Short communication

# Synthesis of novel C2-symmetric chiral crown ethers and their application to enantioselective trifluoromethylation of aldehydes and ketones

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ABSTRACT

Synthesis of novel C2-symmetric chiral crown ethers and their application to enantioselective trifluoromethylation of aldehydes and ketones are discussed. The use of a series of C2-symmetric chiral crown ethers **2** or **3** derived from commercially available (*R*)-1,1′-bi-2-naphthol for the enantioselective trifluoromethylation of 2-naphthyl aldehyde **1a** with (trifluoromethyl)trimethylsilane in the presence of a base was attempted. Iodo-substituted crown ether **2b** was found to be the most effective in the model reaction. Moderate enantioselectivities were observed for the trifluoromethylation of both aryl or alkyl aldehydes and alkyl aryl ketones in 21–44% ees. Although the ees are still improvable, this is the first example of a chiral crown ether-catalyzed enantioselective trifluoromethylation reaction.

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## 1. Introduction

Trifluoromethyl-containing organic compounds have attracted much attention because of their utility in the field of pharmaceuticals, agrochemicals and material sciences [1]. Among a variety of approaches, nucleophilic trifluoromethylation of carbonyl compounds using the Ruppert–Prakash reagent, (trifluoromethyl)trimethylsilane, $Me_3SiCF_3$, is certainly the most basic and important strategy for the preparation of medicinally important trifluoromethylated alcohols [2], and stereoselective variants have been extensively investigated in recent years in the presence of chiral catalysts, including chiral ammonium salts, triaminosulfonium salts and cinchona alkaloids; however, enantioselectivities are low to moderate [3]. Recently, we disclosed the highly enantioselective trifluoromethylation of alkyl aryl ketones with $Me_3SiCF_3$ catalyzed by a combination of ammonium bromides derived from cinchona alkaloids and tetramethylammonium fluoride [4]. However, this catalytic system was not effective for the enantioselective trifluoromethylation of aldehydes, and clearly more efficient catalysts are required to attain sufficient reactivity and selectivity. As mentioned above, most of the elaborated chiral catalysis for the reaction rely on the use of cinchona alkaloid derivatives, studies of which have revealed the limitation of this approach. To address

this issue, we disclose herein the chiral crown ether-catalyzed enantioselective trifluoromethylation of carbonyl compounds for the first time (Scheme 1).

## 2. Results and discussion

Chiral crown ethers are well known as efficient catalysts for a variety of asymmetric reactions such as aldol and Michael addition reactions with high enantiocontrol [5]. Despite the usefulness and
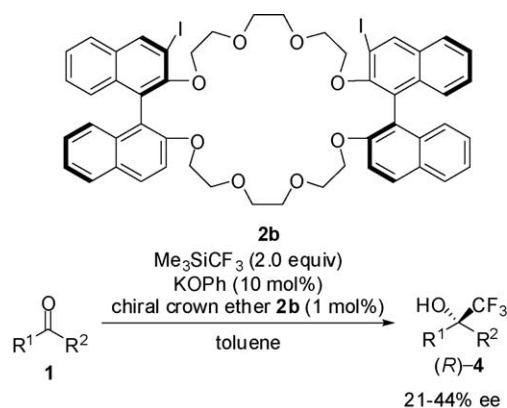


**Scheme 1.** Chiral crown ether-catalyzed enantioselective trifluoromethylation of carbonyl compounds.

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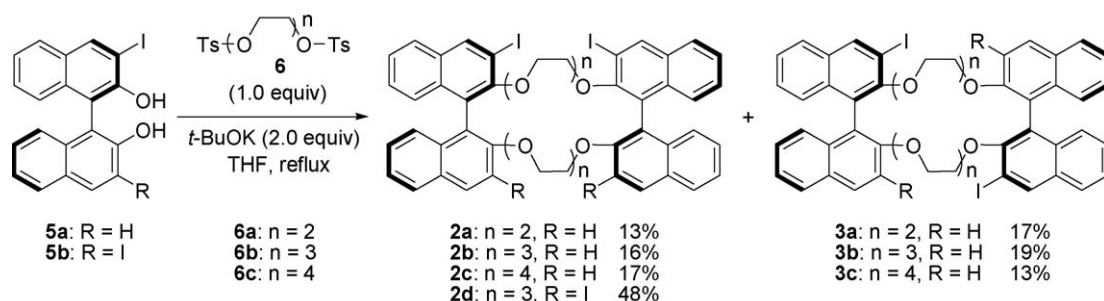
Scheme 2. Synthesis of chiral crown ethers **2a–d** and **3a–c**.

well-documented success of these chiral catalysts for asymmetric reactions, there is no report on their use as catalysts for enantioselective trifluoromethylation reactions [6].

