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Hydrogen-Bond-Directed Catalysis: Faster, Regioselective and Cleaner Heck Arylation of Electron-Rich Olefins in Alcohols

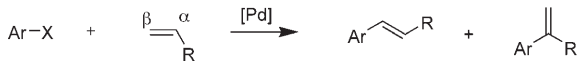
Zeynab Hyder, Jiwu Ruan, and Jianliang Xiao*[a]

Abstract: A general method for the regioselective Heck reaction of electron-rich olefins is presented. Fast, highly regioselective Pd-catalysed α-arylation of electron-rich olefins, vinyl ethers (**1a–d**), hydroxyl vinyl ethers (**1e,f**), enamides (**1g,h**) and a substituted vinyl ether (**1i**) has been accomplished with a diverse range of aryl bromides (**2a–r**), for the first time, in cheap, green and easily available alcohols with no need for any halide scavengers or salt additives. The reaction proceeds with high efficiency, leading exclusively to the α-products, in 2-propanol and particularly in ethylene glycol. In the latter, the arylation can be catalysed at a palladium loading of 0.1 mol% and finish in as short a time as 0.5 h. The remarkable performance of the alcohol solvents in promoting α regiocontrol is attributed to their hydrogen-bond-donating capability, which is believed to facilitate the dissociation of halide anions from Pd^{II}, and hence, the generation of a key ionic Pd^{II}–olefin intermediate responsible for the α product. This belief is further strengthened by the study of a benchmark arylation reaction in 21 different solvents. The study revealed that exclusive α-regioselective arylation takes place in almost all of the protic solvents, and there is a rough correlation between the α-arylation rates and the solvent parameter E_T^N. The method is simpler, cleaner and more general than those established thus far.

Keywords: alcohols · Heck reaction · hydrogen bonds · palladium catalysis · regioselectivity

Introduction

The formation of new sp^2 C–C bonds through the palladium-catalysed Heck reaction is one of the most important tools in synthetic chemistry due to its simplicity, its tolerance of various functional groups and the easy availability of substrates.[1] Most Heck reactions deal with electron-deficient olefins or those with electron-withdrawing substituents, such as -CN or $-CO_2R$, for which arylation or vinylation occurs at the least-substituted terminal β position of the double bond. This chemistry has been exploited in a diverse range of areas, which includes the synthesis of natural products and bioactive compounds.[1,2] However, a regioselectivity issue exists when electron-rich olefins, such as acyclic enol ethers, silanes and enol amides, are employed; these olefins tend to afford a mixture of branched α and linear β regioisomers under normal Heck conditions (Scheme 1).[1e,g,h,i,3–5] They are also generally associated with high catalyst loadings and low turnover frequencies (TOFs).



Scheme 1.

Extensive research by the groups of Cabri,[3a,5] Hallberg and Larhed,[1e,6] and others[7] has led to two effective methods to deal with the regioselectivity issue of electron-rich olefins: 1) when aryl/vinyl halides are the substrates, stoichiometric amounts of silver or thallium salts are added, and 2) organotriflates (or tosylates and mesolates) have been used instead of the halides.[5–7] In both scenarios the branched α-olefinic products are selectively produced. These methods have significantly extended the utility of the Heck reaction and led to a number of interesting applications in chemical synthesis.[6–9] However, there are short comings associated with the methods: silver introduces added cost, thallium salts are toxic and triflates are general-

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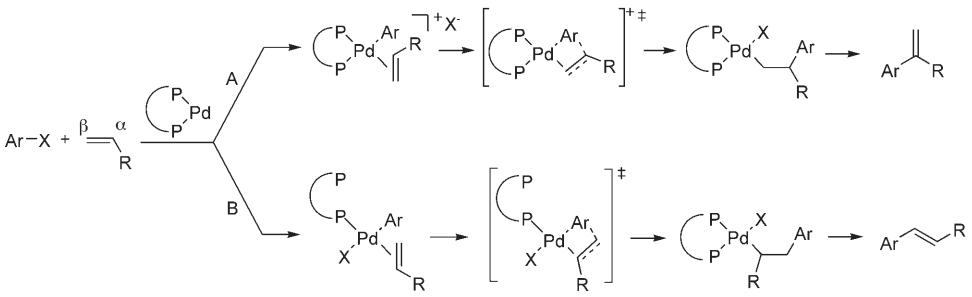
ly commercially unavailable in addition to being base sensitive and thermally labile.

It is now generally accepted that the regioselectivity issue exists because there are two competing reaction pathways in the Heck reaction, as illustrated in Scheme 2.[3,5,6,10] The cat-



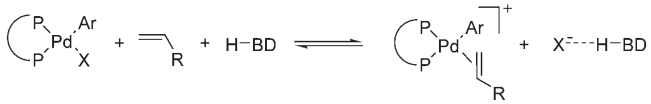
Scheme 2.

ionic pathway (Scheme 2, pathway A) yields the α product, whereas the neutral pathway (Scheme 2, pathway B) produces the β product. Pathway A has a distinguishing feature compared with pathway B: the former involves halide dissociation from Pd^{II}, whereas the latter features phosphorus dissociation. Given the electrophilic nature of cationic Pd^{II}, pathway A is expected to favour electron-rich olefins.[11] Silver and thallium salts act as halide scavengers, thereby promoting pathway A. Similarly, the lability of the Pd–OTf bond facilitates the formation of the cationic Pd^{II}–olefin species, thus leading to regioselective production of the branched product.[12] It is also apparent that a monodentate phosphorous ligand would favour pathway B, whereas a bidentante ligand would be necessary for pathway A.

Recent DFT calculations have given more insight into the mechanisms and show that when following pathway A electron-rich olefins indeed tend to afford the α-arylated olefin, and this is driven primarily by electrostatic and frontier orbital interactions.[13] In fact, the C–C bond forming olefin insertion step may be viewed as an intramolecular nucleophilic attack of the migrating aryl group at the olefin.[13a] More recently, Amatore, Jutand and co-workers showed that isobutyl vinyl ether reacts with [Pd(dppp)(Ph)X] (X = I, OAc; DPPP = 1,3-bis(diphenylphosphino)propane) via indeed a cationic species, $[Pd(Ph)(dppp)(solvent)]^+$, but this can lead to both α and β products.[14] The kinetic study led to the suggestion of an altered mechanism, in which the olefin reacts with the cationic solvato–Pd^{II} species generated from halide dissociation; a higher α regioselectivity results if the subsequent equilibria involving olefin coordination and insertion are in favour of the branched product, and if the concentration of halide anion is low.[14b]

Believing that the cationic Pd^{II}-olefin species in pathway A holds the key to the regioselectivity of electron-rich olefins, we have shown in the last few years that α regiocontrol in the coupling of aryl halides can be readily achieved by using imidazolium ionic liquids as solvents.[15] Under these conditions, we believe that the key cationic Pd^{II} species in pathway A is favoured, thus enhancing selectivity for the α product. Ionic liquids are entirely composed of ions; hence, electrostatic interactions would favour the generation of a Pd^{II}–olefin cation and a halide anion (Scheme 2, pathway A) from two neutral precursors over that of a neutral Pd^{II}–olefin intermediate from the same (Scheme 2, pathway B). The method, alongside those developed by other groups,[16–18] enables a highly regioselective Heck reaction without the use of halide scavengers or triflates, with the possibility for recycling.[15c] One drawback of the chemistry is that little is known about the toxicity of ionic liquids, and they can be expensive and laborious to synthesis.[19]

More recently, we demonstrated that in the presence of hydrogen-bond-donating ammonium salts, such as $[HNEt_3][BF_4]$, the regioselective Heck arylation of electron-rich olefins can be performed equally well in common solvents, such as DMF.[15d] We proposed that before the rate-determining step, which is likely to be the olefin insertion step,[14,15,20] an equilibrium exists in which addition of the potential hydrogen-bond donor shifts the equilibrium to favour the cationic Pd^{II}–olefin intermediate (Scheme 3). This leads to a higher concentration of the

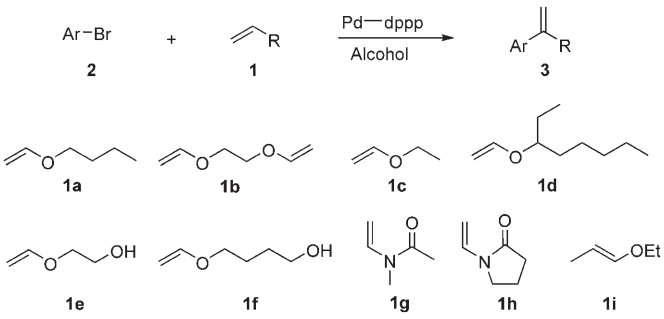


Scheme 3. H-BD: hydrogen-bond donor, for example, $HNEt_3^+$, HOH, HOR.

cationic intermediate, and hence, a higher rate for formation of the α product. We also showed that this acceleration in the α arylation by potential hydrogen-bond-donating ammonium salts is true in common solvents as well as in ionic liquids. However, a negative aspect arising from the application of such salts is that a large quantity of the salt is necessary, namely, 1.5 equiv relative to the substrate, which generates waste that needs to be separated and disposed of, and so has its associated environmental implications. In related work, Vallin, Larhed and Hallberg showed that regiocontrol can be achieved in a mixture of DMF/water or DMF/MeOH,[17] and very recently Larhed and co-workers reported that water can be used as a solvent for fast, highly regioselective arylation.[18] However, the chemistry of the latter appears to be restricted to hydroxyl vinyl ethers.

In continuing our search for a cleaner, more economic method for the regioselective Heck reaction, we now report that the Heck arylation of electron-rich olefins with aryl halides can be most easily performed in alcohols, in a highly regioselective and efficient manner that requires neither ionic

liquids/ionic additives nor halide scavengers (Scheme 4).[21,22] Although alcohols such as 2-propanol and ethylene glycol provide remarkably economic, safe and environmentally attractive alternatives to commonly used dipolar solvents, they have seldom been exploited in metal-catalysed coupling reactions.[23] Of both practical and fundamental significance is that our further studies point to the Heck regioselectivity being directed by polar, protic solvents.



Scheme 4.

