Fluorinated Building Blocks. The Discovery of a Stable Difluoroallenyl Indium and the Synthesis of *gem*-Difluoroallenyl and -propargyl Synthons in Aqueous Media†

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The synthesis of two highly functional fluorinated motifs, TIPS−C≡C−CF_2−, and CF_2=C=C(TIPS)− is described. This approach is mediated by a room-temperature stable ethereal solution of a difluoroallene indium intermediate. This intermediate may be used as "stock solution" in the reaction with aqueous HCHO, to yield CF_2=C=C(TIPS)CH_2OH, and in a reaction with a Schiff base to produce the corresponding *β*,*β*-difluorohomopropargylamine. The synthetic potential of CF_2=C=C(TIPS)CH_2-OH has been demonstrated by its conversion to a difluorodihydrofuran derivative by a facile and efficient 5-*endo*-*trig* cyclization. Homopropargylic *gem*-difluoro alcohols are synthesized by addition of indium to a mixture of an aldehyde and TIPS−C≡C−CF_2Br in predominantly aqueous media.

Introduction

The beneficial effects of fluorine substitution on the physicochemical and physiological properties of organic molecules have spurred remarkable advances in site-specific fluorine substitution methodologies.[1] The development of electrophilic fluorinating reagents[2] and the construction of new fluorine-containing building blocks capable of delivering CF_2 or CFH groups using one-bond disconnections are cases in point.[3] Despite this progress, current methods for the introduction of fluorine in organic molecules have yet to assimilate the emerging concept of "green chemistry".[4] More often than not, reactions employing either fluorinated building blocks, or fluorinating reagents, require an anhydrous environment, low temperatures, and organic solvents. As part of our research on fluorinated synthons,[5] we decided to pursue a "green chemistry" approach for the selective incorporation of fluorine in organic molecules.[6] In this context, we focused our attention on the use of indium to mediate C−C bond forming reactions under environmentally benign conditions. From the environmental standpoint, indium has definite advantages over other metals, not the least of which is the use of water as solvent.[7] Our first aim was to establish a regiocontrolled synthesis of propargyl and allenyl fluorinated building blocks such as **5** and **9**. The latter is an attractive target because of the plethora of synthetic operations propitiated by the allene moiety.[8] Indeed, **9** contains two powerful synthetic handles, a vinyl TIPS substituent and a CH_2OH group on an allene framework that can serve as scaffolding for the synthesis of fluorinated compounds via efficient two-bond disconnections (e.g., Diels−Alder, Pauson−Khand) and other multiple C−C bond forming reactions. Prior to this report, *γ*,*γ*-disubstituted *gem*-difluoroallenes were unknown.[9] The inspiration and stimulus for our research came from the pioneering work of Chan and Li on Barbier−Grignard-type reactions using indium,[7a] Chan and Isaac's[10] indium-mediated regiocontrol in propargyl-allene isomerization, and our own familiarity with propargyl-allenyl-α-fluorophosphonate interconversion.[11]

Our plan to construct a difluoroallene moiety needed a readily available *gem*-difluoropropargyl starting material capable of undergoing a propargyl-allene isomerization. Compound **1** was deemed the candidate of choice

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† In memory of Professor Larry S. Weiler, 1942−1999.

(1) For leading recent references, see: Schlosser, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *110*, 1496. *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V. A., Ed.; Wiley & Sons: West Sussex, 1999.

(2) For a sample of recent reviews see: *Organo-Fluorine Compounds*; Baasner, B., Hagemann, H., Tatlow, J. C., Ed.; Houben-Weyl Methods of Organic Chemistry 4th Edition, Thieme: Stuttgart, 1999; Vol. E 10a. Sankar Lal, G.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737. Umemoto, T. *Chem. Rev.* **1996**, *96*, 1757.

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(4) *Green Chemistry. Frontiers in Benign Chemical Syntheses and Processes*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: Oxford, 1998.

(5) Hammond, G. B.; deMendonca, D. J. *J. Fluorine Chem.* **2000**, *102*, 189. Gu, Y.; Hama, T.; Hammond, G. B. *J. Chem. Soc., Chem. Commun.* **2000**, 395 and references therein.

(6) A practical synthesis of α-trifluoromethylated alcohols in water has been recently accomplished by Loh's group. See: Loh, T.-P.; Li, X.-R. *Tetrahedron Lett.* **1997**, *38*, 869. Loh, T.-P.; Li, X.-R. *Tetrahedron* **1999**, *55*, 5611.

(7) Selected reviews include: (a) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149. (b) Cintas, P. *Synlett* **1995**, 1087. (c) Li, C.-J. *Water as a benign solvent for chemical syntheses*; p 235 in ref 4.

