;[a] P−P = dipamp		X		X			Screening of various complexes

[a] In order of decreasing catalytic activity.

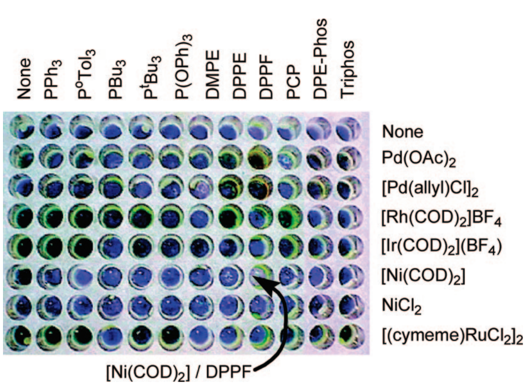
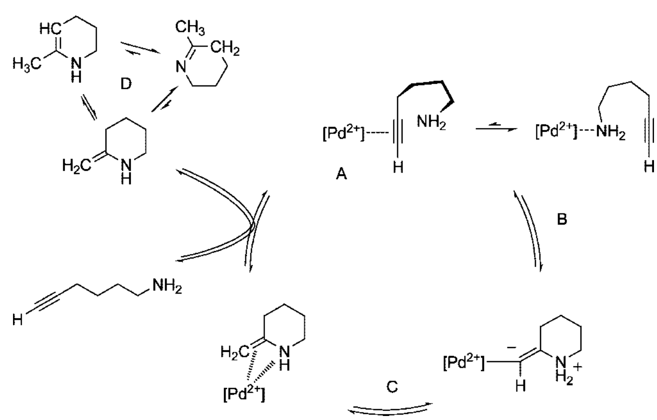
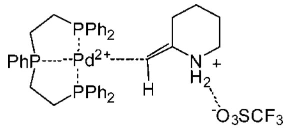


Figure 29. Evaluation of catalysts for the addition of morpholine to cyclohexadiene, visualized by staining with soldium nitroferricyanide(III) dehydrate and acetaldehyde.[254] Lighter colors indicate higher conversions.

Scheme 59

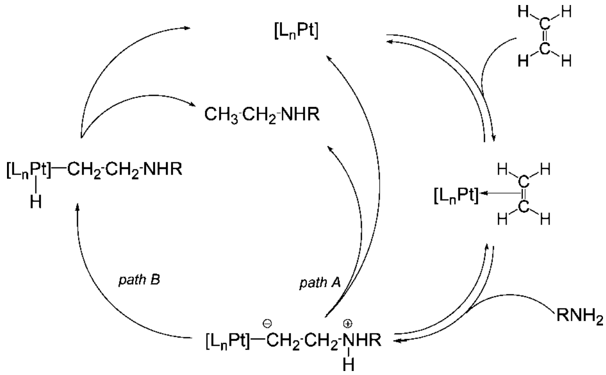


Scheme 60



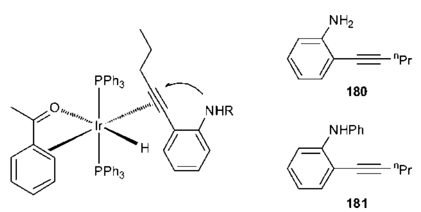
179

Scheme 61[a]

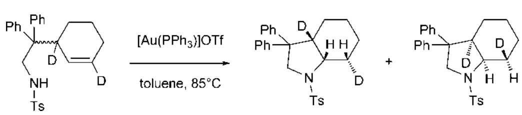


[a] R = Ar;[310] R = C(O)Ar.[309]

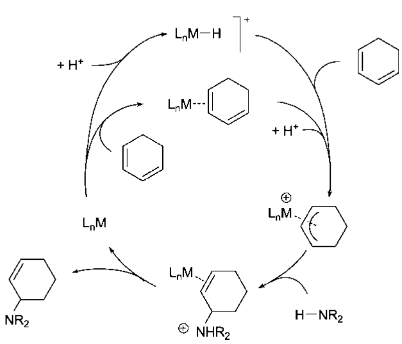
Scheme 62



Scheme 63



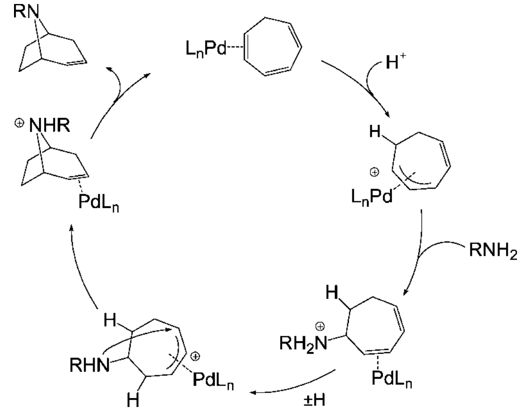
Scheme 64



reaction sequence with η^2-coordination of the diene, reaction with amine, and formation of a β-aminoallyl complex, followed by proton shift and desorption of the product, appears more likely.[255] Variants of these sequences have also been proposed.[450] For addition of primary amines to trienes, intermolecular reaction can be followed by intramolecular ring closure (Scheme 65).[296]

The initiation step for the mechanistic cycle remains ambiguous (Scheme 64). With late transition metals in low oxidation state, formation of a metal hydride by direct protonation of the metal center appears feasible. In case of acids with coordinating anions, this process is better described as oxidative addition of H−X to the metal center.

Scheme 65



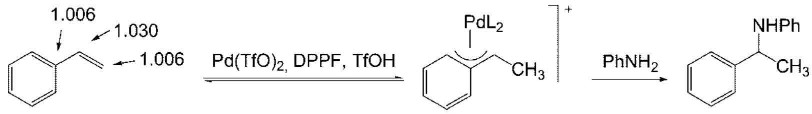
Reaction of the metal hydride with the substrate provides the η^3-allyl complex. The reverse order of protonation of an η^2-alkenyl complex has been suggested for vinylarenes[287] and trienes.[296] The η^3-allyl complexes can be isolated and structurally characterized, and their reactivity is well understood.[287,318,319,382,383] Note that substituted allyl groups can be in syn or anti conformation, which interconvert readily by a η^3-η^1-η^3 mechanism.[287]

Repeatedly, η^3-allyl complexes were identified as the major species during hydroamination indicating that the nucleophilic attack is rate-determining.[254,287,318] Bidentate phosphines with large bite angle destabilize the η^3-allyl complexes. Thus, increase in the rate of nucleophilic attack with increasing bite angle was observed in case of palladium benzyl complexes but not for symmetrical allyl complexes.[287] The nucleophilic attack of amine on η^3-allyl complexes is slower for electron-poor and sterically demanding amines.[287] A substantial kinetic isotope effect was observed during styrene conversion at the benzylic α-carbon atom (Scheme 66)[308] indicating a major σ-bonding change at this carbon during the first irreversible step between free substrate and product. These data suggest that the regioselectivity is determined during the nucleophilic attack of amine and not during the (reversible) formation [254,312] of the η^3-allyl complex. For symmetric allyl complexes, the 1,2 and 1,4 addition are equally likely (Scheme 67), which has been confirmed by deuterium labeling experiments for the reaction between cyclohexadiene and *N*-benzylmethylamine.[254]

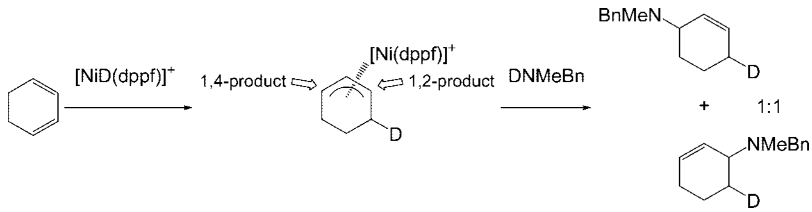
The formation of the C−N bond could be by external attack of amine on the η^3-allyl complex, or it could occur by coordination of amine to the metal center and reductive elimination. With enantio- and diastereomerically pure [Pd(η^3-(*R*)-Tol-BINAP)(1-(2-naphthyl)ethyl)](OTf), predominantly the (*R*)-*N*-1-(2-naphtyl)ethylaniline was obtained consistent with external nucleophilic attack (Scheme 68).[318] However, with excess substrate, the enantioselectivity was opposite indicating that the minor diastereomer produced most of the product. With respect to the overall stereochemistry, the reaction proceeds under retention of the configuration as shown by evaluating the diastereoselectivity for exchange of amines with allylic amines for the catalyst system [Ni(cod)$_2$]/dppf/TfaH (Scheme 69).[254]

For the anti-Markovnikov addition, which was observed with some ruthenium complexes,[267] Michael-type addition to the η^6-arene complex was suggested (Scheme 70).[265] By coordination of the neighboring aryl group, the vinyl group is activated enabling nucleophilic attack of the amine at the β-carbon atom. The product is released by arene exchange. Nucleophilic attack and arene exchange have similar rates.

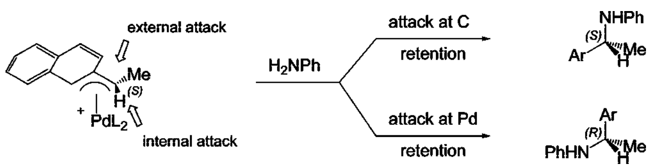
Scheme 66



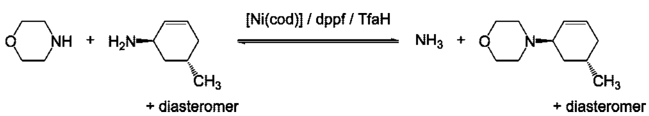
Scheme 67



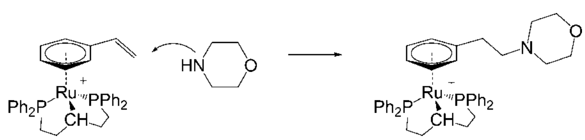
Scheme 68



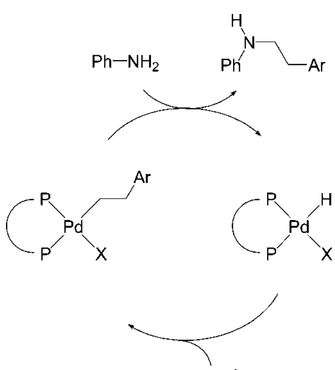
Scheme 69



Scheme 70



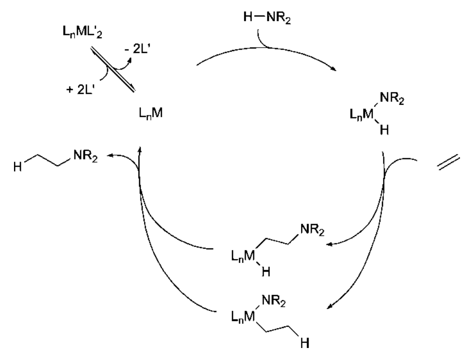
Scheme 71



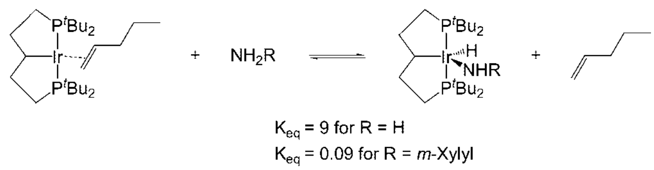
4.1.3. Insertion into the M—H Bond of Metal Hydrides

Formation of a hydride, for example, by initial reduction or protonation of the metal center, insertion of the alkene in the M—H bond, and reaction with the amine, has been invoked for catalysis with palladium complexes (Scheme 71).[323,384] The product distribution is determined by the regioselectivity of the insertion step. In this respect, this reaction pathway has been claimed for formation of the Markovnikov as well as anti-Markovnikov product. However, it appears likely that the steric demand of a large substituent on the alkene allows only for formation of the 2-substitued alkyl complex, whereas steric conflicts would arise between the substituent on the alkene and the phosphine ligand during formation of the 1-substituted palladium ethyl complex.

Scheme 72



Scheme 73



4.1.4. Oxidative Addition

Activation of the amine by oxidative addition to a coordinatively unsaturated late transition metal in low oxidation state has been discussed often as a potential pathway for hydroamination (Scheme 72). This pathway might be effective for the redox couples Ru^0/Ru^{II},[385] Rh^I/Rh^{III},[286,287,378] Ir^I/Ir^{III},[386] Pd^0/Pd^{II}, Pt^0/Pt^{II},[387–389] and Cu^I/Cu^{III}. The initiation step involves ligand dissociation and reduction to a low-valent catalytically active 14 or 16 e^- species. Oxidative addition of the amine provides a hydrido-amido complex. Subsequently, the alkene/alkyne inserts into the M—N or the M—H bond. Reductive elimination of the product regenerates the active low-valent metal species.

The energy profile of the hydroamination of ethyne with hydrido-bridged diplatinum complexes was explored in detail by Tsipis et al. (Figure 30).[387] Dissociation of a dinuclear precursor complex provides the 14 e^- platinum(II) complex $[PtH(NH_2)(PH_3)]$, which reacts with ethyne to the catalytically active species $[PtH(NH_2)(C_2H_2)(PH_3)]$. The ethyne binds trans to the NH_2 ligand and adopts a coplanar orientation with respect to the coordination plane of the Pt^{II} complex. Insertion of ethyne into the Pt—H bond proceeds with an activation barrier of 9.2 kcal/mol followed by coordination of a second alkyne to the empty coordination site. For reductive elimination, which provides the product, a high activation barrier of 27.8 kcal/mol was calculated. The catalytically active species is regenerated by oxidative

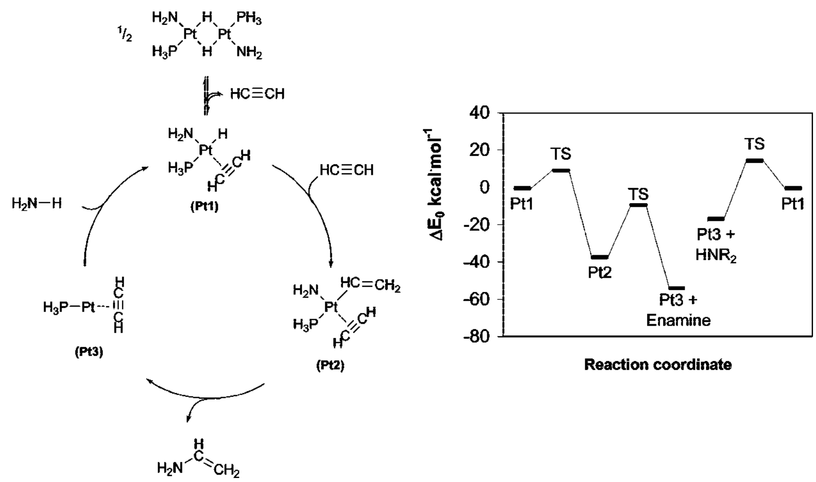
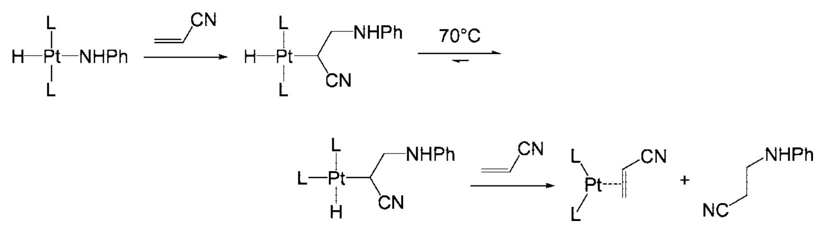
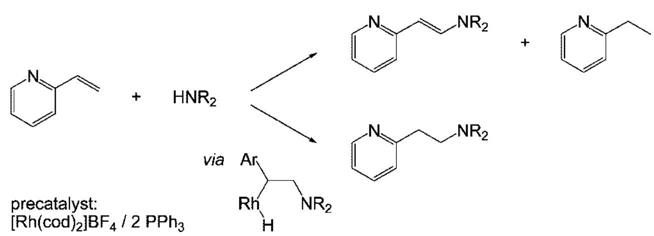


Figure 30. Reaction intermediates and energy diagram calculated for the platinum-catalyzed hydroamination of ethyne with ammonia.

Scheme 74



Scheme 75



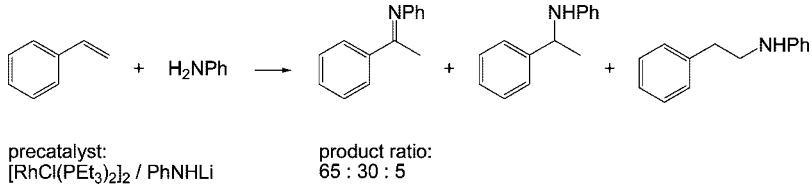
addition of H-NR_2, for which also a high activation energy of 28.5 kcal/mol was calculated. Thus, the theoretical study suggests that reductive elimination and oxidative addition are the limiting steps in the platinum-catalyzed hydroamination.

Oxidative addition of ammonia and 3,5-dimethylaniline has been reported for iridium complexes [Ir(PCP)(1-pentene)] with tridentate pincer ligands.[386] For ammonia, the reaction equilibrium is on the side of the oxidative addition product, while for 3,5-dimethylaniline, the alkene complex is favored (Scheme 73, K_{eq} determined at room temperature). Oxidative addition of aniline has been reported, for example, for $[Ru_3(CO)_{12}]$.[385] However, the rapid hydroamination reaction with Pd^{II} catalyst precursors without initiation phase and the lack of any observed oxidative addition of amines by Pd^0 or Pd^{II} complexes[323] suggests that an alternative mechanism operates for palladium catalysts (*vide supra*).

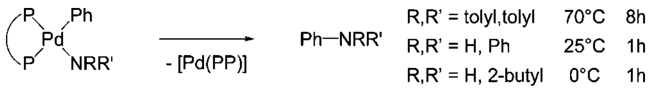
While insertion of the alkene/alkyne into the metal−hydride bond has been suggested by Tsipis, it seems unfavorable relative to insertion into the metal−nitrogen bond. Thus, it has been reported that hydrido-amido complexes $[MH(NR_2)L_n]$, M = Pd, Pt, prefer insertion of alkenes into the M−N bond.[388,389] In addition, reductive eliminations involving carbon−heteroatom bond formation are less common[390,391] and disfavored in comparison to C−H bond formation. Insertion of the alkene/alkyne into M−X requires that both ligands are mutually cis. Thus, the geometry of the hydrido-amido-alkene/alkyne complex determines whether insertion into the M−H or M−N bond occurs during hydroamination. Note that also the regioselectivity is determined during insertion of the alkene/alkyne into the metal−nitrogen or metal−hydrogen bond. For nonactivated alkenes/alkynes, this step is controlled by steric effects, while electronic effects control the regioselectivity in case of activated olefins. Insertion of the alkene/alkyne into the M−H bond with the larger substituent oriented towards the hydrogen atom affords the anti-Markovnikov product. In contrast, insertion into the M−N bond with the larger substituent close to the amide ligand provides the Markovnikov product. At present, there is only little experimental evidence concerning the regioselectivity. Acrylonitrile undergoes regioselective 1,2-insertion into the Pt−N bond of *cis*-$[PtH(NHPh)(PEt_3)_2]$, which converts to $[Pt(\eta^2\text{-}CH_2{=}CHCN)(PEt_3)_2]$ after heating to 70 °C (Scheme 74).[388,389] In the stoichiometric reaction, the anti-Markovnikov product is obtained as the exclusive product (>95%).

Beller et al. reported on the amination of 2- and 4-vinylpyridine with secondary amines (Scheme 75)[286] and the reaction of styrene with morpholine.[287] Either oxidative amination or hydroamination to yield the corresponding enamines or 2-aminoethylaromates occurred. In all cases, only the anti-Markovnikov products were obtained. The kinetic data suggest that the two products were formed in two parallel reactions. The key intermediate is most likely a 2-aminoethyl-hydrido complex formed by oxidative addition of the amine and insertion of the vinyl group. Alternatively, the 2-aminoethyl-hydrido complex might be formed by coordination of the vinyl group, nucleophilic attack of the amine, and proton transfer to the rhodium center (*vide supra*).[378] β-Hydride elimination (see also ref 374) provides the oxidative addition product generating a dihydride rhodium complex, which hydrogenates a vinylpyridine molecule to regenerate the active catalyst. Reductive elimination as alternative reaction pathway provides the hydroamination product (for analogous observations on aryl amide com-

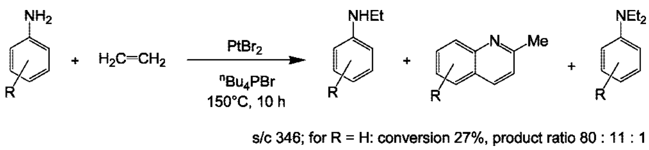
Scheme 76



Scheme 77



Scheme 78



plexes, see ref 391). Note that in the absence of phosphine the hydroamination product is formed exclusively. The regioselectivity observed with $[Rh(cod)]_2BF_4/2PPh_3$ contrasts with that obtained using $[RhCl(PEt_3)_2]_2/PhNHLi$ under basic reaction conditions. When styrene and aniline were converted with the latter catalyst system, the Markovnikov product of oxidative amination was obtained as main product (65%) besides both regioisomeric hydroamination products (Scheme 76).[291] This effect can be attributed to formation of close $[(R_3P)_2Rh(NHPh)_2]^-Li^+$ associates comprising a sterically crowded $Rh(\mu\text{-}N)_2Li$ metallacycle.[392]

The carbon−nitrogen bond-forming reductive elimination might proceed analogous to the elimination of arylsulfides from complexes $[Pd(SR)(Ar)(PR_3)_2]$.[390] Rate acceleration by electron-withdrawing substituents on the aryl group suggests a transition state resembling that of nucleophilic aromatic substitutions. The kinetic details of aryl-amines are consistent with reductive elimination from a four-dentate complex with prior isomerization to cis configuration as in Scheme 74.[391] Note that reductive elimination of arylamines becomes more facile the more electron-rich the amine is (Scheme 77).[391]

Although each single reaction step appears feasible, the reaction pathway to catalytic hydroamination via oxidative addition of amine remains ambiguous so far. For many active metal catalysts, the necessary change in oxidation states by ±2 is not accessible. The key to this reaction pathway is to balance the propensity of metal complexes for oxidative addition of $H{-}NR_2$ and reductive elimination of either R_2N−alkyl/alkenyl or H-(2-amino)alkyl/alkenyl. At the same time, the ligand sphere of the metal complexes must be highly flexible to allow for the appropriate geometry changes. Note that this reaction pathway might provide an opportunity to realize the anti-Markovnikov hydroamination of nonactivated alkenes/alkynes.

4.2. Catalysts and Scope of Reaction

4.2.1. Hydroamination of Ethene

The direct reaction of ethene with amines is of particular interest for the large-scale synthesis of ethylamines. However, all currently known hydroamination catalysts have insufficient activity for this reaction. Besides hydroamination of ethene with late transition metal complexes, catalysis with early transition metal complexes (*vide supra*), as well as strong alkali metal bases, was explored (*vide infra*). The stoichiometric reaction of secondary amines, such as diethylamine, on coordinated ethene in *cis*- or *trans*-$[Pt(C_2H_4)Cl_2L]$ has been known for a long time,[393–398] while reaction of piperidine with $[RhCl(C_2H_4)_2]_2$ leads to displacement of the ethene ligand providing *trans*-$[RhCl(C_2H_4)(C_5H_{10}NH)_2]$.[399] With stoichiometric use of ruthenium complexes, such as $[RuCl_2(PPh_3)_3]$, $[(\eta^6\text{-}C_6H_6)RuCl_2]_2$, or $[(\eta^5\text{-}C_5H_5)Ru(PPh_3)_2(C_2H_4)]^+BF_4^-$, the reaction between ethene and piperidine was mediated.[269]

Catalytic hydroamination of ethene with secondary amines was reported by Coulson in 1971 using Rh and Ir salts.[400] Subsequently only few catalytic systems based on rhodium,[289,290,401,402] and iridium[403] have been shown to exhibit some activity for the addition of amines to ethene. More recently, platinum salts were identified as potential catalysts. Platinum bromide, for example, gave turnover numbers up to 145 in the addition of ethene to aniline.[310] Added proton sources, such as $C_6H_5NH_3^+SO_4^-$, and highly polar solvents, such as the phosphonium salt $^nBu_4P^+Br^-$, led to enhanced reaction rates. The highest initial rate of reaction was reported for the biphasic reaction system comprising $^nBu_4PBr$ and decane (51 $mol_{Product}\cdot mol_{catalyst}^{-1}\cdot h^{-1}$ at 150 °C). Diethylaniline and 2-methyl-quinoline were formed as side products (Scheme 78) at lower initial rates (0.6 and 7.3 $mol_{quinoline}\cdot mol_{catalyst}^{-1}\cdot h^{-1}$, respectively). It is noteworthy that the rate of reaction strongly depended on the nature of the aniline (Figure 31). Anilines with electron-donating substituents (less basic anilines) gave mostly the N-alkylated product Ar-NHEt and less quinoline was formed.

The cationic ruthenium complex $[Ru{=}CHCH{=}C(CH_3)_2(Cl)(PCy_3)_2(CO)]^+BF_4^-$ and the *in situ* mixture of $[Ru(H)(Cl)(PCy_3)_2(CO)]$ and $HBF_4\cdot OEt_2$ were equally effective for the coupling reaction of ethene and aniline to form a 1:1 mixture of *N*-ethylaniline and 2-methylquinoline.[264] The isotope effect of $k_{NH}/k_{ND} = 2.2$ and the Hammet parameter $\rho = -0.43$ for para-substituted anilines suggest that the N−H bond participates in the rate-limiting step. The reaction rate was first-order with respect to aniline and catalyst concentration and independent of ethene concentra-

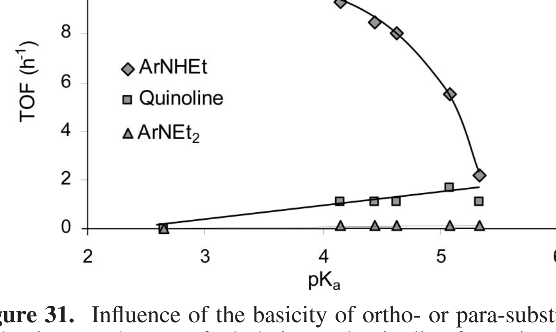
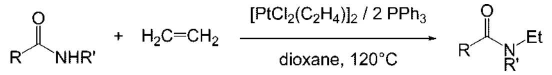


Figure 31. Influence of the basicity of ortho- or para-substituted arylamines on the rate of ethylation and quinoline formation. Each set of three data points represents one arylamine.

