The Stabilizing Effect of Pre-Equilibria: A Trifluoromethyl Complex as CF_2 Reservoir in Catalytic Olefin Difluorocarbenation

Author List

Thomas Louis-Goff,[†,a] Huu Vinh Trinh,[†,a] Eileen Chen,[†] Arnold L. Rheingold,[⊥] Christian Ehm,[‡] Jakub Hyvl*[,†]

[†]Department of Chemistry, University of Hawai'i at Mānoa, 2545 McCarthy Mall, Honolulu, Hawaii 96822, United States

⊥Department of Chemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093, United States

‡ Dipartimento di Scienze Chimiche, Università di Napoli Federico II, Via Cintia, 80126 Napoli (Italy)

[a] These authors contributed equally.

Abstract

A new, efficient, catalytic difluorocarbenation of olefins to give 1,1-difluorocyclopropanes is presented. The catalyst, an organobismuth complex, uses $TMSCF_3$ as a stoichiometric difluorocarbene source. We demonstrate both the viability and robustness of this reaction over a wide range of alkenes and alkynes, including electron-poor alkenes, to generate the corresponding 1,1-difluorocyclopropanes and 1,1-difluorocyclopropenes. Ease of catalyst recovery from the reaction mixture is another attractive feature of this method. In depth experimental and theoretical studies showed that the key difluorocarbene-generating step proceeds through a bismuth non-redox synchronous mechanism generating a highly reactive free CF_2 in an endergonic pre-equilibrium. It is the reversibility when generating the difluorocarbene that accounts for the high selectivity, while minimizing CF_2-recombination side-reactions.

Introduction

Fluorine in organic molecules imparts unique properties such as increased lipophilicity, metabolic stability, and permeability resulting in enhanced biologic activity[1, 2] essential to pharmaceuticals[3] and agrochemicals[4]. 1,1-Difluorocyclopropanes[5, 6] are an important subclass of organofluorine compounds prepared upon difluorocarbenation (1,1-difluorocyclopropanation) of olefins (**Figure 1-A**) where the cyclopropane rings show enhanced reactivity,[5, 6] giving rise to a variety of applications.[7, 8]

Difluorocarbenation is a [2+1] cycloaddition that utilizes singlet difluorocarbene,[9] a highly reactive species, intrinsically electrophilic due to an empty *p*-orbital. It is typically generated (see references [10, 11] for a more detailed overview) by employing either: 1) trifluoromethyl heavy metal complexes $L_xM\text{-}CF_3$ (*e.g.* M = Hg,[12, 13] Cd,[14] Sn;[15] 2) 2,2-difluorocarboxylates;[16, 17, 18] or more recently, 3) silicon based reagents like $TMS\text{-}CF_3$[19] and $TMS\text{-}CF_2Br$.[20] However, each of these methods has disadvantages (e.g. use of toxic heavy metals, high cost, etc.), but all have in common an inability to maintain low CF_2 concentrations. As a consequence, excess reagent (usually 2-7 equiv.) is required due to CF_2-recombination leading to the associated generation of toxic higher perfluoroalkenes.[11] The lack of control of CF_2 concentration in the CF_3^- sources is due to promoters/activators acting via salt metathesis with NaI or TBAT yielding high concentration of the transient CF_3^- anionoid followed by *α*-F-elimination.[11] Thermolysis of difluorocarboxylate reagents face similar CF_2-concentration issues.[17] Moreover, these problems are typically exacerbated in the case of electron-poor alkenes that are less efficient CF_2 trapping agents.

Atom-transfer radical polymerization (ATRP)[21, 22, 23] also produces highly reactive species (radicals) and suggests an excellent solution in that it involves an equilibrium with a heavily favored closed-shell dormant

species. As a result, the concentration of free radicals is kept extremely low and undesired radical recombination or disproportionation is avoided. Extending this approach to the domain of well-defined closed shell chemistry, we envisioned that an endergonic and reversible pre-equilibrium process (**Figure 1-B**) could be used to control CF_2 concentrations. Notably, Seyferth has described a reversible formation of dichlorocarbene from $PhHgCCl_2Br$.[24] Moreover, in principle the difluorocarbene reversible generation was further demonstrated by Eujen and Hoge who showed that when generated at low temperatures from $Cd(CF_3)_2$, CF_2 can readily insert into Sn-X bonds (X = Cl, F).[14] However, it should also be noted that $Cd(CF_3)_2$ is also an excellent CF_3^- source capable of directly alkylating $SnBr_4$.[25]

Bismuth-based reagents are an attractive alternative to heavy main group counterparts due to a benign and environmentally friendly nature.[26] With regard to organofluorination, Kirii has reported that $Bi(CF_3)_3$[27] can induce alkene difluorocarbenation,[28] albeit after activation with aluminum trichloride. More specific to our interests is hypervalent bonding, a privileged approach to activate specific groups, typically accomplished through a pendant arm in complexes with multidentate ligands activating the substituent located *trans* to the hypervalent bond.[29] We hypothesized that hypervalent four-coordinate organobismuth complexes would fit this arrangement as in the 5,6,7,12-tetrahydrodibenz[c,f][1,5]azabismocine **1** (**Figure 1-A**). Bismuth complex **1** exhibits a distorted seesaw geometry, first synthesized by Akiba[30] and further developed by Shimada and Tanaka,[31] that was anticipated to assist in releasing CF_2 from **1-CF$_3$**. Such organobismuth complexes with multidentate ligands are resistant to dismutation, an undesirable substituent scrambling process.[32] Related hypervalent multidentate organobismuth complexes, however operating through Bi^{III}/Bi^{V} redox processes, were recently employed by Cornella in fluorination,[33] and by Ball in arylation reactions[34].[35] Finally, Pd-catalyzed difluorocarbene transfer reactions are reported to furnish fluoroalkylated arenes,[36] but only one system utilizing a cobalt porphyrin catalyst has been claimed to catalytically transfer CF_2; however, the system needs a high $TMSCF_3$ excess (8 eq.) and NaI activation, yields are low (max. 40%) and, curiously, the authors showed the difluorocarbenation only for a single substrate (*n*-butyl acrylate), which raises doubts on the generality of the approach[37].

We present below a highly efficient catalytic process (see **Figure 1-A**) that combines a robust, nontoxic trifluoromethyl bismuth catalyst **1-CF$_3$** with mild and readily available $TMSCF_3$, used for catalyst regeneration. The ensuing reaction is highly atom-efficient stemming from an endergonic, but still feasible, reversible process producing free CF_2 in minute quantities, and thus overcoming the common atom economy disadvantages associated with many of difluorocarbenation methods described above. Our process provides a recyclable system capable of efficiently converting a wide range of alkene substrates into 1,1-difluorocyclopropanes.

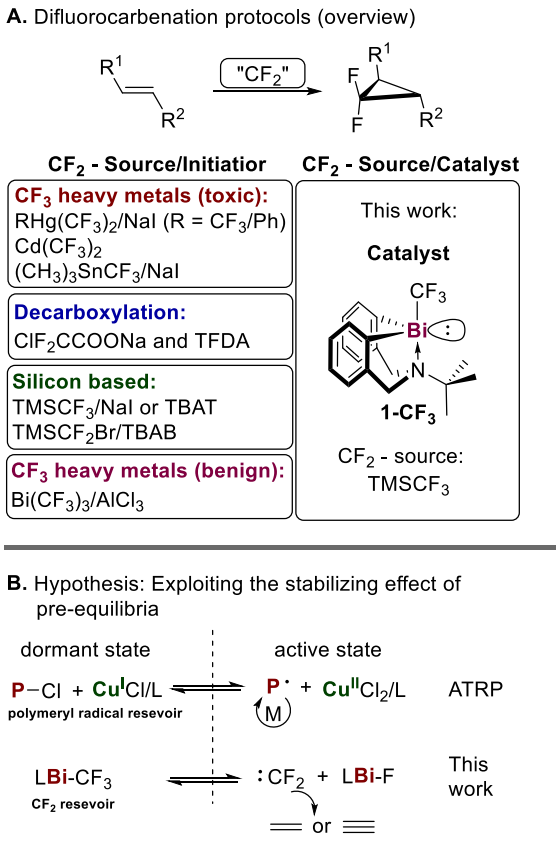


Figure 1. Development of organobismuth-catalyzed olefin difluorocarbenation. (A) Common stoichiometric difluorocarbene sources and the newly developed catalytic Bi-system 12-CF_3-6-*t*Bu-5,6,7,12-tetrahydrodibenz[c,f][1,5]azabismocine (**1-CF_3**). Note: TBAT (tetrabutylammonium difluorotriphenyl-silicate), TBAB (tetrabutylammonium bromide), TFDA (trimethylsilyl fluorosulfonyldifluoroacetate). (B) The origin of the selectivity: equilibrium between dormant and active states in ATRP and in the presented system.

