Trifluoromethylsulfenylation

DOI: 10.1002/anie.201304957

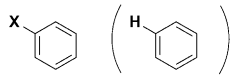
N-Trifluoromethylthiophthalimide: A Stable Electrophilic SCF_3-Reagent and its Application in the Catalytic Asymmetric Trifluoromethylsulfenylation**

*Teerawut Bootwicha, Xiangqian Liu, Roman Pluta, Iuliana Atodiresei, and Magnus Rueping**

Over the years, much attention has been devoted to the development of efficient methods for the stereoselective introduction of fluorinated moieties into organic molecules because of their ability to significantly change the physical and chemical properties of the parent compounds.[1,2] It has been established that the pharmacological properties, including solubility, lipophilicity, metabolic stability, and bioavailability, can be dramatically enhanced by incorporating fluoroalkyl groups into the molecules.[3] Among various established fluoroalkyl groups, the trifluoromethanesulfenyl group (SCF_3) is of current interest because of its remarkable properties, in particular its high stability and electronegativity, which can be useful in the rational modification of drug candidates.[4] The SCF_3 group has the highest lipophilicity value ($\pi_x = 1.44$) compared to the SF_5 ($\pi_x = 1.23$), OCF_3 ($\pi_x = 1.04$), CF_3 ($\pi_x = 0.88$), CH_3 ($\pi_x = 0.52$) groups (Figure 1 a). Compounds with higher lipophilicity show higher permeation across biological membranes, and the incorporation of a SCF_3 group can thus result in enhanced bioavailability, which is of great interest in agrochemical and pharmaceutical research.

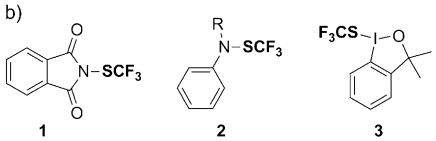
Therefore, the development of powerful methodologies for the formation of C–SCF_3 bonds has recently received much attention.[5] In this context, several new synthetic approaches for the formation of C(sp^2_{aryl})–SCF_3 bonds under mild reaction conditions have been developed employing nucleophilic trifluoromethylsulfenylation reagents, such as $CuSCF_3$.[6] In contrast, there have been only few reports on the use of electrophilic trifluoromethylsulfenylation reagents for the formation of C–SCF_3 bonds,[5a,7–10] with the formation of C(sp^3)–SCF_3 bonds hardly investigated. This development is not surprising, because both the synthesis and stability of electrophilic trifluoromethylsulfenylation reagents can be problematic. Thus, the enantioselective formation of a C–SCF_3 bond with the simultaneous generation of a stereogenic carbon center is a challenging task, prompting us to develop a catalytic asymmetric reaction involving the use of electrophilic SCF_3 reagents. At the outset of our efforts to develop an asymmetric trifluoromethylsulfenylation, only two relatively stable electrophilic SCF_3 sources were known: Munavalli's *N*-trifluoromethylthiophthalimide[8] (**1**) and Billard's trifluoromethanesulfanylamides[9] **2** (Figure 1 b). During our studies, an interesting report by Lu and Shen described the use of the electrophilic hypervalent iodine reagent **3**.[10] In addition, the gaseous and more toxic electrophilic $ClSCF_3$ and F_3CSSCF_3 have previously been applied.[5a]

a)



X	π_x
SCF_3	1.44
SF_5	1.23
OCF_3	1.04
CF_3	0.88
CH_3	0.52
H	0.00

b)



1 2 3

Figure 1. a) π_x = lipophilicity = $\log P_x - \log P_H$ (P = 1-octanol/water partition coefficient). b) Electrophilic SCF_3 sources.

We herein present an enantioselective trifluoromethylsulfenylation using **1** as a moisture- and air-stable electrophilic SCF_3 source.

1-Indanones, especially those with a stereocenter at the C2 position, are important structural motifs that appear in numerous biologically active natural products and pharmaceutical compounds.[11] Thus, indanone-derived β-ketoesters **4** were selected as substrates for the development of a trifluoromethylsulfenylation reaction.

