ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 2508

Received 31st December 2013,
Accepted 9th January 2014

DOI: 10.1039/c3cc49877h

www.rsc.org/chemcomm

Catalytic enantioselective trifluoromethylthiolation of oxindoles using shelf-stable *N*-(trifluoromethylthio)-phthalimide and a cinchona alkaloid catalyst†

Magnus Rueping,*[a] Xiangqian Liu,[a] Teerawut Bootwicha,[a] Roman Pluta[a] and Carina Merkens[b]

The organocatalytic enantioselective trifluoromethylthiolation of oxindoles employing *N*-(trifluoromethylthio)phthalimide as a stable, easy to handle CF_3S-source has been developed. Optically active products with a quaternary stereogenic center bearing a CF_3S-group are obtained in good yields and with good to excellent enantioselectivities.

The development of stereoselective methods that enable the efficient incorporation of fluorinated moieties into organic molecules has been extensively pursued since compounds bearing a fluoroalkyl group at a quaternary stereocenter are potentially important targets in pharmaceutical and agrochemical research.[1,2] In fact, introducing fluoroalkyl groups into the molecules can dramatically alter their chemical and biological properties. Thus medicinal chemists have utilized the fluorine substitution strategy for modulating the pharmacological properties of drugs or lead compounds, such as solubility, lipophilicity, metabolic stability and bioavailability.[3] The trifluoromethanesulfenyl group (CF_3S-) has received particular attention due to its promising applications in drug design and discovery. In the area of medicinal chemistry, the CF_3S-moiety is an intriguing structural motif due to its remarkable properties, especially high stability and electronegativity. In addition, the CF_3S-group has a high lipophilicity value (π_X = 1.44) resulting in a great improvement of the membrane permeability of drug candidates.[4]

Consequently, the development of efficient methods for the incorporation of the trifluoromethanesulfenyl group into organic compounds has attracted great interest from synthetic organic chemists.[5] Numerous efforts have been devoted to the development of efficient methods for the synthesis of trifluoromethylsulfenylated Csp^2 centers through nucleophilic insertion in the presence of metal catalysts.[6,7] In contrast, reports on the direct electrophilic trifluoromethylthiolation are less common, in particular for the Csp^3-SCF_3 bond formation. In this context, Munavalli and co-workers[8a] have reported the trifluoromethylthiolation of enamines employing *N*-(trifluoromethylthio)phthalimide (**1**) as a moisture and air stable electrophilic SCF_3 reagent (Fig. 1).[8] Billard's trifluoromethanesulfenamide (**2**) has shown to be a versatile electrophilic SCF_3 source for the trifluoromethylthiolation of various substrates.[9] Recently, a new electrophilic trifluoromethylsulfenylated hypervalent iodine reagent (**3**) was introduced by Lu and Shen and successfully applied for the direct transfer of the CF_3S-group.[10] Shibata and co-workers developed a hypervalent iodonium ylide reagent (**4**) for the trifluoromethylthiolation of enamines, indoles, and β-ketoesters.[11] We recently reported a safe method for the synthesis of *N*-(trifluoromethylthio)phthalimide (**1**) and its application in the trifluoromethylthiolation of boronic acids and alkynes.[8b] Regarding the development of asymmetric versions of the trifluoromethylthiolation reaction, only a few examples have been reported.[12]

Fig. 1 Electrophilic CF_3S-sources.

Oxindoles bearing a chiral quaternary stereogenic center at the 3-position are important structural motifs found in numerous pharmaceuticals and biologically active compounds.[13] Among these molecules, optically active 3-fluoro aryl oxindoles exhibit significant pharmaceutical properties. Therefore, the development of an efficient method for the preparation of analogous oxindoles bearing a SCF_3-substituted quaternary stereogenic center attracted our attention, as this might lead to further advances in the pharmacological applications.

We herein present the first enantioselective trifluoromethylthiolation of 3-aryl oxindoles using *N*-(trifluoromethylthio)-phthalimide (**1**) as a stable and easy to handle CF_3S-source in the presence of cinchona alkaloids as organocatalysts (Scheme 1).

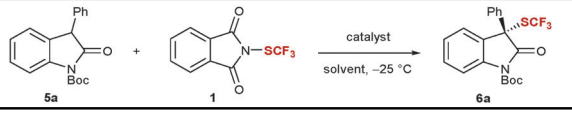
[a] *Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany. E-mail: magnus.rueping@rwth-aachen.de; Fax: +49 (0)241-809-2665*

[b] *Institute of Inorganic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany*

† Electronic supplementary information (ESI) available. CCDC 958955. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc49877h

Scheme 1 Asymmetric trifluoromethylthiolation of 3-aryl oxindoles.

