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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 8231–8234

Palladium-catalyzed arylation of α,α-difluoro-allylic-β-hydroxyester

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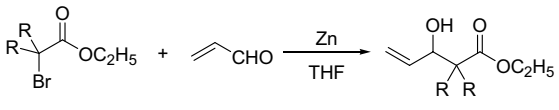
Received 26 June 2006; revised 21 September 2006; accepted 22 September 2006
Available online 10 October 2006

Abstract—The aryl-substituted α,α-difluoro-allylic-β-hydroxyesters and aryl-substituted α,α-difluoroketones were obtained via the coupling reaction of aryl iodides with α,α-difluoro-allylic-β-hydroxyester in the presence of $Pd(OAc)_2$ as the catalyst and Et_3N as the base.

The formation of carbon–carbon bond at unsubstituted vinylic positions by the palladium-catalyzed coupling reaction of aryl or vinyl halides with alkenes, known as the Heck reaction, has become a powerful tool in organic chemistry.[1] Palladium-catalyzed arylation of allylic alcohols with aromatic halides is a convenient synthetic method of aromatic-substituted alkyl aldehydes and ketones.[2] Jeffery[3] reported that a highly selective formation of conjugated aromatic allylic alcohols was achieved from aromatic halides and allylic alcohols in the presence of silver salt, the alteration of the reaction course was rationalized by assuming a four-membered intermediate. Tamaru[4] also utilized *o*-substituted allylic alcohols to coordinate Pd(II) forming a six-membered intermediate without the elimination of proton adjacent to oxygen-bearing carbon. Kang[5] found that the arylation of allylic diols could be highly controlled by the choice of base in the presence of similar reaction system. On the other hand, it is well known that the biological properties can often be influenced by the introduction of fluorine atoms.[6] The physical properties of several electronic and optical devices also depend immensely on the structure of fluoroorganic molecules.[7] It provides the organic chemists with an opportunity to study an extreme case of electronic effect in organic reactions.[6,7] To the best of our knowledge, the palladium-catalyzed arylation of α,α-difluoro-allylic-β-hydroxyester is unprecedented. Herein, we wish to report a Heck reaction in which a strongly electron-withdrawing α,α-difluoroester group coordinates Pd(II) to afford the corresponding aryl-substituted α,α-difluoro-allylic-β-hydroxyesters and aryl-substituted α,α-difluoroketones.

To compare the influence of the difluoromethylene group, the α,α-difluoro-allylic-β-hydroxyester **2a** and its non-fluorinated analogue **2b** were obtained by using the Reformastsky reactions of ethyl bromodifluoroacetate **1a** and its non-fluorinated analogue **1b** with propenal (Scheme 1). Both of the two-step procedure reported by Fried[8] and the modified Reformatsky reaction presented by Shen[9] led successfully to **2** in high yields as expected.



1a: R=F
b: R=H

2a: R=F
b: R=H

Scheme 1.

Keywords: α,α-Difluoro-allylic-β-hydroxyester; Heck reaction; Aryl-substituted α,α-difluoro ketones.
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doi:10.1016/j.tetlet.2006.09.111

By a careful, systematic examination of the influence of a variety of catalysts, such as $PdCl_2(PPh_3)_2$, $Pd(OAc)_2$ and $Pd(OAc)_2$ with ligands (PPh_3); bases, such as K_2CO_3, $NaHCO_3$, Ag_2CO_3, Et_3N and piperidine, and also the reaction temperature, the optimal reaction condition was found for the formation of the desired cinnamyl alcohol and alkyl ketone derivatives to be 1 equiv of aryl iodide **3**, 1.5 equiv of α,α-difluoro-allylic-β-hydroxyester **2a**, 0.05 equiv of $Pd(OAc)_2$ and 1.5 equiv of Et_3N at 80 °C in DMF for 48 h. Tamaru[4] mentioned that 10 equiv of aryl iodides were important to attain a satisfactory yield, but aryl iodides were very expensive. Jeffery[3a] used 2–3 equiv of allylic alcohol. However, the polarity of the product cinnamyl alcohol was close to that of the starting substance, so it was difficult to isolate the product by column chromatography.

