Communication

Selective monodefluorination and Wittig functionalization of gem-difluoromethyl groups to generate monofluoroalkenes

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Selective monodefluorination and Wittig functionalization of *gem*-difluoromethyl groups to generate monofluoroalkenes

Dipendu Mandal†, Richa Gupta† and Rowan D. Young*
Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543

ABSTRACT: Monodefluorination of *gem*-difluoromethyl groups is achieved using a Frustrated Lewis Pair (FLP) approach. Triarylphosphines and group 13 Lewis acids were surveyed as FLP components, with the combination of P(*o*-Tol)$_3$ and B(C$_6$F$_5$)$_3$ found to provide the best results, although the reaction is feasible with more economical components (PPh$_3$ and BF$_3$.OEt$_2$). The α-fluoroalkylphosphonium products arising from the reaction were of lower activity, in regards to further fluoride abstraction, as compared to difluoride starting materials - leading to highly selective monodefluorination. The activated substrates were subject to Wittig reaction protocols to generate a variety of monofluoroalkenes in moderate to high yields.

Introduction:

Lewis acid mediated carbon-fluorine (C-F) bond activation and functionalization has developed greatly within the last decade. The desire to transform C-F bonds into other functional groups is derived from their increasing abundance in societally important chemicals, such as plastics, agrochemicals, pharmaceuticals, refrigerants, and surfactants, and a need to either destroy such chemicals, or convert such chemicals into more useful forms. As such, a number of Lewis acid mediated synthetic methods have been developed.[1]

Despite these recent achievements, Lewis acid controlled C-C bond formation from C-F bonds in polyfluorides generally leads to 'over-reaction', where more than a single fluoride is transformed.[2] As such, stoichiometric monoselective C-F functionalization of polyfluorides is difficult to achieve.[3] Nonetheless, selective functionalization of polyfluorides remains an attractive proposition, as it allows the retention of fluoride in reaction products, and therefore convenient access to a number of fluorine containing motifs. Strategies that employ specific substrates allowing kinetic[3a] (Figure 1A) or thermodynamic[3b-l] (Figure 1B) control of C-F functionalization have been reported. However, a generic approach to selective defluorination is needed to allow the functionalisation of non-specialised polyfluorocarbons with a diverse range of nucleophiles.

The challenge in selective functionalization of polyfluorocarbons arises from the increased stability that C-F bonds offer other proximal C-F positions. Most C-F functionalization methods do not 'deactivate' products from further unwanted functionalization. Thus, post-functionalized products are either as reactive as or more reactive than the polyfluorocarbon starting materials, resulting in a distribution of substitution products.

Upon the realization that no other anionic functional group could be more deactivating than fluoride, we envisaged the incorporation of charge neutral nucleophiles into intermediate carbocations[4] generated from fluoride abstraction. The resulting cationic products would be 'deactivated' towards further fluoride abstraction by Lewis acids (Figure 1C). The cationic products could then be further functionalized once stoichiometric selective fluoride functionalization had been achieved. Indeed, this concept has been utilized by Stephan for hydrodefluorination reactions.[5]

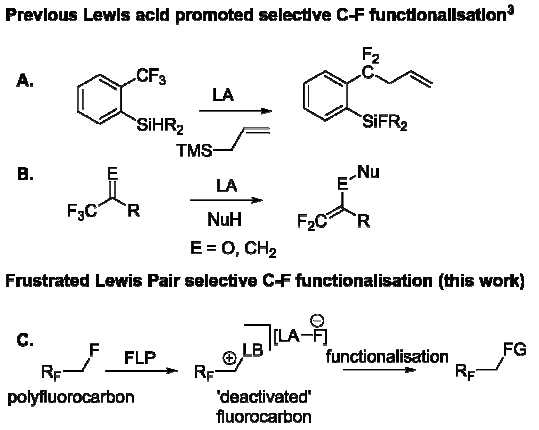

Figure 1. (A, B) Previous examples of Lewis acid promoted selective organofluoride functionalization. (C) Utilising FLP reactivity to 'capture' and 'protect' fluorocarbon fragments. After stoichiometric C-F activation, functionalization of the 'deactivated' fluorocarbon can occur. LA = Lewis acid, LB = Lewis base, FG = functional group.

Importantly, such an approach requires the use of nucleophiles that do not irreversibly bind Lewis acid reagents, preventing Lewis acid fluoride abstraction (akin to catalyst poisoning). Such systems have been heavily reported in Frustrated Lewis Pair (FLP) chemistry.[6]

In utilizing phosphine nucleophiles, the generation of fluoroalkylated phosphonium salts facilitates the ability to enact a number of reported C-C bond forming methodologies.[7] Herein, we report highly selective access to monofluoroalkenes from *gem*-difluoroalkanes using Wittig protocols.[8] Monofluoroalkenes are important synthons in organic and materials chemistries, and are present in a number of agrochemicals, synthetic materials and pharmaceuticals, thus direct access to such compounds from polyfluorides is a highly desirable process.[9]

Proof-of-principle for the concept of selective C-F activation was achieved using 1-difluoromethyl-4-methylbenzene (**1**) as a polyfluorocarbon substrate. With the aim of further functionalization through Wittig protocol, triarylphosphines in combination with [B(C$_6$F$_5$)$_3$] (BCF), [Al(C$_6$F$_5$)$_3$.(C$_7$H$_8$)] (ACF), BF$_3$.(OEt$_2$) and AlBr$_3$ Lewis acids were tested as FLP partners.

