Synthesis of Pharmaceutical Intermediates Aiming at Construction of Optically Active Tertiary Alcohols as a Key Technology

Sumitomo Chemical Co., Ltd.
Fine Chemicals Research Laboratory
Tetsuya IKEMOTO
Osamu TOKUDA
Sumika Electronic Materials (Shanghai) Co., Ltd.
Wei-Guo GAO

We are developing novel synthetic methods of pharmaceutical intermediates aiming at construction of optically active tertiary alcohols. Now, we have found that the tetrasubstituted carbon center was easily constructed by the L-proline catalyzed direct asymmetric aldol reaction between cyclohexanone and ethyl phenylglyoxylate, which gave the corresponding aldol adduct in good yield with excellent diastereo- and enatioselectivity. Herein, we also report a practical synthetic route of (S)-CHPGA as a key intermediate for the preparation of (S)-Oxybutynin.

Introduction

In recent years, there has been a large number of what are called standard preparations, such as asymmetric hydrogenation using asymmetric reduction catalysts typified by BINAP and methods using enzymatic hydrolysis, that are reliable from an industrial point of view for the synthesis of optically active secondary alcohols. Furthermore, there are many producers of pharmaceutical intermediates that cite optically active secondary alcohols as an area of strength. On the other hand, there is a focus on the synthesis of optically active tertiary alcohols as a field where there are few standard industrial preparations and for which organic synthesis is extremely challenging from an academic point of view.

Since optically active tertiary alcohols cannot be synthesized by asymmetric hydrogenation when asymmetric synthesis is presumed, asymmetric carbon-carbon bonds must be constructed. However, ketones, which are sterically difficult to recognize must be used as the electrophilic agent for their construction instead of aldehydes, which are easily recognized. However, even though the construction of asymmetric carbon-carbon bonds with aldehydes is an important academic field in current organic chemistry and many researchers are studying it day in and day out, there are not many industrially reliable preparation methods at present,

and there are even fewer asymmetric reactions that can be used industrially.

Under these circumstances, we assumed that as challenging as this field is, it was a technical area that should be targeted in the field of pharmaceutical intermediates, which will become increasingly competitive in the future. So we decided to carry out the development of a method for synthesizing pharmaceutical intermediates for which the key is the construction of optically active tertiary alcohols. In this paper, we will introduce the development of a method for synthesizing intermediates for medicines for treating frequent urination as an example of this.

Research on Synthesizing Intermediates of "Optically Active Oxybutynin" for Drugs for Treating Frequent Urination

1. History of Development

Oxybutynin hydrochloride is a urological drug developed by Hoechst Marion Roussel (currently Sanofi-Aventis), and it is sold in Japan under the product name Pollakisu®. This is a racemic compound, but the optically active substance (S)-oxybutynin is positioned as a racemic switch product, and we were interested in a method for synthesizing its optically active tertiary alcohol (S)-CHPGA (**Fig. 1**).
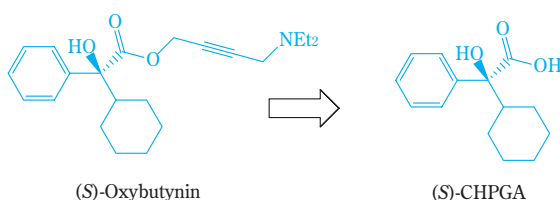
Fig. 1 (S)-CHPGA as an intermediate of (S)-Oxy-butynin

2. Synthesis of CHPGA Racemic Compound

Various methods have been proposed for synthesizing (S)-CHPGA besides optical resolution of the racemic compound, but there have been many problems such as the need for ultra-low temperature reactions. Therefore, we first presumed optical resolution, and carried out research on efficient synthesis of the racemic compound. The Grignard reaction shown in **Fig. 2** is a typical method for synthesizing the CHPGA racemic compound.[1] However, since there is a nucleophilic attack on the sterically crowded carbonyl carbon by the secondary halide Grignard reagent, there are complications at the ester sites with the addition of the Grignard reagent in addition to giving rise to a reduction reaction, and this has not been a method with satisfactory yield and purity. As a result of various investigations targeting a solution for this problem, we found that an adduct could be obtained with a good
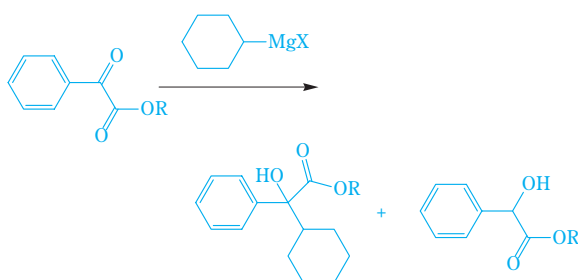