Results and Discussion

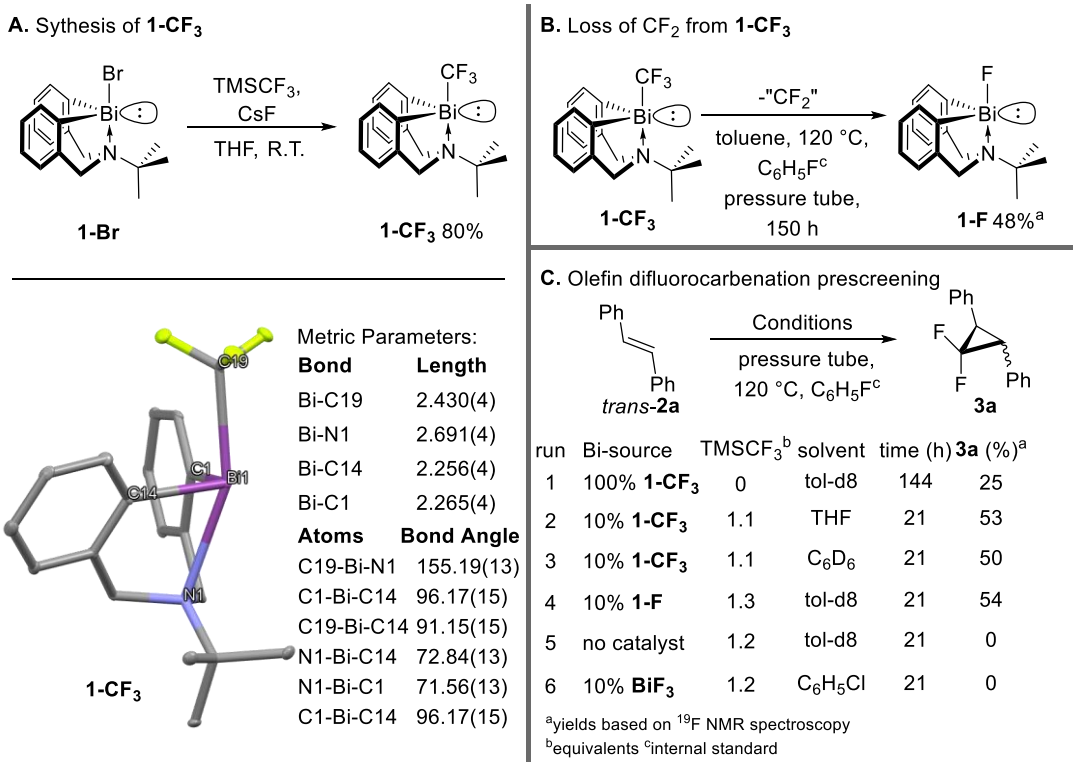
Synthesis of organobismuth catalyst **1-CF_3**.

Bismuth bromide complex **1-Br**[31] was treated with CsF and $TMSCF_3$ providing trifluoromethyl bismuth complex **1-CF_3** in 80% yield (see **Figure 2-A**). The isolated complex is air and moisture stable but decomposes slowly on silica gel. Its structure was confirmed by NMR spectroscopy and elemental analysis. Notably, ^{1}H NMR spectroscopy showed a characteristic downfield doublet for the aromatic protons in *ortho* position to bismuth at 8.22 ppm and second order doublets for the diastereotopic protons in the benzylic position at 4.24 ppm and 3.87 ppm. ^{19}F NMR spectroscopy showed a singlet at 38.8 ppm, closely matching $Bi(CF_3)_3$ (singlet, δ_F = -33.4 ppm).[27] The structure of **1-CF_3** was resolved by single-crystal X-ray crystallography and key structural parameters are presented in **Figure 2-A**. The Bi-N bond length, 2.691(4) Å, falls within the 2.568(3) to 2.896(5) Å range of hypervalent bond lengths previously reported for complexes of **1** by Tanaka and Shimada,[31] indicating the preserved hypervalent character of **1-CF_3**.

Reactivity of **1-CF_3**.

To test the envisioned 'lability' of the CF_3 substituent, we heated **1-CF_3** in solution and observed slow conversion to **1-F** (singlet, δ_F = -188.70 ppm[31]), suggesting indeed the loss of difluorocarbene, CF_2 (**Figure 2-B**). Heating **1-CF_3** at 120 °C for 144h in the presence of the CF_2 acceptor, *trans*-stilbene, *trans*-

2a, led to formation of a 1,1-difluorocyclopropane (**3a,** 25% yield, **Figure 2-C (**run 1), diagnostic triplet at -134 ppm in the ^{19}F NMR spectrum for the major *trans* isomer). When **1-CF$_3$** is used in catalytic amounts (10%) along with 1.1 equivalents of $TMSCF_3$, product **3a** is formed in ≥ 50% yield based on ^{19}F NMR spectroscopy (**Figure 2-C**), in both non-polar and polar solvents (run 2 and 3, for dedicated solvent study see SI). Additionally, the formation of by-product TMSF (singlet, δ_F = -157.1 ppm) and traces of CF_3H (doublet, δ_F = -81.5 ppm) originating from hydrolysis with residual water were observed by ^{19}F NMR spectroscopy.[11] Potentially explosive tetrafluoroethylene and highly toxic higher perfluoroalkenes, common side products in NaI-mediated and Si-induced anionic chain difluorocarbenations, were not observed.[11] Interestingly, the catalytic reaction is much faster and reaches higher yields than the stoichiometric reaction (**Figure 2-C**), an effect that will be explained later. **1-F** or **1-CF$_3$** can be used as pre-catalyst with virtually identical results (run 4). No reactivity was observed in the absence of **1-CF$_3$** or **1-F** (run 5). BiF_3, a simpler inorganic analog of **1-F**, is catalytically inactive (run 6).



Metric Parameters:

Bond	Length
Bi-C19	2.430(4)
Bi-N1	2.691(4)
Bi-C14	2.256(4)
Bi-C1	2.265(4)
Atoms	**Bond Angle**
C19-Bi-N1	155.19(13)
C1-Bi-C14	96.17(15)
C19-Bi-C14	91.15(15)
N1-Bi-C14	72.84(13)
N1-Bi-C1	71.56(13)
C1-Bi-C14	96.17(15)

run	Bi-source	$TMSCF_3$[b]	solvent	time (h)	**3a** (%)[a]
1	100% **1-CF$_3$**	0	tol-d8	144	25
2	10% **1-CF$_3$**	1.1	THF	21	53
3	10% **1-CF$_3$**	1.1	C_6D_6	21	50
4	10% **1-F**	1.3	tol-d8	21	54
5	no catalyst	1.2	tol-d8	21	0
6	10% **BiF$_3$**	1.2	C_6H_5Cl	21	0

[a]yields based on ^{19}F NMR spectroscopy
[b]equivalents [c]internal standard

Figure 2. Development of organobismuth-catalyzed olefin difluorocarbenation. (A) Common stoichiometric difluorocarbene sources and the newly developed catalytic Bi-system 12-CF_3-6-*t*Bu-5,6,7,12-tetrahydrodibenz[c,f][1,5]azabismocine (**1-CF$_3$**). Note: TBAT (tetrabutylammonium difluorotriphenyl-silicate), TBAB (tetrabutylammonium bromide), TFDA (trimethylsilyl fluorosulfonyldifluoroacetate). (B) The origin of the selectivity: equilibrium between dormant and active states in ATRP and in the presented system. (C) Synthesis and X-ray structure of **1-CF$_3$**. C atoms grey, F atoms yellow, N atom blue, Bi atom purple. H atoms removed for clarity. Thermal ellipsoids at 30%. Metric parameters in Å or °. (D) Loss of CF_2 from **1-CF$_3$**, (E) Stoichiometric and catalytic difluorocarbenation of *trans*-stilbene *trans*-**2a** with **1-CF$_3$.**

Optimization, scope and recyclability of the catalytic reaction.

