

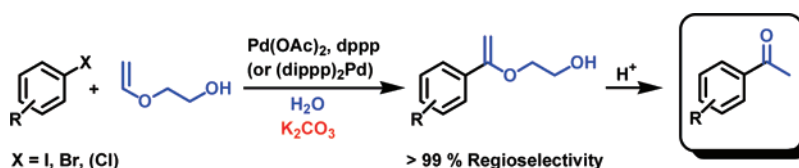
Highly Regioselective Internal Heck Arylation of Hydroxyalkyl Vinyl Ethers by Aryl Halides in Water

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Highly regioselective and fast Pd(0)-catalyzed internal α -arylation of ethylene glycol vinyl ether with aryl halides was shown to be possible in water without the need for any halide scavengers or ionic liquid additives. This presents, to our knowledge, the first case of water being utilized in the selective arylation of electron-rich olefins. Resulting α -products were hydrolyzed and isolated as corresponding acetophenones in good to excellent yields when using aryl bromides and with good to moderate yields in the case of aryl iodides. Microwave irradiation was shown to be beneficial in activation of aryl chlorides toward the internal Heck arylation. The scope of the protocol was further increased to include different hydroxyalkyl vinyl ethers, these all giving selectively only branched α -products. Finally, the active role of the hydroxy group in directing the regioselectivity toward internal arylation of electron-rich olefins, even in nonpolar toluene, was revealed.

Introduction

The first examples of Heck reaction, which is defined as a Pd(0)-mediated coupling of an aryl or vinyl halide or sulfonate ester with an alkene under the influence of base, were independently reported by Heck and Nolley and Mizoroki et al. in the early 1970s.^{1,2} Since then, it has gained more and more interest among scientists and is today known as one of the most versatile carbon–carbon coupling reactions.^{3–6} Especially interesting from an academic point of view has proven to be the control of regioselectivity, which is affected by a variety of different factors such as steric effects, electronic nature of olefin and aryl counterparts, catalytic system, and solvent

used in the reaction.^{7–9} It is today widely acknowledged that electron-deficient olefins such as acrylates and acrylonitriles generally give only terminal products (often referred to as β -products), while electron-rich olefins tend to give mixtures of internal α - and terminal β -products under standard Heck reaction conditions.³

Despite the initial problems relating to the use of acyclic electron-rich olefins, a lot of effort has been put into studying the regiocontrol of the Heck coupling in detail. The early work by Andersson and Hallberg showed the beneficial effect of enol triflates in vinylation of alkyl vinyl ethers, these giving both better regiocontrol favoring the formation of branched products and being superior in reaction rates compared to that of corresponding enol iodides.¹⁰ Complete reversal of regioselectivity, to give exclusively terminal β -products, was shown to be possible by introducing Pd-coordinating amino or phosphine

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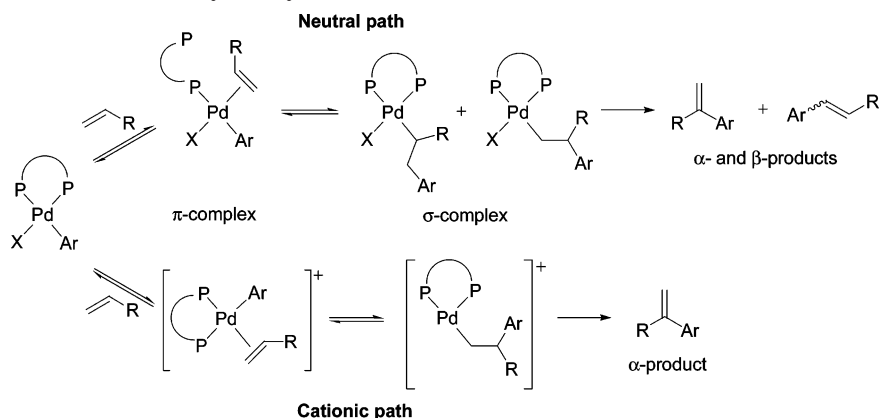
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SCHEME 1. Neutral vs Cationic Pathway in Arylation of Electron-Rich Olefins



