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Palladium-Catalyzed Regioselective Arylation of an Electron-Rich Olefin by Aryl Halides in Ionic Liquids

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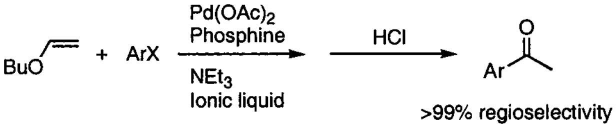
ABSTRACT



Palladium-catalyzed arylation of the electron-rich olefin butyl vinyl ether has been accomplished in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]), using as the arylating agents aryl iodides and bromides instead of the commonly used, but commercially unavailable and expensive, aryl triflates. The reaction proceeds with high efficiency and remarkable regioselectivity, leading almost exclusively to substitution by various aryl groups at the olefinic carbon α to the heteroatom of butyl vinyl ether.

Palladium-catalyzed arylation or vinylation of olefins by aryl or vinyl halides, that is, the Heck reaction, has become one of the most important tools in synthetic chemistry.[1] The reaction works impressively well with a wide range of electron-deficient and unactivated olefins, affording high selectivity to products resulting from arylation or vinylation at the less substituted position of the olefinic double bond. However, with electron-rich acyclic olefins such as enol ethers and enamides, mixtures of regioisomers usually result with standard Heck arylation conditions, thus limiting the applicability of the Heck reaction in synthesis.[1,2] Regioselective substitution at the olefinic carbon α to the heteroatoms of enol ethers or enamides is achievable when the arylating halide is replaced by a triflate or when a stoichiometric quantity of silver triflate or thallium acetate is added.[2] Thallium acetate appears to be preferred with aryl bromides as arylating agents.[2a] The drawback of this approach is that triflates are rarely commercially available and are far more expensive to acquire than the halides, and large amounts of inorganic salts are used and generated. We herein report that palladium-catalyzed, highly regioselective arylation of the electron-rich olefin butyl vinyl ether **1** by aryl halides **2** can readily be accomplished in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]),[3] without resorting, for the first time, to aryl triflates or silver and thallium additives (Scheme 1).[4]

The palladium−phosphine-catalyzed Heck reaction is now generally accepted to proceed via two pathways, one being neutral, resulting in β arylation products such as **3**, and the

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[1] For recent reviews, see: (a) Brase, S.; de Meijere, A. In *Metal-Catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) Link, J. T.; Overman, L. E. In *Metal-Catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (c) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427. (d) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

[2] (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S. *J. Org. Chem.* **1992**, *57*, 1481. (b) Cabri, W.; Candiani, I.; Bedeschi, A. *J. Org. Chem.* **1993**, *58*, 7421. (c) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (d) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 7858.

[3] For recent reviews on reactions in ionic liquids, see: (a) Carlin, R. T.; Wilkes, J. S. In *Advances in Nonaqueous Chemistry*; Mamantov, G., Popov, A., Eds.; VCH: New York, 1994. (b) Chauvin, Y.; Olivier, H. *CHEMTECH* **1995**, *25*, 26. (c) Seddon, K. R. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 351. (d) Olivier, H. *J. Mol. Catal. A: Chem.* **1999**, *146*, 285. (e) Welton, T. *Chem. Rev.* **1999**, *99*, 2071. (f) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772.

[4] Regiocontrol is possible for the coupling of aryl halides and triflates with heterosubstituted olefins that bear additional functionalities capable of chelating to palladium: (a) Andersson, C.-M.; Larsson, J.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 5757. (b) Badone, D.; Guzzi, U. *Tetrahedron Lett.* **1993**, *34*, 3603. (c) Larhed, M.; Andersson, C.-M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 285. (d) Crisp, G. T.; Gebauer, M. G. *Tetrahedron* **1996**, *52*, 12465.

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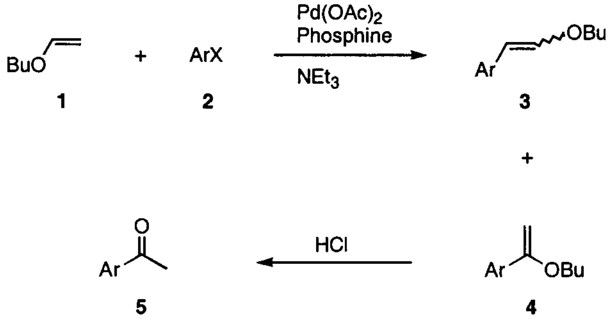
Scheme 1



ArX = 1-bromonaphthalene 2a, 1-iodonaphthalene 2b, 4-bromobenzonitrile 2c, methyl-4-bromobenzoate 2d, 4-bromoacetophenone 2e, 4-bromobenzaldehyde 2f, 1-bromo-4-fluorobenzene 2g, bromobenzene 2h, 4-bromotoluene 2i, 4-bromoanisole 2j.