However, we immediately realized that the development of such a reaction is difficult because electrophilic SCF_3 reagents are 1) rather unreactive electrophiles, and 2) less stable under basic conditions, as well as in the presence of nucleophilic solvents (such as DMSO), highly reactive cationic Lewis acid complexes, and primary and certain secondary amines, in which SCF_3 transfer and formation of the stable R^1R^2N-SCF_3 compounds occurs.

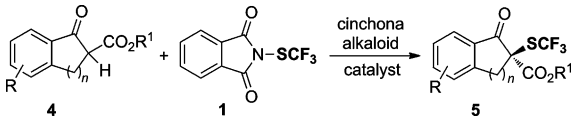
After many attempts, tertiary amines, including cinchona alkaloids, finally proved to be efficient catalysts, allowing the desired enantioselective reaction to proceed (Scheme 1).[12]

Although good reactivity was achieved, the enantioselectivities were not acceptable. In order to obtain decent enantioselectivities, various cinchona alkaloid catalysts were evaluated in the reaction between β-ketoester **4a** and the trifluoromethylthiolating reagent **1** (Table 1, entries 1–7 and 12). Among the catalysts that were evaluated, quinidine

[*] T. Bootwicha, X. Liu, R. Pluta, Dr. I. Atodiresei, Prof. Dr. M. Rueping
Institute of Organic Chemistry, RWTH Aachen University
Landoltweg 1, 52074 Aachen (Germany)
E-mail: magnus.rueping@rwth-aachen.de

[**] X.L. gratefully acknowledges the Chinese Scholarship Council for a fellowship. The absolute configuration was determined by I.A.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201304957.



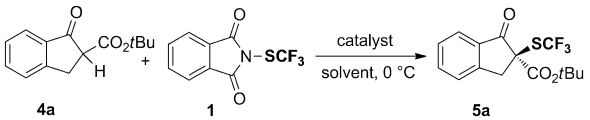
Scheme 1. Catalytic enantioselective trifluoromethylsulfenylation.

proved to be the best for this transformation, providing the corresponding product **5a** in excellent yield (95%) and good enantioselectivity (85% *ee*; Table 1, entry 4). Lowering the catalyst loading to 5 mol% resulted in a decrease in the chemical yield (Table 1, entry 13). Furthermore, four different bis(cinchona alkaloids) were also evaluated. In the case of $(DHQD)_2AQN$ and $(DHQ)_2AQN$, the reactions required 48 h for completion and gave the product in moderate yield and with considerably lower enantiomeric excess (Table 1, entries 5 and 6). When $(DHQD)_2PHAL$ and $(DHQ)_2PHAL$ were applied, longer reaction times were needed and the products were obtained in moderate yields with good enantioselectivities (Table 1, entries 7–12). Although similar enantioselectivities were achieved, the high molecular mass led us to consider quinidine for further optimization of reaction conditions. Thus, various solvents were evaluated (Table 1, entries 14–19). A decrease in the *ee* value was observed when the reaction was performed in ethereal solvents. The yield and enantioselectivity could both be improved by performing the reaction in chlorinated solvents (Table 1, entries 14–17). The desired product **5a** was isolated in good yield with excellent enantiomeric excess (95% *ee*) by using dichloromethane as solvent (Table 1, entry 14). Lowering the reaction temperature to −75°C gave the corresponding product in higher enantiomeric excess with a slight decrease in the chemical yield (93% yield, 98% ee; Table 1, entry 14 vs. 21).

