Organocatalytic Synthesis of Highly Functionalized Heterocycles by Enantioselective aza-Morita–Baylis–Hillman-Type Domino Reactions

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Organocatalytic enantioselective domino reactions are an extremely attractive methodology, as their use enables the construction of complex chiral skeletons from readily available starting materials in two or more steps by a single operation under mild reaction conditions. Thus, these reactions can save both the quantity of chemicals and length of time typically required for the isolation and/or purification of synthetic intermediates. Additionally, no metal contamination of the products occurs, given that organocatalysts include no expensive or toxic metals. The aza-Morita–Baylis–Hillman (aza-MBH) reaction is an atom-economical carbon–carbon bond-forming reaction between α,β-unsaturated carbonyl compounds and imines mediated by Lewis base (LB) catalysts, such as nucleophilic phosphines and amines. aza-MBH products are functionalized chiral β-amino acid derivatives that are highly valuable as pharmaceutical raw materials. Although various enantioselective aza-MBH processes have been investigated, very few studies of aza-MBH-type domino reactions have been reported due to the complexity of the aza-MBH process, which involves a Michael/Mannich/H-transfer/β-elimination sequence. Accordingly, in this review article, our recent efforts in the development of enantioselective domino reactions initiated by MBH processes are described. In the domino reactions, chiral organocatalysts bearing Brønsted acid (BA) and/or LB units impart synergistic activation to substrates, leading to the easy synthesis of highly functionalized heterocycles (some of which have tetrasubstituted and/or quaternary carbon stereocenters) in high yield and enantioselectivity.

Key words heterocycle; organocatalyst; domino; chiral quaternary carbon stereocenter

1. Introduction

Since the initial definition of the domino process by Tietze in 1993,1-4 the development of stereoselective domino reactions has drawn much research attention in organic chemistry.5-7 The efficiencies of enantio- and diastereoselective domino reactions is can be judged by the numbers of bond formations and newly produced chiral centers, and especially, by an increase in molecular complexity. Organocatalytic carbon–carbon bond-forming domino reactions are a particularly attractive aspect of this methodology, as their use enables the construction of complex chiral skeletons directly from readily available compounds in two or more steps by a single operation without the use of toxic metals.7 These sequences can also save on the quantity of chemicals and amount of time required for the isolation and/or purification of synthetic intermediates, allowing for environmentally benign syntheses.

The Morita–Baylis–Hillman (MBH) reaction8,9 is an extremely useful 100% atom-economic C–C-bond formation between the α-position of an electron-deficient alkene and the sp² carbon of an aldehyde catalyzed by nucleophilic amines or phosphines (Chart 1). Although ignored for a long time after its discovery in 1968 by Morita10 (phosphine-catalyzed version) and in 1972 by Baylis and Hillman11 (amine-catalyzed version), by the late 1980s, the MBH reaction and its applications have been of growing interest. Imines can also be used as substrates in the reaction, in which case it is referred to as the aza-MBH reaction.12-34 According to the reaction shown in Chart 1, aza-MBH products are functionalized amines, which are highly valuable synthetic building blocks for pharmaceutically important compounds.11 Accordingly, significant research has been devoted to developing highly active chiral catalysts for MBH and aza-MBH reactions12-34 (Fig. 1).

Chart 2 shows that the aza-MBH reaction involves a Michael addition, Mannich reaction, proton-transfer (H-transfer)
Fig. 1. Highly Active Catalysts for the Enantioselective MBH and aza-MBH Reactions

Biography
Shinobu Takizawa is an Associate Professor (from 2009) at the Institute of Scientific and Industrial Research (ISIR), Osaka University. He received his B.S. in 1995 (under Professor Toru Koizumi) and M.S. in 1997 (under Professor Takefumi Momose) from Toyama Medical and Pharmaceutical University, and a Ph.D. in 2000 (under Professor Yasuyuki Kita) from Osaka University. He was a JSPS research fellow from 1999–2000. He became an Assistant Professor at ISIR, Osaka University in 2000. From 2006–2008, he was a Research Associate at the Scripps Research Institute (under Professor Dale L. Boger). He received the Daiichi Pharmaceutical Co., Ltd. Award in Synthetic Organic Chemistry, Japan (2000), Tetrahedron Letters Most Cited Paper Award (2007), Tetrahedron: Asymmetry Most Cited Paper Awards (2008 and 2009), the Pharmaceutical Society of Japan Award for Young Scientists (2009), the Daiichi-Sankyo Co., Ltd. Award in Synthetic Organic Chemistry, Japan (2009), the Osaka University Presidential Award for Encouragement in Research (2015) and the Pharmaceutical Society of Japan Award for Divisional Scientific Promotion (2019). His current research interest is focused on the development of sustainable synthetic reactions with machine learning optimization.
and \( \beta \)-elimination (retro-Michael reaction) sequence.\(^{35}\) The Michael addition reaction of the Lewis base (LB) catalyst to the electron-deficient alkene produces an enolate \( A \), that reacts with the imine to afford the zwitterionic intermediate \( B \). H-transfer from the \( \alpha \)-carbon atom to the \( \beta \)-amide in the intermediate ketone \( B \), followed by the \( \beta \)-elimination of the LB catalyst, affords an aza-MBH adduct, an allylic amine, with the regeneration of the LB-catalyst.

For a long time, the Mannich reaction of intermediate \( A \) with the imine to generate the two stereocenters in \( B \) was considered to be the rate-determining step (RDS). However, this view was refined as a result of detailed MBH and aza-MBH mechanistic studies by Eberlin and colleagues,\(^{36}\) Raheem and Jacobsen,\(^{18}\) McQuade and colleagues,\(^{37}\) Leitner and colleagues,\(^{38}\) Harvey and colleagues,\(^{39}\) Sunoj and colleagues.\(^{40}\) In the first stage of the reaction, the RDS is the H-transfer that occurs in \( B \) to form \( C \). Later, the Mannich process becomes the RDS, since the aza-MBH product is able to work as a H-transfer reagent.

The stereochemistry considerations are more complex for the aza-MBH reaction. A Brønsted acid (BA) unit on the catalyst promotes H-transfer for one of the four diastereomers of \( B \). Thereafter, a highly enantioselective aza-MBH reaction can be achieved, since the addition of the LB catalyst to the enone, and the attack of the resulting enolate \( A \) to the imine are reversible. However, either the LB catalyst alone or in combination with a protic additive such as a BA co-catalyst can cause the racemization of aza-MBH product via the retro-MBH process. Therefore, the applicability of aza-MBH domino reactions to synthesis is very often limited.

We assumed that if the BA and LB units were appropriately fixed on a single chiral skeleton, the base would selectively react with the electron-deficient alkene (Michael reaction), while the acid in a chiral environment would provide an enantioselective H-transfer reagent. Thus, the spatial arrangement of the acid–base catalyst would be crucial for the stereo-differentiation. Additionally, the irreversible domino cyclization in the final step would prevent subsequent epimerization and reversible reactions, leading to the easy synthesis of highly functionalized heterocycles by a single operation in a one-pot process (Chart 3).

