JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

Organocatalytic Asymmetric Biomimetic Transamination: From α-Keto Esters to Optically Active α-Amino Acid Derivatives

Xiao Xiao,[†] Ying Xie,[†] Cunxiang Su,[†] Mao Liu,[†] and Yian Shi*[,†,‡]

[†]Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

[‡]Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, United States

Supporting Information

ABSTRACT: This paper describes an effective chiral base-catalyzed biomimetic transamination of α-keto esters using simple benzyl amines. A wide variety of α-amino esters containing various functional groups can be synthesized in high enantioselectivity and reasonable yield.

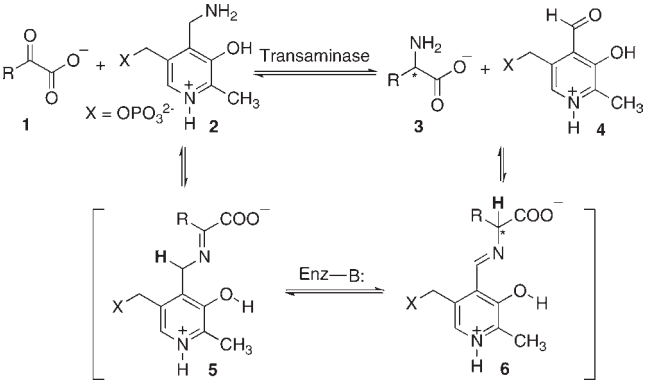
Optically active α-amino acids and their derivatives are an important class of molecules in biological systems and organic synthesis.[1] Various methods have been developed for the synthesis of chiral α-amino acids.[2−4] Transamination of α-keto acids (**1**) from pyridoxamine (**2**) catalyzed by transaminase is an important process to generate α-amino acids in biological systems (Scheme 1).[2] Biomimetic transamination with nonenzymatic catalysts provides an attractive approach to optically active α-amino acids and their derivatives (Scheme 2).[5] Such processes with chiral guanidine[6] and Lewis acid catalysts[7] have been reported, and up to 46% ee has been obtained.[7b,8−12] It appears that high yields can be obtained for the reaction with isolated ketimines.[6] However, many ketimines are difficult to isolate, which potentially limits substrate scope. On the other hand, the in situ process is more complicated, and the reaction efficiency will be highly dependent on the delicate balance among all the steps (Scheme 2), which frequently leads to relatively lower yield. Therefore, the development of an effective catalytic biomimetic transamination with high enantioselectivity and broad substrate scope presents a formidable challenge. During our studies, we have found that α-amino esters (**16**) can be obtained from α-keto esters (**15**) with high enantioselectivity in reasonable yield with quinine derived compound **C7** (Figure 1) as catalyst and *o*-ClPhCH$_2$NH$_2$ (**8a**) as amine donor (Scheme 3).[13] To the best of our knowledge, this represents the first catalytic highly enantioselective synthesis of α-amino esters from α-keto esters via biomimetic transamination. Herein, we wish to report our preliminary results on this subject.

Our initial studies started with ethyl 2-oxo-4-phenylbutanoate (**17a**) as substrate and *o*-ClPhCH$_2$NH$_2$ (**8a**) as amine donor using various chiral bases as catalysts including (−)-sparteine (**C1**) and cinchona alkaloid derivatives (**C2**−**C8**) (Figure 1).[14] As shown in Table 1 (entries 1−8), it was found that the structures of these derivatives have a dramatic effect on both catalytic activity and enantioselectivity. Among these catalysts, demethylated quinine derivative **C7** was found to be the most effective, giving the amino ester in 69% ee (Table 1, entry 7).[15] The corresponding pseudoenantiomeric catalyst derived from quinidine (**C8**) gave the opposite configuration of the amino ester product in 62% ee (Table 1, entry 8). Further studies showed that the ee increased as the size of the ester increased (Table 1, entries 9−11), and 92% ee was obtained with keto ester **17d** (Table 1, entry 11). Various amines donors were also examined. Studies show that the structure of amine has also a large impact on the enantioselectivity (Table 1, entries 12−21), with *o*-ClPhCH$_2$NH$_2$ (**8a**) being the most enantioselective (Table 1, entry 11). In all these cases, high conversions were observed for α-keto esters. However, there were varying amounts of the corresponding ketimines (**11**) and enamines (**12**) still remaining in the reaction mixture, consequently affecting the overall yield of α-amino esters. The relative amounts of the ketimines (**11**), enamines (**12**), and aldimines (**14**) could be a result of equilibrium and could be affected by the structure of benzyl amines (Scheme 2).

