

Highly Enantioselective Copper-Catalyzed Electrophilic Trifluoromethylation of β -Ketoesters

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Supporting Information

ABSTRACT: Enantioselective Cu-catalyzed trifluoromethylation of β -ketoesters using commercially available trifluoromethylating reagents is reported. A number of α -CF₃ β -ketoesters are obtained with up to 99% ee. The trifluoromethylated products were then transformed diastereoselectively to α -CF₃ β -hydroxyesters with two adjacent quaternary stereocenters via a Grignard reaction.

The physical, chemical, and biological properties of organic molecules may be significantly modified in the presence of trifluoromethyl groups.¹ Thus, great efforts have been made to develop reactions to generate trifluoromethylated compounds during the past decades.^{2–4} In particular, the stereoselective introduction of trifluoromethyl groups to generate chiral centers has been of growing interest.⁵ While there is an ever growing number of catalytic enantioselective nucleophilic trifluoromethylations,^{5,6} the corresponding electrophilic variant remains comparatively rare.⁵ To date, the only catalytic enantioselective electrophilic trifluoromethylation has been reported by MacMillan and co-workers in 2010, combining chiral organocatalysis and Lewis acid catalysis and using Togni's reagent (**1c**)⁷ as a CF₃-transfer reagent to obtain enantioenriched α -trifluoromethylated aldehydes.⁸

Enantiopure α -CF₃ β -ketoesters are attractive targets because they possess both a chiral CF₃-containing quaternary stereocenter and an easily derivatized carbonyl group. The non-asymmetric trifluoromethylation has been studied extensively;^{7,9} but surprisingly, only two stoichiometric asymmetric examples have been documented, giving rise to moderate enantioselectivities (up to 71% ee).^{10–12} Therefore, the development of an efficient enantioselective catalytic electrophilic trifluoromethylation of β -ketoesters remains a challenge in organic synthesis.

We recently developed a class of chiral pincer ligands, boxmi (**2**), which proved to be highly efficient as stereodirecting

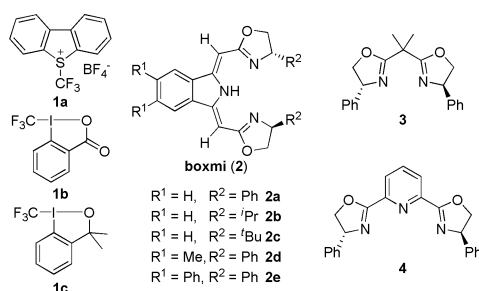
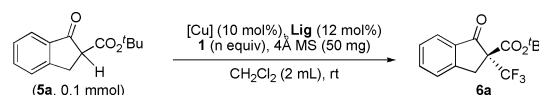


Table 1. Optimization of Reaction Conditions for the Trifluoromethylation of **5a**



entry	[Cu]	Lig	1	<i>n</i>	<i>t</i> (h)	yield (%) ^a	ee (%) ^b
1 ^c	Cu(OTf) ₂	2d	1a	2	48	82	95
2	Cu(OTf) ₂	2d	1b	2	48	NR ^d	—
3	Cu(OTf) ₂	2d	1c	2	15	92	95
4	Cu(OAc) ₂ ·H ₂ O	2d	1c	2	15	90	89
5	Cu(ClO ₄) ₂ ·6H ₂ O	2d	1c	2	15	89	94
6	Cu(OTf)·0.5Stol.	2d	1c	2	15	91	94
7	Cu(BF ₄)·4MeCN	2d	1c	2	15	91	92
8	Cu(OTf) ₂	2a	1c	2	15	91	93
9	Cu(OTf) ₂	2b	1c	2	15	92	73
10	Cu(OTf) ₂	2c	1c	2	15	90	62
11	Cu(OTf) ₂	2e	1c	2	15	89	95
12	Cu(OTf) ₂	3	1c	2	19	89	–49
13	Cu(OTf) ₂	4	1c	2	24	90	0
14	Cu(OTf) ₂	2d	1c	1.5	16	91	95
15	Cu(OTf) ₂	2d	1c	1.2	18	92	95
16	Cu(OTf) ₂	2d	1c	1.1	24	89	93

^aIsolated yields. ^bDetermined by HPLC analysis. ^cAdding 2 equiv of ⁱPr₂NEt as base. ^dNo reaction.

ligands in Cu-catalyzed enantioselective alkylations of β -ketoesters and their subsequent cyclization.¹³ Employing such chiral Cu-pincer systems we now report the highly enantioselective catalytic trifluoromethylation of β -ketoesters under mild conditions by using commercial electrophilic trifluoromethylating agents.

