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PRELIMINARY NOTE

Palladium/Cuprous Iodide Catalyzed Coupling of Substituted Tetrafluorophenyl Halides With 1-Alkynes

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SUMMARY

In the presence of cuprous iodide, the palladium catalyzed coupling reaction of substituted tetrafluorophenyl halides with 1-alkynes gives the corresponding fluoroaryl alkynes in good to excellent yields under mild conditions. Both 4-substituted (methoxy, N,N-dimethylamino, morpholino) tetrafluorophenyl iodides and bromides work well, and alkyl, trimethylsilyl, phenyl, hydroxy, and ether functionalities in the alkyne moiety are tolerated under the reaction conditions. This methodology provides a practical synthesis of substituted fluorinated aryl alkynes.

Fluorinated aryl acetylenes have been demonstrated to be important substances in organic synthesis and material science [1,2]. However, the lack of general methodology for the preparation of this class of compounds has hindered the progress of their development. Recently, we reported the preparation of fluorinated enynes [3] via the reaction of fluorinated vinyl iodides with 1-alkynes in triethylamine solvent catalyzed by palladium/Cu(I)I.

$$\mathrm{RC{\equiv}CH} \quad + \quad \mathrm{R'CF{=}CFI} \xrightarrow[\substack{\mathrm{CuI} \\ \mathrm{Et_3N} \\ \mathrm{RT\text{-}\ 70^{0}C}}]{\mathrm{Pd(PPh_3)_2Cl_2}} \underset{50\text{-}87\%}{\mathrm{RC{\equiv}C\text{-}CF{=}CFR'}}$$

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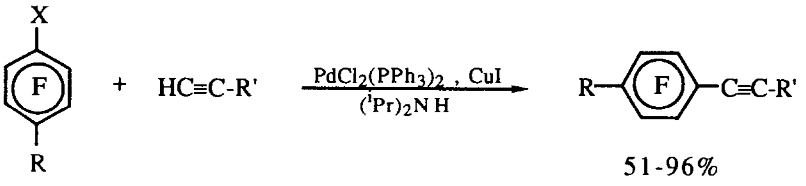
The success of the enyne synthesis prompted us to explore the application of this methodology to fluorinated aryl halides. We now wish to report a facile and practical route for the preparation of substituted tetrafluorophenyl alkyne derivatives.

Tatlow and co-workers [4] have reported that fluorinated aryl acetylenes could be prepared from the reaction of acetylides with polyfluorinated aromatics. Although the use of polyfluorinated benzenes with activating substituents provided good yields of alkynes, polyfluorinated benzenes with deactivating groups did not undergo the desired reaction. In addition, the harsh reaction conditions for this preparation precluded the use of some functionalities.

In contrast to fluorinated aryl alkynes, non-fluorinated aryl alkynes have been prepared via direct reaction of aryl halides with 1-alkynes under palladium catalysis, in the presence of Cu(I)I, under mild conditions [5-8]. Since related conditions had demonstrated success in the synthesis of fluorinated enynes [3], we were encouraged to try a similar approach with fluorinated aryl halides as a route to fluorinated aryl acetylenes. While this work was in progress, a similar approach with iodopentafluorobenzene has also been recently reported [9].

We have found that coupling reactions of fluorinated aryl halides proceed readily with 1-alkynes in the presence of bis(triphenylphosphine)palladium dichloride and cuprous iodide in diisopropylamine to afford the fluorinated aryl alkynes in good to excellent yields under mild conditions.

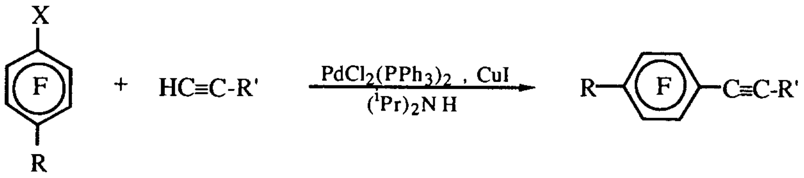


The reaction works well with 4-methoxy-, 4-N,N-dimethylamino-, and 4-morpholino-tetrafluorophenyl iodides. A variety of functionalities in the alkynes are tolerated under the reaction conditions. With 1,4-dibromotetrafluorobenzene and α,ω-diynes, disubstitution occurs to readily afford the 1,4-dialkynyltetrafluorobenzenes. These results are summarized in Table I.

