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Asymmetric Trifluoromethylthiolation of Azlactones under Chiral Phase Transfer Catalysis
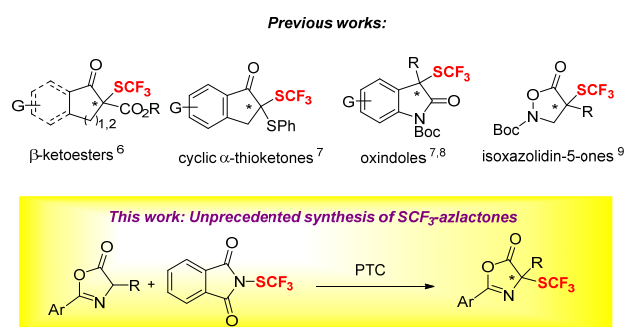
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The first enantioselective method for the installation of the SCF₃ group at the C-4 position of azlactones is described in the present communication under quinidinium phase transfer catalysis. The higher performance of substrates containing electron-rich 2-arylgroups at the azlactone was rationalized using DFT calculations.

Introduction

Over the last recent years, the design of new organofluorinated compounds has become one of the trending topics in the agrochemical and medicinal chemistry field, due to their peculiar physicochemical and biological features, leading to a plethora of reports on innovative fluorine-based drug candidates.[1] Worldwide research groups have thus focused their efforts in the development of diverse synthetic methodologies aimed to the asymmetric incorporation of fluorine atoms or fluoroalkyl groups into organic molecules.[2] In this regard, bioactive compounds bearing the trifluoromethylthio group (SCF₃) have shown a remarkably improved metabolic stability and transmembrane permeability, thanks to both its lipophilic and electron-withdrawing nature (Hansch parameter π= 1, 44).[3] Unsurprisingly, a powerful arsenal of strategies enabling the introduction of this group onto various scaffolds is now available at the synthetic chemist's tool box. Among them, the formation of C(sp²)- and C(sp)-SCF₃ bonds has been satisfactorily achieved through either transition-metal-promoted couplings, organocatalyzed reactions or radical processes.[4] Nevertheless, the direct stereocontrolled nucleophilic or electrophilic installation of the SCF₃ group at C(sp³) centres remains as a challenging task.[5,6]

The most common approach to fulfil this challenge relies on the direct asymmetric functionalization of reactive α-carbon in weakly acidic carbonyl compounds, with electrophilic SCF₃ sources. However, only a limited set of carbonyl substrates has been explored to date, being mainly comprised by β-keto esters,[6] α -thioketones,[7] and oxindoles,[7,8] and isoxazolidin-5-ones.[9] (Scheme 1).

Previous works:

β-ketoesters [6]   cyclic α-thioketones [7]   oxindoles [7,8]   isoxazolidin-5-ones [9]

This work: Unprecedented synthesis of SCF₃-azlactones

Scheme 1. Carbonyl compounds used in the previous asymmetric α–trifluoromethylthiolation reactions and our working plan with azlactones

In this context, azlactones drew our interest because of their synthetic and biological significance, thanks to the wide range of attractive pharmacological activities displayed, as their high versatility as building blocks, arising from presence of both nucleophilic and electrophilic sites.[10] In the light of this, we were intrigued by the possibility of incorporating the SCF₃ group into the azlactone core in an enantioselective fashion, through a phase transfer catalysed process (bottom, Scheme 1).

Initially, aiming to test the feasibility of our idea, azlactone **1a** was chosen as a model substrate, *N*-(trifluoromethylthio)phthalimide **2** as SCF₃ source,[11] in dichloromethane at −20 °C and in the presence of catalytic amount of K₃PO₄.[12] A wide family of different phase transfer catalysts (Table 1. Selected examples taken from ESI) was tested. Derived from this first screening, it was notorious that *O*-alkylated and *O*-acylated forms of the phase-transfer catalyst (**I-III**) were unsuitable for this transformation, leading to good yields but low stereocontrol (entries 1-3). A modest enantioselectivity was achieved with cinchoninium bromide (**IV**) (entry 4). Additionally, although the presence of electron-rich aromatic rings at the *N*-benzyl moiety (catalyst **V**) provided a good yield of **3a**, it turned out to be detrimental for the stereocontrol (entry 5). Conversely, electron-poor *N*-benzyl groups (catalysts **VI-VII**) brought to a slight improvement of the e.r. (entries 6-7). It should be highlighted the importance of the free hydroxyl group by directing/assisting the electrophilic attack of **2** on one of the two enantiotopic faces of **1a** (compare entries 1-7).[13] It is noteworthy that, upon switching from the cinchonine to a quinidine core, the enantiomeric ratio was further improved albeit with a decay of the yield (entry 8), leading to

the identification of **VIII** as the most suitable phase-transfer catalyst. A wide array of parameters was further studied (temperature, solvent, base and catalyst loading) confirming as optimal the preliminarily chosen reaction conditions, as reported in Table 1, entry 8.[14]