Table 56. Coupling of Amides with Ethene Using Late Transition Metal Catalysts[309]



R	R′	*t*, h	yield, %
Ph	H	24[a]	97
p-C_6H_4OMe	H	36	87
p-C_6H_4Br	H	14	85
p-$C_6H_4NO_2$	H	80	70
p-C_6H_4Me	H	12	95
o-C_6H_4Me	H	72	75
2-naphthyl	H	36	91
1-naphthyl	H	72	91
n-Bu	H	20	85
Cy	H	40	84
t-Bu	H	60	82
-$(CH_2)_4$-		36	98
-$O(CH_2)_2$-		36	90

[a] Ratio $[PtCl_2(C_2H_4)]_2$ to PPh_3 1:1

tion. These observations are consistent with a mechanism via N−H bond activation or nucleophilic attack of aniline on a coordinated ethene ligand (*vide supra*). A catalytic mixture of $[PtCl_2(C_2H_4)]_2$ and PPh_3 is effective for the reaction between ethene and less basic benzamides, carboxamides, and carbamates (Table 56). Thus, *N*-ethylbenzamide is obtained in 97% isolated yield after treatment of benzamide with 50 psi ethene using 2.5% catalyst.[309] For substituted benzamides and carboxamides, the rate of hydroamination decreased with increasing steric bulk near the amide nitrogen atom, and for substituted benzamides, the rate decreasted in the order *p*-Me ≈ *p*-Br > *p*-H > *p*-OMe > *p*-NO_2. Note that propene reacted in the same way with valeramide providing *N*-isopropylvaleramide as single isomer in 73% yield (5% catalyst, 80 h).

4.2.2. Higher Alkenes

The hydroamination of norbornene with aniline can be catalyzed with rhodium and platinum complexes when ionic liquids, such as 1-butyl-3-methyl imidazolium bromide ([BMI-]Br), are used as solvent (Table 57). However, long reaction times (6 days) are required for moderate yields of up to 30%.[404] In particular with rhodium catalysts, simultaneous C−H activation is observed giving rise to parallel hydroarylation and enabling domino reaction sequences. This was utilized in the synthesis of quinolines.[86] The intramolecular hydroamination is more facile, and various late transition metal catalysts are known (for references, see Tables 1 and 55). A recent example is the zinc-catalyzed cyclization of substituted aminoalkenes.[352] The zinc catalyst tolerates various heterosubstituents including thiophene, pyridine, and furan. Protecting groups, such as urea, carbamates, and sulfonamides, have been employed, for example, in combination with gold [337,338] and platinum catalysts.[302]

4.2.3. Enantioselective Hydroamination with Late Transition Metals

The Markovnikov addition of amines to alkenes, the 1,2-addition to dienes, and similar hydroamination reactions generate a stereocenter in the amines. Various chiral catalysts have been used to achieve moderate to good enantioselectivities (Table 58). For details, see the review articles on enantioselective hydroamination by Schulz et al.,[11] Hultzsch[29] and Roesky and Müller.[38] In general, the reaction times are quite long, because the reactions need to be performed at low temperatures to enhance stereoselection. Activated alkenes enable the reaction to be run at lower temperatures or for reduced reaction times. Note that several studies have investigated the factors ruling stereoselection. Thus, the ability of chiral diamine silver complexes to bind chiral or prochiral alkenes has been analyzed by NMR spectroscopy and DFT calculations.[405]

The enantioselective hydroamination requires that the reaction is essentially irreversible. In this respect, the addition of aniline to *p*-trifluoromethyl-styrene, vinylnaphthalene, and 1,3-cyclohexadiene showed a constant ee at low and high conversion confirming the irreversibility of the reaction.[255,323] Similarly, the racemization of amine was explored, which occurred with [PdCl(π-allyl)]$_2$/P-N-N-P/TfOH, but not in the absence of acid.[254] The stereochemistry of a single turnover was explored by evaluating the diastereoselectivity for exchange of morpholine with an allylic amine (*trans*-3-amino-5-methylcyclohexene). The reaction occurred with a high stereospecificity with retention of configuration (Scheme 69).[254]

The addition of amines to allenes also generates a stereocenter in the allylic amines formed (Table 59). Chirality in the starting material can be transferred to the product without the use of a chiral catalyst. The excellent stereocontrol and formation of (−)-(*S*)-*N*-(4-phenylbut-3-en-2-yl)benzenamine from (−)-(*R*)-1,3-diphenylpropa-1,2-diene suggests that an internal attack on the coordinated alkene bond occurs (Scheme 79).[343]

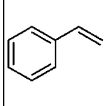
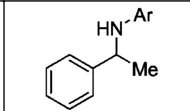
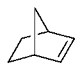
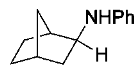
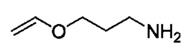
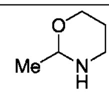
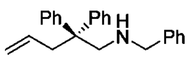
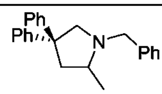
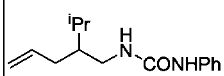
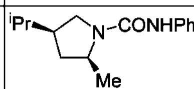
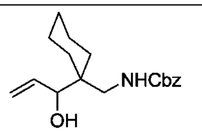
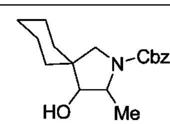
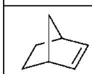
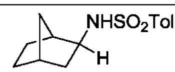
Allylic amination of alkynes proceeds most likely through allene intermediates, which allows control of the stereochemistry with chiral catalysts (Table 59). Although the relative energies of the diastereomeric substrate−catalyst complexes are very close (difference 0.7 kcal/mol), the stereochemistry is decided during formation of the π−allyl complexes.[297] Note that free allenes did not provide stereoselection.

4.2.4. Dienes and Trienes

The telomerization of butadiene in the presence of amines to form long-chain amines has been developed mainly with nickel and palladium catalysts. Although some of these telomerization catalysts produced allylic amines by a 1:1 addition process,[255,407,408] these 1:1 adducts are generally formed as a minor part of the reaction mixture. In contrast, the reverse deamination of allylic amines to generate dienes is well established.[409–414] Recently, palladium catalysts for the 1:1 addition of aromatic amines to dienes, including catalysts that produced allylic amines with high enantioselectivity, were identified.[255] Corresponding nickel catalysts gave good yields with aliphatic and benzylic amines (Table 60).[254] Aromatic and highly hindered amines, such as dicyclohexylamine and 2,2,6,6-tetramethylpiperidine, did not react. Cyclic dienes with ring sizes between 6 and 8 could be used, as well as butadiene, which provided the 1,2-addition product. At prolonged reaction times the terminal allylic amine was formed. The latter results from exchange reactions between product allylic amines and amine reagent. This equilibrium provided the opportunity to determine the relative thermodynamic stability of various allylamines (Scheme 80).

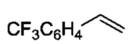
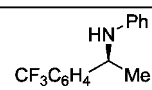
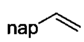
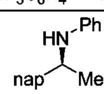
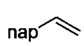
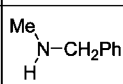
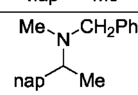
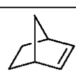
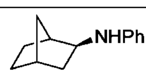
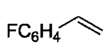
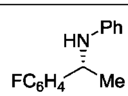
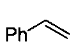
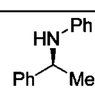
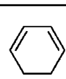
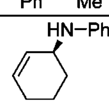
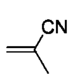
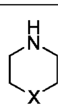
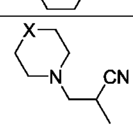
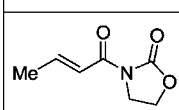
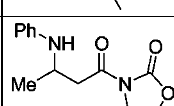
Double addition of aniline to a cyclic triene provides access to the biologically active azabicyclic tropene ring system (Scheme 81).[296]

Table 57. Selected Examples for the Transition Metal Catalyzed Hydroamination of Alkenes

Alkene	Amine	Product	Catalyst	Solvent	*T* /°C	s/c	*t* / h	Yield / %	Ref.
	Ar−NH$_2$		Pd(Tfa)$_2$ / 1.5dppf / 10TfOH	Tol	100	50	7	>99[a] 78 64	323
	Ph−NH$_2$		[RhCl$_3$·3H$_2$O] [RhCl$_3$·3H$_2$O] [Pt(PPh$_2$Me)$_2$Br$_2$] [Pt(PPh$_3$)$_2$Br$_2$]	[BMI]Br ^{n}Bu$_4$PBr ^{n}Bu$_4$PBr ^{n}Bu$_4$PBr	140	100	6 days	8 8 30 13	404
			[Pd(triphos)](TfO)$_2$ / 10TfOH	Tol	60	20	0.6	>99	367
			[Zn((Cy)$_2$ATI)Me]	C$_6$D$_6$	80	40	0.3	91	352
			[Au(NHC)]TfO	MeOH	r.t.	20	22	98[b]	337
			[Au(P^{t}Bu$_2$(*o*-biphenyl))]TfO	Dioxane	60	20	22	91	338
	H$_2$N−SO$_2$Tol		[Pt(COD)](TfO)$_2$	C$_6$H$_4$Cl$_2$	75	10	2	>95	302

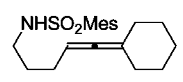
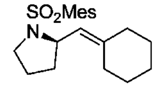
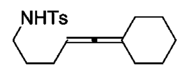
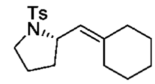
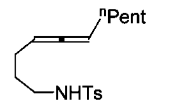
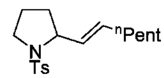
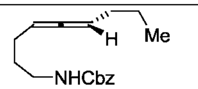
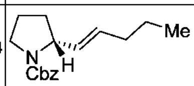
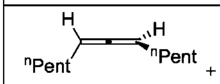
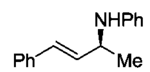
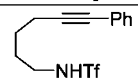
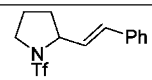
[a] Ar = Ph, *p*-MeOC$_6$H$_4$, *p*-CF$_3$-C$_6$H$_4$, respectively. [b] dr 5.5:1, major diastereomer shown.

Table 58. Selected Examples for the Enantioselective Hydroamination of Alkenes

Alkene	Amine	Product	Catalyst	Solvent	*T* / °C	s/c	*t* / h	Yield / %	*ee* / %	Ref.
	H$_2$N−Ph		[Pd(*R*-BINAP)](TfO)$_2$	Tol	25	10	72	80	81	323
 nap = naphthyl	H$_2$N−Ph		[Pd(*R*-BINAP)](TfO)$_2$	Tol	45	20	36	99	64	323
			Pd(Tfa)$_2$ / 2 PP / TfOH PP = (*R*,*R*)-Et-FerroTANE	Dioxane	50	20	48	36	63	312
	H$_2$N−Ph		[IrCl(P-P)]$_2$ / F$^-$ P-P = (*R*)-Biphemp	neat	75	50	72	24	92	292
	H$_2$N−Ph		[Pd(P-P)(CH$_3$CN)$_2$](TfO)$_2$ P-P = *t*-Bu-SEGPHOS BINAP Ph modified BINAP tms-BINAP	Tol	75	50	40	65 80 80 85	84 69 73 79	294
	H$_2$N−Ph		[Pd(BINAP)-(CH$_3$CN)(H$_2$O)](TfO)$_2$	Tol	100	50	18	75	70	78,82
	H$_2$N−Ph		[Pd(*π*-allyl)Cl]$_2$ / 2 P-N-N-P P-N-N-P = (*R*,*R*)-np-Trost	-	r.t.	40	72	61	91	255
			[Pd(NHC)(CH$_3$CN)](PF$_6$)$_2$[Ni(P-P-P)(THF)](ClO$_4$)$_2$ P-P-P = Pigiphos	THF	-80 r.t.	20 20	72 24	91 99	63[a] 69[b]	295 83,406
	H$_2$N−Ph		[Pd(BINAP)-(CH$_3$CN)(H$_2$O)](TfO)$_2$	Tol	25	10	18	93	93	78,79

[a] For X = S. [b] For X = O.

Table 59. Selected Examples for Stereotransferring or Enantioselective Hydroamination of Allenes and Sterocontrolled Allylic Hydroamination of Alkynes via Intermediate π−Allyl Complexes[a]

Substrate(s)	ee /%	Product	Catalyst	Solvent	T /°C	s/c	t / h	Yield / %	ee /%	Ref.
	–		Ph(CH3)2PAuCl / Ag-(R)-phosphate	C_6H_6	23	20	48	97	96	358
	–		[Au2(P-P)(nb)] P-P = (*R*)-xylyl-BINAP nb = *p*-nitrobenzoate	dce	23	33	17	88	98	333
	96		AuCl	THF	r.t.	100	3	99	94	342
	84		AgOTf	Dioxane	25	20	0.5	96	74	340
 + $PhNH_2$			$AuBr_3$	THF	30	10	1-5	80	99	343
	–		[Pd2(dba)3.CHCl3/ P-P P-P = (*R*,*R*)-renorphos	C_6H_6	100	20	72	65	82	297,311

[a] For an example of benzomorphan synthesis, see ref 628.

Scheme 79

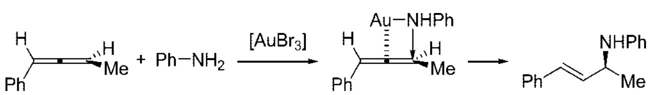
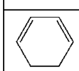
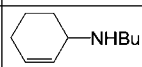
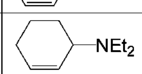
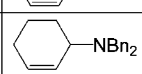
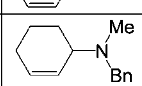
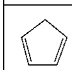
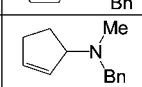
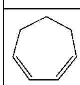
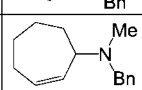
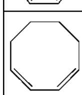
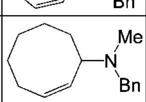
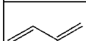
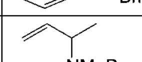


Table 60. Selected Examples for the Transition Metal Catalyzed Hydroamination of 1,3-Dienes with the Catalyst System [Ni(cod)2]/dppf/4HTfa[a 254]

Diene	Amine	Product	T / °C	t / h	Yield / %
	Bu–NH2		25	7	89
	H–NEt2		25	20	78
	H–NBn2		60	72	71
	H–N(Me)Bn		25	20	89
			25	43	91
			25	60	94
			25	84	36
			25	0.5	83

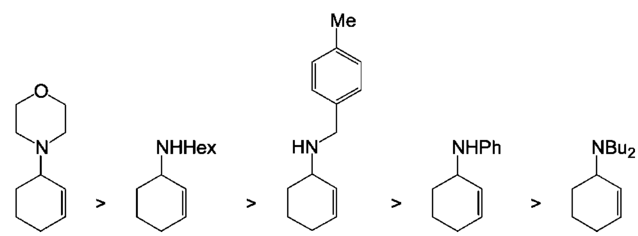
[a] Tol, s/c = 20.

4.3. Nonactivated Alkynes

4.3.1. Synthesis of N-Heterocycles

The high catalytic activity of low-valent late transition metal catalysts has been utilized widely in the synthesis of N-heterocycles via intramolecular hydroamination of aminoalkynes. Five-, six-, and seven-membered nitrogen heterocycles are obtained in excellent yields. For ring sizes ≥5, the reaction is

Scheme 80

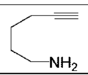
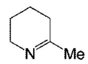
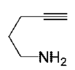
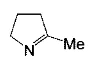
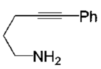
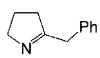
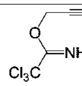
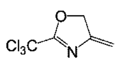


generally highly regioselective to the Markovnikov addition product, whereby the nitrogen atom is attached selectively to the internal carbon atom.

Cationic rhodium(I) and iridium(I) complexes of the general formula $[M(NN)(CO)_2]^+X^-$ with bidentate heterocyclic nitrogen donor ligands NN are efficient catalysts for the regioselective cyclization of 5-amino-pent-1-yne to 2-methyl-1-pyrroline (Table 61).[279] The iridium catalysts were more robust and reuse for at lease three cycles has been demonstrated. The product coordinates quite strongly to the metal center and a significant inhibitory effect was noted.

Low-valent ruthenium complexes with π-acidic ligands, such as $[Ru_3(CO)_{12}]$, $[RuBr(\eta^3\text{-}C_3H_5)(CO)_3]$, and $[Ru(\eta^6\text{-}cot)(dmfm)_2]$ (cot = 1,3,5-cyclooctatriene, dmfm = dimethyl fumarate) showed high catalytic activity for the cyclization of 5-amino-1-phenyl-pent-1-yne to 2-benzyl-1-pyrroline.[268] Interestingly, the catalytic activities of zero-valent and divalent ruthenium complexes without a π-acidic ligand, such as $[RuCl_2(PPh_3)_3]$, were moderate to low. Polar and weakly coordinating solvents, such as diglyme, provided the highest yields. Coordinating solvents such as benzonitrile and nitrobenzene led to drastically reduced yields due to polymerization of 5-amino-1-phenyl-pent-1-yne, while nonpolar solvents, such as mesitylene and decane, provided low conversions. Marked substituent effects were observed in the cyclization of aminoalkynes with low-valent ruthenium complexes with π-acidic ligands, such as $[Ru_3(CO)_{12}]$,[268] the rate of reaction decreasing in the order Ph > H > Me ≫

Table 61. Selected Examples for the Synthesis of N-Heterocycles via Cyclization of Aminoalkynes with Late Transition Metal Catalysts

Aminoalkyne	Product	Catalyst	Solvent	Temp. / °C	s/c	Time / h	Yield / %	Ref.
		[Pd(triphos)](TfO)$_2$ / 10 TfOH	Tol	111	11	0.5	>99	367
		[Cu(C$_6$H$_6$)Cu](TfO)$_2$	Tol	111	100	3.5	>99	256
		[Rh(bim)(CO)$_2$]$^+$BPh$_4^-$	THF	67	67	4.5	75 [1]	279
		[Ir(bim)(CO)$_2$]$^+$BPh$_4^-$		67		4.5	98 [1]	279
		[Rh(bpm)(CO)$_2$]$^+$BPh$_4^-$		67		4	98 [1]	279
		[Ir(bpm)(CO)$_2$]$^+$BPh$_4^-$		67		0.5	98 [1]	279
		[Ru$_3$(CO)$_{12}$]	[3]	110	25	4	78	268
		[Ir(R$_2$PyP)(cod)]BPh$_4$ [4]	CDCl$_3$	60	67	0.17	–	273
		[Cu(CH$_3$CN)$_4$]PF$_6$	CH$_3$CN	82	100	2.2 [5]	–	370
		Zn(TfO)$_2$	Tol	111	100	0.8 [5]	–	370
		[Pd(triphos)](TfO)$_2$	Tol	111	100	0.3 [5]	–	370
		[Ru$_3$(CO)$_{12}$]	diglyme	110 150	25	4	84 >99 [2]	268
		[RuBr(η^3-C$_3$H$_5$)(CO)$_3$]	diglyme	150	25	4	>99 [2]	268
		[Ru(η^6-cot)(dmfm)$_2$]	diglyme	150	25	4	83 [2]	268
		[RuCl$_2$(CO)$_3$]$_2$	diglyme	150	25	4	93 [2]	268
		[(Cp*Mo)$_3$(μ-S)$_4$Pd(dba)]$^+$PF$_6^-$	THF	60	100	0.5	98	293
		[AuCl$_3$]	CH$_3$CN [6]	20	33	0.25	69	335
		[Au(P(C$_6$F$_5$)$_3$)]SbF$_6$	Dce	0	50	9	98	339

[1] Yield determined by NMR. [2] Yield determined by GLC. [3] (BuOCH$_2$CH$_2$)$_2$O was used as solvent. [4] Rate decreasing in the sequence R = ^{i}Pr < Me < Ph < H. [5] Time until complete conversion. [6] Aromatization occurs, when chloroform is used as solvent.

Me$_3$Si. Note that the sequence is entirely different from that observed in catalysis with lanthanide complexes.[96]

Of particular interest is the synthesis of indoles via cyclization of *o*-alkynylanilines (Table 62). Later are readily obtained by reaction of the (substituted) aniline with alkynes or other coupling reactions (*vide infra*). Depending on the activity of the catalyst, the cyclization reaction proceeds quantitatively within several hours. The *o*-alkynylaniline can also be synthesized *in situ* from the corresponding *o*-alkynylchlorobenzene or in a two-step sequential reaction from *o*-iodochlorobenzene.[360]

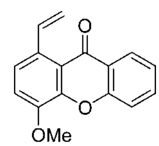
The double hydroamination of *o*-alkynylaniline and terminal alkynes is catalyzed by Lewis acidic gold salts. While the reaction proceeds well with aromatic alkynes, much lower yields are obtained with aliphatic amines (Table 63). Note that the desired product was not obtained when 2-phenyl-1*H*-indole was reacted with phenylacetylene in the presence of catalyst.[334] However, both indole and the double hydroamination product were obtained when 2-(phenylethynyl)aniline was reacted with acetophenone. This suggests that the intermolecular hydroamination is the first step, which is followed by the intramolecular hydroamination.

4.3.2. Synthesis of Complex Molecules in Sequential Reactions

Hydroamination has found a number of applications in the synthesis of complex molecules, such as, naturally occurring multiply substituted nitrogen heterocycles (Table 64).

Indoles were synthesized in a one-pot reaction in three steps: (i) hydroamination of propargyl alcohols with anilines in the presence of [Ru$_3$(CO)$_{12}$], (ii) hydrogen migration of the resulting amino alcohol to amino ketone, and (iii) cyclization to give the indole ring.[415] The ruthenium catalyst is only involved in the hydroamination step. The regioselectivity to the 2-substituted-3-methyl-indole is good (86−92%) with the 3-substituted-2-methyl-indole being the major side product. An ammonium salt, such as NH$_4$PF$_6$, needs to be added as cocatalyst. Aniline hydrochloride is a less effective additive for indole formation; however, if used in 20-fold excess, better selectivities are obtained than with NH$_4$PF$_6$. Electron-donating groups on the aniline ring, such as *p*-OCH$_3$, *p*-CH$_3$, or *p*-Cl, lead to smoother reactions compared with those with electron-withdrawing groups, such as *o*-CO$_2$CH$_3$. The propargyl alcohols can be substituted with alkyl or aryl in the 2-position. A recent study reports on the synthesis of indoles by the zinc-catalyzed hydrohydrazination of terminal alkynes.[350]

[1]Benzopyrano[2,3,4-*i,j*]isoquinolines were synthesized from 1-bromo-4-methoxy-xanthone by assembly of the isoquinoline ring in three steps: vinylation, hydroamination, and ring-closing reduction of the xanthone carbonyl.[416] Lithium amides were chosen as hydroamination agent.[417] The 1-vinylxanthone derivative **182**



182

is a better substrate than styrene because the electron-withdrawing carbonyl group in the *ortho* position to the vinyl group leads to increased electrophilicity of the double bond and stabilizes the benzylic anion generated during the amination process.

The six-membered aromatic heterocycle 1,4-2*H*-1,2,4,5-tetraphenyl-1,4-aza-phosphabenzene was generated via palladium-mediated hydroamination between PhP(C≡CPh)$_2$ and aniline (Scheme 82).[316] Interestingly, the reaction occurs stepwise in the coordination sphere of [PdCl$_2$(CH$_3$CN)$_2$] via an imino-phosphine complex as reaction intermediate. The hydroamination reaction is stereoselective. Using a palladium complex with a chiral ligand sphere, the *P*-chiral enantiomeric imino-phosphines can be synthesized and liberated from the coordination sphere of palladium using KCN.[317]

2-Substituted C5-, C6-, and C7-nitroindoles were synthesized from 2-amino nitrophenols via the stepwise Pd-catalyzed cross-coupling of nitro 2-trifloxyanilides with 1-alkynes followed by *t*-BuOK-mediated heteroannulation.[418] With nitro 2-trifluoroacetamidoaryl triflates, coupling and heteroannulation can also be carried out in a one-pot procedure. The nitroindoles serve as useful precursors to nitrogen-substituted indole derivatives, which exhibit regulatory activities on biomacromolecules. Reaction of aminoalkynes with sulfonyl azides provides tethered ketenimines, which cyclize to the corresponding amidines.[260]

Fluoroanalogues of enamines and β-enaminophosphonates can be prepared by the hydroamination of α-fluoroallenylphosphonates.[419] The reaction proceeds without catalyst and provides a mixture of the *E* and *Z* isomers in the case

Scheme 81

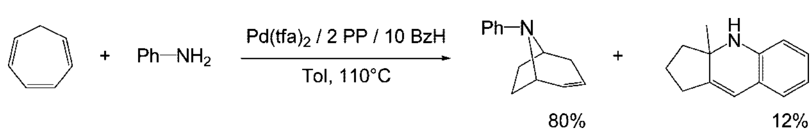
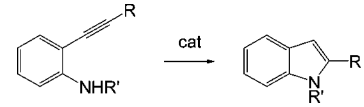


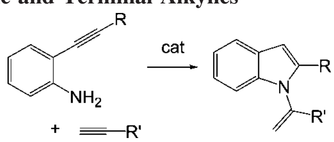
Table 62. Selected Examples for the Synthesis of Indoles via Cyclization of *o*-Alkynylaniline with Late Transition Metal Catalysts



R	R′	catalyst	solvent	*T*, °C	s/c	*t*, h	yield, %	ref
H	H	$[Ru_3(CO)_{12}]$	diglyme	110	25	4	54	268
H	H	$[Rh(N-N)(CO)_2]^+BPh_4^-$	acetone	55	33	2.5	55	285
n-Pr	H	$[Ir(H)(C-O)(PPh_3)_2(C_3H_6O)]^+$	CH_2Cl_2	35	100	1	92	277
Ph	H	$[Ir(H)(C-O)(PPh_3)_2(C_3H_6O)]^+$	CH_2Cl_2	35	100	1	93	277
Ph	H	$[Ir(H)(C-O)(PPh_3)_2(C_3H_6O)]^+BF_4^{-1}$	CH_2Cl_2	40	20	24	100	274
Ph	H	$[Pd(Triphos)](TfO)_2$						
		$[Pd(Triphos)](TfO)_2$	tol	111		8	100	
Ph	H	$Zn(TfO)_2$	tol	111	100	<1	34	370
		$[Cu(CH_3CN)_4]PF_6$	CH_3CN	82		4	100	
n-Bu	CH_3CO	$[Ir(H)(Cl)(C-N-P)(CO)]^a$	Tol	110	100	24	21	274
H	CH_3CO	$[Rh(N-N)(CO)_2]^+BPh_4^-$	acetone	55	66	72	23	281

[a] $NaBAr^F_4$ as cocatalyst.