Toluene was selected as solvent for the substrate screening due to the ease of isolation of the catalyst from the reaction mixture. Improved and more consistent yields are observed when the amount of $TMSCF_3$ is increased to 1.2 equivalents, likely due to scavenging of residual water.[11] The **1-CF$_3$** based catalytic system proved to be both robust and efficient as demonstrated by synthesis of monosubstituted (**3b**), disubstituted

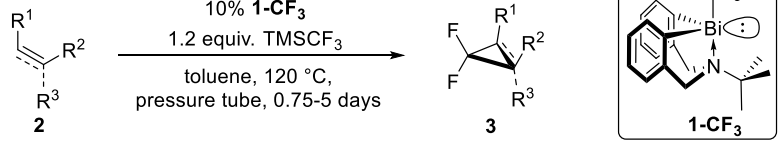
(**3a**, **3c**-**j**, **3l**-**n**, **3q**-**r**), trisubstituted (**3s**), bicyclic (**3l, 3m**, **3s**) 1,1-difluorocyclopropanes and disubstituted (**3o**) and monosubstituted (**3p**) 1,1-difluorocyclopropenes (**Figure 3-A**). Electron-deficient alkenes are in general challenging substrates for difluorocarbenations due to an electrophilic nature of the reaction. In our reaction, the overall yields of electron-poor substrates were not affected; however, the reaction rates were significantly reduced, *e.g.* electron-rich product **3g** formed ~4 times faster than electron-poor product **3e** (*vide infra*, Hammett study). Notably, the most reactive substrate was oct-1-ene **2k** which was fully converted after 18h and the least reactive (the most electron-deficient) substrate was ethyl-cinnamate **2n**, which afforded 95% yield of **3n** after 5 days.

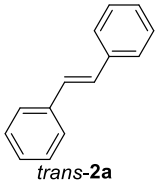
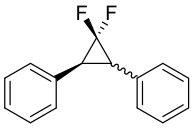
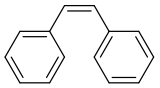
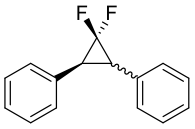
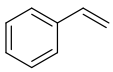
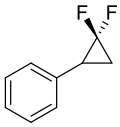
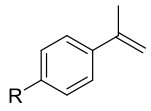
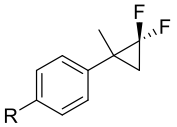
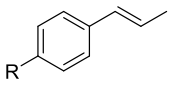
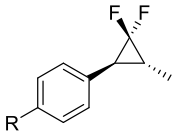
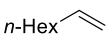
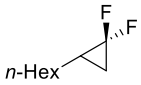
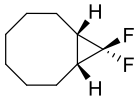
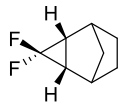
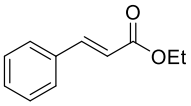
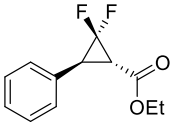
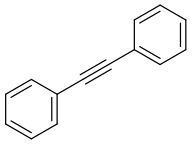
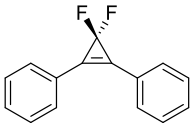
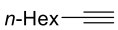
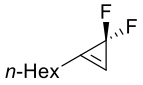
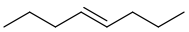
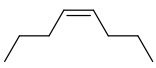
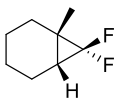
Functional groups like ethers, chlorines, trifluoromethyl groups, and esters were well tolerated, providing 82-99% isolated yields. For ease of isolation, the reactions affording volatile products **3k**, **3l**, **3m**, **3q**, **3r** and **3s** were run in THF. However, the isolated yields were lower (22-77%), despite quantitative ^{19}F NMR yields based on C_6H_5F used as an internal standard (see SI).

The reaction proved to be stereospecific, preserving the configuration of the starting *trans*-*β*-methylstyrenes (products **3i**, **3j** and **3n**) and *cis*- and *trans*-oct-4-ene (products **3q** and **3r**, respectively). Only *cis*- and *trans*-stilbene, afforded virtually the same mixture of *cis* and *trans*-stereoisomers (**3a**) in 1:10 ratio, respectively. A similar observation was reported by Guo-Zhen for reaction with difluorocarbene generated from the Seyferth reagent ($PhHgCF_3$),[38] which was attributed to a radical rearrangement process. In addition, a rearrangement through proposed diradical intermediate was observed in structurally related 1,1-difluoro-vinylcyclopropanes.[39]

Moreover, we were able to recover 45-96% of **1-CF$_3$** from the reaction mixture along with traces of **1-F**. For more polar products (**3d**, **3e**, **3g**, **3j**, **3n**), less **1-CF$_3$** was recovered, likely due to an increased solubility of **1-CF$_3$** in the *n*-hexane/product mixture. In a consecutive three-run experiment under optimized reaction conditions with catalyst isolation (**Figure 3-B**); good yields (70-84%) and catalyst recovery (91-97%) were observed for *cis*-cyclooctene **2l**.

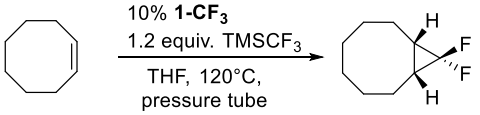
A. Synthetic Scope



Substrate	Product	Substrate	Product
 *trans*-**2a**	 **3a** 94% (87%)[a] *trans*:*cis* = 10:1	 *cis*-**2a**	 **3a** 95% (70%)[a] *trans*:*cis* = 10:1
 **2b**	 **3b** 98% (80%)[a]	 R = H, **2c**; Cl, **2d**; CF_3, **2e**; CH_3, **2f**; OCH_3, **2g**; F, **2h**	 R = H, **3c** 95% (68%)[a]; Cl, **3d** 99% (46%)[a]; CF_3, **3e** 82% (45%)[a]; CH_3, **3f** 83% (68%)[a]; OCH_3, **3g** 98% (49%)[a]; F, **3h** 82% (97%)[a]
 R = H, **2i**; OCH_3, **2j**	 R = H, **3i** 93% (71%)[a] OCH_3, **3j** 98% (60%)[a]	 **2k**	 **3k** 68% (96%)[a]
 **2l**	 **3l** 77% (90%)[a]	 **2m**	 **3m** 22% (93%)[a]
 **2n**	 **3n** 95% (40%)[a]	 **2o**	 **3o** 94% (85%)[a]
 **2p**	 **3p** 98% (80%)[a]	 **2q**	 **3q** 33% (88%)[a]
 **2r**	 **3r** 30% (82%)[a]	 **2s**	 **3s** 26% (93%)[a]

[a] **1-CF_3** recovery

B. Catalyst recovery



2l **3l**

run	**3l** (%)	**1-CF_3** recovery (%)
1	75	96
2	84	97
3	70	91

Figure 3. Synthetic utility. (A) Reaction scope. (B) Catalyst recovery over three runs.

Mechanistic Studies.

Several pathways for the CF_2 transfer were considered. High yields, lack of oligomeric or polymeric side products in difluorocarbenation of styrene (**3c,** *vide supra*), stereoselectivity (reaction scope, *vide supra*) and insensitivity to addition of the radical trap BHT (see SI) speak strongly against a radical mechanism, as described by Wu in a related system.[40] The reaction conditions (i.e. high temperature and long reaction times) and reagent stoichiometry (1.2-fold excess) are distinctively different from NaI-promoted or silicon-induced anionic chain mechanism, recently deconvoluted by Lloyd-Jones,[11] operating through trifluoromethyl anionoid forming difluorocarbene by an α-elimination process. Moreover, in a competitive experiment with 4-fluorobenzaldehyde **4**, selective reaction with the alkene **2h** is observed. Lloyd-Jones observed an elevated amount of the corresponding alcohol **5** indicating a reaction with free trifluoromethyl anionoid (**Figure 4-A**).

