Highly Practical BINOL-Derived Acid–Base Combined Salt Catalysts for the Asymmetric Direct Mannich-Type Reaction

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Abstract: The catalytic asymmetric direct Mannich-type reaction between aldimines and 1,3-dicarbonyl compounds is one of the most important carbon–carbon bond-forming reactions in organic chemistry. The resulting Mannich adducts can be efficiently transformed into pharmaceutically useful, optically active β-amino ketones, β-amino esters, β-lactams, etc. In the course of our study of chiral acid–base combined salt catalysts for asymmetric reactions, we developed a series of simple, practical, chiral BINOL-derived salt catalysts, such as chiral pyridinium 1,1′-binaphthyl-2,2′-disulfonates **1**, chiral lithium(I) binaphtholate **2**, chiral magnesium(II) binaphtholate (**3**), chiral calcium(II) phosphate **4**, and chiral phosphoric acid **5**, which were particularly effective for direct Mannich-type reactions.

Key words: acid–base combined salt catalyst, aldimine, asymmetric catalysis, 1,3-dicarbonyl compound, direct Mannich-type reaction

1 Introduction

Optically active α-branched amines are common, biologically active compounds that are widely found in natural products and medicines. The asymmetric direct Mannich-type reaction between aldimines and carbonyl compounds is highly useful for the synthesis of chiral building blocks of β-carbonyl-α-branched amines, i.e., β-amino carbonyl compounds (Scheme 1).[1] Due to the importance of these enantio-enriched derivatives such as β-lactams in biological and pharmaceutical chemistry, considerable effort has been devoted over the last decade to establishing methodology for direct Mannich-type reactions with chiral metal catalysts[2] or organocatalysts.[3] Among these catalysts, a chiral binaphthyl skeleton has often been used since chiral 1,1′-bi-2-naphthol (BINOL),[4] as the origin of chiral auxiliary, is commercially available in bulk quantities as both *R*- and *S*-enantiomers, inexpensive, easily substituted at the 3,3′-positions by sterically demanding or functional groups, and easily transformed by changing the OH groups at the 2,2′-positions into other functional groups. In the course of our study on the design of chiral acid–base combined catalysts for asymmetric reactions involving carbon–carbon bond formation, we have developed a simple family of chiral binaphthyl-derived salt catalysts.[5] With regard to the asymmetric direct Mannich-type reaction, chiral acid–base combined salt catalysts would be highly attractive since they should activate the substrates (aldimines) and reagents (1,3-dicarbonyl compounds) on the acid moiety and the base moiety, respectively. Generally, the reactivity of 1,3-dicarbonyl compounds varies among diketones, ketoesters, ketolactones, diesters (malonates), ketoamides, ketothioesters, and dithioesters (thiomalonates).[6] Therefore, Brønsted base-assisted effective α-deprotonation from less-reactive 1,3-dicarbonyl compounds leading to the corresponding enolates should be critical, since keto/enol equilibrium is usually disfavorable for the corresponding enolates. To address the problem of the reactivity of 1,3-dicarbonyl compounds, we consider simple, three catalytic systems (types a–c): (a) Brønsted acid–Brønsted base combined salts, (b) cation–anion pair salts, and (c) cation–anion conjugate salts (Scheme 1). Overall, the driving force of direct Mannich-type reactions should be controlled by the balance between the Brønsted or Lewis acidity and the Brønsted basicity in these acid–base catalysts. Here we report the development of chiral acid–base combined salt catalysts for use in asymmetric direct Mannich-type reactions, such as chiral pyridinium 1,1′-binaphthyl-2,2′-disulfonates **1** (type a), chiral lithium(I) binaphtholates **2** (type b), chiral magnesium(II) binaphtholates (**3**, type b), chiral calcium(II) phosphates **4** (type c), and chiral phosphoric acids **5** (type c) (Figure 1).

2 1,1′-Binaphthyl-2,2′-disulfonic Acid (BINSA)–Pyridinium Salts[7]

Chiral organic salts of Brønsted acids and Brønsted bases, such as ammonium sulfonates,[8,9] are some of the most promising catalysts in modern asymmetric syntheses (Scheme 1, type a). In general, acid–base-combined salts have several advantages over single-molecule catalysts with regard to flexibility in the design of their dynamic complexes. In this context, 1,1′-binaphthyl-2,2′-disulfon-

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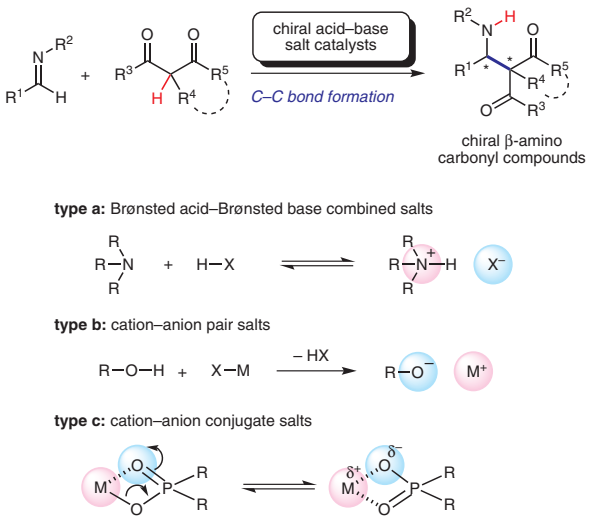
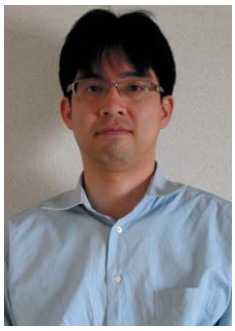


Scheme 1 Catalytic asymmetric direct Mannich-type reactions

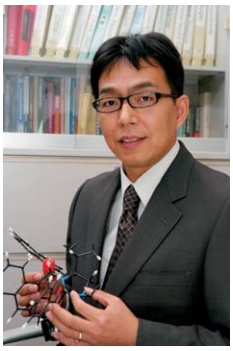
ic acid (BINSA, **6**) should be a promising chiral Brønsted acid catalyst, since both the Brønsted acidity and bulkiness can be easily controlled by complexation with achiral amines (Scheme 2). Remarkably, unlike common binaphthyl compounds, considerable bulkiness can be achieved in situ without directly introducing substituents at the 3,3′-positions in the binaphthyl skeleton. However, at the start of our study, there had been no reports on the practical applications of chiral **6** in asymmetric catalyses after the first synthesis of racemic **6** in 1928 by Barber and Smiles.[10,11]

First, we examined the efficient synthesis of (*R*)-BINSA (**6**) from (*R*)-BINOL via the oxidation of dithiol as a key reaction (Scheme 3). Thermolysis in the Newman–Kwart rearrangement was dramatically improved by using a microwave technique at a milder temperature (200 °C) than reported.[12,13] For the key step of the oxidation of thiols to sulfonic acids, the unprecedented oxidation of dithiol (*R*)-**7** proceeded smoothly to give the product in 82% yield without epimerization under 7 bar of oxygen/potassium

Biographical Sketches



Manabu Hatano was born in Tokyo, Japan, in 1975, and received his Ph.D. from the Tokyo Institute of Technology in 2003 under the direction of Professor Koichi Mikami. He was a JSPS Fellow under the Japanese Junior Scientists Program from 2000 to 2003. In 2003, he joined Professor Kazuaki Ishihara's group at Nagoya University as an assistant professor, and became associate professor in 2007. He has received the Tejima Research Award for Young Scientists (2004), the TORAY Award in Synthetic Organic Chemistry, Japan (2006), the Lectureship Award of the Young Generation Special Forum from the Chemical Society of Japan (2007), and the Encouragement Prize from the Tokai Branch of the Society of Synthetic Organic Chemistry, Japan (2007). His research interests include asymmetric catalysis with carbon–carbon bond-forming reactions with chiral acid–base salt catalysts, the chemistry of ate complexes for efficient catalytic asymmetric reactions, and the design of chiral self-assembled complexes toward supramolecular asymmetric catalysts.



Kazuaki Ishihara was born in Aichi, Japan, in 1963, and received his Ph.D. from Nagoya University in 1991 under the direction of Professor Hisashi Yamamoto. He had the opportunity to work under the direction of Professor Clayton H. Heathcock at the University of California, Berkeley, as a visiting graduate student for three months in 1988. He was a JSPS Fellow under the Japanese Junior Scientists Program from 1989 to 1991. After he completed his postdoctoral studies with Professor E. J. Corey at Harvard University (15 months beginning in 1991), he returned to Japan and joined Professor Hisashi Yamamoto's group at Nagoya University as an assistant professor in 1992, and became associate professor in 1997. In 2002, he was appointed to his current position as a full professor at Nagoya University. He has received the Inoue Research Award for Young Scientists (1994), the Chemical Society of Japan Award for Young Chemists (1996), the Thieme Chemistry Journal Award (2001), the Green and Sustainable Chemistry Award from the Ministry of Education, Culture, Sports, Science, and Technology (2003), the JSPS Prize (2005), the BCSJ Award (2005), the 0th International Conference on Cutting-Edge Organic Chemistry in Asia Lectureship Award (2006), Japan/UK GSC Symposium Lectureship (2007), the IBM Japan Science Prize (2007), and the Mukaiyama Award (2009). His research interests include asymmetric catalysis, biomimetic catalysis induced by artificial enzymes, dehydrative condensation catalysis toward green and sustainable chemistry, and acid–base combination chemistry.

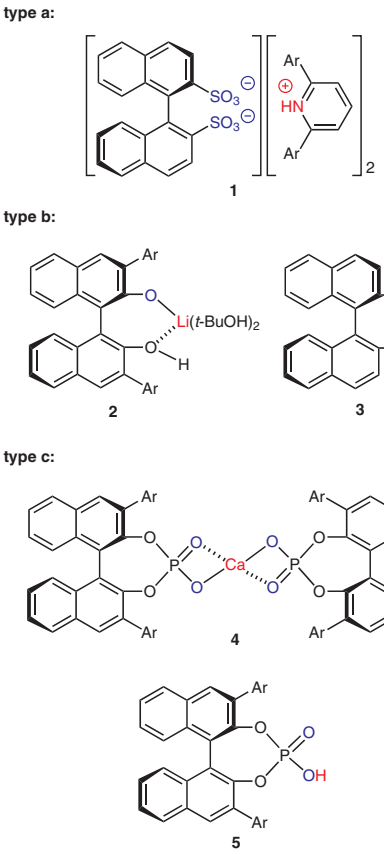
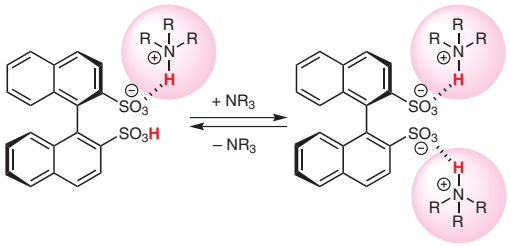


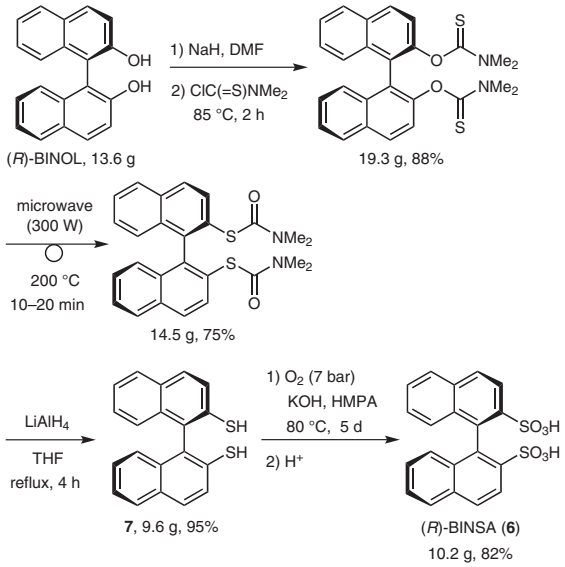
Figure 1 BINOL-derived acid–base combined salt catalysts **1**–**5**



Scheme 2 Dynamics of BINSA **6**–ammonium salts in situ

hydroxide in hexamethylphosphoramide after optimization of the reaction conditions. After protonation by ion-exchange, compound (*R*)-**6** could be prepared, in >10-gram scale, in 51% yield over five steps from (*R*)-BINOL, or in 82% yield in one step from commercially available dithiol (*R*)-**7**.

