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Heck reaction with 3-fluoro-3-buten-2-one

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ABSTRACT

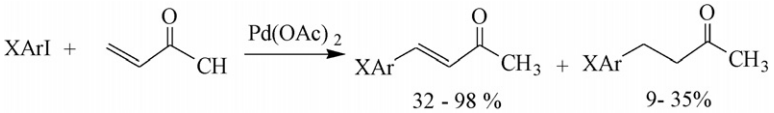
3-Fluoro-3-buten-2-one (**2**) is readily prepared from 1-fluoro-1-chloro-2-methoxy-2-methylcyclopropane (**1**) in 82% yield by heating the cyclopropane in aqueous quinoline solution. Ketone **2** reacts with aryl iodides (**3**) in a Heck reaction catalyzed by $Pd(OAc)_2$ to give *Z*-3-fluorobenzalacetones (**4**) in 36–86% yield.

1. Introduction

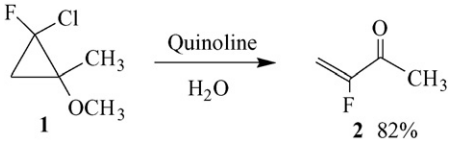
The Heck reaction holds a prominent position among the palladium-catalyzed carbon–carbon bond forming reactions [1,2]. Although a vast amount of information is available for the Heck reactions with regard to substrates and reaction condition [3], very little is known about the use of fluorinated alkene substrates. In 1991, Heitz and Knebelkamp reported that palladium-catalyzed coupling of aryl iodides with 1,1-difluoroethene showed coupling accompanied mostly by loss of a fluorine atom [4]. Ichikawa et al. reported in 2006 several intramolecular cyclizations of 1,1-diffluoroalkenes with palladium catalysis to also gave products with loss of a fluorine atom [5].

2. Results and discussion

In 2003, Cacchi et al. reported that coupling reactions of methyl vinyl ketone with aryl iodides gave good yields of the Heck product accompanied by small amounts of a conjugate addition product [6].



Our interest in new fluorinated intermediates for use in synthetic chemistry led us to develop a Heck procedure with, 3-fluoro-3-buten-2-one (**2**), a fluorinated analog of methyl vinyl ketone. Ketone **2** was previously prepared by Schlosser and co-workers [7] in 50% yield by heating **1** in water. We improved the preparation of the **2** from the cyclopropane **1**, by heating **1** in a solution of quinoline and water to produce **2** in 82%. The ketone distils from the reaction in 82% yield and high purity. If water is not added to the solution 2-fluoro-3-methoxy-1,3-butadiene is formed in 85% yield [8].



When the ketone **2** is subjected to palladium-catalyzed Heck coupling with several aryl iodides (**3**), new *Z*-3-fluorobenzalacetones (**4**) are obtained in high yields with the *Z*-configuration as determined from NMR coupling constants, $J = 36–39$ Hz. No evidence is found for the presence of conjugate addition products or *E* isomers.

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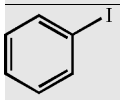
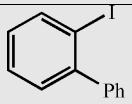
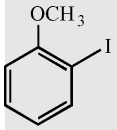
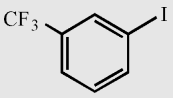
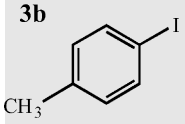
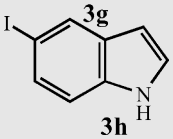
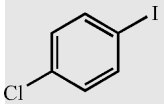
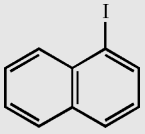
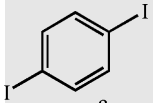
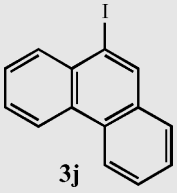
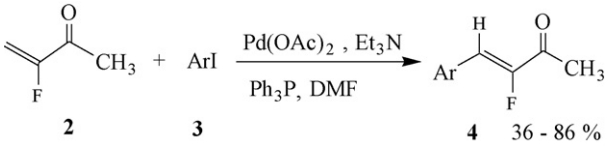
Table 1
Heck reaction products from **2**

