From α-Arylation of Olefins to Acylation with Aldehydes: A Journey in Regiocontrol of the Heck Reaction

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CONSPECTUS

The Pd-catalyzed Mizoroki−Heck reaction of olefins with aryl halides, more often simply called the Heck reaction, was recently recognized with the 2010 Nobel Prize in chemistry. Although highly selective with electron-deficient olefins, which generally yield the linear β-arylated product exclusively, the Heck reaction is less satisfactory with electron-rich olefins. This substrate typically generates a mixture of both α- and β-arylated regioisomeric products, hampering wider application of the reaction in chemical synthesis.

Pioneering studies by a number of researchers revealed that high α-regioselectivity could be obtained under Pd−diphosphine catalysis either through (i) the substitution of aryl triflates for halides or (ii) the addition of stoichiometric silver or thallium salts when aryl halides are used. Under these conditions, the arylation is believed to proceed via an ionic pathway. However, silver introduces added cost, thallium salts are toxic, and triflates are generally commercially unavailable, base sensitive, and thermally labile.

Believing that the ionic pathway would be promoted in an ionic medium, in the early 2000s, we attempted the Pd-catalyzed arylation of the benchmark electron-rich olefin butyl vinyl ether with aryl bromides in an imidazolium ionic liquid. We were delighted to observe that highly regioselective α-arylation could readily be accomplished, with no need for silver additives, thallium additives, or aryl triflates. A range of other electron-rich olefins has since been shown to be viable as well. The high α-selectivity probably results from the high ionic strength of the medium, which facilitates the dissociation of halide anions from the $[L_2Pd(Ar)X]$ intermediate, channeling the arylation into the ionic pathway. Hydrogen bonding interactions may also play a role, however.

We subsequently discovered that the α-arylation can indeed be significantly accelerated by a hydrogen bond donor salt, in both ionic liquids and common solvents. Evidence shows that the concentration of the cationic Pd(II)−olefin species along the ionic pathway is increased as a result of hydrogen bonding between the hydrogen bond donor and the halide anion.

More recently, we reported that cheaper and greener alcohols allow the Heck arylation of electron-rich olefins to proceed in a much faster, productive, and totally α-regioselective manner, circumventing the need for an ionic medium or hydrogen bond donor salt. In particular, aryl chlorides with diverse properties have been demonstrated to be viable substrates for the first time. Significantly, it appears that ethylene glycol facilitates both the oxidative addition of ArCl to Pd(0) and the subsequent dissociation of chloride from Pd(II).

A closely related reaction, acylation of aryl halides with aldehydes, was also developed. Proceeding via the intermediacy of an electron-rich enamine, this Pd−pyrrolidine cooperative catalysis affords alkyl aryl ketones in a straightforward manner, extending the Heck reaction from olefins to aldehydes.
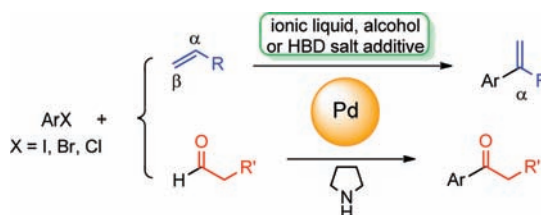
Introduction

The palladium-catalyzed Mizoroki−Heck, or more often the Heck, arylation of olefins with aryl halides was independently discovered by Heck[1] and Mizoroki[2] ca. 40 years ago (eq 1). It has since become one of the most celebrated tools for constructing sp^2 C−C bonds in synthetic chemistry.[3]

Its significance has been highlighted by the 2010 Nobel Prize in chemistry to Professor Richard Heck alongside Professors Ei-ichi Negishi and Akira Suzuki.
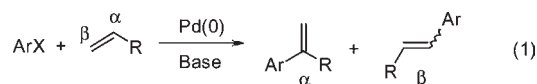
SCHEME 1. Orientation of Addition of Bromobenzene to Olefins Prior to 1979

SCHEME 2. Orientation of Arylation of Electron-Rich and Neutral Olefins Prior to 1995
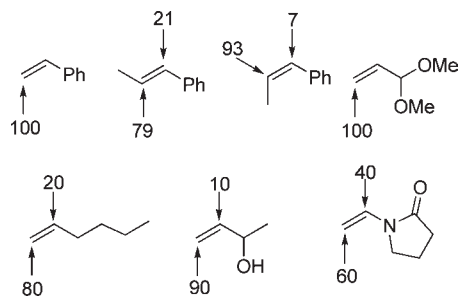
The Heck reaction can give rise to two regioisomeric products (eq 1).[3−5] With electron-deficient olefins, such as acrylonitriles and acrylates, the linear β-arylated products are formed with few exceptions. However, electron-rich olefins, such as acyclic enol ethers and enamides, are problematic, usually affording a mixture of α- and β-arylated products. In his study of the arylation, Heck already noted "Double bonds substituted with electron-donating substituents tend to produce significant amount of 2-aryl adducts in addition to the major 1-aryl isomers."[6] In a 1979 Account, he summarized the orientation of ArBr addition to various olefins.[4] Scheme 1 shows the results concerning electron-rich and neutral olefins.

Since the early studies by Heck and others, extensive effort has been devoted to controlling the regioselectivity in the Heck reaction of electron-rich olefins, that is, those bearing a heteroatom adjacent to the C=C double bond. The progress made in the 1970−80s was documented by Daves and Hallberg,[5b] revealing that the regioselectivity of the arylation is governed by a range of parameters, including the electronic properties of the aromatic rings, ligands, and halide additives.

A significant advance was made by Cabri in the early 1990s.[5a] He found that the regioselectivity could be controlled by the choice of ligands and the leaving groups of aryl substrates, regardless of other variables. Thus, enol ethers were arylated with regioselectivities of >99/1 as measured by the α/β ratios in DMF, when a bidentate ligand was employed and the arylating halides were replaced by triflates, or when a stoichiometric silver or thallium salt was added in the case of aryl halides being the arylating reagents. This approach has since been exploited in a number of reactions including those that lead to bioactive compounds.[3c−e] Scheme 2 shows examples highlighted by Cabri and Candiani in a 1995 Account which were obtained
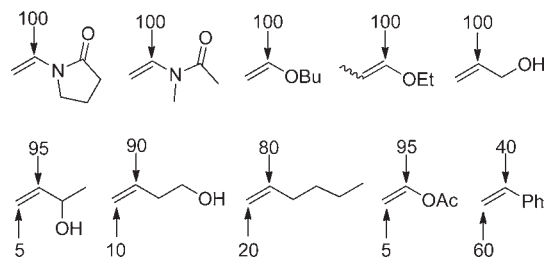
using ArOTf or ArX (X = Br, I) in the presence of a silver or thallium salt.[5a]

It is now generally accepted that the regioselectivity issue exists because there are two competing reaction pathways in the Heck reaction, as illustrated by the simplified mechanism in Scheme 3.[3,5,7,8] The neutral pathway A produces the β product, which is triggered by the dissociation of a neutral ligand from Pd[II]. In contrast, the ionic pathway B, featuring halide dissociation instead, yields the α product.

