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Alkynyl Cinchona Catalysts affect Enantioselective Trifluoromethylation for Efavirenz under Metal-Free Conditions

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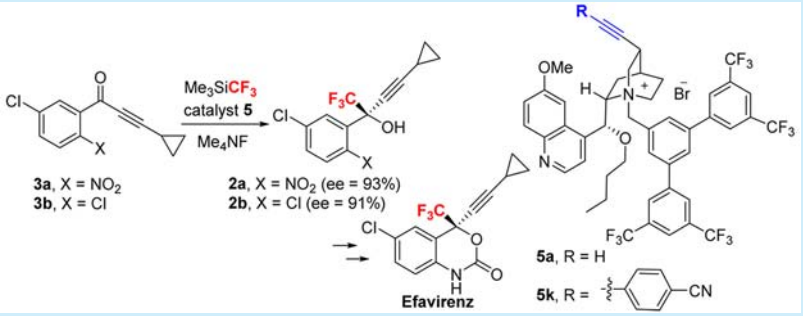
Supporting Information



ABSTRACT: Efavirenz is manufactured worldwide, and its asymmetric synthesis requires a complex organometallic approach, while an organocatalytic approach is far less efficient. The first highly enantioselective approach is disclosed for the synthesis of Efavirenz under nonmetal organocatalysis with up to 93% ee for the Merck intermediate and 91% ee for the Lonsa intermediate using novel alkynyl cinchona catalysts.

Efavirenz, which is one of the most important anti-HIV (Human Immunodeficiency Virus) drugs, reduces the amount of HIV virus in the human body by preventing the enzyme reverse transcriptase from acting.[1] Efavirenz has been marketed with the brand names Sustiva or Stocrin since 1998. The original patent of Efavirenz expired,[2] and its generic versions are now popular with different trade names, including Efavir, Estiva, Viranz, and Efferven. Efavirenz is also used as Atripla in combination with other antiretroviral drugs. The number of people with HIV was estimated to be 36.9 million in 2014, and the Efavirenz market continues to expand. Many pharmaceutical industries manufacture Efavirenz worldwide, but there is still a need to lower its price because 59% of patients still do not have access to this treatment, in particular in low income countries.[3]

Efavirenz is a chiral molecule and has a trifluoromethyl (CF_3)-containing quaternary carbon center with an (*S*)-configuration; thus, the asymmetric construction of this chiral carbon center is the key to success.[4] The asymmetric synthesis of Efavirenz was originally reported by Merck in 1995 by the enantioselective addition of lithium cyclopropyl acetylide to trifluoroacetophenone derivative **1** (X = NHR) in the presence of an excess amount of an ephedrine derivative as a chiral source to furnish **2** (Scheme 1, Approach A, stoichiometric).[5a] Several modifications of this procedure had been reported, but the catalytic version of this process needed a long time to be achieved.[5b] In 2011, Carreira and co-workers succeeded in the first catalytic asymmetric synthesis of Efavirenz by enantioselective alkenylation of **1** (X = NH_2) to **2** under autocatalysis in 99% ee.[6a] However, this autocatalytic system requires two chiral sources and complex ingredients in a substoichiometric amount (18 mol %) of product (Merck intermediate, **2**, X = NH_2), ephedrine derivative (0.3 equiv), diethylzinc (0.24 equiv), and *n*-hexyllithium (0.9 equiv). In 2012, Lonza patented an alternative catalytic approach for Efavirenz from **1** (X = Cl) using a chiral amino alcohol (0.15 equiv) and dimethylzinc (1.5 equiv) for the key asymmetric transformation with 46% ee.[6b] Both methods for the synthesis of Merck and Lonsa intermediates involve organometallic reagents; thus the metal-free, asymmetric catalytic synthesis of Efavirenz is obviously appreciated from a green chemistry point of view. In 2011, we reported the first, nonmetal, catalytic enantioselective approach for the synthesis of Efavirenz based on the enantioselective trifluoromethylation of alkynyl ketone **3** (X = NO_2) with trimethyl(trifluoromethyl)-silane (Ruppert–Prakash reagent, Me_3SiCF_3) using a catalytic amount of cinchonidine derivative **4a** (first generation) and tetramethylammonium fluoride (Me_4NF) (Scheme 1, Approach B, organocatalytic).[7a] This approach is absolutely different from the previously reported methods[5,6,8] for Efavirenz, but the enantioselectivity of **2** (X = NO_2) is modest, with 50% ee. The enantioselectivity was improved to 80% ee with quinine-based