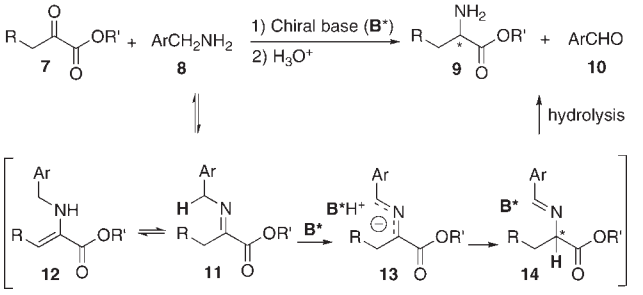
As shown in Table 2, the asymmetric transamination can be extended to a wide variety of α-keto esters to give the corresponding α-amino esters in 88−92% ee and 47−71% yield. Studies showed that introducing various substituents onto the phenyl group of 2-oxo-4-phenylbutanoate (**15a**−**g**) did not affect the ee's (Table 2, entries 1−7). High ee was also obtained when the phenyl group was replaced with other aromatics such as thiophene (Table 2, entry 8). A variety of substituted phenylalanine derivatives were formed in 88−91% ee using this transamination process (Table 2, entries 9−15). Keto esters containing no aromatics were equally effective substrates (Table 2, entries 16−22). Unsaturated α-amino esters can be obtained in high ee's (Table 2, entries 18 and 19). Heteroatoms like O and S are tolerated (Table 2, entries 20−22). However, the current reaction system is not effective for allylglycine partly due to the double bond migration during the transamination. No amino ester product was observed when phenyl keto ester was used likely due to the fact that tautomerization of the conjugated ketimine to the corresponding aldimine is thermodynamically unfavorable.

Received: April 5, 2011
Published: July 19, 2011

Scheme 1. Biological Transamination



Scheme 2. Chiral Base-Catalyzed Biomimetic Transamination



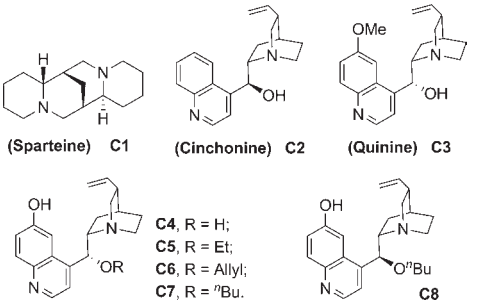
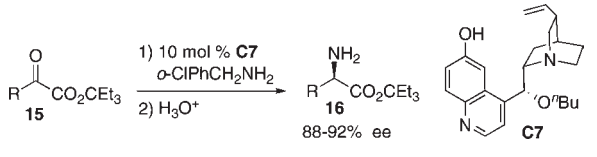


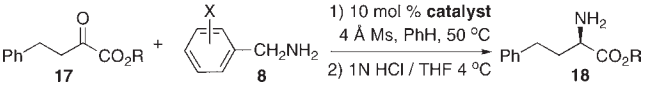
Figure 1. Selected examples of catalyst examined.

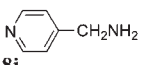
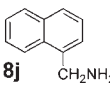
Scheme 3



It appears that the enantioselectivity is primarily influenced by the keto ester moiety, which provides certain degree of predictability for the stereochemical outcome. While a precise understanding of the origin of the enantioselectivity awaits further study, a plausible transition state model is proposed in Figure 2. The (*R*)-amino ester is formed predominately since both transition state **B** in the deprotonation step and transition state **D** in the protonation step are disfavored likely due to the unfavorable interaction between the butyl group of the catalyst and the keto ester substrate.

