Developments in Asymmetric Hydrogenation from an Industrial Perspective

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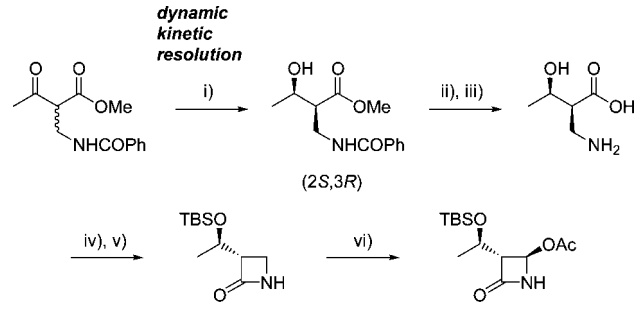
ABSTRACT

Examples of developments in asymmetric hydrogenation from various perspectives, in an effort to improve efficiency, are reported. Discussed in this Account are (1) the improved synthesis of BINAP ligands, (2) the design of SEGPHOS ligands for higher enantioselectivity, (3) a new protocol with fewer reaction steps to synthesize β-aminoesters, and (4) a novel asymmetric hydrogenation mediated by a copper catalyst.

Introduction

Asymmetric hydrogenation is one of the most valuable reactions, investigated in innumerable studies.[1] Since its early years, the reaction has been used for industrial applications, thanks to its prominent catalytic activity and chiral recognition ability.[2] In general, asymmetric hydrogenation is mediated by a complex bearing Rh, Ru, or Ir, among which our focus has been Ru. One reason was that the Ru catalysts have excellent performances, especially when associated with the BINAP ligand,[3,4] which Takasago was already using in the Rh-catalyzed asymmetric isomerization for a L-menthol process.[5] Another reason was that Ru enjoyed a cost advantage relative to other asymmetric hydrogenation metals, such as Rh.[6]

Scheme 1. Synthetic Route to a Key Intermediate of Carbapenem



i) H_2, Ru(II)-cat.; ii) HCl; iii) NaOH
iv) 2,2'-Dithiobis(benzothiazole), PPh_3
v) TBSCl, imidazole; vi) $RuCl_3 \cdot nH_2O$, AcO_2H, AcONa

A representative example of the industrial processes is the synthesis of a key intermediate for carbapenem (Scheme 1).[2a,e] One of the key reactions is asymmetric hydrogenation of an α-substituted-β-ketoester accompanied by dynamic kinetic resolution.[7] This process currently yields more than 100 tons of the product annually.

Numerous efforts have been made so as to improve the efficiency of asymmetric hydrogenations. However, different circumstances affect the goals of development. At Takasago, trends observed in the developments have changed chronologically as follows: (1) In the early stages when the potential usefulness of BINAP was discovered, easier access to the landmark ligand was addressed. Naturally, efforts were made to synthesize BINAP in a more practical fashion. (2) When asymmetric hydrogenations became more frequently investigated, BINAP occasionally failed to afford adequate results. Accordingly, demand for chiral ligands with superior performance increased, which motivated us to develop new ones. (3) When the reaction was regarded as a promising system, an increasing number of processes came to require several additional steps other than asymmetric hydrogenation. Because more effective approaches to a particular target were desired, a new protocol of asymmetric hydrogenation that could offer shorter processes was pursued. (4) Recently, prices for platinum group metals employed for conventional catalyst systems, including Ru, have drastically increased, which brought about cost efficiency uncertainty. The development of an alternative catalyst system for asymmetric hydrogenation using an inexpensive base metal is being pursued.

Outlined in this Account is how we refined asymmetric hydrogenation accordingly. Examples of developments dealt with herein include quests for (1) a practical synthetic route to BINAP using easy-to-handle diphos-