With the optimized reaction conditions in hand, the scope of this asymmetric cinchona alkaloid catalyzed trifluoromethylsulfenylation was investigated (Table 2). In general, the reactions of cyclic five-membered-ring β-ketoesters bearing various electron-donating and electron-withdrawing substituents on positions 4, 5, and 6 of the aromatic ring proceeded smoothly to provide the corresponding products in high yields and excellent enantioselectivities (96–99% *ee*; Table 2, **5a–j**). The effect of the size of the ester group in the β-ketoesters on the enantioselectivity was also investigated. The results of this study showed only a slight influence on the enantioselectivity of the reaction by varying the size of the ester group (Me, *i*Pr, Bn), and the corresponding trifluoromethylsulfenylated products **5k–m** were isolated in good yields and excellent enantioselectivities. Furthermore, the reaction of cyclopentenone-derived *tert*-butyl β-ketoesters also proceeded well under the standard conditions to give the desired products in good yields and good enantioselectivities (Table 2, **5o–q**). Finally, it should be noted that the trifluoromethylsulfenylation of the cyclic six-membered-ring β-ketoester occurred at 0°C to give product **5n** with excellent enantioselectivity (95% *ee*), albeit in low yield (46%; Table 2).

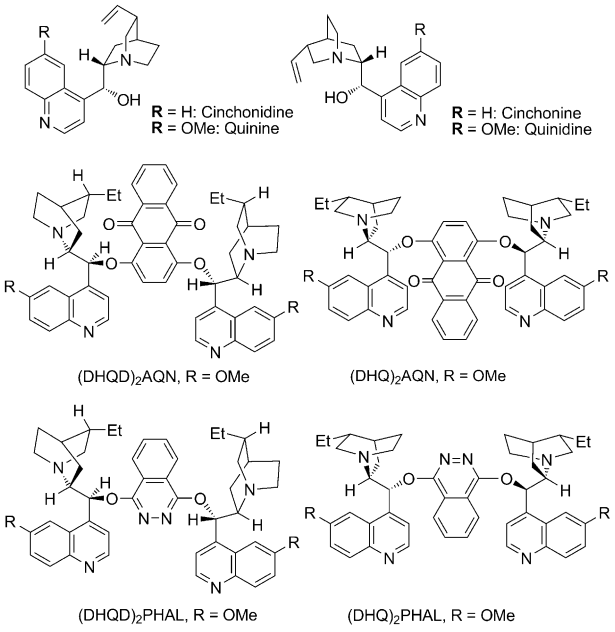
The absolute configuration of the stereogenic carbon center in the trifluoromethylsulfenylated products was determined to be (*S*) by X-ray crystal structure analysis of the

Table 1: Optimization of the reaction conditions for the asymmetric trifluoromethylsulfenylation.



