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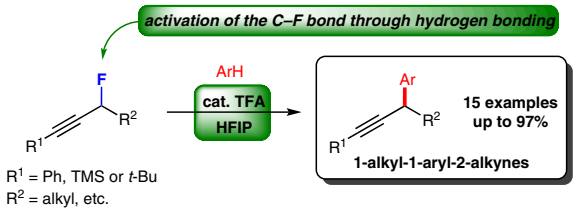
Hydrogen-Bond-Promoted Friedel–Crafts Reaction of Secondary Propargylic Fluorides: Preparation of 1-Alkyl-1-aryl-2-alkynes

Jean-Denys Hamel
Meggan Beaudoin
Mélissa Cloutier
Jean-François Paquin*

CCVC, PROTEO, Département de chimie, Université Laval, 1045 Avenue de la Médecine, Québec, QC G1V 0A6, Canada
jean-francois.paquin@chm.ulaval.ca

Dedicated to Prof. Victor Snieckus on the occasion of his 80th birthday



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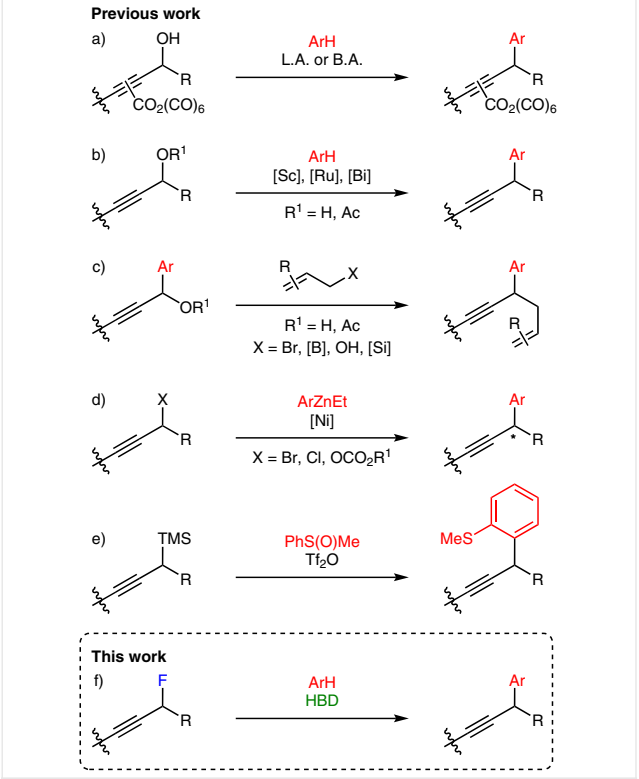
Abstract We report that aromatic propargylation is achievable with secondary propargylic fluorides, thus affording 1-alkyl-1-aryl-2-alkynes. In the present case, hydrogen bonding is responsible for the activation of the C–F bond. A large excess of arene nucleophile is shown to be necessary to achieve good yields.

Key words alkynes, arenes, C–F bond activation, Friedel–Crafts reaction, HFIP, hydrogen bond, propargylation, propargylic fluoride

Alkynes are very valuable in both organic and medicinal chemistry,[1] one of the reasons being that they can easily be transformed into new highly desirable functionalities. While they are well-known substrates for hydrogenation[2] and hydroboration[3] reactions, for example, their reactivity goes far beyond that. This is notably shown by the advent of gold-catalyzed nucleophilic additions,[4] Sonogashira cross-coupling reactions,[5] alkyne click chemistry,[6] and alkyne metathesis.[7]