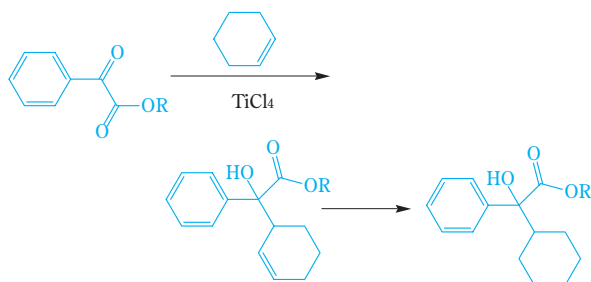**Fig. 2** Conventional synthesis of racemic CHPGA

Fig. 3 Synthesis of racemic CHPGA by carbonyl-ene reaction

yield by reacting cyclohexene and ethyl benzoyl formate in the presence of titanium tetrachloride, that is, a carbonyl-ene reaction (**Fig. 3**).[2] There are many examples of Ene reactions with internal olefin nucleophilic reagents and intramolecular Ene reactions, but not many examples of intermolecular reactions with internal olefins as the nucleophilic reagent are known. We examined this reaction with aluminum chloride, ferric chloride, zirconium tetrachloride and various Lewis acids up through lanthanoid Lewis acids such as ytterbium triflate, but the titanium tetrachloride we selected originally gave the best results. This reaction was verified as a process that is sufficient for industrial application by carrying out plant tests later.

3. Synthesis of Optically Active CHPGA

The optical resolution of racemic compounds is a reliable method, but since half of the optical isomers are discarded, it cannot be said to be a desirable method from the standpoint of costs and green chemistry. Combination with a racemization recovery system can be considered, but in these systems, there is a drop in the purity in the racemization process, so it is difficult to construct a sufficient recovery system. Therefore, we investigated asymmetric synthesis for directly obtaining the optically active compound. First, we will introduce the synthesis methods already known, including the latest results in the following.

(1) Existing Methods Using Asymmetric Synthesis and Their Characteristics
(i) Diastereoselective Addition Reaction Using Asymmetric Auxiliary Groups (**Fig. 4**)[3]

Expensive asymmetric auxiliary groups must be used quantitatively, and when ethyl benzoyl formate is added, the diastereoselectivity is not all that high.
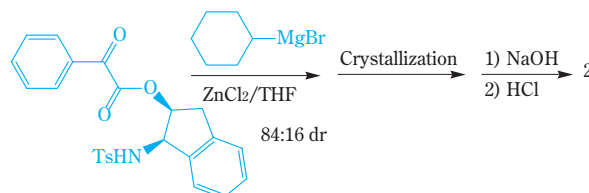

Fig. 4 Diastereoselective organometallic addition with chiral auxiliaries

(ii) Method Using Dioxolone Derived from Optically Active Mandelic Acid (**Fig. 5**)[4], [5]

This uses Seebach's self-renewing diastereoselective

aldol reaction.[6] The use of comparatively inexpensive optically active mandelic acid as the raw material is attractive, but obtaining good diastereoselectivity requires an ultra-low temperature of –78°C, and productivity is difficult.
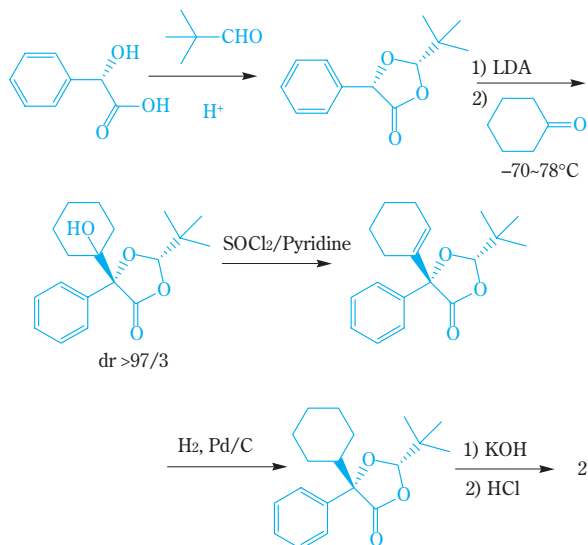