Initially, by using 5-(trifluoromethyl)dibenzothiophenium tetrafluoroborate (Umemoto's reagent,^{9b} **1a**) as the trifluoromethylating agent, the trifluoromethylation of β -ketoester **5a** was performed in CH₂Cl₂ at room temperature with the catalyst generated in situ from 10 mol % of Cu(OTf)₂ and 12 mol % of **2d** in the presence of molecular sieves, under reaction conditions which had been previously optimized for enantioselective alkylations.^{13b} The corresponding product **6a** was obtained in 82% yield with 95% ee (Table 1, entry 1). Screening two types of Togni's reagents revealed that while **1b** was ineffective for this system reagent **1c** gave the product in higher yield with the same enantioselectivity and in a

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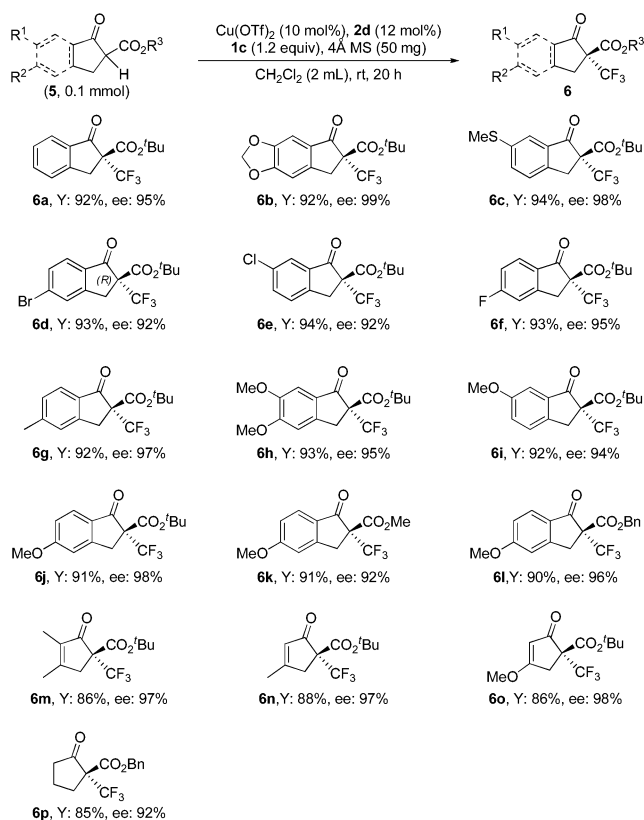
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considerably shorter reaction time (entries 2 and 3). Various copper catalyst precursors were tested in the reaction, and $\text{Cu}(\text{OTf})_2$ was found to be optimal in terms of yield and enantioselectivity (entries 3–7). In contrast to the ligand **2d**, other boxmi derivatives containing different substituents gave lower enantioselectivities or yields (entries 8–11).

Two other bisoxazoline ligands, (*R,R*)-Ph-Box **3**¹⁴ and Nishiyama's (*R,R*)-Ph-Pybox **4**,¹⁵ were also compared under identical reaction conditions. The product was obtained with only –49% and 0% ee respectively (entries 12 and 13), which indicated the greater effectiveness of the boxmi system in obtaining optimum enantioselectivity in the Cu-catalyzed trifluoromethylation of β -ketoesters. Finally, we found that a 1.2 equiv amount of the trifluoromethylating reagent was sufficient for this reaction (entries 14–16).