Results

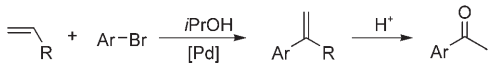
As with the hydrogen-bond-donating ammonium salts, alcohols are also good hydrogen-bond donors and are known to act as receptors for halide anions.[24] This feature could aid the dissociation of a halide anion from Pd^{II}, thereby enhancing the concentration of the ionic Pd^{II}–olefin species in pathway A (Scheme 3).[15d,25,26] In fact, short-chain alcohols are known to have hydrogen-bond-donating capabilities similar to imidazolium ionic liquids.[27] With this in mind, we set out to investigate whether the regioselective Heck arylation of electron-rich olefins could be achieved in a simple alcohol such as 2-propanol.

We first examined the feasibility of the arylation of butyl vinyl ether (**1a**) with 2-bromonaphthalene (**2a**) under the previously established Pd–dppp catalysis.[15] Pd–dppp has been shown to be the most successful catalyst for regioselective Heck arylation reactions in either molecular solvents or ionic liquids.[1,3,5–7,15] As in our previous studies, the catalyst used in this study was derived in situ from $Pd(OAc)_2$ and DPPP. Remarkably, the reaction of **1a** with **2a** at 115 °C was completed in 5 h with no linear product detected; ketone **4a** was isolated in excellent yield after acidification of **3a** (Table 1, entry 1). With such a simple protocol to hand, we started to test the reactions of aryl bromides **2b–n** with a range of alkyl vinyl ethers (**1a–c**,**e**). In a typical reaction, a mixture of **1**, **2**, $Pd(OAc)_2$, DPPP and triethylamine was heated in 2-propanol (2 mL) under reflux in an inert atmosphere of N_2; the ketone was obtained following hydrolysis of **3**. As can be seen in Table 1, good to excellent yields were obtained for all of the reactions, and in no case was the linear olefin detected or isolated. Because some reactions failed to complete within 5 h, as for entry 1, extended times of up to 18–24 h were permitted, so that full conversions were reached. We were also pleased to find that simple removal of the catalyst and resulting salt through a silica plug was sufficient to obtain immaculate purity. However, the *para* analogues (**2h**, **2j** and **2l**) of aryl bromides **2g**, **2i** and **2k** were sluggish when coupled with **1a**, and full conversions were not achieved in 24 h. The coupling of enamides with aryl bromides was even more sluggish, with insignificant amounts of products being detected after a reaction time of 36 h.

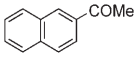
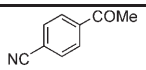
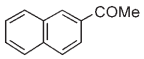
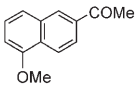
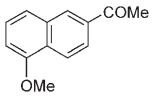
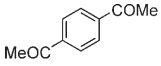
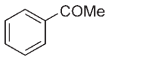
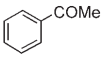
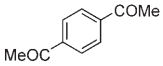
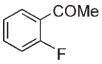
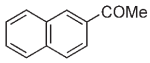
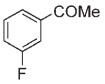
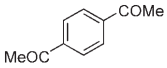
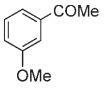
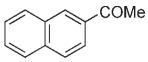
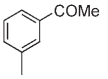
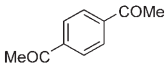
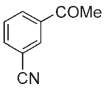
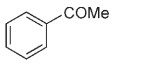
Ethylene glycol allows operation at a higher temperature, and may render ionic pathway A (Scheme 2) more favourable by forming more effective hydrogen bonds with the bromide anion and thus enhancing the concentration of the cationic Pd^{II}–olefin species (Scheme 3).[28] As an examination of feasibility, we tested the arylation of **1a** with **2a** and found that this benchmark reaction was completed within 2 h. To probe the scope of the system, a series of vinyl ethers were then tested in the arylation reaction with a range of aryl bromides (Table 2). Since some substrates necessitated longer times, for example, the enamides, the rest of the reactions were run overnight, and in the case of the enamides up to 36 h was necessary (entries 25–30). The reactions gave ketone products with good to excellent yields regardless of the nature of the substituents on the aryl rings, and again no linear product was observed. Of particular note are *para*-substituted bromides **2h**, **2j** and **2l**, which can now be completely olefinated, as also enamides **1g,h**, which have previously only been successfully arylated in a mixture of ionic liquid and DMSO.[15e] The reaction proceeded cleanly, so that again separation by using a small silica plug was usually sufficient to obtain pure products. When the enamide coupling is carried out in an aprotic solvent, such as dioxane, aryl triflates have been the substrates instead of the halides.[7b] Internal Heck vinylations of enamides have also been performed with high regioselectivity by using vinyl triflates as the substrates.[6b]

In the absence of an acid, the arylation product arising from 2-hydroxyethyl vinyl ether (**1e**) could cyclise to give an alternative method for the synthesis of ketals, which may find uses as intermediates for anti-HIV agents. This was first demonstrated by Hallberg, Larhed and Nilsson by using aryl triflates or halide scavengers for ArX (X = Br, I) in DMF;[6f] however, the reaction can be slow and requires the addition of dry acetic acid to complete ring closure or further heating following the consumption of the arylbromide. When **1e** was arylated in ethylene glycol under the conditions given in Table 2 but without subsequent hydrolysis, the corresponding 5-membered ketals were isolated in good yields (Table 3). An example of 7-membered ketals is also provided (Table 3, entry 10). However, prolonged heating cleanly turned it into 5-membered ketal **3ea**, for which a yield of 73% was obtained (Scheme 5). Apparently, this product arises from **3fa** reacting with the solvent to give a more thermodynamically stable product. The observation also suggests that there may be an exchange between **3ea**, **3fa** and ethylene glycol.

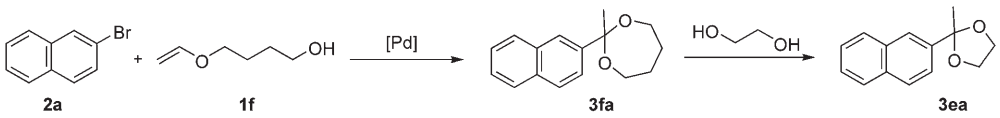
Table 1. Regioselective arylation of olefins **1** in 2-propanol.[a]



1 **2** **3** **4**

Entry	Olefin	ArBr	Product		Yield [%]	Entry	Olefin	ArBr	Product		Yield [%]
1	**1a**	**2a**		**4a**	92[b]	11	**1a**	**2n**		**4n**	83
2	**1a**	**2b**		**4b**	88	12[c]	**1b**	**2a**		**4a**	89
3	**1a**	**2c**		**4c**	94	13[c]	**1b**	**2c**		**4c**	74
4	**1a**	**2d**		**4d**	83	14[c]	**1b**	**2e**		**4e**	81
5	**1a**	**2e**		**4e**	87	15[c]	**1b**	**2d**		**4d**	92
6	**1a**	**2f**		**4f**	91	16	**1c**	**2a**		**4a**	82
7	**1a**	**2g**		**4g**	76	17	**1c**	**2d**		**4d**	79
8	**1a**	**2i**		**4i**	87	18[d]	**1e**	**2a**		**4a**	93
9	**1a**	**2k**		**4k**	85	19[d]	**1e**	**2d**		**4d**	97
10	**1a**	**2m**		**4m**	84	20[d]	**1e**	**2e**		**4e**	85

[a] Reaction conditions: **1** (3.0 equiv), **2** (1.0 mmol), $Pd(OAc)_2$ (4.0 mol%), DPPP (8.0 mol%), NEt_3 (2.5 equiv) and *i*PrOH (2 mL) at 115°C, for 18–24 h; 100% conversion and no linear products, as shown by ^1H NMR analysis; isolated yields are reported; **4** was obtained after acidification of **3**. [b] 5 h reaction time. [c] 0.75 equiv **1b**. [d] Ketals may be formed before the acidification (see Table 3).



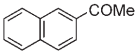
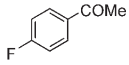
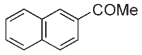
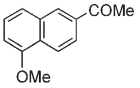
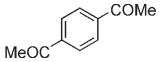
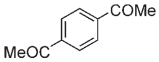
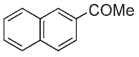
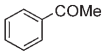
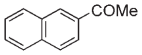
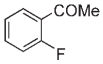
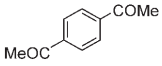
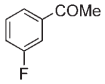
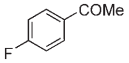
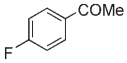
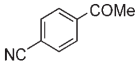
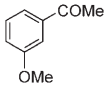
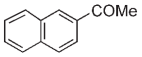
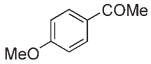
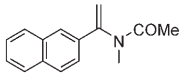
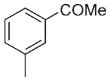
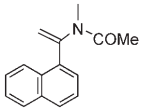
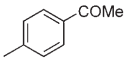
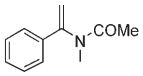
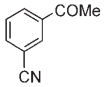
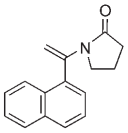
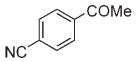
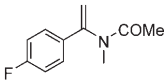
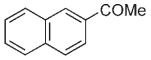
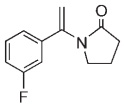
2a **1f** **3fa** **3ea**

Scheme 5.

We have previously shown that ketals are also formed in similar reactions in ionic liquids.[15c,d] In both ethylene glycol and ionic liquids, excellent α regioselectivities were maintained. As aforementioned, hydroxyl vinyl ethers also gave excellent regioselectivity when water was used as the solvent. Larhed and co-workers have also shown that the reaction works to some degree even in toluene.[18] The hydroxyl group thus appears to play a role similar to that of an alcohol solvent (see below).[25] In contrast, when carried out in DMF with a tetradentate phosphine, the reaction of **1e** favoured the β product.[26a]

In the reactions in ethylene glycol described above, the arylation procedure involved heating a mixture of all of the reagents together. It was noted that the ethylene glycol solution turned dark almost immediately, which indicated the formation of palladium black.[29] After a series of test reactions, it became apparent that the presence of the olefin from the beginning of the reaction enhanced the rate of Pd^{II} reduction to palladium black before it formed the Pd–dppp catalyst. In accordance with this finding, when the olefin substrate was added 3–4 min after the solution had been heated the initial yellow-orange solution only turned dark brown slowly, which suggested the presence of more Pd–dppp complex in the catalytic reaction. In a separate experiment, it was observed that in the presence of **1a**, a solution of $Pd(OAc)_2$ in 2-propanol turned dark in less than 1 min at room temperature; in its absence the solution remained yellow for more than 20 h, which again indicated that Pd^{II} is easily reduced by the olefin.

