The Design of Environmentally–Benign, High–Performance Organocatalysts for Asymmetric Catalysis

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Abstract: By the end of the 20th century several advantages of organocatalysis, for example environmental friendliness, operational simplicity, mild reaction conditions etc., had led to its recognition as a powerful principle for the establishment of practical organic synthetic methods. Over the two decades since then tremendous effort has been devoted to the design of novel organocatalysts able to realize unprecedented reactions. In this review our recent results on the design and development of various types of organocatalysts, such as organobase, organoacid, organoacid/base and organoradical catalysts, and their application to a wide variety of synthetic transformations are described.

1. Introduction

Chiral catalysts, which underwent rapid development during the latter half of the twentieth century, are mostly chiral metal catalysts possessing chiral auxiliaries, or biocatalysts. In recent years, the design of new chiral catalysts and new environmentally–benign asymmetric transformations is becoming increasingly important for the construction of new and useful chiral molecules from simple organic resources. In this context, organocatalysis has recently emerged as a field of research providing practical technologies alternative or complementary to the more traditional, transition metal–catalyzed systems. The characteristic features of organocatalysis include its operational simplicity, and the ready availability, easy recovery and reuse, and low associated toxicity of the catalysts, and these make it a highly attractive method for preparing complex and multi–functionalized organic molecules. Accordingly, we have been interested in this exciting field, and have studied and developed our own organocatalytic chemistry since 1998. This review focuses on the design of high–performance organocatalysts, including organobase, organoacid, organoacid/base and organoradical catalysts, for application to various new asymmetric methodologies in order to develop our own unique organocatalytic chemistry.

2. Design of Chiral Phase–Transfer Catalysts as Organobase Catalysts

About 90 (18%) of the top–500 best–selling drug products in the world use α–amino acids as intermediates. These include for example, amoxicillin (antibiotic), captopril, enalapril, lisinopril (antihypertensive drugs), norvir, amiprenavir (anti–HIV drugs) and acyclovir (antiviral drug), etc. Therefore amino acids are indispensable for the preparation of drugs, and have entered the mainstream of medicinal products. Asymmetric synthesis of α–amino acids by enantioselective alkylation of a prochiral, protected glycine derivative using a chiral phase transfer catalyst (chiral PTC) has provided an attractive method for the preparation of both natural and unnatural amino acids (Scheme 1).

However, when we started to look at asymmetric phase–transfer chemistry in 1998, almost all the chiral phase–transfer catalysts that had been developed were cinchona alkaloid derivatives, which unfortunately constituted a major difficulty in rationally designing and fine–tuning of the catalysts to attain sufficient reactivity and selectivity. It was against this background that the structurally rigid, chiral spiro–ammonium salts of type (R,R)–3 and (S,S)–3 possessing 3,3′–diaryl substituents, which are derived from commercially available (R)– or (S)–1,1′–bi–2–naphthol respectively, were designed as new C3–symmetric chiral phase–transfer catalysts, and applied to the asymmetric synthesis of enantio–2a and 2a, respectively (Scheme 2). In the same way, the similar catalysts (S,S)–4 possessing 4,4′,6,6′–tetraaryl substituents also exhibited excellent enantioselectivity in the enantioselective synthesis of 2a. Interestingly, the combination of 0.05 mol % of each of (R,R)–3d and 18–crown–6 at 0 °C for 3 h greatly accelerated the phase–transfer alkylation, giving enantio–2a in 90% yield with 98% ee. It should be noted that without 18–crown–6 the yield is significantly lowered (only 4%). Although the conformationally rigid, N–spiro structure created by two chiral binaphthyl subunits is a characteristic feature of 3 and related catalyst 4, it also imposes limitations on the catalyst design due to the need to use two different chiral binaphthyl moieties. Accordingly, we developed a new C3–symmetric chiral quaternary ammonium bromide 5 incorporating an achiral, conformationally flexible biphenyl subunit. The phase–transfer benzylolation of 1a using the catalyst (S)–5a having a β–naphthyl group on the 3,3′–positions of the flexible biphenyl moiety proceeded smoothly at 0 °C to afford 2a in 85% yield with 87% ee after 18 h.