A broad range of cyclic five-membered ring β -ketoesters was examined with the optimized catalyst and reaction conditions (Scheme 1). Indanone-derived *tert*-butyl β -ketoesters generated

Scheme 1. Enantioselective Trifluoromethylation of Five-Membered Ring β -Ketoesters^a



^aYields refer to isolated products; ee's were determined by HPLC analysis.

the corresponding products in high yields with excellent enantioselectivities (92–99% ee) regardless of the nature and the position of the substituents of the β -ketoesters derivatives (Scheme 1, **6a–6j**). In the presence of either electron-withdrawing or -donating groups, and even methylthio units in the aromatic ring, excellent enantioselectivities were obtained. Methyl and benzyl β -ketoesters also yielded the corresponding products with excellent enantioselectivities (**6k** and **6l**), showing that the size of the ester group only has a slight influence on the enantiocontrol. Furthermore, three

differently functionalized *tert*-butyl esters of cyclopentenone were converted to the corresponding products in high yields with excellent enantioselectivities (**6m–6o**), providing another valuable class of building blocks.¹⁶ Finally, a cyclopentanone-derived benzyl β -ketoester was also successfully employed in the process to generate **6p** with 92% ee.

The absolute configuration of the optically active **6d** was established to be *R* by single crystal X-ray structure analysis (Figure 1). Based on the absolute configuration of the product

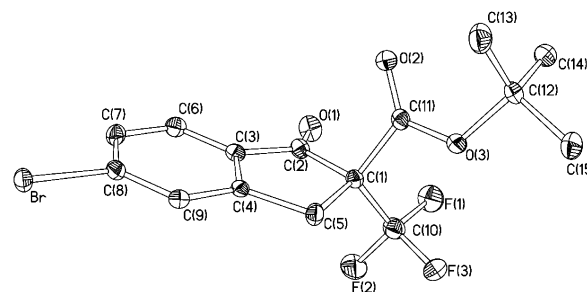


Figure 1. Molecular structure of trifluoromethylated product **6d**; hydrogen atoms omitted for clarity.

formed, we assume that the key reaction intermediate is similar to the one we have proposed previously for the catalytic cycle of the asymmetric alkylation reaction.^{13b}

In contrast to the substrates depicted in Scheme 1, the more easily enolizable cyclic six-membered ring β -ketoester **7a** was trifluoromethylated with a significant decrease in enantioselectivity (63% ee) under the conditions described above (Table 2, entry 1). However, upon using the combination of reagent

Table 2. Optimization of Reaction Conditions for the Trifluoromethylation of **7a**

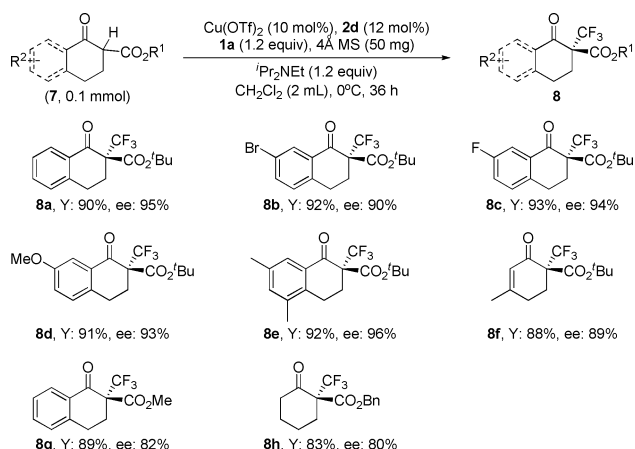
entry	1	base	T (°C)	t (h)	yield (%) ^a	ee (%) ^b
1	1c	—	rt	12	88	63
2	1a	<i>i</i> Pr ₂ NEt	rt	20	90	84
3	1a	<i>i</i> Pr ₂ NEt	0	36	90	95
4	1a	<i>i</i> Pr ₂ NEt	–20	48	11	ND ^c

^aIsolated yields. ^bDetermined by HPLC analysis. ^cNot determined.

1a and diisopropyl ethylamine instead of **1c**, the ee value increased to 84% (entry 2) and the enantioselectivity was further enhanced to 95% ee when the reaction was carried out at 0 °C (entry 3).

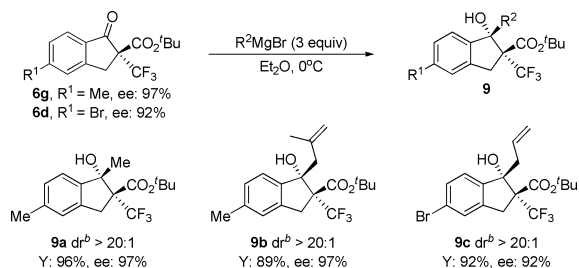
With these optimized reaction conditions we explored the generality of the protocol for six-membered ring β -ketoesters (Scheme 2). Tetralone-derived *tert*-butyl β -ketoesters generated the trifluoromethylated products with excellent enantioselectivities (**8a–8e**). Cyclohexenone-derived *tert*-butyl ester also generated the corresponding product with high ee (**8f**). However, with the corresponding methyl β -ketoester and cyclohexanone-derived benzyl β -ketoester the ee values were reduced to 82% and 80%, respectively (**8g** and **8h**). Unfortunately, acyclic ketoesters proved to be unreactive under these reaction conditions.¹⁷

