

Palladium catalysed regioselective arylation of electron-rich olefins by aryl halides

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Abstract

Palladium catalysed arylation of the electron rich olefin butyl vinyl ether **1** by aryl halides **2** has been accomplished with DPPP/Pd(OAc)₂, (DPPP = 1,3-bis(diphenylphosphino)propane), thus, obviating the need for expensive, commercially unavailable aryl triflates and toxic inorganic additives. In the presence of three equivalents of DPPP, the reaction proceeds with remarkable regioselectivity, leading almost exclusively to substitution by various aryl groups at the olefinic carbon α to the heteroatom of **1**.

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1. Introduction

Palladium catalysed Heck reaction is one of the most important tools in synthetic chemistry (for recent reviews, see [1]). The reaction works impressively well with a wide range of electron-deficient and unactivated olefins, affording high selectivity to product resulting from arylation or vinylation at the less substituted position of the olefin double bond. However, with electron-rich acyclic olefins such as enol ethers and enol amides, mixtures of regioisomers usually result, thus, limiting the applicability of the Heck reaction in synthesis [1,2] (Scheme 1). Regioselective substitution at the olefinic carbon α to the heteroatoms of enol ethers or enol amides is achievable when the arylating halide is replaced by a triflate or when a stoichiometric quantity of silver triflate or thallium salt is

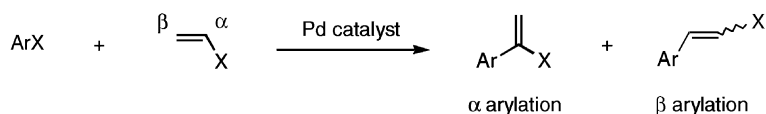
added in the case of aryl halides [2]. Regiocontrol is also possible for olefins bearing additional functionalities capable of chelating to palladium [3]. These approaches have been exploited for the preparation of bioactive compounds [4]. However, they suffer from the high cost of aryl triflates and silver salt and the toxicity of thallium salts.

On the ground of the generally accepted mechanisms for the Heck reaction, which is believed to involve two pathways, one being neutral, favouring β -arylation while the other ionic, favouring α -arylation [1,2,5], we recently reported that the palladium catalysed α -arylation of electron rich olefins by aryl halides can readily be accomplished in a highly regioselective manner in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate without resorting to aryl triflates or the silver salt of triflate [6]. More recently, Hallberg et al. found that similar, regioselective α -arylation of alkyl vinyl ethers with aryl and heteroaryl bromides could be achieved in aqueous DMF [7,8]. These results suggest that the

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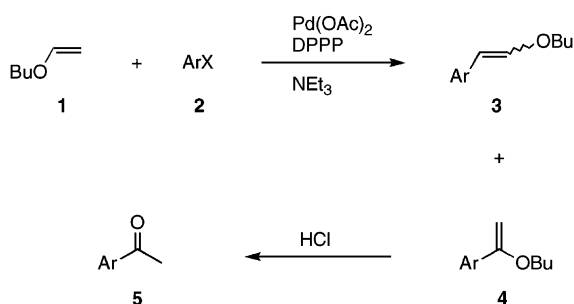
Scheme 1. Formation of regioisomers in the Heck reaction.

Heck coupling pathways can be altered by using substrates containing good leaving groups such as the triflate ion as well as by using solvents capable of stabilising ionic intermediates. We report herein that the regioselectivity of Heck reaction can additionally be affected favourably by the use of bidentate ligands with appropriate choice of ligand to palladium ratios.

2. Results and discussion

Bidentate phosphine ligands play an important role in affecting the regioselectivity of the palladium catalysed Heck reaction [1,2]. Cabri reported that the combination of Pd(OAc)₂ with slightly more than one equivalent of DPPPP furnished high regioselectivity in the coupling of butyl vinyl ether **1** with aryl triflates. However, the reaction became sluggish and much less regioselective when an aryl halide was used as the arylating agent [2c,d]. In our study of this reaction, we have observed that regioselective α -arylation of **1** by aryl halides **2** can be effected by the proper combination of palladium with some bidentate phosphines (Scheme 2).

We first examined the arylation of **1** by 1-bromonaphthalene in DMF by combining Pd(OAc)₂ with one of the three bidentate phosphines, DPPPP, 1,4-bis-



Scheme 2. Regioselective arylation of butyl vinyl ether by aryl halides.

