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Synthesis of a stable indium complex derived from γ-silyl-α,α-difluorobromopropyne: evaluation of experimental parameters

Satoru Arimitsu, Bo Xu, Tara L.S. Kishbaugh, Leanne Griffin, Gerald B. Hammond*

Department of Chemistry and Biochemistry, University of Massachusetts, Dartmouth, 285 Old Westport Road, North Dartmouth, MA 02747, USA

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Abstract

Fluoroallenes are potentially useful cyclization precursors because of the synergistic combination of fluorine's unique stereoelectronic features and the rich chemistry of allenes. We have optimized the experimental conditions needed for the formation of a difluoropropargylindium complex **2**. Sonication, lower reaction temperatures (5 °C), and dilute concentration of the starting material (0.15 M) are required to maximize production of this complex. Although the structure of this complex remains unknown, we have found that the nature of the alkyl substituents on the silyl group does not influence the formation of **2** but it does affects the allenyl **5** to propargyl **4** ratio.

Keywords: Fluoroallenes; Indium; Propargyldifluoro; tri-*iso*-Propylsilyl

1. Introduction

Despite its distinctive stereoelectronic properties and widespread use—from polymers to liquid crystals to pharmaceuticals and agrochemicals—fluorine is not an easy atom to introduce in an organic compound. In particular, methods for the incorporation of fluorine in cyclic, non-aromatic systems are scarce. In this regard, the use of a fluorine substituent as activator and controller (β-cation-destabilizing effect, β-anion-stabilizing effect and leaving group ability as F^-) has only recently been realized for ring construction [1]. Our research addresses the shortage of convergent methods to synthesize alicyclic difluorinated systems by employing fluorinated functionalized allenes as coupling partners in ring construction methodologies.

By developing the chemistry of fluoroallenes as novel fluorine-containing building blocks, we seek to merge the unique stereoelectronic features of fluorine with the rich chemistry of allenes, to create functionalized complex molecules not available through fluorinating agents or other building block approaches. Fluorinated allenes are practically unknown. Indeed, except for the pioneering work of Dolbier on the synthesis of the parent di- and mono-fluoroallene [2], fluorinated allenes have been of interest mainly to theoreticians because of their inaccessibility in terms of synthesis. We are now well qualified to tackle this investigation. After our discovery of fluoroallenylphosphonate, [3] and, more recently, our synthesis of *gem*-difluoroallenol **5a** [4] from tri-*iso*-propylsilyldifluorobromopropyne (**1a**), [5] we have made possible a number of hitherto unknown synthetic pathways such as $Mo(CO)_6$ catalyzed [2 + 2] difluoro allene–alkyne intramolecular cyclization, [6] a facile synthesis of functionalized conjugated dienes, [7] and an extremely mild 'Baldwin-disfavored' intramolecular cyclization [4] (Scheme 1). As shown in Scheme 1, the cornerstone of our investigations on fluorinated synthons for cyclic systems relies on an efficient preparation of **2a**, which is hindered by a competing dimerization leading to **3a**.

2. Results and discussion

Our ultimate goal is the synthesis of a fluorinated allene dianion equivalent $(C{=}C{=}CF_2)^{2-}$, a task which we expected to accomplish by introducing two mutually orthogonal functional groups on the γ-carbon. Hence, our initial task was to optimize the production of **2**. With this purpose in mind we have undertaken an extensive study of the reaction conditions leading to the most efficient production of this intermediate, so

* Corresponding author. Tel.: +1-508-999-8865; fax: +1-508-910-6918.
E-mail address: ghammond@umassd.edu (G.B. Hammond).

