Asymmetric Catalysis

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Which Is the Actual Catalyst: Chiral Phosphoric Acid or Chiral Calcium Phosphate?**

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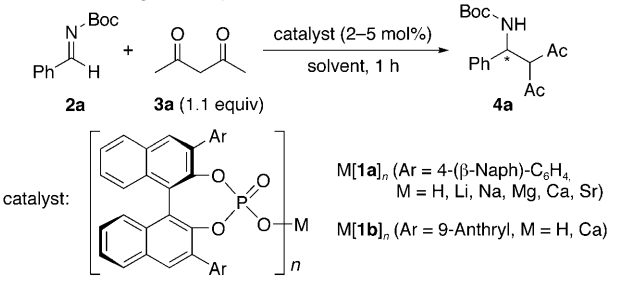
Since Akiyama et al.[1] and Uraguchi and Terada[2] independently reported chiral phosphoric acid catalysts derived from 3,3′-disubstituted 1,1′-bi(2-naphthol) (BINOL), these have become recognized as some of the most useful organocatalysts.[3] However, BINOL-derived phosphoric acids are readily neutralized to adventitious metal salts such as alkali or alkaline-earth metal salts by purification on silica gel. Recent research has been focused on the possibility of metal contaminants in phosphoric acids. Ding and co-workers reported that phosphoric acid washed with HCl improved the catalytic activity in the Baeyer–Villiger reaction.[4] Moreover, Rueping et al. excluded calcium phosphate as the potential active catalyst in their organocatalytic carbonyl-ene reaction.[5] Herein, we report the significance of the acidic purification of chiral phosphoric acids. Not only metal-free chiral phosphoric acid (H[**1b**]) but also chiral calcium phosphate (Ca[**1a**]$_2$) catalyze enantioselective direct Mannich-type reactions of aldimines with 1,3-dicarbonyl compounds (see Table 1). In particular, Ca[**1a**]$_2$ was effective for the enantioselective Mannich-type reaction with less-acidic 1,3-dicarbonyl compounds, including β-ketothioesters and thiomalonates.

The enantioselective direct Mannich-type reaction of aldimine **2a** with acetylacetone (**3a**) catalyzed by H[**1a**] was first developed by Terada and co-workers.[2,6,7] We envisioned that alkali or alkaline-earth metal phosphates might activate 1,3-dicarbonyl compounds more effectively than the corresponding phosphoric acids because of their stronger Brønsted basicity.[8,9] As preliminary experiments, the Mannich-type reaction of **2a** with **3a** was examined using alkali or alkaline-earth metal salts of **1a** (Table 1). Although Li^{I}, Na^{I}, Mg^{II}, and Sr^{II} salts showed disappointing results (entries 1–3 and 5), the Ca^{II} salt (Ca[**1a**]$_2$) catalyzed the reaction, and (*R*)-**4a** was obtained in >99% yield with 92% *ee* in CH_2Cl_2 at room temperature (entry 4).[10] Interestingly, this result obtained with Ca[**1a**]$_2$ was comparable to Terada's result using H[**1a**] purified by silica gel (entry 6). However, with H[**1a**] washed with HCl, poor and opposite enantioselectivity (27% *ee*, *S* configuration) was observed for **4a** (entry 7).[11] Moreover, during optimization, in the absence of Ca^{II}, we found that the sterically demanding H[**1b**], in place of H[**1a**], improved the enantioselectivity to give (*S*)-**4a** with 49% *ee* (entry 8). Further optimization of the reaction conditions with H[**1b**] gave (*S*)-**4a** with 93% *ee* in toluene at −30°C (entry 9), although Ca[**1b**]$_2$ also gave (*S*)-**4a**, albeit with low enantioselectivity (30% *ee*; entry 10).

Table 1: Screening of catalysts.



