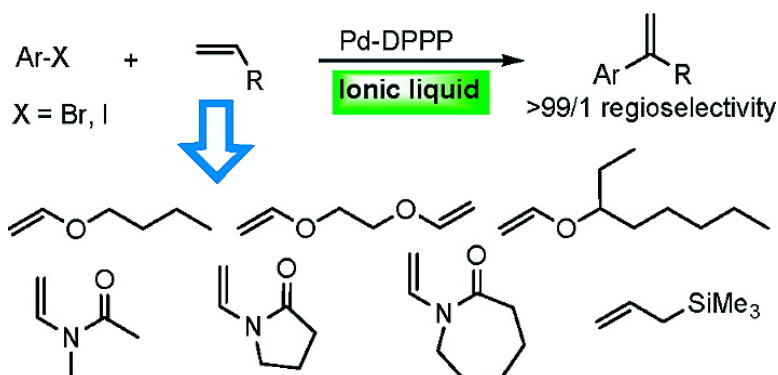


Ionic Liquid-Promoted, Highly Regioselective Heck Arylation of Electron-Rich Olefins by Aryl Halides

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Ionic Liquid-Promoted, Highly Regioselective Heck Arylation of Electron-Rich Olefins by Aryl Halides

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Abstract: Palladium-catalyzed regioselective Heck arylation of the electron-rich olefins, vinyl ethers **1a–d**, enamides **1e–g**, and allyltrimethylsilane **1h**, has been accomplished in imidazolium ionic liquids with a wide range of aryl bromides and iodides instead of the commonly used, but commercially unavailable and expensive, aryl triflates. The reaction proceeded with high efficiency and remarkable regioselectivity without the need for costly or toxic halide scavengers, leading exclusively to substitution by aryl groups of diverse electronic and steric properties at the olefinic carbon α to the heteroatom of **1a–g** and β to the heteroatom of **1h**. In contrast, the arylation reaction in molecular solvents led to mixtures of regioisomers under similar conditions. Several lines of evidence point to the unique regiocontrol stemming from the ionic environment provided by the ionic liquid that alters the reaction pathway. The chemistry provides a simple, effective method for preparing branched, arylated olefins and contributes to the extension of Heck reaction to a wider range of substrates.

Introduction

Palladium-catalyzed arylation or vinylation of olefins by aryl or vinyl halides, that is, the Heck reaction, has become one of the most useful tools for constructing C–C bonds in synthetic chemistry.^{1,2} Thus far, most of the reported Heck reactions deal with olefins bearing electron-withdrawing substituents, such as $-\text{CO}_2\text{R}$ and $-\text{CN}$, which selectively lead to products resulting from arylation or vinylation at the less-substituted (β) position of the olefin double bond. With electron-rich olefins, such as acyclic enol ethers, silanes, and enol amides, an important issue arises; the reaction is rarely regioselective under normal Heck conditions, giving rise to a mixture of α - and β -substituted olefins and thus hampering its wider application in synthesis (eq 1).^{1a,c,d,h,3–6} For instance, arylation of butyl vinyl ether with 4-bromoanisole catalyzed by the well-known Herrmann–Beller palladacycle yielded two olefins, with an α/β ratio of 10/13,^{4m}

and a similar reaction involving 4-dimethylaminobromobenzene catalyzed by Fu's versatile $\text{Pd}-\text{P}(t\text{-Bu})_3$ catalyst led to an α/β ratio of 4/1.^{4h} Poor regioselectivity alongside poor yield has also been observed with some of the most active heterogeneous palladium catalysts.⁴ⁱ In fact, few catalytic systems have been developed which allow for the regioselective, intermolecular

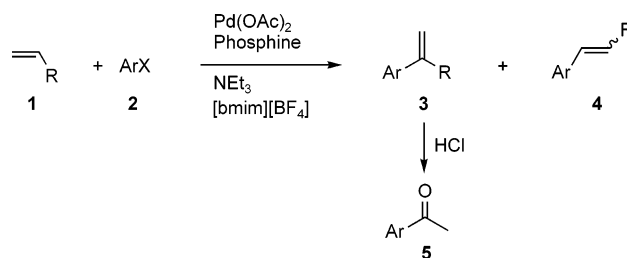
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characterized by dissociation of one of the coordinating neutral phosphorus atoms, while pathway B generates a coordinating site for the incoming olefin by dissociation of the halide anion. Understandably, with monodentate phosphine ligands and aryl halides, the neutral pathway would dominate due to easy dissociation of the ligand and the relatively strong Pd–X bonds formed following oxidative addition of ArX (X = I, Br, or Cl) to the Pd(0) species.^{14,15} In contrast, the liability of the Pd–OTf bond means that the ionic route would be favored when using aryl triflates (X = OTf),^{13i,16} particularly in the presence of a chelating bidentate ligand. Recent theoretical calculations have shed more light on the mechanisms, showing that when following pathway B, electron-rich olefins tend to afford the α -arylated olefin, and this is driven primarily by electrostatic (as a result of charge difference) and frontier orbital interactions.^{13a–c,17} Of further interest is that both experimental and theoretical studies have suggested that for a given olefin, it may be possible to alter the regioselectivity by choosing the reaction pathway.^{3a,13b} In this context, an important observation is that the reaction pathway can indeed be switched from neutral to ionic and vice versa. Thus, when starting with a halide substrate, addition of a halide-sequestering agent, such as AgOTf or TIOAc, alters the reaction route from A to B, and when the substrate is a triflate, addition of halide salts generates the neutral halide-containing species in path A.^{3a,5g,8c,16,18}

In a program aimed at developing metal-catalyzed reactions in ionic liquids,¹⁹ we thought that the ionic pathway might be promoted by using ionic liquids as solvents, producing branched olefins without calling for a halide scavenger. Ionic liquids are entirely composed of ions; hence, electrostatic interactions would favor the generation of a Pd–olefin cation and a halide anion from two neutral precursors over that of a neutral Pd–olefin intermediate from the same.²⁰ In fact, studies by Amatore and Jutand have shown that the neutral complex [(PPh₃)₂Pd(Ar)X] is in equilibrium with [(PPh₃)₂Pd(Ar)(DMF)]⁺ and X[−] (X = Cl, Br, or I) in DMF,^{15a,21} and an earlier study by Milstein has revealed that olefin insertion into the Pd–Ar bond in [L₂Pd–

Scheme 2



R = O^tBu, **1a**; O(CH₂)₂OCH=CH₂, **1b**; OEt, **1c**; O-3-Octyl, **1d**; NMeAc, **1e**; 2-oxopyrrolidinyl, **1f**; 2-oxoazepanyl, **1g**; CH₂SiMe₃, **1h**

(Ar)X] (L₂ = diphosphine) is greatly facilitated in a polar solvent, due to stabilization of the ionic species generated by halide dissociation.²² Additionally, with dialkylimidazolium-based ionic liquid solvents, the acidic C²–H proton of the imidazolium ring is well-known to hydrogen bond to halide anions;²³ so we initially thought this hydrogen bonding might also help accelerate the ionic reaction by contributing to the dissociation from palladium of a halide anion and its stabilization.