(8) For a sample of references published since the year 2000 on the synthesis of allenes, see: Shimizu, T.; Sakamaki, K.; Miyasaka, D.; Kamigata, N. *J. Org. Chem.* **2000**, *65*, 1721. Ma, S.; Zhang, A.; Yu, Y.; Xia, W. *J. Org. Chem.* **2000**, *65*, 2287. Ahmed, M.; Arnauld, T.; Barrett, A. G. M.; Braddock, D. C.; Flack, K.; Procopiou, P. A. *Org. Lett.* **2000**, *2*, 551. For a sample of references published since the year 2000 on reactions of allenes see: Parsons, P. J.; Thompson, P.; Taylor, A.; Sparks, T. *Org. Lett.* **2000**, *2*, 571. Ma, S.; Li, L. *Org. Lett.* **2000**, *2*, 941. Liepins, V.; Karlstroem, A. S. E.; Baeckvall, J.-E. *Org. Lett.* **2000**, *2*, 1237. Chang, H.-M.; Cheng, C.-H. *J. Org. Chem.* **2000**, *65*, 1767. Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630. Yoneda, E.; Kaneko, T.; Zhang, S.-W.; Onitsuka, K.; Takahashi, S. *Org. Lett.* **2000**, *2*, 441.

(9) Dolbier, J. W. R. *Acc. Chem. Res.* **1991**, *24*, 63.

(10) Isaac, M. B.; Chan, T.-H. *J. Chem. Soc. Chem. Commun.* **1995**, 1003.

(11) Zapata, A., Gu, Y., Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 227.

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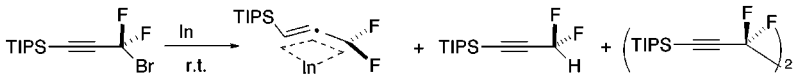
Table 1

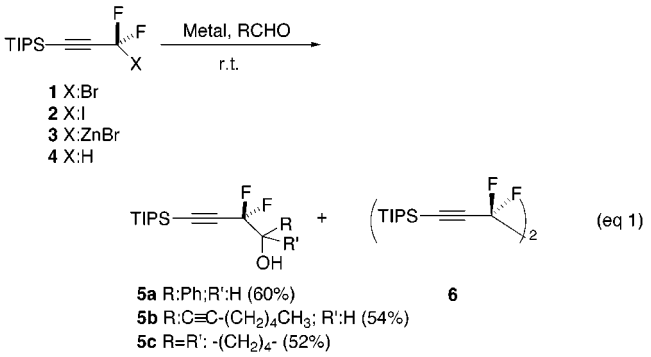


1 7 4 6

entry	In (eq)	Solvent systems (v/v)[a]	1	7	4	6
1	1.2	H_2O	26	0	0.7	1
2		CH_3OH:H_2O (20:80)	0.5	1.4	0.3	1
3		CH_3CN:H_2O (20:80)	0.9	4.1	0.3	1
4		HMPA:H_2O (20:80)	3.4	3.5	0	1
5		THF:H_2O (30:70)	0	6	0	1
6		THF	0	0.6	0.1	1
7		THF:H_2O (20:80)	0	12	0	1
8	0.6		0	5	0	1
9	0.3		2.4	1.7	0	1

[a]A mixture of **1**(1.0 eq) and indium powder in the solvent system (5 mL) was stirred at r.t. for 2-3 h before monitoring the mixture by ^{19}F NMR.

because it could be prepared in multigram quantities in a single, high-yielding step[12] from TIPS-acetylene and CF_2Br_2, an industrial fluorinated feedstock.[13] An earlier report from our laboratory had shown that the zinc-mediated reaction of **1** with a carbonyl electrophile (e.g., benzaldehyde or 1-octynal) led to the formation of **5a**,**b** via a Reformatsky-type reaction (eq 1). Replacing the aldehyde by a ketone (e.g., cyclopentanone) yielded the corresponding tertiary homopropargylic alcohol **5c**.[14] The only byproduct of that reaction was dimer **6**, and the ratio of **5c** to **6** was approximately 4:1. Without the presence of an aldehyde or ketone, the organozinc intermediate **3** (^{19}F NMR δ −94.6 ppm), gradually lost both fluorine atoms yielding *trans*-(TIPS)HC=CHBr after 48 h at room temperature.



We are now pleased to report that indium brings about the conversion of **1** to a stable difluoroallenyl indium intermediate **7** and the synthesis of *gem*-difluoro derivatives **5** and **9** in predominantly aqueous media. The synthetic potential of allenyl alcohol **9** has been further demonstrated by its conversion to the hitherto unknown difluorodihydrofuran **11** via a facile and efficient 5-*endo*-*trig* cyclization.

Results and Discussion

First, we examined the effect of indium on the reaction of **1** with cyclopentanone, anticipating[10] that a mixture of allenyl and homopropargyl alcohols might be obtained. A mixture of **1** (1.0 equiv), cyclopentanone (1.0 equiv), and indium (1.2 equiv) stirred vigorously in water at room temperature led to the formation of **5c** (10%), dimer **6** (11%), a new ^{19}F signal at δ −88 ppm (10%) and unreacted starting material (58%). Assuming that the new signal corresponded to the allenyl alcohol isomer of **5c**, we proceeded to purify it by flash chromatography. However, it was soon noticed that the fraction that contained the new compound darkened immediately after solvent removal. ^{19}F NMR analysis of the residue showed complete disappearance of the signal at δ −88 ppm. This result led us to speculate that this signal probably corresponded to a difluoroallenylindium intermediate, to which we ascribed structure **7**.[15]