Numerous FLP systems incorporating triarylphosphines have been reported. For example, Stephan has reported the activation of H$_2$ using PMes$_3$ and BCF.[10] Furthermore, PMes$_3$ and P(*o*-Tol)$_3$ have been reported to activate CO$_2$ via FLP type reactivity.[11] As such, we surveyed the com-

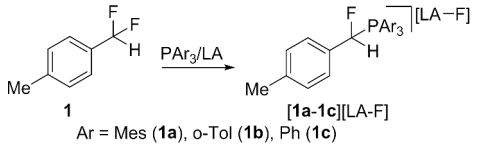

Table 1. Optimization conditions for generation of phosphonium salts [**1a-c**][anion].

Entry	LA	PAr_3	Time (h)	Yield
1	BCF	$PMes_3$	24	20%
2	BCF	$P(o\text{-Tol})_3$	24	100%
3[a]	BCF	$P(o\text{-Tol})_3$	2	100%
4[a]	BCF	PPh_3	24	100%
5[b], 6[c], 7[d]	BCF	$P(o\text{-Tol})_3$	24	<10%
8[e]	ACF	$P(o\text{-Tol})_3$	24	49%
9	$AlBr_3$	$P(o\text{-Tol})_3$	24	0%
10	$BF_3.(OEt_2)$	$P(o\text{-Tol})_3$	24	55%
11	$BF_3.(OEt_2)$	PPh_3	24	93

Conditions: 0.031 mmol FLP, 0.028 mmol **1** in 0.5 mL DCM at 25 °C. Yields determined by ^{19}F NMR spectroscopy. [a] Performed at 40 °C. [b] Toluene solvent. [c] Acetonitrile solvent. [d] Diethyl ether solvent. [e] 1,2-dichlorobenzene solvent.

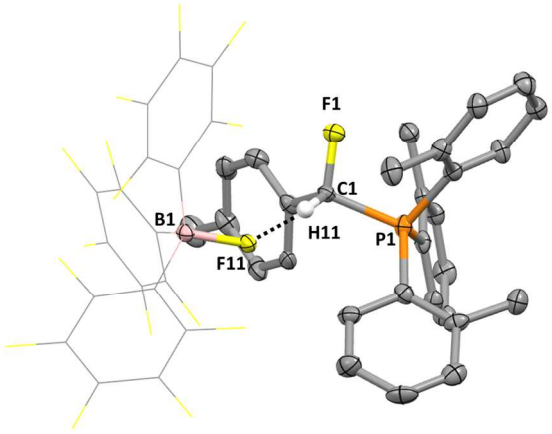

Figure 2. Molecular structure of [**1b**][$BF(C_6F_5)_3$]. Hydrogen atoms (except H11) omitted, thermal ellipsoids shown at 50%. Selected bond distances (Å) and angles (°): P1-C1, 1.894(6); C1-F1, 1.398(6); F11-H11, 2.353; P1-C1-F1, 105.8(3).

mercially available phosphines, $PMes_3$, $P(o\text{-Tol})_3$ and PPh_3.

The reaction between $PMes_3$, BCF and **1** in DCM proceeded very slowly at room temperature to generate [**1a**][$BF(C_6F_5)_3$] with *ca.* 20% yield after 24 hours (Table 1, entry 1). Employing the less sterically crowded phosphine $P(o\text{-Tol})_3$ with BCF and **1** dramatically improved the reaction rate, with quantitative conversion after 24 hours (Table 1, entry 2). Heating a DCM solution of $P(o\text{-Tol})_3$ with BCF and **1** at 40 °C led to complete consumption of **1** in two hours, and quantitative generation of product [**1b**][$BF(C_6F_5)_3$] based on **1** (Table 1, entry 3). Employing PPh_3 as a nucleophile resulted in no reaction at room temperature. However, heating this reaction at 40 °C generated [**1c**][$BF(C_6F_5)_3$] quantitatively after 24 hours of heating (Table 1, entry 4), indicating that the Lewis adduct [BCF-PPh_3][12] may reversibly dissociate at elevated temperatures.[13] For further optimization, $P(o\text{-Tol})_3$ was employed as the nucleophile of choice based on its superior reaction rate.

A survey of solvents (Table 1, entries 5-7) revealed DCM to be the most suitable for the generation of [**1b**][$BF(C_6F_5)_3$].

