

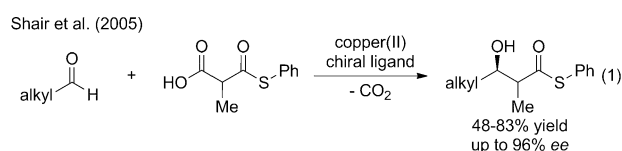
Organocatalytic Enantioselective Decarboxylative Aldol Reaction of Malonic Acid Half Thioesters with Aldehydes**

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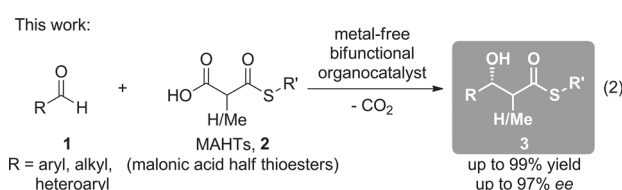
The direct asymmetric aldol reaction is one of the most powerful and fundamental tools for forming new carbon-carbon bonds and chiral hydroxy functional groups simultaneously.^[1] Inspired by nature, the development of prefucionalized metal enolates and metal Lewis acids to mimic type II aldolases have provided a general solution to accessing enantioenriched β -hydroxy carbonyl compounds in cooperation with chiral auxiliaries and metal complexes.^[2] Specifically, the Mukaiyama aldol reaction^[3] is general in scope and is practical for controlling chemo-, stereo-, and enantioselectivity with a pregenerated silyl enol ether. However, to gain access to a variety of aldol products with defined stereochemistry, it is necessary to develop a reaction with a distinct catalytic reaction mode. Since 2000, primary and secondary amine organocatalysts have shown excellent performance, compared to chiral metal Lewis acids, for direct aldol reactions and Mukaiyama-type reactions by forming an enamine intermediate with a carbonyl compound.^[4]

Recent studies by us^[6c] and others^[5–10] using malonic acid half thioesters (**2**, MAHTs) as ester enolate equivalents with various electrophiles were compelling for the application of organocatalytic aldol reactions to mimic polyketide synthases. Moreover, the desired β -hydroxy thioesters **3** could readily be transformed into various functional groups.^[11] In addition, such a reaction generates only CO₂ as a sole by-product.

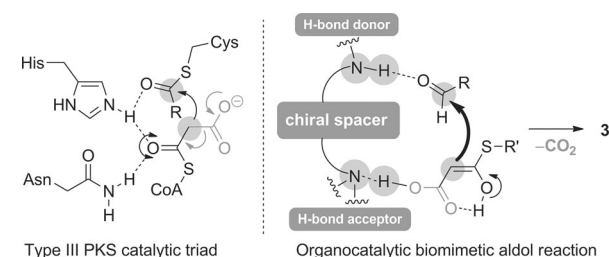
Recently, Shair et al. investigated the aldol reaction with methyl-substituted MAHT (MeMAHT) using a chiral Cu^{II}/bis(oxazoline) catalyst. Aliphatic aldehydes underwent the aldol reaction to afford the α -methyl substituted aldol products with excellent diastereo- and enantioselectivity [Eq. (1)]. However, aromatic and α,β -unsaturated aldehydes



were shown to be poor substrates.^[9b] Herein, we report the first organocatalytic asymmetric aldol reaction of methyl-substituted and unsubstituted MAHTs (**2**) with a variety of aromatic and aliphatic aldehydes to afford enantioenriched β -hydroxythioesters (**3**) by employing a sulfonamide-based organocatalyst [Eq. (2)]. To the best of our knowledge, this is the first example of metal-free enantioselective organocatalytic aldol reaction of MAHTs (**2**) with aldehydes (**1**), as a polyketide synthase mimic,^[12] to provide β -hydroxy thioesters (**3**).



