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Facile Assembly of Chiral Tetrahydrothiopyrans Containing Four Consecutive Stereocenters via an Organocatalytic Enantioselective Michael–Michael Cascade

Shengzheng Wang,[†] Yongqiang Zhang,[†] Guoqiang Dong,[†] Shanchao Wu,[†] Kun Fang,[†] Zhengang Li,[†] Zhenyuan Miao,[†] Jianzhong Yao,[†] Hao Li,[‡] Jian Li,[‡] Wannian Zhang,*[,†] Wei Wang,*[,‡,§] and Chunquan Sheng*[,†]

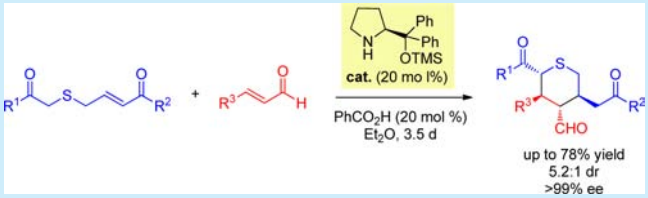
[†]Department of Medicinal Chemistry, School of Pharmacy, Second Military Medical University, 325 Guohe Road, Shanghai 200433, P. R. China

[‡]School of Pharmacy, East China University of Science and Technology, Shanghai 200237, P. R. China

[§]Department of Chemistry and Chemical Biology, University of New Mexico, Albuquerque, New Mexico 87131-0001, United States

Supporting Information

ABSTRACT: An organocatalytic enantioselective Michael–Michael cascade reaction has been implemented for the creation of structurally variant chiral tetrahydrothiopyrans. The process is realized by employment of new bifunctional ketothioether enones and proceeds highly enantioselectively with formation of four consecutive stereogenic centers.



Tetrahydrothiopyrans are abundant in a number of bioactive compounds and promising pharmaceuticals, such as antihypertensive (**a**),[1] anti-Alzheimer's disease (**b**),[2] antidiabetes (**c**,[3] **f**[4]), antimicrobial (**d**),[5] and antimitotic (**e**) agents (Figure 1).[6] There are several established approaches to constructing the molecular architecture in both racemic[7] and optically active forms.[8] In the reported asymmetric approaches, the main strategy relies on the employment of chiral substrates.[8] It is highly appealing to develop a more efficient and atom-economic catalytic enantioselective process to build the valuable chiral tetrahydrothiopyrans.

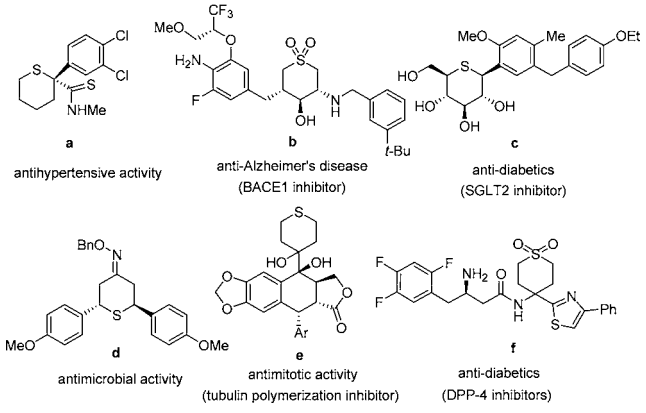


Figure 1. Representative bioactive molecules containing the tetrahydrothiopyran unit.

Organocatalyzed asymmetric Michael–Michael cascade reactions (also called "double Michael") have been intensively studied and have demonstrated their broad synthetic utilities in the past decade.[9] In our own effort, we have developed a series of the organocatalytic "double Michael" cascade reactions to assemble highly functionalized chiral cyclopentanes,[10] tetrahydrothiophenes,[11] pyrrolidines,[12] thiochromanes,[13] chromans,[14] and a 4*H*-chromene scaffold.[15] In the case of six-membered rings, the cascade strategy has been applied for the construction of highly functionalized chiral carbocycles, including cyclohexenes,[16] cyclohexanes,[17] and cyclohexanones.[18] Nevertheless, to the best of our knowledge, the organocatalytic method has not been reported for the preparation of the chiral tetrahydrothiopyrans. Herein, we wish to disclose such an approach to the framework. Notably, a new class of bifunctional ketothioether enone substrates is developed for the purpose. Moreover, four consecutive stereogenic centers are created in a "one-pot" operation under mild reaction conditions.