This review article describes our recent research on the development of organocatalyzed domino reactions initiated by enantioselective MBH-type processes.\(^{41-52}\)

2. Synthesis of Highly Functionalized Isoindolines and Tetrahydropyridines Initiated by Enantioselective aza-MBH Reactions\(^{41,42}\)

Isoindoline skeletons are standard structures in a variety of natural products and pharmaceuticals, such as nuevamine\(^{53}\) and pagoclone,\(^{54}\) as well as their functionalized derivatives.\(^{55}\) As such, these materials show a range of biological potencies.
involving anti-leukemic, anxiolytic, anti-tumoral, and potent endothelin A receptor antagonist activities.\textsuperscript{53–55} Due to the numerous potential applications of these heterocycles, the development of efficient and novel synthetic approaches for isoindolines has received special attention.\textsuperscript{56} However, very few studies have addressed the catalytic preparation of 1,3-disubstituted isoindolines.\textsuperscript{57–58}

We assumed that optically active 1,3-disubstituted isoindoline 3 could be readily synthesized from enone 1 and N-tosylimine 2 bearing a Michael acceptor unit at the o-position with a BA-LB-organocatalyst (Chart 4). Initially, the Michael addition of the LB unit to 1 forms chiral enolate I, which is stabilized by the BA. This then reacts with 2 to generate intermediate II. In the aza-MBH reaction, H-transfer from the α-position of the carbonyl group to the amine group, followed by the β-elimination of the catalyst, proceeds to furnish the normal aza-MBH product 4. Alternatively, the nitrogen anion of intermediate II can undergo an intramolecular reaction with the attached Michael acceptor, resulting in the generation of optically active 3 through intermediate III, together with the regeneration of the chiral catalyst via H-transfer and β-elimination.

Our assumption proved to be correct, thus we consequently developed an enantioselective aza-MBH/intramolecular aza-Michael domino process for the first time, which is promoted by (S)-2-diphenylphosphanyl-[1,1'-binaphthalenyl-2-ol [(S)-5]\textsuperscript{16} The optimal outcome (98% yield, 92% enantiomeric excess (ee)) was obtained when the reaction of methyl vinyl ketone (1a) with imine 2a was carried out in CHCl\textsubscript{3}\textsuperscript{59} (0.2 M for 2) at 10°C in the presence of MS 3 Å\textsuperscript{60} (Table 1, entry 1). Phenyl vinyl ketone (1b) and ethyl vinyl ketone (1c) were also found to be appropriate substrates, providing isoindolines 3\textsubscript{b} and 3\textsubscript{c}, respectively, with high enantioselectivities (entries 2–3). Other α,β-unsaturated carbonyl derivatives, e.g. acrolein and phenyl acrylate (1d, e), promoted the reactions with acceptable outcomes (entries 4–5).

Table 1. Synthesis of 1,3-Disubstituted Isoindolines by a Chiral Organocatalyzed aza-MBH Domino Reaction

| entry | R\textsuperscript{1} | R\textsuperscript{2} | R\textsuperscript{3} | yield of 3 [%]\textsuperscript{15} | ee of 3 [%]\textsuperscript{15} |
|-------|-------------------|-----------------|-----------------|---------------------|----------------------|
| 1     | Me, 1a            | H               | 2a              | 98 (3a)             | 92                   |
| 2     | Ph, 1b            | 2a              | 72 (3b)         | 88                  |
| 3     | Et, 1c            | 2a              | 97 (3c)         | 92                  |
| 4     | H, 1d             | 2a              | 49 (3d)         | 87                  |
| 5     | OPh, 1e           | 2a              | 66 (3e)         | 68                  |
| 6\textsuperscript{11} | 1a               | H               | 2b              | 85 (3f)             | 93                   |
| 7\textsuperscript{2} | 1a               | H               | 2c              | 78 (3g)             | 91                   |
| 8     | 1a                | 5-Me            | 2d              | 75 (3h)             | 89                   |
| 9\textsuperscript{3} | 1a               | 5-F             | 2a              | 80 (3i)             | 92                   |
| 10\textsuperscript{4} | 1a               | 5-Cl            | 2f              | 76 (3j)             | 93                   |
| 11    | 1a                | 6-Cl            | 2g              | 88 (3k)             | 82                   |
| 12    | 1a                | 2h              | 73 (3l)         | 82                   |
| 13    | 1a                | CO\textsubscript{Me} | 2i             | 88 (3m)             | 85                   |

Reaction conditions: 1 (0.10 mmol), 2 (0.050 mmol), catalyst (S)-5 (10 mol %), 0.2 M (concentration of 2) in CHCl\textsubscript{3}, 10 °C. 1) Isolated yield. 2) Determined by HPLC on a chiral stationary phase. 3) No MS was used. 4) MS 4 Å was used.

![Chart 4. First Enantioselective aza-MBH/Intramolecular aza-Michael Domino Process](image-url)
Considering the substituent R on imines 2, isoindolines 3f and 3g were produced in good yield (entries 6–7). High enantiomeric excesses (up to 93% ee) were established irrespective of the electronic nature of the 5-substituent position on the aromatic ring of 2 (entries 8–10). The 6- and 3-substituents lead to 3k–m with high enantiomeric excesses (82–85% ee), respectively (entries 11–13).

Notably, the use of sole LB catalysts, e.g. (S)-2,2′:binaphthyl [(S)-BINAP] and (R)-2,2′:binaphthyl-2′-methoxy-1,1′-binaphthyl [(R)-Me-MOP], led to drastically decreased yields (< 28%) and enantiomeric excesses (< 15%) of 3a, and the pronounced decomposition of 2a was observed. These results indicate the relevant acid–base organocatalyst effectively promotes the aza-MBH domino process with high enantiomeric excess.

Because cis,1,3-disubstituted isoindoline is more thermodynamically stable than the trans-form and, in addition, given that the intramolecular aza-Michael reaction is reversible, cis-3 could be generated as single diastereomer (ΔE = 4.13 kcal/mol on MM2). The absolute and relative configurations of 3b were determined by NMR spectroscopy and X-ray crystallographic analyses. This aza-MBH/intramolecularaza-Michael domino process is found to be cis-selective, with (R,S)-configured 3 generated when using (S)-5 (Fig. 2).

In order to provide mechanistic insight into the present domino process, an intramolecular aza-Michael reaction was carried out, with the racemic 4a catalyzed by (S)-5 in CHCl3 at −20°C. The reaction rate was quite slow, with trace amounts of 3a isolated with the recovery of most of the initial 4a (Eq. 1 in Fig. 2). Under the same conditions, the domino reaction of 1a with 2a afforded 3a in 38% yield, with 94% ee without the generation of 4a (Eq. 2 in Fig. 2). Thus, it is apparent that the intramolecular cyclization of intermediate II furnishes 3 directly without producing 4a (Chart 4).