Seebach's diastereoselective aldol reaction using chiral mandelic acid derivatives

(iii) Method using Sharpless Asymmetric Dihydoxylation (**Fig. 6**)[7]

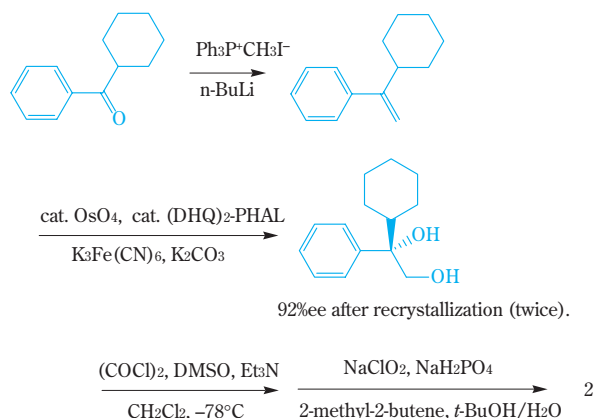Highly toxic osmium tetroxide is used. The asymmetric yield is not always satisfactory in this case.

Fig. 6 Sharpless asymmetric dihydoxylation

(iv) Methods Using Asymmetric Cyanosilylation (**Fig. 7**)[8), 9]

This method was recently reported by the group of Tokyo University Professor Shibazaki et al., and it achieves catalytic asymmetric cyanosilylation of ketones, which has been difficult up to this point. How-

ever, there is a need for separate adjustments to the asymmetric catalyst for industrial use, and in addition, the toxicity is high and comparatively expensive Trimethylsilyl cyanide (TMSCN) must be used.
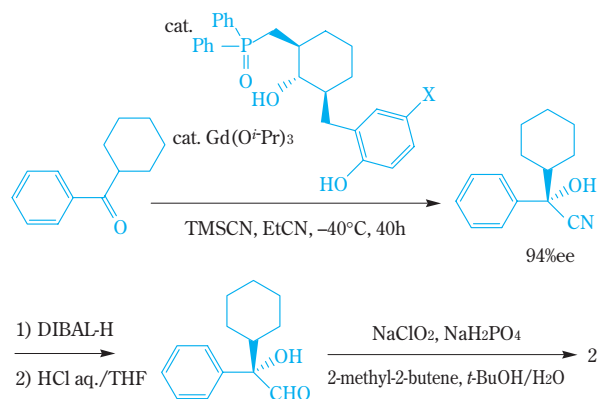

