Organic LETTERS

Letter

pubs.acs.org/OrgLett

Asymmetric Sulfa-Michael Addition to α-Substituted Vinyl Ketones Catalyzed by Chiral Primary Amine

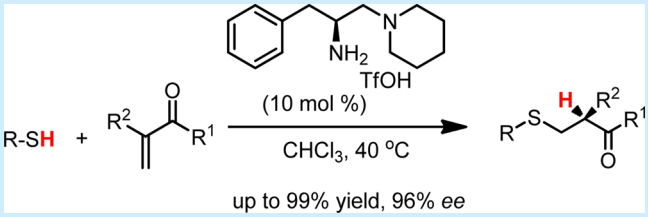
Niankai Fu,[†] Long Zhang,[†,‡] Sanzhong Luo,*[,†,‡] and Jin-Pei Cheng[†,‡]

[†]Beijing National Laboratory for Molecule Sciences (BNLMS), CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100190, P.R. China

[‡]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin, 300071, P.R. China

Supporting Information

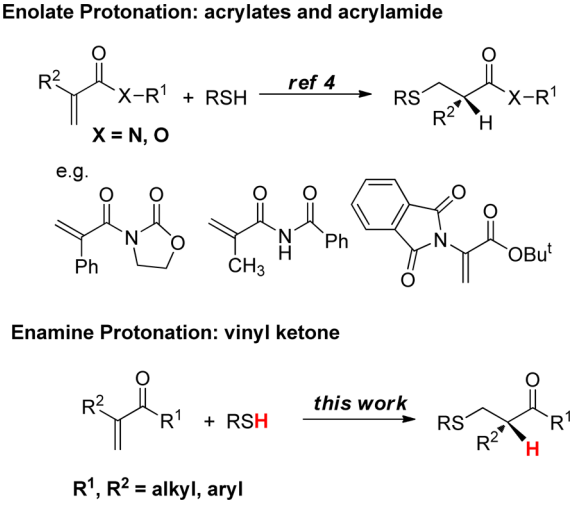
ABSTRACT: The first effective example of asymmetric conjugate addition−protonation reactions of thiols to α-substituted vinyl ketones by chiral primary amine catalysis is reported. A simple chiral primary−tertiary diamine catalyst derived from L-phenylalanine was found to promote the sulfa-Michael addition−protonation reactions with good to excellent enantioselectivity.



Asymmetric sulfa-Michael addition (SMA) of thiol nucleophiles to electron-deficient alkenes is one of the most versatile and reliable methods for the synthesis of chiral sulfur-containing compounds that are of significant potential in pharmaceuticals.[1] Despite tremendous progress on catalytic asymmetric sulfa-Michael addition reactions over the decades,[2] enantioselective sulfa addition to α-substituted vinyl carbonyls that feature stereogenic protonation steps remains a challenging transformation.[3] Since the seminal work by Pracejus et al. in 1977,[4a] much effort has been devoted to the enantioselective protonation of enolates in sulfa-Michael addition.[4,5] However, notable advances have only been achieved lately by catalysis with thioureas,[4d] squaramides,[4e] or strong basic guanidine[4g] derivatives. In these cases, the substrates have been limited to carboxylic acid derivatives such as acrylamide or acrylates wherein the appropriate choice of prochiral templates has been found to be critical to control the enolate configurations (Scheme 1). Effective asymmetric catalysis with α-substituted vinyl ketones has not been achieved so far. In two of the previous studies, the use of acyclic α-substituted vinyl ketones has been attempted but with unfortunately rather poor enantioselectivity, pinpointing the difficulties with this type of substrate.[5b,c]

Recently, we have developed chiral primary−tertiary diamines as effective catalysts for the iminium activation of α-substituted acroleins and vinyl ketones with good activity and high enantioselectivity.[6] These reactions feature enamine protonation as the key stereogenic step. Meanwhile, our detailed mechanistic studies have disclosed a Curtin−Hammett control in the C−C bond formation step for the reactions of α-substituted vinyl ketones, which infers that successful extensions to other nucleophiles in the reactions with vinyl ketones can be readily achieved.[6e] Recently, this idea has been successfully verified by using azoles as nucleophiles.[6f] Herein, we document the first highly enantioselective sulfa-Michael addition−enamine protonation reactions with α-branched vinyl ketones.