As a probe reaction,[3a,14] we examined the catalytic enantioselective direct Mannich-type reaction between *N*-Cbz-phenylaldimine **8a** and acetylacetone (**9a**) in dichloromethane at 0 °C for 30 minutes. The enantioselectivity of **10a** was low (17% ee) when 5 mol% of **6** was used without amines (Table 1). However, we found that **6**–achiral amine combined salts as chiral Brønsted acid–base catalysts prepared in situ were effective (Scheme 1, Figure 1, type a). The preliminary results with **6** (5 mol%)–amines (10 mol%) suggested that pyridines with weak Brønsted basicity would be better Brønsted bases. Even then, the use of pyridine, 2-phenylpyridine, or 2,6-

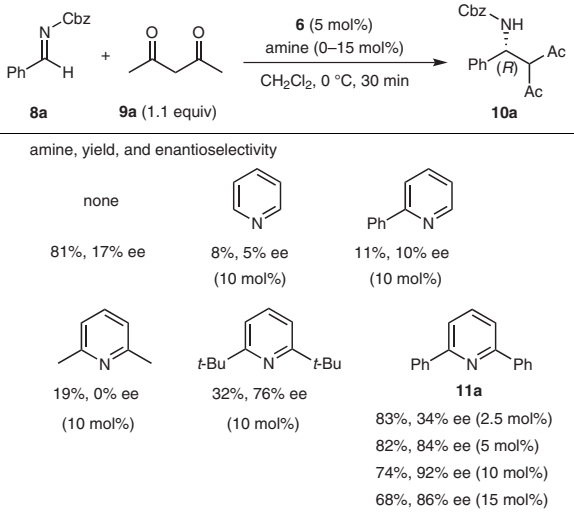


Scheme 3 Synthesis of (*R*)-BINSA **6** from (*R*)-BINOL

lutidine was not effective, partially due to the lower solubility of the corresponding salts. In sharp contrast, 2,6-di-*tert*-butylpyridine improved the enantioselectivity to 76% ee. Ultimately, we found that 2,6-diphenylpyridine (**11a**), which led to a homogeneous catalyst in situ, was an optimal amine, and **10a** was obtained in 74% yield with 92% ee. Interestingly, the enantioselectivity of **10a** was dramatically improved when a greater than 1:1 ratio of **6**/**11a** was examined. However, the addition of excess equimolar amounts of **11a** (15 mol%) per **6** had a slightly negative influence on the catalytic activity. The wide range of suitable ratios of **6**/**11a** may reflect the postulated dynamic structure of the catalysts (Scheme 2).

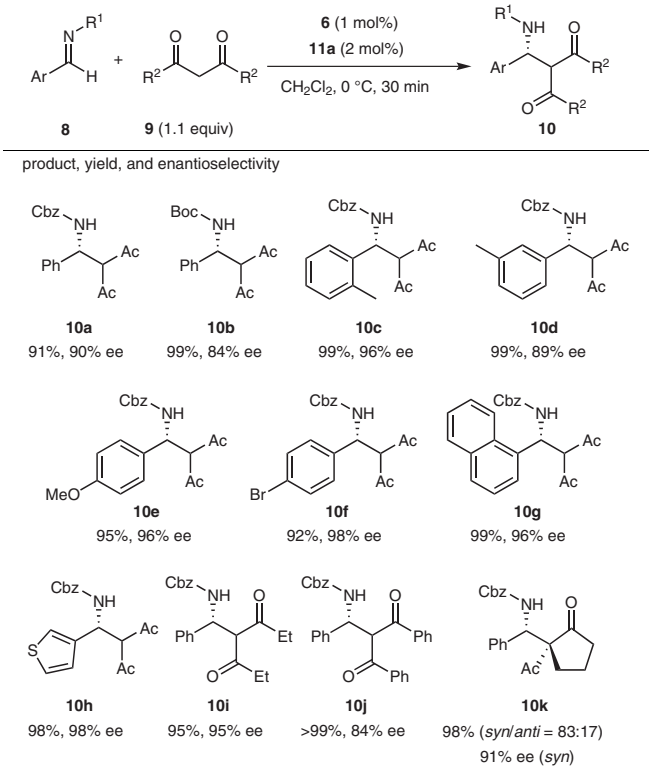
With the optimized reaction conditions in hand, we next examined the scope of aldimines and 1,3-dicarbonyl compounds (Table 2). Fortunately, with the use of 1 mol% of **6**·(**11a**)$_2$, **10a** was obtained in 91% yield with 90% ee. Under these optimized conditions, *N*-Boc-Mannich product

Table 1 Screening of BINSA **6**–Pyridinium Salts

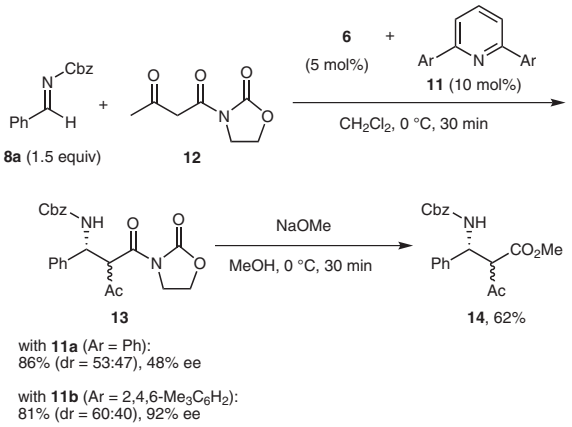


10b was obtained in 99% yield with 84% ee. From **9a** and a variety of *N*-Cbz-arylaldimines bearing electron-donating or electron-withdrawing groups in the aryl moiety, the corresponding adducts **10c–h** were obtained in high to excellent yields (92–>99%) and with high enantioselectivities (89–98% ee). When other diketones such as heptane-3,5-dione and 1,3-diphenylpropane-1,3-dione were reacted with **8a**, the corresponding adducts **10i** and **10j** were obtained with 95% ee and 84% ee, respectively. Moreover, a cyclic 1,3-diketone could also be used, and the corresponding adduct **10k** with a quaternary carbon center was obtained in 98% yield with a *syn*/*anti* diastereomer ratio of 83:17 and high enantioselectivity (91% ee, *syn*).

Table 2 BINSA **6**–Pyridinium Salt Catalysis



A suitable chiral ammonium salt was easily tailor-made for a ketoester equivalent such as 3-acetoacetyloxazolidin-2-one (**12**) (Scheme 4). The chiral ammonium salt **6**·(**11a**)$_2$, which was optimized for the previous reaction, was not effective, and the desired product **13** was obtained in 86% yield with low diastereo- and enantioselectivities. In contrast, the enantioselectivity of **13** increased to 92% ee when 2,6-dimesitylpyridine (**11b**) was used in place of **11a**. In this way, the use of tailor-made salts **6**·(**11**)$_2$ made it possible to avoid preparing single-molecule catalysts in advance and offered a quick solution to this type of optimization problem. Note that compound **13** was easily transformed to β-amino carbonyl compound **14** via deprotection of the oxazolidinone moiety without loss of enantioselectivity.



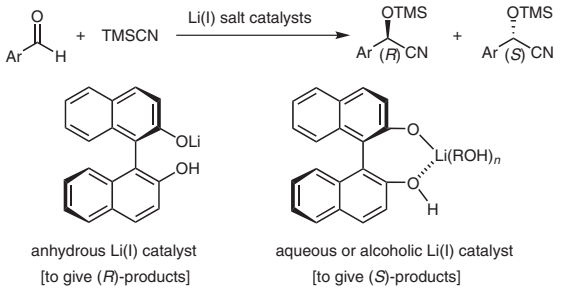
Scheme 4 Reaction of ketoamide **12**

In this reaction, BINSA (**6**) was found to be a highly effective chiral Brønsted acid that could be combined with an achiral Brønsted base (Scheme 1, Figure 1, type a). Combination of the achiral bulky 2,6-diarylpyridine **11** with **6** circumvented the trouble of having to build bulky substituents at the 3,3′-positions as is normally required with analogous binaphthyl phosphoric acid catalysts. We believe that BINSA should be a powerful chiral auxiliary like BINOL, BINAP [2,2′-bis(diphenylphosphino)-1,1′-binaphthalene], BINAM (2,2′-diamino-1,1′-binaphthalene), etc., and could open a new frontier in acid–base chemistry in asymmetric catalyses. In fact, we and other research groups later developed BINSA derivatives and their asymmetric catalyses, and we suspect that BINSA catalysis will be developed further.[15]

3 Lithium(I) Binaphtholate Salts[16]

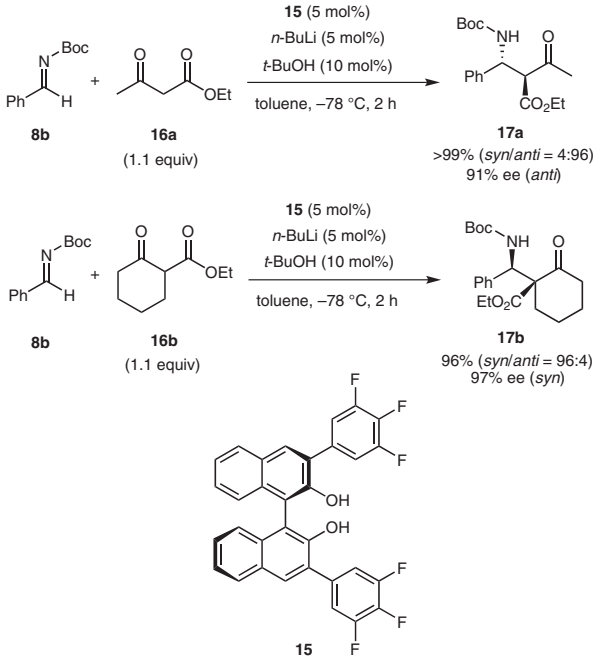
A chiral Li(I)–BINOLate salt is one of the simplest acid–base bifunctional catalysts.[17] In landmark work, Kagan and Holmes developed the trimethylsilylcyanation of aldehydes with the use of anhydrous chiral Li(I)–BINOLate salts.[18] Later, we reported that aqueous or alcoholic Li(I)–BINOLate salts showed dramatically improved catalytic activity as Lewis acid–Lewis base catalysts for trimethylsilylcyanation by activating both the aldehyde and cyanotrimethylsilane.[19] Moreover, an interesting changeover of the stereochemistry of the products was observed with aqueous or alcoholic catalysts in place of anhydrous catalysts. In the further study of Li(I)–BINOLate salts based on the strong basicity of naphtholate oxygen, Li(I)–BINOLate salts should be good Lewis acid–Brønsted base catalysts, which activate both the substrate and the acidic pronucleophile (Scheme 1, Figure 1, type b).

By taking advantage of studies on Li(I)–BINOLate-catalyzed trimethylsilylcyanation, we found that the monolithium salt of 3,3′-Ar$_2$-BINOL in the presence of *tert*-butyl alcohol was effective. In particular, 3,3′-(3,4,5-$F_3C_6H_2)_2$-BINOL (**15**) was the most promising, and we performed a direct Mannich-type reaction between *N*-Boc



Scheme 5 Trimethylsilylcyanation of aldehydes by Li(I)–BINOLates

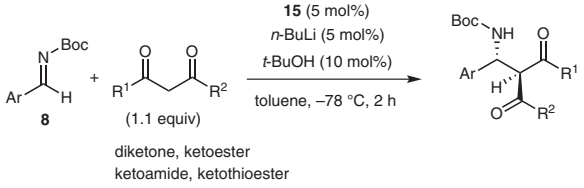
aldimines and some 1,3-dicarbonyl compounds. In summary, an interesting changeover of both the diastereoselectivity and absolute stereochemistry was observed between the acyclic 1,3-dicarbonyl compound **16a** and the cyclic compound **16b** (Scheme 6). *syn*-Product **17b** was obtained from cyclic pronucleophiles while *anti*-product **17a** was obtained from acyclic pronucleophiles.