Very recently, we reported an organocatalytic enantioselective formal [3 + 3] cycloaddition process for the construction of 3,4-dihydro-2*H*-thiopyrans (Scheme 1, eq 1).[19] In this investigation, we discovered that the CH_2 between the carbonyl group and the S atom in bisketone thioethers was highly nucleophilic for initiating the Michael reaction. Inspired by the study and motivated by the lack of efficient approach to the tetrahydrothiopyrans, we determined that it was required to craft a new synthetic methodology. Toward this end, we *de novo* designed a substrate (**1**) bearing the nucleophilic CH_2 as the Michael donor and an α,β-unsaturated ketone as a Michael

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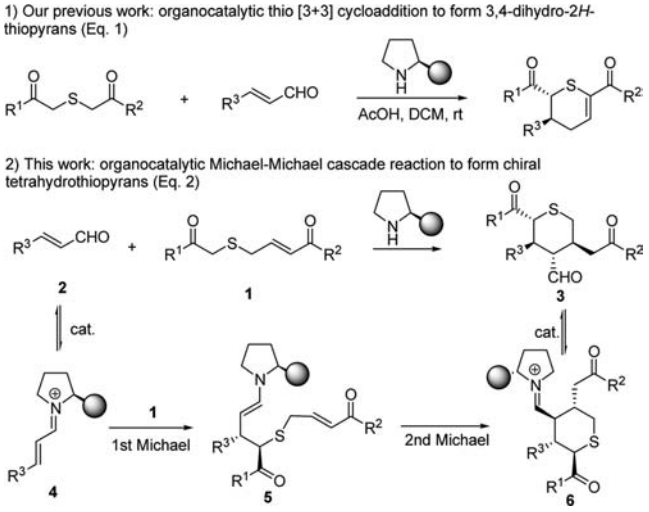
Scheme 1. Organocatalytic Enantioselective Access to Chiral 3,4-Dihydro-2*H*-thiopyrans and Tetrahydrothiopyrans

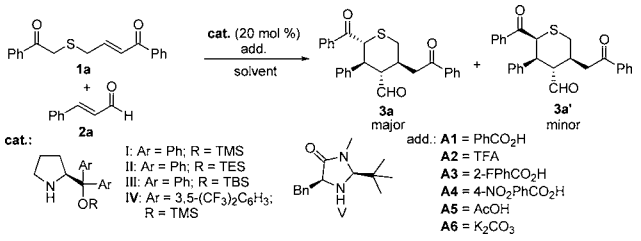


acceptor for a new organocatalytic asymmetric Michael–Michael cascade process (eq 2).

As a proof concept for this proposed Michael–Michael cascade, we probed a model reaction of substrate **1a** with *trans*-cinnamaldehyde **2a** catalyzed by diphenylprolinol silyl ether (**I**) in the presence of $PhCO_2H$ as additive (Table 1).[20] The reaction proceeded smoothly and afforded the desired product **3a** in moderate yield (56%) and with excellent enantioselectivity (ee > 99%) and moderate diastereoselectivity (2.4:1 dr) (entry 1). Encouraged by the results, we screened other secondary amine catalysts **II**–**V**. Similar results were obtained with catalysts **II** and **III** (entries 2 and 3), while **IV** and **V** failed to do so (entries 4 and 5). Accordingly, catalyst **I** was selected for further studies. Reaction media had a significant impact on the reaction efficiency and enantio- and stereoselectivities (entries 6–11). The best results (70% yield, ee > 99%, and 4.0:1 dr) came from Et_2O (entry 11). In contrast, no reaction occurred with THF or acetonitrile (entries 7 and 8). $CHCl_3$ and DCE offered inferior outcomes (entries 9 and 10). Screening acid additives revealed $PhCO_2H$ to be the choice (entries 11–14), while a base was detrimental (entry 15). Furthermore, upon increasing the amount of cinnamaldehyde **2a** to 3.0 equiv or increasing the reaction temperature (35 °C), the yield and diastereoselectivity were reduced slightly (entries 16 and 17). Using the procedure reported by Xu et al.,[21] the reaction time was reduced (1.5 d), but the diastereoselectivity dropped slightly (2.4:1 dr, entry 18). These results led us to select the protocol consisting of catalyst **I** in the presence of $PhCO_2H$ in Et_2O to probe the scope of the Michael–Michael cascade reaction (entry 11).