Among motifs featuring a carbon–carbon triple bond, an intriguing case is that of 1-alkyl-1-aryl-2-alkynes, as it highlights a central carbon atom bonded to four substituents of differing formal hybridizations (H = *s*; alkynyl = *sp*; aryl = sp^2; alkyl = sp^3). Noteworthy, while not of wide use yet in medicinal chemistry, this motif has recently found applications in the development of dihydrofolate reductase inhibitors.[8] However, to this day, only a few methods allow the preparation of 1-alkyl-1-aryl-2-alkynes, most of them relying on propargylic substitution reactions. As part of a Nicholas reaction, $Co_2(CO_6)$-complexed propargylic alcohols were reacted with aromatic nucleophiles in presence of an acid (Scheme 1, a),[9] while aromatic propargylation with propargylic alcohols[10] and acetates[11] was carried out under transition-metal catalysis (Scheme 1, b) via either cationic or metal-allenylidene intermediates. Likewise, propargylic allylation was shown to be an appropriate strategy (Scheme 1, c).[12–15] The asymmetric Negishi cross-coupling of propargylic halides and carbonates with arylzinc reagents also allowed the preparation of enantioenriched 1-alkyl-1-aryl-2-alkynes (Scheme 1, d).[16] Finally, aryl sulfoxides underwent



Scheme 1 Known methodologies for the preparation of 1-alkyl-1-aryl-2-alkynes via propargylic substitution reactions and present work. R = alkyl chain; L.A. = Lewis acid; B.A. = Brønsted acid; * = enantioenriched stereocenter; HBD = hydrogen-bond donor.

ortho propargylation with propargylic silanes via an interrupted Pummerer–allenyl thio-Claisen rearrangement sequence (Scheme 1, e).[17] Overall, compared to their allylic and benzylic counterparts, propargylic substitution reactions are much less developed,[18] and propargylic[10c,19] and Meyer–Schuster[19b,20] rearrangements are processes that sometimes compete.

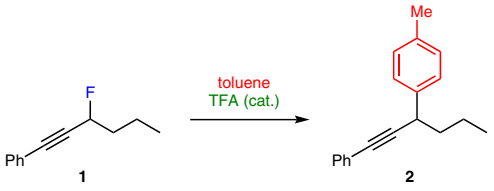
Our group has a longstanding interest in the activation of the C–F bond by means of hydrogen bonding.[21,22] This has led us to the development of the Friedel–Crafts reaction of benzylic fluorides using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as the activator, which allowed the preparation of diarylmethanes.[21c] This system was shown to be autocatalytic through the formation of HF, which is a strong hydrogen-bond donor (HBD). Recently, we have shown that addition of trifluoroacetic acid (TFA) to the reaction mixture results in the shortening of the induction period associated with the formation of the first HF molecules.[21e] We were now interested in applying these findings about the Friedel–Crafts reaction to other activated organic fluorides. Propargylic fluorides appeared to be ideal substrates (Scheme 1, f), as while the chemistry of the carbon–carbon triple bond is well known,[23] to our knowledge no example of C–F bond activation onto this motif has ever been reported. Herein, we thus describe the use of propargylic fluorides in a hydrogen-bond-promoted aromatic propargylation reaction.

Propargylic monofluorides were synthesized by means of nucleophilic addition of acetylides to aldehydes to form propargylic alcohols, followed by deoxofluorination with *N*,*N*-dimethylaminosulfur trifluoride (Me-DAST) (Scheme 2).[23a,24] Through this methodology, a series of (α-alkyl)propargylic fluorides was obtained, as well as a bis(propargylic) fluoride and a primary fluoride.[25]

