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A highly efficient synthesis of triisopropylsilyldifluorobromopropyne yields a versatile *gem*-difluoromethylene building block

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Triisopropylsilyldifluorobromopropyne, readily prepared in excellent yield from the reaction of lithium triisopropylsilylacetylide with CF_2Br_2, provides a convenient entry into a functionalized CF_2 synthon.

The *gem*-difluoromethylene unit is a key structural motif in many fluorine containing compounds of biological and pharmaceutical significance. For this reason, it is an important synthetic target.[1] Two complementary approaches to such important unit exist. These are (i) substitution of a carbonyl or an active methylene group by fluorine;[2] and (ii) use of small *gem*-difluoromethylene-containing building blocks.[3] When it comes to fluorinate complex molecules, the latter approach is preferred because of the reactivity, thermal instability, hazards and cost associated with electrophilic and nucleophilic fluorinating agents. The two most frequently used *gem*-difluoromethylene synthons, $(EtO)_2P(O)CF_2Br$ and $EtOC(O)CF_2Br$, were developed in the late 70s and early 80s by Burton[4] and Fried,[5] respectively. Stimulated by our earlier work in the synthesis of fluorinated phosphonates,[6] we sought a new generation of difluorinated building blocks from inexpensive industrial fluorine feedstock such as CF_2Br_2 (not included in the list of CFCs to be phased out). Our initial target, triisopropylsilyldifluoropropyne **1** (Fig 1), is a highly functionalized three-carbon backbone that contains a propargyl silane moiety. This feature should facilitate multiple synthetic conversions containing the *gem*-difluoromethylene unit.

A literature search revealed that difluoropropargyl substrates, without exception, have been prepared in disappointingly low yields.[7] The low yields obtained have probably contributed to the lack of use of the difluoropropargyl building block in the literature. To our satisfaction, **1** was very efficiently assembled in one step (92% GC-MS, 81% isolated) by the reaction of CF_2Br_2 with lithium triisopropylsilylacetylide. This reaction has been carried out on 5, 16 and 50 g scales and the results have shown excellent reproducibility.[8] We attributed the success of this reaction to the presence of the TIPS group, which possesses remarkably different properties compared to other alkylsilyl groups.[9] Chiefly, the presence of TIPS enhances the stability of the triisopropylsilyldifluoropropyne anion intermediate.[10] Although the reaction mechanism is still unclear, our experimental observation of a typical 5–10 min induction period supports the difluorocarbene based ionic chain path proposed by Wakselman and co-workers.[7a] With a highly efficient preparation of **1** in hand, we explored the synthesis of various *gem*-difluoromethylene-containing compounds. Preliminary results, summarized in Scheme 1,[11] unveiled a highly versatile building block.

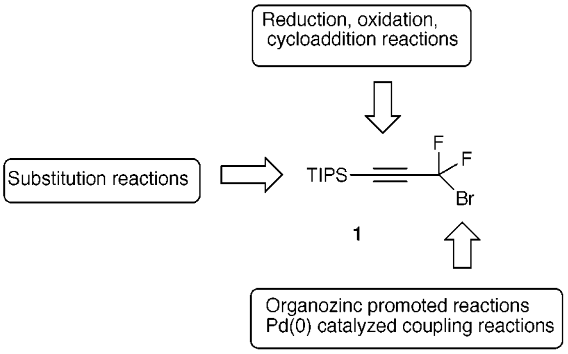
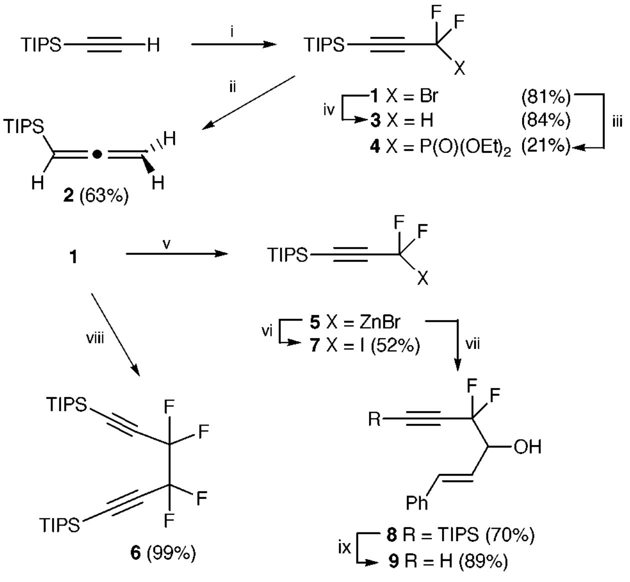


Fig. 1 Building block potential of **1**.

