

Unveiling the impact of a CF₂ motif in the isothiourea catalyst skeleton: Evaluating C(3)-F₂-HBTM and its catalytic activity

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Dedicated to Dr Alan Aitken for his boundless enthusiasm towards heterocyclic chemistry

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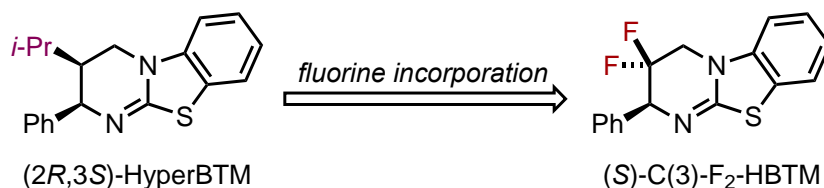
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Abstract

The incorporation of the CF₂ motif within organic structures is known to affect the susceptibility of functional groups to oxidation, as well as altering conformation and reactivity. In this manuscript, the incorporation of the CF₂ functional group within an isothiourea catalyst skeleton to give C(3)-F₂-HBTM is reported. Effective gram-scale routes to both racemic and enantiopure heterocyclic Lewis bases are developed, with preliminary catalytic and kinetic activity evaluated.

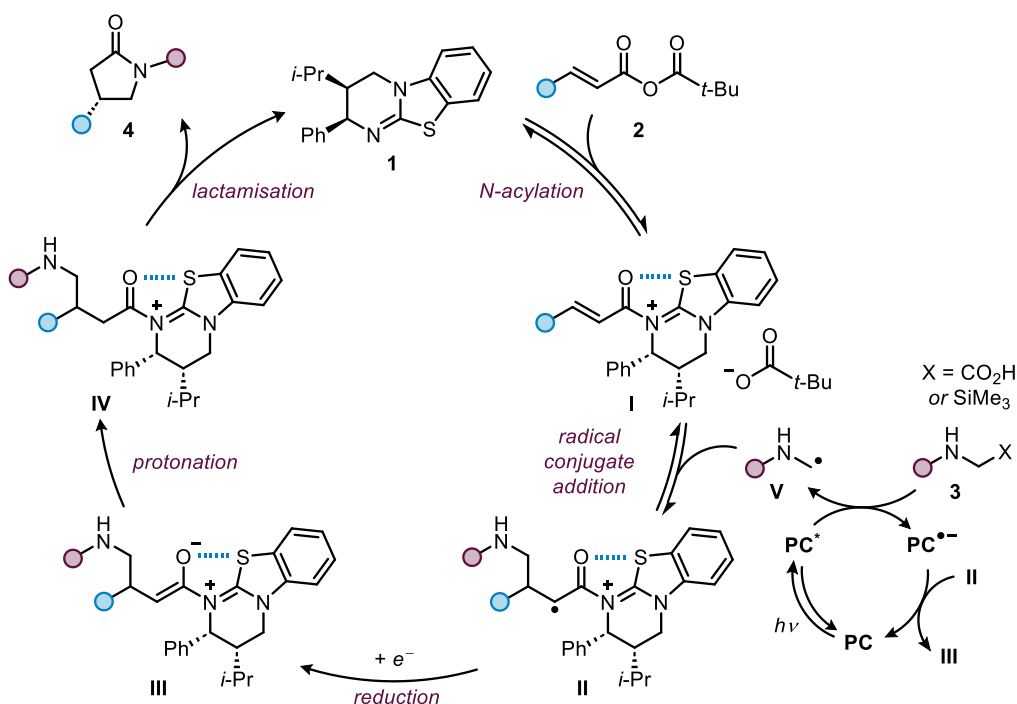


- enhanced photocatalytic stability • gram scale synthesis •
- kinetics and nucleophilicity studies •

Keywords: Isothiourea, fluorination, asymmetric synthesis, photocatalysis

Introduction

Since Birman's seminal work on the kinetic resolution of secondary alcohols,¹⁻² isothioureas have become established as versatile Lewis base organocatalysts in a range of enantioselective protocols.³ Through reaction with an activated carbonyl precursor, a variety of reactive intermediates have been utilised in enantioselective catalysis that encompass acyl ammonium species (for example in kinetic resolution and desymmetrisation),⁴ C(1)-ammonium enolates (for example in cycloadditions and sigmatropic rearrangements)⁵ and α,β -unsaturated acyl ammonium intermediates (for example in enantioselective conjugate additions).⁶⁻⁷ Recently ourselves⁸ and Melchiorre and co-workers⁹ concurrently published the enantioselective synthesis of γ -lactams *via* dual isothiourea/photoredox catalysis. For example, acylation of isothiourea (2*R,3S*)-HyperBTM **1** with a pivaloyl mixed anhydride **2** generated an intermediate α,β -unsaturated acyl ammonium intermediate **I** (Scheme 1). Subsequent enantioselective conjugate addition of α -amino radical **V**, generated using the excited state of a photocatalyst (PC) from amine **3**, generated intermediate **II**. Conjugate addition was expected to be stereodetermining, with selectivity in this step postulated to arise due to a *syn*-coplanar 1,5-O•••S chalcogen bonding interaction¹⁰⁻¹² that provided a conformational lock, with addition *anti*- to the C(2)-Ph stereodirecting group allowing for stereodiscrimination. Reduction of α -carbonyl radical **II** by the reduced state photocatalyst gives both C(1)-ammonium enolate **III** and regenerates the ground state photocatalyst. Protonation of **III** led to acyl ammonium **IV** which after concomitant cyclisation formed the enantioenriched γ -lactam **4** and released the isothiourea catalyst **1** (Scheme 1).



Scheme 1. The dual isothiourea/photoredox catalysed synthesis of enantioenriched γ -lactams **4**

During the course of this investigation, competitive oxidation of the isothiourea HyperBTM **1** by the excited state of the photoredox catalyst was identified as a deleterious organocatalyst degradation pathway.

To circumvent this oxidation, modification of the isothioureia structure was considered. Given that the incorporation of electron-withdrawing fluorine atoms is widely used in medicinal chemistry to lower the susceptibility of functional groups to enzymatic oxidation while also reducing amine basicity, the incorporation of a C(3)-*gem*-difluoro substituent within the isothioureia skeleton was evaluated.¹³⁻¹⁴ The introduction of CF₂ groups into aliphatic chains has been employed for their ability to influence geometric and electronic properties in addition to possessing bioisosterism for carbonyl groups or oxygen atoms.¹⁵⁻¹⁶ The ability of the *gem*-difluoro motif to alter the properties of cyclic aliphatic amine heterocyclic building blocks is finding increasing use in drug design.¹⁷ This fluorination approach was employed elegantly by Melchiorre and co-workers through modification of amine **5** (

Figure 1a).¹⁸ The incorporation of the geminal difluorinated motif resulted in a substantial increase in the oxidation potential of the catalyst **6** over its non-fluorinated counterpart **5** and minimised catalyst degradation. The fluorinated α,β -unsaturated iminium intermediates derived from **6** were also found to be more catalytically competent reactive species in a suite of different dual organocatalysis/photoredox manifolds.¹⁹⁻²⁴ Based upon this precedent, herein, the synthesis of the C(3)-*gem*-difluorinated isothioureia **7** as both a racemate and in enantiopure form, as well as preliminary catalytic reactivity and associated kinetic studies through reaction with benzhydrylium ions is reported (

Figure 1b).

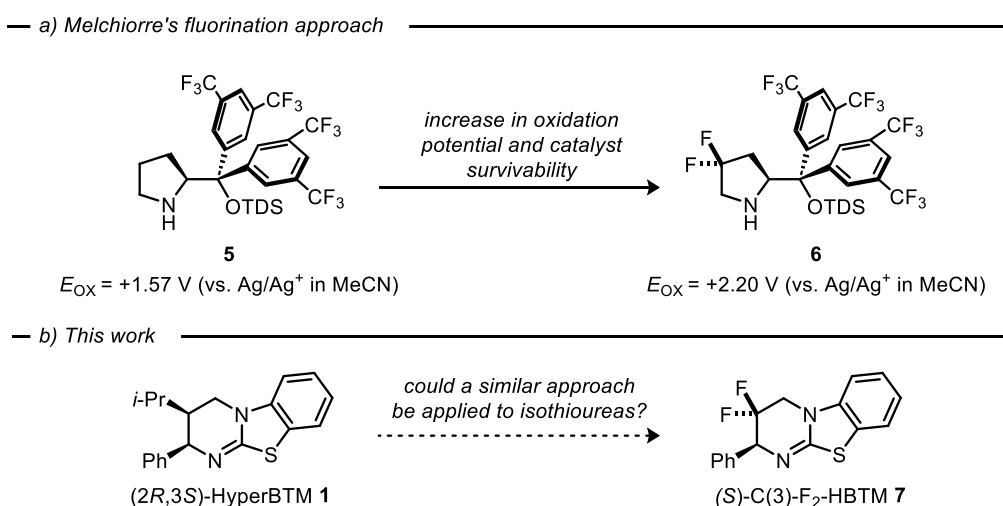


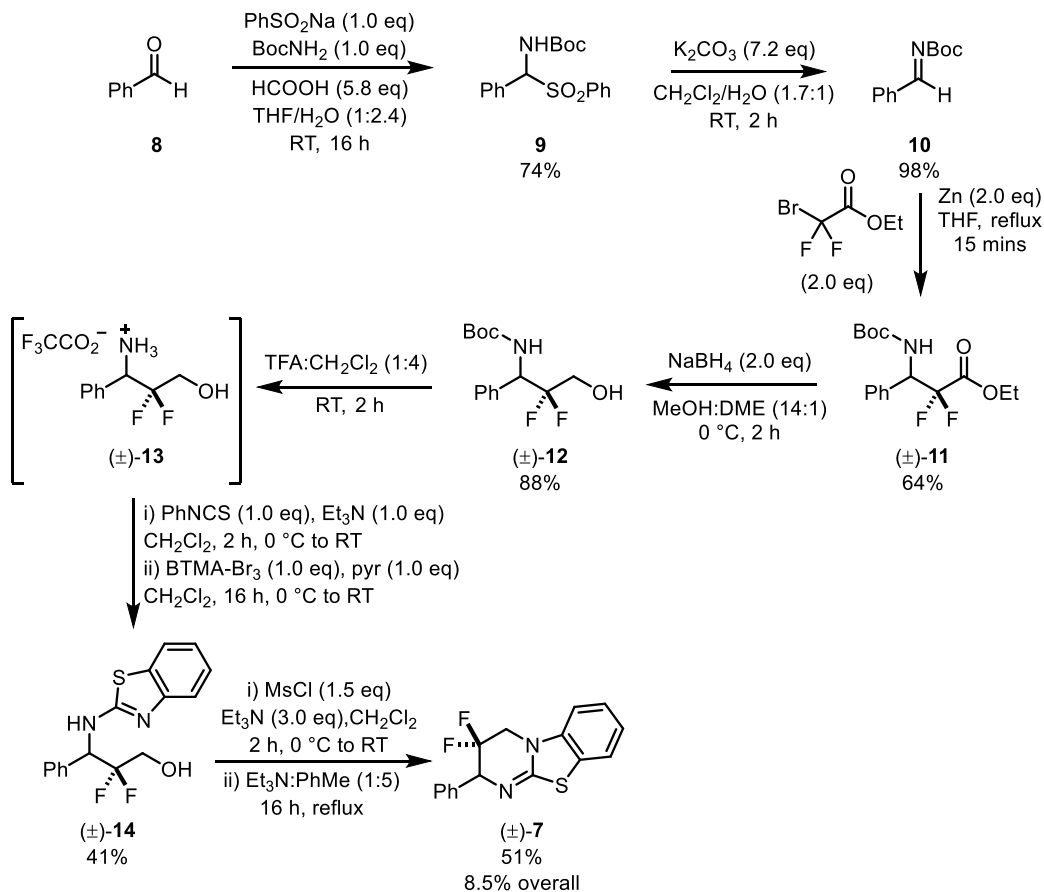
Figure 1. The fluorination approach to increase organocatalyst oxidation potential

