Catalytic Enantioselective Addition to Imines

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Contents

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Haruro Ishitani was born in 1970 in Osaka, Japan. He earned his Ph.D. in 1998 under supervision of Prof. Kobayashi. He is now an assistant professor at the Graduate School of Pharmaceutical Sciences, University of Tokyo. His research interests include development of chiral catalysts and total synthesis of biologically interesting compounds.

1. Introduction

Chiral nitrogen-containing compounds are widely distributed in nature and include many biologically important molecules (Chart 1). In these compounds, the nitrogen-containing units are known to play important roles for their bioactivities. For the synthesis of these chiral nitrogen-containing building blocks, use of imines as electrophiles is the most promising and convenient route.[1] While many approaches using chiral imines or chiral nucleophiles have been reported,[1] these diastereoselective reactions have some disadvantages. First, the procedures to introduce chiral auxiliaries to substrates and to remove them after the diastereoselective reactions are often tedious. Second, more than stoichiometric amounts of chiral sources are needed to obtain chiral compounds according to these reactions.

On the other hand, catalytic enantioselective reactions provide the most efficient methods for the synthesis of chiral compounds,[2] because large quantities of chiral compounds are expected to be prepared using small amounts of chiral sources. While much progress has been made recently in catalytic enantioselective reactions of aldehydes and ketones such as aldol,[3] allylation,[4] Diels−Alder,[5] cyanation reactions,[6] reduction,[1b,2b] etc., progress in catalytic enantioselective reactions of imines is rather slow. There are some difficulties in performing catalytic enantioselective reactions of imines. For example, in the cases of chiral Lewis acid promoted asymmetric

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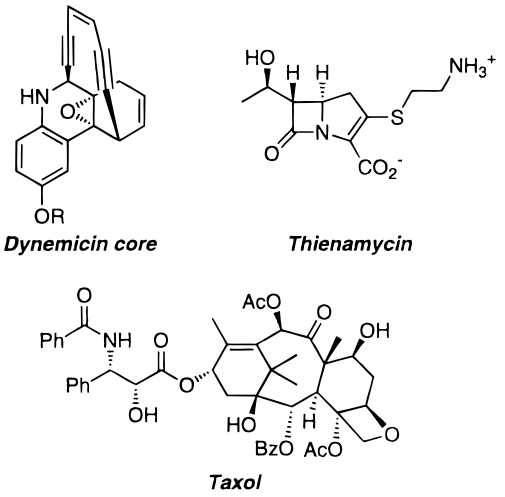
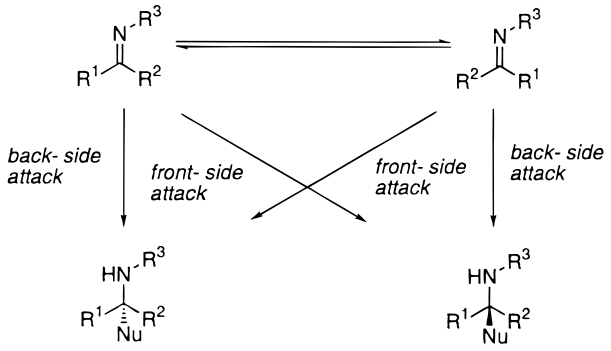
Chart 1



reactions, aldehydes usually coordinate the metal centers of the Lewis acids using one of the lone pairs of carbonyl oxygens (the same sites as aldehyde hydrogens).[7] The structures of these complexes were confirmed by X-ray crystallographic analyses.[8] In addition, Corey et al. proposed that second interactions between counteranions of Lewis acids and formyl hydrogens made the complex rigid.[9] On the other hand, imines often exist as mixtures of geometrical isomers ascribed to the C−N double bonds or under rapid equilibrium states.[10] Therefore, plural transition states exist when Lewis acids coordinate imines, which often decreases selectivities (Scheme 1). In addition, most Lewis acids are trapped by the

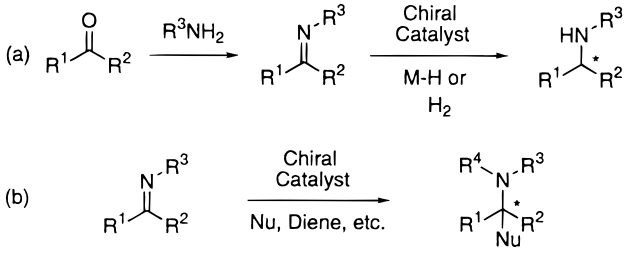
Scheme 1. Relationship between Selectivities and C−N Double Bond Isomerization



basic nitrogen atoms of the starting materials (imines and/or products), and therefore, catalytic reactions using imines as electrophiles and metal catalysts are difficult to perform.

However, several excellent examples of catalytic enantioselective reactions of imines have been reported especially in the past 2 or 3 years, and these works have impacted synthetic organic chemistry as well as other fields of chemistry including their potential contribution to science. This review covers all such works as far as the authors know. It is divided into two parts: reductive amination and carbon−carbon bond-forming reactions (Scheme 2). The former describes enantioselective reductions mainly, while the latter discusses enantioselective

Scheme 2. (a) Synthesis of Chiral Nitrogen-Containing Compounds via Reductive Amination; (b) Synthesis of Chiral Nitrogen-Containing Compounds via Carbon−Carbon Bond-Forming Reaction

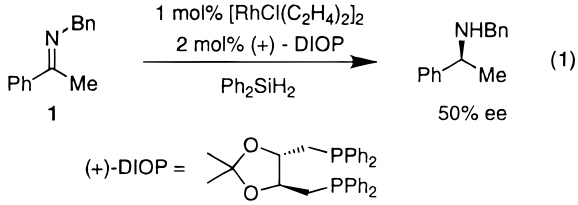


carbon nucleophilic attacks on imines. In principle, asymmetric reactions using more than stoichiometric amounts of chiral sources are not mentioned in this review.

2. Catalytic Enantioselective Reductive Amination via Imines

2.1 Introduction

Reductive amination via imines provides one of the most convenient methods for the synthesis of nitrogen-containing compounds (amines).[2b,11] When imines derived from unsymmetrical ketones are employed in this reaction, a new chiral center is formed at the carbon connected to the nitrogen atom. In 1973, Kagan et al. reported the first example of catalytic enantioselective reductions (hydrosilylation) of imines, and 50% ee of the amine was obtained in the reduction of *N*-(α-methylbenzylidene)benzylamine (**1**).[12] Since then, many chemists have made effort to develop highly enantioselective reduction processes (eq 1).[13]

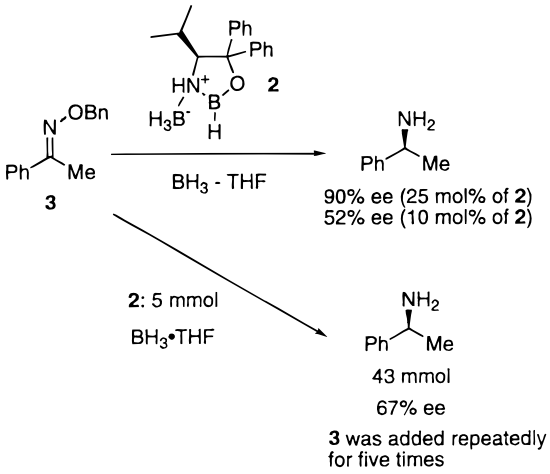


(1)

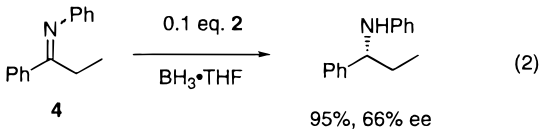
2.2 Reductive Amination Using Hydride Reagents Based on Chiral Borons

Enantioselective reductions of imines with chiral borane-based reducing reagents were investigated early in the 1980s.[14] Itsuno et al. developed catalytic enantioselective reductions of oxime ether **3** using chiral borone **2**, which was prepared by combining borane and a chiral amino alcohol (Scheme 3). While good chemical and optical yields were obtained by using 25 mol % of the chiral source, lower enantioselectivities were obtained when 10 mol % of the chiral amino alcohol was used. Successive addition of substrate **3** realized a more effective semicatalytic process.[15]

Scheme 3. Itsuno's Catalytic and Semicatalytic Enantioselective Reductions



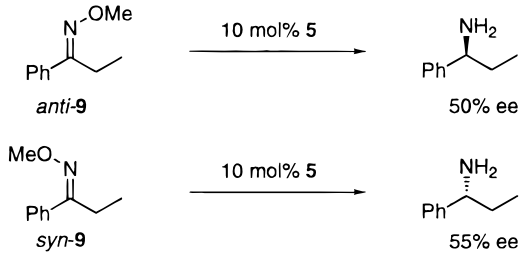
Cho et al. investigated reductions of imines using **2** (0.1 equiv); however, lower enantioselectivities were obtained (eq 2).[16]



(2)

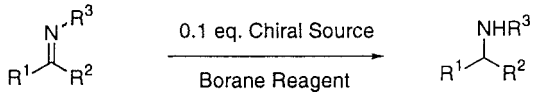
Several catalytic asymmetric hydroborations of imines are summarized in Table 1.[17] Bolm (Table 1, entry 4)[18] and Buono (Table 1, entry 5)[19] et al. independently demonstrated asymmetric reductions of imines using chiral β-hydroxy sulfoximine **5** and oxazaphospholidine **6** as ligands, respectively, although enantioselectivites were moderate to good when using 10 mol % of the chiral sources. Bolm et al. also revealed that the absolute configurations of the reduced products were determined by not only that of the catalyst but also the geometrical structure of the substrates.[18] Namely, *E*-isomer of **9** (anti-**9**) gave (*S*)-enantiomer while *Z*-isomer of **9** (syn-**9**) gave (*R*)-enantiomer (Scheme 4). Fujisawa et al. showed a highly enantioselective reduction of bisimine **7** using 50 mol % of chiral catalyst **8** with 3.0 equiv of BH_3•THF (90% yield, chiral/meso = 95:5, 99% ee).[20] However, even in this case, the selectivity decreased to 73% ee when 10 mol % of **8** was used (Table 1, entry 6).

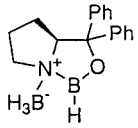
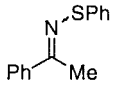
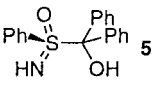
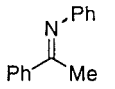
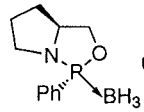
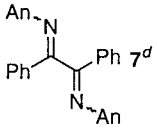
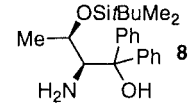
Scheme 4. Asymmetric Reductions of Oxime Ethers



Recently, Mukaiyama et al. developed highly enantioselective borohydride reductions of imines using chiral cobalt(II) complex **10**.[21,22] Namely, under the

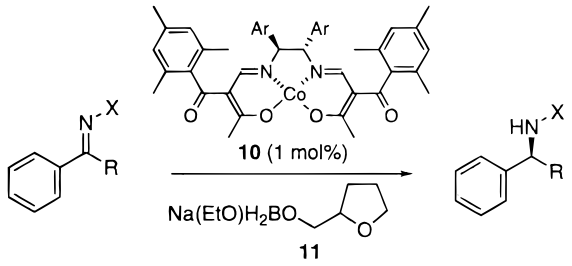
Table 1. Catalytic Asymmetric Hydroborations

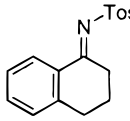
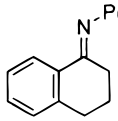
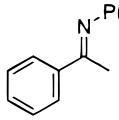
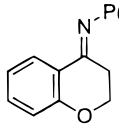


entry	substrate	chiral source	borane	yield/%	ee/%	ref.
1	**3**	**2**	BH_3•THF	quant.	52[a,c]	15
2	**4**	**2**	BH_3•THF	95	66[b]	16
3	**4**		BH_3•THF	92	70[b]	16
4		 **5**	BH_3•SMe_2	64	70[a,c]	18
5		 **6**	BH_3•SMe_2	59	63[b]	19
6	 **7**[d]	 **8**	BH_3•THF	71[e]	73[f]	20

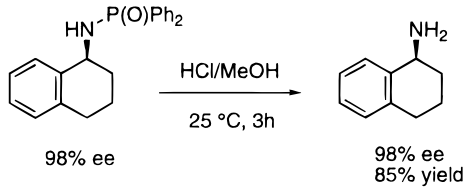
[a]The absolute configuration of the product was determined to be *S*. [b]The absolute configuration of the product was determined to be *R*. [c]The products were isolated as the corresponding primary amine. [d]An = *p*-MeO-Ph. [e]Chiral:meso = 95:5. [f] (*R,R*)-enantiomer.

Table 2. Mukaiyama's Catalytic Enantioselective Borohydride Reductions



entry	imine	Ar	yield/%	ee/%
1		5-xylyl	95	71
2		5-xylyl	85	98
3		mesityl	97	90
4		5-xylyl	81	92

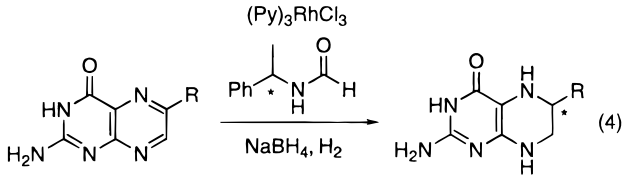
influence of 1 mol % of **10**, *N*-tosyl imines or *N*-diphenylphosphinyl imines were rapidly reduced by pre-modified sodium borohydride **11**, which was prepared from $NaBH_4$, tetrahydrofurfuryl alcohol, and ethanol under mild conditions. The reductions proceeded smoothly under the conditions to afford the corresponding amide derivatives in high yields with high ees (Table 2). Various *N*-diphenylphosphinyl imines derived from aromatic, acyclic, and cyclic ketones were converted to the corresponding amides. The resulting phosphinyl amides were easily hydrolyzed with acidic treatment (eq 3).[23]



(3)

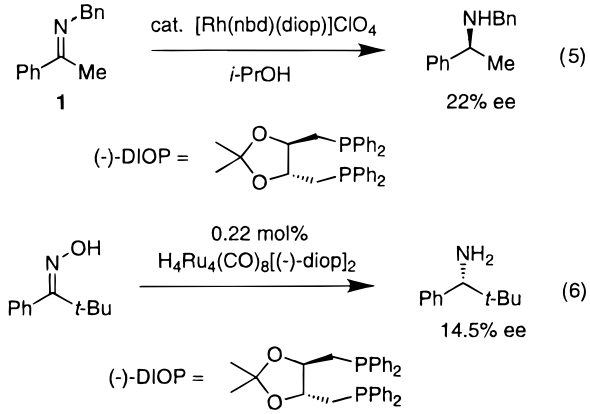
2.3 Reductive Amination Using Hydride Reagents Based on Chiral Early Transition Metals

Reductive amination via catalytic asymmetric hydrogenation of imines was first demonstrated by three groups independently in 1974−1975. In 1974, Boyle et al. performed hydrogenation of a carbon−nitrogen double bond in folic acid using a chiral rhodium complex (eq 4).[24] In 1975, Scorrano et al. investigated asymmetric hydrogenation of imines using a chiral rhodium catalyst. They performed



(4)

reduction of simple imine **1** in the presence of a catalytic amount of $[Rh(nbd)(diop)]^+ClO_4^-$ (eq 5).[25] Botteghi et al. demonstrated asymmetric hydrogenation of a ketone oxime using a chiral ruthenium cluster, $H_4Ru_4(CO)_8[(-)\text{-diop}]_2$ (eq 6).[26]

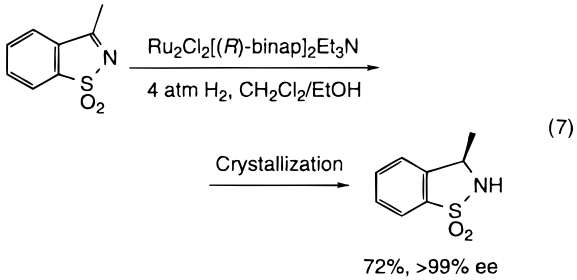


(5)

(6)

While the enantioselectivities according to the above three group's systems were not so good, some improvements on enantioselectivities were achieved in the middle of the 1980s. Markó[27] and Bakos[28] et al. investigated asymmetric hydrogenation of imines using a Rh−chiral diphosphine system. They tested a variety of diphosphine ligands, and finally found that imine **1** was reduced to afford the corresponding amine in an 83% ee (Table 3, entry 5).[28]

Chiral ruthenium complexes are also recognized as effective chiral catalysts in asymmetric reductions of imines.[29] Oppolzer et al. showed that cyclic *N*-arylsulfonyl imines were hydrogenated by a Ru−BINAP complex in good enantioselectivities (eq 7).[30]

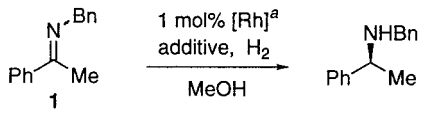


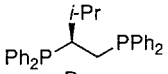
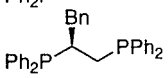
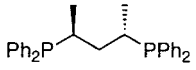
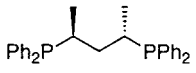
(7)

James et al. investigated an improved enantioselective hydrogenation of imines using a catalyst which was prepared in situ based on rhodium(I) at the end of 1980s.[31] They observed dramatic enhancement of the enantioselectivity when potassium iodide was added and the reaction was performed at −25 °C. Simple acyclic imine **12** was reduced quantitatively in the presence of 1 mol % of the Rh catalyst, and the optical yield of the corresponding amine was 91% ee (Table 4, entry 4).

