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Highly Efficient Synthesis of 1,1-Difluoro-2-substituted-1,3-dienes and Dienynes from *gem*-Difluorohomoallenyl Bromide via Palladium-Catalyzed Cross-Coupling Reactions

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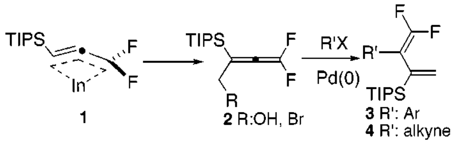
ABSTRACT



A stable *gem*-difluoroallenylindium 1 is readily transformed to a potentially bifunctional electrophile 2, which can then undergo a transition-metal-promoted isomerization–cross-coupling cascade to yield diene 3 and dienyne 4 in very high yields.

It is well-known that the physicochemical properties of organic molecules can be greatly affected when one or more hydrogen atoms are substituted with fluorine.[1] In particular, substitution of a methylene group with CF_2 blocks its metabolic oxidation and enhances the reactivity of a neighboring functionality due to the strong electron withdrawing character of fluorine.[2] Despite progress achieved in the syntheses of acyclic *gem*-difluorinated compounds,[3] the construction of rings containing a CF_2 unit remains a challenge.[4] A convenient synthesis of CF_2-containing cyclic, bicyclic, or heterocyclic systems would facilitate the building of libraries aimed at designing enzyme-activated irreversible inhibitors and other biologically active species. During our research on fluorinated synthons,[5] it occurred to us that if a vinyl CF_2 group were to become an intrinsic component of a substituted allene, diene, or dienyne such as **2**−**4**, the resulting compounds would be ideally suited for the construction of carbocycles, because of the existing wealth of annulation and cycloaddition strategies.[6] To our surprise, an inspection of the pertinent literature revealed only one practical[7] synthesis of substituted 1,1-difluoro-1,3-dienes,[8] other than dienol ethers.[9] This method[10] used a Pd-catalyzed coupling reaction of 2,2-difluorovinylboranes with 1-alkenyl halides and was applied exclusively to *n*- and *sec*-butyl

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[1] Schlosser, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1496−1513. Hudlicky, M.; Pavlath, A. E. *Chemistry of Organic Fluorine Compounds II*; American Chemical Society: Washington, DC, 1995.

[2] For leading references see: O'Hagan, D.; Rzepa, H. S. *J. Chem. Soc. Chem. Commun.* **1997**, 645−652. *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996; Vol. 639.

[3] Tozer, M. J.; Herpin, T. F. *Tetrahedron* **1996**, *52*, 8619−8683. Some recent leading references include: Yamazaki, T.; Hiraoka, S.; Sakamoto, J.; Kitazume, T. *Org. Lett.* **2001**, *3*, 743−746. Zhang, X.; Burton, D. J. *Tetrahedron Lett.* **2000**, *41*, 7791−7794. Huang, X.; He, P.; Shi, G. *J. Org. Chem.* **2000**, *65*, 627−629. Broadhurst, M. J.; Brown, S. J.; Percy, J. M.; Prime, M. E. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3217−3226.

[4] Harrington, P. E.; Li, L.; Tius, M. A. *J. Org. Chem.* **1999**, *64*, 4025−4029.

[5] Zapata, A.; Gu, Y.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 227−234. Lan, Y.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 4217−4221. Wang, Z.; Hammond, G. B. *J. Chem. Soc., Chem. Commun.* **1999**, 2545−2546 and references therein.

[6] Selected reviews, since 1999, include: Molander, G. A. *Pure Appl. Chem.* **2000**, *72*, 1757−1761. Houpis, J. N.; Lee, J. *Tetrahedron* **2000**, *56*, 817−846. Brummond, K. M. *Adv. Cycloaddit.* **1999**, *6*, 211−237. Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111−124. Gevorgyan, V.; Yamamoto, Y. *J. Organomet. Chem.* **1999**, *576*, 232−247. Aggarwal, V. K.; Ali, A.; Coogan, M. P. *Tetrahedron* **1999**, *55*, 293−312. Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, *71*, 1511−1519.