Indeed, we have found that, using the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]) as solvent, the Heck arylation of the electron-rich olefins **1a–h** can be accomplished in excellent regioselectivity with a wide variety of aryl bromides and iodides with no need for aryl triflates or halide scavengers (Scheme 2; the isolated product was ketone **5** in the case of **1a–d**). In line with the reasoning above, Hallberg and co-workers reported, shortly after our initial report,^{19d} that highly regioselective arylation of vinyl ethers by aryl bromides could also be achieved in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF₆])²⁴ as well as in aqueous DMF,²⁵ in which water acts as a polarity promoter and is indispensable.²⁶ However, the DMF–H₂O system was shown to be ineffective toward aryl iodides, and only one example was reported for the reaction in [bmim][PF₆]. More recently, Alper and co-workers reported the arylation of *tert*-butyl vinyl ether by iodobenzene to give a 9/1 α/β regioselectivity using a Pd–bisimidazole catalyst in [bmim][PF₆].^{4a}

Room temperature ionic liquids, such as those based on imidazolium salts, have widely been recognized as one of the most promising alternatives to hazardous organic solvents for clean chemical reactions, due to their extremely low vapor pressure and their novel, tunable physicochemical properties.²⁷ A great number of catalytic reactions have proved feasible in these ionic liquids, with many displaying enhanced reactivities and selectivities, some of which have not been seen in common organic solvents.^{28,29} Herein, we report the details of the regioselective arylation of **1a–h** by activated and deactivated aryl bromides and iodides in [bmim][BF₄] and some observa-

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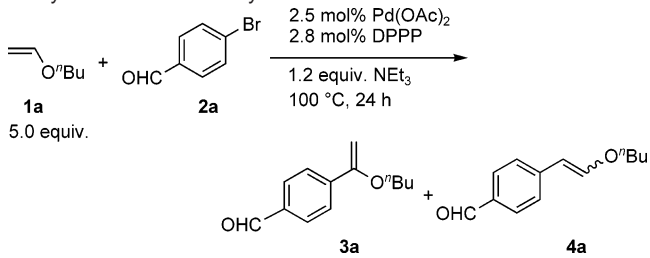
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tions concerning the reaction mechanism. To the best of our knowledge, the catalytic system to be described represents the only reported protocol, with which the intermolecular Heck arylation of the three classes of electron-rich olefins **1a–h** can be affected with both aryl bromides and iodides in a highly regioselective manner with no need for a halide scavenger.

Results and Discussion

Effects of Solvents. To determine if direct, regioselective arylation of electron-rich olefins by aryl halides could occur in ionic liquids without using any inorganic salt additives, we examined the arylation of **1a** by 4-bromobenzaldehyde **2a** in [bmim][BF₄] under conditions previously optimized for triflates using molecular solvents, where the active catalyst was derived in situ from Pd(OAc)₂ and 1.1 equiv of a diphosphine, 1,3-bis-(diphenylphosphino)propane (DPPP).^{9c} For comparison, the same reaction experiment was also carried out in common organic solvents. In a typical reaction, a mixture of **1a**, **2a**, Pd(OAc)₂, and DPPP was heated in a chosen solvent for a certain period of time under an inert atmosphere. The α -arylated product **3a** was isolated, when necessary, as the aryl methyl ketone **5a** following acidification. The results are given in Table 1. Much

Table 1. Solvent Effect on the Heck Arylation of Butyl Vinyl Ether **1a** by 4-Bromobenzaldehyde **2a**^a



solvent	conv. (%) ^b	α/β ^c	<i>E/Z</i> ^d
[bmim][BF ₄]	100	>99/1	
toluene	18	47/53	68/32
dioxane	26	35/65	82/18
acetonitrile	33	45/55	63/37
DMAc	98	24/76	74/26
DMF	100	47/53	80/20
DMSO	100	86/14	79/21

^a See text for detailed procedures. Product was analyzed by ¹H NMR. ^b Conversion of **2a** to **3a** and **4a**. ^c Molar ratio of **3a/4a**. When product **4a** could not be detected by ¹H NMR, a value of >99/1 was assigned. The same applies to other tables. ^d Ratio of trans/cis isomers of **4a**.

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to our delight, **1a** was completely arylated by **2a** in [bmim]-[BF₄] to give essentially exclusively the α -substituted product **3a**; the ¹H NMR spectrum of the reaction mixture after removing the ionic liquid showed no sign of the linear olefin **4a**, suggesting that the ionic pathway B is operative in the ionic liquid. In sharp contrast, with the six molecular solvents, some of which are usually used in Heck reactions, none of the reactions afforded a similar α/β ratio. DMSO produced the highest α -regioselectivity among the molecular solvents, which is consistent with its high polarity that is expected to promote the ionic route.³⁰ In the case of toluene, dioxane, and acetonitrile, the reactions were also markedly slower. These results confirm early observations, that is, mixtures of regioisomers result when electron-rich olefins are arylated with aryl halides in molecular solvents.^{7,8a,9c} Little conversions (<1%) were observed in the ionic liquids [bmim][X] (X = Br or Cl), conceivably due to halide coordination to palladium, which affects generation of the cationic Pd–olefin species (vide infra), and/or the formation of inactive 1-butyl-3-methylimidazol-2-ylidene complexes of palladium.^{19f,31}

The excellent regioselectivity observed in [bmim][BF₄] corroborates the arylation proceeding via the ionic pathway made possible by the ionic medium. Although polar organic solvents, such as DMSO and DMF, may facilitate halide dissociation from palladium and the resulting high concentration of Pd–olefin cations have been shown to give fast rates of olefin insertion into Pd–Ar bonds,^{21,22} it is clear that none of the molecular solvents alone are able to completely alter the reaction pathway. However, as aforementioned, when water was introduced into DMF, the resulting solvent mixture was capable of

(30) The dielectric constants, which can be used as a quantitative measure of solvent polarity, of the six molecular solvents range from 2.2 to 46.5.