Several important findings were reported in 1990, and the following mechanistic investigations were

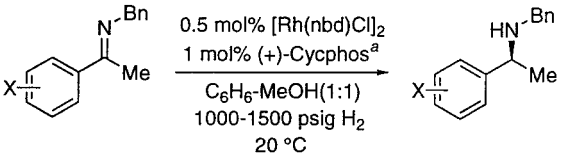
Table 3. Improved Catalytic Enantioselective Hydrogenation



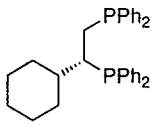
entry	ligand	additive	temp/°C	yield/%	ee/%
1[b]	(+)-DIOP	—	25	97	3[c]
2[b]		—	25	100	66[c]
3[b]		—	25	96	72[c]
4		Et_3N	20	96[d]	73[e]
5		Et_3N	0	100[d]	83[e]

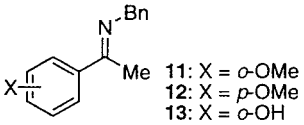
[a]The rhodium catalyst was prepared from $[Rh(nbd)Cl]_2$ and diphosphine. [b]Methanolic benzene (1:1) was used as a solvent. [c]The absolute configuration of the product was determined to be *S*. [d]Conversion yield. [e]The absolute configuration of the product was determined to be *R*.

Table 4. James' Investigation of Rh-Catalyzed Enantioselective Hydrogenation

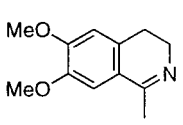


entry	substrate[b]	conditions	yield/%	ee/%
1	**12**	—	quant	71
2	**11**	KI	90	71
3	**12**	KI	quant	84
4	**12**	KI, Tol-MeOH(1:2) -25 °c	quant	91
5	**13**	—	~ 0	
6	**12**	pre-formed $[Rh(nbd)(cycphos)]PF_6$	quant	0
7	**14**	—	~ 0	

[a] (+) - Cycphos = 

[b] 

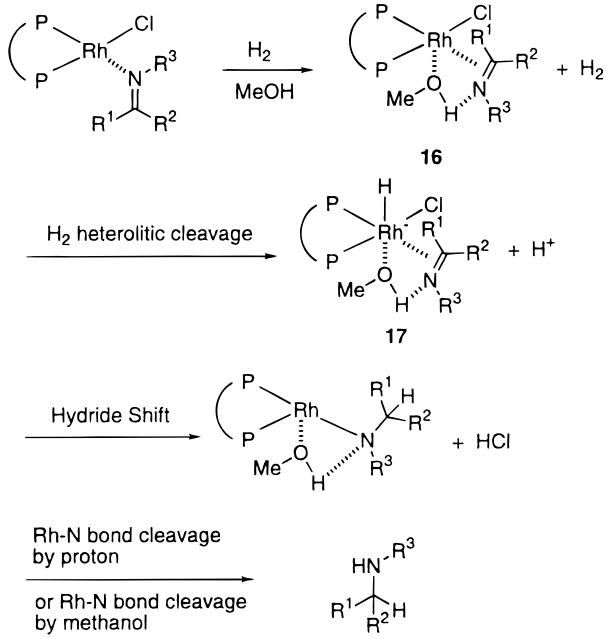
11: X = *o*-OMe
12: X = *p*-OMe
13: X = *o*-OH



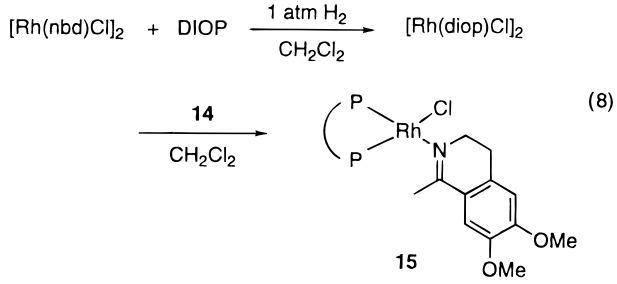
14

published in 1991.[32] They suggested that chelate formation was not essential to obtain high chemical and optical yields. Actually, imine **11** was reduced under the reaction conditions to afford the corresponding amine in a 71% ee, while no product was obtained in the reaction of **13** under the same reaction conditions (Table 4, entries 2 and 5). When

Scheme 5. Proposed Mechanism of Rh−Diphosphine Complex-Catalyzed Enantioselective Hydrogenation



a preformed catalyst was used, the reaction proceeded quantitatively, but no chiral induction was observed (Table 4, entry 6). According to the reaction mechanism of the Rh-mediated hydrogenation suggested by Longley and Wilkinson et al., oxidative addition of hydrogen to rhodium(I) is the first step of the reactions.[33] On the other hand, James et al. suggested that coordination of nitrogen atoms of imines to the rhodium center was the first step of the reactions.[32b] When imine **14** was treated under the reduction conditions, the reaction did not proceed but complex **15**, which existed as a couple of isomers in solution state (eq 8), was isolated. Because of the

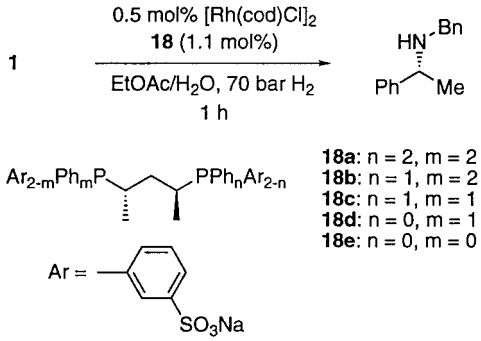


(8)

importance of the solvent system (methanol-benzene (1:1)), they suggested the existence of five-coordinated Rh(I) intermediate such as **16** and the following formation of monohydride species **17** (Scheme 5). While the role of an iodide anion was not clean, they supposed that the iodide prevented the binding of two imines to the metal center.

Bakos and Sinou et al. studied asymmetric hydrogenation of imines in a two-phase system.[34] They used partially sulfonated chiral diphosphine **18b**−**e**(sodium salts) as a water soluble chiral ligand. They found that enantioselectivities of reduced products were strongly dependent on sulfonation degrees of the diphosphine ligands. Namely, almost complete

Table 5. Catalytic Enantioselective Hydrogenation of Imines in a Two-Phase System

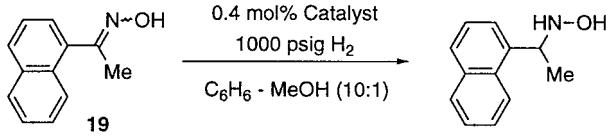


entry	sulfonation degree	solvent	yield/%	ee/%	ref.
1	1.41	H_2O-EtOAc	96	96	34b
2	1.65	H_2O-EtOAc	94	96	34b
3	3.75	H_2O-EtOAc	55	19	34b
4	4.0 (**18e**)	H_2O-EtOAc	quant.	58	35
5	1.0 (**18b**)	H_2O-EtOAc	85	94	35
6	1.0 (**18b**)	EtOAc	quant.	94	35

enantioselectivity was obtained when the sulfonation degrees were kept between 1.2 and 1.7 (Table 5). It is remarkable that this highly enantioselective ligand system included a mixture of epimers based on chirality of phosphorus atoms. On the other hand, a homochiral ligand system using a tetra-sulfonated diphosphine ligand showed lower enantioselectivity (58% ee). de Vries et al. tried to separate and characterize the selective ligand components.[35] Mono- and di-sulfonated ligands were separable by column chromatography, and they revealed that mono-sulfonated ligand **18b**(sodium salt) consisted of equimolar amounts of two epimers. FAB-MS spectra indicated that the structure of the catalyst prepared from **18b**(sodium salt) and $[Rh(cod)Cl]_2$ was Rh(cod)-**18b** in which SO_3^- acted as a counteranion. This catalyst was only soluble in organic solvents and showed the same level of enantioselectivities in both organic and two-phase systems.

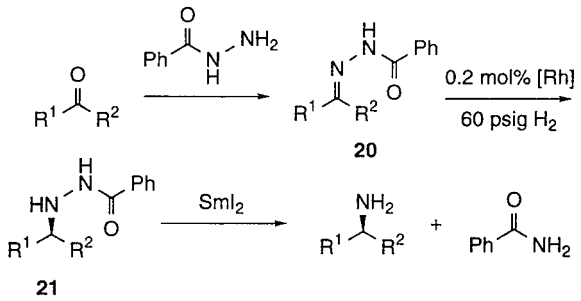
In 1995, Chan et al. reported interesting investigations on the relationship between enantioselectivities and geometry of 1-acetonaphthone oxime **19** in the asymmetric reduction using rhodium(I)-based hydrogenation systems.[36] It was generally recognized that in addition reactions of imines, two geometrical isomers based on C−N double bonds gave enantiomeric pairs of addition products. Hence, to obtain high enantioselectivities, it was important to employ only single geometric isomers. On the other hand, the authors showed that in some chiral transition-metal-catalyzed hydrogenation systems the same sense of chiral induction was observed by using both *E*- and *Z*-oximes (Table 6).

Table 6. Chiral Transition Metal Complex Catalyzed Hydrogenation of Oximes (Relationship between Enantioselectivities and Geometrical Isomers)



entry	catalyst	ee/% from *E*-isomer	ee/% from *Z*-isomer
1	[Rh(nbd)(*S*-binap)]BF_4	30 (*S*)	66 (*S*)
2	[Rh(nbd)(*R,R*-dipamp)]BF_4	8 (*R*)	15 (*R*)
3	[Rh(cod)(*R,R*-diop)]BF_4	14 (*R*)	26 (*S*)

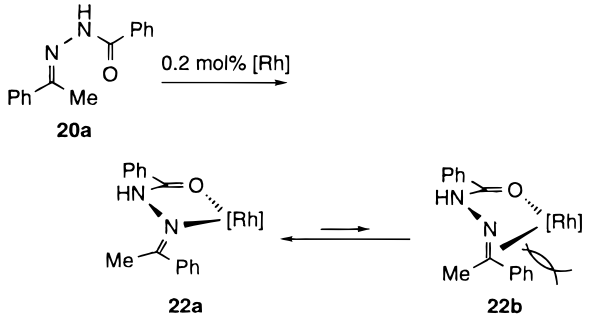
Table 7. Burk's Catalytic Enantioselective Hydrogenation of Hydrazones



entry	hydrazone	time/h	ee/%
1	**20a**: R^1 = Ph, R^2 = Me	24	95
2	**20b**: R^1 = *p*-NO_2.Ph, R^2 = Me	12	97
3	**20c**: R^1 = CO_2Me R^2 = Et	36	91
4	**20d**: R^1 = *i*-Pr, R^2 = Me	36	73
5	**20e**: R^1 = *t*-Bu, R^2 = Me	36	45

Burk et al. developed highly enantioselective hydrogenation of *N*-acylhydrazone derivatives using a cationic Rh(I)−DuPHOS complex.[37] A variety of hydrazones derived from acetophenone or pyruvate series with benzoylhydrazine were hydrogenated enantioselectively up to 95% ee in the presence of 0.2 mol % of a rhodium catalyst. On the other hand, lower selectivities and reaction rates were observed in the reactions using acylhydrazones derived from aliphatic ketones such as **20d** and **20e** (43−73% ees) (Table 7). Assumed reaction mechanism is shown in Scheme 6. While **22a** was the major component between two complexes, the authors expected that

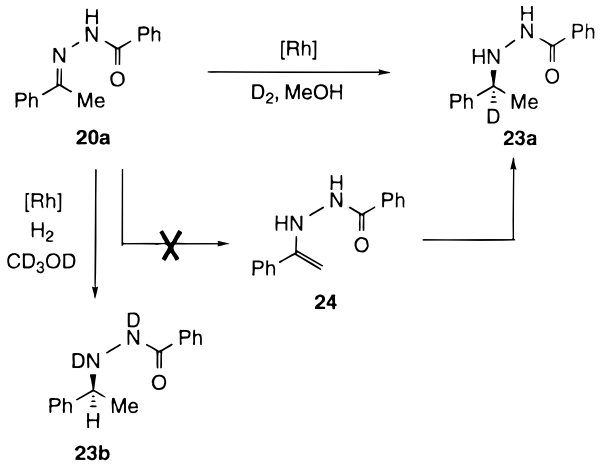
Scheme 6. Assumed Transition State of the Burk Hydrogenation



enantioselection occurred at the state of π-bound intermediate **22b**. Moleculer modeling studies suggested that steric repulsions between alkyl substituents and the DuPHOS moiety disfavored state **22b**. Actually, a significant decrease of enantioselectivities were observed when one of the alkyl substituents was changed from *i*-Pr to *t*-Bu.

They also carried out deuterium incorporation studies (Scheme 7).[37b] When the reduction of **20a** was

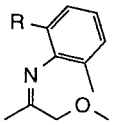
Scheme 7. Deuterium Incorporation Studies of the Burk Hydrogenation



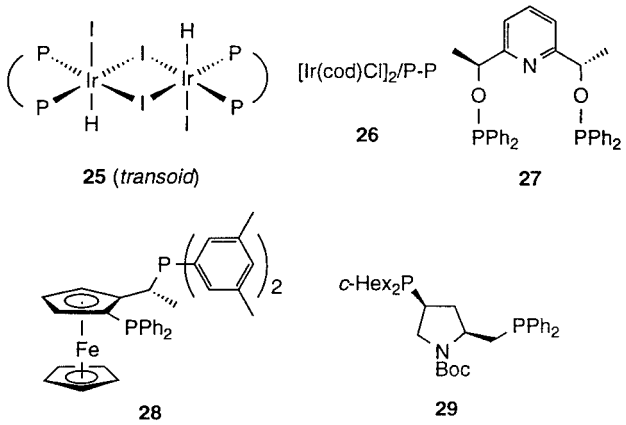
carried out in methanol under D_2, deuterium was detected only at the methine carbon of **23a**. In addition, when **20a** was reduced in methanol-d_4 under H_2, deuterium was detected at the two nitrogen atoms of **23b**. The former results indicated that the reaction did not proceed via enamine tautomer **24**. On the other hand, it was suggested from the latter results that the cleavage of the metal−nitrogen bond was mainly taken place by methanol, although the authors did not mention clearly. It is noted that these results are consistent with the reaction course shown in Scheme 5. It was also shown that the reductive cleavage of the N−N bond of reduction products was successfully carried out using samarium diiodide (SmI_2).