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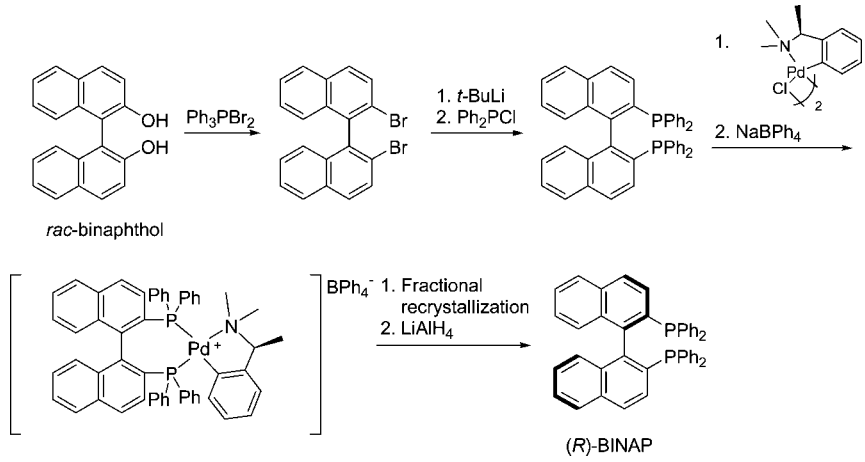
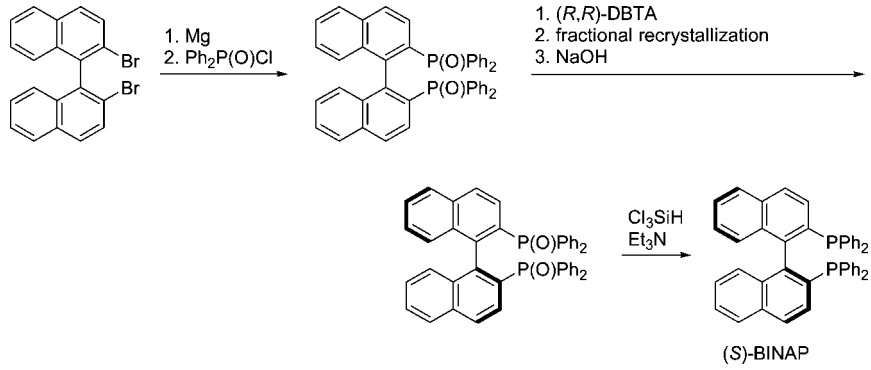
Scheme 2. Synthesis of BINAP (1980)



Scheme 3. Synthesis of BINAP (1986)



phine oxide, (2) a new biaryl diphosphine ligand line, SEGPHOS series, that offers higher performance in enantioselectivity and catalytic activity, (3) an efficient protocol en route to β-aminoesters by reductive amination that reduce the number of reaction steps, and (4) a new catalyst system containing copper, an inexpensive base metal.

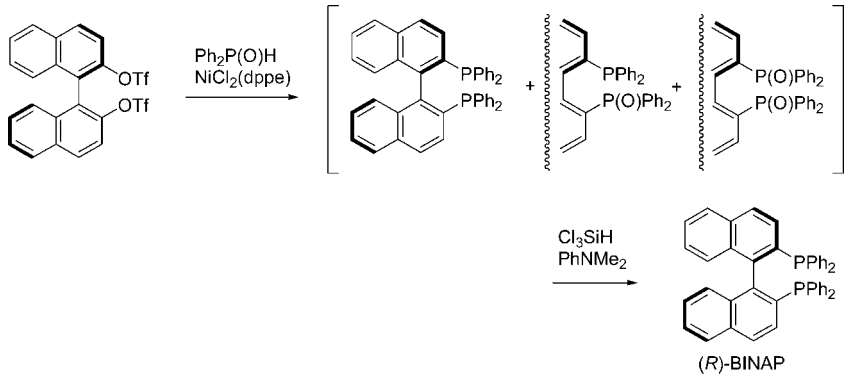
Development of Synthetic Route to BINAP

When BINAP was first reported in 1980, the ligand was synthesized according to the route shown in Scheme 2.[3] Dilithiated binaphthyl, generated from dibromide and butyllithium, was exposed to chlorodiphenylphosphine to afford racemic BINAP. The racemate was then treated with a chiral Pd complex. The resultant diastereomeric mixture was subjected to fractional recrystallization, followed by decomplexation, to afford enantiomerically pure BINAP.

Several years later, a more practical method, which adopted a diphosphine oxide of the ligand as an intermediate, was developed (Scheme 3).[8] The racemic diphosphine oxide, prepared from the corresponding Grignard reagent and diphenylphosphinyl chloride, was treated with dibenzoyltartaric acid (DBTA) to form diastereomeric complexes. Fractional recrystallization of the complexes followed by exposure to a base afforded an enantiomerically pure diphosphine oxide. The diphosphine oxide was then reduced to give the target. This process, which utilizes weak basicity of phosphine oxide moieties, is still a standard method in the synthesis of various biaryl diphosphine ligands.

When BINAP started to be used in large-scale production, one problem arose out of the conventional procedure involving a racemic BINAP derivative; one enantiomer of the ligand was partially used, whereas the other remained unused. This situation was undesirable in terms of inventory control, thereby impacting the total cost. A breakthrough was made by Cai, introducing a route starting from an optically active binaphthol, which was relatively easily available.[9] The ditriflate of the optically active binaphthol was coupled with diphenylphosphine in the presence of a Ni catalyst, giving the optically active BINAP. With this protocol, only the desired enantiomer is synthesized. On the basis of a similar concept, we developed a synthetic route employing diphenylphosphine oxide (Scheme 4).[10] The coupling reaction gave a mixture of BINAP, its monoxide and dioxide, which was then reduced by a silane, leading to BINAP. Use of diphenylphosphine oxide as a coupling partner is advantageous because it is easy to handle compared to diphenylphosphine[9] or chlorodiphenylphosphine,[11] although it does require additional reduction of the phosphine oxide moieties. This protocol is particularly effective in the synthesis of related ligands with various phosphine appendages, avoiding tedious optical resolution studies for each derivative.