With the optimized conditions in hand, the substrate scope and the generality of the reaction were explored (Scheme 2). It was found that a variety of substrates **1** participated in the reaction with structurally diverse enals **2**. It appeared that the aldehydes bearing electron-withdrawing (**3b**–**3e**) or -donating (**3f**–**3h**) groups were both well tolerated and afforded the desired products with good yield (60–74%), moderate diastereoselectivities (2.1:1 to 4.0:1 dr), and excellent enantioselectivities (96–99% ee). Moreover, steric effect had a marginal negative impact on diastereoselectivity (**3g** vs **3h**). Besides phenyl-substituted enals, heterocyclics, such as furanyl and pyridyl (**3i** and **3j**), were also well tolerated and gave rise to

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	add.	solvent	t (d)	% yield[b]	dr[c]	% ee[d]
1	**I**	**A1**	DCM	2	56	2.4:1	>99
2	**II**	**A1**	DCM	2	51	2.3:1	>99
3	**III**	**A1**	DCM	2	53	2.3:1	>99
4	**IV**	**A1**	DCM	2	trace		
5	**V**	**A2**	DCM	2	nr[e]		
6	**I**	**A1**	PhMe	2	72	2.6:1	>99
7	**I**	**A1**	THF	2	nr		
8	**I**	**A1**	ACN	2	trace		
9	**I**	**A1**	$CHCl_3$	3.5	50	2.5:1	>99
10	**I**	**A1**	DCE	3.5	48	2.4:1	>99
11	**I**	**A1**	Et_2O	3.5	70	4.0:1	>99
12	**I**	**A3**	Et_2O	3.5	68	2.9:1	>99
13	**I**	**A4**	Et_2O	2	70	3.0:1	>99
14	**I**	**A5**	Et_2O	3.5	65	3.5:1	>99
15	**I**	**A6**	Et_2O	2	trace		
16[f]	**I**	**A1**	Et_2O	3.5	66	3.8:1	>99
17[g]	**I**	**A1**	Et_2O	1	68	2.6:1	>99
18[h]	**I**	**A1**	Et_2O	1.5	66	2.4:1	>99

[a]Reaction conditions (unless otherwise specified): solvent (2.0 mL), substrate **1a** (0.11 mmol, 1.0 equiv), cinnamaldehyde **2a** (0.13 mmol, 1.2 equiv), catalyst (20 mol %), additive (20 mol %), room temperature. [b]Yield of isolated product after column chromatography. [c]Determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC analysis. [e]No reaction. [f]Cinnamaldehyde **2a** (0.33 mmol, 3.0 equiv), catalyst (20 mol %), additive (20 mol %), reaction performed at rt. [g]Cinnamaldehyde **2a** (0.33 mmol, 3.0 equiv), catalyst (20 mol %), additive (20 mol %), reaction performed at 35 °C. [h]1,3-Bis(3,5-bis(trifluoromethyl)phenyl)thiourea (20 mol %) was added to the reaction.

the products in good yield (68–76%) and with excellent ee values (ee ≥ 99%). Limitations were also realized. No reactions were observed with the aliphatic enals, such as pent-2-enal and 4-methylpent-2-enal.