Table 1. Screening of phase transfer catalysts
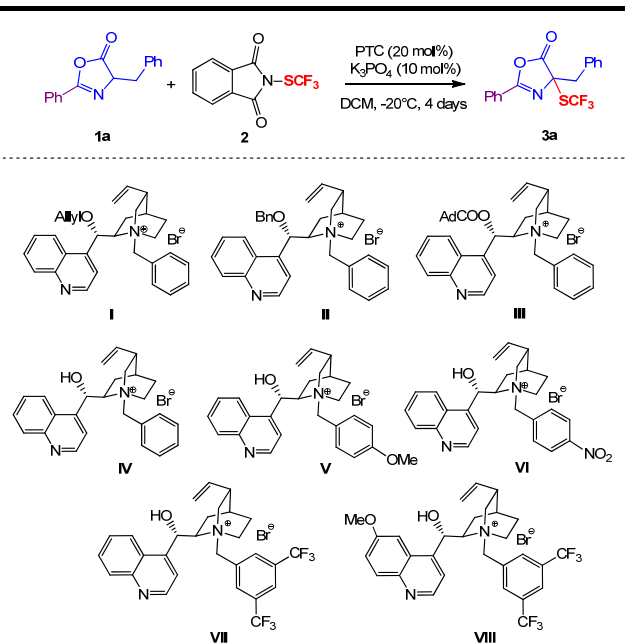
Entry	Catalyst	Yield (%)[a]	er[b]
1	I	80	51:49
2	II	86	52:48
3	III	72	51:49
4	IV	91	72:28
5	V	78	53:47
6	VI	57	77:23
7	VII	74	72:28
8	VIII	49	82:18

Reaction conditions: **1** (0.10 mmol), **2** (0.12 mmol), 0.1 M. [a]Isolated yield. [b]The values of *er* were determined by HPLC.

Attempting to use different SCF₃-sources such as *N*-(trifluoromethylthio)saccharin and *N*-(trifluoromethylthio)succinimide under the best conditions (Table 1, entry 8) affording complex mixtures and degradation of the starting materials. Aiming to increase both, yield and enantiomeric ratio of **3a**, we then decided to properly modify the substrate structure, surveying various substituent at its C-2 position, in the reaction catalysed by **VIII** (see Table 2). It was found that the electronic nature of the C-2 substituent was highly relevant, as the reaction did not take place when electron poor aromatic rings were used, even after extended reaction times, as complete degradation of the starting azlactones was only observed (Table 2, entries 1 and 2). Interestingly, when a chlorine atom was placed in the *para*-position of the aromatic ring, the reaction proceeded smoothly, with better yield

and shorter time compared to the unsubstituted phenyl ring, but the enantioselectivity was lower (Table 2, entries 3 and 4). Finally, when an electron donating group was introduced at the *para*-position of the 2-aryl group (Table 2, entry 5), full conversion was accomplished in very short reaction time (1h), displaying excellent yield and high enantiomeric ratio (Table 2, entry 5).

Table 2. Screening of C-2 substituent

Entry	R	Time	Conv./Yield (%)[a]	er[b]
1	4-CN(C₆H₄) **1b**	7 days	Degradation	-
2	4-CF₃(C₆H₄) **1c**	5 days	Degradation	-
3	4-Cl(C₆H₄) **1d**	19 h	100/83	70:30
4	C₆H₅ **1a**	4 days	50/49	82:18
5	4-OMe(C₆H₄) **1e**	1 h	100/84	94:6

Reaction conditions: **1** (0.10 mmol), **2** (0.12 mmol), 0.1 M. [a]Isolated yield. [b]The values of *er* were determined by HPLC.