Table 63. Selected Examples for the Double Hydroamination of *o*-Alkynylaniline and Terminal Alkynes[334]



R	R′	Catalyst	Solvent	*T*, °C	s/c	*t*, h	yield, %
	Ph						82
	p-$CH_3C_6H_4$						79
Ph	*p*-FC_6H_4	$Au(TfO)_3$	neat	rt	20	3	75
	p-$CH_3OC_6H_4$						69
	1-naphthyl						80
Ph	*n*-Pr	$Au(TfO)_3$	neat	rt	20	3	27[a]
	n-Bu						33[a]
	Ph						53
n-Bu	*p*-$CH_3C_6H_4$	$Au(TfO)_3$	neat	rt	20	3	50
	p-FC_6H_4						42
	p-$CH_3OC_6H_4$						56

[a] Mixture of isomers.

of primary amines, whereas it is selective for the *Z* isomer in the case of secondary amines. In a similar reaction, tungsten vinylidene complexes react readily with amine nucleophiles without the use of a catalyst.[420]

Hydroamination of the alkene moiety in a conjugated spiroketal enol ether system enabled the distereoselective synthesis of analogues of tonghaosu, 2-(2,4-hexadiynylidene)-1,6-dioxaspiro[4.4]-non-3-ene.[421] The latter is an antifeedant of certain plants and vegetables. Hydroamination was catalyzed with ^{n}BuLi, affording the product in good yield for secondary amines, such as morpholine, pyrrolidine, and piperidine. However, primary amines, such as *n*-butylamine, gave much lower yields, and aromatic amines did not react. The excellent regioselectivity is probably the result of a directing effect of lithium coordinated to oxygen atom 6.

4.4. Hydroamination of Alkenes with Weaker Nucleophiles

Hydroamination of alkenes with weaker nucleophiles, like sulfonamines and carbamates as amines sources has been carried out mostly in intramolecular fashion.[422,423] An alternative protocol employing catalytic amounts of *N*-bromosuccinimide (NBS) allows reaction of electron-rich styrenes with *p*-toluenesulfonamide ($TsNH_2$), benzyl carbamide ($CbzNH_2$), and carbamic acid methyl ester as amine sources (Scheme 83).[424] Amine bromide R^3NHBr was identified as an active aminating agent and is thought to react with the quinonoid form of styrene bearing a *para*-(+M)-substituent. The reaction proceeded in Markovnikov fashion with moderate to good yields and can be transferred to the corresponding hydroalkoxylation.

4.5. Catalysis in Aqueous Phase and Ionic Liquids

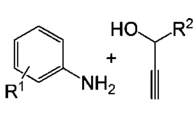
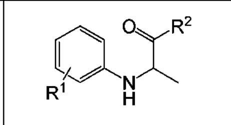
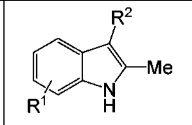
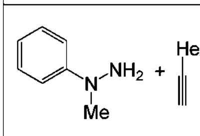
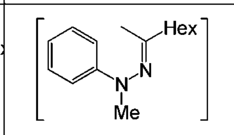
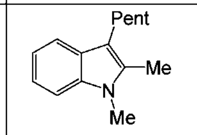
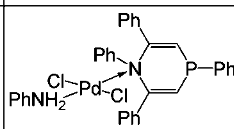
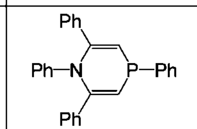
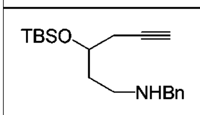
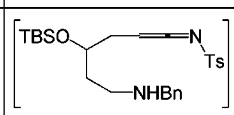
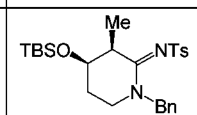
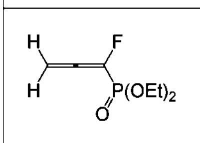
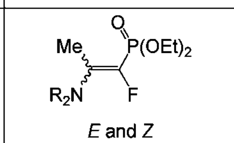
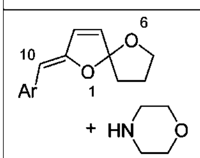
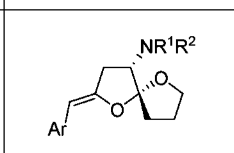
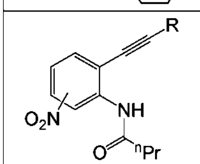
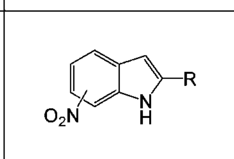
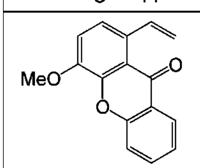
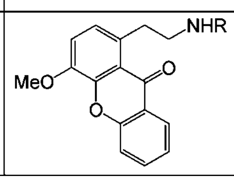
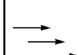
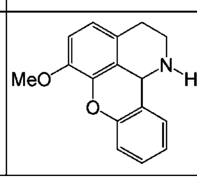
Higher reaction rates in hydroamination with late transition metals are generally observed in solvents with high dielectric constant, such as water or ionic liquids. Probably, the polar environment leads to stabilization of a polar transition state associated with the zwitterionic ammonioalkenyl complex (Scheme 59). As the activation barrier in the rate-determining step is lowered, the overall process is accelerated.

Water was successfully used as solvent for the cyclization of aminoalkynes. The reaction was catalyzed by Pd^{II} and Pt^{II} complexes with water-soluble ligands, such as 1,3,5-triaza-7-phospha-adamantane.[300,301] Similarly, the reaction of 2-ethynylaniline derivatives to indoles is catalyzed by copper(II) salts in a water/methanol mixture, whereby 1-ethylpiperidine was added to ligate the copper ions.[425] Note that copper-catalyzed Michael additions of aliphatic amines to α,β-unsaturated compounds also proceed well in water.[75] Particularly interesting is a two-phase system where the $Zn(TfO)_2$ catalyst for the reaction of phenylacetylene with aryl and alkyl amines was immobilized in the aqueous phase.[426] Rapid extraction of the product into the organic heptane phase prevents hydrolysis to acetophenone. The same catalytic system is also effective for the hydroamination of cyclohexadiene.[427]

Ionic liquids[428] appear particularly favorable for two-phase catalytic systems, in particular, when the substrate or product is sensitive to hydrolysis. Molten salts have been reported to increase rates and turnover numbers in the Rh^{III}-catalyzed hydroamination of norbornene with anilines,[404] the Pt^{II}-catalyzed reaction of aniline with terminal alkynes[298] and hexene,[304] and the Ir-catalyzed cyclization of 5-aminopent-1-yne.[275] Ionic liquids have been used to tune the selectivity between hydroamination and hydroarylation.[429]

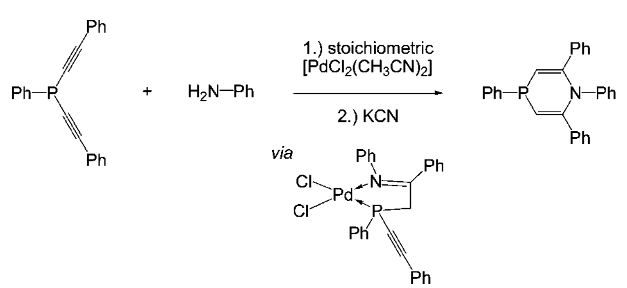
Conversion and selectivity are improved in two-phase systems comprising ionic liquid and an alkane.[355,430] The Lewis acid catalyst $Zn(TfO)_2$ and the Brønsted acid cocatalysts TfOH are very effectively immobilized in the ionic liquid allowing to perform the reaction in continuous operation.[355] The catalyst phase can also be immobilized on a solid support (Figure 32, left). The dry material can then

Table 64. Selected Examples for the Synthesis of Multisubstituted Indoles and Complex Molecules via Hydroamination with Late Transition Metals.[f,g]

Starting material or intermediate	Intermediate after hydroamination step		Target product	Catalyst [a] (s/c)	Exp. conditions	Yield / %	Ref.
				$[Ru_3(CO)_{12}]$ (28) NH_4PF_6	No solvent, 140°C, 7-9 h	75 (R^1=H, R^2=C_2H_5) 91 (R^1=*o*-CH_3, R^2=CH_3)	415
		*in situ*		$ZnCl_2$ (33) or $Zn(TfO)_2$ (100)	THF, 100°C, 24 h	95 ($ZnCl_2$) 94 ($Zn(OTf)_2$)	350
Ph—NH_2 + PhP(C≡CPh)$_2$		KCN →		$[PdCl_2(NCCH_3)_2]$ (1)	CH_3CN, 75°C, 3 h	59	316
		*in situ*		$[Ru_3(CO)_{12}]$ (20), TsN_3 (stoichiometric)	THF, 25°C, 12 h	51, single diastereomer	260
			—	–	THF, r.t., overnight	80 (R=Benzyl, H)[b] 81 (R=Cy, H) 75 (R=Et, Et)	419
			—	^{n}BuLi, TMEDA [d] (1.7)	THF, -78°C, overnight	94 83 90 44 [c]	421
		[e]	—	^{t}BuOK [d] (0.83)	NMP, 60-70°C, 7 h	72-86 (R=Ph, ^{n}Pr)	418
				^{n}BuLi [d] (0.4)	THF, 0°C, overnight	69 (R=Bu) 77 (R=Bn) 85 (R= Allyl)	416

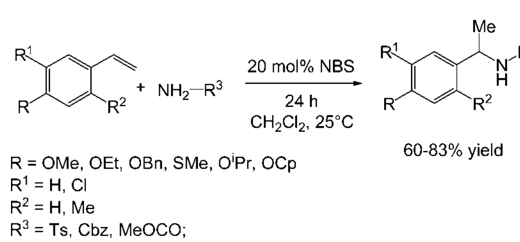
[a] For hydroamination step. [b] *E*/*Z* = 67/33, 70/30, 0/100, respectively. [c] Ar = Ph, *p*-MeO-C_6H_4, *p*-Me-C_6H_4, *p*-$O_2N-C_6H_4$, respectively. [d] Examples included for comparison. [e] The amine is deprotected during workup. [f] Examples for activated substrates and base-catalyzed reactions were included in the table for comparison. For further examples of base-catalyzed reactions, *vide infra.* [g] For an example of benzomorphan synthesis, see ref 627.

Scheme 82



be used in suspension[431] or in fixed bed reactors.[5] Stepwise increase in temperature showed that the addition of aniline to styrene was exclusively in Markovnikov fashion in the kinetic regime, while the anti-Markovnikov product was the main product in the thermodynamic regime at higher temperatures (Figure 32, right). The particular performance of hydroamination catalysts dissolved in ionic liquids might be due to the formation of solvent cages encapsulating the

Scheme 83



complexes.[384,432] Note that this effect also leads to stabilization of sensitive complexes, such as $[Ni(PPP)(THF)]^{2+}$ with a chiral tridentate phosphine ligand.[83,82]

4.6. Hydroamination Using Homogeneous Zinc Catalysts

Aminotroponiminato[351–353] and aminotroponate[354] zinc alkyl complexes catalyze the hydroamination of ami-

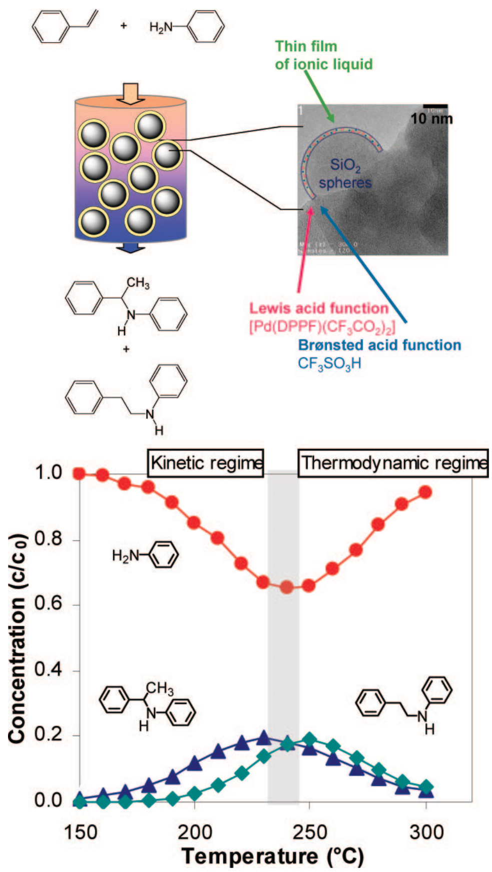


Figure 32. Concept of immobilizing hydroamination catalysts in a supported film of ionic liquid for fixed bed reactors (top) and temperature profile for the reaction of aniline (bottom) and styrene to the Markovnikov product *N*-(1-phenylethyl)aniline and anti-Markovnikov product *N*-(2-phenylethyl)aniline.

noalkynes and *gem*-dialkyl-activated aminoalkenes at elevated temperatures (typically 80−120 °C). Significantly higher catalyst activities were observed when the anilinium borate $[PhNMe_2H][B(C_6F_5)_4]$ was added as cocatalyst. The role of the catalyst is therefore most likely that of a Lewis acid, rather than a lanthanide-like mechanism involving insertion of the unsaturated CC bond in a metal amide bond. The catalysts tolerate a number of functional groups, including amides, sulfonamides, (thio)ethers, furans, thiophenes, pyridines, and thioacetals, because they lack a reactive metal−alkyl bond. The cyclization of secondary amine propargyl ethers gave access to 1,4-oxazines due to a facile double bond migration of the initial hydroamination product leading to the thermodynamically favored vinyl ether (Scheme 84).

Catalytic activity strongly varies with the substituents on nitrogen of the aminotroponiminato ancillary ligand,[351−353] giving optimal activities using cyclohexyl groups (Scheme 85). Attempts to perform diastereoselective transformations have met limited success so far.

5. Heterogeneous Hydroamination Catalysts and Immobilized Early and Late Transition Metal Complexes

There are few reports on heterogeneous catalysts, such as zeolites,[433−436] clays,[437] metal-cation exchanged zeolites,[256,356,357,376,438,439] ion-exchanged montmorillonite,[440−442] oxide-supported Pd complexes,[443−445] tin−silicate MCM-41 supported Au complexes,[332] polymer-supported organolanthanide complexes,[446] two-phase catalytic systems,[430] and metal complexes supported in a thin film of ionic liquid.[5,431]

5.1. Inorganic Solid Catalysts

H-Zeolites, H-MFI, H-mordenite, H-FAU, etc. have been reported as solid catalysts for hydroamination using ammonia.[433−435] Reactions between ammonia and 2-methylpropene were investigated on solid acids (H-zeolites, silica−alumina, silica−titania, and $Cs_xH_{3-x}PW_{12}O_{40}$) and solid base (MgO) using conventional flow reactors at 423−673 K.[434] The catalytic activity was remarkably controlled by the amount and strength of Brønsted-acid sites on these solid catalysts, and linear correlations with the SiO_2/Al_2O_3 ratio of H-MFI, H-mordenite, and H-FAU were observed.[434] However, the scope is mostly restricted to the reaction between ammonia and C2−C4 alkenes.[434,435] The hydroamination of methyl acrylates and amine compounds (aniline, 4-anisidine, 4-nitroaniline, and benzylamine) proceeds on H-Beta and H-FAU, and anti-Markovnikov adducts are obtained as main products.[436] However, the double addition of methyl acrylate to aniline also occurs under reaction conditions. Until now, only one process, synthesis of *t*-butyl amine using ammonia and isobutene catalyzed by H-MFI, has been commercialized.[435]

Various clays have been used as solid supports and catalysts for heterogeneous reactions, and proton-exchanged montmorillonite acts as a good catalyst for C−N bond formation between cyclohexene and *p*-toluenesulfonamide.[437] H-Montmorillonite exhibits good hydroamination performance at 423 K and can be reused without any loss of its catalytic activity to at least the 5th recycle. Its Brønsted-acid site can be applicable for the hydroamination of nonactivated alkenes.

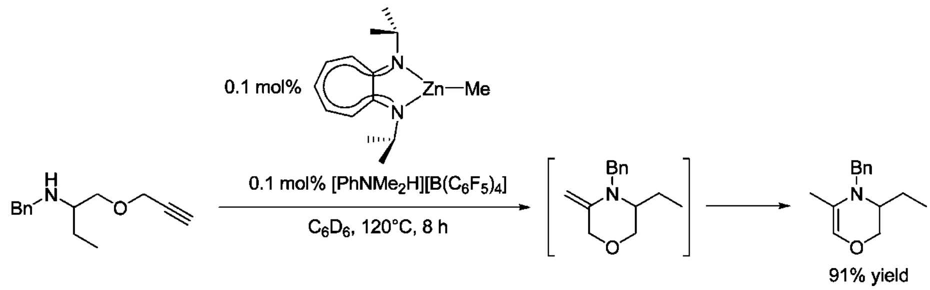
5.2. Metal-Ion Exchanged Zeolites and Clays

There are several reports on metal-ion-exchanged zeolites or clays active for hydroamination.[256,438−442] On beta zeolite, Zn, Cu, Rh, Pd, Pt, Ni, and La have been utilized as metal cation sources. The hydroamination activities are in the order: $Cu^+ > Zn^{2+}, Rh^+ \gg Pd^{2+}, Pt^{2+}, Ni^0, La^{3+}$, and Al^{3+}.[256] The d^8 and d^{10} metal ions exhibit good performance, and a plot of the intrinsic reaction rate per metal center vs the ratio of metal charge and ionic radius shows a volcano-curve-type correlation as shown in Figure 33.[256] The ratio of charge to ionic radius is an approximate measure for the (hard) Lewis acidity of a metal cation, indicating that there is an optimum Lewis acidity required for transition metal cations to catalyze the hydroamination reaction. Very weak Lewis acidity is speculated to lead to an unstable catalyst−substrate complex, while a too stable catalyst−substrate complex prohibits further reactions.

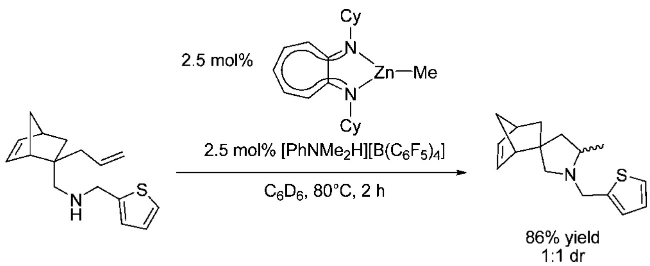
The catalytic activity of the heterogeneous catalyst (Zn/H-beta) in the cyclization of 6-aminohex-1-yne was higher than that of the corresponding homogeneous catalyst $(Zn(TfO)_2)$. When a Brønsted acid (TfOH) was added to the reaction mixture, the catalytic activity of $Zn(TfO)_2$ increased to such an extent that it was similar to the Zn/H-beta catalyst.[366] These observations strongly suggest that the ion-exchanged zeolites are bifunctional catalysts comprising Brønsted-acid sites and Lewis-acidic metal centers.

The catalytic activity of Zn/H-beta increases linearly with Zn loading as shown in Figure 34a.[356,357] A break at 0.26 Zn loading (Zn/Al) indicates a change in the structure of

Scheme 84



Scheme 85



the Zn species on H-beta. At higher Zn loadings, the catalytic activity is almost constant. These observations are explained by preferential coordination of Lewis-acidic Zn^{2+} to ring openings in beta zeolite composed of six oxygen atoms (A) at low zinc content, incorporation of $[Zn-O-Zn]^{2+}$ cations (B) at intermediate zinc content, and finally formation of ZnO (C) at high zinc content (Figure 34b).[256] Zn^{2+} cations immobilized at ion-exchange positions preferentially coordinate to two vicinal Brønsted-acid sites. In the most stable geometry, the Zn^{2+} cations are coordinated in a square-pyramidal fashion to four framework oxygens and two further oxygens at a longer distance as shown in Figure 34b,

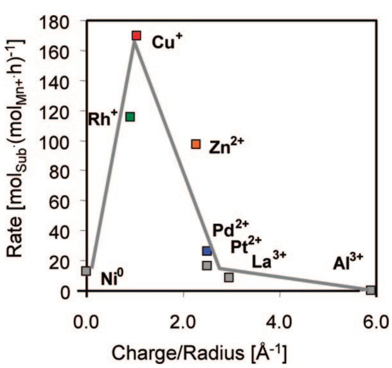


Figure 33. Rate of the cyclization of 6-aminohex-1-yne using ion-exchanged beta zeolite related to the ratio of charge to cation radius.[256]

structure A. This distorted coordination geometry of the Zn cations is suggested to enhance their Lewis acidity, leading to a much higher catalytic activity of Zn/H-beta in hydroamination. Lewis-acidic zinc centers are catalytically active, whereas ZnO is completely inactive for hydroamination reactions.[256,439]

Similar results are obtained for Zn^{2+}-exchanged K-10 montmorillonite clay (Zn/K-10) as catalyst for the addition of aniline to phenylacetylene (Table 65).[440] The catalytic activity increases with increasing zinc contents up to 0.22 $mmol_{Zn^{2+}} g^{-1}$. Further increase shows little effect. In parallel, the Lewis acidity of the catalyst increases up to 0.22 $mmol_{Zn^{2+}} g^{-1}$, whereas the Brønsted acidity decreases. Higher concentrations resulted in incorporation of zinc as ZnO after calcination, which does not contribute to catalytic activity. Silica was a less suitable support and the parent supports hardly showed activity, the sequence being Zn/H-beta ≈ Zn/K-10 > Zn−silica > H-beta > K-10 > silica. Lewis acids such as Al^{3+} present in the parent material after calcination are probably responsible for a small but noticeable activity. The only reaction product was the Markovnikov addition product phenyl-(1-phenylethylidene)amine. High reaction temperatures were favorable. The activation energy was determined to be 50 $kJ \cdot mol^{-1}$ in the temperature range 363−423 K.

5.3. Supported Complexes on Oxide Surfaces

The structures of supported Pd complexes on SiO_2 can be controlled by using Pd^{2+} precursors with different metal conformations.[443,444] The surface structures of supported Pd complexes on SiO_2 reported by H. Alper et al. are shown in Figure 35. A methyl or hydroxyl group easily reacts with a surface hydroxyl group (Si-OH) on SiO_2 when the Pd loading is controlled. The immobilization reactions are stoichiometric, but sometimes several surface structures are obtained (Figure 35A). It appears that Pd complexes stabilized by more basic ligands undergo a more facile reaction with the surface.[443] The catalytic cyclization of 6-aminohex-1-yne on these SiO_2-

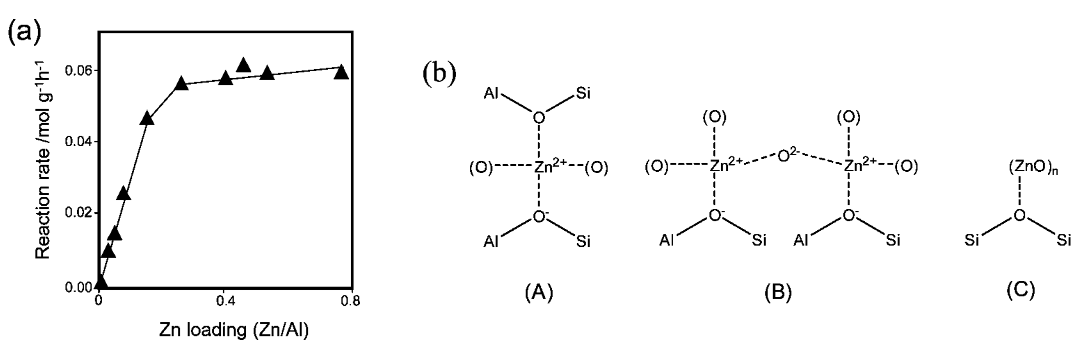
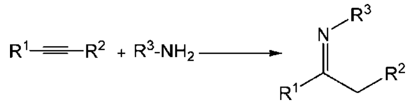


Figure 34. Initial rates (a) for the cyclization of 6-aminohex-1-yne with Zn/H-beta catalyst varying in the Zn^{2+} loading and (b) possible Zn^{2+} sites in the Zn/H-beta catalyst. (O) indicates an oxygen atom in zeolite framework.[256]

Table 65. Intermolecular Hydroamination Reactions with Immobilized and Supported Catalysts [440,442]



alkyne	R^3	catalyst	solvent	T, °C	metal, wt %	t, h	conv, %
phenylacetylene	C_6H_5	Zn/K-10	Tol	130	5	20	77
phenylacetylene	C_6H_5	Zn/H-beta	Tol	111	5	10	48
		Zn/K-10					46
phenylacetylene	C_6H_5	Pd/K-10	Tol	111	5	10	12
		Co/K-10					7
		Mn/K-10					5
phenylacetylene	C_6H_5	Cu/K-10	Tol	110	10	20	99
phenylacetylene	2-$CH_3C_6H_4$	Cu/K-10	Tol	110	10	20	99
phenylacetylene	4-$CH_3C_6H_4$	Cu/K-10	Tol	110	10	20	98
phenylacetylene	4-$CH_3OC_6H_4$	Cu/K-10	Tol	110	10	20	95
phenylacetylene	2-ClC_6H_4	Cu/K-10	Tol	110	10	20	32
phenylacetylene	4-BrC_6H_4	Cu/K-10	Tol	110	10	20	68
phenylacetylene	1-naphtyl	Cu/K-10	Tol	110	10	20	88
1-hexyne	C_6H_5	Cu/K-10	Tol	110	10	20	45
1-heptyne	C_6H_5	Cu/K-10	Tol	110	10	20	55
3-hexyne	C_6H_5	Cu/K-10	Tol	110	10	20	0
diphenylacetylene	C_6H_5	Cu/K-10	Tol	110	10	20	0
4-ethynyltoluene	C_6H_5	Cu/K-10	Tol	110	10	20	87
4-ethynylanisole	C_6H_5	Cu/K-10	Tol	110	10	20	84

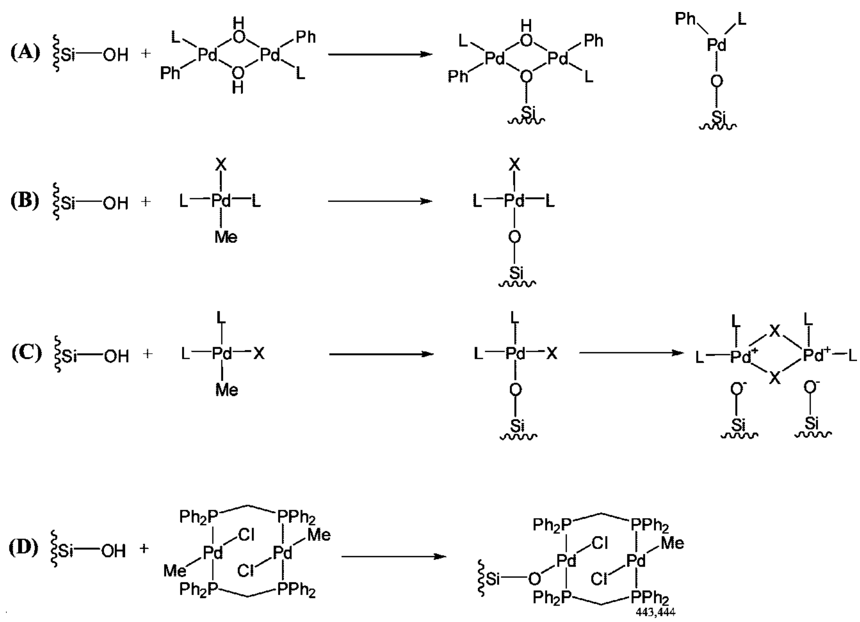


Figure 35. Structures of SiO_2-immobilized Pd^{2+} complexes for alkyne hydroamination.[443,444]

Table 66. Catalytic Performance of SiO_2-Supported Pd Complexes for Cyclization of 6-Aminohex-1-yne[443,444]

type[a]	precursor complex	Pd, wt %	t, h	conv, %	TOF, h^{-1}
A	$[PdPh(OH)(PPh_3)]_2$	1.47	20	33	1.1
B	*trans*-$[PdMe(NO)_3(PMe_3)_2]$	0.50	20	74	6.9
B	*trans*-$[PdMeCl(PMe_3)_2]$	0.42	20	15	1.7
B	*trans*-$[PdMeCl(PPh_3)_2]$	0.037	20	23	29.1
C	*cis*-$[PdMeCl(PMe_3)_2]$	1.12	20	51	2.1
C	*cis*-[PdMeCl(dmpe)]	0.65	20	21	1.5
C	*cis*-[PdMeCl(dppe)]	0.24	20	6	1.2
C	*cis*-[PdMeCl(bipy)]	0.023	20	8	16.3
D	$[Pd_2Me_2Cl_2(dppm)_2]$	0.80	20	39	6.5
D	$[Pd_2Me_2Cl_2(dmpm)_2]$	2.16	20	100	>4.3

[a] Refer to Figure 35.

bound Pd complexes was explored (Table 66).[443,444] Higher conversion is found for those supported Pd complexes containing more basic ligands, due to the higher loadings, and for those complexes containing more weakly coordinating anions. The catalytic activities for the cyclization reaction widely depend on their coordinating ligands and less on the type of the Pd-precursor complexes (Figure 35A−D).