Fig. 7 Shibazaki's asymmetric cyanosilylation

(2) Our Approach to Synthesizing Optically Active Compounds

(i) Asymmetric Ene Reaction Tests

We also carried out racemic compound synthesis using Ene reactions, and initially we looked for possibilities for Ene reactions. First we used a BINOL-TiCl2[10] compound, which was developed by Professor Mikami at Tokyo Institute of Technology and has become the standard for asymmetric Ene reactions, and carried out investigations under various conditions without making any progress at all (**Fig. 8**). At the time, almost no examples of the progress of asymmetric Ene reactions on ketones were known,[11] but recently, Prof. Mikami et al. published an example of a catalytic asymmetric Ene additive reaction progressing on the ketone with a good yield through the use of a cationic palladium complex having Lewis acid properties (**Fig. 9**),[12] so we tried using that asymmetric catalyst. However, while the reaction for extremely electron deficient ketones, such as methyl trifluoroacetyl formate certainly progressed, the reaction for methyl benzoyl formate with a 1,1-methyl benzoyl formate di-substituted olefin such as methylenecyclohexane as the nucleophilic reagent did not progress, to say nothing of there being absolutely no progress in the reaction with internal olefins (**Fig. 10**). To improve the electron attraction of the ester parts, we investigated changing to hexafluoro isopropyl ester and to increase the cationic properties of the catalyst, changing to SEGPHOS ligands instead of BINAP ligands, but the results were the same.
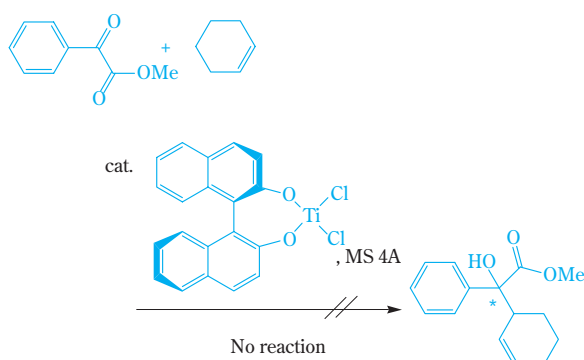
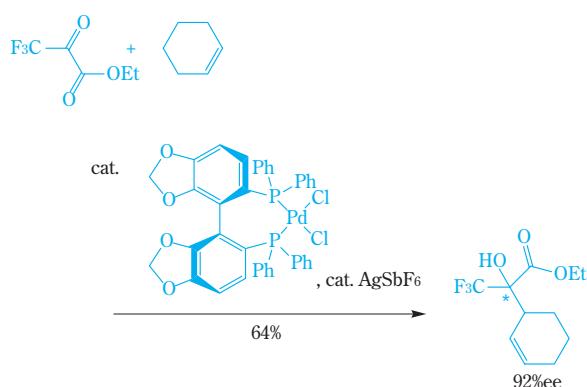**Fig. 8** Asymmetric ene approach using Mikami's BINOL-TiCl2 catalyst

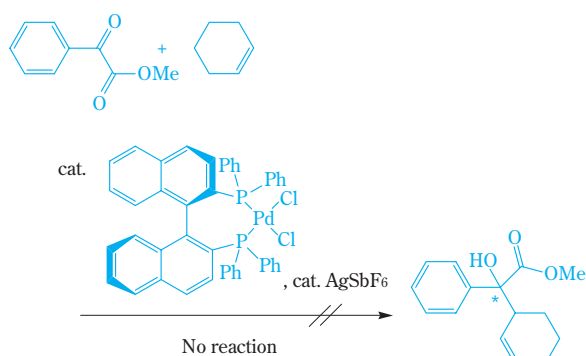**Fig. 9** Dicationic palladium (II) comlexes catalyzed asymmetric ene reactions

Fig. 10 Asymmetric ene approach using dicationic palladium (II) catalyst

Thus, at present, the hurdles for catalytic asymmetric Ene reactions for ethyl benzoyl formate derivatives are very high, and additionally, having determined the inevitability of the cost for the catalyst being high, we decided to shift to investigations of other methods, even though we had developed a provisional asymmetric catalyst.

(ii) Use of the Inexpensive Catalyst "L-Proline"

At the beginning of 2000, there was a report by List,

Barbas et al. of a direct asymmetric aldol reaction[13] using Proline (**Fig. 11**), and in addition, there were reports, one after another from MacMillan et al. of an asymmetric Diels-Alder[14] reaction using a simple asymmetric organic catalyst derived from an amino acid, of an asymmetric dipolar addition reaction,[15] and of an asymmetric Friedel-Crafts reaction[16] (**Fig. 12**). At the time, an asymmetric catalyst meant an organic metal complex having asymmetric ligands if no particular limits were put on it, but their reports changed the concept of asymmetric catalysts that had been held up to that time. There were several reports of asymmetric organic catalysts that did not contain metals before their reports,[17]–[19] but they were extremely limited, and the possibilities were not always suggested. Conversely, their reports truly suggested the possibilities for asymmetric organocatalysis, and the actual development afterwards was startling with a large research area being spoken of.[20]–[22] At present, "asymmetric organocatalysis" has typically come to be defined in a form that includes the field of asymmetric phase-transfer catalysis,[24] the development of which has been
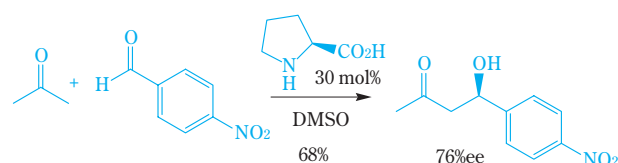