Subsequently, with the optimized reaction scenario, the reaction scope was carried out (Scheme 2), showing that both electron-donating and electron-withdrawing groups at the benzyl substituent of the azlactone core (**3h**, **3i** and **3j**) allowed the incorporation of the SCF₃ group without dramatically altering the good enantioselectivity and excellent yield. The substrate containing a β-naphthylmethyl side chain also reacted successfully under the standard conditions without losing quality in the results (**3f**). Good yield and enantioselectivity were also obtained upon replacing PMP with 3,5-(MeO)₂C₆H₃ at the C-2 position of the core (cf. **3e** and **3g**). Gratefully, the presence of an arylmethyl sidechain proved to be not mandatory to achieve good results. For instance, a homobenzylsubstituted azlactone was smoothly transformed into the corresponding thiofluorinated compound 3k in good yield and enantiomeric ratio. A similar result was obtained with a methionine derivative, affording **3l** albeit requiring a longer stirring time. Moreover, the reaction of substrates containing moderately sterically hindered cyclohexyl, *sec*-butyl and isopropyl chains, occurred smoothly, delivering the desired products **3m**, **3n** and **3o** respectively with e.r.'s from moderate to excellent. In particular, an outstanding result was achieved with the valine-derived azlactone, that was transformed into the corresponding trifluoromethylthiolated product **3o** as a single enantiomer. During our investigation, we encountered some limitations in the scope of this methodology, as outlined in the bottom of Scheme 2. The configuration assignment of the resulting trifluoromethylthiolated azlactones was described as R by a comparison of simulated and experimental electronic circular dichroism spectra of compound **3k** (see ESI for details).
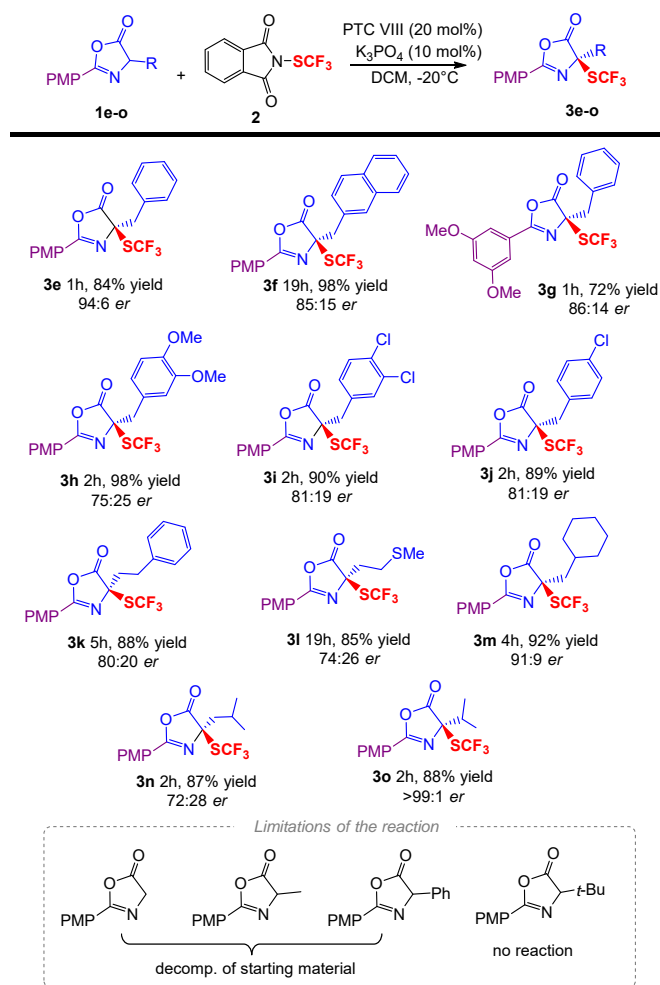
Scheme 2. Azlactone scope: yields of isolated products are given. HPLC was use for *er* meassurements. Reactions conditions: **1** (0.1 mmol), **2** (0.12 mmol), 0.1 M

In the quest for finding a plausible explanation to the relationship observed between the reactivity and the *para*-substituent at the 2-aryl moiety of azlactone, which showed the high efficiency of the *p*-OMe group (See Table 2 and Scheme 3), we performed reactions of azlactones **1a-e** with NBu$_4$Br as PTC, confirming the same reactivity order (CN < CF$_3$ < H < Cl < OCH$_3$). This experimental result suggest that such trend is not due to an interaction between the chiral and non-chiral catalyst and the different substrates, but rather it is solely dependent on the electronic nature of the azlactone. This information realigned our efforts to carry out a theoretical study based on Density Functional Theory (DFT) calculations.[15,16] As a starting point in our simulations, we located the minima in the potential energy surface corresponding to the interaction between the anions derived from azlactones **1a-e** and tetrabutylammonium ion (see structures in the ESI). In all cases, the obtained stabilization energy of the resulting complex between the azlactone anion and the NBu$_4^+$, compared to the separated compounds, oscillated around ~21 kcal·mol-1. The nature of the simulated interaction is rationalised by considering Coulomb attraction forces between the positively charged ammonium species and the negatively charged azlactone, as well as Van der Waals forces between the azlactone phenyl rings and the ammonium aliphatic chains. Since this interaction is very similar in all cases, we concluded that it does not