The α-regioselectivity is probably a result of the polarized nature of the C=C double bond in an electron-rich olefin such as vinyl ethers, in which the HOMO orbital is primarily located on the β-carbon and the α-carbon is more positively charged. Coordination to the cationic Pd[II] center would enhance this polarization, as illustrated by the resonance structures shown in eq 2, rendering the α-carbon more susceptible to attack by the migrating aryl moiety.[9] DFT calculations show that, when following pathway B, electron-rich olefins indeed tend to afford the α-arylated olefin, and this is driven primarily by electrostatic and frontier orbital interactions.[10] Theoretical studies also revealed how an electron-rich olefin is polarized by Pd[II]. Thus, 2,3-dihydrofuran coordinates to a Pd[II]−P^N complex almost exclusively through one of the two olefinic carbons, the C_4 atom, supporting eq 2.[11]
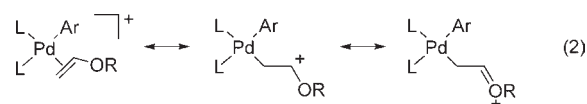
The mechanism in Scheme 3, although simple, explains the salient features of the methods used by Hallberg and Larhed,[3e,12] Cabri,[5a,7a,13] and other researchers[3a,e] in their effort to promote the α-selectivity. Thus, acting as halide scavengers for aryl halides, silver and thallium salts promote the ionic pathway B. Similarly, the lability of the Pd−OTf bond facilitates the formation of the cationic Pd[II]−olefin

SCHEME 3. Two Competing Pathways in the Heck Reaction
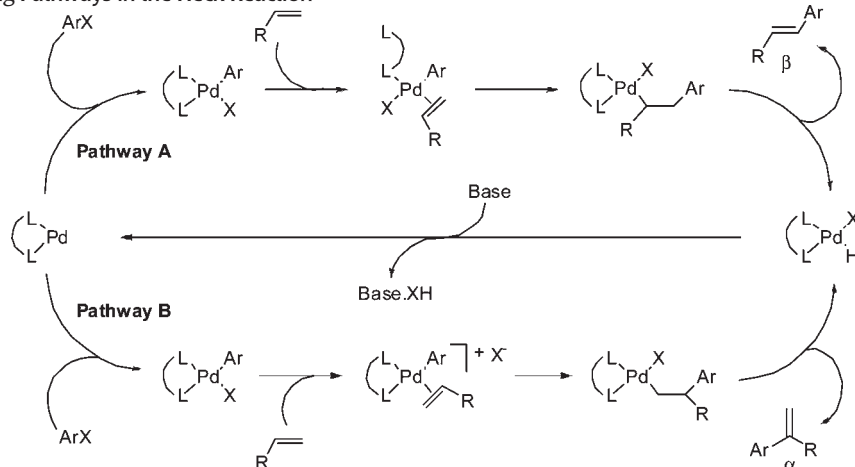
species. It is also apparent that a monodentate ligand would make pathway A more likely, whereas a bidentate ligand would encourage pathway B. These tactics have also been widely exploited in enantioselective Heck reactions, where the ionic pathway is generally believed to give high enantioselectivities.[3c,d]

There are, however, shortcomings associated with these methods. Silver introduces added cost, thallium salts are toxic, and triflates are generally commercially unavailable in addition to being base sensitive and thermally labile. Hence, there clearly exists an incentive to develop cleaner, faster, and more economical α-regioselective catalytic systems that tolerate aryl halides while obviating the need for expensive or toxic inorganic additives. Summarized below is a journey we have undertaken since the early 2000s, aiming to address these issues.

## Promoting the Ionic Pathway with Ionic Liquids

Ionic liquids such as imidazolium salts are entirely composed of ions. Thus, electrostatic interactions would be expected to 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 (pathway B vs A, Scheme 3). This seemingly naive, like−likes−like approach proves to be highly effective. In 2001 in a project aimed to develop catalysis in ionic liquids, we quickly found that by simply switching solvent from the traditional CH_3CN, DMF, or DMSO to the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF$_4$]), the benchmark electron-rich olefin butyl vinyl ether is arylated exclusively α-regioselectively with aryl bromides under the catalysis of Pd−dppp (dppp =1,3-bis(diphenylphosphino)propane).[14] The scope

TABLE 1. Arylation of Vinyl Ethers with Aryl Bromides in [bmim][BF$_4$]

	yield (%)			
	olefin used			
R=	a	b	c	d
R=H	90	97	93	86
F	92	96	96	87
CHO	90	93	96	84
COMe	90	92	94	88
CN	91	94	95	85
OMe	87	81	89	83
CO$_2$Me	90			
Me	88			

	yield (%)
	olefin **b** used
R=F	81
CHO	83
COMe	87
CN	95
OMe	86
Me	80

|	yield (%)
	olefin **b** used
R=F	81
OMe	86

of the reaction was subsequently explored.[15] Selected examples of arylation of vinyl ethers with aryl bromides are shown in Table 1. The arylation proceeded with >99/1 α/β-regioselectivities, furnishing aryl methyl ketones in high yields after acidic hydrolysis of the arylated enol ethers. The regioselectivity was not affected by the electronic property of substituents on the aryl rings, and aryl iodides worked equally well.

Heteroaryl bromides could also be brought to couple with vinyl ethers.[16] Table 2 shows examples obtained with *n*-butyl vinyl ether. Excellent α-selectivities were obtained, providing an alternative way to acetyl heteroaromatics which would be difficult to access via the traditional Friedel−Crafts acylation.

TABLE 2. Arylation with Heteroaryl Bromides in [bmim][BF$_4$]

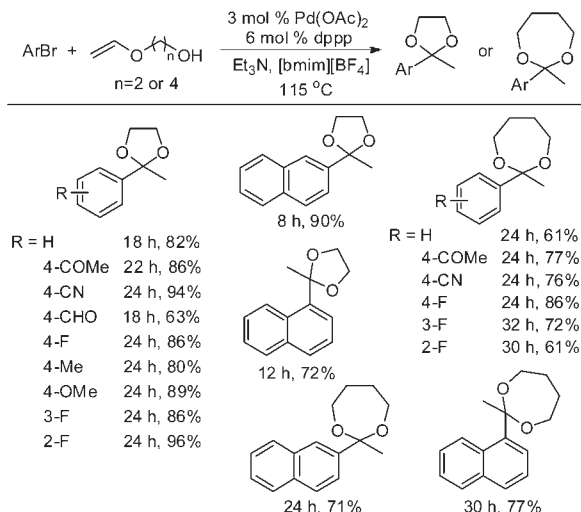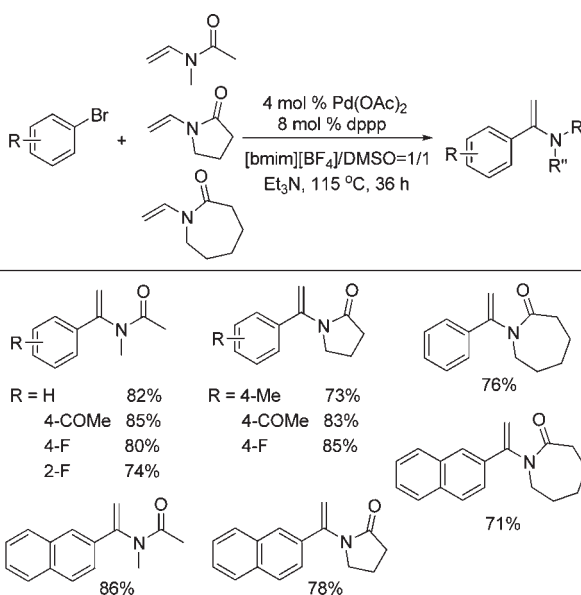|					
81%	88%	75%	91%	82%	89%
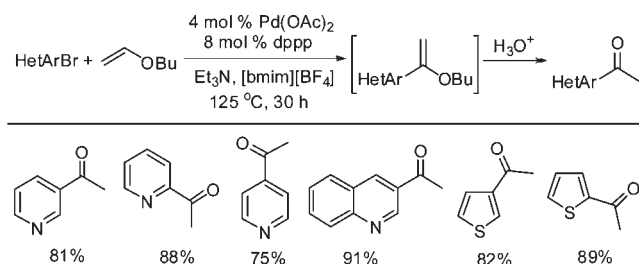
Inspired by the work of Hallberg and Larhed on the arylation of hydroxyalkyl vinyl ethers to synthesize cyclic ketals, using aryl triflates or aryl bromides combined with TlOAc in DMF,[12c] we performed the same reaction with aryl bromides in an ionic liquid. As is shown in Table 3, cyclic ketals are formed in good yields, via the intermediacy of α arylated enol ethers.[17] We further demonstrated that both the catalyst and ionic liquid are recyclable.