To highlight the utility of the enantioselective trifluoromethylation developed in this work, we undertook further

Scheme 2. Enantioselective Trifluoromethylation of Six-Membered Ring β -Ketoesters^a

^aYields refer to isolated products; ee's were determined by HPLC analysis.

transformations of the trifluoromethylated products. The trifluoromethylated β -ketoesters reacted with Grignard reagents (methyl-, 2-methylallyl-, or allylmagnesium bromide) in Et_2O at 0 °C to give the α - CF_3 β -hydroxyesters **9a–9c** in high yields with excellent diastereoselectivities (Scheme 3). The relative

Scheme 3. Highly Diastereoselective Grignard Reaction of α - CF_3 β -Ketoesters^a

^aYields refer to isolated products; ee's were determined by HPLC analysis. ^bDetermined by ^1H and ^{19}F NMR.

stereochemistry of products **9** was assigned by comparison of NMR data and ^1H – ^{19}F NOE experiments¹⁷ which showed that the methyl group and CF_3 group have a relative trans orientation in **9a**. The X-ray structure analysis of *rac*-**9b** also confirmed that the hydroxyl group and CF_3 group are cis oriented relative to each other (Figure 2). This stereochemistry might arise from the formation of a Mg^{2+} chelate with the keto and the ester carbonyl groups, which is attacked by the nucleophile from the less hindered face, that is, opposite to the CF_3 group.¹⁸

Furthermore, in the presence of 5 mol % of $\text{Cu}(\text{OTf})_2$ and 3 equiv of $\text{BF}_3 \cdot \text{Et}_2\text{O}$,^{13b} lactonization and dehydration of α - CF_3 β -hydroxyester **9b** readily occurred in dichloromethane at 0 °C yielding a substituted 9,9a-dihydroindeno[2,1-*c*]pyran-1(3*H*)-one **10** with comparable enantioselectivity (Scheme 4).

In conclusion, we have developed an efficient protocol for enantioselective trifluoromethylation of cyclic β -ketoesters using commercially available reagents via Cu-boxmi catalysis. Both five- and six-membered ring β -ketoesters were converted to the corresponding products in high yields with up to 99% ee under mild conditions. Furthermore, the subsequent Grignard

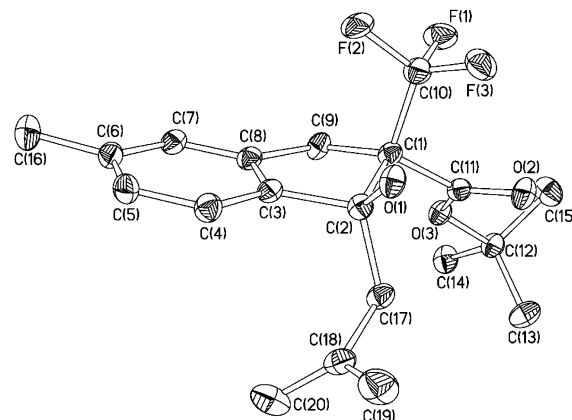
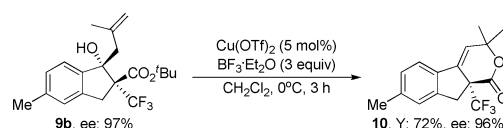


Figure 2. Molecular structure of trifluoromethylated product *rac*-**9b**; hydrogen atoms omitted for clarity.

Scheme 4. Lactonization of α - CF_3 β -Hydroxyester **9b**^a

^aYields refer to isolated products; ee's were determined by HPLC analysis.

reaction constructed two adjacent quaternary stereocenters with a well-defined absolute configuration to give stereochemically pure α - CF_3 β -hydroxyesters.