have major influence on the observed reactivity. In a second step of our simulations, the highest occupied molecular orbitals of the enolates – HOMO – were analysed (Scheme 3). These molecular orbitals show π character and are localized only in the azlactone ring, particularly, higher electron density is observed in the azlactones molecular region between the carbonyl oxygen atom and C-4, consistently with the observed electrophilic attack of SCF$_3$ at the latter position (see a.u. values in Scheme 3 and ESI for different representations and a deeper analysis of the HOMO orbital). The orbital energy increases across the substituent series CN < CF$_3$ < Cl < H < OCH$_3$, which is roughly in accordance with the experimental reactivity behaviour. In an effort to obtain the atomic population, and thus the charges located on each atom, a Natural Bond Orbital (NBO) analysis[17] was lastly performed. This final study was mainly focused on the previously identified two key atoms, the carbonyl oxygen and C-4, unveiling a partial negative charge in both sites. This data suggested an excess of electron density and was consistent with the higher electron density associated to these atoms in the HOMO orbital, displaying a clear charge trend (see Z values in Scheme 3). These computational data reflect very well the observed reactivity trend, wherein enolates with lower electron density at C-4 do not react or react very slow compared to enolates with higher electron density. However, the higher reactivity of the *p*-chloro substrate **1d** compared to its unsubstituted counterpart **1a** is not reproduced by the calculated electron densities, thus suggesting that other factors may work in these borderline cases. In summary, a simple electron density analysis offers an explanation to the general reactivity trend, with more reactive substrates characterized by larger accessibility (higher energy) of the HOMO orbital and enhanced electron density at C-4, suggesting that the rate-determining step is the reaction of azlactone anion with the electrophilic SCF$_3$ source.
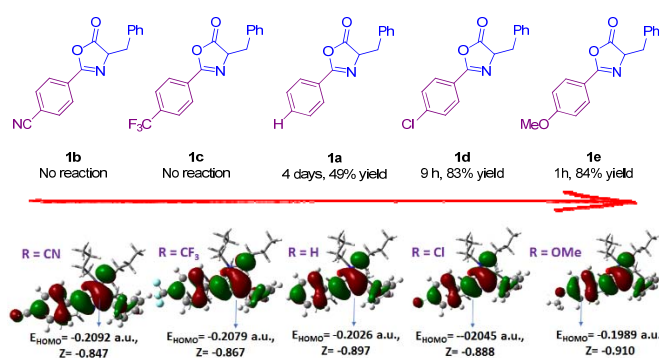
Scheme 3. Reactivity and comparison of the different aryl groups at the azlactones

Experimental section

General procedure for the enantioselective trifluoromethylthiolation of azlactones

In a 4 ml vial, to a mixture of the selected azlactone (1.0 eq., 0.10 mmol), *N*-(trifluoromethylthio)phthalimide **2** (1.2 eq., 0.12 mmol, 29.7 mg), catalyst **VIII** (0.20 eq., 0.02 mmol, 12.6 mg), and K$_3$PO$_4$ (0.1 eq., 0.01 mmol, 2.1 mg) dichloromethane (1.0 mL) was added and the reaction mixture was stirred for the indicated time at -20 °C.

Then, the mixture was filtered and concentrated in vacuo. The crude residue was purified by chromatography (10 g silica gel cyclohexane-ethyl acetate, 99/1 to 80/20) to afford the corresponding product.

4-benzyl-2-(4-methoxyphenyl)-4-(trifluoromethyl)thio)oxazol-5(4H)-one (3e): Obtained after 1 h as a yellow solid (32.0 mg, 84% yield), mp 115-116 °C. ^{1}H NMR (300 MHz, CDCl3) δ 7.85 (d, J = 8.9 Hz, 2H), 7.21 (m, 5H), 6.94 (d, J = 8.9 Hz, 2H), 3.86 (s, 3H), 3.47 (d, J = 13.1 Hz, 1H), 3.32 (d, J = 13.1 Hz, 1H). ^{13}C NMR (75 MHz, CDCl3) δ 174.7, 164.0, 162.2, 131.4, 130.8, 130.4, 128.7 (q, J = 311.1 Hz), 128.5, 128.2, 116.8, 114.4, 76.8 (q, J = 1.1 Hz), 55.6, 42.5 (q, J = 1.1 Hz). ^{19}F NMR (282 MHz, CDCl3) δ -37.5. $[\alpha]_D^{20}$= -65.5° (c = 0.80, CHCl$_3$). Enantiomeric ratio 94:6 determined by SFC analysis (CHIRALPAK® AS-H column (ϕ 0.46 cm x 25 cm), n-hexane:i-PrOH = 95:5, 0.5 mL/min, t_{minor} = 7.2 min, t_{major} = 8.1 min). HRMS (ESI) [M + H$^+$] calcd for C$_{18}$H$_{15}$F$_3$NO$_3$S$^+$ 382.0719, found 382.0710.