Other electron-rich olefins were also examined. Allyltrimethylsilane, the α carbon of which is more positively charged, reacted with aryl bromides of diverse electronic properties, furnishing exclusively the α-arylated allylsilanes (eq 3).[15] Similar regioselective arylation could also be achieved in CH$_3$CN, but aryl triflates were necessary.[12b]

R	COMe	CHO	CO$_2$Me	CN	F	H	Me
yield (%)	93	82	85	65	89	88	89
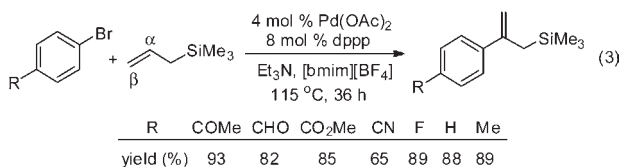
Under the same reaction conditions, however, the arylation of enamides failed. This may partly stem from the nitrogen lone pair being engaged in conjugation with the carbonyl group. Somewhat surprisingly, when DMSO was introduced as cosolvent, regioselective arylation took place.[15] Table 4 summarizes the results obtained in a 1:1 (volume) mixture of [bmim][BF$_4$] and DMSO. All the reactions were α-selective, affording synthetically important α-arylenamides. Further study showed that the amount of ionic liquid in the mixture could be substantially reduced.[18]

Using the DMSO−[bmim][BF$_4$] cocktail, allyl alcohol was arylated with excellent α-regioselectivity (Table 5).[19] Homoallyl alcohol and other unsaturated alcohols were less selective, however. The ability to arylate these alcohols in such a regioselective manner is pleasing, as their Heck reaction usually leads to β-substitution.[19,20] Allyl alcohols with substituent next to the OH group were also arylated, affording up to 70% α-products. It appears that increased steric bulkiness diminishes the α/β ratios.[21]

TABLE 3. Synthesis of Cyclic Ketals in [bmim][BF$_4$]

R = H	18 h, 82%
4-COMe	22 h, 86%
4-CN	24 h, 94%
4-CHO	18 h, 63%
4-F	24 h, 86%
4-Me	24 h, 80%
4-OMe	24 h, 89%
3-F	24 h, 86%
2-F	24 h, 96%

8 h, 90%

12 h, 72%

R = H	24 h, 61%
4-COMe	24 h, 77%
4-CN	24 h, 76%
4-F	24 h, 86%
3-F	32 h, 72%
2-F	30 h, 61%

24 h, 71%

30 h, 77%

TABLE 4. Arylation of Enamides in DMSO−[bmim][BF$_4$]

R = H	82%	R = 4-Me	73%	76%
4-COMe	85%	4-COMe	83%	
4-F	80%	4-F	85%	
2-F	74%			

86%

78%

71%

The ionic liquid protocol also finds use in the arylation of unsaturated ketones. Table 6 shows examples from 5-hexen-2-one. Arylated unsaturated ketones were obtained in up to 99/1 α/β ratios (Table 6).[22] In both this reaction and that of the alcohols, the oxygen atom may coordinate to Pd^{II}, assisting bromide dissociation. It is interesting to note, however, that a similar regioselectivity was observed with 1-hexene when the ionic pathway B was made favorable.[5a]

Good regioselectivities necessitate careful choice of ligands, and dppp appears to be most effective thus far. This is seen in the effect of phosphines on the arylation of butyl vinyl ether with 4-bromobenzaldehyde (Table 7).[15] There

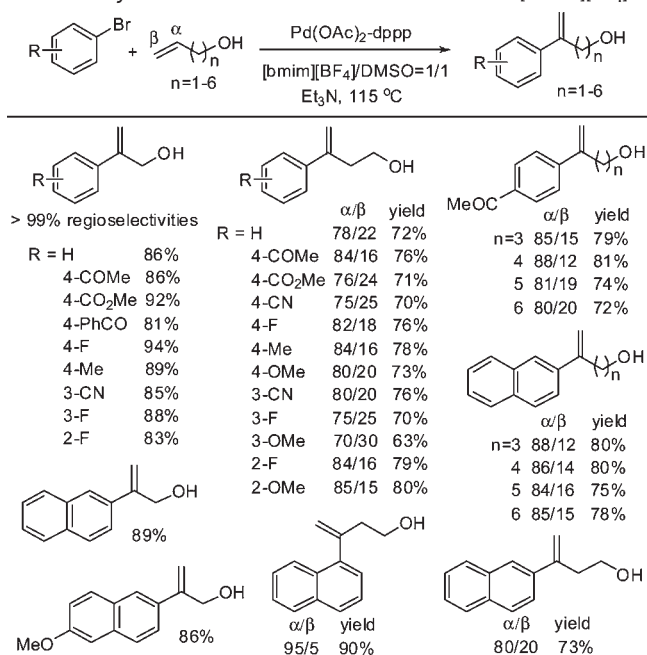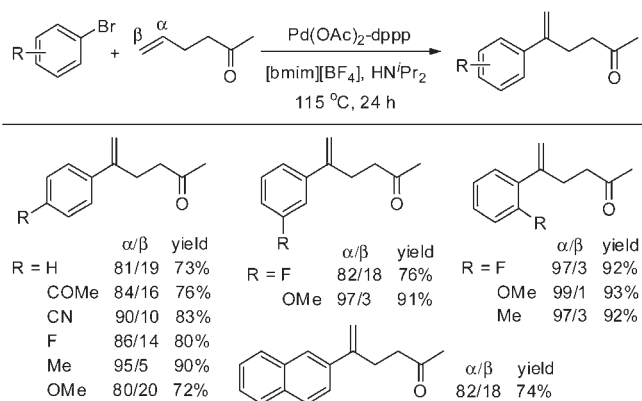**TABLE 5.** Arylation of Unsaturated Alcohols in DMSO–[bmim][BF$_4$]

> 99% regioselectivities

R = H   86%
4-COMe   86%
4-CO$_2$Me 92%
4-PhCO   81%
4-F   94%
4-Me   89%
3-CN   85%
3-F   88%
2-F   83%

R = H	α/β	yield
	78/22	72%
4-COMe	84/16	76%
4-CO$_2$Me	76/24	71%
4-CN	75/25	70%
4-F	82/18	76%
4-Me	84/16	78%
4-OMe	80/20	73%
3-CN	80/20	76%
3-F	75/25	70%
3-OMe	70/30	63%
2-F	84/16	79%
2-OMe	85/15	80%

MeOC	α/β	yield
n=3	85/15	79%
4	88/12	81%
5	81/19	74%
6	80/20	72%

	α/β	yield
n=3	88/12	80%
4	86/14	80%
5	84/16	75%
6	85/15	78%

89%

MeO   86%

α/β	yield
95/5	90%

α/β	yield
80/20	73%

TABLE 6. Arylation of 5-Hexen-2-one in [bmim][BF$_4$]

R = H	α/β	yield
	81/19	73%
COMe	84/16	76%
CN	90/10	83%
F	86/14	80%
Me	95/5	90%
OMe	80/20	72%

R = F	α/β	yield
	82/18	76%
OMe	97/3	91%

R = F	α/β	yield
	97/3	92%
OMe	99/1	93%
Me	97/3	92%

α/β	yield
82/18	74%

appears to be a correlation between the catalyst activity and selectivity with the bite angles of diphosphines.[23] 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. Large bite angles could facilitate the dissociation of halide ions from palladium due to steric repulsions,[24] increasing the concentration of Pd−olefin cations and α-selectivity as a result. However, when the bite angle becomes too large, olefin rotation from the initial out-of-plane coordination to an in-plane position necessary for insertion could be inhibited. Previous studies suggest that the ionic pathway is rate-limited by the olefin insertion step and there is a pre-equilibrium between the neutral [L$_2$Pd(Ar)X] and the ionic [L$_2$Pd(Ar)(olefin)]$^+$ species

