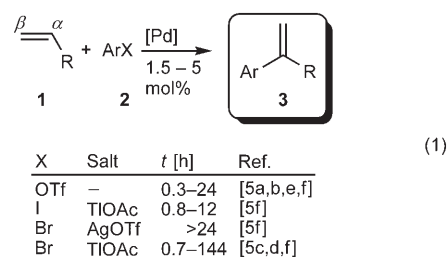


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The Heck Reaction of Electron-Rich Olefins with Regiocontrol by Hydrogen-Bond Donors

Jun Mo and Jianliang Xiao*

Considerable progress has been made in the Heck arylation of electron-deficient olefins in the past several years; these olefins generally form linear products.^[1,2] However, this is not the case with electron-rich olefins, the intermolecular arylation of which is usually complicated by the formation of a mixture of regioisomers. This problem can be addressed by employing aryl triflates or by adding stoichiometric silver or thallium salts when aryl iodides and bromides are chosen.^[3-5] However, triflates are thermally labile and are generally not commercially available, and the inorganic additives create new problems, that is, waste salts, toxicity, and added cost. Additionally, when applied to intermolecular arylation these methods generally afford low turnover numbers (TONs) and turnover frequencies (TOFs), with some reactions requiring exceedingly long times and high catalyst loadings [Eq. (1); OTf = triflate].^[5d]



We recently demonstrated that imidazolium ionic liquids in combination with readily available Pd(OAc)₂ and 1,3-bis(diphenylphosphino)propane (dppp) form an excellent catalytic system, with which electron-rich olefins can be arylated highly regioselectively by aryl halides without recourse to triflates or any halide scavengers, for example, AgOTf or TfOAc.^[6-9] However, the observed TOF (< 2 h⁻¹) and TON (< 40) values are again relatively low. Herein, we report that the regioselective Heck reaction of electron-rich olefins can be greatly accelerated by hydrogen-bond-donating ammonium salts, not only in ionic liquids but in common molecular solvents as well. The use of common solvents would

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further extend the applicability of the Heck chemistry in synthesis, as until now “the use of additives such as AgOTf or TIOAc or of an ionic liquid solvent is generally required to obtain high α/β selectivity in the Heck reaction of aryl halides” for this class of olefin.^[10]

Our recent study indicates that the arylation of electron-rich olefins by Pd–dppp catalysis is inhibited by bromide ions in the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF₄]).^[6a] This behavior is clearly seen in Figure 1 for the arylation of butyl vinyl ether by bromoaceto-

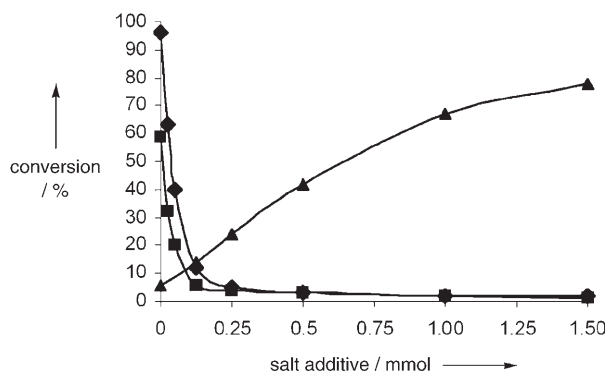
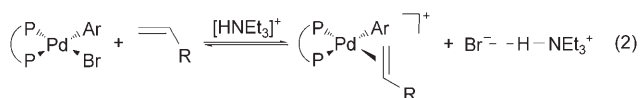


Figure 1. The effect of salt additives on the conversion of bromoacetophenone (**2a**) with butyl vinyl ether (**1a**) at different reaction times: ■ *n*Bu₄NBr, 6 h; ◆ *n*Bu₄NBr, 12 h; ▲ [HNEt₃][BF₄], 1 h. Reaction conditions: **1a** (2.0 mmol), **2a** (1.0 mmol), Pd(OAc)₂ (2.5 mol%), dppp (5.0 mol%), and Et₃N (1.5 equiv) in [bmim][BF₄] (2 mL) at 115 °C.

tophenone. The dramatic decrease in the arylation rate with increasing bromide concentration suggests that there is an equilibrium before the rate controlling step [Eq. (2)]. An

