The enantioselective intramolecular aminative functionalization of unactivated alkenes, dienes, allenes and alkynes for the synthesis of chiral nitrogen heterocycles

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The enantioselective intramolecular aminative functionalization of unactivated alkenes and related π-systems is a straight-forward and atom economical strategy for the synthesis of chiral nitrogen heterocycles. These reactions can be categorized as oxidatively neutral, such as alkene hydroamination, or as oxidative reactions, such as alkene difunctionalization, *e.g.* aminooxygenation and carboamination. This perspective reviews the current work in the field and explores mechanistic trends that are common among the different catalysts and reaction types.

1 Introduction

The asymmetric synthesis of chiral nitrogen heterocycles by aminative functionalization of unactivated π-bonds has been traditionally challenging as the process involves stereocontrolled addition of the amine onto the alkene or equivalent unsaturated bond. This review will discuss recent progress in the use of chiral metal catalysts to enable these cyclization reactions and control the three-dimensional orientation of the C–N bond-forming step. We will focus on the intramolecular addition of amines to unactivated, non-polarized π-systems, which offer different synthetic challenges than polarized π bonds, those conjugated to electron-withdrawing groups, as the latter can undergo intrinsically favorable 1,4-addition processes as well as benefit from Lewis acid activation of the electron withdrawing group (EWG).

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We will present a variety of different metal-catalyzed reactions for the cyclization of amines onto unactivated π-systems that none-the-less share similarities in transition state conformational preferences related to the cyclization process. Lewis acidic π-catalysts are necessary to promote the otherwise intrinsically unfavorable nucleophilic addition of amines onto these electron-rich π systems.

2 Oxidatively neutral cyclizations

Oxidatively neutral aminative π-bond functionalizations are reactions where the substrate and product are in the same net oxidation state. These include the hydroamination of alkenes, dienes, allenes and alkynes and the S_N2' type displacement of allylic leaving groups.

2.1 Enantioselective intramolecular hydroamination of alkenes and dienes

The inter- and intramolecular enantioselective catalytic hydroamination of alkenes, dienes, allenes and alkynes has been reviewed previously.[1–5] This review focuses only on instructive and recent developments. A number of metals can catalyze the enantioselective hydroamination/cyclization of alkenes. It is interesting to note that for these reactions, all of the proposed enantioinduction models have involved "inner sphere" or syn aminometallation processes (*vide infra*). Many of these reactions also occur more readily on terminal rather than internal alkenes, indicating that steric hindrance affects the metal–carbon bond-forming process.

2.1.1 Hydroaminations catalyzed by rare earth metals. The pioneering enantioselective intramolecular hydroaminations of alkenes catalyzed by chiral rare-earth metal catalysts has been reviewed previously.[1–5] Although early studies were conducted with configurationally unstable cyclopentadienyl-based ligands[4], in 2001, Livinghouse and co-workers demonstrated that cyclopentadienyl ligands are not necessary for catalytic hydroamination[6,7] and new, more stable chiral catalysts were subsequently developed.

In 2002, Marks and co-workers reported that upon screening a number of chiral bis(oxazoline) ligands and several lanthanide

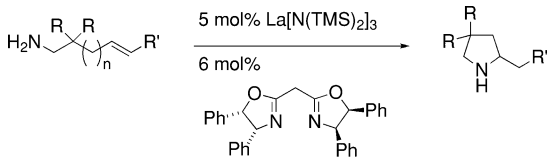
metals, the [(4*R*,5*S*)-Ph_2Box]La[$N(TMS)_2$]$_2$ catalyst provided efficient and moderately enantioselective (up to 67% ee at 23 °C) hydroamination of terminal alkenes and dienes (Table 1).[8]

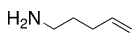
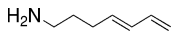
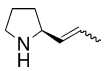
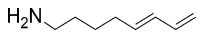
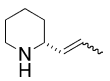
The reaction mechanism was examined in depth.[8] Kinetic studies indicated the hydroamination rate is zero-order in [amine substrate] and first-order in [catalyst]. This is consistent with rate-determining Ln–N alkene insertion. A model that rationalizes the observed pyrrolidine stereochemistry is shown in Scheme 1. In the favored transition state, the metal is trigonal bipyramidyl and the ligand and the approaching olefin adopt equatorial positions while the two amine substituents adopt apical positions. Interestingly, piperidine rings are formed with the opposite enantioinduction (Table 1).

A number of other research groups, including those of Scott[9], Livinghouse[10], Hultzsch[11] and Schulz[12] have also identified chiral and configurationally stable, non-cyclopentadienyl ligands that coordinate with lanthanides and whose complexes thereof catalyze the enantioselective hydroamination of alkenes. The catalyst structures and the enantioselectivity are given for the quantitative cyclizations of 2,2-dimethyl-4-pentenylamine to 2,4,4-trimethylpyrrolidine (Fig. 1).

2.1.2 Hydroaminations catalyzed by group 4 metals. Group 4 metal catalysts are attractive because of their low cost and toxicity.[13] The first enantioselective hydroamination/cyclization of alkenes catalyzed by a chiral zirconium catalyst was reported by Scott and co-workers in 2004.[14] The cationic zirconium catalyst [ZrL_2CH_2Ph][$B(C_6F_5)_4$], 5–10 mol%, enabled the quantitative cyclization of several secondary amines in 20–82% ee (Table 2). Primary amines were unreactive with this catalyst, presumably because the *in situ*-formed zirconium imido species is catalytically inactive.

