



Cite this: *Chem. Commun.*, 2022, 58, 5761

Received 12th February 2022,
Accepted 5th April 2022

DOI: 10.1039/d2cc00886f

rsc.li/chemcomm

Straightforward synthesis of bench-stable heteroatom-centered difluoromethylated entities *via* controlled nucleophilic transfer from activated TMSCHF₂[†]

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The commercially available and experimentally convenient (bp 65 °C) difluoromethyltrimethylsilane (TMSCHF₂) is proposed as a valuable difluoromethylating transfer reagent for delivering the CHF₂ moiety to various heteroatom-based electrophiles. Upon activation with an alkoxide, a conceptually intuitive nucleophilic displacement directly furnishes in high yields the bench-stable analogues.

Among the techniques enabling the modulation of pivotal physical-chemical properties of organic arrays, the introduction of fluorine atoms has become a powerful tool, nowadays thoroughly applied in chemistry.¹ Synthetic chemists tackling the challenge of embodying fluorine into molecules quickly recognized that well-established methodologies in classical halogen chemistry could not be validated for this member of the series.² Ideally, the use of fluorinated carbanion-like entities would enable – upon a conceptually intuitive nucleophile-electrophile logic – the forging of a new carbon–carbon bond presenting the exact and desired fluorination degree of the targeted compound (Scheme 1).³ However, F-containing nucleophiles are notoriously reluctant species mainly due to their inherent limited chemical integrity, which for a long time eclipsed their employment in synthesis.^{2a,4} In this sense, the introduction of trifluoromethyltrimethylsilane (TMSCF₃, Ruppert–Prakash reagent)⁵ allowed productive trifluoromethylations under nucleophilic regimes by exploiting the stabilizing effect imparted by the silicon atom. Analogous nucleophilic difluoromethylations⁶ and monofluoromethylations⁷ remained

somehow obscured and thus, underdeveloped until recently because of the high tendency of MCHF₂ and MCH₂F carbanions to undergo α-elimination. On the other hand, the introduction of difluoromethyltrimethylsilane (TMSCHF₂), a commercially available and experimentally convenient CHF₂-donor source (bp 65 °C)⁸ boosted the flourishing of synthetic protocols for the introduction of this group⁹ featuring some unique properties – H-bond donor, weakly acidic, lipophilic isostere of OH and SH motifs – which make it highly valuable *inter alia* in drug design.¹⁰ Compared to the Ruppert–Prakash reagent, the reactivity of TMSCHF₂ is tamed¹¹ and its proper activation under Lewis basic conditions is essential, as demonstrated by Hu in 2011 in the course of difluoromethylations of ketones and imines,¹² and later extended also to other sp²-hybridized carbon electrophiles by our group.¹³ Collectively, these precedents showcase that replacing a putative ionic (*e.g.* Li) M–CHF₂ bond with a covalent one (*e.g.* Si) represents the *conditio sine qua non* for accessing bench stable difluoromethylating agents. With this rationale in mind, we wondered if a unified strategy enabling the release of the nucleophilic CHF₂ moiety from a competent donor to a recipient heteroatom-centered

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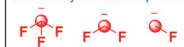
[†] Electronic supplementary information (ESI) available. CCDC 2150362–2150363. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2cc00886f>

Forming C-C bond with fluorinated nucleophiles

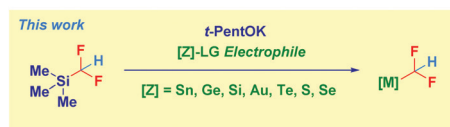


Use of Fluoro-containing carbanions

Inherently unstable species



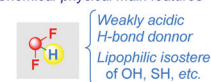
Requirement for stabilizing elements (*e.g.* Si as in TMSCF₃)



■ 20 examples ■ high yielding ■ direct procedure ■ stable structures
■ scalable ■ new CHF₂ delivering agents ■ preliminary reactivity data

The CHF₂ group

Chemical-physical main features



Scheme 1 General context of the presented work.