Scheme 4. Synthesis of BINAP (1997)

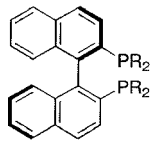


Taking advantage of these protocols, BINAP derivatives with a variety of phosphine appendages were synthesized, expanding the utility of the ligand type (Figure 1).[8,12]

Development of New Biaryl Diphosphine Ligand

The most important parameter that governs enantioselectivity, as well as catalytic activity, is the choice of chiral ligand. Although BINAP provides compounds with reasonably high optical purities in many cases, higher performances are sometimes required. In the late 1990s, we needed to improve the enantioselectivity of the asymmetric hydrogenation of hydroxyacetone, which by BINAP was 89% ee. In order to determine trends that could assist in our further developments, we screened the ligands that were analogous to BINAP. We discovered a close relationship between the dihedral angle of the biaryl backbones (θ) and observed enantioselectivities: BINAP (θ 73.49°): 89.0% ee; BIPHEMP[13] (θ 72.07°): 92.5% ee; MeO-BIPHEP[14] (θ 68.56): 96.0% ee (Figure 2). These observations afforded a working hypothesis that a narrower dihedral angle should make a stronger interaction between the ligand and a substrate, enhancing enantioselectivity. On the basis of this hypothesis, we envisioned that ultimate enantioselectivity could be achieved with ligands having a narrower dihedral angle than that of MeO-BIPHEP. We presumed that the bi-1,3-benzodioxole framework would be a good candidate, which was supported by the calculated dihedral angle of 64.99°.

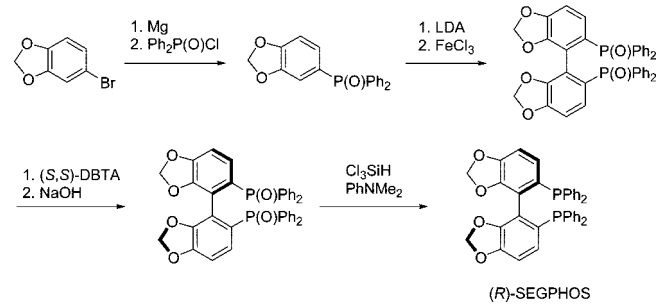
Synthesis of the ligand SEGPHOS[15] is shown in Scheme 5. In the synthesis, we developed a new method for oxidative homoaryl coupling; exposure of an aryllithium to $FeCl_3$ afforded the corresponding biaryl compound in high yield. This method enjoys advantages in terms of cost and waste relative to the conventional iodination/Ullmann coupling using stoichiometric Cu.



R = Ph:	BINAP
4-MeC_6H_4:	Tol-BINAP
4-*t*-BuC_6H_4:	*t*-Bu-BINAP
4-$MeOC_6H_4$:	MeO-BINAP
3,5-$Me_2C_6H_3$:	DM-BINAP
3,5-(*t*-Bu)$_2C_6H_3$:	DB-BINAP
4-MeO-3,5-$Me_2C_6H_2$:	DMM-BINAP
cyclohexyl:	Cy-BINAP
4-FC_6H_4:	*p*-F-BINAP
4-ClC_6H_4:	*p*-Cl-BINAP

FIGURE 1. BINAP series.

Scheme 5. Synthesis of SEGPHOS



As expected, SEGPHOS achieved the highest level of chiral recognition in the asymmetric hydrogenation of hydroxyacetone, affording 98.5% ee. Fortunately, catalytic activity was enhanced as well, realizing turnover numbers (TON) up to 10 000 (cf. BINAP: 3000). Additionally, with other functionalized ketones, SEGPHOS generally gives higher enantioselectivities and catalytic activities than those with BINAP (Scheme 6).[15]

Various modifications of SEGPHOS were also pursued (Figure 3). DM-SEGPHOS and DTBM-SEGPHOS frequently excel in Ru-catalyzed asymmetric hydrogenations,[15] whereas Cy-SEGPHOS and IPR-SEGPHOS are good ligands for the Rh-catalyzed reactions.[16] Ligands with various appendages such as phosphetane,[16] phospholane,[16] and phosphole[17] were also synthesized.

