ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Open Access Article. Published on 10 February 2017. Downloaded on 1/20/2026 9:41:12 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

Check for updates

Cite this: *Org. Chem. Front.*, 2017, **4**, 1051

(1*S*)-(–)-*N*-Trifluoromethylthio-2,10-camphorsultam and its derivatives: easily available, optically pure reagents for asymmetric trifluoromethylthiolation†

He Zhang, Xuebing Leng, Xiaolong Wan and Qilong Shen*

Received 16th January 2017,
Accepted 9th February 2017

DOI: 10.1039/c7qo00042a

rsc.li/frontiers-organic

A family of easily scalable, shelf-stable, optically pure reagents (1*S*)-(–)-*N*-trifluoromethylthio-2,10-camphorsultam **1a–c** was successfully developed. In particular, compound **1c** was shown to be an efficient reagent that is capable of transferring chirality to other prochiral nucleophiles such as β-ketoesters, oxindoles and benzofuranones with good to excellent enantioselectivities.

Introduction

Over the past two decades, fluorine and its magic "fluorine effect" in the discovery of new drug molecules have been well recognized in the fields of the pharmaceutical and agrochemical industries.[1] Consequently, strategic incorporation of a fluorine atom or a fluoroalkyl group into therapeutic or agrochemical agents has become a routine tool to manipulate the target molecule's physical, chemical and biological properties including conformation, pK_a, intrinsic potency, metabolic pathways, and pharmacokinetic properties. In particular, recently, the trifluoromethylthio group (–SCF_3) has gained intense interest, mainly due to its high lipophilicity (Hansch's hydrophobicity parameter $\pi = 1.44$) that may improve the molecule's trans-membrane permeability.[2] Not surprisingly, new reagents and new methods that are able to introduce the trifluoromethylthio group effectively are in high demand.[3] As a matter of fact, in the last five years, a number of electrophilic trifluoromethylthiolating reagents,[4] as well many transition metal-catalyzed trifluoromethylthiolation reactions[5,6] emerged, that now allow for the construction of the C(sp^2)–SCF_3, C(sp^3)–SCF_3 or C(sp)–SCF_3 bonds efficiently.

Despite these impressive advances in developing the methods for the formation of C–SCF_3 bonds, very few methods that could generate optically active compounds with a stereogenic carbon center bearing a trifluoromethylthio group have been reported.[7] In 2013, Shen's and Rueping's groups simultaneously reported the first highly enantioselective cinchona alkaloid-catalyzed asymmetric trifluoromethylthiolation of cyclic β-ketoesters with trifluoromethanesulfenate[7a] or *N*-trifluoromethylphthalimide[7b] as the electrophilic SCF_3 reagent, respectively. Later on, the asymmetric reactions were successfully extended to trifluoromethylthiolation of oxindoles with excellent enantioselectivity.[7e,f] Likewise, Liu and Tan discovered that the organocatalytic asymmetric trifluoromethylthiolation of oxindoles can be achieved when an *in situ* formed electrophilic trifluoromethylthio species generated from trichloroisocyanuric acid (TCCA) and $AgSCF_3$.[7d] Very recently, Zhao's group reported the first chiral sulphide-catalyzed asymmetric trifluoromethylthiolating lactonization of alkenes with *N*-trifluoromethylthiodibenzenesulfonimide.[7g] On the other hand, Gade and co-workers reported the first copper-catalyzed asymmetric trifluoromethylthiolation of cyclic β-ketoesters using the trifluoromethanesulfenate reagent.[7c] Nevertheless, new and highly enantioselective methods for the construction of a stereogenic carbon center bearing a trifluoromethylthio group are still urgently needed.

Chirality transfer from a chiral reagent to a prochiral substrate to give the product in high enantiomeric excess represents a general and efficient method for the production of optically active compounds.[8] In this respect, the design and exploration of optically pure electrophilic trifluoromethylthiolating reagents for asymmetric trifluoromethylthiolation offers a simple and straightforward strategy for the formation of a stereogenic carbon center bearing a trifluoromethylthio group, which would complement the previously reported asymmetric trifluoromethylthiolation methods. Herein, we report the design and synthesis of (1*S*)-(–)-*N*-trifluoromethylthio-2,10-camphorsultam[9] and its derivatives, a family of optically pure reagents that can efficiently transfer their chirality to prochiral

Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, 345 Lingling Lu, Shanghai, 200032, China. E-mail: shen@mail.sioc.ac.cn

† Electronic supplementary information (ESI) available: Synthesis, analytical data, computational details, NMR data of compounds **1a–f**, **3a–n**, **4a–p**, **5a–h** and X-ray crystallography data of **1a–c**, **4i** and **5c**. CCDC 1527557–1527562. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7qo00042a

Open Access Article. Published on 10 February 2017. Downloaded on 1/20/2026 9:41:12 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

substrates such as β-ketoesters, oxindoles and benzofuran-2(3*H*)-ones with good to excellent enantioselectivities.