Polyketide synthases (PKSs) use the catalytic triad to organize and stabilize the reaction intermediates by hydrogen-bonding interactions.^[13] Thus, we presumed that Brønsted acid/base bifunctional moieties in an organocatalyst might be crucial for the deprotonation/stabilization of MAHTs and orientation of the aldehyde for high facial selectivity (Scheme 1). The model reaction was conducted by using the MAHT **2a** and benzaldehyde (**1a**) in MTBE/THF at room temperature with different types of cinchona-based bifunctional catalysts. As shown in Scheme 2, this preliminary



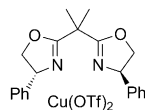
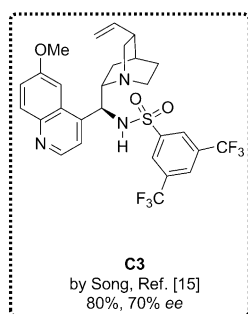
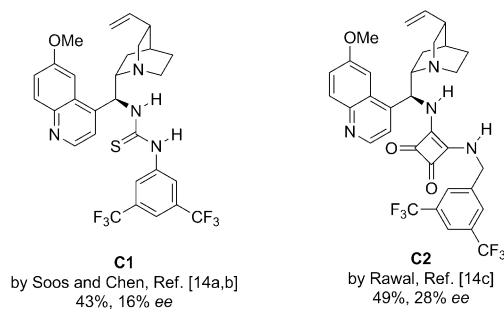
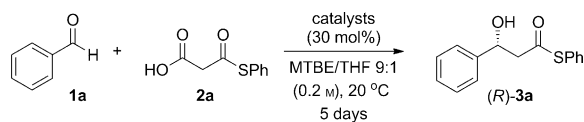
Scheme 1. Reaction mechanism of the polyketide synthase^[13a] and plausible working hypothesis for the organocatalytic aldol reaction of the malonic acid half thioester **2** with a chiral hydrogen-bonding donor/acceptor catalyst.

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no reaction

Scheme 2. Preliminary catalyst screening for the decarboxylative aldol reaction of the MAHT **2a** with benzaldehyde (**1a**). MTBE = *tert*-butyl methyl ether, Tf = trifluoromethanesulfonyl.

catalyst screening revealed that the cinchona-based thiourea **C1**^[14a,b] and squaramide **C2**^[14c] led to low turnover numbers and poor enantioselectivities. Gratifyingly, the sulfonamide-based catalyst **C3**, which was developed previously in our laboratory,^[15] showed distinguished catalytic activity and enantioselectivity (80% yield, 70% *ee*^[16]) compared to **C1** and **C2**. It should be noted here that α -unsubstituted MAHTs such as **2a** were not tolerated under the copper(II)-catalyzed aldol reaction conditions, thus conversion into the desired aldol product was not observed with either aromatic or aliphatic aldehydes (see the Supporting Information).^[9b] These results prompted us to investigate the unique activity and enantioselectivity of the sulfonamide-based catalyst **C3** in detail.

Since the hydrogen-bonding property of **C3** could be easily modulated by changing the substitution of the aromatic functional group, we modified the aromatic moiety in the catalyst to induce higher activity and facial selectivity (Table 1). Sterically bulky substituents and strong π -electron donors showed no significant improvement (entries 3–5). Surprisingly, we could obtain remarkable catalytic activity (99% yield) and enantioselectivity (94% *ee*) with a 1-naphthyl substituent (entry 7). The highly fluorescent dansyl sulfonamide catalyst **C10**, which also bears a 1-naphthyl moiety together with an electron-donating group, showed excellent catalytic performance (entry 8). However, the 2-naphthyl substituent showed only modest activity and enantioselectivity, and might imply a subtle effect from hydrogen