Table 1 Optimization of the reaction conditions[a]



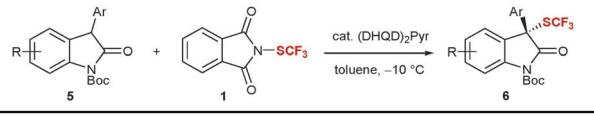
Entry	Catalyst	Solvent	t (°C)	T (h)	Yield[b] (%)	ee[c] (%)
1	Cinchonidine	CH_2Cl_2	−25	48	97	−47
2	Cinchonine	CH_2Cl_2	−25	48	96	50
3	Quinine	CH_2Cl_2	−25	48	69	30
4	Quinidine	CH_2Cl_2	−25	48	96	−29
5	$(DHQD)_2AQN$	CH_2Cl_2	−25	96	45	75
6	$(DHQ)_2AQN$	CH_2Cl_2	−25	96	65	−8
7	$(DHQD)_2PHAL$	CH_2Cl_2	−25	96	10	41
8	$(DHQD)_2Pyr$	CH_2Cl_2	−25	96	44	78
9	$(DHQD)_2Pyr$	$CHCl_3$	−25	96	30	80
10	$(DHQD)_2Pyr$	PhCl	−25	96	49	88
11	$(DHQD)_2Pyr$	$PhCF_3$	−25	96	56	90
12	$(DHQD)_2Pyr$	Toluene	−25	96	60	93
13	$(DHQD)_2Pyr$	*o*-Xylene	−25	96	43	92
14	$(DHQD)_2Pyr$	Et_2O	−25	96	8	86
15	$(DHQD)_2Pyr$	Toluene	0	96	67	90
16	$(DHQD)_2Pyr$	Toluene	RT	96	84	88
17[d]	$(DHQD)_2Pyr$	Toluene	−25	96	67	93
18[e]	$(DHQD)_2Pyr$	Toluene	−25	96	84	93
19[e]	$(DHQD)_2Pyr$	Toluene	−10	48	85	92

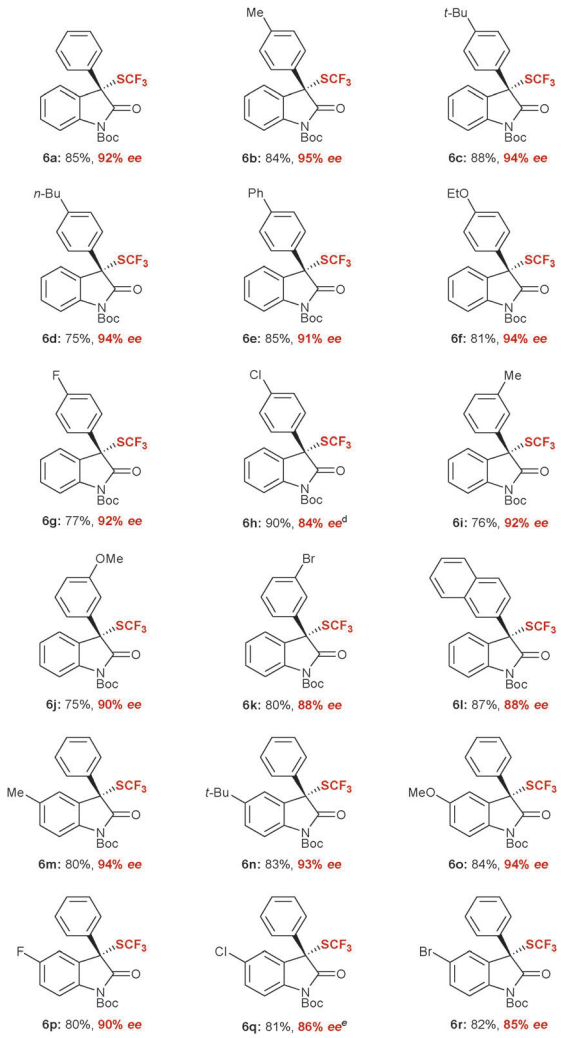
[a] Reaction conditions: **5a** (1.0 equiv.), **1** (1.2 equiv.), catalyst (10 mol%), in 0.07 M solution of solvent at −25 °C for 48–96 h. [b] Yield of the isolated product after column chromatography. [c] Determined by chiral HPLC analysis. [d] 0.1 M solution of toluene. [e] 0.2 M solution of toluene.