Results and Discussion

Racemic Route

Initial work focused on the optimisation of a racemic route to the target. Benzaldehyde **8** was condensed with *tert*-butyl carbamate and sodium benzenesulfinate to give sulfone **9**, followed by treatment with a biphasic basic mixture gave NBoc aldimine **10** on a decagram scale in good yield as previously reported (Scheme 2).²⁵ A Reformatsky reaction with ethyl bromodifluoroacetate gave the *gem*-difluorinated NBoc β -amino ester **11** in good yield. Reduction of **11** with sodium borohydride gave NBoc amino alcohol **12** in an excellent yield of 88%, with subsequent Boc deprotection of **12** with TFA giving the amino alcohol **13** as its trifluoroacetate salt. This salt was treated with 1.0 equivalent of phenyl isothiocyanate generating the

corresponding thiourea *in situ*. Addition of benzyltrimethylammonium tribromide (BTMA-Br₃) into the reaction mixture gave the benzothiazole **14** *via* a Hegerschoff reaction in 41% yield over three steps.²⁶⁻²⁷ The alcohol was activated by treatment with methanesulfonyl chloride and subsequently heated under basic conditions overnight, which gave the racemic C(3)-*gem*-difluorinated isothiurea **7** in 8.5% overall yield over 9 steps.

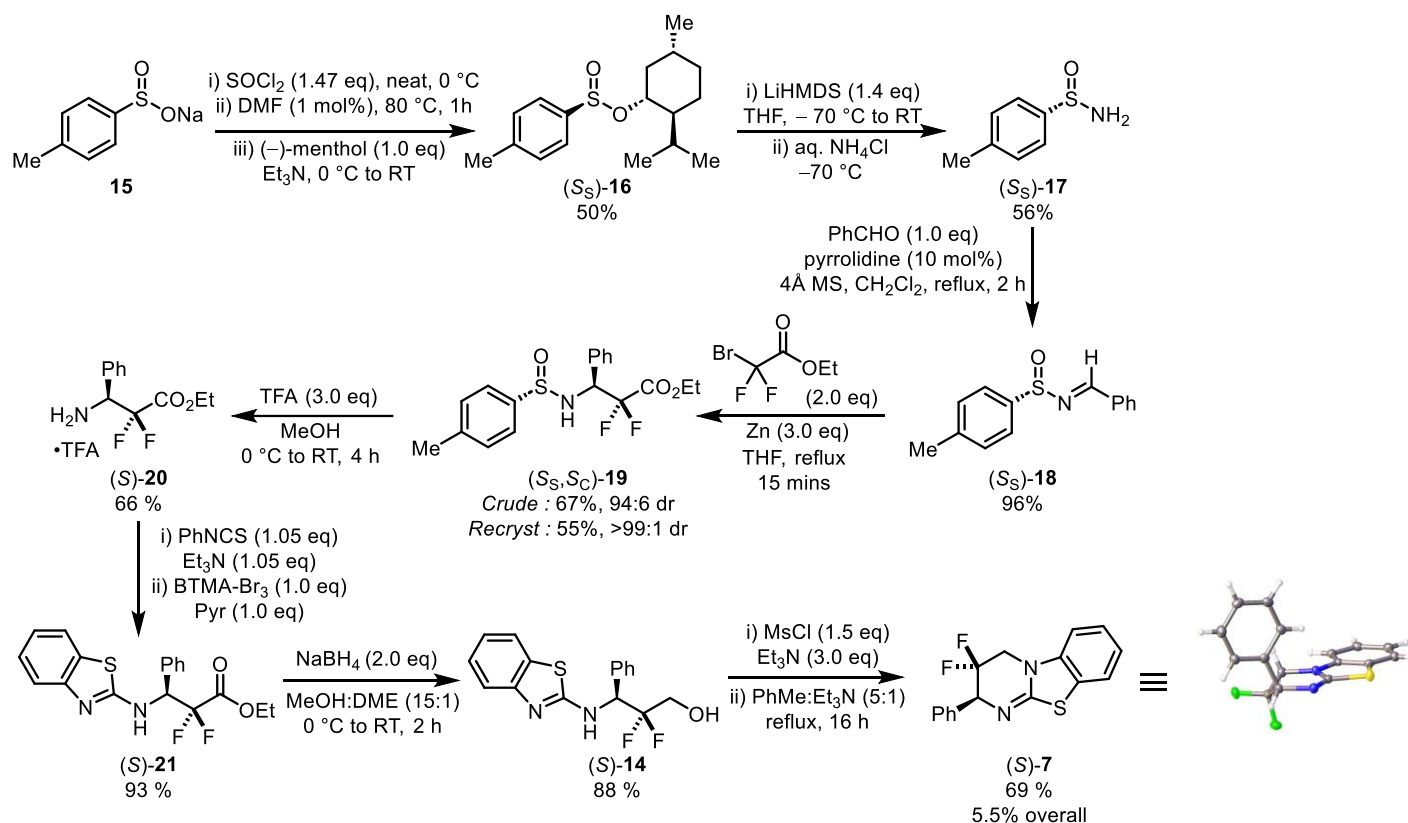


Scheme 2. The synthetic approach to racemic C(3)-F₂-HBTM **7**

Route to enantiomerically pure material

To evaluate the performance of **7** in asymmetric catalysis, access to this compound in enantiopure form was required. The synthesis began by producing Andersen's sulfinate **16** on a decagram scale by the reaction of (–)-menthol with 4-methylbenzenesulfinyl chloride (Scheme 3). Reaction of **16** with LiHMDS, followed by an acidic hydrolysis, led to the corresponding enantiopure sulfinamide **17**.²⁸ Condensation of this sulfinamide **17** with benzaldehyde with catalytic pyrrolidine gave the corresponding sulfinimine **18**.²⁹ A diastereoselective Reformatsky reaction with ethyl bromodifluoroacetate led to the difluorinated sulfinamide **19** with high levels of diastereoselectivity (94:6 dr).³⁰⁻³⁷ Subsequent recrystallization gave diastereomerically pure **19** in a good yield of 55%. Cleavage of the sulfinyl group in acidic methanol led to the difluorinated β-amino ester **20**, which was isolated and stored as its trifluoroacetate salt.³⁸ Reaction of this salt with phenyl isothiocyanate gave the corresponding thiourea *in situ*, which after treatment with BTMA-Br₃ gave the benzothiazole amino ester **21**. Reduction of **21** with sodium borohydride gave the amino alcohol **14**. Ring closure conditions as previously employed for the racemic variant gave the isothiurea **7** as a single enantiomer (>99:1 er) by HPLC analysis on a chiral stationary

phase. A suitable single crystal was grown by vapour diffusion which confirmed the absolute configuration for (S)-**7**.³⁹



Scheme 3. The synthetic route to enantiomerically pure (S)-C(3)-F₂-HBTM **7**

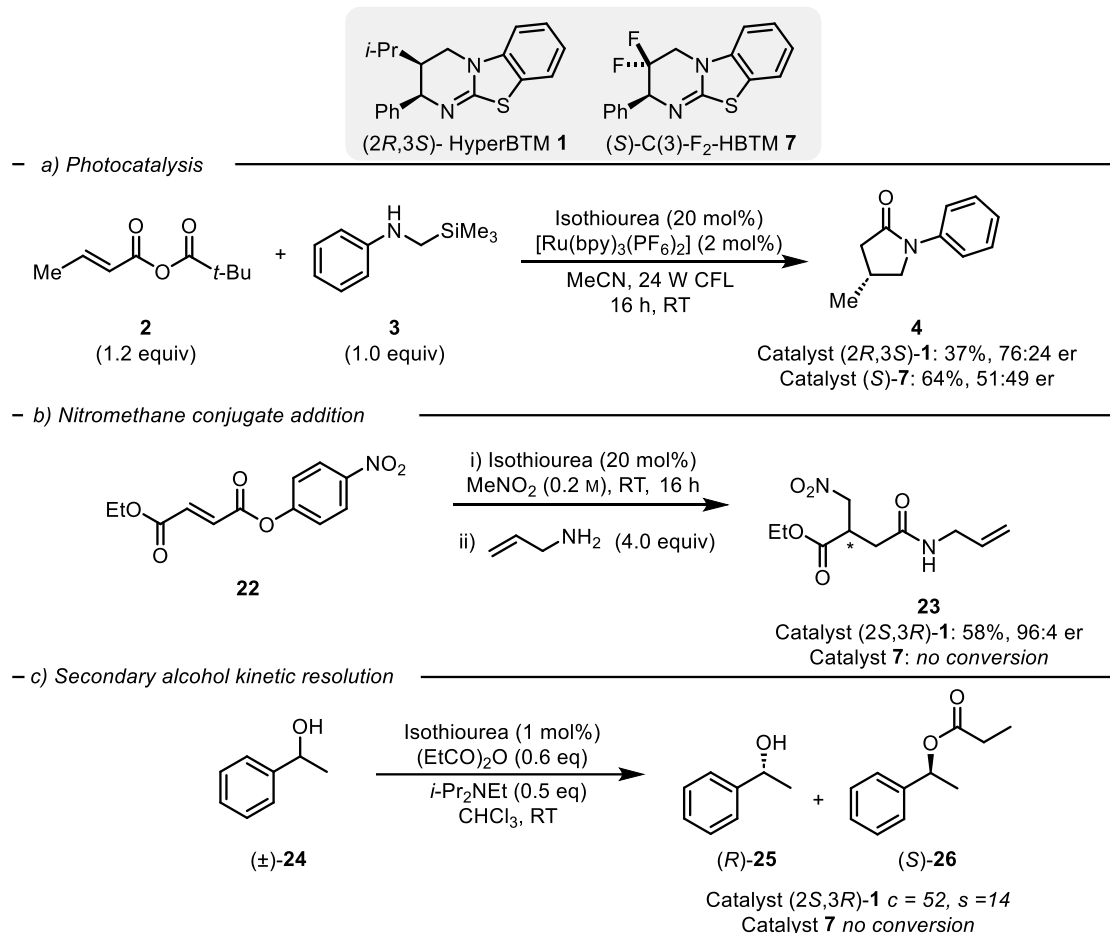
Evaluation of catalytic and physical properties