2-(4-methoxyphenyl)-4-(naphthalen-2-ylmethyl)-4-((trifluoromethyl)-thio)oxazol-5(4H)-one (3f): Obtained after 19 h as a yellow solid (42.3 mg, 98% yield), mp 119-120 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.87–7.81 (m, 2H), 7.77–7.71 (m, 2H), 7.71–7.65 (m, 2H), 7.49–7.37 (m, 2H), 7.35 (dd, J = 8.6, 1.7 Hz, 1H), 6.94–6.87 (m, 2H), 3.83 (s, 3H), 3.65 (d, J = 13.1 Hz, 1H), 3.51 (d, J = 13.1 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 174.7, 164.0, 162.4, 133.1, 132.8, 130.4, 129.9, 129.1, 128.8 (q, J = 309.8 Hz), 128.1, 128.0, 127.6, 126.3, 126.2, 116.8, 114.4, 76.9 (q, J = 1.1 Hz), 55.5, 42.7. ^{19}F NMR (282 MHz, CDCl$_3$) δ -37.5. $[\alpha]_D^{20}$= -47.6° (c = 0.80, CHCl$_3$). Enantiomeric ratio 85:15 determined by HPLC analysis (CHIRALPAK® AS-H column (ϕ 0.46 cm x 25 cm), n-hexane:i-PrOH = 98:2, 0.5 mL/min, t_{minor} = 14.7 min, t_{major} = 17.3 min). HRMS (ESI) [M + H$^+$] calcd for C$_{22}$H$_{17}$F$_3$NO$_3$S$^+$ 432.0876, found 432.0873.

4-benzyl-2-(3,5-dimethoxyphenyl)-4-((trifluoromethyl)thio)oxazol-5(4H)-one (3g): Obtained after 1 h as a white solid (33.3 mg, 81% yield), mp 117118- °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.22 (m, 5H), 7.02 (d, J = 2.3 Hz, 2H), 6.65 (t, J = 2.3 Hz, 1H), 3.81 (s, 6H), 3.48 (d, J = 13.2 Hz, 1H), 3.33 (d, J = 13.2 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 174.4, 162.4, 161.0, 131.2, 130.5, 128.7 (q, 310.2 Hz), 128.6, 128.3, 126.2, 106.6, 105.9, 76.7 (q, J = 1.1 Hz), 55.7, 42.4 (q, J = 1.1 Hz). ^{19}F NMR (282 MHz, CDCl$_3$) δ -37.5. $[\alpha]_D^{20}$= -51.0° (c = 0.80, CHCl$_3$). Enantiomeric ratio 86:14 determined by HPLC analysis (CHIRALPAK® AS-H column (ϕ 0.46 cm x 25 cm), n-hexane:i-PrOH = 99:1, 0.5 mL/min, t_{minor} = 21.4 min, t_{major} = 22.2 min). HRMS (ESI) [M + H$^+$] calcd for C$_{19}$H$_{17}$F$_3$NO$_4$S$^+$ 412.0825, found 412.0826.

4-(3,4-dimethoxybenzyl)-2-(4-methoxyphenyl)-4-((trifluoromethyl)thio)oxazol-5(4H)-one (3h): Obtained after 2 h as a yellow solid (43.2 mg, 98% yield), mp 107-108 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.87 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 6.77–6.67 (m, 3H), 3.86 (m, 3H), 3.79 (s, 3H), 3.68 (s, 3H), 3.42 (d, J = 13.2 Hz, 1H), 3.26 (d, J = 13.2 Hz, 1H). ^{13}C NMR (75 MHz, CDCl3) δ 174.7, 164.1, 162.3, 148.9, 148.5, 130.3, 128.8 (q, J = 310.1 Hz), 123.7, 122.6, 116.8, 114.4, 113.5, 111.0, 76.8 (q, J = 1.1 Hz), 55.7, 55.7, 55.6, 42.1 (q, J = 1.1 Hz). ^{19}F NMR (282 MHz, CDCl$_3$) δ -37.5. $[\alpha]_D^{20}$= -40.2°