Results and discussion

Preparation of (1*S*)-(−)-*N*-trifluoromethylthio-2,10-camphorsultam and *N*-trifluoromethylthio-oxazolidin-2-one and their derivatives

(1*S*)-(−)-*N*-Trifluoromethylthio-2,10-camphorsultam **1a** could be easily synthesized *via* a two-step procedure, as shown in Fig. 1. Reaction of commercially available (1*S*)-(−)-2,10-camphorsultam with *tert*-butyl hypochlorite in methanol at room temperature for 45 min yielded (1*S*)-(−)-*N*-chloro-2,10-camphorsultam in quantitative yield. Without further purification, the *in situ* generated (1*S*)-(−)-*N*-chloro-2,10-camphorsultam was then further treated with $AgSCF_3$ in CH_3CN at room temperature for 1 h to give (1*S*)-(−)-*N*-trifluoromethylthio-2,10-camphorsultam **1a** in 68% yield. The reaction can be easily scaled up to a quantity of 4.7 g without erosion of the yield. Likewise, two analogous compounds **1b** and **1c** were prepared in 73% and 79% yield, respectively. In addition, compounds **1d–f** derived from oxazolidin-2-one were synthesized by the same method in 71–82% yields, as shown in Fig. 1. Compounds **1a–f** were fully characterized by ^1H, ^{13}C, and ^{19}F NMR spectroscopy. The structures of compounds **1a–c** were further unambiguously confirmed by X-ray analysis of their single crystals (Fig. 2).

Asymmetric trifluoromethylthiolation of β-ketoesters with reagent 1c

To probe whether compounds **1a–f** can efficiently transfer their chirality to other substrates, we first studied the reactions of β-ketoesters with compounds **1a–f**. The reaction of β-ketoester **2a** derived indanone with compound **1a** was chosen initially as a model reaction to optimize the reaction parameters. A quick screening of the base disclosed that the

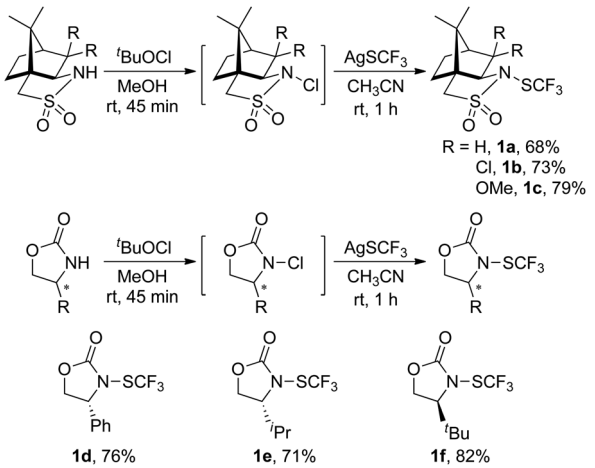


Fig. 1 Preparation of (1*S*)-(−)-*N*-trifluoromethylthio-2,10-camphorsultam and *N*-trifluoromethylthio-oxazolidin-2-one and their derivatives.

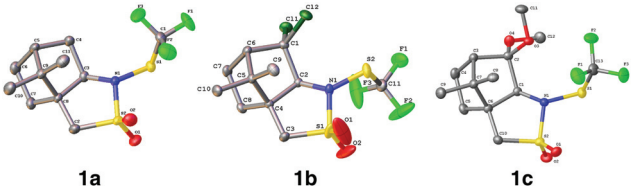
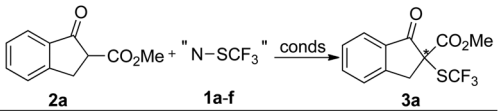


Fig. 2 ORTEP diagrams of compounds **1a–c**.

desired trifluoromethylthio-β-ketoester **3a** was generated in higher yield when the reaction was conducted in THF using K_2CO_3 as the base than those using Cs_2CO_3, Li_2CO_3, K_3PO_4 or DMAP as the base (Scheme 1, entries 1–5). Next, the effect of the solvents was studied. Reactions in THF occurred much faster than those in CH_2Cl_2, Et_2O or toluene (Scheme 1, entries 6–9). For example, reaction of β-ketoester **2a** with compound **1a** occurred in 78% yield with 77% ee after 12 h at −20 °C while reactions in CH_2Cl_2, Et_2O or toluene occurred in less than 10% conversion under otherwise identical conditions. Under the current reaction conditions (K_2CO_3 as the base, THF as the solvent, −20 °C, 12 h), we compared the reactivity of compounds **1a–f**. Interestingly, reactions of compounds **1a–c** derived from (1*S*)-(−)-camphorsultam were much faster and with higher enantioselectivity than reactions of compounds **1d–f** derived from oxazolidin-2-one (Scheme 1, entries 7, 10–14). In addition, compound **1c** with two methoxy groups reacted faster and with higher enantioselectivity than its analogs **1a–b** (Scheme 1, entries 7, 10 and 11). With these promising results in mind, we further optimized the reaction



