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Review

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Hydroxyamide-Based Ligands and Their Use in the Asymmetric Catalysis of Key Organic Transformations

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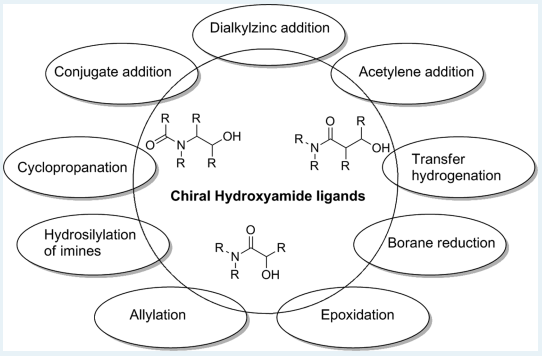
ABSTRACT: Asymmetric ligands whose key functional component consists of an amide and hydroxyl functional groups, in the absence of other co-ordinating groups, are a relatively recent development in asymmetric catalysis. These ligands in combination with ruthenium, zinc, or titanium have catalyzed a range of key organic reactions showing high activity and selectivity. This review looks at the ligands reported and their performance as catalysts.



KEYWORDS: *hydroxyamide, catalyst, ligand, asymmetric synthesis, organic synthesis*

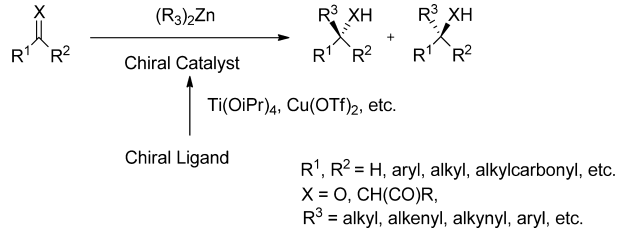
INTRODUCTION

The asymmetric catalysis of organic reactions by metal complexes of amines and amino alcohols or, indeed, their use without metals in organocatalysis is a very active area of research. Many very successful catalytic systems have been reported for key organic reactions. More recently, there has been growing interest in the use of amido alcohols as ligands in metal complexes which show good activity in asymmetric organic transformations. This review seeks to look at ligands of this type and their complexes' use in key synthetic reactions. The review is arranged according to the reactions studied and relates to work reported to the end of 2010.

DIAKYLZINC ADDITION TO CARBONYL GROUPS

The stereoselective creation of stereogenic centers is an important process in organic chemistry. Approaches based on C−C bond formation reactions provide a basic strategy for synthesizing these molecules. The catalytic asymmetric addition of organozinc reagents to carbonyl groups in the presence of chiral ligands (Scheme 1) has proved a very useful and versatile approach, synthesizing optically active secondary alcohols.[1] Many ligands inducing high enantioselectivies have been reported.[2−5] The organozinc reagents, due to their low reactivity, can tolerate the presence of many reactive functional groups and are highly selective in nucleophilic addition reactions to carbonyl compounds.

Scheme 1. Enantioselective Addition of Organozinc Reagents to Carbon Electrophiles



Although many types of ligands can catalyze this reaction, the derivatives of chiral amino alcohols are among the most studied ligand types due to the high stereoselectivities achieved.[1,6] *N,N*-dialkyl-substituted *β*-amino alcohols such as Noyori's DAIB **1** and Nugent's (2*S*)-(−)-3-exo(morpholino)isoborneol [(−)-MIB] **2** are particularly noteworthy (Figure 1).[7,8]

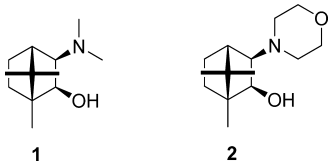


Figure 1. Some established amino alcohol ligands.

The mechanism of diethylzinc addition to benzaldehyde with *β*-amino alcohols as ligands is well-known. The amino alcohol acts as a Lewis base, which activates the zinc reagent and forms a Lewis acidic zinc species, which activates the aldehyde. Upon treatment of an amino alcohol with an alkylzinc reagent, the nitrogen and oxygen donor atoms of the amino alcohol coordinate to the zinc atom, yielding a complex that is capable

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of acting as an alkyl donor. The zinc atom in the five-membered chelate ring is a Lewis acid, which coordinates the aldehyde through the oxygen nonbonding orbital, and hence, the carbonyl carbon atom is activated for nucleophilic attack.[9,10]

Certain chiral β-hydroxyamides have proved to be efficient ligands in the addition of organozincs to carbonyl compounds, as well. These compounds are attractive because they have the advantage of being easily prepared by the reaction of simple and cheap starting materials (e.g., hydroxy acids and amines or acids and amino alcohols), which can be obtained in enantiopure form from the chiral pool. In many cases, titanium(IV) isopropoxide is used as a Lewis acidic additive.

Katsuki and co-workers described the application of 1,1′-bi-2-naphthol-3,3′-dicarboxamides **3a**−**e** as chiral ligands, in the enantioselective addition of diethylzinc to a variety of aldehydes (Figure 2).[11,12] Among the ligands they used, the ligand **3c** gave high yields and excellent enantioselectivities in the reaction of aromatic aldehydes (Scheme 2). The alkylation of phenyl propargyl aldehyde was also studied (Scheme 3). Ligand **3d** induced excellent enantioselectivities with moderate yields in the reaction. The yields could be improved somewhat by increasing the excess of alkylating agent.

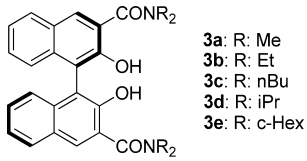
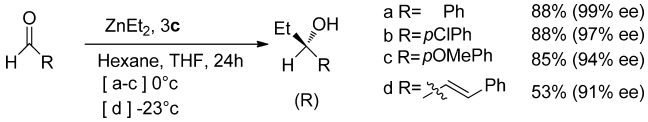
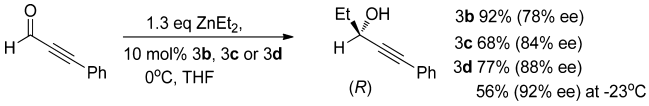


Figure 2. 1,1′-Bi-2-naphthol-3,3′-dicarboxamide ligands.

Scheme 2. Diethylzinc Addition to Aldehydes Using a Napthol Dicarboxamide Ligand



Scheme 3. Alkylation of Phenyl Propargyl Aldehyde



Oppolzer et al. first reported the use of ketopinic acid-derived tertiary amido alcohol **4a** in the addition of diethylzinc to benzaldehyde (68% yield, 91% ee) in 1988.[13] The use of tertiary amido alcohols in this reaction remained largely unexplored until the group of Engel developed ligands **5a**−**9a** (Figures 3, 5), analogues of **4a**, to investigate the influence of the nitrogen's alkyl substitution and the ligand's symmetry on its catalytic activity in the same reaction. These experiments were repeated with the corresponding *N*,*N*-dialkylamino alcohol ligands, **4b**−**8b**.[14,15]

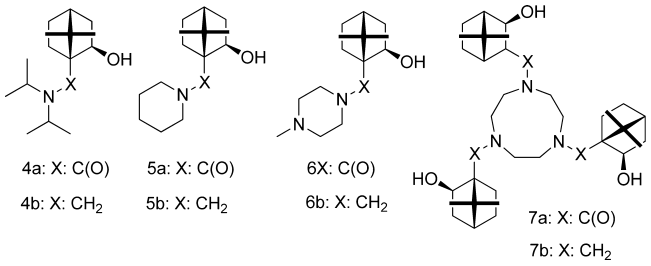


Figure 3. Isoborneol-based hydroxyamides and amino alcohols studied.

The collected data in Table 1 shows that all the ligands promote Re face attack of the prochiral benzaldehyde, giving the *R* product. It also demonstrates that hydroxyamides can be more efficient than the analogous amino alcohols for certain ligand structures and reactions. A bis(hydroxyamide) C_2-symmetric structure is more efficient and selective for these amido isoborneols, whereas a C_1-symmetric structure is better for amino isoborneols.

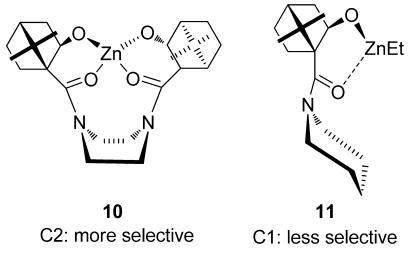


Figure 4. Possible conformations of the C_2-symmetric zinc dialkoxide catalyst, **10**, and the C_1-symmetric **11**.[17]

The authors reasoned that the better catalytic results obtained with **8a** in relation to the related amino alcohols **5b** and **6b** was due to the formation of a more enantioselective and reactive C_2-symmetric zinc dialkoxide catalyst, **10**, instead of the C_1-symmetric **11** (Figure 4). The substitution of the methylamino group of **6a** with the amide present in **8a** must be enough to allow the extra coordination (by the closer carbonyl oxygen), giving rise to the efficient catalyst **10**. It is proposed that the difference in performance between **8a** and **8b**

Table 1. Enantioselective Addition of Diethylzinc to Benzaldehyde in the Presence of Ligands 3a−8a and 3b−7b[17,a]

	hydroxyamides				amino alcohols			
ligand symmetry	ligand	yield (%)	ee (%)	dominant configuration	ligand	yield (%)	ee (%)	dominant configuration
C_1	4a	68	91	*R*	4b	35	82	*R*
	5a	96	48	*R*	5b	96	72	*R*
	6a	93	50	*R*	6b	99	50	*R*
C_2	8a	97	90	*R*	8b	94	56	*R*
	9a	92	73	*R*				
C_3	7a	70	39	*R*	7b	72	12	*R*

[a]Reactions conducted at room temperature for 5 h in hexane using Et_2N 2 mmol, ligand 0.05 mmol, aldehyde 1 mmol; ee determined by GC.

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can be explained by the loss of the usually advantageous C_2 symmetry[14,16] by the metallocatalyst formed in the case of **8b**, which is similar in structure to **11** and gives similar results.

It has been proposed, for a number of reasons, that transition metal complexes derived from C_3-symmetric ligands have even greater potential for asymmetric catalysis than their C_2-symmetric counterparts.[18] Here, the C_3-symmetric ligands **7a** and **7b** promote the reaction poorly. The low enantioselectivity can be explained by the possible coexistence of different catalytic species due to multiple coordination sites in these ligands.

More recently, a paper by the same author[19] screened a selected library of ketopinic acid-derived C_2-symmetric bis-(hydroxyamide) ligands in the enantioselective ethylation of benzaldehyde (Table 2). These ligands included previously reported **8a** and **9a**[14] and Uangs's **12** and **13** (Figure 5).[20,21]

Table 2. Performance of Ligands in the Enantioselective Diethylzinc Addition to Benzaldehyde[19,a]

		1-phenylpropan-1-ol	
ligand	yield (%)	ee (%)	dominant configuration
8a	97	90	*R*
9a	92	73	*R*
12	43	24	*R*
13	45	24	*R*
14	25	40	*R*
15	62	52	*R*
16	95	94	*R*
17	99	86	*R*
18	65	10	*R*

[a]Reactions conducted at room temperature for 5 h in hexane using Et_2N 2 mmol, ligand 0.05 mmol, aldehyde 1 mmol; ee determined by HPLC, and yield, by GC.

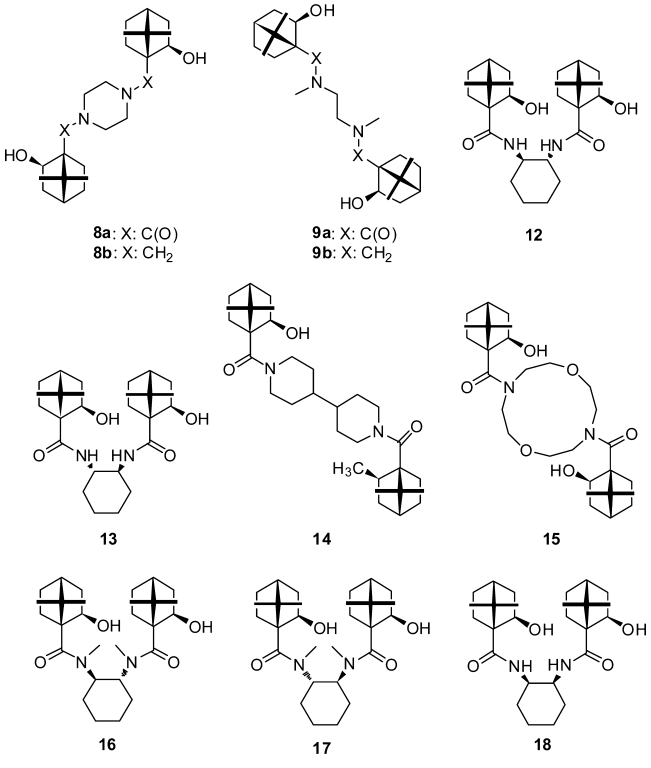

Figure 5. Ketopinic acid-derived bis(hydroxyamide) ligands.