Exclusion of the aforementioned reaction pathways leaves three possible options: reversible or irreversible CF_2 generation, followed by CF_2 addition (**Figure 4-B a.** and **b.**, respectively), or difluorocarbene transfer in a single step mechanism operational in CH_2 transfers of metal carbenoids[41] (**Figure 4-B c.**).

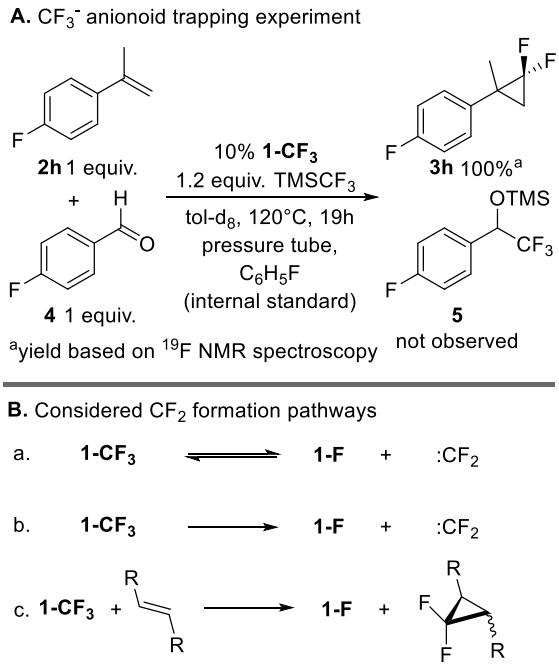
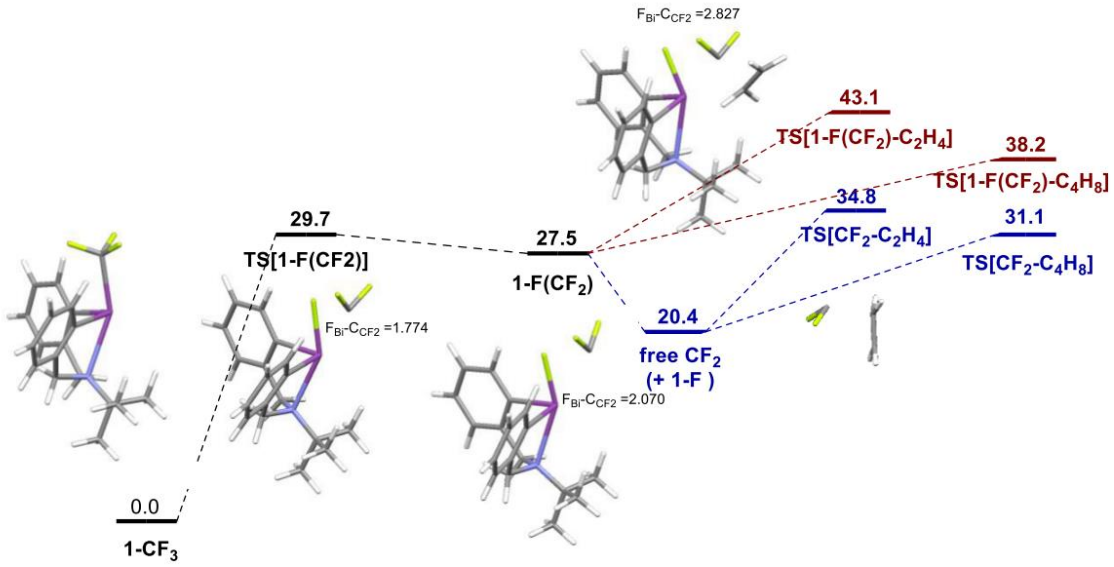


Figure 4. Investigation of CF_2 formation step. (A) Competition experiment with 4-fluoro-α-methyl-styrene/4-fluorobenzaldehyde. (B) Possible difluorocarbenation pathways.

a. DFT study.

To better understand the mechanism, we performed DFT studies on the TPSSh/TZ(PCM)// TPSSh/DZ level of theory. **1-CF_3** has an asymmetric CF_3 unit, as evidenced by three different C-F bond lengths. One Bi-C-F angle deviates significantly from the tetrahedral angle of 109.5°. Asymmetry is well reproduced in the calculations (see **Figure 5-B**).

A. **1-CF_3** Difluorocarbenation PES.



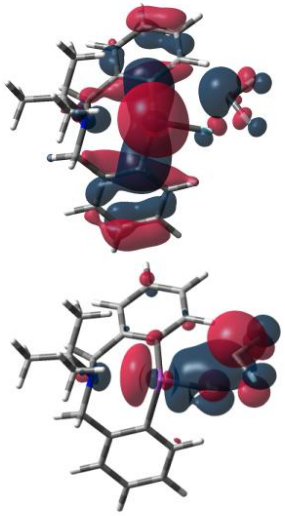
B. Key metric parameters (Å or °).

	metric parameter	X-ray	DFT
1-CF_3	C-F	1.332; 1.358;1.369	1.365; 1372; 1.378
	Bi-C	2.43	2.39
	Bi-C-F	119.8; 111.0; 107.8	117.5; 111.7; 110.0
1-F	Bi-F	2.19	2.109

C. Key metric parameters for difluorocarbenation TS (Å).

metric parameter	TS[CF_2-C_2H_4]		TS[1-F(CF_2)-C_2H_4]	
$C_{carbene}$-C_{alkene}	1.901	2.538	1.880	2.530
C=C	1.380		1.383	
C-F_{BiF}			2.827	
C-Bi_{BiF}			3.209	

D. HOMO (top) and LUMO (bottom) of **1-F(CF_2)**.



E. Relative stabilization of **1-F** over **1-CF_3** (kcal/mol).

	BDH	Δ_{BDH}
	Bi-C	
1-CF_3	55.0	**8.5**
$Bi(CF_3)_3$	46.5	
	Bi-F	
1-F	111.6	**14.8**
$Bi(CF_3)_2$-F	96.8	

F. TS energies, **1-CF_3** vs **$Bi(CF_3)_3$** (kcal/mol).

	α-F elimination TS
1-CF_3	29.7
$Bi(CF_3)_3$	34.2
Δ	**-4.5**

Figure 5. DFT Study. (A) Potential energy surface for the formation of **1-F(CF_2)** (black traces) and the difluorocarbenation pathways via **1-F(CF_2)** (burgundy traces) and free CF_2 (blue traces) for two archetypical alkenes: ethene (C_2H_4) and *trans*-2-butene (C_4H_8) Gibbs free energies, T = 393K. Only ethene DFC TS structures shown for simplicity. (B) Key metric parameters for **1-CF_3** and **1-F** (crystal structure vs. DFT values). (C) Key metric parameters for the TS for difluorocarbenation of ethene via the free carbene pathway and the **1-F(CF_2)** pathway. (D) HOMO (-6.07

eV) and LUMO (-1.40 eV) of **1-F(CF_2)**, showing significant delocalization over the Bi-F and CF_2 fragments. Isovalue 0.03. (E) Trends in Bond dissociation enthalpies (BDH) and the relative stabilization of **1-F** over **1-CF_3**. (F) α-F elimination TS lowering from $Bi(CF_3)_3$ to **1-CF_3**.

1-CF_3 can, via an energetically relatively low lying α-F elimination transition state (**TS[1-F(CF_2)],** $\Delta G^{\ddagger}_{393K}$ = 29.7 kcal/mol, see **Figure 5-A**) with minimal charge separation (q_{CF2} = 0.112 e^-), form **1-F(CF_2)**. This barrier is significantly lower than the 34.2 kcal/mol predicted for *α*-F elimination from $Bi(CF_3)_3$. HOMO and LUMO of **1-F(CF_2)** are delocalized over the **1-F** and CF_2 fragment (see **Figure 5-D**). Wiberg bond indices (WBI) for the Bi-C_{CF2} (0.104) and the C-F_{BiF} bond (0.212) indicate some interaction of **1-F** with the carbene fragment. Additionally, the Bi-F bond (WBI: 0.307 vs 0.420 in **1-F**) is not yet fully formed. Nonetheless, CF_2 is only weakly bound and the calculated bond dissociation energy of CF_2 in **1-F(CF_2)** is only 3.2 kcal/mol.