Alkene hydrogenation can be performed on oxide-supported Pd-monomer complexes using 3-amino-propanol vinyl ether to produce cyclic oxazolin 2-methyl-[1,3]-oxazinane.[445] The same local coordination can be achieved on SiO_2, Al_2O_3, and TiO_2 with *trans*-$PdMeClL_2$ (L = amine or phosphine ligand). Oxide-supported catalysts are prepared by selectively reacting the methyl group of precursor complexes $[PdMeClL_2]$ with surface hydroxyl groups under stoichiometric evolution of CH_4. In consequence, the Pd center is directly coordinated to the surface via lattice-O···Pd linkers as a Pd monomer as was confirmed by Pd K-edge EXAFS. While corresponding homogeneous catalysts are inactive, supported complexes exhibit significant catalytic activities for the cyclization of 3-amino-propanol vinyl ether. The hydroamination activity decreases with the pK_a of the support (SiO_2 > TiO_2 > Al_2O_3) and the basicity of the ligand (dppf > PMe_2Ph > $P(O^iPr)_3$ > cyclohexylamine > 2-methylpiperi-

Table 67. Characteristic Data for the Oxide-Supported Pd Complexes and Catalytic Performance for Hydroamination of 3-Amino Propanol Vinyl Ether[445]

ligand	support	Pd, wt %	CH_4/Pd[a]	Cl/Pd[b]	TOF, h^{-1}
P(O-^{i}Pr)$_3$	SiO_2	0.23	0.9		15.3
PMe_2Ph	SiO_2	0.34	1.0	1.0	18.8
dppf	SiO_2	0.11	0.9	1.1	22.6
TMEDA	SiO_2	0.44	1.1		1.1
cyclohexylamine	SiO_2	0.25	1.1		9.1
methylpiperidine	SiO_2	0.16	1.0	1.1	5.0
		0.16			4.8[c]
methylpiperidine	Al_2O_3	0.25	1.0	1.0	1.6
		0.32			1.8
		0.32			1.7[c]
methylpiperidine	TiO_2	0.28	1.0	1.1	3.7

[a] Amount of CH_4 evolved during the binding of monomeric Pd precursors onto oxide surfaces. [b] Amount of Cl on the supported Pd complexes estimated by XPS. [c] Reused.

dine > TMEDA) as shown in Table 67. This suggests that an electron-rich palladium center is most favorable. The oxide-supported Pd-monomer complexes can be reused for the alkene hydroamination.[445]

A recent report refers to the use of gold(III) complexes supported on MCM-41 mesostructured inorganic oxides.[332] Brønsted or Lewis acid sites on the alumino- or tin−silicate support, respectively, were required to promote the hydroamination of phenylacetylene and styrene. However, only the gold complexes on the tin−silicate support were stable, and the material could be recycled at least 4 times without loss of activity and selectivity.

5.4. Polymer-Supported Organolanthanide Catalysts

Amino-functionalized polystyrene resins are applicable for reversible binding supports of organolanthanide complexes, which are active for intramolecular hydroamination/cyclization.[446] The schematic protocol is presented in Figure 36, in which the precatalyst is bound to the polymer resin in a flexible and accessible way. The Ln−N complex is immobilized on a polymer support (precatalyst), protonolytically released by the substrate to function as conventional homogeneous organolanthanide hydroamination catalyst, and then re-adsorbed as substrate. The reaction provides the sterically more encumbered cyclization product (Figure 36). There are several attractions to this approach: (i) it has potential applicability to most organolanthanide catalysts without having to attach covalently an ancillary ligand to the support; (ii) diverse amine-functionalized polymer supports are commercially available; (iii) the released catalysts have high reactivity and selectivity. The polymer-supported organolanthanide catalysts exhibit similar catalytic activities for hydroamination/cyclization of 2,2-dimethyl-4-penten-1-amine (**7**), 4-penten-1-amine (**27**), and 2,2-dimethyl-5-hexen-1-amine (**51**), which are comparable to those of the homogeneous precursors and are recyclable with only modest loss of activity.[446]

6. Brønsted Acid Catalyzed Hydroamination of Alkenes and Alkynes

Except solid acids (*vide supra*), Brønsted acids have not been used extensively as catalysts in hydroamination processes of alkenes and alkynes because of the more basic character of the nitrogen compared with the π-system of unsaturated compounds. Thus, ammonium salts are formed preferentially instead of the carbenium ions, which result from proton addition to carbon−carbon double or triple bonds. In this way, the nucleophilic character of the nitrogen is destroyed and activation of the π-system to the attack of a nucleophile avoided. Despite these general considerations, it was found that catalytic amounts of Brønsted acids favored the inter- and intramolecular hydroamination of alkenes and alkynes with homogeneous and heterogeneous catalysts (*vide supra*).[320,366,434] A reaction pathway via intermediate protonation of vinylarenes was proposed by Hii et al. also for copper-catalyzed hydroaminations.[331] In nearly all hydroamination reactions, the basicity of the amine or amine derivative plays a key role: more basic amines lead to lower rates of the reaction.[376]

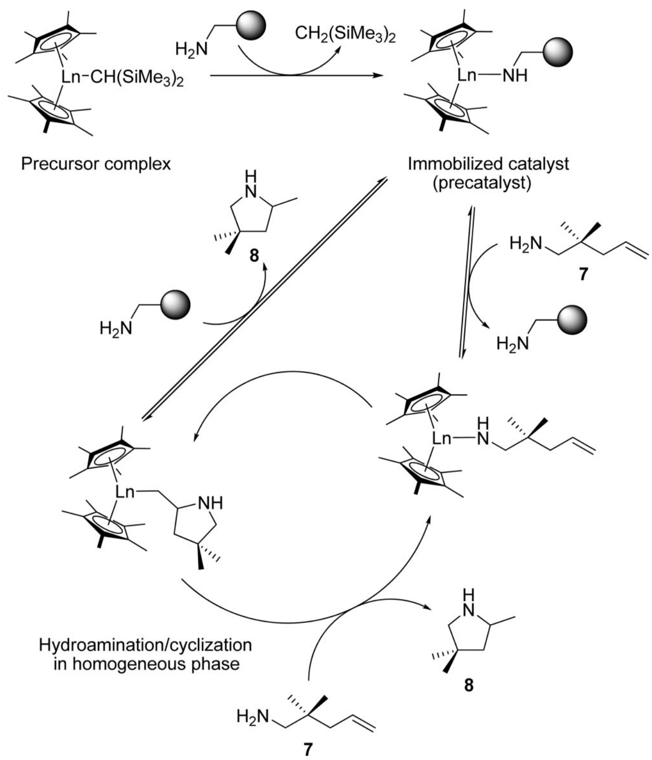
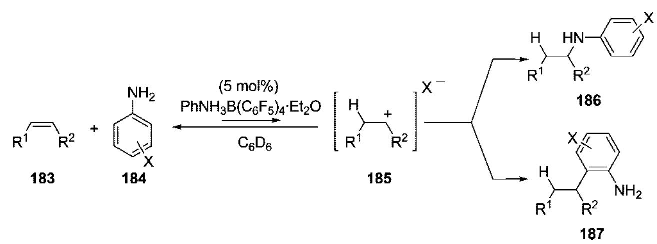


Figure 36. Mechanism of intramolecular hydroamination/cyclization using polymer-supported organolanthanide catalysts.[446]

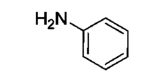
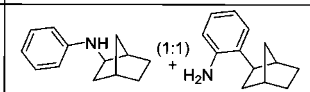
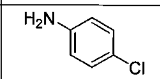
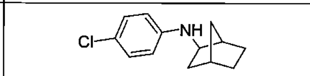
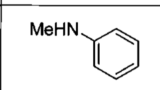
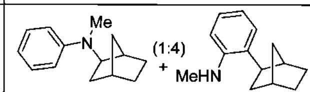
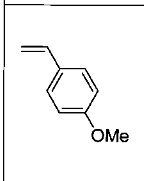
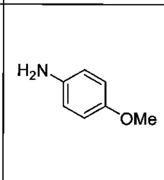
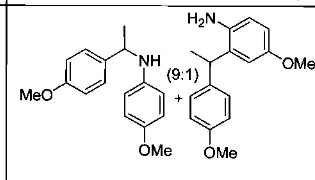
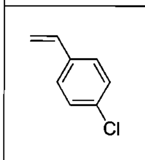
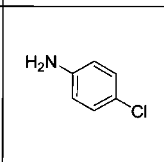
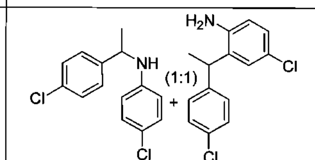
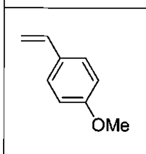
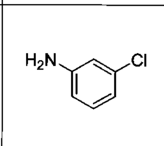
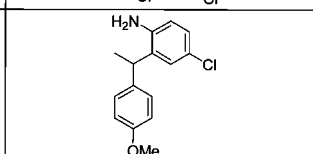
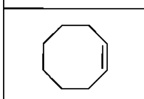
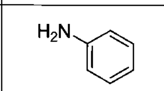
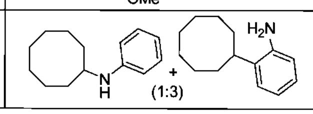
Scheme 86



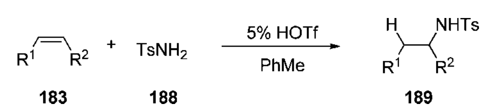
6.1. Intermolecular Brønsted Acid Catalyzed Hydroamination of Alkenes and Alkynes

Hydroamination/hydroarylation of olefins **183** with anilines **184** was performed using $PhNH_3B(C_6F_5)_4 \cdot Et_2O$ (Scheme 86). The addition reactions tolerate substitution on the nitrogen as well as in the aromatic ring of the aniline **184** (see Table 68). Electron-withdrawing substituents on the aniline increase the overall yield of the reaction and favor the formation of the hydroamination product. A stabilized carbocation **185** is supposed to act as a reaction intermediate, and either the nitrogen or the aromatic ring can act as the nucleophile to

Table 68. Selected Examples of Hydroamination and Hydroarylation of Olefins

Olefin **183**	Aniline **184**	Reaction conditions	Reaction products **186** and **187**	Yield / %
		135 °C 48 h		84
		135 °C 48 h		56
		135 °C 48 h		55
		45 °C 51 h		82
		105 °C 1 h		89
		45 °C 12 h		71
		105 °C 56 h		56

Scheme 87

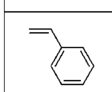
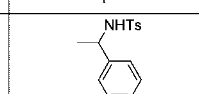
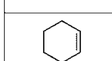
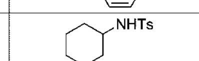
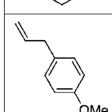
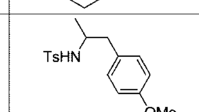
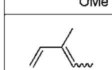
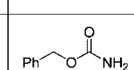
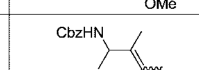
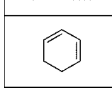
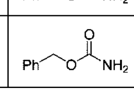
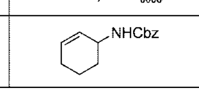


give, after deprotonation, the hydroamination or hydroarylation products **186** or **187**, respectively.[237] Dupont et al. found that intermolecular hydroamination or hydroarylation reactions of norbornene and cyclohexadiene performed with catalytic amounts of Brønsted acids in ionic liquids provided higher selectivity and yields than those performed in classical organic solvents.[429]

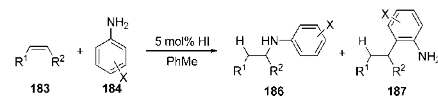
He et al. reported the hydroamination of simple olefins **183** with tosylamide (**188**) under mild conditions mediated by trifluoromethanesulfonic acid at low concentrations to give compounds **189**. Under the same reaction conditions, $CbzNH_2$ could be added to 1,3-dienes to afford allylamines in good yields (Scheme 87 and Table 69).[447] Almost at the same time, Hartwig et al. reported very similar results.[448]

Hydrogen iodide has been recently used as hydroamination catalyst. Marcseková and Doye found that substituted anilines **184** reacted with olefins **183** in the presence of catalytic amounts of aqueous hydrogen iodide to give a mixture of the corresponding hydroamination and hydroarylation products, **186** and **187**, respectively (Scheme 88 and Table 70).[238] The hydroamination reaction is the predominant process; however, the hydroarylation reaction becomes more important in the case of aryl-substituted olefins. The electronic properties of the amine and the olefin play an important role considering the selectivity of the reaction. The authors suggest that a plausible mechanism for this reaction involves

Table 69. Selected Examples of Hydroamination of Olefins with Tosylamide Mediated by Trifluoromethanesulfonic Acid

Olefin **183**	Amine	Reaction conditions	Reaction product **189**	Yield / %
	$TsNH_2$	85 °C 15 h		70
	$TsNH_2$	85 °C 15 h		85
	$TsNH_2$	60 °C 15 h		88
		25 °C 15 h		83
		50 °C 15 h		71

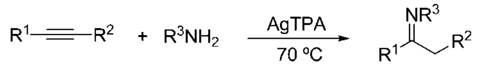
Scheme 88



a first addition of hydrogen iodide to the olefin followed by a nucleophilic substitution.

Silver-exchanged tungstophosphoric acid (AgTPA) catalyst has been used by Lingaiah et al. in the intermolecular hydroamination of alkynes **190** with both aromatic and aliphatic amines **191** under solvent-free conditions. In this way, ketimines **192** were obtained in high yields (Scheme 89).[449]

Scheme 89

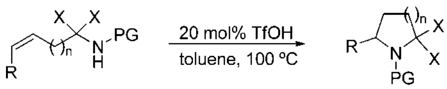


190 191 192

(52-99%)

R^1 = Et, *n*-Pr, *i*-Pr, Ph
R^2 = H, Et, *n*-Pr
R^3 = Ph, 2-ClC_6H_4, 3-ClC_6H_4, 4-FC_6H_4, 4-$NO_2C_6H_4$, 2,3-$F_2C_6H_4$, *n*-C_8H_{17}, *n*-C_7H_{15}, 4-MeC_6H_4, 4-$MeOC_6H_4$

Scheme 90



193 194

6.2. Intramolecular Brønsted Acid Catalyzed Hydroamination of Alkenes

Intramolecular hydroamination is of great interest, because nitrogen-containing heterocycles are synthesized from aminoolefins. The first example of a Brønsted acid-catalyzed intramolecular hydroamination was reported by Schlummer and Hartwig.[422] Aminoalkenes **193** bearing an electron-withdrawing group at the nitrogen atom led to pyrrolidines and piperidines **194** in excellent yields in the presence of a substoichiometric amount of triflic acid in toluene (Scheme 90 and Table 71). Lactams (**193**, X = O) were also prepared under the same reaction conditions starting from amides (Scheme 90 and Table 71). In the case of using sulfuric acid as catalyst, yields were generally lower. In a proposed mechanism, the alkenyl tosylamide is protonated first at the tosylamide group, the proton then transferred intramolecularly to the double bond, and finally, the resulting carbocation is trapped by the sulfonamide, which liberates a proton for continuing the catalytic process. The regiochemistry of the process is determined mostly by the stability of the carbenium ion intermediate, thus, most of these transformations are unfavorable 5-*endo*-trig cyclizations, according to the Baldwin's rules.[450]

Yin and Zhao applied the former methodology to the synthesis of indolines and quinolines using *N*-arylsulfonyl-2-allylanilines as starting materials, the process being carried

Table 71. Selected Examples of Brønsted Acid-Catalyzed Intramolecular Hydroamination of Protected Alkenylamines 193

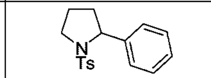
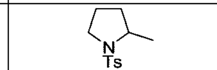
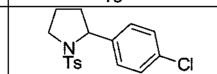
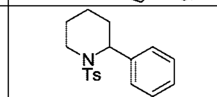
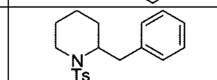
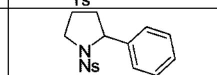
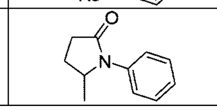
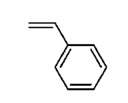
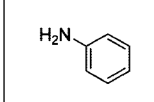
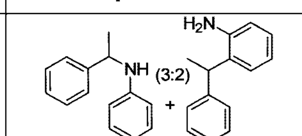
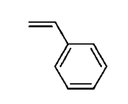
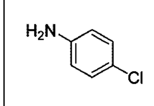
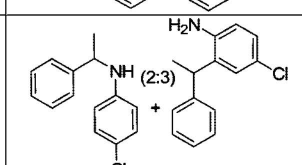
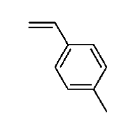
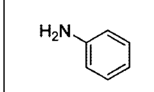
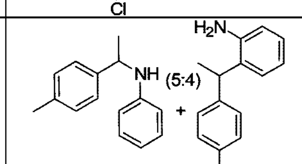
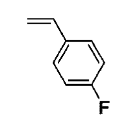
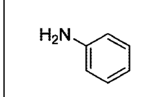
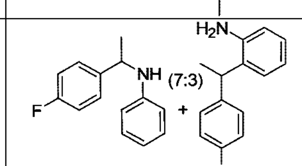
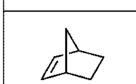
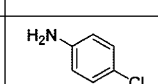
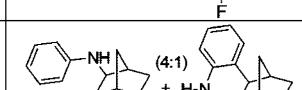
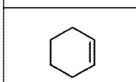
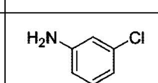
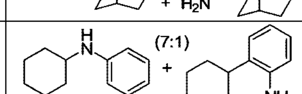
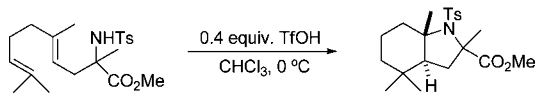
Starting alkenylamine 193				Reaction product 194	Yield / %
R	X	n	PG		
Ph	H	1	Ts		83
H	H	2	Ts		95
4-ClC_6H_4	H	1	Ts		88
Ph	H	2	Ts		83
Ph	H	3	Ts		51
Ph	H	2	Ns		95
H	O	2	Ph		99

Table 70. Selected Examples of Hydroamination and Hydroarylation of Olefins

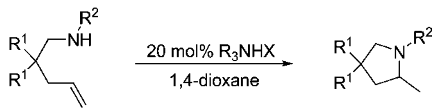
Olefin 183	Aniline 184	Reaction conditions	Reaction products 186 and 187	Yield / %
		135 °C 48 h	 (3:2)	98
		135 °C 24 h	 (2:3)	86
		135 °C 24 h	 (5:4)	80
		135 °C 24 h	 (7:3)	82
		135 °C 24 h	 (4:1)	77
		150 °C 70 h	 (7:1)	17

Scheme 91



195 196

Scheme 92



197 198

out in toluene at 80 °C in the presence of a catalytic amount of triflic acid.[451]

Almost simultaneously to the study of Schlummer and Hartwig,[422] Haskins and Knight demonstrated that triflic acid was an excellent catalyst for inducing overall 5-*endo* cyclization of homoallylic sulfonamides to give pyrrolidines.[452] They applied this methodology to the synthesis of polycyclic compounds through a cationic cascade terminated by a sulfonamide group. For instance, geranyl derivative **195** underwent rapid cyclization at 0 °C to give 90% isolated yield of the trans-annulated pyrrolidine **196**, as a 3:2 epimeric mixture at the amino ester stereogenic center (Scheme 91).

Intramolecular hydroamination reactions of nonactivated alkenes with basic alkylamines using Brønsted acid catalysis were unknown until Ackermann et al. found that ammonium salts of weakly coordinating anions enabled efficient catalysis. The reaction conditions allowed the use of substrates bearing a variety of valuable functional groups, so *bis*-homoallyl amines **197** were converted into pyrrolidines **198** in high yields (Scheme 92 and Table 72).[453] This protocol is not restricted to *gem*-disubstituted substrates and can be applied to primary alkylamines.

7. Base-Catalyzed Hydroamination of Alkenes and Alkynes

The nucleophilic addition of amines to non-activated olefins and alkynes[454] is unfavorable mostly due to the electrostatic repulsion between the lone electron pair on the nitrogen and the π system of multiple bonds. By contrast, the nucleophilic addition of amines takes place smoothly to activated olefins bearing electron-withdrawing substituents. Deprotonation of the amine enables the nucleophilic attack also on nonactivated alkenes. Regarding the mechanism of the base-catalyzed hydroamination of olefins, deprotonation of the amine with a strong alkali base leads to the alkali amide **I** (initiation step). This highly nucleophilic intermediate slowly adds to the olefin to give a more reactive organometallic species **II**, which immediately deprotonates the amine present in the reaction medium to yield the hydroamination reaction product regenerating the alkali amide **I** (Scheme 93).

7.1. Base-Catalyzed Hydroamination of Alkenes

7.1.1. Intermolecular Reactions

The base-catalyzed hydroamination of aliphatic olefins has to be carried out at high temperatures and pressures. Otherwise the process does not take place, or it proceeds with very low yield. Some representative examples are shown in Table 73.

The reaction of amines with 1,3-butadienes in the presence of different bases (alkali metal, alkyllithium, etc.) yields the corresponding 1,4-addition products. Regarding the stereochemistry of the resulting double bond in the products, it varied from predominantly *E* to nearly exclusive *Z*, depending on the structure of the amine and the solvent used. Similarly, arylic olefins react regioselectively with amines in the presence of bases, leading to the hydroamination product resulting from the attack of the nitrogen on the olefinic carbon atom that is not bonded to the aromatic ring. This process is governed by the stability of the intermediate of type **II** (R″ = Ar) shown in Scheme 93. A few representative examples are shown in Table 74.

Beller et al. studied in depth the catalytic hydroamination reaction of ethene with diethylamine in the presence of lithium diethylamide.[463] Several tertiary amines were synthesized and screened as ligands for this reaction (Scheme 94 and Table 75). After optimization of the process, the highest yields and shorter reaction times were found using *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylentriamine (PMDTA) as ligands, but ligand degradation was also observed. Applying this methodology, the hydroamination of substituted olefins was possible at higher temperatures.

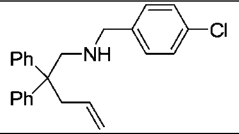
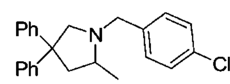
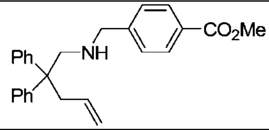
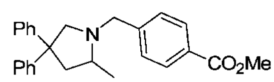
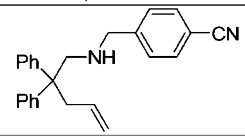
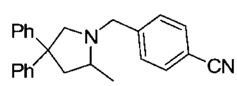
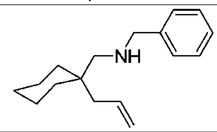
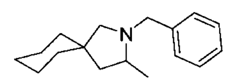
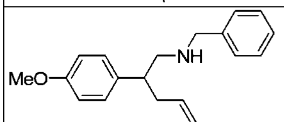
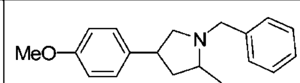
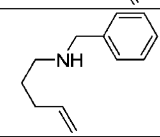
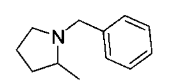
The base-catalyzed hydroamination reaction of styrenes **199** with monobenzylated piperazine (**200**) has been used by Beller's group as a key step in the synthesis of *N*-(heteroarylcarbonyl)-*N*′-(arylalkyl)piperazines **202**, which are central nervous system active compounds.[464] Thus, the reaction of styrenes **199** with *N*-benzylpiperazine (**200**) in the presence of 0.1−0.2 equiv of *n*-BuLi at 65−120 °C yields *N*-benzyl-*N*′-(2-arylethyl)piperazines **201** in good yields. The process takes also place at room temperature in similar or even better yields than at higher temperatures, when it is performed in a 2:1 olefin/amine ratio (Scheme 95, Table 76). A variant involves prior isomerization of allylbenzene to β-methylstyrene.[465]

A better substrate than styrenes **199** for hydroamination is the 1-vinylxanthone derivative **203**, as the electron-withdrawing carbonyl group ortho to the vinyl group ought to increase the electrophilicity of the double bond and stabilize the benzylic anion generated during the amination process. When compound **203** was reacted with different lithium amides in THF the corresponding phenethylamines **204** were obtained in high yields (Scheme 96).[416] This phenethylamines **204** are direct precursors of [1]benzopyrano[2,3,4-*i*,*j*]isoquinolines **205**.