groups to the vinyl ether.^{11–13} However, the major breakthrough came from Cabri et al. who were the first to realize the influence of both leaving group and phosphine ligand to the regioselectivity of the Heck reaction. More precisely, they utilized a variety of bidentate phosphine ligands, 1,3-bis(diphenylphosphino)propane (dppp) being especially advantageous, in conjunction with triflates as leaving groups in highly regioselective internal arylation of electron-rich olefins.^{14,15} Similar results were obtained with aryl halides when thallium or silver salts were used to scavenge halide ions from the solution.¹⁶ On the basis of these findings, Cabri and co-workers proposed that the reaction proceeds via a cationic pathway in which a charged organopalladium intermediate is formed after dissociation of an anionic ligand (Scheme 1).^{17,18} Dissociation of the neutral ligand in the case of strongly Pd(II)-coordinating groups, such as halide ions, results in a shift of the mechanism toward a neutral pathway leading to mixtures of α - and β -products.¹⁹

Although the use of triflates and other sulfonate ester derivatives has proven to be efficient in regioselective α -arylation, they are rarely commercially available and often expensive, thus limiting their applicability.²⁰ Aryl halides, on the contrary, are easily accessible and relatively cheap starting materials for organic synthesis. In the early 21st century, both Hallberg et al. and Xiao et al. reported methodologies for highly regioselective α -arylation of electron-rich butyl vinyl ether with aryl bromides in DMF–water mixtures or in ionic liquids without the need for toxic thallium or expensive silver

additives.^{21–23} In these methods, the DMF–water– K_2CO_3 cocktail or imidazolium-based ionic liquids, [bmim][BF_4] and [bmim][PF_6], were used as solvents to increase the polarity of the reaction mixture to favor the formation of charged intermediate. The applicability of ionic liquids as a sole solvent or as an additive has further on been expanded to include the arylation of a wide range of electron-rich olefins regioselectively with aryl and heteroaryl halides.^{24–28} As further proof of this concept, Jutand et al. reported very recently that $[\text{Pd}(\text{dppp})(\text{S})\text{-Ph}]^+$ (S = solvent) is the most reactive complex formed in the oxidative addition of PhI to the $\text{Pd}(0)/\text{dppp}$ complex, its overall role in directing the regioselectivity increasing at high ionic strengths.²⁹

In addition to finding faster, cheaper, and more operative synthetic routes, there is also an ever-growing need for more environmentally friendly ways to perform organic reactions. Use of ionic liquids has in many cases been confirmed to be efficient, but high costs, often laborious workup procedures, and lack of long-range statistics relating to their possible toxicity and biodegradability in nature have reduced somewhat their use in industrial processes.³⁰ Water, on the other hand, is nontoxic, nonflammable, readily available, and inexpensive. Moreover, because of its polar nature it is an excellent solvent, especially suitable for microwave-assisted organic synthesis and is today widely used in organic transformations as evidenced by increasing numbers of reviews appearing in the literature every year.^{31,32} We herein report, to the best of our knowledge, the first ever

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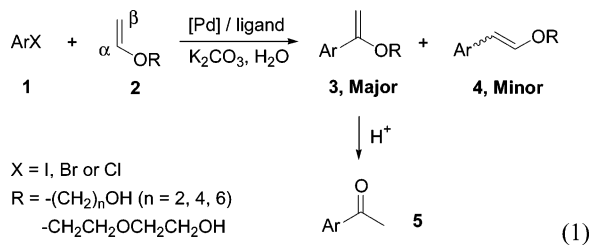
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methodology for highly selective, palladium-catalyzed internal arylation of electron-rich olefins by aryl halides in water (eq 1). In addition, we discuss the unique nature of these olefins in guiding the mechanism toward the cationic pathway, even in nonpolar solvents such as toluene.



Results and Discussion

Reactions with Aryl Bromides and Iodides. In our previous studies on the Heck arylation of electron-rich olefins, we focused mainly on the use of triflates as leaving groups.³³ However, because of the problems relating to sulfonate esters, we were keen to develop further our methodology utilizing aryl halides in the DMF–water system²¹ and thus avoid the use of expensive and laborious ionic liquids. As a starting point, we chose to study a reaction between 4-bromoanisole (**1a**) and ethylene glycol vinyl ether (**2a**), carrying a hydrophilic hydroxy group. Reactions were run in water³⁴ using K₂CO₃ as a base and a catalytic system constructed of Pd(OAc)₂ and dppp. Furthermore, all experiments were run under air using conventional heating, and formed α -products were hydrolyzed and isolated as 4'-methoxyacetophenone (**5a**). Results from the reaction development are summarized in Table 1.