Entry	Catalyst (mol%)[a]	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c] (config.)
1	Li[**1a**] (5)	CH_2Cl_2	RT	99	11 (*S*)
2	Na[**1a**] (5)	CH_2Cl_2	RT	88	9 (*S*)
3	Mg[**1a**]$_2$ (2.5)	CH_2Cl_2	RT	>99	43 (*R*)
4	Ca[**1a**]$_2$ (2.5)	CH_2Cl_2	RT	>99	92 (*R*)
5	Sr[**1a**]$_2$ (2.5)	CH_2Cl_2	RT	>99	59 (*R*)
6	H[**1a**] purified on silica gel (2)	CH_2Cl_2	RT	86[d]	92 (*R*)[d]
7	H[**1a**] washed with HCl (2)	CH_2Cl_2	RT	88	27 (*S*)
8	H[**1b**] washed with HCl (5)	CH_2Cl_2	RT	>99	49 (*S*)
9[e]	H[**1b**] washed with HCl (5)	toluene	−30	>99	93 (*S*)
10	Ca[**1b**]$_2$ (2.5)	CH_2Cl_2	RT	93	30 (*S*)

[a] See the Supporting Information for details on preparation of the catalysts. [b] Yields of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] Compare to the original data by Terada[2]: 99% yield and 95% *ee* (*R*). [e] Used **2a** (1.2 equiv) and **3a** (1 equiv). Reaction time was 12 hours. Boc = *tert*-butoxycarbonyl, Naph = naphthyl.

Based on the unexpected preliminary results with the organocatalysts shown in Table 1, we thoroughly investigated the metal-free phosphoric acid catalysis with H[**1b**] washed with HCl (Scheme 1). Acyclic α-substituted β-diketones smoothly gave the Mannich adducts (**4b–d**) with high enantioselectivities (92–95% *ee*). Cyclic β-diketone and β-ketoesters also gave the corresponding products (**4e–i**) with both high *anti* diastereoselectivities and high enantioselectivities (*syn*/*anti* = <10:>90, 95–98% *ee*). The *anti* diastereom-

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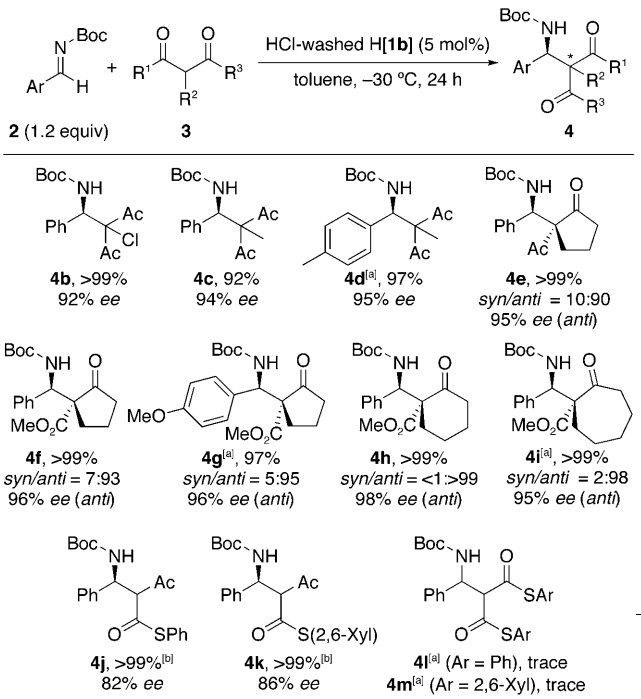
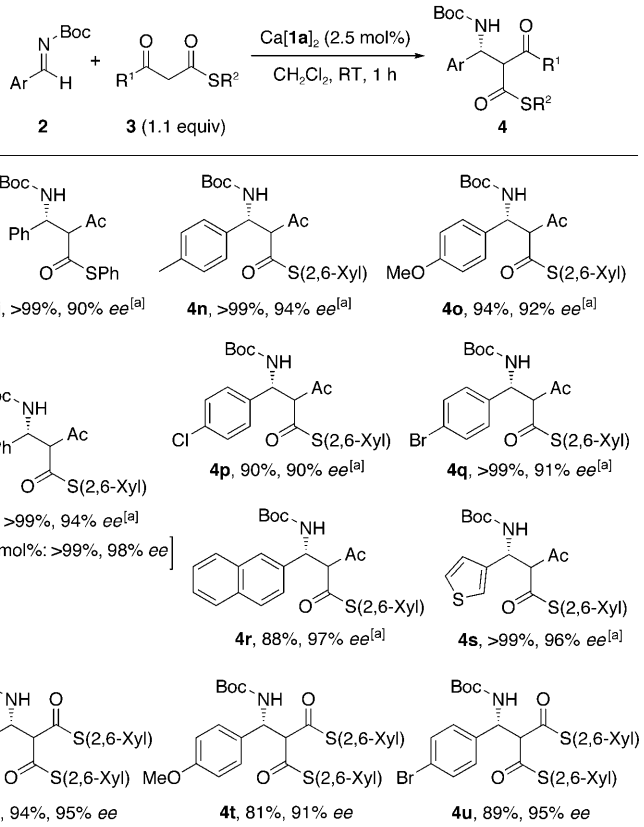