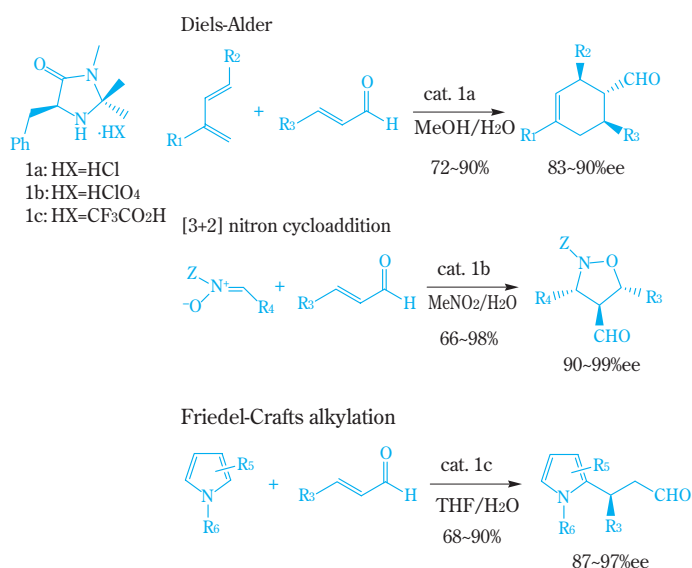**Fig. 11** Proline catalyzed asymmetric direct aldol reaction

Fig. 12 MacMillan's enantioselective organocatalytic reactions

startling, starting from the opportunity of asymmetric phase-transfer catalysts[23] designed by Kyoto University Professor Maruoka et al.
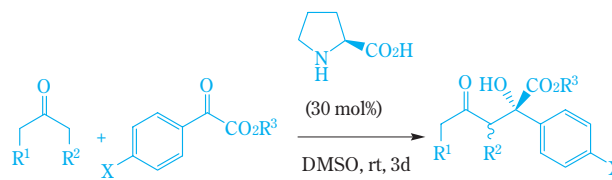
Among the asymmetric organic catalysts, Proline is inexpensive and has a simple structure, but, even compared with similar amino acids, it was recognized to be a specifically acting, high performance catalyst in subsequent research.[25] However, since it is an organic catalyst, the reactivity is, of course, poor, and it is limited to aldehydes such as benzaldehyde. As far as we know, there has only been an example for keto-malonic acid ester, which is an extremely electron deficient ketone, reported.[26]

Thus, it can be assumed that if an additive reaction progresses provisionally for ethyl benzoyl formate, we can expect high selectivity. In our previous investigation of the Ene reaction, we recognized that ethyl benzoyl formate is a good acceptor, so we thought that even though there are no reported examples up to that point, it merited investigation and decided to conduct tests.

As a result, we found that production with good yields was only obtained when DMSO was used as a solvent. Furthermore, the product had a selectivity greater than predicted with a diastereomer ratio greater than 20:1 and an optical purity of 96% ee (**Table 1**). This reaction is the first example of a direct asymmetric aldol reaction for ethyl benzoyl formate using an organic catalyst. As a result of subsequent investiga-

Table 1 Proline catalyzed asymmetric construction of a tetrasubstituted carbon center

entry	solvent	time	Yield[a]	dr	% ee (major)
1	neat	4d	15%	>20/1	96%
2	CHCl3	4d	15%	>20/1	97%
3	THF	4d	10%	>20/1	97%
4	MeOH	4d	35%	>20/1	88%
5	Toluene	4d	<10%	—	—
6	DMF	4d	28%	>20/1	96%
7	DMSO	7d	75%[b]	>20/1	96%
8	NMP	4d	24%	>20/1	96%
9	Dioxane	4d	<10%	>20/1	97%
10	Sulfolane	4d	12%	>20/1	95%

a) Determined by ^{1}H-NMR, b) Isolated Yield

tions into the range of applicability for this reaction, we found that the yield and selectivity improved even further with methyl ester. Furthermore, we found that there was good reactivity for ethyl benzoyl formate without substitutions or with electron withdrawing group substitutions, but with ethyl benzoyl formate with electron donating group substitutions, the selectivity was as good as before, but the reactivity dropped. Furthermore, cyclohexanone was the best nucleophilic reagent, and cyclopentanone and acetone resulted in a reduction in selectivity (**Table 2**).