With *N*-Boc-protected 3-phenyl oxindole (**5a**) as the model substrate and *N*-(trifluoromethylthio)phthalimide (**1**) as the trifluoromethylsulfenylating agent, we searched for the optimal reaction conditions. Initially, various cinchona alkaloid derivatives were evaluated (Table 1 entries 1–8). In the case of monomeric cinchona alkaloid catalysts the desired product **6a** was obtained in high to excellent yields with moderate enantioselectivity (Table 1, entries 1–4). Next, different commercially available bis-cinchona alkaloids were evaluated. It was found that $(DHQ)_2AQN$ was ineffective for this transformation and gave the product with a very low enantiomeric excess (Table 1, entry 6). In contrast, $(DHQD)_2AQN$ gave the product in 45% yield with good enantioselectivity (Table 1, entry 5). When $(DHQD)_2PHAL$ was applied, longer reaction time was needed and the desired product was isolated in only 10% yield with moderate enantioselectivity (Table 1, entry 7). Finally, $(DHQD)_2Pyr$ showed the best catalytic activity, providing the corresponding product **6a** with 78% ee (Table 1, entry 8). The good enantioselectivity obtained with the $(DHQD)_2Pyr$ catalyst warranted further investigation. Thus, various solvents were evaluated (Table 1, entries 9–14). When the reaction was performed in Et_2O, the enantioselectivity of **6a** was improved but the product was isolated in poor yield (Table 1, entry 14). Higher enantiomeric excesses were obtained when the reactions were performed in aromatic solvents (Table 1, entries 10–13), with toluene giving the best results (60%, 93% ee, Table 1, entry 12). Increasing the reaction temperature gave the product in a higher chemical yield but with lower enantiomeric excess (Table 1, entries 15, 16 *vs.* 12). Interestingly, when the reaction was performed at the same temperature, but at a higher concentration, a beneficial effect on the conversion, with virtually no effect on the ee value was observed (Table 1, entries 17, 18 *vs.* 12). To our delight, performing the reaction at a higher temperature (−10 °C) in a 0.2 M solution of toluene required only 48 h for completion and gave the product in good yield with excellent enantioselectivity (85%, 92% ee; Table 1, entry 19 *vs.* 18).

Having established the optimal reaction conditions, we evaluated the scope of this enantioselective cinchona alkaloid-catalyzed trifluoromethylthiolation with various 3-aryl oxindoles **5** (Table 2).

Table 2 Scope of the enantioselective trifluoromethylthiolation[a–c]





[a] Reaction conditions: **5** (1.0 equiv.), **1** (1.2 equiv.), $(DHQD)_2Pyr$ (10 mol%), in 0.2 M solution of toluene at −10 °C for 48–96 h. [b] Yield of the isolated product after column chromatography. [c] ee values were determined by chiral HPLC analysis. [d] The reaction was performed at RT. [e] The reaction was performed at 0 °C.

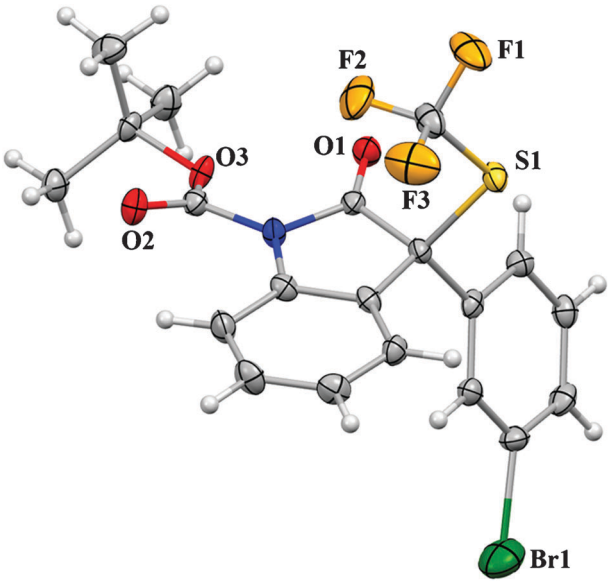


Fig. 2 X-ray crystal structure of product **6k**.

In general, the reactions of 3-aryl oxindoles **5a–l** with different electronic properties and different substitution patterns on the aryl ring at the C_3 proceeded smoothly to provide the corresponding products **6a–l** in good yields and good to excellent enantioselectivities (84–95% ee, Table 2). Moreover, oxindoles **5m–r** bearing various electron-donating and electron-withdrawing substituents at C_5 afforded the desired products **6m–r** in good yields and good to excellent enantiomeric excesses (84–93% ee, Table 2).