Osborn[38] and Spindler[39] et al. developed independently the enantioselective hydrogenation of imines with chiral Ir complexes. The above two groups used different types of catalyst precursors. Namely, the former used [Ir(III)(P−P)HI_2]$_2$ (**25**) prepared from [Ir(I)(P−P)(cod)]BF_4 and LiI (Table 8, entry 1), and the latter used an in situ prepared catalyst (Table 8,

Table 8. Iridium Complex-Catalyzed Enantioselective Hydrogenation

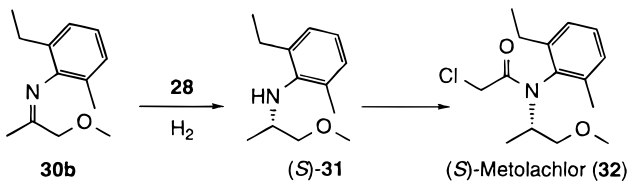
entry	substrate	catalyst	substrate/Ir	ee/%	ref.
1	 **30a**; R = Me	**25** ((+)-DIOP)	2000	63[a]	38a
2	**30a**	**26**/(+)-DIOP/I^-	100	70[a]	39
3	**30a**	**26**/**27**/ClO_4^-	150	55[a]	40
4	**30b**[b]	Ir(I)/**28**/I^-	1,000,000	80[a]	41
5	**14**	**26**/**29**/Phthalimide	100	85-93[a]	42c

[a]The absolute configuration of the amine was determined to be *S*. [b]R = Et. This imine is a starting material for the synthesis of (*S*)-Metolachlor.



entry 2). While both types of catalytic systems showed reasonable catalytic activities (substrate/catalyst ratio), moderate to good enantioselectivities were observed. More recently, Osborn et al. synthesized a new type of C_2-symmetrical tridentate phosphine ligand (**27**), and they used the ligand for in situ preparation of an Ir catalyst in asymmetric hydrogenation of imines (Table 8, entry 3).[40] In addition, Spindler et al. applied their method to an industrial process.[41] Namely, potent herbicide (*S*)-Metolachlor (**32**) was synthesized by means of hydrogenation of imine **30b** using a new type of ferrocenylphosphine-bound iridium catalyst (**28**, Scheme 8). Up to 1 000 000

Scheme 8. Asymmetric Synthesis of Herbicide (*S*)-Metolachlor



of substrate/catalyst ratio was achieved by using this new catalyst. Achiwa et al. also developed a catalyst system based on an Ir-diphosphine complex in asymmetric hydrogenation of cyclic imines.[42] They showed the remarkable effect of diphosphine **29** (*not*

Scheme 9. Pfaltz's Catalytic Enantioselective Hydrogenation

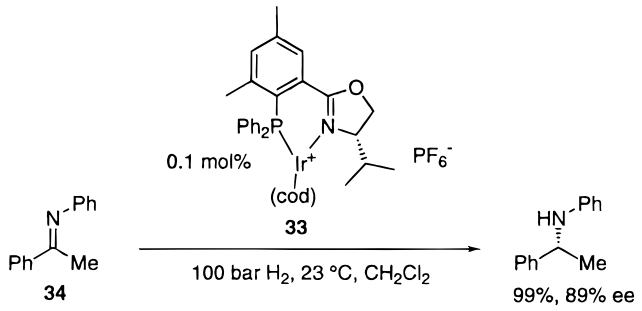
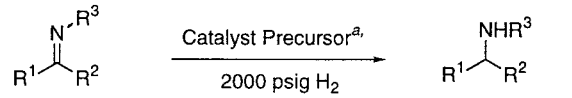
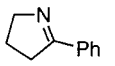
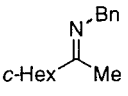
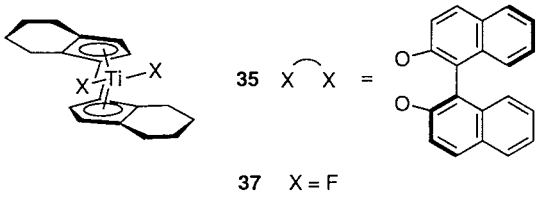


Table 9. Buchwald's Catalytic Enantioselective Hydrogenation



entry	substrate	catalyst/ eq.	yield/%	ee/%
1	**1**	**35**[a] / 0.02	93	85[b]
2	**14**	**35**[a] / 0.05	82	98[c]
3	 **38**	**35**[a] / 0.1	77	98[b]
4		**35**[a] / 0.05	93 85	76[b] 43[b,d]

[a]The catalyst precursor was activated *in situ* by treatment of 2 eq. of BuLi and 3 eq. of $PhSiH_3$. [b]The absolute configuration of the amine was determined to be *R*. [c]The absolute configuration of the amine was determined to be *S*. [d]The reaction was carried out under 500 psig of H_2 atmosphere.

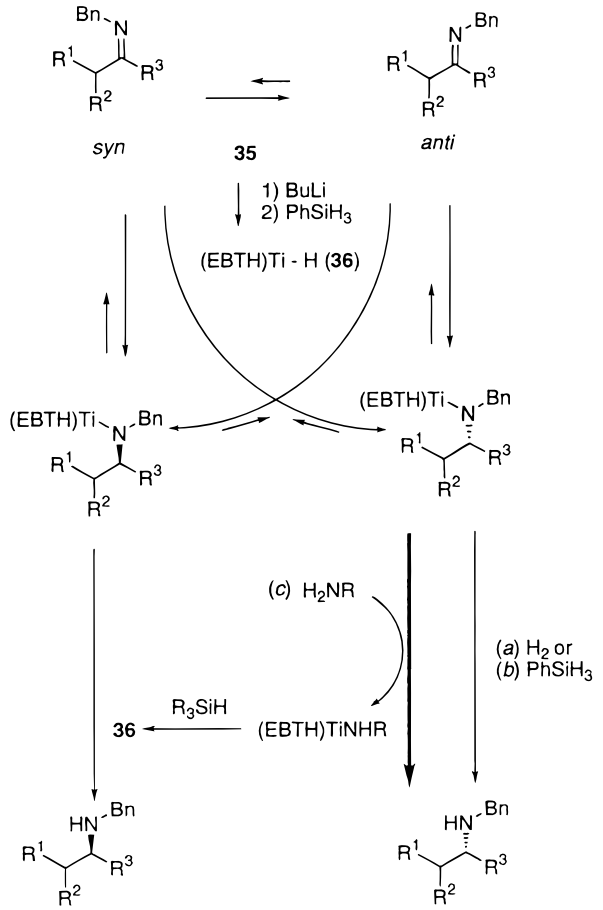


C_2 symmetry) and also revealed that a phthalimide was an effective cocatalyst (Table 8, entry 5).[42c]

Quite recently, Pfaltz et al. also investigated hydrogenation of imines with iridium complexes.[43] They used phosphine-oxazolidine ligand **33** as a chiral source. *N*-Phenyl imine **34** was reduced to corresponding aniline derivative in a 99% yield and a 89% ee with 0.1 mol % of the catalyst (Scheme 9).

Recently, Buchwald et al. developed effective reductive amination using chiral titanocen catalysts.[43] The representative results of their investigations are listed in Table 9. First, the hydrogenation reactions were performed using catalyst **35**. The active intermediate in these hydrogenantions was assumed to be titanocene(III) hydride species **36**. Under hydrogen atmosphere of 80−2000 psig, cyclic imines **14** and **38** were reduced in good to high yields with excellent enantioselectivities (Table 9, entries 1 and 2). Even

Scheme 10. Assumed Catalytic Cycles of the Buchwald System; (*a*) First Report; (*b*) Improved Method Using a Hydrosilane; (*c*) Most Effective Method of Adding a Primary Amine (EBTH = ethylene(bis)tetrahydroindenyl)

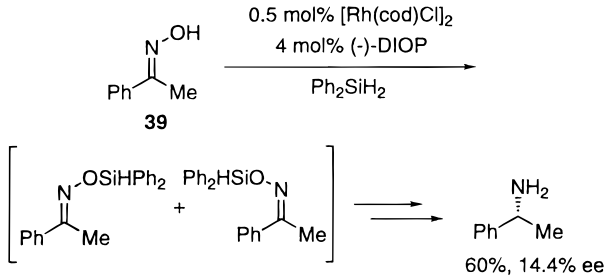


when acyclic imine **1** was employed, the corresponding amine was obtained in good enantioselectivity in the presence of a less amount (2 mol %) of catalyst **35**. It was assumed from kinetic studies that the imines existed under equilibrium conditions in the catalytic cycle as shown in Scheme 10, and this caused pressure dependence of the enantiomeic excesses in these reductions. They improved these results using fluoride **37** as a catalyst and triphenylsilane as a reducing reagent, and much higher enantioselectivities and catalytic efficiency were obtained. The details of their improved investigations are mentioned in the following chapter.

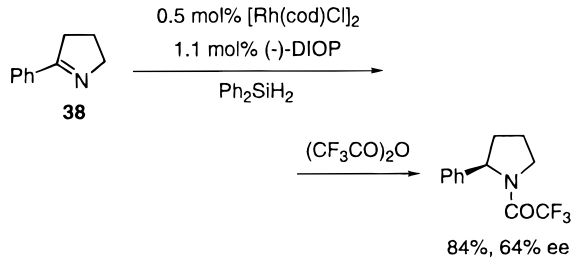
2.4 Reductive Amination Using Late Transition Metal Complexes

As mentioned in 2.1., Kagan et al. reported the first enantioselective hydrosilylation of imines **1** in 1973 (eq 1).[14,45] After nearly 10 years from their findings, Brunner et al. reported the second example of the Rh-catalyzed hydrosilylation of imines.[46a] They performed reactions in the presence of 0.5 mol % of $[Rh(cod)Cl]_2$ as a catalyst precursor and 4 mol % of (−)-DIOP as a chiral ligand (Scheme 11). Under these conditions, oxime (*N*-hydroxylimine) **39** was reduced by diphenylsilane. It was found from ^1H NMR spectroscopic studies that *E*−*Z*-isomerization of an

Scheme 11. Brunner's Catalytic Asymmetric Hydrosilylation



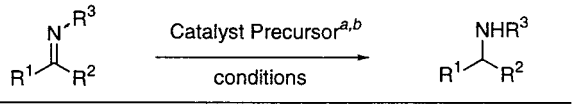
Scheme 12. Brunner's Improved Hydrosilylation Using a Cyclic Imine

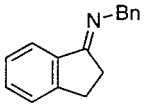


O-silylated oxime occurred, which decreased the enantioselectivity. The enantioselectivity was slightly improved when a cyclic imine was employed (Scheme 12).[46b]

As noticed in the last chapter, the Buchwald's catalytic asymmetric hydrosilylation is quite promising. Chiral titanocene fluoride **37** reacted with triphenylsilane smoothly in the presence of a small amount of pyrrolidine and methanol to produce active titanocene(III) hydride **36**. This process is more effective than the method using **35** under hydrogen atmosphere. An *N*-silylated amine was obtained first, and the following acidic workup gave the corresponding amine in a high enantioselectivity, even in the presence of 0.02−0.1 mol % of the catalyst (Table 10, entries 1 and 2, see also Scheme 10b).[47]

Table 10. Buchwald's Catalytic Enantioselective Hydrosilylation



entry	substrate	catalyst/ eq.	conditions	yield/%	ee/%
1	**38**	**37**[d] / 0.01	$PhSiH_3$	97	99[c]
2	**38**	**37**[a,d] / 0.001	$PhSiH_3$	96	98[c]
3	**1**	**37**[b,d] / 0.005	PMHS[e] /*i*-$BuNH_2$	95	98[c]
4		**37**[b,d] /0.01	PMHS[e] /*i*-$BuNH_2$	96	92[c]

[a] The catalyst precursor was activated *in situ* by treatment of $PhSiH_3$ and pyrrolidine in MeOH. [b]The catalyst precursor was activated *in situ* by treatment of $PhSiH_3$ and piperidine in MeOH. [c]The absolute configuration of the amine was determined to be *S*. [d](*S,S*)-enantiomer of the catalyst was used. [e]Polymethylhydrosiloxane.

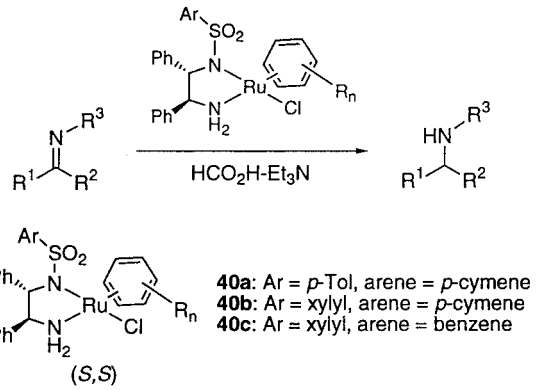
More recently, they revealed that the catalytic recycle turned more efficiently when a primary amine was added as a proton source. They used polymethylhydrosiloxane (PMHS) as a convenient and inexpensive hydride source (Table 10, entries 3 and 4, see also Scheme 10c).[48]

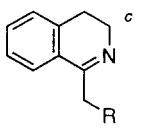
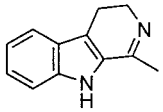
2.5 Transfer Hydrogenation of Imines with Ruthenium Catalysts

Recently, Noyori et al. made effort to develop an effective reductive amination protocol via transfer hydrogenation of imines using stable organic materials as hydride donors.[49] A variety of cyclic imines including **14** were reduced by using a formic acid-triethylamine mixture under mild conditions in the presence of 0.1−1 mol % of chiral diamine-bounded ruthenium complex **40a**−**c** (Table 11). The sense of chiral induction was determined based on the geometry of imines. Consequently, an acyclic imine such as **1** that is easy to isomerize geometrically showed lower enantioselectivity.

It was reported that imine **14** was reduced even in acetone as a solvent. This means that imines are reduced chemoselectively in the presence of ketones in this system.

Table 11. Noyori's Catalytic Enantioselective Transfer Hydrogenation



entry	substrate	catalyst/ eq.	yield/%	ee/%	cofig.
1[a]	**14**	**40a**/0.005	>99	95	*R*
2[a]	**14**	**40a**/0.001	97	94	*R*
3[b]		**40b**[d]/0.005	90	95	*S*
4[b]		**40a**/0.005	86	97	*R*
5[e]	**1**	**40c**/0.005	72	77	*S*

[a]Acetonitrile was used as a solvent. [b]Dimethylformamide was used as a solvent. [c]R= 3,4-Dimethoxyphenyl [d](*R,R*)-Catalyst was used. [e]Dichloromethane was used as a solvent.

3. Carbon–Carbon Bond-Forming Reactions of Imines

3.1 Introduction

Compared with catalytic asymmetric reductions of imines, reports on catalytic asymmetric carbon−carbon bond-forming reactions of imine are fewer.[1a,50−52] This is contrast to the recent results on catalytic enantioselective carbon−carbon bond-forming reactions of carbonyl compounds.[3−6] While rather rapid progress has been made on the enantioselective reactions of carbonyl compounds using chiral Lewis acids (aldol reactions, allylation reactions, Diels−Alder reactions, etc.),[3−6] very few examples have been reported for their aza analogues. Even in achiral reactions, only a few successful examples using small amounts of catalysts under mild conditions were reported.[53−55] The difficulty is mainly ascribed to the existence of basic nitrogen atoms, which often prevent catalytic processes. There are two typical strategies to perform these types of reactions; namely, catalytic activation of organometallic reagents with external chiral ligands (Lewis base approach)[51] and catalytic activation of imines or related compounds with chiral Lewis acids (Lewis acid approach). Historically, Lewis base approaches were investigated relatively faster than Lewis acid approaches. This demonstrates the difficulty to realize catalytic activations of imines with chiral Lewis acids, because most Lewis acids are deactivated by both imines or related compounds and products which work as Lewis bases. In these 2 or 3 years, however, new types of Lewis acids have been developed, and remarkable progress has been made. In this section, recent progresses of catalytic enantioselective carbon−carbon bond-forming reactions are discussed comparing the two different strategies.

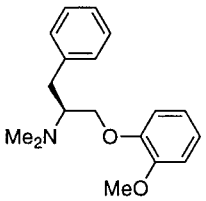
3.2 Catalytic Enantioselective Alkylation of Imines

Despite the usefulness of external ligand controlled addition of organometallic nucleophiles,[56] only a handful of reports have been known. The first report of this type of asymmetric alkylation appeared in 1990. Several examples are summarized in Table 12.