The existence of an allenylindium species is not without precedence in the literature. Chan,[10] as well as Marshall,[16] had speculated that a transient species possessing allenic character was an intermediate in their respective synthesis of allenyl and homopropargyl alcohols. What is unprecedented is the room-temperature stability of **7** in solution. Hence, we sought to optimize its formation by using a binary solvent system (Table 1). A mixture of MeOH/H_2O (entry 2) increased somewhat the production of **7** and so did CH_3CN/H_2O (entry 3) and HMPA/H_2O (entry 4), although starting material was still present in the reaction mixture in these cases. Ultimately, optimal conditions for the production of **7** were found using THF in predominantly aqueous media (entry 7). Because the reaction of indium with **1** occurs under heterogeneous conditions, employing vigorous agitation during the reaction increases the ratio of **7**:**6** from 6:1 to 12:1. The reaction of **1** with 1.2 equivalents of indium in H_2O/THF (80:20) not only produced **7** but also generated substantial amounts of a malleable metallic gray nugget with a very shiny silver inner surface, insinuating that indium metal was present at the end of the reaction. This observation prompted us to reevaluate the stoichiometry

(12) Wang, Z., Hammond, G. B. *J. Chem. Soc., Chem. Commun.* **1999**, 2545.

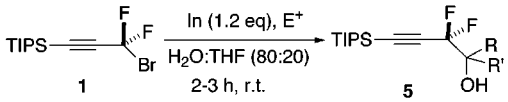
(13) This molecule is not included in the list of banned halofluorocarbons by the Montreal Protocol.

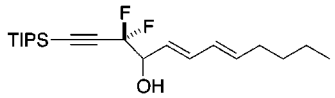
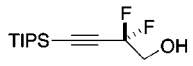
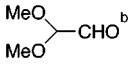
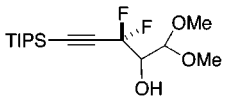
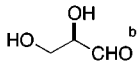
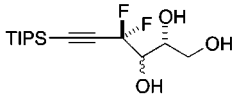
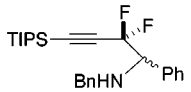
(14) Wang, Z.; Hammond, G. B. *Tetrahedron Lett.* **2000**, *41*, 2339.

(15) The portrayal of **7** in solution as a bridged structure is modeled after Reich's comprehensive study of silyl-substituted allenylpropargyllithium reagents. See: Reich, H. J.; Thompson, J. L. *Org. Lett.* **2000**, *2*, 783. Reich, H. J.; Holladay, J. E.; Walker, T. G.; Thompson, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 9769.

(16) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 696.

Table 2



entry	E^+	**5**[a] (%)	^{19}F NMR (ppm)
1	PhCHO	**5a** (72%)	-92.48, -94.62 $^2J_{FF}$=275 Hz
2	1-octynal	**5b** (67%)	-94.07, -97.22 $^2J_{FF}$=270 Hz
3	2,4-nonadienal	 **5d** (86%)	-94.40, -97.12 $^2J_{FF}$=274 Hz
4	HCHO [b] (37% wt)	 **5e** (38%)[c]	-95.78
5	 (60% wt)	 **5f** (20 %)[c,d]	-93.83, -95.45 $^2J_{FF}$ = 281 Hz
6	 (70% wt)	 **5g**(15%)[c,d,e]	-93.06, -94.43 $^2J_{FF}$ = 281 Hz
7	BnN=CHPh	 **5h**	NO REACTION

[a]Isolated yield. [b]Commercial aqueous solution. [c]Reaction conditions have not been optimized. [d]Stirring 1 to 3 days is needed; the yields were judged from ^{19}F NMR analysis of the crude product. [e]Diastereoselectivity was not determined

of this reaction. Chan had demonstrated that in reactions involving allyl bromide, an allylindium species containing a C−In(I) bond is the reactive intermediate in Barbier-type reactions,[17] but the nature of the indium salt formed, and the question of the stoichiometry of the reaction had not been investigated. According to Chan,[18] the assumption is that allyl bromide reacts with two atoms of indium to give allylindium(I) plus indium(I) bromide. However, it is then possible for indium(I) bromide to disproportionate[19] to indium metal and indium(III) bromide, which is the final indium salt. If this is the case, the silvery nugget found in our reaction could be a mixture of indium and $InBr_3$, the weight of which should decrease as the number of equivalents of indium is reduced. Experimentally, we found this to be the case. Reducing the number of equivalents of indium to 0.6 (entry 8) led to a reduction of the mass of the nugget[20] and the consumption of **1**, albeit at the expense of a smaller **7**:**6** ratio. Using 0.3 equiv of indium led to an even smaller **7**:**6** ratio, but this time, starting material remained present at the end of the reaction (entry 9). The above experiments established that even if only 0.5 equiv of indium is used in the reaction with **1**, the reaction still goes to completion with total consumption of starting material, although the yield of **7** is reduced. This result is explained by noticing that the formation of dimer **6**, a side product of the reaction, is mediated by indium but it does not contain indium, whereas indium is present in **7**. If the rate of formation of **6** is faster than that of **7** then it is to be expected that as the number of indium atoms available for the reaction with **1** decrease, so will the **7**:**6** ratio.[21] The difluoroallenyl indium **7** forms an emulsion in water and is easily extracted into organic solvents.[22] An ethereal solution [^{19}F NMR ($CDCl_3$) δ −88 ppm; ^1H δ 1.08 ppm] was very stable at room temperature and could be stored for weeks without decomposition, allowing us to use it as a "stock solution" for future reactions. The decomposition of **7** occurred upon complete solvent removal. Its ^{13}C NMR (THF-d_8) spectrum exhibited three sets of upfield-shifted

(17) In addition to Et_2O, **7** is soluble in EtOAc and THF. It decomposes gradually in $CDCl_3$, and it forms a milky white suspension in hexane.