(31) McLachlan, F.; Mathews, C. J.; Smith, P. J.; Welton, T. *Organometallics* **2003**, *22*, 5350. (b) Aggarwal, V. K.; Emme, I.; Mereu, A. *Chem. Commun.* **2002**, 1612. (c) McGuinness, D. S.; Cavell, K. J.; Yates, B. F. *Chem. Commun.* **2001**, 355. (d) Mathews, C. J.; Smith, P. J.; Welton, T.; White, A. J. P.; Williams, D. J. *Organometallics* **2001**, *20*, 3848. (e) Hasan, M.; Kozhevnikov, I. V.; Siddiqui, M. R. H.; Femoni, C.; Stenier, A.; Winterton, N. *Inorg. Chem.* **2001**, *40*, 795.

Table 2. Ligand Effect on the Heck Arylation of Butyl Vinyl Ether **1a** by 4-Bromobenzaldehyde **2a** in [bmim][BF₄]

ligand ^a	bite angle (deg) ^b	L/Pd	2.5 mol% Pd(OAc) ₂ Ligand		
			conv. (%) ^c	α/β ^c	E/Z ^c
none			4		
PPh ₃		2.0	66	76/24	75/25
P(2-toly) ₃		2.0	<1		
DPPM	72	1.1	<1		
DPPE	85	1.1	17	>99/1	
DPPP	91	1.1	100	>99/1	
(<i>R</i>)-BINAP	92	1.1	100	93/7	89/11
DPPF	96	1.1	100	50/50	75/25
DPPB	98	1.1	100	45/55	79/21
XANTPHOS	112	1.0	100	31/69	72/28

^a See Experimental Section for ligand nomenclature. ^b From ref 35b. ^c Determined by ¹H NMR.

promoting highly regioselective arylation by aryl bromides, though not aryl iodides.²⁵ 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 rarely noticed in the ionic liquid. Evidently, not only does [bmim][BF₄] promote the ionic pathway in the direct arylation of electron-rich olefins by aryl halides to give preferentially the α-arylated product but also it stabilizes the active palladium–phosphine species in such reactions.

Effects of Ligands. As ligands are known to exert significant effects on palladium-catalyzed Heck arylation reactions in common organic solvents,^{1,3} we were interested in finding out if ligands other than DPPP could also offer high regiocontrol and high activity in the palladium-catalyzed arylation in the ionic liquid [bmim][BF₄]. The results on ligand screening, again using 4-bromobenzaldehyde **2a** as the aryating agent, are given in Table 2. It is clear that the choice of ligand is critical in achieving good selectivities to the α-product alongside high conversions, and as in the case of molecular solvents,^{9c} the combination of Pd(OAc)₂ and DPPP affords the most selective and active catalyst. Thus, with the catalyst so formed, the arylation of **1a** by **2a** was complete within 24 h, leading to an α/β product ratio of >99/1. In contrast, with all the other ligands tested or in the absence of a phosphine, a lower selectivity and/or a lower conversion were observed. BINAP is closest to DPPP in terms of regioselectivity, affording an α/β ratio of 97/3.³² The regioselectivity with DPPP in [bmim][BF₄] resembles that observed with 1-naphthyl triflate in DMF, but the results with DPPE, DPPB, and DPPF differ considerably in the two solvents, with higher rates and/or higher α/β ratios being obtained in DMF.^{9c} The regioselectivity associated with PPh₃ is consistent with recent DFT calculations on a Pd(II)–L (L = H₂PCH₂PH₂ or PH₃) model complex, which predict that vinyl ethers favor α-arylation, regardless of the reaction pathway being ionic or neutral, with the former being more α-selective, provided that

steric effects are minimal.^{13a} The lack of reactivity with P(2-toly)₃ is probably due to the in situ formation of palladacycle species, which normally require a higher temperature to activate aryl bromides.^{4m,33} With DPPM, inactive binuclear palladium species could be generated.³⁴

Of particular note is that the activity and selectivity of the palladium catalysts in the ionic liquid appear to correlate with the bite angles of diphosphines.³⁵ Full conversions were only observed with ligands with relatively large bite angles (ca. >90°), but high regiocontrol was only possible with ligands of medium bite size. While bite angles affect both the oxidative addition and olefin insertion steps, the latter appears to be more likely here.³⁶ Large bite angles could facilitate the dissociation of halide ions from palladium due to steric repulsions, increasing the concentration of Pd–olefin cations and presumably the reaction rate as a result. van Leeuwen and co-workers have recently reported that the cationic palladium species generated from [L₂Pd(Ph)Br] (L₂ = DPPE and XANTPHOS-type diphosphines) through bromide dissociation increases in concentration when the ligand bite angle increases.³⁷ Increasing the ligand bite angle, which leads to increased steric interactions between the inserting olefin and the phenyl rings at the phosphorus, could also promote the α-selectivity by destabilizing the transition state leading to the β-product.^{1c,13b} However, when the bite angle becomes too large, the ligand could inhibit rotation of the olefin from out-of-plane coordination to an in-plane position necessary for insertion, and if the rotation leading to the α-product is severely affected and one of phosphorus atoms dissociates,^{5g,22,35d} reduced α-regioselectivities would result. In contrast, ligands with smaller bite angles would be less inhibitive toward olefin rotation, affording the α-product mainly under the influence of electronic interactions. However, dissociation of the halide ion or the insertion itself could be slow in this case, leading to lower conversions. It thus appears that DPPP is the ligand of choice for the least-resisting insertion pathway.

Comparative Arylation in [bmim][BF₄] and DMF. Encouraged by the results above, we first extended the arylation reaction to the electrophiles **2b,c,e,x** in [bmim][BF₄]. To determine if the ionic liquid would offer the same advantage over common organic solvents for these substrates as well, the same reaction experiments were performed in the most often used solvent DMF. Table 3 summarizes the results obtained. Clearly, in terms of regioselectivity, the ionic liquid is unsurpassed. Thus, with each of the aryl bromides, compound **3** was essentially the only product to be formed. By way of contrast, the same reactions in DMF afforded mixtures of products, with α/β ratios ranging from 46/54 to 69/31, which resemble the results of **2a** reacting with **1a** in DMF and other common solvents.

(32) BINAP also displayed a high regioselectivity in α-vinylation of enamides (ref 10a). For a reference comparing the reactivity of L₂Pd(0) (L₂ = diphosphine, including BINAP) in oxidative addition, see: (a) Amatore, C.; Broeker, G.; Jutand, A.; Khalil, F. *J. Am. Chem. Soc.* **1997**, *119*, 5176. On a related study, see: (b) Alcazar-Roman, L. M.; Hartwig, J. F. *Organometallics* **2002**, *21*, 491.