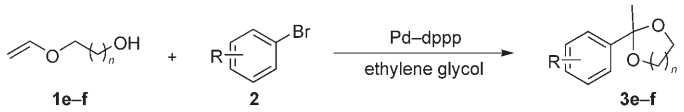
Table 2. Regioselective arylation of olefins **1** in ethylene glycol.[a]

Entry	Olefin	ArBr	Product		Yield [%]	Entry	Olefin	ArBr	Product		Yield [%]
1	**1a**	**2a**		**4a**	93	16	**1b**	**2h**		**4h**	78
2	**1a**	**2b**		**4b**	89	17	**1c**	**2a**		**4a**	74
3	**1a**	**2c**		**4c**	94	18	**1c**	**2d**		**4d**	76
4	**1a**	**2d**		**4d**	83	19	**1d**	**2a**		**4a**	78
5	**1a**	**2e**		**4e**	87	20	**1e**	**2a**		**4a**	88
6	**1a**	**2f**		**4f**	76	21	**1e**	**2d**		**4d**	83
7	**1a**	**2g**		**4g**	91	22	**1e**	**2h**		**4h**	87
8	**1a**	**2h**		**4h**	88	23	**1e**	**2n**		**4n**	89
9	**1a**	**2i**		**4i**	75	24	**1f**	**2a**		**4a**	93
10	**1a**	**2j**		**4j**	79	25[b]	**1g**	**2a**		**3ga**	78
11	**1a**	**2k**		**4k**	77	26[b]	**1g**	**2b**		**3gb**	79
12	**1a**	**2l**		**4l**	89	27[b]	**1g**	**2e**		**3ge**	81
13	**1a**	**2m**		**4m**	83	28[b]	**1h**	**2b**		**3hb**	74
14	**1a**	**2n**		**4n**	84	29[b]	**1g**	**2h**		**3gh**	78
15	**1b**	**2a**		**4a**	87	30[b]	**1h**	**2g**		**3hg**	82

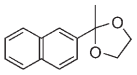
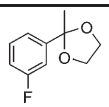
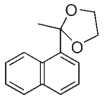
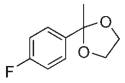
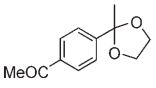
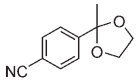
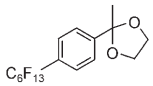
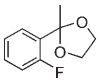
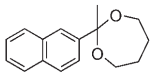
[a] Reaction conditions: **1** (3.0 equiv), **2** (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), DPPP (10.0 mol%) and NEt_3 (2.5 equiv) in ethylene glycol (2 mL) at 145 °C; 100% conversion and no linear products; isolated yields are reported; **4** was obtained after acidification of **3**. [b] Conditions were the same as for [a], omitting aqueous acidic work up.

This simple change in procedure was implemented in the arylation and we were delighted to find that the reaction in ethylene glycol proceeded at a much faster rate, even at lower catalyst loadings. Selected examples are illustrated in Table 4, which includes the coupling of 2-substituted olefin **1i**. For all of the substrates, particularly previously "stubborn" **2h**, **2j** and **2l**, the reaction time reduced dramatically compared with those presented in Tables 1 and 2, at a lower catalyst loading of 1%. More remarkably, the reaction time can be shortened to 0.5 h at a catalyst loading of as low as 0.1 mol% (Table 4, entries 20–22). It is also worth noting the successful arylation of aryl dibromides **2q** and **2r** (Table 4, entries 10 and 11), which required only short times for complete conversions. To the best of our knowledge, these examples represent the fastest rates ever reported for the Heck reaction of electron-rich olefins. We note that the

Table 3. Arylation of hydroxyl vinyl ethers to form cyclic ketals.[a]



1e–f 2 3e–f

Entry	Olefin	ArBr	Product		Yield [%]	Entry	Olefin	ArBr	Product		Yield [%]
1	**1e**	**2a**		**3ea**	88	6	**1e**	**2g**		**3eg**	87
2	**1e**	**2b**		**3eb**	88	7	**1e**	**2h**		**3eh**	85
3	**1e**	**2d**		**3ed**	89	8	**1e**	**2n**		**3en**	86
4	**1e**	**2e**		**3ee**	81	9	**1e**	**2o**		**3eo**	83
5	**1e**	**2f**		**3ef**	77	10	**1f**	**2a**		**3fa**	69

[a] Reaction conditions as in Table 2, without aqueous acidic work up; 100% conversion and no linear products; isolated yields are reported.

catalyst loading could not be decreased to lower than 2.5 mol% when the arylation was carried out in neat water.[18]

An additional advantage of the protocol is that it allows both the Pd–dppp catalyst and solvent to be easily recycled because the product could be extracted with a less polar solvent. To demonstrate this, the regioselective arylation of **1e** with **2a** was examined in ethylene glycol. Following each run, the ketal was extracted with diethyl ether. As shown in Scheme 6, the Pd/DPPP-ethylene glycol mixture was recycled five times with no significant loss in catalytic activity.

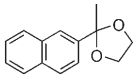
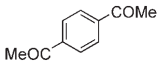
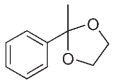
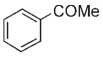
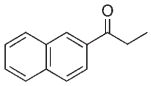
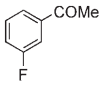
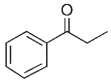
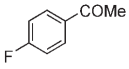
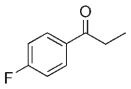
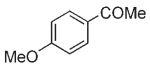
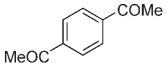
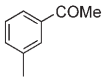
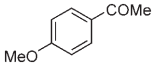
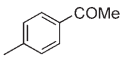
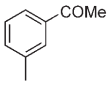
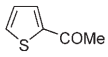
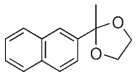
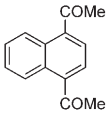
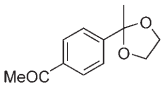
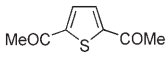
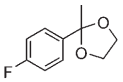
Discussion

The study into the regioselectivity of the Heck reaction has attracted a great deal of attention over the past two decades, culminating with the advent of three effective methods to control α regioselectivity (see above). It is surprising that a simple change of solvents from the common dipolar solvents, such as DMF, or ionic liquids to an alcohol affords complete regiocontrol for electron-rich olefins with no need for any halide scavengers. Naturally, one would like to ask why the alcohol solvents are so effective in promoting the α regioselectivity. We started this study by assuming that alcohols could act as hydrogen-bond donors to stabilise or solvate the dissociated halide anions and thereby enhance the concentration of the key cationic Pd–olefin intermediate (Scheme 3). If this is true, other protic solvents would function in a similar manner. In particular, solvents with high E_T^N values would be expected to give good α regiocontrol because they are in general good hydrogen-bond donors.[28] To a large degree, the previous reports from the groups of Hallberg and Larhed and us on using a mixture of water/DMF,[17] neat water[18] and ammonium salts (e.g., $HNEt_3^+$)[15d] to direct regioselection appear to support this view because all of these media possess hydrogen-bond-donating capabilities. To gather more evidence, we then screened a diverse range of solvents.

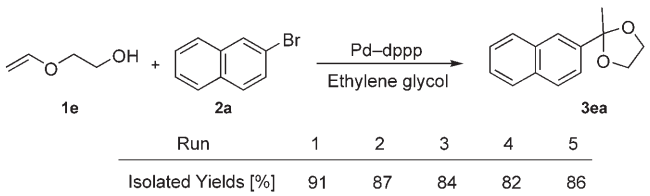
Our study of the arylation of **1a** with **2d** in 21 solvents is summarised in Table 5. Depending on the results used, the reaction of **1a** with **2d** can produce a mixture of α and β regioisomers and the latter, if formed, is usually composed of *E* and *Z* stereoisomers. The solvents examined span a wide range of the solvent spectrum, as reflected in their dielectric constants ε_r (7.2–191.3), dipole moments μ (5.5×10^{-30}–12.9×10^{-30} cm) and E_T^N values (0.23–0.79). When examining the results in Table 5, there appears to be no correlation between ε_r or μ with either conversion or TOF^{α}. However, whereas the E_T^N values do not show a correlation with conversion, there appears to be a link between this parameter and TOF^{α}. In fact, plotting $\ln TOF^{\alpha}$ against E_T^N reveals a roughly linear relationship: the higher the E_T^N values, the faster the α product is formed (Figure 1). Because the E_T^N parameter measures largely the hydrogen-bond-donating capability of a solvent, this rough correlation suggests that ionic pathway A (Scheme 2), and hence, the formation of the α product are accelerated by hydrogen-bond donors, which echoes our proposition mentioned above.

A closer look at Table 5 shows that the α product is exclusively produced in all of the protic solvents except for *N*-methylacetamide. The alcohols deserve particular attention because the β product was never detected in these solvents, and a clear correlation between the hydrogen-bond-donating capabilities and the TOF^{α} exists. All of the terminal alcohols afforded higher TOF^{α} than their internal isomers, of

Table 4. Faster, regioselective arylation in ethylene glycol.[a]

Entry	Olefin	ArBr	Product		Time [h]	Yield [%]	Entry	Olefin	ArBr	Product		Time [h]	Yield [%]
1	**1a**	**2b**		**4b**	0.5	77	12[c]	**1e**	2a		**3ea**	0.5	76
2	**1a**	**2d**		**4d**	0.5	83	13[c]	**1e**	**2e**		**3ee**	2	88
3	**1a**	**2e**		**4e**	0.5	85	14	**1i**	**2a**		**4ia**	3	72
4	**1a**	**2g**		**4g**	1	91	15	**1i**	**2e**		**4ie**	3	75
5	**1a**	**2h**		**4h**	1	89	16	**1i**	**2h**		**4ih**	3	81
6	**1a**	**2j**		**4j**	2	84	17[d]	**1a**	**2d**		**4d**	3	87
7	**1a**	**2k**		**4k**	0.5	78	18[d]	**1a**	**2j**		**4j**	3	74
8	**1a**	**2l**		**4l**	2	71	19[d]	**1a**	**2k**		**4k**	3	72
9	**1a**	**2p**		**4p**	0.5	81	20[c,d]	**1e**	**2a**		**3ea**	0.5	73
10[b]	**1a**	**2q**		**4q**	1	82	21[c,d]	**1e**	**2d**		**3ed**	0.5	76
11[b]	**1a**	**2r**		**4r**	1.5	69	22[c,d]	**1e**	**2h**		**3eh**	0.5	71

[a] Reaction conditions: **1** (3.0 equiv), **2** (1.0 mmol), $Pd(OAc)_2$ (1.0 mol%), DPPP (2.0 mol%) and NEt_3 (2.5 equiv) in ethylene glycol (2 mL) at 145°C, with **1** added 3–4 min after the mixture containing all the other reagents had been heated at 145°C; 100% conversion and no linear products detected; isolated yields are reported; **4** was obtained after acidification of **3**. [b] Conditions were the same as those given in [a]; however, compounds **2q** and **2r** are dibromides, so 6.0 equiv of **1** were used. [c] Conditions were the same as those given in [a], omitting aqueous acidic work up. [d] Conditions were the same as those given in [a] except lower quantities of $Pd(OAc)_2$ (0.10 mol%) and DPPP (0.20 mol%) were used.