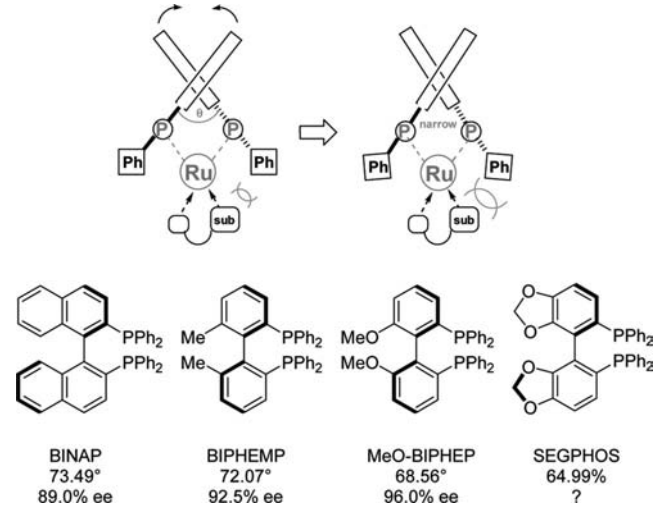
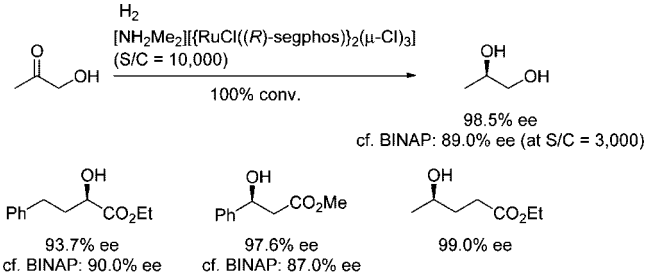


FIGURE 2. Dihedral angle and enantioselectivity in the asymmetric hydrogenation of hydroxyacetone.

Scheme 6. Asymmetric Hydrogenations with SEGPHOS



The effect of the ligand modification in the appendages would be best described using the example of a process that afforded a key intermediate for carbapenem antibiotic by asymmetric hydrogenation with dynamic kinetic resolution (Table 1).[7,15] With BINAP or SEGPHOS, diastereoselectivity was not satisfactory although enantioselectivity is high. In the reaction, diastereoselectivity is as important as enantioselectivity. Studies revealed that substitution at the 3,5-position of the phenyl appendages on the ligand was effective in enhancing diastereoselectivity. Ultimately, when DTBM-SEGPHOS was adopted as a chiral ligand, essentially only one stereoisomer out of the four possible isomers was obtained.

The SEGPHOS family of ligands was also used in other asymmetric reactions (more than 50 applications), in many cases becoming the ligand of choice.[6,18] A representative example is Cu-catalyzed asymmetric hydrosilylations. In the reaction with isophorone, for instance, DTBM-SEGPHOS realized unprecedented high catalytic activity (substrate-to-ligand molar ratio (S/L) 275 000), keeping high enantioselectivity (Scheme 7).[19]

Development of an Efficient Process

In process development, efficiency in the overall process must be pursued rather than in individual reactions. Even if the key reaction per se is excellent, the process cannot be regarded as a good protocol if it has fatal defects (i.e., too long steps, hazardous operation, etc.). Reported in this section is our effort to develop more efficient processes to create β-aminoesters.

β-amino acid derivatives have been attracting attention in the pharmaceutical industry as chiral building blocks.[20] Our conventional protocol to access the compounds consisted of (1) asymmetric hydrogenation of the corresponding β-ketoester, (2) tosylation of the hydroxyl group, (3) introduction of an azide group with sodium azide, and (4) hydrogenolysis of the azide group into amino group (Scheme 8). Although the asymmetric hydrogenation was excellent, the process suffered from some defects. One such defect is the requirement for hazardous azide chemistry. More critically, the process was too long, requiring long lead times and high cost.

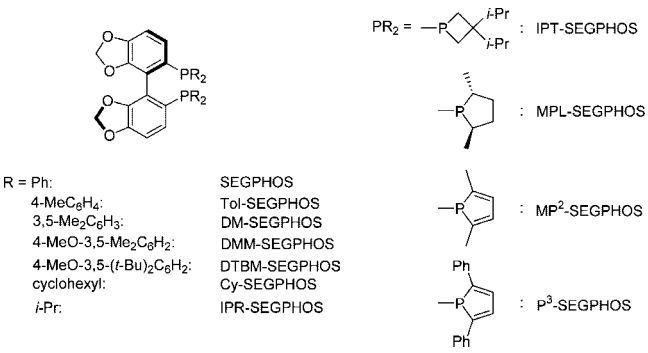


FIGURE 3. SEGPHOS series.

An alternative route known at the time involved the asymmetric hydrogenation of a β-enamidoester (Scheme 9). Although this approach avoided azide chemistry and effective asymmetric hydrogenation of the enamidoester was known,[21] in our eyes, this process was still too long because intrinsically it was accompanied by protection (or enamide formation)/deprotection steps.

