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Palladium-catalyzed regiocontrolled internal heteroarylation of electron-rich olefins with heteroaryl halides

Dan Xu [a], Zhihua Liu [a], Weijun Tang [a], Lijin Xu [a,*], Zeynab Hyder [b], Jianliang Xiao [b,*]

[a] Department of Chemistry, Renmin University of China, Beijing 100872, China
[b] Liverpool Centre for Materials and Catalysis, Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, UK

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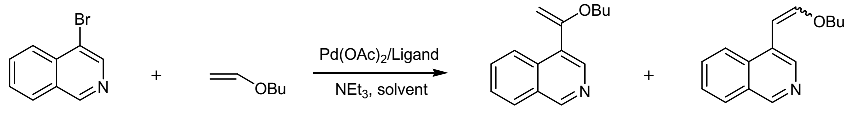
ABSTRACT

A highly efficient palladium-catalyzed Heck coupling reaction of heteroaryl halides with electron-rich vinyl ether and hydroxyalkyl vinyl ethers is described. It was found that the choice of solvent, ligand, and reaction temperature had a fundamental influence on the regioselectivity and reactivity of the reaction, and the combination of $Pd(OAc)_2$ and DPPF in ethylene glycol led to the most effective catalytic system. Under these conditions, a variety of heteroaryl halides reacted very quickly with electron-rich olefins to afford exclusively the branched products in good to excellent yields without employing triflates, halide scavengers, or ionic liquids.

The Pd-catalyzed Heck olefination of heteroaryl halides has emerged as a powerful tool for the synthesis of functionalized heteroaryls.[1] However, most of the published Heck reactions focused on the heteroarylation of electron-deficient olefins, and the coupling reactions of electron-rich olefins with heteroaryl halides have remained largely unexplored.[1,2] This is understandable since the latter is frequently complicated by the formation of mixtures of linear β- and branched α-products due to two possible reaction pathways (Eq. 1).[3,4] Several methods have been successfully developed to circumvent the problem of regioselectivity, but they usually suffer from the use of expensive substrates, or toxic additives or limitations to particular olefins.[5] Considering

Table 1
Solvent and ligand effect on the Heck heteroarylation of vinyl ether[a]



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

Entry	Solvent	Ligand	Temperature (°C)	Time (h)	Conv. (%)[b]	α/β[b]	E/Z[b]
1	Isopropanol	DPPP	Reflux	20	Nd		
2	Ethanol	DPPP	Reflux	20	Nd		
3	Ethylene glycol	DPPP	115	20	40	>99/1	
4	Ethylene glycol	DPPB	115	20	32	>99/1	
5	Ethylene glycol	DPPE	115	20	28	>99/1	
6	Ethylene glycol	DPPM	115	20	<1		
7	Ethylene glycol	rac-BINAP	115	20	50	95/5	70/30
8	Ethylene glycol	DPPF	115	12	100	>99/1	
9	Ethylene glycol	DPPF	140	2	100	>99/1	

[a] Conditions: **1a** (1.0 mmol.), **2a** (2.0 mmol), $Pd(OAc)_2$ (3 mol %), ligand (6 mol %), NEt_3 (2.0 mmol), solvent (2 mL).
[b] Determined by ^{1}H NMR. When no β product was detected, a value >99/1 was assigned.

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[*] Corresponding authors. Tel.: +86 10 62511528; fax: +86 10 62516444 (L.X.).
E-mail address: xulj@chem.ruc.edu.cn (L. Xu).

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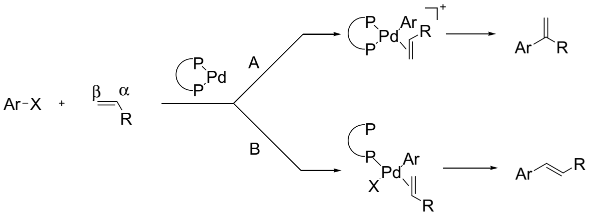
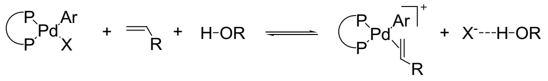
the synthetic potential of this reaction in heterocyclic chemistry, a more effective catalytic system for regioselective heteroarylation of electron-rich olefins would be attractive.