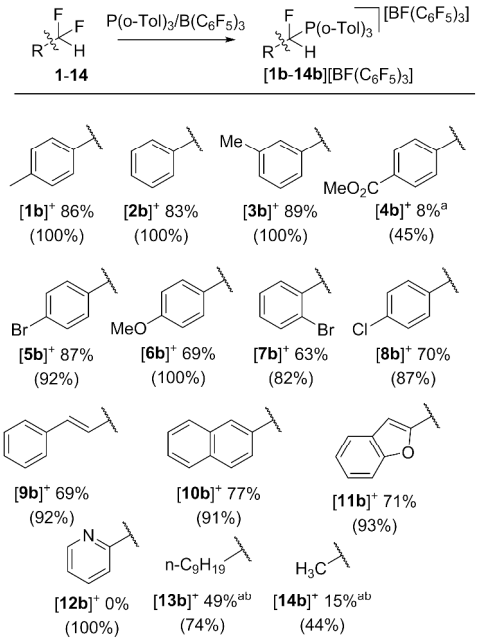

Figure 3. Reaction scope for monodefluorination of *gem*-Difluorocarbons **1-12**. See ESI for reaction conditions. Isolated yields given, reaction conversion indicated in brackets. [a] Yield based on $^{19}F/^{31}P$ NMR. [b] ACF used as Lewis acid.

The use of toluene led to Friedel-Crafts alkylation products, while MeCN masked the reactivity of the Lewis acid resulting in no conversion. In diethyl ether, fluoride abstraction by BCF proceeded, but ether was found to react with the intermediate carbocation to generate 1-fluoromethyl-4-methyl-benzene.[14] The use of pre-dried solvents was essential, with the presence of water giving rise to hydrophosphonium salts, [$HPAr_3$][$B(OH)(C_6F_5)_3$], and compromising reaction yields.

Varying the Lewis acid from BCF to ACF resulted in a rapid clean reaction, but the reaction proceeded to only half conversion (based on **1**). This is possibly due to the formation of a fluoride bridged [$F\{Al(C_6F_5)_3\}_2$]$^-$ anion,[15] resulting in the need of at least two equivalents of ACF for full consumption of **1**. Due to reaction of ACF with chlorinated aliphatic solvents,[16] the reaction was performed in 1,2-dichlorobenzene. Attempts to utilize less expensive Lewis acids gave mixed results (Table 1, entries 9-10). The use of $AlBr_3$ resulted in halodefluorination of **1**, as reported by us previously.[1h] Employing $BF_3.(OEt_2)$ generated [**1b**][BF_4] cleanly, but with a lower yield of 55% over 24 hours. Surprisingly, the combination of $BF_3.(OEt_2)$ and PPh_3 (Table 1, entry 11) performed better than both BCF/PPh_3 and $BF_3.(OEt_2)$/$P(o\text{-Tol})_3$. This may be attributed to the high solubility of the PPh_3-BF_3 adduct (*cf.* the PPh_3-BCF adduct that precipitates from solution at room temperature). The success of $BF_3.(OEt_2)$ and PPh_3 render this strategy cost-effective in larger scale syntheses of α-fluoroalkylphosphonium salts. Indeed, the synthesis of [**1b**][BF_4] was repeated on gram scale with 3.3 mmol of difluoride **1**. In this instance, the reaction was continued for 72 hours at room temperature, providing an isolated yield of 86%.

Phosphonium [**1b**][$BF(C_6F_5)_3$] was recrystallized from DCM/hexane in 86% yield. The ^{31}P NMR spectrum of

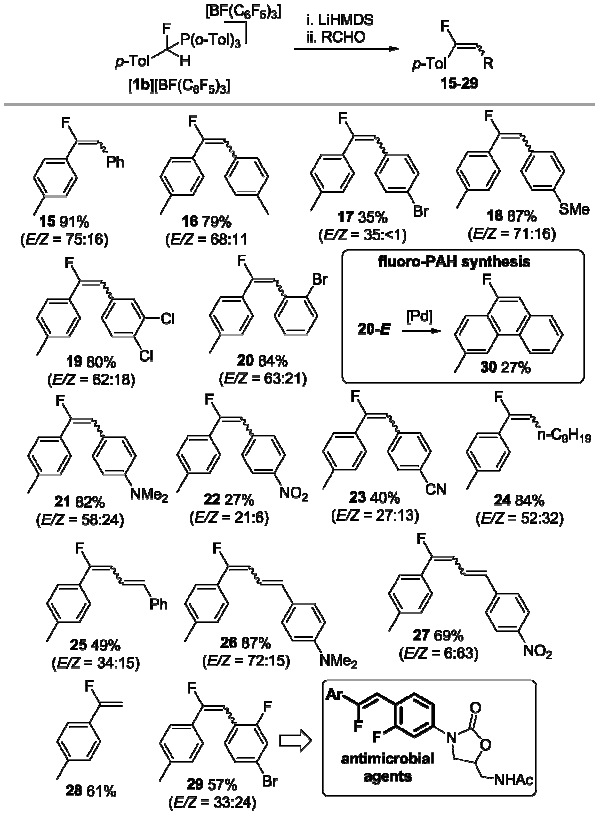

Figure 4. Aldehyde scope of Wittig reaction with α-fluorobenzylphosphonium salt [**1b**][$BF(C_6F_5)_3$]. See ESI for reaction conditions. Yield determined by ^{19}F NMR spectroscopy.