Activating the pronucleophile with CsF (in toluene or DMF) or with TBAT (tetrabutylammonium difluorodiphenylsilicate) was not effective and, the starting chloro-stannatrane **1** was fully recovered (entries 1–3). The adoption of a Lewis base activation protocol with a commercially available solution of potassium *tert*-pentoide (amylate) in toluene enabled a clean

transformation in THF at $-50\text{ }^{\circ}\text{C}$, thus giving **2** in 79% isolated yield (entry 4). Increasing the temperature – *coeteris paribus* – to $-20\text{ }^{\circ}\text{C}$ and $0\text{ }^{\circ}\text{C}$, respectively, was beneficial (entries 5–6). The stoichiometric ratio between TMSCHF_2 and *t*-PentOK could be dwindled to 1.5:1.4 without significantly affecting the transformation efficiency (entry 7), whereas a further decrease was detrimental (entry 8). Some additional aspects merit mention: (a) a slight excess (0.1 equiv.) of the pronucleophile compared to the alkoxide was essential for the complete genesis of the difluoromethyl carbanion-like species and thus, for suppressing the (non isolable) stannatrane nucleophilic substitution adduct $[\text{Sn}-\text{O}(t\text{-Pent})]$, entry 9; (b) using Barbier-type conditions was crucial for observing reactivity, thus remarking the limited chemical integrity of this carbanion (entry 10).

With the optimal conditions for the direct homologative transfer of the CHF_2 unit to a halostannane-type derivative,²⁰ we then investigated the scope of the reaction (Scheme 2). Pleasingly, tricyclohexyl- and tri(*n*-butyl)-stannanes smoothly underwent the transformation, furnishing analogues **3** and **4** in comparable high yield. Switching to aromatic substituents (**5**) on tin did not affect the effectiveness. Previously undisclosed difluoromethyl derivatives of organogermanium compounds could also be prepared under our conditions in the case of both trialkyl-(**6**) and triphenyl-(**7**) systems. This is particularly intriguing since organogermaniums recently emerged as more sustainable and attractive alternatives to the more common organotin compounds.²¹ Notably, dichlorodiphenylgermanium was a competent electrophile for the double functionalization, conducting to the bis-(difluoromethyl) derivative **8** in a very good 83% isolated yield. The difluoromethyl fragment released by the silicon atom of TMSCHF_2 could be efficiently transferred to a different silicon center by reacting with a halo-silane, thus conducting to the unprecedented difluoromethylsilanes **9** (*t*-butyldiphenyl, 78%) and **10** (triphenyl, 81%). The combined electronic and steric factors imparted by these substituents may be advantageously employed for modulating the reactivity of difluoromethylsilane (*vide infra*). Furthermore, the NHC-Au(I)-Cl complex could be engaged in the transformation, giving the corresponding $-\text{CHF}_2$ adduct **11** in high yield. The scalability of the transformation (15 mmol) was deduced by high-yielding processes for compounds **2** (90%) and **10** (85%).

The formal nucleophilic substitution process was not only achieved on heteroatom-halide functionalities but, was also effective in the case of symmetrical RZ-ZR moieties acting as convenient starting materials. An organotellurium analogue smoothly underwent the reaction, giving (12) in a very good 90% isolated yield. Organosulfur compounds acted as competent substrates for the transformation regardless of the different electronic behaviour displayed by the substituent on the aromatic ring, as evidenced by reactions involving the *p*-methoxy-(13) and the 2,4,5-trichloro-(14) systems. Notably, engaging a highly sterically hindered material (2,4,6-*tri*-propyl, 15) aromatic disulfide further validated the protocol. Moreover, an excellent chemoselective profile was deduced in the presence of a nitro moiety which remained unaffected, thus