Of note is the catalytic efficiency of aprotic over protic amide ligands and also that the bis(hydroxyamides) with shorter spacers (2-carbon length) between the amide N's are superior to those with longer spacers. The ligands with longer spacers should form dimetallic, nontetrahedral, C_1-symmetric Zn catalysts similar to **11**. It follows that their catalytic behavior would be similar to less efficient C_1-symmetric catalysts derived from C_1-symmetric hydroxyamide ligands (**5a**–**7a**, Table 1). The catalytic behavior of all the studied aprotic amide-based ligands demonstrates that both the length and the conformational flexibility of the diamine spacer are key structural factors controlling the catalytic activity. The effect of conformational flexibility is evident in the decreased selectivity of **9a**.

The poor efficiency of the protic amide ligands was explained by the formation of bimetallic zinc catalysts as a result of deprotonation of the amides and subsequent O/N zinc chelation, which leads to competitive, undesired pro-*S* transition states, in contrast to the zinc-centered catalyst **10**.

The most efficient ligands, **8a**, **16**, and **17**, were tested in the ethylation of different benzaldehydes, bearing electron-withdrawing or -donating groups to influence their reactivity. Under the optimized conditions (0.02 mol % ligand), the reactions occurred with moderate to excellent yields and enantioselectivities (73–97% ee and 71–92% yield).

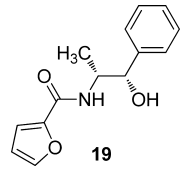

Figure 6. Chiral *β*-hydroxyamide **19** derived from from (1*S*,2*R*)-(+)-norephedrine.

Velmathi et al. developed chiral *β*-hydroxyamide **19** (Figure 6), synthesized from (1*S*,2*R*)-(+)-norephedrine and furoic acid,[22] and applied it to catalyze the enantioselective ethylation of aromatic and heteroaromatic aldehydes to secondary alcohols.

During initial optimization studies with the ligand in the asymmetric addition of diethylzinc to benzaldehyde, it was found that the reaction temperature and ligand concentration had a significant influence on the efficacy of the catalyst. The results indicated that 0 °C, 10 mol % of the **19** in toluene, and reaction times of 24 h were the best conditions to obtain the highest enantioselectivity. To study the effect of $Ti(O^iPr)_4$ as a promoter[23] in this catalytic system, the diethylzinc addition to benzaldehyde was carried out in the presence of $Ti(O^iPr)_4$, and (*R*)-1-phenyl propyl alcohol was formed in 99.8% ee with 90% yield.[22] This performance is identical to the reaction without promoter, the use of which does not seem to be beneficial in the case of this ligand.

The ligand's performance was further studied in the asymmetric diethylzinc addition to other substituted benzaldehydes, salicylaldehydes, and heterocyclic aldehydes without the addition of $Ti(O^iPr)_4$ (Table 3).

The performance of the catalytic system was good in terms of both yield and selectivity across a variety of aldehyde starting materials. The three final entries in Table 3 along with that for *p*-methoxybenzaldehyde show dramatically reduced selectivity. The authors speculate that this altered performance is due to coordination of the additional oxygens or nitrogens in the substrates to the zinc species.

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Table 3. Diethylzinc Addition to Different Aldehydes Using 19 and No Promoter[24,a]

aldehyde	yield (%)	ee (%)	dominant configuration
benzaldehyde	90	99.8	*R*
o-nitro benzaldehyde	70	68	*R*
m-nitro benzaldehyde	82	95	*R*
p-nitro benzaldehyde	92	85	*R*
p-methoxy benzaldehyde	90	30	*R*
p-methyl benzaldehyde	90	76	*R*
p-chloro benzaldehyde	95	99.8	*R*
salicylaldehyde	23	99.8	*R*
5-chloro salicylaldehyde	46	99	*R*
4-hydroxy 3-methoxy benzaldehyde	20	20	*S*
pyrrole-2-carboxaldehyde	99	53	*R*
furfural	96	10	*R*

[a]Reactions conducted at 0 °C for 24 h in toluene using Et_2N 2 mmol, ligand 0.1 mmol, aldehyde 1 mmol; ee determined by HPLC; yields are isolated yields.

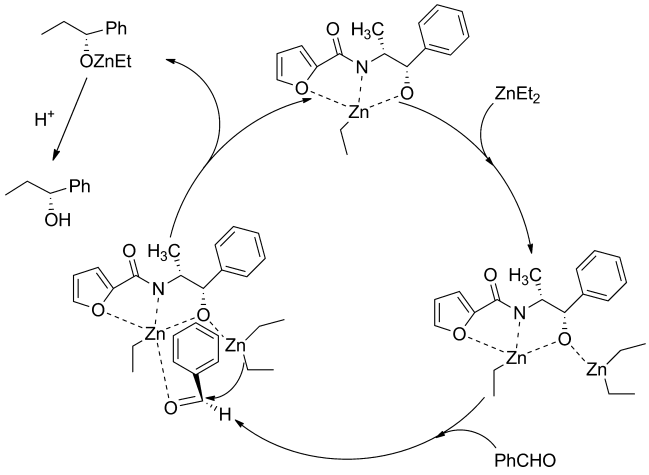

Figure 7. Catalytic cycle for the addition of diethylzinc to benzaldehyde catalyzed by **19**.[24]

The proposed catalytic cycle for the addition of diethylzinc to benzaldehyde catalyzed by **19** is shown in Figure 7. In the first step, the **19** reacts with diethylzinc to yield monomeric alkylzinc complex. This alkoxide can subsequently form a monoalkoxide diethylzinc complex by reaction with another equivalent of diethylzinc. Coordination of the reacting aldehyde followed by alkyl group transfer ultimately leads to the product.

To account for the preferential formation of the *R*-isomer in the addition of diethylzinc to the substrate aldehydes using **19** as catalyst, possible transition state assemblies were proposed by the authors, as shown (Figure 8). They propose that the phenyl group present in the ligand exerts a steric effect with the phenyl group in benzaldehyde, thus favoring transition state I over state II during the reaction. Due to the steric influence of the phenyl groups, the ethyl group of the second coordinating diethyl zinc molecule can only approach the reface of the aldehyde. No molecular modeling is presented in support of this hypothesis, and it is not completely clear from the diagrammatic representation, but it does fit with the observed results

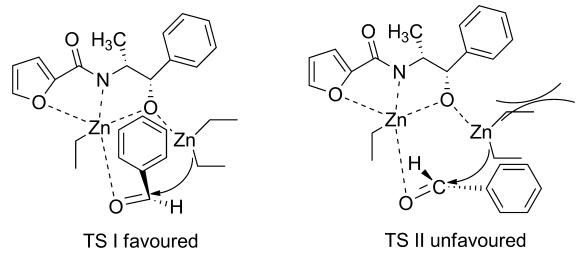

Figure 8. Transition state models I and II for **19** as a catalyst.[24]

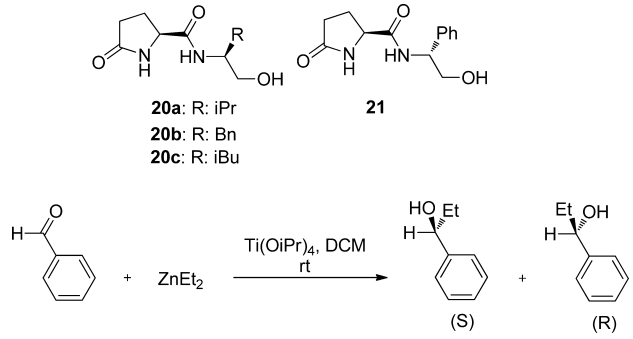

Figure 9. L-Pyroglutamic acid-derived chiral hydroxyamide ligands and their use in an alkylation reaction.

Table 4. Titanium-Promoted Alkylation Using Hydroxyamide Ligands 20a–c and 21[25,a]

ligand	yield (%)	ee (%)	dominant configuration
21	90	74	*R*
20a	88	5	*R*
20b	82	24	*R*
20c	79	6	*R*

[a]Reactions conducted at room temperature for 18 h in CH_2Cl_2 using Et_2Zn 2 mmol, $Ti(O^iPr)_4$ 0.2 mmol, ligand 0.1 mmol, aldehyde 1 mmol; ee determined by HPLC; yields are isolated yields.

O'Leary et al. applied new L-pyroglutamic acid-derived chiral hydroxy amide ligands **20a–c** and **21** (Figure 9) in the enantioselective addition of diethylzinc to benzaldehyde (Table 4).[25] In all cases, conversion was high, but a significant enantioselectivity was achieved only in the case of ligand **21**, where an ee of 74% was achieved.

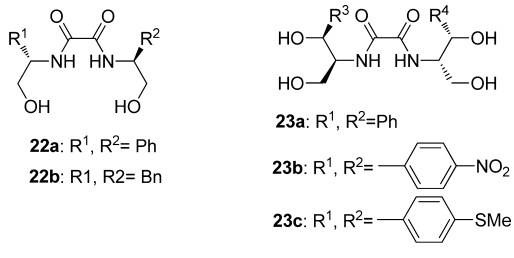

Figure 10. Polydentate oxalamide-based ligands.

Testa and co-workers reported the synthesis of polydentate oxalamide-based ligands[26] (Figure 10) and their use as chiral catalysts for the enantioselective addition of diethylzinc to benzaldehyde. The results showed moderate induction of enantioselectivity (up to 67% for **23b**) and moderate to good yields (up to 85% for **22a**).

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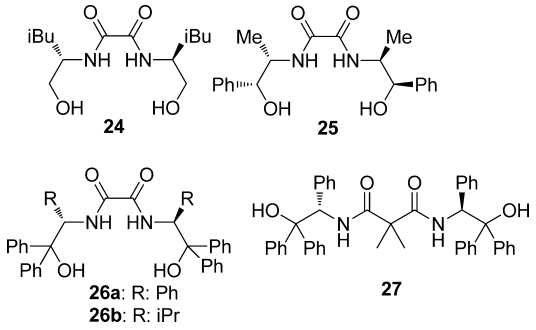
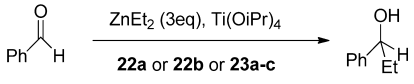


Figure 11. Tetradentate bis(amino alcohol) oxalamides.

Scheme 4. Application of Polydentate Oxalamide-Based Ligands to an Alkylation Reaction



22a: 85% [60% ee (S)]
22b: 82% [23% ee (S)]
23a: 64% [40% ee (S)]
23b: 75% [67% ee (R)]
23c: 57% [15% ee (R)]

Pedro and co-workers had reported the synthesis of **22a–b** prior to Testa, along with other novel chiral tetradentate bis(amino alcohol) oxalamides with C_2 symmetry: **24**, **25**, **26a–b**, **27** (Figure 11).[27] This group applied all of these ligands to the enantioselective addition of diethylzinc to benzaldehyde (Scheme 4). Pedro's results were poorer than Testa's, with enantioselectivities of 39% and 12% for **22a** and **22b**, compared with 60% and 23% for Testa. The difference was probably due to the difference in the amount of ligand used in the reaction (Pedro, 20 mol %; Testa, 25 mol %) and also the solvents used. Testa performed the reactions in toluene, as opposed to DCM. This is in accordance with previous results in which toluene was found to be the most appropriate solvent for this reaction. Ligand **25** was found not to be very selective, which was attributed to mismatching in the asymmetric induction caused by the two stereogenic centers in the molecule. Ligand **27** gave very poor reactivity and no selectivity, which the authors point out is unexpected, given the reported preference of titanium for co-ordinating groups with a 1,3 separation.[28] Ligand **26a** was found to perform best in this reaction and was used in the diethylzinc addition to a range of different aldehydes, both with and without the addition of Ti(O^{i}Pr)$_4$ (Table 5).[27]

With the exception of benzaldehyde, the presence of titanium isopropoxide increased both the yield and enantioselectivity of the reaction. In all cases, opposite configurations of product were obtained, depending on the presence or absence of Ti(IV). This shift in configuration of the product is thought to be due to a different reaction pathway, when titanium is present, involving dinuclear metal complexes of both titanium and zinc atoms as the active catalyst.