Scheme 2 Two-step preparation of propargylic fluorides from acetylides

Secondary propargylic fluoride **1** was selected as the model substrate for the optimization of the Friedel–Crafts reaction with toluene as the nucleophile (Table 1). For the initial experiment, a 3:1 mixture of toluene and HFIP was chosen as the solvent, and TFA was added in catalytic amount. After one hour at room temperature, this resulted in the formation of 1-alkyl-1-aryl-2-alkyne **2** in 74% yield as an inseparable 1:10 mixture of *ortho*/*para* isomers (Table 1, entry 1). We next sought to reduce the amount of arene nucleophile. The use of 25 equivalents of toluene while keeping HFIP as the solvent resulted in a decrease of the yield down to 31% (Table 1, entry 2). Lowering the temperature to 0 °C had little effect on side-product formation, but resulted in improved *ortho*/*para* selectivity (Table 1, entry 3), whereas running the reaction at –30 °C slowed it down to the point where full conversion had not occurred after 18 hours (Table 1, entry 4). As *ortho*/*para* selectivity was not the main concern of this study, we arbitrarily chose to run subsequent reactions at room temperature as shorter induction periods were preferred. Using CH_2Cl_2 (Table 1, entry 5) and $CHCl_3$ (Table 1, entry 6) as 1:1 mixtures with HFIP as solvent resulted in similar yields with slightly improved *ortho*/*para* selectivity. Increasing the CH_2Cl_2/HFIP ratio to 4:1 (Table 1, entry 7) and 10:1 (Table 1, entry 8) resulted in better yields, the latter giving rise to a 74% yield (*ortho*/*para* = 1:9.2). However, the longer induction period associated with the smaller amount of HFIP had to be counterbalanced with longer reaction times. When decreasing further the amount of HFIP to a 20:1 ratio (Table 1, entry 9) or by simply omitting it (Table 1, entry 10), lower yields and *ortho*/*para* selectivities were obtained. Keeping the 10:1 CH_2Cl_2/HFIP mixture as the solvent, but lowering the tem-

Table 1 Optimization of the Friedel–Crafts Reaction of Propargylic Fluoride **1** with Toluene



Entry	Toluene (equiv)	TFA (mol%)	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
1	71[b]	5	toluene/HFIP (3:1)	r.t.	1	74 (1:10)
2	25	5	HFIP	r.t.	1	31 (1:13)
3	25	5	HFIP	0	1	39 (1:20)
4	25	5	HFIP	–30	18	35[c](1:19)
5	25	5	CH_2Cl_2/HFIP (1:1)	r.t.	1	36 (1:12)
6	25	5	$CHCl_3$/HFIP (1:1)	r.t.	1	40 (1:13)
7	25	5	CH_2Cl_2/HFIP (4:1)	r.t.	18	59 (1:9.0)
8	25	5	CH_2Cl_2/HFIP (10:1)	r.t.	18	74 (1:9.2)
9	25	5	CH_2Cl_2/HFIP (20:1)	r.t.	18	61 (1:7.6)
10	25	5	CH_2Cl_2	r.t.	18	54 (1:8.0)
11	25	5	CH_2Cl_2/HFIP (10:1)	0	18	57 (1:12)
12	25	0	CH_2Cl_2/HFIP (10:1)	r.t.	18	65 (1:8.7)
13	25	5	CH_2Cl_2/HFIP (10:1)	r.t.	1	54 (1:9.0)
14	25	0	CH_2Cl_2/HFIP (10:1)	r.t.	1	0

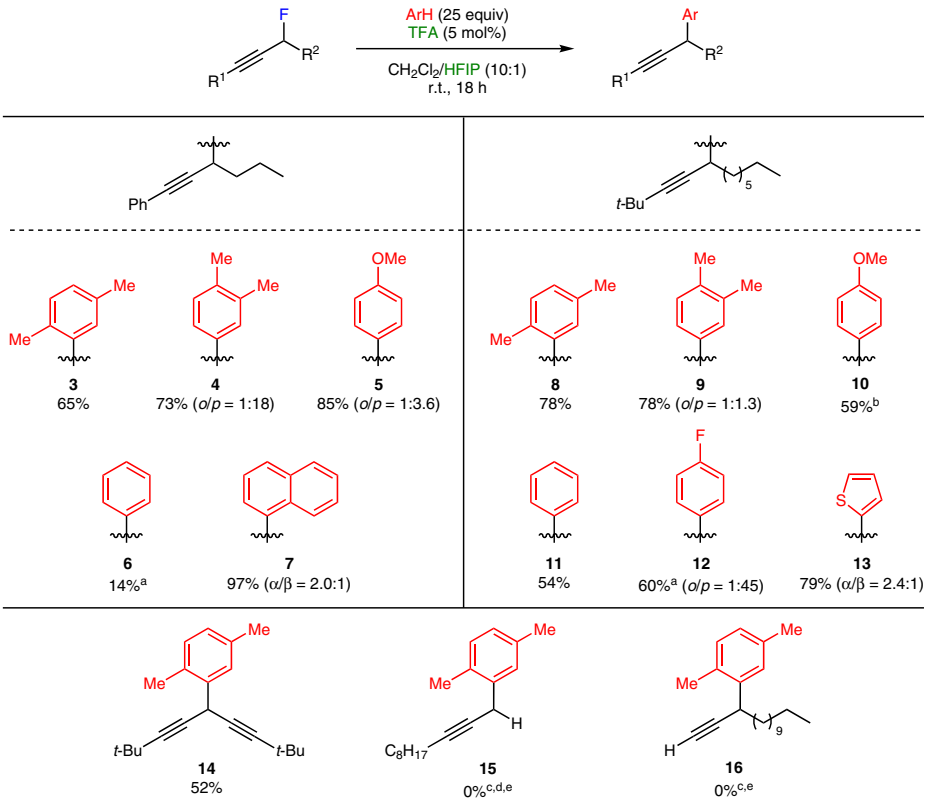
[a] Product isolated as an inseparable mixture of *ortho*/*para* isomers. The *ortho*/*para* ratio is given in parentheses and was determined by ^{1}H NMR analysis by comparing integrations for propargylic protons.
[b] Corresponds to the amount of toluene in the solvent mixture at a concentration of propargylic fluoride of 0.1 M.
[c] Incomplete conversion (ca. 90% as estimated by ^{1}H NMR analysis).