entry	reagent	base	solvent	temp (°C)	time (h)	yield (%)	ee (%)
1	**1a**	K_2CO_3	THF	rt	12	82	34
2	**1a**	Cs_2CO_3	THF	rt	12	31	21
3	**1a**	Li_2CO_3	THF	rt	12	-	-
4	**1a**	K_3PO_4	THF	rt	12	73	26
5	**1a**	DMAP	THF	rt	12	2	-
6	**1a**	K_2CO_3	CH_2Cl_2	-20	12	6	-
7	**1a**	K_2CO_3	THF	-20	12	78	77
8	**1a**	K_2CO_3	Et_2O	-20	12	4	-
9	**1a**	K_2CO_3	toluene	-20	12	7	-
10	**1b**	K_2CO_3	THF	-20	12	63	57
11	**1c**	K_2CO_3	THF	-20	12	83	83
12	**1d**	K_2CO_3	THF	-20	52	62	17
13	**1e**	K_2CO_3	THF	-20	52	34	43
14	**1f**	K_2CO_3	THF	-20	52	40	36
15	**1c**	K_2CO_3	THF	-40	12	61	89
16	**1c**	K_2CO_3	THF	-40	24	53	89[d]
17	**1c**	K_2CO_3	THF	-40	48	73	88[d]
18	**1c**	K_2CO_3	THF	-40	72	89	88[d]

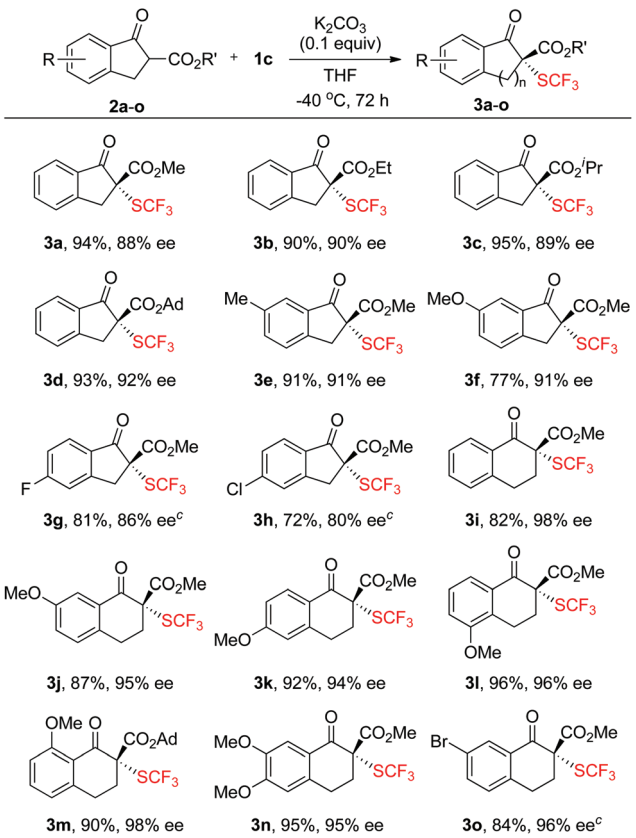
Scheme 1 Optimization of the conditions for the reactions of β-ketoester **2a** with compounds **1a–f**.[a,b,c] [a]Reaction conditions: β-ketoester **2a** (0.050 mmol), reagents **1a–f** (0.055 mmol), base (1.1 mmol) in 0.5 mL of solvent; [b]yields were determined by ^{19}F NMR spectroscopy in the presence of trifluoromethylbenzene as the internal standard; [c]the ee values were determined by HPLC analysis on a chiral stationary phase. [d] 0.1 equivalent of K_2CO_3 was used.

Open Access Article. Published on 10 February 2017. Downloaded on 1/20/2026 9:41:12 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

conditions using compound **1c** as the electrophilic trifluoromethylthiolating reagent. It was found that reactions using 0.1 equivalent of K_2CO_3 as the base worked equally efficient, while reactions conducted at −40 °C occurred slowly but with higher enantioselectivity (Scheme 1, entry 16). Finally, full conversion of the substrate was achieved by elongating the reaction time to 72 h (Scheme 1, entry 18).

Scope of the asymmetric trifluoromethylthiolation of β-ketoesters with reagent 1c

With the optimum reaction conditions in hand, the stage was set to explore the scope and the limitation of the asymmetric trifluoromethylthiolation reactions. A variety of β-ketoesters **2a–o** derived from indanone or tetralone were subjected to the optimized conditions and the results are summarized in Scheme 2. In general, reactions of six-membered ring β-ketoesters occurred with higher enantioselectivities than those of five-membered ring β-ketoesters. Reactions of six-membered ring β-ketoesters typically generated the desired trifluoromethylthiolated compounds in 94–98% ee while reactions of five-membered ring β-ketoesters gave the desired products in 79–92% ee. In addition, reactions of less nucleophilic β-ketoesters with an electron-withdrawing group such as fluoride, chloride, or bromide occurred much slower than those with electron-donating groups. For examples, reactions of β-ketoesters **2g–h** and **2o** required 32 h at −25 °C to convert completely to the desired products (Scheme 2, **3g–h** and **3o**). The effects of the steric hindrance of the ester group of β-ketoesters on the enantioselectivity of the reaction were not significant since the enantioselectivities increased from 88% ee to 92% ee when the ester group of β-ketoester was changed from the methyl group to the adamantyl group (Scheme 2, **3a–d**). Thus, methyl esters of the six-membered ring β-ketoesters reacted with reagent **1c** to form the corresponding trifluoromethylthiolated products in 94–98% ee (Scheme 2, **3i–o**). As a comparison, organo-catalytic or transition-metal catalyzed asymmetric trifluoromethylthiolation of the six-membered ring β-ketoesters typically required the use of steric-bulky *tert*-butyl or adamantyl esters to achieve excellent enantioselectivity.[7] The absolute configuration of compound **3n** was established to be *R* as determined by analysis of the X-ray diffraction data of its single crystal (Fig. 3). The configurations of the rest of the β-ketoesters were assigned based on the same mechanism assumption.