The absolute configuration of the newly created stereogenic carbon center in the trifluoromethylsulfenylated product was determined to be (*S*) by X-ray crystal structure analysis of the optically active product **6k** (Fig. 2).[14]

In conclusion, we have developed a novel asymmetric trifluoromethylthiolation of oxindoles catalyzed by cinchona alkaloids. This transformation utilized air and moisture stable *N*-(trifluoromethylthio)phthalimide as the SCF_3 source. A series of optically active oxindoles bearing a SCF_3-substituted quaternary stereogenic center were obtained in good yields and with good to excellent enantioselectivities. The application of the present method to further challenging substrates is currently ongoing in our laboratories and will be reported in due course.

Notes and references

1 (*a*) *Selective Fluorination in Organic and Bioorganic Chemistry*, ed. J. T. Welch, ACS Symposium Series, Washington, D.C., 1991; (*b*) V. A. Soloshonok, *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedical Targets*, John Wiley & Sons Ltd., 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 and F. Diederich, *Science*, 2007, **317**, 1881; (*f*) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308; (*g*) G. K. S. Prakash and F. Wang, *Chimica Oggi-Chemistry Today*, 2013, **30**, 30.

2 For reviews of stereoselective formation of fluorinated compounds, see: (*a*) C. Bobbio and V. Gouverneur, *Org. Biomol. Chem.*, 2006, **4**, 2065; (*b*) J.-A. Ma and D. Cahard, *Chem. Rev.*, 2008, **108**, PR1; (*c*) D. Cahard, X. Xu, S. Couve-Bonnaire and X. Pannecoucke, *Chem. Soc. Rev.*, 2010, **39**, 558; (*d*) S. Lectard, Y. Hamashima and M. Sodeoka, *Adv. Synth. Catal.*, 2010, **352**, 2708; (*e*) G. Valero, X. Companyó and R. Rios, *Chem.–Eur. J.*, 2011, **17**, 2018; (*f*) C. Ni and J. Hu, *Synlett*, 2011, 770; (*g*) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470; (*h*) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214. Our efforts: (*i*) D. Parmar, M. S. Maji and M. Rueping, *Chem.–Eur. J.*, 2014, **20**, 83; (*j*) M. Rueping, T. Bootwicha, S. Kambutong and E. Sugiono, *Chem.–Asian J.*, 2012, **7**, 1195; (*k*) R. Husmann, E. Sugiono, S. Mersmann, G. Raabe, M. Rueping and C. Bolm, *Org. Lett.*, 2011, **13**, 1044; (*l*) M. Rueping, M. Stoeckel, E. Sugiono and T. Theissmann, *Tetrahedron*, 2010, **66**, 6565; (*m*) M. Rueping, T. Theissmann, A. Kuenkel and R. M. Koenigs, *Angew. Chem., Int. Ed.*, 2008, **47**, 6798–6801.

3 (*a*) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*, ed. R. Filler, Y. Kobayashi and 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 and K. Müller, *ChemMedChem*, 2007, **2**, 1100; (*c*) *Current Fluoroorganic Chemistry. New Synthetic Directions, Technologies, Materials and Biological Applications*, ed. V. A. Soloshonok, K. Mikami, T. Yamazaki, J. T. Welch and J. Honek, ACS Symposium Series 949, Oxford University Press, 2007; (*d*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (*e*) K. L. Kirk, *Org. Process Res. Dev.*, 2008, **12**, 305; (*f*) J.-P. Bégué and D. Bonnet-Delpon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley-VCH, Hoboken, NJ, 2008; (*g*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; (*h*) *Fluorine in Medicinal Chemistry and Chemical Biology*, ed. I. Ojima, Wiley-Blackwell, Chichester, 2009.

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

5 (*a*) V. N. Boiko, *Beilstein J. Org. Chem.*, 2010, **6**, 880; (*b*) A. Tlili and T. Billard, *Angew. Chem., Int. Ed.*, 2013, **52**, 6818; (*c*) H. Liu and X. Jiang, *Chem.–Asian J.*, 2013, **8**, 2546.