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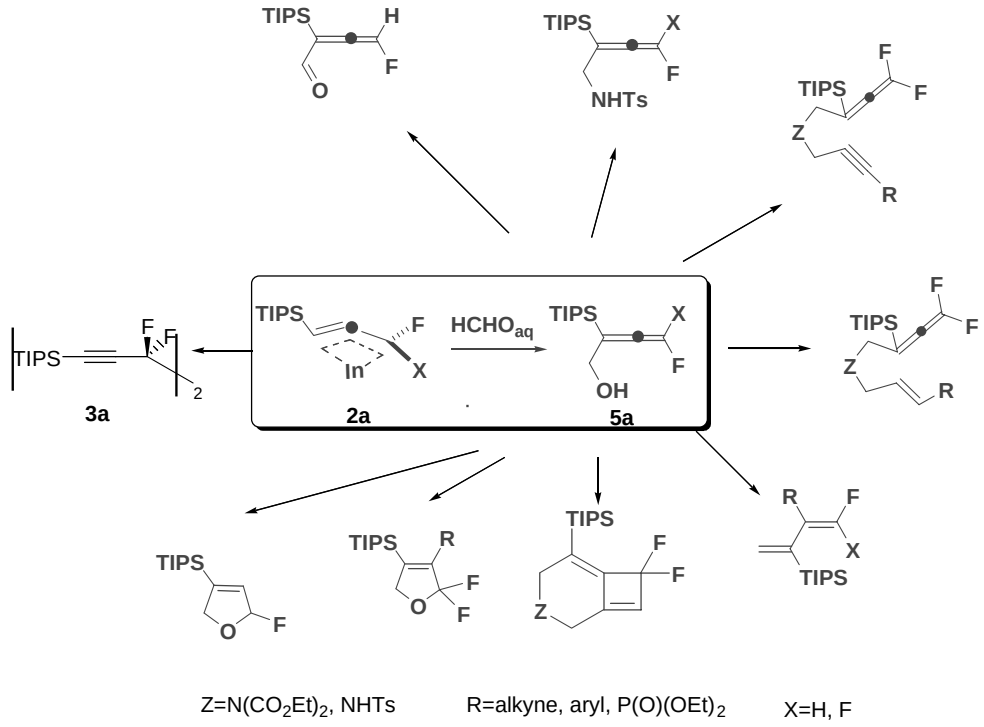


Scheme 1. Cyclization building blocks derived from a single fluorinated allene.

that we might minimize production of dimer **3** and maximize the formation of **2**, thereby gaining a greater understanding of the chemistry of this intriguing organometallic complex.

2.1. Effect of the silyl group on the formation of 2

The synthesis of *tert*-butyldimethylsilyldifluorobromopropyne (**1b**) and phenyldimethylsilyldifluorobromopropyne (**1c**) was carried out according to the methodology used for tri-*iso*-propylsilyldifluorobromopropyne (**1a**) [5] in 58 and 75% unoptimized yields, respectively. The chemical behavior of silyl propynes **1b** and **1c** towards indium was similar to that of **1a**. Compounds **1b** and **1c** furnished the indium intermediate **2b** and **2c**, respectively, accompanied by dimer **3b** and **3c**, in a ratio comparable to that observed for **1a** (Table 1). The reaction was complete after 2 h at rt in all three cases. After the addition of aqueous formaldehyde, the regioselectivity of the reaction varied considerably. Whereas **2a** reacted with formaldehyde to produce allenol **5a** preferentially, **1b** and **1c** produced homopropargyl alcohol **4b** and **4c**, respectively, rather than the desired allenol **5b** and **5c**. The reaction of **2a** with other aldehydes (R = aryl, alkyl), produced exclusively the thermodynamically more stable homopropargyl alcohol [4].

Table 1
Effect of the trialkylsilyl group on the production of the allenol **5**

Entry	R_3Si	Ratio of the intermediate to dimer[a]		Ratio of products[b]	
		2 (δ −88)	**3** (δ −99)	**4** (δ −95)	**5** (δ −106)
1	(*i*-Pr)$_3$Si	7	1	1	6
2	*t*-BuMe$_2$Si	6	1	5	1
3	PhMe$_2$Si	8	1	7	1

[a] A 0.32 M mixture of **1** and indium powder (1.2 eq.) in H_2O: THF (4:1) system was stirred at rt for 2 h before an aliquot in $CDCl_3$ was monitored by ^{19}F NMR.

[b] To the above mixture was added 5 eq. of aqueous HCHO; this mixture was then sonicated for 17 h prior to workup. The ratio is based on the isolated product.

2.2. Effect of metals on the production of 2a

In the presence of zinc, **1a** reacts with aldehydes or ketones to yield the corresponding homopropargyl alcohols in very good yields [8]. We examined the behavior of **1a** toward other metals (Table 2). In all cases studied, a discrete organometallic intermediate, such as the one found with indium (i.e., **2a**), was not observed by ^{19}F NMR; and none of the reactions conditions produced the desired allenol **5a**. The use of cadmium [9,10] gave rise to the homopropargyl alcohol **4a** (entry 1); when lead was used [11,12], the only compound observed was the reduced product TIPS-CC-CF_2H (**6a**) (entry 2). Under a variety of reaction conditions, gallium–which has a similar first ionization potential and reduction potential as indium, [13] only furnished dimer **3a**. Neither magnesium nor aluminum [14] were successful, returning **1a** unchanged (Scheme 2).