Scheme 1. *anti*-Selective catalysis with chiral phosphoric acid, H-[**1b**]. [a] Used **2** (1.5 equiv). [b] Diastereoselectivities for **4j** and **4k** are given in the Supporting Information. Yields of isolated product. The *ee* values were determined by HPLC on a chiral stationary phase.

ers obtained here are valuable because preceding catalysts gave the *syn* diastereomers as major products.[7,12] Furthermore, when *S*-aryl thioacetoacetate was used, the adducts (**4j** and **4k**) were obtained in > 99 % yield with 82–86 % *ee*. Unfortunately, however, reactions with thiomalonates did not proceed, and compounds **4l** and **4m** were obtained only in trace quantities.

The catalysis by the unprecedented, highly *anti*-selective H[**1b**] is thought to proceed through cyclic transition states, as the catalyst can activate both the aldimine and the 1,3-dicarbonyl compound in a synclinal conformation. The coordination of the aldimine to H[**1b**] is sterically controlled, as illustrated by **TS-1** and **TS-2** (Figure 1) because of the steric repulsion between the 9-anthryl moiety of H[**1b**] and the aryl moiety of the aldimine. The bulky *t*Bu moiety in the Boc group, which should show significant repulsion with the 1,3-dicarbonyl compound, would then be directed to the inside of the catalyst cavity. However, this repulsion can be partially relieved by rotation of the ester substituent (R′) on the aldimine in favored **TS-1**, while the ketone moiety cannot, inherently, turn away in disfavored **TS-2**. In **TS-1**, a pronucleophile would be activated by coordination with the Brønsted basic P=O moiety, and subsequent attack on the Brønsted acid (i.e. proton) coordinated aldimine on the *si* face to give the *anti* product.

Next, we investigated the scope of the enantioselective direct Mannich-type reaction with 1,3-dicarbonyl compounds under the optimized reaction conditions for Ca[**1a**]$_2$ (Scheme 2). Unfortunately, the Mannich-type reaction of **2**



Scheme 2. Catalysis with chiral calcium phosphate, Ca[**1a**]$_2$. [a] Diastereoselectivities for **4j**, **4k**, and **4n–s** are given in the Supporting Information. Yields of isolated product. Xyl = xylyl.

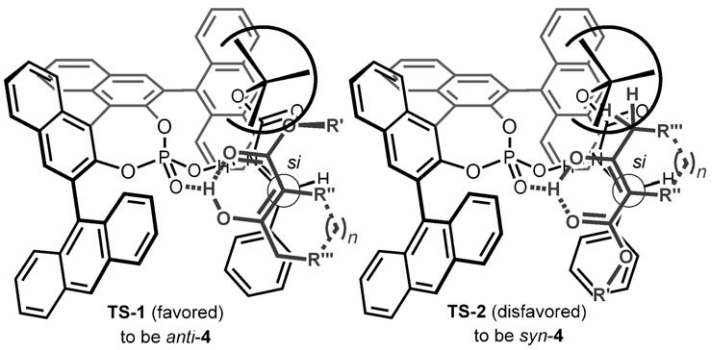


Figure 1. Proposed transition states for H[**1b**]-based catalysis.

with α-substituted β-ketoesters only gave moderate enantio- and diastereoselectivities (see for results for **4f**).[13] Instead, α-nonsubstituted β-ketothioesters[14] were more suitable pronucleophiles. The Mannich-type reaction of **2a** with *S*-phenyl thioacetoacetate proceeded smoothly and afforded the desired product (**4j**) in > 99 % yield with 90 % *ee*. The *S*-2,6-xylyl thioacetoacetate also provided the corresponding products (**4k** and **4n–q**) with good enantioselectivities (90–98 % *ee*) in the reaction of aldimines with Me, MeO, Cl, and Br substituents with 0.5–2.5 mol % of Ca[**1a**]$_2$. The 2-naphthyl and 3-thienyl substrates also gave the