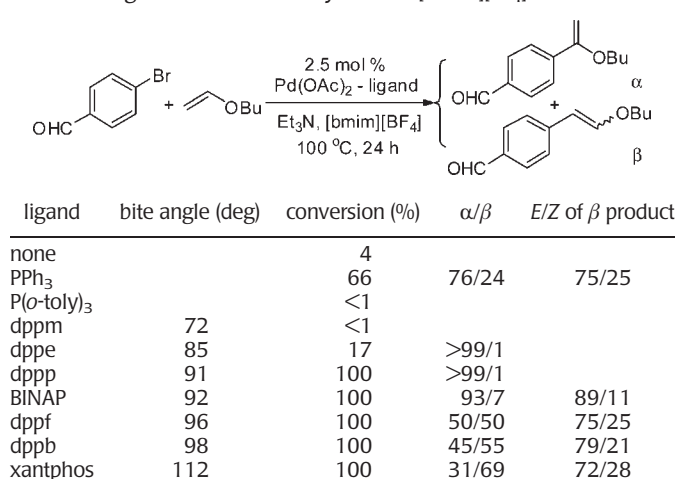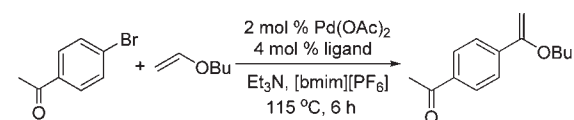**TABLE 7.** Ligand Effect on the Arylation in [bmim][BF$_4$]

ligand	bite angle (deg)	conversion (%)	α/β	E/Z of β product
none		4		
PPh$_3$		66	76/24	75/25
P(o-tolyl)$_3$		<1		
dppm	72	<1		
dppe	85	17	>99/1	
dppp	91	100	>99/1	
BINAP	92	100	93/7	89/11
dppf	96	100	50/50	75/25
dppb	98	100	45/55	79/21
xantphos	112	100	31/69	72/28

TABLE 8. Effect of Ligand Electronic Properties on the Arylation in [bmim][PF$_6$]

R	ligand	conversion (%)
4-CN	4-CN-dppp	74
4-CF$_3$	4-CF$_3$-dppp	60
H	dppp	47
4-Me	4-Me-dppp	41
4-OMe	4-MeO-dppp	29

(pathway B, Scheme 3).[8,25] While ligands with smaller bite angles would be less inhibitive toward olefin rotation, dissociation of the halide ion or the insertion itself could be slow.

We also examined the electronic effect of the ligand. Contrary to the Heck reaction proceeding via the neutral pathway A, where electron-rich monophosphine ligands are generally favored,[3] the results in Table 8 show that the α-arylation of electron-rich olefins benefits from electron-deficient diphosphine ligands.[26] The higher rates associated with these ligands may be attributed to a reduced olefin insertion barrier, and this could in turn stem from an easier rotation of the olefin preceding insertion due to reduced π back-donation from Pd(II), and from an enhanced positive charge on the coordinated olefin.[10,27] DFT calculations revealed indeed a lower insertion barrier for the electron-deficient dppp analogues.[26]

An inevitable question is why the ionic liquid is so effective in promoting the α-arylation. We believe that the formation of the key cationic Pd(II)−olefin species is favored
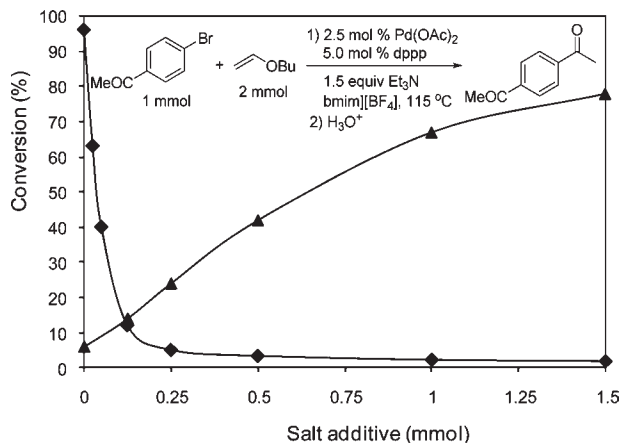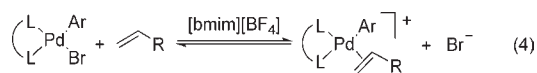
FIGURE 1. Effect of salt additives on the arylation of butyl vinyl ether at different reaction times: (◆) Bu$_4$NBr, 12 h; (▲) [HNEt$_3$][BF$_4$], 1 h.

in ionic liquids. In line with this view, Amatore and Jutand have recently shown that a high ionic strength favors α-arylation.[8] And an earlier study by Milstein et al. revealed that olefin insertion into the Pd−Ar bond in [L$_2$Pd(Ar)X] is greatly facilitated in a polar solvent.[25]

Evidence in support of the ionic pathway B comes from reactions in the presence of added halide anions.[15] As shown in Figure 1 (line ◆), the arylation of butyl vinyl ether with 4-bromoacetophenone was notably slowed even when 1 equiv of Br$^-$ (relative to palladium) was introduced into [bmim][BF$_4$], and the reaction rate was progressively reduced when more Bu$_4$NBr was added. This is consistent with there being an equilibrium (eq 4), which is shifted toward the left on addition of the halide ions. Similar observations have been made in arylation reactions using aryl triflates[7a,28] and in the stoichiometric reaction of [L$_2$Pd(Ar)Cl] with olefins in molecular solvents.[25]

$$\left(\begin{array}{c}L\\L\end{array}Pd\begin{array}{c}Ar\\Br\end{array}\right) + \diagup\!\!\!\diagup R \xrightleftharpoons{[bmim][BF_4]} \left[\begin{array}{c}L\\L\end{array}Pd\begin{array}{c}Ar\\\diagup\!\!\!\diagup R\end{array}\right]^+ + Br^- \quad (4)$$

A further demonstration of the ionic pathway is seen in the competition reaction shown in eq 5.[15] Of the three olefins, only the electron-rich vinyl ether reacted. This is a result of 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 butyl vinyl ether and methyl acrylate, due to preferential coordination of the electron-poor acrylate to a neutral Pd^{II} center.[13b]
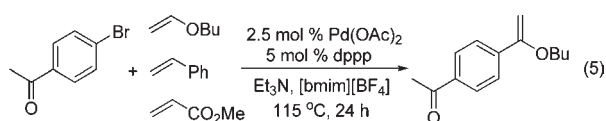

TABLE 9. [H$_2$N^{i}Pr$_2$]$^+$ Accelerated Arylation of Vinyl Ether in DMF

	COMe	CHO	CO$_2$Me	CN	F	H	Me	OMe	![naphthyl]
yield (%)	90	87	88	83	85	91	83	82	89

Speeding up with Hydrogen Bond Donors

The ionic liquid approach enables successful regiocontrol, circumventing the need for silver/thallium salts. However, the observed TOF (<2 h^{-1}) and TON (<40) values were low. The dramatic decrease in the arylation rate with increasing bromide concentration suggests that the HBr generated from each arylation cycle must be effectively scavenged by the base NEt$_3$ (Figure 1 and Scheme 3). The trapping of the bromide anions most likely arises from possible hydrogen bonding between [HNEt$_3$]$^+$ and Br$^-$, rendering the equilibrium in favor of the Pd^{II} cation (eq 4). Thus, we reasoned that introduction of a potential hydrogen bond donor (HBD) should enhance the reaction rates. The remarkable effect of [HNEt$_3$]$^+$ is clearly revealed in Figure 1 (line ▲).[29]

Indeed, in the presence of [HNEt$_3$][BF$_4$] (1.5 equiv), the arylation in [bmim][BF$_4$] becomes much faster, with no compromise on regioselectivity.[29] For instance, the reactions of butyl vinyl ether with various bromides all completed in less than 3 h. This is significant, as the reactions required up to 36 h to complete without [HNEt$_3$][BF$_4$]. Worth noting is that the palladium loading could be lowered to 0.1 mol % in the presence of the HBD, increasing the TOF and TON to ca. 80 h^{-1} and 1000, respectively.

