Organic LETTERS

Letter

pubs.acs.org/OrgLett

Direct Remote Asymmetric Bisvinylogous 1,4-Additions of Cyclic 2,5-Dienones to Nitroalkenes

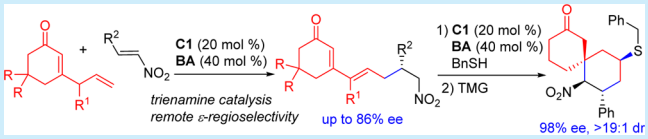
Zhi Zhou,[†] Xin Feng,[†] Xiang Yin,[†] and Ying-Chun Chen*[,†,‡]

[†]Key Laboratory of Drug-Targeting and Drug Delivery System of the Ministry of Education, West China School of Pharmacy, and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China

[‡]College of Pharmacy, Third Military Medical University, Shapingba, Chongqing 400038, China

Supporting Information

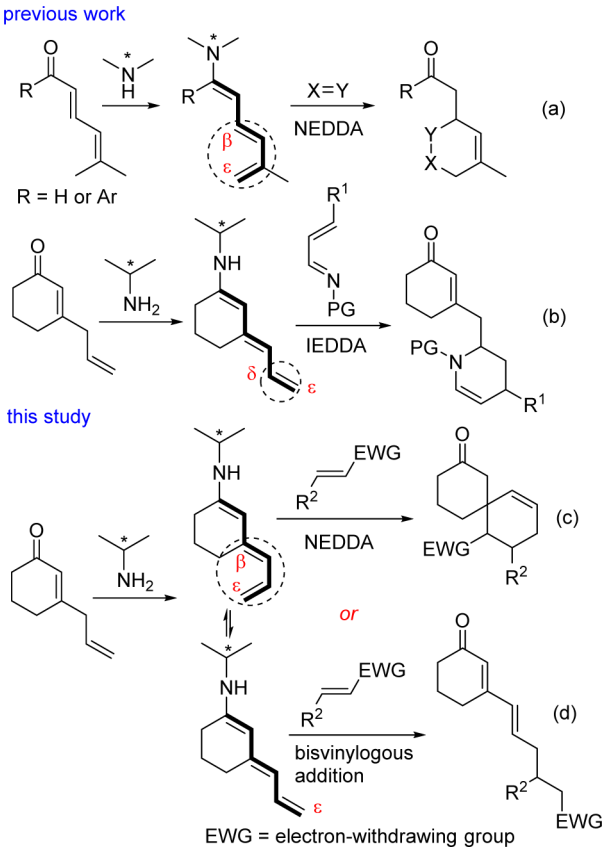
ABSTRACT: Here we report that cyclic 2,5-dienones can act as bisvinylogous precursors through in situ generation of linear trienamine species with a cinchona-derived primary amine, and exclusively remote ε-regioselective 1,4-additions to nitroalkenes were accomplished in moderate to high enantioselectivity. Moreover, a diversity of complex spirocyclic frameworks could be efficiently constructed in an enantioenriched manner from these multifunctional 1,4-adducts via subsequent vinylogous iminium and even cascade iminium catalysis of the same amine.



In 1935, Fuson established the principle of vinylogy; he pointed out that electron density and reactivity could be transmitted along conjugated C=C bonds.[1] While previous asymmetric examples focused mainly on the vinylogous reactions with masked dienolates,[2] recently, significant progress has been made in the direct vinylogous versions with diverse unsaturated substances catalyzed by chiral metal complexes or organic molecules, usually in high γ-regioselectivity.[3] Nevertheless, the application of α,β,γ,δ-unsaturated systems in the ε-regioselective bisvinylogous additions seems to be much more challenging, and very limited attempts were reported in bisvinylogous Mukaiyama aldol or Mannich reactions with previously formed trienol silyl ethers.[4] To the best of our knowledge, direct asymmetric bisvinylogous addition reactions have not been developed yet.