An initial coupling of **1a** with olefin **2a** (5.0 equiv), using 3.7 equiv of K₂CO₃, 2.5 mol % of Pd(OAc)₂, and 5.0 mol % of dppp in 1.0 mL of deionized water, gave full conversion after 2 h of heating at 100 °C, showing a promising α/β ratio of 88:12. However, analysis of the crude product revealed a major loss of material, and disappointing 44% yield of **5a** was recorded by ¹H NMR analysis³⁵ (Table 1, entry 1). Decreasing the temperature to 90 °C was noticed to be beneficial, giving 74% isolated yield of **5a** without any β -product formation (entry 2), but further decrease of the temperature to 80 °C led to only traces of product after 24 h of heating time. In addition to K₂CO₃, a few other bases, namely NEt₃, KOAc, and KHCO₃, were tested in the protocol but neither of these superseded the results obtained with K₂CO₃ (data not reported here).

Additional adjustment of the reaction time and the amount of base needed in the reaction (entries 3–8) provided 73% isolated yield of **5a** after only 80 min of heating at 90 °C using 1.2 equiv of base. The reaction time reported here is considerably shorter than in most of the protocols available today for the α -arylation of electron-rich olefins by organobromides (times varying usually between 24 and 36 h),^{21,22,24–28} which combined with the easy purification makes this methodology highly

TABLE 1. Reaction Development for Arylation of Ethylene Glycol Vinyl Ether in Water^a

entry	2a (equiv)	K ₂ CO ₃ (equiv)	T (°C)	t (min)	3a/4a ^b	5a ^c (%)
1	5.0	3.7	100	120	88:12	44 ^{d,e}
2	5.0	3.7	90	120	99:1	74
3	5.0	3.0	90	120	99:1	70
4	5.0	2.0	90	120	99:1	75
5	5.0	1.2	90	120	99:1	74
6	5.0	1.2	90	100	99:1	69
7	5.0	1.2	90	80	99:1	73
8	5.0	1.2	90	60	99:1	71 ^f
9	5.0	1.2	90	80	99:1	41 ^{f,g}
10	3.0	1.2	90	120	99:1	41 ^f

^a Constant in all experiments: **1a** (0.50 mmol), Pd(OAc)₂ (2.5 mol %), dppp (5.0 mol %), H₂O (1.0 mL). Hydrolysis of **3a** was performed by addition of concd HCl (aq). ^b Determined by ¹H NMR and/or GC/MS.

^c Isolated yield. Purity >95% by GC/MS. ^d Yield determined by comparing to internal standard in ¹H NMR analysis. ^e Major loss of material.

^f Conversion of **1a** to product(s) not complete. ^g Pd(OAc)₂ (1.0 mol %), dppp (2.0 mol %).

advantageous. In addition, the reaction proceeds cleanly in water, without the need for heavy metal additives or inert atmosphere and with no noticeable formation of dehalogenation products, which sometimes has been reported in the literature to occur when using aryl halides in aqueous media.²¹ Unfortunately, we were not able to decrease either the amount of catalyst or the amount of olefin (entries 9 and 10). It should also be noted that omission of the bidentate ligand led to considerable decomposition of the starting material and changing it to monodentate PPh₃ resulted in a loss of regioselectivity.

Having identified proper conditions (Table 1, entry 7), we wanted to test the usefulness of our protocol by screening a variety of substituted aryl bromides (Table 2). We soon discovered that the amount of base becomes crucial when moving from electron-donating to electron-withdrawing substituents on the organobromide; 4-bromobenzophenone (**1h**) is far less reactive than 4-bromoanisole (**1a**) when using only a slight excess of base (Table 2, compare entries 1 and 8, Method A). In fact, only 8% yield of **5h** was recorded after 80 min of heating when using 1.2 equiv of K₂CO₃. Increasing the amount of base to 3 equiv furnished an increase of the reaction rate, giving full conversion and an excellent 99% isolated yield (entry 8, Method B). It is likely that the increase in basicity and ionic strength of the reaction mixture with excess of base promotes ionization and facilitates the olefin insertion step for this electron-poor Pd-aryl intermediate.²¹

Further screening demonstrated the applicability of our aqueous methodology, and yields varying from good to excellent were obtained with a diverse group of aryl bromides (Table 2, entries 1–9). Method B, utilizing a large excess of base, was shown to be more general altogether and absolutely necessary when having electron-withdrawing groups on an aryl counterpart.³⁶ Reactions proceeded in a highly α -selective manner even in the absence of an electron-rich aryl group capable of

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(34) High-quality ultrapure Millipore water was used in all reactions. However, regular tap water provides identical reaction outcome according to GC/MS analysis.