We envisioned that if an unprotected enaminoester could be used as a substrate for asymmetric hydrogenation, it would provide an effective protocol to access a β-aminoester. This idea challenged us to develop a system that could hydrogenate "unprotected" substrates in order to achieve drastic improvements.

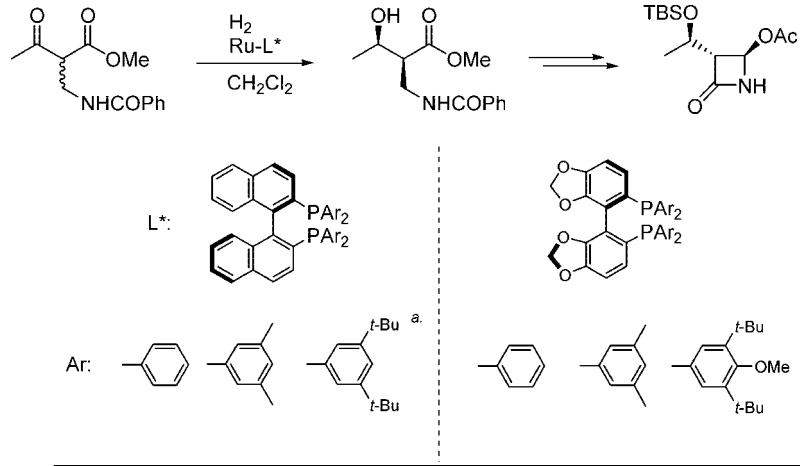
After considerable struggles, we found that a Ru complex was able to hydrogenate the methyl 3-aminocrotonate in the presence of an acid, completing the reaction with moderate ee (Table 2, entry 1). Further study revealed that 2,2,2-trifluoroethanol was effective in enhancing enantioselectivity. When 2,2,2-trifluoroethanol was adopted as a solvent, enantioselectivity was 94% ee (entry 2). Use of the fluorinated alcohol as an additive (1 equiv to substrate) was also effective, although slightly lower enantioselectivity was observed than in the case where it was used as a solvent (entry 3).[22]

Almost at the same time, the Merck group reported a similar protocol employing Rh–ferrocenophosphine (**L1**) complexes that gives excellent enantioselectivity (Scheme 10).[23]

Further investigation in an effort to develop a more effective process led to another breakthrough: a one-pot reductive amination.[24] Asymmetric hydrogenation of a β-ketoester in the presence of a nitrogen source, such as ammonium acetate, afforded the β-aminoester with high enantioselectivity (Table 3, entry 1). A Ru–diacetate complex[25] ligated by Tol-BINAP selectively gave the desired compound **1**. When we carried out the same procedure with a Rh catalyst, a considerable amount of hydroxyester **3** was also produced as a result of competing ketone reduction (entry 2).

Ligand screening at this stage showed that DM-SEGPHOS was the ligand of choice in terms of enantioselectivity, although with slightly lower chemoselectivity (Table 4, entry 5). The low selectivity with DM-SEGPHOS was subsequently overcome with the addition of acetic acid (2 equiv) to the reaction system (entry 6). Choice of acid as additive was particularly important. Use of stronger acid (such as methanesulfonyl acid and trifluoroacetic acid) in place of acetic acid gave a complex mixture, where considerable formation of the hydroxyester was observed. The amount of acetic acid had also impact on selectivity.

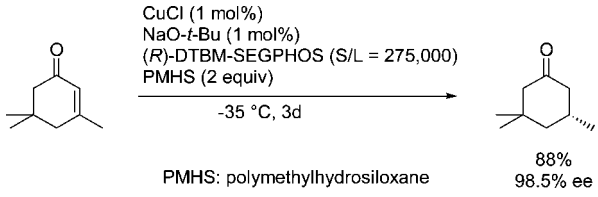
Table 1. Effect of Ligand Modification on a Dynamic Kinetic Resolution



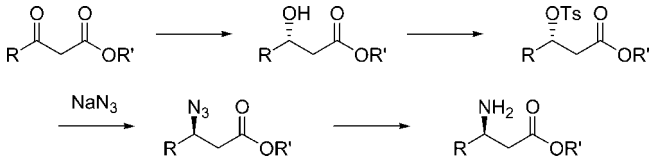
de	74	95	98	80	94	99
ee	90	99	99	N. A.	98	99

[a] CH_2Cl_2/MeOH was used as a solvent.