In a typical experimental procedure, a dry, 50 mL, two-necked, round-bottomed flask equipped with a septum, magnetic stir-bar, and a water condenser topped with a nitrogen inlet, was charged with 1.5 g (5.0 mmol) of 4-methoxy-1-iodotetrafluorobenzene, 0.5 g (6.0 mmol) of 1-hexyne, 0.18 g (5.0 mol%) of $PdCl_2(PPh_3)_2$, 0.03 g (3.0 mol%) of CuI, and 20 mL of $(^iPr)_2NH$. The solution was stirred under a nitrogen atmosphere and heated in an oil bath at 70°C. After complete consumption of starting material (determined by ^{19}F NMR analysis of the reaction mixture) the mixture was cooled to room temperature, gravity filtered, and the solid washed with 20 mL of CH_2Cl_2. The filtrate was concentrated by rotary evaporation, then loaded onto a chromatography column packed with silica gel, and the product was eluted with hexane. Thin-layer chromatography was used to monitor the elution of the product. The fraction which contained the product was concentrated by rotary evaporation. Any last traces of solvent were removed under vacuum. The yield was 1.1g (81%), GLPC purity 95%, of 1-(4-methoxytetrafluorophenyl)-1-hexyne. ^{19}F NMR ($CDCl_3$, $CFCl_3$): δ -139.6 ppm (m); -159.1 ppm (m); ^1H NMR ($CDCl_3$, TMS): δ 4.09 ppm (3H; t; J= 1.4 Hz); 2.50 ppm (2H; t; J= 7.0 Hz); 1.63 ppm (2H; m); 1.52 ppm (2H; m); 0.97 ppm (3H; t; J= 7.0 Hz); ^{13}C NMR ($CDCl_3$, TMS): δ 149.65 (m); 146.30 (m); 142.82 (m); 139.62 (m); 138.60 (m); 102.83 (s); 98.95 (t, J= 32.0 Hz); 65.65 (s); 62.30 (s); 30.70 (s); 22.38 (s); 20.04 (s); 13.97 (s) ppm. IR (CCl_4): 2963 (s); 2875 (m); 2247 (w); 1646 (w); 1510 (s); 1491 (s); 1430 (s); 1380 (w); 1312 (w); 1203 (m); 1166 (m); 1076 (s); 996 (s); 992 (s) cm^{-1}. MS: 260 ($M^{+\cdot}$, 43.61), 245 (100.00), 217 (95.56), 202 (38.06), 193 (27.22), 174 (23.61), 105 (15.69), 43 (63.61).

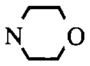
TABLE I

Pd/CuI Catalyzed Reaction of 1-Alkynes with Fluorinated Aryl Halides



R = 1) OMe X = I, Br

2) $N(Me)_2$

3) 

4) Br

Entry	R	X	R'	Temp[a] (°C)	Time[b] (hrs)	Yield[c,d] (%)
1	1	I	$-(CH_2)_3-CH_3$	70	2	81
2	1	I	$-(CH_2)_4-CH_3$	90	3	79
3	1	I	$-(CH_2)_5-CH_3$	70	2	95
4	1	I	$-(CH_2)_6-CH_3$	70	2	96
5	1	I	$-C_6H_5$	70	2	74
6	1	I	$-(CH_2)_3-CN$	90	2	96
7	1	I	$-CH_2-OC_6H_5$	90	12	80
8	1	I	$-CH_2-OH$	90	12	73
9	2	I	$-CH(OH)-CH_3$	60	4	67
10	2	I	$-C(CH_3)_2-OH$	80	2	70
11	3	I	$-(CH_2)_3-CH_3$	80	24	89
12	3	I	$-C_6H_5$	70	12	85
13	4	Br	$-(CH_2)_3-CH_3$ [e]	80	9	74
14	1	I	$-(CH_2)_3-$ [f]	80	12	65

