A Novel Synthesis of Trifluoromethylated Multi-Substituted Alkenes via Regio- and Stereoselective Heck Reaction of (*E*)-4,4,4-Trifluoro-1-phenyl-2-buten-1-one

Tsutomu Konno,* Shigeyuki Yamada, Akinori Tani, Tomotsugu Miyabe, Takashi Ishihara

Department of Chemistry and Materials Technology, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan
Fax +81(75)7247580; E-mail: konno@chem.kit.ac.jp

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Abstract: Treatment of (*E*)-4,4,4-trifluoro-1-phenyl-2-buten-1-one with various aryldiazonium salts in the presence of a palladium catalyst led to a smooth Heck reaction, furnishing α-arylated adducts in good yields.

Key words: Heck reaction, aryldiazonium salts, fluoroorganic compounds

Much attention has been paid to fluorine-containing compounds as agrochemical and pharmaceutical agents due to the unique properties exerted by fluorine atom(s).[1] Fluoroalkyl groups increase lipophilicity allowing for easier drug transportation, cellular absorption, and improve binding within hydrophobic pockets of receptors.[2] Consequently, the development of novel synthetic methods for the preparation of fluorine-containing materials continues to be an important field of research in agricultural, medicinal, and organic chemistry.[3]

Among various types of fluoroorganic molecules, alkenes bearing a fluoroalkyl group, **A**, are one of the most valuable synthetic targets because they are found in the framework of biologically active materials, such as panomifnene (Figure 1).[4]

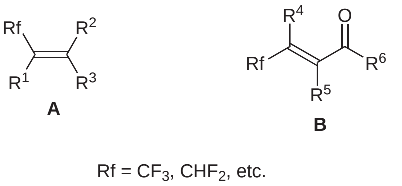
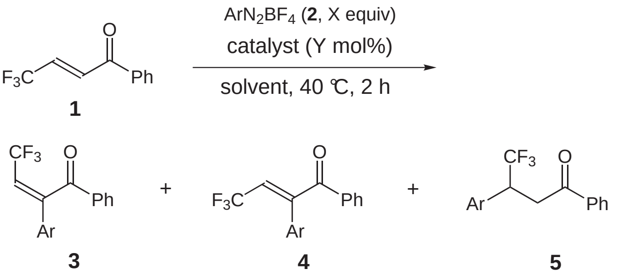


Figure 1

Although several synthetic methods for the preparation of such compounds have been developed by several groups[5] and us,[6] little is known on the stereoselective synthesis of multi-substituted β-fluoroalkylated-α,β-unsaturated carbonyl compounds **B**, which have been widely used as potent synthetic blocks, particularly as Michael acceptors for conjugate additions, or dienophiles and dipolarophiles for cycloaddition reactions.[7] In this communication, we wish to describe the first convenient synthesis of β-fluoroalkylated-α-aryl-α,β-unsaturated carbonyl compounds via a regio- and stereoselective Heck reaction of β-fluoroalkylated-α,β-unsaturated carbonyl compounds with various types of aryldiazonium salts.[8]

Our initial studies were focused on the Heck reaction of (*E*)-4,4,4-trifluoro-1-phenyl-2-buten-1-one (**1a**) with phenyldiazonium salt **2a** (Scheme 1, Table 1, Ar = Ph).



Scheme 1

Thus, treatment of **1a** with 1.2 equivalents of **2a** in the presence of 2.5 mol% $Pd_2(dba)_3 \cdot CHCl_3$ in THF at 40 °C for 2 hours gave the corresponding adduct **3a** in 4% yield, together with 90% of recovered starting material (Table 1, entry 1); only the *Z*-isomer was detected.[9] Various solvents, such as toluene, 1,4-dioxane, diethyl ether, and methanol, did not give satisfactory results (no reaction or low regioselectivity; Table 1, entries 2–5), however, the use of ethanol resulted in the formation of **3a** in 9% yield, as the sole product (Table 1, entry 6). Therefore, we further examined the reaction conditions in THF or EtOH. The addition of various types of phosphine ligands did not lead to an improvement in the yield of the reaction in THF (Table 1, entries 7–10). On the other hand, the reaction in refluxing THF afforded the Heck adducts **3** and **4** in a ratio of 92:8 in 24% combined yield (Table 1, entry 11). Though a prolonged reaction time as well as the use of 2.2 equivalents of **2a** did not bring about a significant change (Table 1, entries 12 and 13), the reaction with 2.2 equivalents of **2a** in the presence of 20 mol% palladium catalyst gave **3a** and **4a** in 61% yield (Table 1, entry 14). Additionally, the reaction with 4.4 equivalents of **2a** at reflux caused a significant improvement in the yield; **3a** and **4a** were obtained in 79% yield in a 90:10 ratio (Table 1, entry 16). We also investigated the reaction in ethanol as shown (Table 1, entries 17–21). In sharp contrast to the reaction in THF, the ligand effect was significant. Thus, when