Scheme 2 Scope of the reactions of β-ketoesters **2a–n** with compound **1c**. [a,b] [a]Reaction conditions: β-ketoester **2a** (0.50 mmol), reagent **1c** (0.55 mmol), K_2CO_3 (0.050 mmol) in 2.5 mL of THF at −40 °C for 72 h; [b]isolated yields; the ee values were determined by HPLC analysis on a chiral stationary phase; [c] reactions were conducted at −25 °C for 32 h.

Scope of the asymmetric trifluoromethylthiolation of oxindoles with reagent 1c or 1b

Having established that compound **1c** is an effective reagent for chirality transfer, we then tried to expand the scope of reagent **1c** for asymmetric trifluoromethylthiolation reaction to other carbon-based nucleophiles. Oxindole represents one of the privileged structural units in many biologically active natural products and the development of highly enantioselective methods for trifluoromethylthiolation of oxindoles would be of great interest to medicinal chemists. As a matter of fact, three different organo-catalytic methods for asymmetric trifluoromethylthiolation of oxindoles have been reported recently.[7d–f] Interestingly, when the reaction of compound **1c** and *N*-methyl oxindole was conducted in THF at −40 °C using 0.1 equivalent of K_2CO_3 as the base, moderate enantioselectivity of the desired product was observed. Instead, switching the base from K_2CO_3 to Cs_2CO_3 and the solvent from THF to Et_2O led to a significant improvement of the enantioselectivity. As summarized in Scheme 3, a variety of 3-aryloxindoles reacted with compound **1c** to give 3-trifluoromethylthio-3-aryloxindoles in excellent yields and with excellent enantioselectivities except for one case in which a cyanomethyl substituent was in the *para*-position of the 3-aryl group (Scheme 3, **4j**). For this particular substrate, using compound

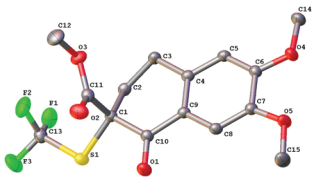
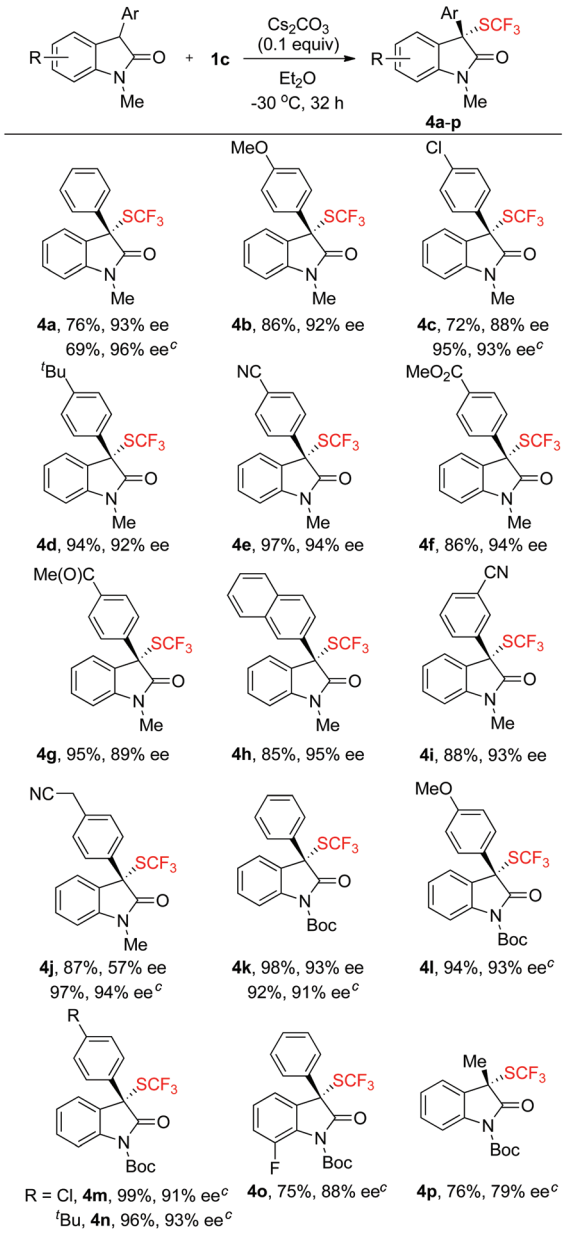


Fig. 3 ORTEP diagram of compound **3n**.