Scheme 1. Organocatalytic Asymmetric Sulfa-Michael Addition−Protonation Reaction

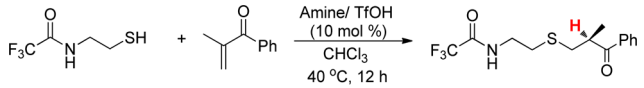


Our initial studies on sulfa-Michael addition−protonation reactions were carried out with odorless thiol **4a** using chiral primary−tertiary diamines as the catalysts. Results from this investigation led to the identification of **3g**/TfOH as the optimal catalyst. In the presence of 10 mol % **3g**/TfOH, the reaction gave the desired product **6a** with 94% isolated yield and in 85% *ee* (Table 1, entry 9). When we decreased the concentration of the reaction mixture from 0.25 to 0.10 M, the enantioselectivity can be slightly improved to 91% *ee* (Table 1, entries 10 and 11). However, further optimization with

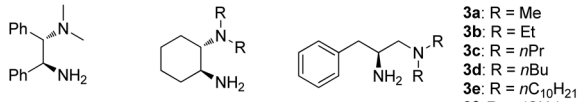
Received: July 27, 2014
Published: August 21, 2014

dx.doi.org/10.1021/ol5022178 | Org. Lett. 2014, 16, 4626−4629

Table 1. Optimization of the Reaction Conditions[a]



4a 5a 6a



1 2 R = *n*Pr

3a: R = Me
3b: R = Et
3c: R = *n*Pr
3d: R = *n*Bu
3e: R = $nC_{10}H_{21}$
3f: R = -$(CH_2)_4$-
3g: R = -$(CH_2)_5$-

entry	amine	additive	yield (%)[b]	*ee* (%)[c]
1	**1**	none	trace	–
2	**2**	none	trace	–
3	**3a**	none	78	−10
4	**3b**	none	85	−37
5	**3c**	none	87	34
6	**3d**	none	90	38
7	**3e**	none	89	58
8	**3f**	none	87	54
9	**3g**	none	94	85
10[d]	**3g**	none	94	88
11[e]	**3g**	none	98	91
12[e]	**3g**	PhCOOH (0.1 equiv)	75	87
13[e]	**3g**	BHT (0.1 equiv)	93	90
14[e]	**3g**	*i*PrOH (0.1 equiv)	87	85

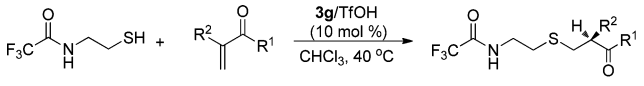
[a]General conditions: **4a** (0.15 mmol), **5a** (0.30 mmol), amine/TfOH (10 mol %) in $CHCl_3$ (0.25 M) at 40 °C, 12 h. [b]Isolated yield. [c]Determined by HPLC analysis. [d]$CHCl_3$ (0.15 M). [e]$CHCl_3$ (0.10 M).

variations on the proton additives or solvents did not result in noticed improvements in the enantioselectivity (Table 1, entries 12−14).