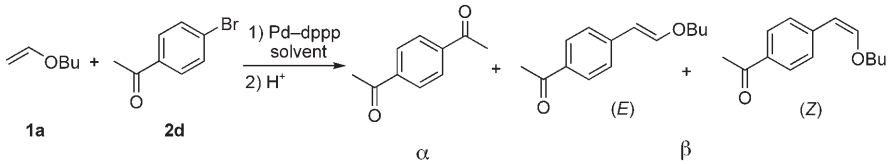
Scheme 6.

which the best hydrogen-bond donor, ethylene glycol, stands out as the best solvent. In sharp contrast, when performed in largely non-protic poly(ethylene glycol) ($M_W = 2000$) using $Pd(OAc)_2$ without ligand, the coupling of **1a** with **2** yields exclusively the β product.[30]

In recent studies by Amatore, Jutand and co-workers,[14] the high α regioselectivity observed in ionic liquids[15] was attributed to the high ionic strength of the solvent, which encourages anion–cation separation and therefore enhances the concentration of the Pd^{II}–olefin cations, and consequently, the selectivity towards the α product. In both our previous[15d] and current investigations, increasing the ionic strength is found to increase the arylation rates. Within the limited range of variation in ionic strength we examined, however, the ionic strength does not appear to impact on the regioselectivity. For instance, introduction of 0.5 equiv $[NEt_4][BF_4]$ (relative to the arylbromide) to the arylation of **1a** with **2d** in DMF resulted in an increase in TOF by 1.5 times. Whereas this is consistent with the kinetic study of Amatore and co-workers, which showed that [Pd(dppp)I(Ph)] reacts faster with an analogue of **1a** at higher ionic strength,[14b] the α/β ratio of the product from **1a** and **2d** remained at approximately 22:78. A similar observation was made with $NaPF_6$.[31]

Thus, it appears that it is the hydrogen-bond-donating capabilities that make simple alcohols such powerful solvents

Table 5. Solvent effect on the Heck arylation of **1a** by **2d**.[a]



Solvent	B.p. [°C]	ε_r	μ [10^{-30} cm]	E_T^N	Conversion[b] [%]	α/β[c]	*E*/*Z*	TOF$^{\alpha}$[d] [h^{-1}]
1,2-dimethoxyethane	84.5	7.2	5.7	0.231	7.4	18:82	79:21	0.4
triethylene glycol dimethyl ether	216	7.6	7.4	0.253	4.4	69:31	80:20	1.0
hexamethylphosphoric triamide	233	29.3	18.5	0.315	60	11:89	74:26	2.1
N,*N*-dimethylformamide	153.1	36.71	12.7	0.386	34	22:78	77:23	2.5
2-methyl-2-propanol	82.3	12.47	5.5	0.389	4.0	>99:1	–	1.4
N,*N*-dimethylacetamide	166.1	37.78	12.4	0.401	42	19:81	76:24	2.6
dimethyl sulfoxide	189	46.45	13.5	0.444	23	44:56	73:27	3.3
3-pentanol	115.3	13.35	5.5	0.463	9.0	>99:1	–	3.0
2-pentanol	119	13.71	5.5	0.488	7.5	>99:1	–	2.5
2-butanol	99.5	16.56	5.5	0.506	10	>99:1	–	3.3
2-propanol	82.2	19.92	5.5	0.546	13	>99:1	–	4.3
2-methyl-1-propanol	107.9	17.93	6.0	0.552	14	>99:1	–	4.7
1-pentanol	138	13.9	5.7	0.568	16	>99:1	–	5.3
1-butanol	117.7	17.51	5.8	0.586	22	>99:1	–	7.3
1-propanol	97.2	20.45	5.5	0.617	30	>99:1	–	10
ethanol	78.3	24.55	5.5	0.654	28	>99:1	–	9.4
N-methylacetamide	206.7	191.3	12.8	0.657	49	60:40	75:25	9.7
triethylene glycol	288	23.69	10.0	0.682	7.5[e]	>99:1	–	15
diethylene glycol	245.7	31.69	7.7	0.713	21[e]	>99:1	–	42
N-methylformamide	200	182.4	12.9	0.722	31[e]	>99:1	–	62
ethylene glycol	197.5	37.7	7.7	0.790	28[e]	>99:1	–	56

[a] Reaction conditions: **1a** (3.0 equiv), **2d** (1.0 mmol), $Pd(OAc)_2$ (1.0 mol%), DPPP (2.0 mol%), and NEt_3 (2.5 equiv) in solvent (2 mL) at 115 °C for 3 h; average of two runs; solvent parameters from reference [28]. [b] Conversion refers to the total conversion of **2d** into the α and β olefins and was determined by ^{1}H NMR spectroscopy. [c] When the β product was not detected by ^{1}H NMR spectroscopy, a >99/1 ratio was assigned. [d] TOF$^{\alpha}$ refers to turnover frequency for the α product calculated using the conversions. [e] 30 min reaction time.

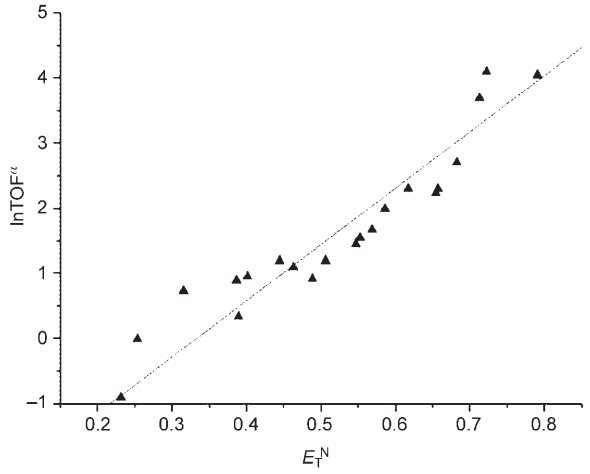
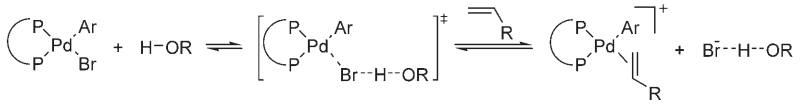


Figure 1. Effect of the solvent parameter E_T^N on TOF$^{\alpha}$ in the arylation of 4-bromoacetophenone with butyl vinyl ether (data taken from Table 5).

in accelerating the α regioselective Heck arylation. In fact, it has long been known that such solvents "exert an electrophilic pull on the departing anions in much the same way that heavy metal ions (Ag^+, Hg^{2+}) catalyse nucleophilic substitution reactions of haloalkanes",[28] which explains why no halide scavengers are necessary in alcohols. Analogous with the S_N1 nucleophilic substitution of haloalkanes,[28] the alcohols may not only solvate the ionised bromide anion, they could also aid its departure from Pd^{II} as illustrated in Scheme 7.[32,33]

Conclusion

This report presents the first general, green method for the Heck arylation of electron-rich olefins. Our results show that highly efficient and regioselective arylation of these olefins with aryl bromides can be readily carried out in simple alcohols to circumvent the need for silver, thallium, or ammonium salts, including ionic liquids. The chemistry is more general, greener and less expensive than the methods reported thus far. We believe that the excellent performance of the catalytic system stems from the solvents being dipo-



Scheme 7.

lar, and more importantly, hydrogen-bond donors. This belief is further strengthened by the study of a benchmark electron-rich olefin reacting with an arylbromide in 21 solvents, which revealed that hydrogen-bond donating, protic solvents accelerate α regioselective arylation. The higher the E_T^N values, the faster this reaction becomes. Whereas the detailed acceleration mechanism is yet to be scrutinised, we may conclude that dipolar, hydrogen-bond donor solvents, such as alcohols, promote the α arylation by facilitating bromide dissociation from Ar–Pd^{II}–Br and suppressing its recombination with the resulting cationic Ar–Pd^{II} species by hydrogen bonding. We note this proposition is not necessarily in conflict with the mechanism suggested by Amatore, Jutand and co-workers.[14b] As pointed out by one of the referees, by quenching the halides by hydrogen bonding with the solvent, the pathway leading to the β product is blocked, thereby rendering the α product favourable.

More than three decades ago, Gutmann recommended that reactive cations are best produced in solvents of high acceptor numbers.[34] These solvents are generally good hydrogen-bond donors, for example, water and short-chain alcohols. This recommendation still appears to be fitting for the Heck reaction of electron-rich olefins.

Experimental Section

General: All reactions were carried out under a nitrogen atmosphere. The olefins (**1**), aryl halides (**2**), $Pd(OAc)_2$, DPPP, triethylamine and all solvents were purchased from Aldrich and were used as received. Chromatographic purifications were performed through a silica gel (mesh 230–400) plug for the ketals and ketones, and by the flash technique for the enamides. ^1H and ^{13}C NMR spectra were recorded on a Gemini 400 spectrometer at 400 (^1H) and 100 MHz (^{13}C); values are given in ppm with reference to TMS as the internal standard in $CDCl_3$. Mass spectra were obtained by chemical ionisation (CI). The products were satisfactorily characterised by ^1H and ^{13}C NMR spectroscopies, MS and HRMS and when possible, comparison of NMR spectra has been made with available literature data, which includes our previous data.[15]

Arylation procedures: A typical procedure is given for the arylation of olefin **1a** in ethylene glycol. An oven-dried, two-necked round-bottom flask containing a stirrer bar was charged with an aryl halide (**2**; 1.0 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), DPPP (41 mg, 0.1 mmol) and solvent (2 mL) under nitrogen at room temperature. Following degassing three times, olefin **1a** (3.0 mmol) and NEt_3 (2.5 mmol) were sequentially injected. The flask was placed in an oil bath, and the mixture was stirred and heated at the desired temperature. After an appropriate reaction time, the flask was removed from the oil bath and cooled to room temperature. A small sample was then taken for analysis by NMR spectroscopy. For products requiring acid hydrolysis, aqueous HCl (5%, 5 mL) was added and following stirring for 0.5 h, CH_2Cl_2 (2 mL) was added. After separation of the CH_2Cl_2 phase, the aqueous layer was extracted with CH_2Cl_2 (2×5 mL), and the combined organic layer was washed with water until neutrality, dried (Na_2SO_4), filtered and concentrated in vacuo. Aryl methyl ketone **4** was isolated from crude product through a silica gel filled Pasteur pipette using CH_2Cl_2 as the eluent, which was then evaporated. Aryl enamides were isolated from the crude product by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (1:99 to 10:90) as the eluent.