perature to 0 °C, resulted in a lower 54% yield, albeit with greater *ortho*/*para* selectivity (Table 1, entry 11). Lastly, we wanted to assess the beneficial or detrimental effect of TFA on yields and also its ability to accelerate the reaction. Performing the reaction at room temperature in absence of TFA resulted in a somewhat lower yield of 65% with similar *ortho*/*para* selectivity (Table 1, entry 12). The effect on the induction period was shown by stopping the reaction after one hour.

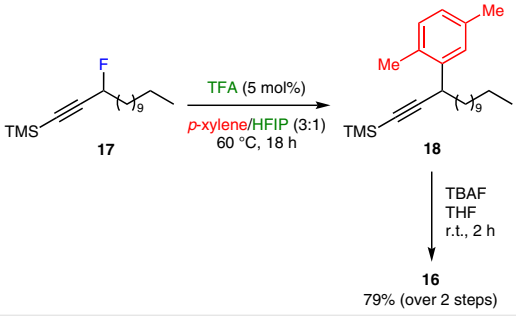
Indeed, while the reaction with TFA afforded **2** in 54% yield (Table 1, entry 13), no conversion was observed in the absence of TFA (Table 1, entry 14). In view of all the data, the reaction conditions outlined in entry 8 (arene: 25 equiv; TFA: 5 mol%; CH_2Cl_2/HFIP (10:1), r.t., 18 h) were determined as the optimal ones.

With the optimized conditions in hand, the scope of the transformation was studied (Scheme 3). A selection of arenes of varying electronic properties reacted well with secondary propargylic fluorides featuring a nonterminal acetylenic unit to form 1-alkyl-1-aryl-2-alkynes **3**–**13** in mostly good yields. Weaker nucleophiles such as benzene and fluorobenzene generally had to be used as co-solvents to overcome their lesser nucleophilicity. Even so, the reaction between **1** and benzene led to a poor 14% yield of **6**, as attack onto the phenyl of another propargylic fluoride was predominant. A bispropargylic fluoride was also shown to be a suitable substrate, as exemplified by the formation of **14** in 52% yield. When a primary propargylic fluoride was treated under the same reaction conditions with *p*-xylene as the nucleophile, the starting material remained intact, and, even when the reaction was heated up to 60 °C in HFIP, **15** was never observed. Similarly, when the reaction was carried out with a terminal propargylic fluoride (R^1 = H), no conversion into **16** was observed, even at elevated temperatures. However, under similar reaction conditions, a TMS-protected propargylic fluoride (R^1 = TMS, **17**) reacted with *p*-xylene so that **18** was formed, albeit with partial fluoride-induced TMS deprotection to the terminal acetylene. Subsequent treatment with TBAF completed the deprotection so that **16** was obtained in 79% yield over two steps (Scheme 4).