Scheme 1. Asymmetric, phase–transfer alkylation of a prochiral, protected glycine derivative.
Interestingly, introduction of the 3,4,5-trifluorophenyl group at the 3,3'-positions of chiral binaphthyl moieties as in (S)-6b resulted in the absolute configuration of product, affording enantioselectivity.

This finding led to the discovery that chiral quaternary ammonium bromide 7 (now registered as Simplified Maruoka Catalyst®), possessing flexible, straight-chain alkyl groups instead of a rigid binaphthyl moiety, functions as an unusually active chiral phase-transfer catalyst. Most notably, the reaction of 1a with various alkyl halides proceeded smoothly under mild phase-transfer conditions in the presence of only 0.05 mol % of (S)-7 to afford the corresponding alkylation products 2a with excellent enantioselectivities (Scheme 3). 

The synthetic utility of our chiral phase-transfer catalysts was highlighted by the facile synthesis of L-Dopa ester and its analogues, which have usually been prepared by either asymmetric hydrogenation of eneamides or enzymatic processes, and have been tested as potential drugs for the treatment of Parkinson’s disease. Catalytic phase-transfer alkylation of glycine tert-butyl ester 1a with the requisite benzyl bromide 8 in toluene—50% KOH aqueous solution proceeded smoothly at 0 °C under the influence of (R,R)-3e (1 mol %) to furnish fully protected L-Dopa tert-butyl ester, which was subsequently hydrolyzed with 1 M citric acid in THF at room temperature to afford the corresponding amino ester 9 in 81% yield with 98% ee. Debenzylation of 9 under catalytic hydrogenation conditions produced the desired L-Dopa tert-butyl ester 10 in 94% yield (Scheme 4).

In addition to chiral α-monoalkyl—α-amino acids, non-proteinogenic, chiral α,α-dialkyl—α-amino acids possessing stereochemically stable, quaternary carbon centers are also significant synthetic targets, not only because they are often effective enzyme inhibitors, but also because they are indispensable for the elucidation of enzymatic mechanisms. Accordingly, numerous studies have been conducted to develop truly efficient methods for their preparation, and phase-transfer catalysis has made some unique contributions. Since the aldime Schiff base 1b can be readily prepared from glycine, direct stereoselective introduction of two different side chains

Our further efforts toward simplifying the catalyst have led to the design of new, polyamine-based, chiral phase-transfer catalysts of type 6 in the expectation of achieving the multiplier effect of chiral auxiliaries as illustrated in Scheme 3. The chiral efficiency of such polyamine-based, chiral phase-transfer catalysts (S)-6 was examined by carrying out asymmetric alkylation of glycine derivatives under phase-transfer conditions. Among various commercially available polyamines investigated, spermidine and spermine-based polyammonium salts were found to show moderate enantioselectivity. Interestingly, introduction of the 3,4,5-trifluorophenyl group at the 3,3'-positions of chiral binaphthyl moieties as in (S)-6b resulted in the absolute configuration of product, affording enantioselectivity.

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(Scheme 2). The observed chiral efficiency could be ascribed to the considerable difference in catalytic activity between the rapidly equilibrated, diastereomeric homo- and heterochiral catalysts; namely, homochiral (S,S)-5a is primarily responsible for the efficient asymmetric phase-transfer catalysis (PTC) to produce 2a with high enantiomeric excess, whereas heterochiral (R,S)-5a displays low reactivity and stereoselectivity. This unique phenomenon provides a powerful strategy for the molecular design of chiral catalysts, and quaternary ammonium bromides possessing a sterically demanding substituent such as (S)-5b and (S)-5c exhibited higher enantioselectivity (92% ee and 95% ee, respectively) in the asymmetric benzylation of 1a.

Scheme 2. Design of new C₃-symmetric, chiral phase-transfer catalysts.
to 1b by appropriate chiral phase-transfer catalysis would provide an attractive and powerful strategy for the asymmetric synthesis of structurally diverse α,α-dialkyl-α-amino acids in one pot (Scheme 5). Of course, asymmetric monoalkylation of aldime Schiff base 11 derived from an α-alkyl-α-amino acid would also provide α,α-dialkyl-α-amino acids as indicated in Scheme 5.