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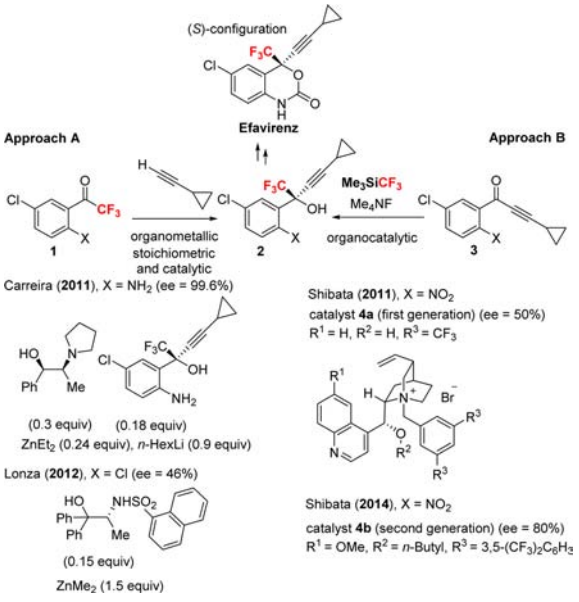
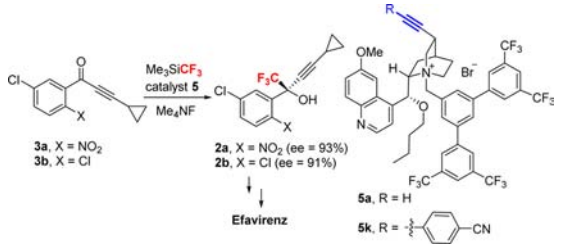
Scheme 1. Organometallic (Stoichiometric and Catalytic) and Organocatalytic Approaches for the Synthesis of Efavirenz



catalyst **4b** (second generation) bearing an *n*-butyloxy group.[7b] The enantioselectivity by an organocatalytic process is still less efficient than that by an organometallic approach.

We disclose herein the first highly enantioselective synthesis of Efavirenz by organocatalysis (Scheme 2). The enantioselectivity

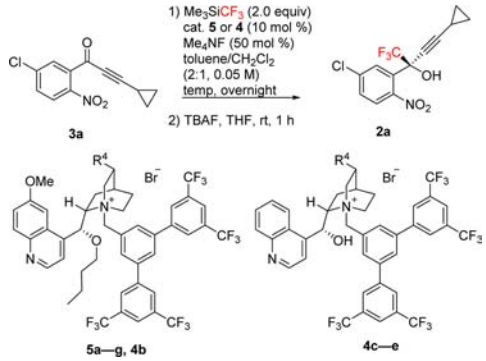
Scheme 2. Highly Enantioselective Synthesis of Efavirenz under Nonmetal Organocatalysis



of **2** from **3** was dramatically improved to over 90% ee by the use of previously unknown, alkynyl cinchona catalysts **5a** and **5k**. Both Merck and Lonza key intermediates **2** for Efavirenz were nicely accessed by this method in high yields with 93% ee and 91% ee, respectively. The synthesis of Efavirenz can be completed in one or two steps from **2** without the major loss of enantiopurity.

Since a large number of catalysts (**3a** to **2a**) have been thoroughly investigated for the improvement of enantioselectivity based on the modification of a second generation catalyst (Figure S1 in Supporting Information (SI)), we almost abandoned this strategy. However, we noticed that a vinyl moiety of cinchona alkaloids was not modified that much. More importantly, quaternary ammonium salts of cinchona alkaloids having an alkynyl group instead of vinyl have rarely been synthesized.[9] We thus synthesized **5a**, a simple ethynyl analogue of our second generation catalyst **4b**, from ethynyl-quinine[10] in two steps in high yields through etherification with *n*-butyl bromide followed by quaternerization using bulky benzyl bromide (see SI for details). With the novel catalyst **5a** in hand, we attempted the trifluoromethylation of **3a** under the best conditions for second generation catalyst **4a** consisting of Me_3SiCF_3 (2.0 equiv), catalyst **5a** (10 mol %), and Me_4NF (50 mol %) in toluene/CH_2Cl_2 (2:1) at −60 °C overnight. Excitingly, 83% ee was achieved instantaneously (Table 1,