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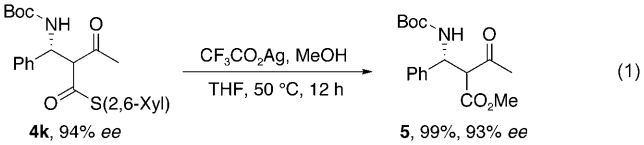
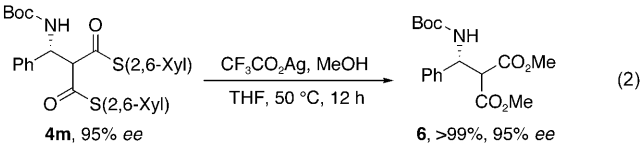
desired products (**4r** and **4s**) with high enantioselectivities (96–97% *ee*). To our great delight, *S*-2,6-xylyl thiomalonate could be used in the presence of Ca[**1a**]$_2$, and the corresponding adducts (**4m**, **4t**, and **4u**) were obtained in high yields with high enantioselectivities (91–95% *ee*). The catalysis with thiomalonates by Ca[**1a**]$_2$ gave results that were in sharp contrast to those by H[**1b**], as the Brønsted basicity of H[**1b**] was not sufficient to promote the reactions through the activation of less-acidic pronucleophiles. To the best of our knowledge, this is the first practical example of the direct Mannich-type reaction of aldimine with β-ketothioesters[7l] and thiomalonate. Moreover, a change in the absolute configuration of the amino stereocenter of the products was observed with H[**1b**] (Scheme 1) versus Ca[**1a**]$_2$ (Scheme 2). It is therefore noteworthy that these catalyses give enantiodivergent methodology while using catalysts with the same absolute configurations.

β-Ketothioester **4k** and thiomalonate **4m** were readily transformed into β-ketoester **5** and malonate **6**, respectively, without racemization by treatment with CF_3CO_2Ag/MeOH[15] in THF at 50 °C [Eqs. (1) and (2); THF = tetrahydrofuran].

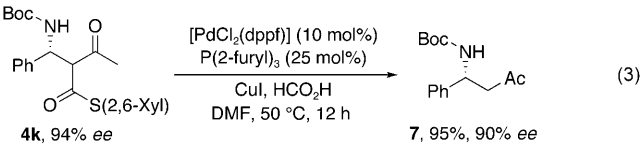


(1)



(2)

Decarboxylations of β-ketoesters and malonates are often difficult as basic conditions are often required. In sharp contrast, compound **4k** was converted into β-amino ketone **7**—which is difficult to obtain directly from **2a** and acetone[16]—by Pd^{II}/HCO_2H catalysis[17] [Eq. (3); DMF = N,N-dimethylformamide, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene]. However, for **5,** decarboxylation with LiOH gave a complex mixture (**7**, 13% yield and 69% *ee*) [Eq. (4)].



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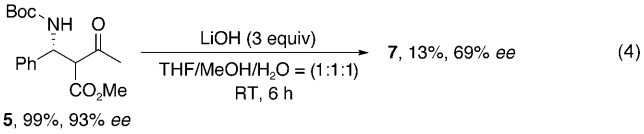
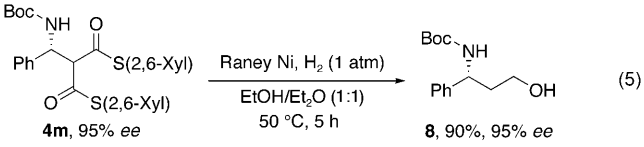


(4)

The reduction of **4m** with Raney Ni under H_2 (1 atm) gave the chiral β-amino alcohol **8** in 90% yield with 95% *ee* [Eq. (5)]. Moreover, β-*N*-Boc-protected thioester **9** was obtained from **4u** in 74% yield with 95% *ee* by decarboxylation in DMSO/H_2O at 110 °C in the presence of NaCl [Eq. (6); DMSO = dimethyl sulfoxide].[18]



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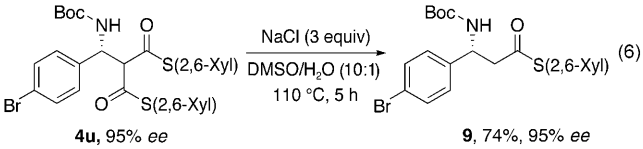

(6)