(35) The ¹H NMR integral of the methoxy group of **5a** was compared to integrals of a known amount of 2,3-dimethylnaphthalene used as an internal standard.

(36) Interestingly, also after addition of extra amount of K₂CO₃ (Method B), reactions with **2a** appear to be homogeneous, not biphasic, at 90 °C.

TABLE 2. Internal Arylation of Ethylene Glycol Vinyl Ether with Aryl Bromides and Iodides in Water^a

$\text{ArX} + \text{CH}_2=\text{CH}-\text{O}-\text{CH}_2-\text{CH}_2-\text{OH} \xrightarrow[\text{K}_2\text{CO}_3, \text{H}_2\text{O}]{\text{Pd}(\text{OAc})_2, \text{dppp}} \xrightarrow{\text{H}^+} \text{Ar}-\text{C}(=\text{O})-\text{CH}_2-\text{CH}_2-\text{OH}$							
entry	ArX	α/β^b (3/4)	product	method ^c	yield (%) ^d		
1		99:1		A	73 88 ^e		
2		99:1		A B	79 84		
3		99:1		A B	84 92		
4		99:1		A B	60 63		
5		99:1		A B	37 ^f 52		
6		99:1		A B	16 ^{g,h} 60 ⁱ		
7		99:1		A B	89 91		
8		99:1		A B	8 ^{f,h} 99		
9		97:3		A B	14 ^{f,h} 61 ^j		
10		99:1		B	28		
11		99:1		B	73		
12		99:1		A	49		
13		99:1		B	65 ^j		
14		99:1		B	32 ^{f,i,j}		

^a The reactions were performed on 0.50 mmol scale with 5.0 equiv of **2a**, 2.5 mol % of Pd(OAc)₂, 5.0 mol % of dppp, and 1.2–3.0 equiv of K₂CO₃ in 1.0 mL of H₂O by heating at 90 °C for 80 min. Hydrolysis of **3** was performed by addition of concd HCl (aq). ^b Determined by GC/MS. ^c Method A: 1.2 equiv of K₂CO₃. Method B: 3.0 equiv of K₂CO₃. ^d Isolated yield. Purity >95% by GC/MS. ^e Reaction was performed on 50 mmol scale. ^f Conversion of **1** to product(s) not complete. ^g Substantial loss of material. ^h Yield determined by comparing to internal standard in ¹H NMR analysis. ⁱ Reaction time of 120 min. ^j Formation of some dehalogenation product.

stabilizing the cationic π -intermediate. The shift toward the neutral pathway giving both internal and terminal products was noticed only with 4-bromonitrobenzene, which gave a substantial loss of material, some dehalogenation product, and a mixture of α - and β -products.³⁷ Two heteroaryl bromides were also tested, but only 2-bromothiophene gave a synthetically meaningful 73% isolated yield of ketone **5k** (entries 10 and 11). Finally, to prove the scalability of this methodology, the reaction was scaled up to 100-fold using 4-bromoanisole as an aryl substrate, giving an impressive 88% isolated yield of 4'-methoxyacetophenone **5a** (entry 1). In addition to aryl bromides, a few substituted aryl iodides were tested. This class of arylpalladium precursors gave generally lower yields than aryl bromides, with dehalogenation becoming a more serious issue as moving toward electron-withdrawing substituents on the benzene ring (entries 12–14). Despite this, reactions with aryl iodides proceeded with full regiocontrol and represent one of the few cases where aryl iodides have been used successfully in regioselective internal arylation of electron-rich olefins.^{16,24}