(c = 0.80, CHCl$_3$). Enantiomeric ratio 75:25 determined by HPLC analysis (CHIRALPAK® AS-H column (ϕ 0.46 cm x 25 cm), n-hexane:i-PrOH = 80:20, 0.5 mL/min, t_{minor} = 11.1 min, t_{major} = 12.1 min). HRMS (ESI) [M + H$^+$] calcd for C$_{20}$H$_{19}$F$_3$NO$_5$S$^+$ 442.0931, found 442.0930

4-(3,4-dichlorobenzyl)-2-(4-methoxyphenyl)-4-(trifluoromethyl)-thio)oxazol-5(4H)-one (3i): Obtained after 2 h as a yellow solid (40.5 mg, 90% yield), mp 109-110 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.89 (d, J = 8.9 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.30 (d, J = 8.2 Hz, 1H), 7.06 (dd, J = 8.2, 2.0 Hz, 1H), 6.97 (d, J = 8.9 Hz, 1H), 3.88 (s, 3H), 3.43 (d, J = 13.4 Hz, 1H), 3.28 (d, J = 13.4 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 174.3, 164.3, 162.7, 132.6, 132.6, 132.5, 131.8, 130.5, 130.4, 129.8, 128.6 (q, J = 310.0 Hz), 116.4, 114.5, 76.2 (q, J = 1.1 Hz), 55.6, 41.5 (q, J = 1.1 Hz). ^{19}F NMR (282 MHz, CDCl$_3$) δ -37.3. $[\alpha]_D^{20}$= -53.8° (c = 0.80, CHCl$_3$). Enantiomeric ratio 81:19 determined by HPLC analysis (CHIRALPAK® IB column (ϕ 0.46 cm x 25 cm), n-hexane:i-PrOH = 99:1, 0.5 mL/min, t_{major} = 17.9 min, t_{minor} = 20.9 min). HRMS (ESI) [M + H$^+$] calcd for C$_{18}$H$_{13}$Cl$_2$F$_3$NO$_3$S$^+$ 449.9940, found 449.4942.

4-(4-chlorobenzyl)-2-(4-methoxyphenyl)-4-(trifluoromethyl)thio)oxazol-5(4H)-one (3j): Obtained after 2 h as a yellow solid (37.0 mg, 89% yield), mp 100-101 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.87 (d, J = 8.9 Hz, 2H), 7.19 (d, J = 8.6 Hz, 2H), 7.14 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.9 Hz, 2H), 3.87 (s, 3H), 3.44 (d, J = 13.3 Hz, 1H), 3.30 (d, J = 13.3 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 174.6, 164.2, 162.4, 134.3, 131.9, 130.5, 130.0, 128.7, 128.7 (q, J = 310.0 Hz), 116.6, 114.5, 76.5 (q, J = 1.1 Hz), 55.6, 41.7 (q, J = 1.1 Hz). ^{19}F NMR (282 MHz, CDCl$_3$) δ -37.4. $[\alpha]_D^{20}$= -52.0 ° (c = 0.80, CHCl$_3$). Enantiomeric ratio 81:19 determined by HPLC analysis (CHIRALPAK® IB column (ϕ 0.46 cm x 25 cm), n-hexane:i-PrOH = 99:1, 0.5 mL/min, t_{major} = 15.1 min, t_{minor} = 16.2 min). HRMS (ESI) [M + H$^+$] calcd for C$_{18}$H$_{14}$ClF$_3$NO$_3$S$^+$ 416.0330, found 416.0335.

2-(4-methoxyphenyl)-4-phenethyl-4-((trifluoromethyl)thio)oxazol-5(4H)-one (3k): Obtained after 5 h as a white solid (34.8 mg, 88% yield), mp 103-104 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.05 (d, J = 8.8 Hz, 2H), 7.34-7.13 (m, 5H), 7.05 (d, J = 8.8 Hz, 2H), 3.93 (s, 3H), 2.78 (m, 1H), 2.65 (m, 1H), 2.56-2.33 (m, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.2, 164.2, 162.7, 138.9, 130.6, 128.8 (q, J = 309.5 Hz), 128.7, 128.4, 126.7, 116.9, 114.5, 75.9 (q, J = 1.1 Hz), 55.6, 38.4 (q, J = 1.1 Hz), 30.1. ^{19}F NMR (282 MHz, CDCl$_3$) δ -37.7. $[\alpha]_D^{20}$= -58.8° (c = 0.80, CHCl$_3$). Enantiomeric ratio 80:20 determined by HPLC analysis (CHIRALPAK® AS-H column (ϕ 0.46 cm x 25 cm), n-hexane:i-PrOH = 98:2, 0.5 mL/min, t_{minor} = 13.2 min, t_{major} = 16.2 min). HRMS (ESI) [M + H$^+$] calcd for C$_{19}$H$_{17}$F$_3$NO$_3$S$^+$ 396.0876, found 396.0870.