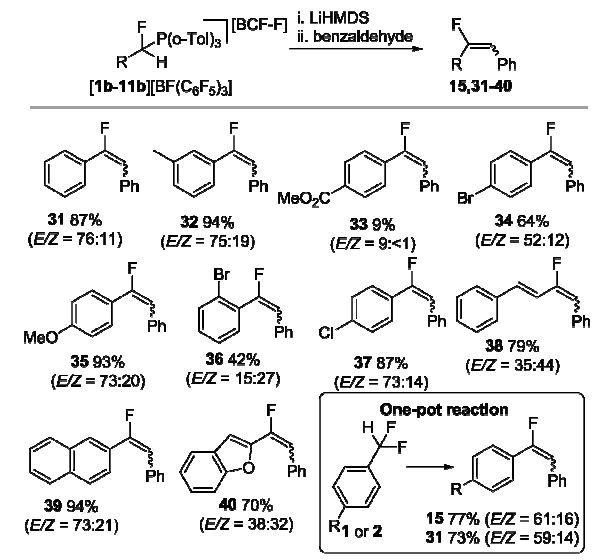

Figure 5. α-Fluoroalkylphosphonium scope of Wittig reaction with benzaldehyde. See ESI for reaction conditions. Yield determined by ^{19}F NMR spectroscopy.

[**1b**][$BF(C_6F_5)_3$] provided clear evidence for retention of a *geminal* fluorine within the product with a signal at 27.8 ppm displaying $^2J_{PF}$ of 82.3 Hz. Fluoride abstraction by BCF was evident in the ^{19}F NMR spectrum of [**1b**][$BF(C_6F_5)_3$], with a broad signal 187.8 ppm corresponding closely to previously reported values for B-F in the $[BF(C_6F_5)_3]^-$ anion.[5b] The residual benzylic fluoride signal was also observed at 189.1 ppm with $^2J_{FP}$ of 82.3 Hz.

A molecular structure of [**1b**][$BF(C_6F_5)_3$ confirmed the spectroscopically implied connectivity (Figure 2). The structure shows close contact between $[\mathbf{1b}]^+$ and the $[BF(C_6F_5)_3]^-$ anion arising from strong hydrogen bonding between the calculated benzylic hydrogen position and the boron fluoride (F11-H11 = 2.353 Å). The *o*-tolyl methyl groups extend into the benzylic region, suggesting that they may influence further reactivity of this position (*vide infra*).

The optimized conditions, employing BCF and P(*o*-Tol)$_3$ (Table 1, entry 2), were applied to a range of *gem*-difluorocarbons (Figure 3). Benzyldifluoride substrates generally performed well. Electron withdrawing substituents (**4**-**5**, **7**-**8**) resulted in lower yields of phosphonium products, primarily due to incomplete conversion. The reaction conditions were found to tolerate substrates containing halide (**5**, **7**, **8**), and ether (**6**) functional groups, but performed poorly in the presence of ester groups (**4**). Unprotected difluoromethylarenes (**2**, **9**, **10**, **11**) also gave high yields, avoiding Friedel-Crafts alkylation reactions.

Extending this reaction to allylic difluorides did not result in rearrangement products, and cinnamyl difluoride (**9**) generated a moderate yield (53%) of phosphonium product [**9b**][$BF(C_6F_5)_3$]. Polyaromatic (**10**) and heteroaromatic (**11**) substrates worked well, however, the pyridyl derivative **12** gave no desired product, with only deprotonation of the difluoromethyl position observed.

Under the standard reaction conditions (Table 1, entry 2), fluoride abstraction of saturated 1,1-difluoroalkanes did not proceed. Thus, the more fluorophilic ACF (2 equivalents) was employed for selective monodefluorination of 1,1-difluorodecane (**13**) and 1,1-difluoroethane (**14**).

Selective monodefluorination of **13** generated [**13b**][$F\{Al(C_6F_5)_3\}_2$] in *ca* 20% yield at room temperature overnight, indicating the greater stability of 1,1-difluoroalkanes as compared to benzylic difluorides. Repeating this reaction at 85 °C for 24 hours improved the yield to 49%. Under the same conditions, monodefluorination of **13** generated [**14b**][$F\{Al(C_6F_5)_3\}_2$] in 14% yield. 1,1-difluorethane is a commercially available refrigerant gas (R-152a), and is considered a possible replacement for the heavily used 1,1,1,2-tetrafluoroethane (R-134a), due to its lower Global Warming Potential. With increased use of 1,1-difluoroethane, methods of recycling used refrigerant gas to generate valuable products will become increasingly important.