(1)

During the course of our research on regiocontrolled arylation of electron-rich olefins,[6] we discovered that Pd-catalyzed highly regioselective Heck reactions of heteroaryl halides with electron-rich olefins could be achieved in an imidazolium ionic liquid [bmim][BF_4].[6c] However, these reactions proceeded slowly, requiring about 30 h for completion. Another concern is that in these reactions pure ionic liquid was used as the bulk solvent, which may create a problem since ionic liquids are by no means cheap as solvents. Following our pursuit for a cleaner, more economic method for the regioselective Heck heteroarylation, herein we report that heteroaryl halides can be efficiently olefinated with electron-rich olefins in a highly regioselective manner in ethylene glycol, which is a low-cost and environmentally benign solvent, without recourse to ionic liquids, triflates, or halide scavengers.[7]

The preliminary experiments were performed with 4-bromoisoquinoline **1a** as the model substrate, and the results are summarized in Table 1. We first investigated the heteroarylation of the benchmark electron-rich olefin butyl vinyl ether **2a**, in different alcohols under the previously established conditions, where the catalyst was generated *in situ* from DPPP (1,3-bis(diphenylphosphino)propane) and $Pd(OAc)_2$.[6] No reaction was observed in either isopropanol or ethanol after 20 h; however, ethylene glycol provided a 40% conversion with the exclusive formation of α-substituted product **3a** (entries 1–3). The better reactivity and α-regioselectivity observed in ethylene glycol may be partly ascribed to its higher boiling point (bp: ethanol, 78 °C; isopropanol, 81–83 °C; and ethylene glycol, 196–198 °C) and better capability to form hydrogen bond with the bromide anion,[8] enhancing the concentration of the cationic Pd(II)-olefin species. In order to improve the rate of this reaction, we then examined the catalytic performance of other bidentate phosphines in ethylene glycol. High regioselectivity was obtained with DPPE (1,2-bis(diphenylphosphino)ethane), DPPB (1,4-bis(diphenylphosphino)butane), or DPPF (1,1′-bis(diphenylphosphino)ferrocene) as the ligand; but DPPM (1,1-bis(diphenylphosphino)methane) inhibited the reaction and rac-BINAP ((±)-2-2′-Bis(diphenylphosphino)-1,1′-binaphthalene) displayed an inferior regioselectivity (entries 4–8). Delightfully, the combination of $Pd(OAc)_2$ and DPPF afforded the most efficient catalyst (entry 8), which may be related to the large bite angle of DPPF.[6e] Ethylene glycol allows operation at a higher temperature, and a faster reaction rate is expected at elevated temperature. Indeed, when the reaction temperature was increased to 140 °C, we were pleased to find that the heteroarylation of **2a** with **1a** was completed in 2 h (entry 9). These results indicate that alcoholic solvents are capable of quenching the halides by hydrogen bonding, thus blocking the pathway to the linear product, and rendering the branched product favorably (Eq. 2).

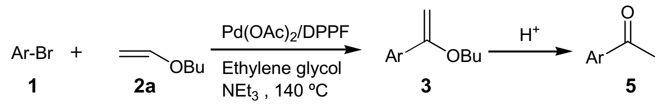


(2)

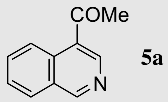
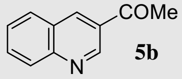
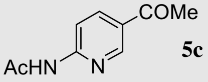
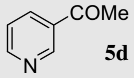
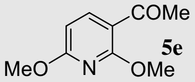
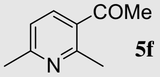
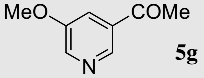
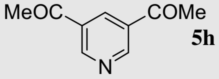
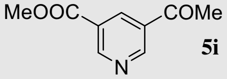
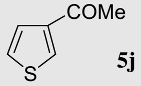
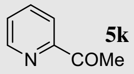
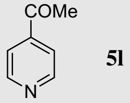
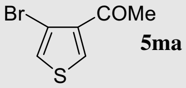
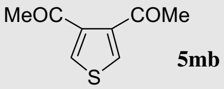
To study the substrate scope of this efficient catalytic system, we then extended the chemistry to other heteroaryl halides. In a

Table 2

Regioselective Heck heteroaryaltion of vinyl ether in ethylene glycol[a]