Dienamine catalysis has been demonstrated to be a powerful protocol for the activation of unmodified α,β-unsaturated carbonyl compounds in various asymmetric vinylogous reactions.[5] Recently, we and the Jørgensen group succeeded in the transmission of HOMO-raising effect to the remoter ε-position of α,β,γ,δ-unsaturated aldehydes or ketones via in situ generation of trienamine intermediates. However, this catalytic mode was dominantly explored in β,ε-regioselective normal-electron-demand Diels–Alder reactions [Scheme 1, (a)].[6] We further developed an inducing strategy with interrupted cyclic α,β,δ,ε-unsaturated ketones and realized a δ,ε-regioselective inverse-electron-demand cycloaddition mode [Scheme 1, (b)].[7] On the basis of the above results, it was envisaged that the latter type of linear trienamine species from cyclic 2,5-dienones would not likely act as electron-rich diene partners in normal-electron-demand Diels–Alder reactions with activated alkenes, probably because of the requisite formation of a sterically hindered spirocyclic chiral center [Scheme 1, (c)]. Therefore, the potential ε-regioselective Michael reaction might be

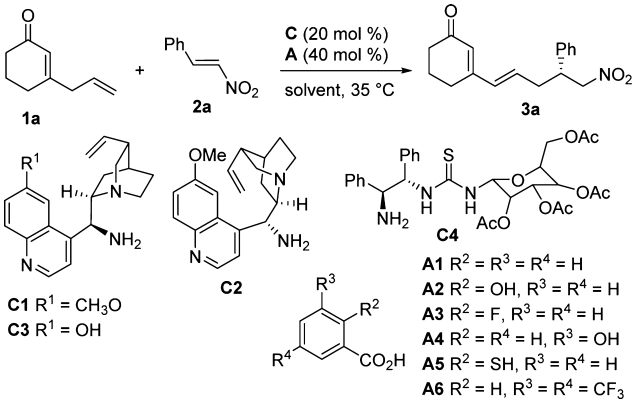
Scheme 1. Diverse Catalytic Modes of Linear Trienamine Intermediates



Received: March 6, 2014
Published: April 24, 2014

   dx.doi.org/10.1021/ol500700d | Org. Lett. 2014, 16, 2370–2373

Table 1. Screening Conditions of Asymmetric Bisvinylogous 1,4-Addition of 2,5-Dienone 1a to Nitroalkene 2a[a]



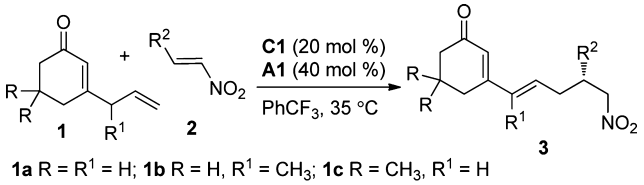
entry	cat.	acid	solvent	time (h)	yield[b] (%)	ee[c] (%)
1	**C1**	**A1**	toluene	67	56	84
2	**C2**	**A1**	toluene	65	54	−83
3	**C3**	**A1**	toluene	64	53	70
4	**C1**	**A1**	*o*-xylene	62	65	79
5	**C1**	**A1**	*m*-xylene	60	67	81
6	**C1**	**A1**	DCM	58		
7	**C1**	**A1**	$PhCF_3$	62	80	85
8	**C1**	**A2**	$PhCF_3$	64	62	86
9	**C1**	**A3**	$PhCF_3$	58	71	83
10	**C1**	**A4**	$PhCF_3$	65	45	73
11	**C1**	**A5**	$PhCF_3$	56	65	86
12	**C1**	**A6**	$PhCF_3$	64	68	84
13[d]	**C4**	**A1**	$PhCF_3$	67	63	84
14[e]	**C1**	**A1**	$PhCF_3$	72	75	84
15[f]	**C1**	**A1**	$PhCF_3$	72	78	82