Following monodefluorination of a range of difluorides, functionalization of these molecules to neutral organic products was undertaken. From a synthetic point-of-view, C-C bond forming reactions are highly valued in organic synthetic chemistry and offer direct routes to complex molecules. Although a range of C-C bond forming reactions have been reported for phosphonium salts, the most widely employed is the Wittig reaction.[17] Fluorinated benzylic phosphonium salts are ideal for Wittig reactions, given the high acidity of the benzylic proton, and the utility of fluorostyrene derivatives.[18]

Addition of 1.1 equivalents of lithium hexamethyldisilazane (LiHMDS) to a sample of [**1b**][$BF(C_6F_5)_3$] in THF quickly turned the colourless solution deep red. New ^{31}P

and ^{19}F NMR signals at δ_P 2.5 and δ_F -233.5 ($^2J_{PF}$ = 60.3 Hz) recorded 30 minutes after base addition confirmed the quantitative conversion of [**1b**][$BF(C_6F_5)_3$] to its corresponding ylide, [**1b**-H].

Subsequent addition of benzaldehyde to the solution resulted in formation of fluoroolefin **15** in 91% yield (*E*/*Z* = 75:16) over 16 hours at room temperature. Interestingly, when [**1c**][$BF(C_6F_5)_3$] is used as a starting material in the same reaction, a yield of 49% (*E*/*Z* = 19:30) is achieved, indicating the ability of the protecting phosphine to affect the efficacy of the Wittig reaction.[19]

Figure 4 lists the scope of aldehydes in the Wittig reaction with [**1b**][$BF(C_6F_5)_3$]. Products from the addition of benzaldehyde derivatives, 4-methylbenzaldehyde (**16**), 4-bromobenzaldehyde (**17**), 4-thiomethoxybenzaldehyde (**18**), 3,4-dichlorobenzaldehyde (**19**), 2-bromobenzaldehyde (**20**), 4-dimethylaminobenzaldehyde (**21**), 4-nitrobenzaldehyde (**22**) and 4-cyanobenzaldehyde (**23**) demonstrate a high functional group tolerance, and provided moderate to high yields with high *E*-selectivity. Benzaldehyde derivatives containing electron donating groups tended to provide higher yields as compared to electron withdrawing groups, however, product **20** (with an *ortho*-bromo substituent) gave a respectable yield of 84%. The combination of high yield and *E*-selectivity provides the perfect platform to access Polycyclic Aromatic Hydrocarbons (PAHs). Indeed, treatment of **20** with a catalytic amount of palladium led to dehydrobrominative aryl-aryl coupling, forming the PAH 10-fluoro-3-methylphenanthrene (**30**) in 27% yield (based on **20**-***E***). Flourinated PAHs have been shown to have enhanced biological activity and are widely used in materials chemistry.[20]

Aliphatic aldehydes also performed well in the Wittig reaction, with *n*-decanal generating **24** in 84% yield (*E*/*Z* = 52:32). Alkenyl groups were tolerated in coupling partners, with cinnamaldehyde generating **25** in 49% yield (*E*/*Z* = 34:15), and its derivatives, 4-dimethylaminocinnamaldehyde and 4-nitrocinnamaldehyde, generating **26** in 87% (*E*/*Z* = 72:15) and **27** in 69% (*E*/*Z* = 6:63) yields respectively. Interestingly, product **27** displays inverse regioselectivity, with the *Z*-isomer favoured.

Paraformaldehyde was used directly as a coupling partner, generating α-fluorostyrene **28** in 61% yield. α-Fluorostyrene derivatives have been used in polymer chemistry, but their synthesis often involves the application of toxic hydrofluoric acid to alkynes.[9,21]

Employing 4-bromo-2-fluorobenzaldehyde led to the formation of **29** in 57% yield. The structure of **29** closely resembles a reported family of antimicrobial agents, and offers a safer method to access these compounds as compared to the reported synthesis that relies upon the use of toxic trialkyltin reagents to install the fluoroalkene motif.[22]

Having established the ease by which *gem*-difluoro substrates may be converted to monofluoroalkenes, we then benchmarked the performance of the Wittig reaction with phosphoniums [**2b**-**11b**][$BF(C_6F_5)_3$] and benzaldehyde under identical conditions to those employed for [**1b**][$BF(C_6F_5)_3$] (Figure 5). Generally, excellent yields (>80%) of monofluoroalkenes were obtained. The exceptions to this were [**4b**][$BF(C_6F_5)_3$] and [**7b**][$BF(C_6F_5)_3$], which gave poor yields of their alkene products **33** (9%) and **36** (42%) respectively. *E*-selectivity once again dominated, with *E*-isomer products generally preferred in greater than 75% bias, however, [**9b**][$BF(C_6F_5)_3$] generated product **38** with similar *E,E*- and *E,Z*-isomer ratios, and [**7b**][$BF(C_6F_5)_3$] actually showed a 2:1 preference for the generation of the *Z*-isomer of **36** over the *E*-isomer.