Next, the structural variation of substrates **1** was probed under the optimized conditions (Scheme 2, **3k**–**3r**). It appeared that substrates **1** containing suitable Michael donors and acceptors allowed the process. With respect to the Michael donor part of substrate **1**, electron-withdrawing (such as bromo and nitro groups, **3k**–**3n**) or electron-donating groups (such as methyl group, **3o**) on the aromatic ring of R^1 were both well tolerated and afforded the desired products with high yield (58–67%), moderate diastereoselectivities (1.7:1–3.1:1 dr), and excellent enantioselectivities (97% to >99% ee). Furthermore, heteroaromatic thienyl could be applicable to the domino processes as well (**3p**). In view of Michael acceptor component in **1**, both aromatic and aliphatic moieties were able to engage in the process. It is observed that the electronic effect plays a critical role in the second Michael reaction. An electron-withdrawing group on the benzene ring (**3q**) could effectively take part in the reaction, while no reaction occurred with the substrates bearing an electron-donating alkoxy functionality under the standard conditions (data not shown).

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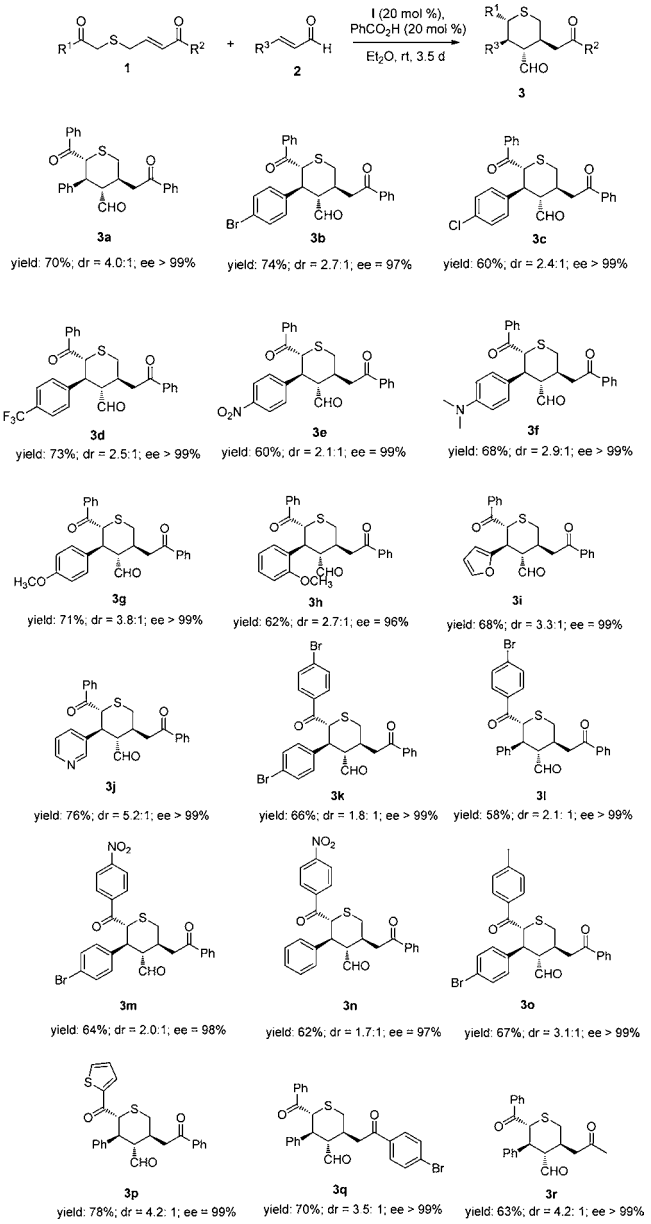
Scheme 2. Scope of I-Catalyzed Michael–Michael Cascade



The absolute configuration of the major isomer products obtained in the Michael–Michael cascade reaction was determined by X-ray crystallography analysis of compound **3b**, whose absolute configuration was determined to be (2*R*,3*S*,4*S*,5*S*) (Figure 2), and that of the minor one (2*S*,3*S*,4*S*,5*S*) was determined by H–H COSY and NOESY COSY analysis based on **3a**′ (Table 1).[22]