Table 2 The scope of the proline catalyzed direct asymmetric aldol reaction between cyclohexanone and phenylglyoxylate
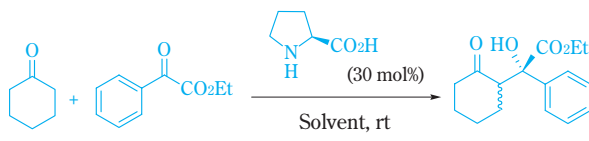

entry	R^1	R^2	R^3	X	Yield	dr	% ee (major)
1	$-(CH_2)_3-$		Me	H	89%	>20/1	98%
2	$-(CH_2)_3-$		Et	Me	45%	>20/1	>99%
3	$-(CH_2)_3-$		Et	CF$_3$	>99%	>20/1	97%
4	$-(CH_2)_3-$		Et	Cl	95%	>20/1	96%
5	H	H	Me	H	92%	—	9%
6	$-(CH_2)_2-$		Me	H	89%	85/15	41%

We initially tried Wolff-Kishner reduction for deriving (S)-CHPGA from the aldol adduct obtained, but it was accompanied by the elimination of hydroxyl groups, and good results were not obtained. As a result of examining various possibilities, we found smooth progress in borane reduction of the ketone and the elimination reaction through the action of LiCl in DMF for a mesylate where hydroxyl groups have been mesylated. By reducing, hydrolyzing and recrystallizing the olefins obtained in this manner by normal methods it is possible to derive (S)-CHPGA (greater than 99% ee) with a good yield (**Fig. 13**).

As described above, we found a direct asymmetric aldol reaction for cyclohexanone and ethyl benzoyl formate using inexpensive L-Proline as the catalyst as a simple method for synthesizing optically active tertiary alcohols, and we showed that (S)-CHPGA, which is a key intermediate for (S)-oxybutynin, can be derived from the aldol adduct obtained by industrial preparation methods. This reaction can easily construct a tetra-
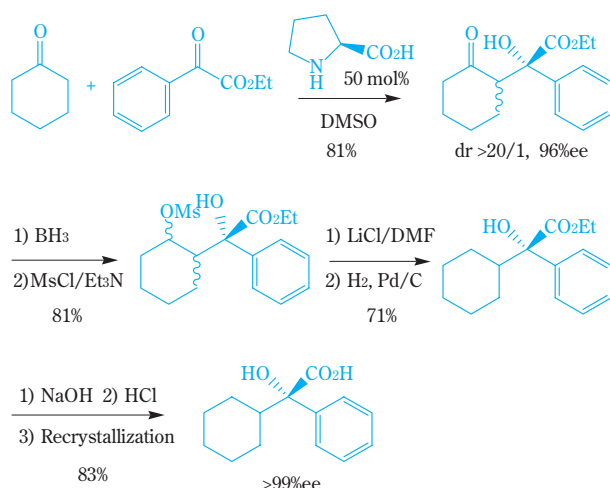
Fig. 13 A practical synthesis of (S)-CHPGA via an organocatalytic asymmetric construction of a tetrasubstituted carbon center

substituted asymmetrical center, so we plan to expand the breadth of the technique so as to expand the range of application by getting feedback into the catalyst design, taking into consideration the reaction mechanism.

Conclusion

While there are more compounds having optically active tertiary alcohol sites among pharmaceutical intermediates than one would think, there are few established methods for actually constructing optically active tertiary alcohols at present, as was mentioned at the beginning of this paper. This is an academically challenging field, and there is no doubt that a large area will be built in the field of research for asymmetric synthesis in the future. Having recognized that there is a chance for business in a field like this, we are continuing research day and night, and, though we did not discuss it because of the limitations of space in this paper, we have developed a new preparation method for antifungal agent intermediates (**Fig. 14**) for which
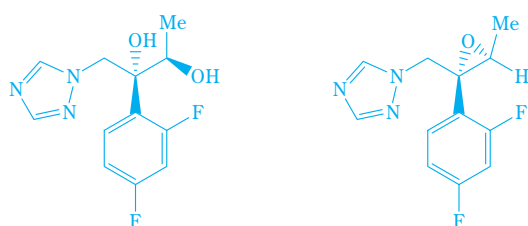

Fig. 14 Key intermediates for the preparation of antifungal agents

the key technology is the construction of optically active tertiary alcohols, and are building up a record.