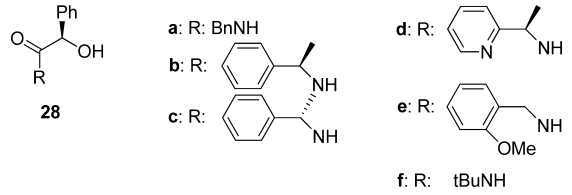


Figure 12. Mandelamide ligands.

The same group described the enantioselective addition of dimethyl and diethylzinc to aromatic and aliphatic aldehydes using easily prepared mandelamide ligands **28a–f** (Figure 12) and titanium isopropoxide, which was necessary for promotion of the reaction.[30] Ligands **28a** and **28e** were the most effective for dimethylzinc addition (up to 85% yield and 78% ee), whereas ligand **28d** performed best in diethylzinc addition (94%, 86% ee). In the case of dimethylzinc addition to aromatic aldehydes, electron-withdrawing groups on the para position were found to decrease the enantioselectivity dramatically, and electron-donating groups promoted it. The electronic character of ortho and meta substituents generally had no substantial effect on enantioselectivity. Ortho substituents, regardless of electronic character, caused a dramatic decrease in enantioselectivity, indicating the importance of steric hindrance near the reaction center.

The *S* configuration was the dominant stereochemical outcome for both alkylzinc additions for each of the mandelamide ligands. Two bimetallic, Ti(IV) transition state structures, related to previously proposed structures for the addition of dialkylzinc to carbonyl compounds, were described to explain the observed stereochemistry (Figure 13). In both, the carbonyl of the aldehyde is coordinated to an octahedral Ti,

Table 5. Diethylzinc Addition to a Range of Different Aldehydes Using Ligand 26a, Both with and without the Addition of Ti(O^{i}Pr)$_4$[29]

aldehyde	yield[a]	ee[a]	dominant[a] configuration	yield[b]	ee[b]	dominant[b] configuration
benzaldehyde	81	58	(*S*)-(−)	92	61	(*R*)-(+)
p-methoxybenzaldehyde	60	36	(*S*)-(−)	26	38	(*R*)-(+)
p-chlorobenzaldehyde	74	60	(*S*)-(−)	21	30	(*R*)-(+)
p-bromobenzaldehyde	41	58	(*S*)-(−)	54	50	(*R*)-(+)
p-trifluoromethylbenzaldehyde	89	56	(*S*)-(−)	36	20	(*R*)-(+)
p-nitrobenzaldehyde	54	46	(*S*)-(−)	12	5	(*R*)-(+)
p-cyanobenzaldehyde	77	50	(*S*)-(−)	6	53	(*R*)-(+)
o-methylbenzaldehyde	19	31	(*S*)-(−)	10	10	(*R*)-(+)
decanal	82	66	(*S*)-(−)	50	41	(*R*)-(+)
dihydrocinnamaldehyde	79	74	(*S*)-(−)	-	-	(*R*)-(+)
cyclohexanecarboxyaldehyde	85	78	(*S*)-(−)	80	67	(*R*)-(+)
2-butylhexanal	35	42	(*S*)-(−)			(*R*)-(+)

[a]Reactions conducted at 0 °C for 24 h in CH_2Cl_2 using Et_2Zn 3 mmol, Ti(O^{i}Pr)$_4$ 1.4 mmol, ligand 0.2 mmol, aldehyde 1 mmol; ee determined by HPLC; yields determined by HPLC. [b]As a, except no Ti(O^{i}Pr)$_4$.

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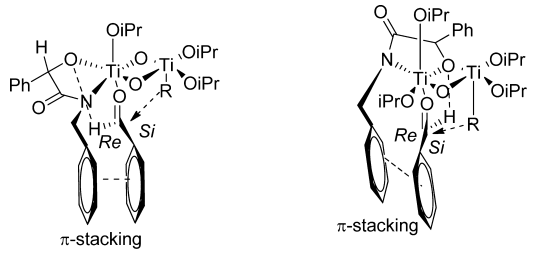
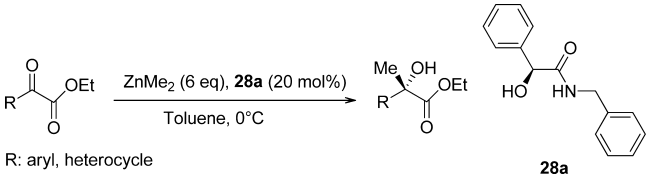


Figure 13. Two bimetallic, Ti(IV) transition state structures described to explain the observed stereochemistry.[34]

and its Si face is exposed to attack from an alkyl group on the second Ti atom. Stabilization for the structure should be provided by hydrogen bonding between the ligand O and the aldehyde H, similar to that described in previous studies,[31−33] and by π-stacking between the aryl aldehyde and the phenyl group of the ligand. Where either aromatic group is missing, for example, with an aliphatic aldehyde, the stereoselectivity of the reaction is reduced, which supports this argument.

Hydroxyamide ligands have also been used to catalyze the enantioselective addition of dimethylzinc to α-ketoesters. Pedro et al. have applied ligands **28a−f** to this reaction without the need for an additional Lewis acid promoter (such as titanium isopropoxide).[35] The additional problem with the reaction of dialkylzinc with α-ketoesters is the competing background addition. Unlike with aldehydes and ketones, the uncatalyzed reaction of Et_2Zn with α-ketoesters is fairly rapid. The chiral catalyst must thus have significant activity; otherwise, uncatalyzed background reaction will reduce overall selectivity. This study based its ligand design on the likelihood that in competition between the chiral ligand and the substrate to coordinate the zinc metal ion, the chiral ligand−Zn complex may be favored by increasing the electron-donating ability of the ligand. This would favor the enantioselective reaction over the achiral background reaction.

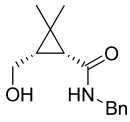
Scheme 5. The Application of Ligand 28a to the Alkylation of α-Ketoesters



They found their results supported this hypothesis. Under the optimized conditions, the best-performing ligand **28a** catalyzed the addition of dimethylzinc to α-ketoesters having aromatic and heteroaromatic substituents with good yields and ee's from moderate (62%) to high (90%) (Scheme 5). It was found that the presence of electron-donating groups on the aromatic ring increases the enantioselectivity of the reaction.

Wang and co-workers reported the use of γ-hydroxyamide, (1*R*,3*S*)-*N*-benzyl-3-(hydroxymethyl)-2,2-dimethylcyclopropanecarboxamide **29** (Figure 14) in the same reaction.[36] Under the optimized conditions, a series of α-ketoesters were examined for the enantioselective Me_2Zn additions in the presence of **29**. The corresponding products were obtained in good yield (60−87%) and moderate enantioselectivities (41−81%).

Du and co-workers developed a series of tris(β-hydroxyamide) ligands **30a−k** and **31a−c** used in the asymmetric addition of



29

Figure 14. γ-Hydroxyamide **29**.

diethylzinc to benzaldehyde in the presence of $Ti(O^iPr)_4$ (Figure 15).[37] Ligand **30d** was the most efficient for this reaction, giving (*R*)-1-phenylpropan-1-ol in 99% yield and 47% ee.

As indicated in the initial introduction, historically the ligands most commonly used in the catalysis of alkylation reactions of this type are amino alcohols, which have been used in this context since the early 1980s. Their performance has been reviewed by Pu.[38] Hundreds of such ligands have been reported, and high selectivity and activity outperforming the hydroxyamides discussed here is observed in most cases. However, given the relatively few reports of the use of hydroxyamide ligands and the excellent performance of some ligands, such as **19**, it is clear that hydroxyamide ligands are excellent prospects for these alkylation reactions.

■ ACETYLENE ADDITION

The enantioselective alkynylation of aldehydes as a method for the synthesis of chiral nonracemic secondary propargylic alcohols is highly convenient, leading to C−C bond formation and stereogenic center formation in one step. Propargylic alcohols are synthetically versatile intermediates with a heteroatom and alkyne center, which has resulted in their use in the efficient synthesis of many natural products and pharmaceuticals.[39−41]

Among the catalytic methods developed for this reaction, the addition of terminal acetylene to aromatic aldehydes is currently considered to be the most practical. Very few chiral ligands that give good activity and selectivity in the catalytic asymmetric alkynylation of aliphatic and vinyl aldehydes have been reported. Carreira reported the use of $Zn(OTf)_2$ and a catalytic amount of (+)-*N*-methyl ephedrine with an amine base gave good activity and stereoselectivity in the addition of terminal acetylides to aliphatic aldehydes.[42] A titanium-based complex of BINOL has been used by Pu's group with good success.[43] An indium(iii) complex of BINOL also formed the basis of a successful system.[44] A number of amido alcohol ligands have been used in these reactions with good success.

Du's ligands **30a**, **30b**, **30e**, and **30f** were used in the catalytic asymmetric alkynylation of aldehydes.[45] In initial screening of the enantioselective addition of phenylacetylene to benzaldehyde, it was found that the use of diethyl zinc, $Ti(O^iPr)_4$ as an additive and one of the ligands **30a**, **30b**, or **30f** gave the corresponding (*R*)-propargyl alcohol in <20% ee. Promisingly, ligand **30e** gave the *S*-enantiomer in 85% yield and 78% ee. By fine-tuning the proportion of **30e**/$Ti(O^iPr)_4$ to a ratio of 1:7, the result was improved, providing the (*S*)-propargyl alcohol in 84% yield and 87% ee. The application of these metal complexes to other substituted benzaldehydes demonstrated their toleration of both electron-withdrawing and electron-donating groups to give products in high yields and enantioselectivities (Scheme 6).

The C_1- and C_2-symmetric ligands **32** and **33** (Figure 16) were synthesized, and their catalytic activity in the enantioselective addition of phenylacetylene to benzaldehyde was evaluated

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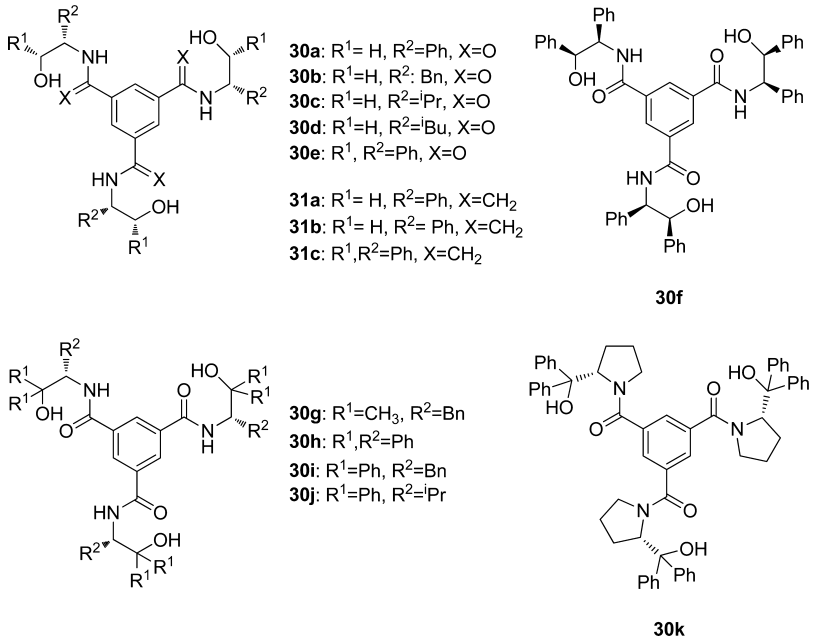
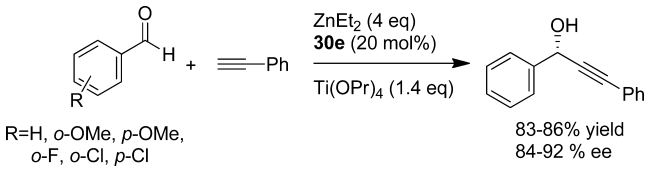


Figure 15. Du's C_3-symmetric tris(β-hydroxyamide) ligands.