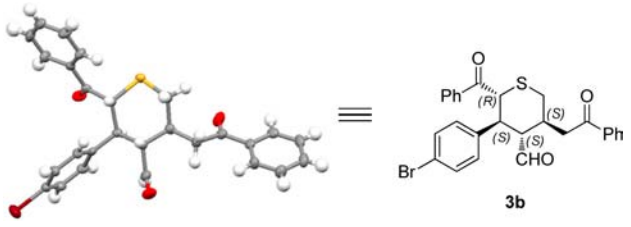
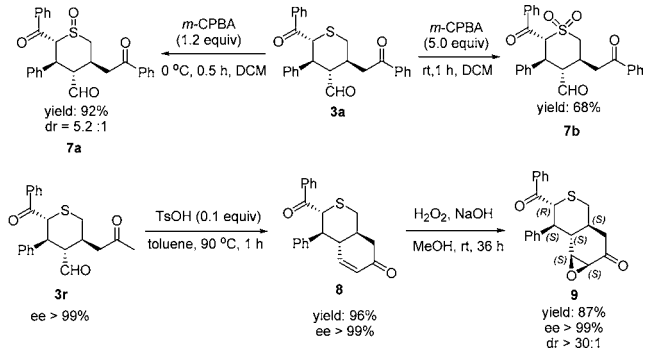


Figure 2. X-ray structure of compound **3b**.

The highly enantioenriched tetrahydrothiopyrans **3** serve as versatile building blocks to construct valuable molecules with rapidly increased molecular complexity and diversity in simple synthetic operation using compounds **3a** and **3r** as examples. Adduct **3a** can be selectively oxidized into the respective sulfoxide **7a** and sulfone **7b** in good yield (92% and 66%) and with good stereocontrol (5.2:1 dr) by controlling the amount of oxidant *m*-CPBA (Scheme 3). Moreover, compound **3r** can be

Scheme 3. Synthetic Elaboration of Michael–Michael Adducts 3a and 3r



transformed into a structurally different framework **8** bearing four stereogenic centers with good yield (96%) via one-step intramolecular aldol condensation reaction. Furthermore, new scaffold **9** could be easily achieved as a single stereoisomer in good yield and with excellent stereocontrol in a one-step oxidation of scaffold **8** (Scheme 3). The absolute configuration of new scaffold **9** bearing six stereogenic centers was further assigned to be (1a*S*,3a*S*,6*R*,7*S*,7a*S*,7b*S*) according to the NOESY and ^{1}H NMR spectra (see Supporting Information).