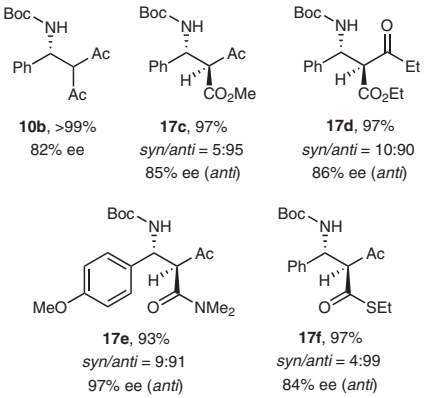
Scheme 6 Reaction of acyclic and cyclic ketoesters with a chiral Li(I)–BINOLate salt

First, we explored the scope of the diastereo- and enantioselective direct Mannich-type reaction with a class of acyclic 1,3-dicarbonyl compounds by using **15** (5 mol%), *n*-butyllithium (5 mol%), and *tert*-butyl alcohol (10 mol%) in toluene at –78 °C for two hours (Table 3). A diketone, ketoesters, ketoamide, and ketothioester gave the corresponding products **10b**, **17c–f** with high enantioselectivities (82–97% ee). Notably, *anti*-products **17c–f** were selectively obtained from acyclic reagents without epimerization at the α-tertiary carbon center. These results are valuable since previous catalysts often gave *syn*/*anti* mixtures, or the stereochemistry has not yet been determined.

Table 3 Reaction of Acyclic 1,3-Dicarbonyl Compounds



Product, yield, diastereoselectivity, and enantioselectivity

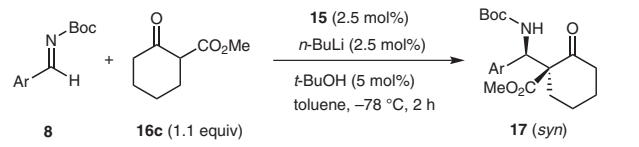


Next, we investigated cyclic 1,3-dicarbonyl compounds (Table 4). For methyl 2-oxocyclohexanecarboxylate (**16c**), a variety of aryl aldimines with an electron-withdrawing group or an electron-donating group and heteroaryl aldimines were acceptable. The reactions proceeded smoothly in toluene at –78 °C within two hours in the presence of 2.5 mol% of the catalyst. The desired products were obtained in high yields with high *syn*-diastereoselectivities (*syn*/*anti* 88:12–97:3) and high enantioselectivities (87–95% ee). One mol% of the catalyst was still effective, and **17g** was obtained in 97% yield with high diastereo- and enantioselectivity. Since the observed TOF was 284 h^{-1} (71% yield at 3 min for **17g**), the high reactivity of this catalyst is quite unlike those of other conventional catalysts.[1–3] Moreover, another advantage is that inexpensive lithium hydroxide can be used as a lithium precursor in place of *n*-butyllithium/*tert*-butyl alcohol in the synthesis of **17g**.

To demonstrate the synthetic utility of this approach, the obtained adduct **17g** (90% ee) was transformed to the useful spiro-β-lactam **18** (Scheme 7). Diastereoselective reduction of **17g** by sodium borohydride was conducted, followed by deprotection of the amino moiety by trifluoroacetic acid and protection of the alcohol with *tert*-butyldimethylsilyl chloride. Subsequent cyclization by treatment with lithium diisopropylamide gave spiro-β-lactam **18** with three consecutive chiral carbon centers in a highly diastereo- and enantioselective manner.

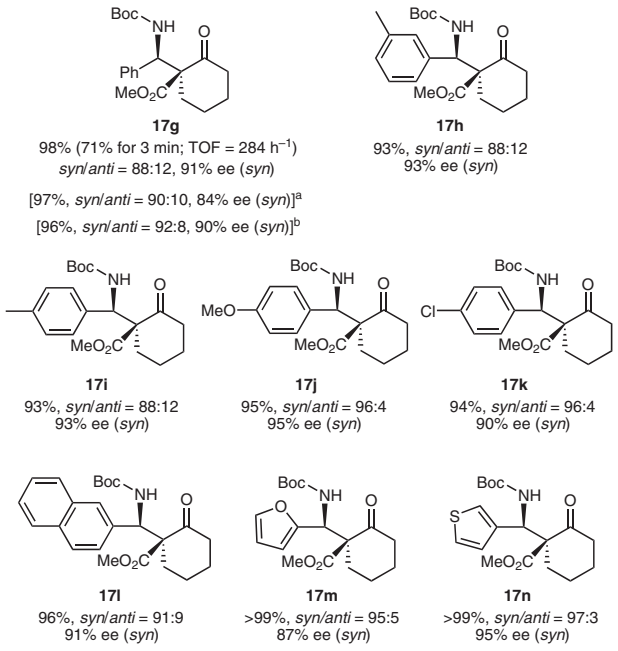
Moreover, from an *S*-heterocyclic ketoester **16d**, the desired adduct **17o** was obtained in 90% yield with a *syn*/*anti* ratio of 88:12 with 93% ee (*syn*) (Scheme 8). Subsequent reduction by sodium borohydride and desulfurization with Raney nickel gave the valuable acyclic β-amino

Table 4 *syn*-Enantioselective Reaction

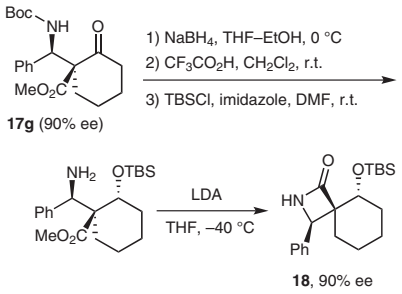


8 **16c** (1.1 equiv) **17** (*syn*)

product, yield, diastereoselectivity, and enantioselectivity



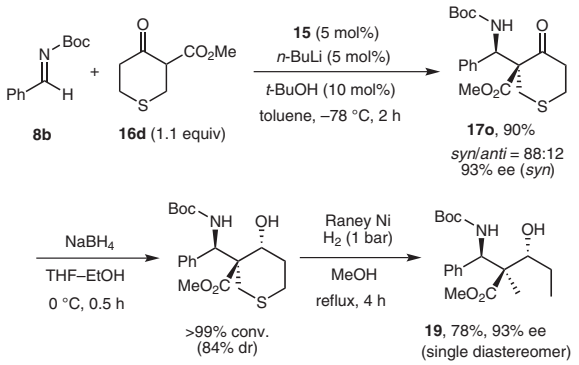
[a] **15** (1 mol%), *n*-BuLi (1 mol%), *t*-BuOH (2 mol%).
[b] LiOH (2.5 mol%) was used in place of *n*-BuLi and *t*-BuOH.



Scheme 7 Transformation to a spiro-β-lactam

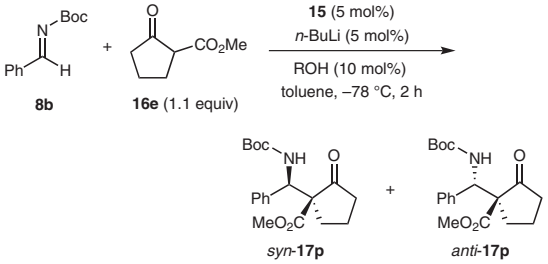
carbonyl compound **19** with three consecutive chiral carbons involving a methyl-substituted quaternary center.

In place of **16c** with a six-membered ring, when **16e** with a five-membered ring was used, a mixture of *syn*- and *anti*-isomers was obtained at a low diastereomeric ratio of 52:48, with high enantioselectivities (90% ee and 97% ee, respectively) (Scheme 9). Very interestingly, we also found that the *syn*- and *anti*-isomers **17p** showed different absolute configurations at the amino-carbon center. Moreover, when 3,5-xylenol was used in place of *tert*-butyl alcohol, **17p** was obtained in a similar diastereoselectivity (*syn*/*anti* = 61:39), and the enantioselectivity of *syn*-**17p** decreased significantly to 43% ee.



8b **16d** (1.1 equiv)

Scheme 8 Transformation to an acyclic β-aminodicarbonyl compound



8b **16e** (1.1 equiv)

Scheme 9 Reaction of a ketoester with a five-membered ring

As shown in Tables 3 and 4 and Scheme 9, *anti*-products were generally obtained from acyclic pronucleophiles, while *syn*-products were generally obtained from cyclic pronucleophiles. Opposite absolute configurations at the amino-carbon center were observed among these *syn*- and *anti*-products. These results, which are shown in Figure 2, strongly suggest that the *syn*- and *anti*-isomers were obtained thorough different reaction pathways, based mainly on structural and/or conformational differences and the acidity of 1,3-dicarbonyl compounds. In particular, cyclic ketoester **16e** with a five-membered ring has an intermediate nature, related to its conformation and acidity,[6,20] among the 1,3-dicarbonyl compounds that were examined. Since **16c** and **16e** should exhibit six- and five-membered ring chelation, respectively, **16c** would be more likely to chelate the lithium(I) center than **16e**, even though these compounds have similar pK_a values.

Two major mechanisms can be considered (Figure 3). On one hand, the aldimine would be activated by the Lewis acidic lithium(I) center (path A). On the other hand, the pronucleophile would be activated as a lithium enolate (path B). In both paths, the addition of *tert*-butyl alcohol would promote the dissociation to a monomeric precursor, Li(I)–BINOLate·(*t*-BuOH)$_n$. Since a more acidic acyclic 1,3-dicarbonyl compound would have a rather flexible conformation, activation of the aldimine on the lithium(I) center would be likely (path A). In path A, alcohols (*t*-BuOH or 3,5-xylenol) would still coordinate to the lithium(I) center, which would not strongly affect the enantioselectivity even in the case of **16e** (Scheme 9, *anti*-**17p**).

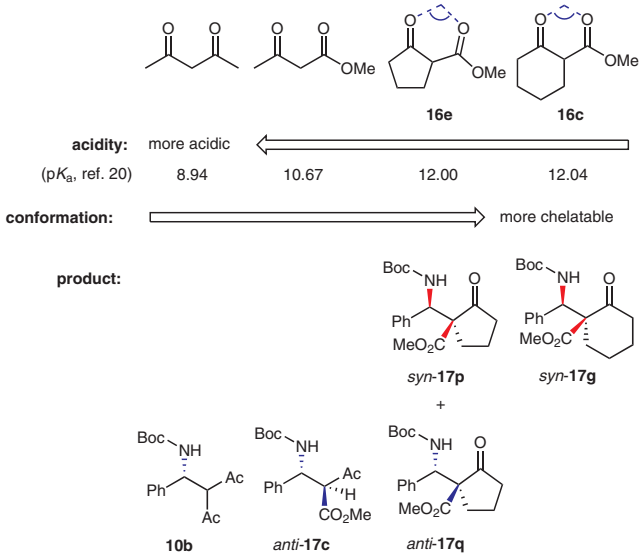


Figure 2 Relation of stereochemistry

In sharp contrast, a less acidic cyclic 1,3-dicarbonyl compound would be preferentially activated as a lithium enolate since the conformationally rigid structure could promote chelation to the lithium(I) center (path B). Ligand **15**, which is then protonated via lithium enolization, would activate the aldimine through hydrogen bonding. However, 3,5-xylenol (pK_a = 10.1), which is more acidic than *tert*-butyl alcohol (pK_a = 15.3), might compete with **15** (pK_a = 7.2) and could trigger a nonselective pathway, particularly in the case of **16e** (Scheme 9, *syn*-**17p**).[20] Therefore, we conjectured that *syn*-isomers would be obtained via path B, while *anti*-isomers would be obtained via path A (Figure 4). In path A, a pronucleophile would be activated by coordination with a Brønsted basic naphtholate oxygen, followed by attack of the lithium-coordinated aldimine on the *re*-face. In path B, the aldimine would be activated on a resulting Brønsted acidic naphthol proton, and the lithium enolate would attack the aldimine on the *si*-face.