(diphenylphosphino)butane (DPPPB), and 1,1-bis(diphenylphosphino)ferrocene (DPPPF). These ligands had previously been shown to be most effective in giving α -substituted product in arylation by triflates [2d]. The results are given in Table 1. As can be seen, the arylation of **1** catalysed by Pd(OAc)₂ in the presence of ca. one equivalent of phosphine afforded a mixture of α and β substituted products in addition to being slow, confirming the observations made by Cabri [2c,d]. The low rates could result from the phosphine ligand being inadequate, some of which may be consumed in the reduction of Pd(II) to an active Pd(0) species [9]. Indeed in the case of aryl triflates, two equivalents of a ligand were sometime necessary to generate a stable and effective palladium catalyst [2c]. In the present study, while slightly faster rates were observed in the presence of two equivalents of ligands, no significant improvement in regioselectivity was observed. However, by increasing the amount of ligand to three equivalents relative to palladium, DPPPP

Table 1
Ligand effect on the Heck arylation of butyl vinyl ether **1** by 1-bromonaphthalene^a

Ligand	L/Pd	Conversion (%) ^b	α/β ^c	<i>E/Z</i> ^d
DPPPP	1.1	54	75/25	77/23
DPPPB	1.1	53	59/41	79/21
DPPPF	1.1	87	50/50	72/28
DPPPP	2	85	61/39	86/14
DPPPB	2	80	62/38	72/28
DPPPF	2	100	53/47	71/29
DPPPP	3	65	>99/1	
DPPPB	3	64	>99/1	
DPPPF	3	100	65/35	68/32

^a Reactions were run with 1.0 mmol **1**, five equivalents of 1-bromonaphthalene, 1.2 equivalents of Et₃N, and 2.5 mol% of Pd(OAc)₂ in DMF at 100 °C for 12 h. The product was identified/analysed by NMR, GC, and GC-MS and by comparison with literature data [12].

^b Conversion of **1** to **3** and **4**.

^c Molar ratio of **4/3**. When the product **3** could not be detected by GC and NMR, a value of >99/1 was assigned.

^d Ratio of *trans/cis* isomers of **3**.

Table 2
Regioselective arylation of **1** catalysed by DPPP/Pd(OAc)₂^a

X	Arylation	Temperature (°C)	Time (h)	α/β ^b	Yield (%) ^{b,c}
OTf	C ₆ H ₅	80	1	>99/1	100 (87)
I	1-C ₁₀ H ₇	80	24	>99/1	100 (89)
I	4-Me-C ₆ H ₄	100	24	10/1	100
I	C ₆ H ₅	100	24	10/1	100 (91)
Br	1-C ₁₀ H ₇	120	36	>99/1	100 (91)
Br	4-OHC-C ₆ H ₄	120	36	>99/1	40
Br	4-MeCO-C ₆ H ₄	120	36	>99/1	100 (89)
Br	4-F-C ₆ H ₄	120	36	>99/1	100 (92)
Br	4-NC-C ₆ H ₄	120	36	>99/1	21
Br	C ₆ H ₅	120	36	>99/1	100 (90)
Br	4-MeO-C ₆ H ₄	120	36	>99/1	60
Br	4-Me-C ₆ H ₄	120	36	>99/1	100 (88)
Br	4-O ₂ N-C ₆ H ₄	120	36	20/1	42
Br	4-MeO ₂ C-C ₆ H ₄	120	36	>99/1	100 (89)

^a For general reaction conditions, see Section 3. DPPP/Pd(OAc)₂ = 3.

^b Determined by GC and ¹H NMR.

^c The values in parentheses indicate isolated yields of the α product after hydrolysis with HCl.

and DPPB become effective, affording remarkably enhanced regioselectivity in favour of α-arylation, as can be judged by the ratio of the α substituted **4** to the β substituted **3** (α/β), albeit with conversions slightly lower than those obtained with two equivalents of ligands. It is somewhat surprising that the regiocontrol exerted by DPPF is lower, although its bite angle is similar to that of DPPB [10]. This could arise from an easier dissociation of the former from palladium, and the higher conversion observed with DPPF is consistent with this view.