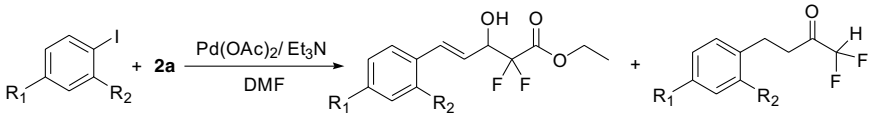
The bases showed an important effect on the reaction. When K_2CO_3 was used in a blank experiment, **2a** disappeared after 48 h. Because K_2CO_3 might be a stronger base than Et_3N in refluxing DMF,[5] **2a** was largely destroyed due to alkaline hydrolysis.[10] Best results were obtained when Et_3N was used as the base.

Under the optimal reaction condition, iodobenzene **3e** reacted with **2a** catalyzed by $Pd(OAc)_2$ to give the corresponding cinnamyl alcohol **5e** in a 72% yield (Table 1, entry 5). In the reactions of the aryl iodides bearing the weak electron-withdrawing substituents, the products were cinnamyl alcohols **5** and coupling products **7**. For example, the major difluoro-substituted cinnamyl alcohol **5b** and the minor coupling product **7b** were obtained in 57% and 19% yields, respectively, in the reaction of **2a** with **3b** (Table 1, entry 2). For methyl 2-iodobenzoate, only the difluoro-substituted cinnamyl alcohol **5g** was obtained, the coupling product **7g** was not found due to the influence of the steric factor (Table 1, entry 7). In the case of strong electron-deficient aryl iodides, no desired product **5** was formed, only the coupling product **7a** was obtained instead (Table 1, entry 1). When **2a** reacted with aryl iodides bearing electron-donating substituents, a mixture of cinnamyl alcohols **5** and α,α-difluoro ketones **6** was formed. For example, in the reaction of **3d,** the major product, difluoro-substituted cinnamyl alcohol **5d** was separated in a 46% yield, ketone **6d** was detected instead of the minor intermediate, 2,2-difluoro-3-oxo-5-arylpentanoic acid ethyl ester **C**, which was unstable and decomposed at a high temperature[11] (Table 1, entry 3). The detailed results for the arylation of α,α-difluoro-allylic-β-hydroxyester are summarized in Table 1.[12]

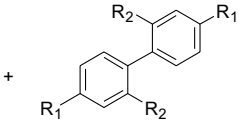
In contrast, the reactions of non-fluorinated **2b** were tried. In the case of methyl 4-iodobenzoate, the result was similar and major product **8b** was obtained along with coupling product **7b** (Table 2, entry 1). Some results were quite different from those of **2a**. For example, iodobenzene **3e** reacted with **2a** to give only one product, cinnamyl alcohol **5e** (Table 1, entry 5), but when **3e** reacted with **2b**, the mixture of cinnamyl alcohol **8e** and keto-ester **9e** was afforded under similar reaction conditions (Table 2, entry 2). Compound **8f** and keto-ester **9f** were also obtained in the reaction of **2b** with **3f** (Table 2, entry 3).

Under similar conditions, 2-iodothiophene **3h** reacted with **2a** to give the difluoro-substituted allylic alcohol **5h** and coupling product **7h** in 51% and 26% yields,

Table 1. Palladium-catalyzed arylation of α,α-difluoro-allylic-β-hydroxyester **2a**