1 **2a** **3** **5**

Entry	Ar-Br	Product	Time (h)	Yield[b] (%)
1	**1a**	 COMe, N **5a**	2	95
2	**1b**	 COMe, N **5b**	2	85
3	**1c**	 COMe, AcHN, N **5c**	0.5	92
4	**1d**	 COMe, N **5d**	1	86
5	**1e**	 COMe, MeO, N, OMe **5e**	0.3	95
6	**1f**	 COMe, N **5f**	0.3	96
7	**1g**	 MeO, COMe, N **5g**	1	89
8	**1h**	 MeOC, COMe, N **5h**	2	90
9	**1i**	 MeOOC, COMe, N **5i**	2	87
10	**1j**	 COMe, S **5j**	1	89
11	**1k**	 N, COMe **5k**	2	90
12[c]	**1l**	 COMe, N **5l**	15	81
13[c]	**1m**	 Br, COMe, S **5ma**	1.5	86
14[c,d]	**1n**	 MeOC, COMe, S **5mb**	1.5	90

[a] Conditions: **1** (1.0 mmol), **2a** (2.0 mmol), $Pd(OAc)_2$ (3 mol %), DPPF (6 mol %), NEt_3 (2.0 mmol), ethylene glycol (2 mL), 140 °C. Compound **5** was obtained after acidification of **4**. 100% conversion and no linear products were observed as shown by ^1H NMR analysis.

[b] Isolated yields.

[c] Compounds **1l:** 4-bromopyridine hydrochloride; **1m**: 3,4-dibromothiophene.

[d] Four equivalents of olefins were employed.

typical reaction, a mixture of **1**, **2a**, Pd(OAc)$_2$, DPPF, and NEt$_3$ was heated in 2 mL ethylene glycol at 140 °C in an inert atmosphere of N$_2$; the ketone **5** was obtained following the hydrolysis of **3**. As shown in Table 2, all the reactions reached completion with >99/1 regioselectivity in favor of the branched products with good to excellent isolated yields.[11] Nearly all the reactions were completed within 2 h, regardless of the nature of the heteroaryl rings. This outcome is remarkable in comparison with our previous results in ionic liquid, in which the reactions required as long as 36 h to complete.[6c] It appeared that the reaction proceeded slightly faster in the olefination of electron-rich heteroaryl bromides (entries 3, 5–7), and somewhat longer reaction times were needed for the electron-deficient ones (entries 8 and 9). For example, only 0.3 h was needed to finish the coupling reaction of **1f** and **2a** (entry 6), while it took 2 h to complete the olefination of **1j** (entry 9), although the former is sterically less favorable. It is notable that the heteroaryl bromides, **1k** and **1l** (4-bromopyridine hydrochloride), which have long been considered as difficult substrates for Heck couplings,[9] could undergo the regioselective olefination smoothly (entries 11 and 12). The slow olefination of **1l** is probably due to the presence of chloride anion, which has been found to inhibit the regioselective coupling of aryl halides with electron-rich olefins.[6b]

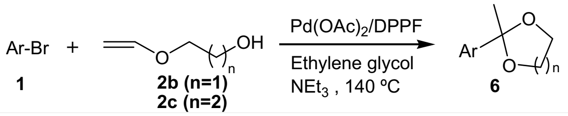
The catalytic system also worked effectively for the olefination of a polyhalohetero-aryl, furnishing mono- or poly-olefinated products in good yields (entries 13 and 14). For example, in the presence of 2 equiv **2a**, compound **1m** (3,4-dibromothiophene) was mono-olefinated to provide the product **5ma** as the main product, leaving another position for further functionalization (entry 13). Indeed, using 4 equiv **2a** led to the di-olefinated product **5mb** (entry 14).