Reactions with Aryl Chlorides. To our disappointment, aryl chlorides showed no reactivity in our Pd(OAc)₂/dppp-mediated aqueous protocol. This is believed to be caused by an inadequate activation of the strong Ar–Cl bond toward oxidative addition by Pd(0)/dppp.^{4,5} In fact, only Xiao et al. have successfully used aryl chlorides in the regioselective arylation of electron-rich butyl vinyl ether, using [HNEt₃][BF₄] as an extra activator.³⁸ However, only a handful of activated organochlorides were arylated under somewhat harsh conditions, partly diminishing the value of this discovery. We were, nevertheless, eager to find a catalytic system to complete our methodology, and thus we turned our attention to electron-rich, chelate-stabilized (dipp)₂Pd(0) (dipp = 1,3-bis(diisopropylphosphino)propane). This catalyst, which can also be formed in situ from Pd(OAc)₂ and dipp, has been extensively used in, for example, carbonylation and dechlorination of aryl chlorides.³⁹ Indeed, by simply replacing the earlier catalytic system by 5 mol % of (dipp)₂Pd(0) we managed to get 38% isolated yield from the reaction between 4-chloroacetophenone (**1o**) and olefin **2a** after 80 min of heating at 90 °C (Table 3, entry 1). The reaction proceeded with excellent regioselectivity (99:1 α/β), giving some acetophenone as a dehalogenated byproduct. Further improvement of the reaction conditions was possible by pre-activating the catalytic system at 50 °C followed by heating at 130 °C for 90 min with high-density microwave irradiation;^{40,41} this gave an excellent 89% isolated yield of **5g** with an α/β ratio of 94:6.

Encouraged by our success, we screened a few other aryl chlorides with varying results using (dipp)₂Pd(0) (Table 3). When employing 4-chloroacetophenone (**1o**) and 2-chloronaphthalene (**1p**) (entries 1 and 2), good yields and regioselectivities were obtained. However, in contrast to the outcome with aryl bromides, unactivated aryl chlorides provided poor yields, implying difficulties in the oxidative addition step (entries 3

(37) Difficulties in using 4-nitrophenyl substrates have been previously reported; see ref 33c.

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(39) For a few examples, see: (a) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *111*, 8742. (b) Ben-David, Y.; Gozin, M.; Portnoy, M.; Milstein, D. *J. Mol. Catal.* **1992**, *73*, 173. (c) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1989**, 1816. (d) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665.

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TABLE 3. Internal Arylation of Ethylene Glycol Vinyl Ether with Aryl Chlorides in Water^a

entry	ArCl	α/β^b (3/4)	product	yield (%) ^c	
1		99:1 94:6		38 ^{d,e,f} 89 ^f	
2		99:1		71 ^{e,f}	
3		95:5		33 ^{e,f}	
4		96:4		15 ^{e,f}	
5		76:24		46 ^g	

^a The reactions were performed on 0.25 mmol scale with 5.0 equiv of **2a**, 5.0 mol % of (dipp)₂Pd, and 3.0 equiv of K₂CO₃ in 1.0 mL of H₂O by irradiating with microwaves at 130 °C for 90 min. Hydrolysis of **3** was performed by addition of concd HCl (aq). ^b Determined by GC/MS. ^c Isolated yield. Purity >95% by GC/MS. ^d Conventional heating at 90 °C for 80 min. ^e Conversion of **1** to product(s) not complete. ^f Formation of some dehalogenation product noticed. ^g 33% of benzophenone formed as a byproduct.

and 4). In the early 1990s, Milstein et al. reported their studies about the Pd/dipp system in promoting the facile oxidative addition of chlorobenzene to Pd(0).^{39d,42,43} The oxidative addition step worked well in several solvents, and polar solvents provided the fastest reaction rates. However, in a base-mediated terminal Heck coupling, half of the catalytic species were deactivated in each catalytic cycle because of formation of a stable dichloride complex (dipp)₂PdCl₂. In light of these results, it might be that unactivated electron-rich aryl chlorides require a higher catalyst concentration compared to more reactive electron-poor analogues, explaining the incomplete conversion. On the other hand, with electron-deficient **1s**, the insertion of olefin becomes rate-limiting, allowing formation of a significant amount of dehalogenation product (entry 5). In addition, poorer regiocontrol was noticed with **1s**, which is likely to be caused by the high reaction temperature and the inability of the electron-deficient ArPd(dipp)Cl intermediate to release the chloride ion, thus forcing the dipp ligand to hand over one of the metal coordination sites for the incoming olefin (Scheme 1, neutral reaction pathway).