Table 1. Studies on Catalysts, α-Keto Esters, and Amine Donors[a]



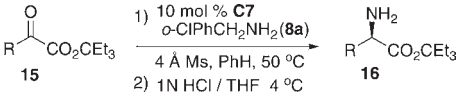
entry	17	Cat	8	conv (%)[b]	ee (%)[c]
1	**17a**, R = Et	**C1**	**8a**, X = *o*-Cl	87	5
2	**17a**	**C2**	**8a**	74	52
3	**17a**	**C3**	**8a**	84	-18
4	**17a**	**C4**	**8a**	96	53
5	**17a**	**C5**	**8a**	89	58
6	**17a**	**C6**	**8a**	95	61
7	**17a**	**C7**	**8a**	89	69
8	**17a**	**C8**	**8a**	86	-62
9	**17b**, R = ^{i}Pr	**C7**	**8a**	92	75
10	**17c**, R = ^{t}Bu	**C7**	**8a**	93	86
11	**17d**, R = CEt_3	**C7**	**8a**	100	**92**
12	**17d**	**C7**	**8b**, X = H	100	83
13	**17d**	**C7**	**8c**, X = *o*-F	100	85
14	**17d**	**C7**	**8d**, X = *o*-MeO	100	50
15	**17d**	**C7**	**8e**, X = *m*-CF_3	79	82
16	**17d**	**C7**	**8f**, X = *m*-Br	88	86
17	**17d**	**C7**	**8g**, X = *p*-NO_2	100	43
18	**17d**	**C7**	**8h**, X = *p*-CN	100	80
19	**17d**	**C7**	 **8i**	100	14
20	**17d**	**C7**	 **8j**	87	79

[a] All reactions were carried out with α-keto ester **17** (0.50 mmol), benzyl amine **8** (0.50 mmol), **catalyst** (0.050 mmol), and 4 Å molecular sieves (0.050 g) in dry benzene for 24 h (for detail, see Method A in Supporting Information). [b] The conversion was determined by ^{1}H NMR of the crude reaction mixture based on α-keto esters **17**. There are varying amounts of the corresponding imines and enamines present in the reaction mixture besides corresponding aldimines. [c] The ee's were determined by chiral HPLC (Chiralpak OD-H column) after the amino esters were converted into their *N*-benzoyl derivatives.

In summary, we have developed an effective biomimetic asymmetric synthesis of α-amino esters from α-keto esters via readily available chiral base-catalyzed transamination from simple benzyl amines. A wide variety of α-amino esters with various functional groups can be obtained with high enantioselectivity in reasonable yield. The current process provides a viable approach to synthesize optically active α-amino acids and their derivatives, which further illustrates the synthetic potential of organocatalytic biomimetic transformations. Further efforts will be devoted to understanding the reaction mechanism as well as developing more effective catalytic systems to expand substrate scope and to explore new transamination processes.

dx.doi.org/10.1021/ja203138q |*J. Am. Chem. Soc.* 2011, 133, 12914–12917

Table 2. Catalytic Asymmetric Transamination of α-Keto Esters[a,b]



entry	amino ester (**16**)[c]	yield (%)[d]	ee (%)[e]
1	**16a**, X = H	70	92
2	**16b**, X = *o*-F	71	92
3	**16c**, X = *p*-Cl	70	90
4	**16d**, X = *o*-OCH_3	66	92
5	**16e**, X = *m*-OCH_3	68	90
6	**16f**, X = *p*-OCH_3	66	90
7	**16g**, X = *p*-$PhCH_2O$	58	91
8	**16h**	71	90
9	**16i**, X = H	56	90
10	**16j**, X = *m*-Cl	63	88
11	**16k**, X = *p*-Cl	50	90
12	**16l**, X = *m*-Me	52	89
13	**16m**, X = *p*-Me	54	91
14	**16n**, X = H	60	88
15	**16o**, X = F	64	90
16	**16p**	57	88
17	**16q**	48	90
18	**16r**	49	90
19	**16s**	61	92
20	**16t**, X = O	59	89
21	**16u**, X = S	59	88
22	**16v**	47	90