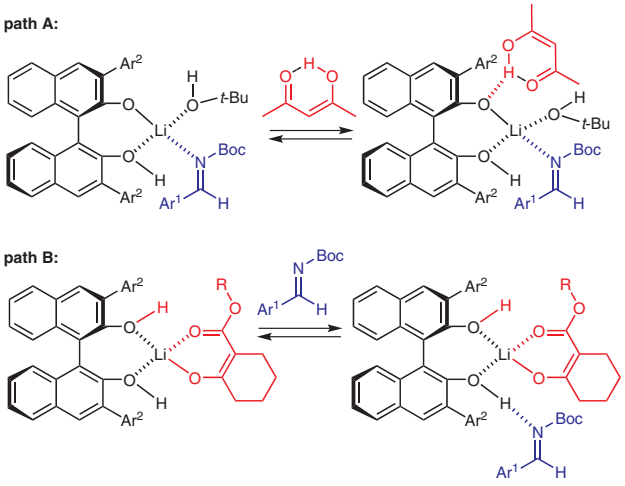


Figure 3 Possible reaction pathways

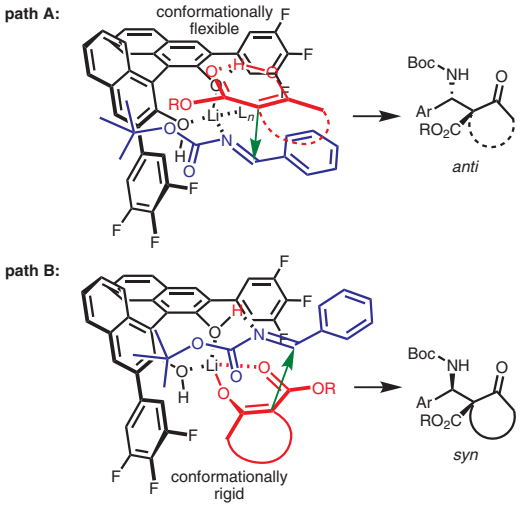
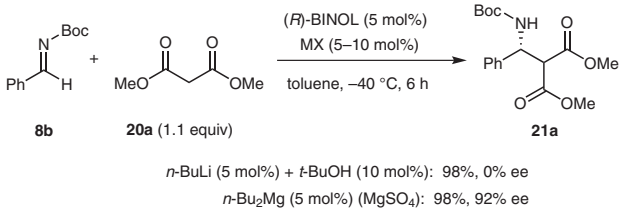


Figure 4 Possible transition states (L = *t*-BuOH)

4 Magnesium(II) Binaphtholate Salts[21]

As shown in Section 3, we developed chiral Li(I)–BINOLate salts as effective acid–base catalysts for direct Mannich-type reactions with 1,3-diketones, 1,3-ketoesters, 1,3-ketoamides, and 1,3-ketothioesters. However, malonates could not be used even in the active lithium(I) catalysis (Scheme 10). Among 1,3-dicarbonyl compounds, the inherent difficulty of the direct Mannich-type reaction with malonates is due to their weak acidity and stronger chelation to the metal center without the generation of an activated metal enolate.[6] To overcome these problems, we next examined a cooperative acid–base catalyst with divalent group II elements instead of lithium(I). An uncommon but easily prepared chiral Mg(II)–BINOLate salt[22] is particularly attractive (Scheme 1, Figure 1, type b). It should have enough Brønsted basicity to generate the magnesium(II) enolate in situ without the release of BINOL, as shown in Figure 5. Therefore, when this cooperative acid–base Mg(II) salt catalyst activates both aldimine and malonate, a divalent magnesium(II) center would be firmly bound to both BINOL and malonate through ionic and coordinate bonds. As expected, Mg(II)–BINOLate effectively catalyzed the reaction of *N*-Boc aldimine **8b** with dimethyl malonate (**20a**), and the corresponding product **21a** was obtained in 98% yield with 92% ee when 5 mol% each of BINOL and dibutylmagnesium were used in the presence of magnesium sulfate as a drying reagent in toluene at –40 °C for six hours (Scheme 10).



Scheme 10 Catalysis by Li(I)– or Mg(II)–BINOLate salts

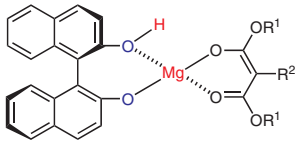


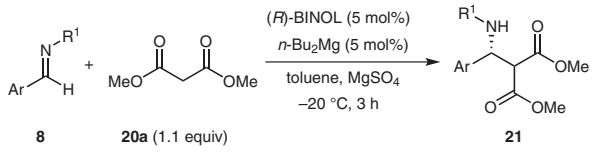
Figure 5 Expected Mg(II)–malonate BINOLate salts in situ

Interestingly, modification of the skeleton of BINOL (e.g., substitution at the 3,3′-positions, etc.) gave the Mannich adducts in low reactivity and/or low enantioselectivity. Therefore, to our delight, we selected simple and inexpensive non-modified BINOL itself for subsequent experiments. We further found that the reactions could proceed at a more practical temperature such as –20 °C for three hours without any loss of enantioselectivity (Table 5). With regard to the protecting group in the N-moiety of aldimines, *tert*-butoxycarbonyl (Boc) showed better enantioselectivity than benzyoxycarbonyl (Cbz). A variety products **21c–e** of aryl aldimines with an electron-withdrawing or electron-donating group and products **21f–h** of heteroaryl aldimines were obtained in high yields and with high enantioselectivities. In the case of the 3,4-dimethoxyphenyl-substituted aldimine, an optimal 1:1 ratio of BINOL/Bu_2Mg (5 mol% each) provided the product **21e** in moderate yield (55%). Interestingly, however, a slight excess of dibutylmagnesium (7.5 mol%) to BINOL (5 mol%) improved the yield and enantioselectivity (91% with 90% ee). A chelatable moiety such as an *ortho*-dimethoxy group may partially ligate the magnesium(II) center, and this may prevent generation of the active catalyst.

We next explored the scope of malonates (Table 6). Not only dimethyl malonate (**20a**) but also dipropyl malonate, dibenzyl malonate, and diallyl malonate could be used successfully, and the corresponding products **21i–k** were obtained from **8b** in almost quantitative yields with 88–92% ee. The reactions of dimethyl α-halomalonates were also examined. Although dimethyl 2-fluoromalonate gave the corresponding adduct **21l** with moderate enantioselectivity (50% ee), the reactions of dimethyl 2-chloromalonate and dimethyl 2-bromomalonate proceeded smoothly with the formation of a chiral quaternary carbon center, and the desired α-halo-β-amino esters **21m** and **21n**, respectively, were obtained in high yields (92–>99%) and with high enantioselectivities (96–97% ee). The reaction proceeded smoothly even in the presence of 2.5 mol% of BINOL and 3.75 mol% of dibutylmagnesium, and α-bromo-β-amino ester **21n** was obtained in 87% yield with 94% ee.

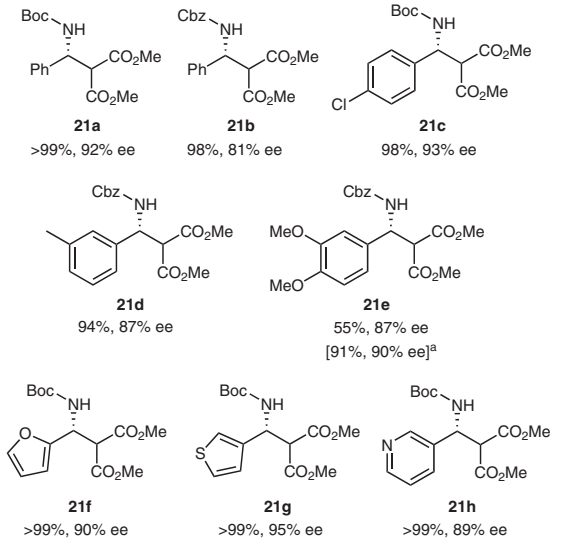
To evaluate the tolerance of this catalyst, a 2-gram-scale (5 mmol) synthesis of **21n** was examined in the reaction of **8b** with dimethyl 2-bromomalonate (Scheme 11). The reaction proceeded smoothly with the use of 5 mol% each of BINOL and dibutylmagnesium in toluene at –20 °C for

Table 5 Reaction of Dimethyl Malonate (**20a**)



8 **20a** (1.1 equiv) **21**

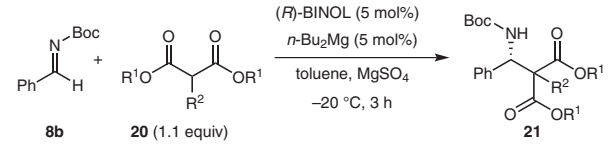
product, yield, and enantioselectivity



21a >99%, 92% ee
21b 98%, 81% ee
21c 98%, 93% ee
21d 94%, 87% ee
21e 55%, 87% ee [91%, 90% ee][a]
21f >99%, 90% ee
21g >99%, 95% ee
21h >99%, 89% ee

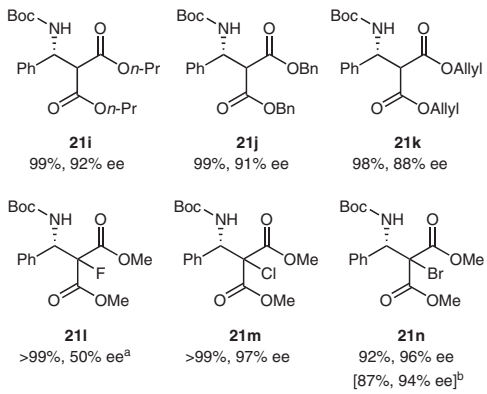
[a] BINOL (5 mol%), Bu_2Mg (7.5 mol%).

Table 6 Scope of Malonates **20**



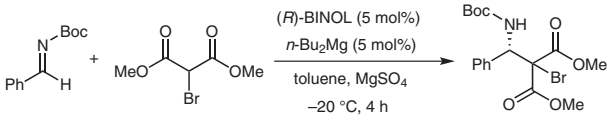
8b **20** (1.1 equiv) **21**

product, yield, and enantioselectivity



21i 99%, 92% ee
21j 99%, 91% ee
21k 98%, 88% ee
21l >99%, 50% ee[a]
21m >99%, 97% ee
21n 92%, 96% ee [87%, 94% ee][b]

[a] Yield and enantioselectivity when BINOL (10 mol%) and Bu_2Mg (10 mol%) were used.
[b] Yield and enantioselectivity when BINOL (2.5 mol%) and Bu_2Mg (3.75 mol%) were used.

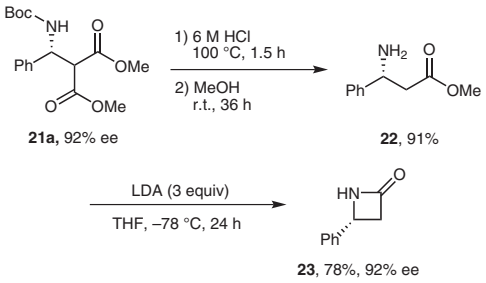


8b (5 mmol) (5.5 mmol) **21n**, 2.07 g
>99%, 99% ee

Scheme 11 Catalytic gram-scale synthesis

four hours, and the desired product **21n** was obtained in quantitative yield (2.07 g) with 99% ee.

With regard to the utility of the resulting Mannich product, we transformed **21a** (92% ee) to the corresponding β-lactam **23** (Scheme 12).[23] Without any loss of enantioselectivity (92% ee), β-phenyl-substituted β-lactam **23** was obtained in 71% yield in three steps via the decarboxylation of **21a** and subsequent cyclization of the synthetically useful optically active β-amino ester **22** by treatment with lithium diisopropylamide.