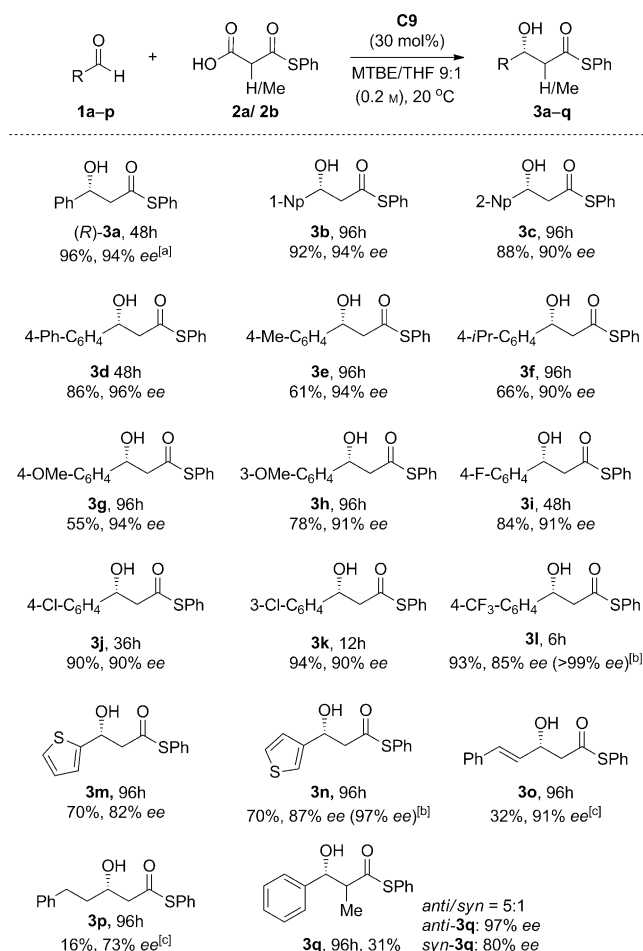
Table 1: Screening of sulfonamide-based catalyst for the aldol reaction of **2a** with benzaldehyde (**1a**).^[a]

Entry	Catalyst	Solvent	<i>t</i>	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	C3	MTBE/THF ^[d]	5 days	80	70
2	C4	MTBE/THF	5 days	91	79
3	C5	MTBE/THF	5 days	67	55
4	C6	MTBE/THF	5 days	73	76
5	C7	MTBE/THF	5 days	78	85
6	C8	MTBE/THF	5 days	79	63
7	C9	MTBE/THF	48 h	99	94
8	C10	MTBE/THF	48 h	93	94
9	C9	CH ₂ Cl ₂	7 days	7	61
10	C9	THF	3 days	91	91
11	C9	1,4-dioxane	7 days	81	93
12	C9	EVE	7 days	47	94
13	C9	EtOAc	7 days	67	94
14	C9	acetone	7 days	56	94

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (3.0 equiv), and catalyst (30 mol%) in 2.5 mL of solvent at 20 °C. [b] Yields of products isolated after purification by column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase (see the Supporting Information). [d] MTBE/THF (9:1, v/v). EVE = ethyl vinyl ether, THF = tetrahydrofuran.

bonding and steric interactions (entry 6). In addition, the solvent has an important effect on reactivity and enantioselectivity. Although a range of aprotic nonpolar and polar solvents afforded high enantioselectivity (entries 9–14), MTBE/THF (entry 7) proved best with respect to both chemical yield and enantioselectivity.

By using **C9** as the optimal catalyst and **2a** as the optimal reaction partner (for effects of the substituents on various MAHTs on the reaction outcome, see the Supporting Information), we explored the scope of the organocatalytic decarboxylative aldol reaction with a variety of aromatic and aliphatic aldehydes. As summarized in Scheme 3, regardless of the electronic nature of the aromatic substituent, high enantioselectivity (up to 96% *ee*) was achieved with electron-donating and electron-withdrawing substituents under the standard reaction conditions.^[17] Heteroaromatic aldehydes were also smoothly converted into the desired products **3m** and **3n** with high enantioselectivity. Nonaromatic aldehydes, such as **1o** and **1p** were tolerated and afforded the desired aldol products **3o** and **3p**, respectively, in good to excellent enantioselectivity, although a significant amount of by-products was observed.^[18] Fortunately, enantiomerically pure aldol products (**3**; >99% *ee*) were easily isolated by

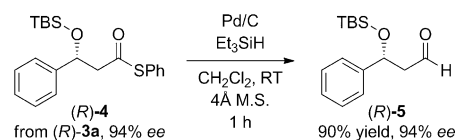


Scheme 3. Substrate scope. General reaction conditions: **1** (0.5 mmol), **2** (3.0 equiv), and **C9** (30 mol%) in 2.5 mL of MTBE/THF (9:1) at 20 °C. [a] Using HQN-1-Np-SA (**C11**) as a catalyst. [b] After single recrystallization. [c] The reactions were performed at 10 °C.