[a] The reactions were carried out with α-keto ester **15** (0.50 mmol), benzyl amine **8a** (0.50 mmol), catalyst **C7** (0.050 mmol), and 4 Å molecular sieves (0.050 g) in dry benzene at 50 °C for 24 h (the imines were generated at 70 °C for 12 h before **C7** was added, for detail, see Method A in Supporting Information) (entries 1−8). [b] The reactions were carried out with α-keto ester **15** (1.0 mmol), benzyl amine **8a** (1.5 mmol for entries 9−15, 1.0 mmol for entries 16−22), **C7** (0.10 mmol), and 4 Å molecular sieves (0.10 g) in dry benzene at 50 °C for 36 h (the imines were generated at 50 °C for 20 min before **C7** was added, for detail, see Method B in Supporting Information). [c] For entries 1 and 17, the absolute configurations (*R*) were determined by comparing the optical rotations with reported ones of α-aminio acids after hydrolysis (refs 16 and 17). The absolute configurations of remaining amino esters were tentatively proposed by analogy. [d] Isolated yield based on α-keto esters **15**. [e] The ee's were determined by chiral HPLC (Chiralpak OD-H column) after the amino esters were converted into their *N*-benzoyl derivatives.

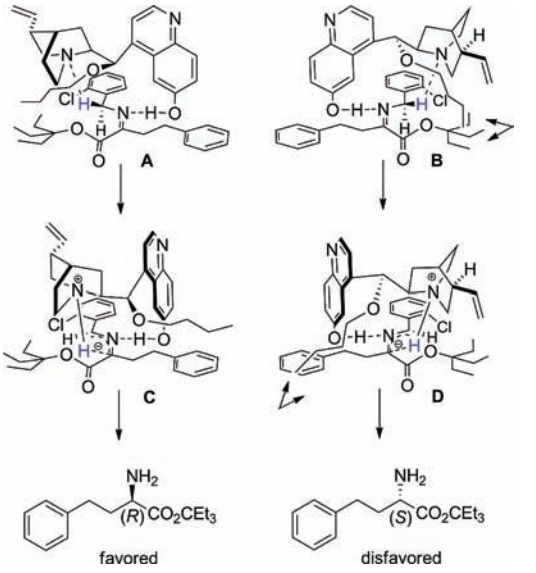


Figure 2. Proposed transition model for transamination.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, characterizations, and data for determination of enantiomeric excess of transamination products and their derivatives along with the ^1H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
yian@lamar.colostate.edu

■ ACKNOWLEDGMENT

We gratefully acknowledge the National Basic Research Program of China (973 program, 2010CB833300) and the Chinese Academy of Sciences for the financial support. This paper is dedicated to Professor Barry M. Trost on the occasion of his 70th birthday.

■ REFERENCES

(1) For a recent book, see: *Amino Acids, Peptides and Proteins in Organic Chemistry*; Hughes, A. B., Ed.; Wiley-VCH: Weinheim, Germany, 2009.

(2) For leading reviews on biological synthesis of α-amino acids, see: (a) Martell, A. E. *Acc. Chem. Res.* **1989**, *22*, 115. (b) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146. (c) Murakami, Y.; Kikuchi, J.; Hisaeda, Y.; Hayashida, O. *Chem. Rev.* **1996**, *96*, 721. (d) De Wildeman, S. M. A.; Sonke, T.; Schoemaker, H. E.; May, O. *Acc. Chem. Res.* **2007**, *40*, 1260. (e) Zhu, D.; Hua, L. *Biotechnol. J.* **2009**, *4*, 1420. (f) Ward, J.; Wohlgemuth, R. *Curr. Org. Chem.* **2010**, *14*, 1914.

(3) For leading reviews on asymmetric synthesis of α-amino acids, see: (a) Cintas, P. *Tetrahedron* **1991**, *47*, 6079. (b) Williams, R. M. *Aldrichimica Acta* **1992**, *25*, 11. (c) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889. (d) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539. (e) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013. (f) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10. (g) Ma, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290. (h) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506. (i) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518. (j) Nájera, C.; Sansano, J. M. *Chem. Rev.* **2007**, *107*, 4584.