As predicted, electrochemical analysis indicated that the incorporation of the difluorinated motif within the catalyst skeleton led to a small but significant increase in the oxidation potential of C(3)-F₂-HBTM **7** ($E_{\text{ox}} = +1.36$ V, 9.1 mM in MeCN, vs. Ag/Ag⁺, Pt working electrode, electrolyte Bu₄NClO₄ 100 mM, with Ferrocene 5 mM) relative to HyperBTM **1** ($E_{\text{ox}} = +1.14$ V, 7.1 mM in MeCN, vs. Ag/Ag⁺, Pt working electrode, electrolyte Bu₄NClO₄ 100 mM, with Ferrocene 5 mM). When **7** was examined in the dual isothiurea photoredox reaction, a significantly enhanced yield of the product **4** was observed (from 37% to 64%) with no catalyst degradation seen, consistent with the incorporation of the difluorinated motif having the desired effect of minimising this competitive process (

Scheme 4a). Disappointingly the product **4** was racemic, which led to us examine the competency of this isothiurea catalyst in a range of alternative well established Lewis base promoted transformations that have previously been reported. No reaction was observed for the conjugate addition of nitromethane to α,β -unsaturated PNP ester **22** (

Scheme 4b).⁴⁰ The kinetic resolution of secondary alcohol **24** gave only trace conversion to the ester **26** when the fluorinated isothiurea **7** was employed (

Scheme 4c).



Scheme 4. Reactivity comparisons between HyperBTM **1** and (*S*)-C(3)-F₂-HBTM **7**; (*c* = conversion, *s* = selectivity factor)⁴¹

The lack of efficiency in established Lewis base catalysed processes when using C(3)-F₂-HBTM **7** led us to question the effect of the fluorinated motif upon catalyst nucleophilicity. To investigate this, the kinetics of C(3)-F₂-HBTM **7** reacting with benzhydrylium ions as reference electrophiles *via* adducts **27** were photometrically investigated by the previously reported stopped-flow method in order to enable a comparison of the nucleophilic reactivity of **7** with that of the HyperBTM **1** and HBTM **28** isothiourea catalysts (Figure 2a).⁴²⁻⁴³ The isothiourea catalyst was employed in excess (at least 4 equiv.) to achieve pseudo first-order kinetics regarding the benzhydrylium ion. The decay of the absorbance of benzhydrylium ions **29** – **37** and hence their concentration (*via* the Beer-Lambert law) was observed at their corresponding absorption maxima and can be fitted using the monoexponential function $A = A_0 \cdot e^{-k_{\text{obs}}t} + C$ to obtain the value of the first order rate constant k_{obs} . Unfortunately, initially applied cations **33** and **34** formed an equilibrium with **7** hindering the observation of a sufficient decay in absorption to apply an exponential fit. Conversely, more electrophilic benzhydrylium ions **35**, **36** and **37** showed acceptable levels of decay to obtain k_{obs} values. A representative sample of such a decay with exponential fit is shown in Figure 3a employing **7** in a 10-fold excess with (pfa)₂CH⁺BF₄⁻ **37**. The good quality of this fit is also highlighted by the residual graph ($A_{\text{obs}} - A_{\text{fit}} < 3\%$) in Figure 3b. The dependency of k_{obs} on the different excess concentrations correlates linearly and the second order rate constant k_1 can be extracted from the slope of the linear regression. For example, k_{obs} at 5 different concentrations of **7** with **37** were measured successfully to give a linear regression yielding $k_1 = 1.13 \cdot 10^6 \text{ M}^{-1} \cdot \text{s}^{-1}$ (Figure 3c). The k_1 values with different benzhydrylium ions can be substituted in the equation

log $k_1 = s_N(N+E)$ to determine the nucleophilicity (N) of the corresponding catalyst *via* linear regression to give $s_N = 0.80$ and $N = 10.80$ (Figure 3d and 3e).⁴⁴

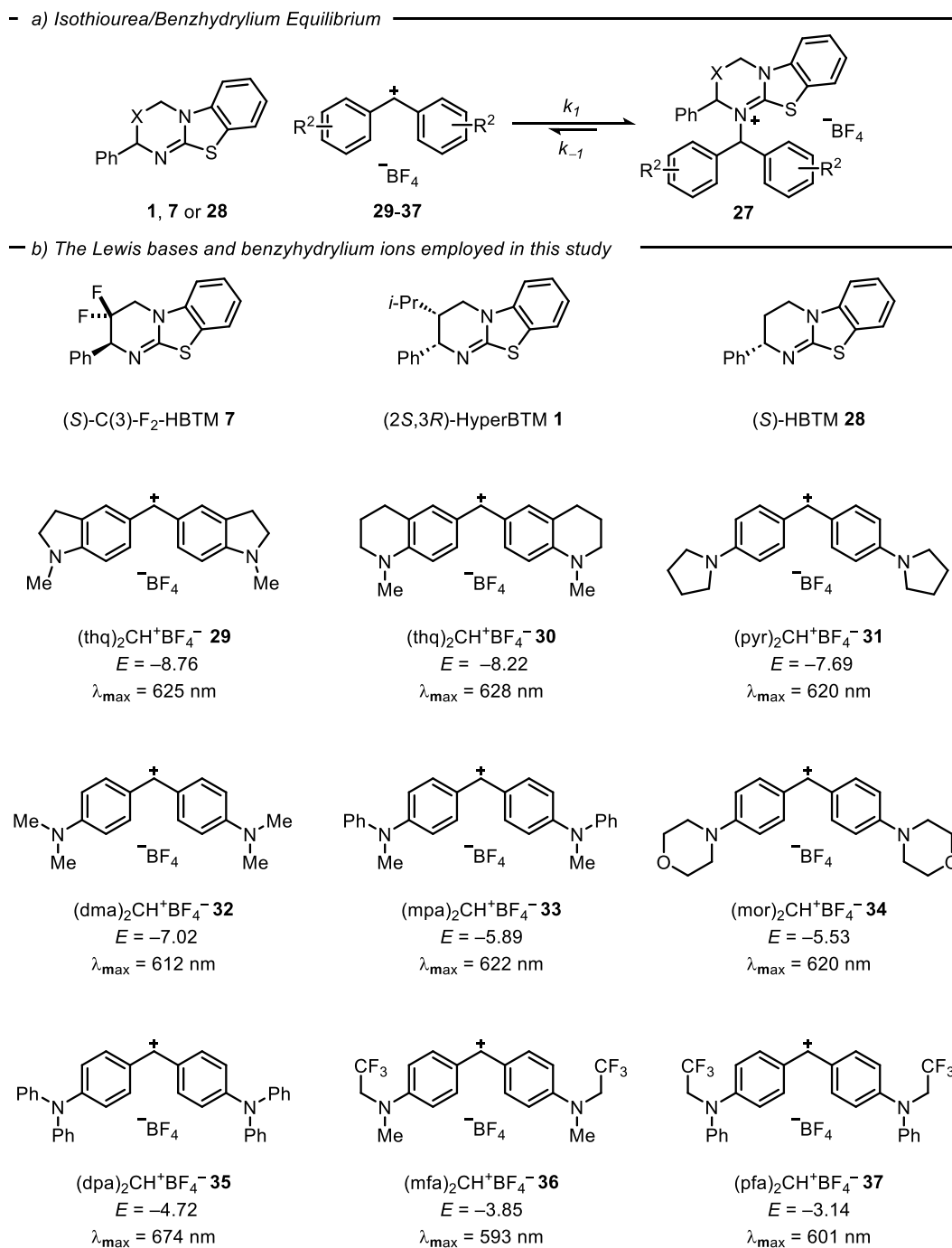
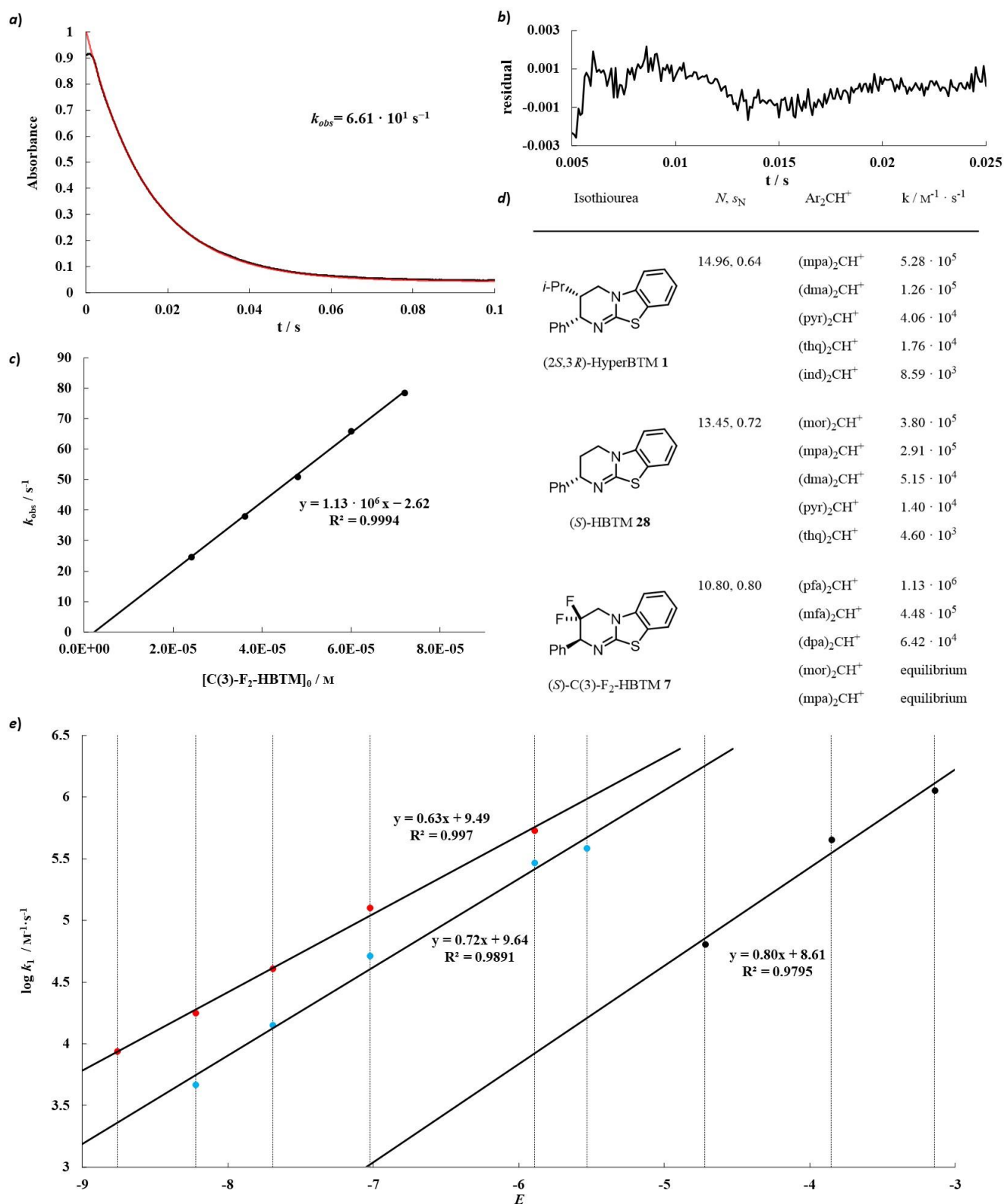