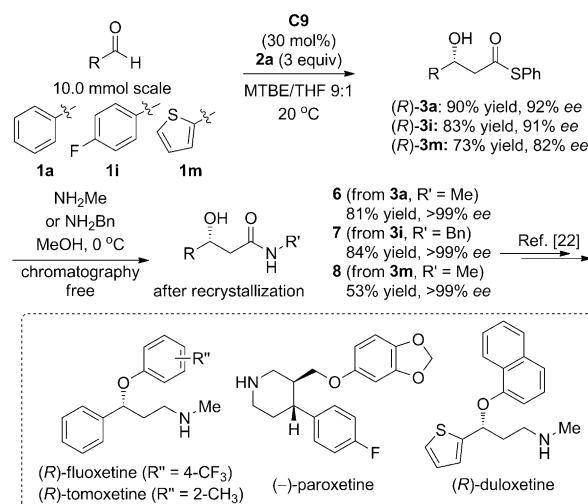
a simple recrystallization because of the crystalline property of the β -hydroxy thioesters **3**. Notably, the present reaction conditions were also compatible with the methyl-substituted MAHT **2b** and afforded *anti*-**3q** selectively with excellent enantioselectivity (97% ee), although the chemical yield still requires further optimization.

To demonstrate synthetic utility of our methodology with enantioenriched β -hydroxy thioesters, the aldol product (*R*)-**4** was subjected to Fukuyama reduction conditions. The desired aldehyde (*R*)-**5** was isolated without erosion of enantiopurity (Scheme 4). Acetaldehyde has long been considered as a problematic nucleophile for aldol reactions because of the severe polymerization and self-aldol reactions of acetaldehyde, and the unstable nature of the aldol products.^[19] No successful suppression of the over-reaction of the product has been reported to date in spite of extensive research.^[20] Thus, α -unsubstituted MAHTs can be used as feasible surrogates for an acetaldehyde nucleophile in the aldol reaction.

Additional synthetic applications of the β -hydroxy thioesters **3** began with preparation of the aldol products **3a**, **3i**, and **3m** on a multigram scale. As summarized in Scheme 5, the aldol reactions were performed on a 10 mmol scale to



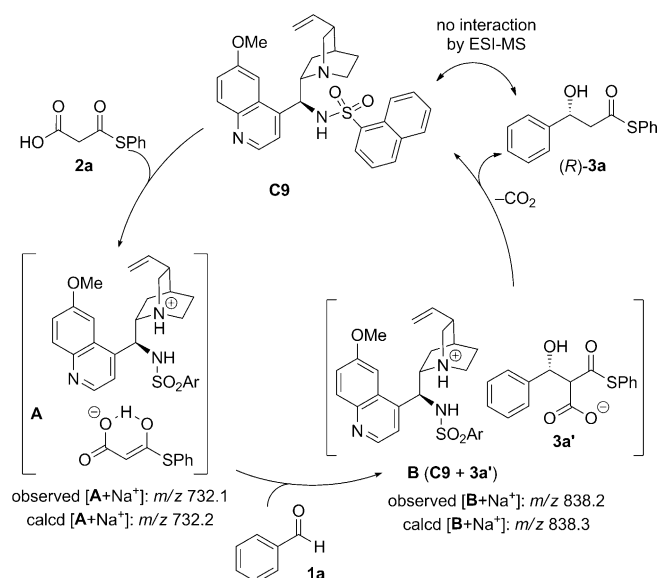
Scheme 4. Facile conversion of the thioesters (*R*)-**4** into the corresponding aldehydes (*R*)-**5** under the Fukuyama reduction conditions.^[21] M.S. = molecular sieves, TBS = *tert*-butyldimethylsilyl.