21a, 92% ee

22, 91%

23, 78%, 92% ee

Scheme 12 β-Lactam synthesis

Although a further mechanistic investigation of the actual catalysts should be necessary to determine which cooperative acid–base system is more favored (Brønsted acid–Brønsted base or Lewis acid–Brønsted base), we show a working model for the possible transition states in Figure 6. We assumed that some monomeric magnesium(II) pathways can explain the favored carbon–carbon bond formation on the *re*-face. In particular, the transition state with the tetrahedral magnesium(II) center by a Brønsted acid–Brønsted base system TS-**24** might be more favored due to the reasonably saturated coordination sites, while other transition states, TS-**25** and TS-**26**, have a vacant site on the magnesium(II) center. TS-**24** would smoothly release the product after carbon–carbon bond formation followed by protonation, and regenerate the Mg(II)–BINOLate salt. However, in contrast to our expectation, we can not completely deny the presence of other dimeric, trimeric, or oligomeric magnesium(II) complexes in the transition states.

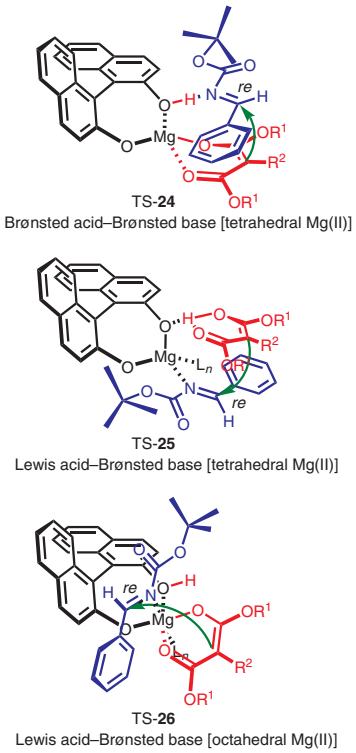


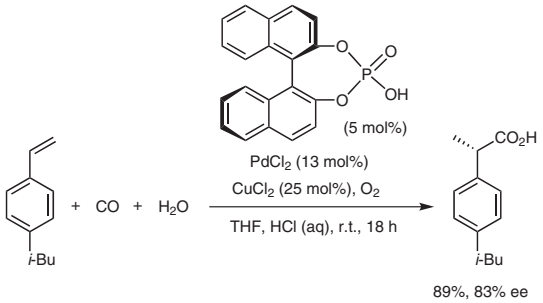
Figure 6 Possible transition states **24**–**26** with monomeric magnesium(II) [L_n = vacant site or solvent]

BINOL is simple, readily available in bulk quantities, and inexpensive. Therefore, this Mg(II)–BINOLate salt catalyst should be extremely practical in academic and industrial process chemistry. In particular, the smooth conversion within 3–4 hours at –20 °C with a catalyst loading of 2.5–5 mol% of the Mg(II)–BINOLate salt is outstanding, and this result is in sharp contrast to the reactions with previous catalysts, which often require 10–20 mol% loading and a longer reaction time (sometimes >12 h).[1–3]

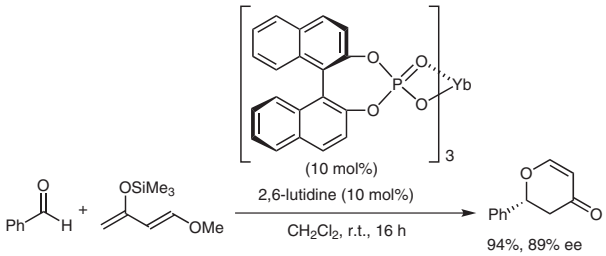
5 Chiral Calcium(II) Phosphate Salts and Chiral Phosphoric Acids[24]

On one hand, since Akiyama et al.[25] and Terada et al.[3a,14] independently reported chiral phosphoric acid catalysts derived from 3,3′-disubstituted BINOL, these have become recognized as some of the most useful organocatalysts.[26] However, BINOL-derived phosphoric acids are readily neutralized to adventitious metal salts such as alkali or alkaline earth metal salts by purification on silica gel. Some researchers have focused on the possibility of metal contaminants in phosphoric acids. Ding et al. reported that HCl-washed phosphoric acid improved catalytic activity in the Baeyer–Villiger reaction.[27] Moreover, Rueping et al. excluded calcium phosphate as a potential active catalyst in their organocatalytic carbonyl-ene reaction.[28]

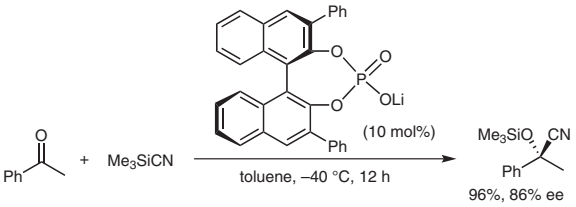
On the other hand, metal phosphates ($[M^{n+}][(RO)_2PO_2^-]_n$) have traditionally been of great value in asymmetric catalyses.[29,30] In particular, in pioneering works, Alper et al. reported the enantioselective hydrocarboxylation of olefins catalyzed by palladium(II) phosphates (Scheme 13),[29a] and Inanaga et al. later reported the hetero-Diels–Alder reaction catalyzed by rare earth metal phosphates (Scheme 14).[29b,c] Based on the bifunctional chemistry between acid (M^{n+}) and base [$(RO)_2PO_2^-$], replacement of the acidic proton (H^+) of phosphoric acids [$(RO)_2PO_2H$] with a metal cation (M^{n+}) should affect the coordination/activation of both the substrates and reagents (Scheme 1, Figure 1, type c). We have developed a catalytic enantioselective trimethylsilylcyanation with the use of chiral lithium(I) phosphate as a bifunctional Lewis acid–Lewis base salt catalyst (Scheme 15).[31] Similarly, a well-designed chiral metal phosphate, which should act as a bifunctional Lewis acid–Brønsted base salt catalyst, is sig-



Scheme 13



Scheme 14



Scheme 15

nificantly attractive for us to promote enantioselective direct Mannich-type reactions of aldimines with 1,3-dicarbonyl compounds (Figure 7).

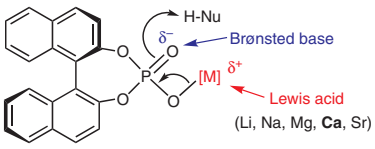
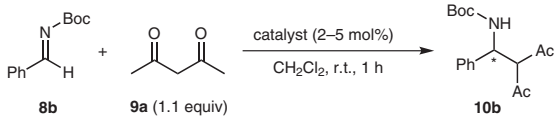


Figure 7 Chiral metal phosphates as bifunctional salt catalysts

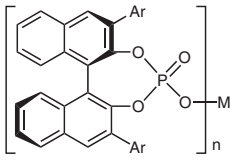
In this context, we recognized the significance of the acidic purification (e.g., treatment with aq HCl) of chiral phosphoric acids to obtain a metal-free, pure organocatalyst. Moreover, both metal-free chiral phosphoric acid H[**27b**] and chiral calcium phosphate Ca[**27a**]$_2$ catalyzed the enantioselective direct Mannich-type reactions of aldimines with 1,3-dicarbonyl compounds. The presence of small amounts of metal contaminants in 'purified' phosphoric acid may trigger unexpected excellent results or may invalidate these evaluations.

The enantioselective direct Mannich-type reaction of aldimine **8b** with acetylacetone (**9a**) catalyzed by H[**27a**] was first developed by Terada et al.[3a,14] We envisioned that alkali or alkaline earth metal phosphates might activate 1,3-dicarbonyl compounds more effectively than the corresponding phosphoric acids due to their stronger Brønsted basicity (Figure 7). In preliminary experiments, the Mannich-type reaction of **8b** with **9a** was examined using alkali or alkaline earth metal salts of **27a** (Table 7). While lithium(I), sodium (I), magnesium(II), and strontium(II) salt catalysts gave disappointing results (entries 1–3 and 5), the calcium(II) salt catalyst Ca[**27a**]$_2$ promoted the reaction, and (*R*)-**10b** was obtained in >99% yield with 92% ee in dichloromethane at room temperature (entry 4). Interestingly, this result with Ca[**27a**]$_2$ was compatible with Terada's result using silica gel purified H[**27a**], which we nearly reproduced ourselves (entry 6). However, with HCl-washed H[**27a**], poor and opposite enantioselectivity [27% ee, (*S*)-configuration] was observed for **10b** (entry 7). In this context, we were prompted to re-evaluate whether metal-free, pure phosphoric acid is the actual active catalyst for the direct Mannich-type reaction. During further investigation in the absence of calcium(II), we found that the enantioselectivity was improved with sterically demanding HCl-washed H[**27b**] in place of HCl-washed H[**27a**] (entry 8). In particular, a remarkable solvent effect was observed when toluene was used, and (*S*)-**10b** was obtained in quantitative yield with 93% ee at –30 °C (entry 9).

Table 7 Screening of Catalysts



catalyst:



M[**27a**]$_n$ (Ar = 4-(2-naphthyl)C$_6$H$_4$ M = H, Li, Na, Mg, Ca, Sr)

M[**27b**]$_n$ (Ar = 9-anthryl, M = H, Ca)

Entry	Catalyst (mol%)	Yield (%)	ee (%) (config)
1	Li[**27a**] (5)	99	11 (*S*)
2	Na[**27a**] (5)	88	9 (*S*)
3	Mg[**27a**]$_2$ (2.5)	>99	43 (*R*)
4	Ca[**27a**]$_2$ (2.5)	>99	92 (*R*)
5	Sr[**27a**]$_2$ (2.5)	>99	59 (*R*)
6[a]	silica gel purified H[**27a**] (2)	86	92 (*R*)
7	HCl-washed H[**27a**] (2)	88	27 (*S*)
8	HCl-washed H[**27b**] (5)	>99	49 (*S*)
9[b]	HCl-washed H[**27b**] (5)	>99	93 (*S*)

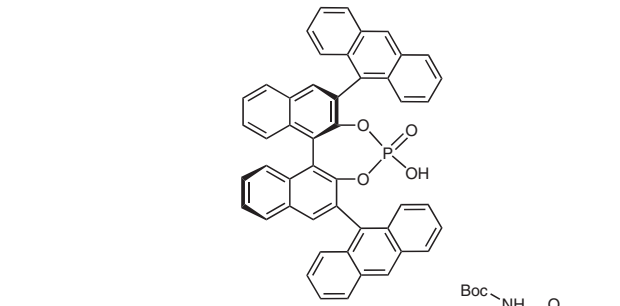
[a] Original data by Terada: 99% yield and 95% ee (*R*) (see ref. 3a).
[b] **8b** (1.2 equiv), **9a** (1 equiv), toluene, –30 °C, 12 h.

During the catalyst screening, we found that silica gel purified H[**27a**] and HCl-washed H[**27a**] gave different ^{1}H NMR spectra in DMSO-d_6. However, lithium(I), sodium(I), magnesium(II), calcium(II), and strontium(II) salts showed the same ^{1}H NMR spectra as silica gel purified H[**27a**]. In the FAB-LRMS analysis of silica gel purified H[**27a**], two major *m*/*z* peaks at 775 and 791 and two minor *m*/*z* peaks at 1529 and 1543 were observed, which indicate $[H[\mathbf{27a}] + Na]^+$, $[Ca[\mathbf{27a}]]^+$, $[2\ (H[\mathbf{27a}]) + Na]^+$, and $[Ca[\mathbf{27a}]_2]^+$, respectively. Therefore, silica gel purified H[**27a**] involved at least sodium(I) and calcium(II) salts.[32] We emphasize that aqueous hydrochloric acid treatment of silica gel purified material is essential for obtaining metal-free, pure phosphoric acid for efficient organocatalysis.