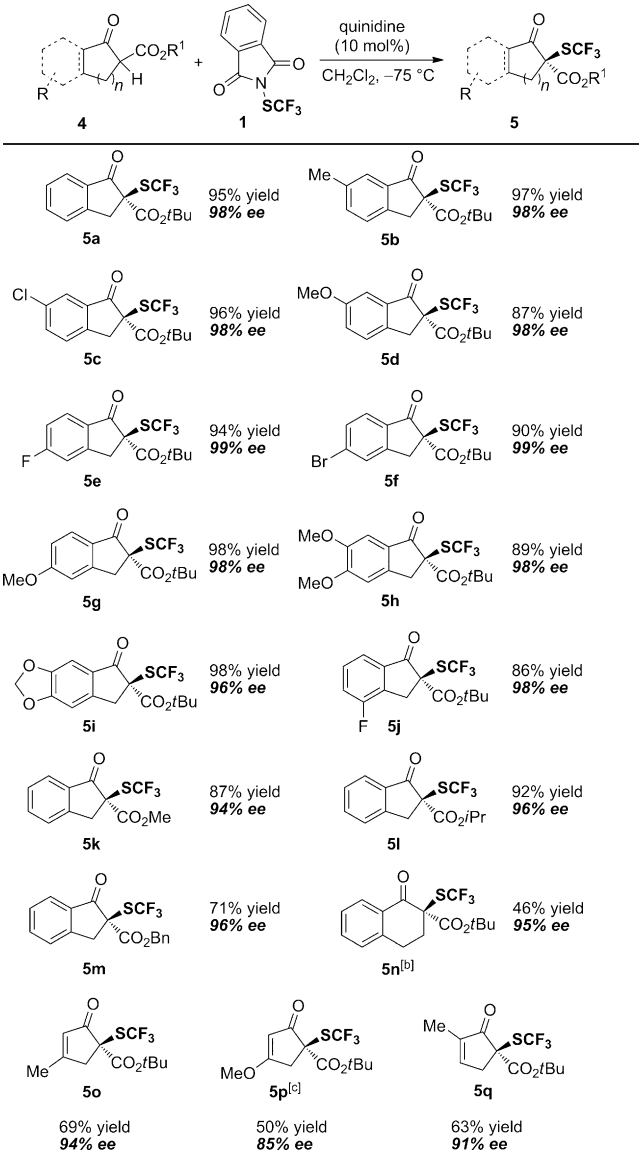
Entry[a]	Catalyst	Solvent	*t* [h]	Yield[b] [%]	*ee*[c] [%]
1	cinchonidine	toluene	48	70	−59
2	cinchonine	toluene	48	45	58
3	quinine	toluene	24	91	−75
4	quinidine	toluene	24	95	85
5	$(DHQD)_2AQN$	toluene	48	76	−41
6	$(DHQ)_2AQN$	toluene	48	76	30
7	$(DHQD)_2PHAL$	toluene	48	56	−88
8	$(DHQD)_2PHAL$	mesitylene	72	43	−85
9	$(DHQD)_2PHAL$	*m*-xylene	72	53	−83
10	$(DHQD)_2PHAL$	CH_2Cl_2	72	77	−73
11[d]	$(DHQD)_2PHAL$	CH_2Cl_2	72	20	−76
12	$(DHQ)_2PHAL$	toluene	48	73	84
13[e]	quinidine	toluene	24	84	85
14	quinidine	CH_2Cl_2	24	98	95
15	quinidine	$CHCl_3$	24	94	94
16	quinidine	$ClCH_2CH_2Cl$	24	98	94
17	quinidine	Cl-benzene	24	98	93
18	quinidine	Et_2O	24	98	72
19	quinidine	THF	24	94	20
20[f]	quinidine	CH_2Cl_2	24	98	96
21[d]	quinidine	CH_2Cl_2	24	93	98

[a] Reaction conditions: **4a** (1.0 equiv), **1** (1.3 equiv), catalyst (10 mol%), in 0.07 M solution of solvent at 0°C for 24–48 h. [b] Yield of the isolated product after column chromatography. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction was performed at −75°C. [e] Using 5 mol% catalyst. [f] The reaction was performed at −20°C.



optically active product **5f** (Figure 2). Having noticed that the use of quinine resulted in the opposite enantiomer (Table 1, entry 3), we utilized quinine under the optimized conditions and obtained the (*R*)-configured trifluoromethylsulfenylated

Table 2: Scope of the enantioselective trifluoromethylsulfenylation.[a]



[a] Reaction conditions: **4** (1.0 equiv), **1** (1.3 equiv), quinidine (10 mol%) in CH_2Cl_2 at −75 °C. Yield of the isolated product after column chromatography. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [b] The reaction was performed at 0 °C for 7 days. [c] The reaction was performed at −40 °C for 72 h.

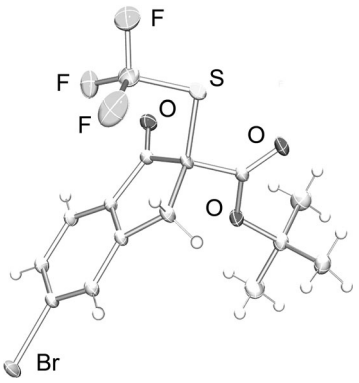
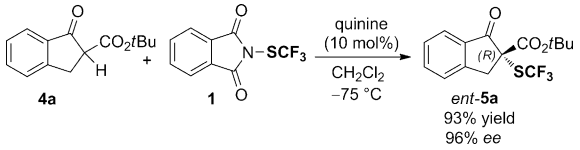
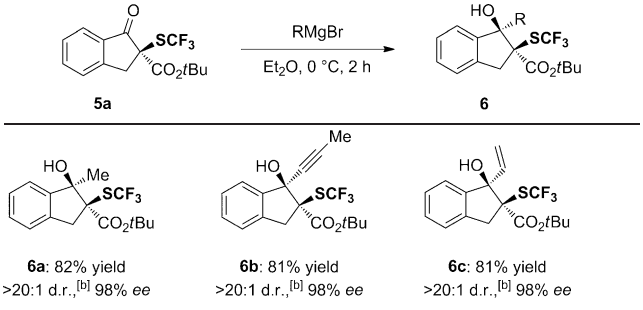