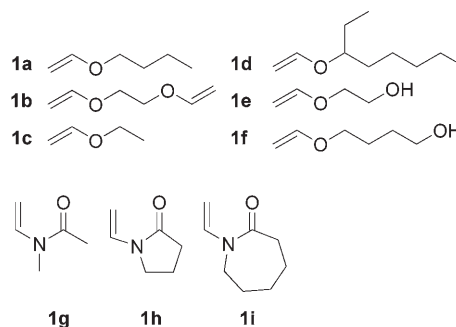
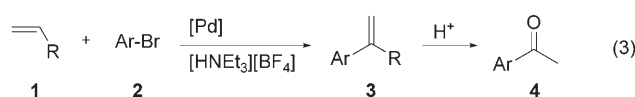


important conclusion then is that the HBr generated from each arylation cycle must be effectively scavenged by NEt₃, as the reaction would otherwise be practically stopped before reaching an approximate conversion of 25%. The trapping of the bromide anions could be brought about by possible hydrogen bonding between [HNEt₃]⁺ and Br[−], thus rendering the equilibrium in favor of the right side [Eq. (2)]. Hydrogen bonding is indicated as the N–H proton of [HNEt₃][BF₄] (0.01M in CDCl₃) moves progressively from δ = 7.55 to 10.91 ppm in the ¹H NMR spectra upon addition of up to two equivalents of [Br][NBu₄]. Indeed, examples of such hydrogen bonds are abundant in the literature.^[11]

Given the adverse effect of the bromide ions, introduction of the potential hydrogen-bond donor [HNEt₃]⁺ should enhance the reaction rates. The accelerating effect of [HNEt₃]⁺ is clearly revealed in Figure 1. A remarkable illustration of the effect is the comparison between the conversion observed in the presence of 1.5 equivalents of [NBu₄][Br] over 12 hours versus that in the presence of

1.5 equivalents of [HNEt₃][BF₄] over 1 hour; the conversions for the former and the latter were 2 and 78%, respectively (Figure 1)! Further evidence in support of the possible involvement of hydrogen bonding came from the observation that replacing [HNEt₃][BF₄] with [NBu₄][BF₄] brought about no significant effect on the reaction rate; but reintroduction of [HNEt₃][BF₄] did considerably accelerate the reaction in [bmim][BF₄] (see the Supporting Information). We also carried out the same arylation in the presence of 1.5 equivalents of [NBu₄][Br] with increasing palladium loading. However, this approach did not lead to any increase in the conversion (<3%), thus indicating that the inhibition of bromide ions takes place before the reductive elimination of HBr.^[12,13]

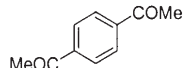
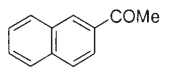
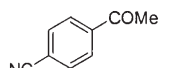
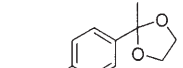
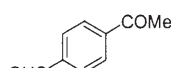
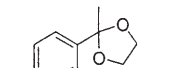
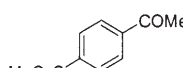
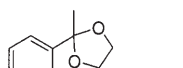
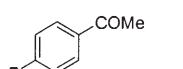
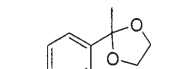
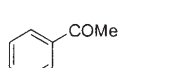
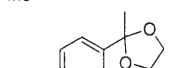
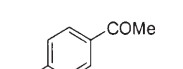
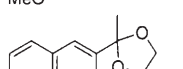
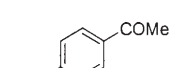
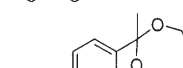
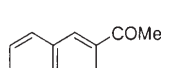
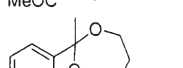
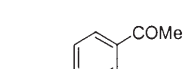
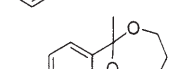
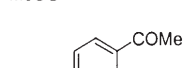
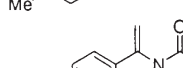
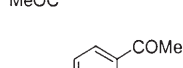
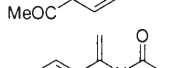
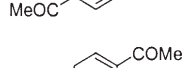
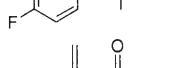
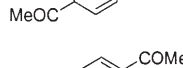

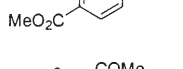
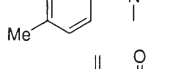
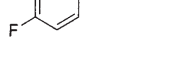
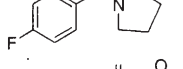