Based on the preliminary results in Table 7, we thoroughly investigated metal-free phosphoric acid catalysis with HCl-washed H[**27b**] in toluene at –30 °C for 24 h (Table 8). Acyclic α-substituted 1,3-diketones smoothly gave the Mannich adducts **10b**,**l**–**n** with high enantioselectivities (92–95% ee). Cyclic 1,3-diketones and β-ketoesters also gave the corresponding products **10o**,**17g**,**p**–**r**) with both high diastereoselectivities and high enantioselectivities (*syn*/*anti*, <10:>90, 95–98% ee. *anti*-Products were selectively obtained by H[**27b**]-catalysis, while *syn*-products were selectively obtained by **15**/*n*-BuLi/*t*-BuOH-catalysis (see Section 3). Remarkably, α-fluoro- and α-chloro-β-ketoesters also gave *anti*-diastereomers with high enantioselectivities as the major products (**17s**–**u**, 92–98% ee). A ketolactone and another functionalized β-ketoester, such as ethyl 4,4,4-trichloroacetoacetate also gave *anti*-adducts **28** and **29**, respectively, as the major diastereomer with high enantioselectivities. Overall, these *anti*-diastereomers obtained in Table 8 are valuable, since conventional catalysts gave the *syn*-diastereomers as major products.[1–3] Furthermore, when *S*-aryl thioacetoacetate was used, the adducts **30a** and **30b** were obtained in >99% yield with 82–86% ee. Unfortunately, however, reactions with thiomalonates did not proceed, and compounds **31a** and **31b** were scarcely obtained by H[**27b**] catalysis.

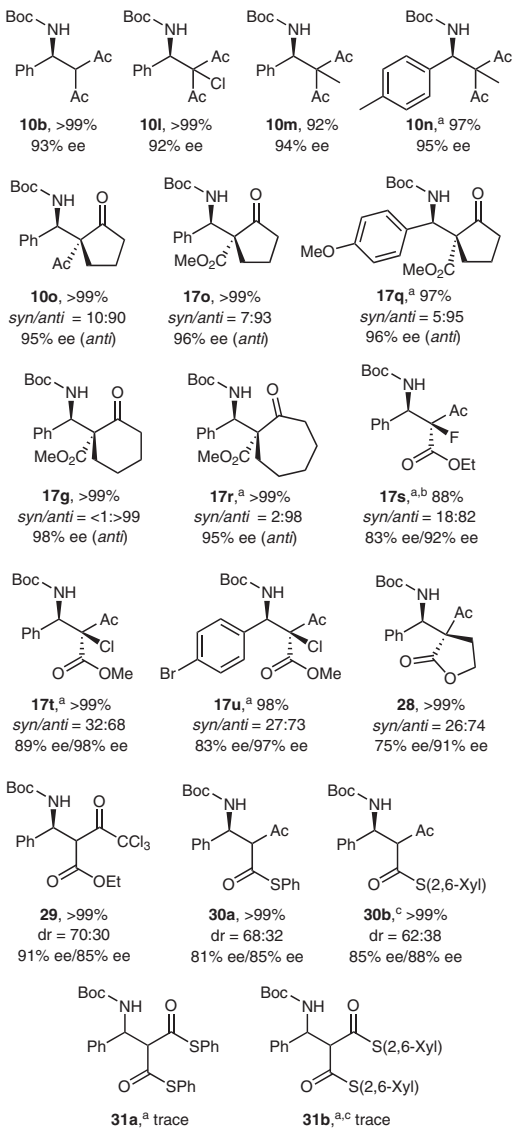
We discuss here a possible mechanism for H[**27b**] catalysis. The unprecedented highly *anti*-selective catalysis is considered to proceed via cyclic transition states, since the H[**27b**] catalyst can activate both the aldimine and the 1,3-dicarbonyl compound in a synclinal conformation (Figure 8). The coordination of the aldimine to H[**27b**] is sterically controlled as illustrated in TS-**32** and TS-**33**, due to steric repulsion between the 9-anthryl moiety of H[**27b**] and the aryl moiety of the aldimine. The bulky *tert*-butyl moiety in *N*-Boc, which should show significant repulsion with the 1,3-dicarbonyl compound, would be directed to inside the catalyst cavity. However, this repulsion can be partially reduced by rotation of the ester substitution (R^1) of the aldimine in favored TS-**32**, while the ketone moiety cannot inherently turn away in disfavored TS-**33**. In TS-**32**, a pronucleophile would be activated by coordination with the Brønsted basic P=O

Table 8 *anti*-Selective Catalysis with a Chiral Phosphoric Acid



8 (1.2 equiv) — diketone, ketoester, ketolactone, ketothioester

product, yield, diastereoselectivity, and enantioselectivity



[a] 1.5 equiv of **8** was used.
[b] Temperature was –20 °C.
[c] 2,6-Xyl = 2,6-$Me_2C_6H_3$.

moiety, followed by attack to the Brønsted acid (i.e., proton) coordinated aldimine on the *si*-face to give the *anti*-product.

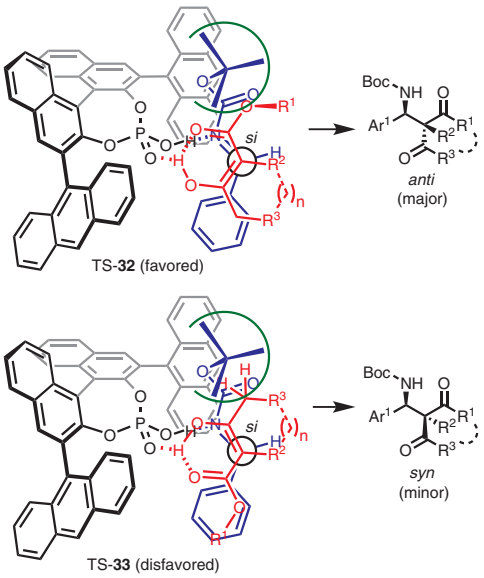


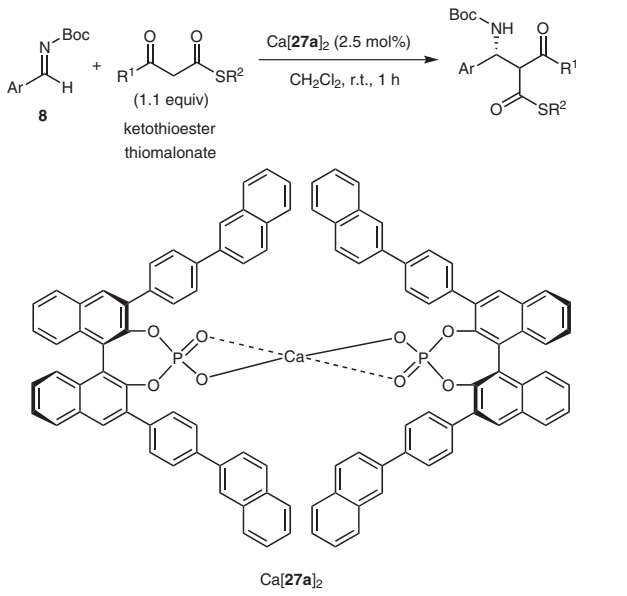
Figure 8 Proposed transition states **32** and **33** for H[**27b**] catalysis

Next, we investigated the scope of the enantioselective direct Mannich-type reaction with 1,3-dicarbonyl compounds under the optimized conditions for Ca[**27a**]$_2$ (Table 9). As a result, we found that β-ketothioesters[33] were suitable pronucleophiles. The Mannich-type reaction of **8b** with *S*-phenyl thioacetoacetate proceeded smoothly afforded the desired product **30a** in >99% yield with 90% ee. *S*-2,6-Xylyl thioacetoacetate also provided the corresponding products **30b–h** with better enantioselectivities (90–98% ee) in the reaction of aldimines with Me, MeO, Cl, and Br substitution with 0.5–2.5 mol% of Ca[**27a**]$_2$. To our great delight, *S*-2,6-xylyl thiomalonate could be used in the presence of 2.5 mol% of Ca[**27a**]$_2$, and the corresponding adducts **31b–d** were obtained in high yields and with high enantioselectivities (91–95% ee). This catalysis with thiomalonates by Ca[**27a**]$_2$ was in sharp contrast to that by H[**27b**], since the Brønsted basicity of H[**27b**] was not sufficient to promote the reactions through the activation of less acidic pronucleophiles.

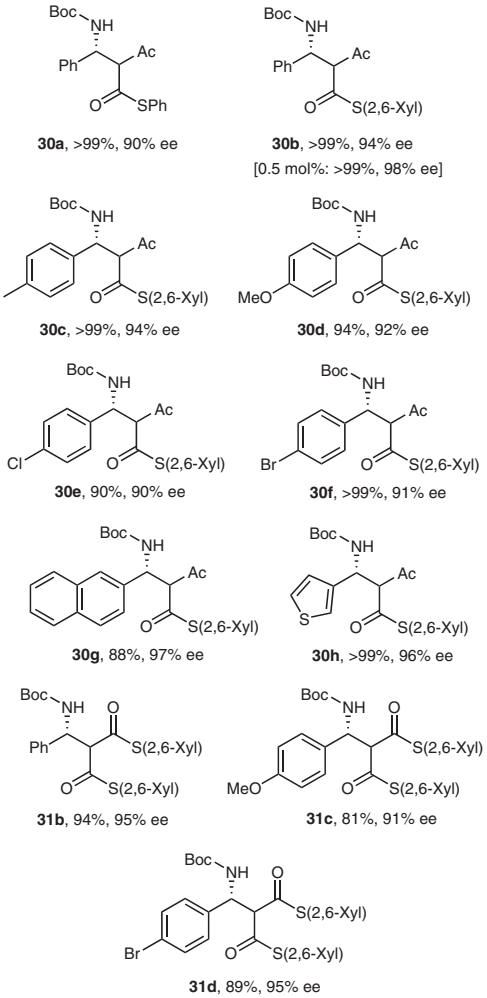
As noted above, H[**27b**] and Ca[**27a**]$_2$ catalysts made it possible to establish the first practical reaction of β-ketothioesters and thiomalonates. Remarkably, a change in the absolute configuration of the amino stereocenter of the products was observed with H[**27b**] (Table 8) vs. with Ca[**27a**]$_2$ (Table 9). Interestingly, these catalyses offer enantiodivergence with the same absolute configuration of the catalysts.

We next demonstrated the synthetic utility of β-ketothioesters and thiomalonates. Thiomalonate **31b** was readily transformed to malonate **21a** without racemization by treatment with silver trifluoroacetate and methanol in tetrahydrofuran at 50 °C (Scheme 16).

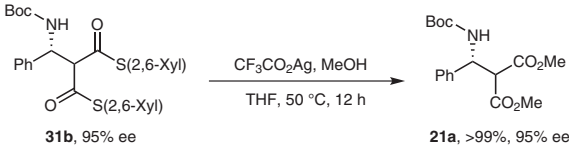
Table 9 Catalysis with a Chiral Calcium Phosphate[a]



product, yield, diastereoselectivity, and enantioselectivity



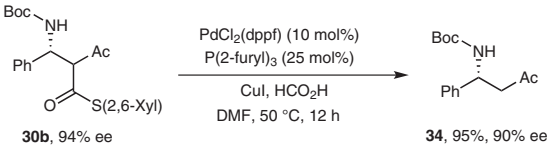
[a] 2,6-Xyl = 2,6-$Me_2C_6H_3$.



31b, 95% ee **21a**, >99%, 95% ee

Scheme 16 Decarboxylation of thiomalonate **31b**

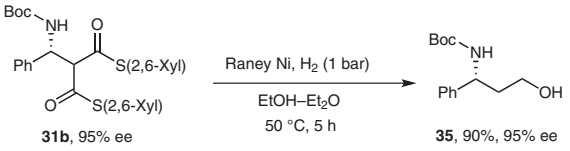
The decarboxylations of β-ketoesters and malonates would be difficult since harsh basic conditions are often required. In fact, a common decarboxylation with lithium hydroxide for **17c** gave a complex mixture with a significant loss of enantioselectivity (**34**, 13% yield and 69% ee). In sharp contrast, compound **30b** was converted into β-amino ketone **34**, which is also difficult to obtain directly from **8b** and acetone,[34] with palladium(II)/formic acid catalysis[35] (Scheme 17).