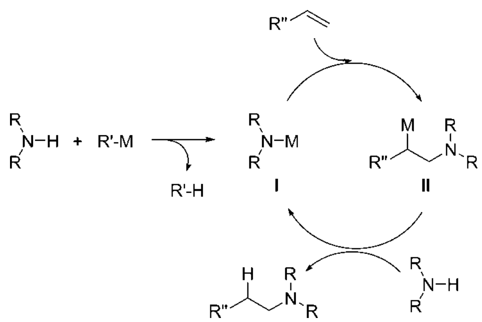
The oxazolidine ring facilitates also the hydroamination of vinylarenes. Seijas et al. studied the addition of the lithium amide derived from *N*-methylbenzylamine to oxazolidine **206**. Very low yields were obtained, when the reaction was performed at −55 °C in THF. An enhancement of the reactivity was achieved by performing the reaction at room temperature leading to compound **207** in 63% yield (Scheme 97).[466] This methodology was used in the synthesis of *N*-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**208**).

The nucleophilic addition of amines to activated olefins, which means olefins bearing electron-withdrawing groups, can take place even without the presence of any catalyst although bases facilitate the process enormously. The conjugate addition of chiral lithium amides to α,β-unsaturated esters is of special interest, because β-aminoesters can be prepared with high stereoselectivity (up to >99% de) through this protocol. Some examples are shown in Table 77.

Table 72. Selected Examples of Hydroamination of Nonactivated Alkenes with Basic Alkylamines

Starting alkylamine **197**	Reaction conditions	Reaction product **198**	Yield / %
	NH_4^+ Tfa^- 130 °C, 24 h		84
	NH_4^+ Tfa^- 130 °C, 24 h		93
	NH_4^+ Tfa^- 130 °C, 24 h		82
	$[PhMe_2NH]^+$ $[B(C_6F_5)_4]^-$ 120 °C, 24 h		84
	$[PhMe_2NH]^+$ $[B(C_6F_5)_4]^-$ 120 °C, 24 h		82 (2.6:1)
	$[PhMe_2NH]^+$ $[B(C_6F_5)_4]^-$ 120 °C, 24 h		74

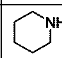
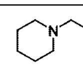
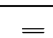
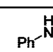
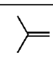
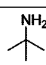
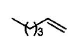
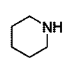
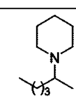
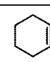
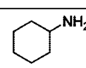
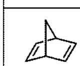
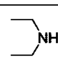
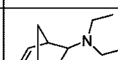
Scheme 93



Several reports have appeared in recent years regarding the use of lithium amides in conjugated addition reactions, acting as nucleophiles instead of as bases.[470] For instance, Tomioka et al. studied the stereoselective addition of lithium amides to α,*β*-unsaturated esters **209** in the presence of the chiral diether **210**. The aminoesters **211** are obtained in high chemical yield and ee (Scheme 98).[471–475]

More recently, the conjugate addition of chiral lithium amides to substituted acrylates has found wide applicability, for instance, in the synthesis of sperabillins B and D,[476] as well as the synthesis of different substituted 3-aminopyrrolidines[477] and of homochiral 3-alkyl-cispentacin and 3-alkyl-transpentancin derivatives, in this last case through a kinetic resolution of *tert*-butyl 3-alkylcyclopentene-1-carboxylates.[478] The highest distereoselectivities of the resulting *β*-aminoesters[479] were obtained using *N*-benzyl or *N*-allyl *N*-α-methylbenzylamides at low temperature (−78 °C). The stereoselectivity of these processes slightly decreases at higher temperatures. Regarding the esters, *tert*-butyl esters led to higher chemical yields than in the case of methyl or ethyl esters. The *tert*-butyl unit seems to prevent 1,2-addition

Table 73. Selected Examples for Alkali Metal-Catalyzed Amination of Aliphatic Olefins

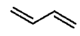
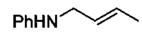
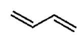
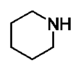
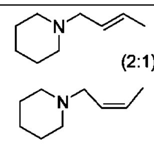
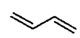
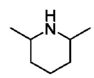
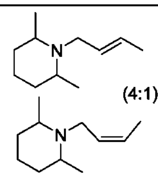
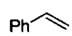
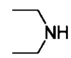
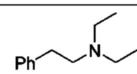
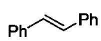
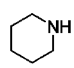
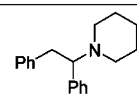
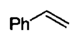
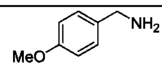
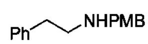
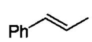
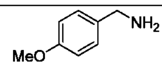
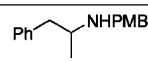
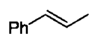
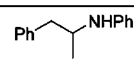
Alkene	Amine	Product	Catalyst	Reaction conditions	Yield / %	Ref.
			Na, Py	100 °C 41-55 bar	80	455
	$PhNH_2$		$NaNH_2$	275 °C 41-55 bar	75	456
	NH_3		Na	250 °C 800-950 bar	32	456
			$NaNH_2$	225 °C	9	456
	NH_3		Na	250 °C 800-950 bar	17	456
			$LiNEt_2$/ TMEDA	150 °C	18	457

of the nucleophile to the carbonyl group. These processes can also be performed using acrylates with straight and branched chains at *β*- as well as at α-positions.

The conjugate addition of chiral *N*-benzyl-*N*-α-methylbenzylamides to α,*β*-unsaturated Weinreb amides **212** proceeds with high diastereoselectivity. The resulting reaction products **213** can be transformed into either *β*-aminoketones **214** by reaction with organomagnesium reagents or *β*-aminoaldehydes **215** upon reduction with DIBAL-H. Davies et al. synthesized (*S*)-coniine (**216**) following this strategy (Scheme 99).[480]

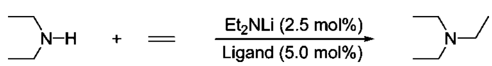
The same protocol has been applied to the synthesis of *syn*-α,*β*-dialkyl amino acid derivatives **218**, which are interesting building blocks because of their sheet-forming

Table 74. Selected Examples for Alkali Metal-Catalyzed Amination of 1,3-Butadienes and Aryl Substituted Olefins

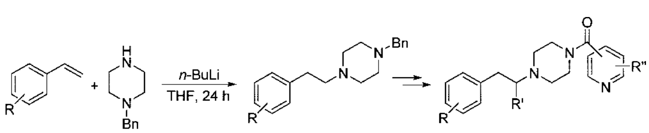
Olefinic substrate	Amine	Product(s)	Catalyst	Reaction conditions	Yield / %	Ref.
	PhNH2		Na	120 °C	79	458
		 (2:1)	*s*-BuLi	50 °C	83	459
		 (4:1)	*s*-BuLi	50 °C	50	459
			*s*-BuLi	50 °C	57	459
			*n*-BuLi	50 °C	10	459
			LiN(SiMe3)2/ TMEDA	120 °C	78	460
			LiN(SiMe3)2/ (-)-sparteine	120 °C	60[a]	460
	PhNH2		*t*-BuOK	120 °C	50	461,462

[a] 14 % ee.

Scheme 94



Scheme 95



199 200 201 202

propensity and their presence in bioactive compounds. The conjugate addition of the chiral lithium amide to α,β-unsaturated tert-butyl esters **217** took place in moderate yields and high diastereoselectivities (Scheme 100).[481]

A different strategy to prepare β-amino acids of type **221** was reported by Davies's group. In this case, the conjugate addition of lithium dibenzyl amide to *N*-acryloyloxazolidinones **219**, followed by alkylation of the resulting enolate provided a highly stereoselective route to β-amino oxazolidinones **220**, which were easily converted into 2-alkyl-3-aminopropionic acids **221** in good yield and high ee (Scheme 101).[482]

Homochiral *anti*-α-*tert*-butylthio-β-amino ester **224** was prepared by a tandem conjugate addition of homochiral

Table 75. Influence of Different Ligands in the Hydroamination of Ethene

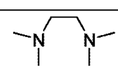
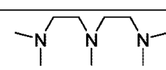
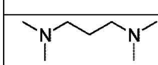
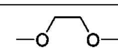
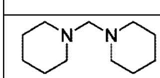
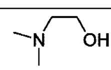
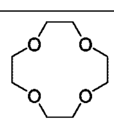
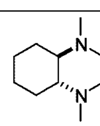
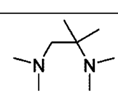
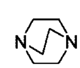
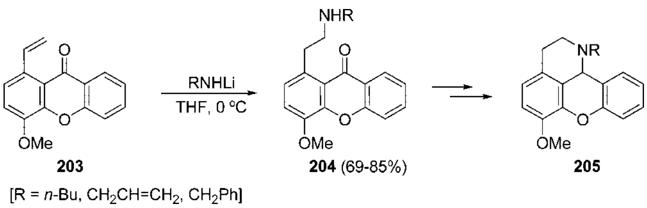
Ligand	Conv. / %	Yield / %	Ligand	Conv. / %	Yield / %
	99	92		99	90
	10	9		-	-
	19	17		-	-
	-	-		-	-
	14	14		7	6

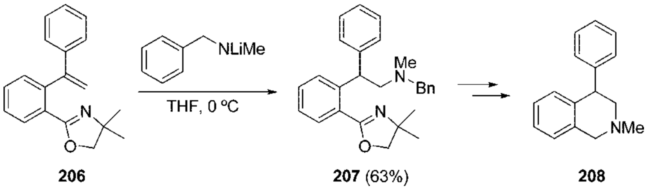
Table 76. Base-Catalyzed Hydroamination of Vinylarenes with Benzylated Piperazine To Give Compounds 201

R	olefin/amine	*n*-BuLi, mol %	*T*, °C	conv, %	yield, %
H	1:1	10	120	94	94
H	2:1	20	20	82	80
4-Cl	1:1	10	65	92	38
4-Cl	1:1	20	120	92	65
4-Cl	2:1	20	20	99	60
4- OMe	1:1	10	65	98	71
4-OMe	1:1	20	120	96	92
4-OMe	2:1	20	20	100	99
4-F	1:1	10	65	28	15
4-F	1:1	20	120	66	57
4-F	2:1	20	20	98	87
3-Br	1:1	10	65	89	40
3-Br	2:1	20	20	90	41
3-CF_3	1:1	10	120	80	60
3-CF_3	2:1	20	20	78	69

Scheme 96



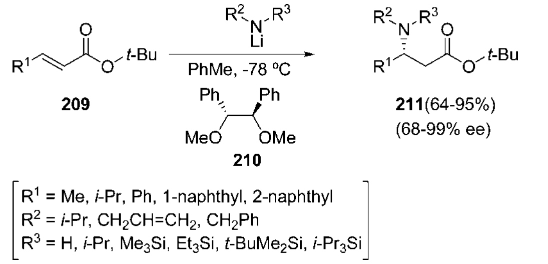
Scheme 97



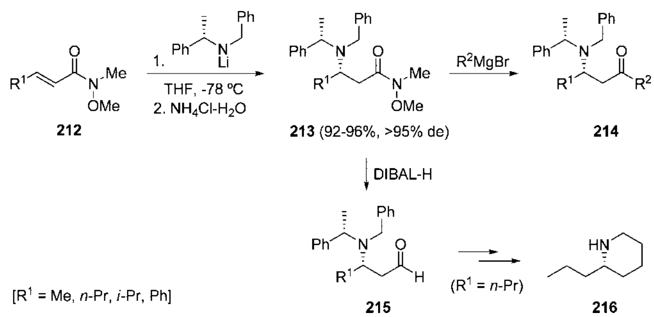
lithium *N*-benzyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to *tert*-butyl cinnamate **222** and enolate **223** trapping with *t*-BuSTs (Scheme 102).[483] This methodology was applied to the synthesis of polysubstituted thiomorpholines.

The addition of homochiral lithium amides to a THF solution of dialkyl (*E*,*E*)-nona-2,7-dienedioate **225** at −78 °C led to the corresponding cyclic 1,2-*anti*-1,6-*anti*-*β*-amino ester **226** derived from a conjugate addition and an intramolecular enolate cyclization in high de (Scheme 103).[484]

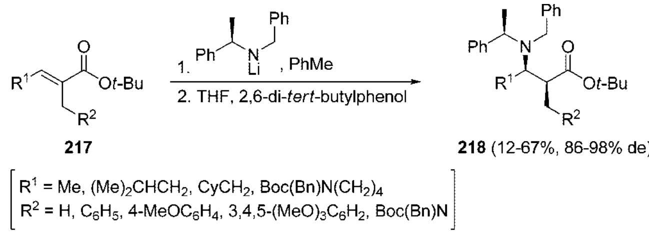
Scheme 98



Scheme 99



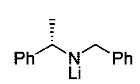
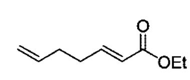
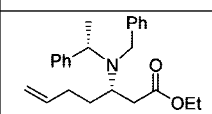
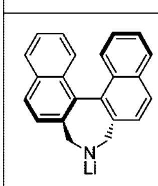
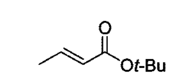
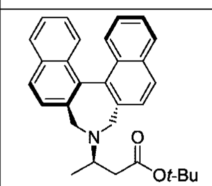
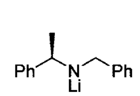
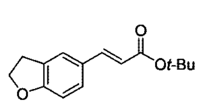
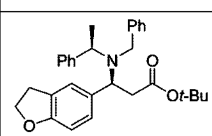
Scheme 100



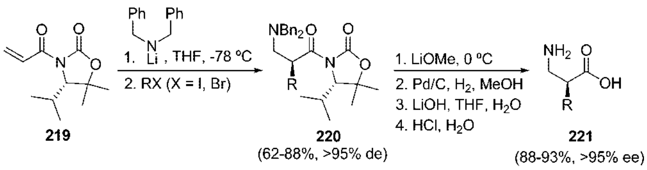
However, the addition of dienedioate to a large excess of lithium amide led predominantly to the reaction product of double addition.

An intermolecular version of the above-mentioned trapping of the enolate resulting from the conjugate addition of a homochiral lithium amide to an α,*β*-unsaturated ester with a second α,*β*-unsaturated acceptor allowed the synthesis of polysubstituted piperidones **230**. Thus, the conjugate addition of lithium (*S*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to acrylates **227** and subsequent coupling

Table 77. Conjugate Addition of Chiral Lithium Amides to α,*β*-Unsaturated Esters

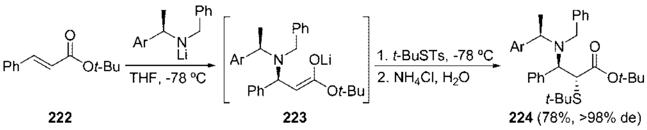
Lithium amide	Activated olefin	Product	*de* (%)	Yield (%)	Ref.
			>95	93	467
			>95	83	468
			95	72	469

Scheme 101



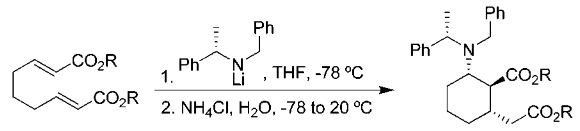
[R = Me, Et, Bn]

Scheme 102

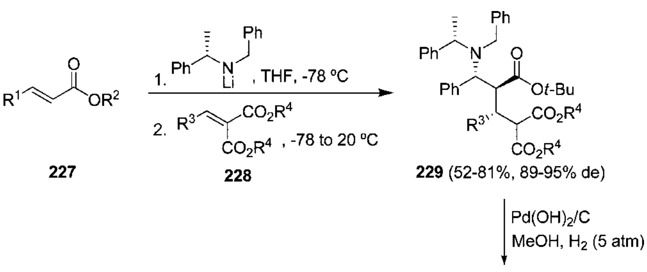


[Ar = $4MeOC_6H_4$]

Scheme 103

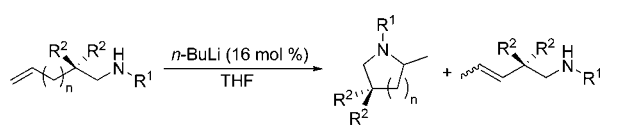


Scheme 104



[R^1 = Me, Ph, 3,4-$(MeO)_2C_6H_3$
R^2 = *i*-Pr, *t*-Bu
R^3 = Me, Et, Ph, 4-BrC_6H_4
R^4 = Me, Et]

Scheme 105



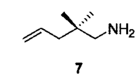
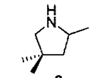
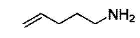
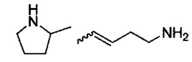
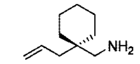
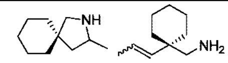
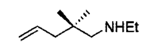
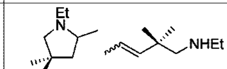
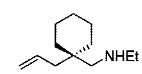
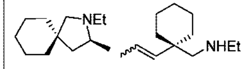
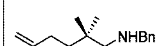
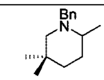
231 232 233
[n = 1, 2]

of the resulting enolate with alkylidene malonates **228** led to amino polyesters **229** with high levels of 2,3-*anti* stereoselectivity. Hydrogenolysis of **229** and concomitant cyclization led to piperidones **230**. Higher yields and diastereoselectivities were observed with β-aryl substituents in both ester and malonate components, although the reaction tolerated both β-alkyl and β-alkenyl functionalities (Scheme 104).[485]

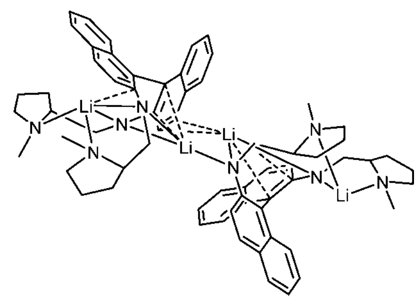
7.1.2. Intramolecular Reactions

Ates and Quinet reported the first intramolecular cyclization of primary and secondary amines onto nonactivated alkenes in THF at 50 or 20 °C using *n*-BuLi (5−16 mol %) as the precatalyst.[486] In general, for primary alkenylamines **231**, a mixture of cyclized product **232** and the isomerized alkene **233** was generated (Scheme 105 and Table 78). However, the alkene isomerization was suppressed in the case of 2,2-disubstituted substrates (*gem*-dialkyl effect).[114] On the other hand, secondary amines under the same reaction conditions yield the desired pyrrolidines or piperidines more rapidly meanwhile olefin isomerization occurs to a lesser extent (see examples in Table 78). The structure of the lithium−substrate complex is critically dependent on the solvent. A 1:1 mixture of tetrahydropyran and toluene is best for hydroamination and avoids alkene isomerization.[487] The butyllithium catalyzed cyclization of 1,5-disubstituted 5-aminoalkenes is stereoselective providing *cis*-2,5-disubstituted pyrrolidines.[488]

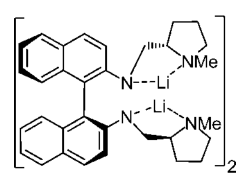
Table 78. Selected Examples for Intramolecular Hydroamination of Primary and Secondary Amines

Substrate	Product(s)	Time (h)	T (° C)	Yield / %
 7	 8	2	50	85
 27	 (32:68)	2	50	75
 86	 (95:5)	24	20	91
	 (>98:2)	5	20	84
	 (>98:2)	5	20	86
		20	50	95

Scheme 106

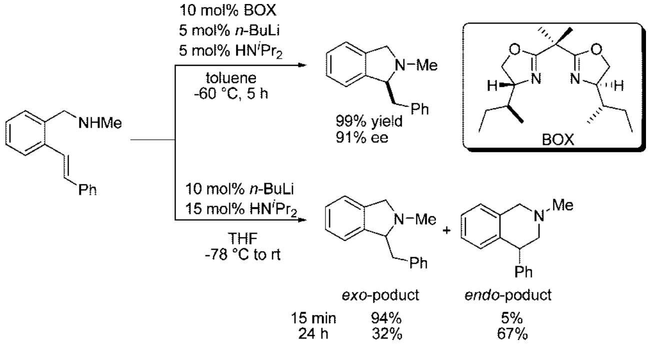


Dimeric proline-derived diamidobinaphthyl dilithium salts **234**, resulting from the deprotonation of the corresponding tetraamines with *n*-BuLi, represent the first example of a chiral main group metal based catalyst for asymmetric intramolecular hydroamination reactions of aminoalkenes.[489] Starting tetraamines were prepared in two steps from Boc-L-proline and racemic aminobinaphthyl (first coupling followed by $LiAlH_4$ reduction), followed by lithiation generating the dilithium salt **234** as a yellow-orange powder, which possesses a dimeric structure (Scheme 106), as revealed by X-ray crystallography. Hultzsch et al. demonstrated that compound **234**



234

Scheme 107



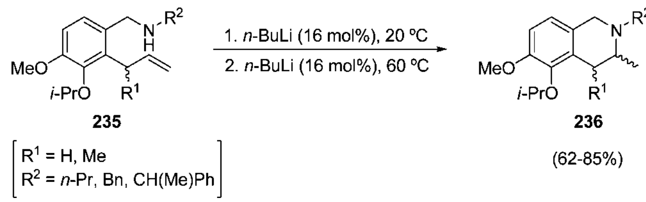
with (*S*,*S*,*S*) configuration is a suitable catalyst for asymmetric intramolecular hydroamination reactions of different aminopentene derivatives (Table 79). The reactions are performed in C_6D_6 and addition of THF significantly reduced the catalytic performance requiring elevated temperatures and resulted in lower enantioselectivities.

More recently, Tomioka et al.[490] have utilized a chiral bisoxazoline ligand in the lithium-catalyzed asymmetric hydroamination/cyclization of amino-substituted stilbenes with enantioselectivities reaching as high as 91% ee (Scheme 107). The reactions were performed in toluene at −60 °C to give the *exo* cyclization product under kinetic control. However, the hydroamination/cyclization reaction in THF solution is reversible, producing the thermodynamically favored *endo* cyclization product.

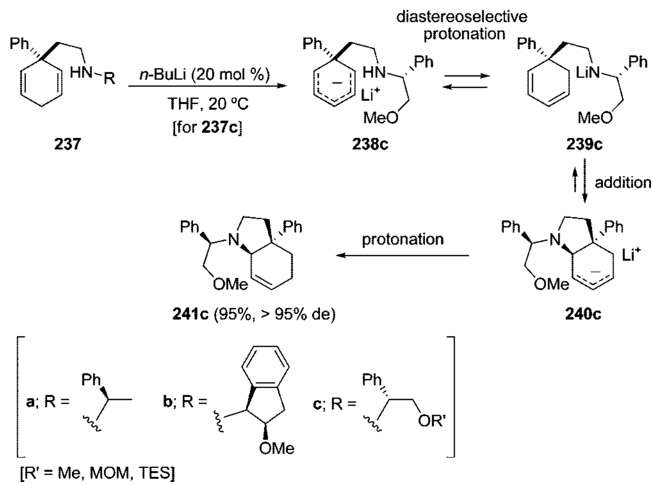
The synthesis of 3-methyltetrahydroisoquinolines (R^1 = H) and 3,4-dimethyltetrahydroisoquinolines (R^2 = Me) **236** from aromatic aminoalkanes **235** using intramolecular hydroamination reactions mediated by substoichiometric amounts of *n*-butyllithium has been reported by van Otterlo et al. (Scheme 108).[491] All attempts to apply this strategy to the stereoselective synthesis of tetrahydroisoquinolines failed. Treatment of enantiomerically pure aminoalkene **235** [R^2 = CH(Me)Ph] with *n*-butyllithium led to a mixture of diastereoisomers. Thus, cyclization involving chiral benzylamine derivatives was not selective under these conditions.

Bicyclic allylic amines **241** have been prepared by intramolecular hydroamination of cyclohexa-2,5-dienes **237** with high selectivity. The reaction does not proceed through a direct hydroamination of one of the diastereotopic olefins

Scheme 108



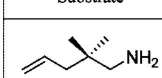
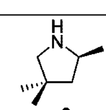
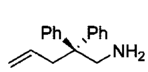
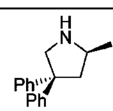
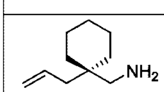
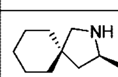
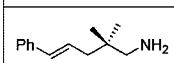
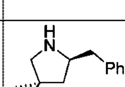
Scheme 109



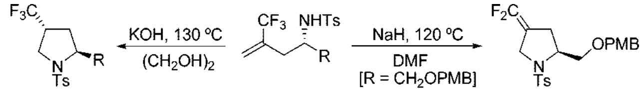
but more likely involves a diastereoselective protonation of a initially formed pentadienyl anion **238**, followed by addition of a lithium amide across the double bond of the resulting 1,3-diene **239**, and final highly regioselective protonation of the allylic anion **240** (Scheme 109).[492] The best results were obtained using phenylglycinol-derived chiral auxiliaries **237c** [R = $CH(Ph)CH_2OR'$], which led to the cyclized product **241c** in excellent yield as a single isomer.