Scheme 5. Utility of the aldol products **3a**, **3i**, and **3m** in the asymmetric syntheses of valuable drug intermediates.

afford the products in an enantioenriched form in good yield. Amide formation using **3a**, **3i**, and **3m** provided the chiral synthons **6**, **7** and **8**, respectively, as precursors for antidepressant drugs such as (*R*)-fluoxetine, (*R*)-tomoxetine, (–)-paroxetine, and (*R*)-duloxetine.^[22] The amides were obtained, without any silica gel chromatography and tedious purification, in high yields as a single enantiomer after a single recrystallization (for detailed experimental results, see the Supporting Information). Although our protocol requires high catalyst loading (30 mol%) to facilitate the reaction, **C9** could be easily recovered from the reaction mixture after a simple acid/base workup to afford the pure catalyst **C9** in greater than 95% yield. The recovered catalyst was successfully reused for the subsequent runs and showed identical activity and enantioselectivity, and can be ascribed to the robustness of the catalyst (for details of catalyst recycling experiments, see the Supporting Information).

To gain insight into the reaction mechanism as well as the observed catalytic activity of **C9**, we conducted in situ electrospray ionization mass spectroscopy analysis of the reaction mixture (see the Supporting Information). In the presence of **C9** under the standard reaction conditions, we observed signals at m/z 732.1 and m/z 838.2, which correspond to the complex **A** + Na⁺ (catalyst/**2a**) and the complex **B** + Na⁺ (catalyst/**3a'**; Scheme 6), respectively.^[23] The observation of the complex **B** indicated that the reaction operates by the aldol addition of **2** to the aldehyde and subsequent decarboxylation to complete the catalytic cycle by releasing **3a**. Other types of catalytic reactions using MAHTs have been



Scheme 6. A proposed reaction mechanism and observation of complex **A** (**C9**/**2a**) and complex **B** (**C9**/**3a'**).

known to proceed by a similar reaction sequence.^[7b,8b,24] When **C1** and **C2** were used as catalysts instead of **C9**, the corresponding complex of the catalyst and **3a** was additionally observed. The formation of a strong complex of either **C1** or **C2** with the aldol product can be ascribed to their efficient bifurcated hydrogen-bonding donor character which might have higher binding affinity than the sulfonamide-based catalysts. Formation of such a stable catalyst–product complex can deplete the effective catalyst concentration during the reaction course, thus resulting in low turnover numbers (Scheme 2). A fine-tuning of the hydrogen-bond donor property of sulfonamide catalysts might be key to the successful enantioselective catalysis by avoiding the catalyst poisoning by the product.

In summary, we disclosed the first successful metal-free biomimetic enantioselective decarboxylative aldol reaction of MAHTs with various aldehydes using sulfonamide-based organocatalysts to afford enantioenriched β -hydroxy thioesters. A range of aromatic and nonaromatic aldehydes were converted into the corresponding aldol products in good to excellent yields and enantioselectivities. The obtained enantioenriched aldol products were easily converted into valuable synthetic intermediates without loss of enantiopurity. In situ ESI-MS analysis provided insight into the origin of the unique catalytic activity of **C9** as well as the reaction sequence. The ready accessibility of the organocatalysts and enantioenriched β -hydroxy thioesters will lead to various applications in the field of natural product synthesis, such as catalytic asymmetric polyketide synthesis.