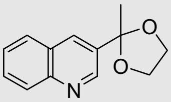
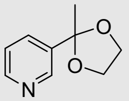
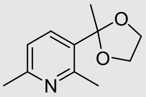
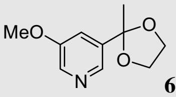
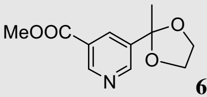
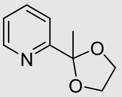
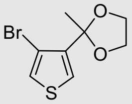
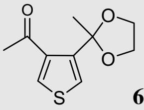
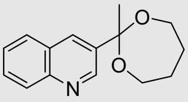
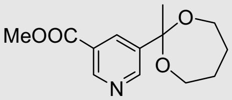
Given the success with **2a**, we hoped that this efficient coupling process could also be extended to other electron-rich olefins. Hallberg and his coworkers first reported the synthesis of cyclic ketals of acetophenones via internal Heck arylation of hydroxyalkyl vinyl ethers with aryl triflates, but the reactions were slow and additional hydrolysis with dry acetic acid to complete ring closing was required.[10] Recently with aryl halides as the substrates, similar regioselective arylation has been successfully carried out in ionic liquids without subsequent hydrolysis.[6b,6d] Very recently, Larhed and his coworkers reported regioselective heteroarylation of hydroxyalkyl vinyl ethers in water, but they only obtained the ketones.[5d] So far there has been no report about the synthesis of cyclic ketals via regioselective heteroarylation of hydroxyalkyl vinyl ethers. To our delight, under the same reaction conditions as for vinyl ether **2a**, the hydroxyalkyl vinyl ethers **2b** and **2c** have proved to be viable substrates. Examples of heteroarylation with different heteroaryl halides are given in Table 3.[11] It is notable that all the reactions were completed again within 2 h with excellent regioselectivities, affording the 5-membered and 7-membered cyclic ketals in good yields without subsequent hydrolysis. Also noteworthy is the successful olefination of **1m** (Table 3, entries 7 and 8). In the presence of 2 equiv **2b**, the compound underwent mono-olefination to produce **6mba** as the main product (entry 7), while using 4 equiv **2b** led to the di-olefinated product **6mbb** (entry 8). The formation of a mono-rather than a di-ketal compound may be due to the steric effects.

In summary, we have developed a general and efficient method for the internal heteroarylation of vinyl ether and hydroxyalkyl vinyl ethers in a green solvent, ethylene glycol. This method allows for highly regioselective heteroarylation of these electron-rich olefins with heteroaryl halides with no necessity for triflates, halide scavengers, or ionic liquids. Ethylene glycol is expected to facilitate the formation of the ionic palladium intermediate, enabling the reaction to proceed via the ionic route and hence to preferentially afford the branched products.

Table 3

Regioselective heteroarylation of hydroxyalkyl vinyl ethers in ethylene glycol[a]



Entry	Ar–Br	Olefin	Product	Time (h)	Yield[b] (%)
1	**1b**	**2b**	 **6bb**	2	92
2	**1d**	**2b**	 **6db**	1	91
3	**1f**	**2b**	 **6fb**	1	89
4	**1g**	**2b**	 **6gb**	1	92
5	**1i**	**2b**	 **6ib**	2	94
6	**1k**	**2b**	 **6kb**	2	87
7	**1m**	**2b**	 **6mba**	1	83
8[c]	**1m**	**2b**	 **6mbb**	2	89
9	**1b**	**2c**	 **6bc**	2	70
10	**1i**	**2c**	 **6ic**	2	75

[a] Conditions: **1** (1.0 mmol), **2b** or **2c** (2.0 mmol), Pd(OAc)$_2$ (3 mol %), DPPF (6 mol %), NEt$_3$ (2.0 mmol), ethylene glycol (2 mL), 140 °C. 100% conversion and no linear products were observed as shown by ^{1}H NMR analysis.

[b] Isolated yields.

[c] Four equivalents of olefins were employed.

Acknowledgments

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11. *General procedure for the olefination of heteroaryls*: An oven-dried, two-necked round-bottomed flask containing a stir bar was charged with heteroaryl halide **1** (1.0 mmol), Pd(OAc)$_2$ (7 mg, 0.03 mmol), DPPF (25 mg, 0.06 mmol), and ethylene glycol (2 mL) under nitrogen at room temperature. Following degassing three times, olefin **2** (2.0 mmol) and NEt$_3$ (2.0 mmol) were injected sequentially. The flask was placed in an oil bath, and the mixture was stirred and heated at 140 °C. The reaction was monitored by TLC. After the reaction went to completion, water was added, and the aqueous phase was extracted with dichloromethane 3 times. For products requiring acid hydrolysis, aqueous HCl (5%, 5 mL) was added and following stirring for 0.5 h, dichloromethane was added. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. The crude product was purified via flash chromatography on silica gel using a mixture of ethyl acetate and hexane (5:95–20:80).