Re-insertion of CF_2 into the Bi-F bond of **1-F** has a very low barrier (2.2 kcal/mol) from **1-F(CF_2)**. Release of CF_2 from **1-F(CF_2)** is exergonic (-7.1 kcal/mol). Overall, formation of **1-F** and free **CF_2** carbene is reversible (re-insertion barrier 9.3 kcal/mol) and endergonic by 20.4 kcal/mol. The concentration of free carbene in reactions catalyzed by **1-CF_3** should always be vanishingly small, making the formation of larger amounts of tetrafluoroethylene, *cyclo*-C_3F_6 or higher perfluoroalkenes as side products unlikely.

Difluorocarbenation barriers from CF_2 and **1-F(CF_2)** were analyzed for two archetypical alkenes: ethene and *trans*-2-butene and can proceed via two different pathways, with participation of **1-F** or without via a free carbene pathway. More electron-rich alkenes like *trans*-2-butene show lower activation barriers via both pathways. The **1-F(CF_2)** pathway offers some enthalpic stabilization (≈ -2.5 kcal/mol). However, the entropy contribution in the **TS[1-F(CF_2)-alkene]** stemming from the 2→1 particle penalty forming the TS from alkene and **1-F(CF_2)**, outweighs this stabilization. In the free CF_2 pathway this penalty is compensated for by the dissociation of **1-F** (*i.e.* **1-CF_3** + alkene vs **1-F** + **TS[CF_2-alkene]**). Overall, difluorocarbenation barriers via the preferred free CF_2 pathway amount to 11-14 kcal/mol from free CF_2 and to 31-35 kcal/mol when the **1-CF_3**/(**1F** + free CF_2) equilibrium is accounted for. The latter agrees nicely with the experiments, which require prolonged heating at high temperatures.

Difluorocarbenation TS (**TS[1F(CF_2)-C_2H_4]** and **TS[CF_2-C_2H_4]**) geometries via both pathways are very early, as evidenced by the long C_{CF2}-C_{ethene} distances (>1.88 Å) and only slightly elongated C=C bond length (1.38 Å), both with and without the presence of **1-F** (see **Figure 5-A and C**). The C-Bi_{BiF} distance is only slightly elongated in the TS compared to **1-F(CF_2)**. Both pathways involve minimal charge separation ($q_{CF2(ethene)}$ = 0.076 e^-). The free carbene pathway prevails for **1-CF_3**. Nonetheless, the α-F elimination **TS[1F(CF_2)]** to form **1-F(CF_2)** is energetically and geometrically late, while the difluorocarbenation **TS[1F(CF_2)-C_2H_4]** is energetically and geometrically early. Therefore, stabilizing **1-F(CF_2)** via variation of the ligand framework should lower both the elimination TS as well as the difluorocarbenation TS according to the Hammond postulate and could eventually lower the Bi-stabilized pathway below the free carbene one.[42]

For *trans*-2-butene, the α-F elimination **TS[1F(CF_2)]** and the difluorocarbenation **TS[1F(CF_2)-C_4H_8]** have nearly identical Gibbs free energies (with 1.4 kcal/mol). Whether the difluorocarbenation is zero order with respect to the reactant thus depends on the substrate. For more electron rich substrates, CF_2 elimination could become rate limiting while for less electron rich substrates difluorocarbenation should be rate limiting. The barrier is then composed of two parts, a pre-equilibrium leading to free carbene and the actual difluorocarbenation barrier. Therefore, DFT supports the reversible two-step difluorocarbenation (**Figure 4-B a.**).

b. <u>Understanding the ease of CF_2 generation from 1-CF_3</u>

As mentioned in the introduction, we assumed at the onset of this project that the hypervalent framework of **1-CF_3** would weaken the Bi-CF_3 bond in comparison to $Bi(CF_3)_3$, thus enabling easier CF_2

release. While the bond order of the Bi-C bond in **1-CF_3** is indeed lower than in $Bi(CF_3)_3$ (0.694 vs 0.800 as judged by the WBI), consistent with a 3c-4e bonding model,[29] the Bi-C_{CF3} bond in **1-CF_3** is actually much stronger (homolytic bond dissociation enthalpy, BDH, 55.0 vs 46.5 kcal/mol, Δ_{BDH} = 8.5 kcal/mol, **Figure 5-E**). Similarly, the Bi-F BDH increases from 96.8 to 111.6 kcal/mol, Δ_{BDH} = 14.8 kcal/mol. However, as envisioned, the CNC framework decreases the endergonicity of the CF_2 release from 26.3 to 20.4 kcal/mol at 393K. This can be understood as a result of stabilizing the Bi-F bond *relative to* the Bi-CF_3 bond. More importantly, as mentioned earlier, the α-F elimination TS is late, both in $Bi(CF_3)_3$ as well as in **1-CF_3** and stabilizing the product (**1-F** over $Bi(CF_3)_2$-F) therefore lowers the TS to a similar degree (Hammond postulate, see also **Figure 5-F**). The ease of CF_2 generation, at least in the present case, can therefore be fully attributed to a selective stabilization of the α-F elimination product **1-F**, not to an inherent destabilization of **1-CF_3**.

c. Mechanistic experiments

To support the reversible CF_2 generation and to unambiguously demonstrate that **1-CF_3** is not formed by CF_3 transmetalation, we selected difluoromethylene phosphobetaine **6**[18] containing a difluorocarbene fragment and not a CF_3 moiety. Indeed, heating of **1-F** in presence of **6** afforded **1-CF_3** in 88% isolated yield (**Figure 6-A**). In addition, we decided to compare kinetic profiles of the stoichiometric reaction of **1-CF_3** with *p*-methoxy-α-methylstyrene **2g** in the presence and absence of **1-F** (**Figure 6-B**). **1-F** addition slows the reaction significantly, indicating that **1-F** retards the reversible preequilibrium CF_2 formation, corroborating the experiment above. This is also consistent with our earlier observation that the CF_2 transfer occurred faster under catalytic compared to stoichiometric conditions (**Figure 2-B** and **C**), since in the former **1-F** is removed from the equilibrium accelerating the addition (Le Chatelier's principle).

Next, we decided to study the catalyst regeneration through trifluoromethylation of **1-F** in the model reaction shown in **Figure 6-C**. Transmetalation from silicon to bismuth was previously reported,[43] and is fast. **1-F**, when treated with $TMSCF_3$ reached 83% isolated yield of **1-CF_3** even at ambient temperature after 4d

The insensitivity to solvent variation and the DFT study are indicative of a concerted mechanism rather than an ionic one. To support this, a Hammett study was conducted (**Figure 6-D**). We selected *para*-substituted α-methylstyrenes (**2d**, **2e**, **2f**, **2g** and **2h**) with the parent α-methylstyrene **2c** serving as reference and used the ratio of products instead of the relative rates k_x/k_H due to the irreversibility of the reaction. A good fit with σ^+ rather than with σ values was observed, with the ρ value to be -0.47. This is close to values obtained for difluorocarbene additions generated from $TMSCF_3$ (TBAT, rt, ρ = -0.64, plotted against σ^+) and difluoromethylene phosphobetaine **6** (65 °C, ρ = -0.57, plotted against σ^+).[11] Corroborating the DFT results, the Hammett study thus indicates a relatively small charge separation in the TS of the rate determining step, consistent with the difluorocarbene addition mechanism.

Catalytic Cycle.