Significantly, the HBD is also shown to accelerate arylation in common solvents.[29] Thus, under conditions used for [bmim][BF$_4$] but replacing the ionic liquid with DMF or DMSO, various aryl bromides reacted with vinyl ethers or enamides, affording α-arylated olefins exclusively (Tables 9 and 10). In contrast, the reaction in the absence of [H$_2$N^{i}Pr$_2$][BF$_4$] was sluggish and much less selective.[7a,13a,13b,15]

Ammonium salts, such as [NBu$_4$][Cl], are known to accelerate the Heck reaction.[30] Under the Jeffery conditions, the Heck reaction presumably proceeds via the neutral pathway, involving anion-ligated palladium species.[31] In contrast, the HBD [H$_n$NR$_{4-n}$]$^+$ ($n = 1, 2$) promoted arylation is typical of the Heck reaction proceeding by the cationic pathway B, and we believe that the primary role of
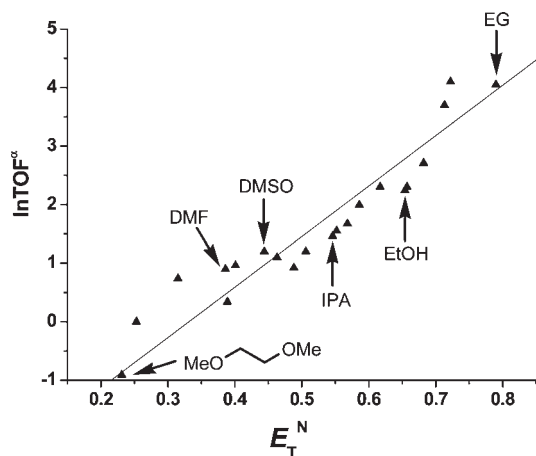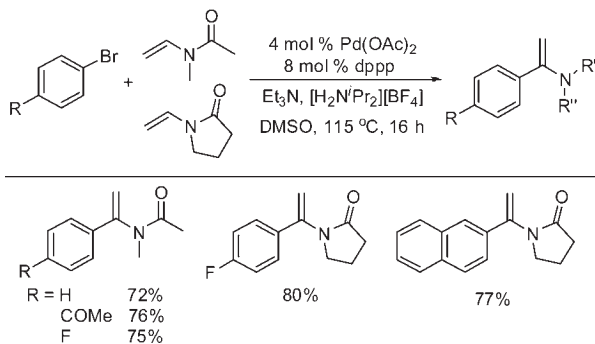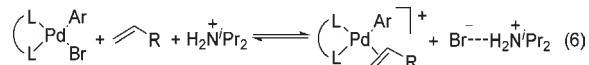
FIGURE 2. Effect of the solvent parameter E_T^N on ln(TOF) in the α-arylation of butyl vinyl ether with 4-bromoacetophenone.

TABLE 10. $[H_2N^iPr_2]^+$ Accelerated Arylation of Enamides in DMSO

$[H_nNR_{4-n}]^+$ is to hydrogen-bond with the bromide anion, shifting the equilibrium shown in eq 6 toward the Pd(II)–olefin cation.

Salty No Longer: α-Arylation in Alcohols

The observations made with the ammonium HBD raise an interesting question. Could much cheaper and environmentally friendlier alcohols be used as solvent to replace the imidazolium or HBD salts? Alcohols are known to act as receptors for halide anions, and in particular ethylene glycol (EG) is a good HBD as judged by its high E_T^N value of 0.790.[32]

This belief was strengthened by the study of an arylation in more than 20 solvents, which revealed that hydrogen-bond donating, protic solvents indeed accelerate α-regioselective arylation.[33] As shown in Figure 2, the higher the E_T^N values, the faster this reaction becomes, with EG affording the fastest arylation.

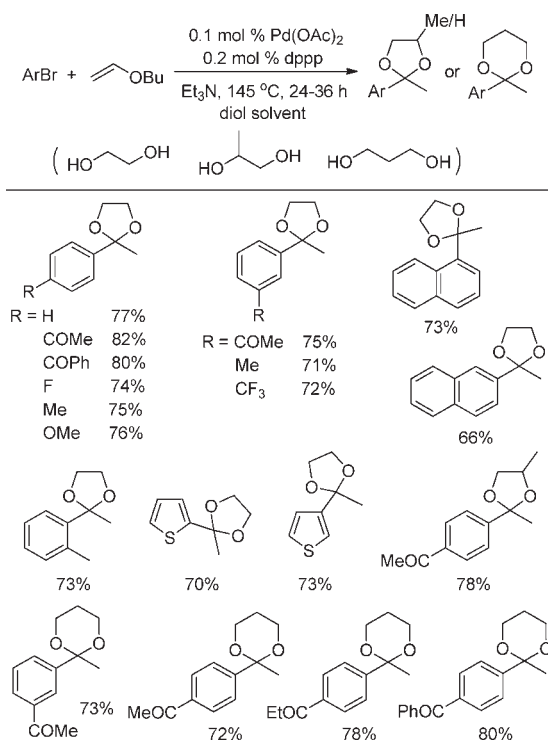**TABLE 11.** Arylation of Butyl Vinyl Ether in EG
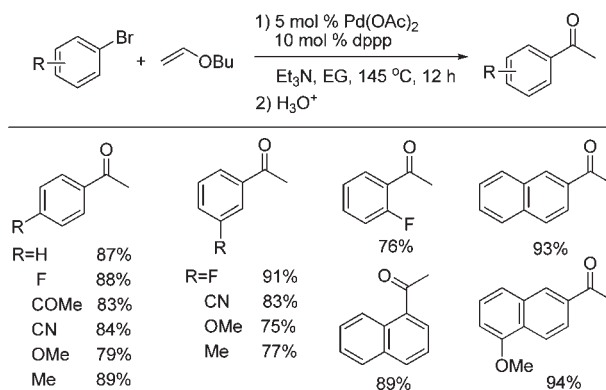
TABLE 12. Arylation of Enamides in EG
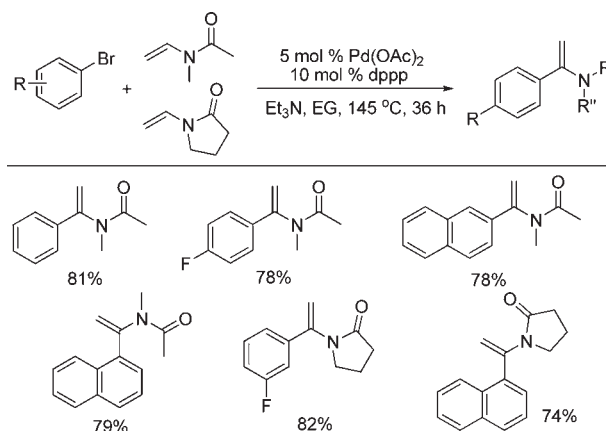
Gratifyingly, the arylation in alcohols such as EG indeed proceeds fast and α-regioselectively.[33a] Examples obtained with butyl vinyl ether and enamides are summarized in Tables 11 and 12. A further study has revealed remarkably high activity (TOF up to 15 625 h^{-1}) and productivity (TON up to 3.75×10^5) in the arylation of vinyl ethers, with the substrate-to-catalyst (S/C) ratio reaching 5×10^5.[34] These numbers far surpass those observed in ionic liquids or when using ammonium HBDs, representing actually the highest values ever reported for the Heck reaction of electron rich olefins. In particular, sterically demanding vinyl ethers also reacted under these conditions, leading to interesting aryl alkyl ketones (eq 7).
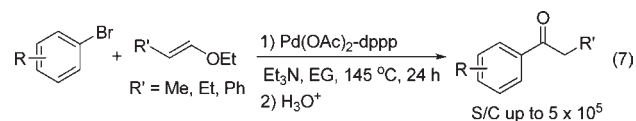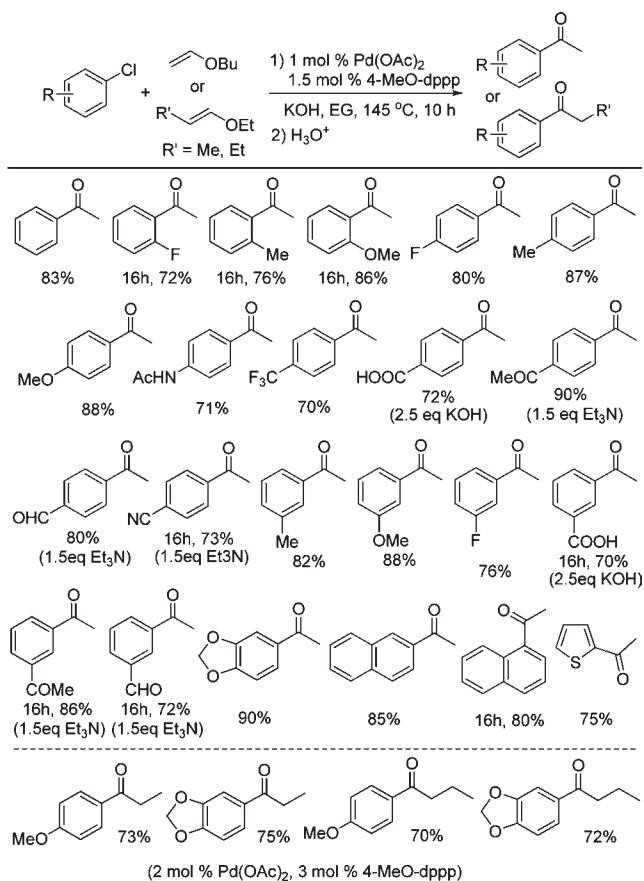