Table 1. Screening of Catalysts 5 or 4 for Enantioselective Trifluoromethylation of 3a to 2a, for Merck Intermediate[a]



entry	catalyst 5	R^4	temp (°C)	yield (%)[b]	ee (%)
1	**5a**	C≡C−H	−60	77	83
2	**5b**	C≡C−Ph	−60	54	55
3	**5c**	C≡C−Br	−60	89	84
4	**5a**	C≡C−H	−80	95	88
5	**5d**	C≡C−Br	−80	73	87
6	**5e**	C≡C−Cl	−80	82	85
7	**5f**	C≡C−C≡C−TIPS[c]	−80	79	74
8[d]	**5a**	C≡C−H	−80	92	89
9[d]	**5a**	C≡C−H	−90	88	93
10	**5g**	Et	−80	52	71
11	**4b**	CH=CH_2	−60	83	75
12	**4c**	Et	−60	80	39
13	**4d**	CH=CH_2	−60	99	45
14	**4e**	C≡C−H	−60	75	54

[a]The reaction of **3a** with Me_3SiCF_3 (2.0 equiv) was carried out in the presence of catalyst **5** or **4** (10 mol %) and Me_4NF (50 mol %) in toluene/CH_2Cl_2 (2:1) (2.0 mL, 0.05 M) overnight, unless otherwise noted. [b]Isolated yield. [c]TIPS: triisopropylsilyl. [d]Solvent (toluene/CH_2Cl_2 = 1:2) was used.

entry 1). This result greatly encouraged us to examine the further modification of catalyst **5** with an alkenyl group in the hope of achieving the improved enantioselectivity of **2a** (Table 1).

Thus, we prepared additional alkynyl derivatives **5b—f** and submitted these catalysts to trifluoromethylation of **2a** under the same conditions at −60 °C. While the ee of phenyl acetylene catalyst **5b** dropped to 55%, alkynyl bromide catalyst **5c** displayed the same high level of enantioselectivity with 84% ee (Table 1, entries 2 and 3). Further improvement was observed at a low temperature (−80 °C) (Table 1, entries 4—7), and the simple alkynyl catalyst **5a** most effectively provided **2a** with a high ee (88%) in 95% yield (Table 1, entry 4), while *bis*-ethynyl catalyst **5f** gave 74% ee for **2a** (Table 1, entry 7). Further fine optimization of the reaction conditions indicated that the use of a solvent system of toluene/CH_2Cl_2 (1:2) slightly increased the ee to 89% (Table 1, entry 8) and the best ee of 93% was observed in toluene/CH_2Cl_2 (1:2), at −90 °C (Table 1, entry 9). The advantage of an alkynyl group is obvious when compared to the results using conventional ethyl **5g** and vinyl **4b** catalysts, which gave 71% ee and 75% ee, respectively (Table 1, entries 10 and 11). To appreciate the advantages of the ethynyl group for the

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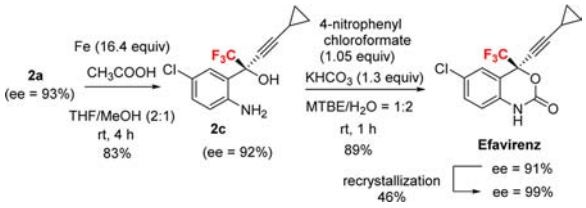
improvement of enantioselectivity, modification of the cinchonidine catalyst, a first generation catalyst **4a**, was next attempted (Table 1, entries 12—14). The same conditions were used for ensuing comparisons. As can be seen, enantioselectivities gradually improved to 39% ee, 45% ee, and 54% ee as the catalyst was changed from ethyl **4c**, vinyl **4d**, and ethynyl **4e**, respectively.

With the enantiomerically enriched **2a** in hand, the synthesis of Efavirenz was completed via the Merck intermediate (Scheme 3). The chemoselective reduction of the nitro group of **2a** by the