30b, 94% ee **34**, 95%, 90% ee

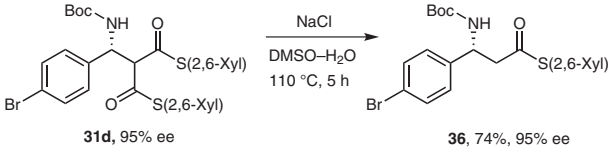
Scheme 17 Decarboxylation of β-ketothioester **30b**

The reduction of **31b** with Raney nickel under hydrogen (1 bar) gave chiral β-amino alcohol **35** in 90% yield with 95% ee (Scheme 18). Moreover, β-Boc-amino thioester **36** was obtained from **31d** in 74% yield with 95% ee through decarboxylation in dimethyl sulfoxide–water at 110 °C in the presence of sodium chloride (Scheme 19).[36]



31b, 95% ee **35**, 90%, 95% ee

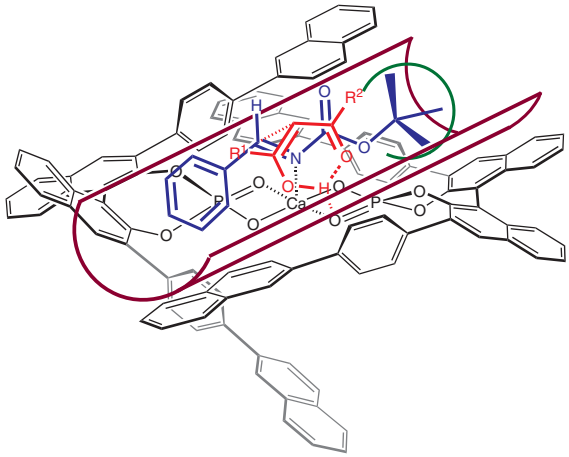
Scheme 18 Transformation to β-amino alcohol **35**



31d, 95% ee **36**, 74%, 95% ee

Scheme 19 Transformation to monothioester **36**

Although the further investigation of calcium(II) catalysis is necessary,[37] Lewis acidic calcium bis(phosphate) salt Ca[**27a**]$_2$, which was generated in situ and found in the FAB-HRMS analysis (*m*/*z* for [Ca[**27a**]$_2$]$^+$; calcd: 1543.3736; found: 1543.3749), might play a role. ^{31}P NMR analysis of Ca[**27a**]$_2$ (CD_2Cl_2) showed a broad peak at δ = 0.05, which suggests an oligomeric structure. However, when **8b** (1 equiv) and **9a** (1.1 equiv) were added to the solution of Ca[**27a**]$_2$ (2.5 mol%), a new sharp singlet was immediately observed at δ = 4.55, which suggests a monomeric structure for Ca[**27a**]$_2$. The calcium(II) center would be highly sterically hindered by the four 4-(β-naphthyl)C_6H_4 moieties, and a half-pipe-like chiral groove was formed around the calcium(II) center (Figure 9). Therefore, a sterically less-hindered cyclic transition state (TS-**37**) would be favored in Ca[**27a**]$_2$ catalysis, and a pronucleophile activated by the Brønsted basic P=O moiety would attack the aldimine activated by the Lewis acidic calcium(II) center on the *re*-face to give the *R*-product.



TS-**37** (favored)

Figure 9 Proposed transition state for Ca[**27a**]$_2$ catalysis

6 Conclusions

In summary, we have developed a series of extremely active and practical acid–base combined salt catalysts for the catalytic asymmetric direct Mannich-type reaction between aldimines and 1,3-dicarbonyl compounds. In particular, we designed several chiral BINOL-derived simple salt catalysts, such as chiral pyridinium 1,1′-binaphthyl-2,2′-disulfonates **1**, chiral lithium(I) binaphtholates **2**, chiral magnesium(II) binaphtholate (**3**), chiral calcium(II) phosphates **4**, and chiral phosphoric acids **5**. These catalysts covered a wide range of 1,3-dicarbonyl compounds with different reactivities [i.e., diketones, ketoesters, ketolactones, diesters (malonate), ketoamides, ketothioesters, dithioesters (thiomalonates)] (Table 10). Pharmaceutically useful, optically active β-amino ketones, β-amino es-

Table 10 Summary

1,3-Dicarbonyl compound	Suitable catalysts
diketone	**1**, **2**, **4**, **5**
ketoester	**2**, **5**
ketolactone	**2**, **5**
diester (malonate)	**3**
ketoamide	**1**, **2**
ketothioester	**2**, **4**
dithioester (thiomalonate)	**4**

ters, β-lactams, etc. were efficiently synthesized and/or transformed in high yield and with high stereoselectivity through this method. Our salt catalysts are significantly attractive for not only academic but also industrial use, since they can be immediately prepared in situ from simple and inexpensive precursors and show extremely high reactivity.

All reactions were carried out under a N_2 atmosphere using standard vacuum-line techniques and glassware that was flame-dried and cooled under N_2 before use. All anhyd solvents and reagents were obtained from commercial sources and distilled before use. All reagents were purchased and used without further purification. ^{1}H NMR spectra were measured on a Jeol ECS-400 (400 MHz) spectrometer at r.t. with the solvent resonance employed as the external standard (TMS δ = 0). ^{13}C NMR spectra were measured on Jeol ECS-400 (100 MHz) spectrometer with the solvent resonance employed as the internal standard ($CDCl_3$ δ = 77.1). ^{19}F NMR spectra were measured on a Jeol ECS-400 (376 MHz) spectrometer with the solvent resonance employed as the internal standard ($CF_3C_6H_5$ δ = –63.24). ^{31}P NMR spectra were measured on a Jeol ECS-400 (161 MHz) spectrometer with the solvent resonance employed as the internal standard (H_3PO_4 δ = 0). HRMS analyses were performed at Chemical Instrument Center, Nagoya University (Jeol JMS-700). IR spectra were recorded on a Jasco FT/IR 460 plus spectrophotometer. HPLC analysis was conducted using Shimadzu LC-10 AD coupled diode array-detector SPD-MA-10A-VP and chiral column of Daicel Chiralcel, Chiralpak. TLC analysis throughout this work, Merck TLC plates (silica gel 60G F254 0.25 mm) were used. The products were purified by neutral column chromatography on silica gel (Kanto Chemical Co., Inc. 37560). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid.

Catalysts, Mannich products, and their derivatives (**6**, **10**, **11**, **13**–**15**, **17**–**19**, **21**–**23**, **27**, **30**, **31**, **34**–**36**) have been fully characterized in the corresponding references.[7,16,21,24]

Chiral BINSA–Pyridinium Salt Catalysis; General Procedure

A well-dried Pyrex Schlenk tube was charged with (*R*)-1,1′-binaphthyl-2,2′-disulfonic acid (BINSA, **6**, 1.0 mg, 0.0025 mmol) and 2,6-diarylpyridine (0.005 mmol) under N_2. MeCN (2 mL) was added, and the soln was stirred at r.t. for 15 min. The volatiles were removed in vacuo, and well-dried $MgSO_4$ (50 mg, 0.42 mmol) and CH_2Cl_2 (1.5 mL) were added, and the suspension was stirred at r.t. for 30 min. The mixture was cooled to 0 °C, aldimine (0.375 mmol) in CH_2Cl_2 (0.5 mL) was added via a cannula, and 1,3-dicarbonyl compound (0.25 mmol) in CH_2Cl_2 (0.5 mL) was then added over 1 h (a syringe pump is useful if available.). The resultant mixture was then stirred at 0 °C for 30 min. Sat. aq $NaHCO_3$ (10 mL) was poured into the mixture, and the product was extracted with EtOAc (2 × 15 mL). The combined extracts were washed with brine (10 mL) and dried (Na_2SO_4). The organic phase was concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 5:1–2:1) to give the desired product. The enantiomeric purity was determined by chiral HPLC.

Chiral Lithium(I)–Binaphtholate Salt Catalysis; General Procedure

A well-dried Pyrex Schlenk tube was charged with (*R*)-3,3′-(3,4,5-$F_3C_6H_2)_2$-BINOL (**15**, 13.6 mg, 0.025 mmol) and *t*-BuOH (4.8 μL, 0.05 mmol) under N_2. Toluene (5 mL) was added, and the soln was stirred at –78 °C for 10 min. 1.5 M *n*-BuLi in *n*-hexane (16.7 μL, 0.025 mmol) was added, and the soln was stirred at –78 °C for 10 min. 1,3-Dicarbonyl compound (1.1 mmol) and aldimine (1 mmol) were added to the soln. The resultant mixture was then stirred at –78 °C for 2 h. The mixture was diluted with 10% HCl–MeOH (1 mL) at –78 °C. After 10 min, H_2O (5 mL) and EtOAc (15 mL) were added. The organic phase was extracted with EtOAc (2 × 15 mL), washed with brine (20 mL), and dried (Na_2SO_4). The organic phase was concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 5:1–2:1) to give the desired product. The enantiomeric purity was determined by the chiral HPLC analysis.

Chiral Magnesium(II)–Binaphtholate Salt Catalysis; General Procedure

A well-dried pyrex Schlenk tube was charged with (*R*)-BINOL (7.1 mg, 0.025 mmol) and well-dried $MgSO_4$ (100 mg) under N_2. Toluene (3 mL) was added, and the suspension was stirred at –20 °C for 5 min. 1.0 M Bu_2Mg in heptane (25.0 μL, 0.025 mmol) was added, and the mixture was stirred at –20 °C for 5 min. Dialkyl malonate (0.55 mmol) and aldimine (0.50 mmol) were added to the mixture. After then, the mixture was stirred at –20 °C for 3 h. The mixture was diluted with 10% HCl–MeOH (2 mL) at –20 °C. After 10 min, H_2O (10 mL) and EtOAc (20 mL) were added. The organic phase was extracted with EtOAc (2 × 20 mL), washed with brine (20 mL), and dried (Na_2SO_4). The organic phase was concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 5:1–2:1) to give the desired product. The enantiomeric purity was determined by the chiral HPLC analysis.

Preparation of Silica Gel Purified H[27a]

'Silica gel purified H[**27a**]' was prepared by the reported procedure[3a] through silica gel column purification but without subsequent treatment with aq HCl. 'Silica gel purified H[**27a**]' can be stored in a cool dark place.

Preparation of HCl-Washed H[27a]

The EtOAc soln of 'silica gel purified H[**27a**]' was thoroughly washed with aq 2 M HCl, and the organic phase was separated. After volatiles were removed under reduced pressure (<7 mbar), 'HCl-washed H[**27a**]' was obtained as a white solid that can be stored in a cool dark place.

Preparation of M[27a]$_n$ Salts

Catalysts M[**27a**]$_n$ were prepared in situ in a Pyrex Schlenk tube for the Mannich reaction. To prepare M[**27a**]$_n$ (2.5–5 mol%) such as Li[**27a**], Na[**27a**], Mg[**27a**]$_2$, Ca[**27a**]$_2$, and Sr[**27a**]$_2$ in situ, Li(O*i*-Pr) (5 mol%), NaOMe (5 mol%), Mg(O*t*-Bu)$_2$ (2.5 mol%), Ca(O*i*-Pr)$_2$ (2.5 mol%), and Sr(O*i*-Pr)$_2$ (2.5 mol%), respectively, were used with 'HCl-washed H[**27a**]' (5 mol%) in CH_2Cl_2–MeOH (1:1, 2 mL), and the soln was stirred at r.t. for 30 min. The volatiles were removed in vacuo, and then CH_2Cl_2 (2 mL) was added and removed in vacuo again. This solvent-removal sequence was repeated two additional times, and the desired M[**27a**]$_n$ was obtained as a white solid. Catalysts M[**27a**]$_n$ were used for the Mannich reaction just after this in situ preparation.

Chiral Phosphoric Acid Catalysis; General Procedure

A well-dried Pyrex Schlenk tube was charged with (*R*)-3,3′-bis(9-anthracenyl)-1,1′-binaphthyl phosphate (HCl-washed H[**27b**]) (17.5 mg, 0.025 mmol) and toluene (4 mL) under N_2. The soln was cooled to –30 °C, and aldimine (0.60 mmol) was added, and then 1,3-dicarbonyl compound (0.50 mmol) in toluene (1 mL) was added over 1 h. After that, the resultant mixture was stirred at –30 °C for 24 h. Sat. aq $NaHCO_3$ (10 mL) was poured into the mixture, and the product was extracted with EtOAc (3 × 15 mL). The combined extracts were washed with brine (10 mL) and dried (Na_2SO_4). The organic phase was concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel, *n*-hex-

ane–Et_2O, 5:1–1:1) to give the desired product. The enantiomeric purity was determined by chiral HPLC.