■ ASSOCIATED CONTENT

■ Supporting Information

Experimental procedures, spectral data for all compounds, and crystallographic results (for **6d** and **9b**) in cif format. The details of NMR data and ^1H – ^{19}F NOE experiments (for **9a**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) (a) Welch, J. T. *Tetrahedron* **1987**, 43, 3123. (b) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004. (c) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, 44, 214. (d) Schlosser, M. *Angew. Chem., Int. Ed.* **2006**, 45, 5432. (e) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, 317, 1881. (f) Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; Wiley-VCH: Hoboken, NJ, 2008. (g) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, 37, 320. (h) Hagmann, W. K. *J. Med. Chem.* **2008**, 51, 4359. (i) Pursor, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, 37,

320. (j) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, 2009. (k) Lin, G.-Q.; You, Q.-D.; Cheng, J.-F. *Chiral Drugs: Chemistry and Biological Action*; Wiley-VCH: Hoboken, 2011.

(2) For reviews on trifluoromethylation reactions, see: (a) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555. (b) Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757. (c) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757. (d) Prakash, G. K. S.; Hu, J. *Acc. Chem. Res.* **2007**, *40*, 921. (e) Ma, J.-A.; Cahard, D. *J. Fluorine Chem.* **2007**, *128*, 975. (f) Uneyama, K.; Katagiri, T.; Amii, H. *Acc. Chem. Res.* **2008**, *41*, 817. (g) Lundgren, R. J.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 9322. (h) Shibata, N.; Matsnev, A.; Cahard, D. *Beilstein J. Org. Chem.* **2010**, *6*, No. 65. (i) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475. (j) Parsons, A. T.; Buchwald, S. L. *Nature* **2011**, *480*, 184. (k) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (l) Qing, F.-L.; Zheng, F. *Synlett* **2011**, 1052. (m) Besset, T.; Schneider, C.; Cahard, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 5048.

(3) For selected examples on the latest copper-catalyzed trifluoromethylation reactions, see: (a) Xu, J.; Fu, Y.; Luo, D.-F.; Jiang, Y.-Y.; Xiao, B.; Liu, Z.-J.; Gong, T.-J.; Liu, L. *J. Am. Chem. Soc.* **2011**, *133*, 15300. (b) Wang, X.; Ye, Y.; Zhang, S.; Feng, J.; Xu, Y.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 16410. (c) Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9120. (d) Chu, L.; Qing, F.-L. *J. Am. Chem. Soc.* **2012**, *134*, 1298. (e) He, Z.; Luo, T.; Hu, M.; Cao, Y.; Hu, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3944. (f) Shimizu, R.; Egami, H.; Hamashima, Y.; Sodeoka, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4577.

(4) For selected examples of the latest on other trifluoromethylation reactions, see: (a) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science* **2010**, *328*, 1679. (b) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648. (c) Cho, E. J.; Buchwald, S. L. *Org. Lett.* **2011**, *13*, 6552. (d) Niedermann, K.; Fröh, N.; Vinogradova, E.; Wiehn, M. S.; Moreno, A.; Togni, A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1059. (e) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6119. (f) Kawai, H.; Tachi, K.; Tokunaga, E.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 7803. (g) Döbele, M.; Wiehn, M. S.; Bräse, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 11533. (h) Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224. (i) Mu, X.; Wu, T.; Wang, H.-Y.; Guo, Y.-L.; Liu, G. *J. Am. Chem. Soc.* **2012**, *134*, 878. (j) Liu, T.; Shao, X.; Wu, Y.; Shen, Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 540. (k) Parsons, A. T.; Senecal, T. D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 2947. (l) Hafner, A.; Bräse, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3713.

(5) For reviews on asymmetric trifluoromethylation reactions, see: (a) Shibata, N.; Mizuta, S.; Kawai, H. *Tetrahedron: Asymmetry* **2008**, *19*, 2633. (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2008**, *108*, PR1. (c) Zheng, Y.; Ma, J.-A. *Adv. Synth. Catal.* **2010**, *352*, 2745. (d) Valero, G.; Companyó, X.; Rios, R. *Chem.—Eur. J.* **2011**, *17*, 2018.

