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Regiospecific Synthesis of Bicyclo- and Heterobicyclo-*gem*-difluorocyclobutenes Using Functionalized Fluoroallenes and a Novel Mo-Catalyzed Intramolecular [2 + 2] Cycloaddition Reaction

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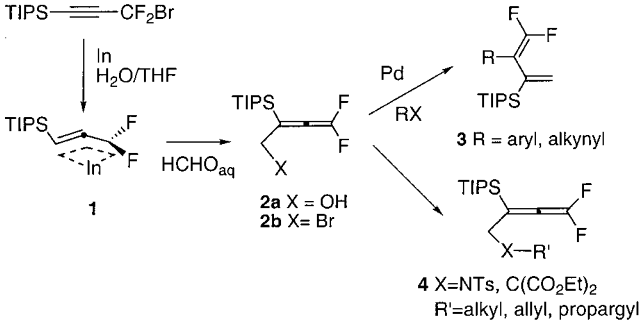
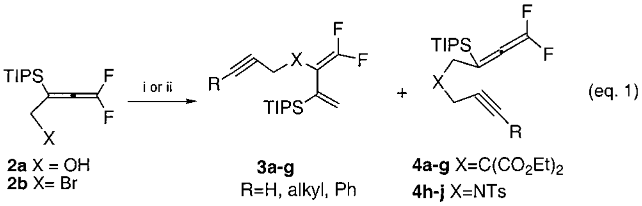
It is well established that the replacement of a hydrogen atom with fluorine in organic compounds brings about major biological and chemical changes.[1] Despite advances in fluorination strategies,[2] the synthesis of alicyclic *gem*-difluoro compounds is approached on a case-by-case basis.[3] A broader synthetic strategy—the cycloaddition of functionalized *gem*-difluoro-allenes—pioneered by Dolbier,[4] has remained largely unexplored, hampered by the difficulty in synthesizing such fluorinated intermediates. Indeed, only few difluoroallenes $R_2C{=}C{=}CF_2$ (R = H, Me, Ph, Bu) have been reported,[5] and even conjugated *gem*-difluorodienes are rare.[6,7] Conceptually, a functionalized difluoroallene such as **4** (Scheme 1) could be prepared by appending an appropriate olefinic or alkynyl fragment to allenylsilane **2**. Allene **4** would be an ideal cyclization partner for the generation of a diverse array of fluorocyclic compounds. We now report the first synthesis of a functionalized *gem*-difluoroallene **4** and its novel molybdenum-catalyzed intramolecular allene−alkyne [2 + 2]-cycloaddition that produced **6**, a hitherto unknown class of CF_2-containing fused cyclobutenes.

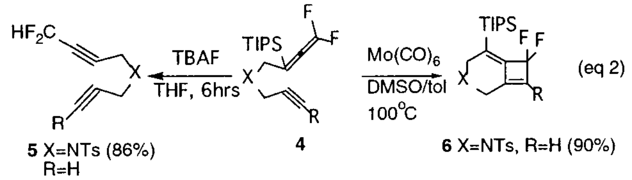
Scheme 1



Our recently discovered difluoroallenyl indium **1** (Scheme 1) reacted nucleophilically with aldehydes to yield the expected homopropargylic alcohols, but in the presence of aqueous formaldehyde, it produced allenyl alcohol **2a**.[8] Conversion of the hydroxyl **2a** into its corresponding halide **2b** was achieved cleanly. Allene **2b** isomerized to the themodynamically more stable conjugated diene isomer under Pd-mediated cross-coupling conditions—including Suzuki and Sonogashira—yielding *gem*-difluoro conjugated diene **3** in high yields.[7] Similarly, displacement of bromide in **2b** with a phosphorus nucleophile produced the corresponding 1,3-dienylphosphonate **3h** (R = $P(O)(OEt)_2$,) in what could be formally construed as a S_N2' reaction. The homologation of the side chain in **2b** was achieved using soft nucleophiles and Trost's Pd-catalyzed alkylation methodology[9] (**4a**−**g** in eq 1 and Table 1). By exercising strict control on the reaction conditions we minimized the formation of the isomeric dienes **3a**−**g**. Surprisingly, the alkylation reaction of **2b** with malononitrile or ethyl cyanoacetate yielded a larger ratio of **3**/**4**. The oxygen in **2a** could be substituted with nitrogen using propargylic amines, under Mitsunobu's conditions[10] (**4h**−**j**). In these cases, the corresponding diene isomer **3** was not found. Prior to our work, microwave spectroscopy and theoretical calculations on the geometries of the parent 1,1-difluoroallene showed that the C═C and C−F bond lengths would decrease with increasing fluorine substitution and FCF bond angles should resemble sp^3 hybridization.[11] Our X-ray data,[12] obtained from crystals of **4h**−**j**, provided the first crystallographic support to the above statements.