(18) For information on ^{13}C NMR chemical shifts of fluoroallenes, see: Zens, A. P.; Ellis, P. D.; Ditchfield, R. *J. Am. Chem. Soc.* **1974**, *96*, 1309.

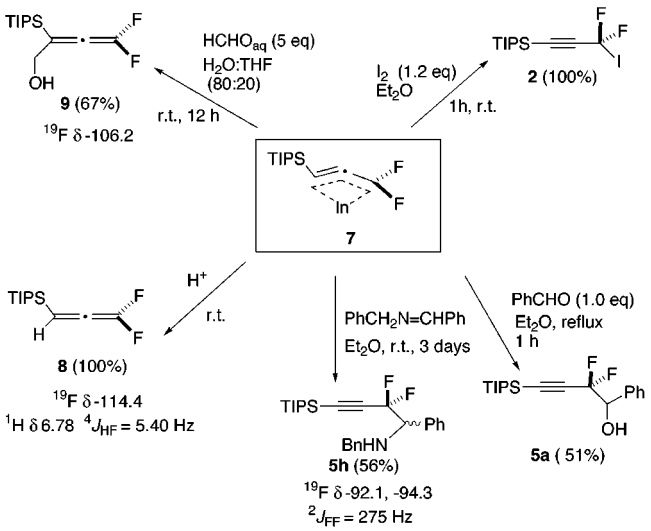
(19) Chan, T.-H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228.

(20) Chan, T.-H. Personal communication.

(21) Taylor, M. J.; Brothers, P. J. In *Chemistry of Aluminium, Gallium, Indium and Thallium*; Downs, A. J., Ed.; Blackie Academic & Professional: London, 1993; p 199.

(22) For example, when **1** (628 mg) was treated with indium (1.2 equiv), 156 mg of the silvery nugget was recovered; however, when **1** (305 mg) was treated with indium (0.6 equiv), only 2.5 mg was recovered.

Scheme 1



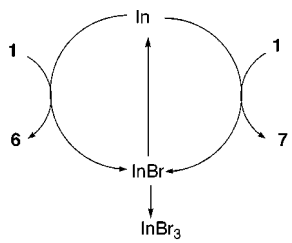
triplets at δ 131.5 (J_{FC} = 283 Hz), 111.2 (J_{FC} = 36 Hz) and 107.9 (J_{FC} = 36 Hz) in addition to the TIPS signals.[23] The upfield shift of the carbon signals could have been caused by the shielding effect of indium on the allene framework. Its IR spectrum showed two medium intensity peaks absorbing at 1811 and 1714 cm^{-1}. We hypothesized that this shift to lower wavenumbers—compared to a normal allene—might have been caused by the combined effect of the electron withdrawing fluorine substituents and the coordination of indium with the sp^2 carbon atoms.

To probe whether a halogen atom was present, **7** was treated with an acidified solution of $AgNO_3$, but no AgBr precipitate was observed. When the iodo analogue **2** was stirred with indium in H_2O:THF (80:20), the disappearance of the signal corresponding to **2** in the ^{19}F NMR spectrum was accompanied by the formation of the fluorine signal corresponding to **7**. The combination of these two results revealed that there was no halide presence in **7**. When **1** was vigorously stirred with nonwater soluble aldehydes such as benzaldehyde, 1-octynal, or 2,4-nonadienal, in the presence of indium in H_2O/THF (80:20) at room temperature, the reaction produced α,α-difluorohomopropargyl alcohol **5a**,**b**,**d** (Table 2) in very good yields.[24] The same reaction using aldehydes sold commercially as aqueous solutions, such as formaldehyde, glyoxal, or D-glyceraldehyde, furnished the partially fluorinated alcohols **5e**−**g**, without the need to protect/deprotect reactive hydroxyl groups or mask water-sensitive functionalities.[25] Modifying the H_2O/THF ratio might improve the yields of alcohols **5e**−**g**. When the carbonyl electrophile was substituted by a Schiff base, there was no reaction (entry 7). However, we were able to prepare **5h** by treating **7** with the same Schiff base (Scheme 1).