Reduction with $LiAlH_4$ gave allene **2**, whereas nucleophilic substitution with $MP(O)(OEt)_2$ afforded difluoropropyne **3** and difluoropropargyl phosphonate **4**, although the latter was obtained in low yield. Because compound **4** is a potential precursor for isosteric and isoelectronic phosphate mimics of enzyme inhibitors,[12] an optimization of this reaction is in progress. Using ultrasound, **1** reacted rapidly with zinc dust yielding the alkynyl organozinc reagent **5** *in situ*. This organozinc intermediate is a useful synthetic building block as can be seen in the Reformatsky-type reactions shown at the bottom of Scheme 1. Addition of Zn to **1** produced dimer **6** in nearly quantitative yield. Compound **6** is a potential intermediate in the synthesis of CF_2CF_2-containing bioactive molecules.[13] If **5** is quenched with powdered iodine, it produces difluoroiodopropyne **7**, another important *gem*-difluoromethylene synthon.[14] Addition of *trans*-cinnamaldehyde to **5** afforded difluoro alcohol **8** in 70% yield. When needed, the TIPS-protecting group can be easily removed, as demonstrated by the conversion of **8** to **9** under mild conditions, and in excellent yield. The latter result will allow an easy entry to the preparation of propargylic, and possibly allylic, α,α-difluorocarbonyl compounds, after oxidation of the alcohol and hydrogenation of the triple bond.



Scheme 1 *Reagents and conditions*: i, BuLi, CF_2Br_2, THF, −20 °C to room temp.; ii, $LiAlH_4$ (0.6 equiv.), THF, −80 °C; iii, NaN $(TMS)_2$, $HP(O)(OEt)_2$ (1.0 equiv.), THF, −10 °C; iv, $HP(O)(OEt)_2$, BuLi (1.5 equiv.), −10 °C; v, Zn (1.2 equiv.),THF, room temp., ultrasound; vi, I_2 (1 equiv.), 0 °C; vii, *trans*-cinnamaldehyde, 20 h, room temp.; viii, **1** (1.0 equiv.), Zn (2.0 equiv.), room temp.; ix, TBAF (1.0 equiv., 1 M in THF), −80 °C.

Other synthetic modifications of **1** and the preparation of a monofluorinated counterpart to **1** are under investigation.

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8 Under Ar atmosphere, a solution of triisopropylsilylacetylene (36 g, 0.2 mol) in THF (300 ml) was cooled to −20 °C. BuLi (125 ml, 1.6 M solution in hexane) was added *via* syringe and the resulting solution was stirred for 30 min before CF_2Br_2 (62 g, 1.5 equiv.) was added. The solution was allowed to warm to room temperature and stirred for 9 h. After solvent removal, NH_4Cl (120 ml) was added and the oily layer was extracted with Et_2O (3 × 100 ml). Standard work-up gave the crude product as a viscous orange oil (92% yield by GC−MS) which was purified by distillation (bp 51–52 °C/0.1 mmHg) to yield **1** (49.9 g, 81%); δ_H(300 MHz, $CDCl_3$) 1.11 (s, TIPS protons); δ_C(75 MHz, $CDCl_3$) 100.61 (t, $^1J_{CF}$ 290), 97.16 (t, $^2J_{CF}$ 36.5), 95.1 (t, $^3J_{CF}$ 4.7), 18.01, 11.28; δ_F −32.60 (s, 2F); *m/z* (GC-MS) 312 (M^+ + 1, 4), 310 (M^+ − 1, 4), 269 (14), 267 (14), 143 (27), 77 (100) (calc. for $C_{12}H_{21}SiF_2Br$: C, 46.33; H, 6.75. Found: C, 46.91; H, 6.83%). The triisopropylsilylacetylene starting material, purchased from GFS Co., contained diisopropylpropenylsilylacetylene (11%) and diisopropylpropylsilylacetylene (14%). Fractional distillation did not remove these impurities. The GC-MS analysis of **1** shows all three components were alkylated and their ratios perfectly match that of the starting material. The calculated C% and H% were based on the formula of triisopropylsilyldifluorobromopropyne. If the two impurities are removed from the calculation, the values found for C% and H% are 46.84 and 6.67%, respectively.