On the basis of the above study, the arylation of **1** in DMF was undertaken for a variety of aryl halides in the presence of Pd(OAc)₂ and three equivalents of DPPP. The results obtained are summarised in Table 2. As can be seen from the table, excellent regioselectivity together with high isolated yields for the aryl methyl ketones **5** was obtained in most of the reactions, regardless of the nature of the substituents on the aromatic ring. Thus, with bromobenzenes bearing either strongly electron withdrawing or electron donating substituents such as -CN, or -OMe, the α/β ratios remained at >99/1, reminiscent of the results obtained with aryl triflates in DMF, where substituents of aryl triflates were found to exert no significant effects on the α/β ratio [2d]. Except for 1-iodonaphthylene, however, poor regioselectivity was obtained with the iodides. Similar observations

were made when such reactions were run in ionic liquids and aqueous DMF [6,7]. With potentially co-ordinating substrates such as 4-bromobenzonitrile, the reaction was slower, so was the reaction involving the electron rich 4-bromoanisole. Similar to the coupling reactions of aryl triflates containing nitro substituents [2d], 1-bromo-4-nitrobenzene displayed both a low reactivity and low regioselectivity. Whilst excellent regioselectivities were obtained in most reactions, the reaction rates were in general slow, as is evident from the prolonged reactions times indicated in Table 2.

It has recently been shown that three equivalents of DPPP react with Pd(OAc)₂ to give Pd(DPPP)₂ and one equivalent of DPPP monoxide in wet DMF, and the co-ordinatively saturated Pd(DPPP)₂ is inactive toward the oxidative addition of PhI at low temperature [9a]. The observed arylation of **1** with the halides **2** must result from the high temperature employed in this study that facilitates the dissociation of phosphorus. In accordance with the generally accepted Heck mechanism, the α-arylation product is derived from an ionic pathway made possible by halide or triflate dissociation from palladium. The unusual regioselectivity in favour of **4** observed here could probably be due to the presence of excess ligands that make easier the dissociation of bromide or iodide ions from palladium. Consistent with the assumption that the reaction

proceeds via the ionic pathway, the coupling of phenyl triflate and **1** in the presence of Pd(OAc)₂ and three equivalent of DPPP was complete within 1 h, leading almost exclusively to the α product. The lability of the Pd–OTf bond [11], resulting from the oxidative addition of phenyl triflate to Pd(0), should promote the ionic pathway.

In summary, the results presented here demonstrate that by a proper choice of ligands and their combination with palladium, it is possible to effect highly regioselective Heck arylation of electron rich olefins without resorting to expensive or toxic triflates or inorganic additives. In the particular case of butyl vinyl ether **1**, the combination of Pd(OAc)₂ with three equivalents of a bidentate phosphine, DPPP, ensures good to excellent α regiocontrol in the arylation of **1** by various aryl halides.

3. Experimental

3.1. General remarks

All reactions were carried out under argon atmosphere. Chromatographic purifications were performed on silica gel (mesh 230–400) by flash technique. Dimethylformamide (DMF) and triethylamine were distilled over CaH₂, and stored over activated 4 Å molecular sieves. Commercial deuterated chloroform for NMR spectroscopy and solvents for chromatography were used without further purification. Butyl vinyl ether **1**, aryl halides and phenyl triflates, Pd(OAc)₂, 1,3-bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, and 1,1-bis(diphenylphosphino)ferrocene were purchased from Lancaster and Aldrich and used as received. ¹H and ¹³C NMR spectra were recorded on a Gemini 300 spectrometer. Mass spectra were obtained by electron ionisation (EI). The products were characterised by ¹H and ¹³C NMR, MS, GC, and GC–MS, and by comparison of their ¹H NMR spectra with available literature data and/or those of authentic samples. The products from this study are known compounds. For their physical and spectroscopic data, see [12].

3.2. General procedure for the arylation of vinyl ether

An oven-dried, two-necked round-bottom flask containing a stir bar was charged with an aryl halide **2**

(2.0 mmol), Pd(OAc)₂ (2.5 mol%), DPPP (7.5 mol%), and DMF (5 ml) under argon at room temperature. The flask was degassed for a few times. Butyl vinyl ether **1** (10.0 mmol) and NEt₃ (2.4 mmol) were injected sequentially. The flask was placed in an oil bath, and the mixture was stirred and heated at the desired temperature. After appropriate reaction time, the flask was removed from the oil bath and cooled to the room temperature. A small quantity of sample was then taken for NMR and GC analysis. To the rest of the mixture, HCl (5%, 10 ml) was added and following stirring for 0.5 h, CH₂Cl₂ (40 ml) was added. The aqueous layer was extracted with CH₂Cl₂ (3 ml \times 40 ml), and the combined organic layer was washed with water until neutrality, dried (Na₂SO₄), filtered, and concentrated in vacuo. The aryl methyl ketone **5** was isolated out of the crude product by flash chromatography on silica gel using a mixture of ethyl acetate and hexane as eluant. The identification and purity of the product were confirmed by NMR, GC and GC–MS.

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