[a]Unless noted otherwise, reactions were performed with 2,5-dienone **1a** (0.15 mmol), nitroalkene **2a** (0.1 mmol), amine **C** (20 mol %), and acid (40 mol %) in solvent (1.0 mL) at 35 °C. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral column. [d]With 20 mol % of acid. [e]With 10 mol % of **C1** and 20 mol % of **A1**. [f]At 1.0 mmol scale.

favored, furnishing the unprecedented direct bisvinylogous conjugate addition via trienamine catalysis [Scheme 1, (d)]. This asymmetric catalytic mode might be extremely challenging because not only would the HOMO-raising power of amine catalyst be diminished, leading to reduced reactivity, but also the reactive ε-site is quite remote from the chiral center of the catalyst, rendering the stereocontrol much more difficult than that of concerted β,ε- or δ,ε-regioselective cycloaddition reactions.[8]

The initial screenings with 2,5-dienone **1a** and diverse Michael acceptors revealed that β-nitrostyrene **2a** is a suitable electrophilic partner under the catalysis of 9-amino-9-deoxyepiquinine **C1** and benzoic acid **A1**.[9] To our gratification, the reaction proceeded smoothly in toluene at 35 °C, successfully furnishing the bisvinylogous 1,4-addition product **3a** with a moderate yield and a good ee value (Table 1, entry 1). It should be noted that this reaction exhibited remarkable chemo- and remote ε-regioselectivity, and a β,ε-regioselective cycloaddition product as that observed in early trienamine catalysis[10] has not been detected. 9-Amino-9-deoxyepiquinidine **C2** afforded the product with an opposite configuration in similar enantioselectivity (entry 2), but amine **C3** with a free 6′-OH group gave poorer results (entry 3). A few solvents were tested (entries 4−7), and better data were produced in $PhCF_3$ (entry 7). Then an array of acid additives were explored in combination with amine **C1** in $PhCF_3$ (entires 8−12), while inferior results were generally obtained in regard to reaction time, yield, and enantiocontrol. After extensively studying more catalytic parameters,[11] it was found that bifunctional primary amine−thiourea[12] **C4** in combination with acid **A1** also could promote the Michael addition in $PhCF_3$, but with similar enantioselectivity and lower yield (entry 13). The reaction still proceeded smoothly with lower catalyst loadings (entry 14). In addition, comparable data were also produced at a larger scale (1 mmol) catalyzed by amine **C1** and benzoic acid **A1** (entry 15).

Table 2. Substrate Scope in Direct Asymmetric Bisvinylogous 1,4-Additions of 2,5-Dienones 1 to Nitroalkenes 2[a]