In summary, we have developed an organocatalytic highly enantioselective Michael–Michael cascade reaction for the preparation of structurally diverse tetrahydrothiopyrans. A new class of ketothioether enones is designed for the cascade process. Notably, heavily functionalized tetrahydrothiopyran molecular architectures with four consecutive stereogenic centers are assembled in good to high yield (up to 78%) and with good diastereoselectivities (up to 5.2:1 dr) and excellent enantioselectivities (up to >99% ee) in a one-pot operation under mild reaction conditions. Moreover, simple synthetic elaboration of the Michael–Michael adducts lead to structurally diverse, complex scaffolds. Further exploration of the new reagents in synthesis is under investigation in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zhangwnk@hotmail.com.
*E-mail: wwang@unm.edu.
*E-mail: shengcq@hotmail.com.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Cook, D. C.; Hart, T. W.; McLay, I. M.; Palfreyman, M. N.; Walsh, R. J. A.; Aloup, J. C. EP326297A1, 1989.
(2) Rueeger, H.; Lueoend, R.; Rogel, O.; Rondeau, J. M.; Mobitz, H.; Machauer, R.; Jacobson, L.; Staufenbiel, M.; Desrayaud, S.; Neumann, U. *J. Med. Chem.* **2012**, *55*, 3364.
(3) Kakinuma, H.; Oi, T.; Hashimoto-Tsuchiya, Y.; Arai, M.; Kawakita, Y.; Fukasawa, Y.; Iida, I.; Hagima, N.; Takeuchi, H.; Chino, Y.; Asami, J.; Okumura-Kitajima, L.; Io, F.; Yamamoto, D.; Miyata, N.; Takahashi, T.; Uchida, S.; Yamamoto, K. *J. Med. Chem.* **2010**, *53*, 3247.
(4) Nitta, A.; Fujii, H.; Sakami, S.; Satoh, M.; Nakaki, J.; Satoh, S.; Kumagai, H.; Kawai, H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7036.
(5) Parthiban, P.; Aridoss, G.; Rathika, P.; Ramkumar, V.; Kabilan, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2981.
(6) Abad, A.; Lopez-Perez, J. L.; del Olmo, E.; Garcia-Fernandez, L. F.; Francesch, A.; Trigili, C.; Barasoain, I.; Andreu, J. M.; Diaz, J. F.; San Feliciano, A. *J. Med. Chem.* **2012**, *55*, 6724.
(7) (a) Whitehead, E. V.; Dean, R. A.; Fidler, F. A. *J. Am. Chem. Soc.* **1951**, *73*, 3632. (b) Fehnel, E. A.; Oppenlander, G. C. *J. Am. Chem. Soc.* **1953**, *75*, 4660. (c) Nagasawa, K.; Yoneta, A. *Chem. Pharm. Bull.* **1985**, *33*, 5048. (d) Cui, Y.; Floreancig, P. E. *Org. Lett.* **2012**, *14*, 1720. (e) Bondalapati, S.; Gogoi, P.; Indukuri, K.; Saikia, A. K. *J. Org. Chem.* **2012**, *77*, 2508.
(8) (a) Aggarwal, V. K.; Angelaud, R.; Bihan, D.; Blackburn, P.; Fieldhouse, R.; Fonquerna, S. J.; Ford, G. D.; Hynd, G.; Jones, E.; Jones, R. V. H.; Jubault, P.; Palmer, M. J.; Ratcliffe, P. D.; Adams, H. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2604. (b) Gunasundari, T.; Chandrasekaran, S. *J. Org. Chem.* **2010**, *75*, 6685. (c) Zhang, J.; Niu, Y.; Cao, X.; Ye, X.-S. *Tetrahedron* **2012**, *68*, 4242. (d) Periasamy, M.; Gurubrahamam, R.; Muthukumaragopal, G. P. *Tetrahedron: Asymmetry* **2013**, *24*, 568.