Scheme 6. Enantioselective Addition of Phenylacetylene to Aldehydes Catalyzed by 30e



against tris(β-hydroxyamide), **30e**. Under the same optimized conditions used for **30e**, the catalysts formed from **32** and **33** resulted in yields of 86% and 82% and ee's of 51% and 62%, respectively. Increasing the catalytic amount of ligand had no appreciable effect on enantioselectivity, demonstrating the efficacy of C_3-symmetry for this particular ligand type and reaction.

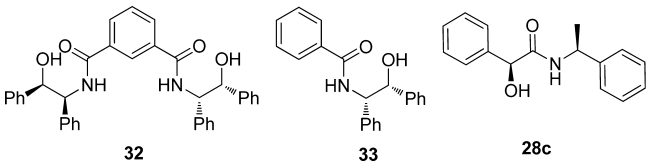


Figure 16. Symmetric and nonsymmetric ligands.

Blay and Pedro have reported that (*S*,*S*)-mandelamide **28c** (Figure 16) could catalyze the asymmetric additions of aryl-, alkyl-, and silylalkynylzinc reagents to aromatic and heteroaromatic aldehydes with good yields (up to 94%) and good enantioselectivities (up to 92% ee).[46,47] It is noteworthy that to improve the enantioselectivity of the reaction, the authors preformed the alkynylzinc reagent in the presence of the ligand prior to the addition of aldehyde. It was necessary to heat phenylacetylene with dimethylzinc at 70 °C in toluene in the presence of **28c** and then to add the aldehyde at 0 °C, which is different from the procedure described by Pu in the initial work in this area,[48] in which the ligand is added into the system after the formation of alkynylzinc reagent. In this case, the amount of dimethylzinc used also proved critical, leading the authors to speculate that it must be involved in the deprotonation of the ligand at 70 °C, a process that is not achieved by the alkynylzinc reagent at the lower temperature used in Pu's method. This study did not use $Ti(O^iPr)_4$ as an additive to avoid the side reaction in which the aldehyde is alkylated.

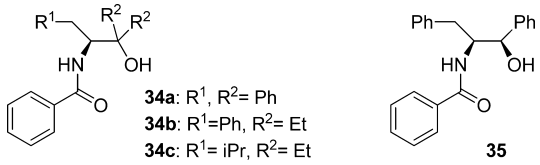


Figure 17. Hydroxyamide ligands prepared by Hui and used in the addition of phenylacetylene to aldehydes.

Hui et al. reported the facile synthesis of β-hydroxyamide ligands **34a**–**35c** and **35** (Figure 17) from chiral amino alcohols and the application of their titanium(IV) complexes to the enantioselective addition of phenylacetylene to aromatic and aliphatic aldehydes in the presence of diethylzinc at room temperature.[49] Ligand **34b** proved to be by far the most efficient, consistently affording high yields (up to 96%) and ee's (up to 97%). The ligand was used in relatively large amounts (20 mol %), and the ligand performance was found to be adversely affected by the introduction of less flexible aromatic groups alpha to the hydroxyl group and nonaromatic groups at R^1. The titanium tetraisopropoxide/ligand ratio was also found to be critical to the enantioselectivity, 3:1 being the best ratio.

One such ligand was immobilized on amorphous silica gel using Seebach's strategy,[50] to afford silica-immobilized ligand **36** (Figure 18).[51] Ligand **36** was used in the asymmetric addition of phenylacetylene to aromatic aldehydes to afford the propargylic alcohols (Table 6).

The isolated yields were high (84–95%), and good enantioselectivities (69–81%) were achieved by using silica-immobilized chiral ligand **36**. The best enantioselectivity (81% ee) was obtained in the alkynylation of 2-naphthaldehyde. The performance in terms of enantioselectivity and conversion,

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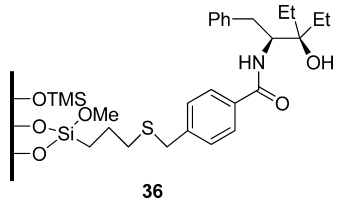
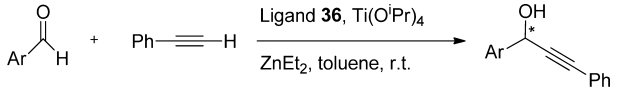


36

Figure 18. Covalently immobilized hydroxyamide ligand.

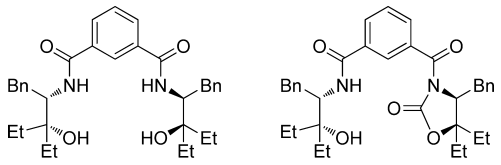
Table 6. Asymmetric Addition of Phenylacetylene to Aromatic Aldehydes Using the Immobilized Ligand 36[52,a]



aldehydes	yield (%)	ee (%)
benzaldehyde	95	78
2-chlorobenzaldehyde	87	69
3-chlorobenzaldehyde	86	74
4-chlorobenzaldehyde	84	72
4-tolualdehyde	89	70
2-naphthaldehyde	93	81

[a]Reaction conducted in toluene at room temperature for 18 h. Ligand 0.2 mmol, $Ti(O^iPr)_4$ 0.6 mmol, $ZnEt_2$ 3 mmol, phenylacetylene 3 mmol, ArCHO 1 mmol. Yields are isolated yields; ee's determined using HPLC.

while good, does fall short of that obtained with the homogeneous system. The reusability of silica-immobilized ligand **36** was checked by using benzaldehyde as a representative substrate. After each catalytic cycle, ligand **36** was recovered and dried for the next catalytic cycle. A small reduction in yields (95−86%) and enantioselectivities (78−75%) was observed over five runs.



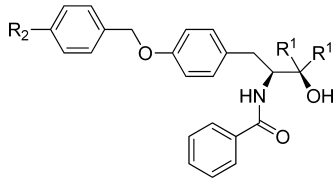
37 38

Figure 19. Ligands used by Hui and Xu in the asymmetric addition of alkynylzinc to aldehydes.

Hui and Xu reported the synthesis of new C_2-symmetric bis(hydroxyamide) ligand **37** and ligand **38** (Figure 19) and their use in the asymmetric addition of alkynylzinc reagents to aldehydes.[53]

Ligand **37** proved to be an effective ligand for the $Ti(O^iPr)_4$ catalyzed addition of phenylacetylene to a variety of aldehydes, providing high yields (82−94%) and enantioselectivities (87−98%) for aromatic aldehydes and more moderate yields (83−87%) and selectivities (52−67% ee) for aliphatic aldehydes under the optimized reaction conditions. Ligand **38** was used to investigate whether each hydroxyamide moiety in the bis(hydroxyamide) **37** could act as an independent coordinating ligand in the alkynylzinc addition reaction. It was applied to the enantioselective addition of phenylacetylene to benzaldehyde, providing the desired propargylic alcohol in good yield and 78% ee under the same conditions used for **37**, and under slightly altered conditions, enantioselectivities of up to 94% were achieved. The authors assert that this means the hydroxyamide units can act as independent ligands, which is supported by their previously reported similar result with the mono hydroxyamide ligands.

In an effort to develop new hydroxyamide ligands with greater efficiency in catalyzing the asymmetric alkynylzinc addition to aliphatic and vinyl aldehydes Xu reported novel L-tyrosine-derived ligands **39a−c** (Figure 20).[54] Ligand **39b** proved to be the best in optimization studies in which phenylacetylene was added to *n*-butyraldehyde.



39a: R^1=Bn, R^2= H
39b: R^1= Et, R^2= H
39c: R^1= Bn, R^2= OMe

Figure 20. L-Tyrosine-derived ligands **39a−c**.

The generality of the success of ligand **39b** in the asymmetric phenylacetylene addition to aliphatic and vinyl aldehydes was examined using $Ti(OiPr)_4$ as a promoter under the optimized reaction conditions, and the results are summarized in Table 7. The chiral propargyl alcohols could be obtained in 88−96% ee for aliphatic and vinyl aldehydes. Aliphatic aldehydes with bulky groups gave slightly lower enantioselectivities. The catalytic system was also tested with the typical aromatic aldehydes, for example, benzaldehyde, which proceeded smoothly to give the product in 85% yield and 92% ee.

Table 7. Asymmetric Phenylacetylene Addition to Aliphatic and Vinyl Aldehydes Using Ligand 39b and $Ti(OiPr)_4$ As a Promoter[55,a]

aldehydes	yield (%)	ee (%)	dominant configuration
propioaldehyde	75	90	*R*
n-butyraldehyde	85	91	*R*
isobutyraldehyde	87	92	*R*
3-methylbutanal	83	90	*R*
n-heptanal	80	91	*R*
pivaldehyde	81	88	*R*
cyclohexanaldehyde	81	88	*R*
2-phenylacetaldehyde	79	94	*R*
trans-cinnamaldehyde	83	96	*R*
acrylaldehyde	71	90	*R*
(*E*)-but-2-enal	86	90	*R*
benzaldehyde	85	92	*R*

[a]Reaction conducted in toluene at room temperature for 18 h. Ligand 0.2 mmol, $Ti(O^iPr)_4$ 0.6 mmol, $ZnEt_2$ 3 mmol, phenylacetylene 3 mmol, ArCHO 1 mmol. Yields are isolated yields; ee's determined using HPLC.

In an effort to develop recyclable ligands, Hui and Xu reported the synthesis of polymer-supported chiral β-hydroxy amides and C_2-symmetric β-hydroxy amides (Figure 21) and successfully used them for the titanium-promoted enantioselective addition of phenylacetylene to aldehydes.[56]

C_1-symmetric monomer **40** was chosen as a model ligand for the system and, when applied to the asymmetric addition of phenylacetylene to benzaldehyde, gave 1,3-diphenylprop-2-yn-1-ol in 85% yield and 89% ee. A polymeric version of this

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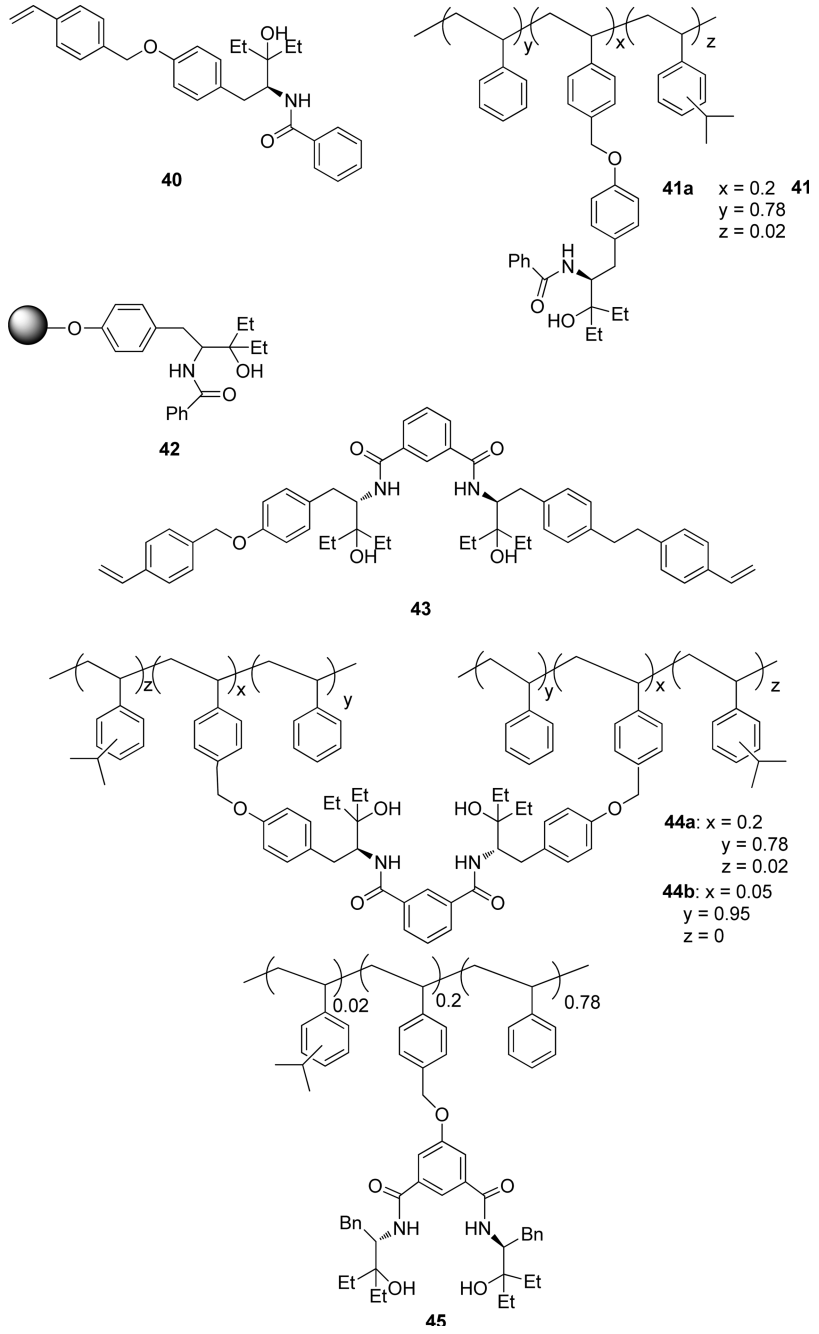