Although, in theory, an intramolecular cycloaddition of **4c**−**j** could be used to prepare bicyclic fluorinated compounds, there are but a handful reports detailing intramolecular metal-mediated allene cycloadditions,[13] none of which involved allene−alkyne [2 + 2] cycloadditions. Equipped with an efficient synthesis of functionalized *gem*-difluoroallenes **4**, we attempted the Co-mediated Pauson−Khand reaction,[14] and although we succeeded in isolating the stable Co−alkyne complex, the subsequent [2 + 2 + 1] cycloaddition did not occur. Use of ancillary agents such as NMO or DMSO at various temperatures did not bring about the cyclization either. We then decided to adopt Brummond's conditions,[15] using molybdenum to affect the cycloaddition (eq 2).



The intramolecular cyclization of **4** did not produce the Pauson−Khand product but a novel fused cyclobutene **6**,[16] in 90% yield. No traces of the [3.2.0] exocyclic difluoromethylene regioisomer could be detected. TIPS cleavage of **4** using TBAF resulted in the efficient formation of diyne **5**.

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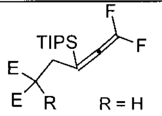
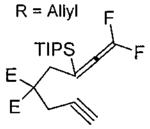
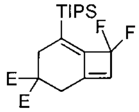
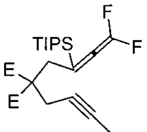
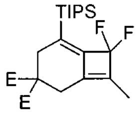
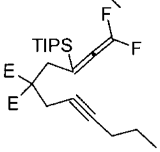
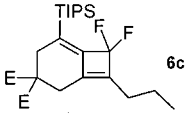
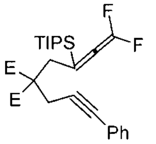
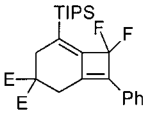
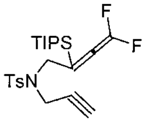
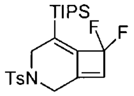
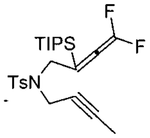
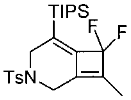
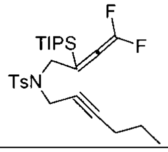
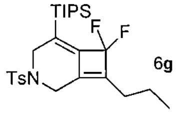
Table 1. Synthesis of Functionalized Difluoroallene Derivatives and Their Mo(CO)$_6$-Catalyzed Intramolecular [2 + 2] Cycloaddition[a]

Entry	Substituted Difluoroallenes	Ratio of **4/3**[c]	Yield[b]	Product	Yield[b]
1	 R = H	10:1	**4a/3a** (85%)	—	—
2	R = CH$_3$	4:1	**4b/3b** (82%)	—	—
3	R = Allyl	5:1	**4c/3c** (64%)	—	—
4		3:1	**4d/3d** (88%)		**6a** (81%)
5		4:1	**4e/3e** (84%)		**6b** (72%)
6		2:1	**4f/3f** (79%)		**6c** (88%)
7		2:1	**4g/3g** (76%)		**6d** (75%)
8		—	**4h** (83%)		**6e** (86%)[d]
9		—	**4i** (48%)		**6f** (92%)
10		—	**4j** (44%)		**6g** (81%)

[a] No products were detected without Mo(CO)$_6$ or at a lower temperature (80 °C). [b] Isolated yields. [c] The ratio of **4/3** is based on ^{19}F NMR. [d] When 1.5 equiv Mo(CO)$_6$ was used, the yield is 90%.