Open Access Article. Published on 10 February 2017. Downloaded on 1/20/2026 9:41:12 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.



Scheme 3 Scope of the reactions of oxindoles with compound **1c** or **1b**. [a,b] [a]Reaction conditions: oxindole (0.50 mmol), reagent **1c** (0.55 mmol), Cs_2CO_3 (0.050 mmol) in 2.5 mL of Et_2O at −30 °C for 32 h; [b]isolated yields; the ee values were determined by HPLC analysis on a chiral stationary phase; [c] reactions were conducted with compound **1b**.

1b as the chiral electrophilic trifluoromethylthiolating reagent greatly improved the enantioselectivity from 57% ee to 94% ee (Scheme 3, **4j**). A few other examples also support that reactions of oxindoles with compound **1b** occurred with higher enantioselectivities than those with compound **1c** (Scheme 3, **4a**, **4c** and **4j**). Because of the mild reaction conditions, various common functional groups such as the fluoride, chloride, bromide, cyano or ester group were tolerant. Nevertheless, reaction of 3-alkylated oxindoles with compound **1b** occurred with moderate enantioselectivity (Scheme 3, **4p**).

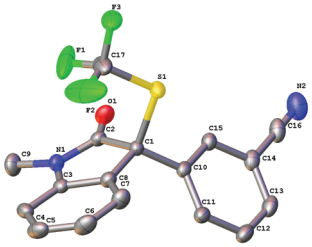
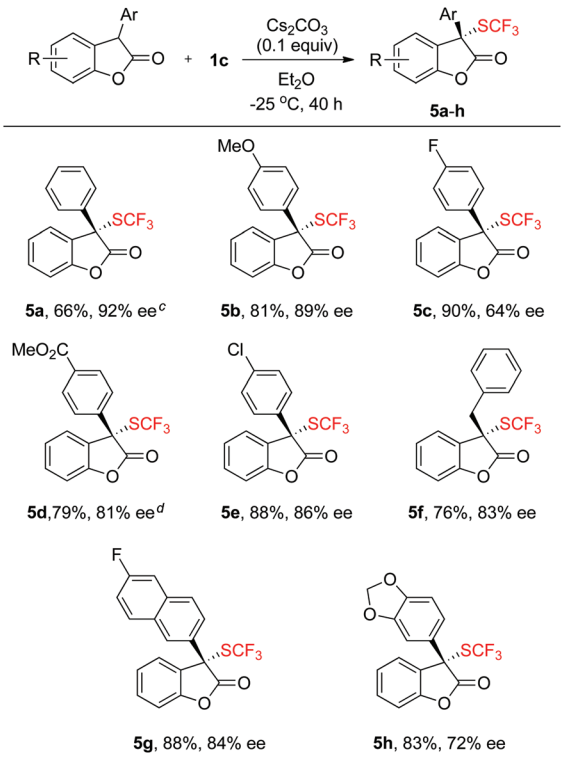


Fig. 4 ORTEP diagram of compound **4i**.

The absolute configuration of the optically active compound **4i** was established to be *S* as determined by analysis of the X-ray diffraction data of its single crystal (Fig. 4). The configurations of other oxindole derivatives were assigned based on the assumption that the reaction proceeded *via* a similar mechanistic pathway.

Scope of the asymmetric trifluoromethylthiolation of benzofuran-2(3*H*)-ones with reagent 1c

To further expand the scope of the asymmetric trifluoromethylthiolation of compound **1c**, we studied the reactions of 2-aryl or 2-alkyl benzofuran-2(3*H*)-ones with compound **1c**, as summarized in Scheme 4. In general, good to excel-



Scheme 4 Scope of the reactions of benzofuran-2(3*H*)-ones with compound **1c**. [a,b] [a]Reaction conditions: benzofuran-2(3*H*)-ones (0.5 mmol), reagent **1c** (0.55 mmol), Cs_2CO_3 (0.05 mmol) in Et_2O (2.5 mL) at −25 °C for 40 h; [b]isolated yields; the ee values were determined by HPLC analysis on a chiral stationary phase; [c]reactions were conducted at −35 °C for 40 h; [d] reactions were conducted at 10 °C for 32 h.

