

Efficient synthesis of alkyl aryl ketones & ketals *via* palladium-catalyzed regioselective arylation of vinyl ethers†

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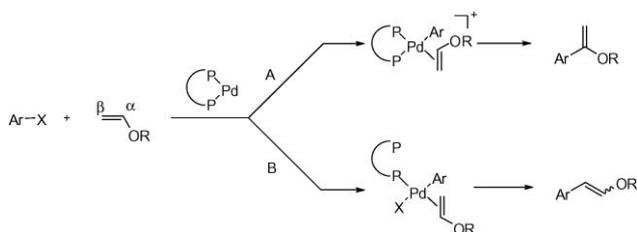
The combination of Pd(OAc)₂ with 1,3-bis(diphenylphosphino)propane (dppp) in ethylene glycol constitutes a high-performance catalytic system for highly regioselective arylation of a range of electron-rich vinyl ethers by aryl bromides to provide, upon hydrolysis, alkyl aryl ketones and cyclic ketals in good yields with up to 3.75 × 10⁵ TON and 15625 h⁻¹ TOF.

Alkyl aryl ketones have been widely applied in the pharmaceutical, fragrance, dye and agrochemical industries.¹ In general the preparation of these compounds employs the traditional Friedel–Crafts acylation, which involves handling hazardous reagents and fails with electron-deficient arenes; thus the development of efficient alternative routes has been an active topic in both academia and industry.² Since the discovery of palladium-catalyzed cross-coupling reactions, a great deal of interest has been devoted to the development of Pd-catalyzed protocols to access these ketones, and a range of efficient routes have been described in the literature.^{3–5} Among these reported methods, the Pd-catalyzed Heck reaction of aryl halides with the electron-rich olefin vinyl ethers is very attractive due to its simplicity, its tolerance of various functional groups and the easy availability of reagents.⁵ However, this arylation is rarely regioselective under normal Heck conditions, giving rise to a mixture of α- and β-arylated vinyl ethers and thus hampering its wider application in synthesis.

It is generally believed that this regioselectivity problem arises from two competing reaction pathways, which result in different regioisomers (Scheme 1).^{5b–d} Several methods have been successfully developed to overcome this problem. The success is usually

attributed to promoting the ionic pathway A, which leads to internal α-arylated vinyl ethers. Earlier studies by Hallberg and Cabri revealed that the poor regioselectivity could be greatly improved by employing aryl triflates or by adding stoichiometric silver or thallium salts when aryl iodides and bromides are chosen.⁶ However, triflates are thermally labile and are rarely commercially available, and the inorganic additives create new problems such as toxicity and high cost. The regioselectivity enhancement has been observed by changing the reaction medium. For example, good β-regioselectivities have been achieved with poly(ethylene glycol) or aqueous DMF as the reaction medium in the presence of a Pd(OAc)₂ or Pd–P(tBu)₃ catalyst.^{7a–b} Recent work by Hallberg and us has shown that the use of imidazolium-based ionic liquids or DMF–water mixtures in combination with Pd–dppp catalysis provides excellent α-regioselectivity in the coupling reaction of vinyl ethers with aryl bromides.^{7c–e} It is assumed that the ionic or polar environment provided by the solvent enables formation of the cationic species in a more facile way. The recent kinetic studies of Amatore, Jutand and co-workers support this view.⁸ Interestingly it has been found that ammonium salts, such as [HNEt₃][BF₄] or [H₂NiPr₂][BF₄], could act as hydrogen-bond donor to increase both the rate and regioselectivity in the arylation of vinyl ethers not only in ionic liquids but also in molecular solvents, presumably by facilitating dissociation of bromide anion from Pd(II).^{9a} Following this leading report, inexpensive and environmentally benign alcohol solvents, such as ethylene glycol (EG) and *i*PrOH, which possess large hydrogen-bond-donating ability, have been found to efficiently promote α-regioselectivity in the arylation of several vinyl ethers with aryl bromides.^{9b–c} In addition, Larhed *et al.* reported that ethylene glycol vinyl ether could undergo fast and highly regioselective α-arylation in water, although other vinyl ethers failed.^{9d}