Figure 2. The kinetic study of isothioureas **1**, **7** or **28** with benzhydryliums **27**

In general, the equilibrium in

Figure 2a shifts further towards the starting materials with benzhydrylium ions of decreasing electrophilicity, meaning that other benzhydrylium ions that would react at a slower rate than **33** would also show a strong equilibrium with no sufficient signal decay within the observed time regime.⁴⁵ Due to this constraint only three rate constants k_1 were obtained. Additionally, due to equilibria present, product

identification was difficult due to potential mixtures of adduct and starting materials. Hence, it is assumed that adduct formation proceeds in analogy to previously identified and characterised substrates formed from **1** and **28**. Comparing the rate constant of C(3)-F₂-HBTM **7** to HyperBTM **1** and HBTM **28** (N 14.96, 13.45; s_N 0.63, 0.72; respectively)⁴⁶ significantly reduced nucleophilicity (approximately 4 or 2.5 orders of magnitude respectively) was observed. This, together with the observation of equilibria during the measurements confirms the hypothesis that the incorporation of the *gem*-difluoro motif within C(3)-F₂-HBTM **7** leads to lower catalytic reactivity due to the low propensity of **7** to form the catalytically active acyl ammonium species. It is apparent that the incorporation of the electron withdrawing *gem*-difluoro motif drastically alters the nucleophilicity of the Lewis base, although the relevance of electronic dipolar effects and changes to conformational preference have not been studied.



a) Absorbance at 601 nm during the reaction of **7** ($c = 6 \cdot 10^{-5} \text{ M}$) with (pfa)₂CH⁺BF₄⁻ **37** ($c = 6 \cdot 10^{-6} \text{ M}$) at 20 °C in CH₂Cl₂ as an average of 5 runs and exponential fit using ExpoFit programme; the concentration is the concentration in the mixing cell. **b)** Difference of observed and fitted absorbance in the fitted region. **c)** Determination of the second-order rate constant $k_1 = 1.13 \cdot 10^6 \text{ M}^{-1} \cdot \text{s}^{-1}$ from the dependency of k_{obs} on the concentration of C(3)-F₂-HBTM **7**. **d)** Plot of $\log k_1$ for the reactions of HyperBTM **1** (red), HBTM **28** (blue) and C(3)-F₂-HBTM **7** (black) with benzhydrylium ions (in order from left to right: (ind)₂CH⁺BF₄⁻ **29**, (thq)₂CH⁺BF₄⁻ **30**,

(pyr)₂CH⁺BF₄⁻ **31**, (dma)₂CH⁺BF₄⁻ **32**, (mpa)₂CH⁺BF₄⁻ **33**, (mor)₂CH⁺BF₄⁻ **34**, (dpa)₂CH⁺BF₄⁻ **35**, (mfa)₂CH⁺BF₄⁻ **36**, (pfa)₂CH⁺BF₄⁻ **37** against their corresponding *E* parameter (indicated by dashed lines) at 20 °C in CH₂Cl₂, with data from ref 37.

Figure 3. Kinetics measurements of isothioureas **1** and **7**

Conclusions

In conclusion, effective synthetic routes to the difluorinated isothiurea C(3)-F₂-HBTM **7** in both racemic and enantiopure form have been established. Electrochemical analysis indicated that the incorporation of the difluorinated motif within the catalyst skeleton led to a small but significant increase in the oxidation potential of C(3)-F₂-HBTM **7** (*E*_{ox} = +1.36 V) relative to HyperBTM **1** (*E*_{ox} = +1.14 V). However catalytic reactions using C(3)-F₂-HBTM **7** led to either significantly reduced product conversion (zero in some cases) or poor enantiocontrol (generating racemic material). Kinetic measurements indicate that C(3)-F₂-HBTM **7** is significantly less nucleophilic than HyperBTM **1**, which is proposed as the origin of the reduced catalytic scope.

Experimental Section

General. Analytical thin layer chromatography was performed on pre-coated aluminium plates (Kieselgel 60 F254 silica) and visualisation was achieved using ultraviolet light (254 nm) and/or staining with either aqueous KMnO₄ solution, ethanolic phosphomolybdic acid, or ethanolic Vanillin solution followed by heating. Manual column chromatography was performed in glass columns fitted with porosity 3 sintered discs over Kieselgel 60 silica using the solvent system stated. Melting points were recorded on an Electrothermal 9100 melting point apparatus, (dec) refers to decomposition. Optical rotations were measured on a Perkin Elmer Precisely/Model-341 polarimeter operating at the sodium D line with a 100 mm path cell at 20 °C.

Zinc dust was activated immediately prior to reaction *via* the following literature procedure.⁴⁶ Zinc (120 g) was stirred in 2% aq. HCl (300 mL) for 1 minute, the acid removed *via* filtration. The solid was washed with sequentially with 1 x 300 mL portion of 2% aq. HCl, 3 x 300 mL portions of H₂O, 2 x 200 mL portions of absolute ethanol and 2 x 200 mL portions of Et₂O. The solid was dried *in vacuo* at 50 °C for 6 hours.

'Chiral HPLC analysis' refers to HPLC analysis on a chiral stationary phase using either DAICEL CHIRALCEL OD-H and OJ-H columns or DAICEL CHIRALPAK AD-H, AS-H, IA, IB, IC and ID columns using the method stated. HPLC traces of enantiomerically enriched compounds were compared with authentic racemic spectra. Infrared spectra were recorded on a Shimadzu IRAffinity-1 Fourier transform IR spectrophotometer fitted with a Specac Quest ATR accessory (diamond puck).

¹H, ¹³C(¹H), and ¹⁹F(¹H) NMR spectra were acquired on either a Bruker AV300, AV400, AVII 400 or a AVII 500 spectrometer in the deuterated solvent stated. All chemical shifts are quoted in parts per million (ppm) relative to the residual solvent peak. All coupling constants, *J*, are quoted in Hz. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and multiples thereof. The abbreviation Ar denotes aromatic and app denotes apparent.

An Applied Photophysics SX.20 stopped-flow spectrophotometer system was used for monitoring the kinetics of the reactions of benzhydrylium ions with isothioureas. Cyclic voltammetry data was collected on a CH Instruments, Inc. CHI6330E Electrochemical Workstation with a Pt working electrode, Ag counter electrode and Ag/Ag⁺ (filled with electrolyte solution) reference electrode. Mass spectrometry (*m/z*) data were acquired

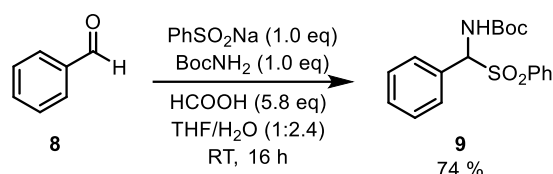
by either electrospray ionisation (ESI), chemical ionisation (CI), electron impact (EI), atmospheric solids analysis probe (ASAP), atmospheric pressure chemical ionization (APCI) or nanospray ionisation (NSI) at the University of St Andrews Mass Spectrometry Facility ([A] quoted).

Further general experimental details are available in the supplementary information file available in the online version.

The research data supporting this publication can be accessed at: "Unveiling the Impact of a CF₂ motif in the Isothiourea Catalyst Skeleton: Evaluating C(3)-F₂-HBTM and its Catalytic Activity". University of St Andrews Research Portal. <https://doi.org/10.17630/71039bf0-a0c5-44da-9934-0759efd35343>

Racemic Synthesis

Step 1) Synthesis of *tert*-butyl (phenyl(phenylsulfonyl)methyl)carbamate (**9**)



The following procedure was adapted from the literature.²⁵

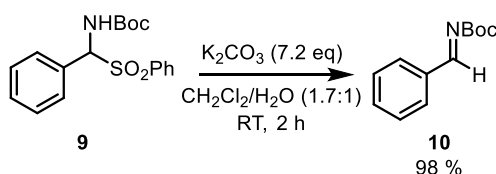
Tert-Butyl carbamate (23.44g, 200 mmol, 1.0 equiv) was added with stirring to a solution of THF:H₂O (74 mL:180 mL). Benzaldehyde (20.74 mL, 204 mmol, 1.02 equiv.), benzene sulfinic acid sodium salt (32.84 g, 200 mmol, 1.0 equiv.) and formic acid (43.6 mL, 1.16 mol, 5.8 equiv.) were added sequentially at room temperature and the resulting mixture was stirred at room temperature overnight. The resulting solid was collected *via* vacuum filtration with transfer from the reaction flask completed with a H₂O rinse (50 mL). The filter cake was rinsed sequentially with H₂O (2 x 200 mL) and CH₂Cl₂:Hexane (9:1, 100 mL). The resulting filter cake was transferred to a shallow Pyrex oven dish and dried in an oven at 90 °C for 2 hours to afford (±)-**9** as a snow white solid (51.30 g, 148 mmol, 74%).