(33) Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917.

(34) Puddephatt, R. *J. Chem. Soc. Rev.* **1983**, *12*, 99.

(35) For reviews on bite angle effects in catalysis, see: (a) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741. (b) Dierkes, P.; van Leeuwen, P. W. N. M. *J. Chem. Soc., Dalton Trans.* **1999**, 1519. (c) Casey, C. P.; Whiteker, G. T. *Isr. J. Chem.* **1990**, *30*, 299. For a study on the effect of diphosphines in amination of aryl halides, see: (d) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694.

(36) The 14e species L₂Pd(0) (Scheme 1, L₂ = diphosphine) is expected to be more active in oxidative addition with L₂ having a smaller bite angle: (a) Otsuka, S. *J. Organomet. Chem.* **1980**, *200*, 191. (b) Hofmann, P.; Heiss, H.; Mueller, G. Z. *Naturforsch.* **1987**, *B42*, 395. (c) Ref 35b.

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Table 3. Heck Arylation of Butyl Vinyl Ether **1a** by Aryl Halides **2** in [bmim][BF₄] and DMF

ArX ^a	solvent	T (°C)	time (h)	conv. ^b (%)	α/β ^c	EI ^z ^c	yield ^d (%)
<i>p</i> -CHOPh 2a	[bmim][BF ₄]	100	24	100	>99/1		90
<i>p</i> -NCPh 2b	[bmim][BF ₄]	100	36	61	>99/1		57
<i>p</i> -MeOCPh 2c	[bmim][BF ₄]	120	24	21	>99/1		
<i>p</i> -FPh 2e	[bmim][BF ₄]	100	24	30	>99/1		25 ^e
1-naph 2x ^f	[bmim][BF ₄]	80	36	45	>99/1		40
2a	DMF	100	24	100	47/53	80/20	30
2b	DMF	120	18	100	61/39	77/23	54
2c	DMF	120	24	100	46/54	76/24	54
2e	DMF	100	18	100	63/37	64/36	59 ^e
2x	DMF	80	24	100	69/31	66/34	54

^a X = Br. ^b Conversion to **3** and **4**; determined by ¹H NMR. ^c Determined by ¹H NMR before acidification. ^d Isolated yield of **5** after acidification of **3**. ^e Determined by ¹H NMR and GC. ^f X = I.

Surprisingly, somehow for these aryl substrates, the reaction became sluggish with the isolated yields for ketones **5** being lower in comparison with that of **2a** in [bmim][BF₄]. Thus, the arylation by **2b** resulted in a conversion of only 61% in 36 h, whereas with **2a**, the reaction was complete within a reaction time of 24 h. This is not the case with the reactions in DMF, where full conversions were obtained with all of the bromides under similar reaction conditions. The lower rates associated with [bmim][BF₄] result presumably from a decrease in the quantity of the phosphine ligand as a consequence of its probable involvement in the reduction of Pd(II) to Pd(0), with itself being turned into a monophosphine ligand, DPPP monoxide [DPPP(O)].³⁸ Palladium without a phosphine ligand or with a monodentate phosphine displays a low activity in the arylation reaction in [bmim][BF₄] (Table 2), and the active catalyst involved in the arylation is generally believed to be the 14e species L₂Pd(0) (Scheme 1).¹ Consistent with this assumption, replacement of Pd(OAc)₂ by a Pd(0) complex, Pd₂(dba)₃ (dba = dibenzylideneacetone), or more simply, addition of 1 equiv more of DPPP led to a marked increase in the rate of arylation in [bmim][BF₄].³⁹ For example, the conversion rose from 21 to 90% when Pd₂(dba)₃ was employed to replace Pd(OAc)₂ in the coupling of 4-bromoacetophenone **2c** with **1a**. The higher rates and lower regioselectivities with DMF are indicative of both neutral and ionic pathways being operative in this solvent, where the active species may be Pd(0)–DPPP(O). We have previously demonstrated that using 2 equiv of DPPP does not improve the regioselectivities in DMF, and while 3 equiv of DPPP does, the reaction is slow with a limited scope.⁴⁰

Arylation of Olefins 1a–h in [bmim][BF₄]. On the basis of the above studies, the arylation of **1a** in [bmim][BF₄] was undertaken with a variety of aryl bromides in the presence of Pd(OAc)₂ and 2 equiv of DPPP. The results obtained are

Table 4. Heck Arylation of Butyl Vinyl Ether **1a** by Aryl Bromides **2a–q** in [bmim][BF₄]^a

R	product ^b	yield ^c (%)	R	product ^b	yield ^c (%)
<i>p</i> -CHO 2a	5a	93	<i>m</i> -COMe 2j	5j	87
<i>p</i> -NC 2b	5b	94	<i>m</i> -CHO 2k	5k	83
<i>p</i> -COMe 2c	5c	92	<i>m</i> -F 2l	5l	81
<i>p</i> -CO ₂ Me 2d	5d	90	<i>m</i> -Me 2m	5m	80
<i>p</i> -F 2e	5e	96	<i>m</i> -MeO 2n	5n	86
H 2f	5f	97	<i>o</i> -F 2o	5o	81
<i>p</i> -Me 2g	5g	88	<i>o</i> -OMe 2p	5p	86
<i>p</i> -MeO 2h ^d	5h	81	1-naph 2q ^e	5q	95
<i>m</i> -NC 2i	5i	95			

^a Reaction time of 24 h for **2a,c,g,q**; 36 h for others. ^b All reactions gave 100% conversion and >99/1 α/β selectivity as determined by ¹H NMR before acidification. ^c Isolated yield of **5**. ^d With 4.0 mol % Pd(OAc)₂ and 8.0 mol % DPPP. ^e 1-Bromonaphthalene.

summarized in Table 4. As can be seen, excellent regioselectivities together with high isolated yields for the aryl methyl ketones **5** were obtained in all of the reactions in the ionic liquid, regardless of the nature of the substituents on the aryl rings. Thus, bromobenzenes bearing either strongly electron-withdrawing or electron-donating para substituents, such as –CN or –OMe, all furnished good to excellent isolated yields, with α/β ratios of >99/1. The same reaction can be equally applied to meta-substituted bromobenzenes having either electron-withdrawing or electron-donating groups, as demonstrated by the substrates **2i–n**. We were pleased that the protocol worked even for some sterically hindered substrates, such as **2o–q**, given that a bulky bidentate ligand is bonded to the palladium center. However, the sterically more demanding 2-bromo-1,3-dimethylbenzene furnished a conversion of only 9% in a 24 h reaction time. The reactions proceeded smoothly in general, leading to relatively clean products even without chromatographic purification (see Supporting Information for an example). Under the given conditions, all of the reactions shown in Table 4 went to completion, but shorter times should be possible since the reaction time was not optimized for each individual reaction (vide infra). The remarkable regioselectivities observed with [bmim][BF₄] suggest that the neutral path A (Scheme 1) is either completely suppressed or its involvement in the arylation in the ionic liquid is insignificant. The protocol provides a practically useful supplement to the known methodologies for the synthesis of important aromatic ketones⁴¹ and particularly to Friedel–Crafts acylation, which is neither effective toward