The altered procedure was the same as above, except that the catalyst loading was lowered and **1a** was introduced 3–4 min after the mixture containing all the other reagents had been heated at 145 °C. The reaction time was significantly shorter with the new procedure (Table 4). The solvent effect was studied by using the new procedure. The identity and purity of the product was confirmed by ^1H and ^{13}C NMR spectroscopies, MS and HRMS.

1-(Naphthalen-2-yl)ethanone (4a): ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.40$ (s, 1H), 8.00–7.98 (m, 1H), 7.91–7.89 (m, 1H), 7.84–7.81 (m, 2H), 7.57–7.49 (m, 2H), 2.67 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.5$, 136.0, 134.8, 132.9, 130.6, 130.0, 128.9, 128.8, 128.2, 127.2, 124.3, 27.1 ppm; CIMS: *m/z* (%): 188 (100) $[M+NH_4]^+$, 171 (90); HRMS: *m/z* calcd for $C_{12}H_{11}O$ $[M+H]^+$: 171.0810; found: 171.0811.

1-(Naphthalen-1-yl)ethanone (4b): ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.76–8.74 (m, 1H), 7.90–7.87 (m, 1H), 7.83–7.77 (m, 2H), 7.56–7.52 (m, 1H), 7.47–7.43 (m, 1H), 7.40–7.36 (m, 1H), 2.65 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 202.2$, 136.0, 134.4, 133.4, 130.6, 129.0, 128.8, 128.4, 126.8, 126.2, 124.7, 30.3 ppm; CIMS: *m/z* (%): 188 (88) $[M+NH_4]^+$, 171 (100); HRMS: *m/z* calcd for $C_{12}H_{11}O$ $[M+H]^+$: 171.0810; found: 171.0809.

1-(5-Methoxynaphthalen-2-yl)ethanone (4c): ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.24$ (s, 1H), 7.89–7.88 (m, 1H), 7.86–7.85 (m, 1H), 7.62–7.60 (m, 1H), 7.09–7.01 (m, 2H), 3.81 (s, 3H), 2.56 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.2$, 160.2, 137.7, 133.1, 131.5, 130.4, 128.5, 127.5, 125.1, 120.1, 106.2, 55.8, 26.9 ppm; CIMS: *m/z* (%): 201 (100) $[M+H]^+$; HRMS: *m/z* calcd for $C_{13}H_{13}O_2$ $[M+H]^+$: 201.0916; found: 201.0916.

1,1′-(1,4-Phenylene)diethanone (4d): ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.94 (s, 4H), 2.55 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 197.7$, 140.5, 128.8, 27.2 ppm; CIMS: *m/z* (%): 180 (100) $[M+NH_4]^+$; HRMS: *m/z* calcd for $C_{10}H_{14}NO_2$ $[M+NH_4]^+$: 180.1024; found: 180.1025.

Acetophenone (4e): ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.97$–7.94 (m, 2H), 7.58–7.53 (m, 1H), 7.48–7.43 (m, 2H), 2.60 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.4$, 137.6, 133.4, 128.9, 128.7, 27.0 ppm; CIMS: *m/z* (%): 121 (100) $[M+H]^+$, 105 (86), 83 (30); HRMS: *m/z* calcd for C_8H_9O $[M+H]^+$: 121.0653; found: 121.0656.

1-(2-Fluorophenyl)ethanone (4f): ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.83$–7.77 (m, 1H), 7.47–7.41 (m, 1H), 7.21–7.11 (m, 1H), 7.09–7.07 (m, 1H), 2.57 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 196.2$, 162.6 (d, *J*(C,F) = 255 Hz), 135.0 (d, *J*(C,F) = 9.0 Hz), 131.0 (d, *J*(C,F) = 2.0 Hz), 126.1 (d, J_{CF} = 24 Hz), 124.7 (d, J_{CF} = 3.0 Hz), 117.0 (d, *J*(C,F) = 24 Hz), 31.7 ppm; CIMS: *m/z* (%): 156 (100) $[M+NH_4]^+$; HRMS: *m/z* calcd for $C_8H_{11}FNO$ $[M+NH_4)^+$: 156.0825; found: 156.0828.

1-(3-Fluorophenyl)ethanone (4g): ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.75$–7.71 (m, 1H), 7.65–7.61 (m, 1H), 7.48–7.41 (m, 1H), 7.29–7.23 (m, 1H), 2.60 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 197.0$, 163.25 (d, *J*(C,F) = 248 Hz), 139.6 (d, *J*(C,F) = 6.0 Hz), 130.6 (d, *J*(C,F) = 8.0 Hz), 124.5 (d, *J*(C,F) = 3.0 Hz), 120.4 (d, *J*(C,F) = 22 Hz), 115.3, 26.9 ppm; CIMS: *m/z* (%): 156 (100) $[M+NH_4]^+$; HRMS: *m/z* calcd for $C_8H_{11}FNO$ $[M+NH_4]^+$: 156.0825; found: 156.0827.

1-(4-Fluorophenyl)ethanone (4h): ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.01$–7.96 (m, 2H), 7.16–7.10 (m, 2H), 2.59 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 196.9$, 166.1 (d, *J*(C,F) = 250 Hz), 134.0 (d, *J*(C,F) = 3.0 Hz), 131.3 (d, *J*(C,F) = 9.0 Hz), 116.0 (d, *J*(C,F) = 22 Hz), 26.8 ppm; CIMS: *m/z* (%): 156 (100) $[M+NH_4]^+$; HRMS: *m/z* calcd for $C_8H_{11}FNO$ $[M+NH_4]^+$: 156.0825; found: 156.0829.

1-(3-Methoxyphenyl)ethanone (4i): ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.53–7.44 (m, 2H), 7.36–7.30 (m, 1H), 7.10–7.06 (m, 1H), 3.81 (s, 3H), 2.56 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.2$, 160.3, 139.4, 129.9, 121.5, 120.0, 112.8, 55.8, 27.0 ppm; CIMS: *m/z* (%): 168 (100) $[M+NH_4]^+$, 151 (32) $[M+H]^+$; HRMS: *m/z* calcd for $C_9H_{11}O_2$ $[M+H]^+$: 151.0759; found: 151.0759.

1-(4-Methoxyphenyl)ethanone (4j): ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.78$ (d, *J* = 8.9 Hz, 2H), 6.78 (d, *J* = 8.9 Hz, 2H), 3.71 (s, 3H), 2.39 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 196.9$, 163.8, 130.9, 130.8, 114.0, 55.7, 26.5 ppm; CIMS: *m/z* (%): 168 (36) $[M+NH_4]^+$, 151 (100) $[M+H]^+$; HRMS: *m/z* calcd for $C_9H_{11}O_2$ $[M+H]^+$: 151.0759; found: 151.0759.

1-*m*-Tolylethanone (4k): ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.76$–7.71 (m, 2H), 7.35–7.28 (m, 2H), 2.58 (s, 3H), 2.41 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 198.7$, 138.7, 137.6, 134.2, 129.2, 128.9, 126.0, 27.0,

21.7 ppm; CIMS: *m/z* (%): 152 (100) $[M+NH_4]^+$, 135 (32); HRMS: *m/z* calcd for $C_9H_{11}O$ $[M+H]^+$: 135.0810; found: 135.0811.

1-*p*-Tolylethanone (4l): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.85$ (d, $J=8.0$ Hz, 2H), 7.23 (d, $J=8.0$ Hz, 2H), 2.55 (s, 3H), 2.39 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=198.1$, 144.2, 135.2, 129.6, 128.8, 26.8, 21.9 ppm; CIMS: *m/z* (%): 152 (100) $[M+NH_4]^+$, 135 (76); HRMS: *m/z* calcd for $C_9H_{11}O$ $[M+H]^+$: 135.0810; found: 135.0809.

3-Acetylbenzonitrile (4m): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.26$–8.18 (m, 2H), 7.88–7.84 (m, 1H), 7.68–7.62 (m, 1H), 2.64 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=196.3$, 138.1, 136.4, 132.7, 132.4, 130.1, 118.4, 113.4, 27.0 ppm; CIMS: *m/z* (%): 163 $[M+NH_4]^+$, (100); HRMS: *m/z* calcd for $C_9H_{11}N_2O$ $[M+NH_4]^+$: 163.0871; found: 163.0867.

4-Acetylbenzonitrile (4n): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.06$ (d, $J=6.6$ Hz, 2H), 7.79 (d, $J=6.6$ Hz, 2H), 2.65 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=197.2$, 142.0, 133.2, 129.2, 117.7, 115.6, 27.1 ppm; CIMS: *m/z* (%): 163 $[M+NH_4]^+$, (100); HRMS: *m/z* calcd for $C_9H_{11}N_2O$ $[M+NH_4]^+$: 163.0871; found: 163.0866.

***N*-Methyl-*N*-(1-(naphthalen-2-yl)vinyl)acetamide (3ga)**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.82$–7.68 (m, 4H), 7.48–7.38 (m, 3H), 5.72 (s, 1H), 5.22 (s, 1H), 3.07 (s, 3H), 1.96 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=171.4$, 149.5, 134.0, 133.7, 133.1, 129.6, 128.9, 128.0, 127.1, 126.0, 125.3, 123.9, 113.2, 36.1, 22.2 ppm; CIMS: *m/z* (%): 226 (100) $[M+H]^+$; HRMS: *m/z* calcd for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1232; found: 226.1227.

***N*-Methyl-*N*-(1-(naphthalen-1-yl)vinyl)acetamide (3gb)**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.18$–8.14 (m, 1H), 7.82–7.64 (m, 2H), 7.50–7.28 (m, 4H), 5.39 (s, 1H), 5.14 (s, 1H), 3.01 (s, 3H), 2.12 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=169.6$, 148.2, 133.7, 133.2, 129.4, 129.1, 128.0, 127.1, 126.9, 125.6, 123.9, 124.0, 113.6, 35.3, 24.2 ppm; CIMS: *m/z* (%): 226 (100) $[M+H]^+$; HRMS: *m/z* calcd for $C_{15}H_{16}NO$ $[M+H]^+$: 226.1232; found: 226.1233.