2-(4-methoxyphenyl)-4-(2-(methylthio)ethyl)-4-((trifluoromethyl)thio)oxazol-5(4H)-one (3l): Obtained after 19 h as a pink solid (31.0 mg, 85% yield), mp 97-98 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.02 (d, J = 9.0 Hz, 2H), 7.02 (d, J = 9.0 Hz, 2H), 3.92 (s, 3H), 2.67-2.41 (m, 4H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.2, 164.3, 159.7, 130.7, 116.9, 128.8 (q, = 310.0 Hz), 114.5, 75.3 (q, J = 1.1 Hz), 55.6, 35.8, 28.4, 15.2. ^{19}F NMR (282 MHz, CDCl$_3$) δ -37.5. $[\alpha]_D^{20}$= -29.4° (c = 0.50, CHCl$_3$). Enantiomeric ratio 74:26 determined

by HPLC analysis (CHIRALPAK® AS-H column (ϕ 0.46 cm x 25 cm), *n*-hexane:*i*-PrOH = 98:2, 0.5 mL/min, t_{minor} = 15.5 min, t_{major} = 17.9 min). HRMS (ESI) [M + H$^+$] calcd for $C_{14}H_{15}F_3NO_3S_2^+$ 366.0440, found 366.0447.

4-(cyclohexylmethyl)-2-(4-methoxyphenyl)-4-((trifluoromethyl)thio)oxazol-5(4H)-one (3m): Obtained after 4 h as a white solid (35.6 mg, 92% yield), mp 114-115 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.00 (d, J = 8.9 Hz, 2H), 7.01 (d, J = 8.9 Hz, 2H), 3.90 (s, 3H), 2.10 (dd, J = 14.0, 5.3 Hz, 1H), 1.96 (dd, J = 14.0, 6.6 Hz, 1H), 1.78–1.52 (m, 5H), 1.50 – 1.38 (m, 1H), 1.29 – 1.08 (m, 3H), 1.08 – 0.87 (m, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 176.0, 164.1, 162.1, 130.5, 128.8 (q, J = 310.1 Hz), 117.1, 114.5, 76.1 (q, J = 1.1 Hz), 55.6, 43.8, 34.4, 34.2, 33.6, 26.0, 25.9. ^{19}F NMR (282 MHz, CDCl$_3$) δ -37.9. $[\alpha]_D^{20}$= -43.3° (c = 0.60, CHCl$_3$). Enantiomeric ratio 91:9 determined by HPLC analysis (CHIRALPAK® AS-H column (ϕ 0.46 cm x 25 cm), *n*-hexane:*i*-PrOH = 99.5:0.5, 0.3 mL/min, t_{minor} = 17.3 min, t_{major} = 18.8 min). HRMS (ESI) [M + H$^+$] calcd for $C_{18}H_{21}F_3NO_3S^+$ 388.1189, found 388.1193.

4-isobutyl-2-(4-methoxyphenyl)-4-((trifluoromethyl)thio)oxazol-5(4H)-one (3n): Obtained after 2 h as a white solid (30.2 mg, 87% yield), mp 102-103 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.07–7.93 (m, 2H), 7.07–6.95 (m, 2H), 3.90 (s, 3H), 2.14 (dd, J = 13.8, 5.6 Hz, 1H), 1.98 (dd, J = 13.8, 6.9 Hz, 1H), 1.88–1.68 (m, 1H), 1.00–0.86 (m, 6H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 175.9, 164.1, 162.1, 130.5, 128.8 (q, J = 309.7 Hz), 117.1, 114.5, 76.1 (q, J = 1.1 Hz), 55.6, 45.0, 25.4, 23.8, 23.0. ^{19}F NMR (282 MHz, CDCl$_3$) δ -37.9. $[\alpha]_D^{20}$= -39.9 ° (c = 0.80, CHCl$_3$). Enantiomeric ratio 72:28 determined by HPLC analysis (CHIRALPAK® IB column (ϕ 0.46 cm x 25 cm), *n*-hexane:*i*-PrOH = 99.2:0.8, 0.35 mL/min, t_{major} = 17.8 min, t_{minor} = 19.1 min). HRMS (ESI) [M + H$^+$] calcd for $C_{15}H_{17}F_3NO_3S^+$ 347.0803, found 347.0800.