other ionic, leading to α arylation products such as **4**.[1,2,5] The neutral route is characterized by phosphine dissociation from palladium, whereas the ionic route proceeds by dissociation of halide or triflats ions. Understandably, the ionic pathway is favored by the use of aryl triflates and bidentate phosphines.[2,6] In continuing our study on catalysis in ionic liquids,[7] we wondered whether the compulsory use of a triflate or addition of silver salts could be avoided when the Heck arylation is carried out in an ionic liquid such as [bmim][BF$_4$]. Generation of the olefin-coordinated cationic palladium species in the ionic pathway from a neutral palladium−aryl halide complex and a neutral olefin could be facilitated in an ionic environment provided by the ionic liquids.[8] In fact, earlier studies have already shown that the reaction of [LPdArX] (L = diphosphine, X = halide) with olefins can be greatly accelerated in a polar solvent via stabilization of the ionic species generated.[5b]

To determine if direct, regioselective arylation of electron-rich olefins by aryl halides could occur in ionic liquids without using triflates or silver salts, we first examined the arylation of **1** by 1-bromonaphthalene **2a** in [bmim][BF$_4$] under conditions previously established for triflates in DMF, where the active catalyst is derived in situ from Pd(OAc)$_2$ and 1.1 equiv of 1,3-bis(diphenylphosphino)propane (DPPP).[2a] For comparison, we also carried out the same reaction in four molecular solvents: toluene, acetone, DMF, and DMSO. A typical reaction consisted of simply heating a mixture of **1**, **2a**, Pd(OAc)$_2$, and DPPP in a chosen solvent under an atmosphere of argon. The α arylated product **4** was isolated as the aryl methyl ketone **5** following acidification (Scheme 1).[9] The results are given in Table 1. Among all these solvents, the only one capable of effecting the regioselective arylation of **1** was [bmim][BF$_4$], as evidenced by the ratio of α substituted **4** to β substituted **3** (α/β). In the four molecular solvents with widely differing polarities,[10] some of which are commonly used in Heck reactions, none of the reactions affords an α/β ratio close to that observed in the ionic liquid. Of further interest is the observation that while decomposition of palladium complexes to various degrees into palladium black always accompanied the arylation in the molecular solvents, palladium black was never observed in the ionic liquid. Evidently, not only does [bmim][BF$_4$] promote the ionic pathway in the direct arylation of electron-rich olefins by aryl halides to preferentially give the α arylated product, it also plays a role in stabilizing the active palladium−phosphine species involved in such reactions.

Table 1. Solvent Effect on the Heck Arylation of Butyl Vinyl Ether **1** by 1-Bromonaphthalene **2a** in Various Solvents[a]

solvent	convn, %[b]	α/β[c]	*E*/*Z*[d]
toluene	23	46/54	68/32
acetonitrile	36	69/31	75/25
DMF	100	60/40	77/23
DMSO	100	75/25	79/21
[bmim][BF$_4$]	50	>99/1	

[a] Reactions were run with 1.0 mmol of **1**, 5 equiv of **2a**, 1.2 equiv of Et$_3$N, 2.75 mol % of DPPP, and 2.5 mol % of Pd(OAc)$_2$ at 100 °C for 18 h. The product was identified/analyzed by NMR, GC, and GC-MS and by comparison with literature data and/or authentic samples.[9] [b] Conversion of **1** to **3** and **4**. [c] Molar ratio of **4**/**3**. When the product **3** could not be detected by GC and NMR, a value of >99/1 was assigned. [d] Ratio of *trans*/*cis* isomers of **3**.

Table 1 also shows that the arylation by Pd(OAc)$_2$ in the presence of ca. 1 equiv of DPPP is slower in [bmim][BF$_4$] than in DMF and DMSO. The lower rates associated with the ionic liquid could result from the phosphine ligand being inadequate, some of which may be consumed in the reduction of Pd(II) to Pd(0).[1] The active catalyst involved in the arylation is generally believed to be a Pd(0) species.[1,2] Consistent with this interpretation, palladium without a phosphine ligand displayed negligent activity in the arylation reaction in [bmim][BF$_4$], and addition of an additional 1 equiv of DPPP or replacement of Pd(OAc)$_2$ by a Pd(0) complex Pd$_2$(dba)$_3$ (dba = dibenzylideneacetone) led to a marked increase in the arylation rate. For example, the conversion of **2e** rose from 21 to 90% when the Pd(0) precatalyst was employed to replace Pd(OAc)$_2$ in the coupling with **1**.

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(5) (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417. (b) Portnoy, M.; Ben-David, Y.; Rousso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465.

(6) In contrast to halide ions, triflate can easily dissociate from the ArPd(II)X species formed in the Heck reaction: (a) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810. (b) Brown, J. M.; Hii, K. K. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 657.