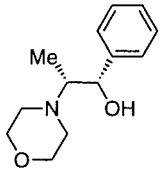
Tomioka et al. first reported stoichiometric asymmetric additions of organolithium reagents.[57] Nonenolizable imines such as those derived from aryl aldehydes and α,β-unsaturated aldehydes were successfully converted to optically active amines in high selectivities. Their catalytic version was also reported.[58a] In the presence of 50 mol % of chiral tridentate amino ether **41a**, the addition of methyllithium to *N*-benzylidene *p*-methoxyaniline (**42a**) proceeded smoothly at −43 °C in toluene to afford the corresponding *N*-*p*-methoxyphenyl phenethylamine in a 96% yield with a 62% ee (Table 12, entry 2). When 10 mol % of **41a** was used in the reaction of **42a** with MeLi, lower ee was observed (Table 12, entry 3). While imines derived from arylaldehydes or α,β-unsaturated aldehydes were employed in these reactions, no examples of imines derived from aliphatic aldehydes were reported. Since achiral reactions of noncomplexed methyllithium undergo competitively under the reaction conditions, the enantioselectivities in their first trial are low to moderate even in stoichiometric reactions. They demonstrated

Table 12. Enantioselective Alkylations of Imines

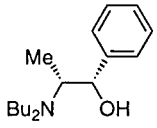
entry	aldimine	alkylmetal	ligand/eq.	temp./°C	yield/%	ee/%	config.	ref.
1	**42a**	MeLi	**41a** / 2.6	-42	95	66	*R*	58a
2	**42a**	MeLi	**41a** / 0.5	-42	96	62	*R*	58a
3	**42a**	MeLi	**41a** / 0.1	-42	90	47	*R*	58a
4	**42b**	MeLi	**41a** / 2.6	-100	97	90	*R*	58b
5	**43**	Et_2Zn	**41b** / 1.0	0	89	90	*S*	59
6	**43**	Et_2Zn	**41b** / 0.5	0	69	85	*S*	59
7	**43**	Et_2Zn	**41c** / 0.1	0	12	75	*S*	59



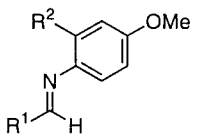
41a



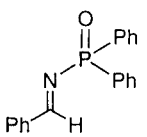
41b



41c

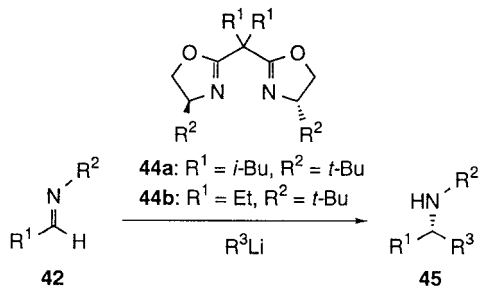


42a: R^1 = Ph, R^2 = H
42b: R^1 = Ph, R^2 = Me
42c: R^1 = $Ph(CH_2)_2$, R^2 = H



43

Table 13. Denmark's Enantioselective Alkylations of Imines



entry	imine	R^3	ligand/eq.	yield/%	ee/%[a]
1	**42a**	Me	**44a**/1.0	95	85
2	**42a**	Me	**44b**/0.1	98	68
3	**42c**	Me	**44b**/0.2	81	82
4	**42c**	CH_2=CH	**44b**/0.2	82	82[b]

[a]The absolute configuration of the adduct was determined to be *R*. [b]The absolute configuration was not determined.

that the enantioselectivity was improved to 90% by using sterically more influencable imine such as **42b** in the presence of 2.6 equiv of **41a** (Table 6, entry 4).[58b]

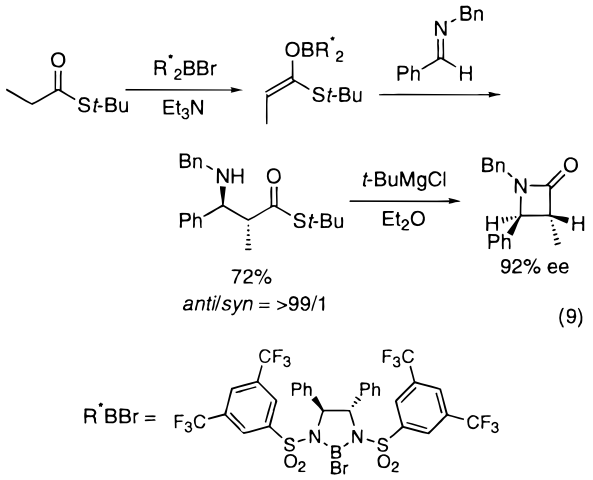
Soai et al. investigated enantioselective alkylations using dialkylzinc reagents.[59a] They used *N*-diphenylphosphinyl imines as electrophiles, and under the influence of an equimolar amount of a chiral amino alcohol such as **41b** or **41c**,[59] diethylzinc reacted with imine **43** to afford the corresponding amide derivative in a high yield with a high enantioselectivity (Table 12, entry 5). The catalytic reactions were also investigated. Namely, when 50 mol % of chiral ligand **41b** was used, the enantioselectivity was still high, but in the case using 10 mol % ligand **41c**, the enantioselectivity was further decreased and the chemical yield was only 12% (Table 12, entries 6 and 7).

While the two groups' methods still suffered from limitation of substrates, Denmark's method seems to be more promising.[60] They first searched reaction conditions under which the reaction of MeLi with an imine proceeded sluggishly in the absence of an external ligand. Consequently, they found that at −78 °C, a toluene solution of MeLi reacted with **42a** to afford the corresponding amine in only 6% yield after 4 h. On the other hand, in the presence of a stoichiometric amount of chiral bis-oxazolidine ligand **44**, an enantiomerically enriched phenethylamine derivative was obtained by addition of MeLi to imine **42a** in a 95% yield with an 85% ee. When a catalytic amount of the ligand (10 mol %) was used in this reaction, the corresponding amine was obtained in a 68% ee. It was gratifying that an enolizable imine such as **42c** was also employed in this reaction. In the presence of 20 mol % of bis-oxazolidine ligand **44b**, imine **42c** was methylated at −63 °C in an 81% yield with an 82% ee (Table 13).

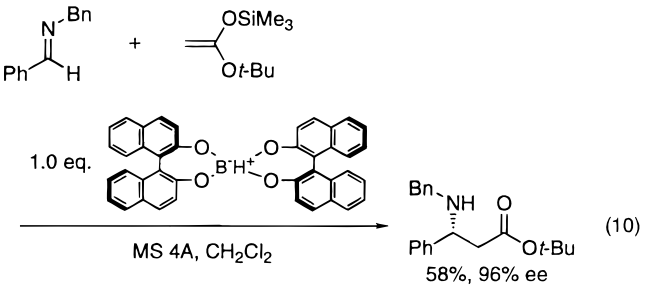
Quite recently, two independent groups investigated enantioselective alkylatyion of imines in the presence of external chiral ligands.[61] In both cases, enantioselectivities were modelate to good when using catalytic amounts of the chiral ligands.

3.3 Catalytic Enantioselective Mannich-Type Reactions

Asymmetric Mannich-type reactions provide useful routes for the synthesis of optically active β-amino ketones or esters, which are versatile chiral building blocks in the preparation of many nitrogen-containing biologically important compounds.[1a,62] While several diastereoselective Mannich-type reactions have already been reported,[63] very little is known about the enantioselective versions. In 1991, Corey et al. reported the first example of the enantioselective synthesis of β-amino acid esters using chiral boron enolates (eq 9).[64] Yamamoto et al. reported enantio-

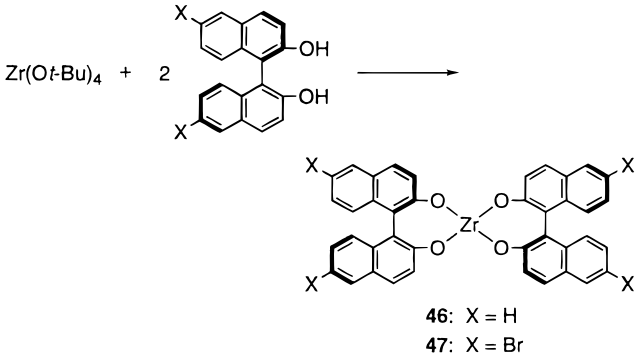


selective reactions of imines with a ketene silyl acetal using a stoichiometric amount of a Brønsted acid-assisted chiral Lewis acid (eq 10).[65] However, in all cases stoichiometric amounts of chiral sources were needed. Asymmetric Mannich-type reactions using small amounts of chiral sources have not been reported before 1997, as far as we know.



In 1997, we reported the first truly catalytic enantioselective Mannich-type reactions of imines with silyl enolates using a novel zirconium catalyst.[66] Our approach is based on chiral Lewis acid-catalyzed reactions (Lewis acid approach). Although asymmetric reactions using chiral Lewis acids are of great current interest as one of the most efficient methods for the preparation of chiral compounds,[2] examples using imines as electrophiles are rare as mentioned previously. We thought that this was due to two main difficulties. First, many Lewis acids are deactivated

Scheme 13. Preparation of Chiral Zirconium Catalyst

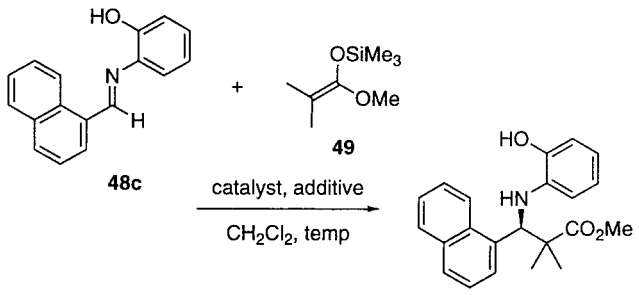


or sometimes decomposed by the nitrogen atoms of starting materials or products, and even when the desired reactions proceed, more than stoichiometric amounts of the Lewis acids are needed because the acids are trapped by the nitrogen atoms. Second, imine−chiral Lewis acid complexes are rather flexible and often have several stable conformers (including *E*/*Z*-isomers of imines),[10] while aldehyde−chiral Lewis acid complexes are believed to be rigid. Therefore, in the additions to imines activated by chiral Lewis acids, plural transition states would exist to decrease selectivities. To solve these problems, various metal salts were first screened in the achiral reactions of imines with silylated nucleophiles. After careful investigation of the catalytic ability of the salts, unique characteristics in zirconium(IV) (Zr(IV)) were found and it was decided to design a chiral Lewis acid based on Zr(IV) as a center metal.[67,68] On the other hand, as for the problem of the conformation of the imine−Lewis acid complex, utilization of a bidentate chelation was planned (see below).

A chiral zirconium catalyst was prepared in situ according to Scheme 13.[69] In the presence of 20 mol % of catalyst **46**, imine **48c** prepared from 1-naphthaldehyde and 2-aminophenol was treated with the ketene silyl acetal derived from methyl isobutylate (**49**) in dichloromethane at −15 °C. The reaction proceeded smoothly to afford the corresponding adduct in a quantitative yield, and the enantiomeric excess of the product was 34% (Table 14). The ee was improved to 70% when *N*-methylimidazole (NMI) was used as an additive. Moreover, the ee was further improved when catalyst **47** was used,[70] and the desired adduct was obtained in a 95% ee when the reaction was carried out at −45 °C. When the imine prepared from aniline or 2-methoxyaniline was used under the same reaction conditions, the corresponding *β*-amino esters were obtained in good yields but with less than 5% ees. It should be noted that the same high level of ee was obtained when 2 mol % of the catalyst was employed (Table 14).

Other examples are shown in Table 15. Not only imines derived from aromatic aldehydes but also imines from heterocyclic aldehydes worked well in this reaction, and good to high yields and enantiomeric excesses were obtained. As for aliphatic aldehydes, while lower selectivities were obtained by using the imines prepared from the aldehydes and 2-aminophenol, high ee was obtained by using the imine which was prepared from the aldehydes and 2-amino-3-methylphenol. Similar high levels of ees were also obtained when the silyl enol ether derived from *S*-ethyl thioacetate (**50**) was used.

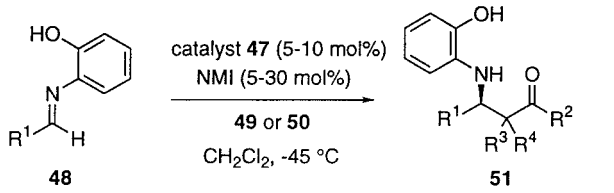
Table 14. Catalytic Enantioselective Mannich-Type Reactions (1)

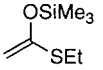
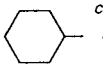


entry	catalyst (mol%)	additive (mol%)	temp/°C	yield/%	ee/%
1	**46** (20)	—	-15	quant.	34
2	**46** (20)	NMI (20)	-15	80	70
3	**47** (20)	NMI (20)	-15	73	90
4	**47** (20)	NMI (20)	-45	83	95
5	**47** (10)	NMI (10)	-45	quant.	92
6	**47** (5)	NMI (5)	-45	69	95
7	**47** (5)	DMI (5)	-15	quant.	91
8	**47** (2)	NMI (2)	-45	75	86

NMI: *N*-Methylimidazole; DMI: 1,2-Dimethylimidazole

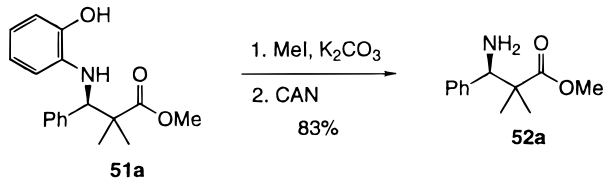
Table 15. Catalytic Enantioselective Mannich-Type Reactions (2)



entry	Imine; R^1	silyl enolate	yield/%[a]	ee/%[b]
1	Ph (**48a**)	**49**	70 (**51a**)	87
2	*p*-Cl-Ph (**48b**)	**49**	86	83
3	1-Nap (**48c**)	**49**	quant.	92
4	Ph (**48a**)	 **50**	78	88
5	*p*-Cl-Ph (**48b**)	**50**	88	86
6	1-Nap (**48c**)	**50**	quant.	>98
7	 (**48d**)	**50**	89	89
8	 (**48e**)[c]	**50**	45	80

[a]Isolated yields after acidic work-up. [b]Determined by HPLC analyses. [c]The aldimine prepared from cyclohexanecarboxaldehyde and 2-amino-3-methylphenol was used. When the reaction was carried out at -23 °C, 71% yield and 71% ee were obtained.