3 5 6



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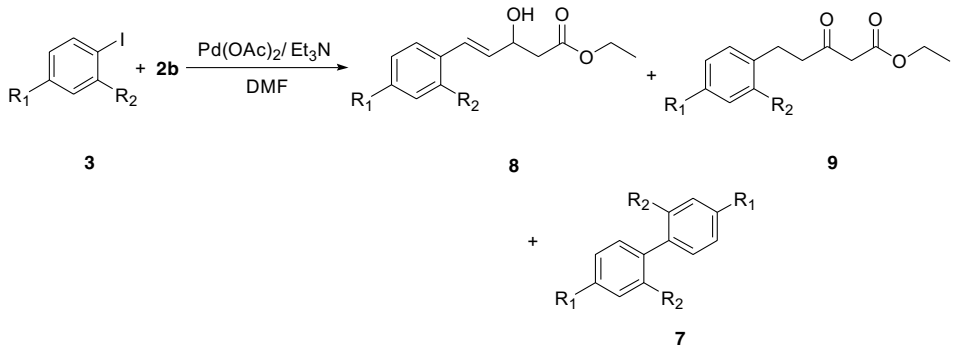
Entry	R_1	R_2	Conversion[a] (%)	Yield of **5**[b] (%)	Yield of **6**[b] (%)	Yield of **7**[b] (%)
1	NO_2	H (**3a**)	0[c]	0	0	46 (**7a**)[d]
2	$COOCH_3$	H (**3b**)	83	57 (**5b**)	0	19 (**7b**)
3	CH_3	H (**3c**)	86	52 (**5c**)	24 (**6c**)	0
4	OCH_3	H (**3d**)	81	46 (**5d**)	29 (**6d**)	0
5	H	H (**3e**)	92	72 (**5e**)	0	0
6	H	CH_3 (**3f**)	84	50 (**5f**)	27 (**6f**)	0
7	H	$COOCH_3$ (**3g**)	69	45 (**5g**)	0	0

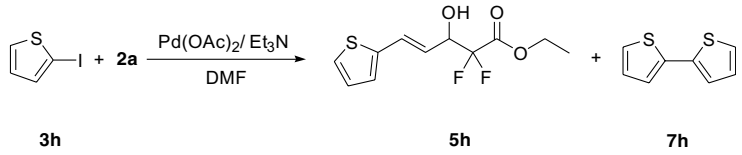
[a] Conversion determined by GC.
[b] Isolated yield.
[c] GC showed **2a** did not decrease.
[d] The reaction at 80 °C for 24 h.

Table 2. Palladium-catalyzed arylation of allylic-β-hydroxyester **2b**



Entry	R_1	R_2	Conversion[a] (%)	Yield of **7**[b] (%)	Yield of **8**[b] (%)	Yield of **9**[b] (%)
1	$COOCH_3$	H (**3b**)	79	20 (**7b**)	53 (**8b**)	0
2	H	H (**3e**)	87	0	33 (**8e**)	38 (**9e**)
3	H	CH_3 (**3f**)	82	0	27 (**8f**)	23 (**9f**)

[a] Conversion determined by GC.
[b] Isolated yield.



Scheme 2.

respectively (Scheme 2). Besides the two-molecule coupling product, four and six-molecule coupling products were detected in the mass spectrometry. The reason might be that the coupling reaction of **3h** occurred easily. When 2-iodothiophene reacted with **2b**, the products were complicated.

A plausible mechanism for the difference between the reactions of α,α-difluoro-allylic-β-hydroxyester **2a** and its non-fluorinated analogue **2b** with iodobenzene **3e** is illustrated in Figure 1. Werner has shown that in the presence of the strongly electron-withdrawing polyfluoroalkyl group, ketone was formed as the major product along with the minor cinnamyl alcohol.[13] We presume that there is an important role of the ester functionality, which can be explained by the simultaneous coordination of palladium with two oxygens (intermediate **A**), or the chelation of ester group to palladium intermediate **B**. when R = F, intermediate **B** is more stable than **A** for the strongly electron-withdrawing α,α-difluoroester group to coordinate Pd(II) forming a six-membered intermediate, intermediate **B** might be unfavorable for *syn* palladium hydride elimination of the hydrogen on the hydroxy-bearing carbon atom, resulting in the formation of **5e** rather than **C**; while R = H, both intermediates **A** and **B** can exist, palladium hydride elimination of the hydrogen on the exocyclic phenyl-bearing methylene carbon would give **8e** and elimination of the hydrogen on the endocyclic hydroxy-bearing carbon could give **9e** (Fig. 1). Electron-donating groups on the phenyl ring might decrease the chelation of difluoroester, the equilibrium could increase intermediate **A**, which would afford major products cinnamyl alcohols **5** and the minor products α,α-difluoro ketones **6**. Electron-withdrawing groups on the phenyl ring might increase the chelation of difluoroester, so no products **6** were found.