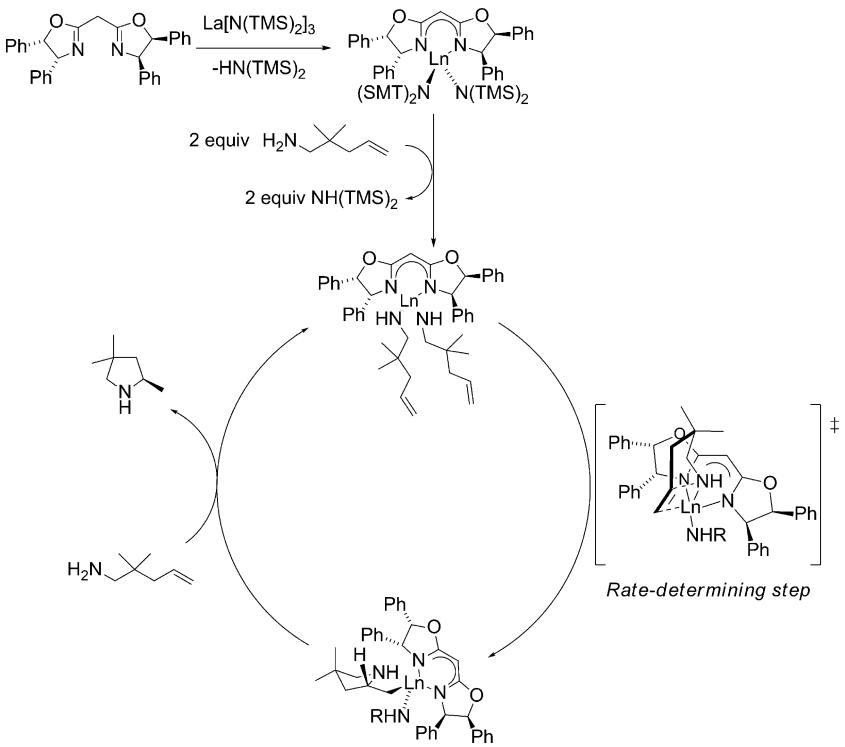
Table 1 Lanthanide-catalyzed enantioselective hydroamination of alkenes and dienes[8]



Entry	Substrate	Product	$N_t(h^{-1})$	Temp (°C)	ee (%)[a]
1			25	23	67
2			0.09	23	40
3			3.0	23	17
4			4.0	60	56
5			0.6	60	54

[a] Determined by chiral HPLC analysis.

A few years after Scott's report, Schafer and Bergman independently reported the successful enantioselective cyclization/



Scheme 1 Proposed mechanism of Marks' enantioselective lanthanide catalyzed alkene hydroamination with a C_2-symmetric bis(oxazoline) ligand.

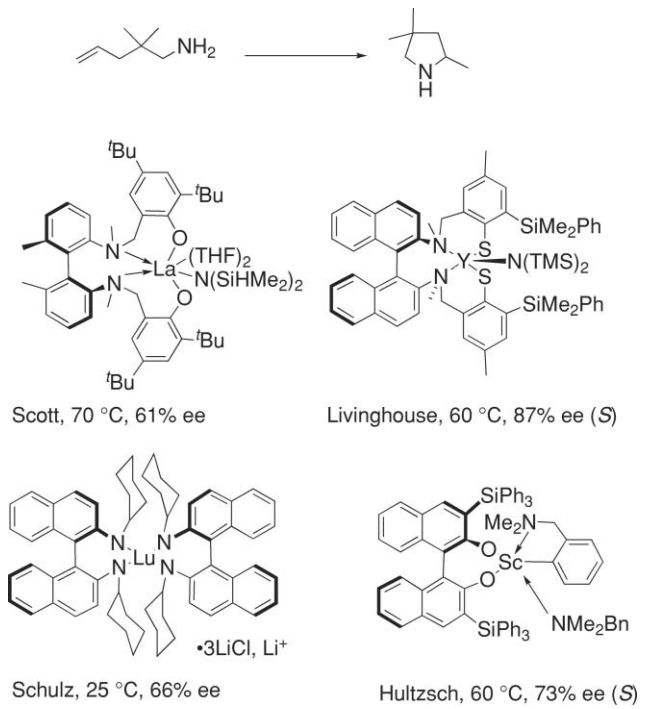
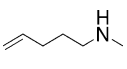
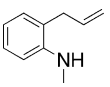
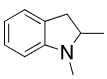
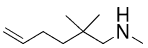
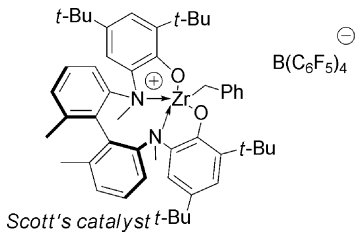


Fig. 1 Other lanthanide–ligand complexes used for asymmetric alkene hydroamination.

Table 2 Hydroamination/cyclization catalyzed by Scott's zirconium catalyst[14]

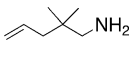
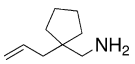
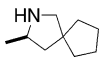
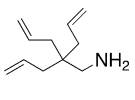
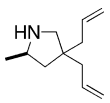
Entry[a]	Substrate	Product	ee (%)[b]
1			64
2			20
3			82

[a] Conditions: C_6D_5Br at 100 °C, *ca.* 10 mol% catalyst, 3–4 h. [b] NMR analysis of (*R*)-(+)-Mosher's acid salt.

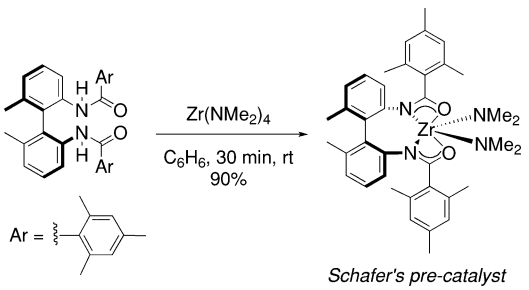


hydroamination of primary amines.[13,15] Schafer and co-workers synthesized an axially chiral amidate ligand and treated the ligand with $Zr(NMe_2)_4$ to obtain the zirconium amidate precatalyst (Table 3). Hydroamination/cyclization of a number of primary 4-pentenyl amines was achieved with 10 mol% of Schafer's catalyst in refluxing toluene for 2–12 h, providing isolated pyrrolidines in 82–96% yield and 62–93% ee (Table 3). All of the substrates contain

Table 3 Hydroamination/cyclization catalyzed by Shafer's zirconium catalyst[13]

Entry[a]	Substrate	Product	Yield (%)[b]	ee (%)[c]
1			80	93
2			91	88
3			88	74

[a] Conditions: toluene at 110 °C, 10 mol% catalyst, 2–12 h. [b] Isolated yield. [c] Determined by NMR analysis following derivatization with (*S*)-(+)-Mosher's acid chloride.



β-quaternary carbons, which is likely important to both the rate and selectivity of the reaction. The authors note that piperidines could also be formed, but with much lower enantioselectivity.