Scheme 3. Synthesis of Efavirenz via the Merck Intermediate



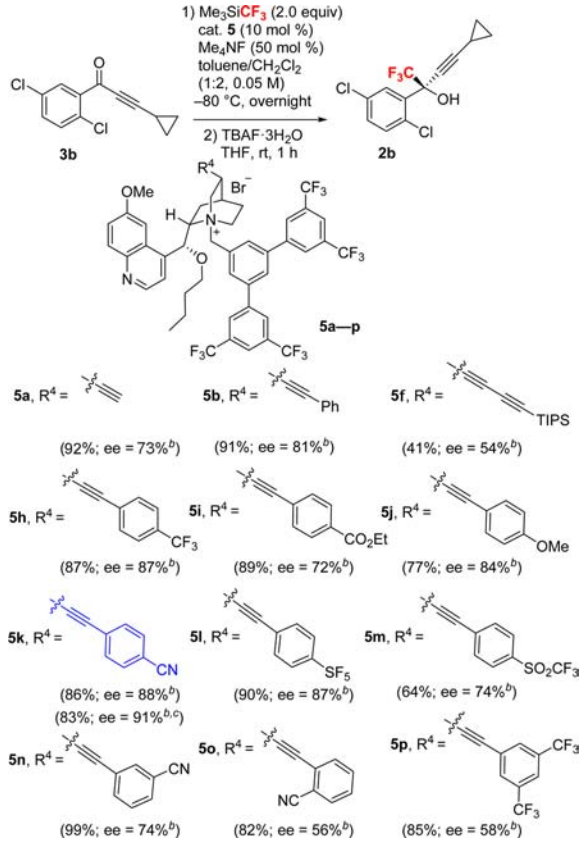
iron/AcOH system in THF/MeOH at rt for 4 h furnished Merck's aniline derivative **2c** in 83% yield. Treatment of **2c** with 4-nitrophenyl chloroformate in the presence of $KHCO_3$ in methyl *tert*-butyl ether (MTBE)/H_2O at rt for 1 h afforded Efavirenz in 89% yield. The enantiopurity of Efavirenz increased easily from 91% ee to 99% ee by a single recrystallization step from *n*-hexane/CH_2Cl_2.

We finally focused on the catalytic enantioselective synthesis of **2b**, which is a Lonza intermediate that may become important for use in processing since it can be transformed into *rac*-Efavirenz by a flow system in a single step;[11] however, the enantioselective synthesis of **2b** remains a challenge with 46% ee under organometallic catalysis.[6b] We applied our organocatalytic trifluoromethylation using catalyst **5a** to dichlorophenyl alkenyl ketone **3b** with Me_3SiCF_3 under the best conditions described in Table 1. The Lonza intermediate **2b** was obtained in 92% yield with good enantioselectivity (73% ee) by **5a** (Scheme 4). Fortunately, the phenylethynyl catalyst **5b** gave a promising enantioselectivity of 81% ee, while *bis*-ethynyl catalyst **5f** showed a moderate ee of 54%. Encouraged by the result using phenylethynyl catalyst **5b**, the modification of the catalyst structure was further investigated to discover a suitable arylethynyl group. After several attempts, catalyst **5k** having a 4-cyano phenyl group displayed the highest enantioselectivity of 88% ee among 12 catalysts. Other catalysts without alkynes were not efficient (Figure S2, SI). Enantioselectivity increased slightly to 91% ee by **5k** in the solvent system of toluene/CH_2Cl_2 (2:1).

The trifluoromethylated adduct **2b** was easily transformed into Efavirenz in a batch, as a single step via copper-catalyzed cyclization of an aryl isocyanate generated in situ using $CuSO_4$ and NaOCN in the presence of a diamine ligand, *trans-N,N′*-dimethyl-1,2-cyclohexanediamine (CyDMEDA)[5b] in 28% yield with 90% ee (Scheme 5).

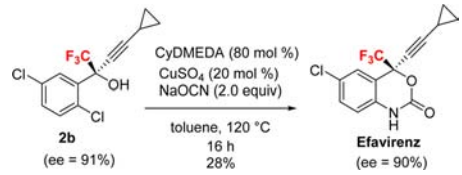
To understand the high enantioselectivity achieved in the trifluoromethylation of **3** to **2**, we examined the three-dimensional arrangements of catalysts **4b**, **5a**, and **5k** by DFT calculations (B3LYP/6-31G(d) level of theory) based on previous reports (Figure 1a—c).[11] The initial structure was generated from the X-ray crystallographic analysis of a related cinchona alkaloid.[11a,c] Geometry-optimized molecular structures of the starting alkenyl ketones **3** were also obtained as well by DFT calculations with the B3LYP/6-31G(d) level of theory

Scheme 4. Screening of Catalysts 5 for Enantioselective Trifluoromethylation of 3b to 2b, the Lonsa Intermediate[a]



[a]The reaction of **3b** with Me_3SiCF_3 (2.0 equiv) was carried out in the presence of catalyst **5** (10 mol %) and Me_4NF (50 mol %) in toluene/CH_2Cl_2 (1:2) (2.0 mL, 0.05 M) overnight, unless otherwise noted. [b]Isolated yield and ee of **2b** by catalyst **5**. [c]Solvent (toluene/CH_2Cl_2 = 2:1) was used.