Ichikawa and et al. reported a divergent chemical synthesis of prolines bearing fluorinated one-carbon units at the 4-position via nucleophilic 5-*endo-trig* cyclizations.[493] Thus, pyrrolidines **243** bearing a trifluoromethyl group at the 4-position with 2,4-*anti* stereoselectivity were prepared by heating tosylamides **242** at 130 °C with an excess of KOH in ethylene glycol. A nucleophilic addition takes place in a 5-*endo-trig* fashion under these protic conditions. Meanwhile, the reaction of tosylamide **242** [R = CH_2OPMB] with NaH at 120

Table 79. Selected Examples for Asymmetric Intramolecular Hydroamination of Aminopentene Derivatives[489]

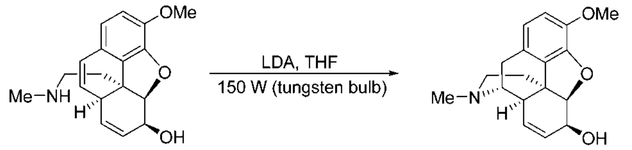
Substrate	Product	Cat. / mol %	*T* / °C	*t* / h	Yield / %	*ee* / %
 **7**	 **8**	**234** (5) **234** (2.5) **234**·4THF (5)	22 22 80	43 45 407	96 93 66	68 67 53
 **84**	 **85**	**234** (5) **234**·4THF (5)	22 80	0.8 27	97 70	31 24
 **86**	 **87**	**234** (5) **234**·4THF (5)	20 60	2 91	98 64	74 69
		**234** (5)	22	0.08	98	17

Scheme 110



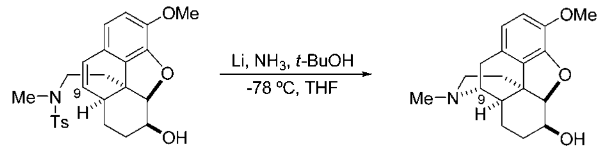
243 242 244 (90%)
(68-85%; *anti*:*syn* = 70:30-92:8)
[R = CH_2OPMB, Ph, 2,4-$(OMe)_2C_6H_3$]

Scheme 111



245 246 (57%)

Scheme 112



247 248 (85%)

°C in DMF (aprotic basic conditions) yielded the pyrrolidine **244** bearing a difluoromethylene group at the 4-position through a S_N2'-type 5-*endo-trig* cyclization (Scheme 110).

The last step of the enantioselective synthesis of (−)-codeine (**246**) reported by Trost and Tang consisted of an intramolecular hydroamination.[4,494] Simply treating amine **245** with LDA or *n*-butyllithium under refluxing THF led to the recovery of the starting material. However, subjecting the solution of the amine **245** and LDA in THF to irradiation with a 150 W tungsten bulb led to cycloaromatization to form (−)-codeine (**246**) (Scheme 111). The addition is facilitated by single electron transfer, which is promoted by irradiation.[495–497]

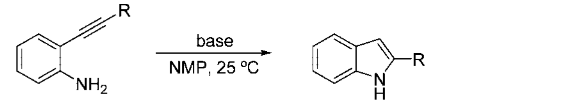
Parker and Fokas followed a similar strategy for the synthesis of codeine derivatives. In this case, the C(9)−N bond connection was accomplished through an intramolecular addition of the anion (or N-centered radical) generated by reductive detosylation of the tosylamide **247**. Although the reductive desulfonation of olefinic sulfonamides had not previously resulted in a cyclization event, treatment of compound **247** with Li/NH_3 in the presence of *t*-BuOH afforded (±)-dihydroisocodeine (**248**) in good yield (Scheme 112).[498]

7.2. Base-Catalyzed Hydroamination of Alkynes

The base-catalyzed hydroamination of alkynes[499] with substituted anilines and heterocyclic amines was first reported by Knochel et al. in 1999.[500] The reaction is performed in the presence of a catalytic amount of cesium hydroxide and using *N*-methylpyrrolidine (NMP) as solvent to yield the corresponding mixtures of *cis*/*trans*-enamines in good yields. An intramolecular version of this reaction has been applied to the synthesis of 2-substituted indoles **250** starting from 2-(2-alkynyl)anilines **249** (Scheme 113).[501] It is worth noting that this intramolecular process proceeds at ambient temperature in the presence of several functional groups. Lane and Snieckus studied the intramolecular cyclization of a 2-ethynylbenzenesulfonamide in the synthesis of a saccharin derivative.[502]

Recently, Borhan et al. have reported a mild aza-Payne/hydroamination reaction of aziridinols **251** mediated by

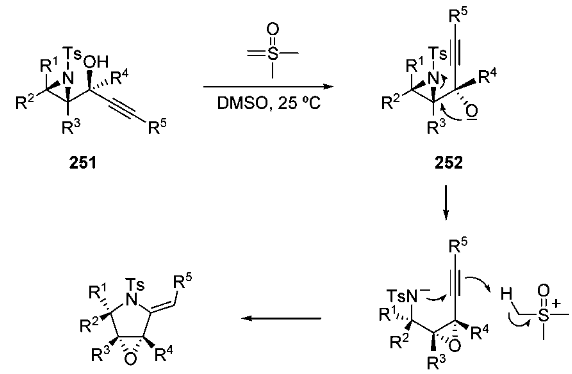
Scheme 113



249 250 (61-90%)

[base = *t*-BuOK, *t*-BuOCs, KH
R = H, *n*-Bu, Cy, $(CH_2)_2OH$, $CH(OEt)_2$, $(CH_2)_3Cl$, 2-$NH_2C_6H_4$, 2-thienyl]

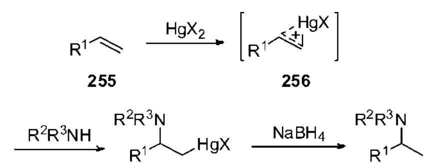
Scheme 114



251 252 253 254 (57-82%)

[R^1 = H, Me, *n*-Bu
R^2 = Me, *n*-C_7H_{15}, CH_2OBn, 4-$OMeC_6H_4$
R^3 = H, Me
R^4 = H, Me
R^5 = H, Ph]

Scheme 115



255 256 257 258

dimethylsulfoxonium methylide that yields highly functionalized pyrrolidine ring systems **254** in a one-pot reaction at room temperature. The hydroamination reaction can be run catalytically in ylide, but the aza-Payne rearrangement from alkoxide **252** to epoxy amide **253** requires an excess of ylide (2−4 equiv). Under these reaction conditions, the epoxy amide **253** led to the corresponding pyrrolidine derivative **254** (Scheme 114).[503] Regarding the stereochemistry of the enamide moiety in **254**, the *Z*-configuration may result from prior coordination of the sulfoxonium to the opposite face of the alkyne, thus leading to a rapid proton transfer and the observed stereochemistry.

8. Amino- and Amidomercuration−Demercuration of Alkenes and Alkynes

The mercury(II) salt-promoted amination of alkenes and alkynes, followed by a demercuration reaction usually performed by sodium borohydride, represents an umpolung process since an amine as nucleophile is able to add to a nonactivated olefin or alkyne, which normally react with electrophiles.[504] This reaction was reviewed first by Lattes et al.[505] as a part of a general account on amination of alkenes and by Alonso et al. covering the addition of amines to alkynes.[9] In Scheme 115, a simple example of a Markovnikov-type reaction of a terminal olefin **255** with a mercury(II) salt is shown. The reaction involves in the first step

Scheme 116

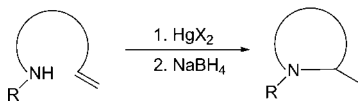
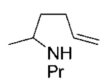
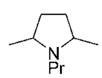
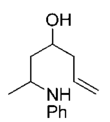
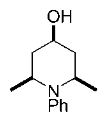
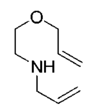
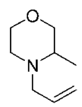
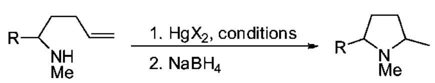


Table 80. Selected Examples of Intramolecular Aminomercuration−Demercuration[505]

Starting material	Product	HgX_2	Solvent[a]	Yield (%)[b]
		$HgCl_2$	THF-H_2O	60 (1:1)
		$Hg(OAc)_2$	THF	57 (8:1)
		$Hg(OAc)_2$	THF-H_2O	53

[a] For the mercuration step. [b] Overall yield based on the starting amine.

Scheme 117



259 260 (28-96%)

conditions	*trans/cis* ratio
$HgCl_2$, H_2O-THF or $Hg(OAc)_2$, THF	84/16-93/7
$HgCl_2$, THF or $CHCl_3$	2/98-36/64

(solvomercuration [506,507]) a mercurinium ion **256**, which suffers the nucleophilic attack of an amine to give the aminomercurial **257**, finally reduced to the amine **258**.

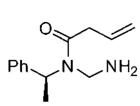
8.1. Aminomercuration−Demercuration of Alkenes

In this section, the literature appearing after 1983[505] will be considered concerning both intra- and intermolecular reactions.

8.1.1. Intramolecular Reactions

The intramolecular version of the aminomercuration−demercuration reaction shown in Scheme 116 was initially described by Lattes et al.[508−510] Table 80 shows some selected examples of this tandem process.

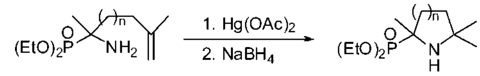
Since then, this tandem process has been applied for the synthesis of different nitrogen-containing heterocycles, for instance, *N*-substituted 2,5-dialkylpyrrolidines **260**, starting from unsaturated amines **259**, as a mixture of cis/trans diastereomers, the corresponding ratio being strongly dependent on the reaction conditions (kinetic or thermodinamic control) (Scheme 117).[511,512]



263

The same reaction was applied to unsaturated α-aminophosphonates **261** to give the expected pyrrolidine ($n = 1$)

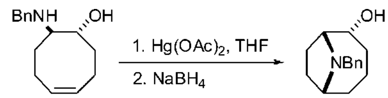
Scheme 118



261 262 (55%)

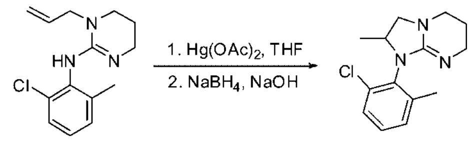
[n = 1,2]

Scheme 119

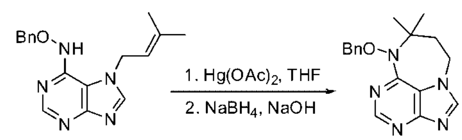


264 265 (70%)

Scheme 120



266 267 (45%)



268 269 (69%)

or piperidine ($n = 2$) derivatives **262**, which have been used for the preparation of the corresponding nitroxides (Scheme 118).[513−518]

An asymmetric version of the reaction described in Scheme 117 starting from the unsaturated chiral amidal **263** was used to prepare chiral perhydropyrimidin-4-ones (as separable diastereomeric mixture), as a protected form of β-aminoacids.[519]

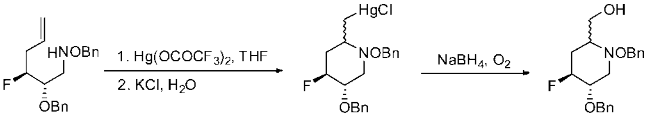
When the starting unsaturated amine has a cyclic structure, as in compound **264**, the corresponding aza-bicyclic system **265** was obtained, after a tandem aminomercuration−demercuration (Scheme 119).[9] It is worth noting that the aminomercuration is preferred to the possible oxymercuration and that the other possible aza-bicyclo[3.3.1] was not observed.[520]

The intramolecular aminomercuration−demercuration has also been applied to the preparation of more complex polynitrogenated heterocycles. Two examples are included in Scheme 120, the first one to generate the bicyclic guanidine **267** from compound **266**[521] and the second one to build the intermediate **269** (from **268**) in the synthesis of asmarines.[522]

Fluorinated analogues of nojirimycin and mannojirimycin have been prepared using an intramolecular aminomercuration as the key step, followed by an oxidation (instead of the most common mercury−hydrogen exchange), so the corresponding hydroxy derivatives were isolated. Thus, for instance, the treatment of the hydroxylamine **270** with mercury(II) trifluoroacetate gave, after anion exchange with potassium chloride, a mixture of two chloromercury derivatives **271**, which were easily separated by chromatography. The final treatment of each mercurial with sodium borohydride under an oxygen atmosphere (radical conditions[523]) gave the corresponding products **272** (Scheme 121).[524,525]

In the field of aza-sugars, carbohydrate-derived δ-aminoalkenes have been cyclized under different conditions

Scheme 121



270 271 (96%, 62:38) 272 (70-74%)

(iodine- or mercury(II)-promoted amination) to study the stereoselection of the process.[526] This chemistry was employed for the preparation of *N*-acetylglucosaminidase inhibitors from a methyl manopyranoside, the key step being shown in Scheme 122 for the transformation of compound **273** into a mixture of diastereomers **274** and **275**, which then were oxidized as it was above mentioned (Scheme 121).[527] The same methodology was used to prepare the enantiomerically pure cyclic aminoalditols 1-deoxynojirimycin and 1-deoxymannojirimycin.[528]

Dhavale et al. have recently reported the mercury(II)-promoted cyclization of some unsaturated amines derived from carbohydrates to synthesize castanospermine analogues. An example is shown in Scheme 123, in which compound **276** is transformed into the pyrrolidine derivative **277** through a tandem mercuration–demercuration.[529,530] It is noteworthy that in this transformation a 5-*endo-trig* cyclization occurred in an exclusive manner, this regiochemistry not being common in intramolecular aminomercuration reactions.

The intramolecular aminomercuration–demercuration methodology has also been applied to synthesize different alkaloid derivatives such as deoxocassine,[531] mesembranol,[532,533] or madangamine A.[534] In Scheme 124, the key steps for the last two cases are shown: in the first case, the unsaturated amine **278** is mercurated and reduced to yield the protected precursor of mesembranol **279**, whereas in the preparation of madangamine the mercuration of the bicyclic amine **280** was followed by oxidation as it was above described (Scheme 121) to yield the tricyclic alcohol **281**.

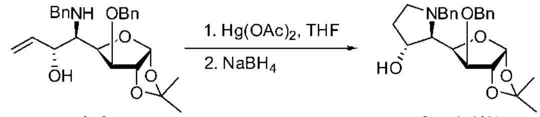
Recently, a similar technology (mercuration-demercuration) has been used for the preparation of the alkaloid vittatine, for which the key step was the transformation of the unsaturated amine **282** into the protected product **283** (Scheme 125).[535]

8.1.2. Intermolecular Reactions

Since the first report on the intermolecular aminomercuration–demercuration by Lattes et al.,[536] this reaction (see Scheme 115) has been widely used as a method to prepare substituted amines from primary or secondary amines and nonactivated olefins.[505] Some selected examples of this tandem process are shown in Table 81.

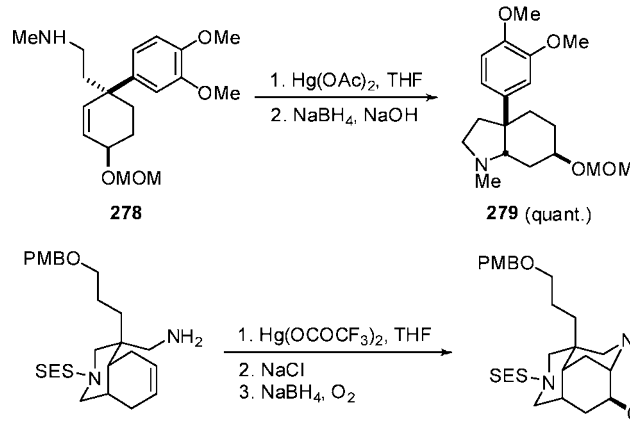
The mechanism of the aminomercuration of olefins, involving different possible mercury(II) salt–amine complexes,[537] has been investigated.[538] The classical tandem aminomercuration–demercuration of unsaturated silanes **284** with aniline[539] or the allylnaphthyl acetate **285** with piperidine[540] has been used to prepare the corresponding substituted amines.

Scheme 123



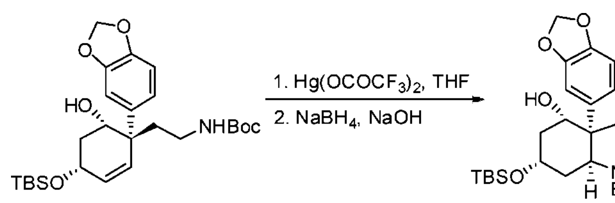
276 277 (74%)

Scheme 124

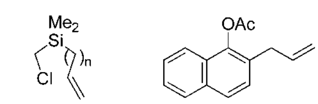


278 279 (quant.) 280 281 (39%)

Scheme 125



282 283 (75%)



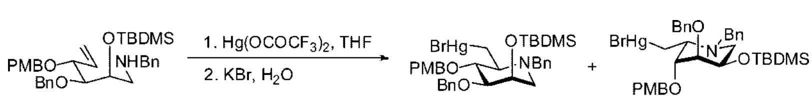
284 (n = 0, 1) 285

Other methodologies based on the aminomercuration of olefins have been developed avoiding the reduction with sodium borohydride as the second step in the whole process. Thus, the use of mercury(II) tetrafluoroborate allows an interesting catalytic version of the aminomercuration of allylic alcohols using aromatic amines. For instance, the reaction of allyl alcohol **286** with aniline **287** under THF reflux using 1% of the mentioned metallic salt produced the corresponding *N*-allylanine **288** (Scheme 126).[541] A mechanism involving a dehydroxymercuration, which regenerates an active mercury(II) species, was proposed.

The same *in situ* generated mercury(II) salt has been used for the chemo- and stereoselective diamination of limonene **289** with aniline. Also in this case, an aminodemercuration takes place to introduce the second amine to yield the final diamine **290** (Scheme 127).[542]

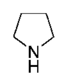
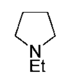
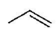
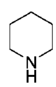
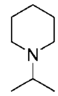
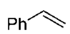
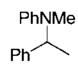
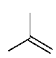
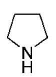
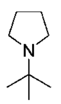
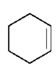
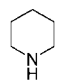
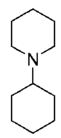
Another interesting variant of the aminomercuration on olefins consists in performing the reductive demercuration in the

Scheme 122



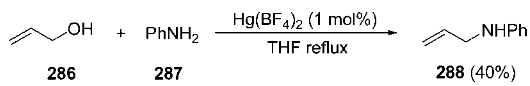
273 274 (78%) 275 (16%)

Table 81. Selected Examples of Intermolecular Aminomercuration−Demercuration[505]

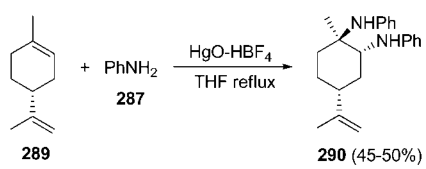
Alkene	Amine	Product	HgX_2	Solvent[a]	Yield (%)[b]
			$HgCl_2$	Amine	60
	$PhNH_2$	PhNHEt	$Hg(OAc)_2$	THF	43
			$HgCl_2$	Amine	45
	PhNHMe		$Hg(OAc)_2$	THF	50
			$HgCl_2$	Amine	70
			$HgCl_2$	Amine	40

[a] For the mercuration step. [b] Overall yield based on the starting amine.

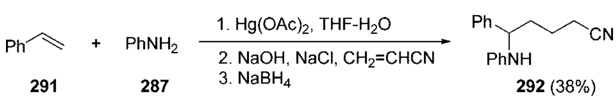
Scheme 126



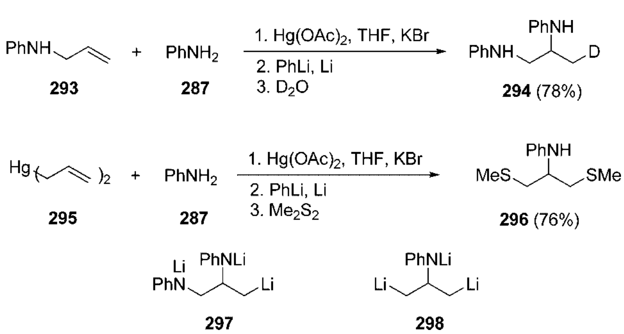
Scheme 127



Scheme 128



Scheme 129



presence of an electrophilic olefin. Since the reduction has been proven to be a radical process,[523] the *in situ* generated radical is trapped by the activated olefin present in the reaction medium generating a new carbon−carbon bond. Scheme 128 shows an example of this tandem reaction starting from styrene (**291**) and aniline and using acrylonitrile as the radical trapping reagent, giving the coupling product **292**.[543]

Scheme 130

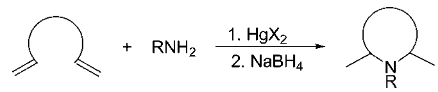
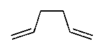
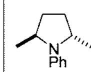
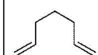
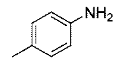
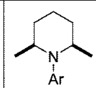
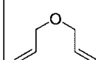
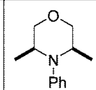
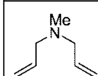
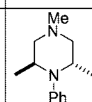
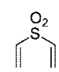
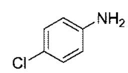
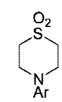


Table 82. Selected Examples of Intermolecular Aminomercuration−Demercuration of Dienes[505]

Diene	Amine	Product	HgX_2	Solvent[a]	Yield (%)[b]
	$PhNH_2$		$Hg(OAc)_2$	THF	99 (49:1)
			$Hg(OAc)_2$	THF	70 (1.5:1)
	$PhNH_2$		$Hg(OAc)_2$	THF	71 (1.4:1)
	$PhNH_2$		$Hg(OAc)_2$	THF	36 (1.4:1)
			$Hg(OAc)_2$	THF	35

[a] For the mercuration step. [b] Overall yield based on the starting amine.

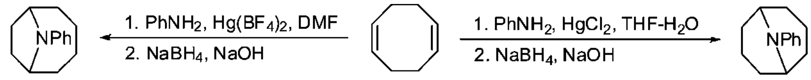
Finally, an interesting transformation of the aminomercurials prepared by aminomercuration of olefins is the mercury−lithium transmetallation initially reported by Barluenga et al. for this type of compound.[544] A couple of examples are included in Scheme 129, in which once starting materials **293** and **295** were mercurated in the presence of aniline, the mercury−lithium exchange followed by reaction with an electrophile (deuterium oxide or dimethyl disulphide, respectively) yielded the expected compounds **294** and **296**, respectively. Before addition of the final electrophile, trianions **297** and **298** were postulated as intermediates in the process.[545]

A special case concerning the intermolecular aminomercuraton appears when a suitable diene reacts with a primary amine, because then a double addition can take place giving a cyclic compound in only one step as it is indicated in Scheme 130.

From the literature up to 1983,[505] some selected examples of nitrogen-containing heterocycles prepared using the aminomercuration−demercuration technology from dienes and primary amines are included in Table 82.

Among different dienes, 1,5-cyclooctadiene (**299**) represents a special case because in the cyclization by aminomercuration two possible bicyclic compounds can be obtained. In fact, depending on the mercury(II) salt, the reaction gave exclusively one or the other bicycle; whereas for nonionic salts, such as mercury(II) chloride, the thermodynamically most stable aza-bicyclo[3.3.1]nonane **300** was obtained after reduction, in the case of using mercury(II) tetrafluoroborate, the corresponding kinetically most stable aza-bicyclo[4.2.1]nonane **301** was the only reaction product isolated after the same work-up (Scheme 131).[546] A nucleophilic demercuration of the same aminomercurial intermediates has also been reported to prepare the functionalized azabiciclononanes.[547]

Scheme 131



301 (60%) **299** **300** (64%)

8.2. Aminomercuration−Demercuration of Alkynes

As was mentioned in the introduction of this section, the aminomercuration of alkynes either in the stoichiometric or in the catalytic version was covered in the review of Alonso et al.[9] The first process, initially described by Hudrlik and Hudrlik,[548] requires a second reduction step, the structure of the corresponding reaction products being dependent of the substitution in the aminic component; whereas with secondary amines enamines are produced, in the case of primary amines, the corresponding imines are the only isolated reaction products (Scheme 132).[9]

Due to the proven toxicity of mercury compounds, a far more interesting chemistry has been developed using catalytic amounts of the mercury(II) salts in the aminomercuration of alkynes. Since the first report of Kozlov et al.,[549] this reaction has allowed the preparation of different enamines or imines without the need for the reduction step. Some selected examples are collected in Table 83.

8.3. Amidomercuration−Demercuration of Alkenes

The amidomercuration−demercuration of alkenes, both in the intra- and intermolecular versions, was almost unknown in the last review article that appeared in 1983 on amination of alkenes,[505] so practically all the reported information on both processes will be considered in this section.

8.3.1. Intramolecular Reactions

Harding et al. have used extensively the intramolecular amidomercuration mainly for the preparation of nitrogenated five-membered heterocycles. Thus, the unsaturated carbamate **302** was mercurated with mercury(II) acetate and then treated with iodine affording the corresponding iodinated pyrrolidine **303**, an intermediate in the synthesis of the alkaloid pseudoconhydrine (Scheme 133).[550]

The same group has also employed the mercuration−demercuration methodology to prepare racemic[551] or enantio-enriched[552] substituted oxazolidines. In Scheme 134, this chemistry is illustrated with two significant examples in which unsaturated carbamates **304** and **306** were transformed into the corresponding heterocycles **305** and **307**, respectively.

Takahata, Momose, et al. reported on a stereoselective intramolecular amidomercuration to prepare 2,5-disubstituted pyrrolidines[553] in a route to synthesize pyrrolizidine[554,555] and indolizidine[556–558] alkaloids. Some selected examples are included in Scheme 135. The chiral unsaturated carbamate **308** was successively mercurated and oxidized to yield the chiral pyrrolidine **309**, an intermediate in the synthesis of pyrrolizidine alkaloids. In the case of compound **310**, the mercuration was followed by radical addition to methyl acrylate during the reduction step yielding the expected *cis*-pyrrolidine **311** used to prepare indolizidine derivatives.