(7) (a) Chen, W.; Xu, L.; Chatterton, C.; Xiao, J. *Chem. Commun.* **1999**, 1247. (b) Xu, L.; Chen, W.; Xiao, J. *Organometallics* **2000**, *19*, 1123.

(8) This is what one would expect on the basis of Hughes−Ingold rules: Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed; VCH: Weinheim, 1988.

(9) The products from this study are known compounds. For their physical and spectroscopic data, see: (a) Ichinose, N.; Mizuno, K.; Otsuji, Y.; Caldwell, R.; Helms, A. M. *J. Org. Chem.* **1998**, *63*, 3176. (b) Kusama, H.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2379. (c) Hachiya, I.; Moriwaki, M.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2053. (d) Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1118. (e) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1990**, *55*, 3564. (f) Pouchert, C. J. *The Aldrich Library of NMR Spectra*, 2nd ed.; Aldrich Chemical Co.: Milwaukee, 1983. (g) Buckingham, J. *Dictionary of Organic Compounds*, 5th ed.; Chapman Hall: New York, 1982. (h) Reference 2b.

(10) The dielectric constants, which can be used as a quantitative measure of solvent polarity, of the four molecular solvents range from 2.4 to 46.5.

On the basis of the above studies, the arylation of **1** in [bmim][BF_4] was undertaken for a variety of aryl halides in the presence of $Pd(OAc)_2$ and 2 equiv of DPPP. The results obtained are summarized in Table 2. As shown in the table, excellent regioselectivity together with high isolated yields for the aryl methyl ketones **5** was obtained in all the reactions in the ionic liquid, regardless of the nature of the substituents on the aromatic ring. Thus, with bromobenzenes bearing either strongly electron withdrawing or electron donating substituents such as -CN or -OMe, the α/β ratios remained $> 99/1$, suggesting that the neutral pathway is either completely suppressed or its involvement in the arylation is insignificant compared with the ionic pathway in the ionic liquid. Similar observations were made in DMF, that is, the nature of the substituents of aryl triflates exerted no significant effects on the α/β ratio.[2a] Under the conditions given in Table 2, all the reactions went to completion. However, since the reaction times were not optimized, shorter times are possible for complete conversions. For example, the coupling of bromobenzene **2h** with **1** was complete within a 20 h reaction time.

Table 2. Heck Arylation of Butyl Vinyl Ether **1** by Aryl Halides **2a**−**j** in [bmim][BF_4][a]

substrate	temp, °C	time, h	convn, %	α/β	yield, %[b]
2a	100	24	100	>99/1	95
2b	80	24	100	>99/1	94
2c	110	36	100	>99/1	94
2d	120	36	100	>99/1	90
2e	120	36	100	>99/1	92
2f	100	24	100	>99/1	93
2g	120	24	100	>99/1	97[c]
2h	100	24	100	>99/1	95[c]
2i	120	36	100	>99/1	88
2j[d]	120	24	100	>99/1	87

[a] 2 equiv of DPPP. Other reaction conditions except temperature and time were given in Table 1. [b] Isolated yield of **5**. [c] Determined by NMR and GC of the acidified mixture. [d] 5 mol % of $Pd(OAc)_2$ was used.

As may be expected, replacement of aryl halides with the corresponding triflates gives faster rates in [bmim][BF_4]. Thus, the arylation of **1** by phenyl triflate afforded a 100% conversion within 2 h with an $\alpha/\beta > 99/1$. In contrast, in the case of **2h**, the reaction was only 20% complete under otherwise identical conditions. These observations seem to indicate that the rate-determining step of the arylation of **1** by aryl halides **2** in [bmim][BF_4] is the same as that proposed for the normal Heck reaction involving deactivated aryl halides, namely, oxidative addition of the aryl halides to a Pd(0) species.[1] In DMF with triflates as substrate, the rate-controlling step has been proposed to be the migratory insertion of olefins into Pd−Ar bonds.[2a]

It has been speculated for some time that the unique ionic environment imposed by an ionic liquid on a chemical reaction may change its course and so one could expect to see a general "ionic liquid effect".[3] The results presented in this paper demonstrate that there exists such an ionic liquid effect, and this effect can be exploited for interesting but traditionally formidable chemical syntheses. Until now, the Heck arylation of electron-rich olefins by aryl halides has been hampered by low regioselectivity, unless commercially unavailable and expensive triflates or silver salts are used. With the environmentally attractive ionic liquids such as [bmim][BF_4] as the reaction media, highly regioselective and efficient arylation can now readily be achieved by directly employing the easily accessible aryl halides. The key to the success of the chemistry probably lies in the accelerating effect of the ionic liquid on the ionic pathway of the Heck reaction.

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