Spectroscopic data was in agreement with the literature²⁵

Mp 150-151 °C (hexane:CH₂Cl₂) (Lit.²⁵ 164-165 °C (hexane:CH₂Cl₂))

¹H NMR (400 MHz, DMSO-*d*₆) δ_H: 1.15 (9H, s, C(CH₃)₃), 5.97 (1H, *d*, *J* 10.7, CH), 7.38 – 7.45 (3H, m, ArH), 7.57 – 7.66 (4H, m, ArH), 7.66 – 7.75 (1H, m, ArH), 7.82 – 7.89 (2H, m, ArH), 8.68 (1H, *d*, *J* 10.7, NH).

Step 2) Synthesis of *tert*-butyl benzylidenecarbamate (**10**)



The following procedure was adapted from the literature.²⁵

Sulfone **9** (18.5g, 53.1 mmol, 1.0 equiv.) and CH₂Cl₂ (270 mL) were added to a solution of potassium carbonate (52.8 g, 382 mmol, 7.2 eq) in H₂O (160 mL) at room temperature. The resulting biphasic mixture was vigorously stirred at room temperature for 2 hours (~900 rpm). The mixture was transferred to a separatory

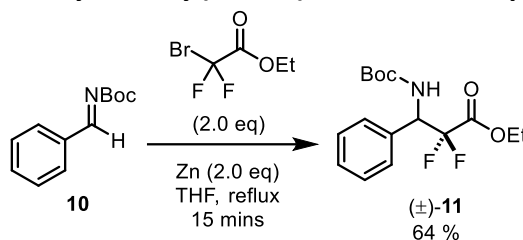
funnel followed by a CH₂Cl₂ rinse (50 mL) of the reaction flask. The aqueous phase was extracted with CH₂Cl₂ (3 x 30 mL). The organic phases were combined, washed (brine), dried (Na₂SO₄), the solvent removed under reduced pressure and dried *in vacuo* to give the crude imine **10** as a clear, colourless oil (10.71 g, 52.1 mmol, 98%).

NB Substantial hydrolysis of the imine **10** was observed after several days under ambient conditions in CDCl₃ in an NMR tube, whereas the neat oil is stable under N₂ at 4 °C for >2 weeks.

Spectroscopic data was in agreement with literature.²⁵

¹H NMR (500 MHz, CDCl₃) δ_H: 1.59 (9H, s, C(CH₃)₃), 7.45-7.49 (2H, m, ArH), 7.53-7.59 (1H, m, ArH), 7.89-7.94 (2H, m, ArH), 8.87 (1H, s, CH).

Step 3) Synthesis of ethyl 3-((*tert*-butoxycarbonyl)amino)-2,2-difluoro-3-phenylpropanoate (**11**)



The following procedure was adapted from the literature.^{30, 32}

A flame dried 3-necked round bottomed flask was charged with activated Zn dust (3.92 g, 60.0 mmol, 2.0 equiv.) under N₂. Anhydrous THF (150 mL) was transferred *via* cannula and the resulting mixture heated to reflux with vigorous stirring. To this refluxing mixture, a solution of imine **10** (6.15 g, 30.0 mmol, 1.0 equiv.) and ethyl bromodifluoroacetate (12.18 g, 60.0 mmol, 2.0 equiv.) in anhydrous THF (60 mL) was added dropwise over a period of 15 minutes. The resulting mixture was stirred at reflux for a further 15 min before being allowed to cool to room temperature. Sat. aq. NH₄Cl (150 mL) and H₂O (150 mL) were slowly added sequentially. The resulting mixture was transferred to a separatory funnel with H₂O (50 mL) and Et₂O (50 mL) rinses of the reaction flask. Et₂O (100 mL) was added and after shaking, the organic phase was set aside and the aqueous phase extracted with Et₂O (3 x 100 mL). The organic phases were combined, washed sequentially (sat. aq. NaHCO₃ and brine), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude oily residue. After purification *via* column chromatography (0 to 20% Et₂O in hexane, R_f = 0.28 (9% EtOAc in hexane)) gave the NBoc amino ester **11** as a clear, colourless oil which crystallized on standing overnight to give a colourless, translucent crystalline solid (6.32 g, 19.2 mmol, 64%).

Note: There is the presence of small amount of an unidentified impurity in the ¹⁹F and ¹H NMR spectrum but this was readily purged during the next step

Mp 74-76 °C (EtOAc:Hexane)

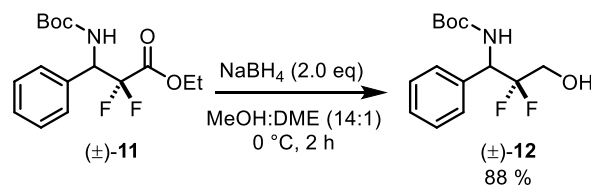
v_{max} (solid) 3366, 2976, 1757, 1711, 1530, 1368, 1306, 1246, 1156.

¹H NMR (500 MHz, CDCl₃) δ_H: 1.26 (3H, t, *J* 7.1, OCH₂CH₃), 1.42 (9H, s, C(CH₃)₃), 4.21-4.30 (2H, m, OCH₂CH₃), 5.30-5.46 (2H, m, NH and PhCH), 7.30-7.41 (5H, m, ArH).

¹³C(¹H) NMR (126 MHz, CDCl₃) δ_C: 13.9 (OCH₂CH₃), 28.3 (C(CH₃)₃), 56.7 (app. t, ²J_{CF} 24.5, PhCHCF₂), 63.3 (OCH₂CH₃), 80.8 (C(CH₃)₃), 114.1 (app. t, ¹J_{CF} 256.3, CF₂) 128.4 (ArCH), 128.9 (ArCH), 129.1 (ArCH), 133.7 (ArC), 154.7 (C(O)NH), 163.1 (app. t, ²J_{CF} 31.8, CO₂Et).

¹⁹F(H) NMR (470 MHz, CDCl₃): -112.02 (d, ²J_{FF} 256.4), -115.48 (d, ²J_{FF} 256.5).

HRMS (ESI⁺) C₁₆H₂₁F₂NNaO₄ [M+Na]⁺ found 352.1321, requires 352.1331 (-2.8ppm)

Step 4) Synthesis of (±)-tert-butyl (2,2-difluoro-3-hydroxy-1-phenylpropyl)carbamate (12)

The following procedure was adapted from the literature.⁴⁷

The NBoc amino ester **11** (3.29 g, 10.0 mmol, 1.0 equiv.) was dissolved in MeOH:DME (18.8 ml:1.3 mL) and cooled to 0 °C and sodium borohydride (760 mg, 20.0 mmol, 2.0 equiv.) added portionwise at 0 °C with vigorous stirring. The resulting mixture was stirred at 0 °C until gas evolution ceased, whereupon starting material consumption was confirmed *via* TLC analysis. Sat. aq. NaHCO₃ (100 mL) was added slowly, followed by a further 100 mL of H₂O. The mixture was transferred to a separatory funnel with H₂O (30 mL) and CH₂Cl₂ (30 mL) rinses of the reaction flask. The aqueous phase was extracted with CH₂Cl₂ (3 x 80 mL), the organic phases were combined, washed sequentially (sat. aq. NaHCO₃ and brine), dried (Na₂SO₄) and concentrated under reduced pressure to give a white solid residue. Hexane (50 mL) was added to the residue and the mixture sonicated for 5 minutes and the resulting white solid collected *via* vacuum filtration, washed with hexane (30 mL) and dried *in vacuo* to give NBoc amino alcohol **12** as a white solid (2.53 g, 8.82 mmol, 88%).

Mp 147-150 °C (Et₂O)

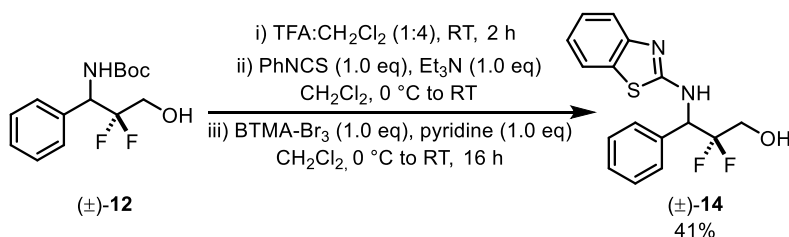
v_{max} (solid) 3335, 2950, 1676, 1533, 1159, 1057, 1045.

¹H NMR (400 MHz, CDCl₃) δ_H: 1.46 (9H, s, C(CH₃)₃), 3.63-3.91 (3H, m, CH₂ and OH), 5.09-5.23 (1H, m, PhCH), 5.23-5.32 (1H, m, NH), 7.32-7.45 (5H, m, ArH).

¹³C(¹H) NMR (101 MHz, CDCl₃) δ_C: 28.4 (C(CH₃)₃), 54.9 (dd, *J* = 33.0, 21.6, PhCHCF₂), 62.1 (dd, *J* 37.1, 27.9, CF₂CH₂OH), 81.6 C(CH₃)₃, 121.6 (t, *J* 250.0, CF₂), 128.6 (ArCH), 128.9 (2 x ArCH), 134.2 (ArC), 156.6 (C(O)NH).

¹⁹F(¹H) NMR (377 MHz, CDCl₃): -111.56 (d, ²*J*_{FF} 257.1), -121.60 (d, ²*J*_{FF} 257.4).