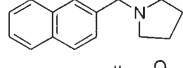
Based on these investigations, the arylation of electron-rich olefins **1a–i** was carried out with a variety of aryl bromides in [bmim][BF₄] in the presence of [HNEt₃][BF₄] [Eq. (3)]. As can be seen from Table 1, all the reactions



finished with >99:1 regioselectivity of the branched/linear products with good-to-excellent yields. In the case of butyl vinyl ether **1a** (Table 1, entries 1–9), the reactions were all completed in less than 3 hours, regardless of the nature of the substituents on the aryl rings. The isolated products were the ketone **4**, following the acidification of **3**. This outcome is remarkable in comparison with the previous results, in which the reactions needed up to 36 hours for completion without [HNEt₃][BF₄].^[6a] The vinyl ethers **1b–d** underwent similar, fast arylation by bromoacetophenone **2a** (Table 1, entries 10–12). Most interestingly, the palladium loading could be lowered to 0.1 mol% in the presence of the hydrogen-bond donor, thus bringing the TOF and TON values to up to 83 h^{−1} and 1000, respectively (Table 1, entries 13–18). This result represents the highest TON value ever reported for the internal arylation of electron-rich olefins.

The hydroxyalkyl vinyl ethers **1e–f** could also be arylated, with cyclization of the resulting products to give cyclic ketals. This chemistry was shown to be feasible in dimethylformamide (DMF) by Larhed and Hallberg using aryl triflates or halide scavengers for ArX (X = Br, I); however, the reaction tends to be slow.^[5d] Under the present conditions, the reaction was completed within 4 hours, thus providing a practical

Table 1: [HNEt₃]⁺-Accelerated regioselective arylation of olefins **1a–i**.^[a]

Entry	Olefin	ArBr	Product	t [h]	Yield [%]	Entry	Olefin	ArBr	Product	t [h]	Yield [%]		
1	1a	2a		4a	1.5	94	18 ^[d]	1a	2i		4i	12	91
2	1a	2b		4b	3	89	19	1e	2a		3ea	2	88
3	1a	2c		4c	1.5	90	20	1e	2e		3ee	2	96
4	1a	2d		4d	1.5	95	21	1e	2f		3ef	2	97
5	1a	2e		4e	1.5	96	22	1e	2g		3eg	2	90
6	1a	2f		4f	1.5	94	23	1e	2h		3eh	4	88
7	1a	2g		4g	2	88	24	1e	2i		3ei	4	89
8	1a	2h		4h	3	87	25	1f	2a		3fa	4	83
9	1a	2i		4i	1.5	93	26	1f	2f		3ff	4	91
10 ^[b]	1b	2a		4a	2	97	27	1f	2g		3fg	4	87
11	1c	2a		4a	2	92	28 ^[d]	1g	2a		3ga	4	84
12	1d	2a		4a	2	86	29 ^[d]	1g	2e		3ge	4	81
13 ^[c]	1a	2a		4a	12	91	30 ^[d]	1g	2f		3gf	4	80
14 ^[c]	1a	2d		4d	12	93	31 ^[d]	1g	2g		3gg	4	74
15 ^[c]	1a	2e		4e	12	94	32 ^[d]	1h	2e		3he	4	86
16 ^[c]	1a	2f		4f	12	90	33 ^[d]	1h	2i		3hi	4	83
17 ^[c]	1a	2g		4g	16	87	34 ^[d]	1i	2i		3ii	4	70

[a] Reaction conditions: **1** (2.0 equiv), **2** (1.0 mmol), [HNEt₃][BF₄] (1.5 equiv), Pd(OAc)₂ (2.5 mol%), dppp (5.0 mol%), and *i*Pr₂NH (1.5 equiv) in [bmim][BF₄] (2 mL) at 115 °C; 100% conversion and >99:1 regioselectivity for all, as determined by ¹H NMR spectroscopic analysis. Yields of the isolated products; **4** was obtained after acidification of **3**. [b] 0.75 equivalents of **1b** were used. [c] Pd(OAc)₂ (0.1 mol%) and dppp (0.2 mol%) were used. [d] Conditions: **1g–i** (1.0 mmol), Pd(OAc)₂ (4 mol%), dppp (8 mol%) in DMSO (1 mL), and [bmim][BF₄] (1 mL).

alternative to the synthesis of ketals, which may find use in the synthesis of anti-HIV agents (Table 1, entries 19–27).^[14]

Recently, we reported the first examples of the regioselective arylation of **1g–i** by aryl halides in a mixed solvent of [bmim][BF₄] and dimethyl sulfoxide (DMSO).^[6a,15] Again the reactions appeared to be sluggish and required more than 30 hours to complete. In stark contrast, under similar conditions but in the presence of [HNEt₃][BF₄], all the reactions went to completion within 4 hours (Table 1, entries 28–34).