Despite all the above advances, it is surprising that less attention has been placed on enabling the regioselective arylation more economically and practically.¹⁰ In most of the cases, effort has been made to exclusively deal with the improvement of regioselectivity, and high catalyst loading is generally required, typically 2.5 mol%, thus limiting its attractiveness in large scale commercial applications. When compared to the exceedingly high catalytic efficiency achieved in other Pd-catalyzed coupling reactions,¹¹ such as Heck arylation of electron-deficient olefins and Suzuki reactions, it appears that there is much room for improvement in terms of rates and turnover numbers. From the viewpoints of both academic interest and practical applications, it is highly desirable to develop high-performance catalytic system for regioselective arylation of vinyl ethers to prepare alkyl aryl ketones. Following our continuing interest in the highly regioselective arylation of electron-rich olefins,^{7a–b,9a–c} herein we report that the combination



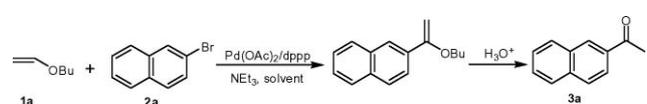
Scheme 1 The two competing pathways.

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Table 1 Solvent and S/C effect on the Heck arylation of n-butyl vinyl ether^a


Entry	Solvent	S/C	Temp./°C	Time/h	Yield [%] ^b
1	EG	1000	145	0.5	90
2	Isopropanol	1000	Reflux	18	89
3	[bmim][BF ₄]	1000	115	12	91
4	[bmim][BF ₄]	1000	145	10	90
5 ^c	EG	10000	145	8	87
6 ^c	EG	500000	145	24	75

^a Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), Pd(OAc)₂/dppp=1/2, NEt₃ (2.0 mmol), solvent (3 ml), no linear product observed. ^b Isolated yield after acid hydrolysis. ^c **1a** (1.0 mmol), vinyl ether (2.0 mmol), Pd(OAc)₂/dppp(1/2) and NEt₃ (2.0 mmol) in 2.0 ml EG stock solution.

of Pd(OAc)₂ and dppp in ethylene glycol results in a high-performance catalytic system, which allows for regioselective α -arylation of a series of vinyl ethers, producing alkyl aryl ketones, after aqueous hydrolysis, and cyclic ketals in acceptable to good yields with up to 3.75×10^5 TON and 15625 h^{-1} TOF.

We first examined the feasibility of arylation of vinyl ether under a low catalyst loading of 0.1 mol%. Under the previously established conditions,⁹ butyl vinyl ether **1a** was arylated by 2-bromo-naphthalene **2a** in EG at 145 °C with NEt₃ as the base, with the catalyst generated *in situ* from Pd(OAc)₂ and 2 equiv. dppp. In order to prevent the formation of palladium black, the olefin was added 3–4 min after the mixture of other reagents in EG had been heated.^{9b} To our delight, **1a** was completely arylated by **2a** in just 0.5 h without any linear product detected, and the subsequent hydrolysis afforded the corresponding methyl ketone in 90% yield (Table 1, entry 1). For comparison, the same reaction was also carried out in *i*PrOH under identical conditions. Although virtually the same yield of methyl ketone was obtained, the reaction time was much longer, at 18 h (Table 1, entry 2). It has been reported that the ionic liquid [bmim][BF₄] is capable of facilitating highly regioselective arylation of **1a** in the presence of 0.1 mol% Pd-dppp catalyst and 1.5 equiv. hydrogen-bond donor [HNET₃][BF₄] at 115 °C.^{9a} We then examined the reaction of **1a** with **2a** in a mixture of [bmim][BF₄] and [HNET₃][BF₄] under the same reaction conditions. Indeed, excellent regioselectivity and a slightly better yield were achieved; however, the reaction went to completion in a much longer time of 12 h (Table 1, entry 3). When increasing the reaction temperature to 145 °C, it still required 10 h to finish but with retained regioselectivity (Table 1, entry 4). Clearly, EG proved to be much more effective than other solvents.

The good performance of Pd-dppp in EG prompted us to further enhance the catalytic efficiency. It is important to note when carrying out the regioselective Heck reactions in a dilute solution, naked Pd may catalyze the arylation in a “ligand free” fashion, producing the linear product. In order to avoid the formation of linear product, a stock solution containing Pd/dppp was prepared in advance by heating Pd(OAc)₂ with dppp in EG for 12 h at 60 °C under an inert atmosphere. As can be seen from Table 1, when the substrate-to-catalyst (S/C) ratio was raised to 10000, the reaction still proceeded smoothly to provide high yield

and excellent regioselectivity albeit with a longer reaction time being required (Table 1, entry 5). It is worthy to note that the reaction performed well even under still lower catalyst loading (S/C = 500000), giving 3.75×10^5 TON and 15625 h^{-1} TOF. These values represent the highest TON and TOF ever reported for the Heck reaction of electron-rich olefins (Table 1, entry 6). Many Pd-catalyzed Heck reactions have been reported to suffer from the fast decomposition of catalyst, and 1–10 mol% catalyst loadings are usually used.^{3,5} The thermal stability of the Pd-dppp system may be partly attributed to EG, which could act as a ligand, inhibiting decomposition of the catalyst into inactive Pd(0). As we pointed out before,^{9b} EG is an excellent hydrogen bond donor and promotes the dissociation of bromide anion from Pd(II), thus facilitating the arylation. Taken together, these features may account for the excellent performance of EG at extremely low catalyst loadings.