A variety of transformations were carried out to demonstrate the synthetic utility of the highly functionalized aza-MBH domino product 3a (Chart 5). The allyl alcohol 6 can be generated by Luche reduction of isoindoline 3a using Yb(OTf)3. Treatment of the major diastereomer 6 with Mg/MeOH cleaves the N-Ts group to afford the amino alcohol 7 in 98% yield (step b). α-Methyl ketone 8 is obtained in good yield as a single diastereomer without over-reduction by 1,4-conjugate reduction of 3a using Zn powder/NH₂Cl. The Michael addition of dibenzyl malonate to 3a with DBU furnishes 9 in 90% yield with high diastereoselectivity (d.r. 96:4). Moreover, 3a is readily hydrolyzed to β-amino acid 10 by exposure to aqueous LiOH/tetrahydrofuran (THF), preserving its high optical purity.

Tetrahydropyridines are also known to exhibit interesting bioactivities, such as their antioxidant, antibiofilm, anti-inflammatory, and pluripotent inhibitory properties against human cancer cell lines. In 2011, we reported another aza-MBH-type domino reaction (Chart 6). (S)-3-[(N-isopropyl-N-3-pyridinylamino)methyl]BINOL (11), as an acid-base organocatalyst, is the most efficient for the domino reaction of acrolein (1d) and N-tosylarylimines 3 derived from benzaldehydes. Regardless of whether the aromatic substituent of 3 is electron-withdrawing or electron-donating, the acid-base organocatalyst (S)-11 promotes the aza-MBH/intermolecularaza-Michael/aldol/dehydration sequence to afford highly functionalized tetrahydropyridines in up to 60% yield and 93% ee.

3. Synthesis of Azetidines with a Chiral Tetrasubstituted Carbon Stereocenter by Formal [2 + 2] Cycloaddition

Optically active azetidines, which represent an important class of four-membered N-heterocycles, have received considerable attention due to their utilization as organocatalysts, and their pharmaceutical and biological potencies. In general, synthetic access to optically rich azetidines are multi-

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**Fig. 2. X-Ray Structure of (R,S)-3b (CCDC 784114)**
The [2 + 2] cycloaddition is one of the most powerful methods for the formation of a strained four-membered ring. As the first to achieve the aza-MBH-type reaction of allenates with aldimines, in 2003, Shi and colleagues reported the construction of azetidines through DABCO-catalysed formal [2 + 2] cycloaddition, with further enantioselective contributions by Zhu and colleagues. However, few reports have described the formal enantioselective [2 + 2] cycloaddition using ketimines, which can construct tetrasubstituted carbon units. Ketimines are well-known to be considerably less unstable and reactive than aldimines, although the enantioface differentiation of ketimines is more difficult due to smaller steric and electronic differences between the two substituents on the prochiral carbon. Thus, effective enantioselective formation of chiral tetrasubstituted carbon stereocenters through the formal [2 + 2] cycloaddition of ketimines remains a challenge in asymmetric synthesis.

As the initial step in the development of the aza-MBH reaction of ketimines, the reaction of 13a and ethyl allenoate (14a) was tested utilizing 20 mol % of chiral organocatalysts. Amongst the catalysts we tested, β-isocupreidine (β-ICD), an acid–base organocatalyst known to promote enantioselective MBH reactions, provides 15a in 49% yield with 80% ee (Table 2, entry 1). By contrast, cinchonidine, quinidine and (S)-11 show no catalytic activity (entries 3–5). Noticeably, neither the formation of 16a nor (Z)-15a is isolated in any reaction. However, ethyl 2-oxo-2-phenylacetate is observed as a by-product through the hydrolysis of 13a.

To prevent the decomposition of moisture-sensitive ketimine, MS 4 Å was added to the reaction media; this improves the yield (69%) and maintains high enantioselectivity (87% ee) (entry 2). The optimal result was obtained when the reaction of 13 with 14 was carried out in a mixed solvent comprising THF/1,4-dioxane (1/2) at −5°C with MS 3 Å (Chart 7). The highly E-selective and (R)-configured azetidines 15 (83–90% ee) were obtained under these optimal conditions, irrespective of the electronic nature of substituent groups on the aromatic ring of 13. The reactions of 13d (Ar = 3-tol, R1 = Et) and 13f (Ar = benzo[d][1,3]dioxol-5-yl, R1 = Bn) and using benzyl allenoate 14b (R2 = Bn) lead to the generation of the E-selective 15d, 15h and 15i (70–79% yields) along with the acyclic α-adducts 17d, 17h and 17i (6–18% yields). Optically pure 15i was isolated after a single recrystallization.

Various transformations were carried out to demonstrate
the synthetic utility of the highly functionalized azetidine 15 (Chart 8). Allyl alcohol 18 is formed by the diisobutylaluminium hydride (DIBAL)-H reduction of 15f without over-reduction. β-Lactam 19 is isolated in 96% yield by oxidation with O₃. The treatment of lactam 19 with Mg/MeOH cleaves the amide bond to afford acyclic α,α-disubstituted amino acid derivative 20 in good yield. Azetidine 15k can react with phenylboronic acid through Suzuki–Miyaura cross-coupling to afford biphenyl 21 quantitatively. The absolute configurations of 15 were assigned by the comparison of their optical rotations with that of the synthetic analogue reported in the literature after the transformation to 3-phenyl-1-tosylpyrrolidine-2,5-dione (23) via hydrogenation, followed by the amidation of 19.

Chart 9 shows our proposed mechanism for the formal [2 + 2] cycloaddition of 13 with 14 using β-ICD as a chiral catalyst. The addition of β-ICD to 14 gives the resonance-stabilized zwitterionic intermediate I, which can react with 13 via two different pathways. The addition of the γ-carbanion to 14 yields intermediate IIa, which upon [2 + 2] cyclization af-
Chart 9. Proposed Reaction Mechanism for the Formal [2 + 2] Cycloaddition

Table 3. Catalyst Search for the Formal [4 + 2] Cycloaddition of 24a with 25

| entry | chiral phosphine | time (h) | temp (°C) | ratio of 26a 26a\(^\text{a}1\) | % total yield\(^1\) | % ee of 26a\(^2\) | % ee of 26a\(^\text{a}1\)\(^2\) |
|-------|------------------|----------|-----------|--------------------------|----------------|----------------|------------------|
| 1     | (S)-BINAP or (S)-Me-MOP | 24        | reflux    | -                        | no reaction    | -              | -                |
| 2     | (R)-QUINAP       | 24        | reflux    | -                        | no reaction    | -              | -                |
| 3     | (S)-S or (S)-27 | 24        | reflux    | -                        | no reaction    | -              | -                |
| 4     | (R)-DIOP         | 24        | reflux    | 1.3:1                    | 35             | 55             | 11               |
| 5     | (S,R)-BPPFA      | 24        | reflux    | 1.2:1                    | 34             | 70             | 6                |
| 6     | (S,R)-BPPFOH     | 24        | reflux    | 1.2:8                    | 23             | 84             | 9                |
| 7     | (R)-SITCP        | 3         | 25        | 5:1                      | 83             | 86             | 8                |
| 8\(^3\) | (R)-SITCP       | 3         | 25        | >20:1                    | 88             | 90             | -                |