The absolute stereochemistry of the major products was rationalized as having been formed *via* a proposed transition state which minimizes steric interactions between the amine backbone and the catalyst during the stereochemistry-determining [2 + 2] syn aminozirconation step (Fig. 2).

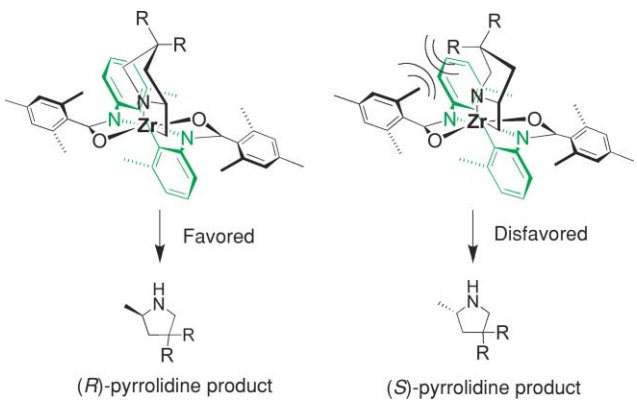
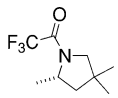
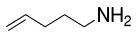
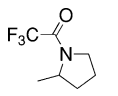
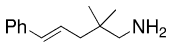
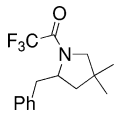
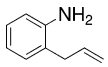
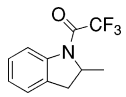
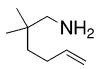
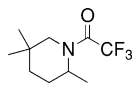


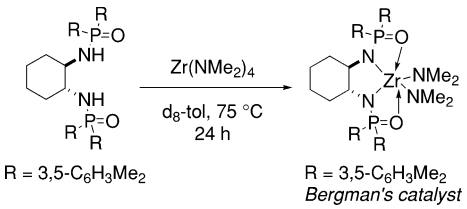
Fig. 2 Origin of the enantioselectivity in the hydroamination reactions with Schafer's catalyst.

Bergman and co-workers synthesized a chiral neutral zirconium catalyst by reaction of chiral diphosphinic amide ligands with $Zr(NMe_2)_4$ (Table 4).[15] They demonstrated that indolines, pyrrolidines and piperidines can be cyclized using 10–20 mol% of their catalyst in 33–99% isolated yield and 33–80% ee (Table 4).

Table 4 Hydroamination/cyclization catalyzed by Bergman's zirconium catalyst[15]

Entry[a]	Substrate	Product	Yield (%)	ee (%)[b]
1			95	80
2			33	62
3			93	62
4			93	70
5			99	51

[a] Conditions: toluene at 85–135 °C, 10–20 mol% catalyst, 24–72 h, then trifluoroacetic anhydride. [b] ee determined by chiral GC or HPLC.



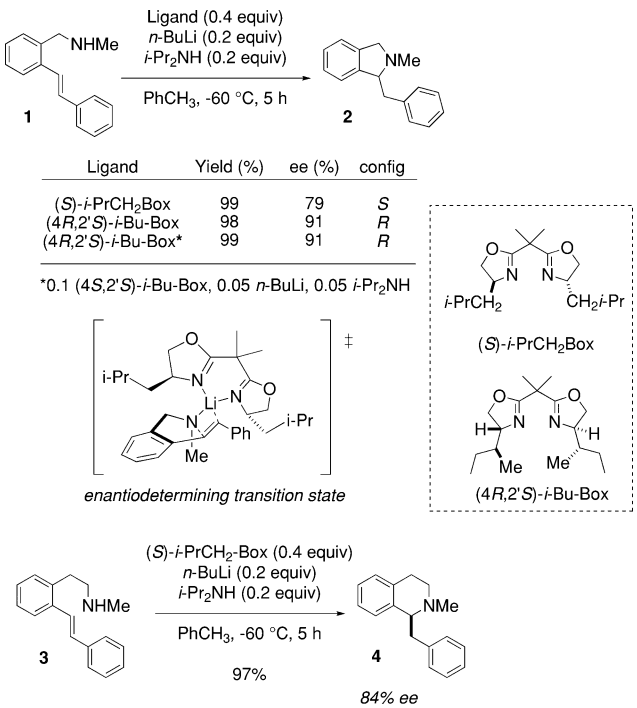
Both Schafer and Bergman believe their reactions involve a [2 + 2] addition of a zirconium imido intermediate to the alkene. In support of this, Schafer demonstrated that secondary amines are unreactive with her catalyst.[13]

2.1.3 Main group metals: organolithium catalysts. The first lithium-based chiral hydroamination reaction was reported by Hultzsch and co-workers in 2006 using diamidobinaphthyl ligands as the source of chirality.[16] Shortly thereafter, Tomioka and co-workers reported an organolithium-catalyzed reaction with chiral bis(oxazoline) ligands.[17] The stereoselective C–N bond formation is thought to occur *via* a syn aminometallation mechanism.[17]

Hultzsch demonstrated that treatment of the L-proline derived axially chiral (*S,S,S*)-diaminobinaphthyl ligand (Table 5) with two equivalents of n-BuLi provided the corresponding dilithium salt as a yellow-orange powder. The crystal structure indicated a dimeric structure involving four highly coordinated lithium atoms. Treatment of the primary amine substrates with 5 mol% of Hultzsch's lithium catalyst in toluene at room temperature provided efficient cyclization in 79–86% isolated yield (96–98% NMR yield) of various pyrrolidines with % ee's ranging from 17–74% (Table 5).[16] Although the styrenyl substrate (entry 4) was considerably more reactive than the substrates with terminal olefins, the enantioselectivity was significantly diminished. In these reactions it was noted that addition of THF reduced catalytic performance and eroded enantioselectivity.

Hultzsch *et al.* demonstrated that the presence of multiple lithium and amine atoms in the catalyst is necessary for high catalyst reactivity. While $LiN(SiMe_3)_2$ was a poor catalyst, a catalyst system comprised of $LiN(SiMe_3)_2$ and (–)-sparteine gave improved rates, though poor selectivity.