More complex polyhydroxylated pyrrolidines have been prepared from the intermediate **313** generated by a tandem mercuration−oxidation of the unsaturated compound **312** (Scheme 136).[559,560]

Scheme 132

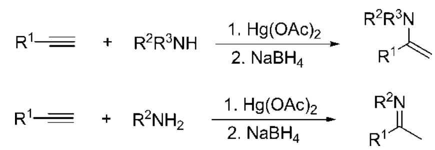
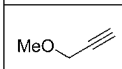
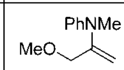
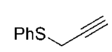
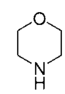
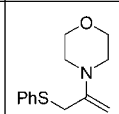
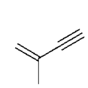
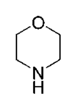
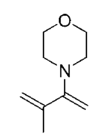
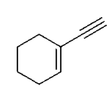
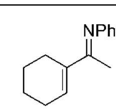
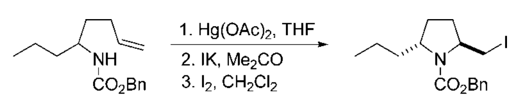


Table 83. Selected Examples of Catalytic Aminomercuration of Alkynes[9]

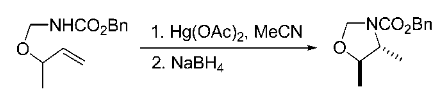
Starting material	Amine	Product	HgX_2 (%)	Yield (%)
	PhNHMe		$HgCl_2$ (5)	41
			$HgCl_2$ (25)	55
			$Hg(OAc)_2$ (75)	61
	$PhNH_2$		$HgCl_2$ (50)	45

Scheme 133

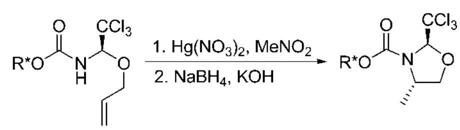


302 **303** (78%)

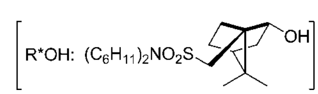
Scheme 134



304 **305** (60-90%)



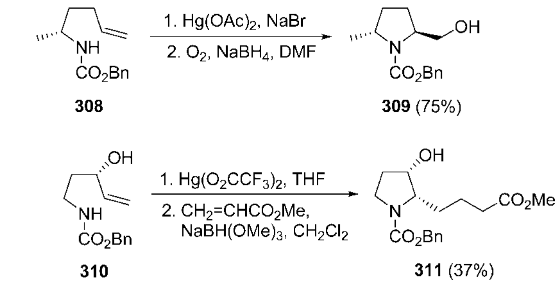
306 **307** (74%)



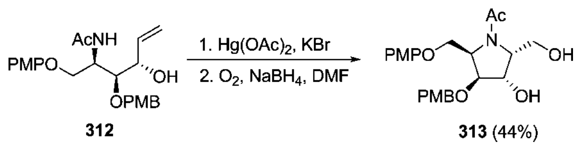
The alkaloid pseudohygroline was prepared by mercuration of compound **314** followed by radical reduction giving the pyrrolidine **315**, a direct precursor of the natural product (Scheme 137).[561]

Tackas et al. described the use of an amidal as a removable auxiliary in amidomercuration reactions. For instance, compound **316** was successively mercurated and reduced to give almost exclusively the corresponding *endo*,*trans*-**317** (less than 0.5% of the *exo*,*cis*-isomer) as a protected form of the corresponding amino alcohol (Scheme 138).[562]

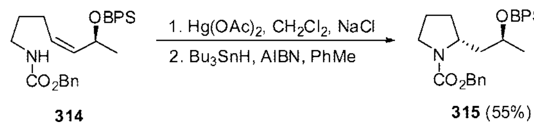
Scheme 135



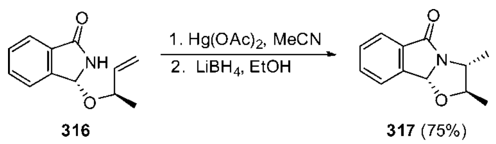
Scheme 136



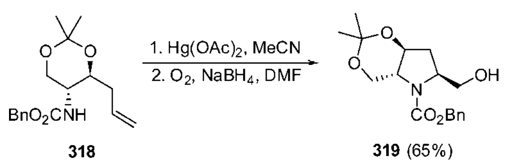
Scheme 137



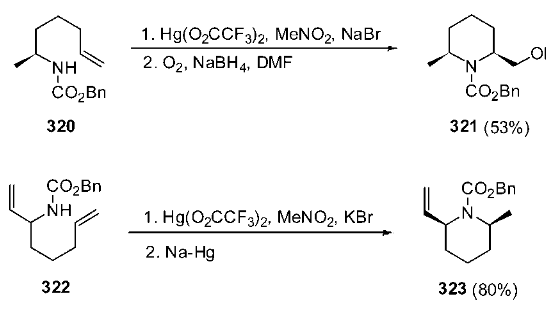
Scheme 138



Scheme 139



Scheme 140

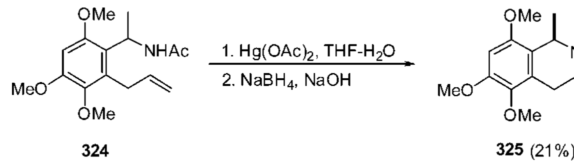


In a recent method to prepare the alkaloid bulgecinine, the chiral unsaturated carbamate **318** was cyclized and oxidized to yield the pyrrolidine **319**, easily transformed into the natural product by oxidation, methylation, and deprotection (Scheme 139).[563]

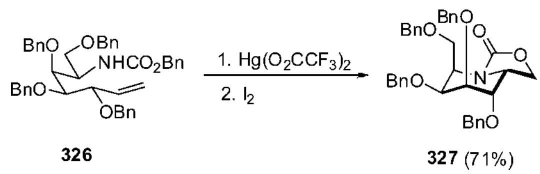
The formation of six-membered heterocycles can be easily achieved through a mercuration process.[564–566] Simple 2,6-dialkylpiperidines, such as **321** or **323**, are thus the resulting products starting from the unsaturated carbamates **320** and **322**, respectively (Scheme 140).[564]

Substituted tetrahydroquinolines are easily accessible by intramolecular amidomercuration,[567–569] as is exemplified in Scheme 141 for the preparation of compound **325** in low yield starting from the unsaturated amide **324**.

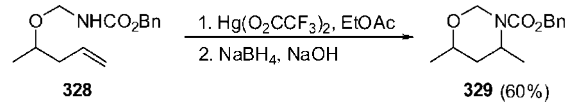
Scheme 141



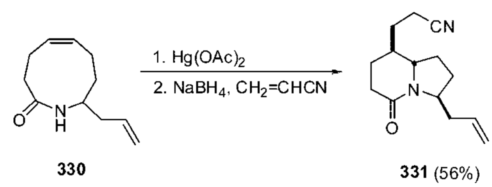
Scheme 142



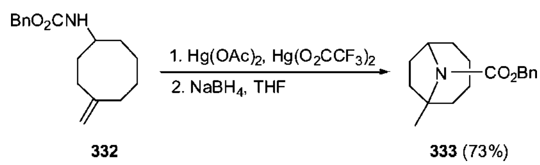
Scheme 143



Scheme 144



Scheme 145



Martin et al. have prepared aza-sugars starting from protected polyhydroxy unsaturated carbamates by using a mercury(II) salt. Thus, the tandem mercuration−iodination of compound **326** yielded the bicycle **327** in a one-pot reaction (Scheme 142).[570]

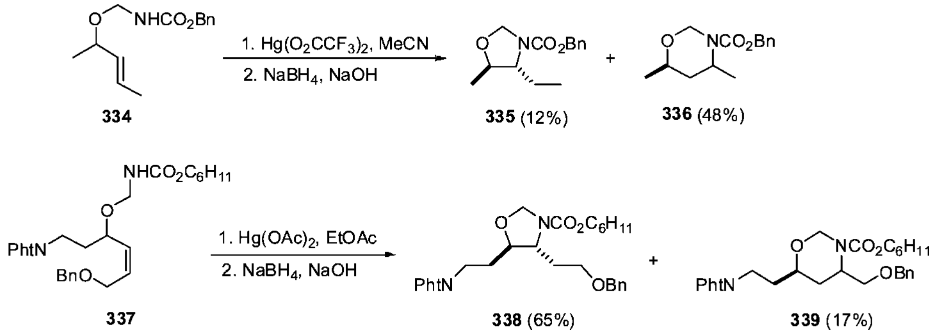
As it was above mentioned (Scheme 134)[551,552] for the five-membered rings, Harding et al. have also applied the same technology to prepare substituted 1,3-oxazines. In Scheme 143, an example is shown for the transformation of the unsaturated carbamate **328** into a 3:1 cis/trans mixture of diastereomers **329**.[571,572]

In the final part of this section, the formation of both five- and six-membered rings at the same time by an intramolecular amidomercuration will be considered. Starting from 1,5-cyclooctadiene is possible to prepare (five steps) the nine-membered lactam **330**, which after mercuration and reductive trapping with acrylonitrile provided the bicyclic lactone **331** (Scheme 144).[573] This strategy was used to prepare a non-peptide mimic of erabutoxin starting also from 1,5-cyclooctadiene through 14 steps.[574]

A related aza-bicycle **333** was synthesized from the exocyclic carbamate **332** by a tandem amidomercuration−reduction and used in the synthetic approach to homotropane analogues (Scheme 145).[575]

In some cases, depending on the substituents in the starting unsaturated carbamate, a mixture of five- and six-membered rings is obtained. This is the case for the mercuration−demercuration of compounds **334** and **337**, for which a mixture of

Scheme 146



heterocycles **335/336** and **338/339**, respectively, is obtained (Scheme 146).[576,577]

In other cases, the unsaturated chain in the starting material fixes the structure of the final heterocycle. For example, the mercuration−demercuration of compounds **340** and **342** gave the benzofused bicycles **341** and **343**, respectively, as the major products (ca. 12:1 diastereomer ratio), the corresponding stereochemistry being dependent on the size of the newly formed ring (Scheme 147).[578,579]

A rather similar case happens starting from simpler carbamates,[580–582] as for compounds **344** and **346**, for which the expected five- and six-membered heterocycles **345** and **347** are the only reaction product isolated (Scheme 148). It is worth noting that whereas for the pyrrolidine the trans isomer was the only one formed, for the piperidine a 1:2 mixture in favor of the cis isomer was produced.

8.3.2. Intermolecular Reactions

The addition of primary amides to nonactivated olefins has been achieved by using mercury(II) nitrate as the metallic promoter. The process, which usually is followed by a mercury/hydrogen exchange, can also be applied to urethanes and urea. Scheme 149 shows representative examples of the three reactions, starting from the olefins **348**, **291**, and **351** and giving the expected compounds **349**, **350** and **352**, respectively.[583]

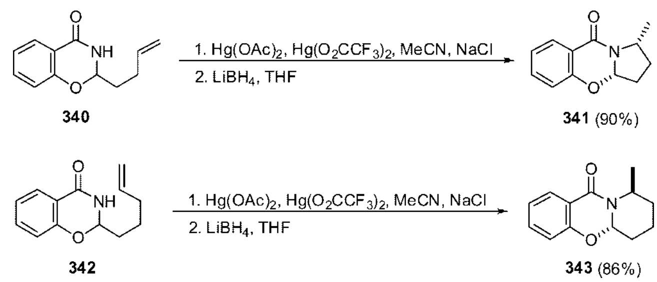
When the former amidomercuration reaction was followed by a radical addition to electrophilic olefins (instead of the shown reduction), a new carbon−carbon bond is formed. For example, starting from cyclohexene and using acrylonitrile as radical acceptor, the reaction yielded the expected coupling product **353** (Scheme 150).[584]

In the synthesis of the 7-methoxybenzolactam-V8, one of the key steps is the intermolecular amidomercuration−oxidation of compound **354** to give the expected product **355** (Scheme 151).[585]

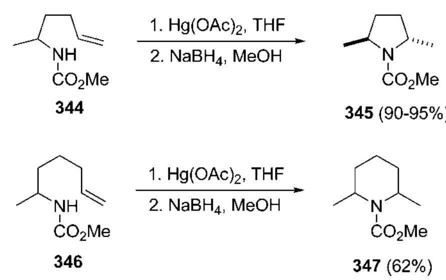
In the case of the amidomercuration of a diene, a monomercuration of tebaine (**356**) with acetamide is the key step to yield the aminomercural **357**, easily transformed into isoneopine (**358**) by simple hydrolysis and final reduction (Scheme 152).[586]

The double addition to dienic compounds using primary carbamates represents a versatile procedure to synthesize heterocycles, the reaction being highly stereoselective compared with the corresponding aminomercuration (Table 82). Thus, either 1,4- or 1,5-hexadiene (**359**) gave the corresponding *cis*-pyrrolidine **360** as the only reaction product isolated after the corresponding final reduction (Scheme 153).[587] The application of the same methodology to diallylether (**361**) yielded exclusively the corresponding *trans*-morpholine (**362**). However, in the case of 1,5-cyclooctadiene (**299**) a 1:1 mixture of the two possible bicycles **363/364** is obtained.[587]

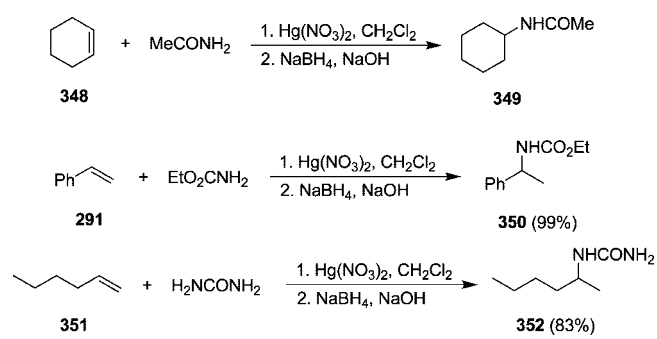
Scheme 147



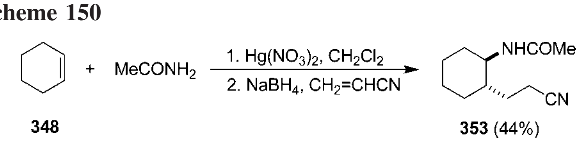
Scheme 148



Scheme 149



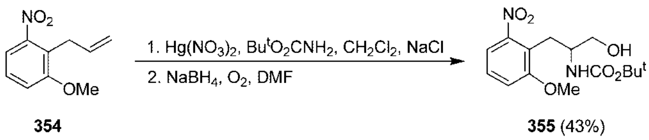
Scheme 150



8.4. Other Aminomercuration−Demercuration Reactions

Other nucleophiles, different from amines or amides, have been reported to be used in mercuration processes. These procedures were not covered in former reviews, so they will be included in this section.

Scheme 151



8.4.1. Sulfonamidomercuration Reactions

The mercury(II) nitrate-promoted addition of *p*-toluene sulfonamide ($TsNH_2$) to nonactivated alkenes represents an indirect way of aminomercuration with ammonia since after the second reduction step the final hydrolysis would liberate the NH_2 group. Scheme 154 shows some examples of this process starting from propylene (**365**), diallyl (**359**), or 1,5-cyclooctadiene (**299**), so the expected products **366**−**369**, respectively, were isolated. The reaction is very stereoselective for the case of diallyl giving exclusively the *cis*-pyrrolidine **367**. For 1,5-cyclooctadiene, a mixture of both regioisomers is obtained (Scheme 154).[588,589]

8.4.2. Phosphoramidomercuration Reactions

Diethyl phosphoramidate (**371**) can be added to nonactivated olefins in the presence of mercury(II) nitrate so that after *in situ* reduction the expected *N*-alkylphosphoramidates were formed in moderate yields. The corresponding reaction with *tert*-butylethylene (**370**) gave the corresponding product **372** (Scheme 155).[590]

8.4.3. Azidomercuration Reactions

To the best of our knowledge the addition of the ion azide as nucleophile promoted by a mercury(II) salt has been used only in the field on carbohydrates. Starting from the unsaturated derivative **373**, a mixture of the azido compounds **374** and **375** were obtained (Scheme 156).[591]

8.4.4. Acetamidomercuration Reactions Using Acetonitrile

When the mercuration of an olefin is performed in acetonitrile, the solvent acts as nucleophile giving after demercuration the corresponding acetamides. The reaction initially described 40 years ago[592] has proven to be high-yielding and rather general for a series of olefins.[593] For instance, cyclohexene (**348**) reacts with mercury(II) nitrate in the presence of acetonitrile to yield the expected amide **349** (Scheme 157).[593] The corresponding intramolecular version of this process, as well as some mechanistic studies, has also been reported.[594]

8.4.5. Nitromercuration Reactions

The nitromercuration of olefins, initially described by Bachman and Whitehouse, is a general method to prepare β-nitromercurals.[595] Corey and Estreicher[596] took advantage of this chemistry to synthesize nitroalkenes by simple treatment of the nitromercural with sodium hydroxide. This methodology is illustrated in Scheme 158 for the nitromercuration of cyclohexene (**348**), which gave the nitromercural **376** that upon treatment with sodium hydroxide produces a reductive elimination yielding the final nitrocyclohexene (**377**). Strictly, this reaction is not a typical nitration of alkenes, because the double bond is regenerated in the final product. However, we have included this chemistry here because in the nitromercuration step a nitrogenated nucleophile (the nitro group) is added to the double bond with the help of the mercury(II) salt.

9. Hydroamination of Alkenes and Alkynes under Microwave Irradiation

Transition metal catalyzed homogeneous reactions frequently take long reaction times. However, it is known that these processes can be accelerated under microwave irradiation,[597–599] making these methodologies synthetically more attractive.

9.1. Hydroamination of Alkenes under Microwave Irradiation

A variety of phosphine−gold(I) complexes have been demonstrated to be efficient catalysts for intramolecular hydroamination reactions of alkenes of type **378** and **379** to give heterocycles **380** and **381**, respectively. The use of microwave irradiation allows completion of the reaction in a much shorter time than that needed under conventional thermal conditions (Scheme 159 and Table 84).[341]

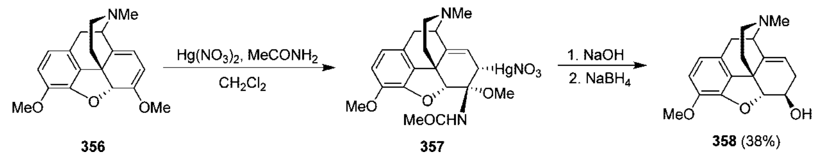
Noticeably, the intermolecular hydroamination of nonactivated alkenes under microwave irradiation worked smoothly and the corresponding products were isolated in good yields with reaction times of 40−60 min (Table 84).

The addition of primary and secondary lithium amides to styrene to give β-phenylethylamines occurs at 0 °C.[600] However, in the case of the lithium salt of aniline, no reaction was observed after 24 h under the same reaction conditions. It had been previously reported that styrenes undergo hydroamination in a sealed tube at high temperatures.[601] Microwave irradiation promoted also hydroamination of styrenes **382** with aniline derivatives **383** yielding β-phenylethylamines **384** in short reaction times (Scheme 160).

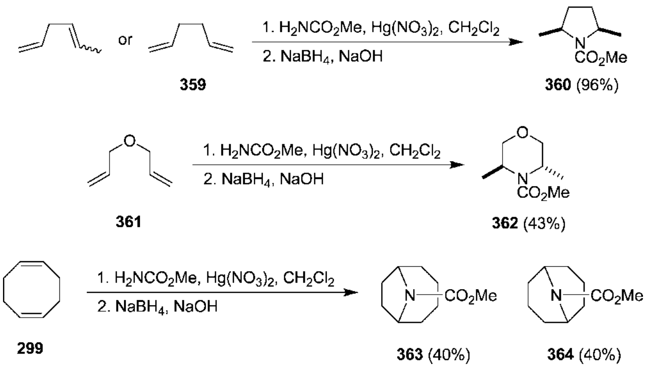
Improved yields were obtained for a 1:10:1 ratio of styrene, aniline, and potassium *tert*-butoxyde. However, when the reagents ratio was 1:1:2 in the case of **382** (R^1 = Cl; R^2 = R^3 = R^4 = H) and aniline (**287**), the additional cyclization product **385** was achieved in very good yield (Scheme 161). This microwave-enhanced cyclization to indoline **385** gave a yield almost twice as high with 400 times faster reaction time than the yields previously reported with conventional heating.[461]

Chemler et al. reported the copper(II) carboxylate-promoted intramolecular carboamination of nonactivated alkenes. Through this methodology *N*-functionalized pyrrolidines **389** and **390** and piperidines are accessible. Both aromatic and aliphatic γ- and δ-alkenyl *N*-arylsulfonamides **386** undergo the oxidative cyclization reaction. Terminal olefins are more reactive than internal ones, and the reaction times were considerably reduced by the use of microwave heating. The yields are also enhanced by the use of soluble copper(II) carboxylate salts, especially copper(II) neodecanoate (ND). The *cis* substitution pattern predominates in the synthesis of 2,5-disubstituted pyrrolidines. Regarding the mechanism, the N−C bond seems to be formed via intramolecular aminocupration to give intermediate **387**, whereas the C−C bond is formed via intramolecular addition of a primary carbon radical **388** to an aromatic ring leading to **389** after re-aromatization (Scheme 162 and Table 85).[602]

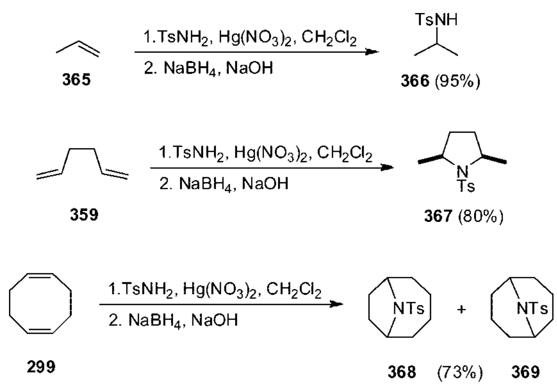
Scheme 152



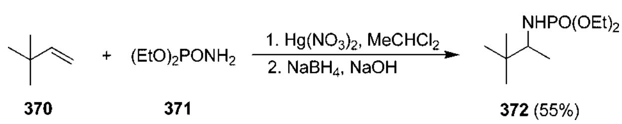
Scheme 153



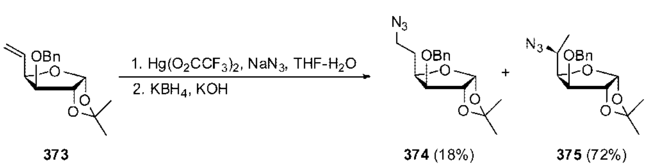
Scheme 154



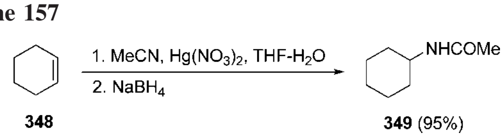
Scheme 155



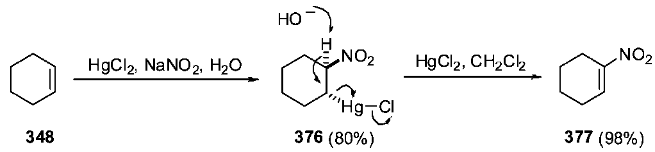
Scheme 156



Scheme 157



Scheme 158



Scheme 159

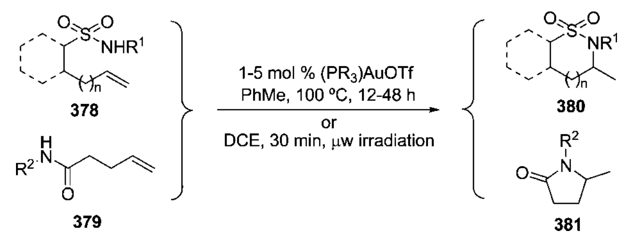
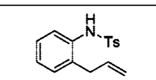
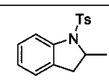
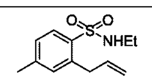
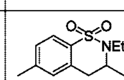
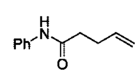
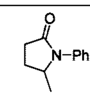
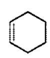
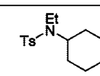
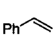
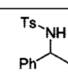
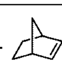
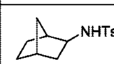
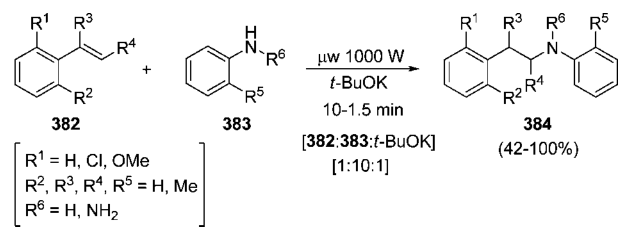


Table 84. Selected Examples for Thermal and Microwave Gold(I)-Catalyzed Inter- And Intramolecular Hydroamination of Nonactivated Alkenes

Reactant(s)	Product	Reaction conditions	Yield / %
		80 °C, 12 h	99
		43 W, 20 min	86
		100 °C, 24 h	95
		43 W, 40 min	90
		100 °C, 30 h	50
		43 W, 30 min	57
TsNHEt + 		43 W, 60 min	50
$TsNH_2$ + Ph		30 W, 40 min	43
$TsNH_2$ + 		48 W, 40 min	95

Scheme 160

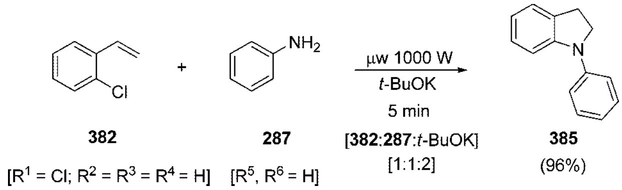


9.2. Hydroamination of Alkynes under Microwave Irradiation

Irradiation of reaction mixtures containing an alkyne **391**, an amine **392**, and a catalytic amount of Cp_2TiMe_2 (**96**) in toluene with microwaves at a frequency of 2.45 GHz and a power output of 180−300 W results in fast reactions to give the corresponding imines **393**. These imines are easily converted into secondary amines **394** upon palladium catalytic hydrogenation or reduction with either $LiAlH_4$ or $NaCNBH_3$/*p*-TsOH (Scheme 163 and Table 86).[603,604]

It is worth pointing out that the microwave-assisted intermolecular hydroamination reactions go to completion within 1/10th of the time required for reactions run in an oil bath at 105 °C. In addition, terminal alkynes undergo hydroamination for the first time in fair yields when irradiated with microwaves with Cp_2TiMe_2 (**96**) as a catalyst. Regarding the regiochemistry, the addition of amines to terminal alkynes

Scheme 161



Scheme 162

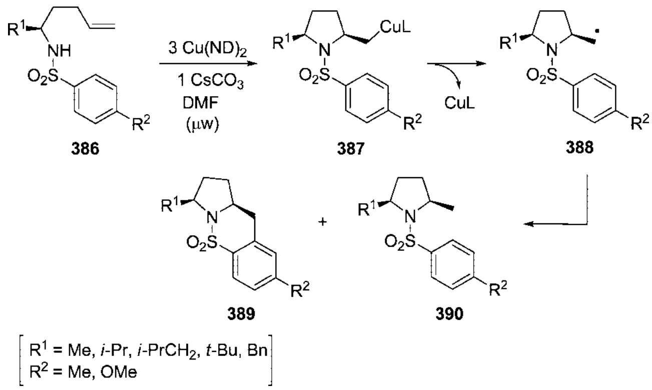
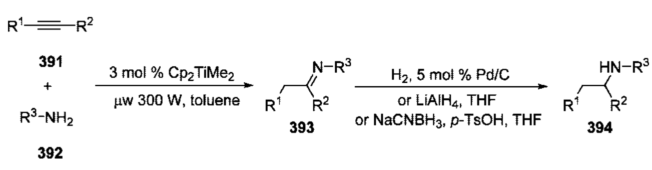


Table 85. Selected Examples for Thermal and Microwave Copper(II) Carboxylate-Promoted Intramolecular Carboamination of Nonactivated Olefins

R^1	R^2	reaction conditions[a]	yield of **389**, %	yield of **390**, %
Me	Me	200 °C, 72 h	48	15
		210 °C (μw), 3h	48	15
i-Pr	Me	190 °C, 72 h	49	25
		210 °C (μw), 3h	51	28
i-Pr	OMe	190 °C, 72 h	49	23
		210 °C (μw), 3h	51	23
i-PrCH$_2$	Me	200 °C, 72 h	49	20
		210 °C (μw), 3h	49	19
t-Bu	Me	200 °C, 72 h	34	15
		210 °C (μw), 3h	31	17
Bn	Me	200 °C, 72 h	50	22
		210 °C (μw), 3h	47	21

[a] μw denotes microwave.