Figure 21. C_1 and C_2-symmetric monomers and their polymer-supported analogues.

monomer was obtained by copolymerization with other styrene type monomers. When the polymer-immobilized ligand **41a** was used (20% loading), the product was isolated in 80% yield and an ee of 88% using 30 mol % of the ligand and a 3.5:1 ratio of $Ti(O^iPr)_4$ to ligand. Polymer **41b**, with a lower ligand loading of 10% and 20 mol % ligand gave the enantioenriched product in 87% ee with a yield of 85%. These results are comparable to that obtained with the nonimmobilized ligand. The polymeric **41b** was also tested in the reaction of a variety of other aromatic and aliphatic aldehydes, giving consistent reactivity and selectivity.

This group also immobilized the ligand on a Merrifield resin to give **42**; however, the titanium-promoted reaction using 20 mol % of the ligand gave the propargyl alcohol in only 58% yield and 49% ee. The poorer performance in this case is attributed to interference between adjacent catalytic sites, given the loading was 98%.

C_2-symmetric monomers and their polymer-supported analogues were also applied to the titanium-promoted addition of phenylacetylene to benzaldehyde. Use of monomer **43** led to good catalytic activity with a yield of 93% and an ee of 92%. The polymeric ligands **44a** and **44b** were also tested in the same reaction and found to have moderate activities, with yields of 66% and 83% and ee's of 56% and 78%, respectively. The authors attributed the reduced reactivity with these ligands compared with **41b** to their higher mechanical robustness, leading to reduced ability to swell. Polymer-supported ligand **45** also provided moderate results, with a yield of 80% and an ee of 74%.

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The reusability of the ligand **41b** was examined with benzaldehyde as the substrate. The resin was reused three times to afford 1,3-diphenylprop-2-yn-1-ol in high yields with enantioselectivities decreasing from 87% to 80%.

O'Leary et al. applied amide ligands **22a−c** and **23** in the titanium isopropoxide-promoted enantioselective addition of phenylacetylene to benzaldehyde. Conversions were high (from 78 to 89%); however, the enantioselectivities were low (11−34%).[25]

Wang reported the application of ligands **46a−f** (Figure 22) derived from the L-Phe-based N-CBZ-protected dipeptides in the asymmetric addition reaction of phenylacetylene to acetophenone (Table 8).[57] The alkynylzinc reagents were generated in situ from phenylacetylene with diethylzinc at room temperature. There were no additional metal promoters in the asymmetric addition reaction.

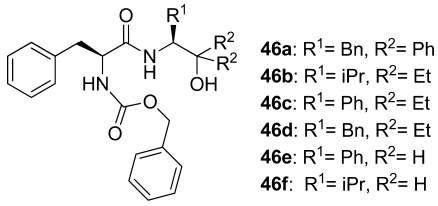
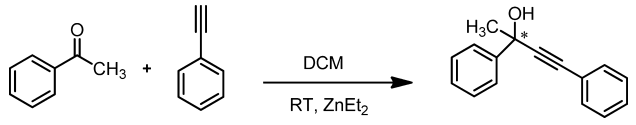


Figure 22. Ligands **46a−f** derived from the L-Phe-based N-CBZ-protected dipeptides.

Table 8. Use of Ligands 46a−f in the Alkynylation Reaction[57,a]



ligand	yield (%)	ee (%)
46a	85	10
46b	72	10
46c	66	6
46d	76	15
46e	43	5
46f	72	72

[a]Reaction conducted in CH_2Cl_2 at room temperature for 24−48 h. Et_2Zn/phenylacetylene/ketones/ligand ratio was 3.0:3.0:1.0:0.1. Yields are isolated yields; ee's determined using HPLC.

Ligands **46a** and **46f** gave good yields of the desired product, but only **46f** gave a satisfactory ee of 72%. Under the optimized reaction conditions, ligand **46f** was employed to induce the enantioselective addition of phenylacetylene to various aromatic ketones. The enantioselectivities were up to 91% ee, and yields up to 90% were obtained. Under the same conditions, ligand **46f** was used in the addition of phenylacetylene to the aliphatic ketone isopropyl methyl ketone. The enantioselectivity was found to be 54% ee with a yield of 80%.

As indicated earlier, very few chiral ligands, apart from these hydroxyamides, have been reported that give good activity and selectivity in this reaction.[42−44] The better ones that have been reported have tended to give the products in ee's in or around 90%, with some examples using BINOL reaching 99% ee. The activity of the reactions using these ligands has been poorer, with yields typically between 70 and 80%. The hydroxyamides discussed herein compare very favorably in performance. Notably, in all cases, hydroxyamide and other catalyst loading is high, typically 20 mol %, with only one example for which a hydroxyamide was used in 10 mol %. This catalyst loading is an impediment to their wider use, and catalysts of greater activity are needed.

■ ASYMMETRIC TRANSFER HYDROGENATION REACTION

The asymmetric transfer hydrogenation reaction, using 2-propanol or formic acid as hydrogen source, is an extremely mild reduction method and has been the focus of much research.[58−61] The use of Ru(II) complexes of chiral amino alcohols or diamines has been highly successful in this area. Adolfsson had studied a range of amido oxazolines as ligands for ruthenium and used the resulting complexes with very limited success;[62] however, the precursor amido alcohols proved to be effective ligands, and the resulting catalysts gave encouraging selectivity in the transfer hydrogenation reaction (Figure 23). Where the R group was a phenyl group, the reactivity was low, but the selectivity was good. Other stereoisomers of **48** gave better activity, but yields remained below 80%. The importance of both stereocenters was tested by using the glycine derivative **47**, which was less selective than **48**, and thus, it was apparent that both centers had an influence of the stereochemistry of the outcome.

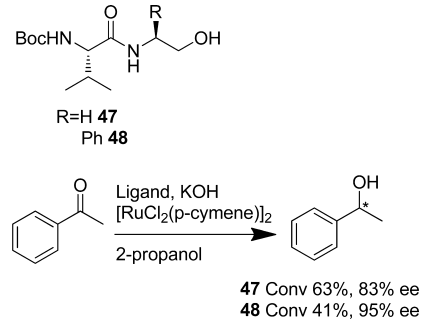


Figure 23. Initial study on the application of hydroxyamides to the transfer hydrogenation reaction.

The Boc protection of the N terminus of the peptidic ligand proved crucial because the deprotected ligands showed no catalytic activity. They also determined that the ruthenium precursor with *p*-cymene gave catalysts of similar activity to the less hindered ruthenium benzene precursor; however, selectivity was superior when the former was used. Reduction of other acetophenones was also achieved, with a notable increase in conversion when the aromatic group bore electron-withdrawing groups with no decrease in selectivity.

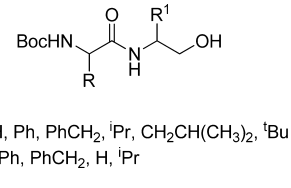


Figure 24. Range of ligands applied to transfer hydrogenation reaction.

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This initial study was followed by a larger one in which 45 dipeptide amido alcohol ligands (Figure 24) were prepared.[63] In addition, the N-terminal protection was investigated using a variety of protecting groups and none. Ligands with two stereocenters gave lower activity. The most active ligands were those derived from phenylglycine and 2-aminoethanol, though these proved disappointing with regard to stereoselectivity. They also found that some diastereomeric ligands gave dramatically different activity, indicating a matched−mismatched situation.

The ligands gave almost universally high stereoselectivity (>85% ee). The amino alcohol was found to influence the stereoselectivity when no chiral center was present on the aminoacid portion. However, where there was a chiral center on the amino acid residue, this determined the absolute configuration of the product.

The protecting group on the nitrogen proved very important. They studied a number of ligands (Figure 25) and discovered that the nitrogen did need to be protected or the catalyst became inactive and the only protecting groups that worked were the carbamate protecting groups (with the exception of Fmoc). The carbamate protecting groups Boc, Alloc, and Z proved to give similar conversion and selectivity (78−81% and 93−95%ee). The free hydroxyl is also critical because O-methylation gave a very poor catalyst.

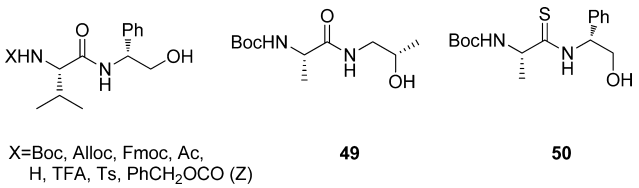

Figure 25. Ligands prepared to study the importance of the protecting group and SAR's.

A second generation of the catalysts focused particularly on the use of chiral secondary alcohols, leading to ligands such as **49**.[64] Thirty-six similar ligands were studied, and in the standard reduction of acetophenone, a catalyst derived from **49** gave superior activity (90%) and selectivity (96% ee). A number of other ligands gave similarly good results. The selectivity is again largely controlled by the configuration of the amino acid residue, but they also report a definite match−mismatch situation in which the amino alcohol configuration is varied. This paper gives a number of experimental details that ultimately aided with the proposal of a mechanism. Three equivalents of base is required, and the best results are achieved with a 1:1 ligand/Ru ratio.

Thioamide-based ligands such as **50**, when used in catalysis in combination with either ruthenium or rhodium sources, gave opposite selectivity to the related amide ligands.[65] Interestingly, although in both cases, the reversal of selectivity was observed, with ruthenium, the amide was more selective, whereas with rhodium, the thioamide ligand gave the greater selectivity.

Where the ligands were generated from the 1,2-disubstituted amino alcohols, they showed very poor activity,[64,66] and when a chiral tertiary alcohol was incorporated into the ligand, the resulting complex was not an effective catalyst .[67]

In a communication in 2005, Adolfsson reported the in situ formation of the hydroxyamide from N Boc-protected aminoacid nitrophenylester and an amino alcohol (Figure 26).[68] The ligands−ruthenium complex, formed in the same pot by addition of the base and ruthenium source, was then used in the transfer hydrogenation reaction, giving results comparable to the catalysts generated by the conventional manner. The ligand shown in Figure 26 was the most successful.