(6) For selected examples on catalytic nucleophilic asymmetric trifluoromethylation, see: (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1994**, *35*, 3137. (b) Caron, S.; Do, N. M.; Arpin, P.; Larivée, A. *Synthesis* **2003**, *11*, 1693. (c) Roussel, S.; Billard, T.; Langlois, B. R.; Saint-Jalmes, L. *Chem.—Eur. J.* **2005**, *11*, 939. (d) Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Lett.* **2007**, *36*, 666. (e) Nagao, H.; Kawano, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 2406. (f) Mizuta, S.; Shibata, N.; Akiti, S.; Fujimoto, H.; Nakamura, S.; Toru, T. *Org. Lett.* **2007**, *9*, 3707. (g) Zhao, H.; Qin, B.; Liu, X.; Feng, X. *Tetrahedron* **2007**, *63*, 6822. (h) Billard, T.; Langlois, B. R. *Eur. J. Org. Chem.* **2007**, 891. (i) Hu, X.-L.; Wang, J.; Li, W.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. *Tetrahedron Lett.* **2009**, *50*, 4378. (j) Kawai, H.; Kusuda, A.; Nakamura, S.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6324.

(7) (a) Eisenberger, P.; Gischig, S.; Togni, A. *Chem.—Eur. J.* **2006**, *12*, 2579. (b) Kieltisch, I.; Eisenberger, P.; Togni, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 754.

(8) (a) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986. MacMillan also reported the catalytic asymmetric radical trifluoromethylation; see: (b) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875.

(9) (a) Umemoto, T.; Ishihara, S. *Tetrahedron Lett.* **1990**, *31*, 3579. (b) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156. (c) Ma, J.-A.; Cahard, D. *J. Org. Chem.* **2003**, *68*, 8726. (d) Petrik, V.; Cahard, D. *Tetrahedron Lett.* **2007**, *48*, 3327. (e) Noritake, S.; Shibata, N.; Nakamura, S.; Toru, T.; Shiro, M. *Eur. J. Org. Chem.* **2008**, 3465. (f) Matsnev, A.; Noritake, S.; Nomura, Y.; Tokunaga, E.; Nakamura, S.; Shibata, N. *Angew. Chem., Int. Ed.* **2010**, *49*, 572. (g) Nomura, Y.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 1885. (h) Shibata, N.; Suzuki, S.; Furukawa, T.; Kawai, H.; Tokunaga, E.; Yuan, Z.; Cahard, D. *Adv. Synth. Catal.* **2011**, 353, 2037.

(10) (a) Petrik, V.; Ma, J.-A.; Cahard, D. *Proceedings of ECSOC-10, 10th International Electronic Conference on Synthetic Organic Chemistry*, 2006. (b) Noritake, S.; Shibata, N.; Nomura, Y.; Huang, Y.; Matsnev, A.; Nakamura, S.; Toru, T.; Cahard, D. *Org. Biomol. Chem.* **2009**, *7*, 3599.

(11) The stoichiometric asymmetric electrophilic trifluoromethylation of ketones, see: Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59*, 5692.

(12) For selected examples on diastereoselective trifluoromethylation of chiral substrates, see: (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169. (b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 961. (c) Itoh, Y.; Mikami, K. *Tetrahedron* **2006**, *62*, 7199. (d) Matoušek, V.; Togni, A.; Bizet, V.; Cahard, D. *Org. Lett.* **2011**, *13*, 5762. (e) Herrmann, A. T.; Smith, L. L.; Zakarian, A. *J. Am. Chem. Soc.* **2012**, *134*, 6976.

(13) (a) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *Chem.—Eur. J.* **2011**, *17*, 14922. (b) Deng, Q.-H.; Wadepohl, H.; Gade, L. H. *J. Am. Chem. Soc.* **2012**, *134*, 2946.

(14) Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, B. A.; Barnes, D. M. *J. Am. Chem. Soc.* **1993**, *115*, 5328.

(15) Nishiyama, H.; Kondo, M.; Nakamura, T.; Itoh, K. *Organometallics* **1991**, *10*, 500.

(16) (a) Kato, K.; Suzuki, H.; Tanaka, H.; Miyasaka, T. *Tetrahedron: Asymmetry* **1998**, *9*, 911. (b) Liu, L.-Z.; Han, J.-C.; Yue, G.-Z.; Li, C.-C.; Yang, Z. *J. Am. Chem. Soc.* **2010**, *132*, 13608.

(17) See Supporting Information for details.

(18) Emelen, K. V.; Wit, T. D.; Hoornaert, G. J.; Compennolle, F. *Org. Lett.* **2000**, *2*, 3083.