RESEARCH ARTICLE

Synthesis of Chiral Hypervalent Trifluoromethyl Organobismuth Complexes and Enantioselective Olefin Difluorocarbenation Screenings

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Abstract: Two hypervalent trifluoromethyl organobismuth complexes were prepared from commercially available chiral amines, (*R*)-1-cyclohexylethylamine and (*1R*, *2R*, *3R*, *5S*)-(−)-isopinocampheylamine; however, only the complex from the latter amine was prepared as a single stereoisomer. Both organobismuth complexes were fully characterized by NMR spectroscopy and single-crystal X-ray crystallography, revealing that the structures were similar to previously reported complexes with a hypervalent Bi-N bond. The complexes were catalytically active in olefin difluorocarbenation with Ruppert-Prakash reagent (TMS-CF_3) used as a terminal source of CF_2. The catalyst derived from isopinocampheylamine was screened with three prochiral olefins of various reactivity in DCM and toluene. All reactions afforded the 1,1-difluorocyclopropanes in good yields, but no enantiomeric excess was observed.

Introduction

The significance of fluorinated compounds is well established in medicinal chemistry due to an enhancement of biological activities in comparison with its non-fluorinated analogs.[1] This improvement is manifested through increased lipophilicity and thus permeability, enhanced metabolic stability due to a strong C-F bond, and other synergistic properties.[2] Thus, the development of new methods or strategies capable of introducing fluorine or organofluorine fragments selectively and under mild conditions into the target molecule is an active research field.[3]

One of the important classes of organofluorines are 1,1-difluorocyclopropanes due to properties suitable for materials science, and synthetic applications tied to enhanced reactivity stemming from the alleviation of ring strain.[4] The most common synthetic approach to these compounds is a [2+1] cycloaddition, utilizing alkenes and difluorocarbene, a singlet form of carbene. Difluorocarbene is electrophilic, and the reaction follows the expected trend in which the electron-rich olefins are more reactive and afford better yields than electron-deficient alkenes.[5] Over time, many CF_2 generating reagents have been developed,[6] but currently, the TMS-CF_3 (Ruppert-Prakash reagent) and its derivatives such as TMS-CF_2Cl and TMS-CF_2Br are the preferred method for olefin difluorocarbenation due to a combination of low toxicity (vs Sn and Hg-based reagents), higher boiling point (HCF_3 is a gas), relatively low price (~$15/g for TMS-$CF_3$), and mild activation of these reagents (NaI or tetrabutylammonium difluorotriphenylsilicate (TBAT), CsF), which mechanisms were recently deconvoluted in an extensive study by Lloyd-Jones.[7]

Synthetic methodologies for a highly stereoselective organofluorination are limited in number but are of high interest due to their potential applications.[8] To the best of our knowledge, there is no known enantioselective olefin difluorocyclopropanation and the synthesis of enantiomerically pure 1,1-difluorocyclopropanes has been achieved by enantioselective reduction of 1,1-difluorocyclopropenes[9] or, in a large scale synthesis, by classical resolution or chromatographic separation of ester diastereomers[10]. This is in a direct contrast to enantioselective ketone trifluoromethylation, another application of TMS-CF_3, in which the enantioselectivity is induced through a chiral phase transfer catalyst.[11] This approach inspired us to design a catalyst generating CF_2 in a chiral environment.

In the last 10 years, chemists have focused on development of reactions catalyzed by main-group-based catalysts instead of the transition metal-based analogs. Most of the work stems from group V.A (pnictogens) with a particular focus on phosphorus and bismuth, but less so on arsenic and antimony.[12] The main group elements are a less toxic (except As and Sb), cheaper, and more sustainable alternative to the 2nd and 3rd row transition metals. Our group recently contributed to this field by the development of a hypervalent organobismuth catalyst for olefin difluorocarbenation.[13] This novel catalytic system offers some advantages over the current protocols such as high efficiency toward the CF_3^- containing reagent (TMS-CF_3) due to a reversible and highly endergonic process forming CF_2 in minute quantities. The method does not require an external source of activation, and forms TMS-F as the only by-product. Based on this seminal work,

we envisaged a chiral hypervalent organobismuth catalyst, synthesized by introduction of a chiral fragment into the catalyst scaffold, capable of enantioselective olefin difluorocarbenation. There are several examples of chiral organobismuth compounds, namely bismuthonium(V) salts,[14] chlorobismuthanes,[15] and triarylbismuthanes[16]. The only chiral organobismuth complex with a cyclic tridentate scaffold with a hypervalent bond (Bi-S and Bi-O) was reported by Yin.[17] However, these complexes utilized asymmetric C,E,C-chelating (E = O, S) ligands and were prepared as racemates. Our strategy relied on installing a chiral substituent through an abundant chiral primary amine, such as (*R*)-1-cyclohexylethylamine and (*1R*, *2R*, *3R*, *5S*)-(−)-isopinocampheylamine, targeting **1a** and **1b** as single stereoisomers, respectively (Figure 1).

Here, we present the synthesis of chiral trifluoromethyl 5,6,7,12-tetrahydrodibenz[*c,f*][1,5]azabismocine complexes (**1**) through an established procedure from the corresponding bismuth bromide, CsF and TMS-CF_3. Target **1b** was successfully synthesized as a single stereoisomer and was tested in catalytic olefin difluorocarbenation with TMS-CF_3 as stoichiometric CF_2 source, on three prochiral olefin substrates and in two different solvents.