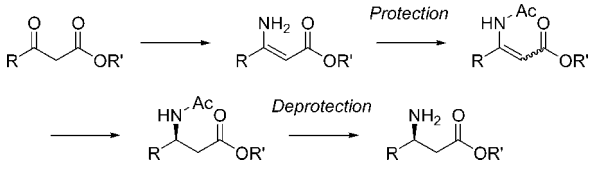
Scheme 7. Cu-Catalyzed Asymmetric Hydrosilylation Accelerated by DTBM-SEGPHOS



Scheme 8. Conventional Synthetic Route to β-Aminoesters



Scheme 9. β-Aminoester Synthesis via Asymmetric Hydrogenation of Enamides

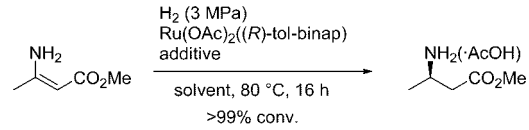


When more acetic acid (4 equiv) was added, population of the hydroxyester was increased to 4% (cf. ca. 1% with 2 equiv).

The optical purity of the resultant β-aminoester was improved by recrystallization after derivation to the tosyl salt. By the recrystallization, nearly enantiomerically pure salt of methyl 3-aminobutyrate (98% ee) was obtained in acceptable yield (66% yield from methyl acetoacetate) (Scheme 11).

With the new protocol in hand, access to a β-aminoester, which previously required four steps, has ultimately been reduced to one step. The scope of the protocol was expanded to produce a variety of β-aminoesters with high optical purities (Figure 4).

Table 2. Asymmetric Hydrogenation of an Enaminoester



entry	S/C[a]	solvent	additive A (equiv)	additive B (equiv)	selectivity (%)	% ee
1	200	MeOH	AcOH (1)		97	54
2	100	CF_3CH_2OH			96	94
3	200	MeOH	AcOH (1)	CF_3CH_2OH (1)	98	83

[a] Substrate-to-catalyst molar ratio.

Development of a Catalytic System Containing an Inexpensive Base Metal

For more than a quarter century, we have employed Ru complexes as catalysts for asymmetric hydrogenation. One of the reasons was that Ru is relatively inexpensive compared to Rh. Recently, however, the price of Ru has increased by more than 20 times compared with that in 2003, reaching US $800 per ounce.[26] Although this situation will not necessarily continue in the future, this radical fluctuation is not desirable from an industrial point of view, as it brings about a considerable impact on the cost stability of the catalysis.

One possible countermeasure is to develop a new catalyst system employing an inexpensive base metal. Requirements necessary for the new system include (1) the metal should be inexpensive and easily available, (2) the metal must have the ability to hydrogenate, (3) the metal should have chiral recognition ability when bearing a chiral ligand, and (4) asymmetric hydrogenation using the metal should be novel. Taking these requirements into consideration, we focused on Cu as a strong candidate because (1) copper is one of the most abundant and least expensive metals; (2) copper is a useful catalyst in het-

Scheme 10. Merck's Method

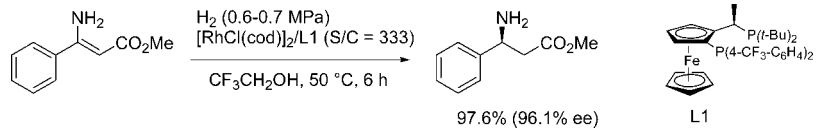
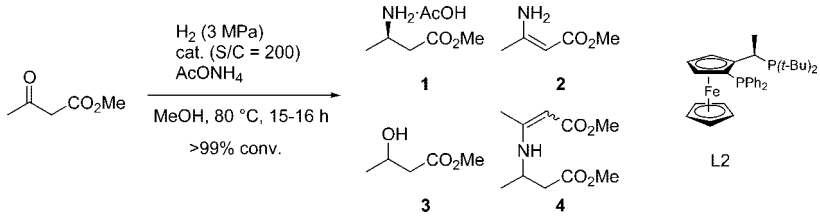
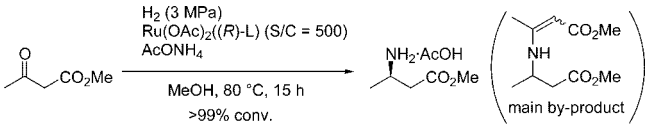


Table 3. Asymmetric "One-Pot" Reductive Amination



		selectivity			
entry	cat.	**1** (% ee)	**2**	**3**	**4**
1	$Ru(OAc)_2$((*R*)-tol-binap)	83 (82)	3	<1	14
2	$[RhCl(cod)]_2$ + L2	65 (73)	1	29	5

Table 4. Ligand Screening in the Reductive Amination



entry	L	selectivity (%)	% ee
1	BINAP	45	47
2	Tol-BINAP	55	84
3	DM-BINAP	75	84
4	SEGPHOS	52	61
5	DM-SEGPHOS	36	94
6[a]	DM-SEGPHOS	93	93

[a] The reaction was carried out at S/C = 1000 at 90 °C with the addition of AcOH (2 equiv).