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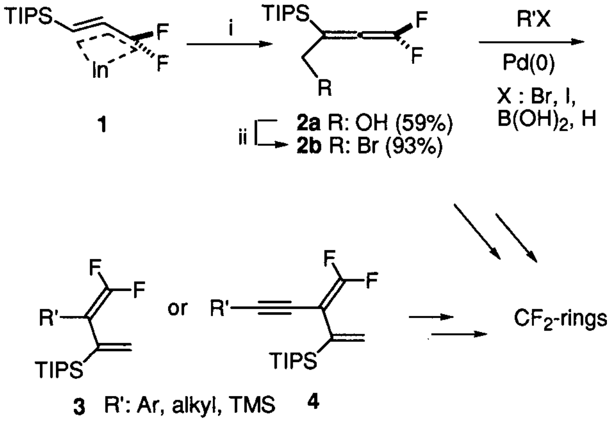
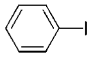
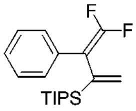
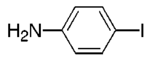
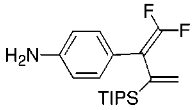
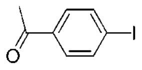
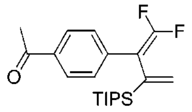
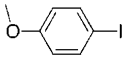
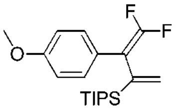
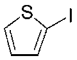
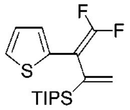
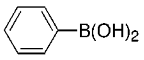
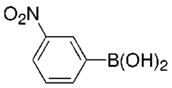
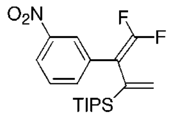
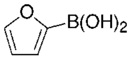
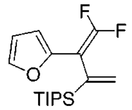
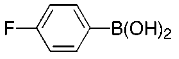
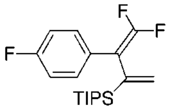
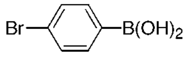
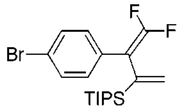
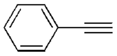
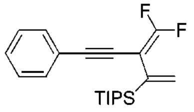
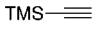
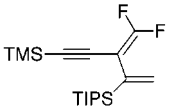
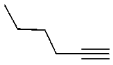
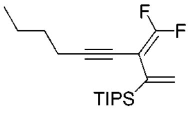
Scheme 1. Synthetic Approach for the Construction of CF_2-Containing Cyclic Systems[a]



[a] (i) HCHO(aq), ultrasound, r.t., 1d, 60%. (ii) TEA/MsCl, CH_2Cl_2, 0 °C; LiBr (1.0 equiv), acetone, 5 h, 93%.

Table 1. Pd-Catalyzed Cross-Coupling Reactions of **2b**

R'X	product	yield
		**3a** (90%)[a, b]
		**3b** (95%)[a]
		**3c** (82%)[a]
		**3d** (86%)[a]
		**3e** (75%)[a]
	**3a**	(89%)[c]
		**3f** (93%)[c]
		**3g** (77%)[c]
		**3h** (91%)[c]
		**3i** (63%)[c]
		**4a** (92%)[d]
		**4b** (95%)[d]
		**4c** (96%)[d]

[a] Zn, DMF, Pd(PPh$_3$)$_4$, 5h, 60 °C. [b] Yield using PhBr is 82%. [c] Pd$_2$(dba)$_3$/PPh$_3$, toluene, 2 M Na_2CO_3, 100 °C, 5−16 h. [d] Pd(PPh$_3$)$_2$Cl$_2$, CuI, TEA, THF, reflux 5 h.

boranes. In the case of *gem*-difluoroallenes, Dolbier has reported the only existing synthesis of $R_2C{=}C{=}CF_2$ (R = Me, Ph).[11] Our group's recent discovery of a room-temperature-stable, difluoroallenylsilane indium **1** has allowed access, for the first time, to densely functionalized *gem*-difluoroallenes.[12] We now report an efficient synthesis of 1,1-difluoro-2-substituted-1,3-dienes **3** and 1,1-difluoro-2-ethylidene-1,3-enynes **4** from homoallenylbromide **2b** using palladium catalyzed, cross-coupling reactions.[13]

A solution of **1**—prepared by stirring TIPS−C≡C−CF_2Br with indium in H_2O/THF (80/20) at room temperature—reacted with aqueous formaldehyde to give homoallenyl alcohol **2a** in 59% yield (50 mmol scale). In addition to a vinyl-CF_2 group, **2** boasts two bifunctional electrophiles—a vinyl silane and a potential leaving group in the 4-position. Indeed, **2** could be envisioned as a "CF_2 diversity engine" because allenes are excellent synthetic manifolds. The palladium-mediated cross-coupling reaction of zinc reagents with aryl or vinyl halides[14] needed the conversion of the hydroxyl in **2a** to its corresponding bromide **2b**, not a trivial task when a vinylsilane is present, due to possible dehydration and concomitant enyne formation.[15] The conversion of **2a** to **2b** was carried out in multigram scale, by treating **2a** with MsCl−TEA at 0 °C,[16] followed by nucleophilic substitution with 1 equiv of LiBr in acetone at room temperature (93% yield). When **2b** was treated with silver-

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(7) Other, less satisfactory, approaches, include: double dehydrobromination of 1,3-dibromo-1,1-difluorobutanes (Elsheimer, S.; Foti, C. J.; Bartberger, M. D. *J. Org. Chem.* **1996**, *61*, 6252−6255.) and carbolithiation−elimination of 1-CF_3 olefins (Begue, J. P.; Bonnet-Delpon, D.; Bouvet, D.; Rock, M. H. *J. Org. Chem.* **1996**, *61*, 9111−9114. Hanzawa, Y.; Ishizawa, S.; Kobayashi, Y.; Taguchi, T. *Chem. Pharm. Bull.* **1990**, *38*, 1104−1106.).