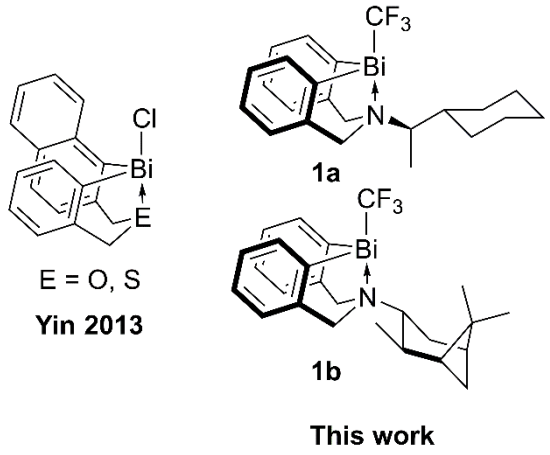
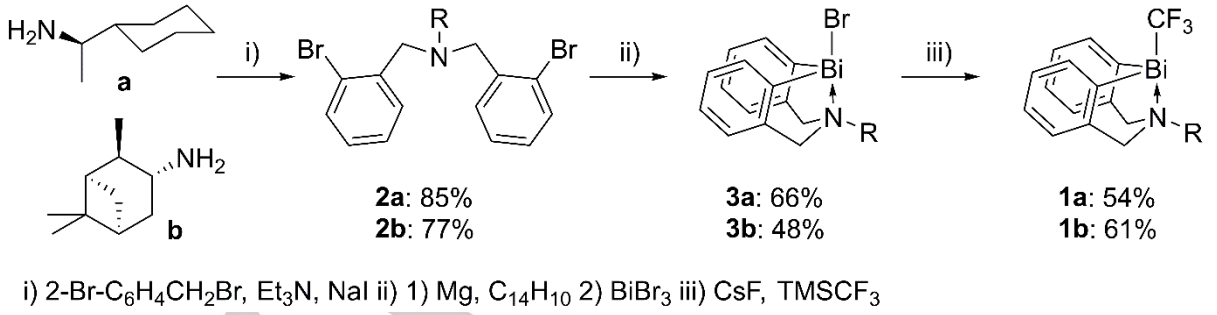


Figure 1. Chiral hypervalent organobismuth complexes.

Results and Discussion

Dialkylation of (*R*)-1-cyclohexylethylamine with two equivalents of 2-bromobenzylbromide in the presence of triethyl amine and catalytic amount of NaI in DMF afforded ligand **2a** in 85% yield (Scheme 1). Analogously, ligand **2b** was prepared from (*1R*, *2R*, *3R*, *5S*)-(−)-isopinocampheylamine and isolated in 77% yield. Both ligands were fully characterized by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy and HRMS. Notably, the ^{1}H NMR spectrum showed one set of signals for aromatic protons of the 2-bromophenyl groups; however, two sets of signals, specifically two doublets at 3.80 ppm and 3.64 ppm for **2a** and 3.88 ppm and 3.80 ppm for **2b**, were observed for the benzylic protons due their diastereotopic nature. In addition, the structure of **2a** was unambiguously confirmed by a single crystal X-ray crystallography (see SI).



Scheme 1. Syntheses of organobismuth complexes **1a/b**.

Treatment of ligand **2a** with Mg powder and catalytic amount of anthracene formed the Grignard reagent. After filtration, the Grignard reagent was treated with $BiBr_3$ affording the corresponding organobismuth bromide complex **3a** in 66% yield. Similarly, complex **2b** afforded bismuth bromide **3b** in 48% yield. Both bismuth bromide complexes were fully characterized by ^{1}H and ^{13}C{^{1}H} NMR spectroscopy and elemental analysis. In the ^{1}H NMR spectrum, the benzylic protons in both complexes were inequivalent displaying four separate signals. Some aromatic protons and carbons in ^{13}C{^{1}H} NMR spectrum in **3a** still showed one set of signals similar to the ligand **2a**. However, in the intermediate **3b**, the aromatic protons and carbons showed two sets of signals due to their diastereotopic nature. This can be due to a confinement of the bulky isopinocampheyl group to the tetracyclic 5,6,7,12-tetrahydrodibenz[c,f][1,5]azabismocine scaffold and perhaps limited rotation in comparison to the flexible 1-cyclohexylethyl substituent in ligand **2a** with a free rotation around C-C single bonds. Notably, the aromatic protons *ortho* to the bismuth atom are significantly downfield shifted to 8.80 ppm (**3a**) and 8.82 ppm (**3b**) which is due to the Inverse Halogen