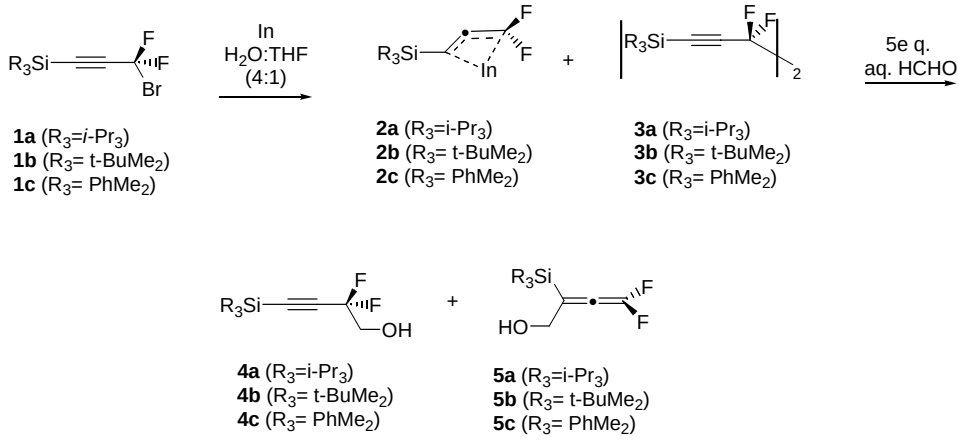
2.3. Effects of addition

We had found earlier that prior formation of the indium complex **2a** is necessary for good conversion to the allenol

Table 2
Effect of metals on the reactivity of **1a**

Entry	Metal	Solvent	Ratio of products[a]				
			1a (δ −32)	**4a** (δ −95)	**3a** (δ −99)	**5a** (δ −106)	**6a** (δ −105)
1	Cd	DMF sonication	0	30	1	0	1
2	Pb	THF sonication	0	0	0	0	1
3	Ga	H_2O: THF sonication	1	0	1	0	0
4	Mg	THF Rt, reflux, sonication	1	0	0	0	0
5	Al	THF or H_2O: THF	1	0	0	0	0
6	Al + 10% $PbCl_2$	THF	1	0	0	0	0

[a] Determined by ^{19}F NMR of the crude sample mixture after workup.



Scheme 2.

5a [4]. In fact, if all of the reagents, including the aqueous solution of formaldehyde, are mixed at once (entry 1, Table 3), only the homopropargyl alcohol **4a** is produced, as a minor product. Dimer **3a** was the major component in the reaction mixture. On the other hand, if **2a** is allowed to form first and none of **1a** remains in solution prior to the addition of formaldehyde, the major component in the reaction mixture is the desired **5a** (entry 2).

Presumably, dimerization could be minimized either by dilution or by keeping the effective concentration of **1a** small near the source of indium. In order to assess this hypothesis, a THF solution of **1a** was added via a syringe pump to an aqueous slurry of indium over the course of 3 h. As can be seen in Table 4, this proved to be a positive development (compare entry 1 to the other entries). Notably, dilution increases the ratio of **2a** to **3a** (compare entries 3 and 5). Furthermore, sonication is more efficient than stirring (compare entries 2 and 3) (Scheme 3).

Table 3
Effect of the order of addition on the production of 5a

Entry	Order of addition	Ratio of products[a]		
		4a (δ −95)	**3a** (δ −99)	**5a** (δ −106)
1	in situ	2	3	0
2	stepwise	1	1	6

[a] Determined by ^{19}F NMR of the crude sample mixture after workup.

2.4. Effect of temperature

Early on, we had observed that the amount of dimer **3a** produced seemed to be contingent upon the temperature of the reaction. The temperature of the ultrasound bath quickly reaches 45 °C if nothing is done to cool the bath; reactions performed at this temperature had, on average, a higher percentage of **3a** (entry 1, Table 5). Although sonication at 25 °C, (entry 2), provided a better result, it was very difficult to maintain that temperature in the ultrasound bath. At lower

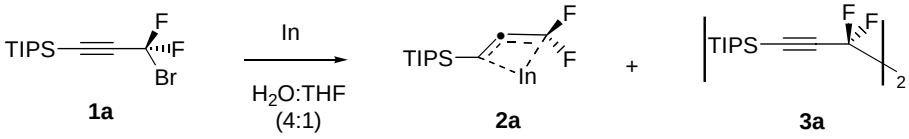
Table 4
The effect of slow addition of 1a on the formation of **2a** and **3a**

Entry	Concentration (M)	Mixing[a]	Rate of addition	Ratio of products[b,c]	
				2a (δ −88)	**3a** (δ −99)
1	0.32	Stirring	In situ	7	1
2	0.13	Sonication	Over 3 h	18	1
3	0.13	Stirring	Over 3 h	15	1
4	0.5	Stirring	Over 3 h	11	1
5	1.0	Stirring	Over 3 h	10	1

[a] Reactions carried out with stirring were at rt; reactions which were sonicated quickly reach ~45 °C.