The fact that this Mo-mediated [2 + 2]-intramolecular allene−alkyne cycloaddition is an intriguing departure from the expected Pauson−Khand reaction prompted us to probe the reaction further (Table 1). In all cases, *gem*-difluorocyclobutenes **6a**−**g** were obtained in very good or excellent yield. Crystallographic data obtained from crystals **6e**−**g** helped to secure the identity of this novel functionalized *gem*-difluoro bicyclo [4.2.0] system.[17]

This cycloaddition, initially performed with 1.5 equiv of molybdenum was repeated using catalytic amounts of molybdenum (10 mol %) with equal success. Mechanistically, this reaction represents a "formal" [2 + 2] cycloaddition, with the molybdenum metallocycle undergoing a reductive elimination, rather than a CO insertion. This behavior has been observed for other metals but not for molybdenum. As we never observed the P−K product, the relative rate of reductive elimination must be much faster than the rate of carbonylation. Moreover, since the electron-withdrawing *gem*-difluoro substituent would be expected to favor both processes, it is interesting that reductive elimination wins. We are currently investigating this and other modes of metal-mediated cyclizations using mono- and difluorinated allenes.

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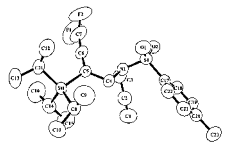
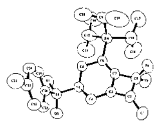
Supporting Information Available: Experimental procedures and spectroscopic and analytical data for the substrates and products (PDF). X-ray crystal data for **4h**−**i** and **6e**−**g** (CIF). This material is available free of charge via the Internet at htt://pubs.acs.org.

References

(1) Recent books include: Hiyama, T. Organofluorine Compounds. *Chemistry and Applications*; Springer-Verlag: Berlin, 2000. Baasner, B., Hagemann, H., Tatlow, J. C., Eds. *Organo-Fluorine Compounds*; Thieme: Stuttgart, 1999; Vol. Vol. E10a.
(2) Leading references include: Soloshonok, V. A.; Ed. *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Wiley & Sons: West Sussex, 1999. Percy, J. M. *Top. Curr. Chem.* **1997**, *193*, 131−195.
(3) Ichikawa, J. *Pure Appl. Chem.* **2000**, *72*, 1685−1689 and references therein.
(4) Shtarov, A. B.; Krusic, P. J.; Smart, B. E.; Dolbier, W. R., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 9956−9962. Dolbier, W., Jr.; Burkholder, C.; Wicks, G.; Palenik, G.; Gawron, M. *J. Am. Chem. Soc.* **1985**, *107*, 7183−7184.
(5) Dolbier, W. R., Jr. *Acc. Chem. Res.* **1991**, *24*, 63−69.
(6) Amii, H.; Kobayashi, T.; Terasawa, H.; Uneyama, K. *Org. Lett.* **2001**, *3*, 3103−3105. Yokomatsu, T.; Katayama, S.; Shibuya, S. *Chem. Commun.* **2001**, 1878−1879.
(7) Shen, Q.; Hammond, G. B. *Org. Lett.* **2001**, *3*, 2213−2215.
(8) Wang, Z.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 6547−6552.
(9) Trost, B. M.; Tour, J. M. *J. Org. Chem.* **1989**, *54*, 484−486.
(10) Edwards, M. L.; Stemerick, D. M.; McCarthy, J. R. *Tetrahedron Lett.* **1990**, *131*, 3417−3420.
(11) Dixon, D.; Smart, B. *J. Phys. Chem.* **1989**, *93*, 7772−7780. Recently, the X-ray of tetrafluorobutatriene was reported by Bash, A.; Lentz, D.; Luger, P.; Messerschmidt, M.; Olesch, C.; Patzschke, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 296−299.
(12) An ORTEP view of **4h**.



(13) Relevant references include: Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263−3283. Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92. Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553−11554. Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 11295−11305. Llerena, D.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1996**, *37*, 7027−7030.
(14) Ishizaki, M.; Suzuki, D.; Hoshino, O. *J. Fluor. Chem.* **2001**, *111*, 81−90.
(15) Brummond, K. M.; Lu, J.; Petersen, J. *J. Am. Chem. Soc.* **2000**, *122*, 4915−4920.
(16) Only the parent 3,3-difluorocyclobutene is known: Dolbier, W. R., Jr.; Al-Fekri, D. M. *J. Org. Chem.* **1987**, *52*, 1872−1874.
(17) ORTEP view of **6f**.



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