

A FACILE, GENERAL METHOD FOR THE PREPARATION OF FLUORINATED ENYNES

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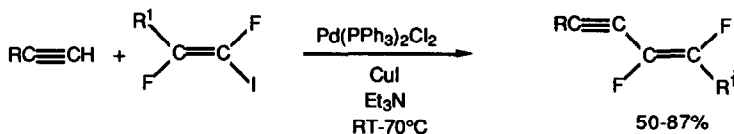
Abstract: Fluorinated vinyl iodides, $R^1CF=CFI$ [where $R^1=F, CF_3, Ph, (iPrO)_2P(O)$], couple directly with 1-alkynes in the presence of palladium and cuprous iodide in triethylamine to give excellent yields of the fluorinated enynes.

Recent reports have demonstrated the importance of enynes in organic synthesis. Conjugated enynes react selectively with electrophiles at the double bond to provide an efficient method for the assembly of multifunctional molecules¹ and they have been utilized as essential components in the synthesis of natural products². Thus, one would anticipate that fluorine-containing enynes would also be useful as building blocks to partially fluorinated multifunctional molecules or partially fluorinated natural products. However, the lack of general synthetic methodology for the preparation of fluorinated enynes has hampered development along these lines. In this communication we wish to describe a facile, direct, and practical method for the general preparation of this class of compounds.

Recently, Normant reported that fluorinated enynes can be prepared by the Pd-catalyzed coupling reaction of either F-containing vinyl iodides with terminal alkynyl zinc reagents, or 1-haloalkynes with fluorinated vinyl zinc reagents³. Although this procedure provided the enynes in reasonable yields, this approach necessitated either the prior generation of the requisite alkynyl zinc reagent, fluorinated vinyl zinc reagent or the 1-haloalkyne.

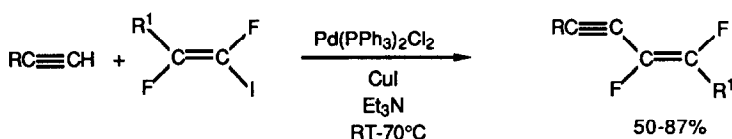
In contrast to Normant's approach, non-fluorinated enynes have been prepared *via* the direct reaction of vinyl halides with terminal alkynes by catalysis with palladium⁴, cuprous iodide⁵ or both⁶, and this direct entry to enynes has been applied to natural product synthesis⁷. Consequently, it was of interest to determine whether the direct catalyzed coupling reaction of fluorinated vinyl iodides with terminal alkynes could be accomplished, thus avoiding the prior generation of either an alkynyl or a fluorovinyl zinc reagent or a 1-haloalkyne.

We have now found that direct coupling of fluorinated vinyl iodides or substituted fluorinated vinyl iodides proceeds readily with 1-alkynes in the presence of bis(triphenylphosphine)palladium dichloride and cuprous iodide in triethylamine to afford good yields of the desired conjugated enynes under mild conditions (RT to 70° C). The results of this exploratory study are summarized in Table I. The coupling reaction works well with perfluorovinyl,



as well as phenyl and phosphoryl substituted fluorinated iodides. In all cases, the stereochemistry in the vinyl iodide was preserved in the enyne product. In Table I, entry 11, the terminal dialkyne gave the dienyne when two equivalents of the vinyl iodide were employed. The reaction can also be carried out in a variety of solvents, such as DMF, DMSO, HMPA, CH₃CN, dioxane, chloroform, benzene and hexane with yields of 56-85%. In addition to bis(triphenylphosphine)palladium dichloride, bis(triphenylphosphine)palladium acetate or tetrakis(triphenylphosphine)palladium could also be utilized to catalyze the coupling process with cuprous iodide in triethylamine.

Table I Pd⁰-Catalyzed Reaction of 1-Alkynes with Fluorinated Vinyl Iodides



Entry	R	R ¹	Catalyst	Yield % ^{a,b}
1	n-C ₃ H ₇	F	Pd(PPh ₃) ₂ Cl ₂	50
2	n-C ₄ H ₉	F	Pd(PPh ₃) ₂ (OAc) ₂	69
3	n-C ₅ H ₁₁	F	Pd(PPh ₃) ₂ Cl ₂	59
4	n-C ₆ H ₁₃	F	Pd(PPh ₃) ₂ Cl ₂	66
5	Ph	F	Pd(PPh ₃) ₂ Cl ₂	53
6	Ph	Ph	Pd(PPh ₃) ₂ Cl ₂	73
7	n-C ₅ H ₁₁	CF ₃	Pd(PPh ₃) ₂ Cl ₂	62
8	n-C ₇ H ₁₅	CF ₃	Pd(PPh ₃) ₂ Cl ₂	67
9	Ph	(iPrO) ₂ P(O)	Pd(PPh ₃) ₂ Cl ₂	87
10	n-C ₆ H ₁₃	(iPrO) ₂ P(O)	Pd(PPh ₃) ₂ Cl ₂	77
11	HC≡C(CH ₂) ₄	CF ₃	Pd(PPh ₃) ₂ Cl ₂	49 ^c