Dependence (IHD).[18] Both intermediates were characterized by a single crystal X-ray crystallography (discussed *vide infra*).
Finally, the bismuth bromide **3a** was treated with CsF and TMS-CF_3 providing the trifluoromethyl bismuth complex **1a** in 54% yield. A related procedure using **3b** provided the corresponding trifluoromethyl complex **1b** in 61% yield. Both isolated complexes are air stable; however, slow decomposition on silica gel was observed. The complexes were fully characterized by ^{1}H, $^{13}C\{^{1}H\}$ and ^{19}F NMR spectroscopy and elemental analysis. The ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra showed C_1 symmetry similar to starting bismuth bromide complexes **3a/b**. The ^{19}F NMR spectra showed one singlet at -38.5 ppm for **1a** and -38.6 ppm for **1b**, closely matching the CF_3 chemical shift of *p*-Tol_2BiCF_3 (singlet, δ_F = -38.6 ppm) and the hypervalent *t*$BuN(CH_2C_6H_4)_2BiCF_3$ complex (singlet, δ_F = -38.8 ppm).[13] Both products were characterized by a single crystal X-ray crystallography (full discussion, *vide infra*). Surprisingly, the single-crystal X-ray crystallography and erosion in optical activity revealed that a racemization process of the (*R*)-1-cyclohexylethylamine substituent in **1a** has occurred. This can be rationalized by acidification of the α-proton due to coordination of amine group to the Lewis acidic bismuth center, creating a tetracoordinate amino group formally bearing a positive charge. The presence of CF_3^-, a relatively strong base, would deprotonate this α-proton forming a carbanion followed by an inversion and protonation. Fortunately, the racemization did not take place in the case of **1b**. We hypothesize that this is due to a lower accessibility of the corresponding α-proton, shielded by two methyl groups (position 2 and 4). Moreover, the tetrasubstituted nitrogen (if the hypervalent Bi-N bond is included) would be moved from a more accessible equatorial position to a more hindered axial position of the cyclohexane boat conformation of the isopinocampheyl substituent.
The structural identity of bismuth bromide **3b** (see SI) and CF_3 products **1a** and **1b** (Figure 2) were unambiguously confirmed by a single-crystal X-ray crystallography. In all three structures, the bismuth center adopts a distorted see-saw geometry with phenyl substituents located in equatorial positions and nitrogen and bromine/CF_3 substituents residing in axial positions. All key parameters are summarized in Table 1.

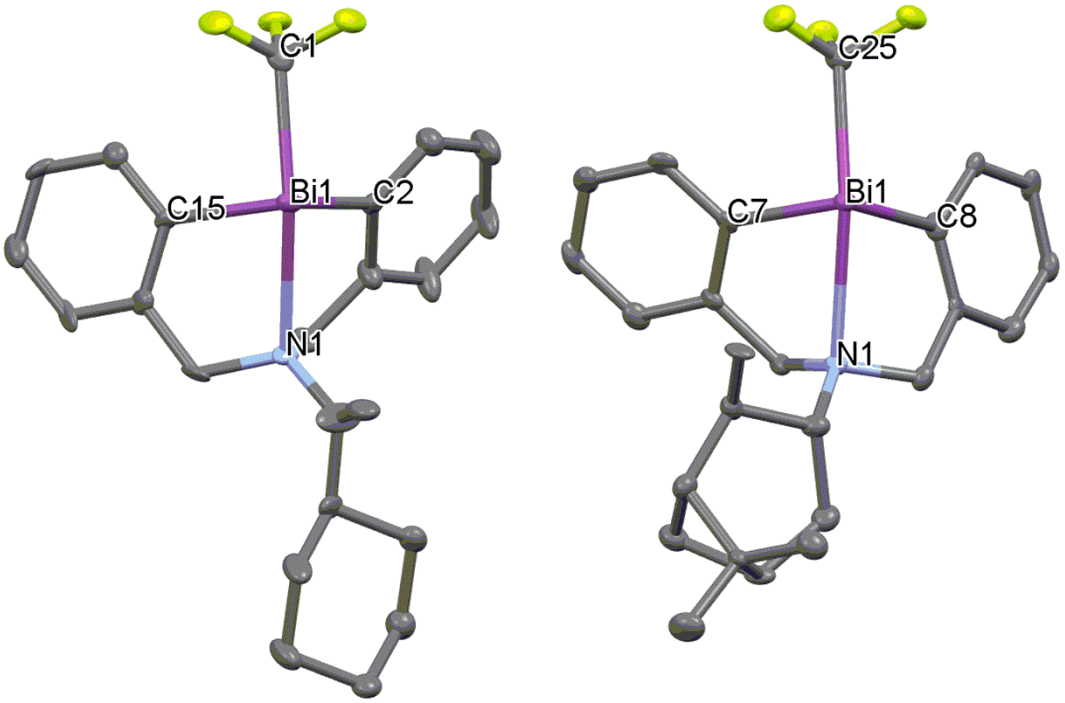


Figure 2. X-ray Structure of **1a** and **1b**; C Atoms Gray, F Atoms Yellow, N Atom Blue, and Bi Atom Purple; H Atoms Are Removed for Clarity; Thermal Ellipsoids Are at 30% Probability.

The newly synthesized complexes did not significantly differ in bond lengths and angles from the previously synthesized *tert*-butyl derivate *t*BuN($CH_2C_6H_4$)$_2$BiCF$_3$.[13] Most importantly, the complexes **1a** and **1b** maintained the hypervalent Bi-N bond, falling within the 2.568(3) to 2.896(5) Å range, previously reported by Tanaka and Shimada[19] for closely related complexes. The presence of the hypervalent bond is essential for CF_3 activation and maintaining activity of the complexes necessary for CF_2 generation as described in our previous work.[13]

The Bi-N bond in **3b** was much shorter in comparison to **1a** and **1b** due to an increased ability of the Bi-Br bond to act as acceptor in comparison to Bi-C bond.[19] The Bi-N bond length of complex **3b** is 2.547(9) Å and as expected, the Bi-Br bond length is 2.795(1) Å in **3b**, thus elongated in comparison with derivatives with a weaker hypervalent donor, e.g. Bi-Br bond length is 2.741(1) Å in $Ph_2BiBr(THF)$,[20] illustrating the donor-acceptor interaction[15b, 21]. The Bi-Br bond length in **3b** was significantly longer in comparison to Bi-CF_3 bonds in **1a/b** due to a larger sum of van der Waals diameters.