Scheme 5. Synthesis of Efavirenz via the Lonsa Intermediate



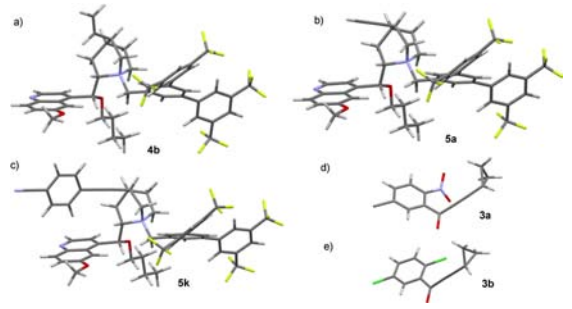


Figure 1. (a) DFT calculated 3D-arrangements of **4b**; (b) **5a**; (c) **5k**; (d) **3a**; (e) **3b**.

(Figure 1d and 1e). The structural difference of the best catalyst **5a** from a previous one, **4b**[7b] (Table 1, entry 11), is only the ethynyl group; thus, the 3D conformation of **5a** and **4b** is

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apparently similar. However, as is obvious from the optimized structures, catalyst **5a** has a closed structure between the ethynyl group and the quinoline ring (Figure 1b). A closed space limitation was also observed for catalyst **5k** having an arylethynyl group (Figure 1c). In contrast, the space over the quinoline ring of catalyst **4b** was more open (Figure 1a). The other spaces around both catalysts **4** and **5** were almost fully occupied by the sterically demanding 3,5-*bis*-CF_3-aryl groups and *n*-butyl ether of **5a,k**.

Thus, the transition-state arrangements shown in Figure 2 are plausible (Figure 2). The alkenyl ketones **3a,b** can be stabilized

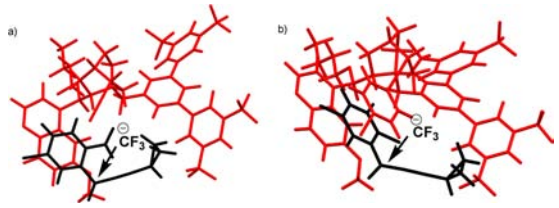

Figure 2. (a) Plausible transition state structures for the formation of **2a** by **5a** from **3a**; (b) formation of **2b** by **5k** from **3b**.

by a $\pi-\pi$ interaction with the quinoline ring. The methoxy group (OMe) of quinoline assists the positioning of ketones **3** by a steric interaction, while a corresponding cinchonidine variant without an OMe group tends to lower the enantioselectivity.[7b] The CF_3 anion approaches from the *Si*-face of ketones **3a,b**.

We disclosed the highly organocatalyzed enantioselective trifluoromethylation of alkenyl aryl ketones with the Ruppert–Prakash reagent to provide trifluoromethyl alcohols in high yields with high enantioselectivities. These are the key intermediates of the anti-HIV drug, Efavirenz. Previously unknown ethynyl and arylethynyl cinchona alkaloid ammonium salts were found to be very effective for this transformation. Over 90% ee has been achieved for the first time under a nonmetal system. Both Merck and Lonsa key intermediates for Efavirenz were accessed with 91–93% ee, both of which were nicely converted into Efavirenz in one or two steps without a major loss of enantiopurity of the trifluoromethylated alcohols. Application of this method for the asymmetric flow synthesis of Efavirenz is now being investigated.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02807.

Experimental procedures, NMR spectra, and HPLC charts (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Wilkins, E.; Fisher, M.; Brogan, J.; Talbird, S. E.; La, E. M. *HIV Med.* **2016**, *17*, 505. (b) Mandala, D.; Thompson, W.; Watts, P. *Tetrahedron* **2016**, *72*, 3389. (c) Roshni, P. R.; Thampi, A.; Ashok, B. A.; Joy, J.; Thomas, T.; Kumar, K. P. G. *Int. J. Pharm. Sci. Rev. Res.* **2016**, *36*, 8. (d) Larru, B.; Eby, J.; Lowenthal, E. D. *Pediatr. Health, Med. Ther.* **2014**, *5*, 29.