In this context, the structurally new, chiral crown ethers derived from commercially available (R)-1,1′-bi-2-naphthol were designed as new C2-symmetric chiral phase-transfer catalysts **2** and **3** for the enantioselective trifluoromethylation [7].

Syntheses of these catalysts **2** and **3** were accomplished as shown in Scheme 2. The hydroxy groups in 3-iodobinaphthol **5a** or 3,3′-diiodobinaphthol **5b** were alkylated by the method of Cram et al. [8] with oligo-ethylene glycol ditosylates **6a–c** in the presence of t-BuOK in THF to afford the targets **2a–d** and **3a–c** in moderate yields whose mass spectra confirmed that they had a dimeric structure. The iodo-crown ethers, except for **2d**, were obtained as mixtures of regio isomers **2** and **3**. Structural assignments to the two isomers **2** and **3** could not be derived from their $^1$H NMR spectra or optical rotations. Finally, we ascertained compounds **2b** and **3b** on the basis of the X-ray crystallographic analysis of **3b** (Fig. 1). The crown ethers **2a/3a**, and **2c/3c** were tentatively assigned on the analogy of their RF values on TLC to those of **2b** and **3b**.

With the novel C2-symmetric chiral catalysts **2a–d** and **3a–c** in hand, enantioselective trifluoromethylation of 2-naphthaldehyde (**1a**) with Me₃SiCF₃ was examined as a model reaction in toluene (Table 1). A catalyst screening was employed first. The crown ethers **2a** and **3a**, which have a 22-membered ring, gave trifluoromethylated alcohol **4a** in high yields with 10–11% ees in the presence of KOPh (runs 1–2). When the reaction was performed in the presence of catalyst **2b** having a 28-membered ring, **4a** was obtained with a higher enantioselectivity of 33% (run 3). However, regio-isomeric catalyst **3b** did not improve the results (run 4). Attempts at trifluoromethylation using catalysts **2c** and **3c** having a 34-membered ring, also failed to improve the selectivity (runs 5–6). These results indicate that the 28-membered ring seems to be effective for this type of reaction. When the reaction was examined by the use of tetra-iodo crown ether **2d**, however, a poorer enantioselectivity was observed (run 7). We next screened a range of additives as combination catalysts with the chiral crown ether **2b** in toluene; however, the

enantioselectivities of **4a** never exceeded 33% (runs 8–11). Eventually, the enantioselectivity increased slightly to 40% when the reaction was performed at −50 °C in the presence of 1 mol% of **2b** (run 13).

The scope of our trifluoromethylation reaction using the **2b**/KOPh catalyst was next investigated in terms of substrates (Table 2). As expected, the **2b**/KOPh combination is a general catalyst for the enantioselective trifluoromethylation of aryl aldehydes **1b–e** that have functional groups, but trifluoromethylation of bromo-substituted aryl aldehyde **1e** shows a somewhat low enantioselectivity of 29% (entry 5). The aryl group of the substrates seems to be indispensable to achieve better enantioselectivity. 2-Phenylacetaldehyde (**1f**) and cinnamaldehyde (**1g**) were trifluoromethylated under the same conditions to give the products **4f, g** with 21–24% ees (entries 6 and 7). For aryl ketones, **1h–j** that have enolizable protons as well as a bromo moiety, the trifluoromethylation proceeded nicely to provide corresponding alcohols **4h–j** with a quaternally carbon centre in high yields with 31–38% ees (entries 8–10). The absolute configuration of the **4a** was determined by comparing HPLC retention times with that of reported value [3a], and the configurations for the remaining trifluoromethylated alcohols **4b–j** were tentatively assumed by analogy [4].

**Table 1**
Optimization of reaction conditions for the enantioselective trifluoromethylation of **1a** with Me₃SiCF₃ catalyzed by chiral crown ethers.



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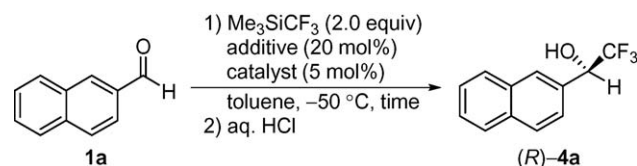
| Run | Catalyst (mol%) | Additive | Time (h) | Yield (%) | ee[a] |
|-----|-----------------|----------|----------|-----------|-------|
| 1[b] | **2a** (2.5) | KOPh | 4 | 89 | 11 |
| 2[b] | **3a** (2.5) | KOPh | 2 | 95 | 10 |
| 3[b] | **2b** (5.0) | KOPh | 3 | 99 | 33 |
| 4[b] | **3b** (5.0) | KOPh | 2 | 91 | 10 |
| 5[c] | **2c** (2.5) | KOPh | 7 | 88 | 7 |
| 6[d] | **3c** (2.5) | KOPh | 42 | 29 | 3 (S) |
| 7[c] | **2d** (5.0) | KOPh | 17 | 90 | 4 |
| 8[d] | **2b** (5.0) | KOH | 24 | 56 | 28 |
| 9[b,c] | **2b** (5.0) | t-BuOK | 36 | 65 | 28 |
| 10[e] | **2b** (5.0) | KF | 43 | 82 | 25 |
| 11[e] | **2b** (5.0) | K₂CO₃ | 53 | no reaction | – |
| 12[b] | **2b** (2.5) | KOPh | 10 | 96 | 33 |
| 13[b] | **2b** (1.0) | KOPh | 1 | 88 | 40 |