Reaction conditions: 24a (0.082 mmol), 25 (0.164 mmol), and chiral phosphine catalyst (20 mol %). 1) Determined using NMR. 2) Determined by HPLC on a chiral stationary phase. 3) MS 4A was added.
forinds intermediate III. To suppress steric interactions between the aryl substituent of the ketimine and the quinoline catalyst, the β-ICD-mediated reaction favors the (R)-configuration product. Thereafter, E-15 would be formed by steric repulsion between the CO₂R² functionality and Ts group in the fragmentation of III with the regeneration of the catalyst. By contrast, the addition of the α-carbanion to the ketimine to give 16 was not supported, probably due to steric hindrance by the ketimine (intermediate IIb). The use of methyl-capped β-ICD resulted in low selectivity and activity, suggesting that the phenolic hydroxyl group on β-ICD may play a crucial role in the intramolecular activation of the substrates to fruitfully mediate the aza-MBH-type reactions with high enantioselectivity (Chart 10).

4. Synthesis of Tetrahydropyridines with a Chiral Tetrasubstituted Carbon Stereocenter by Formal [4 + 2] Cycloaddition

In 2003, Kwon presented the first synthesis of tetrahydropyridine frameworks using aldmines and α-substituted allenoates promoted by PBu₃ as a LB organocatalyst through formal [4 + 2] cycloaddition. After this success, the LB-catalyzed formal [4 + 2] reaction has been recognized as one of the most concise methods for the preparation of six-membered N-heterocycles. Later, an enantioselective Kwon reaction was successfully developed by Wurz and Fu and Zhao and colleagues, independently. In 2012, Ye first presented the achiral LB-mediated [n + 2] reaction of ketimines for the formation of azetidines, dihydropyroles and tetrahydropyridines, thereby making an important contribution to the challenging field of creating tetrasubstituted carbon stereocenters. Despite the potential of such six-membered N-heterocycles with a tetrasubstituted carbon stereocenter in the pharmaceutical sciences, no enantioselective formal [4 + 2] cycloaddition of ketamines has been reported.

As the initial step in the development of a formal enantioselective [4 + 2] cycloaddition of ketamines, the reaction of cyclic ketimine 24a with α-methyl allenoate 25 using various chiral LB organocatalysts was studied (Table 3). The first trials revealed that chiral axially triaryl phosphines, such as (S)-BINAP, (S)-MeMOP, (S)-1-(2-diphenylphosphinopheno-l-naphthyl)isoquinoline, (S)-QUINAP, (S)-5, or (S)-27, which are effective in activating α,β-unsaturated carbonyl compounds in the MBH process, are inactive in the transformation (entries 1–3). However, when 25 was added to the reaction mixture, resulting in the recovery of 24a. The absolute configuration of 24a was determined by X-ray crystallographic analysis (Fig. 3).

Next, the scope of substrates was evaluated (Chart 11). Highly enantioselective and excellent regioselective cyclization occurred under the optimized conditions, irrespective of the electronic nature of the substituent on the aromatic ring (26a–h). The introduction of the bulky 2-naphthyl group into the ketimine allowed the maintenance of excellent regioselectivity (26i). However, because of diminished enantioselectivities (26j and 26k), a heteroaryl substituent and an ester moiety were successfully introduced. Even at an increased reaction temperature and prolonged reaction time, the alkyl-substituted ketimine 26l failed to yield any product, resulting in the recovery of 24l. The absolute configuration of 26c was determined by X-ray crystallographic analysis (Fig. 3).

Chart 11. Substrate Scope for the Formal [4 + 2] Cycloaddition of 24 with 25

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On the basis of the observed results and previous reports,75,78,79 we propose that the reaction proceeds as shown in Chart 12. The addition of a phosphine unit on the catalyst to 25 triggers the formation of zwitterionic species I. The nucleophilic spiro-type phosphine catalyst results in the kinetically favored γ-addition to 24 through intermediate Ia. After the formation of intermediate IIa, intramolecular cyclization produces 26 with regeneration of the (R)-SITCP catalyst. To prevent steric interactions between the phenyl substituent in the catalyst and the R substituent of cyclic ketimines 25, the reaction using (R)-SITCP favors the formation of the (R)-configuration products 26a–i or the (S)-configuration products 26j and 26k. A H-source such as H2O or 2-naphthol 82 could support the formation of intermediate Ib, leading to β-adduct 26’. The addition of MS 4 Å to the reaction media may prevent unfavorable outcomes (Table 3, entries 7 and 8).

5. Stereoselective Synthesis of α-Methylidene-γ-lactams by Amidation/Rauhut–Currier Sequence

α-Alkylidene-γ-lactam derivatives are found in a vast number of biologically active compounds.83 As the lactams exhibit multiple medicinal benefits similar to those of their lactone analogues, including low toxicity, excellent synthetic methods for the lactams have been explored by many chemists.83 To date, several enantioselective and catalytic syntheses of the lactams have been studied84; however these lactam syntheses often require complex synthetic building blocks and are subject to side-reactions owing to the highly reactive exo-alkylidene moiety. Therefore, the development of an easy synthesis to γ-lactams, especially enantioselective synthesis, remains a great challenge for researchers in this field.

α-Substituted α,β-unsaturated carbonyl compounds can be readily accessed by the Rauhut–Currier (RC) reaction, also called the vinylogous MBH reaction, through the coupling of two different α,β-unsaturated enones wherein one acts as a latent enolate.85 As part of our research into the development of enantioselective domino reactions,41–52,86–90 we became interested in designing sequences to address optically active α-methylidene-γ-lactams. We envisioned that the amidation of 28 with 27, followed by the BA-LB-catalyzed carbon–carbon bond-forming reaction of intermediary 29, would result in the generation of α-methylidene-γ-lactams 30 in high yield with high enantiocontrols (Chart 13).
First of all, we chose readily available 27 and dienone 28a as model substrates to determine the optimal sequential conditions. Among the organocatalysts we tested, acid–base catalyst 31 (Chart 13), derived from (S)-valine, showed high catalytic activity (Table 4). When 150 mol% of (S)-31 was utilized, the desired lactam 30a (85% yield, 84% ee) was generated as a single diastereomer, and the corresponding RC precursor 29a was not observed (entry 1). As catalyst 31-HCl salt is generated as an inactive catalyst in situ, various achiral bases that can trap the generated HCl to restore the catalytic activity of 31 were studied. Consequently, the addition of N,N-diisopropylethylamine (DIPEA) or N,N,N’,N’-tetramethyl-1,8-naphthalenediamine (proton sponge) was found to restore the catalytic activity. In the presence of 20 mol% of catalyst 31 with DIPEA or the proton sponge (1.5 eq.), product 30 was formed in 82% yield with 76% ee (DIPEA), and in 51% yield with 64% ee (proton sponge) (entries 2 and 5). By contrast, DBU and tetramethylguanidine do not impart any improvement to the process (entries 3 and 4). Thereafter, 30a was isolated in 92% yield with 80% ee when utilizing catalyst 31 (20 mol%) under reflux conditions (entry 6). As DIPEA itself was not observed (entry 1). As catalyst 31-HCl salt does not mediate the reaction at all (entry 7), DIPEA probably functions as a restoration reagent for the catalytic activity of (S)-31. These outcomes suggest that catalyst 31 functions as a LB and Brønsted base (BB) catalyst for the sequential processes.