Although further investigation of the Ca^{II}-based catalysis is necessary,[10,19] the Lewis acidic calcium bis(phosphate) salt Ca[**1a**]$_2$ might play a role. This salt was generated in situ and identified in the FAB-HRMS analysis (*m/z* for $[Ca[\mathbf{1a}]_2]^+$; calcd: 1543.3736, found: 1543.3749). The ^{31}P NMR analysis of Ca[**1a**]$_2$ in CD_2Cl_2 showed a broad peak at 0.05 ppm, which suggests an oligomeric structure. However, when **2a** (1 equiv) and **3a** (1.1 equiv) were added to the solution of Ca[**1a**]$_2$ (2.5 mol%), a new, sharp singlet was observed at 4.55 ppm at 1 minute (just beginning) to 24 hours, which suggests a monomeric structure of Ca[**1a**]$_2$. Therefore, other possible candidates, such as calcium mono(phosphate) salt, Ca^{II}-free organocatalyst (i.e. H[**1a**] washed with HCl, 2.02 ppm in the ^{31}P NMR spectrum), or Ca^{II}-enolate, are unlikely. The Ca^{II} center would be highly sterically hindered by the four 4-(β-naphthyl)-C_6H_4 moieties, and a half-pipe-like chiral groove would be formed around the Ca^{II} center (Figure 2). Therefore, the less sterically hindered cyclic transition state (**TS-3**) would be favored in Ca[**1a**]$_2$-based catalysis, and pronucleophiles activated by the Brønsted basic P=O moiety would attack the aldimine activated by the Lewis acidic Ca^{II} center on the *re* face to give the *R* products.

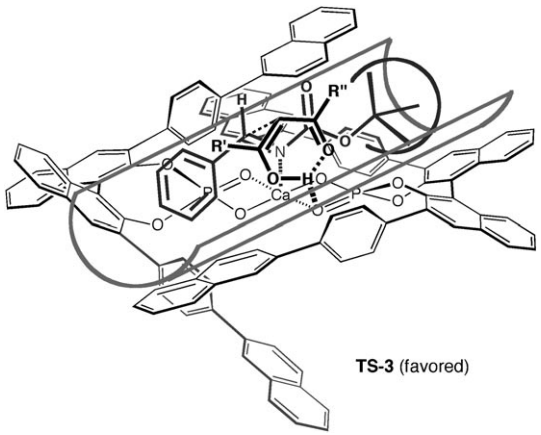

Figure 2. Proposed transition state for Ca[**1a**]$_2$-based catalysis.

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In summary, we have developed a highly enantioselective direct Mannich-type reaction of aldimines with a broad range of 1,3-dicarbonyl compounds involving unprecedented β-ketothioesters and thiomalonate conversions with the use of a chiral phosphoric acid in the presence or absence of Ca^{II}. The presence of small amounts of metal contaminants in "purified" phosphoric acid may trigger unexpected excellent results or may invalidate these evaluations, and the further application of this approach to another asymmetric catalysis with chiral alkali or alkaline-earth salts is now underway.

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[10] During the preparation of this manuscript, Kobayashi and co-workers reported that the chiral calcium catalyst with a neutral tridentate pybox ligand was effective for the enantioselective direct Mannich-type reaction of aldimines with less-acidic malonates. T. Poisson, T. Tsubogo, Y. Yamashita, S. Kobayashi, *J. Org. Chem.* **2010**, *75*, 963. pybox = 2,6-bis(2-oxazolin-2-yl)pyridine).

[11] We found that different ^{1}H NMR spectra, in [D_6]DMSO, were observed for H[**1a**] purified on silica gel and H[**1a**] washed with HCl. Li^I, Na^I, Mg^{II}, Ca^{II}, and Sr^{II} salts showed the same ^{1}H NMR spectra as H[**1a**] purified on silica gel. In the FAB-LRMS analysis of H[**1a**] purified on silica gel, two major *m*/*z* peaks at 775 and 791 and two minor *m*/*z* peaks at 1529 and 1543 were observed, which indicate $[H[\mathbf{1a}] + Na]^+$, $[Ca[\mathbf{1a}]]^+$, $[2(H[\mathbf{1a}]) + Na]^+$, and $[Ca[\mathbf{1a}]_2]^+$, respectively. Therefore, H[**1a**] purified on silica gel involved at least Na^I and Ca^{II} salts, although the ratio of Na^I/Ca^{II} was not determined.

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