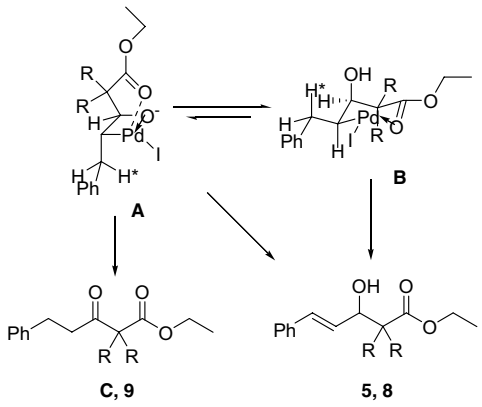


Figure 1. (H* is favorable for *syn* β-elimination).

In summary, the aryl-substituted α,α-difluoro-allylic-β-hydroxyesters and aryl-substituted α,α-difluoroketones were obtained via the coupling reaction of aryl iodides with α,α-difluoro-allylic-β-hydroxyester in the presence of $Pd(OAc)_2$ as the catalyst and Et_3N as the base in a moderate yield under mild conditions. A plausible mechanism for the formation of α,α-difluoro-allylic-β-hydroxyester **2a** and its non-fluorinated analogue **2b** was proposed.

Acknowledgement

This research work was supported by the National Natural Science Foundation of China and Shanghai Science and Technology Committee (03QB14012).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.09.111.

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12. *Typical procedure*: Under an inert atmosphere, palladium acetate (11 mg; 0.05 mmol) was added to a solution of α,α-difluoro-β-hydroxyester (270 mg; 1.5 mmol), *p*-methoxyiodobenzene (234 mg; 1 mmol) and Et_3N (152 mg; 1.5 mmol) in dry *N*,*N*-dimethylformamide (2 mL). The reaction mixture was stirred vigorously at 80 °C for 48 h. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (5 mL) and water (10 mL). The organic layer was separated, the aqueous layer was extracted with ethyl acetate (10 mL × 3) and the organic layers were combined, washed with water and then dried over anhydrous Na_2SO_4. After concentrated under reduced pressure, the residue was chromatographed on silica gel eluting with petroleum ether–ethyl acetate (5:1) to give **5d** (107 mg) in 46% yield and **6d** (50 mg) in 29% yield. For **5d**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.25 (t, 3H, $J = 7.1$ Hz), 2.61 (br, 1H), 3.73 (s, 3H), 4.27 (q, 2H, $J = 7.1$ Hz), 4.61–4.64 (m, 1H), 6.01 (dd, 1H, $J = 7.1$ Hz, $J = 15.9$ Hz), 6.65 (d, 1H, $J = 15.9$ Hz), 6.79 (d, 2H, $J = 8.6$ Hz), 7.26 (d, 2H, $J = 8.6$ Hz). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −121.9 (dd, 1F, $J_{F-F} = 258.5$ Hz, $J_{H-F} = 14.1$ Hz), −115.8 (dd, 1F, $J_{F-F} = 258.5$ Hz, $J_{H-F} = 9.4$ Hz). ^{13}C NMR ($CDCl_3$, 125.8 MHz): δ 14.6, 56, 63.8, 73.8 (t, $J = 26.5$ Hz), 114.6 (t, $J = 256.4$ Hz), 114.8, 114.8, 119.8, 128.8, 128.8, 129.1, 136.3, 160.6, 164.1 (t, $J = 31.6$ Hz). HRMS: calcd for $C_{14}H_{16}F_2O_4$: 286.1017, found: 286.1017. For **6d**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.81 (d, 2H, $J = 6.8$ Hz), 2.86 (d, 2H, $J = 6.8$ Hz), 3.69 (s, 3H), 5.57 (t, 1H, $J = 53.9$ Hz), 6.74 (d, 2H, $J = 7.3$ Hz), 7.02 (d, 2H, $J = 7.3$ Hz). ^{19}F NMR ($CDCl_3$, 470 MHz): δ −128.5 (d, 2F, $J_{H-F} = 51.7$ Hz). ^{13}C NMR ($CDCl_3$ 125.8 MHz): δ 28.2, 38.7, 55.9, 110.5 (t, $J = 252.9$ Hz), 114.7, 114.7, 129.9, 129.9, 132.6, 158.9, 199.6 (t, $J = 26.2$ Hz). HRMS: calcd for $C_{11}H_{12}F_2O_2$: 214.0805, found: 214.0804.
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