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- (41) Cacchi, S.; Fabrizi, G.; Gavazza, F.; Goggiani, A. *Org. Lett.* **2003**, *5*, 289 and references therein. (b) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563. (c) Duris, F.; Barbieri-Baudry, D.; Dormond, A.; Desmurs, J. R.; Bernard, J. M. *J. Mol. Catal. A: Chem.* **2002**, *188*, 97. (d) Kaur, J.; Griffin, K.; Harrison, B.; Kozhevnikov, I. V. *J. Catal.* **2002**, *208*, 448. (e) Frost, C. G.; Wadsworth, K. J. *Chem. Commun.* **2001**, 2316. (f) Walter, D. S. In *Comprehensive Organic Functional Group Transformations*; Patten, G., Ed.; Pergamon: Oxford, 1995; Vol. 3, p 277.

Table 5. Heck Arylation of **1a** by Aryl Iodides **2** in [bmim][BF₄]

R	product ^a	yield (%) ^b
<i>p</i> -CO ₂ Me 2s	5c	96
<i>p</i> -CHO 2t	5a	96
H 2u	5f	91
<i>p</i> -Me 2v	5g	98
<i>p</i> -MeO 2w	5h	98
1-naph 2x^c	5q	94

^a All reactions gave 100% conversion and >99/1 α/β selectivity as determined by ¹H NMR before acidification of **3**, which led to **5**. ^b Isolated yield of **5**. ^c 1-Iodonaphthalene.

electron-deficient arenes nor as regioselective as the current method for the introduction of an acetyl group.⁴²

Olefin **1a** can also be arylated with aryl iodides. When going from bromides to iodides, both electrostatic and hydrogen-bonding interactions would be expected to become weaker, which could render the ionic pathway less favorable as compared with that in the case of bromides.²³ This may explain why the aforementioned DMF–H₂O system failed with this class of substrates.²⁵ The arylation of **1a** with aryl iodides in [bmim][BF₄] was carried out in the presence of Pd(OAc)₂ and 2 equiv of DPPP at 80 °C in a 24 h reaction time. As can be seen from Table 5, the reactions of both electron-rich and electron-deficient aryl iodides afforded, again, excellent regioselectivities and high isolated yields for the ketones after acidic hydrolysis. Without chelation assistance, regioselective arylation of electron-rich olefins with aryl iodides and bromides is possible generally only in the intramolecular version of the reaction, as aforementioned.

The vinyl ethers **1b–d** have also proven to be viable substrates. Examples of arylation with activated and deactivated aryl bromides and an iodide are given in Table 6. All of the reactions proceeded with >99/1 α/β -regioselectivities and furnished aryl methyl ketones in yields of >80% after hydrolysis. The divinyl ether **1b** was generally more effective, requiring smaller amounts (0.75 equiv versus 5 equiv in the case of **1a,c,d**) and delivering better yields.

Enamides are another class of electron-rich olefins, and their arylation could lead to synthetically and catalytically important α -arylenamides.⁴³ Somewhat surprisingly, there appears to be no literature examples in which enamides are α -arylated with aryl halides, although 1-naphthyl triflate and recently vinyl triflates have been shown to react with enamides, regioselectively furnishing branched olefins.^{9a,10a} More recently, Larhed and co-workers have reported successful regioselective coupling of **1e–g** with arylboronic acids in 1,4-dioxane, using a phenanthroline ligand for palladium under an atmosphere of oxygen.¹⁷ Applying the conditions established for the vinyl ethers, we were disappointed to find that enamides **1e** and **1f** showed little sign of coupling with the bromoacetophenone **2c** in [bmim][BF₄].

Table 6. Heck Arylation of Vinyl Ethers **1b–d** with Aryl Halides **2** in [bmim][BF₄]

R'	product ^a	1b	1c	1d
yield (%) ^b				
H 2f	5f	93	90	86
<i>p</i> -F 2e	5e	96	92	87
<i>p</i> -NC 2b	5b	95	91	85
<i>p</i> -COMe 2c	5c	94	90	88
<i>p</i> -CHO 2a	5a	96	90	84
<i>p</i> -MeO 2h^c	5h	89	87	83
1-naph 2x^d	5q	95	92	89

^a All reactions gave 100% conversion and >99/1 α/β selectivity as determined by ¹H NMR before acidification of **3**, which led to **5**. ^b Isolated yield of **5**. ^c Reaction time of 36 h. ^d 1-Iodonaphthalene, 80 °C reaction temperature.

Table 7. Heck Arylation of Enamides **1e–g** by Aryl Bromides **2**

aryl bromides	enamides	products ^a	yield (%) ^b
2c	1e	3ec	85
2e	1e	3ee	80
2f	1e	3ef	82
2o	1e	3eo	74
2r^c	1e	3er	86
2c	1f	3fc	83
2e	1f	3fe	85
2g	1f	3fg	73
2r	1f	3fr	78
2f	1g	3gf	76
2r	1g	3gr	71

^a Full conversions and >99/1 α/β selectivity for all as determined by ¹H NMR. ^b Isolated yield. ^c 2-Bromonaphthalene.

Unexpectedly, when DMSO was introduced as cosolvent, smooth, regioselective arylation of **1e–g** took place. Table 7 summarizes the results obtained with Pd–DPPP in a 1:1 (volume) mixture of [bmim][BF₄] and DMSO. It must be pointed out that in neat DMSO, a mixture of species was formed in which the only olefinic product, **3**, was insignificant. In comparison with Larhed's oxidative coupling using the more costly arylboronic acids,¹⁷ the reactions of Table 7 required harsher conditions but afforded in general higher regioselectivities (>99/1 versus 92/8–99/1) and higher yields (71–86% versus 31–96%). With both methods, aryl substrates bearing the strongly electron-withdrawing –CN group failed to give good conversions, however. The role of DMSO is not entirely clear to us; it may facilitate β -hydrogen elimination by replacing the coordinated amine from palladium. Amine coordination could occur following aryl insertion, impeding the access of β -hydrogen to palladium.⁴⁴

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(43) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142 and references therein.