The unprecedented stability of difluoroallenyl indium **7** encouraged us to investigate its behavior toward some of the electrophiles used in Table 2. When an ether solution of **7** was stirred with benzaldehyde at room temperature there was no reaction even after 40 h. Only after refluxing the same mixture for 1 h the formation of **5a** was effected, although in lower yield than that shown under entry 1 in Table 2. The reaction of **7** with aqueous formaldehyde did produce **5e** only as the minor product, the major product being the isomeric allenyl alcohol **9**[26] (compare with entry 4). By substituting an aldehyde with an imine electrophile, the nucleophilic attack of **7** on the carbon terminus of the Schiff base yielded *gem*-difluoroamine **5h**. Quenching **7** with HCl produced difluoroallene **8** in approximate 50% yield according to ^{19}F NMR. However, when $HP(O)(OEt)_2$ was used as the proton source, the yield of **8** was quantitative. Finally, addition of iodine crystals to an ether solution of **7** afforded **2** in quantitative yield.[27]

It is clear from the results described above that when **1** was treated with indium in the presence of a carbonyl electrophile, only a propargyl-containing product (i.e., **5**) was generated, whereas **7** produced either allenyl- or propargyl-containing products (i.e., **5**, **8**, **9**). How can we account for the regiochemistry observed? We have speculated that perhaps **7** is not a real intermediate, but a transition state in an equilibrating mixture of bridged structures possessing allenyl and propargyl character such as **10A** and **10P**, respectively. Assuming that **10P** is more reactive (kinetically favored), it would be trapped by a carbonyl electrophile as soon as it was formed via a well-established six-membered transition state[28] to yield **5a**−**g** (path A, Scheme 2). Under refluxing conditions, the less reactive (thermodynamically stable) species **10A** is converted to **10P** via **7**, ultimately reacting with benzaldehyde to yield **5a** through path A. The preferential formation of allene **9** in Scheme 1 could be justified assuming that the smaller size and stronger electrophilicity of formaldehyde, as compared to benzaldehyde, allows the former to react, albeit slowly, with **10A**, using also a six-membered transition state (Scheme 2, path B, R = H). A similar argument would justify the synthesis of allene **8** in Scheme 1. By substituting an aldehyde with an imine electrophile, the nucleophilic attack of **7** on the carbon terminus of the Schiff base yielded *gem*-difluorohomoallenylamine **5h**. The regiochemistry of this reaction could be the result of a combination of steric and electronic effects.[29] The fact that **5h** can be prepared from **1** has potentially important repercussions because it may

(23) A plausible diagram showing both reaction paths is shown below:



(24) It is remarkable that the yields of **5a**,**b**,**d** using indium, in reaction vessels held at room temperature, open to the atmosphere, and in predominantly aqueous media, are better than those obtained by the use of zinc under anhydrous conditions and organic solvents (compare results of eq 1).

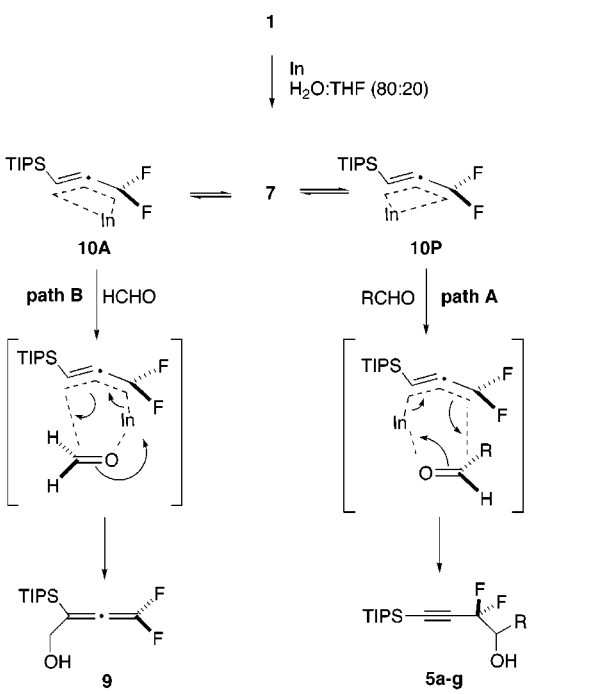
(25) These commercial aldehydes are unfit for traditional organometallic manipulations requiring anhydrous conditions.

(26) $H_2C{=}C{=}CF_2$ ^{19}F NMR δ −107 ppm. See: Berger, S.; Braun, S.; Kalinowski, H.-O. *NMR Spectroscopy of the Nonmetallic Elements*; John Wiley & Sons: Chichester, 1997; p 439.

(27) Even though we had prepared **2** in 73% yield by the reaction of lithium TIPS-acetylide with CF_2I_2, the prohibitive cost of commercial CF_2I_2 will make the indium route attractive for large-scale synthesis of **2**.

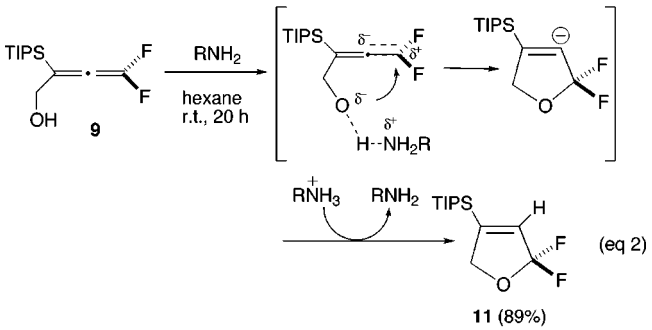
(28) There is enough supporting evidence to accept the six membered transition state in the reaction of of organoindiums with carbonyl compounds. See: Isaac, M. B.; Chan, T.-H. *Tetrahedron Lett.* **1995**, *36*, 8957. Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201.