Figure 2. X-ray crystal structure of product **5f**. Thermal ellipsoids set at 50% probability.[13]



Scheme 2. Switching to (*R*) configuration by employing quinine as the catalyst in the enantioselective trifluoromethylsulfenylation.

Table 3: Synthesis of α-SCF_3 β-hydroxyesters.[a]



[a] Reaction conditions: **5a** (1 equiv), RMgBr (3 equiv) in 0.05 M solution of dry Et_2O at 0 °C for 2 h. Yield of the isolated product after column chromatography. The *ee* values were determined by HPLC analysis on a chiral stationary phase. [b] Determined by ^1H NMR spectroscopy.

ester *ent*-**5a** in 93% yield and excellent enantiomeric excess of 96% *ee* (Scheme 2).

To demonstrate the utility of the optically active trifluoromethylsulfenylated β-ketoesters, we next examined the transformation of **5a** to the corresponding α-SCF_3 β-hydroxyesters **6**. We anticipated that the keto group present in compound **5a** can be derivatized by nucleophilic addition of an appropriate nucleophile. Gratifyingly, when the reaction of **5a** with various Grignard reagents RMgBr (R = methyl, 1-propynyl, vinyl) was performed in Et_2O at 0 °C, the corresponding α-SCF_3 β-hydroxyesters **6a–c** were obtained in good yields with excellent diastereoselectivities (Table 3). The X-ray crystal structure analysis of **6a** shows that the hydroxy and SCF_3 groups in α-SCF_3 β-hydroxyesters **6** are in a *cis* orientation (see the Supporting Information). Coordination of the keto and ester carbonyl groups with Mg^{2+} results in a six-membered-ring chelate, which is preferably attacked from the less sterically hindered face opposite to the SCF_3 group.

In conclusion, we have developed a highly enantioselective cinchona alkaloid catalyzed trifluoromethylsulfenylation of β-ketoesters with *N*-trifluoromethylthiophthalimide as electrophilic SCF_3 source. This enantioselective method enables the construction of a quaternary carbon stereocenter that bears a SCF_3 group. In general, the products are obtained in good yields with excellent enantioselectivities. Depending on the employed alkaloid quinine or quinidine, either the (*R*)- or (*S*)-configured product can be obtained. Furthermore, the highly diastereoselective addition of Grignard reagents allows

the formation of the corresponding α-SCF_3 β-hydroxyesters in high yields. The application of the present protocol to further challenging substrates is currently ongoing in our laboratories and will be reported in due course.[14]

Experimental Section

General procedure: In a screw-capped reaction tube, β-ketoester **4a** (0.07 mmol, 1.0 equiv) and quinidine were dissolved in dichloromethane (1.0 mL) and *N*-trifluoromethylthiophthalimide **1** (0.09 mmol, 1.3 equiv) was added at −75 °C. The resulting solution was stirred at −75 °C until the reaction was completed (TLC monitoring). The crude reaction mixture was directly charged on silica gel and purified by column chromatography (*n*-hexane/Et_2O = 90:10) to afford the desired product **5a**.