Finally, the practical utility of this reaction was demonstrated through one-pot reactions performed in two steps (Figure 5). [**1b**][$BF(C_6F_5)_3$] was initially generated from **1**, P(*o*-Tol)$_3$ and BCF in DCM over 16 hours before the solvent system was exchanged for THF, and LiHMDS and benzaldehyde were introduced to generate **15** in an overall yield of 77% (based on **1**). An analogous procedure generated **31** in 73% yield (based on **2**).

In conclusion, we have developed a simple methodology that preserves fluorofunctionality from *geminal*-difluorocarbon starting materials. This is achieved via protection of the monodefluorinated product from further fluoride abstraction as a phosphonium cation. This methodology was successfully applied to benzylic, allylic and aliphatic 1,1-difluorocarbons. Although many coupling reactions are possible from our isolated phosphonium salts, we demonstrated the utility of this methodology through a series of Wittig reactions to generate monofluoroolefins.

ASSOCIATED CONTENT

The Supporting Information, including experimental details, is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

*rowan.young@nus.edu.sg

† These authors contributed equally.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For examples see: (a) Zhu, J.; Pérez, M.; Stephan, D. W. *Angew. Chem. Int. Ed.* **2016**, *55*, 8448. (b) Champagne, P. A.; Benhassine, Y.; Desroches, J.; Paquin, J.-F. *Angew. Chem. Int. Ed.* **2014**, *53*, 13835; (c) Terao, J.; Nakamura, M.; Kambe, N. *Chem. Commun.* **2009**, 6011; (d) Terao, J.; Begum, S. A.; Shinohara, Y.; Tomita, M.; Naitoh, Y.; Kambe, N. *Chem. Commun.* **2007**, 855; (e) Gu, W.; Haneline, M. R.; Douvris, C.; Ozerov, O. V. *J. Am. Chem. Soc.* **2009**, *131*, 11203; (f) Ooi, T.; Uraguchi, D.; Kagoshima, N.; Maruoka, K. *Tetrahedron Lett.* **1997**, *38*, 5679; (g) Hirano, K.; Fujita, K.; Yorimitsu, H.; Shinokubo, H; Oshima, K. *Tetrahedron Lett.* **2004**, *45*, 2555; (h) Goh, K. K. K.; Sinha, A.; Fraser, C.; Young, R. D. *RSC Adv.* **2016**, *6*, 42708; (i) Jaiswal, A. K.; Goh, K. K. K.; Sung, S.; Young, R. D. *Org. Lett.* **2017**, *19*, 1934; (j) Dryzhakov, M.; Richmond, E.; Li, G.; Moran, J. *J. Fluor. Chem.* **2017**, *193*, 45; (k) Dryzhakov, M.; Moran, J. *ACS Catalysis* **2016**, *6*, 3670; (l)

Scott, V. J.; Çelenligil-Çetin, R.; Ozerov, O. V. *J. Am. Chem. Soc.* **2005**, *127*, 2852; (m) Douvris, C.; Ozerov, O. V. *Science* **2008**, *321*, 1188; (n) Panisch, R.; Bolte, M.; Müller, T. *J. Am. Chem. Soc.* **2006**, *128*, 9676; (o) Douvris, C.; Nagaraja, C. M.; Chen, C.-H.; Foxman, B. M.; Ozerov, O. V. *J. Am. Chem. Soc.* **2010**, *132*, 4946; (p) Klahn, M.; Fischer, C.; Spannenberg, A.; Rosenthal, U.; Krossing, I. *Tetrahedron Lett.* **2007**, *48*, 8900; (q) Caputo, C. B.; Hounjet, L. J.; Dobrovetsky, R.; Stephan, D. W. *Science* **2013**, *341*, 1374.

(2) Munoz, S. B.; Ni, C.; Zhang, Z.; Wang, F.; Shao, N.; Mathew, T.; Olah, G. A.; Prakash, G. K. S. *Eur. J. Org. Chem*. **2017**, 2322