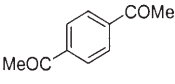
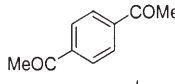
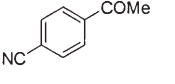
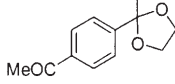
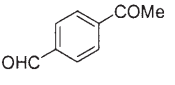
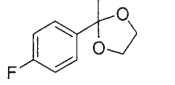
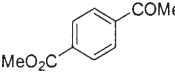
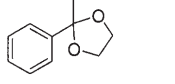
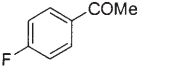
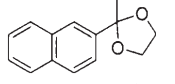
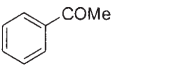
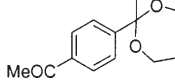
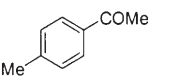
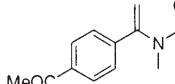
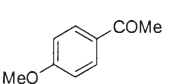
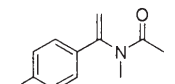
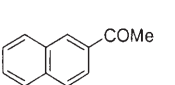
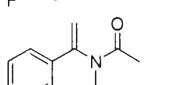
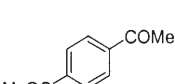
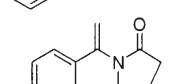
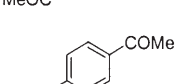
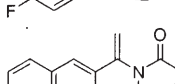
The acceleration of the reaction rates was also seen in common solvents. Thus, under conditions identified for [bmim][BF₄] but replacing the ionic liquid with DMF, bromoacetophenone **2a** was olefinated with butyl vinyl ether **1a** with a 38% conversion in 1 hour and gave the α -arylated olefin exclusively according to ¹H NMR spectroscopic analysis. By way of contrast, the reaction in the absence of [HNEt₃][BF₄] was sluggish and much less selective toward

the α -olefin in DMF (75:25 regioselectivity), thus suggesting that the ammonium additive exerts a significant promotion effect on the ionic pathway of the Heck reaction.^[3,4] A limited screening shows that the combination of [H₂NiPr₂][BF₄] with DMF is a good choice in terms of effectiveness and cost (see the Supporting Information). Under such conditions, the conversion of **2a** is 12 times that observed without the ammonium salt with exclusive α regioselectivity.

The wider applicability of the new chemistry is demonstrated with the arylation of olefins **1a–h** with aryl bromides **2a–i** (Table 2). Thus, in the presence of [H₂NiPr₂][BF₄] in DMF, all the reactions shown in Table 2 finished with > 99:1 regioselectivity in favor of the branched products with high yields. Relative to those in [bmim][BF₄] (Table 1), however, the reactions in DMF generally required longer reaction times to complete.

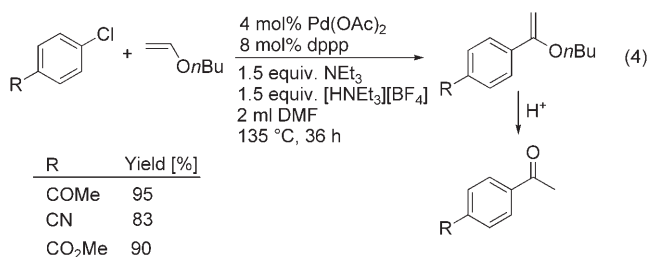
Under the action of the ammonium additive, aryl chlorides could also, for the first time, be coupled regiose-

Table 2: [H₂NiPr₂]⁺-Accelerated regioselective arylation of olefins **1a–h** in DMF.^[a]