Received: June 9, 2013
Published online: October 7, 2013

Keywords: cinchona alkaloids · fluorine · indanones · organocatalysis · trifluoromethylsulfenylation

[1] a) *Selective Fluorination in Organic and Bioorganic Chemistry* (Ed.: J. T. Welch), ACS Symposium Series, Washington, **1991**; b) V. A. Soloshonok, *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets*, Wiley, New York, **1999**; c) *Organofluorine Compounds, Chemistry and Applications* (Ed.: T. Hiyama), Springer, New York, **2000**; d) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis Reactivity, Applications*, Wiley-VCH, Weinheim, **2004**; e) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881 – 1886; f) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308 – 319.

[2] For reviews of stereoselective formation of fluorinated compounds, see: a) C. Bobbio, V. Gouverneur, *Org. Biomol. Chem.* **2006**, *4*, 2065 – 2075; b) J.-A. Ma, D. Cahard, *Chem. Rev.* **2008**, *108*, PR1 – PR43; c) D. Cahard, X. Xu, S. Couve-Bonnaire, X. Pannecoucke, *Chem. Soc. Rev.* **2010**, *39*, 558 – 568; d) S. Lectard, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.* **2010**, *352*, 2708 – 2732; e) G. Valero, X. Companyó, R. Rios, *Chem. Eur. J.* **2011**, *17*, 2018 – 2037; f) C. Ni, J. Hu, *Synlett* **2011**, 770 – 782; g) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470 – 477; h) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem.* **2013**, *125*, 8372 – 8423; *Angew. Chem. Int. Ed.* **2013**, *52*, 8214 – 8264.

[3] a) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications* (Eds.: R. Filler, Y. Kobayashi, L. M. Yagupolskii), Elsevier, Amsterdam, **1993**; b) M. Morgenthaler, E. Schweizer, A. Hoffmann-Röder, F. Benini, R. E. Martin, G. Jaeschke, B. Wagner, H. Fischer, S. Bendels, D. Zimmerli, J. Schneider, F. Diederich, M. Kansy, K. Müller, *ChemMedChem* **2007**, *2*, 1100 – 1115; c) *Current Fluoroorganic Chemistry. New Synthetic Directions, Technologies, Materials and Biological Applications* (Eds.: V. A. Soloshonok, K. Mikami, T. Yamazaki, J. T. Welch, J. Honek), ACS Symposium Series 949, Oxford University Press, **2007**; d) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320 – 330; e) K. L. Kirk, *Org. Process Res. Dev.* **2008**, *12*, 305 – 321; f) J.-P. Bégué, D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley-VCH, Hoboken, NJ, **2008**; g) W. K. Hagmann, *J. Med. Chem.* **2008**, *51*, 4359 – 4369; h) *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, Chichester, **2009**.

[4] a) A. Leo, C. Hansch, D. Elkins, *Chem. Rev.* **1971**, *71*, 525 – 616; b) C. Hansch, A. Leo, S. H. Unger, K. H. Kim, D. Nikaitani, E. J. Lien, *J. Med. Chem.* **1973**, *16*, 1207 – 1216; c) F. Leroux, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827 – 856.

[5] a) V. N. Boiko, *Beilstein J. Org. Chem.* **2010**, *6*, 880 – 921; b) A. Tlili, T. Billard, *Angew. Chem.* **2013**, *125*, 6952 – 6954; *Angew. Chem. Int. Ed.* **2013**, *52*, 6818 – 6819; c) H. Liu, X. Jiang, *Chem. Asian J.* **2013**, DOI: 10.1002/asia.201300636.