**Scheme 5.** New strategy for asymmetric synthesis of α,α-dialkyl-α-amino acids.

The possibility of a one-pot, asymmetric double alkylation has been realized by using a N-spiro, chiral quaternary ammonium bromide of type 3e (Scheme 6). In addition, asymmetric monoalkylation of α-alkyl-α-amino acid derivatives appears feasible by using (S,S)-3e or (S)-7 to furnish various types of α,α-dialkyl-α-amino acids (Scheme 7).

**Scheme 6.** One-pot dialkylation sequence for asymmetric synthesis of α,α-dialkyl-α-amino acids.

**Scheme 7.** Asymmetric synthesis of α,α-dialkyl-α-amino acids by asymmetric alkylation of α-alkyl-α-amino acid derivatives.

Peptide modification provides a useful strategy for efficient target screening and optimization of lead structures in the application of naturally occurring peptides as pharmaceuticals. The introduction of side chains directly to a peptide backbone represents a powerful method for the preparation of unnatural peptides. An achiral glycine subunit has generally been used for this purpose. However, control of the stereochemical outcome of these transformations in an absolute sense is not easy, especially in the modification of linear peptides, and hence development of an efficient and practical approach to establish sufficient stereoselectivity and general applicability has been crucially important. Accordingly, we examined the chirality transfer in the diastereoselective alkylation of the dipeptide, Gly-L-Phe derivative 15 (Scheme 8).

**Scheme 8.** Stereoselective alkylation of peptides under asymmetric phase-transfer catalysis.

The catalytic asymmetric cyanation of imines, the Strecker reaction, represents one of the most direct and viable methods for the asymmetric synthesis of α-amino acids and their derivatives. Numerous recent efforts in this field have led to the establishment of highly efficient and general protocols, although the use of either alkylmetal cyanide or anhydrous hydrogen cyanide, generally at low temperature, is inevitable. We disclosed the first example of a phase-transfer-catalyzed, highly enantioselective Strecker reaction of aldimes using aqueous KCN based on the molecular design of chiral quaternary ammonium salt (R)-17, having a tetranaphthyl backbone, as a highly efficient organocatalyst (Scheme 9).

**Scheme 9.** Asymmetric Strecker reaction under phase-transfer catalysis.
The fluoride-mediated generation of nucleophiles from organosilicon compounds for selective bond-forming reactions is very useful in organic synthesis. This approach implies the possibility of developing an asymmetric version based on the use of a chiral, nonracemic fluoride ion source as represented by chiral quaternary ammonium bifluorides of type 18. Indeed, the asymmetric nitroaldol reaction and conjugate addition of silyl nitronates are found to be highly efficient under the influence of chiral quaternary ammonium bifluorides (S,S)-18a~b (Scheme 10).

Scheme 10. Asymmetric reaction of silyl nitronates with chiral quaternary ammonium bifluorides.

3. Design of Organoacid Catalysts

3.1 With Axially Chiral Dicarboxylic Acids Based on Binaphthyl Structures

Over the last decade, chiral organoacid catalysis has attracted great attention as a useful tool for asymmetric transformations. Several types of Brønsted acid, including urea/thioureas, diols and phosphoric acids, have been widely utilized as chiral organoacid catalysts. On the other hand, one archetypal class of Brønsted acids, the carboxylic acids, had rarely been employed in chiral organoacid catalysts, an exception being the mandelic acid-based catalyst developed by Yamamoto and Momiyama. Because the acidity of carboxylic acids lies between that of thioureas and phosphoric acids, they would be expected to show unique reactivity, unachievable with other organoacid catalysts. In this context, our group designed the new binaphthyl-based organoacid catalysts (R)–19a~d containing a dicarboxylic acid core, and successfully demonstrated their synthetic versatility in asymmetric reactions (Scheme 11).

Scheme 11. Design of axially chiral, dicarboxylic acid catalysts based on binaphthyl structures.

We first revealed the unique catalytic activity of (R)–19a in the asymmetric Mannich reaction of N–Boc imines with diazoacetates, furnishing β–amino–α–diazoesters in high yields with excellent enantioselectivities (Scheme 12a). Although the chiral phosphoric acid–catalyzed Mannich reaction of N–acyl imines with diazoacetates had previously been reported by Terada, the use of the dicarboxylic acid catalyst was found to be crucially important in the case of N–Boc imines. The use of diazoacetamide instead of diazo ester was possible, leading to an asymmetric synthesis of trans–aziridines in good yields with excellent diastereoselectivity and enantioselectivity (Scheme 12b). We further applied our dicarboxylic acid (R)–19c to asymmetric reactions using in situ–generated, acyclic azomethine imines, which had not previously been employed in asymmetric catalysis (Scheme 12c).