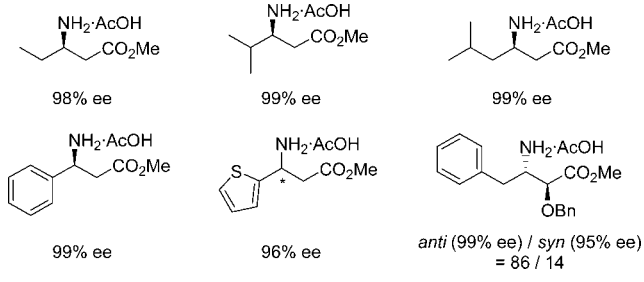
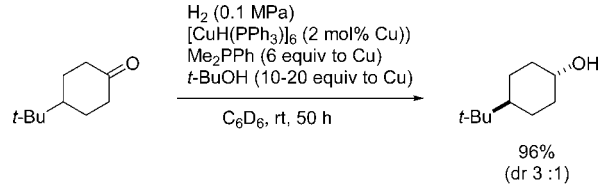


FIGURE 4. Scope of the reductive amination.

erogeneous[27] and homogeneous[28] hydrogenation; (3) excellent enantioselectivities with copper catalysts were proved in asymmetric reductions such as hydrosilylation,[29] hydroboration,[30] and transfer hydrogenation;[31] and (4) no

Scheme 12. Homogeneous Cu-Catalyzed Hydrogenation



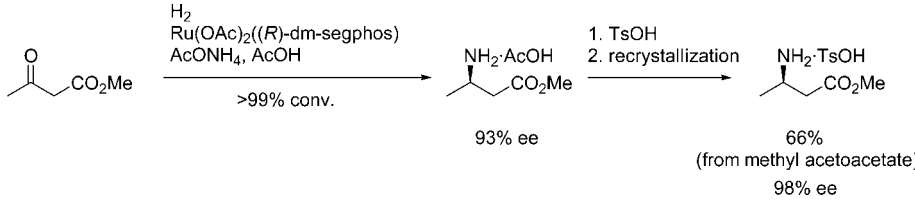
homogeneous asymmetric hydrogenation mediated by a copper catalyst has been reported to date.[32]

As for the ability of homogeneous hydrogenation with Cu, a landmark study by Stryker's group showed its potential usefulness. They proved that a hexamer of CuH ($[CuH(PPh_3)]_6$)[33] can catalyze the hydrogenation of ketones and enones with turnover numbers of up to 50 based on the Cu atom (Scheme 12).[28d]

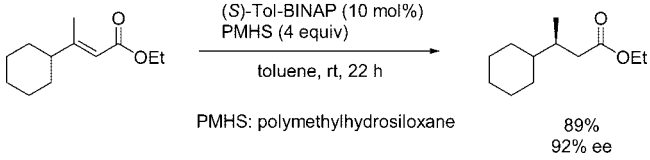
On the other hand, excellent chiral recognition ability with Cu has been frequently documented by groups worldwide, specifically in asymmetric hydrosilylation. Buchwald first reported a Cu-catalyzed asymmetric hydrosilylation, reducing α,β-unsaturated carbonyl compounds in high enantioselectivity (Scheme 13).[34] The scope was then expanded to ketones[35] and imines[36] as well as variously activated olefins.[19,37]

At the start of the Cu-catalyzed asymmetric hydrogenation project, our first priority was a reasonable turnover numbers (TON) (i.e., 1000), an indispensable requirement for industrial use. The initial investigation was carried out using a catalyst system similar to that

Scheme 11. Improvement of Optical Purity



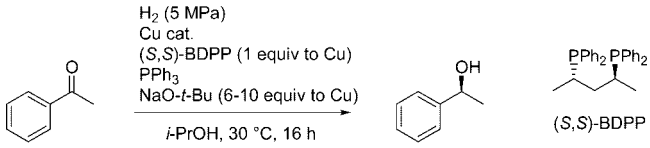
Scheme 13. Cu-Catalyzed Asymmetric Hydrosilylation of an α,β-Unsaturated Ester



PMHS: polymethylhydrosiloxane

89%
92% ee

Table 5. Cu-Catalyzed Asymmetric Hydrogenation of Acetophenone



entry	Cu cat.	S/C	PPh_3 (equiv to Cu)	conversion (%)	ee (%)
1	CuCl	300		21	40
2	CuCl	300	3	>99	48
3[a]	$[CuH(PPh_3)]_6$	500	1	>99	47
4	$[Cu(NO_3)(PPh_3)_2]$	1000		>99	47
5[b]	$[Cu(NO_3)(PPh_3)_2]$	3000	3	97 (94)[c]	48
6	$[Cu(NO_3)(P(3,5\text{-xylyl})_3)_2]$	500		>99	56