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Table 1 Investigation of the Reaction Conditions

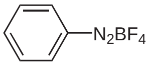
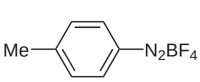
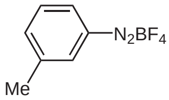
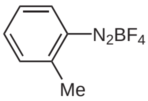
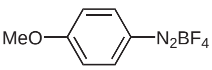
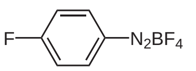
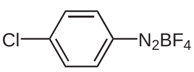
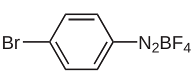
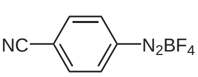
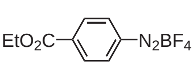
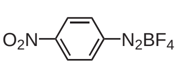
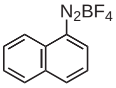
Entry	X (equiv)	Catalyst	Y (mol%)	Solvent	Yield[a] **3a** + **4a** (%)	Ratio[a] **3a**/**4a**	Yield[a] (%) **5a**	Recovery[a] (%) of **1a**
1	1.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$	5	THF	4	100:0	0	90
2	1.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$	5	Toluene	0	–	0	97
3	1.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$	5	1,4-Dioxane	10	80:20	2	67
4	1.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$	5	$\mathrm{Et_2O}$	0	–	0	89
5	1.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$	5	MeOH	10	80:20	0	35
6	1.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$	5	EtOH	9	100:20	3	90
7	1.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$ + 2 $\mathrm{PPh_3}$	5	THF	0	–	0	quant.
8	1.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$ + 2 P(*o*-Tol)$_3$	5	THF	0	–	0	93
9	1.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$ + 2 P(*c*-hex)$_3$	5	THF	2	100:20	0	85
10	1.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$ + dppe	5	THF	0	–	0	quant.
11[b]	1.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$	5	THF	24	92:8	4	59
12[b,c]	1.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$	5	THF	28	75:25	9	71
13[b]	2.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$	5	THF	8	88:12	2	90
14[b]	2.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$	20	THF	61	82:18	12	17
15[b]	3.3	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$	20	THF	63	83:17	12	22
16	4.4	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$	20	THF	79	90:10	11	2
17	2.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$	20	EtOH	51	92:8	3	32
18	2.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$ + 2 $\mathrm{PPh_3}$	20	EtOH	45	93:7	7	36
19	2.2	$[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$+ 2 P(*o*-Tol)$_3$	20	EtOH	82 (69)	94:6	11	0
20	2.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$ + 2 P(*c*-Hex)$_3$	20	EtOH	47	89:11	4	33
21	2.2	0.5 $[\mathrm{Pd_2(dba)_3\cdot CHCl_3}]$ + dppe	20	EtOH	17	88:12	0	76

[a] Determined by ^{19}F NMR spectroscopy. Isolated yield in parentheses.
[b] Carried out at reflux.
[c] Reaction time, 12 h.

P(*o*-Tol)$_3$ was used the starting material was completely consumed and the corresponding arylated adducts **3a** and **4a** were obtained in 82% yield in a ratio of 94:6 (Table 1, entry 18), though the Michael adduct **5a** also formed as a by-product. Additionally, bulky or bidentate ligands resulted in a significant decrease in the yield (Table 1, entries 20 and 21). With the optimum reaction conditions determined (Table 1, entries 16 and 19),[10] we conducted the Heck reaction with various types of aryldiazonium salts (Table 2).

Both *para*- and *meta*-substituted aryldiazonium salts participated well in the Heck reaction to give the corresponding adducts in good yields with a high *Z*-stereoselectivity (Tables 2, entries 3 and 5). When the reaction was carried out in THF at reflux, a slight decrease in the yield as well as the stereoselectivity was detected (Table 2, entries 4 and 6). Very interestingly, the Heck reaction with *ortho*-tolyl or *para*-anisyldiazonium salt in THF at reflux took place smoothly to afford the corresponding Heck adducts in 75% or 71% yield, respectively (Table 2, entries 8 and 10), whereas the reactions in ethanol at 40 °C resulted in very low yields of the products (Table 2, entries 7 and 9). Various halogen-substituted aryldiazonium salts successfully gave the desired materials in 62–74% yield with high *Z*-stereoselectivity, though the Michael adducts **5** formed in 10–20% yield (Table 2, entries 11–16). However, aryldiazonium salts substituted by stronger electron-withdrawing groups, such as cyano, ethoxycarbonyl, and nitro groups on the benzene ring, did not lead to satisfactory results when the reaction was performed in ethanol at 40 °C; the starting diazonium salt **2** was almost completely recovered (Table 2, entries 17, 19, and 21). Interestingly, the reaction with ethoxycarbonyl-substituted aryldiazonium salt in THF at reflux gave the Heck adducts **3** and **4** in 64% yield in a ratio of 80:20 (Table 1, entry 20). On the other hand, the reaction with the cyano- or nitro-substitut-