HRMS (ESI)⁺ C₁₄H₁₉F₂NO₃Na [M+Na]⁺ found 310.1216, requires 310.1225 (-2.9 ppm)

Step 5) Telescoped synthesis of (±)-3-(benzo[d]thiazol-2-ylamino)-2,2-difluoro-3-phenylpropan-1-ol (14)

The following procedure was adapted from the literature.²⁷

Trifluoroacetic acid (31 mL) was added to a mixture of the NBoc amino alcohol **12** (4.50 g, 15.7 mmol, 1.0 eq) in CH₂Cl₂ (125 mL). The resulting mixture was stirred at room temperature for 2 hours then concentrated under reduced pressure. Residual trifluoroacetic acid was removed by azeotroping the crude mixture with toluene (3 x 75 mL) and further drying *in vacuo*. The crude residue was redissolved in anhydrous CH₂Cl₂ (38 mL) under N₂ and cooled to 0 °C and triethylamine (2.19 mL, 15.7 mmol, 1.0 equiv.) added. Phenyl isothiocyanate (1.87 mL, 15.7 mmol, 1.0 equiv.) was added dropwise at 0 °C and the mixture warmed to room temperature and stirred for 2 hours. The mixture was cooled to 0 °C and pyridine (1.26 mL, 15.7 mmol, 1.0 equiv.) added. A solution of benzyltrimethylammonium tribromide (6.12 g, 15.7 mmol, 1.0 equiv.) in

anhydrous CH_2Cl_2 (38 mL) was added dropwise at 0 °C. The resulting mixture was stirred overnight at room temperature. 1M aq. NaOH (100 mL) was added slowly and the mixture stirred for 30 mins. The mixture was transferred to a separatory funnel and the aqueous phase extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure. Purification *via* column chromatography (0 to 33% Et_2O in hexane, $R_f = 0.17$ (33% Et_2O in hexane)) gave the title compound **14** as an off-white solid (2.07 g, 6.46 mmol, 41%)

Mp 154-155 °C (EtOAc:Hexane)

ν_{max} (solid) 3334, 3200, 1535, 1526, 1447, 1219, 1063

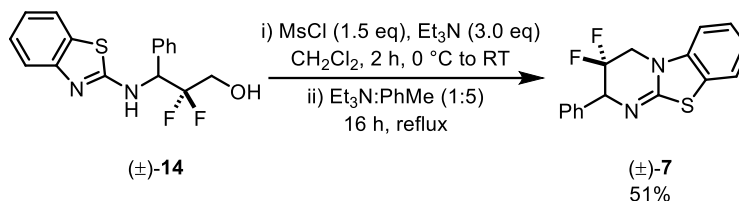
^1H NMR (400 MHz, CDCl_3) δ_{H} : 3.71-3.83 (1H, m, $\text{CH}_A\text{H}_B\text{OH}$), 3.84-4.00 (1H, m, $\text{CH}_A\text{H}_B\text{OH}$), 5.54-5.68 (2H, m, CHPh and OH), 5.94 (1H, dd, J 10.7, 5.1, NH), 7.15-7.20 (1H, m, ArCH), 7.32-7.38 (1H, m, ArCH), 7.40-7.47 (3H, m, ArCH), 7.47-7.54 (2H, m, ArCH), 7.56-7.61 (2H, m, ArCH).

^{13}C (^1H) NMR (101 MHz, CDCl_3) δ_{C} : 58.8 (dd, $^3J_{\text{CF}}$ 35.9, 21.4, CHPh), 61.6 (dd, $^3J_{\text{CF}}$ 38.8, 26.6, CH_2OH), 119.6 (ArCH), 121.2 (ArCH), 121.6 (dd, $^2J_{\text{CF}}$ 252.1, 249.7, CF_2), 123.2 (ArCH), 126.6 (ArCH), 128.7 (ArCH), 129.19 (ArCH), 129.24 (ArCH), 130.2 (ArC), 134.2 (ArC), 150.6 (ArC), 166.7 (ArC).

^{19}F (^1H) NMR (377 MHz, CDCl_3): -109.12 (d, $^2J_{\text{FF}}$ 258.1), -122.16 (d, $^2J_{\text{FF}}$ 258.3).

HRMS (ESI⁺) $\text{C}_{16}\text{H}_{15}\text{ON}_2\text{F}_2\text{S}$ [$\text{M} + \text{H}$]⁺ found 321.0863, requires 321.0868 (-1.4 ppm)

Step 6) Synthesis of (\pm)-3,3-difluoro-2-phenyl-3,4-dihydro-2H-benzo[4,5]thiazolo[3,2-a]pyrimidine (7)



Methanesulfonyl chloride (509 μL , 6.58 mmol, 1.50 equiv.) was added dropwise to amino alcohol **14** (1.41 g, 4.39 mmol, 1.0 equiv.) and triethylamine (1.84 mL, 13.2 mmol, 3.0 equiv.) in anhydrous CH_2Cl_2 (29 mL) under N_2 at 0 °C. The mixture was warmed to room temperature and stirred for 2 hours until starting material consumption was confirmed by NMR spectroscopy (Note 1). The mixture was concentrated under reduced pressure and anhydrous toluene (58 mL) and triethylamine (12 mL) were added under N_2 and the resulting mixture was heated at reflux overnight. The mixture was allowed to cool to room temperature and concentrated under reduced pressure. CH_2Cl_2 (40 mL) was added and washed (aq. sat. NaHCO_3). The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL). The organic phases were combined, washed (brine), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude residue. The crude residue was purified *via* column chromatography (15% to 20% THF in hexane). However, NMR analysis of the isolated compound indicated the presence of an aromatic impurity. A further attempt at purification *via* column chromatography (0 to 0.5% MeOH in CH_2Cl_2) removed some of the impurity but not all. Recrystallisation from CHCl_3 :cyclohexane gave the title compound **7** as an analytically pure clear colourless, crystalline solid (0.68 g, 2.26 mmol, 51%).

Note: A 0.1 mL aliquot of the crude reaction mixture was concentrated under reduced pressure and dissolved in 0.6 mL CDCl_3 and analysed *via* ^1H NMR, the disappearance of the starting material alcohol signals at ~ 3.68 and ~ 3.86 ppm was used to monitor starting material consumption.

Mp 179-180 °C (CHCl_3 :cyclohexane)

v_{\max} (solid) 1614, 1584, 1472, 1452, 1354, 1267, 1227, 1161, 1099

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ_{H} : 3.90 (1H, ddd, J 14.9, 12.2, 8.3, CH_AH_B), 4.01 (1H, dddd, J 15.3, 12.0, 8.3, 2.4, CH_AH_B), 4.94 (1H, ddd, J 13.6, 7.9, 2.4, PhCH), 6.72-6.77 (1H, m, ArH), 7.10 (1H, app. td, J 7.7, 1.1, ArH), 7.24-7.28 (1H, m, ArH), 7.33-7.43 (6H, m, ArH).

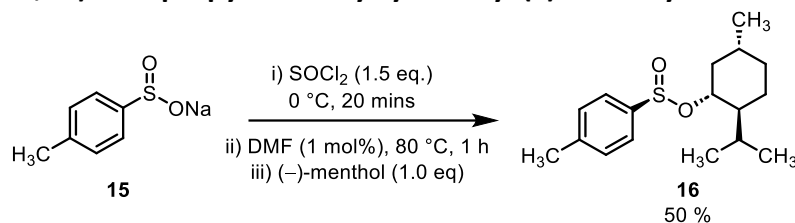
$^{13}\text{C}(^1\text{H}) \text{NMR}$ (126 MHz, CDCl_3) δ_{C} : 46.4 (app. t, $^2J_{\text{CF}}$ 33, CH_2), 63.4 (dd, J 24.0, 21.9, PhCH), 107.8 (ArCH), 116.1 (dd, $^1J_{\text{CF}}$ 250.0, 246.4, CF_2), 122.4 (ArCH), 123.0 (ArCH), 123.8 (ArC), 126.4 (ArCH), 128.46 (ArCH), 128.49 (ArCH), 128.7 (ArCH), 136.0 (d, $^3J_{\text{CF}}$ 3.6, ArC), 139.3 (ArC), 157.6 (ArC).

$^{19}\text{F}(^1\text{H}) \text{NMR}$ (470 MHz, CDCl_3): -104.6 (d, $^2J_{\text{FF}}$ 250.7), -112.5 (d, $^2J_{\text{FF}}$ 250.8).

HRMS (ESI) $^+$ $\text{C}_{16}\text{H}_{13}\text{N}_2\text{F}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ found 303.0756, requires 303.0762 (-1.9 ppm)

Synthesis in enantiopure form

Step 1) Synthesis of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (*S*)-4-methylbenzenesulfinate (**16**)



The following procedure was adapted from the literature.²⁸

Sodium *para*-toluenesulfinate **15** (50.0 g, 284 mmol, 1.0 equiv.) was added portionwise to thionyl chloride (30.0 mL, 414 mmol, 1.47 equiv.) at 0 °C over 10 minutes. After the addition of sodium *para*-toluenesulfinate was complete, DMF (0.22 mL) was added, a drying tube fitted with CaCl_2 was added and the resulting mixture heated at 80 °C for 1 hour. Toluene (100 mL) was added and the mixture concentrated under reduced pressure to remove residual thionyl chloride. Anhydrous CH_2Cl_2 (300 mL) was added to the residue and the mixture cooled to 0 °C. (-)-Menthol (42.0 g, 269 mmol, 0.96 equiv.) in triethylamine (44 mL) was added dropwise to the mixture at 0 °C, the mixture stirred at room temperature for 2 hours. The mixture was poured into a mixture of brine (50 mL) and 1 M aq. HCl (50 mL) in a separatory funnel and shaken. The aqueous phase was extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, washed sequentially (1M aq. HCl (2 x 50 mL), sat. aq. NaHCO_3 (2 x 50 mL)) and brine (100 mL)), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude residue. The crude residue was dissolved in acetone (100 mL), ~4 drops of 37% aq. HCl were added and the residue was mixed and placed in a -20 °C freezer overnight. The solid formed was collected *via* vacuum filtration cold and washed with a small amount of cold acetone (-20 °C). The solid was collected and dried *in vacuo* and the mother liquor concentrated to roughly half volume, 1-2 drops of aq. 37% HCl was added to the mother liquor and the mixture left to stand overnight in a -20 °C freezer. This process was repeated until appreciable amounts of crystals could no longer be recovered from the mother liquor. The crops of crystals were combined, recrystallized from a minimum amount of hot acetone, placed in a -20 °C freezer and collected *via* vacuum filtration, washed with cold acetone (-20 °C) and dried *in vacuo* to give the title compound **16** as clear, colorless needle like crystals (41.75 g, 141 mmol, 50%).

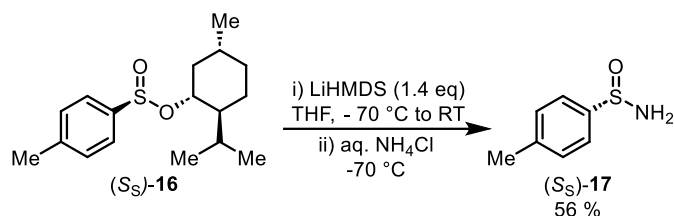
Mp 93-95 °C (acetone) (Lit.⁴⁹ 110 °C)

Specific Rotation $[\alpha]_{\text{D}^{20}} -206.6$ (c 1.0 in CHCl_3) (Lit.⁴⁹ $[\alpha]_{\text{D}^{20}} -202$ (c 2.0 in acetone))

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ_{H} : 0.71 (3H, d J 6.0, CH_3), 0.81-0.92 (4H, m, CH_3 and CH), 0.96 (3H, d J 6.5, CH_3), 0.98-1.09 (1H, m, CH_2), 1.16-1.28 (1H, m, CH_2), 1.30-1.40 (1H, m, CH), 1.42-1.53 (1H, m, CH), 1.64-1.72 (2H, m,

CH_2), 2.09-2.18 (1H, m, CH), 2.24-2.31 (1H, m, CH_2), 2.42 (3H, s, ArCH_3), 4.12 (1H, td, J 10.8, 4.5, CH), 7.30-7.34 (2H, m, ArCH), 7.58-7.62 (2H, m, ArCH).