The fact that a primary propargylic fluoride did not react supports the claim that the reaction presumably goes through the intermediacy of a carbocation, as is the case for benzylic fluorides.[21a] Indeed, the developing primary carbocation is presumably too high in energy for the C–F bond to

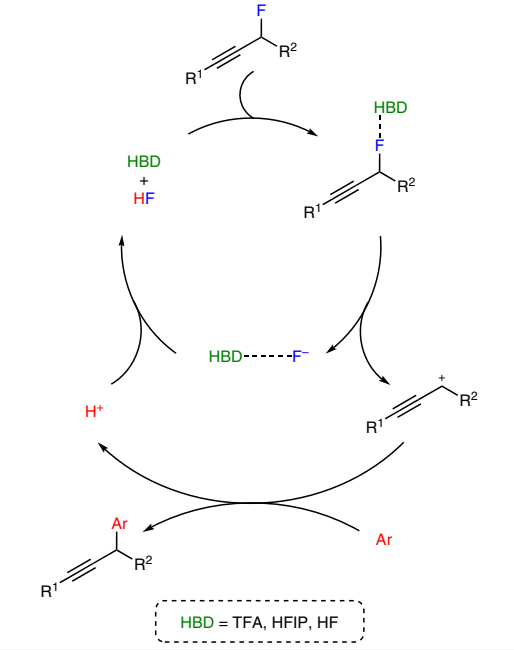


Scheme 3 Scope of the hydrogen-bond-promoted Friedel–Crafts reaction of propargylic fluorides. The yields given are for isolated products, and the ratio of isomers is given in parentheses with the major isomer shown. [a] The reaction was carried out using arene/HFIP (3:1) as the solvent. [b] The reaction was carried out using CH_2Cl_2/HFIP (3:1) as the solvent. [c] The reaction was carried out at 60 °C. [d] The reaction was carried out using HFIP as the solvent. [e] No conversion.



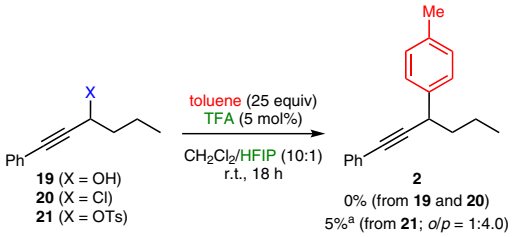
Scheme 4 Friedel–Crafts reaction of TMS-protected propargylic fluoride **17**

break, which would account for the lack of reactivity under the reaction conditions. Also in analogy with benzylic fluorides, TFA, the best HBD initially in the system, would catalyze the abstraction of the first fluoride. Electrophilic aromatic substitution would follow, ultimately generating the desired 1-alkyl-1-aryl-2-alkyne and HF. This HF, a better HBD than TFA, would in turn catalyze the Friedel–Crafts reaction at an even faster rate, making the transformation autocatalytic (Scheme 5).



Scheme 5 Proposed mechanism; HBD = hydrogen bond donor

Finally, we desired to assess the selectivity of this system towards C–F bond activation. We thus exposed propargylic substrates featuring either a better hydrogen-bond acceptor (propargylic alcohol **19**) or a better leaving group (propargylic chloride **20** and propargylic tosylate **21**) to the optimized reaction conditions (Scheme 6), upon which no conversion was observed for **19**[26] and **20**. Conversely, **21** was too reactive[27] and **2** was formed in 5% yield albeit full conversion of the starting material, with what appear as elimination and polymerization side reactions prevailing over the desired reactivity.



Scheme 6 Reactivity of other propargylic substrates. [a] Estimated by ^{1}H NMR analysis using 1,4-dimethoxybenzene as an internal standard.

To summarize this work, we have demonstrated that the C–F bond of secondary propargylic fluorides can be activated by means of hydrogen bonding.[28] The resulting carbocationic intermediate was trapped with arene nucleophiles to form 1-alkyl-1-aryl-2-alkynes in what is essentially a Friedel–Crafts-type propargylation reaction. A large excess of arene nucleophile is, however, necessary to control the reactivity.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589057.