Finally, we would like to thank Professor Keiji Maruoka and Dr. Taichi Kano of the Graduate School of Kyoto University and Professor Koichi Mikami of the Graduate School of Tokyo Institute of Technology, who gave us helpful advice for carrying out this research.

References

1) SS Pharmaceuticals, JP11-193271 (1999).
2) Sumika Fine Chemicals, JP2002-205972 (2002).
3) C. H. Senanayake, K. Fang, P. Grover, R. P. Bakale, C. P. Vandenbossche, and S. A. Wald, *Tetrahedron Lett.*, **40**, 819 (1999).
4) P. T. Grover, N. N. Bhongle, S. A. Wald, and C. H. Senanayake, *J. Org. Chem.*, **65**, 6283 (2000).
5) X. Su, N. N. Bhongle, D. Pflum, H. Butler, S. A. Wald, R. P. Bakale, and C. H. Senanayake, *Tetrahedron: Asymmetry*, **14**, 3593 (2003).
6) D. Seebach, R. Naef, and G. Calderani, *Tetrahedron*, **40**, 1313 (1984).
7) P. Gupta, R. A. Fernandes, and P. Kumar, *Tetrahedron Lett.*, **44**, 4231 (2003).
8) S. Masumoto, M. Suzuki, M. Kanai, and M. Shibasaki, *Tetrahedron Lett.*, **43**, 8647 (2002).
9) S. Masumoto, M. Suzuki, M. Kanai, and M. Shibasaki, *Tetrahedron*, **60**, 10497 (2004).
10) K. Mikami, M. Terada, and T. Nakai, *J. Am. Chem. Soc.*, **112**, 3949 (1990).
11) D. A. Evans, S. W. Tregay, C. S. Burgey, N. A. Paras, and T. Vojkovsky, *J. Am. Chem. Soc.*, **122**, 7936 (2000).
12) K. Aikawa, S. Kainuma, M. Hatano, and K. Mikami, *Tetrahedron Lett.*, **45**, 183 (2004).
13) B. List, R. A. Lerner, and C. F. Barbas III, *J. Am. Chem. Soc.*, **122**, 2395 (2000).
14) K. A. Ahrendt, C. J. Borths, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **122**, 4243 (2000).
15) W. S. Jen, J. J. M. Wiener, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **122**, 9874 (2000).
16) N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, **123**, 4370 (2001).
17) U. Eder, G. Sauer, and R. Wiechert, *Angew. Chem., Int. Ed. Engl.*, **10**, 496 (1971).
18) Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **39**, 1615 (1974).
19) U. –H. Dolling, P. Davis, and E. J. J. Grabowski, *J.*

Am. Chem. Soc., **106**, 446 (1984).

20) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, **43**, 5138 (2004).

21) J. Seayad and B. List, *Org. Biomol. Chem.*, **3**, 719 (2005).

22) *J. Org. Chem. Soc. Jpn*, **63**, 46 (2005).

23) T. Ooi, M. Kameda, and K. Maruoka, *J. Am. Chem. Soc.*, **121**, 6519 (1999).

24) K. Maruoka and T. Ooi, *Chem. Rev.*, **103**, 3013 (2003).

25) K. Sakthivel, W. Notz, T. Bui, and C. F. Barbas III, *J. Am. Chem. Soc.*, **123**, 5260 (2001).

26) A. Bøgevig, N. Kumaragurubaran, and K. A. Jørgensen, *Chem. Commun.*, **2002**, 620.

■ **P R O F I L E**

Tetsuya IKEMOTO

Sumitomo Chemical Co., Ltd.
Fine Chemicals Research Laboratory
Senior Research Associate, Ph. D.

Wei-Guo GAO

Sumika Electronic Materials (Shanghai) Co., Ltd.
Manufacturing Department
Manager, Ph. D.

Osamu TOKUDA

Sumitomo Chemical Co., Ltd.
Fine Chemicals Research Laboratory
Research Associate