A series of aryl bromides were then subjected to olefination by **1a** at a high S/C ratio ranging from 100000 to 500000, and the desired methyl aryl ketones were isolated after acidification of the reaction mixture.¹² The results obtained are listed in Table 2. As can be seen, although necessitating longer reaction time (24 h) for completion, both electron-rich and electron-deficient aryl bromides examined underwent successful olefination by **1a** to provide aryl methyl ketones in moderate to good yields, and in no case was the linear product detected or isolated. Of particular note are aryl bromides **2b–e**, which can be smoothly olefinated at a high S/C ratio of 500000, resulting in up to 355000 TON and 14791 h^{-1} TOF (Table 2, entries 1–4). The coupling procedure also tolerated the presence of the *ortho*- and *meta*-substituents (Table 2, entries 9–13). Dual transformation could be achieved in the case of dibromide **2p** to give the diketone in good yield (Table 2, entry 14). With palladacycle or PdCl₂ as the catalyst, Herrmann *et al.* achieved up to 400 TON in the Heck coupling of **1a** with aryl bromide in ionic liquid [NBu₄][Br]; but only poor regioselectivity was observed.^{10a} Santelli and co-workers reported a Pd-tetraphosphine catalytic system, which allowed the Heck reaction of aryl halides with vinyl ethers to proceed in DMF at low catalyst loadings, affording up to 61000 TON; but the reaction suffered from poor regioselectivity.^{10b–c} Our reaction is not limited to **1a**, and the hydroxyalkyl vinyl ethers **1b** could also be arylated to give cyclic ketals at low catalyst loadings without adding any acid, and again no linear product was observed (Table 2, entries 15–16). It is notable that the reaction of 1-bromonaphthalene with **1b** led to a remarkable TON of 3.75×10^5 , and the TOF thus reached 15625 h^{-1} (Table 2, entry 15). This is the best result reported to date in the regioselective arylation of hydroxyalkyl vinyl ethers.

Most of the reported studies have so far focused on the regioselective arylation of alkyl vinyl ethers by aryl halides to provide methyl aryl ketones as the products.^{6–9} In contrast, the reaction of 2-substituted vinyl ethers with aryl halides to access products other than methyl ketones has been rarely investigated.^{10c–d} To further test the effectiveness of our catalytic system, the arylation of 2-substituted vinyl ethers with aryl bromides was then carried out at low catalyst loading; this would lead to products other than methyl ketones after hydrolysis. Since these olefins are less reactive than **1a**, a higher catalyst loading was required.^{10c–d} As can be seen in Table 3, the Pd-dppp catalyst in EG allowed complete reactions of aryl bromides with 2-substituted vinyl ethers **1c–f** in 24 h regardless of the nature of substituents on the aryl ring,

Table 2 Heck arylation of vinyl ethers **1a–b** in EG under low catalyst loadings^a

Entry	Olefin	Ar–Br	S/C	Product	Yield [%] ^b
1		2b	5×10^5		74
2	1a	2c	5×10^5		71
3	1a	2d	5×10^5		71
4	1a	2e	5×10^5		69
5	1a	2f	1×10^5		72
6	1a	2g	1×10^5		71
6	1a	2h	1×10^5		70
7	1a	2i	1×10^5		73
8	1a	2j	1×10^5		72
9	1a	2k	1×10^5		71
10	1a	2l	1×10^5		73
11	1a	2m	1×10^5		75
12	1a	2n	1×10^5		76
13	1a	2o	1×10^5		73
14 ^c	1a	2p	1×10^5		73
15 ^d		2e	5×10^5		75
16 ^d	1b	2c	5×10^5		70

^a Conditions: aryl bromide (1.0 mmol), vinyl ether (2.0 mmol), Pd(OAc)₂/dppp(1/2) and NEt₃ (2.0 mmol) in 2.0 ml EG stock solution, 145 °C, 24 h; the ketone was obtained after acidification. All reactions gave >99/1 regioselectivity as determined by ¹H NMR. ^b Isolated yield after acid hydrolysis. ^c 4 Equiv. olefin was employed. ^d Conditions were the same as for *a*, but omitting aqueous acidic work-up.