The derivative **1a** showed to be a slightly more distorted in comparison to **1b**, which might be due to the bulkier 1-ethylcyclohexyl group in comparison to isopinocampheyl group. This is reflected in the angle between the apical groups N-Bi-CF_3 in which **1a** has more acute angle, 152.2(3), in comparison to 153.2(2) in **1b**, which should be ideally 180 degrees. In a similar vein, the angles between the equatorial groups should be ideally 90 degrees, and **3b** with 96.0(4) angle was more acute than 99.1(3) in **1a** and 99.0(3) in **1b**, where the angles were comparable.

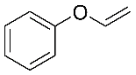
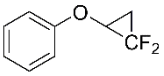
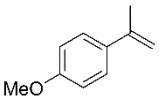
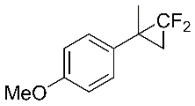
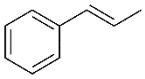
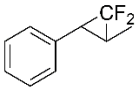
Table 1. Summary of bond distances and angles around bismuth centers for compounds **3b**, **1a**, and **1b**. Metric parameters in Å or °.

bond/angle[a,b]	3b	1a	1b
Bi-N	2.547(9)	2.672(8)	2.720(6)
Bi-C^1	2.25(1)	2.241(9)	2.256(7)
Bi-C^2	2.24(1)	2.258(8)	2.251(8)
Bi-X	2.795(1)	2.36(1)	2.375(8)
N-Bi-C^1	72.4(3)	72.4(3)	71.5(2)
N-Bi-C^2	75.6(3)	71.8(3)	71.9(2)
N-Bi-X	157.7(2)	152.2(3)	153.2(2)
C^1-Bi-C^2	96.0(4)	99.1(3)	99.0(3)
C^1-Bi-X	92.2(3)	89.0(3)	92.9(3)
C^2-Bi-X	90.5(3)	91.7(3)	89.8(3)

[a] C^1 corresponds to C2 in **1a** and C8 in **1b** in Figure 2. [b] C^2 corresponds to C15 in **1a** and C7 in **1b** in Figure 2.

As complex **1a** racemized during the synthesis, only **1b** was obtained as a single stereoisomer, which could be tested in the enantioselective catalytic olefin difluorocarbenation. In general, the optimization of an enantioselective reaction is handled through several parameters including the ligand, temperature, concentration, solvent, and the substrate.[22] In our case, the ligand is covalently bound to the metal and is part of the complex, thus it cannot be exchanged. The temperature has significant impact on enantioselectivity, *e.g.*, if the barriers of two enantioselective pathways differ by 1 kcal/mol, then the obtained enantiomeric ratio would be 84/14 at -60 °C, and 80/20 at 0 °C. Since the studied system requires high reaction temperature (120 °C) and longer reaction times (0.5d-5d), this parameter could not be easily optimized without a large extension of the reaction times. Similarly, the concentration cannot be effectively altered due to the highly endergonic process in CF_2 formation where only minute amounts of CF_2 is produced at a time. Based on our previous work, the reaction is limited to aprotic solvents, and toluene (entries 1, 3, and 5) and DCM (entries 2, 4, and 6) were chosen for the study (Table 2). Three prochiral olefin substrates with various reactivity were selected; phenyl vinyl ether (entries 1, 2), as being the most reactive, α-methyl-*p*-methoxystyrene (entries 3, 4) having a moderate reactivity, and the least reactive is the *trans*-ß methyl styrene (entries 5, 6). These reactions were run under standard conditions 10 mol% of the catalyst **1b** with 1.2 equiv. of TMS-CF_3 at 120°C until full conversion. The yields ranged from 71 to 91%, similar to the results from our original achiral *t*BuN($CH_2C_6H_4$)$_2$BiCF$_3$ complex. However, the catalyst recovery was somewhat lower due to a higher lipophilicity of the complex **1b** in comparison to the original *t*BuN($CH_2C_6H_4$)$_2$BiCF$_3$. Unfortunately, none of the experiments lead to an observable enantiomeric ratio, affording racemic mixtures (Table 2, entries 1-6). We hypothesize that this is simply a consequence of CF_2 being added to the olefin, outside the coordination sphere of the chiral catalyst. As described previously, the reaction is assumed to produce free CF_2, and hence, the only chiral induction would be provided in close proximity to the catalyst. Since our options to optimize this reaction are limited only to substrate and the solvent, our future efforts are focused on development of a more active catalyst capable of producing CF_2 at lower temperature, which might increase the enantioselectivity.

Table 2. Enantioselective olefin difluorocarbenation. [a]

entry	substrate	product	solvent	% Yield	% **1b** recovery	e.r.
1			tol-d_8	72	70	50:50
2			DCM-d_2	86	5	50:50
3			tol-d_8	91	80	50:50
4			DCM-d_2	71	67	50:50
5			tol-d_8	85	73	50:50
6			DCM-d_2	89	67	50:50

[a] Conditions: TMS-CF_3 (1.2 equiv.), 10% of **1b**, solvent (DCM-d_2 or tol-d_8), 120 °C.

Conclusion

Two chiral hypervalent trifluoromethyl bismuth complexes **1a** and **1b** were prepared and fully characterized. However, only derivative **1b** was prepared as a single stereoisomer. All prepared complexes were structurally analogous to previously reported structures including the Bi-N hypervalent bond. Complex **1b** showed to be catalytically active in olefin difluorocarbenation with TMS-CF_3 as a terminal source of CF_2. The catalyst was screened with three prochiral olefins of various reactivity, all affording the 1,1-difluorocyclopropanes in good yields. The catalyst recovery was somewhat lower in comparison to previously reported values, due to increased lipophilicity of the catalyst. Unfortunately, none of the tested substrates afforded an observable enantiomeric excess. We are currently exploring new catalyst designs with a higher activity allowing to lower the reaction temperature and thus providing a new parameter for the enantioselective optimization.