[a] Determined by chiral HPLC.
[b] Additive (10 mol%) was used.
[c] The reaction was carried out at −50 to −40 °C.
[d] The reaction was carried out at −50 to −20 °C.
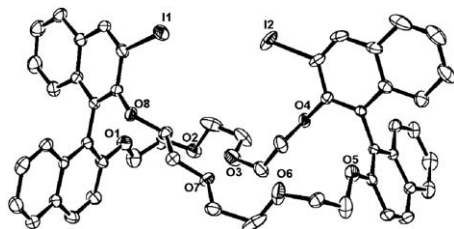[e] The reaction was carried out at −50 °C to rt.



Fig. 1. ORTEP view of crown ether **3b** with thermal ellipsoids drawn at the 30% probability. The hydrogen atoms are omitted for clarify.

**Table 2**
Enantioselective trifluoromethylation of ketones and aldehydes **1a–j** with Me$_3$SiCF$_3$ catalyzed by chiral crown ether **2b**.

1) Me$_3$SiCF$_3$ (2.0 equiv)
KOPh (10 mol%)
catalyst **2b** (1 mol%)
toluene, −50 °C, time
2) aq. HCl (R$^2$ = H) or
TBAF/H$_2$O, THF (R$^2$ = Me)

.

| Entry[a] | 1 | R$^1$ | R$^2$ | Time (h) | Yield (%) | ee[b] |
|---|---|---|---|---|---|---|
| 1 | **1a** | 2-Naphthyl | H | 1 | 88 | 40 |
| 2 | **1b** | Ph | H | 1 | 84 | 44 |
| 3[c] | **1c** | 4-MeC$_6$H$_4$ | H | 14 | 80 | 39 |
| 4[c] | **1d** | 4-MeOC$_6$H$_4$ | H | 14 | 84 | 43 |
| 5[c] | **1e** | 4-BrC$_6$H$_4$ | H | 2 | 87 | 29 |
| 6 | **1f** | PhCH$_2$CH$_2$ | H | 4 | 72 | 24 |
| 7[d] | **1g** | PhCH=CH | H | 6 | 90 | 21 |
| 8[e] | **1h** | 2-Naphthyl | Me | 6 | 91 | 34 |
| 9[e] | **1i** | Ph | Me | 6 | 66 | 38 |
| 10[e] | **1j** | 4-BrC$_6$H$_4$ | Me | 6 | 80 | 31 |

[a] Concentration was 0.13 M.
[b] Determined by chiral HPLC.
[c] The reaction was carried out at −50 to −40 °C.
[d] The reaction was carried out at −50 to −20 °C.
[e] The reaction was carried out at −40 to −30 °C.

## 3. Conclusion

In conclusion, we have synthesized novel C2-symmetrical chiral crown ethers and investigated their utility for the enantioselective trifluoromethylation of aryl aldehydes and alkyl aryl ketones. As far as we know, this is the first example of a chiral crown ether-catalyzed enantioselective trifluoromethylation reaction. The amount of chiral catalysts can be reduced to 1 mol%. Despite the fact that the ees are still improvable, the model reported in this work could spark the imagination of chemists to design new chiral crown ethers to improve the stereochemical outcome. Further structural optimization of chiral crown ethers in combination with additives for this reaction should achieve high enantioselectivity. We are now working in this direction.

## 4. Experimental

### 4.1. Preparation of chiral crown ether 2b

To a suspension of potassium *tert*-butoxide (621 mg, 5.54 mmol) and 3-iodobinaphthol **5a** (1.14 g, 2.77 mmol) in THF (23 ml) under a nitrogen atmosphere, a solution of triethyleneglycol di-*p*-toluene-sulfonate **6b** (1.27 g, 2.77 mmol) in THF (7.0 ml) was added. The reaction mixture was heated at reflux for 12 h and concentrated under reduced pressure. The residue was shaken with water and CH$_2$Cl$_2$, and the organic layer was washed with brine and dried over Na$_2$SO$_4$. After removal of solvent, the residue was purified by column chromatography on alumina (diethyl ether: ethyl acetate = 7:3). Crown ether **2b** was obtained in 17% yield as a less polar isomer, and **3b** was obtained in 19% yield as a polar isomer on the basis of their polarity under alumina column chromatography.