Thereafter, the scope of the amidation/RC sequence was investigated (Chart 14). The high enantiocontrol of lactams 30b–i was achieved (70–86% ee) when utilizing substrates 28 with various substituents [R1 = 4-tol (28b), 2-tol (28c), 4-Br-C6H4 (28d), 4-Br-C6H4 (28e), 3-Cl-C6H4 (28f), Me (28g), Et (28h) or vinyl (28i); R2 = Ts; R3 = H]. The acid–base catalyst 31 also mediates the reaction of 28j–k with methanesulfonyl amide (R1 = Ph or Me, R2 = Ms, R3 = H) to afford 30j–k in good yields, however, with slightly decreased enantioselectivities. The formation of structural motifs having two contiguous quaternary carbon stereocenters is considered to be particularly challenging in synthetic chemistry. 29) The reaction of 28l (R1 = R3 = Me, R2 = Ts) is allowed as a suitable substrate for the enantioselective sequence, affording the corresponding lactam 30l in 84% ee.

When the amidation of acryloylchloride (27) with dienone 28 is carried out utilizing powdered NaOH, RC precursor 29 bearing an acrylamide unit can be isolated. The study of this stepwise transformation is shown in Chart 15. Upon comparison of the results for the stepwise transformation and one-pot amidation/RC sequence, in all entries, the stepwise transformation displayed better enantioselectivities. However, RC precursors 29c–e (R1 = 2-tol, 4-Br-C6H4 or 4-Br-C6H4; R2 = Ts, R3 = H) and 29j (R1 = Ph, R2 = Ms, R3 = H) could not be isolated, due to their instability. The one-pot procedure may be useful as an alternative synthetic method for highly functionalized α-methylidene-γ-lactams 30.

Encouraged by the success of the stepwise process, next, the recovery and reuse of the catalyst 51 was tested. 29) After completion of the reaction of 29g, the organocatalyst 51 and RC product 30g were separated by simple acid/base extraction. Recovered catalyst 51 was then directly utilized for the next reaction without any purification. Even after being reused at least five times, our acid–base organocatalyst 51 retained its activity to give the product 30g in 95% yield with 94% ee.
Moreover, optically pure 30g is easily accessible by the single recrystallization of the optically pure RC product from CH2Cl2/hexane. The absolute configuration of (R,R)-30g formed by the reaction with catalyst (S)-51 was confirmed by single crystal X-ray analysis (Fig. 4).

Chart 16 shows a plausible mechanism for the present sequence consisting of an amidation step and an RC cycle. In the first amidation step, organocatalyst 31, working as a BB, abstracts a proton from the nitrogen atom of substrate 28 and immediately reacts with 27, leading to the precursor 29 together with the protonated catalyst 31. Without any inhibition of the amidation and RC processes, DIPEA efficiently restores the BB catalytic activity of 31 from protonated 31 in situ (Table 4, entry 7). In the later RC cycle, the Michael addition of catalyst 31 to the acrylamide moiety of 29 forms the ammonium intermediate A (Int. A), stabilized by the BA unit of catalyst 31(94) which reacts in a manner influenced by the interactions between the TsN and R substituent of the substrate and iPr substituent of the chiral catalyst 31. Thus, the present organocatalyzed reaction may impart the (R,R)-configuration to intermediate B (Int. B), which is formed by the second Michael reaction. H-Transfer from the α-position of a carbonyl group of the lactam to the enolate anion in Int. B through the BA unit(94) leads to the optically active lactam 30, along with regeneration of the catalyst 31 via the β-elimination of the LB moiety in (S)-31. In the presence of D2O (excess), the reaction of 29g produced the partially α-deuterated 30g [D content (%): α: 50, α': 0], thereby indicating that the intramolecular Michael process of Int. A includes irreversibility under optimized reaction conditions (Eq. 1 in Chart 16).

In 2012, we also found that the desymmetrization of the prochiral substrate 32, which is readily prepared from commercially available phenols(95) via a manner similar to RC, is an atom-economical and concise way to afford α-methylidene-γ-butyrolactones 33.43,45) The nucleophilic phosphine and Brønsted acidic sulfonamide in catalyst 34 synergistically work to mediate the intramolecular RC reaction and afford the medicinally important lactones with high chemo-, diastereo- and enantioselectivities (Chart 17).

6. Synthesis of Tetrahydrobenzofuranones Bearing a Chiral Tetrasubstituted Carbon Stereocenter via LB-Catalyzed β,γ-Umpolung Sequence of Allenoates(97)

As we described in Sections 3 and 4 in this review article, the organocatalyzed cyclization of allenoates has been widely explored as an extremely powerful method for the construction of structurally divergent hetrocycles.44,46,96) In 1995, Lu first reported achiral LB-catalyzed [3 + 2] annulation of allenoates with imines or enones (Chart 18, A) through α- or γ-zwitterionic intermediates.97) Aided by the development of an enantioselective version developed by Zhang,98) [n + 2] annulations were deeply considered for the construction of heterocycles and carbocycles.96) Within this related field, the γ-umpolung (polarity reversing) addition of nucleophiles to electron-deficient allenes and alkynes produces γ-substituted

![Chart 16. Plausible Reaction Mechanism](image)

![Chart 17. Facile Synthesis of α-Methylidene-γ-butyrolactones via Intramolecular RC Reactions Promoted by Chiral Acid–Base Organocatalysts](image)
α,β-unsaturated enones (Chart 18, B). Based on the pioneering efforts of Cristau\(^{99}\) (stoichiometric process), Trost\(^{100}\) (catalytic process for alkynes), Lu\(^{101}\) (for allenes) and Zhang\(^{102}\) (enantioselective version), there has been increasing interest in γ-umpolung additions of various nucleophiles to electron-deficient allenes and alkynes.\(^{103}\) As part of our research into chiral LB catalysis,\(^{41–52}\) we became interested in designing new sequences to approach important structures via nucleophilic attack to the γ-position of allenoates. Before the elimination of the LB catalyst, if the zwitterionic intermediate C would react with electrophiles, the result may be a formal dual umpolung coupling (Chart 18).