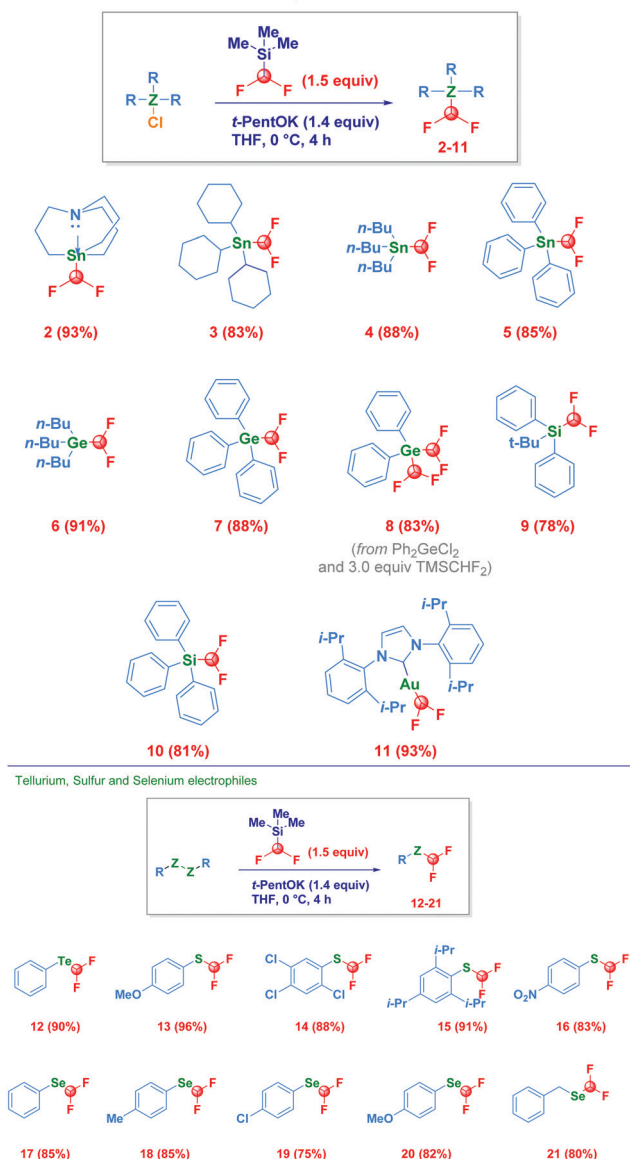
Reaction scheme showing the synthesis of compound **2** from compound **1** using a trimethylsilyl fluoride activator.

Compound **1** (a macrocyclic organotin(II) chloride) reacts with the **Activator** (Me_3SiF) in a **Solvent** at a specific **temperature** to yield compound **2** (a macrocyclic organotin(IV) fluoride).

Entry	Activator (equiv.)	TMSCHF ₂ (equiv.)	Solvent/Temp. (°C)	Yield of 2 (%) ^a
1	CsF (1.8)	2.0	Toluene/90	—
2	CsF (1.8)	2.0	DMF/90	—
3	TBAT (1.8)	2.0	DMF/90	—
4	<i>t</i> -PentOK (1.8)	2.0	THF/-50	79
5	<i>t</i> -PentOK (1.8)	2.0	THF/-20	87
6	<i>t</i> -PentOK (1.8)	2.0	THF/0	94
7	<i>t</i> -PentOK (1.4)	1.5	THF/0	91
8	<i>t</i> -PentOK (1.2)	1.1	THF/0	83
9 ^b	<i>t</i> -PentOK (1.5)	1.5	THF/0	85
10 ^c	<i>t</i> -PentOK (1.4)	1.5	THF/0	—

^a Yields refer to isolated and purified compound on a model reaction run at 0.68 mmol scale. ^b 1H-NMR and GCMS analyses of the reaction crude indicate the presence of a stannatrane-O-T-Pent adduct whose purification was unfortunately not effective. ^c Reaction carried out under *non* Barbier-type conditions. Entries 1–3 run for 6 h. Entries 4–10 run for 1 h.