(3) For examples mediated by Lewis acids see: (a) Yoshida, S.; Shimomori, K,; Kim, Y.; Hosoya, T.; *Angew. Chem. Int. Ed.* **2016**, *55*, 10406; (b) Bégué, J. -P.; Bonnet-Delpon, D.; Rock, M. H. *Synlett*, **1995**, 659; (c) Bégué, J. -P.; Bonnet-Delpon, D.; Rock, M. H. *Tetrahedron Lett.*, **1995**, *36*, 5003; (d) Bégué, J. -P.; Bonnet-Delpon, D.; Rock, M. H.; *J. Chem. Soc. Perkin Trans*., **1996**, 1409; (e) Ichikawa, J.; Fukui, H.; Ishibashi, Y. *J. Org. Chem.*, **2003**, *68*, 7800; (f) Fujita, M.; Obayashi, M.; Hiyama, T.; *Tetrahedron*, **1988**, *44*, 4135; (g) Cunico, R. F.; Motta, A. R. *Org. Lett*. **2005**, *7*, 771; (h) Yang, J.; Mao, A.; Yue, Z.; Zhu, W.; Luo, X.; Zhu, C.; Xiao, Y.; Zhang, J. *Chem.Commun*. **2015**, *51*, 8326; (i) Ichikawa, J.; *J. Synth. Org. Chem. Jpn*., **2010**, *68*, 1175; (j) Fuchibe, K.; Takahashi, M.; Ichikawa, J.; *Angew. Chem. Int. Ed*., **2012**, *51*, 12059; (k) Fujita, T.; Takazawa, M.; Sugiyama, K.; Suzuki, N.; Ichikawa, J. *Org. Lett*., **2017**, *19*, 588; (l) Fuchibe, K.; Hatta, H.; Oh, K.; Oki, R.; Ichikawa, J. *Angew. Chem. Int. Ed.,* **2017**, *56*, 5890; (m) Bergeron, M.; Guyader, D.; Paquin, J. -F. *Org. Lett*., **2012**, *14*, 5888. Electroreductive and radical promoted strategies for single C-C bond formation in polyfluorides have also had varying degrees of success in selective C-F functionalisation, see: (n) Saboureau, C.; Troupel, M.; Sibille, S.; Perichon, J. *J. Chem. Soc. Chem. Comm*. **1989**, 1138; (o) Chen, K.; Berg, N.; Gschwind, R.; Konig, B. *J. Am. Chem. Soc*. **2017**, *139*, 18444; (p) Wang, H.; Jui, N. T. *J. Am. Chem. Soc.* **2018**, *140*, 163.

(4) Fadeev, D. S.; Chuikov, I. P.; Mamatyuk, V. I. *J. Fluorine Chem.*, **2016**, *182*, 53.

(5) (a) Caputo, C. B.; Stephan, D. W. *Organometallics*, **2012**, *31*, 27; (b) Mallov, I.; Ruddy, A. J.; Zhu, H.; Grimme, S.; Stephan, D. W. *Chem. Eur. J.*, **2017**, *23*, 17692.

(6) (a) Stephan, D. W.; Erker, G. *Angew. Chem. Int. Ed.* **2015**, *54*, 6400; (b) Stephan, D. W.; *Acc. Chem. Res.,* **2015**, *48*, 306.

(7) (a) Deng, Z.; Lin, J. -H.; Cai, J.; Xiao, J. -C. *Org. Lett*., **2016**, *18*, 3206; (b) Li, Q.; Lin, J. -H.; Deng, Z. -Y.; Zheng, J.; Cai, J.; Xiao, J. -C. *J. Fluorine Chem*., **2014**, *163*, 38; (c) Zheng, J.; Cai, J.; Lin, J. -H.; Guo, Y.; Xiao, J. -C. *Chem. Commun*., **2013**, *49*, 7513; (d) Zheng, J.; Lin, J. -H.; Cai, J.; Xiao, J. -C. *Chem. Eur. J*., **2013**, *19*, 15261; (e) Deng, Z.; Lin, J. -H.; Xiao, J. -C. *Nature Commun*., **2016**, *7*, 10337; (f) Hwang, K. L.; Na, Y.; Lee, J.; Do, Y.; Chang, S. *Angew. Chem. Int. Ed.*, **2005**, *44*, 6166.

(8) (a) Vedejs, E.; Peterson, M. J. *Top. Stereochem*. **1994**, *21*, 1; (b) Appel, M.; Blaurock, S.; Berger, s. *Eur. J. Org. Chem.*, **2002**, *1143*.

(9) (a) Hara, S. *Top. Curr. Chem.*, **2012**, *327*, 59; (b) Landelle, G.; Bergeron, M.; Turcotte-Savarda, M. -O.; Paquin, J. -F. *Chem. Soc. Rev*., **2011**, *40*, 2867.

(10) Welch, G. C.; Stephan, D. W. *J. Am. Chem. Soc*., **2007**, *129*, 1880.

(11) (a) Ménard, G.; Stephan, D. W.; *J. Am. Chem. Soc*., **2010**, *132*, 1796; (b) Menard, G.; Stephan, D. W. *Angew. Chem., Int. Ed*., **2011**, *50*, 8396; (c) Ménard, G.; Gilbert, T. M.; Hatnean, J. A.; Kraft, A.; Krossing, I.; Stephan, D. W. *Organometallics*, **2013**, *32*, 4416

(12) Massey, A. G.; Park, A. J. *J. Organomet. Chem*., **1964**, *2*, 245

(13) The Lewis adduct $[Ph_3P\text{-}B(C_6F_5)_3]$ has previously been shown to undergo dissociation at elevated temperatures, see: (a) Welch, G. C.; Holtrichter-Roessmann, T.; Stephan, D. W. *Inorg. Chem.*, **2008**, *47*, 1904; (b) Dureen, M. A.; Brown, C. C.; Stephan, D. W. *Organometallics*, **2010**, *29*, 6594.