Scheme 12. Asymmetric reactions of N–Boc imines with diazo compounds.

a) N Boc + CO2Bu (R)-19a (5 mol%) CH2Cl2, MS4A 0 °C
b) N Boc + PhH PhCl2 toluene, MS4A 0 °C

c) RCHO + CO2R (R)-19c (5 mol%) PhCF3, MS4A 

The asymmetric imino azah–enamine reactions between N–Boc imines and N,N–dialkyl hydrazones was also achieved by using the dicarboxylic acid (R)–19a (Scheme 13a). Aldehyde N,N–dialkylhydrazones are known as a useful class of acyl anion equivalent. However, asymmetric reactions using such hydrazones had been limited to the case of the formaldehyde derivatives. The use of dicarboxylic acid catalyst enabled expansion of the reaction to aryl aldehyde N,N–dialkylhydrazones. We have also succeeded in extending this reaction to vinylogous azah–enamines (Scheme 13b). Here the N–benzoyl protecting group of the imine had a significant effect on the product yield as well as enantiomeric excess.


a) N Boc + H N N R R (R)-19d (5 mol%) CH2Cl2, MS4A −20 ~ −30 °C
b) N Bz + H N N R R (R)-19d (10 mol%) CH2Cl2, MS4A −35 °C

Quinone imines and quinone imine ketals have been widely utilized as useful synthetic intermediates; however, their application in asymmetric catalysis has rarely been reported. In this context noteworthy is the arylation of enecarbamates catalyzed by the dicarboxylic acid (R)–19a which has been successfully developed to furnish α–amino–β–aryl ethers in high yields
with excellent diastereo- and enantioselectivities (Scheme 14). In 2013, the in situ-assembled, boronate ester-assisted, chiral carboxylic acid-catalyzed, asymmetric aziridinations.

### 3.2 With Chiral Organoacid Catalysts based on Boronic Acids

In 2013, the in situ-assembled, chiral organoacid catalyst composed of a chiral diol and a 2-boronobenzoic acid was developed (Scheme 15). In this system, a chiral diol controls the chiral environment, while an achiral Brønsted acid governs the acidity of catalyst, thus providing an opportunity for fine-tuning of both chiral environment and catalyst acidity independently and without the need for extensive synthetic efforts to prepare a variety of different catalysts. Screening chiral diols and boronobenzoic acids revealed that the combination of chiral diol 20 and 2-boronobenzoic acid 21 enabled highly enantioselective trans-aziridinations of N-Boc imines with N-phenyldiazoacetamide. We tentatively propose that in situ-generated (S,S)-22 should be viewed as the true catalyst. By employing 10 mol % of chiral 3-borono-BINOL 23 with 50 mol % of α-nitrobenzoic acid (α-NBA) as a co-catalyst, theaza-Michael adducts derived from quinone imine ketals and a hydroxamic acid were obtained in high yields with excellent enantioselectivities (Scheme 16). Mechanistic studies suggest that the in situ-formed dimer of the boronic acid catalyst should activate both the hydroxamic acid and the quinone imine ketal (Scheme 17).

The asymmetric Mannich reaction is a useful method for the preparation of optically active β-amino carbonyl compounds. Asymmetric Mannich reactions catalyzed by proline or its derivatives generally provide syn-Mannich adducts as the major diastereomer, while only a few secondary amine catalysts have shown the opposite anti-selectivity in similar reactions. In this context, our newly designed, axially chiral sulfonamide (S)-24 successfully realized the opposite anti-selectivity in the Mannich reaction between aldehydes with imines (Scheme 19). In addition to simple aliphatic aldehydes, employing an α-aminoacetaldehyde as nucleophile also provided an anti–vicinal diamine. Furthermore, asymmetric Mannich reaction of highly reactive acetaldehyde with N-Boc imine also proceeded smoothly to give the corresponding adduct with virtually perfect enantioselectivity. A similar tendency can also be seen with asymmetric cross-aldol reactions. Although proline-catalyzed aldol reactions furnished anti–aldol adducts predominantly, our catalyst (S)-
In enamine catalysis, the direct cross-aldol reaction between two simple aliphatic aldehydes has remained a challenging problem because simple aliphatic aldehydes can act as both nucleophile and electrophile. This tends to cause the formation of mixtures including the two cross-aldol adducts and the two homo-aldol adducts, all as stereoisomers. To overcome this hurdle, we employed α-chloroaldehydes as acceptor in the amine-catalyzed cross-aldol reaction (Scheme 21). We envision that the introduction of chloro group on α-position of aldehyde would inhibit or slow down the formation of enamine intermediate, and also expected that α-chloroaldehyde, which is electronically activated by the α-chloro group, would react predominantly with the enamine intermediate. In the presence of biphenyl-based amino sulfonamide (S)-25, the reaction between 3-methylpropanal and α-chloroaldehyde gave a syn-cross-aldol product selectively, while conversely the use of proline as catalyst afforded an anti-cross-aldol product. The chloro group on the aldol–products was readily removed by treatment with LiAlH₄, affording the chiral 1,3-diols.