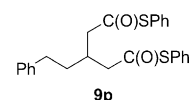
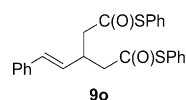
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- [1] For recent reviews of catalytic, enantioselective aldol reactions, see: a) C. Palomo, M. Oiarbide, J. M. García, *Chem. Soc. Rev.* **2004**, 33, 65–75; b) B. M. Trost, C. S. Brindle, *Chem. Soc. Rev.* **2010**, 39, 1600–1632.
- [2] T. D. Machajewski, C.-H. Wong, *Angew. Chem.* **2000**, 112, 1406–1430; *Angew. Chem. Int. Ed.* **2000**, 39, 1352–1374.
- [3] For a review of catalytic, enantioselective Mukaiyama aldol reactions with silyl ketene acetals, see: E. M. Carreira in *Comprehensive Asymmetric Catalysis*, Vol. 3 (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 997–1065; For an excellent example of organocatalytic Mukaiyama aldol reaction, see: P. García-García, F. Lay, F. P. García-García, C. Rabalakos, B. List, *Angew. Chem.* **2009**, 121, 4427–4430; *Angew. Chem. Int. Ed.* **2009**, 48, 4363–4366.
- [4] For recent reviews, see: a) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, 37, 580–591; b) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, 107, 5471–5569; c) L. M. Geary, P. G. Hultin, *Tetrahedron: Asymmetry* **2009**, 20, 131–173; d) M. M. Heravi, S. Asadi, *Tetrahedron: Asymmetry* **2012**, 23, 1431–1465; e) V. Bisai, A. Bisai, V. K. Singh, *Tetrahedron* **2012**, 68, 4541–4580.
- [5] For the reviews, see: a) Y. Pan, C.-H. Tan, *Synthesis* **2011**, 2044–2053; b) L. Bernardi, M. Fochi, M. C. Franchini, A. Ricci, *Org. Biomol. Chem.* **2012**, 10, 2911–2922.
- [6] For the catalytic enantioselective decarboxylative Michael addition reactions of MAHTs, see: a) J. Lubkoll, H. Wennemers, *Angew. Chem.* **2007**, 119, 6965–6968; *Angew. Chem. Int. Ed.* **2007**, 46, 6841–6844; b) M. Furutachi, S. Mouri, S. Matsunaga, M. Shibasaki, *Chem. Asian J.* **2010**, 5, 2351–2354; c) H. Y. Bae, S. Some, J. H. Lee, J.-Y. Kim, M. J. Song, S. Lee, Y. J. Zhang, C. E. Song, *Adv. Synth. Catal.* **2011**, 353, 3196–3202.
- [7] For the catalytic enantioselective decarboxylative Mannich reactions of MAHTs, see: a) A. Ricci, D. Pettersen, L. Bernardi, F. Fini, M. Fochi, R. P. Herrera, V. Sgarzani, *Adv. Synth. Catal.* **2007**, 349, 1037–1040; b) Y. Pan, C. W. Kee, Z. Jiang, T. Ma, Y. Zhao, Y. Yang, H. Xue, C.-H. Tan, *Chem. Eur. J.* **2011**, 17, 8363–8370; c) N. Hara, S. Nakamura, M. Sano, R. Tamura, Y. Funahashi, N. Shibata, *Chem. Eur. J.* **2012**, 18, 9276–9280.
- [8] For the achiral decarboxylative aldol reactions of MAHTs, see: a) G. Lalic, A. D. Aloise, M. D. Shair, *J. Am. Chem. Soc.* **2003**, 125, 2852–2853; b) N. Blaquiere, D. G. Shore, S. Rousseaux, K. Fagnou, *J. Org. Chem.* **2009**, 74, 6190–6198; c) X.-J. Li, H.-Y. Xiong, M.-Q. Hua, J. Nie, Y. Zheng, J.-A. Ma, *Tetrahedron Lett.* **2012**, 53, 2117–2120.
- [9] For the catalytic enantioselective decarboxylative aldol reactions of MAHTs, see: a) S. Orlandi, M. Benaglia, F. Cozzi, *Tetrahedron Lett.* **2004**, 45, 1747–1749; b) D. Magdziak, G. Lalic, H. M. Lee, K. C. Fortner, A. D. Aloise, M. D. Shair, *J. Am. Chem. Soc.* **2005**, 127, 7284–7285; c) K. C. Fortner, M. D. Shair, *J. Am. Chem. Soc.* **2007**, 129, 1032–1033; d) D. J. Schipper, S. Rousseaux, K. Fagnou, *Angew. Chem.* **2009**, 121, 8493–8497; *Angew. Chem. Int. Ed.* **2009**, 48, 8343–8347; e) N. Hara, S. Nakamura, Y. Funahashi, N. Shibata, *Adv. Synth. Catal.* **2011**, 353, 2976–2980.
- [10] For the catalytic enantioselective decarboxylative amination reactions of MAHTs, see Ref. [7b].
- [11] T. Miyazaki, X. Han-ja, H. Tokuyama, T. Fukuyama, *Synlett* **2004**, 477–480.
- [12] For reviews, see a) J. Staunton, K. J. Weissman, *Nat. Prod. Rep.* **2001**, 18, 380–416; b) A. Hill, *Nat. Prod. Rep.* **2006**, 23, 256–320; c) S. Smith, S.-C. Tsai, *Nat. Prod. Rep.* **2007**, 24, 1041–1072.
- [13] For examples, see a) M. B. Austin, M. Izumikawa, M. E. Bowman, D. W. Udary, J.-L. Ferrer, B. S. Moore, J. P. Noel, *J. Biol. Chem.* **2004**, 279, 45162–45174; b) Y.-M. Zhang, J. Hurlbert, S. W. White, C. O. Rock, *J. Biol. Chem.* **2006**, 281,