Step 2) Synthesis of (S)-4-methylbenzenesulfinamide (17)



The following procedure was adapted from the literature.³⁸

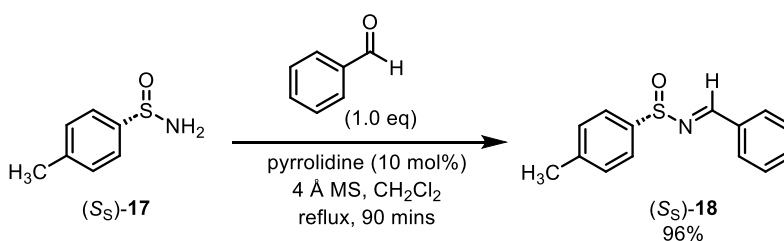
(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl (S)-4-methylbenzenesulfinate **16** (30.31 g, 103 mmol, 1.0 equiv.) was added to a flame dried three-necked RBF under N_2 and anhydrous THF (220 mL) added *via* cannula. The mixture was cooled to -78 °C with the aid of a liquid nitrogen/acetone bath and lithium bis(trimethylsilyl)amide (139 mL, 139 mmol, 1.35 equiv, 1.0 M in THF) was added *via* cannula at -78 °C. The resulting mixture was warmed to room temperature and stirred for 4 ½ hours. The mixture was cooled to -78 °C and aq. 30% NH_4Cl (120 mL) was added slowly at -78 °C. The mixture was warmed to room temperature and H_2O (80 mL) added. The aqueous phase was extracted with Et_2O (3 x 150 mL) and the organic phases were combined, washed (H_2O , 2 x 120 mL), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude residue. The residue was triturated with cold pentane to give the title compound **17** as a fluffy, white solid (9.02 g, 58.1 mmol, 56%).

Mp 119-120 °C (pentane) (Lit.³⁸ 110-112 °C)

Specific Rotation $[\alpha]_{\text{D}^{20}} +44.6$ (c 0.7 in CHCl_3) (Lit.³⁸ $[\alpha]_{\text{D}^{20}} +79.7$ (c 1.2 in CHCl_3))

^1H NMR (500 MHz, CDCl_3) δ_{H} : 2.42 (3H, s, CH_3), 4.24 (2H, br s, NH_2), 7.29-7.34 (2H, m, ArCH), 7.61-7.66 (2H, m, ArCH)

Step 3) Synthesis of (S)-*N*-benzylidene-4-methylbenzenesulfinamide (18)



The following procedure was adapted from the literature.²⁹

A 500 mL three-necked flask was charged with 4 Å MS (60 g) and flame-dried *in vacuo*. Once the flask had cooled to room temperature and back filled with N_2 x 3, anhydrous CH_2Cl_2 (180 mL) was added *via* cannula. (S)-4-methylbenzenesulfinamide **17** (8.85 g, 57.0 mmol, 1.0 equiv.), benzaldehyde (5.82 mL, 6.04 g, 57.0 mmol, 1.0 equiv.) and pyrrolidine (468 μL , 405 mg, 5.7 mmol, 0.1 equiv.) were sequentially added. The resulting mixture was stirred at reflux for 90 minutes. After cooling to room temperature, the mixture was filtered

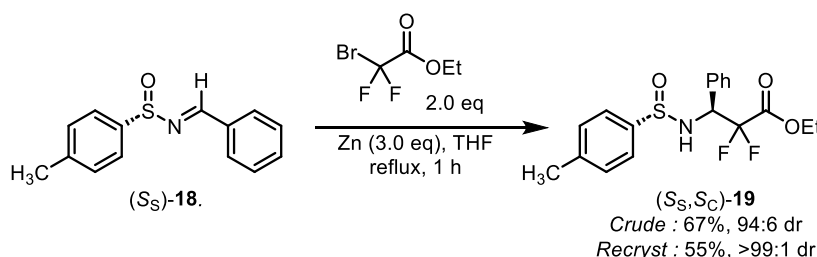
through a pad of Celite[®], the pad washed with CH₂Cl₂ (100 mL) and the filtrate concentrated under reduced pressure. Upon standing at room temperature for ~5 minutes, the resulting oil crystallised, providing the title compound **18** after drying *in vacuo* (13.25 g, 54.5 mmol, 96%).

Mp 81-82 °C (CH₂Cl₂) (Lit.³⁸ 80-81 °C)

Specific Rotation $[\alpha]_{D}^{20} +112.6$ (c 1.0 in CHCl₃) (Lit.³⁸ $[\alpha]_{D}^{20} +122.8$ (c 1.2 in CHCl₃))

¹H NMR (400 MHz, CDCl₃) δ_H : 2.40 (3H, s, CH₃), 7.29-7.34 (2H, m, ArH), 7.42-7.54 (3H, m, ArH), 7.60-7.66 (2H, m, ArH), 7.82-7.87 (2H, m, ArH), 8.75 (1H, s, CH).

Step 4) Synthesis of ethyl (S)-2,2-difluoro-3-phenyl-3-(((S)-p-tolylsulfinyl)amino)propanoate (**19**)



The following procedure was adapted from the literature.^{30, 32}

A flame-dried three-necked flask under N₂ was charged with activated zinc dust (8.02 g, 122.7 mmol, 3.0 equiv.). Anhydrous THF (205 mL) was added *via* cannula and the mixture heated to reflux. A solution of ethyl bromodifluoroacetate (10.50 mL, 16.62 g, 2.0 equiv.) and sulfinimine **18** (9.96 g, 40.9 mmol, 1.0 equiv.) in anhydrous THF (80 mL) was added dropwise at reflux. The mixture was stirred at reflux for approx. 75 mins. The mixture was allowed to cool to room temperature and sat. aq. NH₄Cl (200 mL) and H₂O (200 mL) added slowly with vigorous stirring and the mixture transferred to a separatory funnel. The organic phase was decanted and the aqueous phase extracted with EtOAc (3 x 100 mL). The organic phases were combined, washed (brine), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude residue. Purification *via* column chromatography (0 to 25% EtOAc in petrol, R_f = 0.3 (25% EtOAc in petrol)) gave the title compound **19** with a diastereomeric ratio of 96:4. Recrystallisation from EtOAc:hexane gave the title compound **19** as a single diastereoisomer (8.26 g, 22.5 mmol, 55%).

Note: Diastereomeric ratio was judged by ¹H NMR analysis by evaluating the integral ratio of the diagnostic ArCH₃ signals at δ 2.43 ppm (*major*) and δ 2.36 ppm (*minor*)

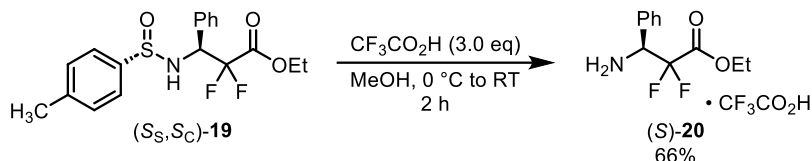
Mp 120-121 °C (EtOAc:Hexane) (Lit.^{30, 32} 119-120 °C)

Specific Rotation $[\alpha]_{D}^{20} +139.9$ (c 0.95 in CHCl₃) (Lit.^{30, 32} $[\alpha]_{D}^{20} +116.2$ (c 1.04 in CHCl₃))

¹H NMR (400 MHz, CDCl₃) δ_H : 1.18 (3H, t J 7.2, OCH₂CH₃), 2.43 (3H, s, CH₃), 4.09-4.24 (2H, m, OCH₂CH₃), 4.87-5.01 (2H, m, NH and PhCH), 7.29-7.35 (2H, m, ArH), 7.37-7.44 (5H, m, ArH), 7.54-7.59 (2H, m, ArH).

¹⁹F(¹H) NMR (377 MHz, CDCl₃): -114.11 (d, ²J_{FF} 256.0), -112.09 (d, ²J_{FF} 256.2)

Step 5) Synthesis of (S)-3-ethoxy-2,2-difluoro-3-oxo-1-phenylpropan-1-ammonium trifluoroacetate (**20**)



The following procedure was adapted from the literature.³⁸

Trifluoroacetic acid (5.99 mL, 8.92 g, 78.3 mmol, 3.0 equiv.) was added dropwise to a solution of **19** (9.58 g, 26.1 mmol, 1.0 equiv.) in methanol (96 mL) under N₂ at 0 °C. The mixture was warmed to room temperature and stirred for 2 hours. The mixture was concentrated under reduced pressure, Et₂O (100 mL) was added and the mixture sonicated for 5 minutes. The resulting solid was collected *via* vacuum filtration, washed (Et₂O) and dried *in vacuo* to give the title compound **20** as a fluffy white solid (5.91 g, 17.2 mmol, 66%).

Mp 137-138 °C (Et₂O)

Specific Rotation $[\alpha]_{D^{20}} -2.3$ (c 1.0 in MeOH)

v_{max} (solid) 2864, 2654, 1761, 1659, 1622, 1553, 1184, 1142, 1115

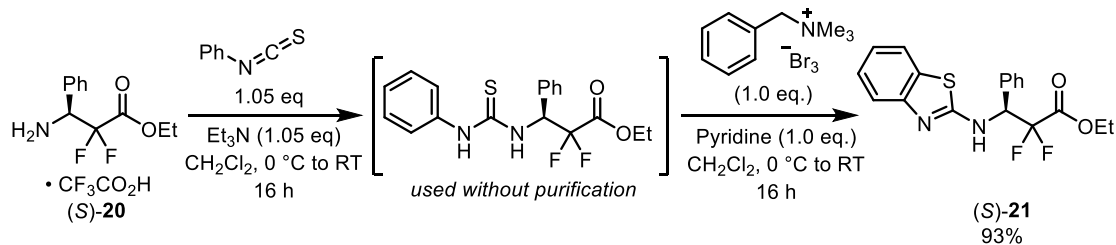
¹H NMR (500 MHz, CD₃CN) δ_H : 1.16 (3H, t *J* 7.1, OCH₂CH₃), 4.21 (2H, q *J* 7.1, OCH₂CH₃), 4.99 (1H, dd *J* 17.0, 9.8, PhCH), 5.80 (br s, NH₃, exchange with H₂O in the CD₃CN so integral not accurate), 7.41-7.50 (5H, m, ArH).