and the subsequent hydrolysis provided alkyl aryl ketones with moderate to good yields. As with the arylation of **1a** in EG, only α -arylated products were detected. The reaction is sensitive to the nature of substituents of 2-substituted vinyl ethers, however, and this is exemplified by the observation that lower S/C ratios ranging from 5000 to 200 are required to efficiently arylate the bulkier vinyl ethers **1d–1f** (Table 3, entries 7–16), whilst the arylation of **1c** could proceed smoothly at a higher S/C ratio of 100000 (Table 3, entries 1–6). The best result was observed in the coupling reaction of **1c** with **2b**, affording a TON of 73000 (Table 3, entry 2).

In summary, the results presented in this paper show that Pd-dppp in EG is a high-performance catalyst capable of catalyzing highly regioselective arylation of a series of electron-rich vinyl ethers, showing remarkably high activity (TOF up to 15625 h⁻¹)

Table 3 Heck arylation of 2-substituted vinyl ethers **1c–f** in EG at low catalyst loadings^a

Entry	Olefin	Ar–Br	S/C	Product	Yield [%] ^b
1		2a	1×10^5		71
2	1c	2b	1×10^5		73
3	1c	2g	1×10^5		69
4	1c	2i	1×10^5		69
5	1c	2j	1×10^5		70
6	1c	2k	1×10^5		65
7		2b	5×10^3		72
8	1d	2d	5×10^3		74
11		2a	5×10^3		76
12	1e	2b	5×10^3		78
13	1e	2c	5×10^3		73
14	1e	2j	5×10^3		77
15		2b	2×10^2		69
16	1f	2g	2×10^2		65

^a Conditions: aryl bromide (1.0 mmol), vinyl ether (2.0 mmol), Pd(OAc)₂/dppp(1/2) and NEt₃ (2.0 mmol) in 2.0 ml EG stock solution, 145 °C, 24 h; the ketone was obtained after acidification. All reactions gave >99/1 regioselectivity as determined by ¹H NMR. ^b Isolated yield after acid hydrolysis.

and productivity (TON up to 3.75×10^5). It is noteworthy that the efficacy of the chemistry stems from the use of EG as a solvent, which may play a role in stabilizing the Pd-dppp catalyst and facilitating the formation of the ionic palladium intermediate. The latter feature enables the reaction to proceed *via* the ionic route and hence to preferentially afford the branched products. The chemistry provides a straightforward and convenient route to the synthesis of alkyl aryl ketones and cyclic ketals, displaying great potential for practical applications.

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- General procedure for regioselective Heck arylation of vinyl ethers: A stock solution of 0.1 mol% (1 mmol, 2.2 mg) palladium acetate together with 0.2 mol% dppp (2 mmol, 8.2 mg) was prepared in 10 mL degassed ethylene glycol, which was used as the mother solution to which subsequent dilutions were made. To ensure the mixture was homogeneous, the solution was left stirring under nitrogen at 60 °C for 12 h. The solution turned deep orange, with no sign of residue indicating that the Pd/dppp was dissolved homogeneously. To make a 1×10^{-2} mol% stock solution, 1 mL was taken from this mother solution and added (under nitrogen) to 9 mL of degassed ethylene glycol. This procedure was followed to make more dilution solutions when necessary. An oven-dried, two necked round-bottom flask containing a stirrer bar was charged with an aryl halide (1.0 mmol), Pd-dppp stock solution (2.0 mL) under nitrogen atmosphere at room temperature. After degassing three times, NEt_3 (2.0 mmol) was injected. The vinyl ether (2.0 mmol) was added after 2–4 min of pre-mixing at 145 °C in an oil bath. After an appropriate reaction time, the flask was removed from the oil bath and cooled to room temperature. For products requiring acid hydrolysis, aqueous HCl (5%, 5 mL) was added and following stirring for 0.5–3 h, CH_2Cl_2 (2.0 mL) was added. After separation of the CH_2Cl_2 phase, the aqueous layer was extracted with CH_2Cl_2 (3×5 mL), and the combined organic layer was washed with water until neutrality, dried (Na_2SO_4), filtered and concentrated in vacuo. The product was purified *via* flash chromatography on silica gel using a mixture of ethyl acetate and hexane (for details, please see Electronic Supplementary Information†).