- 17390–17399; c) J. M. Jez, M. B. Austin, J.-L. Ferrer, M. E. Bowman, J. Schröder, J. P. Noel, *Chem. Biol.* **2000**, *7*, 919–930.
- [14] a) B. Vakulya, S. Varga, A. Csampai, T. Soos, *Org. Lett.* **2005**, *7*, 1967–1969; b) B.-J. Li, L. Jiang, M. Liu, Y.-C. Chen, L.-S. Ding, Y. Wu, *Synlett* **2005**, 603–606; c) J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–14417.
- [15] a) S. H. Oh, H. S. Rho, J. W. Lee, J. E. Lee, S. H. Youk, J. Chin, C. E. Song, *Angew. Chem.* **2008**, *120*, 7990–7993; *Angew. Chem. Int. Ed.* **2008**, *47*, 7872–7875; b) S. E. Park, E. H. Nam, H. B. Jang, J. S. Oh, S. Some, Y. S. Lee, C. E. Song, *Adv. Synth. Catal.* **2010**, *352*, 2211–2217.
- [16] The absolute configuration of **3a** was established to be *R* by conversion into the corresponding (*R*)- β -hydroxymethylester. See the Supporting Information.
- [17] The enantiomer can be obtained using the quinidine-derived catalyst **QD-1-Np-SA (C12)**. However, the enantioselectivity was lower than that obtained with the quinine analogue (e.g., 78% *ee* with **2a**). However, fortunately, the crystalline property of most of the aldol products **3** enabled facile recrystallization of **3** to improve the enantiopurity of the products.
- [18] The low yields of **3o** and **3p** could be ascribed to the formation of side products such as **9o** and **9p**, respectively (see the Supporting Information). In all cases, S-phenyl thioacetate was also formed during the reaction. However, the use of S-phenyl thioacetate as a substrate resulted in almost no reaction leading to the desired aldol product in the presence of the catalyst **C9**.



- [19] Y. Hayashi, T. Itoh, S. Aratake, H. Ishikawa, *Angew. Chem.* **2008**, *120*, 2112–2114; *Angew. Chem. Int. Ed.* **2008**, *47*, 2082–2084.
- [20] For recent selected examples, see: a) S. S. V. Ramasastry, H. Zhang, F. Tanaka, C. F. Barbas III, *J. Am. Chem. Soc.* **2007**, *129*, 288–289; b) S. Luo, H. Xu, L. Zhang, J.-P. Cheng, *J. Am. Chem. Soc.* **2007**, *129*, 3074–3075. For the Mannich-type reaction with acetaldehyde, see: J. W. Yang, C. Chandler, M. Stadler, D. Kampen, B. List, *Nature* **2008**, *452*, 453–455.
- [21] For a review of Fukuyama reduction, see: T. Fukuyama, H. Tokuyama, *Aldrichimica Acta* **2004**, *37*, 87–96.
- [22] For selected references concerning the asymmetric syntheses of Fluoxetine, (–)-Paroxetine, and Duloxetine, see the Supporting Information page 116.
- [23] MS (ESI+): calcd for (**A**+Na⁺): *m/z* 732.2 (100.0%), 733.2 (42.2%); observed: 732.1 (100%), 733.2 (40%); calcd for (**B**+Na⁺): *m/z* 838.3 (100.0%), 839.3 (49.8%); observed: 838.2 (100%), 839.2 (48%). See the Supporting Information.
- [24] J. Baudoux, P. Lefebvre, R. Legay, M. Lasne, J. Rouden, *Green Chem.* **2010**, *12*, 252–259.