Reactions with Different Olefins. To further explore the scope of this highly selective internal Heck arylation, a few additional examples of electron-rich olefins were screened. Results from these experiments are summarized in Table 4. Reactions were run using exactly the same conditions as in

TABLE 4. Arylation of Some Vinyl Ethers and Allyl Alcohol with 4-Bromoanisole in Water^a

entry	olefin	α/β^b	5a (%) ^c	4 (%) ^c	1a (%) ^c
1		99:1	73 ^d	-	-
2		99:1	23 26 ^e	-	52 58
3		99:1	24 29 ^e	-	41 45
4		99:1	17	-	27
5		-	-	-	-
6		80:20	16	4	nd ^g
7		61:39	21	13	36
8		78:22	25	nd ^h	40
9		-	-	-	-

^a The reactions were performed on 0.50 mmol scale with 5.0 equiv of olefin, 2.5 mol % of Pd(OAc)₂, 5.0 mol % of dipp, and 3.0 equiv of K₂CO₃ in 1.0 mL of H₂O by heating at 90 °C for 80 min. Hydrolysis of **3** was performed by addition of concd HCl (aq). ^b Determined by GC/MS. ^c Isolated yield. Purity >95% by GC/MS. ^d With 1.2 equiv of K₂CO₃. ^e Reaction time of 6 h. ^f No product formation noticed. ^g nd = not determined. Reaction not complete even though amount of remaining starting material was not verified. ^h Formed β -products were not isolated after the reaction.

Method B reported in Table 2, making a direct comparison possible. Remarkably, all hydroxyalkyl vinyl ethers **2a–d** were arylated in water with **1a** in highly regioselective manner and without any byproduct formation (Table 4, entries 1–4). The yields from the arylations of heavier olefins **2b–d** were moderate at best, and unfortunately, prolongation of the reaction time to 6 h had only a slight positive effect on the yields (entries 2 and 3). For alkyl vinyl ethers lacking the hydroxy functionality, the regioselectivity decreased gradually with elongated alkyl chains (Table 4, entries 6 and 7). A similar regiochemical outcome was obtained with ethylene glycol butyl vinyl ether (**2h**) (entry 8). This can be explained by insolubility of **2f–h** in water, providing a two-phase reaction system with a nonpolar organic layer as the probable arylation media. Moreover, [2-(dimethylamino)ethoxy]ethane (**2e**) and allyl alcohol (**2i**) showed no reactivity in the aqueous protocol (entries 5 and 9).⁴⁴

Reactions in Toluene. In 2006, Mo and Xiao suggested a hydrogen bond-induced regiocontrol and acceleration of the reaction rate in α -arylation of electron-rich olefins by aryl halides in ionic liquids or DMF.³⁸ In this study, they proposed that the HNET₃⁺ ion from the additive [HNET₃]⁺[BF₄][−] was capable of forming a hydrogen bond with the bromide ion in

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(43) Portnoy, M.; Ben-David, Y.; Rouso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465.

(44) Noncyclic, N-alkylated enamides have been reported to undergo unselective arylation in water–DMF mixtures; see ref 21.

TABLE 5. Comparative Arylation of Ethylene Vinyl Glycol Ether in Toluene or in Solventless Reaction^a

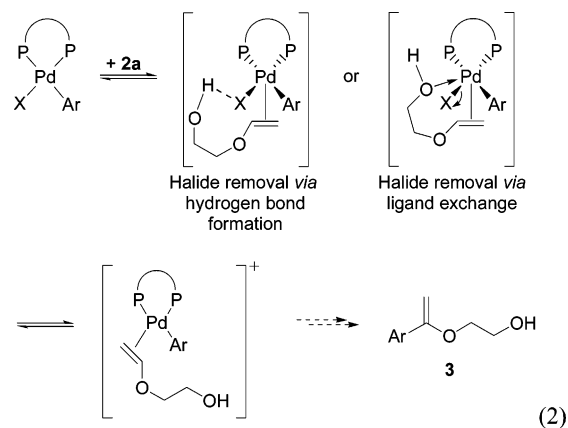
ArX +		2.5 mol% Pd(OAc) ₂ 5.0 mol% dppp K ₂ CO ₃ 1 mL toluene or neat 90 °C, 80 min		H ⁺			
1	2a					5	
entry	ArX	method ^b	product	toluene α/β^c	5 (%) ^d	no solvent α/β^c	5 (%) ^d
1	1a	A	5a	99:1	81	99:1	86
2	1a	B	5a	73:27	24 ^{e,f}		
3	1c	A	5c	99:1	88		
4	1h	B	5h	96:4	62 ^g		