Scheme 14. Removal of the *N*-(2-Hydroxyphenyl) Group



51a **52a**

The *N*-substituent of the product was easily removed according to Scheme 14. Thus, methylation of the phenolic OH of **51a** using methyl iodide and potassium bicarbonate and deprotection using cerium ammonium nitrate (CAN)[71] gave *β*-amino ester **52a**. The absolute configuration assignment was made by comparison of the optical rotation of **52a** with that in the literature.[72]

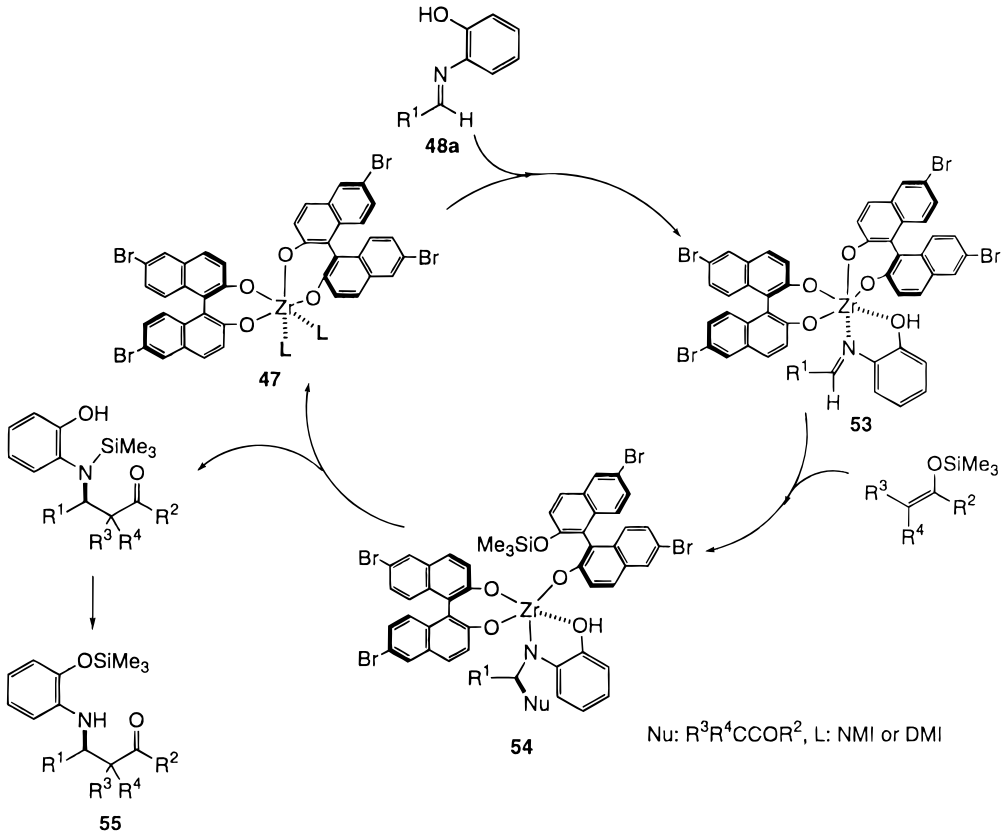
The assumed catalytic cycle of this enantioselective reaction is shown in Scheme 15. Catalyst **47** coordinates imine **48a** to form zirconium complex **53**. A silyl enolate attacks the imine to produce **54**, whose trimethylsilylated oxygen atom attacks the zirconium center to afford the product along with the regeneration of catalyst **47**. The product was obtained as a trimethylsilylated form (**55**) without the acidic work up.

The precise role of NMI or 1,2-dimethylimidazole (DMI) is not yet clear. White precipitates were observed after combining $Zr(O\text{-}t\text{-}Bu)_4$ and 6,6′-dibromo-1,1′-bi-2-naphthol in dichloromethane, and the precipitates dissolved completely when NMI or DMI was added. From these observations, it was assumed that a monomeric catalyst would be produced by adding NMI or DMI, while an oligomeric structure would be formed without the ligand. It was also found that the catalyst was obtained as a white powder after removal of the solvent. The powder did not contain *t*-BuOH and was effective in the asymmetric Mannich-type reactions.

The present Mannich-type reactions were then applied to the synthesis of chiral *β*-amino alcohols.[73] *β*-Amino alcohol units are often observed in biologically interesting compounds,[74] and several methods for the synthesis of these units have been developed. Among them, catalytic asymmetric processes are the most effective and promising. Asymmetric ring opening of symmetric epoxides by nitrogen nucleophiles in the presence of a chiral Lewis acid catalyst[75] and ring opening of chiral epoxides or aziridines which are prepared by catalytic asymmetric reactions are useful methods.[76] Recent progress has been made by Sharpless et al. to introduce direct asymmetric aminohydroxylation (AA) of alkenes.[77] Sharpless's AA method has realized a high degree of enantioselectivities to afford syn-*β*-amino alcohols directly. An alternative approach for the synthesis of chiral *β*-amino alcohols using catalytic diastereo- and enantioselective Mannich-type reactions of α-alkoxy enolates with imines has been developed (Scheme 16).[78,79]

The reaction of imine **48a** with α-TBSO-ketene silyl acetal **56a** using 10 mol % of zirconium catalyst **47**, which was prepared from $Zr(O\text{-}t\text{-}Bu)_4$, 2 equiv of (*R*)-6,6′-dibromo-1,1′-bi-2-naphthol, and NMI, proceeded smoothly to afford the corresponding α-alkoxy-*β*-amino ester **57a**+**58a** in a 76% yield with moderate syn-selectivity. The enantiomeric excess of the syn-adduct **57a** was proven to be less than 10% (Table 16, entry 1). Various reaction conditions were then

Scheme 15. Assumed Catalytic Cycle of the Mannich-Type Reaction



Scheme 16. Syntheses of syn- and anti-β-Amino Alcohols

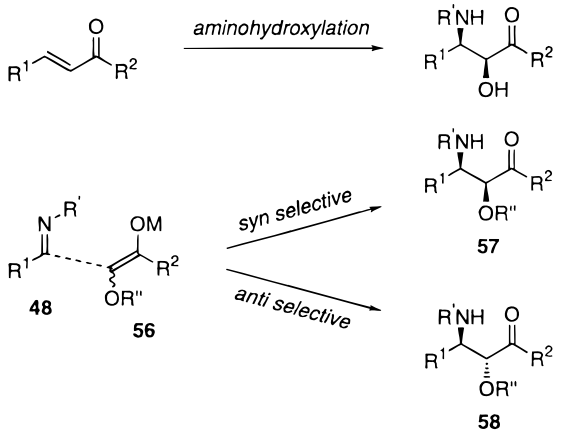
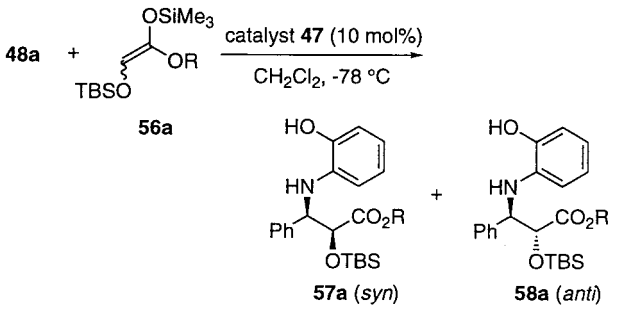
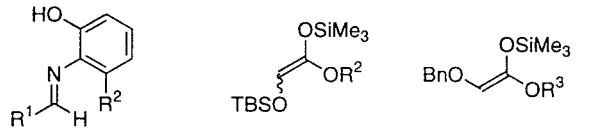


Table 16. Stereoselective Synthesis of β-Amino Alcohols via Mannich-Type Reactions



entry	enolate	yield/%	*syn*(57a)/*anti*(58a)	ee/% (57a)
1[a,b]	**56a**[d]	76	66/34	6
2[b]	**56a**[d]	62	90/10	63
3	**56a**[d]	90	94/ 6	82
4	**56b(E)**[e]	90	91/ 9	89
5[c]	**56b(E)**[e]	quant.	96/ 4	95
6[c]	**56b(Z)**[f]	65	>99/ 1	96

[a]NMI (12 mol%) was used. [b]The reaction was carried out at -45 °C. [c]Toluene was used as a solvent. [d]E/Z = 93/7. [e]E/Z = 87/13. [f]E/Z = 1/99.



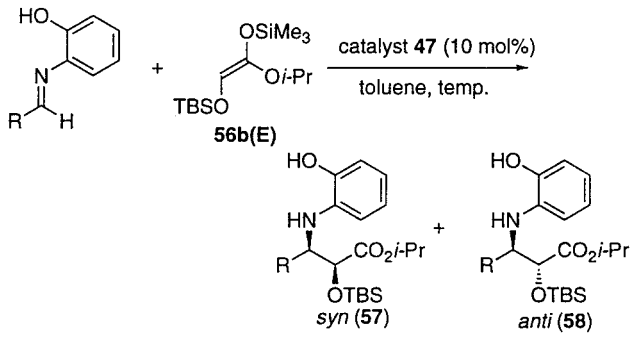
48a: R^1 = Ph, R^2 = H
48b: R^1 = *p*-Cl-Ph, R^2 = H
48c: R^1 = 1-Nap, R^2 = H
48d: R^1 = 2-Furyl, R^2 = H
48e: R^1 = *c*-C_6H_{11}, R^2 = Me
48f: R^1 = *c*-C_6H_{11}, R^2 = H

56a: R^2 = Me
56b: R^2 = *i*-Pr

56c: R^3 = *i*-Pr
56d: R^3 = *p*-MeO-Ph
56e: R^3 = *c*-C_6H_{11}

screened, and it was found that when DMI was used instead of NMI, the selectivity increased dramatically (Table 16, entry 2). Moreover, the diastereo- and enantioselectivities were improved when the reaction was carried out at −78 °C (Table 16, entry 3). The O-substituents of ketene silyl acetals and solvents also influenced the yield and selectivity, and finally

Table 17. Enantioselective Synthesis of syn-β-Amino Alcohols



entry	aldimine	temp./°C	yield/%	*syn*/*anti*	ee/% (57)
1	**48a**	-78	quant	96/ 4	95
2	**48b**[a]	-78	73	92/ 8	98
3	**48c**	-78	65	>99/ 1	91
4	**48d**	-45	68	82/18	92

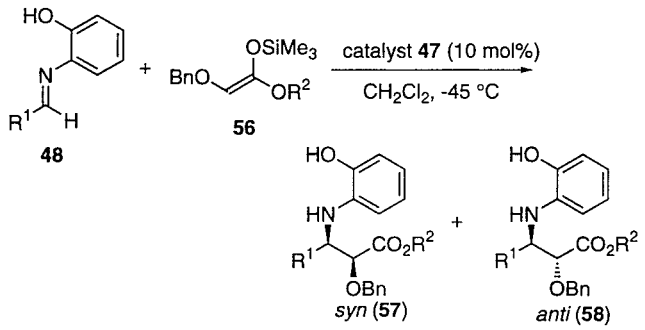
[a]Dichloromethane was used as a solvent, and 30 mol% of DMI was added.

the best result (quantitative, syn/anti = 96/4, syn = 95% ee) was obtained when the reaction was carried out in toluene using ketene silyl acetal **56b(E)** (Table 16, entry 5). It was also interesting from a mechanistic point of view that geometrically isomeric ketene silyl acetal **56b(Z)** gave excellent diastereo- and enantioselectivities (Table 16, entry 6). Other substrates were tested, and the results are shown in Table 17. In all cases, the desired adducts including syn-β-amino alcohol units **57** were obtained in high diastereo- and enantioselectivities.

On the other hand, it was found that anti-β-amino alcohol derivatives **58** were obtained by the reaction of imine **48a** with α-BnO-ketene silyl acetal **56c** under the almost same reaction conditions. Namely, in the presence of 10 mol % of the above catalyst, imine **48a** reacted with **56c** smoothly to give the corresponding adduct (**57c**+**58c**) quantitatively with anti preference, and the enantiomeric excess of the anti-adduct **58c** was 95%. It was exciting that both syn- and anti-amino alcohol units were prepared by choosing the protective groups of the α-alkoxy parts of the silyl enolates. Several imines were then tested (Table 18). In most cases, the desired anti-adducts were obtained in high yields with high diastereo- and enantioselectivities. While higher diastereoselectivities were obtained using a ketene silyl acetal derived from a *p*-methoxyphenyl (PMP) ester, higher enantiomeric excesses were observed in the reactions using a ketene silyl acetal derived from isopropyl or cyclohexyl ester. In the reaction of the imine derived from cyclohexanecarboxaldehyde, use of 2-amino-3-methyl phenol instead of 2-aminophenol was effective in affording the corresponding *anti*-adduct in high selectivities.

These reactions provide an efficient method for the synthesis of both syn- and anti-amino alcohol units with high yields and high selectivities. The protocol

Table 18. Enantioselective Synthesis of anti-β-Amino Alcohols



entry	aldimine	silyl enolate	yield/%	*syn*/*anti*	ee/% (**58**)
1	**48a**[a]	*i*-Pr (**56c**)[e]	quant.	32/68	95
2	**48a**[b]	*p*-MeO-Ph (**56d**)[f]	91	6/94	80
3	**48c**[c]	*c*-C_6H_{11} (**56e**)[e]	80	8/92	96
4	**48d**[b]	**56d**[f]	68	13/87	80
5	**48b**[a,c]	**56c**[e]	quant.	43/57	91
6	**48b**[b]	**56d**[f]	72	8/92	76
7	**48e**[d]	**56e**[e]	41	18/82	92

[a]DMI (30 mol%) was used. [b]NMI (20 mol%) was used. [c]The reaction was carried out at -78 °C. [d]The imine was prepared from cyclohexanecarboxaldehyde with 2-amino-3-methylphenol *in situ* in the presence of MS 4A. [e]E/Z = <1/>99. [f]E/Z = 4/96.

includes catalytic diastereo- and enantioselective carbon−carbon bond-forming processes, and the syn- and anti-selectivities were controlled by choosing the protective groups of the α-alkoxy parts and of the ester parts of the silyl enolates. Since both enantiomers of the chiral source, (*R*)- and (*S*)-6,6′-dibromo-1,1′-bi-2-naphthol, are commercially available, all four stereoisomers of β-amino alcohol units can be prepared according to this method.

The utility of this protocol has been demonstrated by the concise synthesis of (*2R*,*3S*)-3-phenylisoserine·hydrochloride (**59**), which is a precursor of the C-13 side chain of paclitaxel, known to be essential for its biological activity.[80] The catalytic asymmetric Mannich-type reaction of imine **48a** with ketene silyl acetal **56b(E)** using the chiral zirconium catalyst prepared using (*S*)-6,6′-dibromo-1,1′-bi-2-naphthol proceeded smoothly in toluene at −78 °C to afford the corresponding syn-adduct **57a** quantitatively in excellent diastereo- and enantioselectivities (syn/anti = 95/5, syn = 94% ee). Methylation (MeI, K_2CO_3) of the phenolic OH of the adduct (**57a**) and deprotection using cerium ammonium nitrate (CAN) gave β-amino ester **60**. Hydrolysis of the ester and deprotection of the *tert*-butyldimethylsilyl (TBS) group were performed using 10% HCl to afford **59** quantitatively (Scheme 17).[81]

Tomioka et al. also reported catalytic asymmetric Mannich-type reactions of lithium enolates with imines in 1997.[82] Their method is based on an external chiral ligand accelerated reaction (Lewis-base approach). In their report, stoichiometric reac-

Scheme 17. Synthesis of Phenylisoserine·hydrochloride

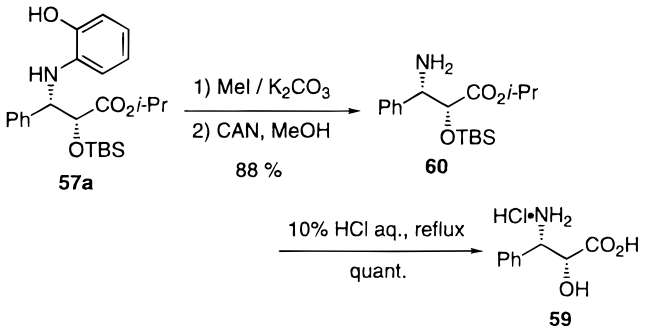
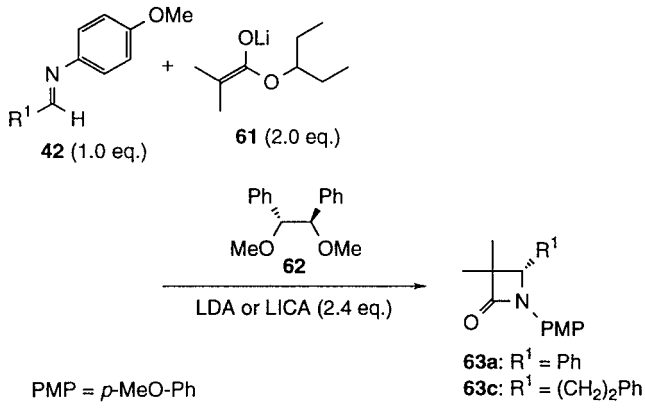


Table 19. Tomioka's Enantioselective Mannich-Type Reactions



entry	**62**/eq.	imine[a]	nucleophile	yield/%	ee/%
1	2.6	**42a**	**61** (2.0 eq) + LICA (2.2 eq)	85	88
2	2.6	**42c**	**61** (2.0 eq) + LDA (2.2 eq)	80	90
3	0.2	**42a**	**61** (2.0 eq) + LICA (2.4 eq)	80	75
4	0.2	**42c**	**61**[b] (2.0 eq) + LDA (4.4 eq)	75	82