1a R = R^1 = H; **1b** R = H, R^1 = CH_3; **1c** R = CH_3, R^1 = H

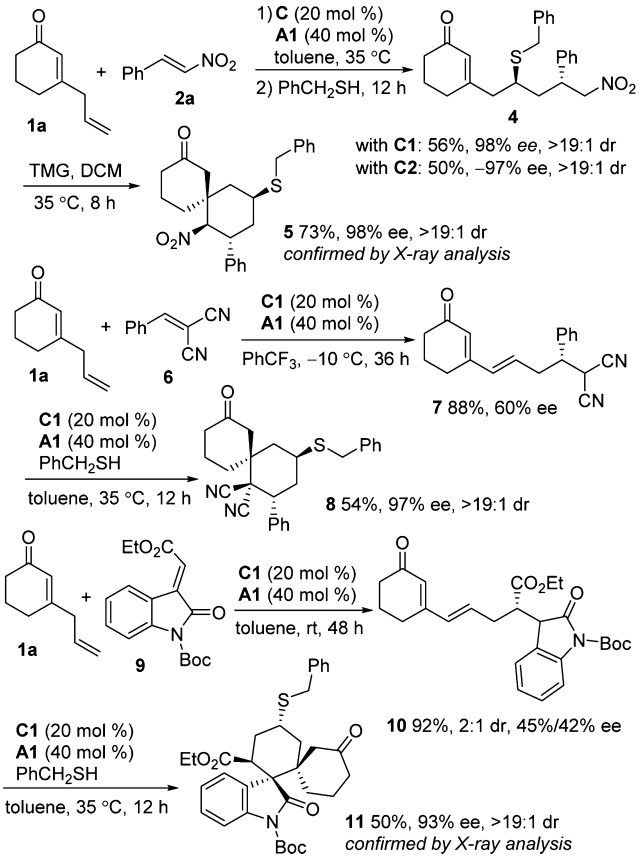
entry	1	R^2	time (h)	yield[b] (%)	ee[c] (%)
1	**1a**	Ph	62 (68)	**3a**, 80 (71)	85 (−83)
2	**1a**	3-FC_6H_4	60	**3b**, 77	86
3	**1a**	2-BrC_6H_4	52 (48)	**3c**, 76 (70)	86 (−84)
4	**1a**	4-BrC_6H_4	50	**3d**, 79	85
5	**1a**	4-Br-2-FC_6H_3	60	**3e**, 82	85
6	**1a**	3,4-$Cl_2C_6H_3$	50	**3f**, 81	85
7	**1a**	4-$CF_3C_6H_4$	56 (50)	**3g**, 81 (72)	85 (−86)
8	**1a**	3-MeC_6H_4	62	**3h**, 80	81
9	**1a**	4-MeC_6H_4	48	**3i**, 76	80
10	**1a**	4-$MeOC_6H_4$	58 (56)	**3j**, 84 (68)	81 (−81)
11	**1a**	1-naphthyl	54	**3k**, 78	79
12	**1a**	2-furyl	65	**3l**, 80	81
13	**1a**	2-thienyl	58	**3m**, 85	82
14	**1a**	*n*-propyl	85	**3n**, 56	60
15	**1a**	isopropyl	80	**3o**, 60	67
16	**1b**	Ph	100	**3p**, 62	84
17	**1c**	Ph	110	**3q**, 60	83

[a]Unless noted otherwise, reactions were performed with 2,5-dienone **1** (0.15 mmol), nitroalkene **2** (0.1 mmol), amine **C1** (20 mol %), and acid **A1** (40 mol %) in $PhCF_3$ (1.0 mL) at 35 °C. Data in parentheses were obtained with amine **C2**. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral column.

Subsequently, a number of nitroalkenes were used in the reactions with 2,5-dienone **1a** catalyzed by amine **C1** and benzoic acid **A1**. As summarized in Table 2, nitroalkenes bearing diversely substituted aryl or heteroaryl groups could be well tolerated, and the corresponding bisvinylogous Michael addition adducts were generally obtained in good yield and enantioselectivity (Table 2, entries 1−13). Alkyl-substituted nitroalkenes showed lower reactivity, and moderate data were attained after longer times (entries 14 and 15). In addition, 2,5-dienones **1b** and **1c** also smoothly produced the bisvinylogous adducts (entries 16 and 17), and the sole isomer was observed in the case of **1b** with a γ-methyl group. Unfortunately, more sluggish reactions were observed for ε-substituted 2,5-dienones, and both diastereo- and enantioselectivity were disappointing. We also tested more examples with amine **C2**, and the products with an opposite configuration were attained in similar enantiocontrol (data in parentheses).

dx.doi.org/10.1021/ol500700d | *Org. Lett.* 2014, 16, 2370−2373

Scheme 2. Sequential Trienamine−Vinylogous Iminium or Even Iminium Catalysis To Access Complex Spirocyclic Products