Table 2 The Heck Reaction with Various Aryldiazonium Salts

Entry	Diazonium salt	Method[a]	Yield[b] **3** + **4** (%)	Ratio[b] **3/4**	Yield[b] **5** (%)
1		A	82 (69)	94:6	11
2		B	79	90:10	11
3		A	57 (48)	93:7	10
4		B	35	86:14	9
5		A	73 (57)	95:5	9
6		B	48	88:12	10
7		A	9	44:56	0
8		B	75 (63)	48:52	6
9		A	5	100:0	4
10		B	71 (55)	92:8	17
11		A	74 (58)	89:11	15
12		B	69	8:20	13
13		A	67 (50)	89:11	10
14		B	68	79:21	19
15		A	65 (74)	88:12	12
16		B	62	79:21	19
17		A	0	–	0
18		B	0	–	trace
19		A	28	86:16	6
20		B	64 (63)	80:20	15
21		A	11	100:0	0
22		B	38	69:31	11
23		C	41	73:27	10
24		B	23	83:17	0
25		B	36	58:42	9

[a] Method A: **2** (2.2 equiv), EtOH, 40 °C, 2 h; Method B: **2** (4.4 equiv), THF, reflux, 2 h; Method C: **2** (4.4 equiv), THF, reflux, 10 h.

[b] Determined by ^{19}F NMR spectroscopy. Isolated yields are in parentheses.

ed aryldiazonium salts in THF did not lead to dramatic changes (Table 2, entries 18, 22, and 23). Additionally, the 1-naphthyldiazonium salt gave very poor results (Table 2, entries 24 and 25).

In summary, we have developed an easy access to a variety of β-fluoroalkylated-α-aryl-α,β-unsaturated carbonyl compounds via a regio- and stereoselective Heck reaction with readily available aryldiazonium salts. Various aryldiazonium salts bearing an electron-donating group and halogens at the *para*-, *meta*-, or *ortho*-position of the benzene ring could participate nicely in the Heck reaction, the corresponding *Z*-isomer was formed preferentially. On the other hand, aryldiazonium salts having an electron-withdrawing group or bulky salts did not give satisfactory results.

Further investigations of the Heck reaction of various fluoroalkylated alkenes are currently underway in our laboratory.

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(9) The stereochemistry was determined on the basis of the chemical shifts in the ^{1}H NMR spectra according to the literature; see ref. 8.

(10) **Method A; Typical Procedure**: To a solution of $Pd_2(dba)_3 \cdot CHCl_3$ (10 mol%) and P(*o*-Tol)$_3$ (40 mol%) in EtOH was added (*E*)-4,4,4-trifluoro-1-phenyl-2-buten-1-one (50 mg, 0.25 mmol) and *p*-fluorophenyldiazonium tetrafluoro-borate (115 mg, 0.55 mmol) at r.t., and the resulting mixture was stirred at 40 °C for 2 h. After cooling to r.t., the mixture was poured into a sat. aq solution of NH_4Cl, and the resulting mixture was extracted three times with Et_2O. The combined organic layers were washed with a sat. solution of NaCl, dried over anhyd Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding Heck adduct (43 mg, 0.45 mmol; *Z*/*E*, 89:11; 58% yield).
Z-Isomer: ^{1}H NMR ($CDCl_3$) δ = 6.15 (q, *J* = 7.1 Hz, 1 H), 7.02–7.07 (m, 2 H), 7.38–7.47 (m, 4 H), 7.50–7.60 (m, 1 H), 7.86–7.92 (m, 2 H). ^{19}F NMR ($CDCl_3$): δ = –59.1 (d, *J* = 7.1 Hz, 3 F), –110.2 to –110.3 (m, 1 F).
E-Isomer: ^{1}H NMR ($CDCl_3$): δ = 6.09 (q, *J* = 7.1 Hz, 1 H). ^{19}F NMR ($CDCl_3$): δ = –57.3 (d, *J* = 7.1 Hz, 3 F), –111.78 to –111.84 (m, 1 F).
Method B: The reaction was carried out in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ in THF at reflux. The workup was the same as Method A.