In summary, we propose a reaction mechanism where **1-CF_3** reversibly forms difluorocarbene and **1-F**. Free difluorocarbene reacts with alkenes yielding 1,1-difluorocyclopropane products and **1-F**. **1-F** is then trifluoromethylated by $TMSCF_3$ producing TMSF and regenerating **1-CF_3** through a pentacoordinated silicon intermediate[44], thus completing the catalytic cycle (**Figure 6-E**). The catalyst acts as controlled CF_2 reservoir effectively keeping the concentration of free CF_2 exceedingly low, eliminating the formation of potentially explosive tetrafluoroethylene, or highly toxic perfluoroalkenes by bimolecular pathways. The stabilizing role of pre-equilibria in the chemistry of highly reactive intermediates, *e.g.* radicals, has for example also been noted for ATRP polymerization, but also for well-defined closed-shell species, e.g. in hydrodefluorination using highly reactive Cp_2Ti-H.[45]

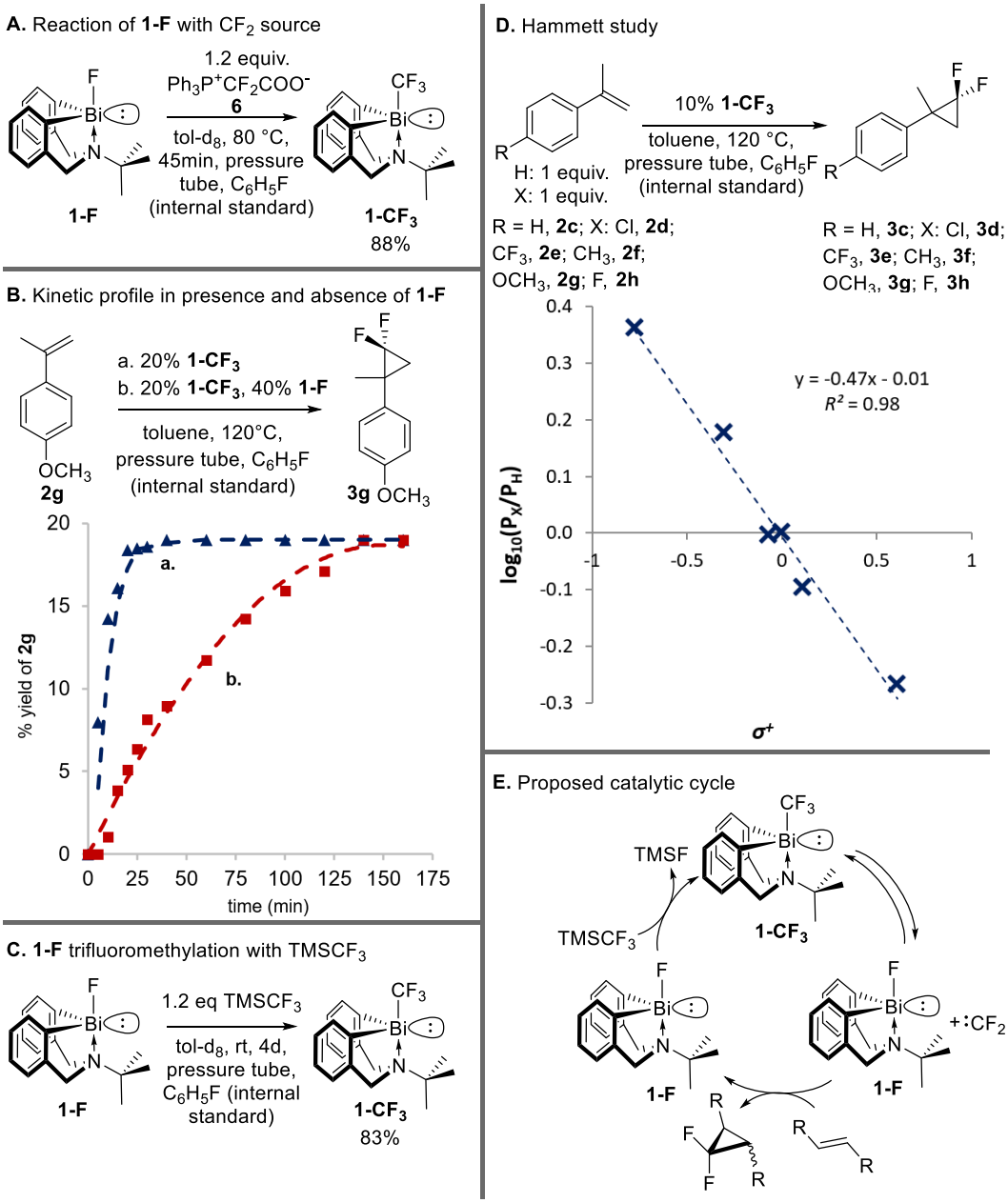


Figure 6. (A) Difluorocarbenation of **1-F** with difluoromethylene phosphobetaine **6**. (B) Kinetic profiles for difluorocarbenation with (red trace) addition of **1-F** and without (blue). (C) Transmetallation of **1-F**. (D) Hammett study of *para*-substituted *α*-methylstyrenes. R = CF_3, Cl, H, Me, OMe, F. (E) Proposed catalytic cycle.

Conclusion

Hypervalent trifluoromethyl bismuth complex **1-CF_3** catalyzes the formation of 1,1-difluorocyclopropanes with excellent efficiency, promising improved synthetic access to medicinally relevant targets. Additional advantages of our system include $TMSCF_3$ as the stoichiometric source of difluorocarbene, high recyclability of the catalyst, stereospecificity, and overall robustness. Experiments and DFT studies indicate a reversible formation of difluorocarbene where **1-CF_3** acts catalytically to release small quantities of the highly reactive CF_2 species, thus explaining the high efficiency. Finally, we argue that the data support our assertion that CF_2 is the actual species that reacts with alkene substrates. We are currently exploring the

effects of ligand variation on the **1-CF_3**/CF_2 equilibrium, in efforts to lower the reaction temperature and reduce the reaction times.

Methods

Representative procedure for alkene difluorocarbenation.

Under nitrogen atmosphere, **1-CF_3** (0.262g, 0.5mmol) was suspended in 2.5ml toluene. To this suspension was added fluorobenzene (0.471ml 5mmol) as internal standard, and then *trans*-stilbene *trans*-**2a** (0.901g, 5 mmol). Lastly, TMS-CF_3 (0.812ml, 5.5 mmol) was added to the Schlenk bomb. The reaction was heated to 120 °C until the disappearance of starting material was observed by ^{1}H NMR spectroscopy, about 40 hours. The reaction was cooled to room temperature, solvent was removed *in vacuo*, and the product *trans*-1,1-difluoro-2,3-diphenylcyclopropane, **3a,** was extracted with hexanes and filtered to afford 1.08g (94%) **3a**, with 0.229g (87% mass recovery) of the **1-CF_3** catalyst.

DFT study.

All geometries were fully optimized by using the Gaussian 16 software package[46] in combination with an external optimizer (PQS, OPTIMIZE routine of Baker[47-48]) and the BOpt software package.[49] Following the protocol proposed in ref. [50], all relevant minima and transition states were fully optimized at the TPSSh level[51] of theory employing correlation-consistent polarized valence double-ζ Dunning (DZ) basis sets with cc-pVDZ quality[52, 53] from the basis set exchange library,[54] using a small core pseudo-potential on Bi. The density fitting approximation (Resolution of Identity, RI)[55, 56, 57, 58] was used at the optimization stage and for single-point energy corrections. All calculations were performed at the standard Gaussian16 SCF convergence using an ultrafine grid [Scf=Tight and Int(Grid=ultrafine)]. The nature of each stationary point was checked with an analytical second-derivative calculation (no imaginary frequency for minima, exactly one imaginary frequency for transition states, corresponding to the reaction coordinate). The accuracy of the TS was confirmed with IRC scans. Transition states were located using a suitable guess and the Berny algorithm (Opt=TS)[59] or a relaxed potential energy scan to arrive at a suitable transition-state guess, followed by full optimization.

