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# Selectivity in Palladium Catalyzed Arylation: Synthetic Application Leading to Aromatized Ionone Natural Products

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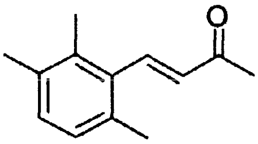
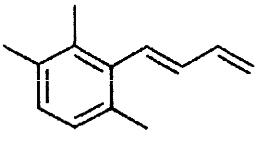
***Abstract***: The selectivity in aromatic substitution *vs* conjugate addition during palladium catalyzed reactions has been controlled simply by changing the base. These reaction conditions have been applied to the syntheses of aromatized β-ionone natural products **1** and its dihydro-derivatives **7**. © 1998 Elsevier Science Ltd. All rights reserved.

The metabolites derived from carotenoids involve several ionone based flavour substances. For example compound **1** is a metabolite isolated from the urine of mares,[1] exhibiting floral notes even at a very low concentration of 0.01 ppm. Compounds **2** and **3** which could be derived from **1**, are constituents of rum and cognac[2] and contribute towards its flavour (Fig. 1). Compound **1** has been prepared earlier by a lone procedure using aldol condensation involving 2,3,6-trimethylbenzaldehyde and acetone.[3] The benzaldehyde derivative was prepared from pseudocumene *via* 4 steps namely sulfonation, bromination, desulfonation, and Grignard reaction. This lengthy procedure leading to 2,3,6-trimethylbenzaldehyde however, lacked reproducibility and further, the strong acidic conditions used for the reaction disfavoured its utilization to the large scale preparation of **1**.

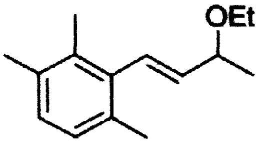
**Figure 1**



**1**



**2**



**3**

An obvious solution for effecting an efficient synthesis of compounds **1**, **2** and **3** is the utilization of palladium catalyzed Heck arylation reaction (Scheme 1).

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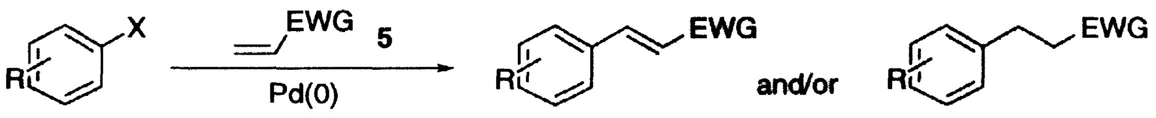
However, in Heck arylation to electron deficient olefins, two competing reaction pathways operate, namely aryl substitution and 1,4-conjugate addition, leading to either a mixture of E/Z isomers or 1,4-conjugate addition products respectively.[5b] In this direction, we report herein a simple procedure to control the stereoselectivity of aryl substitution *vs* 1,4-conjugate addition by simply changing the base from sodium hydrogencarbonate to triethylamine and the application of this procedure to the syntheses of compounds **6** and its dihydro derivatives **7** (Scheme 1).

**Scheme 1**



**4a**: X=OTf
**b**: Br

**6**

**7**

In order to optimize the reaction conditions for aromatic substitution reaction of 3-butene-2-one leading to aromatized ionone **1**, 2,3,6-trimethylphenyl triflate **4a** was prepared from 2,3,6-trimethylphenol since 2,3,6-trimethylbromobenzene **4b** was not available easily. Some representative results are listed in Table 1. Among the Pd catalyst used such as $Pd(OAc)_2$, $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$, only $PdCl_2(PPh_3)_2$ provided a mixture of aromatized ionone **1** and its dihydroderivative (R=2,3,6-trimethyl) **7**[7] in 24% yield with triethylamine as a base in DMF (entry 1). When dppp was added to the reaction mixture and reaction temperature was raised to 150 °C in a sealed tube, the yield of **1** increased to 76% (entry 3). Addition of LiBr further improved the yield to 87% (entry 4), though still **1** accompanied by a small amount of 1,4-conjugate addition product **7**. Since it is known that triethylamine can act as a hydride source in Pd catalyzed reactions,[7] an alternate amine base without having an $\alpha$-hydrogen atom like DBU, or bulkier base such as Hunig base or tributylamine was employed to prevent co-ordination with Pd, furnished a mixture of **1** and **7** without any selectivity in low yield. Finally, sodium hydrogencarbonate[4] was found to be the best base affording **1** selectively in 84% yield (entry 5). It is noteworthy that there was no contamination of the product with **7** or Z-isomer of **1** when $NaHCO_3$ was used as a base. These results are contrary to the one reported in the literature precedent[5] thereby establishing the supremacy of this procedure over the earlier reported method. The reaction conditions employed in this procedure are of general nature and can be applied not only to various positional isomers of **4a** (entries 7~9) but also to triflates having either electron donating or withdrawing group as shown in entries 10~12. It has also been observed that even in the absence of LiBr, the reaction afforded aromatized ionone **1**, though the rate of reaction became sluggish. Under the experimental condition employed, 2,3,6-trimethylbromobenzene **4b** could also provide exclusively **1** in 80% yield.