Over the years, a number of closely related theories have been presented as to the mechanism of the asymmetric transfer hydrogenation catalyzed by ruthenium complexes of these amido alcohols. Most of the early theories were based on the mechanism described by Noyori for amine type systems.[69] More recently, three comprehensive studies by Adolfsson have brought some clarity to the situation.[70−72] The proposed mechanism is supported by the observation that the alkali cation has an effect on the reaction selectivity, with lithium being the best cation. The reaction must involve a fairly tight catalytic complex because when the ion was enlarged by using sodium or potassium with or without a crown ether or lithium in combination with a cryptand, the selectivity dropped. The effect of the crown ethers or cryptand is to further increase the size of the cation, loosening the complex, leading to lower selectivity. With already selective ligands, the ion effect on selectivity was small, but using lithium as the anion with ligands that performed poorly with other anions increased the ee by up to 40%. Where the second generation ligands are used in combination with lithium, the alcohol configuration was found to have a greater influence on the stereochemical outcome of the reaction, which otherwise is dominated by the amino acid residue, indicating an interaction between the lithium and the alcohol during the reaction. The mechanism was then developed with support from DFT calculations and work on the kinetics, including kinetic isotope effect experiments (Scheme 7).

Structure activity studies indicated all of the ligand functionalities interact with the ruthenium center in the initially formed complex **51**. As previously indicated, 3 equiv of base is optimum, and <2 equiv results in virtually no activity. Adolfsson

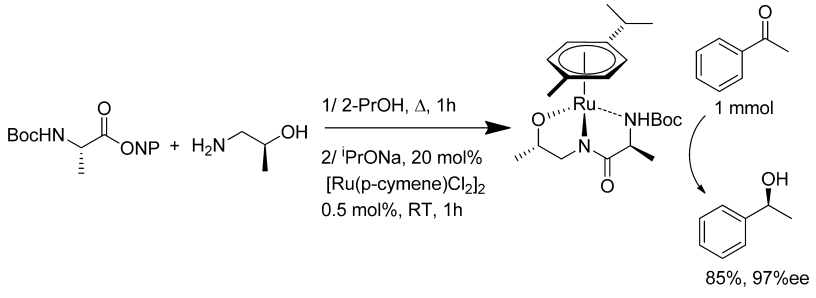

Figure 26. One-pot catalyst preparation and use.[68]

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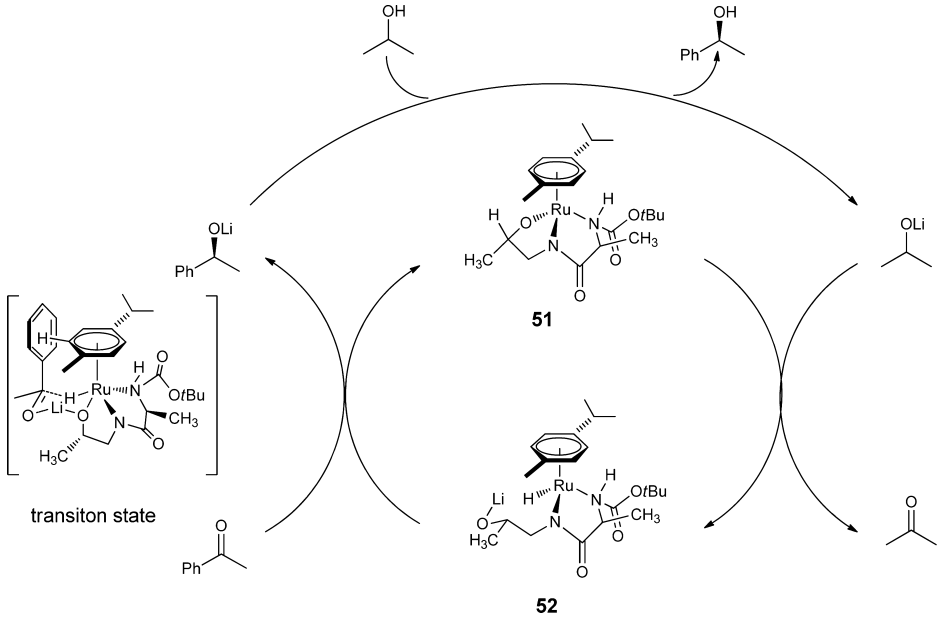
Scheme 7. Proposed Mechanism of the Reaction[72]



thus concluded that two of the sites (alcohol and amide) are deprotonated by the isopropoxide base present in the ATH reaction mixture. The carbamate binds in a neutral fashion. The third equivalent of base is involved in a different process because if the carbamate was also deprotonated, an inactive anionic ruthenium complex would be formed.

As the reaction proceeds, an alkali metal alkoxide interacts with the catalyst. The release of the ligand alkoxide coordinating to ruthenium allows the alkali metal ion to be transferred to the oxygen of the ligand, while the hydride is transferred to the now vacant coordination site on the ruthenium leading to **52**. The acetophenone enters the coordination sphere of the bimetallic catalyst through attraction by the Lewis acidic lithium ion, and once it coordinates, transfer of the hydride to the activated substrate can occur via the transition state shown, and the cycle is completed by proton transfer from the 2-propanol to the lithium salt of the product. The structure of the postulated transition state, particularly the CH-π interaction, explains the high degree of stereoselectivity achieved as it stabilizes the transition state for the transfer of the hydride.[72] It also accounts somewhat for the better selectivity observed with these systems in the reduction of alkyl aromatic ketones as distinct from dialkyl ketones.

Adolfsson has done extensive work on the kinetics of the reduction process. One interesting discovery during this study was the fact that the rate of the reaction when conducted in a solvent mixture (IPA and THF) was not directly dependent on the concentration of the hydrogen donor. Indeed, the initial reaction rate in the reduction of acetophenone was found to be at a maximum in a mixed solvent with IPA at 6.4 M concentration.[72] They speculated that one possible reason for this rate change was the altered polarity of the system that uses THF, which may make key components taking part in the reaction more soluble. This discovery was then exploited in the reduction of a variety of acetophenones that were previously difficult substrates with catalyst **51**. Some of the reported reductions are shown in Table 9. It is interesting to note that the catalyst loading in these cases has been reduced to 0.5 mol % from the previously used 1 mol %, but it still gives good activity and selectivity.

This area of asymmetric transfer hydrogenation reactions is a very active area of research, as illustrated by the recent review.[58] It is clear from that review that there are very many good catalytic systems to effect these transformations based on ruthenium, iridium, and rhodium along with ligands with amine, sulfonylamide, amino alcohol, oxazoline and various types of phosphorus-based functional groups. It is also clear that these hydroxyamide-based catalytic systems perform very well in comparison with the other reported systems. The yields are still in need of improvement, but the selectivity, particularly with the more challenging acetophenones shown in Table 9, compares very well with other catalytic systems.

■ ASYMMETRIC BORANE REDUCTION

Du et al. reported the use of C_3-symmetric, tripodal ligands in the asymmetric borane reduction of prochiral ketones.[73] Under the optimized reaction conditions, ligand **30k** was found to be the best ligand, and it was applied to the asymmetric borane reduction of a variety of aromatic and aliphatic ketones.

As the results summarized in Table 10 show, high yields and enantioselectivities (up to 97%) were obtained for prochiral ketones containing electron-donating or electron-withdrawing groups, except 3,5-dinitro acetophenone (Table 10, entries 1−9). A slightly decreased ee was obtained with a substituent at the ortho position, probably as a result of the steric effect (entry 7). Reduction of the aliphatic ketone 3,3-dimethylbutan-2-one was also achieved in high enantioselectivity.

In contrast, much lower enantioselectivity (11%) was obtained in the reduction of acetophenone in the presence of the amino alcohol analogue of **30K**; namely, **53** (Figure 27). This result indicates that the amido group is important for the catalyst enantioselectivity and, indeed, that reduction of the amide of the ligand is not key to the reaction.

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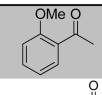
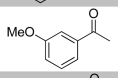
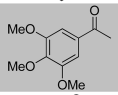
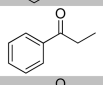
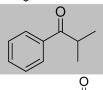
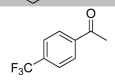
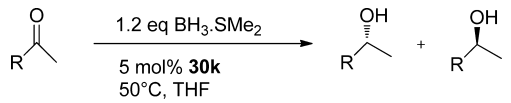
Table 9. Asymmetric Transfer Hydrogenation Reaction of Various Acetophenones Using [Ru 51] Propan-2-ol/THF[72,a]

Substrate	Time(min)	Yield(%)[a]	ee(%)[b]
	60	45	>99
	30	80	>99
	45	79	98
	30	70	>99
	45	75[b]	>99
	90	82	98
	120	18[b]	>99
	15	89	96

[a]Reaction was carried out at 30 °C with {Ru (*p*-cymene)Cl_2}$_2$ 0.0125 mmol, LiCl (21.2 mg, 0.5 mmol), propan-2-ol (9.75 mL), ligand (0.0275 mmol in 0.25 mL propan-2-ol), THF (12.5 mL), substrate 5 mmol, and *i*PrONa (0.25 mmol in 2.5 mL 2-propanol). [a] isolated yields, [b] determined by GLC analysis.

Table 10. Asymmetric Borane Reduction of Ketones Using Ligand 30k[73,a]

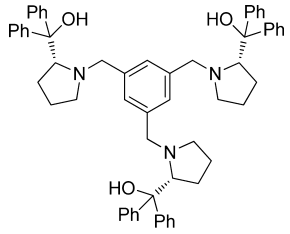


entry	R	yield (%)	ee (%)	dominant configuration
1	Ph	96	94	*R*
2	*p*-FC_6H_4	94	97	*R*
3	*p*-ClC_6H_4	91	97	*R*
4	*p*-BrC_6H_4	93	96	*R*
5	*p*-$MeOC_6H_4$	90	91	*R*
6	*p*-$NO_2C_6H_4$	94	97	*R*
7	*o*-$MeOC_6H_4$	91	87	*R*
8	2-naphthyl	94	95	*R*
9	*tert*-butyl	99	89	*R*
10	3,5-$NO_2C_6H_4$	94	74	*R*

[a]Reaction was carried out on a 0.5 mmol scale in 2 mL of THF for 1 h, molar ratio of acetophenone−BH_3 = 1:1.2. Yields are isolated yields; ee's were determined by HPLC.

Du later studied the catalytic activity of a series of bis(hydroxyamide)s **54a−c** and **55** synthesized from diphenylamine-2,2-dicarboxylic acid and chiral amino alcohols (Figure 28).[74]

The ligands were applied to the enantioselective borane reduction of 1-acetylnaphthalene using 1.2 equiv of BH_3-THF complex at 50 °C. The activity of the catalytic systems were good (87−93% yield); however, ligands **54a−c** gave poor selectivities (23−52% ee). Ligand **55** proved the most stereoselective in the reaction (91% ee) and was applied to a range of aromatic prochiral ketones under optimized catalytic conditions (Table 11).



53

Figure 27. Amino alcohol analogue of **30K**.

Excellent yields and enantioselectivities were achieved in the cases of both electron-donating and -withdrawing groups substituted onto the aromatic ketones. Generally, electron-deficient ketones gave better results than electron-rich ketones. The dominant configuration of the product was determined to be *R*, except in the case where R^1 was 1-naphthyl and R^2 was phenyl. Here, $\pi-\pi$ stacking was proposed to influence the stereochemical outcome more than steric hindrance and give predominantly the *S* enantiomer.

C_1-symmetric ligand **56** was synthesized to further study the catalyst system. Its catalytic performance was compared with **55** in the enantioselective reduction of 1-acetylnaphthalene under the same conditions. The enantioselectivity decreased from 97 to 92% ee, indicating a certain synergy between the two pyrrolidineamide units in the catalytic complex. The nature of the catalytic species and a transition state for the reduction reaction was postulated by the authors to account for the stereochemical outcome. The catalytic species when ligand **55** is used involves one boron and the ligand with the boron being coordinated to one NH and bonded to the two oxygens ligand alcohols. The transition state involves the ketone co-ordinating to the boron through the carbonyl oxygen, thus bringing the reaction center into the chiral pocket where it is reduced by another borane. Presumably, this borane is held in place by interaction with the carbonyl of the reagent and that of the ligand. The transition state proposed is not supported by calculation and, although it is consistent with the chemical outcome of the reaction, is only a postulation (Figure 29).

Many catalytic systems have been investigated for this type of reaction.[76] Among them, the CBS system developed by Corey attracts the most attention because it is highly enantioselective.[77,78] In addition to the CBS system, other active catalysts derived from amino alcohols, such as chiral phosphinamido alcohols,[79] phosphoramido alcohols,[80] and sulphonamide alcohols,[81] have also been developed. The hydroxyamide ligands described here are very competitive with the previously reported catalytic systems, given their consistently high activity combined with high enantioselectivity across a wide variety of substrates with acceptable catalyst loading (5−10 mol %).