Final single-point energies were calculated at the TPSSh level of theory[60] employing triple-ζ Dunning (TZ) basis sets (cc-pVTZ quality).[52] Grimme dispersion corrections without damping (keyword -zero) were added at this stage using the standalone dftd3 program.[61, 62] Solvent effects (toluene, ε = 2.3741) were included with the polarizable continuum model approach (PCM).[63] Enthalpies and Gibbs free energies were then obtained from TZ single-point energies and thermal corrections from the TPSSh/cc-pVDZ-(PP) vibrational analyses; entropy corrections were scaled by a factor of 0.67 to account for decreased entropy in the condensed phase.[64, 65, 66] NBO 3.1 was used for NBO analysis.[67] Optimization in solvent and inclusion of dispersion corrections (via B97D functional) was tested and found to give essentially identical results.

Notes

The authors declare the following competing financial interest(s): A provisional patent on this work, application no. 63/122,374, has been filed by University of Hawai'i.

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Author Contributions

T. L.-G., H.V.T. and J.H. were involved in the discovery and development of the catalyst and the difluorocarbenation method. E.C. contributed to the synthesis of catalyst. C.E. designed and performed the computational investigations and contributed to elucidation of the mechanism. A.R. resolved the X-ray structure. J.H. directed the investigation and wrote the manuscript with major contributions from C.E.

Data Availability

The X-ray crystallographic coordinates for structure **1-CF_3** reported in this article have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition number CCDC 2050813. The data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. All other data generated or analysed during this study are included in this published article (and its supplementary information files).

References

1. Gillis, E.P., Eastman, K.J., Hill, M.D., Donnelly, D.J. & Meanwell, N.A. Applications of Fluorine in Medicinal Chemistry. *J. Med. Chem.* **58**, 8315-8359 (2015).

2. Furuya, T., Kamlet, A.S. & Ritter, T. Catalysis for fluorination and trifluoromethylation. *Nature* **473**, 470-477 (2011).

3. Wang, J. *et al.* Fluorine in pharmaceutical industry: fluorine-containing drugs introduced to the market in the last decade (2001-2011). *Chem. Rev.* **114**, 2432-2506 (2014).

4. Jeschke, P. The unique role of fluorine in the design of active ingredients for modern crop protection. *Chembiochem* **5**, 571-589 (2004).

5. Dolbier, W.R., Jr. & Battiste, M.A. Structure, synthesis, and chemical reactions of fluorinated cyclopropanes and cyclopropenes. *Chem. Rev.* **103**, 1071-1098 (2003).

6. Fedorynski, M. Syntheses of gem-dihalocyclopropanes and their use in organic synthesis. *Chem. Rev.* **103**, 1099-1132 (2003).

7. Lenhardt, J.M. *et al.* Trapping a diradical transition state by mechanochemical polymer extension. *Science* **329**, 1057-1060 (2010).

8. Bychek, R.M., Levterov, V.V., Sadkova, I.V., Tolmachev, A.A. & Mykhailiuk, P.K. Synthesis of Functionalized Difluorocyclopropanes: Unique Building Blocks for Drug Discovery. *Chem. Eur. J.* **24**, 12291-12297 (2018).

9. Brahms, D.L.S. & Dailey, W.P. Fluorinated Carbenes. *Chem. Rev.* **96**, 1585-1632 (1996).

10. Hu, J. & Ni, C. Recent Advances in the Synthetic Application of Difluorocarbene. *Synthesis* **46**, 842-863 (2014).

11. Garcia-Dominguez, A. *et al.* Difluorocarbene Generation from TMSCF3: Kinetics and Mechanism of NaI-Mediated and Si-Induced Anionic Chain Reactions. *J. Am. Chem. Soc.* **142**, 14649-14663 (2020).

12. Nowak, I., Cannon, J.F. & Robins, M.J. Synthesis and properties of gem-(difluorocyclopropyl)amine derivatives of bicyclo[n.1.0]alkanes. *Org. Lett.* **6**, 4767-4770 (2004).

13. Seyferth, D. & Hopper, S.P. Halomethyl metal compounds. LX. Phenyl(trifluoromethyl)mercury. Useful difluorocarbene transfer agent. *J. Org. Chem.* **37**, 4070-4075 (1972).

14. Eujen, R. & Hoge, B. Donor-free bis(trifluoromethyl) cadmium, (CF3)2Cd: a readily available low-temperature difluorocarbene source. *J. Organomet. Chem.* **503**, C51-C54 (1995).

15. Seyferth, D., Dertouzos, H., Suzuki, R. & Mui, J.Y.P. Halomethyl-metal compounds. XIII. Preparation of gem-difluorocyclopropanes by iodide ion-induced CF2 transfer from trimethyl(trifluoromethyl)tin. *J. Org. Chem.* **32**, 2980-2984 (1967).

16. Csuk, R. & Eversmann, L. Synthesis of difluorocyclopropyl carbocyclic homo-nucleosides. *Tetrahedron* **54**, 6445-6456 (1998).

17. Dolbier, W.R. *et al.* Trimethylsilyl fluorosulfonyldifluoroacetate (TFDA): a new, highly efficient difluorocarbene reagent. *J. Fluor. Chem.* **125**, 459-469 (2004).

18. Zheng, J., Lin, J.H., Cai, J. & Xiao, J.C. Conversion between difluorocarbene and difluoromethylene ylide. *Chem. Eur. J.* **19**, 15261-15266 (2013).

19. Wang, F. *et al.* Synthesis of gem-difluorinated cyclopropanes and cyclopropenes: trifluoromethyltrimethylsilane as a difluorocarbene source. *Angew. Chem. Int. Ed.* **50**, 7153-7157 (2011).

20. Li, L., Wang, F., Ni, C. & Hu, J. Synthesis of gem-difluorocyclopropa(e)nes and O-, S-, N-, and P-difluoromethylated compounds with TMSCF(2)Br. *Angew. Chem. Int. Ed.* **52**, 12390-12394 (2013).

21. Wang, Y. *et al.* Improving the “Livingness” of ATRP by Reducing Cu Catalyst Concentration. *Macromolecules* **46**, 683-691 (2013).

22. Patten, T.E. & Matyjaszewski, K. Atom Transfer Radical Polymerization and the Synthesis of Polymeric Materials. *Adv. Mater. (Weinheim, Ger.)* **10**, 901-915 (1998).

23. Matyjaszewski, K. & Xia, J. Atom Transfer Radical Polymerization. *Chem. Rev.* **101**, 2921-2990 (2001).

24. Seyferth, D., Mui, J.Y.-P. & Damrauer, R. Halomethyl-metal compounds. XIX. Further studies of the aryl(bromodichloromethyl)mercury-olefin reaction. *J. Am. Chem. Soc.* **90**, 6182-6186 (1968).

25. Krause, L.J. & Morrison, J.A. Trifluoromethyl group 2B compounds: bis(trifluoromethyl)cadmium.base. New, more powerful ligand-exchange reagents and low-temperature difluorocarbene sources. *J. Am. Chem. Soc.* **103**, 2995-3001 (1981).

26. Mohan, R. Green bismuth. *Nat. Chem.* **2**, 336 (2010).

27. Naumann, D. & Tyrra, W. The preparations and properties of tris(perfluoroorgano)bismuth compounds Bi(Rf)3 (Rf = CF3, C2F5, n-C3F7, n-C4F9, n-C6F13, n-C8 F17, C6F5). *J. Organomet. Chem.* **334**, 323-328 (1987).

28. Kirii, N.V., Pazenok, S.V., Yagupolskii, Y.L., Naumann, D. & Turra, W. Carbenoid Reactions of Organoelemental Compounds Containing Trifluoromethyl Groups: VII.2* Difluorocyclopropanation of Olefins and Dienes with a System Tris(trifluoromethyl)bismuth-Aluminum Chloride2*2*. *Russ. J. Org. Chem.* **37**, 207-209 (2001).

29. Raţ, C.I., Silvestru, C. & Breunig, H.J. Hypervalent organoantimony and -bismuth compounds with pendant arm ligands. *Coord. Chem. Rev.* **257**, 818-879 (2013).

30. Ohkata, K., Takemoto, S., Ohnishi, M. & Akiba, K.-y. Synthesis and chemical behaviors of 12-substituted dibenz[c,f][1,5]azastibocine and dibenz[c,f][1,5]azabismocine derivatives: evidences of 10-Pn-4 type hypervalent interaction. *Tetrahedron Lett.* **30**, 4841-4844 (1989).