**2b**: off-white solid; $^1$H NMR (CDCl$_3$, 200 MHz) δ 3.02–3.79 (m, 20H), 4.01–4.13 (m, 2H), 4.24-4.33 (m, 2H), 7.02–7.38 (m, 12H), 7.47 (d, J = 9.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 7.6 Hz, 2H), 7.97 (d, J = 9.0 Hz, 2H), 8.46 (s, 2H); $^{13}$C NMR (CDCl$_3$, 150.9 MHz) δ 69.2, 69.5, 69.8, 70.1, 70.6, 72.3, 92.7, 114.8, 119.1, 123.8, 125.1, 125.3, 125.9, 126.6, 126.7, 126.9, 127.9, 129.0, 130.1, 132.3, 133.7, 134.1, 138.85, 138.88, 153.7, 154.3; IR (KBr) 3464, 3056, 2871, 1621, 1593, 1508, 1468, 1396, 1348, 1270, 1227, 1135, 1089, 881, 811, 749 cm$^{-1}$; MS (ESI, m/z) 1075 (M+Na$^+$), 1091 (M+K$^+$).

**3b**: off-white solid; $^1$H NMR (CDCl$_3$, 200 MHz) δ 3.09–3.22 (m, 4H), 3.34–3.49 (m, 10H), 3.58–3.78 (m, 6H), 3.99–4.09 (m, 2H), 4.20−4.31 (m, 2H), 7.05−7.34 (m, 12H), 7.41 (d, J = 9.2 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.83 (d, J = 7.4 Hz, 2H), 7.95 (d, J = 8.8 Hz, 2H), 8.46 (s, 2H); $^{13}$C NMR (CDCl$_3$, 150.9 MHz) δ 69.4, 69.6, 69.9, 70.6, 70.7, 72.4, 93.1, 114.5, 119.0, 123.8, 125.1, 125.3, 125.6, 128.0, 126.6, 126.7, 126.9, 127.9, 129.0, 130.1, 132.2, 133.7, 134.1, 138.87, 138.89, 153.7, 154.2; IR (KBr) 3435, 3056, 2925, 2872, 1621, 1593, 1509, 1469, 1348, 1270, 1134, 1089, 1051, 811, 749; MS (ESI, m/z) 1091 (M+K$^+$).

### 4.2. Trifluoromethylation of aldehyde 1a catalyzed by chiral crown ether 2b

Potassium phenoxide (3.3 mg, 0.025 mmol) and **2b** (2.6 mg, 0.0025 mmol) in toluene (2.0 ml) were stirred under a nitrogen atmosphere at room temperature for 30 min. Me$_3$SiCF$_3$ (73.9 μl, 0.500 mmol) was added at −50 °C, and **1a** (39.0 mg, 0.250 mmol) was added to the reaction mixture. After the reaction mixture was stirred at the same temperature by monitoring with TLC, it was quenched with sat. NH$_4$Cl aq. The aqueous layer was extracted with AcOEt, and the combined organic layers was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to furnish the crude **4a** as trimethylsilyl ether. The trimethylsilyl ether was treated with 1.0 ml 1N HCl aq. in THF (1.0 ml) at room temperature for 1 h. The resulting mixture was extracted with AcOEt, and the combined organic layers was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure to furnish crude **4a**. The residue was purified by column chromatography on silica gel (hexane:ethyl acetate = 9:1) to give **4a** (49.6 mg, 88%, 40% ee). **4a** white solid; $^1$H NMR (CDCl$_3$, 200 MHz) δ 2.67 (d, J = 3.8 Hz), 5.12–5.23 (m, 1H), 7.47–7.57 (m, 3H), 7.81−7.93 (m, 4H); $^{13}$C NMR (CDCl$_3$, 50.3 MHz) δ 73.0 (q, J = 31.9 Hz), 124.09, 124.10 (d, J = 281.0 Hz), 126.4, 126.7, 127.1, 127.5, 128.0, 128.3, 131.0, 132.7, 133.5; $^{19}$F NMR (CDCl$_3$, 188 MHz) δ −77.9 (d, J = 6.4 Hz, 3F); IR (KBr) 3366, 3065, 1509, 1366, 1260, 1197, 1175, 1125, 1067, 892, 821, 792, 752, 701 cm$^{-1}$; MS (EI, m/z) 226 (M$^+$); The product was determined as 40% ee by HPLC (Chiralcel OJ-H, Hexane: *i*-PrOH = 90:10, flow rate 1.0 ml/min, λ = 254 nm) t$_R$ (major) = 12.1 min and t$_R$ (minor) = 18.4 min.

## Acknowledgements

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