Tin, Germanium, Silicon and Gold electrophiles



Scheme 2 Difluoromethyl-group transfer under the nucleophilic regime from TMSCH₂ to different heteroatom-based electrophiles.

furnishing exclusively the difluoromethyl sulfide (**16**). We further extended the technique to diselenides, it being applicable to both aromatic (**17–20**) and alkyl analogues (**21**). The proposed strategy favourably compares with reported protocols, as for example the use of the non-commercially available PhSeCN with the same TMSCH₂F₂²² or, the use of the gaseous species chlorodifluoromethane.²³

With the aim to gain insights into structural features of difluoromethyl-tin analogues **2** and **5**, their crystallographic X-ray analysis revealed some important aspects (Fig. 1). In the case of stannatrane, the Sn1–C1 bond has a length of 2.233 Å, significantly longer compared to classical organotin (R₃SnR¹).²⁴ This element is in agreement with the reasons accounting for the chemical profile of the stannatrane

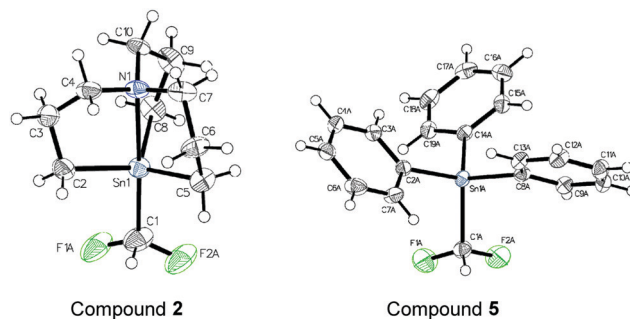


Fig. 1 X-ray structures of selected difluoromethyltin derivatives (**2** CCDC 2150362 and **5** CCDC 2150363).

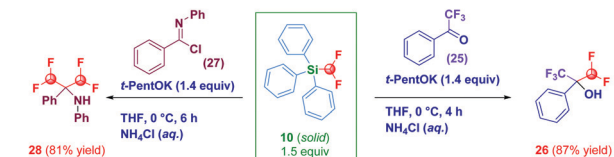
backbone: the enlarged Sn–C bond makes it more labile and thus, confers a high reactivity. In fact, the analogous bond Sn1–C1 in the triphenyltin analogue **5** is 2.197 Å. Moreover, the Sn1–N1 distance in the stannatrane is 2.478 Å, whereas the two carbon-fluorine bonds in both structures are comparable (1.313 Å and 1.317 Å in stannatrane **2** and, 1.225 Å and 1.338 Å in triphenyltin- **5**). The angle C1–Sn1–C2 (102.66°) matches with the analogous C1–Sn1–C5 (103.77°) and C1–Sn1–C8 (102.27°) in the stannatrane, which also shows a characteristic planar orientation N1–Sn1–C6 (178.61°). The absence of the rigidifying backbone in **5** is evident from the values of the angles C1–Sn1–C8 (107.36°), C1–Sn1–C14 (110.30°) and C1–Sn1–C2 (103.13°).

The synthetic potential of selected prepared compounds was then evaluated (Scheme 3). Difluoromethyl stannatrane **2** acted as a versatile coupling agent in two recently developed protocols by Biscoe,^{18a,d} namely: (a) the Pd-catalyzed cross-coupling with bromobenzene furnishing **22** in 76% yield and, (b) the Pd-catalyzed acylation with an acyl chloride **23** which resulted in the clean formation of difluoromethylketone **24** in 83% yield (path a). As an additional proof of the enhanced reactivity conferred by the stannatrane backbone, it is worth noting that Sn-CHF₂ analogues **3**, **4** and **5** did not promote at any extent both transformations. Intrigued by the solid physical state of the triphenylsilane derivative **10**, upon the usual activation with potassium *tert*-pentoxide and reaction with

a) Use of CHF₂-stannatrane in Pd-catalyzed cross-coupling and acylation



b) Use of CHF₂-triphenylsilane in nucleophilic additions



Scheme 3 Synthetic uses of CHF₂-stannatrane and CHF₂-triphenylsilane.