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11 *Selected data* for **2**: δ_H(300 MHz, $CDCl_3$) 1.06 (s, TIPS protons), 4.81 (t, 1H, $^4J_{HH}$ 7.23), 4.30 (d, 2H, $^4J_{HH}$ 7.23); *m/z* (GC-MS) 196 (M^+), 157, 153, 125, 97, 83, 67. For **3**: δ_H(300 MHz, $CDCl_3$) 1.09 (s, TIPS protons), 6.17 (t, $^2J_{HF}$ 54.8); δ_F −105.49 (s); *m/z* (GC-MS) 232 (M^+), 189, 161, 133, 105, 81, 77. For **4**: δ_H(300 MHz, $CDCl_3$) 1.11 (s, 21H, TIPS protons), 1.39 (t, 6H, $^3J_{HH}$ 7.00), 4.32 (m, 4H); δ_F −96.79 (d, $^2J_{PF}$ 109.01); δ_P 4.23 (t, $^2J_{PF}$ 109.10); *m/z* (GC-MS) 325 (M^+ − 43), 297, 269, 153, 109, 81. For **6**: δ_H(300 MHz, $CDCl_3$) 1.10 (s, TIPS protons); δ_F −99.01 (s, 4F); *m/z* (GC-MS) 462 (M^+), 377, 307, 239, 183, 115, 77. For **7**: δ_H(300 MHz, $CDCl_3$) 1.11 (s, TIPS protons); δ_F −28.13 (s); *m/z* (GC-MS) 315 (M^+ − 43), 265, 237, 189, 165, 119, 105, 77. For **8**: δ_H(300 MHz, $CDCl_3$) 7.41–7.26 (m, 5H), 6.82 (d, 1H, $^3J_{HH}$ 15.9), 6.26 (dd, 1H, $^3J_{HH}$ 15.9, $^3J_{HH}$ 6.2), 4.55 (m, 1H, CHOH), 2.05 (s, 1H, OH), 1.06 (s, 21 H, TIPS protons); δ_F −94.3 (d, 1F, $^2J_{FF}$ 274), −96.7 (d, 1F, $^2J_{FF}$ 274). For **9**: δ_H(300 MHz, $CDCl_3$) 7.45–7.30 (m, 5H), 6.85 (dd, 1H, $^4J_{HH}$ 0.9, $^3J_{HH}$ 15.9), 6.24 (dd, 1H, $^3J_{HH}$ 15.9, $^3J_{HH}$ 6.3), 4.55 (m, 1H, CHOH), 2.85 (t, 1H, $^3J_{HF}$ 5.0), 2.04 (s, 1 H); δ_F −95.9 (d, 1F, $^2J_{FF}$ 277), −96.9 (d, 1F, $^2J_{FF}$ 277); *m/z* (GC-MS) 206 (M^+, 5),170 (3), 159 (2), 133 (100), 115 (30), 77 (26), 55 (46).

12 The major by-product is **3**, an indication that, compared to the bromide, the triisopropylsilyldifluoropropyne anion is a better leaving group. For a leading reference on fluorinated phosphate mimics, see: D. O’Hagan and H. S. Rzepa, *Chem. Commun.*, 1997, 645.

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14 We have also prepared **8** in 73% yield by the reaction of lithium triisopropylsilylacetylide with CF_2I_2. However, the prohibitive cost of commercial CF_2I_2 will most likely limit its use in large-scale synthesis.

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