(2) Young, D. S.; Britcher, F. S.; Payne, S. L.; Tran, O. L.; William, L. C., Jr. Benzoxazinones as Inhibitors of HIV Reverse Transcriptase. World Patent 9520389, Aug 3, 1995.

(3) (a) Nakakeeto, O. N.; Elliott, B. V. *Globalization and Health* **2013**, *9*, 6. (b) Global HIV and AIDS statistics, https://www.avert.org/global-hiv-and-aids-statistics (accessed Oct 2016).

(4) (a) Li, S.; Ma, J. A. *Chem. Soc. Rev.* **2015**, *44*, 7439. (b) Wu, G.; Huang, M. *Chem. Rev.* **2006**, *106*, 2596. (c) Huang, Y.; Yang, X.; Chen, Z.; Verpoort, F.; Shibata, N. *Chem. - Eur. J.* **2015**, *21*, 8664. (d) Wang, J.; Sánchez-Roselló, M.; Aceña, J. L.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. *Chem. Rev.* **2014**, *114*, 2432.

(5) (a) Parsons, R. L., Jr.; Fortunak, J. M.; Dorow, R. L.; Harris, G. D. G.; Kauffman, S.; Nugent, W. A.; Winemiller, M. D.; Briggs, T. F.; Xiang, B.; Collum, D. B. *J. Am. Chem. Soc.* **2001**, *123*, 9135. (b) Tan, L.; Chen, C.; Tillyer, R. D.; Grabowski, E. J. J.; Reider, P. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 711.

(6) (a) Chinkov, N.; Warm, A.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 2957. (b) Dai, D.; Long, X.; Luo, B.; Kulesza, A.; Reichwagen, J.; Guo, Y. Process for Preparation of Efavirenz by Cyclization. World Patent 2012097510, Jul 26, 2012.

(7) (a) Kawai, H.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Eur. J. Org. Chem.* **2011**, *2011*, 5959. (b) Okusu, S.; Kawai, H.; Yasuda, Y.; Sugita, Y.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Asian J. Org. Chem.* **2014**, *3*, 449.

(8) For asymmetric synthesis of Efavirenz analogues, see: (a) Jiang, B.; Dong, J. J.; Si, Y. G.; Zhao, X. L.; Huang, Z. G.; Xu, M. *Adv. Synth. Catal.* **2008**, *350*, 1360. (b) Xie, H.; Zhang, Y.; Zhang, S.; Chen, X.; Wang, W. *Angew. Chem., Int. Ed.* **2011**, *50*, 11773. (c) Yuan, H.-N.; Wang, S.; Nie, J.; Meng, W.; Yao, Q.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2013**, *52*, 3869. (d) Wang, J.; Liu, X.; Feng, X. *Chem. Rev.* **2011**, *111*, 6947. (e) Zhang, F.-G.; Zhu, X.-Y.; Li, S.; Nie, J.; Ma, J.-A. *Chem. Commun.* **2012**, *48*, 11552. (f) Zhang, F.-G.; Ma, H.; Zheng, Y.; Ma, J.-A. *Tetrahedron* **2012**, *68*, 7663. (g) Zhang, F.-G.; Ma, H.; Nie, J.; Zheng, Y.; Gao, Q.; Ma, J.-A. *Adv. Synth. Catal.* **2012**, *354*, 1422. (h) Cai, H.; Nie, J.; Zheng, Y.; Ma, J.-A. *J. Org. Chem.* **2014**, *79*, 5484.

(9) One compound is registered in the ScFinder database: Baptiste, T.; Plaquevent, P. D.; Christophe, J.; Dominique, C. In *A panoply of polymer-anchored cinchona alkaloids for asymmetric phase-transfer catalysis*, International Sixth International Electronic Conference on Synthetic Organic Chemistry (ECSOC-6), Basel, Switzerland, Sept 1–30, 2002.

(10) (a) Braje, W. M.; Frackenpohl, J.; Schrake, O.; Wartchow, R.; Beil, W.; Hoffmann, H. M. R. *Helv. Chim. Acta* **2000**, *83*, 777. (b) Kacprzak, K. M.; Lindner, W.; Maier, N. M. *Chirality* **2008**, *20*, 441.

(11) (a) Matoba, K.; Kawai, H.; Furukawa, T.; Kusuda, A.; Tokunaga, E.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 5762. (b) Kawai, H.; Yuan, Z.; Kitayama, T.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 5575. (c) Kawai, H.; Kusuda, A.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6324.

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