Although enantioselectivity in direct bisvinylogous 1,4-additions with nitroalkenes is not excellent, it was pleasing that a highly stereoselective 1,6-thiol addition reaction with 2,4-dienone **3a** could be achieved via vinylogous iminium catalysis of the same chiral amine.[13] In fact, as outlined in Scheme 2, even the sequential trienamine−vinylogous iminium catalysis with amine **C1** or **C2** and acid **A1** could proceed smoothly in a one-pot pathway, directly furnishing the major separable sulfide product **4** in excellent diastereo- and enantioselectivity, albeit with moderate yields. Furthermore, an intramolecular nitro-Michael addition was efficiently promoted by adding TMG (tetramethylguanidine), giving densely adorned spirocyclic product **5** as a single diastereomer.[14] Encouraged by the above results, Michael acceptors **6** and **9** were further tested. Although the early bisvinylogous Michael adducts **7** and **10** were obtained in low to modest ee values, the subsequent cascade vinylogous iminium−iminium catalysis proceeded effectively, directly delivering separable spirocycle **8** and a highly complicated bisspirocyclic substance **11**, respectively, in excellent stereocontrol.[15] Thus, such a [4 + 2] annulation process also accomplished the β,ε-functionalization of cyclic 2,5-dienone substrates, as proposed in Scheme 1, (c).

In conclusion, we have developed the first direct asymmetric bisvinylogous 1,4-additions of cyclic 2,5-dienones to electron-deficient alkenes via induced trienamine catalysis. These reactions exhibited exclusive remote ε-regioselectivity, and moderate to high enantioselectivity was obtained by employing readily available chiral primary amines derived from cinchona alkaloids. Moreover, the sequential vinylogous iminium−iminium catalysis could be further conducted with the obtained bisvinylogous 1,4-adducts by using the same amine catalyst, efficiently furnishing enantioenriched spirocyclic or even bisspirocyclic architectures with highly structural and stereochemical complexity. These procedures efficiently provide an alternative synthetic protocol for β,ε-functionalizations of cyclic 2,5-dienone substrates in a [4 + 2] cycloaddition manner. We believe that the current work would help develop more reaction versions in the field of asymmetric trienamine catalysis. More results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization of new products, CIF files of enantiopure products **5** and **11**, NMR spectra, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ycchen@scu.edu.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the financial support from the NSFC (21122056, 21372160, and 21321061) and the National Basic Research Program of China (973 Program, 2010CB833300).

■ REFERENCES

(1) Fuson, R. C. *Chem. Rev.* **1935**, *16*, 1.

(2) For reviews, see: (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. (b) Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682. (c) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895.

(3) For recent reviews, see: (a) Cui, H.-L.; Chen, Y.-C. *Chem. Commun.* **2009**, 4479. (b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076. (c) Pansare, S. V.; Paul, E. K. *Chem.—Eur. J.* **2011**, *17*, 8770. For selected examples, see: (d) Poulsen, T. B.; Alemparte, C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 11614. (e) Liu, T.-Y.; Cui, H.-L.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *J. Am. Chem. Soc.* **2007**, *129*, 1878. (f) Trost, B. M.; Hitce, J. *J. Am. Chem. Soc.* **2009**, *131*, 4572. (g) Shepherd, N. E.; Tanabe, H.; Xu, Y.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 3666. (h) Feng, X.; Cui, H.-L.; Xu, S.; Wu, L.; Chen, Y.-C. *Chem.—Eur. J.* **2010**, *16*, 10309. (i) Ube, H.; Shimada, N.; Terada, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 1858. (j) Jiang, L.; Lei, Q.; Huang, X.; Cui, H.-L.; Zhou, X.; Chen, Y.-C. *Chem.—Eur. J.* **2011**, *17*, 9489. (k) Zhang, W.; Tan, D.; Lee, R.; Tong, G.; Chen, W.; Qi, B.; Huang, K.-W.; Tan, C.-H.; Jiang, Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 10069. (l) Curti, C.; Rassu, G.; Zambrano, V.; Pinna, L.; Pelosi, G.; Sartori, A.; Battistini, L.; Zanardi, F.; Casiraghi, G. *Angew. Chem., Int. Ed.* **2012**, *51*, 6200. (m) Yin, L.; Takada, H.; Kumagai, N.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 7310. (n) Zhu, B.; Zhang, W.; Lee, R.; Han, Z.; Yang, W.; Tan, D.; Huang, K.-W.; Jiang, Z. *Angew. Chem., Int. Ed.* **2013**, *52*, 6666.