Experimental Section

General Methods. All reactions were carried out under nitrogen atmosphere using standard Schlenk techniques or an Innovative Technology Inc. glovebox. All reagents and solvents were purchased from commercial suppliers. Solvents were purified through an alumina column solvent system and further dried with molecular sieves. Specific rotation data was collected on a JASCO DIP-370 Digital Polarimeter with a Sodium Lamp and reported as an average of 10 runs. EA samples were analyzed with a PerkinElmer 2400 Series II Analyzer at the University of Rochester by Bill Brennessel. HPLC Chromatograms were collected on an Agilent 1200 series binary HPLC pump on Lux 5µ Amylose 1 100mm x 4.6mm chiral column. Column conditions are as follows: 1.0mg/mL flow rate with an isocratic flow rate of either 50% water (0.1% formic acid)/50% acetonitrile (0.1% formic acid) or 40% water (0.1% formic acid)/60% acetonitrile (0.1% formic acid) and UV detection of 254 nm. Varian Unity Inova 500 MHz was used for ^1H, $^{13}C\{^1H\}$ and ^{19}F NMR in the characterization of novel bismuthanes **1a**, **1b**, **3a**, and **3b**. Agilent 300 MHz DD2 was used in the characterization of chiral amines **2a** and **2b**. The chemical shifts for ^1H and $^{13}C\{^1H\}$ NMR spectra are given in parts per million (ppm); ^1H and $^{13}C\{^1H\}$ were referenced internally according to the residual solvent resonances. Coupling constants are given in Hertz (Hz) and the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet; app, apparent; br, broad. High-resolution mass spectra (HRMS) data were collected with an Agilent 6410 Triple Quadrupole LC/MS and reported exact masses were calculated based on an algorithm using MS (ESI) m/z for $[M]^+$ within 5 ppm of the expected target mass.

(*R*)-*N*,*N*-bis(2-bromobenzyl)-1-cyclohexylethan-1-amine (2a): 2-bromobenzyl bromide (12.98 g, 51.93 mmol) and NaI (47 mg, 0.31 mmol) were combined in a sealed Schlenk flask. (*R*)-1-cyclohexylethylamine (3.17 g, 24.9 mmol), Et_3N (7.04 g, 69.6 mmol), and 40 mL of DMF were added. The reaction mixture was gradually warmed to 85°C and stirred overnight. The temperature was raised to 120°C and stirred for 50 hours. The reaction mixture was diluted with H_2O (35 mL) and extracted with Et_2O (3 x 30 mL). The organic layer was combined and washed with H_2O (3 x 20 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product was passed through a short silica gel column in EtOAc. The filtered product was recrystallized from hot isopropyl alcohol to afford **2a** as white crystals (9.85 g, 21.2 mol) in 85% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (dd, J = 7.6, 1.2 Hz, 2H), 7.49 (dd, J = 7.8 Hz, 1.2 Hz; 2H), 7.27 (app td, J = 7.6 Hz, 1.2, 2H), 7.06 (app td, J = 7.8 Hz, 1.6, 2H), 3.80 (d, J = 15.2 Hz, 2H), 3.64 (d, J = 15.2 Hz, 2H), 2.43 – 2.31 (m, 1H), 2.31 – 2.21 (m, 1H), 1.77 – 1.57 (m, 4H), 1.46 – 1.31 (m, 1H), 1.24 – 1.02 (m, 6H), 0.87 – 0.71 (m, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 139.3, 132.6, 130.6, 128.1, 127.3, 124.5, 59.1, 53.6, 41.6, 31.4, 30.9, 26.7, 26.6, 26.5, 10.5. HRMS: calcd for $C_{22}H_{28}Br_2N$ $[M]^+$: 463.0510 m/z, found: 463.0509 m/z. Specific Rotation: $[\alpha]_D^{20}$ -0.113 (*c* 1.0, $CHCl_3$).

(*1R,2R,3R,5S*)-*N,N*-bis(2-bromobenzyl) isopinocampheylamine (2b): 2-bromobenzyl bromide (13.67 g, 54.70 mmol) and NaI (52 mg, 0.35 mmol) were combined in a sealed Schlenk flask. (*1R*,*2R*,*3R*,*5S*)-(−)-isopinocampheylamine (4.02 g, 26.2 mmol), Et_3N (7.48 g, 73.9 mmol), and 40 mL of DMF were added. The reaction mixture was gradually warmed to 85°C and stirred overnight. The temperature was then raised to 120°C and stirred for 50 hours. The reaction mixture was diluted with H_2O (35 mL) and extracted with Et_2O (3 x 30 mL). The organic layer was combined and washed with H_2O (3 x 20 mL), dried over $MgSO_4$, and concentrated under vacuum. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was passed through a short silica gel column in EtOAc. The filtered product was recrystallized from acetonitrile to afford **2b** as white crystals (9.87 g, 20.1 mmol) in 77% yield. ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, J = 7.7 Hz, 1.6 Hz, 2H), 7.47 (dd, J = 7.7 Hz, 1.2 Hz, 2H), 7.23 (app td, J = 7.7 Hz, 1.2 Hz, 2H), 7.04 (app td, J = 7.7 Hz, 1.6 Hz, 2H), 3.88 (d, J = 14.7 Hz, 2H), 3.80 (d, J = 14.7 Hz, 2H), 3.26 – 3.15 (m, 1H), 2.38 – 2.18 (m, 2H), 2.06 – 1.93 (m, 3H), 1.80 – 1.73 (m, 1H), 1.19 (s, 3H), 1.01-0.96 (m, 4H), 0.87 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$) δ 139.5, 132.5, 131.1, 128.3, 127.2, 124.4, 59.0, 54.8, 48.2, 41.9, 40.8, 39.4, 33.8, 28.3, 27.7, 23.4, 21.3. HRMS: calcd for $C_{24}H_{30}Br_2N$ $[M]^+$: 489.0667 m/z, found: 489.0669m/z. Specific Rotation: $[\alpha]_D^{20}$ -0.761 (*c* 1.0, $CHCl_3$).