4-isopropyl-2-(4-methoxyphenyl)-4-((trifluoromethyl)thio)oxazol-5(4H)-one (3o): Obtained after 19 h as a white solid (29.3 mg, 88% yield), mp 98-99 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.06–7.96 (m, 2H), 7.04–6.96 (m, 2H), 3.89 (s, 3H), 2.39 (hept, J = 6.5 Hz, 1H), 1.20 (d, J = 6.8 Hz, 3H), 1.03 (d, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 174.4, 163.0, 161.2, 129.5, 128.0 (q, 309.7 Hz), 116.0, 113.4, 79.1 (q, J = 1.1 Hz), 54.6, 34.8, 16.2, 15.8. ^{19}F NMR (282 MHz, CDCl$_3$) δ -37.5. $[\alpha]_D^{20}$= -61.3° (c = 0.80, CHCl$_3$). Enantiomeric ratio >99:<1 determined by HPLC analysis (CHIRALPAK® AS-H column (ϕ 0.46 cm x 25 cm), *n*-hexane:*i*-PrOH = 99.5:0.5, 0.3 mL/min, t_{major} = 16.8 min. HRMS (ESI) [M + H$^+$] calcd for $C_{14}H_{15}F_3NO_3S^+$ 334.0719, found 334.0714.

4-benzyl-2-phenyl-4-((trifluoromethyl)thio)oxazol-5(4H)-one (3a): Obtained after 19 h as a white solid (17.2 mg, 49% yield), mp 104-105 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ = 7.90 (dd, J = 8.4 Hz, 1.4 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1.5 Hz, 1H), 7.46 (t, J = 7.7 Hz, 2H), 7.24-7.18 (m, 5H), 3.49 (d, J = 13.2 Hz, 1H), 3.35 (d, J = 13.2 Hz, 1H). ^{13}C NMR (300 MHz, CDCl$_3$) δ = 174.5, 162.5, 133.7, 131.3, 130.6, 129.2 (q, J = 298 Hz), 128.9, 128.5, 128.34, 128.27, 124.7, 42.5. ^{19}F NMR (300 MHz, CDCl$_3$): δ = -37.51 (s, 3 F). $[\alpha]_D^{20}$= -41.1° (c = 0.80, CHCl$_3$). Enantiomeric ratio 82:18 determined by HPLC analysis (CHIRALPAK® AS-H column (ϕ 0.46 cm x 25 cm), *n*-hexane:*i*-PrOH = 90:10, 0.5

mL/min, t_{minor} = 9.3 min, t_{major} = 11.1 min). HRMS (ESI) [M + H$^+$] calcd for $C_{17}H_{13}F_3NO_2S^+$ 352.3174, found 352.3170.

4-benzyl-2-(4-chlorophenyl)-4-((trifluoromethyl)thio)oxazol-5(4H)-one (3d): Obtained after 19 h as a white solid (32.0 mg, 83% yield), mp 118-119 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.83 (d, J = 6.9 Hz, 2H), 7.44 (d, J = 6.9 Hz, 2H), 7.21 (s, 5H), 3.48 (d, J = 13.2 Hz, 1H), 3.34 (d, J = 13.2 Hz, 1H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 174.2, 161.7, 140.3, 131.1, 130.5, 129.6, 129.4, 128.7 (q, J = 309.9 Hz), 128.5, 128.3, 123.0, 77.2, 42.4 (q, J = 1.1 Hz). ^{19}F NMR (282 MHz, CDCl$_3$) δ -37.5. $[\alpha]_D^{20}$= -38.2° (c = 0.80, CHCl$_3$). Enantiomeric ratio 70:30 determined by HPLC analysis (CHIRALPAK® AS-H column (ϕ 0.46 cm x 25 cm), *n*-hexane:*i*-PrOH = 99:1, 0.5 mL/min, t_{minor} = 13.3 min, t_{major} = 17.5 min). HRMS (ESI) [M + H$^+$] calcd for $C_{17}H_{12}ClF_3NO_2S^+$ 386.0224, found 386.0228.

Conclusions

In conclusion, we have developed the first enantioselective direct installation of SCF$_3$ group at the C-4 position of azlactones by employing a phase transfer catalyzed methodology, affording a wide array of products with benzyl, homobenzyl and aliphatic α-side chains with high yields and good enantioselectivity. The most effective cinchona alkaloid derived catalyst is characterized by the electron poor nature of *N*-benzyl group and the presence of a free hydroxyl moiety. The absolute configuration of products has been determined by circular dichroism. In addition, DFT calculations gave interesting mechanistic insights and provided an explanation for the best performance achieved with substrates containing an electron-rich 2-aryl group. Further investigation aimed to expand the scope of enantioenriched trifluoromethylthiolated aza-compounds are currently under way.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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