[6] a) Q.-Y. Chen, J.-X. Duan, *J. Chem. Soc. Chem. Commun.* **1993**, 918 – 919; b) D. J. Adams, J. H. Clark, *J. Org. Chem.* **2000**, *65*, 1456 – 1460; c) D. J. Adams, A. Goddard, J. H. Clark, D. J. Macquarrie, *Chem. Commun.* **2000**, 987 – 988; d) W. Tyrra, D. Naumann, B. Hoge, Y. L. Yagupolskii, *J. Fluorine Chem.* **2003**, *119*, 101 – 107; e) G. Teverovskiy, D. S. Surry, S. L. Buchwald, *Angew. Chem.* **2011**, *123*, 7450 – 7452; *Angew. Chem. Int. Ed.* **2011**, *50*, 7312 – 7314; f) C.-P. Zhang, D. A. Vicic, *J. Am. Chem. Soc.* **2012**, *134*, 183 – 185; g) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang, F.-L. Qing, *Angew. Chem.* **2012**, *124*, 2542 – 2545; *Angew. Chem. Int. Ed.* **2012**, *51*, 2492 – 2495; h) C. Chen, L. Chu, F.-L. Qing, *J. Am. Chem. Soc.* **2012**, *134*, 12454 – 12457; i) C.-P. Zhang, D. A. Vicic, *Chem. Asian J.* **2012**, *7*, 1756 – 1758; j) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan, K.-W. Huang, *Angew. Chem.* **2013**, *125*, 1588 – 1592; *Angew. Chem. Int. Ed.* **2013**, *52*, 1548 – 1552; for the nucleophilic trifluoromethylthiolation of benzyl and allyl bromides with [(bpy)Cu(SCF_3)], see: k) D. Kong, Z. Jiang, S. Xin, Z. Bai, Y. Yuan, Z. Weng, *Tetrahedron* **2013**, *69*, 6046 – 6050; l) J. Tan, G. Zhang, Y. Ou, Y. Yuan, Z. Weng, *Chin. J. Chem.* **2013**, *31*, 921 – 926.

[7] a) W. A. Sheppard, *J. Org. Chem.* **1964**, *29*, 895 – 898; b) K. Bogdanowicz-Szwed, B. Kawalek, M. Lieb, *J. Fluorine Chem.* **1987**, *35*, 317 – 327.

[8] S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. W. Wagner, H. D. Durst, *Synth. Commun.* **2000**, *30*, 2847 – 2854.

[9] a) A. Ferry, T. Billard, B. R. Langlois, E. Bacqué, *J. Org. Chem.* **2008**, *73*, 9362 – 9365; b) A. Ferry, T. Billard, B. R. Langlois, E. Bacqué, *Angew. Chem.* **2009**, *121*, 8703 – 8707; *Angew. Chem. Int. Ed.* **2009**, *48*, 8551 – 8555; c) L. D. Tran, I. Popov, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 18237 – 18240; d) A. Ferry, T. Billard, E. Bacqué, B. R. Langlois, *J. Fluorine Chem.* **2012**, *134*, 160 – 163; e) F. Baert, J. Colomb, T. Billard, *Angew. Chem.* **2012**, *124*, 10528 – 10531; *Angew. Chem. Int. Ed.* **2012**, *51*, 10382 – 10385; f) J. Liu, L. Chu, F.-L. Qing, *Org. Lett.* **2013**, *15*, 894 – 897; g) Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro, N. Shibata, *J. Am. Chem. Soc.* **2013**, *135*, 8782 – 8785.

[10] X. Shao, X. Wang, T. Yang, L. Lu, Q. Shen, *Angew. Chem.* **2013**, *125*, 3541 – 3544; *Angew. Chem. Int. Ed.* **2013**, *52*, 3457 – 3460.

[11] E. Fillion, D. Fishlock, A. Wilsily, J. M. Goll, *J. Org. Chem.* **2005**, *70*, 1316 – 1327.

[12] Recent reviews for the application of organocatalysis in the synthesis of bioactive molecules and natural products: a) R. Marcia de Figueiredo, M. Christmann, *Eur. J. Org. Chem.* **2007**, 2575 – 2600; b) E. Marqués-López, R. P. Herrera, M. Christmann, *Nat. Prod. Rep.* **2010**, *27*, 1138 – 1167.

[13] CCDC 963612 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.

[14] This Communication is published back-to-back with the following study: X. Q. Wang, T. Yang, X. Cheng, Q. Shen, *Angew. Chem.* **2013**, *125*, 13098 – 13102; *Angew. Chem. Int. Ed.* **2013**, *52*, 12860 – 12864.