(4) (a) Ratjen, L.; García-García, P.; Lay, F.; Beck, M. E.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 754. (b) Abels, F.; Lindemann, C.; Schneider, C. *Chem.—Eur. J.* **2014**, *20*, 1964.

(5) (a) Ramachary, D. B.; Reddy, Y. V. *Eur. J. Org. Chem.* **2012**, 865. (b) Bencivenni, G.; Galzerano, P.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20642. (c) Bergonzini, G.; Vera, S.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2010**, *49*, 9685. (d) Stiller, J.; Marqués-López, E.; Herrera, R. P.; Fröhlich, R.; Strohmann, C.; Christmann, M. *Org. Lett.* **2011**, *13*, 70.

(e) Cassani, C.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 5590. (f) Bastida, D.; Liu, Y.; Tian, X.; Escudero-Adán, E.; Melchiorre, P. *Org. Lett.* **2013**, *15*, 220.

(6) For an early example, see: (a) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053. For reviews, see: (b) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248. (c) Li, J.-L.; Liu, T.-Y.; Chen, Y.-C. *Acc. Chem. Res.* **2012**, *45*, 1491. (d) Arceo, E.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 5290. (e) Kumar, I.; Ramaraju, P.; Mir, N. A. *Org. Biomol. Chem.* **2013**, *11*, 709. (f) Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Chem. Sci.* **2013**, *4*, 2287.

(7) (a) Feng, X.; Zhou, Z.; Ma, C.; Yin, X.; Li, R.; Dong, L.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2013**, *52*, 14173. (b) For an example with 2,5-dienals, see: Prieto, L.; Talavera, G.; Uria, U.; Reyes, E.; Vicario, J. L.; Carrillo, L. *Chem.—Eur. J.* **2014**, *20*, 2145.

(8) For reviews on remote asymmetric synthesis and catalysis, see: (a) Clayden. *J. Chem. Soc. Rev.* **2009**, *38*, 817. (b) See ref 6f. For selected examples, see:. (c) Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67. (d) Malkov, A. V.; Liddon, A. J. P. S.; Ramírez-López, P.; Bendová, L.; Haigh, D.; Kočovský, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 1432. (e) Mikami, K.; Narisawa, S.; Shimizu, M.; Terada, M. *J. Am. Chem. Soc.* **1992**, *114*, 6566. (f) Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16454. (g) Lewis, C. A.; Gustafson, J. L.; Chiu, A.; Balsells, J.; Pollard, D.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 16358. (h) van Leeuwen, P. W. N. M.; Rivillo, D.; Raynal, M.; Freixa, Z. *J. Am. Chem. Soc.* **2011**, *133*, 18562. (i) Trost, B. M.; Morris, P. J.; Sprague, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 17823.

(9) For a comprehensive review of cinchona-based primary aminocatalysis, see: Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9748.

(10) (a) Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 8638. (b) Xiong, X.-F.; Zhou, Q.; Gu, J.; Dong, L.; Liu, T.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2012**, *51*, 4401. (9) See ref 7b..

(11) For more details, see the Supporting Information.

(12) For selected examples with bifunctional primary amine−thiourea catalysts, see: (a) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (b) Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578. (c) Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 1891. (d) Liu, K.; Cui, H.-F.; Nie, J.; Dong, K.-Y.; Li, X.-J.; Ma, J.-A. *Org. Lett.* **2007**, *9*, 923. (e) Uehara, H.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2009**, *48*, 9848. For a review, see: (f) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. *Org. Biomol. Chem.* **2013**, *11*, 7051.

(13) (a) Tian, X.; Liu, Y.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2012**, *51*, 6439. (b) Tian, X.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 5360.

(14) For a recent review on catalytic synthesis of chiral spirocyclic compounds, see: Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060.

(15) The minor diastereomers of products **8** and **11** could be isolated in about 10% yields, also with excellent enantioselectivity (99% ee). See the Supporting Information.