(k) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406. (l) Perdih, A.; Dolenc, M. S. *Curr. Org. Chem.* **2007**, *11*, 801. (m) Connon, S. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 1176. (n) Michaux, J.; Niel, G.; Campagne, J. M. *Chem. Soc. Rev.* **2009**, *38*, 2093.

(4) For leading reviews on asymmetric hydrogenation of α,β-dehydro-α-amino acid derivatives, see: (a) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106. (b) Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J. *J. Mol. Catal.* **1983**, *19*, 159. (c) Kreuzfeld, H. J.; Döbler, C.; Schmidt, U.; Krause, H. W. *Amino Acids* **1996**, *11*, 269. (d) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (e) Jerphagnon, T.; Renaud, J.; Bruneau, C. *Tetrahedron: Asymmetry* **2004**, *15*, 2101. (f) Gridnev, I. D.; Imamoto, T. *Acc. Chem. Res.* **2004**, *37*, 633. (g) Jäkel, C.; Paciello, R. *Chem. Rev.* **2006**, *106*, 2912. (h) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; De Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267. (i) Shultz, C. S.; Krska, W. *Acc. Chem. Res.* **2007**, *40*, 1320. (j) Gridnev, I. D.; Imamoto, T. *Chem. Commun.* **2009**, 7447.

(5) For leading references on 1,3 proton shift of imines, see: (a) Ingold, C. K.; Wilson, C. L. *J. Chem. Soc.* **1933**, 1493. (b) Guthrie, R. D.; Meister, W.; Cram, D. J. *J. Am. Chem. Soc.* **1967**, *89*, 5288. (c) Corey, E. J.; Achiwa, K. *J. Am. Chem. Soc.* **1969**, *91*, 1429. (d) Jaeger, D. A.; Cram, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 5153. (e) Jaeger, D. A.; Broadhurst, M. D.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 717. (f) Babler, J. H.; Invergo, B. J. *J. Org. Chem.* **1981**, *46*, 1937. (g) Buckley, T. F.; Rapoport, H. *J. Am. Chem. Soc.* **1982**, *104*, 4446. (h) Ono, T.; Kukhar, V. P.; Soloshonok, V. A. *J. Org. Chem.* **1996**, *61*, 6563. (i) Cainelli, G.; Giacomini, D.; Trerè, A.; Boyl, P. P. *J. Org. Chem.* **1996**, *61*, 5134. (j) Ohkura, H.; Berbasov, D. O.; Soloshonok, V. A. *Tetrahedron* **2003**, *59*, 1647. (k) Han, J.; Sorochinsky, A. E.; Ono, T.; Soloshonok, V. A. *Curr. Org. Synth.* **2011**, *8*, 281.

(6) For a leading reference on chiral guanidine-catalyzed asymmetric synthesis of α-amino acids, see: Hjelmencrantz, A.; Berg, U. *J. Org. Chem.* **2002**, *67*, 3585.

(7) For leading references on chiral Lewis acid-catalyzed asymmetric synthesis of α-amino acids, see: (a) Knudsen, K. R.; Bachmann, S.; Jørgensen, K. A. *Chem. Commun.* **2003**, 2602. (b) Bachmann, S.; Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2004**, *2*, 2044.

(8) For leading references on metal complexes promoted transamination of α-keto acids, see: (a) Bernauer, K.; Deschenaux, R.; Taura, T. *Helv. Chim. Acta* **1983**, *66*, 2049. (b) Deschenaux, R.; Bernauer, K. *Helv. Chim. Acta* **1984**, *67*, 373.

(9) For leading references on cinchona alkaloid-catalyzed asymmetric synthesis of β-fluoroalkyl-β-amino acids, see: (a) Soloshonok, V. A.; Kirilenko, A. G.; Galushko, S. V.; Kukhar, V. P. *Tetrahedron Lett.* **1994**, *35*, 5063. (b) Michaut, V.; Metz, F.; Paris, J.; Plaquevent, J. *J. Fluorine Chem.* **2007**, *128*, 500.