6 (*a*) Q.-Y. Chen and J.-X. Duan, *J. Chem. Soc., Chem. Commun.*, 1993, 918; (*b*) D. J. Adams and J. H. Clark, *J. Org. Chem.*, 2000, **65**, 1456; (*c*) D. J. Adams, A. Goddard, J. H. Clark and D. J. Macquarrie, *Chem. Commun.*, 2000, 987; (*d*) W. Tyrra, D. Naumann, B. Hoge and Y. L. Yagupolskii, *J. Fluorine Chem.*, 2003, **119**, 101; (*e*) G. Teverovskiy, D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 7312; (*f*) C.-P. Zhang and D. A. Vicic, *J. Am. Chem. Soc.*, 2012, **134**, 183; (*g*) C. Chen, Y. Xie, L. Chu, R.-W. Wang, X. Zhang and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2012, **51**, 2492; (*h*) C.-P. Zhang and D. A. Vicic, *Chem.–Asian J.*, 2012, **7**, 1756; (*i*) L. D. Tran, I. Popov and O. Daugulis, *J. Am. Chem. Soc.*, 2012, **134**, 18237; (*j*) Z. Weng, W. He, C. Chen, R. Lee, D. Tan, Z. Lai, D. Kong, Y. Yuan and K.-W. Huang, *Angew. Chem., Int. Ed.*, 2013, **52**, 1548; (*k*) M. Rueping, N. Tolstoluzhsky and P. Nikolaienko, *Chem.–Eur. J.*, 2013, **19**, 14043. For the nucleophilic trifluoromethylthiolation of benzyl and allyl bromides with (bpy)-Cu(SCF_3), see: (*l*) D. Kong, Z. Jiang, S. Xin, Z. Bai, Y. Yuan and Z. Weng, *Tetrahedron*, 2013, **69**, 6046.

7 For a transition metal-free oxidative trifluoromethylthiolation, see: C. Chen, L. Chu and F.-L. Qing, *J. Am. Chem. Soc.*, 2012, **134**, 12454.

8 (*a*) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. W. Wagner and H. D. Durst, *Synth. Commun.*, 2000, **30**, 2847; (*b*) R. Pluta, P. Nikolaienko and M. Rueping, *Angew. Chem., Int. Ed.*, 2013, DOI: 10.1002/anie.201307484.

9 (*a*) A. Ferry, T. Billard, B. R. Langlois and E. Bacqué, *J. Org. Chem.*, 2008, **73**, 9362; (*b*) A. Ferry, T. Billard, B. R. Langlois and E. Bacqué, *Angew. Chem., Int. Ed.*, 2009, **48**, 8551; (*c*) A. Ferry, T. Billard, E. Bacqué and B. R. Langlois, *J. Fluorine Chem.*, 2012, **134**, 160; (*d*) F. Baert, J. Colomb and T. Billard, *Angew. Chem., Int. Ed.*, 2012, **51**, 10382; (*e*) J. Liu, L. Chu and F.-L. Qing, *Org. Lett.*, 2013, **15**, 894; (*f*) S. Alazet, L. Zimmer and T. Billard, *Angew. Chem., Int. Ed.*, 2013, **52**, 10814; (*g*) Q. Xiao, J. Sheng, Z. Chen and J. Wu, *Chem. Commun.*, 2013, **49**, 8647; (*h*) J. Sheng, S. Li and J. Wu, *Chem. Commun.*, 2014, **50**, 578; (*i*) S. Alazet, K. Ollivier and T. Billard, *Beilstein J. Org. Chem.*, 2013, **9**, 2354.

10 X. Shao, X. Wang, T. Yang, L. Lu and Q. Shen, *Angew. Chem., Int. Ed.*, 2013, **52**, 3457.

11 Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro and N. Shibata, *J. Am. Chem. Soc.*, 2013, **135**, 8782.
12 (*a*) T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei and M. Rueping, *Angew. Chem., Int. Ed.*, 2013, **52**, 12856; (*b*) X. Wang, T. Yang, X. Cheng and Q. Shen, *Angew. Chem., Int. Ed.*, 2013, **52**, 12860; (*c*) Q.-H. Deng, C. Rettenmeier, H. Wadepohl and L. H. Gade, *Chem.–Eur. J.*, 2014, **20**, 93.
13 For selected reviews, see: (*a*) S. Hibino and T. Choshi, *Nat. Prod. Rep.*, 2001, **18**, 66; (*b*) B. S. Jensen, *CNS Drug Rev.*, 2002, **8**, 353; (*c*) H. Lin and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2003, **42**, 36; (*d*) A. B. Dounay and L. E. Overman, *Chem. Rev.*, 2003, **103**, 2945; (*e*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748.
14 CCDC 958955 contains the supplementary crystallographic data for this paper.