(14) Carbocation mediated hydride abstraction from ethers has been reported. See: Holthausen, M. H.; Mahdi, T.; Schlepphorst, C.; Hounjet, L. J.; Weigand, J. J.; Stephan, D. W. *Chem. Commun*., **2014**, *50*, 10038.

(15) Chen, M. -C.; Roberts, J. A. S.; Marks, T. J. *Organometallics*, **2004**, *23*, 932.

(16) Chakraborty, D.; Chen, E. Y. -X. *Inorg. Chem. Commun.* **2002**, *5*, 698.

(17) Maercker, A. *Org. React*. **2011**, *14*, 270.

(18) (a) Knebelkamp, A.; Heitz, W. *Makromol. Chem., Rapid Commun.*, **1991**, *12*, 597; (b) Fustero, S.;Simón-Fuentes, A.; Barrio, P.; Haufe, G. *Chem. Rev.*, **2015**, *115*, 871; (c) Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. *Nature*, **2016**, *531*, 459.

(19) For examples of phosphines that dictate product selectivity in Wittig reactions, see: (a) Vedejs, E.; Marth, C. *Tetrahedron Lett*. **1987**, *28*, 3445; (b) Vedejs, E.; Peterson, M. *J. Org. Chem*. **1993**, *58*, 1985; (c) Vedejs, E.; Cabaj, J.; Peterson, M. J. *J. Org. Chem*. **1993**, *58*, 6509; (d) Lawrence, N. J.; Beynek, H. *Synlett* **1998**, 497; (e) Wang, Z.; Zhang, G.; Guzei, I.; Verkade, J. G. *J. Org. Chem*., **2001**, *66*, 3521; (f) Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; Vicente, J. *J. Am. Chem. Soc*., **2003**, *125*, 6034.

(20) (a) Prasad, G. K. B.; Mirsadeghi, S.; Boehlert, C.; Byrd, R. A.; Thakker, D. R. *J. Biol. Chem*., **1988**, *263*, 3676; (b) Hiszpanski, A. M.; Woll, A. R.; Kim, B.; Nuckolls, C.; Loo, Y. -L.; *Chem. Mater*., **2017**, *29*, 4311; (c) Fuchibe, K.; Shigeno, S.; Zhao, N.; Aihara, H.; Akisaka, R.; Morikawa, T.; Fujita, T.; Yamakawa, K.; Shimada, T.; Ichikawa, J. *J. Fluorine Chem.*, **2017**, *203*, 173; (d) Fuchibe, K.; Imaoka, H.; Ichikawa, J. *Chem. Asian J*., **2017**, *12*, 2359; (e) *Fluorinated Polycyclic Aromatic Hydrocarbons (PAHs) and Heterocyclic Aromatic Hydrocarbons (Hetero-PAHs); Synthesis and Utility,* Okazaki, T.; Laali, K. K. Advances in Organic Synthesis, Vol. *2*, 353-380, Bentham: UAE, 2006.

(21) (a) Matsuda, K.; Sedlak, J. A.; Noland, J. S.; Gleckler, G. C.

J. Org. Chem., **1962**, *27*, 4015; (b) Majumdar, R. N.; Niknam, M. K.; Nguyen, H. A.; Harwood, H. J. *Makromol. Chem., Rapid Commun.*, **1982**, *3*, 421; (c) *New Monomers and Polymers,* Majumdar, R.; Harwood, H. J. Polymer Science and Technology, Vol. *25*, 285-309, Springer: Berlin, 1984.

(22) Sciotti, R. J.; Pliushchev, M.; Wiedeman, P. E.; Balli, D.; Flamm, R.; Nilius, A. M.; Marsh, K.; Stolarik, D.; Jolly, R.; Ulrich, R.; Djuric, S. W. *Bio. Med. Chem. Lett.*, **2002**, *12*, 2121.

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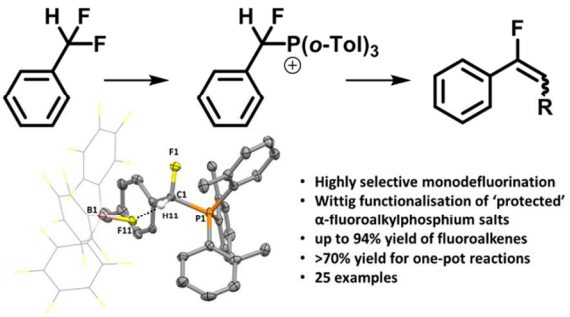
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