Heteroaryl bromides could also be brought to arylate the electron-rich olefins. However, better yields were obtained with Pd–dppf than Pd–dppp.[35] As shown in Table 13, high

TABLE 13. Arylation with Heteroaryl Bromides in EG
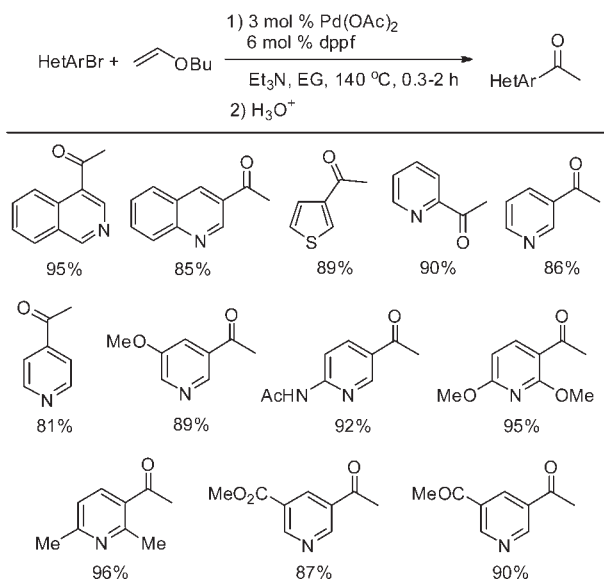
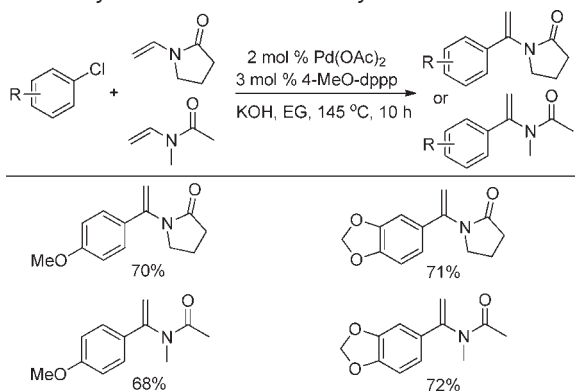**TABLE 14.** Synthesis of Cyclic Ketals via α-Arylation in Diols

TABLE 15. Arylation of Vinyl Ethers with Aryl Chlorides in EG

other than EG were also used. Further investigation established that the ketal results from nucleophilic attack at the isolable α-arylated vinyl ether by the diol under acid catalysis. As noted earlier, the use of hydroxylalkyl vinyl ether was required to obtain cyclic ketals.[12c,17,29,33a]

Having succeeded in the α-arylation with aryl bromides and iodides, we sought to extend the chemistry into the cheaper and more widely available aryl chlorides. Their reaction is much more challenging, however, as catalysts capable of coupling aryl chlorides[3a,f] are generally less active and, without exception, give rise to a mixture of products when used for electron-rich or deactivated olefins (eq 8).[29,37,38]
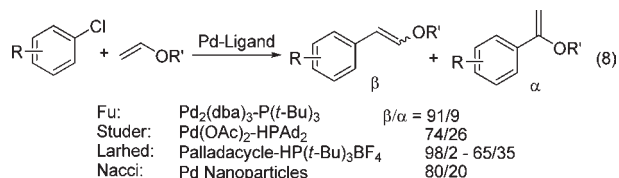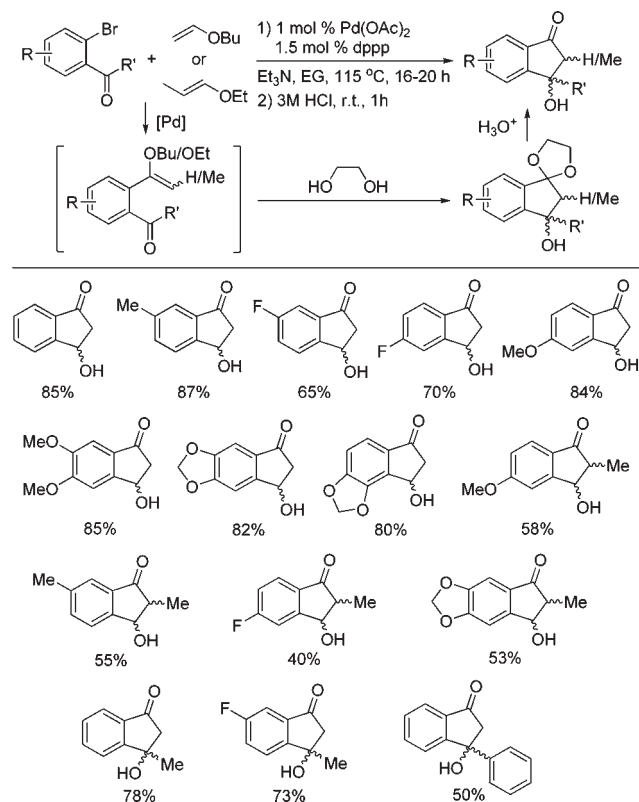

To tackle this issue, we reasoned that an electron rich ligand would be necessary, since the overall Heck reaction is almost certainly turnover-limited by the oxidative addition

yields of acetyl heteroaromatics were furnished, although a higher catalyst loading was necessary.