¹³C(1H) NMR (126 MHz, CD₃CN) δ_C : 13.9 (OCH₂CH₃), 57.9 (app. t, ²*J*_{CF} 23.5, PhCH), 65.0 (OCH₂CH₃), 114.4 (app t, ¹*J*_{CF} 257.7, CF₂), 129.8 (ArCH), 130.0 (ArCH), 130.5 (app. d, ³*J*_{CF} 4.8, ArC), 131.3 (ArCH), 162.0 (m, CO₂Et).

¹⁹F NMR (377 MHz, CDCl₃): -116.93 (dd, ²*J*_{FF} 256.9 ³*J*_{HF} 16.7), -110.51 (dd, ²*J*_{FF} 257.3 ³*J*_{HF} 10.4), -76.34 (s, CF₃).

HRMS (ESI⁺) C₁₁H₁₄O₂NF₂ [M]⁺ found 230.0979, requires 230.0987 (-3.6 ppm)

Step 6) Synthesis of ethyl (S)-3-(benzo[d]thiazol-2-ylamino)-2,2-difluoro-3-phenylpropanoate (**21**)



The following procedure was adapted from the literature.²⁷

Triethylamine (2.33 mL, 1.69 g, 16.7 mmol, 1.05 equiv.) was added to amino ester **20** (5.46 g, 15.9 mmol, 1.0 equiv.) in CH₂Cl₂ (32 mL) under N₂. The resulting mixture was cooled to 0 °C and phenyl isothiocyanate (1.99 mL, 2.26 g, 16.7 mmol, 1.05 equiv.) added dropwise at 0 °C. The mixture was warmed to room temperature and stirred overnight. The mixture was transferred to a separatory funnel, with CH₂Cl₂ rinses (3 x 10 mL) of the reaction flask. Sat. aq. NaHCO₃ (100 mL) was added and the mixture shaken, after decanting the organic layer the aqueous phase was extracted with CH₂Cl₂ (3 x 30 mL). The organic phases were combined, washed (brine), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude thiourea, which was used without further purification. This residue was dissolved in CH₂Cl₂ (40 mL), pyridine (1.28 mL, 1.26 g, 15.9 mmol, 1.0 equiv.) added and the mixture cooled to 0 °C. A solution of benzyltrimethylammonium tribromide (6.20 g, 15.9 mmol, 1.0 equiv.) in CH₂Cl₂ (40 mL) was added dropwise at 0 °C. The mixture was warmed to room temperature and stirred overnight. Sat. aq. NaHCO₃ (150 mL) was added and the mixture stirred at room temperature for 30 minutes. The aqueous phase was extracted with CH₂Cl₂ (3 x 30 mL), the organic phases were combined, washed (brine), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude

residue. Purification *via* column chromatography ((0 to 25% EtOAc in petrol), R_f 0.58 (25% EtOAc in petrol)) gave the title compound **21** as a white, crystalline solid (5.38 g, 14.8 mmol, 93%).

Mp 154-155 °C (EtOAc:Hexane)

Specific Rotation $[\alpha]_{D^{20}} +91.1$ (c 1.0 in CHCl_3)

ν_{max} (solid) 3350, 2980, 1757, 1533, 1207, 1193

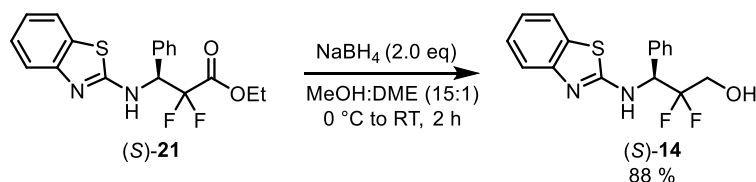
^1H NMR (500 MHz, CDCl_3) δ_{H} : 1.22 (3H, t J 7.1, OCH_2CH_3), 4.20-4.28 (2H, m, OCH_2CH_3), 5.73 (1H, dd J 17.6, 8.5, PhCH), 6.23 (1H, br s, NH), 7.08-7.13 (1H, m, ArH), 7.27-7.32 (1H, m, ArH), 7.35-7.41 (3H, m, ArH), 7.44-7.52 (2H, m, ArH), 7.53-7.59 (2H, m, ArH).

^{13}C (^1H) NMR (101 MHz, CDCl_3) δ_{C} : 13.9 (OCH_2CH_3), 60.6 (dd, $^2J_{\text{CF}}$ 27.0, 23.5, PhCH), 63.6 (OCH_2CH_3), 113.9 (app. t, $^1J_{\text{CF}}$ 257.7, CF_2), 120.0 (ArCH), 121.0 (ArCH), 122.5 (ArCH), 126.2 (ArCH), 128.5 (ArCH), 128.9 (ArCH), 129.4 (ArCH), 133.0 (ArC), 151.8 (ArC), 162.8-163.6 (m, CO_2Et), 165.4 (ArC).

^{19}F (^1H) NMR (377 MHz, CDCl_3): -116.01 (d, $^1J_{\text{FF}}$ 258.1), -110.52 (d, $^1J_{\text{FF}}$ 258.7)

HRMS (ESI $^+$) $\text{C}_{18}\text{H}_{17}\text{F}_2\text{N}_2\text{O}_2\text{S}$ [M+H] $^+$ found 363.0969, requires 363.0973 (-1.2 ppm)

Step 7) Synthesis of (*S*)-3-(benzo[d]thiazol-2-ylamino)-2,2-difluoro-3-phenylpropan-1-ol (**14**)

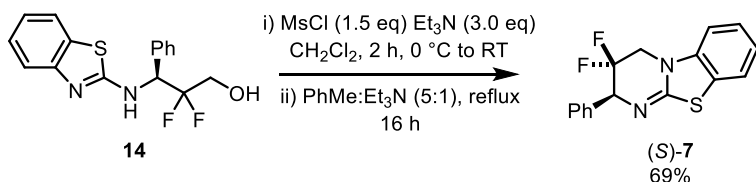


The following procedure was adapted from the literature.⁴⁸

Amino ester **21** (5.00 g, 13.7 mmol, 1.0 equiv.) was added to MeOH/1,2-DME (25.6 mL:1.78 mL, 15:1) and cooled to 0 °C and sodium borohydride (1.4 g, 27.5 mmol, 2.0 equiv.) was added portionwise over 5 minutes at 0 °C with vigorous gas evolution observed. The reaction mixture was stirred at 0 °C for 90 mins after which time, the thick reaction mixture had impeded effective stirring. Starting material consumption was confirmed *via* TLC analysis of the remaining liquid. The mixture was transferred to a large separatory funnel with 15% isopropanol in CHCl_3 (3 x 50 mL) rinses of the reaction flask. H_2O (150 mL) and aq. sat. NaHCO_3 (150 mL) were added and mixture shaken. After decanting the organic phase, the aqueous phase was extracted with 15% isopropanol in CHCl_3 (3 x 100 mL). The organic phases were combined, dried (Na_2SO_4) and concentrated under reduced pressure to roughly 30 mL volume. Hexane (350 mL) was added and the mixture sonicated thoroughly for 5 minutes. The resulting solid was collected *via* vacuum filtration, washed with hexane (2 x 100 mL) and dried *in vacuo* to give the title compound **14** as a fine, white, amorphous solid (3.86 g, 12.1 mmol, 88%).

Specific Rotation $[\alpha]_{D^{20}} +121.0$ (c 1.0 in CHCl_3)

Step 8) Synthesis of (*S*)-3,3-difluoro-2-phenyl-3,4-dihydro-2H-benzo[4,5]thiazolo[3,2-*a*]pyrimidine (**7**)



Triethylamine (4.59 mL, 3.34 g, 33.0 mmol, 3.0 equiv.) was added to a suspension of amino alcohol **14** (3.53 g, 11.0 mmol, 1.0 equiv.) in anhydrous CH₂Cl₂ (73 mL) under N₂. The mixture was cooled to 0 °C and methanesulfonyl chloride (1.28 mL, 1.89 g, 16.5 mmol, 1.5 equiv.) added dropwise at 0 °C. The mixture was allowed to warm to room temperature and stir for 2 hours whereupon starting material consumption was confirmed *via* ¹H NMR analysis (Note 2). Methanol (5.0 mL) was added and the mixture stirred at room temperature for 10 minutes. The mixture was concentrated under reduced pressure to give a sticky oil. Anhydrous toluene (120 mL) and triethylamine (20 mL) were added under N₂ and the mixture heated at reflux overnight. After cooling to room temperature, the mixture was transferred to a separatory funnel, aq. sat. NaHCO₃ (150 mL) and EtOAc (100 mL) added the mixture shaken. The organic phase was set aside and the aqueous phase extracted with EtOAc (3 x 75 mL). The organic phases were combined, washed sequentially (aq. sat. NaHCO₃ and brine), dried (Na₂SO₄) and concentrated under reduced pressure to give the crude residue which was purified *via* column chromatography (0 to 20% EtOAc in Hexane). The resulting solid was recrystallized from CHCl₃:cyclohexane (Note 2) to give the title compound **7** as a white, crystalline solid (2.31 g, 7.6 mmol, 69 %).

Notes: 1) A 0.1 mL aliquot of the crude reaction mixture was concentrated under reduced pressure and dissolved in 0.6 mL CDCl₃ and analysed *via* ¹H NMR, the disappearance of the starting material alcohol signals at ~3.68 and ~3.86 ppm was used to monitor starting material consumption. 2) The enantiomeric ratio of both the amorphous solid after column chromatography and the crystalline compound were checked and found to remain unchanged after the recrystallisation.

Specific Rotation [α]_D²⁰ -138.3 (c 1.0 in CHCl₃)

Chiral HPLC analysis Chiralcel OD-H (90:10 hexane:IPA, flow rate 1.0 mLmin⁻¹, 211 nm, 30 °C) t_R (S): 21.5 min, t_R (R) 32.2 min, >99:1 er

A sample for single crystal X-Ray analysis was prepared *via* vapour diffusion by dissolving ~10 mg of sample in CHCl₃ (~1 mL) in a small, uncapped vial. This vial was placed carefully within a larger vial containing ~5 mL cyclohexane, the larger vial was capped and the vial left at room temperature for several days until suitable crystals had formed.

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Supplementary Material

Further experimental details including ¹H, ¹⁹F and ¹³C NMR spectra for synthesised compounds are provided as supplementary material in the online version of the text.

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