Tomioka and co-workers demonstrated the enantioselective hydroamination/cyclization of the secondary amine styrenyl substrates **1** and **3** (Scheme 2).[17] Under optimal conditions, using chiral bis(oxazoline) ligands (*S,S*)-*i*-PrCH_2-Box and (4*R*,2′*S*)-*i*-Bu-Box, they obtained high yields of isoindoline **2** and tetrahydroisoquinoline **4** with 91% and 84% ee, respectively. The (*S*)-*i*-PrCH_2-Box ligand favored formation of the *S*-product while the pseudo-enantiomeric (4*R*,2′*S*)-*i*-Bu-Box ligand favored formation of the *R*-adduct. The reactions proceeded at low temperature (–60 °C) and with high yield (>90%) with a catalyst mixture comprised of a 1:1:2 ratio of *n*-BuLi to *i*-Pr_2NH to bis(oxazoline). Chiral ligand loading was typically 40 mol% but could be as low as 10 mol% with substrate **2**. A transition state that could rationalize the formation of the *S*-stereoisomer using the (*S*)-*i*-PrCH_2-Box ligand with substrate **2** is shown in Scheme 2, where a dominant stereocontrol element could be minimization of steric interactions between the alkene undergoing addition and the nearest oxazoline ring (lower right quadrant).

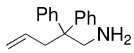
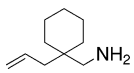
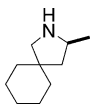
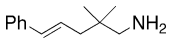
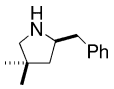
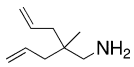
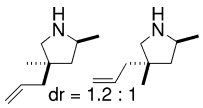


Scheme 2 Chiral bis(oxazoline) ligands in enantioselective lithium-catalyzed hydroamination reactions.

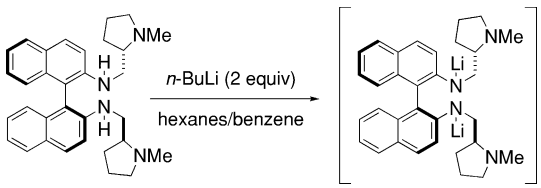
2.2 Enantioselective intramolecular hydroamination of allenes

Allenes are often more reactive than alkenes in addition chemistry due to the 10 kcal of strain associated with the cumulated

Table 5 Hydroamination/cyclization catalyzed by Hultzsch's lithium catalyst[16]

Entry[a]	Substrate	Product(s)	Time (h)	Yield (NMR, isolated)[b]	ee (%), config.
1			42	96, 86	68, *S*
2			0.8	97	31, *S*
3[d]			2	98, 82	74, *S*
4			0.08	98	17
5			2	98, 79	64, 72

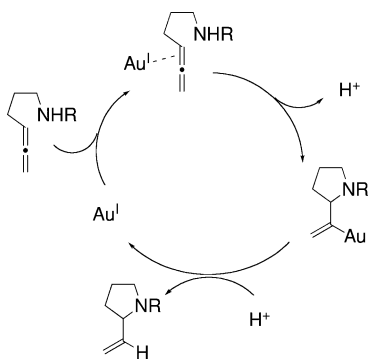
[a] Conditions: 5 mol% catalyst, C_6D_6, 22 °C, Ar atm. [b] NMR yield relative to ferrocene internal standard. [c] Enantiomeric excess was determined by ^{19}F NMR of the Mosher amides. [d] Reaction in toluene.



double bond.[18,19] A number of transition metals have demonstrated utility in the intramolecular aminofunctionalization of allenes.[20] Highly enantioselecctive hydroamination of allenes have only been reported using gold catalysts (*vide infra*). Although chiral palladium[21] and titanium-catalyzed[22] intramolecular enantioselective hydroaminations have been tried, the levels of asymmetric induction obtained were quite low.

The use of chiral gold(I) complexes has enabled the enantioselective cyclization of heteroatoms onto allenes.[23–25] Toste and co-workers reported the first intramolecular enantioselective hydroamination of γ- and δ-*N*-allenyl sulfonamides catalyzed by gold(I) complexes in 2007.[26,27] Widenhoefer and co-workers reported their results with γ-*N*-allenyl carbamates in the same year.[28,29] An outer-sphere, *trans* aminometallation has been proposed for the stereochemistry-determining C–N bond forming step (Scheme 3).[24,25,29]

Toste and co-workers explored the use of two kinds of chiral catalysts in the intramolecular hydroamination of allenes. In their first report, chiral dinuclear gold(I)-phosphine complexes such as **5–7**, where chirality is derived from the phosphine ligand, catalyzed the enantioselective hydroamination/cyclization of a number of γ- and δ-*N*-allenyl sulfonamides (Table 6).[26] Isolated yields ranged from 41–99% and the ee's ranged from 70–99%. They found that the nature of the achiral counterion influenced the efficiency and selectivity of the reactions; the optimized catalysts had the electron-withdrawing p-nitrobenzoate

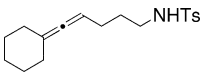
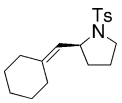
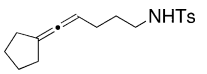
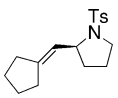
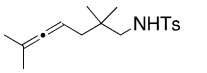
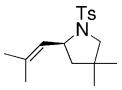
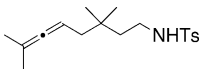
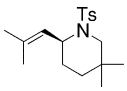


Scheme 3 Proposed catalytic cycle for the gold-catalyzed hydroamination of allenes.

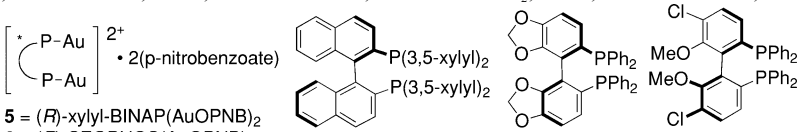
counterions. To obtain high enantioselectivities, highly substituted allene substrates were necessary (Table 6).

In a similar manner, Widenhoefer and co-workers also employed chiral dinuclear gold(I)-phosphine catalysts in their hydroamination/cyclization reactions of *N*-carbamoyl allenes (Table 7).[28,29] Interestingly, allenylcarbamates failed to undergo hydroamination in Toste's reaction,[26] while allenylsulfonamides failed to give appreciable enantioselectivity in Widenhoefer's reaction.[28] In Widenhoefer's reaction, the allene substrates are not required to be highly substituted to obtain respectable enantioselectivities.