Scheme 2



pave the way for an expedient preparation of *gem*-difluorinated-β-amino acids (via ozonolysis of the triple bond in **5h**) or -α-amino acids (by substituting the phenyl group in the Schiff base with a carboxylic acid).

Cyclization methodologies, especially intramolecular, are of paramount importance in the synthesis of organic compounds. Among the ring closure rules proposed by Baldwin[30] almost 25 years ago, only very few exceptions of nucleophile-driven, disfavored *5-endo-trig* cyclization are known. Ichikawa and co-workers[31] have recently reported a successful *5-endo-trig* cyclization of a terminally difluorinated homoallylic alcohol via the corresponding alkoxide, the process being facilitated by the electron withdrawing role of the geminal fluorine atoms.[32] Their cyclization needed strong basic conditions (NaH in DMF, 0−60 °C, 2 h). In our case, allenyl alcohol **9** underwent a mild conversion to the hitherto unknown 2,2-difluoro-2,5-dihydrofuran **11** at room temperature in hexane using hexylamine (eq 2). This reaction worked



equally well using other primary aliphatic amines such as cyclohexylamine, benzylamine, or (*R*)-(+)-α-methylbenzylamine. The reaction failed to work with a less basic amine such as *p*-iodoaniline. To our knowledge, the only reported partially successful attempt to synthesize a similar difluorodihydrofuran, albeit without the TIPS group, was carried out by Bunnelle and co-workers via a DAST fluorination of γ-thiolactone. Because the reaction worked in very low yield, their product could only be tentatively identified on the basis of GC−MS.[33] The mechanism for our base-mediated rearrangement probably involves an initial nucleophilic attack by oxygen on the distal double bond of the allene aided by the neighborhood group participation of the CF_2-containing terminal olefin. After cyclization, the negative charge on the ring would be stabilized by a favorable β-effect of the silicon atom. Abstraction of the acidic proton from the alkylammonium cation furnished **11**.

In sum, the results presented suggest that our methodology has the potential to provide a practical route to a library of partially fluorinated propargylic and allenic molecules built using water-soluble substrates. In addition, the synthesis of **8** and **9** could provide a vantage point for the assembly of other γ,γ-disubstituted *gem*-difluoroallenes.

Experimental Section

The solvents are reagent grade and used without purification. The indium metal powder (100 mesh) and all other commercial reagents were purchased from Aldrich and used as received. All reaction were done under air atmosphere and the reaction progress were monitored using one of the following techniques: ^{19}F NMR, TLC and GC-MS. Analytical TLC was performed using Macherey-Nagel Polygram Sil G/UV_{254} precoated plastic plates and visualized using phosphomolybdic acid (5% in methanol). Flash chromatography (eluent: hexane/ethyl acetate) was performed using silica gel 230−400 mesh, 40−63μm (Lagand Chemicals). IR spectra were recorded on a Bruker Vector-22 FT-IR spectrophotometer. ^1H, ^{19}F, and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300, 282 and 75 MHz, respectively. ^{19}F NMR spectra were referenced against external $CFCl_3$ and were broadband decoupled from hydrogen nuclei. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

The Formation of Difluoroallenyl In(I) Intermediate (7). To a vigorously stirred suspension of **1** (1227 mg, 3.94 mmol) in 10 mL of H_2O/THF (80/20,v/v) was added indium powder (499 mg, 1.2equiv), and the resulting mixture was stirred at room temperature for 2 h. TLC showed that both **7** and **6** are formed, accompanied by the absence of starting material. Their ratio can be judged by ^{19}F NMR. **7** was easily extracted by 20 × 3 mL ethyl ether and stored for future use.

General Procedure for the Preparation of Compounds 5a,b,d. To a vigorously stirred suspension of **1** (542 mg, 1.74 mmol) and benzaldehyde (177 μL, 1.0 equiv) in H_2O/THF (5 mL 80/20, v/v) was added indium powder (240 mg, 1.2 equiv). The mixture was stirred at room temperature for 2 h until the absence of **1** (^{19}F δ −32 ppm) was observed. Then saturated NH_4Cl (5 mL) was added, the milk-white suspension was extracted by ethyl acetate (15 × 3 mL), dried over $MgSO_4$, and concentrated to give the crude product as yellow oil. Purification by silica gel flash chromatography furnished **5a**. Com-

(29) One of the reviewers commented that it is possible that the indium species formed in situ with the electrophile present is radicaloid in nature, while the preformed reagent **7** is more electrophilic. This would certainly be consistent with the observed regiochemistry and would fit the kinetic/thermodynamic profile.

(30) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. Baldwin, J. E.; Cutting, J.; W., D.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

(31) Ichikawa, J.; Wada, Y.; Okauchi, T.; Minami, T. *J. Chem. Soc., Chem. Commun.* **1997**, 1537.