[a] Oil bath temperature

[b] Reaction time

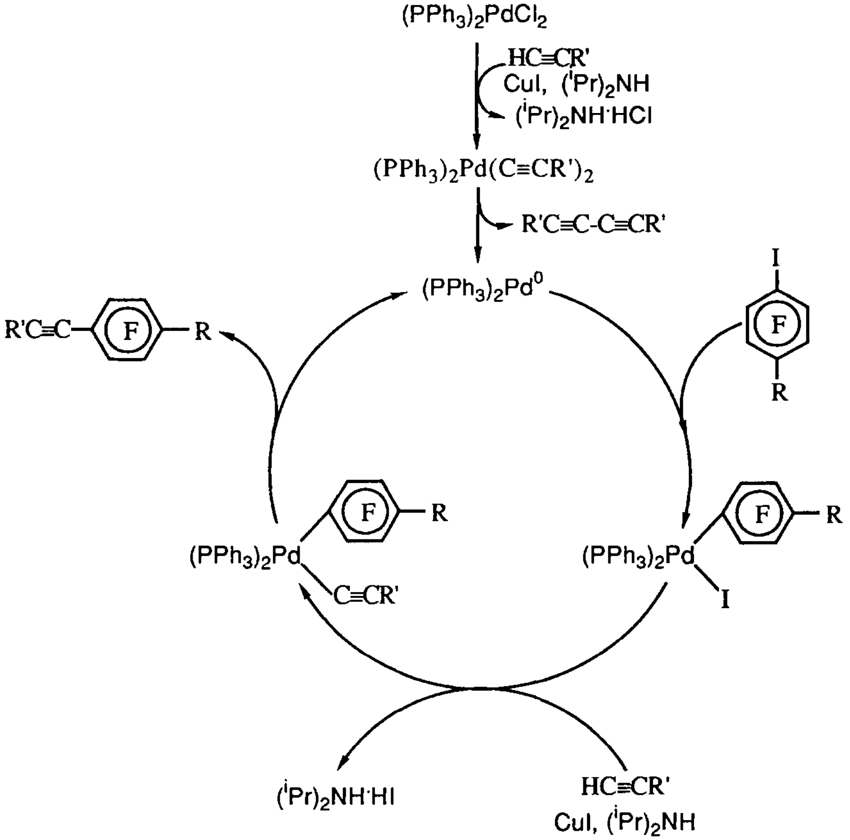
[c] Isolated yields

[d] All products gave satisfactory ^{19}F, ^{1}H, and ^{13}C NMR, FT-IR, and GC/MS data.

[e] 1,4-dialkynyl tetrafluorobenzene

[f] α,ω-diyne

When triethylamine was used as the base in the 1,4-dibromotetrafluorobenzene reaction with diynes, a mixture of 1,4-dialkynyl tetrafluorobenzene and 4-bromotetrafluorophenyl alkyne was observed by ^{19}F NMR analysis of the reaction mixture.



Scheme 1.

Although a detailed mechanistic study has not been carried out, it seems likely that the coupling reaction proceeds through a reactive Pd^0 intermediate via a series of oxidative addition and reductive elimination steps as outlined in Scheme I. The alkylation of the initial catalyst or the oxidative adduct of the in-situ generated Pd^{0} catalyst in the catalytic cycle is catalyzed by cuprous iodide in the presence of diisopropylamine.

In conclusion, a useful, practical coupling reaction of substituted tetrafluorophenyl halides with a wide variety of alkynes under mild conditions has been described. The ready availability of the catalysts, and alkyne precursors, the ease of preparation of substituted fluorinated aryl halides, the simplicity of the experimental procedure, and the high yields obtained make this approach a useful route to fluorinated aryl alkynes.

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