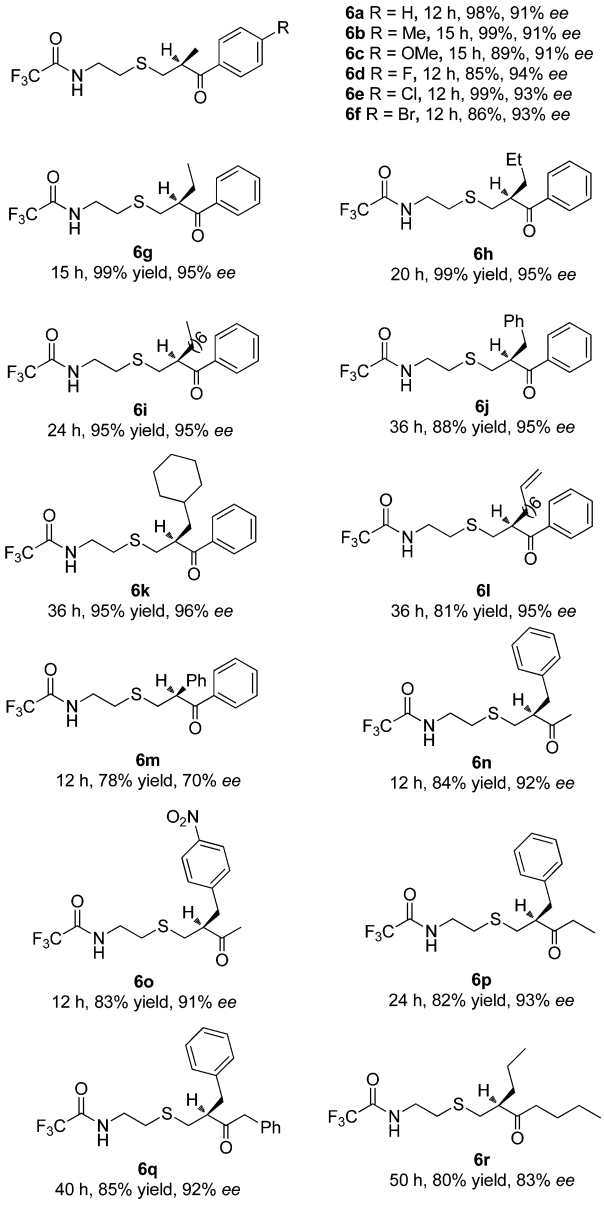
With the optimized conditions in hand, the scope of the catalytic system was examined. An array of α-substituted vinyl ketones were tested in this reaction, resulting in high yields of products **6a−r** with good to excellent enantioselectivity (Scheme 2). Aromatic α-substituted vinyl ketones were identified as one class of preferred substrates, and phenyl groups bearing either electron-rich (**6b**, **6c**) or electron-deficient (**6d−6f**, 85−99% yields, 93−94% *ee*) substituents are equally applicable. Additionally, it was found that increasing the bulkiness of the α-substituent led to better enantioselectivity (Scheme 2, **6g−6l**). When the α-substituted group was changed to a bulky cycohexyl moiety, the enantioselectivity can reach up to 96% *ee* (Scheme 2, **6k**). However, when changing the α-substituted group to phenyl, the enantioselectivity dropped to 70% *ee* (Scheme 2, **6m**). Additionally, different types of aliphatic enones, such as methyl, ethyl, benzyl, and *n*-butyl vinyl enones, can also be well applied to this reaction system with good enantioselectivity (Scheme 2, **6n−6r**).

The scope of the reaction with respect to different types of sulfur sources were also investigated (Scheme 3). As seen from the results in Scheme 3, the use of other types of protecting groups on 2-aminoethanethiol led to some loss of enantioselectivity, but the reactions still proceeded smoothly to furnish the desired products with good activity and enantioselectivity (Scheme 3, **7a−7c**). Meanwhile, thioglycolate and its analogues were good alternative sulfur sources for this catalytic system, affording the desired adducts with good yields and enantioselectivity (Scheme 3, **7d−7f**). Benzylthiol and thiophenol can also be applied in the reactions; however, the

Scheme 2. Substrate Scope for α-Substituted Vinyl Ketones[a]



4a 5 6



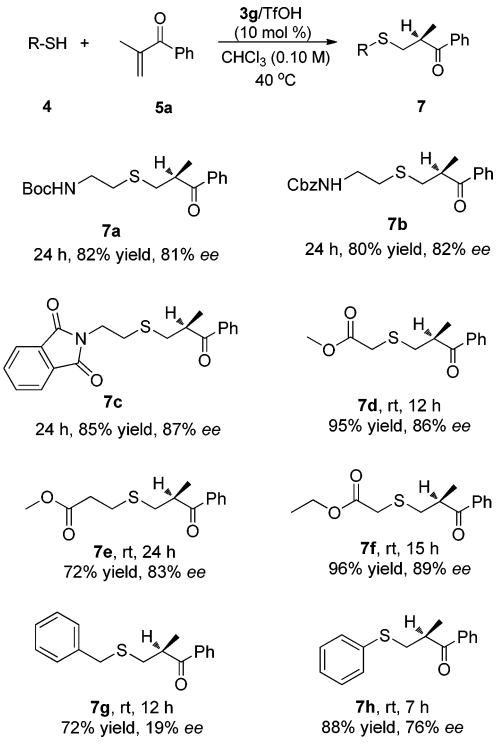
[a]General conditions: **4a** (0.15 mmol), **5** (0.30 mmol), **3g**/TfOH (10 mol %) in $CHCl_3$ (0.10 M) at 40 °C, 12−50 h.

enantioselectivity with benzylthiol was poor due to significant background reactions (Scheme 3, **7g** and **7h**).

