

Regioselective Heck arylation of unsaturated alcohols by palladium catalysis in ionic liquid†

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In contrast to almost all of the known examples of Heck arylation of unsaturated alcohols, which yield predominately β -arylated products, arylation under the Pd-DPPP catalysis in ionic liquid leads preferentially to aryl substitution at the α carbon, providing an easy pathway to this valuable class of olefins.

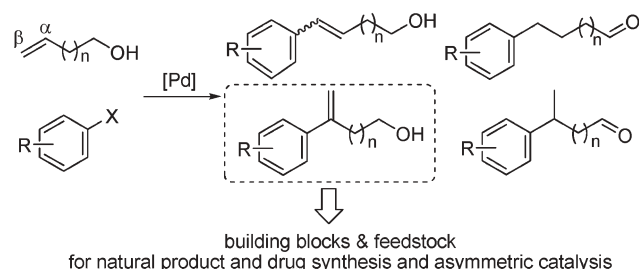
Regioselective Heck arylation of unsaturated alcohols at the internal α position of the C=C double bonds leads to interesting compounds, which could be used as substrates for asymmetric catalysis and building blocks for the synthesis of bioactive compounds, such as natural products, antimalarials, and anticancer and non-steroidal anti-inflammatory agents.¹ However, such chemistry has remained largely unexplored so far.² The Heck reaction of unsaturated alcohols proceeds, with few exceptions, by substitution at the external β position, frequently affording a mixture of carbonyl compounds and substituted unsaturated alcohols (Scheme 1).^{3–5} In fact, there appear to be only two reports in the literature, describing the preferential α arylation of allyl alcohols and homoallyl alcohol with aryl triflates;^{6,7} complex mixtures were formed with the corresponding iodides.⁶ Herein we report the first examples of regioselective, internal α arylation of a wide range of unsaturated alcohols by using the more easily accessible and less costly aryl bromides.⁸

It is now generally believed that the Heck reaction proceeds via two pathways, one being neutral which favours β arylation and the other ionic which favours α substitution.^{9,10} For electron deficient olefins, which usually form the β products, there is little problem concerning the regioselectivity of arylation.² This is not the case

with relatively electron-rich olefins such as allyl alcohol, however. For these olefins, the arylation is usually complicated by the formation of mixtures of regioisomers.^{2d-e,6,9} The regioselective arylation of this class of olefins is most frequently carried out by employing aryl triflates and, when aryl iodides and to a much less degree aryl bromides are chosen, stoichiometrical silver or thallium salts are generally needed,^{2d-e,9} and this is the case for the literature examples aforementioned.^{6,7} Under these conditions, the arylation is channelled into the ionic pathway, thus affording the branched olefins. A drawback of the chemistry is that triflates are base-sensitive, thermally labile and rarely commercially available, and the inorganic additives create new problems, *i.e.* waste salts, toxicity and added cost.

In the course of developing metal-catalysed reactions in ionic liquids,^{11,12} we recently found that the readily available Pd(OAc)₂ and 1,3-bis(diphenylphosphino)propane (DPPP) in combination with imidazolium ionic liquids, *e.g.* 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]), constitute an excellent catalytic system, with which highly regioselective α arylation of several classes of electron-rich olefins can be accomplished with a wide range of aryl halides with no need for any halide scavengers.¹¹ Evidence suggests that the unique regiocontrol stems from the ionic pathway being made favorable by the ionic liquid solvent.^{11,13} We now disclose that the unsaturated alcohols **1a–f** can also be α -arylated with the aryl bromides **2a–p** in a highly regioselective manner in the presence of an ionic liquid, without recourse to aryl triflates nor to any halide scavengers (Scheme 2).

We initially attempted the arylation of allyl alcohol **1a** in the ionic liquid [bmim][BF₄] under conditions employed for other electron-rich olefins.^{11b} However little conversion was observed. After a number of screenings, we were delighted to find that **1a** could be smoothly arylated highly regioselectively in a mixture of [bmim][BF₄] and DMSO, in which enamides had previously been

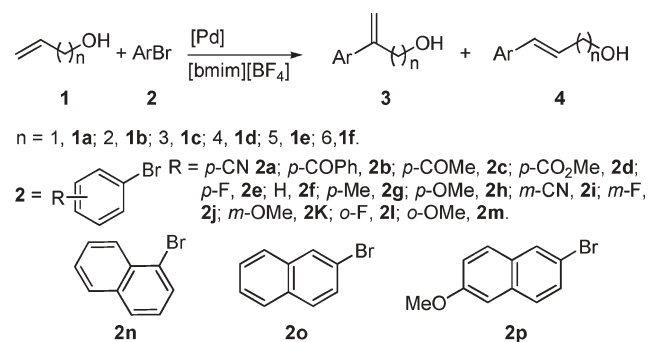


Scheme 1 Formation of isomeric products in the Heck arylation of unsaturated alcohols.

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† Electronic supplementary information (ESI) available: general experimental procedures, spectral data for all compounds, and ¹H and ¹³C NMR spectra for all compounds. See DOI: 10.1039/b608033b



Scheme 2 Heck arylation of the unsaturated alcohols **1a–f** by aryl bromides **2a–p**.

Table 1 Heck arylation of allyl alcohol **1a**^a

$\text{1a} + \text{ArBr (2)} \xrightarrow[\text{DMSO}]{\text{Pd-DPPP, [bmim][BF}_4\text{]}}$ $\text{Ar-CH=CH-CH}_2\text{OH (3a)}$ <p>>99% Regioselectivity</p>			
Entry	2	3	Yield (%) ^b
1			81 ^c
2			86
3			92
4			94
5			86
6			89
7			85
8			88
9			83 ^c
10			89
11			86 ^c

^a See ESI for procedures. 4% Pd(OAc)₂ and 8% DPPP were used at 115 °C for 36 h in 2 mL [bmim][BF₄]-DMSO (1 : 1). The regioselectivity was determined by ¹H NMR. Average of two runs.