Table 6 Au(I)-catalyzed hydroamination/cyclization of *N*-sulfonylallenes[26]

Entry[a]	Substrate	Conditions	Product	Yield (%)	ee (%)
1		A		88	98
2		A		75	83
3		B		94	93
4		C		70	98

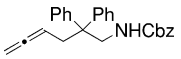
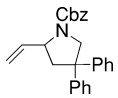
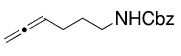
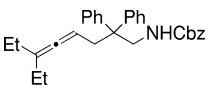
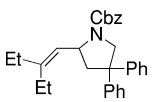
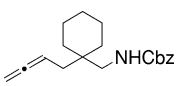
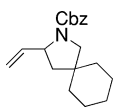
[a] Conditions: A = 3 mol% of **5**, 0.3 M in DCE, 23 °C; B = 5 mol% of **6**, 0.3 M in $MeNO_2$, 50 °C; C = 5 mol% of **7**, 0.3 M in $MeNO_2$, 50 °C.



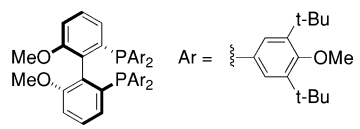
5 = (*R*)-xylyl-BINAP(AuOPNB)$_2$
6 = (*R*)-SEGPHOS(AuOPNB)$_2$
7 = (*R*)-ClMeOBiPHEP(AuOPNB)$_2$

(*R*)-xylyl-BINAP (*R*)-SEGPHOS (*R*)-ClMeOBIPHEP

Table 7 Au(I)-catalyzed hydroamination/cyclization of *N*-carbamoyl allenes[28]

Entry[a]	Substrate	Conditions	Product	Yield (%)	ee (%)
1		A		97	81
2		B		99	34
3		C		83	91
4		A		98	50

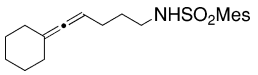
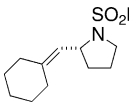
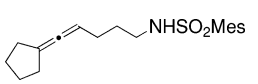
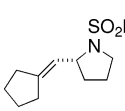
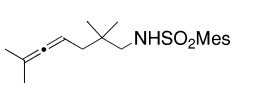
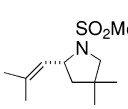
[a] Conditions: A = 2.5 mol% [(*S*)-DTBM-MeOBIPHEP]Au_2Cl_2, 5 mol% $AgClO_4$, 0.30 M in toluene, –40 °C, 24 h; B = same as A except –20 °C; C = same as A except 0 °C, 24 h then rt, 24 h.



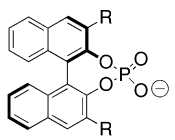
Ligand = (*S*)-DTBM-MeOBIPHEP

Toste and co-workers subsequently reported that a mononuclear gold(I) complex with an achiral phosphine ligand [$Ph(CH_3)_2P$] and a chiral binaphthol-derived phosphate counterion proved highly effective in catalyzing the enantioselective cyclization of γ-*N*-allenyl sulfonamides in benzene at 23 °C (Table 8).[27]

Table 8 Chiral anion strategy for Au(I)-catalyzed hydroamination/cyclization of allenes[27]

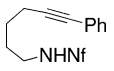
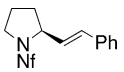
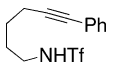
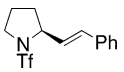
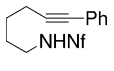
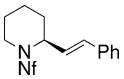
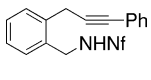
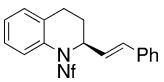
Entry[a]	Substrate	Product	Yield (%)	ee (%)
1			97	96
2			88	98
3			84	99

[a] Conditions: 5 mol% $Ph(CH_3)_2PAuCl$, 5 mol% Ag-(*R*)-**8**, benzene, 23 °C, 48 h.

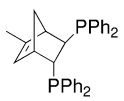


(*R*)-**8**, R = 2,4,6-*i*-Pr_3-C_6H_2

Table 9 Palladium-catalyzed hydroamination/cyclization of alkynes[32]

Entry[a]	Substrate	Product	Yield (%)	ee (%)
1			93	92
2			90	88
3			92	79
4			90	95

[a] Conditions: 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 10 mol% $PhCO_2H$, 20 mol% ligand in PhH at 100 °C, 48 h.

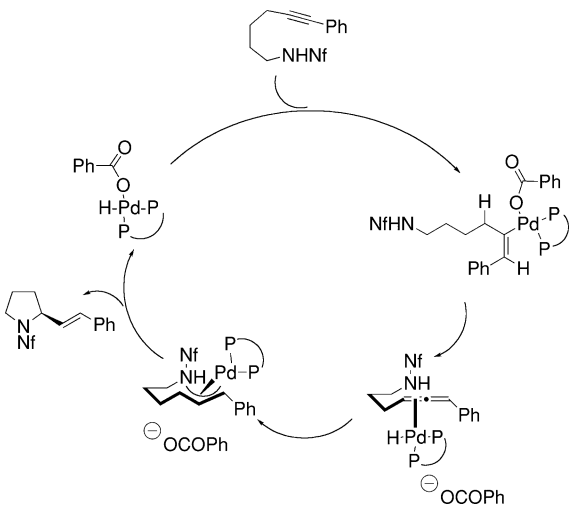


Ligand = (*R, R*)-methyl Norphos

2.3 Enantioselective intramolecular hydroamination of alkynes

Yamamoto and co-workers have reported the enantioselective synthesis of pyrrolidines and piperidines *via* palladium-catalyzed intramolecular alkyne hydroamination.[21,30–32] The reactions occur in good yield (87–93%) and enantioselectivity (79–95% ee) in benzene at 100 °C for 48 h. These conditions require 10 mol% palladium catalyst loading and 20 mol% of the methyl Norphos bisphosphine ligand (Table 9). Generally, the (*R,R*)-ligand provides the *S*-product. The nonafluorobutanesulfonyl (Nf) nitrogen substituent provided the highest yields and selectivities. Interestingly, neither the corresponding allene or diene substrates provided analogous enantioselectivities.