We then turned our attention towards aromatic 1, 4-conjugate addition reaction involving electron deficient olefins **5** leading to dihydro-derivative **7**. In this connection, it was observed that Cacchi *et al.* had reported that aryliodides in presence of an excess amount of formic acid[4d] gave conjugate addition products during which ammonium formate reduced palladium complex to produce alkyl palladium hydride.

After a detailed investigation, we found that catalytic system $PdCl_2(PPh_3)_2$/dppp/$Et_3N$ in DMF furnished the dihydro-derivative (R=2,3,6-trimethyl) **7** exclusively in 75% yield. Other hydride or proton source such as calcium hydride, $H_2O$, EtOH, trifluoromethanesulfonic acid did not give satisfactory results.

**Table 1. Selective Heck arylation**

| Entry | Triflate **4a**, R= | olefin | Reaction condition[a,b,c] | substitution product **6** (%) |
|---|---|---|---|---|
| 1 | 2,3,6-trimethyl | 3-butene-2-one | $Et_3N$, 120 °C[d] | 24[e] |
| 2 | | | $Et_3N$, 150 °C, 20hr | 32[e] |
| 3 | | | $Et_3N$, dppp (5mol%), 150 °C, 20hr | 76[e] |
| 4 | | | $Et_3N$, dppp (5mol%), LiBr (50mol%), 150 °C, 20hr | 87[e] |
| 5 | | | $NaHCO_3$, dppp (5mol%), 150 °C, 6.5hr | 86 |
| 6 | | | $NaHCO_3$, dppp (5mol%), LiBr (50mol%), 150 °C, 6.5hr | 84 |
| 7 | 2,3,5-trimethyl | | | 85 |
| 8 | 2,4,6-trimethyl | | | 72 |
| 9 | 2,4,5-trimethyl | | | 86 |
| 10 | 4-chloro | | | 50 |
| 11 | 4-methoxy | | | 76 |
| 12 | 3,4-methylenedioxy | | | 69 |
| 13 | 2,3,6-trimethyl | 4-pentene-3-one | | 81 |
| 14 | | 3-methyl-3-butene-2-one | | 66 |
| 15 | | methyl propenoate | | 69 |

[a] $PdCl_2(PPh_3)_2$ (5 mo%) was used.

[b] DMF was used as a solvent.

[c] Reaction was carried out in a sealed tube.

[d] Reaction was carried out under nitrogen in a flask.

[e] A mixture with 1,4-conjugate arylation product

Some representative results are listed in Table 2. 2,3,6-Trimethylbromobenzene **4b** provided a mixture of **1** and **7** in 1 : 0.58 ratio, probably due to the liberation of bromide ion under the experimental conditions employed.

Detailed reaction mechanism which is responsible for the presently described selectivity is yet to be investigated. However, it was generally known that $NaHCO_3$ decomposes at the reaction temperature (150 °C) into $CO_2$, $H_2O$ and $Na_2CO_3$. Potassium carbonate did not give satisfactory results. Based on the results reported by Murahashi,[7] in their 1,4-conjugate addition reaction of cyclic unsaturated systems, Stokker[8] and Konopelski[9] have proposed that triethylamine co-ordinates with the Pd intermediate formed followed by hydride transfer from the $\alpha$-proton of nitrogen atom to Pd providing palladium hydride complex which finally collapses to 1,4-conjugate addition product by elimination of Pd(0). However, in the present case, we are unable at this stage to comment on the mechanism of the reaction since it has been observed that even bases which do not have any α-hydrogen atom furnished 1,4-conjugate addition product albeit in low yield.

In conclusion, we have demonstrated that under the Heck arylation reaction conditions to electron deficient olefin, aryl substitution product was obtained predominantly in the presence of sodium hydrogencarbonate as a base whereas 1,4-conjugate addition product can be obtained selectively using triethylamine with $PdCl_2(PPh_3)_2$ in DMF.

**Table 2. 1,4-Conjugate arylation.**

| Entry | Triflate **4a** R= | olefin | Reaction condition | 1,4-conjugate arylation product **7** (%) |
|---|---|---|---|---|
| 1 | 2,3,6-trimethyl | 3-butene-2-one | $PdCl_2(PPh_3)_2$ (5 mo%), $Et_3N$ dppp (5 mo%), DMF, 150 °C sealed tube, 5~6hr | 75 |
| 2 | 2,3,5-trimethyl | | | 56 |
| 3 | 2,4,6-trimethyl | | | 67 |
| 4 | 2,4,5-trimethyl | | | 36 |
| 5 | 4-chloro | | | 37 |
| 6 | 4-methoxy | | | 56 |
| 7 | 3,4-methylenedioxy | | | 45[a] |
| 8 | 2,3,5-trimethyl | 4-pentene-3-one | | 57 |
| 9 | 2,3,6-trimethyl | | | 75 |
| 10 | | acrylonitrile | | 69 |

[a] Subsitution product (14%) was accompanied.

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