Ethyl (*S*)-2-[(*R*)-(*tert*-Butoxycarbonylamino)(phenyl)methyl]-2-fluoro-3-oxobutanoate (17s)

***anti*-Isomer (Major)**

92% ee; HPLC (Daicel Chiralpak AD-H × 2, *n*-hexane–*i*-PrOH 20:1, 0.5 mL/min): t_R = 60.2 [minor, (*R*,*S*)], 63.7 min [major, (*S*,*R*)].

$[\alpha]_D^{26}$ –3.0 (*c* 1.2, $CHCl_3$).

IR (neat): 3372, 2980, 2935, 1758, 1733, 1704, 1497, 1367, 1255, 1164, 1016 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.2 Hz, 3 H), 1.38 (s, 9 H), 2.36 (d, *J* = 4.6 Hz, 3 H), 4.02–4.16 (m, 2 H), 5.41 (d, *J* = 9.2 Hz, 1 H), 5.68 (dd, *J* = 26.6, 10.1 Hz, 1 H), 7.28–7.39 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 26.4, 28.1 (3 C), 57.0 (d, J_{C-F} = 19.1 Hz), 62.8, 80.5, 101.2 (d, J_{C-F} = 204.0 Hz), 128.1 (2 C), 128.3, 128.5 (2 C), 135.9, 154.4, 164.0 (d, J_{C-F} = 24.8 Hz), 199.6 (d, J_{C-F} = 25.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –175.8.

HRMS (FAB+): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{24}FNNaO_5$: 376.1536; found: 376.1536.

***syn*-Isomer (Minor)**

83% ee; HPLC (Daicel Chiralpak AD-H × 2, *n*-hexane–*i*-PrOH 20:1, 0.5 mL/min): t_R = 73.8 [minor, (*S*,*S*)], 107.3 min [major, (*R*,*R*)].

$[\alpha]_D^{26}$ –13.2 (*c* 1.3, $CHCl_3$).

IR (neat): 3364, 2979, 2934, 1756, 1733, 1498, 1367, 1248, 1165, 1065 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, *J* = 7.1 Hz, 3 H), 1.39 (s, 9 H), 1.99 (d, *J* = 4.6 Hz, 3 H), 4.17–4.41 (m, 2 H), 5.50 (d, *J* = 10.1 Hz, 1 H), 5.67 (dd, *J* = 27.3, 10.3 Hz, 1 H), 7.28–7.34 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 26.4, 28.1 (3 C), 56.9 (d, J_{C-F} = 19.1 Hz), 63.1, 80.3, 101.9 (d, J_{C-F} = 203.1 Hz), 128.3 (2 C), 128.4, 128.6 (2 C), 135.6, 154.3, 164.3 (d, J_{C-F} = 26.7 Hz), 199.9 (d, J_{C-F} = 28.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –175.2.

HRMS (FAB+): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{24}FNNaO_5$: 376.1536; found: 376.1534.

Methyl (*S*)-2-[(*R*)-(*tert*-Butoxycarbonylamino)(phenyl)methyl]-2-chloro-3-oxobutanoate (17t)

Diastereomeric mixture; HPLC (Daicel Chiralpak AD-H × 3, *n*-hexane–*i*-PrOH 95:5, 0.3 mL/min): *anti*-isomer (major) t_R = 91.0 [major, (*S*,*R*)], 97.0 min [minor, (*R*,*S*)], *syn*-isomer (minor) t_R = 77.4 [minor, (*S*,*S*)], 94.6 min [major, (*R*,*R*)].

IR (*syn*/*anti* mixtures, neat): 3437, 2979, 1718, 1493, 1367, 1243, 1166, 1050 cm^{-1}.

HRMS (FAB+): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{22}ClNNaO_5$: 378.1084; found: 378.1083.

***anti*-Isomer (Major)**

^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H), 2.34 (s, 3 H), 3.74 (s, 3 H), 5.68 (d, *J* = 9.2 Hz, 1 H), 5.87 (d, *J* = 9.2 Hz, 1 H), 7.27–7.34 (m, 3 H), 7.34–7.42 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6, 28.2 (3 C), 53.8, 58.3, 77.8, 80.2, 128.1 (2 C), 128.3, 128.8 (2 C), 136.2, 154.3, 166.3, 198.9.

***syn*-Isomer (Minor)**

^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H), 2.34 (s, 3 H), 3.77 (s, 3 H), 5.59 (d, *J* = 9.8 Hz, 1 H), 6.12 (d, *J* = 9.8 Hz, 1 H), 7.27–7.34 (m, 3 H), 7.34–7.42 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.6, 28.2 (3 C), 53.8, 58.6, 77.5, 80.4, 128.1 (2 C), 128.4, 128.8 (2 C), 135.8, 154.4, 166.7, 198.3.

Methyl (*S*)-2-[(*R*)-(4-Bromophenyl)(*tert*-butoxycarbonylamino)methyl]-2-chloro-3-oxobutanoate (17u)

Diastereomeric mixture; HPLC (Daicel Chiralpak AD-H × 3, *n*-hexane–*i*-PrOH 95:5, 0.3 mL/min): *anti*-isomer (major) t_R = 102.0 [major, (*S*,*R*)], 111.2 min [minor, (*R*,*S*)]; *syn*-isomer (minor) t_R = 84.6 [minor, (*S*,*S*)], 121.2 min [major, (*R*,*R*)].

IR (*syn*/*anti* mixtures, neat): 3433, 2979, 2932, 1720, 1489, 1366, 1245, 1166, 1011 cm^{-1}.

HRMS (FAB+): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{21}BrClNNaO_5$: 456.0189; found: 456.0184.

***anti*-Isomer (Major)**

^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 2.34 (s, 3 H), 3.76 (s, 3 H), 5.63 (d, *J* = 9.2 Hz, 1 H), 5.86 (d, *J* = 9.2 Hz, 1 H), 7.26 (d, *J* = 8.7 Hz, 2 H), 7.44 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5, 28.1 (3 C), 53.9, 57.9, 77.1, 80.4, 122.4, 130.6 (2 C), 131.2 (2 C), 135.3, 154.2, 166.1, 198.7.

***syn*-Isomer (Minor)**

^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 2.34 (s, 3 H), 3.78 (s, 3 H), 5.55 (d, *J* = 10.6 Hz, 1 H), 6.10 (d, *J* = 10.6 Hz, 1 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 7.45 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5, 28.1 (3 C), 53.9, 58.1, 77.1, 80.6, 122.6, 130.6 (2 C), 131.2 (2 C), 134.9, 154.3, 166.5, 197.9.

***tert*-Butyl {(*R*)-[(*R*)-3-Acetyl-2-oxotetrahydrofuran-3-yl](phenyl)methyl}carbamate (28)**

Diastereomeric mixture.

***anti*-Diastereomer (Major)**

Pale yellow oil; R_f = 0.7 (*n*-hexane–EtOAc, 2:1); HPLC (OD-H × 2, *n*-hexane–*i*-PrOH 4:1, 0.5 mL/min, 210 nm): t_R = 20.1 (major), 35.2 min (minor).

IR (neat): 3368, 2978, 1769, 1713, 1366, 1160, 1023 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.30 (m, 1 H), 1.39 (s, 9 H), 2.07 (m, 1 H), 2.49 (s, 3 H), 2.89 (m, 1 H), 3.59 (m, 1 H), 5.10 (br, 1 H), 5.80 (br, 1 H), 7.20–7.42 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 25.5, 28.3, 56.4, 66.2, 67.0, 80.8, 127.3, 128.5, 128.9, 137.1, 154.6, 173.3, 201.1.

HRMS (FAB+): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{23}NNaO_5$: 356.1474; found: 356.1476.

***syn*-Diastereomer (Minor)**

Colorless solid; mp 145–146 °C; R_f = 0.45 (*n*-hexane–EtOAc, 2:1); HPLC (OD-H × 2, *n*-hexane–*i*-PrOH 4:1, 0.5 mL/min, 210 nm): t_R = 27.9 (minor), 38.4 min (major).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H), 2.15–2.50 (m, 2 H), 2.45 (s, 3 H), 3.69 (m, 1 H), 4.36 (m, 1 H), 5.30 (br, 1 H), 6.63 (br, 1 H), 7.25–7.45 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.2, 28.3, 29.9, 53.1, 65.6, 67.5, 80.3, 128.1, 128.9, 129.0, 137.1, 155.0, 175.9, 203.5.

HRMS (FAB+): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{23}NNaO_5$: 356.1474; found: 356.1471.

Ethyl 2-[(*S*)-(*tert*-Butoxycarbonylamino)(phenyl)methyl]-4,4,4-trichloro-3-oxobutanoate (29)

Diastereomeric mixture; HPLC (Daicel Chiralpak AD-H × 2, *n*-hexane–EtOH 40:1, 0.5 mL/min): major diastereomer t_R = 30.7 (major), 40.4 min (minor); minor diastereomer t_R = 36.7 (minor), 38.4 min (major).

IR (*syn*/*anti* mixtures, neat): 3444, 2980, 1762, 1721, 1496, 1367, 1250, 1168, 1084, 1027 cm^{-1}.

HRMS (FAB+): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{22}Cl_3NNaO_5$: 460.0461; found: 460.0451.

Major Diastereomer

^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 6.4 Hz, 3 H), 1.42 (s, 9 H), 4.28–4.44 (m, 2 H), 4.58–4.78 (m, 1 H), 5.53–5.70 (m, 1 H), 6.26 (d, *J* = 9.6 Hz, 1 H), 7.24–7.34 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 28.2 (3 C), 55.2, 56.4, 62.7, 80.0, 95.7, 126.4 (2 C), 128.0, 128.6 (2 C), 138.1, 154.8, 165.7, 184.6.

Minor Diastereomer

^1H NMR (400 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.2 Hz, 3 H), 1.42 (s, 9 H), 4.28–4.44 (m, 2 H), 4.58–4.78 (m, 1 H), 5.53–5.70 (m, 1 H), 5.77 (d, *J* = 8.3 Hz, 1 H), 7.24–7.34 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 28.2 (3 C), 55.0, 56.6, 60.4, 80.1, 95.5, 126.8 (2 C), 128.1, 128.7 (2 C), 138.5, 154.9, 165.9, 182.1.

Chiral Calcium(II) Phosphate Salt Catalysis; General Procedure

A well-dried Pyrex Schlenk tube was charged with (*R*)-3,3′-bis(4-naphthalen-2-ylphenyl)-1,1′-binaphthyl phosphate (HCl-washed H[**27a**], 18.8 mg, 0.025 mmol) and Ca(O*i*-Pr)$_2$ (2.0 mg, 0.0125 mmol) under N_2. CH_2Cl_2–MeOH (1:1, 2 mL) was added, and the soln was stirred at r.t. for 30 min. The volatile solvents were then removed in vacuo, and CH_2Cl_2 (2 mL) was added and removed in vacuo again. This solvent-removal sequence was repeated two additional times, and Ca[**27a**]$_2$ was obtained in situ as a white solid. CH_2Cl_2 (4 mL) was then added, and the soln was stirred at r.t. for 15 min. To the soln was added aldimine (0.50 mmol). 1,3-Dicarbonyl compound (0.55 mmol) in CH_2Cl_2 (1.0 mL) was then added over 1 h (a syringe pump is useful if available.). The resultant mixture was stirred at r.t. for 1 h. Sat. aq NH_4Cl (10 mL) was poured into the mixture, and the product was extracted with EtOAc (3 × 15 mL). The combined extracts were washed with brine (10 mL) and dried (Na_2SO_4). The organic phase was concentrated under reduced pressure and the crude product was purified by column chromatography (silica gel, *n*-hexane–Et_2O, 5:1–1:1) to give the desired product. The enantiomeric purity was determined by chiral HPLC.

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