This journal is © the Partner Organisations 2017

Open Access Article. Published on 10 February 2017. Downloaded on 1/20/2026 9:41:12 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

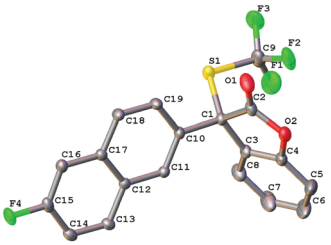


Fig. 5 ORTEP diagram of compound **5g**.

lent enantioselectivities (64–92% ee) were achieved for the reactions of 2-aryl or 2-alkyl benzofuran-2(3*H*)-ones with compound **1c** when the reactions were conducted at −25 °C for 40 h using Cs_2CO_3 as the base. Reaction of methyl 4-(2-oxo-2,3-dihydrobenzofuran-3-yl)benzoate with compound **1c** was slow at −25 °C but occurred to full conversion after 32 h at 10 °C to give the corresponding product in 81% ee (Scheme 4, **5d**). Reaction of alkyl substituted oxindoles occurred also smoothly to give the desired product in 76% yield and 83% ee (Scheme 4, **5f**). Likewise, the absolute configuration of compound **5g** was established to be *S* as determined by analysis of the X-ray diffraction data of its single crystal (Fig. 5). The configurations of the rest of the lactones were assigned based on the same mechanism assumption.

Experimental

General procedure for the preparation of optically active electrophilic trifluoromethylthiolating reagent 1a

To a solution of (1*S*)-(−)-2,10-camphorsultam (2.15 g, 10.0 mmol) in methanol (15.0 mL) and in a 50 mL round-bottom flask covered with aluminum foil was added *tert*-butyl-hypochlorite (2.71 g, 25.0 mmol) under an argon atmosphere. The solution was then stirred at room temperature for 45 min. The solution was evaporated under reduced pressure to give (1*S*)-(−)-*N*-chloro-2,10-camphorsultam quantitatively, which was used directly without further purification.[10]

To an oven dried 500 mL Schlenk flask equipped with a stir bar was added dry (1*S*)-(−)-*N*-chloro-2,10-camphorsultam (2.50 g, 10.0 mmol). The flask was fitted with a glass stopper and evacuated and refilled with argon three times. Dry MeCN (30.0 mL) was injected into the flask, then $AgSCF_3$ (2.49 g, 12.0 mmol) was added. The mixture was stirred vigorously at room temperature for 1 h. The CH_3CN was then evaporated under reduced pressure. And the residue was extracted with CH_2Cl_2 (3 × 30.0 mL). The solution was combined and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by recrystallization from a solution of THF and petroleum ether to give (1*S*)-(−)-*N*-trifluoromethylthio-2,10-camphorsultam **1a** as a white solid (2.14 g, 68% yield).

General procedure for asymmetric trifluoromethylthiolation of β-ketoesters

β-Ketoester **2a** (95.1 mg, 0.500 mmol, 1.0 equiv.), potassium carbonate (7.90 mg, 0.0500 mmol, 0.1 equiv.) and reagent **1c** (206 mg, 0.550 mmol, 1.1 equiv.) were added into a flame-dried Schlenk tube. The tube was put into liquid nitrogen, and dry tetrahydrofuran (2.5 mL) was added under an argon atmosphere. The resulting solution was stirred at −40 °C for 72 h (or −25 °C for 32 h). After the reaction was complete as monitored by ^{19}F NMR spectroscopy, the reaction was quenched by addition of HCl (2.0 M). The mixture was extracted with Et_2O (3 × 10.0 mL). The organic phase was separated and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum. The residue was purified by flash chromatography to give the trifluoromethylthiolated product **3a** (*R*)-methyl-1-oxo-2-((trifluoromethyl)thio)-2,3-dihydro-1*H*-indene-2-carboxylate **3a** as a white solid (136 mg, 94% yield). HPLC: (IE-3 (0.46 × 25 cm, 3 μm), hexane/^{i}PrOH = 97/3, 0.7 mL min^{-1}, 214 nm), t_R (major) = 12.13 min, t_S (minor) = 12.93 min (88% ee); $[\alpha]_D^{25}$ = −99.2 (*c* = 0.110, $CHCl_3$, 88% ee).

General procedure for asymmetric trifluoromethylthiolation of oxindoles with reagent 1c

Oxindole (112 mg, 0.500 mmol, 1.0 equiv.), cesium carbonate (16.3 mg, 0.0500 mmol, 0.1 equiv.) and compound **1c** (206 mg, 0.550 mmol, 1.1 equiv.) were added into a flame-dried Schlenk tube. The tube was put into liquid nitrogen. Dry ethyl ether (2.5 mL) was added under an argon atmosphere. The resulting solution was stirred at −30 °C for 32 h. After the reaction was complete as monitored by ^{19}F NMR spectroscopy, the reaction was quenched with HCl (2.0 M). The mixture was extracted with Et_2O (3 × 10.0 mL). The combined organic phase was separated and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum. The residue was purified by flash chromatography to give (*S*)-1-methyl-3-phenyl-3-((trifluoromethyl)thio)indolin-2-one **4a** as a white solid (122 mg, 76% yield). HPLC: (AD-H (0.46 × 25 cm, 5 μm), hexane/^{i}PrOH = 95/5, 0.7 mL min^{-1}, 214 nm), t_S (major) = 9.83 min, t_R (minor) = 9.04 min (93% ee); $[\alpha]_D^{25}$ = +102.4 (*c* = 0.140, $CHCl_3$, 93% ee).