To evaluate the practicality of this catalytic process, a gram scale synthesis of **6a** using **3g**/TfOH as the catalyst was performed, and the reaction furnished the desired product with a 95% yield and 93% *ee* [eq 1 in Scheme 4]. Product **6a** can be conveniently hydrogenated to the chiral alcohol **8** without erosion of the enantioselectivity [eq 2 in Scheme 4]. Cleavage of the trifluoroacetyl group of **8** at this stage can be readily achieved, maintaining the same enantioselectivity [eq 3 in Scheme 4]. Meanwhile, the asymmetric sulfa-Michael addition protonation products can be selectively oxidized to the

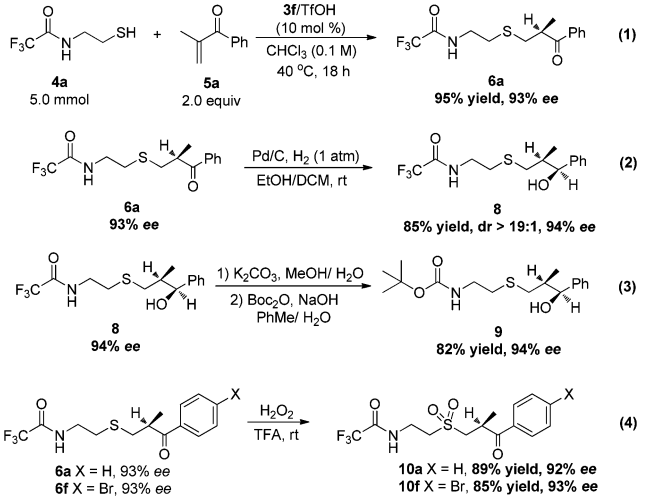
dx.doi.org/10.1021/ol5022178 | *Org. Lett.* 2014, 16, 4626−4629

Scheme 3. Substrate Scope for Sulfur Sources[a]



[a]General conditions: **4** (0.15 mmol), **5a** (0.30 mmol), **3g**/TfOH (10 mol %) in $CHCl_3$ (0.10 M) at 40 °C.

Scheme 4. Gram Scale Reaction and the Subsequent Synthetic Transformations



corresponding sulfones under mild conditions [eq 4 in Scheme 4]. Finally, the absolute configuration of sulfone **10f** was determined by X-ray analysis. The configurations of the sulfa-Michael addition products were tentatively assigned to be *R* accordingly.[7]

In summary, we have developed highly efficient conjugate addition−protonation reactions of thiols to α-substituted vinyl ketones by chiral primary amine catalysis. This is the first highly efficient method for the asymmetric sulfa-Michael addition reaction using simple α-substituted vinyl ketones as the Michael acceptors. Odorless thiols easily prepared from 2-amino-ethanethiol can be well applied in this reaction system. Furthermore, thioglycolate and its analogues which are relatively cheap and less toxic are also good alternative sulfur sources for this catalytic system. Additional investigations into the mechanism of the asymmetric induction and the extension of the methodology to other types of additions are ongoing.[8]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and copies of ^1H and ^{13}C NMR spectra and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: luosz@iccas.ac.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Natural Science Foundation of China (21390400, 21025208, and 21202171) and the National Basic Research Program of China (2011CB808600) for financial support.

■ REFERENCES

(1) (a) Fraústo da Silva, J. R.; Williams, R. J. P. *The Biological Chemistry of the Elements*; Oxford University Press: New York, 2001. (b) *Organosulfur Chemistry in Asymmetric Synthesis*; Toru, T., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, 2008.

(2) (a) For a review, see: Enders, D.; Luttgen, K.; Narine, A. A. A. *Synthesis* **2007**, 959. For selected examples, see: (b) Saito, M.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **2000**, 1851. (c) Saito, M.; Nakajima, M.; Hashimoto, S. *Tetrahedron* **2000**, *56*, 9589. (d) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (e) Uraguchi, D.; Kinoshita, N.; Nakashima, D.; Ooi, T. *Chem. Sci.* **2012**, *3*, 3161. (f) Palacino, C.; Connon, S. J. *Chem. Commun.* **2012**, *48*, 2849. (g) Yang, W.; Du, D. *Org. Biomol. Chem.* **2012**, *10*, 6876. (h) Kimmel, K. L.; Robak, M. T.; Thomas, S.; Lee, M.; Ellman, J. A. *Tetrahedron* **2012**, *68*, 2704. (i) Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 12974. (j) Kawatsura, M.; Komatsu, Y.; Yamamoto, M.; Hayase, S.; Itoh, T. *Tetrahedron Lett.* **2007**, *48*, 6480. (k) Yang, Z.; Liu, J.; Liu, X.; Wang, Z.; Feng, X.; Su, Z.; Hu, C. *Adv. Synth. Catal.* **2008**, *350*, 2001. (l) Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2009**, 6145. (m) Yang, Y.; Dong, S.; Liu, X.; Lin, L.; Feng, X. *Chem. Commun.* **2012**, 5040. (n) Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 418. (o) Dong, X.; Fang, X.; Tao, H.; Zhou, X.; Wang, C. *Adv. Synth. Catal.* **2012**, *354*, 1141. (p) Fang, X.; Li, J.; Wang, C. *Org. Lett.* **2013**, *15*, 3448. (q) Sundararajan, G.; Prabagaran, N. *Org. Lett.* **2001**, *3*, 389. (r) McDaid, P.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 338. (s) Shirakawa, S.; Kimura, T.; Murata, S.; Shimizu, S. *J. Org. Chem.* **2009**, *74*, 1288. (t) Rana, N. K.; Selvakumar, S.; Singh, V. K. *J. Org. Chem.* **2010**, *75*, 2089. (u) Ricci, P.; Carone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth. Catal.* **2008**, *350*, 49. (v) Dai, L.; Wang, S.-X.; Chen, F.-E. *Adv. Syth. Catal.* **2010**, *352*, 2137. (w) Bonollo, S.; Lanari, D.; Pizzo, F.; Vaccaro, L. *Org. Lett.* **2011**, *13*, 2150. (x) Tian, X.; Cassani, C.; Liu, Y.; Moran, A.; Urakawa, A.; Galzerano, P.; Arceo, E.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 17934. (y) White, J. D.; Shaw, S. *Chem. Sci.* **2014**, *5*, 2200.