(44) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Sausalito, CA, 1999; Chapter 7.2. DMSO was also found to improve regioselectivities of the arylation of unfunctionalized cycloalkenes by aryl bromides: (b) Hartung, C. G.; Köhler, K.; Beller, M. *Org. Lett.* **1999**, *1*, 709.

Table 8. Heck Arylation of Allyltrimethylsilane **1h** by Aryl Halides **2a–g** in [bmim][BF₄]

substrate	product ^a	conv. (%) ^b	yield (%) ^c
2a	3ha	92	82
2b	3hb	81	65
2c	3hc	100	93
2d	3hd	91	85
2e	3he	100	89
2f	3hf	100	88
2g	3hg	96	89

^a All reactions gave >99/1 β/γ selectivity as determined by ¹H NMR. ^b Determined by ¹H NMR. ^c Isolated yield.

To further explore the scope of this highly regioselective Heck arylation method, the arylation of allyltrimethylsilane **1h** was examined. The arylated branched allylsilanes are important intermediates in organic synthesis, including palladium-catalyzed C–C bond formation.⁴⁵ Unfortunately, under traditional Heck reaction conditions, arylation of allyltrimethylsilane with aryl halides affords linear arylated silanes, even in the presence of silver additives.^{46,47} In contrast, when performed in the ionic environment provided by [bmim][BF₄], arylation with aryl bromides of diverse electronic properties proceeded regioselectively to give branched allylsilanes in good to excellent yields. Thus, the aryl bromides **2a–g** reacted with allyltrimethylsilane **1h**, furnishing exclusively the β -arylated allylsilanes in 65–93% isolated yields in the presence of Pd(OAc)₂ and DPPP in [bmim][BF₄] (Table 8). Similar regioselective arylation of allyltrimethylsilane could also be achieved in CH₃CN, but aryl triflates were necessary, according to Hallberg and co-workers.^{10g} In addition to relying on triflates, the yields (31–85%) were generally lower in comparison with those of the ionic liquid protocol described here, however. Hallberg has suggested that the reaction proceeds via the ionic pathway, with the key step being migration of the aryl group to the positively charged carbon β to and stabilized by the SiMe₃ unit [which could be understood as arising from the olefin acting as a Lewis base attacking the electrophilic palladium(II)]. The excellent β -selectivities we observed in the ionic liquid are in line with this view. DMSO was not required in this case, however, probably because product inhibition via chelation is unlikely. Owing to its superior selectivity and yield and functional group compatibility, the present method compares favorably with available methods in the literature for the preparation of β -arylated allylsilanes.⁴⁸

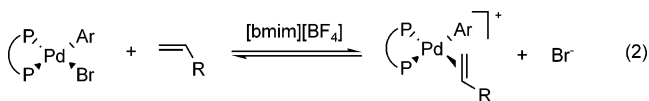
- (45) Barbero, A.; Castroño, P.; Pulido, F. *J. Org. Lett.* **2003**, *5*, 4045. (b) Furman, B.; Dzedzic, M. *Tetrahedron Lett.* **2003**, *44*, 8249. (c) Furman, B.; Dzedzic, M. *Tetrahedron Lett.* **2003**, *44*, 6629. (d) Kuroda, C.; Kasahara, T.; Akiyama, K.; Amemiya, T.; Kunishima, T.; Kimura, Y. *Tetrahedron* **2002**, *58*, 4493. (e) Mendez, M.; Echavarren, A. M. *Eur. J. Org. Chem.* **2002**, *15*. (f) Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491. (g) Ofial, A. R.; Mayr, H. *J. Org. Chem.* **1996**, *61*, 5823. (h) Takeda, T.; Takagi, Y.; Takano, H.; Fujiwara, T. *Tetrahedron Lett.* **1992**, *33*, 5381. (i) Pernez, S.; Hamelin, J. *Tetrahedron Lett.* **1989**, *26*, 3419. (46) Karabelas, K.; Westerlund, C.; Hallberg, A. *J. Org. Chem.* **1985**, *50*, 3896. (47) For an example of regioselective intramolecular vinylation of allylsilane with vinyl triflates and iodides, see: Tietze, L. F.; Modi, A. *Eur. J. Org. Chem.* **2000**, 1959. (48) Monfray, J.; Gelas-Mialhe, Y.; Gramain, J.-C.; Remuson, R. *Tetrahedron Lett.* **2003**, *44*, 5785. (b) Ref 10g and references therein.

Table 9. Effect of Bromide Ion on the Heck Arylation of **1a** by **2c** in [bmim][BF₄]

ⁿ Bu ₄ NBr (mmol)	Pd(OAc) ₂ / ⁿ Bu ₄ NBr	Conv. (%) ^a	
		6 h	12 h
		59	96
0.025	1:1	32	63
0.05	1:2	20	48
0.13	1:5	6	12
0.25 ^b	1:10	4	5
0.50	1:20	3	3

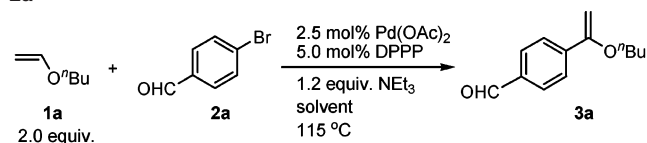
^a Determined by ¹H NMR after acidification of **3c** at the time indicated; average of three runs. ^b Employing the same quantity of ⁿBu₄NCl afforded similar conversions: 5% (6 h) and 7% (12 h).

Mechanistic Observations. As aforementioned, it is generally agreed that the Heck reaction proceeds via a neutral and/or an ionic pathway, and when the latter is in operation, electron-rich olefins lead in general to α -arylation.^{1,9–11,13} Except for intramolecular arylation reactions, where aryl iodides can be employed and coordination of the olefin may assist the dissociation of the iodide generating a palladium–olefin cation (Scheme 1),⁶ the vast majority of the Heck arylation reactions that follow the ionic mechanism rely on aryl triflates as substrates. In fact, Brown has shown that the complex [L₂Pd(Ar)I] (L₂ = DPPF), in which the Ar group bears an *ortho*-vinyl ether substituent, is thermally stable in THF and undergoes intramolecular cyclization (at –40 °C in *d*₆-acetone) only when the iodide is removed with AgOTf.⁴⁹ The results we obtained with aryl bromides and iodides, without using any halide scavenger, are consistent with those of the arylation proceeding via the ionic pathway, with dissociation of the halide anion from palladium promoted by the ionic liquid. More direct supporting evidence comes from reactions in the presence of added halide anions. Thus, as shown in Table 9, the arylation of **1a** by **2c** was notably slowed even when 1 equiv of Br[–] (relative to palladium, in the form of ⁿBu₄NBr) was introduced into the solvent [bmim][BF₄], and the reaction rate was progressively reduced when more ⁿBu₄NBr was added. A similar effect was also observed with ⁿBu₄NCl. This is consistent with there being an equilibrium, as shown in eq 2, which is shifted toward the left on addition of the halide ions, reducing the concentration of cationic Pd–olefin species and consequently the reaction rate.⁵⁰ Similar observations have been made in arylation reactions using aryl triflates^{5g,9c} and in the stoichiometric reaction of [L₂Pd(Ar)Cl] (L₂ = diphosphine) with olefins,²² using molecular solvents in both cases, and these have been taken as evidence in support of the ionic mechanism.