***N*-Methyl-*N*-(1-phenylvinyl)acetamide (3ge)**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.31$–7.25 (m, 5H), 5.58 (s, 1H), 5.11 (s, 1H), 2.98 (s, 3H), 1.91 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=171.0$, 149.4, 135.9, 129.3, 125.9, 112.6, 53.9, 35.7, 22.0 ppm; CIMS: *m/z* (%): 176 (100) $[M+H]^+$; HRMS: *m/z* calcd for $C_{11}H_{14}NO$ $[M+H]^+$: 176.1075; found: 176.1074.

1-(1-(Naphthalen-1-yl)vinyl)pyrrolidin-2-one (3hb): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.91$–7.88 (m, 1H), 7.83–7.79 (m, 2H), 7.48–7.38 (m, 4H), 5.80 (s, 1H), 5.11 (s, 1H), 3.18 (t, $J=7.0$ Hz, 2H), 2.48 (t, $J=8.0$ Hz, 2H), 1.85–1.81 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=174.5$, 142.3, 135.9, 133.7, 131.7, 129.3, 128.8, 127.5, 127.1, 126.8, 125.7, 125.1, 108.5, 48.9, 32.8, 18.4 ppm; CIMS: *m/z* (%): 238 (100) $[M+H]^+$; HRMS: *m/z* calcd for $C_{16}H_{16}NO$ $[M+H]^+$: 238.1232; found: 238.1231.

***N*-(1-(4-Fluorophenyl)vinyl)-*N*-methylacetamide (3gh)**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.41$–7.37 (m, 2H), 7.10–7.05 (m, 2H), 5.62 (s, 1H), 5.21 (s, 1H), 3.08 (s, 3H), 2.02 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=171.2$, 163.7 (d, J(C,F)=249 Hz), 148.6, 127.9 (d, J(C,F)=8.0 Hz), 124.0, 116.4 (d, J(C,F)=24 Hz), 112.4, 35.8, 22.1 ppm; CIMS: *m/z* (%): 194 (100) $[M+H]^+$; HRMS: *m/z* calcd for $C_{11}H_{13}FNO$ $[M+H]^+$: 194.0981; found: 194.0976.

1-(1-(3-Fluorophenyl)vinyl)pyrrolidin-2-one (3hg): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.34$–7.27 (m, 2H), 7.18–6.98 (m, 2H), 5.39 (s, 1H), 5.24 (s, 1H), 3.63–3.46 (m, 2H), 2.58–2.43 (m, 2H), 2.17–2.05 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=172.8$, 163.2 (d, J(C,F)=245 Hz), 143.2, 139.1 (d, J(C,F)=8.0 Hz), 130.3 (d, J(C,F)=8.0 Hz), 128.7, 122.4, 115.6 (d, J(C,F)=21 Hz), 109.4, 49.9, 32.2, 18.9 ppm; CIMS: *m/z* (%): 206 (100) $[M+H]^+$; HRMS: *m/z* calcd for $C_{12}H_{13}FNO$ $[M+H]^+$: 206.0981; found: 206.0985.

2-Methyl-2-(naphthalen-2-yl)-1,3-dioxolane (3ea): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.86$ (s, 1H), 7.74–7.69 (m, 3H), 7.49–7.46 (m, 1H), 7.36–7.33 (m, 2H), 3.97–3.92 (m, 2H), 3.70–3.65 (m, 2H), 1.64 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=139.7$, 132.0, 129.2, 127.2, 127.0, 126.6, 125.1, 125.0, 122.9, 122.7, 107.9, 63.5, 26.6 ppm; CIMS: *m/z* (%): 215 (100) $[M+H]^+$; HRMS: *m/z* calcd for $C_{14}H_{15}O_2$ $[M+H]^+$: 215.1072; found: 215.1077.

2-Methyl-2-(naphthalen-1-yl)-1,3-dioxolane (3eb): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.51$ (d, $J=9.0$ Hz, 1H), 7.72–7.64 (m, 3H), 7.40–7.27 (m, 3H), 3.97–3.93 (m, 2H), 3.68–3.65 (m, 2H), 1.78 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=137.4$, 133.5, 129.3, 128.0, 127.6, 125.3, 124.7, 124.3, 123.8, 122.6, 108.6, 61.2, 26.5 ppm; CIMS: *m/z* (%): 215 $[M+H]^+$ (100); HRMS: *m/z* calcd for $C_{14}H_{15}O_2$ $[M+H]^+$: 215.1072; found: 213.1078.

1-(4-(2-Methyl-1,3-dioxolan-2-yl)phenyl)ethanone (3ed): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.83$ (d, $J=8.0$ Hz, 2H), 7.47 (d, $J=8.0$ Hz, 2H), 3.96–3.91 (m, 2H), 3.67–3.64 (m, 2H), 2.48 (s, 3H), 1.54 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=197.9$, 148.9, 137.1, 128.7, 125.9, 108.8, 64.9, 27.7, 26.9 ppm; CIMS: *m/z* (%): 207 (100) $[M+H]^+$; HRMS: *m/z* calcd for $C_{12}H_{15}O_3$ $[M+H]^+$: 207.1021; found: 207.1023.

2-Methyl-2-phenyl-1,3-dioxolane (3ee): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.38$–7.35 (m, 2H), 7.20–7.11 (m, 3H), 3.90–3.85 (m, 2H), 3.63–3.58 (m, 2H), 1.53 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=143.9$, 128.5, 128.2, 125.7, 109.2, 64.8, 28.0 ppm; CIMS: *m/z* (%): 165 $[M+H]^+$, (100); HRMS: *m/z* calcd for $C_{10}H_{13}O_2$ $[M+H]^+$: 165.0916; found: 165.0919.

2-(2-Fluorophenyl)-2-methyl-1,3-dioxolane (3ef): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.43$–7.40 (m, 1H), 7.20–7.14 (m, 1H), 7.01–6.96 (m, 2H), 4.00–3.96 (m, 2H), 3.76–3.72 (m, 2H), 1.67 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=160.4$ (d, J(C,F)=248 Hz), 128.9 (d, J(C,F)=9.0 Hz), 128.8 (d, J(C,F)=4.0 Hz), 126.2 (d, J(C,F)=3.0 Hz), 122.5 (d, J-(C,F)=4.0 Hz), 115.4 (d, J(C,F)=22 Hz), 106.3 (d, J(C,F)=4.0 Hz), 63.7, 25.1 ppm; CIMS: *m/z* (%): 183 (100) $[M+H^+]$, 167 (43); HRMS: *m/z* calcd for $C_{10}H_{12}FO_2$ $[M+H]^+$: 183.0821; found: 183.0825.

2-(3-Fluorophenyl)-2-methyl-1,3-dioxolane (3eg): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.24$–7.08 (m, 3H), 6.91–6.85 (m, 1H), 3.97–3.93 (m, 2H), 3.70–3.67 (m, 2H), 1.55 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=161.8$ (d, J(C,F)=244 Hz), 145.3 (d, J(C,F)=6.0 Hz), 128.8 (d, J(C,F)=8.0 Hz), 119.9 (d, J(C,F)=3.0 Hz), 113.5 (d, J(C,F)=21 Hz), 111.5 (d, J-(C,F)=22 Hz), 107.3 (d, J(C,F)=2.0 Hz), 63.5 (d, J(C,F)=9.0 Hz), 26.5 ppm (d, $J_{CF}=17$ Hz); CIMS: *m/z* (%): 183 (100) $[M+H]^+$, 167 (53); HRMS: *m/z* calcd for $C_{10}H_{12}FO_2$ $[M+H]^+$: 183.0821; found: 183.0825.

2-(4-Fluorophenyl)-2-methyl-1,3-dioxolane (3eh): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.37$–7.30 (m, 2H), 6.91–6.85 (m, 2H), 3.94–3.87 (m, 2H), 3.69–3.62 (m, 2H), 1.52 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=163.3$ (d, J(C,F)=246 Hz), 140.1 (d, J(C,F)=3.0 Hz), 128.0 (d, J(C,F)=9.0 Hz), 112.7 (d, J(C,F)=21 Hz), 109.4, 65.3, 28.5 ppm; CIMS: *m/z* (%): 183 (100) $[M+H]^+$; HRMS: *m/z* calcd for $C_{10}H_{12}FO_2$ $[M+H]^+$: 183.0821; found: 183.0825.

4-(2-Methyl-1,3-dioxolan-2-yl)benzonitrile (3en): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.58$–7.52 (m, 4H), 4.00–3.97 (m, 2H), 3.69–3.66 (m, 2H), 1.63 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=147.7$, 131.2, 125.2, 117.7, 110.8, 107.2, 64.1, 27.1 ppm; CIMS: *m/z* (%): 207 (100) $[M+NH_4]^+$; HRMS: *m/z* calcd for $C_{11}H_{12}NO_2$ $[M+H]^+$: 190.0868; found: 190.0865.

2-(4-Perfluorohexylphenyl)-2-methyl-1,3-dioxolane (3eo): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.67$–7.59 (m, 4H), 4.08–4.02 (m, 2H), 3.80–3.71 (m, 2H), 1.63 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=149.1$, 133.1-(t, J(C,F)=24 Hz), 132.6, 126.5 (t, J(C,F)=7 Hz), 108.6, 65.0, 27.8 ppm. The carbons in the perfluorocarbon chain were not observed.

2-Methyl-2-(naphthalen-2-yl)-1,3-dioxopane (3fa): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.01$ (s, 1H), 7.88–7.81 (m, 3H), 7.67–7.65 (m, 1H), 7.49–7.46 (m, 2H), 3.86–3.81 (m, 2H), 3.68–3.63 (m, 2H), 1.74–1.58 (m, 4H), 1.51 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=142.5$, 133.5, 133.2, 128.8, 128.4, 128.2, 127.9, 126.3, 125.2, 124.7, 103.1, 63.6, 29.9, 27.8 ppm; CIMS: *m/z* (%): 243 (100) $[M+H]^+$, 188 (85); HRMS: *m/z* calcd for $C_{16}H_{19}O_2$ $[M+H]^+$: 243.1385; found 243.1384.