^a The reactions were performed on 0.50 mmol scale with 5.0 equiv of **2a**. Hydrolysis of **3** was performed by addition of concd HCl (aq). ^b Method A: 1.2 equiv of K₂CO₃. Method B: 3.0 equiv of K₂CO₃. ^c Determined by GC/MS. ^d Isolated yield. Purity >95% by GC/MS. ^e **2g** used instead of **2a**. ^f Conversion of **1a** to product(s) not complete. ^g 20% benzophenone formed as a byproduct.

an oxidative addition intermediate, thus promoting the formation of the cationic π -complex leading to internal arylation products. To be able to conclude whether our results with hydroxyalkyl vinyl ethers were based purely on the better solvation of these olefins in alkaline water or whether the hydroxy group itself could play an active role in the reaction mechanism, the influence of nonpolar toluene on the outcome of the reaction was investigated (Table 5). Much to our surprise, reactions in toluene proceeded with excellent regioselectivities, and yields comparable to those from the earlier reactions in aqueous media were isolated in the case of 4-bromoanisole (**1a**) and 2-bromonaphthalene (**1c**) (Tables 2 and 5). A somewhat lower yield and regioselectivity was recorded with electron-poor 4-bromobenzophenone (**1h**); this gave also 20% of dehalogenation product (benzophenone), implicating problems in the insertion of the olefin. Additionally, **2a** was successfully arylated with **1a** without any cosolvent present, giving an excellent 86% isolated yield of ketone **5a** with no β -product formation. Finally, a loss of selectivity as well as noticeable reduction of the reaction rate in toluene was noticed when changing the olefin **2a** to butyl vinyl ether **2g**, lacking the OH functionality (Table 5, entry 2).

Reaction Pathway. Data from experiments in nonpolar toluene together with the information gained from the reactions in water with a variety of olefins clearly prove that the hydroxy group has a major influence on the outcome of the reaction (Tables 4 and 5). This can be seen in excellent regioselectivities obtained with hydroxyvinyl ethers **2a–d** as well as faster reaction rates of ethylene glycol vinyl ether-mediated reactions when compared to other olefins included in this study. In fact, several researchers have noticed the increase in selectivity of the reaction as a result of coordination of OH group or similar functionality to the catalyst.^{11,12,45} Interestingly, Santelli et al. have suggested that coordination of the hydroxy

group to the Pd(II) center leads to highly β -selective synthesis of protected arylacetaldehydes from ethylene glycol vinyl ether via terminal Heck arylation.^{45a,c} While we have no definitive answer what is behind the excellent α -selectivity in our case, we suggest that the reaction proceeds via a pentacoordinate π -complex (eq 2). This mechanistic suggestion is partly supported by Overman et al.'s proposition for asymmetric intramolecular Heck reactions with aryl halides where axial olefin coordination is essential for chiral discrimination.^{46,47} Here we propose that the hydroxy group assists the dissociation of bromide ion either via hydrogen bond formation or via a ligand exchange–isomerization reaction sequence after the axial coordination of the olefin to the ArPd(dppp)X complex, generating the key cationic π -intermediate. The fact that olefins **2e** and **2h**, capable of binding to the Pd(II) complex via lone pair on oxygen (weak coordination) or nitrogen (strong coordination) atoms,^{13,48,49} failed in this aqueous regioselective internal Heck protocol (Table 4, entries 5 and 8) points toward halide removal via hydrogen bond formation. This hypothesis is further strengthened by the large difference in reactivities of olefins **2a** and **2d**, both having an oxygen atom linked to vinyl ether by a two-carbon spacer. As the efficiency of the halide removal can be expected to be related to the length of the carbon tether linking the double bond and OH-group moieties, the rate of the overall reaction is anticipated to decrease with olefins **2b–d**, which was, in fact, shown to be the case in our preparative experiments (Table 4). Finally, we believe that the same mechanism prevails also in nonpolar toluene where internal hydrogen bonding is further favored. However, as the ability of toluene to promote the internal arylation gets weaker with electron-poor aryl rings, the aqueous methodology is presumed to be more general.