To investigate the utility of the proposed sequence, an LB-mediated desymmetrization of the prochiral substrates 35 and 14 was designed (Chart 19). The addition of an LB to 14 formed the zwitterionic intermediate I, which can act as a BB for 35, resulting in key intermediates II and III. The γ-addition of III to II would afford the transit intermediate IV and generate an allylic ether 36 after elimination of the LB-catalyst. Alternatively, the tethered ylide IV could react intramolecularly with the dienone via a β-addition, leading to V and the chiral tetrahydrobenzofuranone 37 through H-transfer and elimination of the catalyst. Tetrahydrobenzofuranone structures are useful to a large number of natural products (e.g. sorbicillactone A, loukacinol A, and cryptocaryone) working as anti-human immunodeficiency virus (HIV), anti-cancer, and glucose-transport inhibitors.\(^{104}\) Our designed sequence would be an atom-economic and concise way to produce optically active tetrahydrobenzofuranones.

**Chart 18. LB-Catalyzed Processes of Allenoates with Nucleophiles and/or Electrophiles**

**Chart 19. LB-Organocatalyzed Chemo-, Regio-, Diastereo- and Enantioselective β,γ-Umpolung Sequence**

**Chart 20. Substrate Scope for the β,γ-Umpolung Sequence of Allenoates**

Reaction conditions: 14 (1.5 eq.), 35 and (R)-(S)-STCP (20 mol %) in CH₂Cl₂/toluene (1:1) at 0 °C for 48 h (37a-f and 37h-i), for 8 h (37g), for 24 h (37h) and for 72 h (37g). Ee of 37 was determined by HPLC on a chiral stationary phase.
25°C. Accordingly, PPh₃ was found to mediate the reaction using phosphine catalysts. In this reaction, chiral triaryl phosphines were utilized. Thereafter, we tested various chiral phosphines with trace amounts of DMAP or DABCO, barely catalyzing the annulation, yielding 14a in 14% yield, <32% ee. Biaryl phosphines [e.g. (S,R)-BPPFA and (R,R)-DIOP] also showed low activities (36a: <14% yield, <6% ee). During our catalyst screening, the C₂-symmetrical chiral LB-catalyst, (R)-SITCP, was also found to provide promising results. The (R)-SITCP catalyzed reaction between 14a and 35a led to 37a in 57% yield with 84% ee within 30 min.

Finally, the optimal outcome (37a: E:Z = 1:1 20, 78% yield, 93% ee) was obtained using 35a, 14a (1.5 eq.) and (R)-SITCP (20 mol %) in a mixed solvent consisting of CH₂Cl₂/toluene (1/1) at 0°C (Chart 20). Under this optimized conditions, highly Z-selective tetrahydrobenzofuranones 37 were isolated in moderate to good yield (44–78%) with high enantioselectivity (up to 96% ee), irrespective of the electronic nature of substituent R² in 35. Alkyl substituent R², such as the methyl and trifluoromethyl groups in 35l and 35m, respectively, led to the desired products 37l and 37m with 90% ee and 92% ee. The reaction using benzyl alkenolate (14b: R¹ = Bn) was confirmed by the crystalline sponge method(85) to be the Z-configuration of the olefin part, and (R,R)-form (Fig. 5).

No conversion of 35p or 36a was observed when methyl-capped 35p or allylic ether 36a were utilized in the reaction (Eqs. 1 and 2 in Fig. 5). Therefore, the free hydroxy group on 35 is crucial for promoting the γ-addition, and allylic ether 36 is ruled out as a reaction intermediate to afford 37. In the presence of D₂O (3 eq.), the reaction of 14a with 35a yielded the partially deuterated 37a [D content (%): α: 60, γ: 17, δ: 50] (Eq. 3 in Fig. 5), supporting the idea that anionic species are generated at the α-, γ-, and δ-positions in situ.

These outcomes support the mechanism for the designed β,γ-umpolung sequence (Chart 21). The nucleophilic attack of the phosphine unit on (R)-SITCP to the β-position of 14 initiated the reaction, generating the resonance-stabilized betaine I with an anionic character at the carbon atom in the α- and γ-positions. The subsequent protonation of the α-position from the hydroxy group on 35 furnished theolphilic nature of the intermediate II, enabling a nucleophilic γ-addition of III to II. Next, ylide IV was generated, which then underwent an enantioselective intramolecular Michael addition to one of the enone units. To suppress steric interactions between the indane aromatic section of the catalyst and the R² substituent of dienone 35, the (R,R)-SITCP catalysis favored the formation of the (R,R)-configuration. Later, tetrahydrobenzofuranone 37 was provided by the fragmentation of V, with a stabilizing P⁺-O⁻ interaction(106) between a less hindered carbonyl group in CO₂R¹ and a monoarylpheine group in (R)-SITCP, resulting in the Z-form along with regenerated catalyst. As an intermolecular oxy-Michael process includes the reversibility of the alcohol addition under basic conditions,(107) these outcomes indicate that the intramolecular Michael addition from IV to V is the RDS for the present sequence.

As the initial step in the development of the designed sequence, achiral LB catalysts were tested with 14a (R¹ = Et) and 35a (R² = Ph) as model substrates in dichloromethane at 25°C. Accordingly, PPh₃ was found to mediate the reaction efficiently. The product 37a (R¹ = Et, R² = Ph) is detected as an E:Z mixture (1:1) in 72% yield, together with allylic ether 36a (R¹ = Et, R² = Ph) and the self-condensation product 14a (Chart 19). By contrast, amine catalysts, such as DBU, DMAP or DABCO, barely catalyzed the annulation, yielding trace amounts of 37a. Thereafter, we tested various chiral phosphine catalysts. In this reaction, chiral triaryl phosphines such as (S)-BINAP, (S)-QUINAP and (S)-Me-MOP showed no activity. The acid–base organocatalysts (S)-S(60) and (S)-34, as highly active chiral organocatalysts for enantioselective MBH and RC reactions, afforded 36a in low yields and selectivities (<31% yield, <32% ee). Biaryl phosphines [e.g. (S,R)-BPPFA and (R,R)-DIOP] also showed low activities (36a: <14% yield, <6% ee). During our catalyst screening, the C₂-symmetrical chiral LB-catalyst, (R)-SITCP,(80) was also found to provide promising results. The (R)-SITCP catalyzed reaction between 14a and 35a led to 37a in 57% yield with 84% ee within 30 min.

Finally, the optimal outcome (37a: E:Z = 1:1 20, 78% yield, 93% ee) was obtained using 35a, 14a (1.5 eq.) and (R)-SITCP (20 mol %) in a mixed solvent consisting of CH₂Cl₂/toluene (1/1) at 0°C (Chart 20). Under this optimized conditions, highly Z-selective tetrahydrobenzofuranones 37 were isolated in moderate to good yield (44–78%) with high enantioselectivity (up to 96% ee), irrespective of the electronic nature of substituent R² in 35. Alkyl substituent R², such as the methyl and trifluoromethyl groups in 35l and 35m, respectively, led to the desired products 37l and 37m with 90% ee and 92% ee. The reaction using benzyl alkenolate (14b: R¹ = Bn) was confirmed by the crystalline sponge method(85) to be the Z-configuration of the olefin part, and (R,R)-form (Fig. 5).

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Further ground-breaking discoveries in the near future are to be expected.