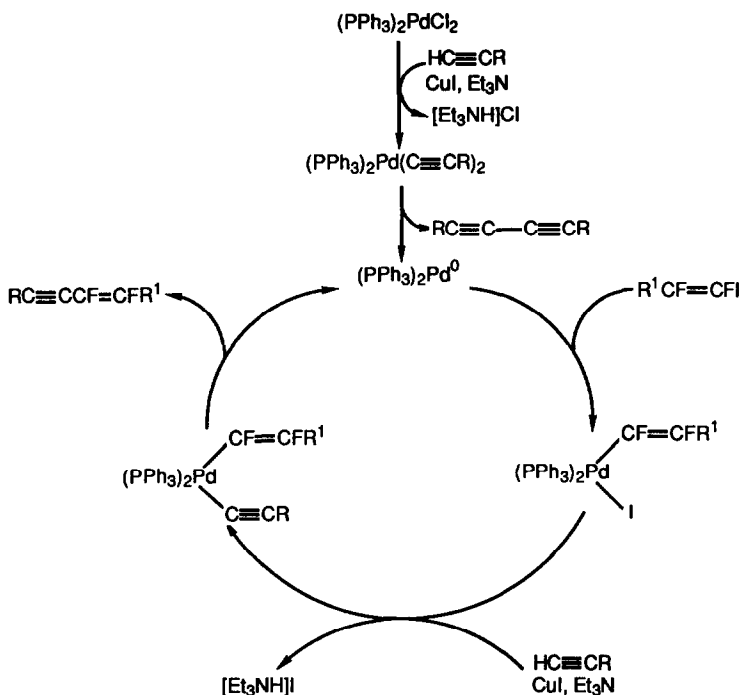
a) isolated yields

b) all products gave satisfactory ¹⁹F, ¹H NMR, IR, and MS data

c) two equivalents of *Z*-CF₃CF=CFI used; product is



Although a detailed mechanistic study has not been carried out, it seems likely that the coupling reaction proceeds through a reactive Pd⁰ intermediate *via* a series of oxidative addition and reductive elimination steps. The alkylation of the initial catalyst or the oxidative adduct of the *in situ* generated Pd⁰ catalyst in the catalytic cycle in Scheme I is catalyzed by cuprous iodide in the presence of triethylamine.



Scheme 1

In a typical experimental procedure, a two-necked flask fitted with a septum, stir bar and condenser topped with a nitrogen inlet was charged with 0.70 g (1 mmol) of Pd(PPh₃)₂Cl₂, 0.19 g (1 mmol) of CuI, and 30 mL of Et₃N. Then, 2.0 g (21 mmol) of 1-heptyne and 5.2 g (20 mmol) of *Z*-pentafluoropropenyl iodide⁸ were added to the catalytic mixture *via* syringe. The resultant mixture was stirred at room temperature for 6 hours. The volatile components of the reaction mixture were then removed *via* distillation at reduced pressure. The resulting mixture of triethylamine and enyne was added to 200 mL of 10% HCl. The organic layer was separated and the aqueous layer extracted with ether (2x100 mL). The combined organic layers were washed with water and dried over anhydrous MgSO₄. After evaporation of the ether, the residue was distilled to give 2.8 g (62%) of *E*-CF₃CF=CFC≡C(CH₂)₄CH₃, 100% GLPC purity, bp 116-118°C/80 mm Hg. ¹⁹F NMR (*vs.* CFCl₃) (CDCl₃): δ -68.2 ppm (dd, J=19.5 Hz, J=12 Hz, 3 F), -137.4 ppm (dq, J=139 Hz, J=19.5 Hz, J=5 Hz, 1 F), -165 ppm (dq, J=139 Hz, J=12 Hz, 1 F); ¹H NMR (CDCl₃) δ 2.46 ppm (m, 2 H), 1.58-1.32 ppm (m, 6 H), 0.93 ppm (t, J=6 Hz, 3H). IR: 2920 (s), 2850 (m), 2225 (m), 1680 (m), 1360 (s), 1270 (s), 1200-1150 (vs), 1060 (s) cm⁻¹. GC/MS: 226 (M⁺, 0.60), 197 (53.16), 127 (43.97), 119 (39.08), 115 (53.16), 55 (100), 41 (75.86).

The ready availability of suitable catalysts and alkyne precursors, the simplicity of the experimental procedure, and the mild reaction conditions make this direct preparation of fluorinated enynes an attractive entry to this class of partially fluorinated building blocks.

Acknowledgement

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