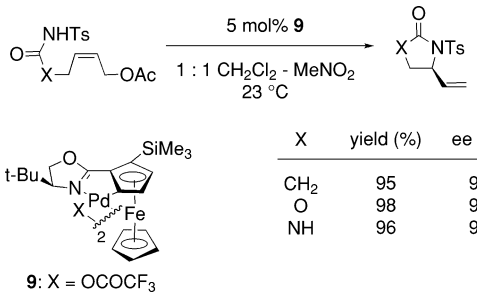
The reaction is thought to involve addition of a palladium hydride onto the alkyne followed by beta-hydride elimination to form the allene. Subsequent hydropalladation would provide the π-allyl species, which may undergo nucleophilic *trans* addition by the amine to provide the nitrogen heterocycle and re-generate the catalyst (Scheme 4).



Scheme 4 Proposed catalytic cycle for the intramolecular hydroamination of alkynes.

2.4 Enantioselective intramolecular aminative S_N2' displacement of allylic acetates

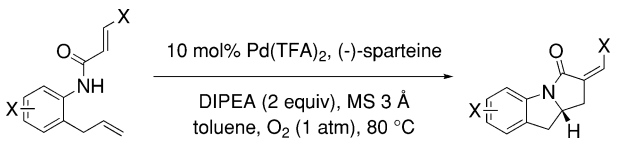
In 2002, Overman and co-workers reported a novel nitrogen heterocycle forming reaction that involves a formal enantioselective intramolecular S_N2' displacement of an allylic acetate,

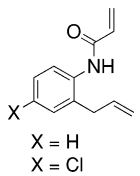
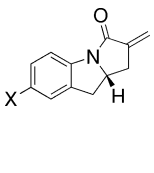
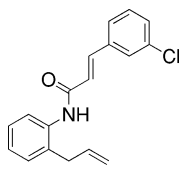
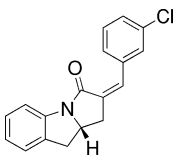
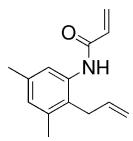
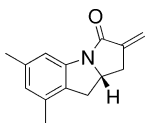


X	yield (%)	ee (%)
CH_2	95	90
O	98	93
NH	96	90

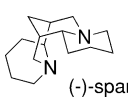
Scheme 5 Palladium-catalyzed enantioselective S_N2'-type cyclization.

Table 10 Palladium-catalyzed enantioselective alkene carboamination[44]



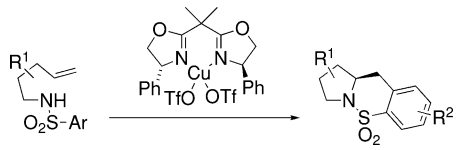
Entry[a]	Substrate	Product	Yield (%)[b]	ee (%)[c]
1	 X = H, X = Cl		78	86
2[d]			61	75
3[d,e]			60	80
4			63	91

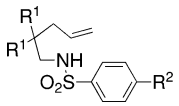
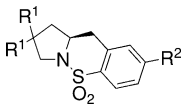
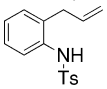
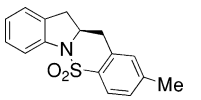
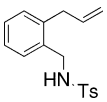
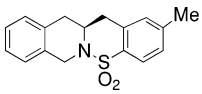
[a] Conditions: 10 mol% $Pd(TFA)_2$, 40 mol% (–)-sparteine, 26–48 h. [b] Yield of isolated product. [c] Enantiomeric excess was determined by HPLC analysis using a Chiralcel OD column. [d] 20 mol% $Pd(TFA)_2$ and 80 mol% (–)-sparteine was used. [e] Absolute configuration determined by X-ray crystallography.



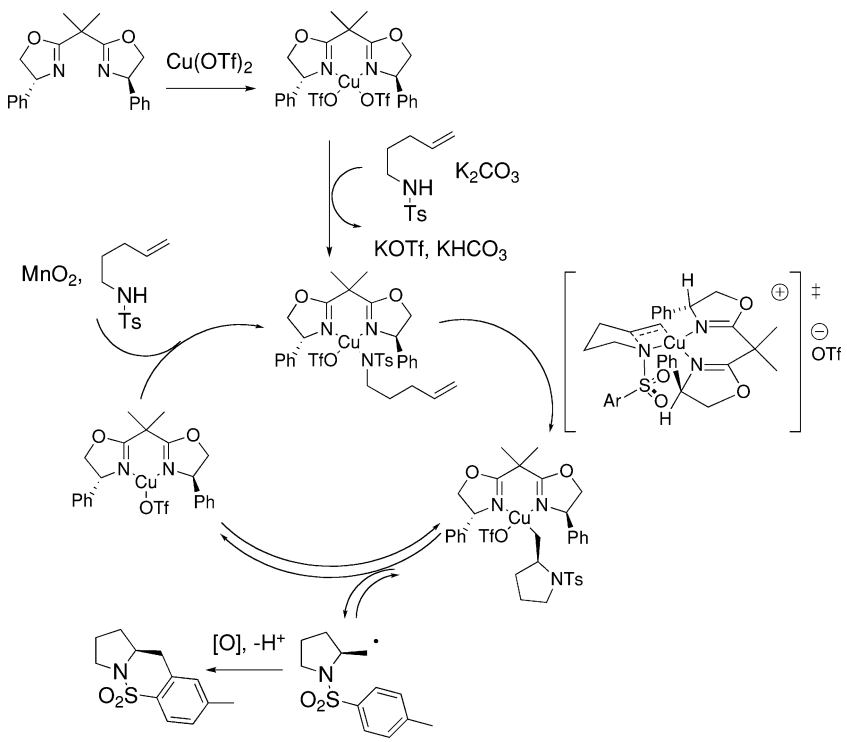
(-)-sparteine

Table 11 Copper-catalyzed enantioselective intramolecular carboamination[45]



Entry[a]	Substrate	Product	Yield (%)[b]	ee (%)[c]
				
1	$R^1 = Me$, $R^2 = Me$		85	92
2	$R^1 = Me$, $R^2 = H$		73	92
3	$R^1 = Me$, $R^2 = Cl$		45	92
4	$R^1 = Me$, $R^2 = OMe$		75	94
5	$R^1 = Ph$, $R^2 = Me$		78	94
6	$R^1 = H$, $R^2 = H$		77	82
7			75	46
8[d]			63	72

[a] Conditions: $Cu(OTf)_2$ (20 mol%) and (*R*,*R*)-Ph-box (20 mol%) were complexed in $PhCF_3$ at 50 °C for 1 h (sealed tube). Substrate, MnO_2 (300 mol%) and K_2CO_3 (100 mol%) were added, the reaction tube was sealed and heated at 120 °C for 24 h. [b] Yields refer to isolated product. [c] Enantiomeric excess was measured by chiral HPLC. [d] Reaction was run for 96 h.