(3) For reviews on enantioselective protonation, see: (a) Yanagisawa, A.; Yamamoto, H. In *Comprehensive Asymmetric Catalysis Vol. III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Heidelberg, 1999; pp 1295−1306. (b) Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. *Tetrahedron: Asymmetry* **2004**, *15*, 3653. (c) Fehr, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2566. (d) Blanchet, J.; Baudoux, J.; Amere, M.; Lasne, M.-C.; Rouden, J. *Eur. J. Org. Chem.* **2008**, 5493. (e) Mohr, J.

dx.doi.org/10.1021/ol5022178 | *Org. Lett.* 2014, 16, 4626−4629

T.; Hong, A. Y.; Stoltz, B. M. *Nat. Chem.* **2009**, *1*, 359. (f) Oudeyer, S.; Brière, J.-F.; Levacher, V. doi: 10.1002/ejoc.201402213.

(4) (a) Pracejus, H.; Wilcke, F.-W.; Hanemann, K. *J. Prakt. Chem.* **1977**, *319*, 219. (b) Kumar, A.; Salunkhe, R. V.; Rane, R. A.; Dike, S. Y. *J. Chem. Soc., Chem. Commun.* **1991**, 485. (c) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (d) Rana, N. K.; Singh, V. K. *Org. Lett.* **2011**, *13*, 6520. (e) Dai, L.; Yang, H.; Niu, J.; Chen, F.-E. *Synlett* **2012**, *23*, 314. (f) Unhale, R. A.; Rana, N. K.; Singh, V. K. *Tetrahedron Lett.* **2013**, *54*, 1911. (g) Leow, D.; Lin, S.; Chittimalla, S. K.; Fu, X.; Tan, C.-H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5641. (h) Cho, B.; Tan, C.-H.; Wong, M. W. *J. Org. Chem.* **2012**, *77*, 6553.

(5) Examples of metal-catalyzed asymmetric sulfa-Michael addition−protonation reactions: (a) Emori, E.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 4043. (b) Hui, Y.; Jiang, J.; Wang, W.; Chen, W.; Cai, Y.; Lin, L.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 4290. (c) Kitanosono, T.; Sakai, M.; Ueno, M.; Kobayashi, S. *Org. Biomol. Chem.* **2012**, *10*, 7134.

(6) For an account, see: (a) Zhang, L.; Luo, S. *Synlett* **2012**, 1575. For examples, see: (b) Li, J.; Li, X.; Zhou, P.; Zhang, L.; Luo, S.; Cheng, J.-P. *Eur. J. Org. Chem.* **2009**, 4486. (c) Li, J.; Fu, N.; Zhang, L.; Zhou, P.; Luo, S.; Cheng, J.-P. *Eur. J. Org. Chem.* **2010**, 6840. (d) Fu, N.; Zhang, L.; Li, J.; Luo, S.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2011**, *50*, 11451. (e) Fu, N.; Zhang, L.; Luo, S.; Cheng, J.-P. *Chem.—Eur. J.* **2013**, *19*, 15669. (f) Fu, N.; Zhang, L.; Luo, S.; Cheng, J.-P. *Org. Chem. Front.* **2014**, *1*, 68.

(7) CCDC 1014215 (**10f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(8) A possible transition state model is described in the Supporting Information.