If the assertion above is true, it must mean that the HBr generated in the last step of the Heck cycle (Scheme 1) is

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Table 10. Effect of Ionic Liquid Cation on the Arylation of **1a** by **2a**

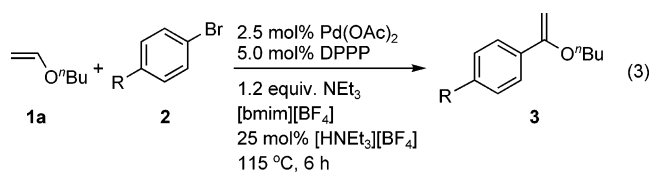
Solvent	Conv. (%), 4 h ^a	Conv. (%), 8 h ^a
 [bmim][BF ₄]	20	42
 [bdmim][BF ₄]	25	55

^a Determined by NMR at the time indicated; >99/1 α/β ratios; average of two runs.

effectively scavenged by NEt₃ in the ionic liquid. It also means that the aforesaid hydrogen bond contribution to the dissociation of Br⁻ from palladium is insignificant, if any. Indeed, the arylation of **1a** by **2a** proceeded even slightly faster in 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([bdmim][BF₄]), in which the H² ring proton was replaced with a methyl group (Table 10). The H² proton is the most acidic among the three imidazolium ring protons and usually forms the strongest hydrogen bonds with anions.²³

So how were the bromide anions removed during the arylation reactions? No precipitated salt was visible in any of the reactions in [bmim][BF₄], and the salt [HNEt₃][Br] (prepared from NEt₃ and HBr) is actually quite soluble in this ionic liquid (>1.5 M); hence, the bromide ions were not removed by precipitation.⁵¹ While we have no clear answer to the question, one possible explanation might be that the bromide ions form tight ion pairs with protonated NEt₃, [H-NEt₃]⁺, via hydrogen bonding. In line with this, introduction of additional hydrogen bond donor [H-NEt₃]⁺ (in the form of its BF₄⁻ salt) into the reaction of **1a** with **2** resulted in significantly faster rates, as shown by the examples given in eq 3, using both electron-deficient and -rich aryl bromides. Thus, for instance, the arylation of **1a** by **2c** gave a full conversion in 6 h when 10 equiv (relative to the catalyst) of [HNEt₃][BF₄] was added; in its absence, the conversion was 96% in 12 h (Table 9). These results are remarkable, as they resemble those obtained by using stoichiometric Ti(OAc)₄ in the arylation of **1a** by **2c** under similar conditions, which led to a full conversion within 6 h ($\alpha/\beta > 99/1$) by forming insoluble TiBr.

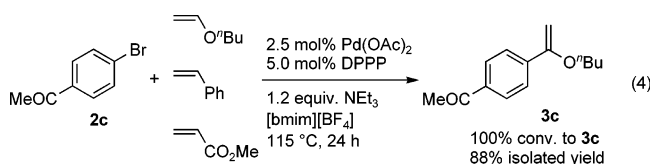
A further demonstration of the ionic Heck pathway operating in the ionic liquid is seen in the competition reaction of butyl vinyl ether **1a**, styrene, and methyl acrylate with 4'-bromoacetophenone **2c**. Of the three olefins, only the electron-rich **1a** reacted in [bmim][BF₄], affording ketone **3c** in 88% isolated



2 = **2c** (R = *p*-Ac), **2e** (R = *p*-F), **2f** (R = H), **2g** (R = *p*-Me)

100% conversion with $\alpha/\beta > 99/1$ for all, based on two runs for each.

yield after hydrolysis of **3c** (eq 4). This result can be viewed as resulting from preferential bonding of an electron-deficient Pd(II) cation with an electron-rich olefin. By way of contrast, in DMF, the opposite chemoselectivity was observed when 1-naphthyl iodide was reacted with a mixture of **1a** and methyl acrylate, due to preferential coordination of the electron-poor methyl acrylate to an electron-rich, neutral Pd(II) center. Preferential reaction of the vinyl ether **1a** was observed only when the naphthyl iodide was replaced with the corresponding triflate.^{9b}



Conclusions

The past several years have witnessed great strides in developing active and productive catalysts for the Heck reaction.^{1,2} These catalysts in general do not lead to regioselective reactions in intermolecular arylation of electron-rich olefins with aryl halides, however. For these olefins, the arylation is most frequently carried out by employing commercially inaccessible aryl triflates, and when aryl halides are chosen, stoichiometrical silver or thallium salts are generally needed. This paper demonstrates that imidazolium ionic liquids in combination with the readily available Pd(OAc)₂ and DPPP form an excellent catalytic system, with which highly regioselective and yielding arylation of several classes of electron-rich olefins can be accomplished with a wide range of aryl halides with no need for any halide scavengers. Specifically, we demonstrated that vinyl ethers, enamides, and allyltrimethylsilane can be arylated under Pd–DPPP catalysis by various aryl bromides and iodides in the ionic liquid [bmim][BF₄] or in [bmim][BF₄]–DMSO in the case of the enamides, with all of the reactions furnishing essentially only the branched olefins in high isolated yields. The chemistry thus provides a viable synthetic pathway to α -arylated vinyl ethers and enamides, aryl ketones, and β -arylated allylic silanes that are of value to synthetic chemistry. While the detailed reaction mechanism remains to be delineated, our results suggest that the reaction proceeds via the ionic pathway, hence, giving rise to the branched product. The ionic liquid plays a pivotal role in making this possible, presumably by facilitating the dissociation of halide anions from palladium. Given the designer properties of ionic liquids,²⁷ improvements on the current method in terms of reaction rates and catalyst loadings and solutions to other difficult substrates for the Heck and related reactions are foreseeable.²⁸