An interesting observation was made during the study of the arylation of butyl vinyl ether in EG.[36] Cyclic ketal was formed before the acidic hydrolysis and could actually be isolated. The results are shown in Table 14, where diols

TABLE 16. Arylation of Enamides with Aryl Chlorides in EG

TABLE 17. Arylation of Styrenes in EG

TABLE 18. Heck Aldol Annulation Reaction of Aryl Bromides with Vinyl Ethers in EG
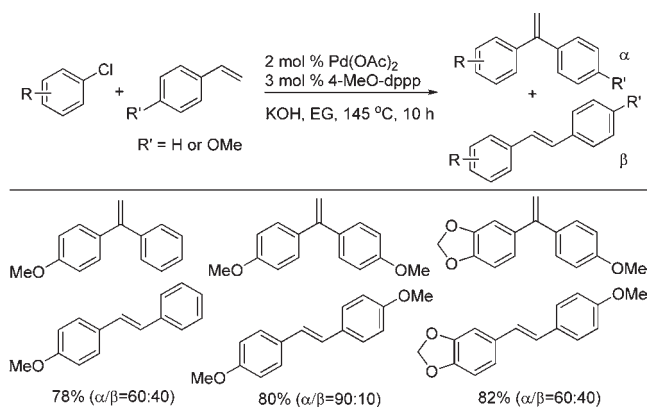
of ArCl to Pd(0);[3a,f,39] further, the ligand should be bidentate, and in addition the reaction medium should be highly ionizing. The latter two conditions are necessary in order to channel the arylation into the ionic pathway B, without which the arylation would stop at the [Pd(dppp)(Ph)Cl] intermediate,[8b] even if the oxidative addition occurred. Delightfully, by combining the highly ionizing power of EG and 4-MeO-dppp (Table 8), we were able to accomplish, for the first time, the arylation of electron-rich olefins with a wide range of aryl chlorides, in a highly α-regioselective manner.[40] Tables 15 and 16 show examples of α-arylation of vinyl ethers and enamides, which tolerates both activated and unactivated aryl chlorides.

Styrenes were also arylated under similar conditions. Surprisingly, somehow, electron-rich substrates such as 4-methoxystyrene led mainly to α-arylated products, thus offering a convenient means for synthesizing the pharmaceutically useful 1,1-diarylalkene derivatives (Table 17).[40]

Further study allowed us to develop a one-pot method to access multisubstituted 1-indanones when 2-halo-

benzaldehydes were used.[41] In this EG-participating cascade reaction, the Heck reaction first installs an enol functionality on the aromatic ring; this is followed by an aldol-type annulation with the neighboring carbonyl group, resulting in the formation of 1-indanones (Tables 18 and 19). EG promotes both the Heck reaction and the nucleophilic attack via hydrogen bonding. Little 1-indanones were produced when the reaction was carried out in DMF or DMSO. The method works for both aryl bromides and chlorides.

The success in ArCl with EG can be at least attributed to the equilibrium (eq 9) being shifted to the right. However, the Pd-(4-MeO-dppp)-catalyzed arylation is almost certainly turnover-limited by the oxidative addition of ArCl,[3a,f,39] and the various evidence we collected is supportive of this view. For instance, the analogous but electron-deficient 4-CF$_3$-dppp ligand led to insignificant yields, and a Hammett plot on *para*-substituted aryl chlorides revealed a positive ρ value of 2.1. In addition, it is worth pointing out that the arylation hardly proceeds when the solvent is changed to DMF or DMSO.
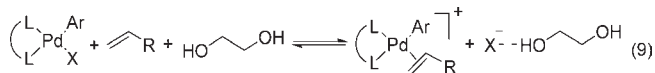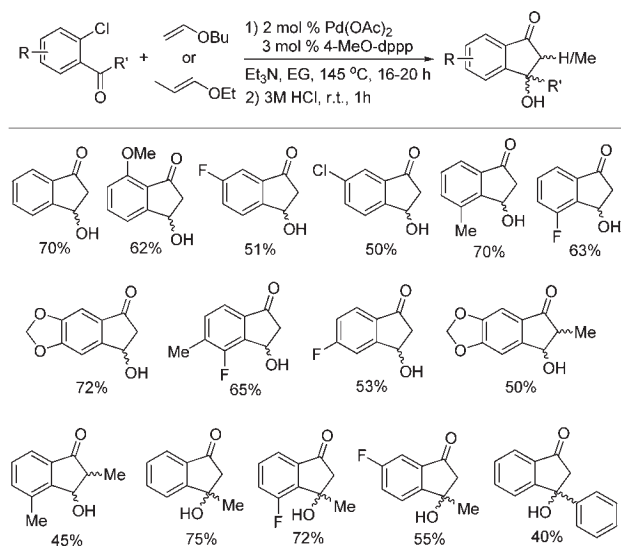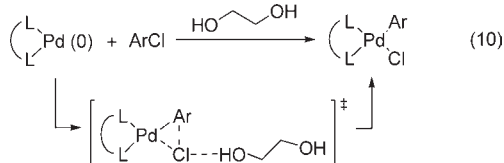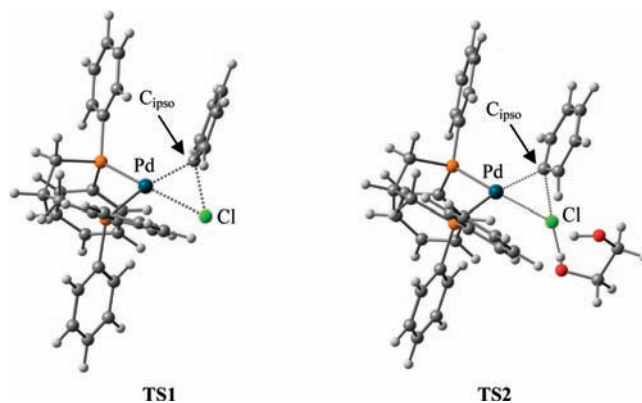
TABLE 19. Heck Aldol Annulation Reaction of Aryl Chlorides with Vinyl Ethers in EG

FIGURE 3. Calculated transition state for the oxidative addition of PhCl to [Pd(dppp)]: TS1 in vacuo; TS2 with one explicit ethylene glycol molecule. Carbon, gray; hydrogen, white; phosphorus, orange; palladium, dark blue; chlorine, green; oxygen, red. Selected distances [Å], TS1: Pd−C_{ipso} 2.124, C_{ipso}−Cl 2.115, Pd−Cl 2.613; TS2: Pd−C_{ipso} 2.070, C_{ipso}−Cl 2.228, Pd−Cl 2.832, Cl−HO 2.30.

An inevitable question then is this: is the oxidative addition accelerated by EG (eq 10)? DFT calculations show indeed that EG interacts with the chloride at the transition state (TS) of PhCl oxidative addition to Pd(dppp), significantly lowering the energy barrier by 13.03 kal/mol relative to that in vacuo (TS1 vs TS2, Figure 3). At TS2, the chloride atom bonds to one of the hydroxyl groups of EG through the hydrogen atom, displaying a Cl···H distance of 2.30 Å. Thus, EG plays a double role in the arylation of ArCl, facilitating oxidative addition of the halides and promoting the subsequent dissociation of chloride from Pd^{II} to enable the ionic pathway B.[40]


## Beyond the Heck Reaction: Acylating Aryl Halides with Aldehydes

In continuing study into the arylation of electron-rich olefins, we developed in 2008 a new protocol for the acylation of aryl bromides with aldehydes, which involves palladium−pyrrolidine cooperative catalysis, affording synthetically significant alkyl aryl ketones in a straightforward manner.[42] The α-regioselective arylation presented above provides an indirect method for accessing these ketones. However, the availability of the vinyl ethers and enamides is