[a]See Table 12. [b]The corresponding ester was used. The lithium enolate was prepared *in situ*.

tions were mainly mentioned and a few catalytic processes were introduced. First, it was found that the reactions of lithium enolates with imines were accelerated by addition of external chiral ligands. They also revealed that the reactions were accelerated in most cases in the coexistence of excess amounts of lithium amides. Actually, the reaction of lithium ester enolate **61** with imine **42a** did not take place at −20 °C. On the other hand, in the presence of excess of lithium amide (lithium cyclohexylisopropyl amide (LICA)) and a stoichiometric amount of chiral bidentate ether **62**, the reaction took place very smoothly at −60 °C to afford the corresponding β-lactam **63a** in 85% yield with 88% ee. They also investigated the asymmetric version using a small amount of a chiral source, and two examples were reported (Table 19). When the reaction of imine **42a** with **61** was performed in the presence of 20 mol % of **62** and an excess of LICA, the corresponding **63a** was obtained in 80% yield with 75% ee. The reaction of imine **42c** with in situ prepared lithium enolate

Scheme 18. Catalytic Enantioselective Mannich-Type Reactions of α-Imino Esters

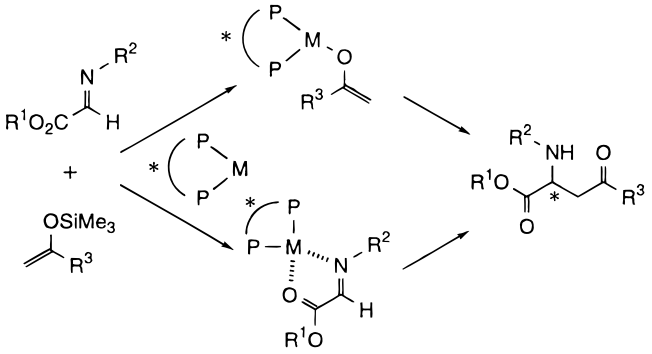
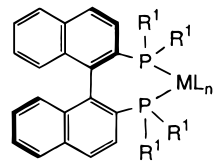
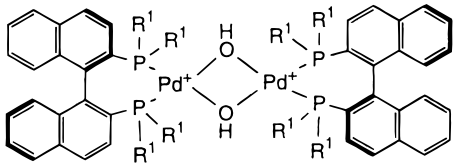


Chart 2



64a: $ML_n = Pd(OH_2)_2$, R^1 = Ph
64b: $ML_n = AgSbF_6$, R^1 = Ph
64c: $ML_n = Pd(ClO_4)_2$, R^1 = Ph
64d: $ML_n = CuClO_4$, R^1 = *p*-Tol



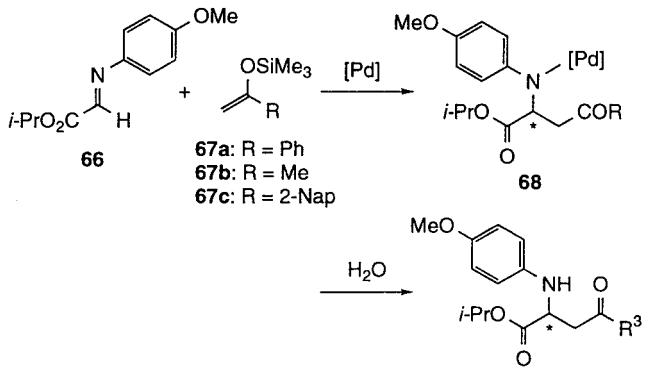
65: R^1 = Ph

61, an example of aliphatic imines, was also demonstrated to afford the corresponding lactam **63c** in 75% yield with 82% ee. In both cases, although reasonable level of enantioselectivities were attained, the selectivities were decreased by reducing the amounts of the chiral source.

Quite recently, very similar and comparable two results were reported by Sodeoka[83] and Lectka.[84] Although both groups used chiral late transition metal−phosphine complexes as catalysts, Sodeoka proposed that their reactions underwent via chiral palladium enolates, while Lectka proposed that their catalyst behaved as a Lewis−acid catalyst (Scheme 18).

Sodeoka et al. first tried to use Pd(II) diaquo complex **64a** (Chart 2), which was effective for catalytic asymmetric aldol reactions,[85] but the attempts at catalytic asymmetric Mannich-type reactions were failed. After careful examination of reaction conditions, they finally found that a new type of Pd(II) binuclear complex **65**[86] was quite effective for condensation of imine **66** derived from glyoxylate and anisidine with silyl enol ether **67**. The results are shown in Table 20.[83] The desired γ-oxo-α-amino acid derivative (**69a**) was obtained in 95% with 90% ee. In the reaction of **66** with acetone silyl enolate, both chemical yield and selectivity slightly decreased. The products in these reactions (alanine derivatives) are known as potent inhibitors of kynurenine 3-hydroxylase and kynureninase and expected to be potential

Table 20. Sodeoka's Catalytic Enantioselective Mannich-Type Reactions



66
67a: R = Ph
67b: R = Me
67c: R = 2-Nap
68
69a: R = Ph
69b: R = Me
69c: R = 2-Nap

entry	[Pd]/eq.	silyl enolate	solvent	yield/%	ee/%
1	**64a**/0.1	**67a**	DMF	60	0
2	**65**/0.05	**67a**	DMF	95	90
3	**65**/0.03	**67a**	CH_2Cl_2	45	53
4	**65**/0.05	**67b**	DMF	79	53
5	**65**/0.05	**67c**	DMF	82	83

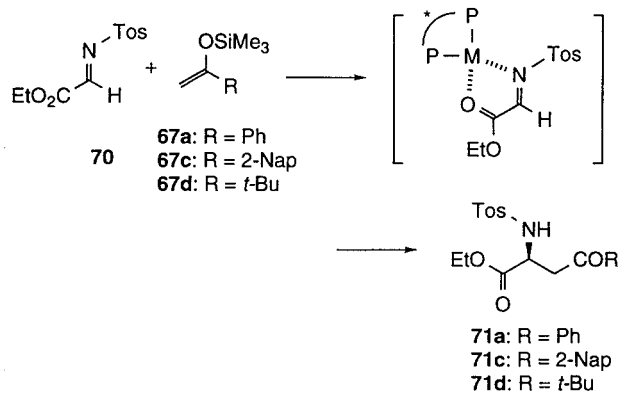
drugs for the treatment of neurodegenerative disorders that function by controlling the concentration of quinolonic acid in the brain.[87,88]

It was shown that water played an important role in Sodeoka's system. Namely, water activated the Pd(II) complex to generate a cation complex, and also cleaved N−Pd bond of **68** to regenerate the chiral catalyst. In these reactions, use of solvents including a small amount of water was essential.

Lectka et al. used some water-free late transition metal−phosphine cation complexes as Lewis acids, and glyoxylate−tosylamine imine **70** reacted with silyl enol ethers steroselectively.[84] They proposed that **70** coordinated to the metal center such as Ag(I) (**64b**), Pd(II) (**64c**), and Cu(I) (**64d**) in a bidentate manner. The copper-based catalyst (**64d**) was the most effective, and the desired product **71** was obtained in high yields with high enantioselectivities (Table 21). Although reaction systems and results of these two groups are very close, it should be noted that different types of solvents are used in these reactions.

Quite recently, acylhydrazones were successfully used in catalytic enantioselective Mannich-type reactions. While acylhydrazones are imine equivalents, they have some advantages over imines; for example, most acylhydrazones including those derived from aromatic, α,β-unsaturated, and even aliphatic aldehydes are stable crystals, easy to handle at room temperature. In the presence of a catalytic amount of a new zirconium catalyst, prepared from Zr(O-*t*-Bu)$_4$ and (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol (3-Br−BINOL),[89] 4-(trifluoromethyl)benzoylhydrazones reacted with silyl enolates to afford the corresponding

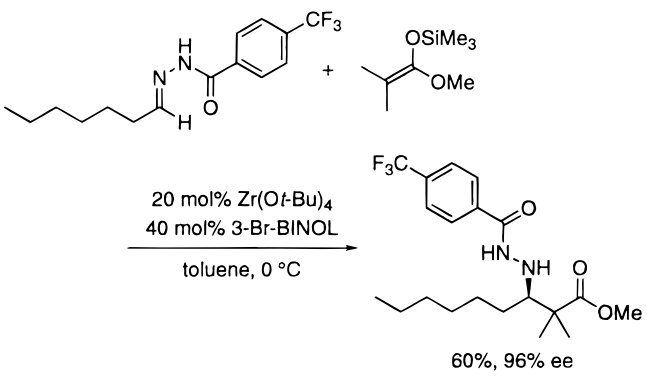
Table 21. Lectka's Catalytic Enantioselective Mannich-Type Reactions



entry	catalyst/eq.	silyl enolate	solvent	yield/%	ee/%
1	**64b**/0.1	**67a**	THF	95	90
2	**64c**/0.1	**67a**	CH_2Cl_2	91	80
3	**64d**/0.05	**67a**	THF	91	98
4	**64d**/0.019	**67a**	THF	92	96
5	**64d**/0.05	**67c**	THF	91	92
6	**64d**/0.05	**67d**	THF	65	90

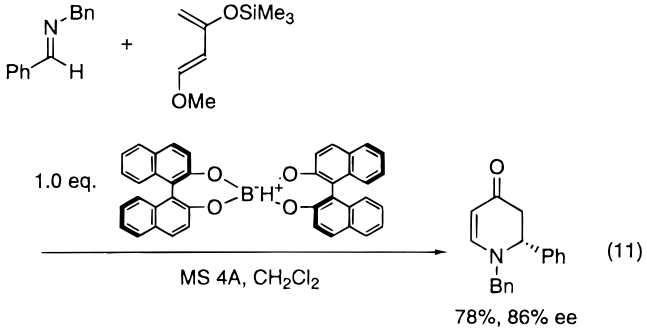
adducts, β-*N*′-acylhydrazinocarbonyl compounds, in good yields with high enantiomeric excesses (Scheme 19).[90] Reductive cleavage of the nitrogen−nitrogen bond of the hydrazino compound using samarium diiodide gave a chiral β-aminocarbonyl compound. In addition, the hydrazino compound was also successfully converted to chiral β-lactam and pyrazolidinone derivatives.

Scheme 19. A New Asymmetric Mannich-Type Reaction Using a Hydrazone Derivative



3.4 Catalytic Enantioselective Aza Diels–Alder Reactions

Asymmetric aza Diels−Alder reactions provide a useful route to optically active nitrogen-containing heterocyclic compounds such as piperidines and tetrahydroquinolines.[50,91] Although successful examples of diastereoselective approaches using chiral auxiliaries have been reported,[92] there have been few reports on enantioselective reactions. Yamamoto et al. reported elegant enantioselective aza Diels−Alder reactions of imines with Danishefsky's diene using chiral boron compounds (eq 11), however, stoichiometric amounts of chiral sources were needed.[65,93] On



the other hand, it was shown that lanthanide triflates are excellent catalysts for achiral aza Diels−Alder reactions.[68a,94] While stoichiometric amounts of Lewis acids are required in many cases, a small amount of the triflate effectively catalyzes the reactions. On the basis of these findings, chiral lanthanides were used in catalytic asymmetric aza Diels−Alder reactions.[95] Chiral lanthanide Lewis acids were first developed to realize highly enantioselective Diels−Alder reactions of 2-oxazolidin-1-one with dienes.[96a−c,e]

The reaction of *N*-benzylideneaniline with cyclopentadiene was performed under the influence of 20 mol % of a chiral ytterbium Lewis acid prepared from ytterbium triflate ($Yb(OTf)_3$),[97] (*R*)-1,1′-bi-naphthol (BINOL), and trimethylpiperidine (TMP). The reaction proceeded smoothly at room temperature to afford the desired tetrahydroquinoline derivative in 53% yield; however, no chiral induction was observed. At this stage, it was indicated that bidentate coordination between a substrate and a chiral Lewis acid would be necessary for reasonable chiral induction. Then, the reaction of *N*-benzylidene-2-hydroxyaniline (**48a**) with cyclopentadiene (**73**) was examined. It was found that the reaction proceeded smoothly to afford the corresponding 8-hydroxyquinoline derivative (**74a**)[7] in a high yield (Scheme 20). It is noted that some

Scheme 20. Catalytic Enantioselective Aza Diels−Alder Reaction (1)

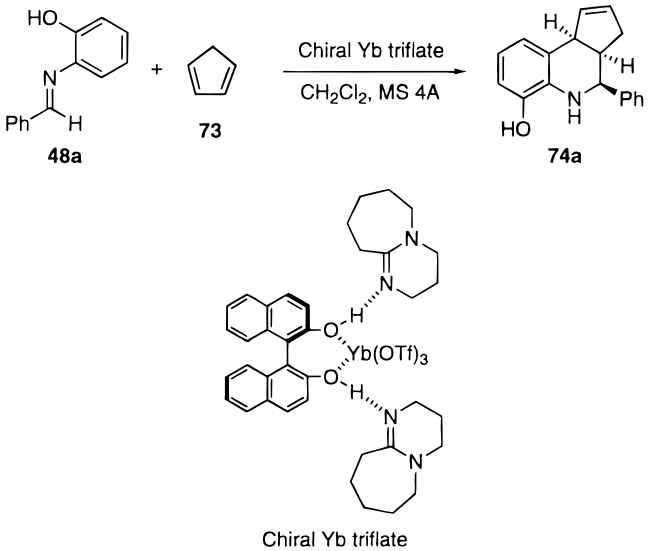
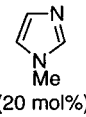
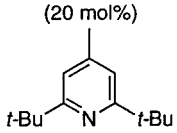


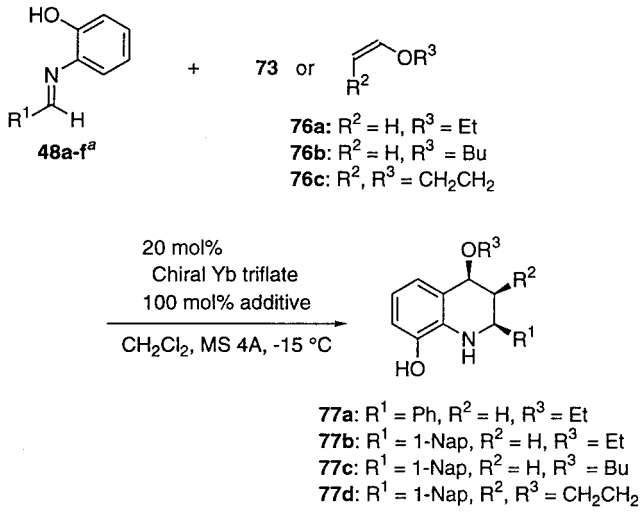
Table 22. Effect of Additives in Asymmetric Aza Diels-Alder Reaction

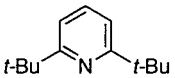
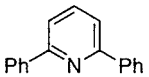
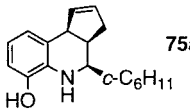
entry	additive	temp./°C	yield/%	*cis*/*trans*	ee/% (*cis*)
1	—	0	71	98/2	62
2	—	-15 to 0	48	99/1	68
3	 (20 mol%)	-15 to 0	21	98/2	91
4	 **75a** (100 mol%)	-15	92	>99/1	71

interesting biological activities were reported in 8-hydroxyquinoline derivatives.[98] The enantiomeric excess of the cis-adduct in the first trial was only 6%; however, the selectivity increased when diazabicyclo-[5.4.0]undec-7-ene (DBU) was used instead of TMP (Table 22). It was also indicated that the phenolic hydrogen of **48a** would interact with DBU, which should interact with the hydrogen of (*R*)-BINOL,[96d] to decrease the selectivity. Additives which interact with the phenolic hydrogen of **48a** were then examined. When 20 mol % of NMI was used, 91% ee of the cis adduct was obtained, but the chemical yield was low. It was found that the desired tetrahydroquinoline derivative was obtained in a 92% yield with high selectivities (cis/trans = >99/1, 71% ee), when 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, **75a**) was used.