(32) Very recently Yamazaki's group have carried out extensive ab initio calculations of the reaction path of a novel DAST-promoted intramolecular rearrangement in which oxygen attacked an exocyclic CF_2 alkene on a glucose derivative. Their results revealed that the fluorine atoms stabilized both transition states and product by their strong electronegative character. See: Yamazaki, T.; Hiraoka, S.; Sakamoto, J.; Kitazume, T. *J. Phys. Chem. A* **1999**, *103*, 6820.

(33) Bunnelle, W. H.; McKinnis, B. R.; Narayanan, B. A. *J. Org. Chem.* **1990**, *55*, 768.

pound **5a** can also be conveniently prepared with a slightly lower yield (51%) by refluxing an ethereal solution of **7** (1 mmol, 5 mL of 0.2 M solution) and benzaldehyde (102 μL, 1.0 equiv).

1-(Triisopropylsilyl)-3,3-difluoro-4-phenyl-1-butyn-4-ol (5a). Yield of **5a** (424 mg, 72%): ^{1}H NMR δ 7.52−7.34 (m, 5H), 4.94 (dd, 1H, $^3J_{FH}$ = 7.37 Hz, $^3J_{FH}$ = 10.39 Hz), 2.04 (s, 1H), 1.02 (s, 21H); ^{13}C NMR δ 135.16, 128.94, 128.19, 127.95, 113.05 (t, $^1J_{FC}$ = 238.22 Hz), 96.21 (t, $^2J_{FC}$ = 37.51 Hz), 93.77 (t, $^3J_{FC}$ = 5.32 Hz), 76.40 (t, $^2J_{FC}$ = 28.45 Hz), 18.34, 10.82; EI-MS *m/e* 338 (M^+, 3), 289 (7), 263 (30), 207 (14), 154 (43), 107 (76), 79 (100).

1-(Triisopropylsilyl)-3,3-difluoro-1,5-undecadiyne-4-ol (5b). 1 (180 mg), yield of **5b** (138 mg, 67%): ^{1}H NMR δ 4.54 (m, 1H), 2.21 (dt, 2H, $^3J_{HH}$ = 7.06 Hz, $^5J_{HH}$ = 1.99 Hz), 2.04 (s, 1H), 1.52−1.26 (m, 6H), 1.12 (s, 21H), 0.90 (t, 3H, $^3J_{HH}$ = 7.10 Hz); ^{13}C NMR δ 111.57 (t, $^1J_{FC}$ = 238.97 Hz), 96.08 (t, $^2J_{FC}$ = 37.13 Hz), 93.02 (t, $^3J_{FC}$ = 5.66 Hz), 89.03, 74.03 (t, $^3J_{FC}$ = 4.11 Hz), 66.52 (t, $^2J_{FC}$ = 32.98 Hz), 30.99, 27.89, 22.13, 18.66, 18.07, 14.00, 10.88; EI-MS *m/e* 355 (M^+, 3), 304 (12), 261 (2), 241 (15), 157 (17), 109 (18), 77 (100). Anal. Calcd for $C_{20}H_{34}SiF_2O$: C, 68.13; H, 9.64. Found: C, 68.08; H, 9.74.

1-(Triisopropylsilyl)-3,3-difluoro-5,7-dienedodecyn-4-ol (5d). 1 (246 mg), yield of **5b** (252 mg, 86%): ^{1}H NMR δ 6.40 (m, 1H), 6.05 (m, 1H), 5.77 (m, 1H), 5.59 (m, 1H), 4.37 (m, 1H), 2.17−2.08 (m, 2H), 2.06 (s, 1H), 1.40−1.37 (m, 4H), 1.08 (s, 21H), 0.90 (t, 3H, $^3J_{HH}$ = 7.12 Hz); ^{13}C NMR δ 137.73, 135.87, 128.94, 123.23, 112.97 (t, $^1J_{FC}$ = 238.07 Hz), 96.59 (t, $^2J_{FC}$ = 37.58 Hz), 93.12 (t, $^3J_{FC}$ = 5.51 Hz), 75.06 (t, $^2J_{FC}$ = 28.90 Hz), 32.30, 31.24, 22.18, 18.41, 13.88, 10.87; EI-MS *m/e* 370 (M^+, 2), 257 (4), 215 (2), 171 (2), 139 (100), 79 (24). Anal. Calcd for $C_{21}H_{36}SiF_2O$: C, 68.06; H, 9.79. Found: C, 68.18; H, 9.92.

General Procedure for the Preparation of Compounds 5e−g. To a suspension of **1** (1.2 g, 3.9 mmol) in H_2O/THF (6 mL, 80/20, v/v) was added HCHO (37 wt % solution in water, 375 mg, 1.2 equiv) and indium powder (531 mg, 1.2 equiv). The resulting mixture was vigorously stirred (with occasional shaking) at room temperature for 2 h. Standard workup (saturated NH_4Cl treatment, ethyl acetate extraction) and flash chromatography gave **5e** as colorless oil.