12-bromo-6-((*R*)-1-cyclohexylethyl)-5,6,7,12-tetrahydrodibenzo[*c*,*f*][1,5]azabismocine (3a): Under nitrogen atmosphere, **2a** (4.65 g, 9.99 mmol), anthracene (89 mg, 0.50 mmol) and magnesium powder (0.693 g, 28.5 mmol) were combined and suspended in 15 mL of THF and stirred overnight. The formed suspension was filtered over celite to remove excess of magnesium powder and the filtrate was added dropwise into stirring solution of $BiBr_3$ ·THF (7.81 g, 15.0 mmol) in THF (35 mL). The reaction mixture was stirred overnight, then filtered through celite, the celite was washed with DCM (15 mL x 3), and the combined filtrate was concentrated *in vacuo.* The obtained solid was then washed with hexanes (3 x 15 ml), dissolved in DCM (25 mL) and filtered through a silica gel plug. The filtrate was concentrated *in vacuo* affording **3a** as off-white solid (3.92 g, 6.60 mmol) in 66% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82-8.78 (m, $2H_{3,3'}$), 7.50-7.47 (m, $2H_{2,2'}$), 7.43-7.39 (m, $2H_{6,6'}$), 7.37-7.33 (m, $2H_{1,1'}$), 4.36 (d, *J* = 14.8 Hz, $1H_{7,8}$), 4.33 (d, *J* = 14.8 Hz, $1H_{7,8}$), 4.17 (d, *J* = 14.8 Hz, $1H_{7,8}$), 4.16 (d, *J* = 14.8 Hz, $1H_{7,8}$), 2.94 (qd, *J* = 6.9, 1.5 Hz, $1H_{10}$), 1.81 – 1.61 (m, $5H_{cyclohexane}$), 1.53 – 1.46 (m, $1H_{cyclohexane}$), 1.33 – 1.22 (m, $1H_{cyclohexane}$), 1.20 (d, *J* = 6.9 Hz, 3H), 1.18 – 0.93 (m, $4H_{cyclohexane}$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 167.9 ($C_{4,4'}$), 167.7 ($C_{4,4'}$), 149.6 ($C_{5,5'}$), 149.0 ($C_{5,5'}$), 140.2 ($C_{3,3'}$), 131.4 ($C_{2,2'}$), 128.3 ($C_{1,1'}$), 127.9 ($C_{6,6'}$), 127.8 ($C_{6,6'}$), 65.0 (C_{10}), 61.5 ($C_{7,8}$), 61.1 ($C_{7,8}$), 41.7 (C_{11}), 33.4 ($C_{cyclohexane}$), 28.8 ($C_{cyclohexane}$), 26.9 ($C_{cyclohexane}$), 26.1 ($C_{cyclohexane}$), 26.1 ($C_{cyclohexane}$), 12.9 (C_9). EA: Anal. Calc. for $BiC_{22}H_{27}NBr$: C, 44.46; H, 4.58; N, 2.36. Found**:** C, 44.32; H, 4.36; N, 2.45. Specific Rotation: $[\alpha]_D^{20}$ +0.176 (*c* 1.0, $CHCl_3$)

12-bromo-6-((*1R,2R,3R,5S*)-isopinocampheyl)-5,6,7,12-tetrahydro dibenzo[*c*,*f*][1,5]azabismocine (3b): Under nitrogen atmosphere, **2b** (3.11 g, 6.33 mmol), anthracene (56 mg, 0.31 mmol) and magnesium powder (0.404 g, 16.6 mmol) were combined and suspended in 20 mL of THF and stirred overnight. The formed suspension was filtered over celite to remove excess magnesium powder and the filtrate was added dropwise into stirring solution of $BiBr_3$ ·THF (4.94 g, 9.49 mmol) in THF (25 mL). The reaction mixture was stirred overnight, then filtered through celite, the celite was washed with DCM (15 mL x 3), and the combined filtrate was concentrated *in vacuo.* The obtained solid was then washed with hexanes (3 x 15 ml), dissolved in DCM (25 mL) and filtered through a silica gel plug. The filtrate was concentrated *in vacuo* to afford **3b** as off-white solid (1.87 g, 3.01 mmol) in 48% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83-8.80 (m, $2H_{3,3'}$), 7.51-7.48 (m, $2H_{2,2'}$), 7.44-7.42 (m, $2H_{6,6'}$), 7.37-7.34 (m, $2H_{1,1'}$), 4.47 (d, *J* = 14.6 Hz, $1H_{7,8}$), 4.44 (d, *J* = 14.6 Hz, $1H_{7,8}$), 4.23 (d, *J* = 14.6, $1H_{7,8}$), 4.21 (d, *J* = 14.6, $1H_{7,8}$), 3.51-3.47 (m,$1H_9$), 2.39-2.31 (m, $2H_{10ab,17ab}$), 2.26-2.23 (m, $1H_{16}$), 2.03-1.95 (m, $2H_{11,17ab}$), 1.88 (td, *J* = 5.5, 2.2 Hz, $1H_{15}$), 1.24-1.22 (m, $6H_{18,13,14}$), 1.07 (d, *J* = 10.4 Hz, $1H_{10ab}$), 0.94 (s, $3H_{13,14}$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 168.2 ($C_{4,4'}$), 167.3 ($C_{4,4'}$), 149.3 ($C_{5,5'}$), 148.8 ($C_{5,5'}$), 140.3 ($C_{3,3'}$), 140.2 ($C_{3,3'}$), 131.5 ($C_{2,2'}$), 128.39 ($C_{1,1'}$), 128.33 ($C_{1,1'}$), 127.9 ($C_{6,6'}$), 127.8 ($C_{6,6'}$), 62.8 (C_9), 61.3 ($C_{7,8}$), 60.3 ($C_{7,8}$), 48.6 (C_{15}), 41.4 (C_{11}), 38.9 (C_{12}), 38.2 (C_{16}), 32.6 (C_{17}), 31.8 (C_{10}), 27.2 ($C_{13,14}$), 23.9 ($C_{13,14}$), 23.6 (C_{18}). EA: Anal. Calc. for $BiC_{24}H_{29}NBr$: C, 46.47; H, 4.71; N, 2.26. Found**:** C, 45.38; H, 4.56; N, 2.18. The elemental analysis was consistently low in C content. Specific Rotation: $[\alpha]_D^{20}$ -0.501 (*c* 1.0, $CHCl_3$).