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(25) All our efforts towards the preparation of an (α-aryl)propargylic fluoride failed as spontaneous decomposition kept occurring upon purification. Since decomposition only occurred after purification, a sample of crude (α-aryl)propargylic fluoride was directly engaged in a Friedel–Crafts reaction. However, decomposition still prevailed over the desired reactivity when using CH_2Cl_2/HFIP (30:1) as the solvent.

(26) At this point, the reasons for the absence of reaction with alcohol **20** are not understood. Our current hypothesis is that **20** is involved in a strong hydrogen-bond network, as an alcohol is capable, at the same time, of accepting and donating hydrogen bonds, with HFIP and/or TFA, which would overall protect it from further reaction. For examples of hydrogen bonded complexes with HFIP, see: (a) Berrien, J.-F.; Ourévitch, M.; Morgant, G.; Ghermani, N. E.; Crousse, B.; Bonnet-Delpon, D. *J. Fluorine. Chem.* **2007**, *128*, 839. (b) Berkessel, A.; Adrio, J. A.; Hüttenhain, D.; Neudörfl, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 8421. (c) Further experiments were performed and no reaction was observed when running the reaction at r.t. or 40 °C using either 5 or 50 mol% of TFA. At best, a low conversion (ca. 13%) to the trifluoroacetate of **20** was observed under more forcing conditions (i.e., TFA (50 mol%), DCE/HFIP (9 :1), 70 °C, 18 h).

(27) Compound **21** principally led to side reactions even under reaction conditions where HFIP was omitted, affording **2** in 29% NMR yield (*o*/*p* = 1:7.7). It should also be mentioned that **21** was also subject to rapid decomposition during column chromatography or during evaporation postpurification.

(28) **Representative Procedure for the Friedel–Crafts Reaction of Propargylic Fluorides – Synthesis of 1-Methyl-4-(1-phenylhex-1-yn-3-yl)benzene (2)**

A solution of TFA (8.7 µL, 0.114 mmol) in CH_2Cl_2 (13 mL) was prepared. 3-(Fluorohex-1-ynyl)benzene (**1**, 40 mg, 0.227 mmol) was then charged in a vial and dissolved in this TFA/CH_2Cl_2 solution (1.3 mL, resulting in 5 mol% of TFA). Toluene (0.60 mL, 5.68 mmol) was added, followed by HFIP (0.13 mL). The resulting solution was stirred at r.t. for 18 h. The reaction was quenched with sat. $NaHCO_3$ and stirred until no more gas evolved. It was then extracted with CH_2Cl_2 (3×). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The desired product (41.5 mg, 74%, *o*/*p* = 1:9.2) was isolated as a colorless oil by flash chromatography using hexanes. IR (ATR, ZnSe): ν = 2957, 2925, 2871, 1686, 1599, 1450, 1281, 812, 754, 689 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.57 (d, 0.11 H, minor, *J* = 7.7 Hz) 7.44–7.42 (m, 2 H), 7.31–7.24 (m, 4.89 H), 7.14 (d, 2 H, *J* = 7.8 Hz), 4.04 (dd, 0.11 H, minor, *J* = 9.1, 5.1 Hz), 3.81 (dd, 0.89 H, major, *J* = 8.4, 6.1 Hz), 2.39 (s, 0.32 H), 2.34 (s, 2.68 H), 1.85–1.72 (m, 2 H), 1.59–1.44 (m, 2 H), 0.99–0.93 (m, 3 H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 139.5, 136.3, 131.8, 130.6 (minor), 129.3, 128.3, 127.8, 127.7 (minor), 127.5, 126.7 (minor), 126.4 (minor), 124.0, 92.1, 83.1, 41.0, 39.4 (minor), 38.0, 34.7 (minor), 29.9 (minor), 21.2, 21.1 (minor), 20.8, 19.4 (minor), 14.0; ESI-HRMS: *m*/*z* calcd for $C_{19}H_{21}[M + H]^+$: 249.1638; found: 249.1634