We have also achieved the direct asymmetric α-amination of aldehydes by using the C₂-symmetric amino diol (S)-26a as catalyst (Scheme 22, left). In the presence of (S)-26a, the reaction between 3-methylbutanal and nitrosobenzene as aminating agent provided a hydroxyamination product with excellent enantioselectivity, in sharp contrast to the asymmetric aminohydroxylation (α-oxygenation) of aldehydes with nitrosobenzene catalyzed by proline or its analogues. In a similar manner, the hitherto difficult asymmetric α-iodination of various aldehydes proceeded smoothly when catalyzed by (S)-26b to furnish α-iodoaldehydes in high yields with excellent enantioselectivities (Scheme 22, right).

Scheme 22. Asymmetric α-functionalization of aldehydes.

At the time we started our work various asymmetric conjugate additions of enamines had been developed, but success with three-carbon Michael acceptors, i.e., acrylate, acrylamide and acrylonitrile, had proved elusive, probably due to their low reactivity. Against this background, we successfully utilized methylenealenate or 1,1,1,3,3,3-hexafluoropropyl acrylate as a three-carbon Michael acceptor for the asymmetric conjugate addition of aldehydes in the presence of the biphenyl-based amino diol (S)-27a or (S)-27b (Scheme 23).

Scheme 23. Asymmetric conjugate addition of aldehydes.

4.2 With Chiral Primary Amino Sulfonamide Catalyst

When compared to chiral secondary amine catalysts, chiral primary amine catalysts have been less investigated in enamine catalysis. However, they often realize unique reactivity and selectivity, which are not achievable by the use of secondary amine catalysts. Besides the biaryl-based secondary amine catalysts mentioned above, we designed and developed the new chiral, bifunctional primary amine catalyst (S,S)-28 based on a dihydroanthracene framework (Scheme 24). Using this catalyst, the highly enantioselective conjugate addition of hetero-substituted aldehydes to electron-deficient olefins was developed.

Scheme 24. Chiral primary amine-catalyzed asymmetric conjugate addition.
chiral quaternary ammonium salts can provide them with novel catalytic activity (Scheme 25). Indeed, in 2007 a novel bifunctional $N$–spiro chiral quaternary ammonium catalyst (S)–29a having a dialkylhydroxymethyl substituent at the 3,3'-positions of the biphenyl moiety was found to be effective for the asymmetric epoxidation of enones (Scheme 26a). In contrast, the reaction with catalyst (S)–29b having no hydroxyl group under otherwise identical conditions resulted in almost total loss of catalytic activity as well as a decrease in stereoselectivity. The bifunctional phase–transfer catalyst (S)–30a having the combination of thiomorpholine and bis (dialkylhydroxymethyl) substituents catalyzed the highly enantioselective fluorination of $\beta$-keto esters with $N$–fluorobenzenesulfonyl fluoride (Scheme 26b).

Scheme 25. Design of bifunctionalized phase–transfer catalysts.

Scheme 26. Asymmetric epoxidation of enones and fluorination of $\beta$-keto esters.