Scheme 6 Proposed catalytic cycle for the enantioselective copper-catalyzed alkene carboamination.

catalyzed by chiral palladium(II) catalyst **9** (Scheme 5).[33,34] In this reaction, allylic tosylamides afford chiral vinyl-substituted nitrogen heterocycles. The reaction is proposed to involve a syn aminopalladation onto the alkene followed by reductive elimination of a palladium(II) acetate complex.[33]

3 Oxidative cyclizations

When a substrate is oxidatively cyclized, it experiences a net oxidation upon conversion to the product. Reactions that fit into this category include carboamination, aminooxygenation, oxidative amination, diamination and aminohalogenation of alkenes. Enantioselective versions of only the first two cyclization reactions have been developed. Racemic metal-catalyzed/promoted intramolecular alkene oxidative aminations,[35] diaminations[36–40] and aminohalogenations[41–43] have been reported, but no enantioselective versions of these reactions have yet appeared.

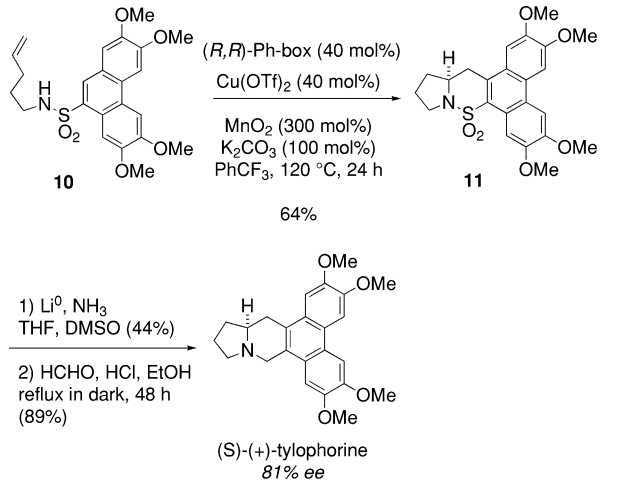
3.1 Enantioselective intramolecular carboamination of alkenes

The intramolecular carboamination of alkenes is an efficient method for the synthesis of nitrogen heterocycles from alkenyl amines. In these reactions, a new carbon–nitrogen and a new carbon–carbon bond are formed in the alkene addition reaction. Thus far, two examples of enantioselective intramolecular alkene carboaminations have been published, one using a chiral palladium catalyst[44] and the other using a chiral copper catalyst[45] (*vide infra*).

3.1.1 Palladium-catalyzed enantioselective carboamination. The first intramolecular catalytic enantioselective alkene carboamination was reported by Dan Yang and co-workers in 2006.[44] This palladium-catalyzed reaction provides chiral indolines in moderate to good yields and 75–91% enantiomeric excess using 5–20 mol% $Pd(TFA)_2$ and 20–80 mol% (–)-sparteine as the chiral catalyst (Table 10). The absolute configuration of one of the products was determined to be *S*. This reaction involves an intramolecular aminopalladation followed by intramolecular alkene insertion and terminates with a beta-hydride elimination. O_2 (1 atm) was used as the stoichiometric oxidant. No model for the enantioselective C–N bond formation has been put forth but the basic reaction conditions[46] and good % ee at elevated (80 °C) temperature may indicate a tight, syn-aminopalladation enantiodetermining transition state.

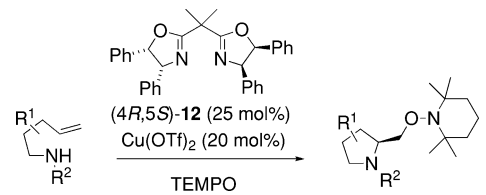
3.1.2 Copper-catalyzed enantioselective carboamination of alkenes. We reported a copper-catalyzed enantioselective alkene carboamination in 2007.[45] This reaction provides chiral polycyclic sultams in moderate to good yields and 46–94% ee (Table 11). The pre-complexed catalyst is composed of 20 mol% $Cu(OTf)_2$ and 20 mol% (*R,R*)-Ph-Box, a bis(oxazoline) ligand, and the stoichiometric oxidant is MnO_2. 4-Pentenylarylsulfonamides provided the highest enantioselectivity.

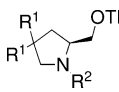
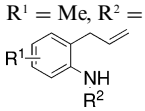
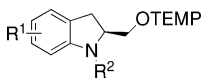
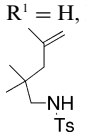
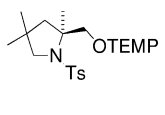
The absolute configurations of two products (not shown) were determined by X-ray crystallography to be *S*; the rest are assigned by analogy. The enantioinduction is rationalized as shown in Scheme 6, which involves a presumed rate-determining syn-aminocupration transition state. In this transition state, steric interactions between the substrate's N-substituent and the oxazoline substituent on the ligand that it is nearest to are minimized. The



Scheme 7 Application of the copper-catalyzed carboamination to the total synthesis of (+)-tylophorine.

Table 12 Copper-catalyzed enantioselective intramolecular aminooxygenation[49]



Entry[a]	Substrate	Product	Yield (%)[b]	ee (%)[c]
				
1[d]	R^1 = Me, R^2 = Ts		97	88
2[d]	R^1 = Ph, R^2 = Ts		97	92
3[d,e]	R^1 = H, R^2 = Ts		74	75
4[d,e]	R^1 = Me, R^2 = Ns		86	89
				
5	R^1 = H, R^2 = Ts		97	90
6	R^1 = p-F, R^2 = Ts		83	89
7	R^1 = p-Cl, R^2 = Ts		73	91
8	R^1 = p-OMe, R^2 = Ts		82	86
9	R^1 = H, R^2 = Ns		75	61
10	R^1 = H, R^2 = Ms		57	50
11[d,e]			61	82

[a] Conditions: $Cu(OTf)_2$ (20 mol%) and (4*R*,5*S*)-**12**(25 mol%) were complexed in $PhCF_3$ at 50 °C for 1 h (sealed tube). Substrate, TEMPO (300 mol%) and K_2CO_3 (100 mol%) were added, the reaction tube was sealed and heated at 110 °C for 24 h. [b] Yields refer to isolated product. [c] Enantiomeric excess was measured by chiral HPLC analysis. [d] Reaction was run at 120 °C under O_2 (1 atm). [e] 40 mol% $Cu(OTf)_2$ and 50 mol% ligand was used.

carbon–carbon bond is subsequently formed *via* homolysis of the unstable carbon–copper(II) bond to form a primary radical that adds to the neighboring aryl ring.[47] Rearomatization, probably facilitated by oxidation of the aryl radical to the aryl cation, then provides the sultam product.