ArI (**3**)	% 4	δF, *J* (Hz)	ArI (**3**)	% 4	δF, *J* (Hz)
 **3a**	86	−123.9 (33.9)	 **3f**	73	−126.8 (36.7)
 **3b**	82	−125.6 (37.7)		51	−124.4 (35.4)
 **3c**	75	−123.7 (33.6)	 **3h**	78	−123.8 (36.7)
 **3d**	62	−125.2 (36.6)	 **3i**	44	−124.0 (36.4)
 **3e** [a]	59(s), 70(d)	−124.0 (36.7), −123.0 (36.3)	 **3j**	36	−124.2 (36.3)

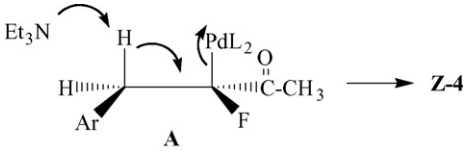
Single (s) addition and double (d). Each compound is contaminated with about 1% of the other compound.

Our reactions used $Pd(OAc)_2$ in DMF solution with triphenylphosphine as the ligand and triethylamine as the base. The results are presented in Table 1.



2 **3** **4** 36 - 86 %

The *trans* relationship between the aryl and acyl groups observed in the Heck reaction with methyl vinyl ketone is still observed in the configuration of **4**. The required *syn* elimination [9] in the intermediate **A** below to give **Z-4** must show little steric interaction between the aryl group and the fluorine atom.



A

In conclusion, we have shown that 3-fluoro-3-buten-2-one (**2**) can be readily prepared and reacted smoothly in Heck reactions with aryl iodides to give *Z*-3-fluorobenzalacetones (**4**) in good yield with *Z* stereoselectivity. Neither conjugate addition nor fluoride elimination was observed. This is possibly the first reported Heck reaction of a simple fluorinated alkene.

3. Experimental procedure

3.1. Preparation of 3-fluoro-3-buten-2-one (2)

A mixture of 1-chloro-1-fluoro-2-methoxy-2-methylcylopropane (4 g, 0.029 mol), water (6.32 g), quinoline (6.32 g) and hydroquinone (4–5 crystals) was heated in an oil bath (80 °C) for 6 h. The reaction mixture was allowed to cool to room temperature and then distilled under reduced pressure. The receivers were cooled in dry ice-acetone. 3-Fluoro-3-buten-2-one (**2**) was obtained as a clear colorless liquid (2.07 g, 82%). Three crystals of hydroquinone were added to the distilled 3-fluorobut-3-en-2-one and stored in the refrigerator until used in Heck reaction. H NMR ($CDCl_3$, TMS) δ 2.4 (d, *J* = 1.5 Hz, 3H, CH_3), δ 5.30 (m, 2H, vinyl; ^{19}F NMR ($CFCl_3$) δ −116.2 (m)

3.2. General procedure for the palladium (II)-catalyzed Heck reaction

Aryl halide (**3**), 3-fluoro-3-buten-2-one (**2**), triethylamine, palladium (II) acetate, triphenylphosphine, and dimethyl formamide (5 ml) were weighed into a 10 ml round-bottomed vial in the ratio 1:3:3:0.05:0.1 mol, respectively. The vial was equipped with a triangular magnetic spinning bar and sealed with a screw cap. The reaction mixture was heated for 20 h at 90 °C (oil bath temperature), allowed to cool and then extracted with diethyl ether/water (30:70). The organic layer was washed with saturated $NaHCO_3$, saturated NaCl and several portions of 15% hydrochloric acid solution, and dried over anhydrous Na_2SO_4. The residue

formed after evaporation of the ether was chromatographed on 200–425 mesh silica gel eluting with a n-hexane/ethyl acetate mixture.

3.3. Analytical data for Heck reaction products, 4

F NMR data are given in Table 1 ($CFCl_3$).