1-(Thiophen-2-yl)ethanone (4p): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.71$–7.70 (m, 1H), 7.65–7.63 (m, 1H), 7.14–7.12 (m, 1H), 2.57 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=191.8$, 145.0, 134.2, 132.9, 128.5, 27.3 ppm; CIMS: *m/z* (%): 144 (100) $[M+NH_4]^+$, 124 (39); HRMS: *m/z* calcd for C_6H_7SO $[M+H]^+$: 127.0218; found: 127.0221.

1,1′-(Naphthalene-1,4-diyl)diethanone (4q): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.53$–8.50 (m, 2H), 7.81 (s, 2H), 7.63–7.61 (m, 2H), 2.74 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=202.5$, 140.1, 130.1, 128.5, 126.4, 126.0, 30.9 ppm; CIMS: *m/z* (%): 230 (100) $[M+NH_4]^+$.

1,1′-(Thiophene-2,5-diyl)diethanone (4r): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.60$ (s, 2H), 2.51 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 191.2, 150.1, 132.2, 27.3 ppm; CIMS: *m/z* (%): 186 (100) $[M+NH_4]^+$.

1-(Naphthalen-2-yl)propan-1-one (4ia): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.40 (s, 1H), 7.98–8.00 (m, 1H), 7.89–7.87 (m, 3H), 7.54–7.42 (m, 2H), 3.02 (q, $J = 7.2$ Hz, 2H), 1.24 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 201.2$, 136.0, 134.7, 133.9, 133.0, 130.0, 128.8, 128.3, 127.2, 126.3, 124.4, 32.3, 8.9 ppm; CIMS: *m/z* (%): 202 (70) $[M+NH_4]^+$, 185 $[M+H]^+$, (100); HRMS: *m/z* calcd for $C_{13}H_{13}O$ $[M+H]^+$: 185.0966; found: 185.0971.

Propiophenone (4ie): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.98$–7.95 (m, 2H), 7.57–7.53 (m, 1H), 7.49–7.43 (m, 2H), 3.01 (q, $J = 7.2$ Hz, 2H), 1.23 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 201.2$, 137.3, 133.3, 129.0, 128.4, 32.2, 8.7 ppm; CIMS: *m/z* (%): 152 (100) $[M+NH_4]^+$, 135 (68) $[M+H]^+$; HRMS: *m/z* calcd for $C_9H_{11}O$ $[M+H]^+$: 135.0810; found: 135.0806.

1-(4-Fluorophenyl)propan-1-one (4ih): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.90–7.92 (m, 2H), 7.06–7.02 (m, 2H), 2.90 (q, $J = 7.2$ Hz, 2H), 1.15 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 199.6$, 166.0 (d, J-(C,F) = 254 Hz), 133.7 (d, J(C,F) = 3.0 Hz), 131.0 (d, J(C,F) = 9.0 Hz), 116.0 (d, J(C,F) = 22 Hz), 32.1, 8.6 ppm; CIMS: *m/z* (%): 153 (67) $[M+H]^+$, 123 (100); HRMS: *m/z* calcd for $C_9H_{10}FO$ $[M+H]^+$: 153.0716; found: 153.0716.

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[1] For reviews, see: a) J. P. Knowles, A. Whiting, *Org. Biomol. Chem.* **2007**, *5*, 31; b) M. Oestreich, *Eur. J. Org. Chem.* **2005**, 783; c) R. B. Bedford, C. S. J. Cazin, D. Holder *Coord. Chem. Rev.* **2004**, *248*, 2283; d) M. Shibasaki, E. M. Vogl, T. Ohshima, *Adv. Synth. Catal.* **2004**, *346*, 1533; e) M. Larhed, A. Hallberg in *Handbook of Organopalladium Chemistry for Organic Synthesis, Vol. 1* (Ed.: E.-I Negishi), Wiley-Interscience, New York, **2002**, p. 1133; f) N. J. Whitcombe, K. K. Hii, S. E. Gibson, *Tetrahedron* **2001**, *57*, 7449; g) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009; h) L. S. Hegedus in *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed., University Science Books, Sausalito, CA, **1999**, Chapter 4.6; i) G. T. Crisp, *Chem. Soc. Rev.* **1998**, *27*, 427.

[2] For applications of the Heck reaction, see: a) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4516; *Angew. Chem. Int. Ed.* **2005**, *44*, 4442; b) V. Farina, *Adv. Synth. Catal.* **2004**, *346*, 1553; c) H.-U. Blaser, A. Indolese, F. Naud, U. Nettekoven, A. Schnyder, *Adv. Synth. Catal.* **2004**, *346*, 1583; d) A. Zapf, M. Beller, *Top. Catal.* **2002**, *19*, 101; e) J. G. de Vries, *Can. J. Chem.* **2001**, *79*, 1086; f) J. T. Link, L. E. Overman in *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, New York, **1998**, Chapter 6.

[3] a) W. Cabri, I. Candiani, *Acc. Chem. Res.* **1995**, *28*, 2; b) G. D. Daves Jr. , A. Hallberg, *Chem. Rev.* **1989**, *89*, 1433.

[4] For examples of regioisomer formation, see: a) F. Berthiol, H. Doucet, M. Santelli, *Appl. Organomet. Chem.* **2006**, *20*, 855; b) I. Kondolff, H. Doucet, M. Santelli, *Organometallics* **2006**, *25*, 5219; c) F. Berthiol, H. Doucet, M. Santelli, *Eur. J. Org. Chem.* **2005**, 1367; d) S. B. Park, H. Alper, *Org. Lett.* **2003**, *5*, 3209; e) V. Calo, A. Nacci, A. Monopoli, M. Spinelli, *Eur. J. Org. Chem.* **2003**, 1382; f) J. C. Hierso, A. Fihri, R. Amardeil, P. Meunier, H. Doucet, M. Santelli, B. Donnadieu, *Organometallics* **2003**, *22*, 4490; g) K. Maeda, E. J. Farrington, E. Galardon, B. D. John, J. M. Brown, *Adv. Synth. Catal.* **2002**, *344*, 104; h) A. Schnyder, T. Aemmer, A. F. Indolese, U. Pittelkow, M. Studer, *Adv. Synth. Catal.* **2002**, *344*, 495; i) M. Feuerstein, H. Doucet, M. Santelli, *Tetrahedron Lett.* **2002**, *43*, 2191; j) A. Littke, G. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 6989.

[5] a) W. Cabri, I. Candiani, A. Bedeschi, R. Santi, *J. Org. Chem.* **1993**, *58*, 7421; b) W. Cabri, I. Candiani, A. Bedeschi, S. Penco, R. Santi, *J. Org. Chem.* **1992**, *57*, 1481; c) W. Cabri, I. Candiani, A. Bedeschi, R. Santi, *J. Org. Chem.* **1992**, *57*, 3558.

[6] a) A. Arefalk, M. Larhed, A. Hallberg, *J. Org. Chem.* **2005**, *70*, 938; b) K. S. A. Vallin, Q. Zhang, M. Larhed, D. P. Curran, A. Hallberg, *J. Org. Chem.* **2003**, *68*, 6639; c) P. Nilsson, M. Larhed, A. Hallberg, *J. Am. Chem. Soc.* **2003**, *125*, 3430; d) A. Bengston, M. Larhed, A. Hallberg, *J. Org. Chem.* **2002**, *67*, 5854; e) K. Olofsson, H. Sahlin, M. Larhed, A. Hallberg, *J. Org. Chem.* **2001**, *66*, 544; f) P. Nilsson, M. Larhed, A. Hallberg, *J. Am. Chem. Soc.* **2001**, *123*, 8217; g) K. S. A. Vallin, M. Larhed, K. Johansson, A. Hallberg, *J. Org. Chem.* **2000**, *65*, 4537; h) K. Olofsson, M. Larhed, A. Hallberg, *J. Org. Chem.* **2000**, *65*, 7235; i) K. Olofsson, M. Larhed, A. Hallberg, *J. Org. Chem.* **1998**, *63*, 5076; j) M. Larhed, A. Hallberg, *J. Org. Chem.* **1997**, *62*, 7858; k) M. Larhed, A. Hallberg, *J. Org. Chem.* **1996**, *61*, 9582.

[7] a) A. L. Hansen, T. Skrydstrup, *Org. Lett.* **2005**, *7*, 5585; b) A. L. Hansen, T. Skrydstrup, *J. Org. Chem.* **2005**, *70*, 5997; c) T. Tu, X.-L. Hou, L.-X. Dai, *Org. Lett.* **2003**, *5*, 3651; d) J. C. Barcia, J. Cruces, J. C. Estévez, R. J. Estévez, L. Castedo, *Tetrahedron Lett.* **2002**, *43*, 5141; e) L. Maik, S. Stroemberg, M. Svensson, B. Åkermark, *Organometallics* **1999**, *18*, 970.

[8] For other examples of regioselective Heck reaction of electron-rich olefins, see: a) V. Calò, A. Nacci, A. Monopoli, V. Ferola, *J. Org. Chem.* **2007**, *72*, 2596; b) Y. Fall, F. Berthiol, H. Doucet, M. Santelli, *Synthesis* **2007**, 1683; c) G. K. Datta, H. Von Schenck, A. Hallberg, M. Larhed, *J. Org. Chem.* **2006**, *71*, 3896; d) V. Calò, A. Nacci, A. Monopoli, V. Ferola, *Eur. J. Org. Chem.* **2006**, 3791; e) A. Svennebring, P. Nilsson, M. Larhed, *J. Org. Chem.* **2004**, *69*, 3345; f) S. Bouquillon, B. Ganchegui, B. Estrine, F. Hénin, J. Muzart, *J. Organomet. Chem.* **2001**, *634*, 153.

[9] For examples of the Heck branched products leading to bioactive compounds, see: a) A. Arefalk, J. Wannberg, M. Larhed, A. Hallberg, *J. Org. Chem.*, **2006**, *71*, 1265; b) T. Tu, X.-L. Hou, L.-X. Dai, *Org. Lett.* **2003**, *5*, 3651; c) J.-Y. Legros, G. Primault, J.-C. Fiaud, *Tetrahedron* **2001**, *57*, 2507; d) H. Sakagami, K. Ogasawara, *Heterocycles* **2001**, *54*, 43; e) J. Wu, J. F. Marcoux, I. W. Davies, P. J. Reider, *Tetrahedron Lett.* **2001**, *42*, 159; f) T. Wegge, S. Schwarz, G. Seitz, *Tetrahedron: Asymmetry* **2000**, *11*, 1405; g) E. J. Homan, M. Th. M. Tulp, J. E. Nilsson, H. V. Wikstrom, C. J. Grol, *Bioorg. Med. Chem.* **1999**, *7*, 2541; h) L. Savelon, J. G. Bizot-Espiard, D. H. Caignard, B. Pfeiffer, P. Renard, M. C. Viaud, G. Guillaumet, *Bioorg. Med. Chem.* **1998**, *6*, 1963; also see references [1d] and [2a].