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References and Notes

1) Tietze L. F., Beifuss U., Angew. Chem. Int. Ed. Engl., 32, 131–163 (1993).
2) Tietze L. F., Chem. Rev., 96, 115–136 (1996).
3) Tietze L. F., Modi A., Med. Res. Chem., 20, 304–322 (2000).
4) Tietze L. F., Brasche G., Gericke K., “Domino Reaction in Organic Synthesis,” Wiley-VCH, Weinheim, 2006.
5) Tietze L. F., “Domino Reactions: Concepts for Efficient Organic Synthesis,” Wiley-VCH, Weinheim, 2013.
6) Pellissier H., Adv. Synth. Catal., 361, 1733–1755 (2019).
7) Pellissier H., Adv. Synth. Catal., 354, 237–294 (2012).
8) Morita K., Suzuki Z., Hirose H., Bull. Chem. Soc. Jpn., 41, 2815 (1968).
9) Baylis A. B., Hillman M. E. D., German Patent 2155113, 1972; US Patent 3743669, 1972 [Chem. Abstr., 77, 34714Q (1972)].
10) Perlmutter P., Too C. C., Tetrahedron Lett., 25, 5951–5952 (1984).
11) Fan Y. C., Kwon O., Chem. Commun., 49, 11588–11619 (2013).
12) Iwabuchi Y., Nakatani M., Yokoyama N., Hatakeyama S., J. Am. Chem. Soc., 121, 10219–10220 (1999).
13) Yamada Y. M. A., Ikegami S., Tetrahedron Lett., 41, 2165–2169 (2000).
14) Yang K.-S., Lee W.-D., Pan J.-F., Chen K., J. Org. Chem., 68, 915–919 (2003).
15) McDougal N. T., Schaus S. E., J. Am. Chem. Soc., 125, 12094–12095 (2003).
16) Shi M., Chen L.-H., Chem. Commun., 1310–1311 (2003).
17) Sohtome Y., Tanatani A., Hashimoto Y., Nagasawa K., Tetrahedron Lett., 45, 5589–5592 (2004).
18) Raeeem I. T., Jacobsen E. N., Adv. Synth. Catal., 347, 1701–1708 (2005).
19) Wang J., Li H., Yu X., Zu L., Wang W., Org. Lett., 7, 4293–4296 (2005).
20) Matsui K., Takizawa S., Sasai H., J. Am. Chem. Soc., 127, 3680–3681 (2005).
21) Matsui K., Takizawa S., Sasai H., Synlett, 2006, 761–765 (2006).
22) Matsui K., Tanaka K., Horii A., Takizawa S., Sasai H., Tetrahedron Lett., 41, 2165–2169 (2000).
23) Tietze L. F., Beifuss U., Angew. Chem. Int. Ed. Engl., 32, 131–163 (1993).
24) Tietze L. F., Chem. Rev., 96, 115–136 (1996).
25) Tietze L. F., Modi A., Med. Res. Chem., 20, 304–322 (2000).
26) Tietze L. F., Brasche G., Gericke K., “Domino Reaction in Organic Synthesis,” Wiley-VCH, Weinheim, 2006.
27) Tietze L. F., “Domino Reactions: Concepts for Efficient Organic Synthesis,” Wiley-VCH, Weinheim, 2013.
28) Pellissier H., Adv. Synth. Catal., 361, 1733–1755 (2019).
29) Pellissier H., Adv. Synth. Catal., 354, 237–294 (2012).
30) Morita K., Suzuki Z., Hirose H., Bull. Chem. Soc. Jpn., 41, 2815 (1968).
31) Baylis A. B., Hillman M. E. D., German Patent 2155113, 1972; US Patent 3743669, 1972 [Chem. Abstr., 77, 34714Q (1972)].
32) Perlmutter P., Too C. C., Tetrahedron Lett., 25, 5951–5952 (1984).
33) Fan Y. C., Kwon O., Chem. Commun., 49, 11588–11619 (2013).
34) Iwabuchi Y., Nakatani M., Yokoyama N., Hatakeyama S., J. Am. Chem. Soc., 121, 10219–10220 (1999).
35) Yamada Y. M. A., Ikegami S., Tetrahedron Lett., 41, 2165–2169 (2000).
36) Yang K.-S., Lee W.-D., Pan J.-F., Chen K., J. Org. Chem., 68, 915–919 (2003).
37) McDougal N. T., Schaus S. E., J. Am. Chem. Soc., 125, 12094–12095 (2003).
38) Shi M., Chen L.-H., Chem. Commun., 1310–1311 (2003).
39) Sohtome Y., Tanatani A., Hashimoto Y., Nagasawa K., Tetrahedron Lett., 45, 5589–5592 (2004).
40) Raeeem I. T., Jacobsen E. N., Adv. Synth. Catal., 347, 1701–1708 (2005).
41) Wang J., Li H., Yu X., Zu L., Wang W., Org. Lett., 7, 4293–4296 (2005).
42) Matsui K., Takizawa S., Sasai H., J. Am. Chem. Soc., 127, 3680–3681 (2005).
43) Matsui K., Tanaka K., Horii A., Takizawa S., Sasai H., Tetrahedron Lett., 41, 2165–2169 (2000).
23) Utsumi N., Zhang H., Tanaka F., Barbis C. F. III, Angew. Chem. Int. Ed., 46, 1878–1880 (2007).
24) Aberrmil N., Masson G., Zhu J., J. Am. Chem. Soc., 130, 12096–12097 (2008).
25) Yukawa T., Seelig B., Xu Y., Morimoto H., Matsunaga S., Berkesel A., Shibasaki M., J. Am. Chem. Soc., 132, 11998–11999 (2010).
26) Song H.-L., Yuan K., Wu X.-Y., Chem. Commun., 47, 1012–1014 (2011).
27) Zhong F., Wang Y., Han X., Huang K.-W., Lu Y., Org. Lett., 13, 1310–1313 (2011).
28) Takizawa S., Kiriya K., Ieki K., Sasai H., Chem. Commun., 47, 9227–9229 (2011).
29) Hyodo K., Nakamura S., Shibata N., Angew. Chem. Int. Ed., 51, 10337–10341 (2012).
30) Rémon E., Bayard J., Takizawa S., Roussevin Y., Sasai H., J. Org. Lett., 15, 1870–1873 (2013).
31) Takizawa S., Rémén E., Arteaga F. A., Yoshida Y., Sridharan V., Bayard J., Juge E., Sasai H., Chem. Commun., 49, 8392–8394 (2013), see also cited references.
32) Nakamoto Y., Urabe F., Takahashi K., Ishii H., Hatakeyama S., Chem. Eur. J., 19, 12653–12656 (2013).
33) Jenegepp F., P. Bächle F., Pfaltz A., Chem. Eur. J., 22, 17595 (2016).
34) Takenaga N., Adachi S., Furusawa A., Nakamura K., Suzuki N., Tetrahedron, 72, 6892–6897 (2016).
35) Declerck V., Martinez J., Lamy F., Chem. Rev., 109, 1–48 (2009).
36) Santos L. S., Pavon C. H. Almeida W. P., Coelho F., Eberlin M. N., Angew. Chem. Int. Ed., 43, 4330–4333 (2004).