1-(Triisopropylsilyl)-3,3-difluoro-1-butyn-4-ol (5e). Yield of **5e** (384 mg, 38%): ^{1}H NMR (C_6D_6) δ 3.59 (t, 2H, $^3J_{FH}$ = 12.49 Hz), 1.71(s, 1H), 0.98 (s, 21H); ^{13}C NMR (C_6D_6) δ 113.05 (t, $^1J_{FC}$ = 234.75 Hz), 98.68 (t, $^2J_{FC}$ = 37.56 Hz), 92.37 (t, $^3J_{FC}$ = 5.87 Hz), 66.58 (t, $^2J_{FC}$ = 31.10 Hz), 18.74, 11.98; EI-MS *m/e* 262 (M^+, 9), 219 (70), 191 (35), 169 (19), 115 (4), 91 (20), 77 (100). Anal. Calcd for $C_{13}H_{24}SiF_2O$: C, 59.50; H, 9.22. Found: C, 59.57; H, 9.23.

1-(Triisopropylsilyl)-3,3-difluoro-1-butyn-4-phenyl-4-*N*-benzylamine (5h). To a vigorously stirred suspension of **1** (426 mg, 1.37 mmol) in H_2O/THF (3 mL, 80/20, v/v) was added indium powder (189 mg, 1.2 equiv). After the alleneindium intermediate was generated (^{19}F δ −88 ppm, ratio **7**:**6** = 6/1), the milky white emulsion was extracted with ether (10 × 3 mL), and the ethereal phase was thoroughly dried over $MgSO_4$, filtered, and concentrated to a volume of 3 mL. *N*-Benzylidenebenzylamine (257 μL, 1.0 eq) was added and the solution was stirred at room temperature until the disappearance of the allene indium ^{19}F NMR signal. Standard workup and flash chromatography furnished **5h** as yellow oil (245 mg, 56% based on **7**): ^{1}H NMR δ 7.89−7.24 (m, 8H), 4.90 (dd, 1H), 4.81 (s, 2H), 2.03 (s, 1H), 1.02 (s, 21H); ^{13}C NMR δ 139.20, 134.39, 130.70, 129.67, 128.76, 128.53, 127.80, 126.92, 113.10 (t, $^1J_{FC}$ = 238.27 Hz), 96.36 (t, $^2J_{FC}$ = 37.56 Hz), 93.41 (t, $^3J_{FC}$ = 5.86 Hz), 76.13 (t, $^2J_{FC}$ = 28.17 Hz), 64.95, 18.30, 10.78; EI-MS *m/e* 295 (2), 263 (9), 207 (4), 193 (5), 154 (26), 127 (35), 107 (70), 79 (100).

1,1-Difluoro-3-(triisopropylsilyl)-1,2-butadiene-4-ol (9). To a suspension of **1** (710 mg, 2.28 mmol) in H_2O/THF (6 mL, 80/20, v/v) was added indium powder (314 mg, 1.2 equiv). The mixture was vigorously stirred for 1−2 h to ensure the depletion of **1** (ratio **7**:**6** = 10/1). Then HCHO (37 wt % solution in water, 926 mg, 5 equiv) was added and the mixture stirred for 12−20 h at room temperature until the disappearance of the alleneindium intermediate (^{19}F δ −88 ppm) was observed. Standard workup and flash chromatography furnished **9** as colorless oil (334 mg, 67% based on **7**): ^{19}F NMR (C_6D_6) δ −106.17; ^{1}H NMR (C_6D_6) δ 4.08 (t, 2H, $^5J_{FH}$ = 6.57 Hz), 1.79 (s, 1H), 1.08 (s, 21H); ^{13}C NMR (C_6D_6) δ 175.80 (t, $^2J_{FC}$ = 35.21 Hz), 161.10 (t, $^1J_{FC}$ = 258.8 Hz), 138.10 (t, $^3J_{FC}$ = 6.46 Hz), 64.81 (t, $^4J_{FC}$ = 3.54 Hz), 18.88, 11.65; EI-MS *m/e* 219 (M^+ − 43, 20), 197 (13), 169 (6), 157 (17), 131 (78), 103 (70), 75 (100). Anal. Calcd for $C_{13}H_{24}SiF_2O$: C, 59.50; H, 9.22. Found: C, 59.66; H, 9.28.

2,2-Difluoro-4-(triisopropylsilyl)-2,5-dihydrofuran (11). To a solution of **9** (50 mg, 0.19 mmol) in 3 mL hexane was added 1-hexylamine (25 mg, 1.0 equiv). The resulting solution was stirred at room temperature until the disappearance of starting material was observed (about 20 h), and then the solvent was removed and crude product was purified by flash chromatography yielding **11** (45 mg, 89%): ^{19}F NMR δ −58.72; ^{1}H NMR δ 6.03 (pentet, 1H), 4.89 (dt, 2H, $^4J_{FH}$ = 12.63 Hz, $^4J_{HH}$ = 2.30 Hz), 1.10 (s, 21H); ^{13}C NMR δ 147.86 (t, $^3J_{FC}$ = 3.85 Hz), 134.23 (t, $^1J_{FC}$ = 247.61 Hz), 130.10 (t, $^2J_{FC}$ = 32.75 Hz), 79.56, 17.95, 11.26; EI-MS *m/e* 262 (M^+, 2), 219 (60), 191 (31), 163 (62), 129 (20), 87 (15), 77 (100). Anal. Calcd for $C_{13}H_{24}SiF_2O$: C, 59.50; H, 9.22. Found: C, 60.16; H, 9.25.

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