General procedure for asymmetric trifluoromethylthiolation of benzofuranones with compound 1c

Benzofuranone (105 mg, 0.500 mmol, 1.0 equiv.), cesium carbonate (16.3 mg, 0.0500 mmol, 0.1 equiv.) and compound **1c** (206 mg, 0.550 mmol, 1.1 equiv.) were added into a flame-dried Schlenk tube. The tube was put into liquid nitrogen. Dry ethyl ether (2.5 mL) was added under an argon atmosphere. The resulting solution was stirred at −25 °C for 40 h. After the reaction was complete as monitored by ^{19}F NMR spectroscopy, the reaction was quenched with HCl (2.0 M). The mixture was extracted using Et_2O (3 × 10.0 mL). The organic phase was separated and dried over anhydrous Na_2SO_4. After filtration, the solvent was removed under vacuum. The residue was purified by flash chromatography to give (*S*)-3-phenyl-3-((trifluoromethyl)thio)benzofuran-2(3*H*)-one **5a** as a colorless oil

Open Access Article. Published on 10 February 2017. Downloaded on 1/20/2026 9:41:12 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

(102 mg, 66% yield). HPLC: (IE-3 (0.46 × 25 cm, 3 μm), hexane/^{i}PrOH = 98/2, 0.7 mL min^{-1}, 214 nm), t_S (major) = 8.25 min, t_R (minor) = 7.93 min (92% ee); $[\alpha]_D^{25}$ = +92.9 (*c* = 0.050, $CHCl_3$, 92% ee).

Conclusions

In summary, a family of easily scalable, shelf-stable, optically pure reagents (1*S*)-(−)-*N*-trifluoromethylthio-2,10-camphorsultam **1a–c** was successfully developed. Among them, compound **1c** was shown to be an efficient reagent that is capable of transferring its chirality to other prochiral nucleophiles, as demonstrated by its reactions with β-ketoesters, oxindoles and benzofuranones with good to excellent enantioselectivities. The studies for further applications of reagent **1c** toward the construction of a stereogenic tertiary carbon center bearing a trifluoromethylthio group are undergoing currently in our laboratory.

Acknowledgements

The authors gratefully acknowledge the financial support from the National Natural Science Foundation of China (21625206, 21632009, 21372247, 21572258, and 21421002) and the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20000000).

Notes and references

1 (*a*) R. Filler, *Biomedical Aspests of Fluorine Chemistry*, Kodansha, Tokyo, 1982; (*b*) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (*c*) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359; (*d*) N. A. Meanwell, *J. Med. Chem.*, 2011, **54**, 2529; (*e*) J. Wang, M. Sánchez-Roselló, J. Aceña, C. Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432.

2 (*a*) A. Leo, C. Hansch and D. Elkins, *Chem. Rev.*, 1971, **71**, 525; (*b*) C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165; (*c*) G. Landelle, A. Panossian and F. R. Leroux, *Curr. Top. Med. Chem.*, 2014, **14**, 941.

3 (*a*) F. Leroux, P. Jeschke and M. Schlosser, *Chem. Rev.*, 2005, **105**, 827; (*b*) B. Manteau, S. Pazenok, J.-P. Vors and F. R. Leroux, *J. Fluorine Chem.*, 2010, **131**, 140; (*c*) V. N. Boiko, *Beilstein J. Org. Chem.*, 2010, **6**, 880; (*d*) G. Landelle, A. Panossian, S. Pazenok, J.-P. Vors and F. R. Leroux, *Beilstein J. Org. Chem.*, 2013, **9**, 2476; (*e*) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem., Int. Ed.*, 2013, **52**, 8214; (*f*) X.-X. Shao, C.-F. Xu, L. Lu and Q. Shen, *Acc. Chem. Res.*, 2015, **48**, 1227; (*g*) X.-H. Xu, K. Matsuzaki and N. Shibata, *Chem. Rev.*, 2015, **115**, 731; (*h*) C.-F. Ni, M.-Y. Hu and J.-B. Hu, *Chem. Rev.*, 2015, **115**, 765.

4 Selected examples for transition metal-catalyzed or -mediated trifluoromethylthiolation methods: (*a*) G. Teverovskiy, D. S. Surry and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2011, **50**, 7312; (*b*) C. P. Zhang and D. A. Vicic, *J. Am. Chem. Soc.*, 2012, **134**, 183; (*c*) C. Chen, Y. Xie, L.-L. Chu, R.-W. Wang, X.-G. Zhang and F.-L. Qing, *Angew. Chem., Int. Ed.*, 2012, **51**, 2492; (*d*) Z. Weng, W. He, C. Chen, R. Lee, D. Dan, Z. Lai, D. Kong, Y. Yuan and K.-W. Huang, *Angew. Chem., Int. Ed.*, 2013, **52**, 1548; (*e*) G. Danoun, B. Bayarmagnai, M. F. Grünberg and L. J. Gooßen, *Chem. Sci.*, 2014, **5**, 1312; (*f*) R. Pluta, P. Nikolaienko and M. Rueping, *Angew. Chem., Int. Ed.*, 2014, **53**, 150; (*g*) K. Kang, C.-F. Xu and Q. Shen, *Org. Chem. Front.*, 2014, **1**, 294; (*h*) W.-Y. Yin, Z.-F. Wang and Y. Huang, *Adv. Synth. Catal.*, 2014, **356**, 2998; (*i*) J. Sheng, S.-Y. Li and J. Wu, *Chem. Commun.*, 2014, **50**, 578; (*j*) H.-Y. Xiong, T. Besset, D. Cahard and X. Pannecoucke, *J. Org. Chem.*, 2015, **80**, 4204; (*k*) G. Yin, I. Kalvet, U. Englert and F. Schoenebeck, *J. Am. Chem. Soc.*, 2015, **137**, 4164; (*l*) G. Yin, I. Kalvet and F. Schoenebeck, *Angew. Chem., Int. Ed.*, 2015, **54**, 6809.