[b] The progress of the reaction was monitored by analyzing an aliquot in $CDCl_3$ by ^{19}F NMR.

[c] Reactions in which the propyne was added slowly, were complete 1 h after addition; reactions in which the propyne was added to the indium in one aliquot were complete after 2 h.



Scheme 3.

Table 5
Effect of temperature on the reaction of **1a** with indium

Entry	Temp. (°C)	Ratio of products[a]		
		1a (δ −32)	**2a** (δ −88)	**3a** (δ −99)
1	45	0	3	2
2	25	0	29	1
3	0–5	27	14	1
4[e]	5–10	0	8	1

[a] A 0.5 M mixture of **1a** and indium powder (1.2 eq.) in H_2O/ THF (4:1) was sonicated for 6 h before monitoring by ^{19}F NMR.

temperatures (entries 3 and 4), the reaction becomes more sluggish, requiring between 6-8 h to complete, as compared with 2 h at room temperature. At 0–5 °C (entry 3), the predominantly aqueous solution froze partially, causing inefficient mixing of the sample with the metal, and a large proportion of unreacted starting material remained. If the temperature was kept between 5–10 °C, the solution did not freeze and the reaction was complete in 8 h, yet the ratio of **2a** to dimer **3a** was far from optimum (entry 4). We examined the stability of a mixture of **2a** and **3a** in solution (diethyl ether or THF-H_2O), and found that in either solution, at room temperature, **2a** was converted into **3a** over a 24 h period. If the solution of **2a** and **3a** was kept between 0 and 10 °C, the mixture showed little change even after three weeks.

2.5. Effects of concentration

The effect of substrate concentration when the ultrasound bath was set at a temperature of 5–10 °C was investigated. We noticed that as the concentration decreased, so did the rate of reaction, but at 0.15 M, the ratio of **2a** to **3a** reached its maximum (entry 2, Table 6). At 0.05 M (entry 3), starting material **1a** remained in the mixture even after 6 h. The optimal results obtained in entry 2 have been consistently reproduced. Replacing water with saturated aqueous NH_4Cl in the reaction solvent at 0.5 M reduced the proportion of unreacted starting material (entry 4) but it showed no improvement when compared with water at lower concentrations (compare entries 2–3 with entries 5–6).

3. Conclusion

We have optimized the experimental conditions needed for the formation of the indium complex **2**. Sonication, lower reaction temperatures (5 °C), and dilute concentration of the starting material (0.15 M) are required to maximize production of **2a**. Although the structure of this complex remains unknown, we have found that the nature of the alkyl substituents on the silyl group does not influence the formation of **2**; however, the presence of a tri-*iso*-propylsilyl group is indispensable for the synthesis of fluorinated allenyl alcohol **5a**.

4. Experimental

All moisture sensitive reactions were done using flame-dried glassware flushed with argon, magnetic stirring, and dry, freshly distilled solvents. THF was dried using a solvent purification system (Glass Contour, Laguna Beach, CA, USA). Other solvents were HPLC grade and were used without purification. TIPS-acetylene was purchased from GFS Chemicals Inc. (Columbus, OH, USA) and used without further purification. Other commercial reagents were purchased from Aldrich and used as received. Standard work-up involves washing ether extraction layer with sat.

Table 6
Effect of concentration on the production of **2a** and **3a**

Entry	Solvent (4:1)	Concentration (M)	Ratio of Products[a]		
			1a (δ −32)	**2a** (δ −88)	**3a** (δ −99)
1	H_2O: THF	0.5	27	14	1
2	H_2O: THF	0.15	0.3	21	1
3	H_2O: THF	0.05	8	12	1
4	sat. aq. NH_4Cl:THF	0.5	0.5	18	1
5	sat. aq. NH_4Cl:THF	0.15	1	26	1
6	sat. aq. NH_4Cl:THF	0.05	3	11	1

[a] A mixture of **1a** and indium powder (1.2 eq.) in the indicated solvent system was sonicated at 5 °C for 6 h before monitoring by ^{19}F NMR.

NH_4Cl, then brine; drying over $MgSO_4$; and concentration *in vacuo*. All reactions were monitored using one of the following techniques: TLC, GC–MS, and/or ^{19}F NMR. 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 was performed using silica gel 230–400 mesh, 40–63 microns (Lagand Chemicals). ^1H, ^{19}F and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300, 282, and 75 MHz respectively. ^{19}F NMR spectra was referenced against external $CFCl_3$. ^{19}F NMR spectra was broadband decoupled from hydrogen nuclei. Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA, USA.