(*Z*)-4-Phenyl-3-fluoro-3-buen-2-one (**4a**): ^{1}H NMR ($CDCl_3$, TMS) δ 2.4 (s, 3H, CH_3), 6.8 (d, 1H, J = 33.9 Hz), 7.5 (m, 5H, arom); ^{13}C NMR ($CDCl_3$, TMS) δ 25 (s, CH_3), 115 (s, CH), 128–132 (m, arom), 154 (d, CF, J = 301.8 Hz), 192.4 (d, C=O). Anal. calcd for $C_{10}H_9FO$: C, 73.16, H, 5.53, F, 11.57. Found, C, 73.00, H, 5.67, F, 11.34.

(*Z*)-4-(2-Methoxyphenyl)-3-fluoro-3-buten-2-one (**4b**): ^{1}H NMR ($CDCl_3$, TMS) δ 2.4 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3), 7.0 (d, 1, CH, J = 37.7 Hz)), 7.4–7.9 (m, 4H, arom); ^{13}C NMR ($CDCl_3$, TMS) δ 25 (s, CH_3), 56 (s, O-CH_3), 120 (s, CH), 125–130 (arom), 154.0 (d, CF, J = 301 Hz), 192 (d, C=O). Anal. calcd for $C_{11}H_{11}FO_2$: C, 68.03, H, 5.71, F, 9.87. Found, C, 68.12, H, 5.45, F, 9.79.

(*Z*)-4-(4-Methylphenyl)-3-fluoro-3-buten-2-one (**4c**): ^{1}H NMR ($CDCl_3$, TMS) δ 2.2 (s, 3H, CH_3), 2.5 (s, 3H, Ph-CH_3), 6.8 (d, 1H, J = 33.6 Hz), 7.2–7.7 (m, 5H, arom); ^{13}C NMR ($CDCl_3$, TMS) δ 21 (s, CH_3), 26 (s, CH_3), 116 (s, CH), 127–141 (m, arom), 154 (d, CF, J = 294.3 Hz), 193 (d, C=O). Anal. calcd for $C_{11}H_{11}FO$: C, 74.14, H, 6.22, F, 10.66. Found, C, 74.15, H, 6.35, F, 10.39.

(*Z*)-4-(4-Chlorophenyl)-3-fluoro-3-buten-2-one (**4d**): ^{1}H NMR ($CDCl_3$, TMS) δ 2.2 (s, 3H, CH_3), 6.8 (d, 1H, J = 36.6 Hz), 7.2–7.6 (m, 4H, arom); ^{13}C NMR ($CDCl_3$, TMS) δ 26 (s, CH_3), 116 (s, CH), 127–141 (m, arom), 154 (d, CF, J = 294.3 Hz), 193 (d, C=O). Anal. calcd for $C_{10}H_8ClFO$: C, 60.47, H, 4.06, F, 4.57. Found, C, 60.55, H, 4.24, F, 4.50.

(*Z*)-4-(4-Iodophenyl)-3-fluoro-3-but-2-one (**4es**): ^{1}H NMR ($CDCl_3$, TMS) δ 2.4 (s, 3H, CH_3), 6.8 (d, CH, J = 36.7 Hz), 7.4–7.6 (m, 4H, arom); ^{13}C NMR ($CDCl_3$, TMS) δ 26 (s, CH_3), 116 (s, CH), 127–141 (m, arom), 154 (d, CF, J = 305.4 Hz) 193 (d, C=O). Anal. calcd for $C_{10}H_8FIO$: C, 41.41, H, 2.78, F, 6.55. Found, C, 41.70, H, 2.58, F, 6.56.

(*Z,Z*)-1,4-bis(3-fluoro-3-buten-2-one)benzene (**4ed**): ^{1}H NMR ($CDCl_3$, TMS) δ 2.5 (s, 6H, 2CH_3), 6.8 (d, 2H, J = 36.3 Hz), 7.8–7.6 (m, 4H, arom); ^{13}C NMR ($CDCl_3$, TMS) δ 26 (s, 2CH_3), δ 115 (s, CH), 128–132 (m, arom), 154 (d, CF, J = 271.7 Hz), 193 (d, C=O). Anal. calcd for $C_{14}H_{12}F_2O_2$: C, 67.20, H, 4.83, F, 15.18. Found, C, 67.02, H, 4.77, F, 15.33.