^b Isolated yield of the branched products **3a**. ^c 72 h.

regioselectively arylated.^{11b} This finding has since led to the successful arylation of a range of unsaturated alcohols. Thus, as can be seen from Table 1, under the catalysis of Pd-DPPP in [bmim][BF₄]-DMSO, **1a** is arylated by various aryl bromides to give the α-arylated **3a** with excellent regioselectivities and high isolated yields. Interestingly, no isomerization of **3a** to the carbonyl compounds was observed. This is in contrast to reactions carried out in the absence of a ligand or when using monodentate ligands in molecular solvents.^{3,4} The presence of DPPP is expected to inhibit this isomerization. The coupling reactions appear to work better with arylating reagents bearing electron withdrawing substituents and with those that are less sterically demanding.

Table 2 Heck arylation of homoallyl alcohol **1b**^a

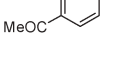
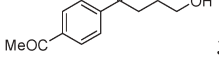
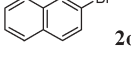
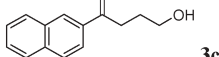
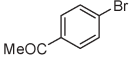
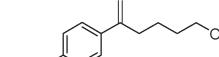
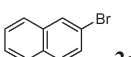
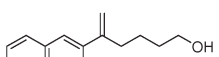
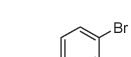
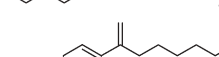
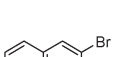
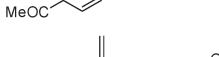
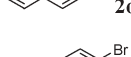
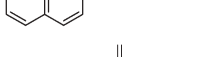
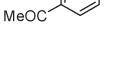
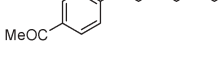
$\text{1b} + \text{ArBr (2)} \xrightarrow[\text{DMSO}]{\text{Pd-DPPP, [bmim][BF}_4\text{]}}$ $\text{Ar-CH=CH-CH}_2\text{CH}_2\text{OH (3b)}$			
Entry	2	3	α/β ^b Yield (%) ^c
1			75/25 70
2			84/16 76
3			76/24 71
4			82/18 76
5			78/22 72
6			84/16 78
7			80/20 73
8			80/20 76
9			75/25 70
10			70/30 63
11			84/16 79
12			85/15 80
13			95/5 90
14			80/20 73

^a 1% Pd(OAc)₂ and 2% DPPP were used at 115 °C for 24 h.

^b Determined by ¹H NMR. ^c Isolated yield of **3**.

This does not necessarily mean that the arylation with other substrates is slowed down by the oxidative addition of the aryl bromides to L₂Pd(0), since the reaction of **1b** with these bromides proceeds in faster rates (*vide infra*). Regardless of the mechanism, the chemistry provides one of the easiest pathways for accessing this class of compounds, which can be used as substrates for various asymmetric catalytic reactions, or for the synthesis

Table 3 Heck arylation of unsaturated alcohols **1c–f**^a

$ \begin{array}{c} \text{1} + \text{ArBr} \xrightarrow[\text{[bmim][BF}_4\text{]}]{\text{Pd-DPPP, DMSO}} \text{Ar-3} + \text{Ar-4} \\ \text{1} \quad \quad \quad \text{2} \quad \quad \quad \text{3} \quad \quad \quad \text{4} \end{array} $			
Entry	2	3	Yield α/β (%)
1			85/15 79
2			88/12 80
3			88/12 81
4			86/14 80
5			81/19 74
6			84/16 75
7			80/20 72
8			85/15 78

^a The conditions were the same as in Table 2.

of profens *via* a two-step process involving oxidation and asymmetric hydrogenation^{1c,14} and antimalarials *via* Mukaiyama hydroperoxysilylation.^{1a}

We next investigated the arylation of the homoallyl alcohol **1b**. Table 2 summarizes the results obtained. As can be seen, bromobenzenes bearing various substituents at various positions are all effective substrates, furnishing the α products with good to excellent regioselectivities. Although the regioselectivities are lower than those observed with **1a**, the reactions proceeded more readily, requiring a reduced catalyst loading and shorter reaction time. Unlike the arylation of **1a**, **1b** could be arylated in [bmim][BF₄], albeit with slightly lower α/β ratios (76/24 in the case of **2c**). In molecular solvents such as DMF and dioxane, the product was dominated by β-arylated species (60–80%).

The Heck arylation of unsaturated alcohols with different chain lengths has also proved to be viable, as demonstrated by the examples of **2c** and **2o** in Table 3. These reactions afforded good α regioselectivities for the branched alcohols. When *n* = 3 or 4, the regioselectivities were slightly higher; but further increase in the chain length reduced the selectivity. Few literature examples are known of the arylation of long chain unsaturated alcohols (*n* ≥ 2)

and as indicated earlier, those that are known are dominated by β arylation.^{4a}

In summary, we have developed a general and efficient method for the internal arylation of unsaturated alcohols by using Pd-DPPP in [bmim][BF₄]-DMSO. The method allows for highly regioselective arylation of these alcohols, including in particular allyl alcohol, with aryl bromides with no need for halide scavengers. In contrast to almost all the known arylation reactions of this class of olefins, the reactions presented here afford preferentially the branched olefins that are usually difficult to access.

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