31. Shimada, S., Yamazaki, O., Tanaka, T., Suzuki, Y. & Tanaka, M. Synthesis and structure of 5,6,7,12-tetrahydrodibenz[c,f][1,5]azabismocines. *J. Organomet. Chem.* **689**, 3012-3023 (2004).

32. Louis-Goff, T., Rheingold, A.L. & Hyvl, J. Investigation into the Organobismuth Dismutation and Its Use for Rational Synthesis of Heteroleptic Triarylbismuthanes, Ar12Ar2Bi. *Organometallics* **39**, 778-782 (2020).

33. Planas, O., Wang, F., Leutzsch, M. & Cornella, J. Fluorination of arylboronic esters enabled by bismuth redox catalysis. *Science* **367**, 313-317 (2020).

34. Jurrat, M., Maggi, L., Lewis, W. & Ball, L.T. Modular bismacycles for the selective C-H arylation of phenols and naphthols. *Nat. Chem.* **12**, 260-269 (2020).

35. Ruffell, K. & Ball, L.T. Organobismuth Redox Manifolds: Versatile Tools for Synthesis. *Trends in Chemistry* **2**, 867-869 (2020).

36. Fu, X.P. *et al.* Controllable catalytic difluorocarbene transfer enables access to diversified fluoroalkylated arenes. *Nat. Chem.* **11**, 948-956 (2019).

37. Goswami, M., de Bruin, B. & Dzik, W.I. Difluorocarbene transfer from a cobalt complex to an electron-deficient alkene. *Chem. Commun.* **53**, 4382-4385 (2017).

38. GUOZHEN, J., GUOFEI, C., ZONGMEI, W. & Xi-Kui, J. The Formation of Trans Cycloadduct from the Reaction of Difluorocarbene with Cis-Difluorostilbene. *Acta Chim. Sinica* **45**, 904–909 (1987).

39. Dolbier, W.R. Thermal rearrangements of gem-difluorocyclopropanes. *Acc. Chem. Res.* **14**, 195-200 (1981).

40. Wu, S.-H., Liu, W.-Z. & Jiang, X.-K. Mechanistic Studies on Zinc-Induced Addition of CF2Br2 to Olefins. A Novel Radical Reductive Cyclopropanation on the Zinc Surface. *J. Org. Chem.* **59**, 854-857 (1994).

41. Rasmussen, T. *et al.* On the Mechanism of the Copper-Catalyzed Cyclopropanation Reaction. *Chem. - Eur. J.* **8**, 177-184 (2002).

42. Hammond, G.S. A Correlation of Reaction Rates. *J. Am. Chem. Soc.* **77**, 334-338 (1955).

43. Preda, A.M. *et al.* Heteroaryl bismuthines: a novel synthetic concept and metalpi heteroarene interactions. *Dalton Trans.* **46**, 8269-8278 (2017).

44. Johnston, C.P. *et al.* Anion-Initiated Trifluoromethylation by TMSCF3: Deconvolution of the Siliconate-Carbanion Dichotomy by Stopped-Flow NMR/IR. *J. Am. Chem. Soc.* **140**, 11112-11124 (2018).

45. Ehm, C., Krüger, J. & Lentz, D. How a Thermally Unstable Metal Hydrido Complex Can Yield High Catalytic Activity Even at Elevated Temperatures. *Chem. - Eur. J.* **22**, 9305-9310 (2016).

46. Frisch, M. J.; Trucks, G. W.; et al. Gaussian 16, Revision A.03; Gaussian, Inc.: Wallingford, CT, 2016. For a full citation, see the Supporting Information.

47. J. Baker, 2.4 ed., Parallel Quantum Solutions, Fayetteville, AR, 2001.

48. Baker, J. An algorithm for the location of transition states. *J. Comput. Chem.* **7**, 385-395 (1986).

49. Budzelaar, P.H.M. Geometry optimization using generalized, chemically meaningful constraints. *J. Comput. Chem.* **28**, 2226-2236 (2007).

50. Ehm, C., Budzelaar, P.H.M. & Busico, V. Calculating accurate barriers for olefin insertion and related reactions. *Journal of Organometallic Chemistry* **775**, 39-49 (2015).

51. Tao, J., Perdew, J.P., Staroverov, V.N. & Scuseria, G.E. Climbing the Density Functional Ladder: Nonempirical Meta\char21{}Generalized Gradient Approximation Designed for Molecules and Solids. *Physical Review Letters* **91**, 146401 (2003).

52. Balabanov, N.B. & Peterson, K.A. Systematically convergent basis sets for transition metals. I. All-electron correlation consistent basis sets for the 3d elements Sc–Zn. *The Journal of Chemical Physics* **123**, 064107 (2005).

53. Balabanov, N.B. & Peterson, K.A. Basis set limit electronic excitation energies, ionization potentials, and electron affinities for the 3d transition metal atoms: Coupled cluster and multireference methods. *The Journal of Chemical Physics* **125**, 074110 (2006).

54. Pritchard, B.P., Altarawy, D., Didier, B., Gibson, T.D. & Windus, T.L. New Basis Set Exchange: An Open, Up-to-Date Resource for the Molecular Sciences Community. *J. Chem. Inf. Model.* **59**, 4814-4820 (2019).

55. Whitten, J.L. Coulombic potential energy integrals and approximations. *J. Chem. Phys.* **58**, 4496 (1973).

56. Baerends, E.J., Ellis, D.E. & Ros, P. Self-consistent molecular Hartree—Fock—Slater calculations I. The computational procedure. *Chem. Phys.* **2**, 41-51 (1973).

57. Feyereisen, M., Fitzgerald, G. & Komornicki, A. Use of approximate integrals in ab initio theory. An application in MP2 energy calculations. *Chem. Phys. Lett.* **208**, 359-363 (1993).

58. Vahtras, O., Almlöf, J. & Feyereisen, M.W. Integral approximations for LCAO-SCF calculations. *Chem. Phys. Lett.* **213**, 514-518 (1993).

59. The Berny algorithm was never fully published, see the Gaussian documentation for detials.

60. Tao, J.M., Perdew, J.P., Staroverov, V.N. & Scuseria, G.E. Climbing the density functional ladder: Nonempirical meta-generalized gradient approximation designed for molecules and solids. *Phys. Rev. Lett.* **91** (2003).

61. Grimme, S. Density functional theory with London dispersion corrections. *Wiley Interdisciplinary Reviews-Computational Molecular Science* **1**, 211-228 (2011).

62. Grimme, S., Ehrlich, S. & Goerigk, L. Effect of the damping function in dispersion corrected density functional theory. *J. Comput. Chem.* **32**, 1456-1465 (2011).

63. Tomasi, J. Thirty years of continuum solvation chemistry: a review, and prospects for the near future. *Theor. Chem. Acc.* **112**, 184-203 (2004).

64. Tobisch, S. & Ziegler, T. Catalytic Oligomerization of Ethylene to Higher Linear α-Olefins Promoted by the Cationic Group 4 [(η5-Cp-(CMe2-bridge)-Ph)MII(ethylene)2]+ (M = Ti, Zr, Hf) Active Catalysts: A Density Functional Investigation of the Influence of the Metal on the Catalytic Activity and Selectivity. *J. Am. Chem. Soc.* **126**, 9059-9071 (2004).

65. Dunlop-Brière, A.F., Budzelaar, P.H.M. & Baird, M.C. α- and β-Agostic Alkyl–Titanocene Complexes. *Organometallics* **31**, 1591-1594 (2012).

66. Raucoules, R., de Bruin, T., Raybaud, P. & Adamo, C. Theoretical Unraveling of Selective 1-Butene Oligomerization Catalyzed by Iron−Bis(arylimino)pyridine. *Organometallics* **28**, 5358-5367 (2009).

67. Glendening, E.D., Landis, C.R. & Weinhold, F. Natural bond orbital methods. *Wiley Interdisciplinary Reviews: Computational Molecular Science* **2**, 1–42 (2012).