37) Price K. E., Broadwater S. J., Walker B. J. McQuade D. T., J. Org. Chem., 70, 3980–3987 (2005).
38) Buskens P., Klanckermayer J., Lettner W., J. Am. Chem. Soc., 127, 16762–16763 (2005).
39) Robiette R., Aggarawal V. K., Harvey J. N., J. Am. Chem. Soc., 129, 15513–15525 (2007).
40) Roy D., Patel C., Sunoj R. B., J. Org. Chem., 74, 6936–6943 (2009).
41) Takizawa S., Inoue N., Hirata S., Sasai H., Angew. Chem. Int. Ed., 49, 9725–9729 (2010).
42) Takizawa S., Inoue N., Sasai H., Tetrahedron Lett., 52, 377–380 (2011).
43) Takizawa S., Nguyen T. M.-N., Grossmann A., Enders D., Sasai H., Angew. Chem. Int. Ed., 51, 5423–5426 (2012).
44) Takizawa S., Arteaga F. A., Yoshida Y., Suzuki M., Sasai H., Org. Lett., 15, 4412–4415 (2013).
45) Takizawa S., Nguyen T. M.-N., Grossmann A., Suzuki M., Enders D., Sasai H., Tetrahedron, 69, 1202–1209 (2013).
46) Takizawa S., Arteaga F. A., Yoshida Y., Suzuki M., Sasai H., J. Org. Chem., 79, 412–415 (2014).
47) Takizawa S., Kishi K., Yoshida Y., Mader S., Arteaga F. A., Lee S., Hoshino M., Rueping M., Fujita M., Sasai H., Angew. Chem. Int. Ed., 54, 15511–15515 (2015).
48) Ngo T.-T.-D., Kishi K., Sako M., Shigenobu M., Bournand C., Toffano M., Guillot R., Baltaze J.-P., Takizawa S., Sasai H., Vo-Thanh G., ChemistrySelect, 1, 544–5420 (2016).
49) Takizawa S., Sako M., Kishi K., Shigenobu M., Vo-Thanh G., Sasai H., Chem. Pharm. Bull., 65, 997–999 (2017).
50) Kishi K., Arteaga F. A., Takizawa S., Sasai H., Chem. Commun., 53, 7724–7727 (2017).
51) Takizawa S., Kishi K., Kusaba M., Bai J., Suzuki T., Sasai H., Het- erocycles, 95, 761–767 (2017).
52) Kishi K., Takizawa S., Sasai H., ACS Catal., 8, 5228–5232 (2018).
53) Moniet J. L., Hindenlang D. M., Shamma M., J. Org. Chem., 44, 4347–4351 (1979).
54) Stuk T. L., Assink B. K., Bates R. C. Jr., Erdman D. T., Fedij V., Jennings S. M., Lassig J. A., Smith R. J., Smith T. L., Org. Pro- cess Res. Dev., 7, 851–855 (2003).
55) Leonard M. S., ARKIVOC, 2013, 1–6 (2013).
56) Albano G., Aronica L. A., Tetrahedron, 69, 1209–1227 (2013).
57) Yao Y., Gilbertson S. R., Chem. Commun., 54, 11292–11295 (2018), see also cited references.
58) Das B. G., Shah S., Singh V. K., Org. Lett., 21, 4981–4985 (2019).
59) Solvent effects were crucial factors to help accelerate the domino reaction without the formation of undesired aza-MBH adducts 4.
60) The addition of MS 3 (or 4A) was beneficial to suppress the de- composition of moisture sensitive N-tosylimines 2.
61) Kurihara T., Fukunaga K., Sakaguchi T., Hirano H., J. Heterocycl. Chem., 12, 989–993 (1975).
62) Ruano J. L. G., Fernández-Ibáñez M. A., Fernández-Salas J. A., Maestro M. C., Márquez- López P., Rodríguez-Fernández M. J., J. Org. Chem., 74, 1200–1204 (2009).
63) Nyasse B., Grehn L., Ragnarsson U., Chem. Commun., 1997, 1017–1018 (1997).
64) Meng X., Huaï H., Chen Y., Ren, Chem. Eur. J., 14, 6852–6856 (2008).
65) Doddugon Y., Rodríguez J., Contantinou T., Bugaut X., Eur. J. Org. Chem., 2018, 2432–2442 (2018), see also cited references.
66) Menguy L., Couty P., Tetrahedron Asymmetry, 21, 2385–2389 (2010).
P., Hirata S., Murai K., Fujioka H., Sasai H., Org. Lett., 19, 5426–5429 (2017).
90) Sako M., Ichinose K., Takizawa S., Sasai H., Chem. Asian J., 12, 1305–1308 (2017).
91) Tello-Aburto R., Kalstabakken K. A., Harned A. M., Org. Biomol. Chem., 11, 5596–5604 (2013).
92) Büschleb M., Dorich S., Hanessian S., Tao D., Schenthal K. B., Overman L. E., Angew. Chem. Int. Ed., 55, 4156–4186 (2016).
93) For selected reviews on the recovery and reuse of chiral organocatalysts, see: Itsuno S., Hassan M., RSC Adv., 4, 52023–52043 (2014).
94) Bharadwaj K. C., RSC Adv., 5, 75923–75946 (2015).
95) Vedejs E., Denmark S. E., “Lewis Base Catalysis in Organic Synthesis,” Wiley-VCH, Weinheim, 2016.
96) Zhang C., Lu X., J. Org. Chem., 60, 2906–2908 (1995).
97) Zhu G., Chen Z., Jiang Q., Xiao D., Cao P., Zhang X., J. Am. Chem. Soc., 119, 3836–3837 (1997).
98) Cristau H.-J., Viala J., Christol H., Tetrahedron Lett., 23, 1569–1572 (1982).
99) Trost B. M., J. Am. Chem. Soc., 116, 3167–3168 (1994).
100) Zhang C., Lu X., Synlett, 1995, 645–646 (1995).
101) Recent report on γ-umpolung addition of allenolate, see: Lorton C., Voituriez A., J. Org. Chem., 83, 5801–5806 (2018).
102) Ren Y., Yuan C., Qian Y., Chai H.-B., Chen X., Goetz M., Kehrmann A. D., J. Nat. Prod., 2014, 550–556 (2014).
103) Inokuma Y., Yoshioka S., Ariyoshi J., Arai T., Hitorya Y., Takada K., Matsunaga S., Rissanen K., Fujita M., Nature (London), 495, 461–466 (2013).
104) Dudding T., Kwon O., Mercier E., Org. Lett., 8, 3643–3646 (2006).
105) Scherer M., Gademann K., Org. Lett., 19, 3915–3918 (2017).
106) Vilaivan T., Bhanthumnavin W., Molecules, 15, 917–958 (2010).
107) Szőllősi G., Catal. Sci. Technol., 8, 389–422 (2018), see also cited references.