6-(1-cyclohexylethyl)-12-(trifluoromethyl)-5,6,7,12-tetrahydro dibenzo[*c*,*f*][1,5]azabismocine (1a): To a stirred suspension of **3a** (1.50 g, 2.52 mmol) in THF (35 mL), CsF (0.575 g, 3.79 mmol) was added, followed by addition of $TMSCF_3$ (0.467 g, 3.28 mmol) under nitrogen atmosphere. After 1 hour, CsF (0.575 g, 3.79 mmol) and $TMSCF_3$ (0.467 mg, 3.28 mmol) was added a second time. Following the second addition, $TMSCF_3$ (0.467 mg, 3.28 mmol) was added in two portions in 50-minute intervals until full conversion of the starting material was reached; the reaction was monitored by ^{1}H and ^{19}F NMR spectroscopy. The solvent was removed *in vacuo* and the crude product was extracted with toluene (3 x 15 ml) and DCM (2 x 10 ml) and filtered through celite. The filtrate was concentrated *in vacuo*. The crude product was then recrystallized with hexane/ethanol slow evaporation, decanted, and the crystals washed with cold ethanol (3 x 15 mL) to afford **1a** (0.576 g, 0.987 mmol) as colorless crystals. The decant was concentrated to a solid, washed with cold ethanol (3 x 15 mL) and dried to afford a second crop of **1a** (0.219 g, 0.375 mmol) as white crystalline solid. The **1a** (0.795 g, 1.36 mmol) was obtained in an overall 54% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (app d, *J* = 7.4 Hz, $2H_{3,3'}$), 7.41 – 7.36 (m, $2H_{2,2'}$), 7.33 – 7.28 (m, $4H_{1,1',6,6'}$), 4.10 (d, *J* = 14.9 Hz, $1H_{7,8}$), 4.09 (d, *J* = 14.8 Hz, $1H_{7,8}$), 3.92 (d, *J* = 14.9 Hz, $1H_{7,8}$), 3.91 (d, *J* = 14.8 Hz, $1H_{7,8}$), 2.75 (qd, *J* = 6.9, 1.8 Hz, $1H_{10}$), 1.84 – 1.62 (m, $5H_{cyclohexane}$), 1.44 (m, $1H_{cyclohexane}$), 1.35 – 1.24 (m, $1H_{cyclohexane}$), 1.18 – 1.04 (m, $7H_{cyclohexane}$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.4 ($C_{4,4'}$), 157.1 ($C_{4,4'}$), 148.0 ($C_{5,5'}$), 147.6 ($C_{5,5'}$), 146.6 (CF_3, q, $J_{C\text{-}F}$ = 402.2 Hz), 139.0 ($C_{3,3'}$), 138.9 ($C_{3,3'}$), 130.3 ($C_{2,2'}$), 128.9 ($C_{6,6'}$), 128.8 ($C_{6,6'}$), 128.1 ($C_{1,1'}$), 62.2 (C_{10}), 58.0 ($C_{7,8}$), 57.7 ($C_{7,8}$), 40.3 (C_{11}), 33.4 ($C_{cyclohexane}$), 29.0 ($C_{cyclohexane}$), 27.0 ($C_{cyclohexane}$), 26.3 ($C_{cyclohexane}$), 26.2 ($C_{cyclohexane}$), 12.5 (C_9). ^{19}F NMR (471 MHz, $CDCl_3$) δ -38.50. EA: Anal. Calc. for $BiC_{19}H_{21}NF_3$: C, 47.35; H, 4.66; N, 2.40. Found**:** C, 47.39; H, 4.56; N, 2.37. Specific Rotation: $[\alpha]_D^{20}$ +0.038 (*c* 1.0, $CHCl_3$).