(10) For leading references on chiral base-catalyzed asymmetric synthesis of chiral amines, see: (a) Willems, J. G.; Vries, J. G.; Nolte, R. J.; Zwanenburg, B. *Tetrahedron Lett.* **1995**, *36*, 3917. (b) Soloshonok, V. A.; Yasumoto, M. *J. Fluorine Chem.* **2007**, *128*, 170.

(11) For leading references on biocatalytic transamination of α-keto esters and ketones, see: (a) Kuang, H.; Distefano, M. D. *J. Am. Chem. Soc.* **1998**, *120*, 1072. (b) Savile, C. K.; Janey, J. M.; Mundorff, E. C.; Moore, J. C.; Tam, S.; Jarvis, W. R.; Colbeck, J. C.; Krebber, A.; Fleitz, F. J.; Brands, J.; Devine, P. N.; Huisman, G. W.; Hughes, G. J. *Science* **2010**, *329*, 305.

(12) For leading references on synthesis of α-amino acids with chiral pyridoxamine analogues, see: (a) Breslow, R.; Hammond, M.; Lauer, M. *J. Am. Chem. Soc.* **1980**, *102*, 421. (b) Tachibana, Y.; Ando, M.; Kuzuhara, H. *Chem. Lett.* **1982**, 1765. (c) Tachibana, Y.; Ando, M.; Kuzuhara, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3652. (d) Zimmerman, S. C.; Breslow, R. *J. Am. Chem. Soc.* **1984**, *106*, 1490. (e) Ando, M.; Kuzuhara, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 244. (f) Bandyopadhyay, S.; Zhou, W.; Breslow, R. *Org. Lett.* **2007**, *9*, 1009.

(13) For leading references on synthesis of α-amino acids by asymmetric reduction of α-imino esters, see: (a) Berkowitz, D. B.; Schweizer, W. B. *Tetrahedron* **1992**, *48*, 1715. (b) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266. (c) Versleijen, J. P.; Sanders-Hovens, M. S.; Vanhommerig, S. A.; Vekemans, J. A.; Meijer, E. M. *Tetrahedron* **1993**, *49*, 7793. (d) Murahashi, S.-I.; Watanabe, S.; Shiota, T. *J. Chem. Soc., Chem. Commun.* **1994**, 725. (e) Burk, M. J.; Martinez, J. P.; Feaster, J. E.; Cosford, N. *Tetrahedron* **1994**, *50*, 4399. (f) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Börner, A. *Chem. Commun.* **2000**, 1867. (g) Abe, H.; Amii, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 313. (h) Kadyrov, R.; Riermeier, T. H.; Dingerdissen, U.; Tararov, V.; Börner, A. *J. Org. Chem.* **2003**, *68*, 4067. (i) Nolin, K. A.; Ahn, R. W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 12462. (j) Tararov, V.; Börner, A. *Synlett* **2005**, 203. (k) Shang, G.; Yang, Q.; Zhang, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 6360. (l) Li, G.; Liang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 5830. (m) Kang, Q.; Zhao, Z.; You, S. *Adv. Synth. Catal.* **2007**, *349*, 1657. (n) Kang, Q.; Zhao, Z.; You, S. *Org. Lett.* **2008**, *10*, 2031. (o) Zhu, C.; Akiyama, T. *Adv. Synth. Catal.* **2010**, *352*, 1846.

(14) For recent leading reviews on cinchona alkaloids catalyzed reactions, see: (a) Tian, S.; Chen, Y.; Hang, J.; Mcdaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (b) Bogle, K. M.; Hirst, D. J.; Dixon, D. J. *Tetrahedron* **2010**, *66*, 6399. (c) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229.

(15) For leading references related to catalyst **C7**, see: (a) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (b) Li, H.; Wang, B.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732. (c) Liu, Y.; Sun, B.; Wang, B.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 418.

(16) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761.

(17) Craig, J. C.; Lee, S. C.; Zdansky, G.; Fredga, A. *J. Am. Chem. Soc.* **1976**, *98*, 6456.