[10] a) F. Ozawa, A. Kubo, T. Hayashi, *J. Am. Chem. Soc.* **1991**, *113*, 1417; b) Y. Sato, M. Sodeoka, M. Shibasaki, *Chem. Lett.* **1990**, 1953.

[11] C. Hahn, *Chem. Eur. J.* **2004**, *10*, 5888.

[12] a) A. Jutand, *Eur. J. Inorg. Chem.* **2003**, 2017; b) J. M. Brown, K. K. Hii, *Angew. Chem.* **1996**, *108*, 679; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 657; c) A. Jutand, A. Mosleh, *Organometallics* **1995**, *14*, 1810.

[13] For DFT studies, see: a) R. J. Deeth, A. Smith, J. M. Brown, *J. Am. Chem. Soc.* **2004**, *126*, 7144; b) H. von Schenck, B. Akermark, M. Svensson, *J. Am. Chem. Soc.* **2003**, *125*, 3503; c) K. K. Hii, T. D. W. Claridge, J. M. Brown, A. Smith, R. J. Deeth, *Helv. Chim. Acta* **2001**, *84*, 3043; d) R. J. Deeth, A. Smith, K. K. Hii, J. M. Brown, *Tetrahedron Lett.* **1998**, *39*, 3229; e) K. Albert, P. Gisdakis, N. Rosch, *Organometallics* **1998**, *17*, 1608.

[14] a) C. Amatore, B. Godin, A. Jutand, F. Lemaitre, *Chem. Eur. J.* **2007**, *13*, 2002; b) C. Amatore, B. Godin, A. Jutand, F. Lamaître, *Organometallics* **2007**, *26*, 1757.

[15] a) J. Mo, L. J. Xu, J. W. Ruan, S. F. Liu, J. L. Xiao, *Chem. Commun.* **2006**, 3591; b) S. F. Liu, N. Berry, N. Thomson, A. Pettman, Z. Hyder, J. Mo, J. L. Xiao, *J. Org. Chem.* **2006**, *71*, 7467; c) Z. Hyder, J. Mo, J. L. Xiao, *Adv. Synth. Catal.* **2006**, *348*, 1699; d) J. Mo, J. L. Xiao, *Angew. Chem.* **2006**, *118*, 4258; *Angew. Chem. Int. Ed.* **2006**, *45*, 4152; e) J. Mo, L. J. Xu, J. L. Xiao, *J. Am. Chem. Soc.* **2005**, *127*, 751; f) L. J. Xu, W. P. Chen, J. Ross, J. L. Xiao, *Org. Lett.* **2001**, *3*,

295; for a recent review, see: g) S. F. Liu, J. L. Xiao *J. Mol. Catal. A* **2007**, *270*, 1.

[16] a) S. B. Park, H. Alper, *Chem. Commun.* **2004**, 1306; b) V. Caló, A. Nacci, A. Monopoli, A. Detomaso, P. Iliade, *Organometallics* **2003**, *22*, 4193; c) K. S. A. Vallin, P. Emilsson, M. Larhed, A. Hallberg, *J. Org. Chem.* **2002**, *67*, 6243.

[17] The arylation can also be performed in a DMF-water mixture: K. S. A. Vallin, M. Larhed, A. Hallberg, *J. Org. Chem.* **2001**, *66*, 4340; this paper also shows, albeit with one example, that the regioselective Heck reaction is feasible by using a mixture of DMF and MeOH.

[18] R. K. Arvela, S. Pasquini, M. Larhed, *J. Org. Chem.* **2007**, *72*, 6390.

[19] For studies on the toxicity and environmental impacts of ionic liquids, see: a) A. Romero, A. Santos, J. Tojo, A. Rodriguez, *J. Hazard. Mater.* **2008**, *151*, 268; b) A. Y. O. Matsuo, G. A. Lamberti, D. J. Couling, R. J. Bernot, K. M. Docherty, J. K. Dixon, E. J. Maginn, *Green Chem.* **2006**, *8*, 82; c) M. T. Garcia, N. Gathergood, P. J. Scammells, *Green Chem.* **2005**, *7*, 9; d) J. Bernd, R. Stoermann, J. Ranke, K. Moelter, F. Stock, B. Oberheitmann, W. Hoffmann, J. Hoffmann, M. Nuechter, B. Ondruschka, J. Filser, *Green Chem.* **2003**, *5*, 136.

[20] M. Portnoy, Y. Ben-David, I. Rousso, D. Milstein, *Organometallics* **1994**, *13*, 3405.

[21] For reviews on green chemistry and pharmaceutical synthesis including solvent usage, see: a) D. J. C. Constable, P. J. Dunn, J. D. Hayler, G. R. Humphrey, J. L. Leazer, R. J. Linderman, K. Lorenz, J. Manley, B. A. Pearlman, A. Wells, A. Zaksh, T. Y. Zhang, *Green Chem.* **2007**, *9*, 411; b) M. Butters, D. Catterick, A. Craig, A. Curzons, D. Dale, A. Gillmore, S. P. Green, I. Marziano, J.-P. Sherlock, W. White, *Chem. Rev.* **2006**, *106*, 3002; c) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337; d) A. D. Curzons, D. J. C. Constable, D. N. Mortimer, V. L. Cunningham, *Green Chem.* **2001**, *3*, 1.

[22] Part of this paper was presented at an AstraZeneca meeting on February 22, 2007 and at GlaxoSmithKline on April 27, 2007. Very recently, two communication papers appeared reporting the Heck arylation of *N*-acyl-*N*-vinylamine and **1a**, respectively, in 2-propanol: a) Z. H. Liu, D. Xu, W. J. Tang, L. J. Xu, J. Mo, J. L. Xiao, *Tetrahedron Lett.* **2008**, *49*, 2756; b) T. He, X. Tao, X. Wu, L. Cai, V. W. Pike, *Synthesis* **2008**, 887.

[23] For recent examples of coupling reactions in alcohols, see: a) R. Giri, N. Maugel, J. Li, D. Wang, S. P. Breazzano, L. B. Saunders, J. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510; b) S. Tandukar, S. Ayusman, *J. Mol. Catal. A* **2007**, *268*, 112; c) L. Wang, P. H. Li, Y. C. Zhang, *Chem. Commun.* **2004**, 514; d) J. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 1340; e) F. Y. Kwong, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 3517.

[24] D. K. Smith, *Org. Biomol. Chem.* **2003**, *1*, 3874. For a review, see: J. M. Llinares, D. Powell, K. Bowman-James, *Coord. Chem. Rev.* **2003**, *240*, 57.

[25] Larhed shows that the hydroxyl vinyl ether **1e** reacts with aryl bromides regioselectively in toluene and suggests this may be due to the dissociation of bromide from Ar-Pd-Br being facilitated by -OH hydrogen bonding to the bromide.[18]

[26] The hydroxy group of a substrate could also affect selectivities in the Heck reaction by coordinating to palladium: a) I. Kondolff, H. Doucet, M. Santelli, *Eur. J. Org. Chem.* **2006**, 765; b) M. Oestreich, F. Sempere-Culler, A. B. Machotta, *Angew. Chem.* **2005**, *117*, 152; *Angew. Chem. Int. Ed.* **2005**, *44*, 149; c) S-K. Kang, H.-W. Lee, S.-B. Jang, T.-H. Kim, S.-J. Pyun, *J. Org. Chem.* **1996**, *61*, 2604.

[27] a) C. Chiappe, D. Pieraccini, *J. Phys. Org. Chem.* **2005**, *18*, 275; b) S. V. Dzyuba, R. A. Bartsch, *Tetrahedron Lett.* **2002**, *43*, 4657; c) M. J. Muldoon, C. M. Gordon, I. R. Dunkin, *J. Chem. Soc. Perkin Trans. 2* **2001**, *4*, 433; d) A. J. Charmichael, K. R. Seddon, *J. Phys. Org. Chem.* **2000**, *13*, 591.

[28] The dielectric constants of 2-propanol and ethylene glycol are 19.9 and 37.7, respectively. The E_T^N values of 2-propanol and ethylene glycol are 0.546 and 0.790, respectively; this parameter measures largely the hydrogen-bond-donating capability of a solvent; C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed., Wiley-VCH, Weinheim, **2003**.

[29] G. Rothenberg, S. C. Cruz, G. P. F. van Strijdonck, H. C. J. Hoefsloot, *Adv. Synth. Catal.* **2004**, *346*, 467.

[30] a) S. Chandrasekhar, Ch. Narsihmulu, S. S. Sultana, N. R. Reddy, *Org. Lett.* **2002**, *4*, 4399; b) P. Ribiere, V. Declerck, Y. Nedellec, N. Yadav-Bhatnagar, J. Martinez, F. Lamaty, *Tetrahedron* **2006**, *62*, 10456.

[31] The effect of higher equivalents of salt was also investigated. However, the reduced solubility of the salt in the solvent obscured the results obtained. On the other hand, we note that the ionic strength of an ionic liquid, such as [bmim][BF_4] (bmim = 1-butyl-3-methylimidazolium), is significantly higher than that of the solution we examined, assuming the ionic strength can be calculated with $I = 0.5\Sigma Z_i^2 C_i$, in which Z_i is the charge of ion i and C_i is the concentration of the ion, and the salt is fully ionised in the solvent.

[32] The standard molar Gibbs energies of transfer of single bromide anions from water is $\Delta G = 7$ to ethylene glycol, 18.2 to EtOH, 22.0 to *i*PrOH, 27.4 to DMSO, 36.2 to DMF, 44.0 to DMA and 46.0 to HMPA (all in kJ mol^{-1}).[35] This provides an estimate on how well the Br^- ions are solvated by the alcohols in comparison with the dipolar, aprotic solvents commonly used in the Heck reaction.

[33] A solvato alcohol–Pd^{II} species could be formed before olefin coordination,[14b] which may also facilitate bromide dissociation.

[34] V. Gutmann, *Electrochim. Acta* **1976**, *21*, 661.

[35] Y. Marcus, *Pure Appl. Chem.* **1983**, *55*, 977.

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