(9) For recent selected examples of organocatalytic Michael-Michael cascade reactions, see: (a) Enders, D.; Huttl, M. R.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (b) Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Org. Lett.* **2007**, *9*, 1833. (c) Companyo, X.; Zea, A.; Alba, A. N.; Mazzanti, A.; Moyano, A.; Rios, R. *Chem. Commun.* **2010**, *46*, 6953. (d) Wang, X. F.; Hua, Q. L.; Cheng, Y.; An, X. L.; Yang, Q. Q.; Chen, J. R.; Xiao, W. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 8379. (e) Zhang, X.; Zhang, S.; Wang, W. *Angew. Chem., Int. Ed.* **2010**, *49*, 1481. (f) Wang, X.-F.; Hua, Q.-L.; Cheng, Y.; An, X.-L.; Yang, Q.-Q.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 8379. (g) Wang, X.-F.; An, J.; Zhang, X.-X.; Tan, F.; Chen, J.-R.; Xiao, W.-J. *Org. Lett.* **2011**, *13*, 808. (h) Jia, Z. X.; Luo, Y. C.; Wang, Y.; Chen, L.; Xu, P. F.; Wang, B. *Chem.—Eur. J.* **2012**, *18*, 12958. (i) Wang, C.; Yang, X.; Raabe, G.; Enders, D. *Adv. Synth. Catal.* **2012**, *354*, 2629. (j) Jia, Z. X.; Luo, Y. C.; Cheng, X. N.; Xu, P. F.; Gu, Y. C. *J. Org. Chem.* **2013**, *78*, 6488. (k) Mao, H.; Lin, A.; Tang, Y.; Shi, Y.; Hu, H.; Cheng, Y.; Zhu, C. *Org. Lett.* **2013**, *15*, 4062. (l) Yang, W.; Yang, Y.; Du, D. M. *Org. Lett.* **2013**, *15*, 1190. (m) Zhang, Y.; Wang, S.; Wu, S.; Zhu, S.; Dong, G.; Miao, Z.; Yao, J.; Zhang, W.; Sheng, C.; Wang, W. *ACS Comb. Sci.* **2013**, *15*, 298. (n) Zhang, J.-X.; Li, N.-K.; Liu, Z.-M.; Huang, X.-F.; Geng, Z.-C.; Wang, X.-W. *Adv. Synth. Catal.* **2013**, *355*, 797. (o) Meninno, S.; Croce, G.; Lattanzi, A. *Org. Lett.* **2013**, *15*, 3436. (p) Weber, M.; Frey, W.; Peters, R. *Chem.—Eur. J.* **2013**, *19*, 8342. (q) Li, X.; Yang, C.; Jin, J. L.; Xue, X. S.; Cheng, J. P. *Chem. Asian J.* **2013**, *8*, 997.
(10) Zu, L.; Li, H.; Xie, H.; Wang, J.; Jiang, W.; Tang, Y.; Wang, W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3732.
(11) (a) Li, H.; Zu, L.; Xie, H.; Wang, J.; Jiang, W.; Wang, W. *Org. Lett.* **2007**, *9*, 1833. (b) Yu, C.; Zhang, Y.; Song, A.; Ji, Y.; Wang, W. *Chem.—Eur. J.* **2011**, *17*, 770.
(12) Li, H.; Zu, L.; Xie, H.; Wang, J.; Wang, W. *Chem. Commun.* **2008**, 5636.
(13) Wang, J.; Xie, H.; Li, H.; Zu, L.; Wang, W. *Angew. Chem., Int. Ed.* **2008**, *47*, 4177.
(14) Zu, L.; Zhang, S.; Xie, H.; Wang, W. *Org. Lett.* **2009**, *11*, 1627.
(15) Zhang, X.; Zhang, S.; Wang, W. *Angew. Chem., Int. Ed.* **2010**, *49*, 1481.
(16) McGarraugh, P. G.; Jones, J. H.; Brenner-Moyer, S. E. *J. Org. Chem.* **2011**, *76*, 6309.
(17) (a) Hong, B.-C.; Sadani, A. A.; Nimje, R. Y.; Dange, N. S.; Lee, G.-H. *Synthesis* **2011**, 1887. (b) Rajkumar, S.; Shankland, K.; Goodman, J. M.; Cobb, A. J. A. *Org. Lett.* **2013**, *15*, 1386. (c) Hong, B.-C.; Nimje, R. Y.; Lin, C.-W.; Liao, J.-H. *Org. Lett.* **2011**, *13*, 1278. (d) Hong, B.-C.; Liao, W.-K.; Dange, N. S.; Liao, J.-H. *Org. Lett.* **2013**, *15*, 468. (e) Rajkumar, S.; Shankland, K.; Brown, G. D.; Cobb, A. J. A. *Chem. Sci.* **2012**, *3*, 584.
(18) Wu, L.-Y.; Bencivenni, G.; Mancinelli, M.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7196.
(19) Wang, S.; Zhang, Y.; Dong, G.; Wu, S.; Zhu, S.; Miao, Z.; Yao, J.; Li, H.; Li, J.; Zhang, W.; Sheng, C.; Wang, W. *Org. Lett.* **2013**, *15*, 5570.
(20) For leading works in using diarylprolinol silyl ethers in organocatalysis, see: (a) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 794. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212.
(21) Wang, Y.; Yu, T.-Y.; Zhang, H.-B.; Luo, Y.-C.; Xu, P.-F. *Angew. Chem., Int. Ed.* **2012**, *51*, 12339.
(22) See Supporting Information.