Since both enantiomers of the Ph-box ligand are commercially available, this protocol provides access to either enantiomer of the product. The SO_2 group in the sultam products can be reductively removed (Li, NH_3) to provide the chiral pyrrolidine.[45]

This enantioselective carboamination reaction was used in our concise total synthesis of (*S*)-(+)-tylophorine (Scheme 7).[48] Copper-catalyzed enantioselective carboamination of sulfonamide **10** provided sultam **11** in 64% yield. Reductive removal of SO_2 followed by Pictet–Spengler reaction of the resulting pyrrolidine with formaldehyde provided (*S*)-(+)-tylophorine in 81% ee as determined by chiral HPLC. The yield in the SO_2 removal is low due to concurrent loss of methoxy groups under the reaction conditions.

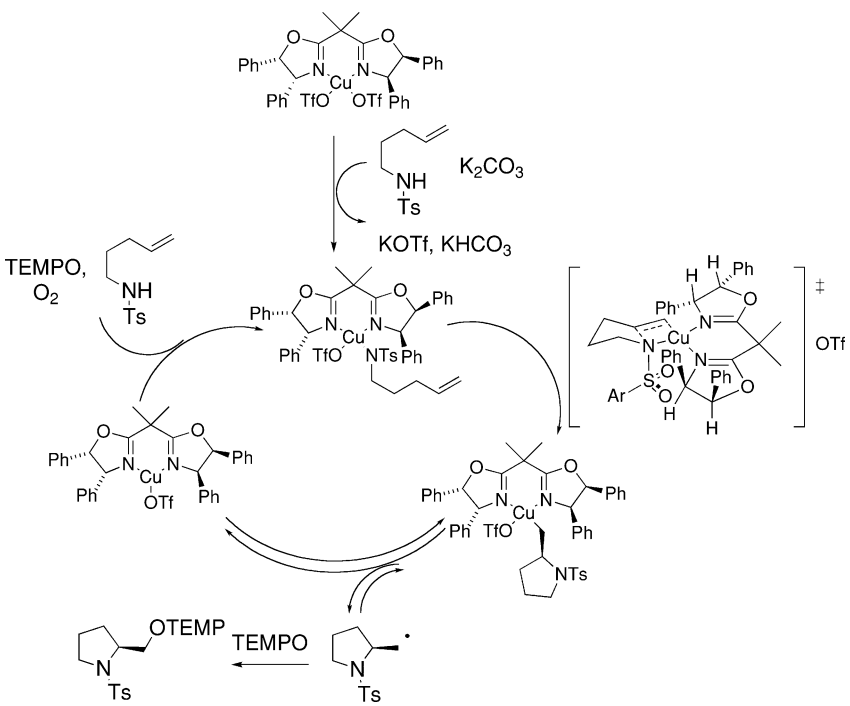
3.2 Catalytic enantioselective intramolecular aminooxygenation of alkenes

We reported the first enantioselective intramolecular alkene aminooxygenation in 2008.[49] This reaction is also catalyzed by chiral copper-bis(oxazoline) complexes and provides access to methyleneoxy-functionalized indolines and pyrrolidines in good to excellent yields and with good enantioselectivity (Table 12). In these reactions, tetramethylaminopyridyl radical (TEMPO) serves as both the oxygen source and as the oxidant. However, an O_2 atmosphere is required for complete conversion of the 4-pentenylsulfonamides to their corresponding pyrrolidines. For this reaction, the (4*R*,5*S*)-diphenylbis(oxazoline) ligand **12** provided the highest enantioselectivity. Arylsulfonyl N-substituents gave the highest reactivity and selectivity (compare entries 5 and 10). The TEMPO adducts can be subsequently reduced to provide the corresponding aminoalcohols or oxidized to provide the aldehydes without reduction of enantiomeric excess.[49]

A rate-determining syn-aminocupration is invoked to rationalize the observed product stereoselectivity (Scheme 8). Homolysis of the resulting carbon–copper bond then provides a primary radical which combines with TEMPO radical to give the observed aminooxygenation product. TEMPO and/or O_2 serve to reoxidize Cu(I) to Cu(II).

4 Summary and future outlook

As can be seen from the new methodologies summarized in this review, the catalytic asymmetric amination of alkenes, dienes, allenes and alkynes has experienced a flurry of progress in recent years. It is interesting that most, but not all of these transformations are thought to occur *via* syn aminometallation processes, which can offer tight transition states for translation of the ligand chirality to the forming nitrogen-bearing stereocenter. Notable exceptions are the gold-catalyzed allene hydroaminations and the palladium-catalyzed alkyne hydroamination. It is expected that application of these methods in the context of fine chemical synthesis and medicinal chemistry, and in the total synthesis of natural products will continue and likely will drive further advances in the field. In this respect, a number of challenges still remain. The intramolecular catalytic enantioselective oxidative amination, diamination and aminohalogenation of alkenes have yet to be reported. Additionally, many of the existing reactions still require significant thermal activation to occur, indicating the need for more active catalysts to be developed. More active catalysts could also further expand the substrate scope. Furthermore, a more rigorous understanding of the factors involved in



Scheme 8 Proposed cycle for the copper-catalyzed enantioselective alkene aminooxygenation.

determining enantioselectivity could lead to more rationally designed ligands and better pairing of substrates and catalysts. Advances in these areas and others will further establish the enantioselective amination of unactivated π bonds as a method of choice for the synthesis of chiral nitrogen heterocycles.

Acknowledgements

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