Conclusion

We have demonstrated that aryl and heteroaryl bromides and iodides can be efficiently converted to corresponding acetophenones in high yields in water using ethylene glycol vinyl ether as the olefin and potassium carbonate as the base. This palladium(0)-catalyzed method is highly advantageous as no heavy metal additives or ionic liquids are necessary, it proceeds

(45) For a few examples, see: (a) Kondolff, I.; Doucet, H.; Santelli, M. *Eur. J. Org. Chem.* **2006**, 765. (b) Oestreich, M.; Sempere-Culler, F.; Machotta, A. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 149. (c) Kondolff, I.; Doucet, H.; Santelli, M. *Synlett* **2004**, 1561. (d) Kang, S.-K.; Lee, H.-W.; Jang, S.-B.; Kim, T.-H.; Pyun, S.-J. *J. Org. Chem.* **1996**, *61*, 2604. (e) Kang, S.-K.; Jung, K.-Y.; Park, C.-H.; Namkoong, E.-Y.; Kim, T.-H. *Tetrahedron Lett.* **1995**, *36*, 6287. (f) Jeffery, T. *Tetrahedron Lett.* **1993**, *34*, 1133. (g) Bernocchi, E.; Cacchi, S.; Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1992**, *33*, 3073.

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cleanly without any noticeable byproduct formation, avoids the need for inert atmosphere, and allows for easy purification of the products. Moreover, the reactions proceed faster than in most of the protocols available in the literature today, and for the first time, water can be utilized as a sole solvent in regioselective internal Heck arylation of electron-rich olefins, making this protocol more environmentally benign. Additionally, by using microwave irradiation in conjunction with reactive (dipp)₂Pd catalyst, a limited number of aryl chlorides were transformed into analogous aryl methyl ketones. Finally, the unique nature of hydroxyalkyl vinyl ethers was demonstrated in directing the mechanism toward the cationic pathway leading to internal arylation products, even in the absence of a polar solvent supporting the stabilization of charged intermediates.

Experimental Section

General Experimental Procedure for Internal Heck Reactions Using Aryl Bromides or Aryl Iodides (Tables 1, 2, and 4). A mixture of corresponding aryl bromide or aryl iodide (0.50 mmol), olefin (2.5 mmol), Pd(OAc)₂ (2.8 mg, 0.0125 mmol), dppp (10.3 mg, 0.025 mmol), K₂CO₃ (83–207 mg, 0.60–1.5 mmol), and 1.0 mL of water was stirred in a sealed vessel (capable to withhold elevated pressure) in a preheated oil bath at 90 °C for 80 min. After cooling, 2.0 mL of ethyl acetate was added to the reaction mixture, which was stirred for 5 min before analysis of the organic layer with GC/MS. A quantity of 0.5 mL of concentrated HCl (aq) was added to the mixture, followed by stirring at room temperature for 1–3 h. Completion of hydrolysis was verified with GC/MS. The reaction was worked up by extraction with ethyl acetate and 10% K₂CO₃ (aq). Products were purified by flash chromatography on silica gel. Eluents: isohexane/ethyl acetate.

Experimental Procedure for Large-Scale Internal Heck Reaction Using 4-Bromoanisole and Ethylene Glycol Vinyl

Ether (Table 2, Entry 1). A mixture of 4-bromoanisole (9.35 g, 50 mmol), ethylene glycol vinyl ether (22.4 mL, 250 mmol), Pd(OAc)₂ (0.28 g, 1.25 mmol), dppp (1.03 g, 2.5 mmol), K₂CO₃ (8.29 g, 60 mmol), and 100 mL of water was stirred in a 250-mL round-bottom flask at 90 °C for 80 min under reflux. After cooling, 50 mL of ethyl acetate was added to the reaction mixture, which was stirred for 5 min before analysis of the organic layer with GC/MS. Thereafter, 25 mL of concentrated HCl (aq) was slowly added to the mixture, followed by stirring at room temperature for 1 h. Completion of hydrolysis was verified with GC/MS. Reaction was worked up and purified as described above.

General Experimental Procedure for Microwave-Assisted Internal Heck Reactions Using Aryl Chlorides (Table 3). A mixture of corresponding aryl chloride (0.25 mmol), (dipp)₂Pd (8.2 mg, 0.0125 mmol), K₂CO₃ (104 mg, 0.75 mmol), and 1.0 mL of water was stirred in a sealed vessel suitable for microwave experiments in a preheated oil bath at 50 °C for 15 min. Ethylene glycol vinyl ether (112 μL, 1.25 mmol) was added, the vessel was sealed, and the reaction mixture was irradiated with microwaves at 130 °C for 90 min. Reactions were hydrolyzed, worked up, and purified as previously described.

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Supporting Information Available: Full details of experimental procedures and spectroscopic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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