The authors thank the University of Vienna, the University of Torino and FWF (project P33130) for financial support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- 3 For the concept of using metalated α -halogenated synthons, see: (a) L. Castoldi, S. Monticelli, R. Senatore, L. Ielo and V. Pace, *Chem. Commun.*, 2018, **54**, 6692; (b) L. Ielo, V. Pillari, M. Miele, D. Castiglione and V. Pace, *Synlett*, 2021, 551For recent examples from our group, see: (c) R. Senatore, M. Malik, T. Langer, W. Holzer and V. Pace, *Angew. Chem., Int. Ed.*, 2021, **60**, 24854; (d) L. Ielo, L. Castoldi, S. Touqeer, J. Lombino, A. Roller, C. Prandi, W. Holzer and V. Pace, *Angew. Chem., Int. Ed.*, 2020, **59**, 20852; (e) L. Ielo, S. Touqeer, A. Roller, T. Langer, W. Holzer and V. Pace, *Angew. Chem., Int. Ed.*, 2019, **58**, 2479; (f) V. Pace, L. Castoldi, E. Mazzeo, M. Rui, T. Langer and W. Holzer, *Angew. Chem., Int. Ed.*, 2017, **56**, 12677.
- 4 (a) A. D. Dilman and V. V. Levin, *Acc. Chem. Res.*, 2018, **51**, 1272; (b) G. K. S. Prakash and J. Hu, *Acc. Chem. Res.*, 2007, **40**, 921.
- 5 X. Liu, C. Xu, M. Wang and Q. Liu, *Chem. Rev.*, 2015, **115**, 683.
- 6 J. B. I. Sap, C. F. Meyer, N. J. W. Straathof, N. Iwumene, C. W. am Ende, A. A. Trabanco and V. Gouverneur, *Chem. Soc. Rev.*, 2021, **50**, 8214.
- 7 Probably monofluoromethylating agents are the most elusive carbanion-like species, see: (a) G. Parisi, M. Colella, S. Monticelli, G. Romanazzi, W. Holzer, T. Langer, L. Degennaro, V. Pace and R. Luisi, *J. Am. Chem. Soc.*, 2017, **139**, 13648; (b) S. Monticelli, M. Colella, V. Pillari, A. Tota, T. Langer, W. Holzer, L. Degennaro, R. Luisi and V. Pace, *Org. Lett.*, 2019, **21**, 584For a review, see; (c) M. Reichel and K. Ragghiosoff, *Angew. Chem., Int. Ed.*, 2020, **59**, 12268.
- 8 M. Miele and V. Pace, *Aust. J. Chem.*, 2021, **74**, 623.
- 9 For comprehensive reviews, see: (a) D. E. Yerien, S. Barata-Vallejo and A. Postigo, *Chem. – Eur. J.*, 2017, **23**, 14676; (b) N. Levi, D. Amir, E. Gershonov and Y. Zafrani, *Synthesis*, 2019, 4549. For ground-breaking works on CHF₂ chemistry, see: (c) P. S. Fier and J. F. Hartwig, *J. Am. Chem. Soc.*, 2012, **134**, 5524; (d) L. Xu and D. A. Vicić, *J. Am. Chem. Soc.*, 2016, **138**, 2536; (e) M. Bos, W.-S. Huang, T. Poisson, X. Pannecoucke, A. B. Charette and P. Jubault, *Angew. Chem., Int. Ed.*, 2017, **56**, 13319.