[a] Without NaO-*t*-Bu. [b] Reaction time was 96 h. [c] Isolated yield.

used by Buchwald for hydrosilylation[34a] (Table 5, entry 1). A catalyst system consisting of CuCl, NaO-*t*-Bu, and (*S*,*S*)-BDPP[38] (S/C = 300) hydrogenated acetophenone in moderate enantioselectivity albeit with only 21% conversion. We used BDPP as the chiral ligand because a preliminary screening showed that BDPP gave the highest conversion among those tested. In addition, use of BDPP was desirable because it could be synthesized at low cost (two steps from easily available chiral 2,4-pentanediol), which is an important element in the development of an inexpensive system. As was suggested by Stryker,[28b] conversion improved with the addition of PPh_3, giving complete conversion with 48% ee (entry 2). Use of $[CuH(PPh_3)]_6$ also led to the reaction's completion even without NaO-*t*-Bu, with additional PPh_3 (entry 3). We settled on the catalyst precursor $Cu(NO_3)(PPh_3)_2$,[39] a Cu complex bearing PPh_3, that improved the catalytic activity up to the targeted TON of 1000 (entry 4). The reaction at S/C = 3000 also led to near completion of the reaction with additional PPh_3 and an extended reaction time (entry 5). Further study showed that use of $Cu(NO_3)(P(3,5\text{-xylyl})_3)_2$ slightly improved the enantioselectivity (entry 6).[40]

As catalytic activity reached an acceptable level, we extensively screened chiral ligands again so as to improve enantioselectivity (Figure 5). However, the screening indicated that BDPP was still the ligand of choice in terms of enantioselectivity and catalytic activity. A structurally similar CHIRAPHOS[41] ligand resulted in almost no reaction, whereas ligands with a flexible C3–C4 linker, such as DIOP,[42] BPPM,[43] and Josiphos,[44] afforded completion of the reaction, albeit with lower enantioselectivities

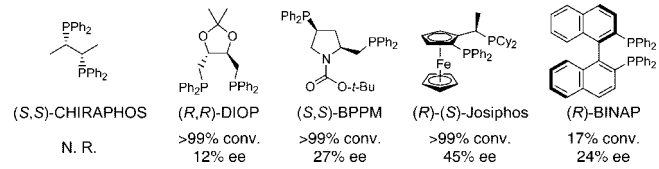
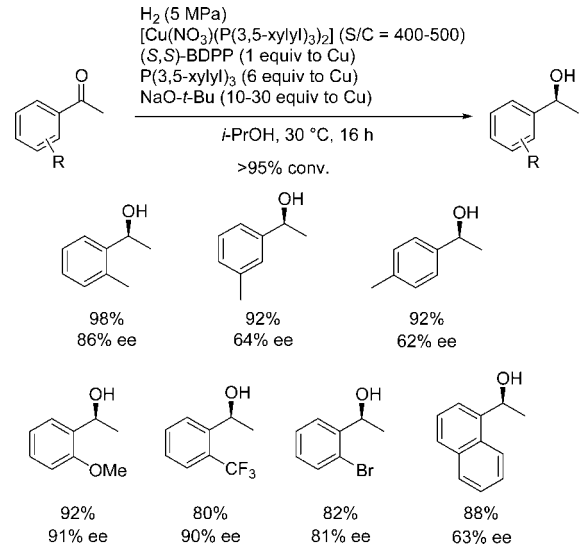


FIGURE 5. Ligand screening with the conditions from Table 5, entry 4 (S/C = 500).

Scheme 14. Asymmetric Hydrogenation of Substituted Acetophenones



relative to BDPP. A biaryldiphosphine ligand (e.g., BINAP), an excellent type of ligand for the hydrosilylation, resulted in lower conversion and ee.

This protocol was effective for the acetophenone-type substrate with various substituents (Scheme 14). Particularly when the catalyst system was applied to the reaction with 2′-substituted acetophenones, high enantioselectivities up to 91% ee were observed.[40] Although catalytic activity and enantioselectivity are still modest compared to Noyori's Ru system,[45] the copper catalysis may offer a more effective and economical protocol. Further expansion of the scope is under investigation.

Conclusions

Some examples of our efforts to improve asymmetric hydrogenation have been outlined in this paper. As the environment surrounding asymmetric hydrogenation has been changing drastically in recent years, it is very important to carry out developments in a timely manner. On-demand development should further popularize the reaction. Increasing demand for "green chemistry"[46] should be a favorable wind for asymmetric hydrogenation. In the future, it may also be important to create an environment where chemists in the industry feel free to employ catalysis (e.g., easier availability of catalysts and ligands,[47] etc.). It is of great interest to see how this reaction will contribute to society.

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(47) Based on this philosophy, Takasago's chiral ligands and Ru catalysts became commercially available.

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