Entry	Olefin	ArBr	Product	t [h]	Yield [%]	Entry	Olefin	ArBr	Product	t [h]	Yield [%]		
1	1a	2a		4a	4	90	12	1d	2a		4a	4	88
2	1a	2b		4b	8	83	13 ^[c]	1e	2a		3ea	8	85
3	1a	2c		4c	4	87	14 ^[c]	1e	2e		3ee	8	90
4	1a	2d		4d	4	88	15 ^[c]	1e	2f		3ef	8	86
5	1a	2e		4e	4	85	16 ^[c]	1e	2i		3ei	12	84
6	1a	2f		4f	4	91	17 ^[c]	1f	2a		3fa	16	78
7	1a	2g		4g	6	83	18 ^[d]	1g	2a		3ga	16	76
8	1a	2h		4h	10	82	19 ^[d]	1g	2e		3ge	16	75
9	1a	2i		4i	4	89	20 ^[d]	1g	2f		3gf	16	72
10 ^[b]	1b	2a		4a	4	92	21 ^[d]	1h	2e		3he	16	80
11	1c	2a		4a	4	90	22 ^[d]	1h	2i		3hi	16	77

[a] Reaction conditions: **1** (2.0 equiv), **2** (1.0 mmol), [H₂NiPr₂][BF₄] (1.5 equiv), Pd(OAc)₂ (2.5 mol%), dppp (5.0 mol%), and NEt₃ (1.5 equiv) in DMF (2 mL) at 115 °C; 100% conversion and > 99:1 regioselectivity for all, as determined by ¹H NMR spectroscopic analysis. Yield of the isolated products; **4** was obtained after acidification of **3**. [b] 0.75 equivalents of **1b** were used. [c] The reaction was continued, upon addition of dry HOAc (5 mL) at 80 °C, for a further 2 h at 80 °C before workup. [d] Reaction conditions: **1g–h** (1.0 mmol), Pd(OAc)₂ (4 mol%), and dppp (8 mol%) in DMSO (2 mL).

lectively with electron-rich olefins. For example, the vinyl ether **1a** was smoothly arylated by activated chlorides [Eq. (4)], thus furnishing the corresponding ketones in high



yields. However, these reactions necessitated harsher conditions and failed with deactivated chlorides under the conditions employed.

In conclusion, we have demonstrated that ammonium salts that can act as hydrogen-bond donors exert a remarkable accelerating effect on the rates of the regioselective arylation of electron-rich olefins by aryl halides in ionic liquids and common solvents. More than two decades ago, tetraalkylammonium salts, such as [NBu₄][Cl], were discovered to accelerate the Heck reaction.^[16] The Jeffery conditions can be successfully employed for palladium catalysts containing monodentate phosphines or no ligands. Under such conditions, the Heck reaction presumably proceeds by the neutral pathway,^[3] which involves anion-ligated palladium species, as indicated by the extensive studies of Amatore and Jutand.^[17] In contrast, the Pd–dppp catalysis described herein is typical of the Heck reaction proceeding by the cationic pathway,^[3,4] although the detailed mechanism of the rate acceleration by [H_nNR_{4-n}]⁺ (*n* = 1, 2) remains open for discussion, particularly with regard to the proposed effect of hydrogen bonding on the equilibrium shown in Equation (2). To the best of our knowledge, the chemistry presented represents the first generic method to conduct the regioselective Heck reaction of electron-rich olefins with aryl halides with no need for silver or thallium-based halide scavengers.

Experimental Section

A typical procedure for the arylation of vinyl ether **1a**: 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 (6 mg, 0.025 mmol), dppp (21 mg, 0.05 mmol), [HNEt₃][BF₄] (284 mg, 1.5 mmol), and [bmim][BF₄] (2 mL) under nitrogen at room temperature. Following degassing three times, **1a** (204 mg, 2.0 mmol) and HN*i*Pr₂ (153 mg, 1.5 mmol) were injected sequentially. The flask was placed in an oil bath, and the reaction 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 spectroscopic analysis. To the rest of the mixture, aqueous HCl (5%, 5 mL) was added and following stirring 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 layers were washed with water until neutral, dried (Na₂SO₄), filtered, and concentrated in vacuo. The aryl methyl ketone **4** was isolated by flash chromatography on silica gel using a mixture of ethyl acetate

and hexane (1:99 to 10:90) as the eluent. The identity and purity of the product was confirmed by ¹H and ¹³C NMR spectroscopic, mass-spectrometric, high-resolution mass-spectrometric, and elemental analysis.

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