Experimental Section

All reactions were carried out under a nitrogen atmosphere. Chromatographic purifications were performed on silica gel (mesh

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230–400) by the flash technique. 1-Butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]) was prepared according to the literature method.⁵² After vacuum-drying at 80 °C for 8 h, the ionic liquid was stored under nitrogen at ambient temperature, and prior to use, it was vacuum-dried again at 80 °C for 1 h. However, our more recent experiments have shown that water (up to 10 wt %) does not have an adverse effect on the arylation of this study. AgNO₃ titration showed the chloride content of the ionic liquid to be below detection limit (<0.2%). Vinyl ethers **1a–d**, enamides **1e–g**, allyltrimethylsilane **1h**, aryl halides **2a–x**, Pd(OAc)₂, 1,2-bis(diphenylphosphino)methane (DPPM), 1,2-bis(diphenylphosphino)ethane (DPPE), 1,3-bis(diphenylphosphino)propane (DPPP), 1,4-bis(diphenylphosphino)butane (DPPB), 1,1-bis(diphenylphosphino)ferrocene (DPPF), (*R*)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl [(*R*)-BINAP], 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XANTPHOS), and triethylamine were purchased from Lancaster and Aldrich and were used as received. ¹H and ¹³C NMR spectra were recorded on a Gemini 400 spectrometer at 400 (¹H) and 100 MHz (¹³C) in parts per million with reference to TMS internal standard in CDCl₃. Mass spectra were obtained by chemical ionization (CI). All of the products were satisfactorily characterized by ¹H and ¹³C NMR, MS, HRMS, and/or elemental analysis, and when possible, comparison of their NMR spectra has been made with available literature data and/or those of authentic samples. The following compounds have all been reported previously: (*E/Z*)-4-(2-butoxyethenyl)benzaldehyde **4a**,⁴⁸ (*E/Z*)-4-(2-butoxyethenyl)benzoxonitrile **4b** [127087-66-5],^{9c} (*E/Z*)-1-butoxy-2-(4-acetylphenyl)ethylene **4c**,^{9a} (*E/Z*)-1-(2-butoxyethenyl)naphthalene **4q** [127087-65-4],^{9c} ketones **5a** [3457-45-2],⁵³ **5b** [1443-80-7],⁵⁴ **5c** [1009-61-6],⁵⁴ **5d** [3609-53-8],⁵⁴ **5e** [403-42-9],⁵⁴ **5f** [98-86-2],⁵⁴ **5g** [122-00-9],⁵⁴ **5h** [100-06-1],⁵⁴ **5i** [6136-68-1],⁵⁴ **5j** [586-37-8],⁵⁴ **5k** [41908-11-6],⁵⁵ **5l** [455-36-7],⁵⁴ **5m** [585-74-0],⁵⁴ **5n** [586-37-8],⁵⁴ **5o** [445-27-2],⁵⁴ **5p** [4079-52-1],⁵⁴ and **5q** [941-98-0],⁵⁴ 4-(1-trimethylsilylamethylvinyl)benzaldehyde (**3ha**) [137190-14-8],⁵⁶ 4-(1-trimethylsilylamethylvinyl)benzoxonitrile (**3hb**),^{10g} 1-[4-(1-trimethylsilylamethylvinyl)phenyl]ethanone (**3hc**),^{10g} [2-(4-fluorophenyl)allyl]trimethylsilane (**3he**) [139214-37-2],⁵⁷ (2-phenylallyl)-trimethylsilane (**3hf**) [77130-15-5],⁵⁸ and trimethyl-(2-*p*-tolylallyl)silane (**3hg**) [139214-35-0].⁵⁸

General Procedure for the Heck Arylation of Vinyl Ethers in Ionic Liquid. An oven-dried, two-necked round-bottom flask containing a stir bar was charged with an aryl halide **2** (1.0 mmol), Pd(OAc)₂ (0.025 mmol), DPPP (0.05 mmol), and [bmim][BF₄] (2 mL) under

nitrogen at room temperature. After the mixture was degassed three times, vinyl ether **1** (5.0 mmol) and NEt₃ (1.2 mmol) were injected sequentially. 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 NMR analysis. In all of the reactions, the β-arylated product was not detected. To the rest of the mixture was added aqueous HCl (5%, 5 mL), and after the mixture was stirred for 0.5 h, CH₂Cl₂ (20 mL) was added. After separation of the CH₂Cl₂ phase, the aqueous layer was extracted with CH₂Cl₂ (2 × 20 mL), and the combined organic layer was washed with water (until neutral), dried (Na₂SO₄), filtered, and concentrated in vacuo. The aryl methyl ketone **5** was isolated out of the crude product by flash chromatography on silica gel using a mixture of ethyl acetate and hexane (1/99–10/90) as eluant. The identity and purity of the product were confirmed by ¹H and ¹³C NMR, MS, HRMS, and elemental analysis and by comparison of their NMR spectra with available literature data. The isolated yields of the products are given in Tables 4–6. Similar procedures were adopted for the arylation in molecular solvents.

General Procedure for the Heck Arylation of Enamides in Ionic Liquid–DMSO. An oven-dried, two-necked round-bottom flask containing a stir bar was charged with an aryl bromide **2** (1.0 mmol), enamide **1** (1.0 mmol), Pd(OAc)₂ (0.04 mmol), DPPP (0.08 mmol), DMSO (1 mL), and [bmim][BF₄] (1 mL) under nitrogen at room temperature. After the mixture was degassed three times, NEt₃ (1.2 mmol) was injected. The flask was placed in an oil bath, and the mixture was stirred and heated at 115 °C. After a reaction time of 36 h, the flask was removed from the oil bath and cooled to room temperature for workup using a procedure similar to that given above. The isolated yields of the products are given in Table 7.

General Procedure for the Heck Arylation of Allyltrimethylsilane in Ionic Liquid. An oven-dried, two-necked round-bottom flask containing a stir bar was charged with an aryl bromide **2** (1.0 mmol), Pd(OAc)₂ (0.04 mmol), DPPP (0.08 mmol), and [bmim][BF₄] (2 mL) under nitrogen at room temperature. After the mixture was degassed three times, allyltrimethylsilane **1h** (4.0 mmol) and NEt₃ (1.2 mmol) were injected sequentially. The flask was placed in an oil bath, and the mixture was stirred and heated at 115 °C. After a reaction time of 36 h, the flask was removed from the oil bath and cooled to room temperature for workup using a procedure similar to that given above. The isolated yields of the products are given in Table 8.

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Supporting Information Available: Experimental procedures for the arylation reactions, analytic data for all the products, and sample ¹H NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA0450861

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