- 10 (a) C. D. Sessler, M. Rahm, S. Becker, J. M. Goldberg, F. Wang and S. J. Lippard, *J. Am. Chem. Soc.*, 2017, **139**, 9325; (b) Y. Zafrani, G. Sod-Moriah, D. Yeffet, A. Berliner, D. Amir, D. Marciano, S. Elias, S. Katalan, N. Ashkenazi, M. Madmon, E. Gershonov and S. Saphier, *J. Med. Chem.*, 2019, **62**, 5628.
- 11 T. Hagiwara and T. Fuchikami, *Synlett*, 1995, 717.
- 12 Y. Zhao, W. Huang, J. Zheng and J. Hu, *Org. Lett.*, 2011, **13**, 5342.
- 13 (a) M. Miele, A. Citarella, N. Micale, W. Holzer and V. Pace, *Org. Lett.*, 2019, **21**, 8261; (b) A. Citarella, D. Gentile, A. Rescifina, A. Piperno, B. Moggetti, G. Gribaudo, M. T. Sciortino, W. Holzer, V. Pace and N. Micale, *Int. J. Mol. Sci.*, 2021, **22**, 1398; (c) M. Miele, R. D'Orsi, V. Sridharan, W. Holzer and V. Pace, *Chem. Commun.*, 2019, **55**, 12960; (d) M. Miele, A. Citarella, T. Langer, E. Urban, M. Zehl, W. Holzer, L. Ielo and V. Pace, *Org. Lett.*, 2020, **22**, 7629.
- 14 G. K. S. Prakash, S. K. Ganesh, J.-P. Jones, A. Kulkarni, K. Masood, J. K. Swabeck and G. A. Olah, *Angew. Chem., Int. Ed.*, 2012, **51**, 12090.
- 15 W. R. Cullen, J. R. Sams and M. C. Waldman, *Inorg. Chem.*, 1970, **9**, 1682.
- 16 E. Vedejs, A. R. Haight and W. O. Moss, *J. Am. Chem. Soc.*, 1992, **114**, 6556.
- 17 (a) N. Srivastav, R. Singh and V. Kaur, *RSC Adv.*, 2015, **5**, 62202; (b) J. G. Verkade, *Acc. Chem. Res.*, 1993, **26**, 483; (c) E. Fillion and N. J. Taylor, *J. Am. Chem. Soc.*, 2003, **125**, 12700; (d) A. Kavooosi and E. Fillion, *Angew. Chem., Int. Ed.*, 2015, **54**, 5488.
- 18 (a) C.-Y. Wang, G. Ralph, J. Derosa and M. R. Biscoe, *Angew. Chem., Int. Ed.*, 2017, **56**, 856; (b) C.-Y. Wang, J. Derosa and M. R. Biscoe, *Chem. Sci.*, 2015, **6**, 5105; (c) X. Ma, B. Murray and M. R. Biscoe, *Nat. Rev. Chem.*, 2020, **4**, 584; (d) L. Li, C.-Y. Wang, R. Huang and M. R. Biscoe, *Nat. Chem.*, 2013, **5**, 607.
- 19 (a) C. Cordovilla, C. Bartolomé, J. M. Martínez-Ilarduya and P. Espinet, *ACS Catal.*, 2015, **5**, 3040; (b) S. Touqeer, L. Castoldi, T. Langer, W. Holzer and V. Pace, *Chem. Commun.*, 2018, **54**, 10112.
- 20 E. Le Grogne, J.-M. Chrétien, F. Zammattio and J.-P. Quintard, *Chem. Rev.*, 2015, **115**, 10207.
- 21 M.-Y. Xu, W.-T. Jiang, Y. Li, Q.-H. Xu, Q.-L. Zhou, S. Yang and B. Xiao, *J. Am. Chem. Soc.*, 2019, **141**, 7582.
- 22 T. Dong, J. Nie and C.-P. Zhang, *Tetrahedron*, 2018, **74**, 5642.
- 23 H. Suzuki, M. Yoshinaga, K. Takaoka and Y. Hiroi, *Synthesis*, 1985, 497.
- 24 F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, S1.
- 25 S. Meyer, J. Häfliger and R. Gilmour, *Chem. Sci.*, 2021, **12**, 10686.