■ SILYLCYANATION

Uang et al. described a highly enantioselective addition of trimethylsilylcyanide to aldehydes catalyzed by chiral titanium complexes of hydroxyamide ligands (Figure 30).[20,21] In the case of addition to benzaldehyde, optimum results were obtained when the reaction was carried out at −78 °C in dichloromethane using the complex prepared from 16.5 mol % of ligand **12** and 15 mol % of titanium tetraisopropoxide in the presence of 4 Å molecular sieves. In the absence of molecular sieves, the reaction was extremely slow, and no sign of reaction was

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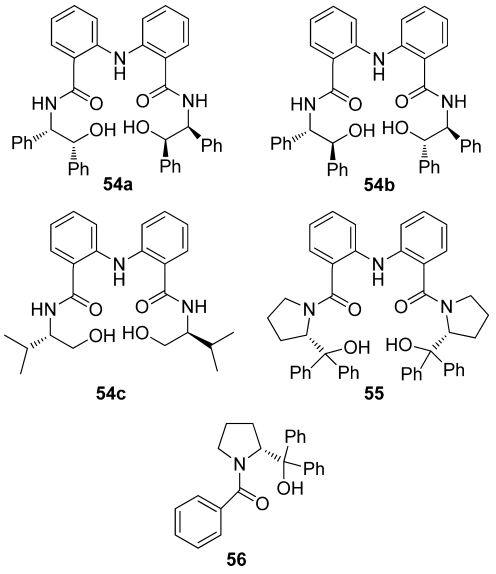
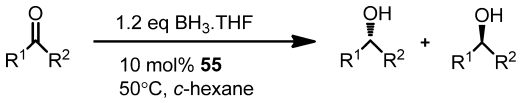


Figure 28. A series of bis(hydroxyamide)s prepared from diphenylamine-2,2-dicarboxylic acid.

Table 11. Borane reduction of aromatic ketones using ligand 55[74,a]



R^1	R^2	yield (%)	ee (%)	dominant configuration
1-naphthyl	Me	94	97	*R*
C_6H_5	Me	87	96	*R*
4-MeC_6H_4	Me	93	90	*R*
4-$MeOC_6H_4$	Me	93	93	*R*
4-FC_6H_4	Me	85	97	*R*
2-BrC_6H_4	Me	96	90	*R*
4-$NO_2C_6H_4$	Me	99	91	*R*
C_6H_5	Et	85	90	*R*
1-naphthyl	C_6H_5	86	81	*S*
c-C_6H_{11}	Me	55	79	*R*

[a]Reactions were conducted on a 0.5 mmol scale at 50 °C in *c*-hexane under the catalysis of 10 mol % **55**. Yields are isolated yields; ee's were determined by HPLC.

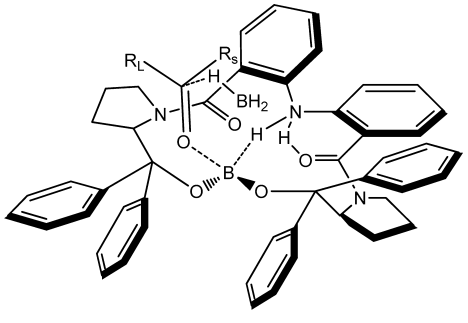


Figure 29. Proposed transition state showing the ketone co-ordinating to the boron with another borane involved in the reduction.[75]

observed after 24 h at −30 °C. The asymmetric induction achieved by **12** was high for a range of aromatic (>94% ee) and aliphatic (>87% ee) aldehydes (Table 12). Ligand **13**, a stereoisomer of **12**, gave very poor selectivity in this reaction (4% ee).

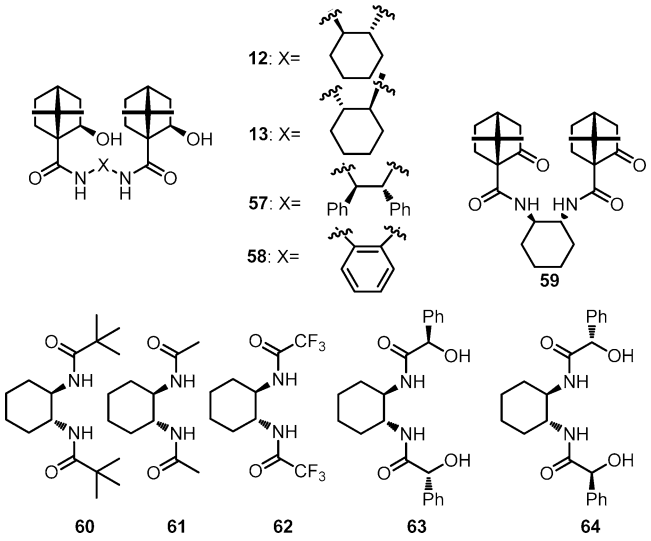


Figure 30. Hydroxyamide ligands used in silylcyanation reactions.

Ligand **57**, with vicinal phenyl groups replacing the cyclohexane moiety in **12**, was synthesized, and its catalytic performance was examined with the same aldehydes. The enantioselectivities were again excellent and, indeed, better than with **12** (Table 12). It was proposed that the bulkier phenyl group increased the energy difference between the two diastereomeric transition structure orientations, thereby giving better enantioselectivity. Ligand **58** was synthesized to study the effect of the chirality of the diamide moiety in **57** in the enantioselective addition of trimethylsilylcyanide to benzaldehyde. The enantioselectivity under the optimum conditions was decreased to 61% ee, demonstrating the importance of the chirality of the diamide backbone on the selectivity in the reaction.

Ketoamide **59** was found to give no enantioselectivity in the silylcyanation of benzaldehyde, as was the case with cyclohexanamides **60**−**62**, suggesting that the hydroxyl groups in the ligand structure of **12** and **57** have a privileged effect on the formation of efficient chiral catalysts for this reaction. *α*-Hydroxyamides **63** and **64** gave low enantioselectivities (up to 13%), in contrast to **12**, probably resulting from the less hindered phenyl groups when compared with the isoborneol structure.

A wide range of catalysts are available for the preparation of cyanohydrins that include the use of enzymes, synthetic peptides, chiral Lewis bases, and chiral transition metal complexes.[83] A recent review of chemical methods for the enantioselective synthesis of cyanohydrins discusses catalytic systems based on Salen, BINOL, phosphine, and amino alcohol ligands using ruthenium, titanium, aluminum, and other metals.[84] The performance of the hydroxyamide ligands discussed here compares very well with the large number of previously reported systems in terms of the stereoselectivity that is achieved. The yields achieved do fall somewhat short of some other systems, and the reported results do not refer to the synthetically more challenging ketone starting materials, which should be the focus of further developments.

■ ENANTIOSELECTIVE EPOXIDATION OF OLEFINS

In 1978, Schurig et al. reported the preparation of an optically active Mo(VI)-oxodiperoxo complex of ligand **65** (Figure 31) and its application in the enantioselective epoxidation of *trans*-but-2-ene.[85] The olefin could be transformed into the *trans*-(1*R*,2*R*)-but-2-ene oxide with a yield of 70% and an ee of up to

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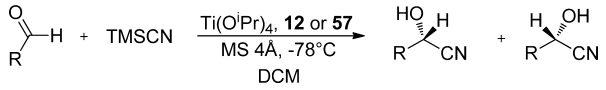
Table 12. Silylcyanation of Aromatic Aldehydes with Ligands 12 and 57[82,a]



	ligand 12			ligand 57		
aldehyde	yield (%)	ee (%)	dominant configuration	yield (%)	ee (%)	dominant configuration
benzaldehyde	79	94	*S*	87	93	*S*
3-phenoxybenzaldehyde	57	97	*S*	54	95	*S*
4-methoxybenzaldehyde	53	97	*S*	47	99	*S*
2-naphthaldehyde	76	96	*S*	67	99	*S*
(*E*)-cinnamaldehyde	51	95	*S*	49	97	*S*
3-phenylpropionaldehyde	62	98	*S*	61	97	*S*
2-methylbenzaldehyde	68	97	*S*	56	94	*S*
cyclohexanecarboxaldehyde	94	87	*S*	90	>99	*S*
valeraldehyde	96	89	*S*	92	97	*S*

[a]Reactions were conducted in CH_2Cl_2 at −78 °C and monitored by TLC. Ligand 0.33 mmol, 4 A ° molecular sieves 130 mg, $Ti(O^iPr)_4$ 0.3 mmol, TMSCN 3.5 mmol, aldehyde 2 mmol. Yields are isolated yields and ee's were determined by HPLC.

34%. Shortly afterward, Kagan et al. reported a catalytic version of this reaction in which they showed that a range of olefins could be epoxidized enantioselectively using only 10 mol % of the ligand. The highest ee obtained was only 35%, again for the epoxidation of *trans*-but-2-ene. The authors worried that kinetic resolution of a racemic epoxide could have led to the enantio-enriched product, but by careful monitoring of the enantiomeric composition of the epoxides during the reaction, they confirmed that the enantioselection occurs during the epoxidation itself .[86]

Schurig et al. prepared a number of other chiral Mo(VI)-oxodiperoxo complexes based on a series of enantiomerically pure hydroxyamides, such as (*S*)-piperidine lactamide (PLA) **65** (Figure 31), and evaluated them in a series of stoichiometric epoxidations of olefins.[87] Prochiral, chiral racemic, and chiral nonracemic olefins were used in this study. The best results were obtained using *trans*-but-2-ene with the complex derived from **65**, [$MoO(O_2)_2$·PLA (49% ee)], and (*S*)-3-methylpent-1-ene with either $MoO(O_2)_2$·PLA (51% ee for the 2*S*,3*S* diastereomer and 49% for the 2*R*,3*S* diastereomer) or with $MoO(O_2)_2$·DMLA **66** (51% for the 2*S*,3*S* diastereomer and 49% for the 2*R*,3*S* diastereomer).

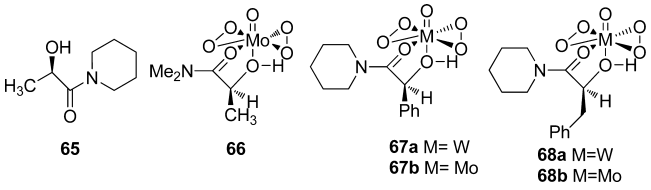
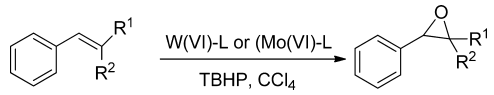


Figure 31. Ligands and complexes used in epoxidation reactions.

In 2000, Yoon reported the preparation of the W(VI) and Mo(VI)-oxodiperoxo complexes based on (*R*)-piperidinyl phenylacetamide **67** and (*R*)-piperidinylmandelamide **68** and the first report of a catalytic epoxidation using this type of complex when both (*E*)- and (*Z*)-β-methylstyrene were transformed to the corresponding epoxides.[88] Using only 10 mol % of the isolated Mo(VI)-oxodiperoxo complexes of **67** and **68** in concert with *tert*-butyl-hydroperoxide (TBHP), which was used as the terminal oxidant, they were able to achieve moderate to good ee's (26−81%). The highest ee (81%) (Scheme 8) was obtained using (*E*)-β-methylstyrene and complex **68b**, with moderate yields.

The use of hydroxyamides as ligands in the epoxidation reaction has been reported rarely, and those reports to date do not bear comparison with the large number of highly successful and well established asymmetric epoxidation systems available.[89,90]

Scheme 8. Epoxidation of Styrene Derivatives



NOZAKI−HIYAMA−KISHI REACTION

Kibayashi et al. applied tertiary β-hydroxyamides **69a−b** (Figure 32) in the chromium-mediated allylation of aromatic aldehydes in an early example of the Nozaki−Hiyama−Kishi reaction.[91] The reaction consists of the initial formation of a chromium(III) complex **70** from chromium(II) chloride and the lithium alkoxide derived from the chiral hydroxyamide and butyl lithium. The addition of allyl bromide gives the chromium(III) species, which reacts with the added aldehyde to yield the homoallylic alcohol **71** with induced stereoselectivity (Scheme 9).