As described in section 2, phase–transfer reactions catalyzed by quaternary ammonium salts are generally believed to require base additives to promote the reaction. However, we recently discovered that some base–free, neutral phase–transfer reactions could be promoted by the use of chiral bifunctional ammonium bromides as catalyst (Scheme 27). By using (S)–30b or (S)–30c, the asymmetric conjugate additions of 3-phenylindole or tert-butyldimethylsilylcarbamate to $\beta$-nitrostyrene proceeded smoothly under neutral conditions in a water–rich solvent. It should be noted that both reactions in toluene without water do not proceed at all, implying that water is essential for promotion of the reactions.

5. Design of Organoradical Catalysts

5.1 With Organo Thiol Radical Catalyst

In comparison with the organobase, organoaicid and organoaicid/base catalysts mentioned above, the research field of organoradical catalysts has, as yet, rarely been explored. In this context, we recently succeeded in developing rationally designed, organic thiol radical catalysts (Scheme 28). The thiol radical, which can be easily generated from the corresponding thio or disulfide, has been utilized as an organoradical catalyst for several radical reactions. However, research efforts focused on the rational design of organic thiol radical catalysts for the realization of asymmetric radical reactions or high performance catalytic activity have been rare. In 2014, we developed novel, chiral organic thiol radical catalysts based on the indanol unit for the highly diastereoselective radical [3+2] cyclization between vinylcyclopropanes and alkenes. Our initial attempts using binaphthyl–based chiral disulfide or thiol catalysts failed to give high enantioselectivity of product (up to ~40% ee). Thus, our attention was turned to designing a novel, chiral thiol radical catalyst. Finally, chiral thiols of type (R)–31 based on an indanol structure were found to be effective for the present reaction. Under photo-irradiation the radical cyclization reactions of vinylcyclopropanes and electron–rich alkenes in the presence of (R)–31 and BPO smoothly proceeded, affording substituted cyclopentanes with high diastereoselectivity (Scheme 29).

Scheme 27. Asymmetric conjugate additions under base–free, neutral, phase–transfer conditions.


Scheme 29. Enantioselective, radical cyclization catalyzed by chiral thiol.

The bulky achiral disulfide 32 was also found to be employable for the thiol–radical catalyzed [3+2] cyclization reactions of $N$–tosyl vinylaziridines with alkenes (Scheme 30). In this reaction the sterically hindered substituents of the catalyst were crucially important to circumvent catalyst deactivation. This reaction’s utility was demonstrated by a modification of $C_{60}$ fullerene with vinyl aziridine to give a functionalized fullerene...

Scheme 31. Radical hydroacylation of electron-deficient olefins with acyl radicals.

6. Conclusion
Over the last two decades, a wide variety type of organocatalysts have been developed by many research groups. In this context, we have originally designed several organocatalysts, such as organobase, organoacid, organoacid/base and organo-radical catalysts, and revealed their unique reactivity and selectivity as described in this review. We believe that further studies toward a design of a conceptually novel organocatalysts may lead to develop more practical and environment benign organic synthetic chemistry.

References
PROFILE

Ryu Sakamoto is an assistant professor of Kyoto University. He received his Ph.D. degree from Kyoto University in 2014 under the supervision of Professor Keiji Maruoka. He then serves as a JSPS postdoctoral fellow with Professor Keisuke Suzuki at the Tokyo Institute of Technology. He became an Assistant Professor in 2015 at the Graduate School of Science, Kyoto University. His research interests involve development of novel organocatalysts and establishment of new radical reactions.

Keiji Maruoka graduated from Kyoto University (1976) and received his Ph.D. (1980) from University of Hawaii (Thesis Director: Prof. H. Yamamoto). After having stayed at Nagoya University as an assistant professor, a lecturer and an associate professor, he promoted to a full professor at Hokkaido University (1995–2001), and currently is a professor of chemistry in Kyoto University since 2000. Recently, he was awarded the Inoue Science and Technology Award (2012), Humboldt Research Award (2011), the Award by the Ministry of Education, Culture, Sports, Science and Technology (2006), the Japan Chemical Society Award (2007), Molecular Chirality Award (2007), Novartis Lectureship Award (2007/2008), Arthur C. Cope Scholar Awards (2011), Medal of Honor with Purple Ribbon (2011), Torey Science & Technology Award (2012), and Noyori Prize (2016). He has a wide range of research interests in synthetic organic chemistry, and his current research interests include bidentate Lewis acids in organic synthesis and practical asymmetric organocatalysis using high–performance organocatalysts such as Maruoka catalysts, etc.