Other substrates were tested, and the results are summarized in Table 23. Vinyl ethers (**76a**−**c**) also worked well to afford the corresponding tetrahydroquinoline derivatives (**77a**−**c**) in good to high yields with good to excellent diastereo- and enantioselectivities (Table 23, entries 1−9). Use of 10 mol % of the chiral catalyst also gave the adduct in high yields and selectivities (Table 23, entries 2 and 6). As for additives, 2,6-di-*tert*-butylpyridine (DTBP, **75b**) gave the best result in the reaction of **48a** with ethyl vinyl ether (**76a**), while higher selectivities were obtained when DTBMP (**75a**) or 2,6-diphenylpyridine (DPP, **75c**) was used in the reaction of **48c** with **76a**. This could be explained by the slight difference in the asymmetric environment created by $Yb(OTf)_3$, (*R*)-BINOL, DBU, and the additive. While use of butyl vinyl ether (**76b**) decreased the selectivities (Table 23, entry 7), dihydrofurane (**76c**) reacted smoothly to achieve high levels of selectivity (Table 23, entries 8 and 9). It was found that imine **48f** prepared from cyclohexanecarboxaldehyde and 2-hydroxyaniline was unstable and difficult to purify. The asymmetric aza Diels−Alder reaction was successfully carried out using the three-component coupling procedure (successively adding the aldehyde, the amine, and cyclopentadiene) in the presence of $Sc(OTf)_3$[96e,97a] (instead of $Yb(OTf)_3$), (*R*)-BINOL, DBU, and DTBMP (**75a**) (Table 23, entry 10).

Table 23. Catalytic Enantioselective Aza Diels−Alder Reactions Using Azadienes



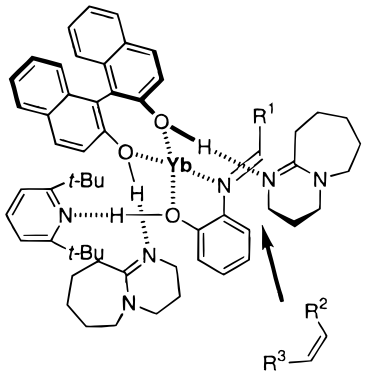
entry	product	additive	yield/%	*cis*/*trans*	ee/% (*cis*)
1[b]	**77a**	 **75b**	58	94/6	61
2[b,c]	**77a**	**75b**	52	94/6	77
3	**77b**	**75b**	69	>99/<1	86
4	**77b**	 **75c**	65	99/1	91
5	**77b**	**75a**	74	>99/<1	91
6[c]	**77b**	**75a**	62	98/2	82
7	**77c**	**75a**	80	66/34	70
8	**77d**	**75a**	90	91/9	78
9	**77d**	**75c**	67	93/7	86
10[d]		**75a**	58	>99/<1	73

[a]See Table 16. [b]The reaction was carried out at -45 °C. [c]Ten mol% of the chiral Yb triflate was used. [d]Chiral Sc catalyst was used.

The assumed transition state of this reaction is shown in Scheme 21. $Yb(OTf)_3$, (*R*)-(+)-BINOL, and DBU form a complex with two hydrogen bonds, and the axial chirality of (*R*)-(+)-BINOL is transferred via the hydrogen bonds to the amine parts. The additive would interact with the phenolic hydrogen of the imine, which is fixed by bidentate coordination to Yb(III). Since the top face of the imine is shielded by the amine, the dienophiles approach from the bottom face to achieve high levels of selectivity.

Characteristic points of this reaction are as follows: (i) Asymmetric aza Diels−Alder reactions between achiral azadienes and dienophiles have been achieved using a catalytic amount of a chiral source. (ii) The unique reaction pathway in which the chiral

Scheme 21. Assumed Transition State[a]



[a] Triflate anions are omitted for clarification

Lewis acid activates not dienophiles but dienes, is revealed. In most asymmetric Diels–Alder reactions reported using chiral Lewis acids, the Lewis acids activate dienophiles.[1,11] (iii) A unique lanthanide complex including an azadiene and an additive, which is quite different from the conventional chiral Lewis acids, has been developed.

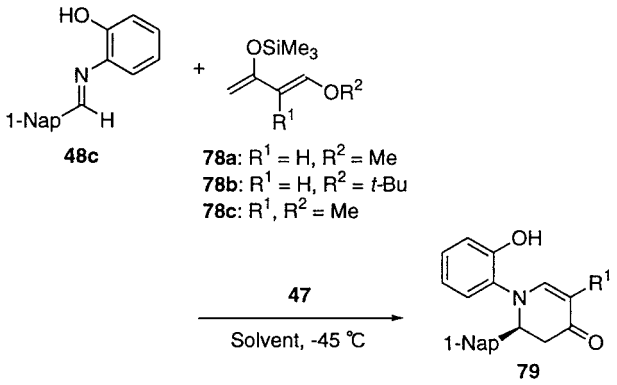
While the above results have demonstrated the catalytic enantioselective aza Diels–Alder reactions of azadienes, the catalytic enantioselective aza Diels–Alder reactions of azadienophiles were reported using a chiral zirconium compound.[99]

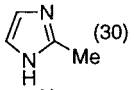
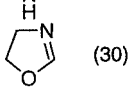
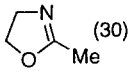
Chiral zirconium compound **47**[66,73] was prepared from Zr(O-*t*-Bu)$_4$, 2 equiv of (*R*)-6,6′-bromo-1,1′-binaphthol ((*R*)-Br–BINOL), and 2–3 equiv of a ligand, and the model reaction of the imine **48c** with Danishefsky's diene (**78a**) was investigated. It was found that ligands and solvents influenced the yields and enantioselectivities strongly (Table 24). The importance of the free hydroxyl group of the imine for the selectivity was already found.[66,73,95] Actually, when the imine prepared from aniline or 2-methoxyaniline was used under the same reaction conditions, the corresponding pyridone derivatives were obtained in good yields but low ees (aniline, 68% yield, 4% ee; 2-methoxyaniline, 74% yield, 25% ee). For ligands, NMI gave the best result. When the chiral catalyst (10 mol %) was prepared in dichloromethane, the desired aza Diels–Alder reaction of **48c** with diene (**78a**) proceeded smoothly, but the enantiomeric excess of the adduct was only 40%. On the other hand, the enantioselectivity was improved to 61% ee when the catalyst was prepared in benzene by stirring for 1 h at room temperature, the mixture was evaporated to remove benzene and *t*-BuOH under reduced pressure, and the reaction was then carried out in dichloromethane. While use of a bulky diene (4-*tert*-butoxy-2-(trimethylsiloxy)-1,3-butadiene, (**78b**))[100c] decreased the selectivity in this case, a higher enantiomeric excess was obtained when the catalyst was prepared in toluene. The best result was finally obtained when the preparation of the catalyst and the successive reaction was carried out in toluene (without removing the solvent).[101]

The effect of the metals used was shown in Table 25. The group 4 metals titanium, zirconium, and hafnium were screened, and it was found that a chiral hafnium catalyst gave high yields and enantioselectivities in the model reaction of **48c** with Danishefsky's diene (**78a**), while lower yields and enantiomeric excesses were obtained using a chiral titanium catalyst.[102]

Several examples of the catalytic aza Diels–Alder reactions using the chiral zirconium catalyst are shown in Table 26. In most cases, high chemical

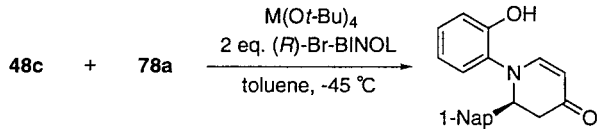
Table 24. Catalytic Enantioselective Aza Diels–Alder Reactions Using Imino Dienophile (1)



entry	additive/mol%	solvent	yield/%	ee/%
1	NMI (30)	CH_2Cl_2	74	40
2	NMI (30)	C_6H_6↑ -CH_2Cl_2	81 (83)	61 41[a]
3	NMI (30)	Toluene ↑ -CH_2Cl_2	81	71
4	NMI (30)	Toluene	86	82
5	DMI (20)	Toluene	76	59
6	 (30)	Toluene	28	24
7	 (30)	Toluene	86	50
8	 (30)	Toluene	81	46
9	———	Toluene	65	10[b]

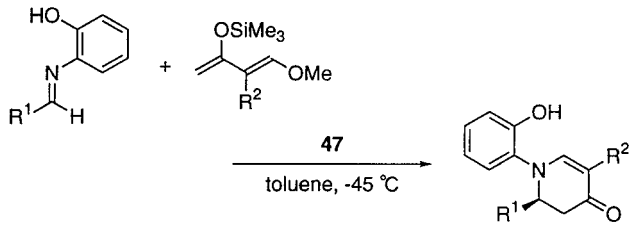
[a] 4-*t*-Butoxy-2-trimethylsilyloxy-1,3-butadiene (**78b**) was used. [b] Reverse enantioselectivity was observed.

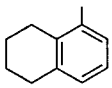
Table 25. Effect of Metals



entry	M (Catalyst)	mol%	yield/%	ee/%
1	Zr (**47**)	10	86	82
2	Zr (**47**)	20	96	88
3	Hf	10	89	73
4	Hf	20	96	84
5	Ti	10	68	39
6	Ti	20	70	62

Table 26. Catalytic Enantioselective Aza Diels–Alder Reactions Using Imino Dienophiles (2)



entry	R^1	diene	amount of **47**/mol%	yield/%	ee/%
1	**48c**	**78a**	5	72	67
2			10	86	82
3			20	96	88
4		**78c**	10	79	89
5			20	93	93
6		**78a**	10	92	80
7	*o*-Me-Ph (**48g**)	**78a**	10	81	76
8			20	83	82
9		**78c**	20	97	77
10	**48a**	**78c**	20	83	65
11	 (**48h**)	**78a**	10	86	64
12	**48e**	**78c**	10	47	78
13			20	51	86

yields and good to high levels of enantioselectivities were obtained in the presence of 5−20 mol % of the chiral catalyst **47**. 4-Methoxyl-3-methyl-2-(trimethylsiloxy)-1,3-butadiene (**78c**)[103] also worked well under standard conditions, and the desired 2,3-dihydro-4-pyridone derivatives were obtained in high yields with high enantioselectivities. As for the R^1 group in Table 26, ortho-substituted aromatics gave higher selectivities. For example, while the imine **48a** reacted with **78c** to afford the corresponding adduct in a 65% ee, a 74% ee of the pyridone derivative was obtained in the reaction of the imine derived from *o*-tolualdehyde (**48g**) with **78c** under the same reaction conditions. The imine derived from 2-thiophenecarboxaldehyde (**48h**) reacted with **78a** smoothly to give the corresponding pyridone derivative in a high yield with a good enantiomeric excess. In the reaction of the imine derived from cyclohexanecarboxaldehyde (**48f**) with **78c**, a low enantiomeric excess of the adduct was observed under standard reaction conditions. It was assumed that the low selectivity was ascribed to the isomerization of the cis and trans conformations of the imine. To prevent the isomerization, the imine **48e**, derived from cyclohexanecarboxaldehyde and 2-amino-3-methylphenol, was used. As expected, the enantiomeric excess of the corresponding pyridone derivative was improved to 86% ee.

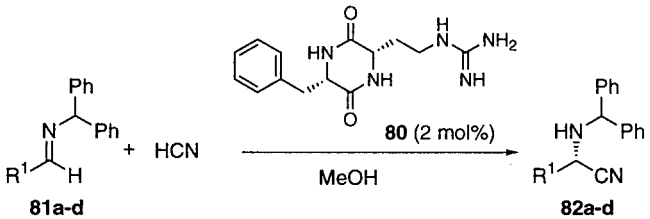
3.5 Catalytic Enantioselective Cyanation of Imines

Asymmetric cyanation of imines provides one of the most important tools for construction of small and functionalized nitrogen-containing molecules. The two-step protocol for α-amino acid synthesis via condensation of aldehydes, amines (ammonia), and cyanides is so-called "Strecker synthesis" including acidic hydrolysis of nitrile groups to carboxylic acids.[54,104,105] "Strecker reaction", cyanation of imines, is also well recognized.[88,106] These asymmetric versions give optically active α-amino nitriles which are key intermediates for syntheses of natural and unnatural α-amino acids. Although there have been many reports on these types of diastereoselective reactions,[107−109] examples of catalytic enantioselective cyanation of imines are limited.

In 1996, Lipton et al. reported the first catalytic asymmetric synthesis of α-amino nitriles by means of external chiral ligand-controlled additions of hydrogen cyanide to imines.[110] Although hydrogen cyanide is highly toxic, it is inexpensive and suitable for industrial use. They exemplified several imines derived from aldehydes and benzhydrylamine and revealed that imines of aromatic aldehydes except for those bearing electron-deficient groups were suitable for their reaction system. Namely, in the presence of 2 mol % of chiral ligand **80**, imine **81a** and **81b** reacted with hydrogen cyanide in MeOH to afford the corresponding amino nitriles **82a** and **82b** in 97 and 90% yields with >99 and 96% ees, respectively. However, the reactions of imine **81c** and **81d** were nonselective (Table 27).

Recently, Jacobsen et al. investigated to search for more effective ligands using combinatorial techniques.[111] Combinatorial chemistry is now recognized as a potentially powerful tool for discovery and optimization of chiral ligands for asymmetric synthesis.[112,113] They prepared three parallel libraries individually (Chart 3). Library **1** consisted of 12 different metal ions; however, no metal ion gave the best result (up to 19% ee). Library **2** and Library **3**

Table 27. Lipton's Catalytic Enantioselective Strecker-Type Reactions



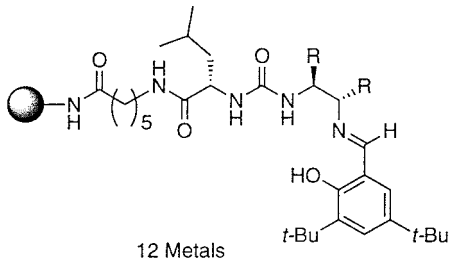
81a-d **82a-d**

81a, **82a**: R^1 = Ph
81b,**82b**: R^1 = *p*-Meo-Ph
81c, **82c**: R^1 = 2-Furyl
81d, **82d**: R^1 = *i*-Pr

entry	imine	yield/%	ee/%
1	**81a**	97	>99
2	**81b**	90	96
3	**81c**	94	32
4	**81d**	81	<10

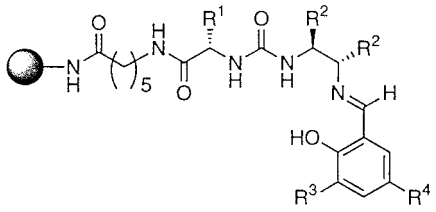
Chart 3. Ligand Library for Catalytic Enantioselective Strecker-Type Reactions

Library 1



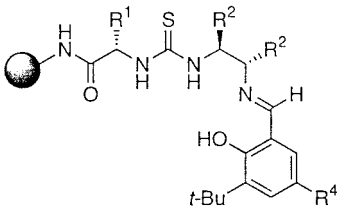
12 Metals

Library 2



4 (R^1) x 2 (R^2) x 6 (R^3, R^4) = 48

Library 3



11 (R^1) x 3 (R^2) x 4 (R^4) = 132

t-Leu-CH-OMe (**84**): R^1 = *t*-Bu, R^2 =  R^4 = OMe

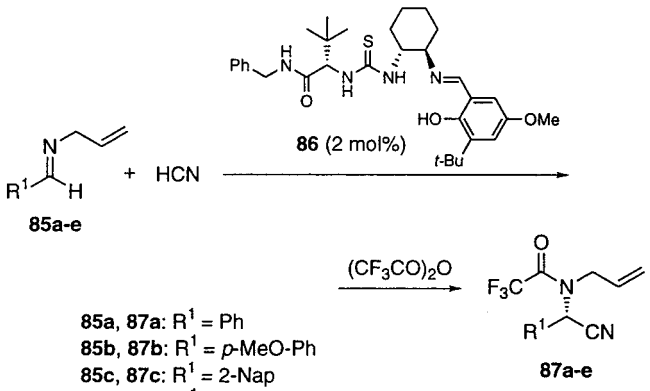
consisted of 48 and 132 different ligands, respectively, and it was shown that the structurally different Library **3** was more effective. Namely, direct attachment of amino acid components to polystyrene matrix gave more enantiomerically enriched products, and replacement of an urea-type linker to a thiourea-type linker improved the selectivity. Finally, the most effective catalyst **84** (*t*-Leu-CH-OMe type) for the reaction of imine **85a** with hydrogen cyanide was determined.