Scheme 163



gives access to both the Markovnikov and the anti-Markovnikov products, the regioselectivities being different for terminal arylic or alkylic derivatives (Table 86).

Dovey et al. reported a synthesis of functionalized pyrroles using a two-step sequence. This process involves the propargylation of secondary enamines **395** using *n*-BuLi and propargyl bromide to give first compound **396**, followed by intramolecular hydroamination catalyzed by silver nitrate. The operating mechanism is assumed to involve activation of the triple bond by the silver ion **397**, affording the cyclic intermediate **398**, which after rearrangement leads to the pyrrole **399** (Scheme 164).[364] A similar gold-catalyzed procedure for the preparation of pyrroles has also been reported.[605] The cyclization reaction can be performed under microwave irradiation using a domestic microwave oven (700 W). In this case, yields are typically comparable to those obtained at room temperature. However, reaction times are reduced from 16−20 h to 1 min.

The previously reported methodology was extended to the synthesis in good yields of N-bridgehead pyrroles **402**, the pyrrole analogues of pyrrolizidines ($n = 1$), indolizidines ($n = 2$), and pyrroloazepines ($n = 3$). Hydroamination is brought about using microwave irradiation of cyclic secondary vinylogous carbamates **400** to afford first the enamine intermediate **401** and, after rearrangement, the thermodynamically more stable pyrrole derivative **402** (Scheme 165).[606]

Metal-free hydroamination of alkynes was achieved recently in superheated water[607] under microwave irradiation. Thus, heating a mixture of *p*-methoxyphenylacetylene (**403**) and 4-bromoaniline (**404**) in water at 200 °C for 20 min in a microwave oven, afforded the ketimine **405** in 87% yield (Scheme 166).[608] In the absence of metals activating the alkyne or the amine, the mechanism of this reaction remains unclear. A possible explanation involves the dissociation constant of water, which is increased by 3 orders of magnitude at temperatures at or greater than 200 °C allowing it to act as an acid, base, or acid−base bicatalyst.

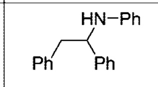
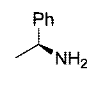
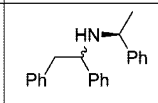
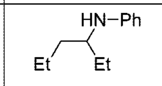
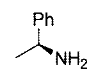
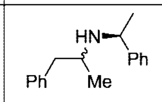
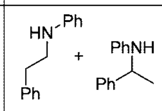
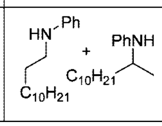
10. Radical Hydroamination of Alkenes

The addition of N-centered radicals **I** to olefins is well-established.[609] However, the hydrogen transfer from the NH group to the resulting C-centered radical **II** is not a favored process (Scheme 167). In consequence, the radical hydroamination of olefins has not been investigated as intensively as, for instance, the transition metal catalyzed hydroamination.

N-Centered radicals are generally obtained via *N*-halo, *N*-hydroxypyridine-2(1*H*)thione (*N*-PTOC), and *N*-phenylthio derivatives either photochemically or by using a co-reducing agent.[610] In general, most of these precursors are unstable and have to be prepared *in situ*. Studer and Kemper demonstrated that 3-aminyl- or 3-amidyl-1,4-cyclohexadienes **406** are stable precursors of N-centered radicals under neutral conditions. The reaction of substituted 1,4-cyclohexadienes **406** with nonactivated and electron-rich olefins **407** in benzene (0.4 M) in the presence of di-*tert*-butylperoxide (DTBP) at 140 °C gave the hydroamination product **409** (Scheme 168 and Table 87).[611] The addition of the N-radical **I** to olefin **407** afforded the C-centered radical **II**, which after hydrogen abstraction from cyclohexadiene **406** yielded the desired hydroamination product **409** and a new stabilized radical intermediate **408**. Chain propagation occurs through aromatization of **408** to give the aromatic compound **410**[612] and the N-centered radical **I**. Thus, 3-amino-1,4-substituted cyclohexadienes **406** can be considered as hydroamination reagents since no additional reducing reagents are necessary. Regarding the regiochemistry, in unsymmetrical substituted olefins, hydroamination occurs with good to excellent anti-Markovnikov selectivity. Better yields were obtained when the reactions were performed in the presence of thiols as polarity reversal catalysts.[613] It is worth noting that many functional groups are tolerated under these reaction conditions (Table 87).

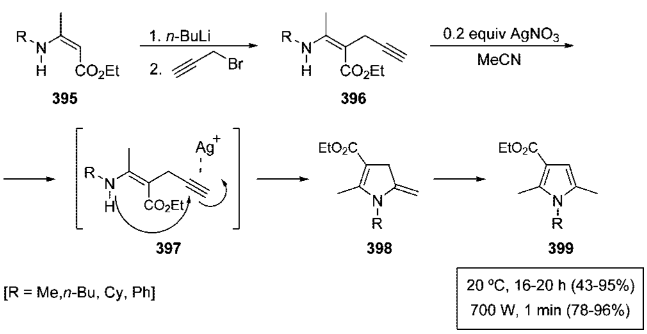
The intramolecular addition of iminyl radicals derived from oximes to alkenes has been extensively studied by Zard et al.[614,615] Iminyl radicals are also accessible from *O*-nitrophenyloximes in the presence of electron donor species. This methodology has been used by Narasaka et al. in the synthesis of different nitrogenated heterocycles. Thus, the

Table 86. Selected Examples for the Microwave-Assisted Cp_2TiMe_2-Catalyzed Hydroamination of Alkynes

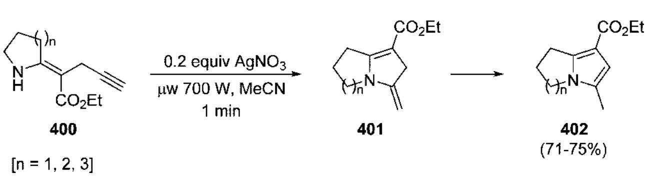
Alkyne	Amine	Product	Microwave irradiation	t / h	Reduction	Yield / %
Ph—≡—Ph	$PhNH_2$		300 W	3	H_2, Pd/C	93
Ph—≡—Ph			300 W	3	$NaCNBH_3$	78[a]
Et—≡—Et	$PhNH_2$		255 W	3	H_2, Pd/C	54
Ph—≡—Me			300 W	3	H_2, Pd/C	70[a]
Ph—≡	$PhNH_2$		180 W	2	$NaCNBH_3$	67 (3:1)
$C_{10}H_{21}$—≡	$PhNH_2$		180 W	2	$NaCNBH_3$	49 (1:7)

[a] Mixture of diastereomers.

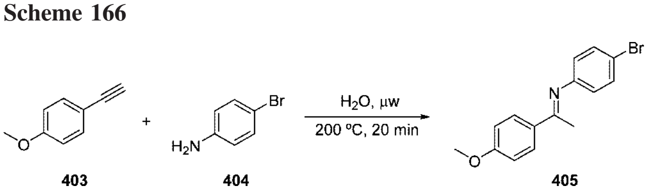
Scheme 164



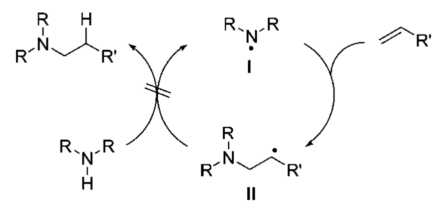
Scheme 165



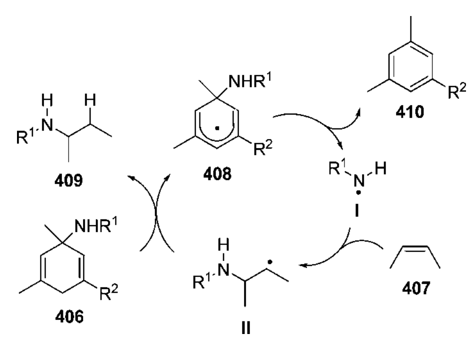
Scheme 166



Scheme 167



Scheme 168

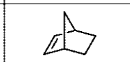
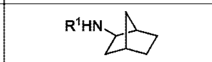
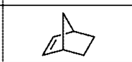
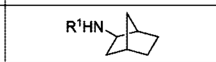
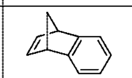
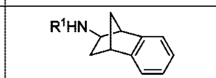
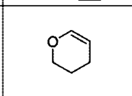
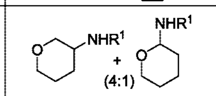
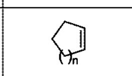
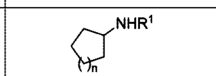
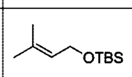
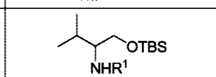
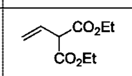
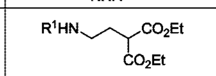
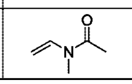
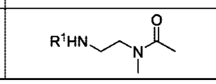


treatment of *cis*-2-allyl-4-phenylcyclohexanone (E)-O-(2,4-dinitrophenyl)oxime (**411**) with sodium hydroxide, 3,4-(methylenedioxy)phenol (sesamol), and 1,4-cyclohexadiene (CHD) in 1,4-dioxane at 50 °C afforded cyclic imine **414** in high yield. The reaction only proceeds under strongly basic conditions. Concerning a possible mechanism, the addition of one electron to the O-aryloxime **411** gave the radical anion intermediate **412**, which decomposed to give 2,4-dinitrophenoxide and an iminyl radical. This intermediate immediately cyclized to afford a new radical **413**, and after hydrogen abstraction from CHD, the imine **414** was obtained (Scheme 169).[616,617]

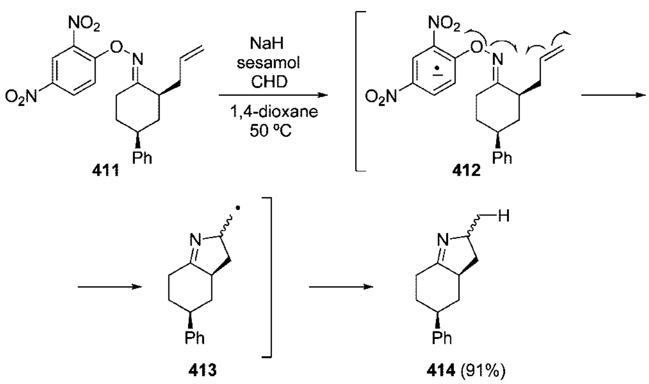
Photolysis of a mixture of γ,δ-unsaturated O-(p-cyanophenyl)oximes **415**, 1,5-dimethoxynaphthalene (DMN), and CHD in acetonitrile led to dihydropyrrole derivatives **418**. The reaction is initiated by one-electron transfer from DMN to compound **415** to give the anion radical **416**, which underwent elimination of p-cyanophenoxide and radical cyclization to afford alkyl radical **417** and, after hydrogen trapping from CHD, the expected 3,4-dihydro-2H-pyrrole **418** (Scheme 170 and Table 88).[618]

The cyclization of alkyl ketone O-acetyloximes proceeded by photosensitized electron transfer only in the presence of acetic acid.[619,620] However, acetic acid did not affect the

Table 87. Selected Examples of N-Centered Radical Hydroamination of Olefins from 3-Amino-Substituted 1,4-Cyclohexadienes

Cyclohexadiene 406 R^1	Cyclohexadiene 406 R^2	Olefin 407	Reaction product 409	Yield / %
Boc	CO_2Me			56
Moc	CO_2Me			45
Boc	CO_2Me			40
Moc	CO_2Me			60
Moc	CO_2Me			48 (n = 1) 51 (n = 2) 42 (n = 8)
Moc	CO_2Me			41
Moc	CO_2Me			40
Moc	CO_2Me			55

Scheme 169



Scheme 170

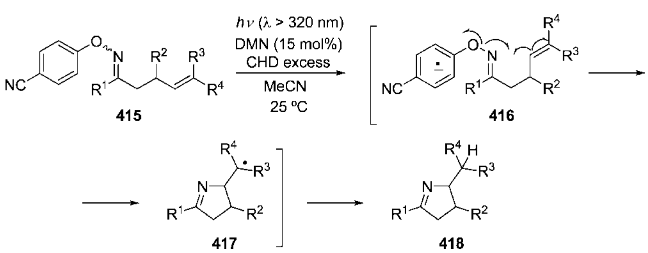
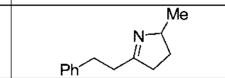
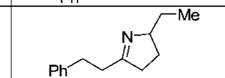
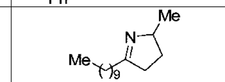
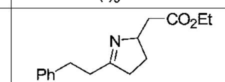
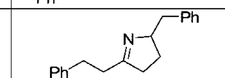
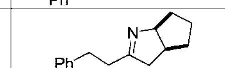
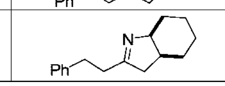
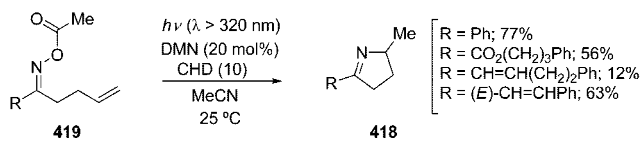


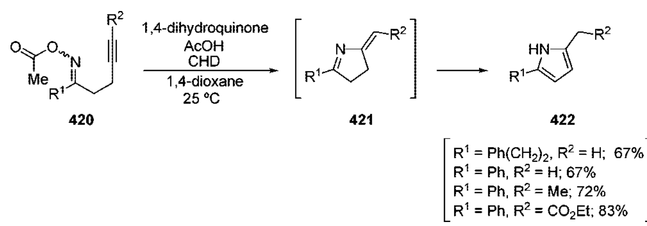
Table 88. Selected Examples of Photochemical Transformation of γ,δ-Unsaturated *O*-(*p*-Cyanophenyl)oximes 415 to 3,4-Dihydro-2*H*-pyrrole 418

Oxime 415 R^1	R^2	R^3	R^4	Reaction product 418	Yield / %
$Ph(CH_2)_2$	H	H	Me		75
$Ph(CH_2)_2$	H	H	Me		78
n-$C_{10}H_{21}$	H	H	H		75
$Ph(CH_2)_2$	H	H	CO_2Et		64
$Ph(CH_2)_2$	H	H	Ph		13
$Ph(CH_2)_2$	$(CH_2)_2$		H		78
$Ph(CH_2)_2$	$(CH_2)_3$		H		69

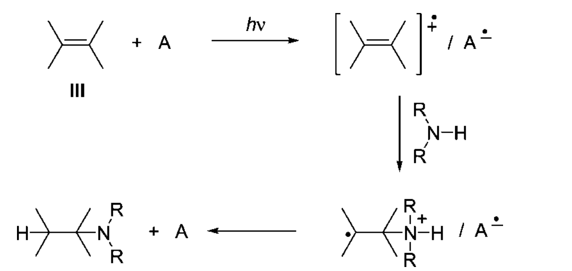
Scheme 171



Scheme 172



Scheme 173



radical cyclization of aryl and α,β-unsaturated ketone oximes **419** (R = CH=CHR′). The cyclization of these conjugated ketone oximes **419** took place in shorter reaction times than that of nonconjugated oximes, 2-methyldihydropyrroles **418** being obtained in moderate yields (Scheme 171).[620]

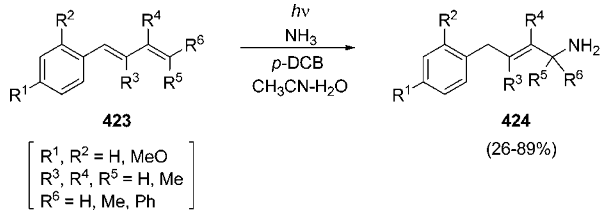
This methodology could also be applied to the preparation of pyrroles from *O*-acetyloximes having an alkynyl moiety as shown Scheme 172. Alkynyl ketoximes **420** were first transformed into the corresponding product of intramolecular hydroamination **421**, which immediately isomerized to 2,5-disubstituted pyrroles **422** in moderate to good yields. Substituents at the triple bond did not show any influence in the process (Scheme 172).[621]

It is known that the photoinduced addition of alkyl amines and NH_3 to carbon−carbon double bonds in stilbenes, styrenes, and 1,1-diarylalk-1-enes[622–624] occurs through generation of the cation radicals derived from olefins **III** by photoinduced electron transfer to an electron acceptor (A) and subsequent addition of the amines to the cation radicals followed by electron transfer and final protonation (Scheme 173).

Yasuda et al. have studied the photoamination of 1-aryl-1,3-dienes **423** with NH_3 in the presence of *p*-dicyanobenzene (DCB). In these processes, 4-amino-1-aryl-2-butenes **424** were isolated as the main reaction products, resulting in a selective 1,4-addition of NH_3 to the dienic system (Scheme 174).[625]

More recently, Yasuda et al. also reported that 1,2,4-triphenylbenzene (1,2,4-TPB) photosensitized the hydroami-

Scheme 174



Scheme 175

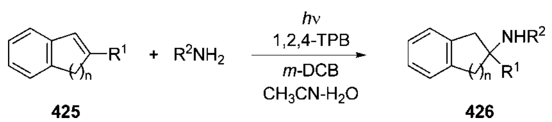
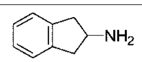
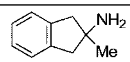
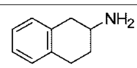
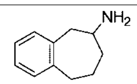
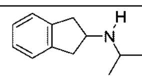
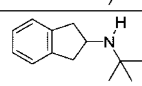


Table 89. Selected Examples of Photosensitized Hydroamination of 1,2-Benzo-1,3-cycloalkadienes 425

Benzoalkadiene **425**		R^2NH_2	Reaction product **426**	Yield / %
R^1	n			
H	1	NH_3		79
Me	1	NH_3		83
H	2	NH_3		63
H	3	NH_3		57
H	1	*i*-$PrNH_2$		52
H	1	*t*-$BuNH_2$		49

nation of 1,2-benzo-1,3-cycloalkadienes **425** with ammonia or primary amines in the presence of *m*-dicyanobenzene (*m*-DCB) to give 4-amino-1,2-benzocycloalkanes **426** in reasonable yields (Scheme 175 and Table 89).[626] It was found that the relationships in oxidation potentials between the sensitizers and the substrates and the positive charge distribution of the cation radicals of the substrates were important factors for the efficient amination.

11. Conclusions

The addition of amines to nonactivated CC multiple bonds (hydroamination) is a highly desired but difficult chemical transformation. In particular, the conversion of nonactivated alkenes poses considerable constraints, while the hydroamination of alkynes finds first applications in the synthesis of natural products. The challenge for the development of hydroamination catalysts lies in the repulsive forces, which arise during approach of the electron-rich π-system of the CC multiple bond and the electron pair on the amine nitrogen atom. Thus, either the reactivity of one of the two reaction partners has to be reversed, or an alternative reaction pathway has to be provided by the catalyst. The reaction enthalpy, which is slightly negative for most hydroamination reactions, prohibits accelerating the reaction by using high temperatures because the thermodynamic equilibrium is encountered. In consequence, a highly efficient catalyst is required. So far, the search for the “Grubbs catalyst” of hydroamination, combining high activity for a variety of substrates, tolerance for functional groups with high robustness, stability, and easy operation, is ongoing.

From a synthetic point of view, the most important feature of the addition of amines and their derivatives to alkenes and alkynes lies in the fact that an amine, which is a typical nucleophile, can be added to a nonactivated olefin, which normally reacts with electrophiles. Thus, this process represents a typical example of umpolung reactivity for the two main components of the reaction, the amine and the alkene or alkyne. The amino- and amidomercuration–demercuration of olefins, dienes, and alkynes both in intra- and intermolecular fashion represents an easy way to generate amines, amides, and saturated nitrogenated heterocycles in a regioselective manner and under very mild reaction conditions.

Particularly active hydroamination catalysts are needed to accomplish olefin hydroamination in a synthetically valuable fashion, while industrial applications place particularly high constraints with respect to catalyst stability. As minimum requirements, TON > 1000 and TOF > 200 h^{-1} are generally considered.[44] Since the last comprehensive review in 1998,[8] much progress has been made in the development of catalysts for hydroamination. Efficient lanthanide and actinide catalysts for the hydroamination of alkenes have been developed, but intermolecular reactions are generally slow. Group 4 metal catalysts have similar performance and are easier to handle. Late transition metal catalysts are known for this reaction, being less sensitive to air and more tolerant of polar functional groups. However, intermolecular hydroamination of alkenes that are catalyzed by late transition metals provide low rates and have limited scope.

The development of more active catalysts faces the challenge of having to develop a catalyst without knowing the particular reaction mechanism. For early transition metals, activation of the amine by deprotonation and coordination to the metal center followed by insertion of the alkene appears most likely. For late transition metals, activation of the alkene for nucleophilic attack of the amine is a plausible reaction pathway. However, alternative reaction mechanisms have been proposed and cannot be excluded based on current evidence. This variability is reflected in the survey of the known catalysts for hydroamination, which provided a variety of excellent candidates for next generation catalysts.

Although further progress must be made to develop transition metal catalyzed hydroamination, specific applications have been realized and are used routinely in organic syntheses. In particular, late transition metal catalysts for addition of arylamines to alkynes, vinylarenes, and dienes have been developed. These catalysts tolerate the types of functionality commonly found in natural products and pharmaceutically active materials. First applications include the total synthesis of natural products and other complex molecules. In particular, the synthesis of N-heterocycles from amino-alkenes and -alkynes commences to be a routine technique. A number of domino reactions and sequential one-pot reactions have been developed for the synthesis of more complex molecules. It is thus predicted that the hydroamination reaction will soon become part of the standard toolbox of the organic chemist.

On the other hand, however, the factors governing the regioselectivity of intermolecular hydroamination are little understood. The anti-Markovnikov hydroamination of alkenes, which has been classified as one of the ten biggest challenges in catalysis, remains an open issue. Some first successful examples have demonstrated that this reaction is possible. Further mechanistic studies and a deeper understanding of the system are required.

Considerable progress has also been made in the development of solid catalysts. Late transition metal cations bound to the surface of a zeolite or an oxide show high activity in the hydroamination of alkynes and slightly activated alkenes, like vinyl ethers and styrene. Ionic complexes can be immobilized in an ionic liquid, and the reaction can be performed either as a two-phase reaction or with an immobilized film of the ionic liquid phase on a solid support. A particular advantage is the high stability of the immobilized catalysts, which enables use of higher reaction temperatures. At temperatures around 200 °C, the thermodynamic limit of the reaction is obtained. Note that for the addition of aniline to styrene in the thermodynamic regime, equilibrium between Markovnikov and anti-Markovnikov products was observed. In this case, the product distribution is determined by the relative stability of the two regioisomers.

In summary, much progress has been made, and hydroamination is just about to become a standard tool when a C−N bond needs to be made. For more widespread applications, a deeper understanding of the mechanistic details is required. The latter is also a precondition for the development of more active catalysts and catalysts specific for the anti-Markovnikov hydroamination.

12. Abbreviations

Ac^-	CH_3COO^-
Ar	aryl
bim	bis(1-methylimidazol-2-yl)methane
BHT	butylated hydroxytoluene
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
bpm	bis(1-pyrazolyl)methane
Bn	benzyl
Bz^-	$C_6H_5COO^-$
Cbz	benzyloxycarbonyl
CGC	$Me_2Si(C_5Me_4)(^tBuN)^{2-}$
chd	1,3-cyclohexadiene
cod	1,5-cyclooctadiene
coe	*cis*-cyclooctene
cot	1,3,5-cyclooctatriene
Cp	η^5-C_5H_5
Cp*	η^5-C_5Me_5
Cy	cyclohexyl
$(Cy)_2$ATI	*N*-cyclohexyl-2-(cyclohexylamino)troponiminate
dba	dibenzylidenacetone
dipamp	1,2-bis[(*o*-methoxyphenyl)(phenyl)phosphino]ethane
dmfm	dimethyl fumarate
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
ebi	ethylenebis(η^5-indenyl)
ebthi	ethylene-1,2-bis(tetrahydroindenyl)
Et	ethyl
HTfa	trifluoroacetic acid
Ind	indenyl
NHC	N-heterocyclic carbene
N−N	bidentate heterocyclic N donor
Mes	2,4,6-trimethylphenyl
nor	norbornadiene
pip	2-methylpiperidine
nap	naphthyl
^{i}Pr	isopropyl
P−C−P	tridentate P, C, P donor ligand
PhMCP	phenylmethylenecyclopropane
PMB	*para*-methoxybenzyl
P−N	bidentate P−N ligand
P−NHC	bidentate phosphine−NHC ligand
P−P	bidentate phosphine ligand
P−P−P	tridentate phosphine ligand
^{i}PrAT	2-(isopropylamino)troponate
$(^i$Pr$)_2$ATI	*N*-isopropyl-2-(isopropylamino)troponiminate
pta	1,3,5-triaza-7-phosphaadamantane
py	pyridine
PNNP	tetradentate phosphine−amine−amine−phosphine ligand
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
Tfa^-	CF_3COO^-
Ts^-	$CH_3C_6H_4SO_3^-$
TfO^-	$CF_3SO_3^-$
TfOH	CF_3SO_3H
TOF	turnover frequency
triphos	bis(2-diphenylphosphinoethyl)phenylphosphine

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14. References

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