TABLE 20. Acylation of Aryl Bromides with Aldehydes
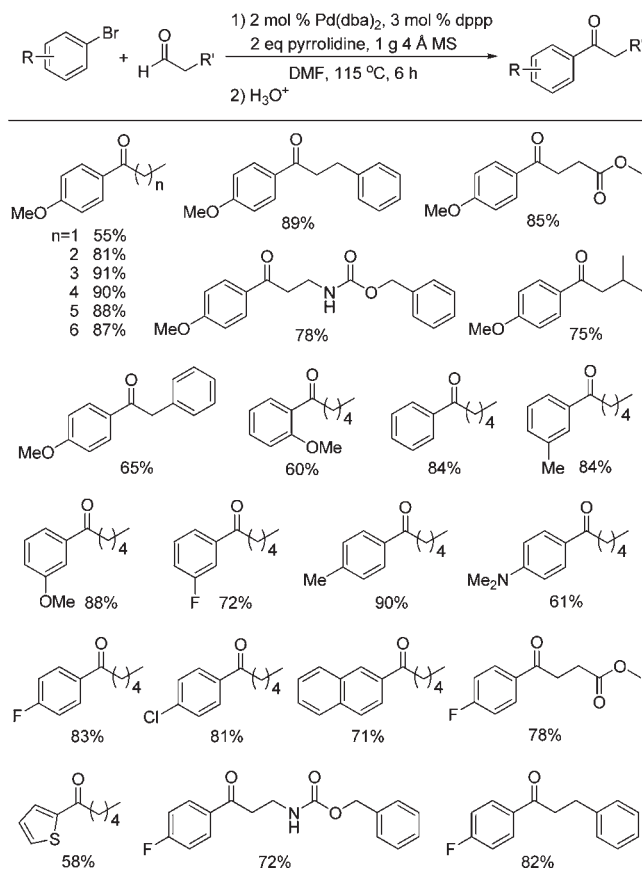
relatively limited. Realizing that, in the presence of a secondary amine, such as pyrrolidine, an aldehyde can equilibrate with an enamine, which is an electron-rich olefin, we thought that it might be possible to couple aryl halides with

TABLE 21. Acylation of Aryl Chlorides with Aldehydes
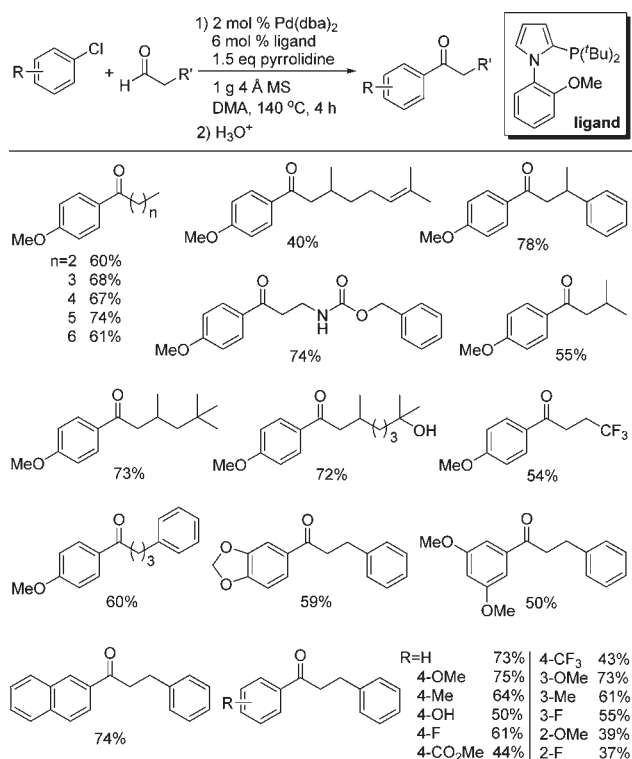
aldehydes via the intermediacy of enamine to give ketone following hydrolysis (eq 11).
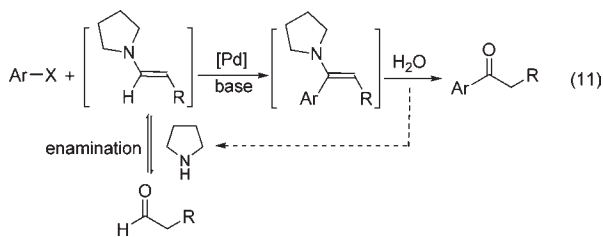
The hypothesis led to an exciting outcome. As is shown in Table 20, various aldehydes underwent acylation with aryl bromides under the palladium–pyrrolidine catalysis. Pyrrolidine is necessary for the acylation, as lower yields resulted with other amines. In contrast to the arylation of vinyl ethers, the acylation appears to be less sensitive to the ligand used, presumably due to the pyrrolidine moiety being more electron donating.

Aryl chlorides were also acylated, but a bulky, electron-rich monophosphine was necessary.[43] A wide range of aryl chlorides reacted, affording moderate to good yields of alkyl aryl ketones (Table 21). Preformed enamine could also be used to form the same product, supporting the intermediacy of enamine. In both acylation reactions, pyrrolidine is a co-catalyst. Indeed, catalytic pyrrolidine is feasible provided an

SCHEME 4. Regioselectivities (α/β Ratio) Observed in Our Studies
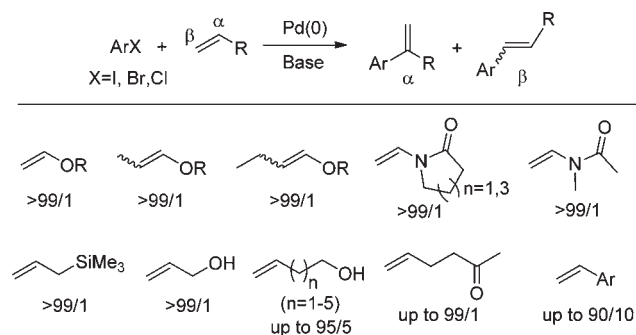
additional base such as K_2CO_3 is added. The chemistry extends the Heck reaction from olefins to aldehydes, permitting direct access to alkyl aryl ketones via acylation of aryl halides.

Concluding Remarks

The regioselectivity issue in the arylation of electron-rich olefins was noted in the early development of the Heck reaction, and it has since been extensively studied. The early success is summarized in Schemes 1 and 2, culminating in the discovery of using aryl triflates, halide scavengers, and bidentate ligands. Bearing in mind the textbook-type mechanism shown in Scheme 3, we thought if we were able to encourage the formation of the cationic Pd(II) species and so the ionic pathway B, we would be able to direct the arylation to give the α-product. Our journey started with ionic liquids, the slow rate in which prompted the finding of the promoting role of HBDs. Realizing the ability of hydrogen bonding led us to where we are now, that is, regiocontrol with an alcohol medium. All three methods afford total α-regiocontrol in the arylation of the typical electron-rich olefins such as vinyl ethers and enamides with aryl halides, circumventing the need for halide scavengers.[44] Scheme 4 summarizes the regioselectivities obtained in our hands. Gratifyingly, along the journey, the arylation protocol evolves to become more productive, powerful, and greener, with the cheap and less toxic EG delivering unprecedented productivity and tolerating aryl chlorides of diverse properties.

BIOGRAPHICAL INFORMATION

Jiwu Ruan received his B.Sc. degree in chemistry from Sichuan University in 1994 and obtained his Ph.D. degree in organic chemistry from Sun Yat-sen University in 2004 under the direction of Professor Lianquan Gu. He then joined Professor Albert S. C. Chan's group as a postdoctoral researcher at the Hong Kong Polytechnic University. He has been a postdoctoral researcher at Professor Jianliang Xiao's group since 2005.

Jianliang Xiao received his B.Eng. in chemical engineering at Northwest University. This was followed by a M.Eng. in catalytic engineering with Profs. Chi Wu and Junyu Wang at the Research Institute of Petroleum Processing and a Ph.D. in chemistry with Prof. Marty Cowie at the University of Alberta. After a postdoctoral appointment with Prof. Richard Puddephatt, he joined the ERATO Molecular Catalysis Project directed by Prof. Noyori. In 1996 he took up a Principal Scientist position at the University of Liverpool and was appointed to a Lectureship in the Chemistry Department in 1999; this was followed by promotion to full Professor in early 2005. He was awarded the UK Prize for Process Chemistry Research 2008.

FOOTNOTES

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