On the basis of these preliminary studies, they performed solution-phase asymmetric reactions (Table 28). A variety of imines derived from aromatic and aliphatic aldehydes reacted with HCN to give the corresponding amino nitriles **87a**−**e** under the influence of 2 mol % of **86** in satisfactory yields and selectivities.

The authors also reported another approach for catalytic enantioselective cyanation of imines (Table 29).[114] They evaluated the reaction of a series of imine **85** with hydrogen cyanide in the presence of 5 mol % of chiral salen-bounded aluminum catalyst **88**. While imines derived from aliphatic aldehydes did not give enough selectivities, the selectivities were slightly improvement when imine **89** was used instead of **85e**.

The zirconium catalyst **47**, which was effective in the catalytic enantioselective Mannich-type reactions[66,73] and aza Diels−Alder reactions,[99] was used in asymmetric Strecker-type reactions. In the presence of 10 mol % of zirconium catalyst **47**, imine **48a** was treated with Bu_3SnCN[115] in dichloromethane at

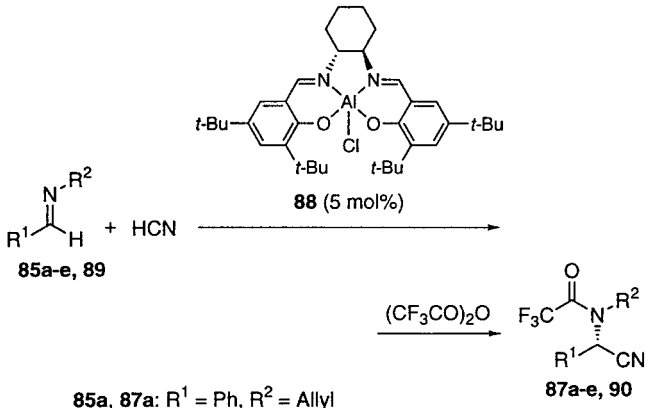
Table 28. Jacobsen's Catalytic Enantioselective Strecker-Type Reactions (1)



85a, 87a: R^1 = Ph
85b, 87b: R^1 = *p*-MeO-Ph
85c, 87c: R^1 = 2-Nap
85d, 87d: R^1 = *c*-C_6H_{11}
85e, 87e: R^1 = *t*-Bu

entry	imine	yield/%	ee/%
1	**82a**	78	91
2	**82b**	92	70
3	**82c**	88	88
4	**82d**	77	83
5	**82e**	70	85

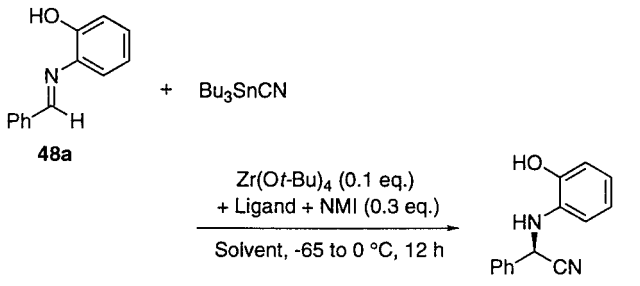
Table 29. Jacobsen's Catalytic Enantioselective Strecker-Type Reactions (2)



85a, 87a: R^1 = Ph, R^2 = Allyl
85b, 87b: R^1 = *p*-MeO-Ph, R^2 = Allyl
85c, 87c: R^1 = 2-Nap, R^2 = Allyl
85d, 87d: R^1 = *c*-C_6H_{11}, R^2 = Allyl
85e, 87e: R^1 = *t*-Bu, R^2 = Allyl
89, 90: R^1 = *t*-Bu, R^2 = Bn

entry	imine	yield/%	ee/%
1	**85a**	91	95
2	**85b**	93	91
3	**85c**	93	93
4	**85d**	77	57
5	**85e**	69	37
6	**89**	88	49

Table 30. Chiral Zirconium-Catalyzed Enantioselective Strecker-Type Reactions (1)



ligand (equiv)	solvent	yield/%	ee/%
(*R*)-6-Br-BINOL (0.2)	CH_2Cl_2	70	55
(*R*)-6-Br-BINOL (0.2)	toluene-benzene (1:1)	72	69
(*R*)-6-Br-BINOL (0.1) + (*R*)-3-Br-BINOL (0.1)	toluene-benzene (1:1)	92	91
(*R*)-6-Br-BINOL (0.1) + (*R*)-3-Br-BINOL (0.1)	toluene	93	86
(*R*)-6-Br-BINOL (0.1) + (*R*)-3-Br-BINOL (0.1)	toluene-C_2H_5CN (1:1)	91	86
(*R*)-6-Br-BINOL (0.1) + (*R*)-3-Br-BINOL (0.1)	benzene-CH_2Cl_2 (1:1)	97	83
(*R*)-6-Br-BINOL (0.1) + (*R*)-3-Br-BINOL (0.1)	CH_2Cl_2	85	71

−45 °C. The reaction proceeded smoothly to afford the corresponding α-amino nitrile in a 70% yield, but the enantioselectivity was moderate (55% ee). After several reaction conditions were examined, the best results (92% yield, 91% ee) were obtained when the reaction was carried out in benzene−toluene (1:1) using a chiral zirconium catalyst, prepared from 1 equiv of Zr(O-*t*-Bu)$_4$, 1 equiv of (*R*)-6-Br−BINOL and (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol ((*R*)-3-Br−BINOL),[89] and 3 equiv of NMI (Table 30). The free hydroxyl group of the imine **48a** was important in obtaining both high yield and high selectivity in this case. When the imine prepared from aniline or 2-methoxyaniline was used under the same reaction conditions, the corresponding α-amino nitrile derivatives were obtained in much lower yields and lower ees (aniline, 29% yield, 1% ee; 2-methoxyaniline, 45% yield, 5% ee).

It was very interesting to find that use of a mixture of (*R*)-6-Br−BINOL and (*R*)-3-Br−BINOL gave the best results. The structure of the zirconium catalyst was carefully examined, and it was indicated from NMR studies that a zirconium binuclear complex **91** was formed under the conditions used (Scheme 22). The binuclear complex consists of 2 equiv of zirconium, (*R*)-6-Br−BINOL, and NMI, and 1 equiv of (*R*)-3-Br−BINOL. The structure was indicated to be very stable and very likely because the complex was formed even when different molar ratios of Zr(O-*t*-Bu)$_4$, (*R*)-6-Br−BINOL, (*R*)-3-Br−BINOL, and NMI were combined. Actually, formation of **88** was confirmed by ^{1}H and ^{13}C NMR spectra when 1 equiv of Zr(O-*t*-Bu)$_4$ and (*R*)-6-Br−BINOL, 0.5−1 equiv of (*R*)-3-Br−BINOL, and 2−3 equiv of NMI were combined.[116]

Scheme 22. Preparation of a Chiral Zirconium Binuclear Complex

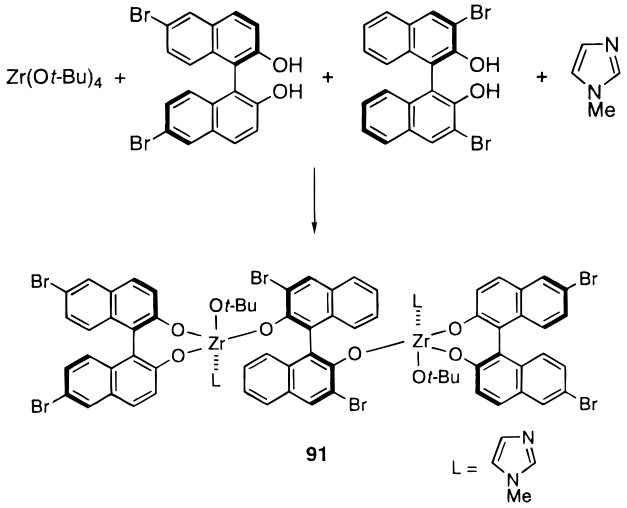
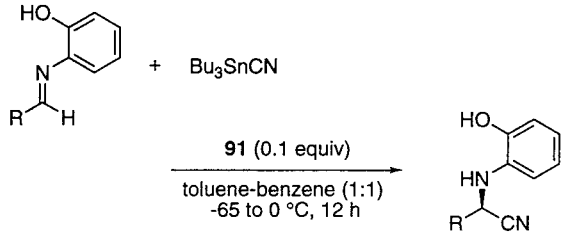
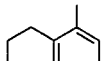
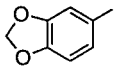


Table 31. Chiral Zirconium-Catalyzed Enantioselective Strecker-Type Reactions (2)



entry	R	yield/%	ee/%
1	Ph (**48a**)	92	91
2	*p*-Cl-Ph (**48b**)	90	88
3	1-Nap (**48c**)	98	91
4	*p*-MeO-Ph	97	76
5	*o*-Me-Ph (**48g**)	96	89[a]
6	*o*-Me-Ph (**48g**)	93	89 (*S*)[b]
7		85	87
8		89	80
9	 (**48h**)	89	92
10	$Ph(CH_2)_2$	55	83[c]
11	*i*-Bu	79	83[c]
12	C_8H_{17}	72	74[c]

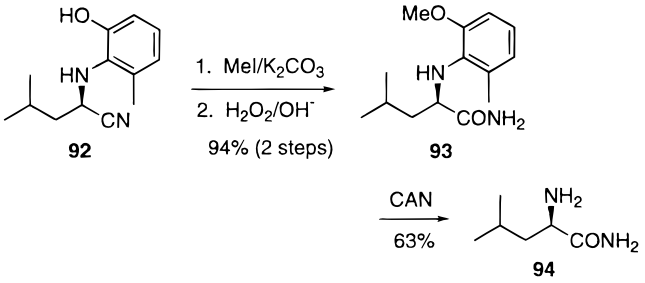
[a]When 0.05 equiv of **91** was used, 94% yield and 87% ee were obtained. [b]0.1 equiv of ***ent*-91** was used. [c]The imine was prepared from the corresponding aldehyde and 2-amino-3-methylphenol *in situ* in the presence of MS 4A.

Several examples of the Strecker-type reactions are summarized in Table 31. Imines derived from

various aromatic aldehydes as well as aliphatic and heterocyclic aldehydes reacted with Bu_3SnCN smoothly to afford the corresponding α-amino nitrile derivatives in high yields with high enantiomeric excesses. Since both enantiomers of the chiral sources (6-Br−BINOL and 3-Br−BINOL) are readily available, both enatiomers of α-amino nitrile derivatives can be easily prepared according to this protocol. In addition, it is noteworthy that Bu_3SnCN has been successfully used as a safe cyanide source. Bu_3SnCN is stable in water, and no HCN is produced. This is in contrast to trimethylsilyl cyanide (TMSCN) that easily hydrolyzes to form HCN even in the presence of a small amount of water.[117] After the reaction was completed, all tin sources were quantitatively recovered as bis(tributyltin) oxide, which was already reported to be converted to tributyltin chloride[118] and then to Bu_3SnCN.[119]

α-Amino nitrile **92** was easily converted to leucinamide according to Scheme 23. Thus, after methyl-

Scheme 23. Preparation of (*R*)-Leucinamide



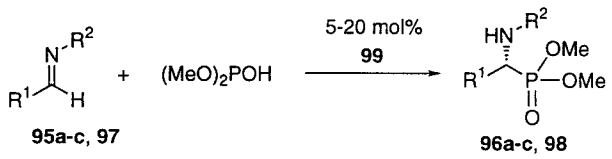
ation of the phenolic OH of **92** using methyl iodide and potassium bicarbonate, the nitrile group was converted to an amide moiety.[120] Treatment of **93** with cerium ammonium nitrate (CAN) gave leucinamide **94**. The absolute configuration assignment (*R*) was made by comparison of its hydrochloride with the authentic sample.[121]

3.6 Miscellaneous

Hydrophosphonylation of imines provides an useful route for synthesis of biologically interesting α-amino phosphonates.[122] Despite the importance of these compounds, there have been few reports focused on catalytic enantioselective reactions. Shibasaki et al. developed the first practical method to synthesize α-amino phosphonates by using a chiral rare earth catalyst.[123] In the presence of 5−20 mol % of chiral catalyst **99**,[124] the reaction of acyclic or cyclic imines (**95a**−**c**, **97**) with dimethyl phosphite proceeded smoothly to afford the corresponding α-amino phosphonates (**96a**−**c**, **98**) in high yields with high enantioselectivities (Table 32).

Quite recently, Yamamoto et al. reported catalytic enantioselective allylation of imines with allyltributylstannane in the presence of a chiral Pd(II)−η^3-π-allyl complex (**100**).[125] They proposed that the chiral Pd(II) catalyst reacted first with allyltributylstannane to afford nucleophillic bis-π-palladium species **101** (Table 33).[55d]

Table 32. Shibasaki's Catalytic Enantioselective Hydrophosphonylation of Imines



entry	aldimine	catalyst (mol%)	yield/%	ee/%
1	**95a**	**99a** (5)	82	92
2	**95b**	**99a** (20)	80	91
3	**95c**	**99a** (20)	73	75
4	**97**	**99b** (10)	80	95[a]

[a] (*R*)-Enantiomer was obtained

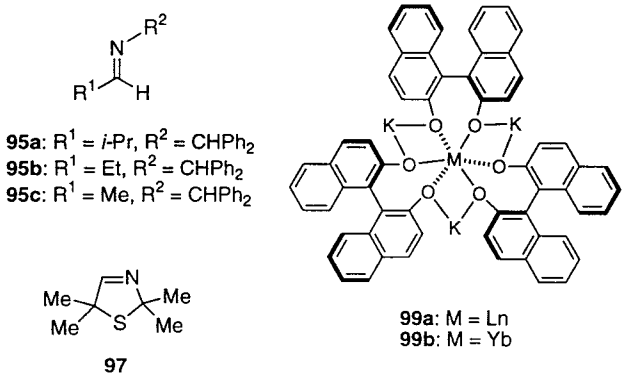
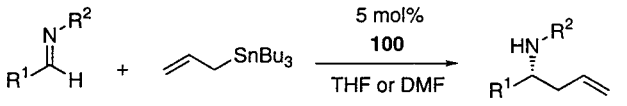
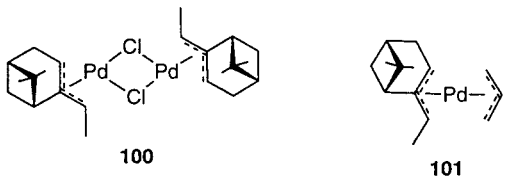


Table 33. Yamamoto's Catalytic Enantioselective Allylation of Imines



entry	R^1	R^2	time/h	yield/%	ee/%
1	Ph	Bn	90	62[a]	81
2	Ph	Bn	119	72[b]	80
3	Ph	PMB[c]	116	61[b]	82
4	2-Nap	Bn	62	69[a]	79
5	*c*-C_6H_{11}	Bn	111	44[a]	40

[a] DMF was used as a solvent. [b] THF was used as a solvent. [c] *p*-$MeOC_6H_4CH_2$



4. Conclusions

Catalytic enantioselective reactions of imines have been surveyed. The challenges to establish highly efficient catalytic enantioselective processes for the synthesis of chiral nitrogen-containing compounds have just begun. Several methodologies seem to be

promising; however, there are a number of problems which must be overcome. For instance, substrate limitation is still problems in most reductive amination. In carbon−carbon bond-forming reactions, substrates are limited to aldimines at present. Instability of imines, especially the imines having α-protons, are still common problems to perform reactions efficiently. Development of reactions which proceed under mild conditions and more stable imine equivalents is strongly in demand. As mentioned in this review, several efforts have supplied important information how to overcome these problems, and the authors hope that it will not need long time before establishing really practical ways to obtain optically pure nitrogen-containing compounds.

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