12-trifluoromethyl-6-((*1R,2R,3R,5S*)-isopinocampheyl)-5,6,7,12-tetrahydro dibenzo[*c*,*f*][1,5]azabismocine (1b): To a stirred suspension of **2b** (0.500 g, 0.806 mmol) in THF (15 mL), CsF (0.184 g, 1.21 mmol) was added, followed by addition of $TMSCF_3$ (0.149 mg, 1.05 mmol) under nitrogen atmosphere. After 1 hour, CsF (0.184 g, 1.21 mmol) and $TMSCF_3$ (0.149 mg, 1.05 mmol) was added a second time. Following the second addition, $TMSCF_3$ (0.149 mg, 1.05 mmol) was added in two portions in 50-minute intervals until full conversion of the starting material was reached; the reaction was monitored by ^{1}H and ^{19}F NMR spectroscopy. The solvent was removed *in vacuo* and the crude product was extracted with DCM (3 x 15 ml) and filtered through silica gel. The filtrate was concentrated *in vacuo.* The crude product was then recrystallized with hexanes to afford **1b** (0.300 g, 0.492 mmol) as colorless crystals in 61% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 7.3 Hz, $2H_3$), 7.41-7.38 (m, $2H_2$), 7.35 – 7.29 (m, $4H_{1,6}$), 4.22 (d, *J* = 14.8 Hz, $1H_{7,8}$), 4.13 (d, *J* = 14.8 Hz, $1H_{7,8}$), 3.98 (d, *J* = 14.8 Hz, $1H_{7,8}$), 3.95 (d, *J* = 14.8 Hz, $1H_{7,8}$), 3.32-3.28 (m, $1H_9$), 2.36 – 2.21 (m, $3H_{10ab,16,17ab}$), 2.07 – 1.98 (m, $2H_{11,17ab}$), 1.85-1.82 (m, $1H_{15}$), 1.22 (s, $3H_{13,14}$), 1.16 (d, *J* = 7.0 Hz, $3H_{18}$), 1.08 (d, *J* = 10.1 Hz, $1H_{10ab}$), 0.91 (s, $3H_{13,14}$). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.3 ($C_{4,4'}$), 157.1 ($C_{4,4'}$), 146.9 (CF_3, q, $J_{C\text{-}F}$ = 400.7 Hz) 147.6 ($C_{5,5'}$), 147.4 ($C_{5,5'}$), 139.1 ($C_{3,3'}$), 139.0 ($C_{3,3'}$), 130.4 ($C_{2,2'}$), 130.3 ($C_{2,2'}$), 128.94 ($C_{6,6'}$), 128.91 ($C_{6,6'}$), 128.2 ($C_{1,1'}$), 128.1 ($C_{1,1'}$), 60.1 (C_9), 57.2 ($C_{7,8}$), 57.0 ($C_{7,8}$), 48.4 (C_{15}), 41.4 (C_{11}), 39.0 (C_{12}), 37.8 (C_{16}), 31.6 (C_{10}), 30.7 (C_6), 27.3 ($C_{13,14}$), 23.9 (C_{18}), 23.6 ($C_{13,14}$). ^{19}F NMR (471 MHz, $CDCl_3$) δ -38.55. EA: Anal. Calc. for $BiC_{25}H_{29}NF_3$: C, 49.27; H, 4.80; N, 2.30. Found**:** C, 49.25; H, 4.57; N, 2.36. Specific Rotation: $[\alpha]_D^{20}$ -0.375 (*c* 1.0, $CHCl_3$)

General procedure for the catalytic difluorocarbenation of alkene substrates with 1b (Table 2). Under a nitrogen atmosphere, **1b** (31 mg, 0.051 mmol) was suspended in 0.5 mL of solvent (toluene-d_8 or DCM-d_2) in a pressure tube, followed by addition of TMS-CF_3 (0.087 mL, 0.60 mmol), fluorobenzene (0.047 mL, 0.50 mmol) and 0.50 mmol of alkene substrate. The reaction was heated to 120 °C until the full conversion of alkene, as determined by ^{1}H NMR and ^{19}F NMR spectroscopy. Then, the solvent was removed *in vacuo*, and the crude mixture was filtered through a silica gel plug (~2.5 cm in a glass pipette) with pentane (5x1 mL), followed by concentration *in vacuo* affording the corresponding products. The silica gel plug was washed with DCM (5 x 2mL) and the DCM filtrate was concentrated *in vacuo* recovering catalyst **1b**.

Supplementary material

The available Electronic Supplementary Information (ESI) contains ^{1}H, ^{19}F and $^{13}C\{^1H\}$ NMR data and HPLC chromatograms for all complexes and products of screening. Deposition Number(s) <url href="https://www.ccdc.cam.ac.uk/services/structures?id=doi:10.1002/cplu.202200450"> 2224774 (for **2a**), 2224803 (for **3b**), 2224777 (for **1a**), 2224804 (for **1b**) </url> contain(s) the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe <url href=" http://www.ccdc.cam.ac.uk/structures ">Access Structures service</url>.

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Conflict of interest

The authors declare no competing conflict of interest. All contributing authors have approved the final version.

Keywords: chiral • 1,1-difluorocyclopropane • enantioselective difluorocyclopropanation • main-group catalysis • organobismuth

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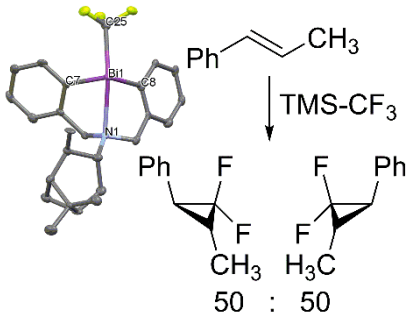

Progress toward Enantioselective Difluorocyclopropanation: This work presents synthesis and characterization of chiral hypervalent trifluoromethyl organobismuthanes. One complex was synthesized as a single stereoisomer and was screened in catalytic olefin difluorocarbenation with prochiral olefins and TMS-CF_3, as a terminal source of CF_2. The screened catalyst showed a good catalytic activity; however, enantiomeric excess in the formed 1,1-difluorocyclopropanes was not observed.