(*Z*)-3-Fluoro-4-(2-biphenyl)-3-fluoro-3-buten-one (**4f**): mp 44–47, ^{1}H NMR ($CDCl_3$, TMS) δ 2.3 (s, 3H, CH_3), 6.8 (d, 1H, J = 36.7), 7.4–8.0 (m 9H, arom); ^{13}C NMR ($CDCl_3$, TMS) δ 25 (s, CH_3), δ 115 (s, CH), 130–143 (m, arom), 153.0 (d, CF, J = 288 Hz), 192 (d, C=O). Anal. calcd for $C_{16}H_{13}FO$: C, 79.98, H, 5.45, F, 7.91. Found, C, 80.11, H, 5.56, F, 8.00.

(*Z*)-4-(3-Trifluoromethylphenyl)-3-fluoro-3-buten-2-one (**4g**): ^{1}H NMR ($CDCl_3$, TMS) δ 2.2 (s, 3H, CH_3), 6.8 (d, 1H, J = 35.4 Hz), 7.2–7.6 (m, 4H, arom); ^{13}C NMR ($CDCl_3$, TMS) δ 26 (s, CH_3), 119 (s, CH), 127–141 (m, arom and CF_3), 154 (d, CF, J = 294.3 Hz), 193 (d, C=O); ^{19}F NMR ($CDCL_3$, $CFCl_3$) δ −64.0 (CF_3). Anal. calcd for $C_{11}H_8F_4O$: C, 56.90, H, 3.47, F 32.73. Found, C, 56.86, H, 3.35, F, 32.88.

(*Z*)-4-(1-*H*-indol-5-yl)-3-fluoro-3-buten-2-one (**4h**): mp 57–59; ^{1}H NMR ($CDCl_3$, TMS) δ 2.4 (s, 3H, CH_3), δ 6.6 (m), 7.0 (d, CH, J = 36.7 Hz), δ 7.4–8.0 (m, 5H, arom), 8.4 (br, H–N); ^{13}C NMR ($CDCl_3$, TMS) δ 26 (s, CH_3), 120 (CH), 104, 112, 118, 125, 128, 137 (arom), δ 153 (d, CF, J = 256.4 Hz), δ 192.68 (d, C=O). Anal. calcd for $C_{12}H_{10}FNO$: C, 70.93, H, 4.96, F, 9.35. Found, C, 70.66, H, 5.12, F, 9.55.

(*Z*)-3-Fluoro-4-(1-naphthyl)-3-fluoro-3-buten-one (**4i**): mp 66–67, ^{1}H NMR ($CDCl_3$, TMS) δ 2.3 (s, 3H, CH_3), 6.8 (d, 1H, J = 36.4)), 7.2–7.6 (m, 7H, arom); ^{13}C NMR ($CDCl_3$, TMS) δ 25 (s, CH_3), 119.6 (s, CH), 125–133 (m, arom), 153.0 (d, CF, J = 290 Hz), 194 (d, C=O). Anal. calcd for $C_{14}H_{11}FO$: C, 78.49, H, 5.18, F, 8.87. Found, C, 78.19, H, 5.37, F, 9.04.

(*Z*)-3-Fluoro-4-(9-phenanthryl)-3-fluoro-3-buten-one (**4j**): mp 79–82, ^{1}H NMR ($CDCl_3$, TMS) δ 2.3 (s, 3H, CH_3), 6.76 (d, 1H, J = 36.3 Hz), 7.4–7.8 (m, 9H, arom); ^{13}C NMR ($CDCl_3$, TMS) δ 25 (s, CH_3), 120 (s, CH), 122–138 (m, arom), 153.0 (d, CF, J = 299 Hz), 192 (d, C=O). Anal. calcd for $C_{18}H_{13}FO$: C, 81.80, H, 4.96, F, 7.19. Found, C, 81.83, H, 4.77, F, 7.32.

Acknowledgment

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