5 Reviews for electrophilic trifluoromethylthiolating reagents: (*a*) F. Toulgoat, S. Alazet and T. Billard, *Eur. J. Org. Chem.*, 2014, 2415; (*b*) H. Chachignon and D. Cahard, *Chin. J. Org. Chem.*, 2016, **34**, 445; (*c*) S. Barata-Vallejo, S. Bonesi and A. Postigo, *Org. Biomol. Chem.*, 2016, **14**, 7150.

6 Selected examples for trifluoromethylthiolation with electrophilic trifluoromethylthiolating reagents: (*a*) A. Ferry, T. Billard, B. R. Langlois and E. Bacqué, *J. Org. Chem.*, 2008, **73**, 9362; (*b*) S. Alazet, L. Zimmer and T. Billard, *J. Fluorine Chem.*, 2015, **171**, 78; (*c*) Y.-D. Yang, A. Azuma, E. Tokunaga, M. Yamasaki, M. Shiro and N. Shibata, *J. Am. Chem. Soc.*, 2013, **135**, 8782; (*d*) X.-X. Shao, X.-Q. Wang, T. Yang, L. Lu and Q. Shen, *Angew. Chem., Int. Ed.*, 2013, **52**, 3457; (*e*) E. V. Vinogradova, P. Müller and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2014, **53**, 3125; (*f*) S. Munavalli, D. K. Rohrbaugh, D. I. Rossman, F. J. Berg, G. W. Wagner and H. D. Durst, *Synth. Commun.*, 2000, **30**, 2847; (*g*) C. Xu, B. Ma and Q. Shen, *Angew. Chem., Int. Ed.*, 2014, **53**, 9316; (*h*) P.-P. Zhang, M. Li, X.-S. Xue, C.-F. Xu, Q.-C. Zhao, Y.-F. Liu, H.-Y. Wang, Y.-L. Guo, L. Lu and Q. Shen, *J. Org. Chem.*, 2016, **81**, 7486.

7 (*a*) T. Bootwicha, X. Liu, R. Pluta, I. Atodiresei and M. Rueping, *Angew. Chem., Int. Ed.*, 2013, **52**, 12856; (*b*) X.-Q. Wang, T. Yang, X.-L. 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; (*d*) X.-L. Zhu, J.-H. Xu, D.-J. Cheng, L.-J. Zhao, X.-Y. Liu and B. Tan, *Org. Lett.*, 2014, **16**, 2192; (*e*) M. Rueping, X. Liu, T. Bootwicha, R. Pluta and C. Merkens, *Chem. Commun.*, 2014, **50**, 2508; (*f*) T. Yang, Q. Shen and L. Lu, *Chin. J. Chem.*, 2014, **32**, 678; (*g*) X. Liu, R. An, X.-L. Zhang, J. Luo and X. D. Zhao, *Angew. Chem., Int. Ed.*, 2016, **55**, 5846.

8 (*a*) I. Farnadez and N. Khiar, *Chem. Rev.*, 2003, **103**, 3651; (*b*) J. M. Brunel, *Chem. Rev.*, 2007, **107**, PR1.

 This journal is © the Partner Organisations 2017

Open Access Article. Published on 10 February 2017. Downloaded on 1/20/2026 9:41:12 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

9 Review about camphorsultam-based optically pure reagents: (*a*) M. M. Heravi and V. Zadsirjan, *Tetrahedron: Asymmetry*, 2014, **25**, 1061. Reports on camphorsultam-based optically pure fluorinating reagents: (*b*) E. Differding, G. W. Ruegg and R. W. Lang, *Tetrahedron Lett.*, 1991, **32**, 1779; (*c*) F. A. Davis, P. Zhou, C. K. Murphy, G. Sundarababu, H. Qi, W. Han, R. M. Przeslawski, B.-C. Chen and P. J. Carroll, *J. Org. Chem.*, 1998, **63**, 2273; (*d*) Y. Takeuchi, Z. Liu, A. Satoh, T. Shiragami and N. Shibata, *Chem. Pharm. Bull.*, 1999, **47**, 1730; (*e*) Z.-P. Liu, N. Shibata and Y. Takeuchi, *J. Org. Chem.*, 2000, **65**, 7583.

10 L. Duhamel, G. Ple and P. Angibaud, *Synth. Commun.*, 1993, **23**, 2423.