5. General procedure for the synthesis of 1-trialkylsilyl-3-bromo-3,3-difluoropropyne

Under Ar atmosphere, *n*-butyl lithium (1.1 eq., 1.6 M in hexane) was added dropwise via syringe to a −78 °C solution of the trialkylsilylacetylene in THF (0.6 M). The resulting solution was stirred for 30 min to 1 h before CF_2Br_2 (1.5 eq.) was added slowly via cannula. The solution was allowed to warm to rt over 9 h before being quenched by the addition of sat. aq. NH_4Cl. It was extracted with ether (4×). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to yield a viscous orange oil which was purified by distillation (bulb-to-bulb in the case of **1b** and **1c**) to yield **1** as a colorless oil.

tri-*iso*-Propylsilyldifluorobromopropyne (**1a**): IR (neat); *v*: 2947 (s), 2869 (s), 2190 (m), 1464 (s), 1187 (s), 1098 (s), 947 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 1.11 (s); ^{19}F NMR ($CDCl_3$) δ: −32.6 (s, 2F); ^{13}C NMR ($CDCl_3$) δ: 100.61 (t, 290 Hz), 97.16 (t, 36.5 Hz), 95.1 (t, 4.7 Hz),18.01, 11.28; EIMS (probe) 70 eV, m/z (rel. int.): 312 (M^+ +1, 4), 310 (M^+ −1, 4), 269 (14), 267 (14), 143 (27), 77 (100). Anal. Calcd. for $C_{12}H_{21}SiF_2Br$: C, 46.33; H, 6.75. Found: C, 46.91; H, 6.83. The tri-*iso*-propylsilyl acetylene starting material, purchased from GFS Co., contained di-*iso*-propylpropenylsilyl acetylene (11%) and di-*iso*-propylpropylsilyl acetylene (14%). Fractional distillation did not remove these impurities. The GC–MS analysis shows all three components were alkylated and their ratios perfectly match that of the starting material. The calculated C% and H% was based on the formula of TIPS-difluorobromopropyne. If the two impurities are removed from the calculation, the values found for C% and H% are 46.84 and 6.67%, respectively.

tert-Butyldimethylsilyldifluorobromopropyne (**1b**): IR (neat); *v*: 2932 (s), 2887 (m), 2861 (s), 2192 (m), 1472 (s), 1183 (s), 1096 (s), 946 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 0.19 (s, 6 H) 0.97 (s, 9H); ^{19}F NMR ($CDCl_3$) δ: −32.8 (s, 2F); ^{13}C NMR ($CDCl_3$) δ: 104.7 (t, 290 Hz), 96.4 (t, 36 Hz), 95.4 (t, 3 Hz), 26.0,16.8, −5.26. EIMS (probe) 70 eV, m/z (rel. int.): 270 (M^+ +1, 5), 268 (M^+ −1, 5), 189 (5), 132 (20), 57 (100), 43 (80).

Phenyldimethylsilyldifluorobromopropyne (**1c**): IR (neat) *v*: 3277 (s), 3070 (s), 3023 (m), 2961 (s), 2035 (s), 1429 (s), 1251 (s), 1118 (s), 821 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ: 7.57–7.39 (m, 5H), 0.509 (s, 6H); ^{19}F NMR ($CDCl_3$) δ: −33.3(s, 2F); ^{13}C NMR ($CDCl_3$) δ: 133.9, 133.2, 130.4, 129.8, 128.2, 122.8, 100.9 (t, 287 Hz), −1.60. EIMS (probe) 70 eV, m/z (rel. int.): 290 (M^+ +1, 3), 288 (M^+ −1, 3), 275 (4), 273 (4), 209 (38), 159 (16), 132 (100), 77 (10).

6. Optimized production of 2a and 5a

To a 0.15 M solution of **1** in H_2O: THF (4:1) is added indium (1.2 eq.). This mixture is sonicated at 5 °C for 8 h. The temperature in the Bransonic® ultrasound bath was adjusted every 30–45 min by additional ice. An aliquot was analyzed in either C_6D_6 or $CDCl_3$ by ^{19}F NMR to monitor rate of conversion to **2a**. For the formation of **4a** and **5a**, the ultrasound bath was charged with water at rt, and 5 eq. of 37% aq. HCHO was added to **2a**. This mixture was sonicated for an additional 17 h. Standard workup produced **4a** and **5a**, with some contamination by **3a**. The alcohols, **4a** and **5a**, can be separated from **3a** by column chromatography (20:1; Hexanes:EtOAc).

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