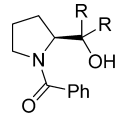


Figure 32. Tertiary β-hydroxyamide ligands applied to the NHK reaction.

The chromium complex is considered to constitute preferential coordination between chromium and the nitrogen atom rather than the oxygen atom of the amide group to form a five-membered chelate ring in a /trans planar structure that is quite rigid, which helps to differentiate the enantiotopic faces during the NHK coupling. The allyl coupling to benzaldehyde was undertaken using allylchromium complexes **72** derived from *N*-benzoyl-L-prolinol derivatives **69a−b** (Table 13). Derivative **69b** proved to be the most efficacious in chiral induction, affording predominantly the *R* enantiomer with an enantiomeric excess of 82%.

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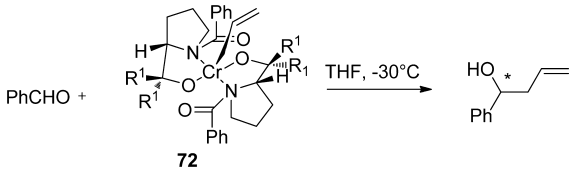
Table 13. Nozaki–Hiyama–Kishi Reaction[91,a]



β-hydroxyamide	yield (%)	ee (%)
69a	72	30
69b	62	82

[a]Reactions were conducted in THF at −30 °C for 1−12 h using $CrCl_2$ 2.0 mmol, lithium alkoxide 2 mmol, allyl bromide 1.0 mmol, and aldehyde 0.5 mmol.

The enantioselective NHK reaction has been developed substantially since the initial Kibayashi report discussed here. Many successful ligands have been reported for these reactions since that early report, including salen, amino oxazoline, and amido oxazoline ligands, and it is the last two that have proved the most successful, with enantioselectivities and yields in excess of 90% becoming commonplace.[92]

HYDROSILYLATION OF IMINES

Onomura reported the use of *N*-picolinoylpyrrolidine hydroxyamide derivative **73** to activate trichlorosilane in the hydrosilylation of aromatic imines to amines.[93] The catalytic activity of **73** was investigated using a range of aromatic imines and enamines with similar stereoselectivities in each case (Table 14) (67−80% ee for imine substrates derived from methyl ketones).

The authors proposed a working hypothesis for the transition state of the reduction of aromatic imines with **73** in which the silane coordinates to the pyridine nitrogen and the carbonyl oxygen of the amide. The approach of the imine is controlled by the hydrogen bonding of the imine nitrogen with the alcohol. The imine tends to approach in one orientation, which has less steric interation with the phenyl group of the ligands (Figure 33). Although, in general, in this review, ligands with amines or other ligating groups have been excluded in this case, the pyridine-based ligand is included because of the clear indication that both the amide and alcohol are involved in the key step of the reaction mechanism.

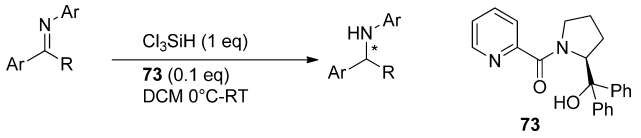
Although the reduction of imines is possible in many ways, the lack of any metal involvement in this organocatalytic process gives the reactions some advantage in terms of usability. Several peptidic organocatalysts have been reported for this reaction.[95,96] The performance of the hydroxyamide catalysts discussed here is competitive with those peptidic catalysts, albeit that the enantioselectivity is in need of some improvement.

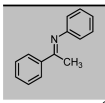
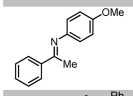
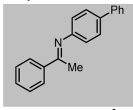
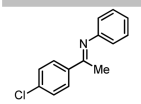
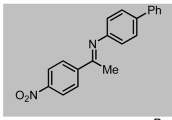
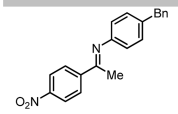
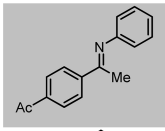
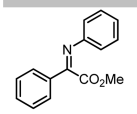
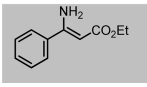
SIMMONS–SMITH CYCLOPROPANATION

Katsuki and co-workers reported the synthesis of BINOL derivatives, 1,1′-bi-2-naphthol-3,3′-dicarboxamides, and their application as chiral ligands in the asymmetric Simmons–Smith cyclopropanation of *E*-allylic alcohols.[12]

Ligand **3b**, with the diethylamide group, exhibited the highest enantioselectivity of 94% ee. The reaction of both conjugated and nonconjugated *E*-allylic alcohols, catalyzed by **3b**, showed good enantioselectivity (87−94% ee) in moderate yields (50−78%) (Scheme 10). However, in the case of *Z*-allylic alcohol, a lower chemical yield and enantioselectivity were observed, although only two examples were reported.

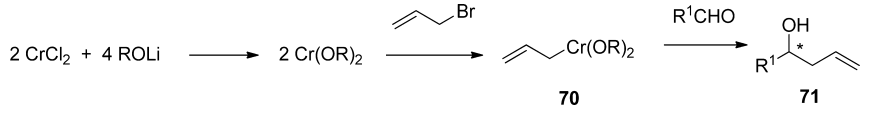
Table 14. Hydrosilylation of Aromatic Imines[94,a]



Aromatic imines	Yield (%)	ee (%)	Dominant Configuration
	86	73	*S*
	90	75	*S*
	90	71	*S*
	73	71	*S*
	84	73	*S*
	67	80	*S*
	24	67	nd
	80	45	*R*
	65	41	*S*

[a]Reactions were conducted in CH_2Cl_2 at room temperature over 4 h using Cl_3SiH 0.45 mmol, imine (0.3 mmol) and ligand 0.03 mmol. Yields are isolated yields, and ee's were determined by HPLC.

Scheme 9. Reaction Scheme for the NHK Reaction



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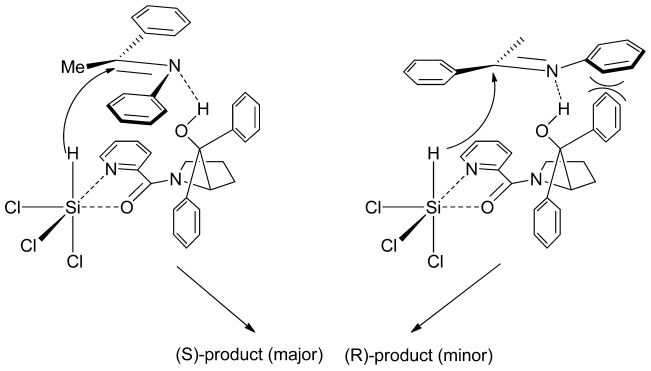
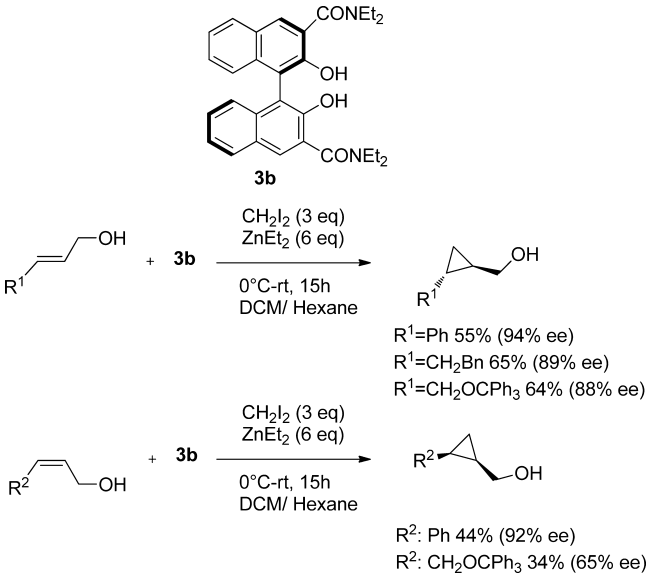


Figure 33. Proposed transition state of the reduction of aromatic imines.[94]

Scheme 10. The Preparation of Cyclopropanes by the Simmons–Smith Reaction



The Simons–Smith reaction is a well-known cyclopropanantion method, and many ligands that give good enantioselection, including amino alcohols, amides, BINOL-derived phosphorus-based ligands, and others,[97] have been reported. The results for the hydroxyamides are limited, but the initial reports do seem to indicate potential for good enantioselectivity, but the yields reported are somewhat short of the established catalysts.

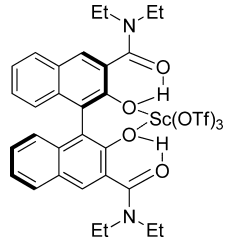


Figure 34. Ligand **3b** as its proposed Sc(III) complex.

MICHAEL ADDITION

Katsuki also reported the use of the optically active *N,N,N′,N′*-tetraalkyl-BINOL-3,3′-dicarboxamides such as **3b** as chiral auxiliaries for asymmetric Michael addition reactions (Scheme 11).[98,99] Because an intramolecular hydrogen bond between phenolic hydrogen and carbonyl oxygen was considered to fix the conformation of the amide moiety in **3b**, it was expected that the $Sc(OTf)_3$ complex (Figure 34) would serve as a chiral catalyst for the Michael addition reaction. Although antiselectivity was high (>50:1), both the chemical yield (48%) and enantioselectivity (18%) were only modest.

The authors reasoned that the amide alkyl groups of ligand **3b** directing away from the reaction site could not induce asymmetry in the product effectively.

ENANTIOSELECTIVE CONJUGATE ADDITION OF NUCLEOPHILIC RADICALS TO ENOATES

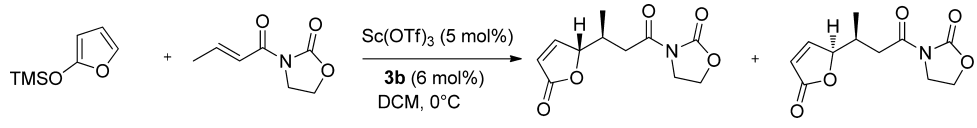
Sibi and Manyem have reported that lanthanide triflate along with proline-derived ligand **74** is a catalyst for the enantioselective conjugate addition of nucleophilic radicals to enoates (Scheme 12).[100]

The enantioselectivity obtained in the reaction (23%) was much lower than that obtained by related carbamate analogues (>80%), and the reaction completion was also significantly slower and yields were moderate.

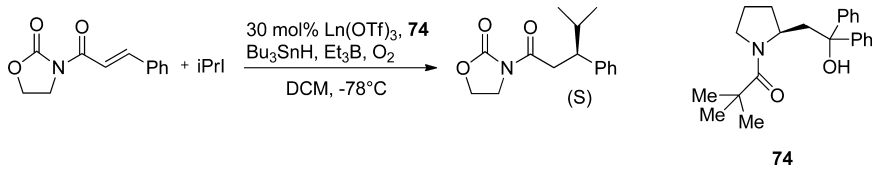
CONCLUSION

Asymmetric ligands whose key functional component consists of amide and hydroxyl functional groups, in the absence of other co-ordinating groups, are showing real promise as part of catalytic systems for a wide range of reactions. In general, these ligands are remarkably easy to synthesize, which favors their use, as does the fact that they are very versatile in terms of stereochemistry and substitution patterns. Two main routes are used: (1) an activated acid (acid chloride,[27,74] anhydride,[22] or ester with TBD[25]) reacting with an amino alcohol or (2) an

Scheme 11. Asymmetric Michael Addition Reactions



Scheme 12. The Addition of Nucleophilic Isopropyl Radical to an *α,β*-Unsaturated Enoate



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acid derivative (acid chloride[21] or parent acid[19]) reacting with an amine, the alcohol being generated subsequently by reduction of a ketone in the molecule. For ligands that have largely been researched for only the last 12 years, they have found application to a large number of synthetically key reactions. In many cases, the activity and selectivity has been optimized somewhat through a number of generations of ligand. That being said, there is undoubtedly more progress yet to come. One feature that is striking in reviewing the literature in this area is the lack of characterization of the metal complexes involved, and should this change, it will surely give insights that will help the development of the next generations of the ligands.

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Notes

The authors declare no competing financial interest.

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