(8) This is in stark contrast to the diverse syntheses of terminal *gem*-difluoroolefins: Percy, J. M. *Top. Curr. Chem.* **1997**, *193*, 131−195.

(9) The synthesis of 2-O-subsbstituted dienes from difluoroenol carbamate has been reported recently by DeBoos, G. A.; Fullbrook, J. J.; Owton, M. W.; Percy, J. M.; Thomas, A. C. *Synlett.* **2000**, 963−966.

(10) Ichikawa, J.; Ikeura, C.; Minami, T. *Synlett* **1992**, 739−740.

(11) Dolbier, J. W. R.; Burkholder, C. R.; Winchester, W. R. *J. Org. Chem.* **1984**, *49*, 1518−1522.

(12) Wang, Z.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 6547−6552.

(13) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067−3125.

(14) For a review of coupling of fluorinated vinyl zinc reagents see: (a) Burton, D. J.; Lu, L. *Top. Curr. Chem.* **1997**, *193*, 45−89. (b) Burton, D. J.; Yang, Z. Y.; Morken, D. A. *Tetrahedron* **1994**, 2993−3063.

(15) Trost, B. M.; Tour, J. M. *J. Org. Chem.* **1989**, *54*, 484−486.

activated zinc in THF—even at refluxing temperatures—no reaction was detected. However, substituting DMF as solvent and keeping the reaction temperature at 60 °C for 3 h had the desired effect, as ^{19}F NMR analysis of the reaction mixture signaled the disappearance of starting material and the appearance of two new doublets at δ −75.9 ppm and −83.8 ppm, to which we assigned structure **3** (R′ = ZnBr). The formation of this intermediate could be explained by assuming that allene **2** (R = ZnBr) was generated first but it isomerized rapidly to the thermodynamically more stable diene **3** (R′ = ZnBr). Aryl halide was then added to this dienyl zinc, in the presence of $Pd(PPh_3)_4$, and the expected coupling product **3a**−**e** was obtained in high yield (Table 1). Both bromo- and iodo-substituted benzenes can be effectively used in the coupling reaction, although the yields using the former are slightly lower. Notably, the zinc reagent was inert toward the ketone group (see **3c**). A heterocyclic iodide could also be used successfully (**3e**) but when 5-iodouracil was used, there was no reaction, perhaps due to the acidity of the imide hydrogen. The Suzuki reaction has an exceptional tolerance of functional groups and the ability to couple sterically demanding substrates.[17] We found that refluxing **2b** with aryl boronic acids in toluene under palladium catalysis led to the preparation of aryl-substituted 1,3-difluorodienes, also in very satisfactory yields (**3a**, **3f**−**i**).

The lower yield observed with **3i** is due to the formation of the biphenyl analogue (11%), resulting from an additional coupling of **3i** with the boronic acid. One of the most straightforward methods for the preparation of conjugated enynes is the Sonogashira reaction.[18] We had hoped that **2b** could also be employed in the synthesis of vinyl CF_2-substituted enynes,[19] and were very pleased to find that its reaction with terminal alkynes resulted in almost quantitative yields of **4a**−**c**. The readily available starting materials and high efficiency of these methodologies should find utility in organic synthesis. Further transformations of **2** are under study.

Acknowledgment. The financial support of the National Science Foundation (CHE-9711062) and the Petroleum Research Fund (PRF#36602-AC1) is acknowledged with gratitude.

Supporting Information Available: The preparation and characterization of compounds **2**−**4** and the ^{13}C NMR spectra of **3h**, **3i**, and **4a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) At room temperature, in the presence of an aliphatic amine, **2a**, undergoes a facile 5-*endo-trig* cyclization to give 2,2-difluoro-4-TIPS-2,5-dihydrofuran in excellent yield (see ref 12).

(17) Suzuki, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH Verlag: Weinheim, 1998; p 49−98.

(18) Shen, W.; Thomas, S. A. *Org. Lett.* **2000**, *2*, 2857−2860. Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729−1731. Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551−8553.

(19) For recent examples of the Sonogashira reaction applied to the synthesis of other fluorinated enynes see: Qing, F.-L.; Gao, W.-Z.; Ying, J. *J. Org. Chem.* **2000**, *65*, 2003−2006. Jennings, M. P.; Cork, E. A.; Ramachandran, P. V. *J. Org. Chem.* **2000**, *65*, 8763−8766.