Electron-Deficient Phosphines Accelerate the Heck Reaction of Electron-rich Olefins in Ionic Liquid

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Abstract: Using various substrates and ligands, we show that electron-deficient, bidentate phosphines are the ligands of choice for palladium-catalyzed arylation of electron-rich olefins. This is in contrast to the reaction of electron-deficient olefins, which benefit from electron-rich monodentate phosphines. A tentative explanation is offered based on DFT calculations.
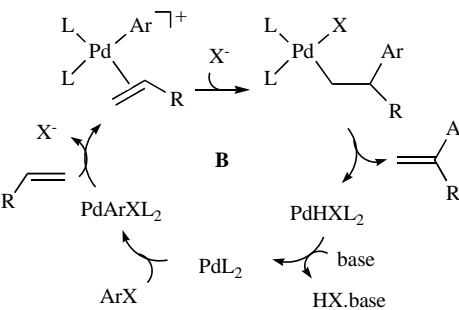
Keywords: Heck reaction, palladium, phosphine ligand, olefin, catalysis.

The Heck reaction has been well known as one of the most versatile methods for the formation of C–C bonds in synthetic chemistry [1, 2]. This chemistry can occur under diverse conditions and catalysts. Depending on the conditions, the Heck reaction is believed to follow one of the two different mechanisms, neutral pathway A or ionic pathway B, as shown in Scheme **1**.

In general, the Heck arylation of electron-deficient olefins provides a terminally arylated linear product *via* the neu-

generally favored, particularly when deactivated aryl bromides and chlorides are concerned [5-9]. We now report that contrary to this belief, the palladium-catalyzed Heck reaction of electron-rich olefins is accelerated with electron-deficient, bidentate phosphine ligands.

Ever since the pioneering work of Cabri [10], the easily-available 1,3-bis(diphenylphosphino)propane (DPPP) has established itself as the prototype ligand in the Heck reaction of electron-rich olefins [3, 10, 11]. However, there appears to

Scheme 1. The Heck reaction and its neutral (**A**) and ionic (**B**) pathways.

tral pathway **A**, while that of electron-rich olefins provides an internally arylated branched product *via* the ionic pathway **B** [1a, 3]. A variety of factors are known to affect the outcome of the Heck reaction including its regioselectivity [4-9], and the property of ligand is no exception. In the case of electron-deficient olefins reacting *via* pathway **A**, studies from a number of groups have shown that electron-rich, basic, sterically demanding monodentate phosphine ligands are

be no study into how the electronic properties of this type ligand may impact on the Heck reaction [12]. In continuing our research in using ionic liquids to promote the ionic Heck pathway [11a-f, 13], we synthesized a series of substituted DPPP ligands, in which the phenyl rings are *para*-substituted with -Me, -OMe, -CF$_3$, and -CN [14], as shown in Fig. (**1**). This substitution would ensure that the observed effects on the Heck reaction stem from ligand electronic rather than steric properties. The Hammett constants are also provided, reflecting the electron-withdrawing/donating capabilities of the substituents used. With these ligands in hand, we subsequently studied the Heck reaction of a series of electron-rich olefins in an ionic liquid, [bmim][PF$_6$] (bmim: 1-butyl-3-

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methylimidozolium). Previous studies by our group and that of Hallberg and Larhed have shown that electron-rich olefins can be readily regioselectively arylated with aryl halides in imidazolium ionic liquids without recourse to any halide scavengers [11a-f, 15].
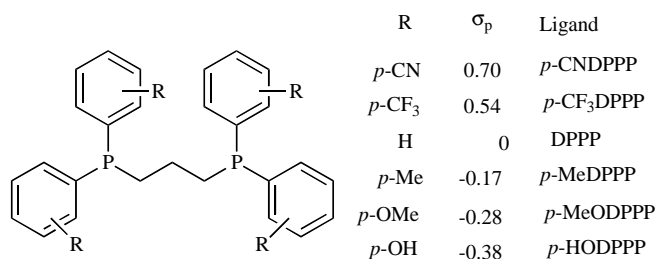
R	σ_p	Ligand
p-CN	0.70	*p*-CNDPPP
p-CF$_3$	0.54	*p*-CF$_3$DPPP
H	0	DPPP
p-Me	-0.17	*p*-MeDPPP
p-OMe	-0.28	*p*-MeODPPP
p-OH	-0.38	*p*-HODPPP

Fig. (1). DPPP and derivatives.

In our initial investigation, the arylation of the benchmark electron-rich olefin *n*-butyl vinyl ether was examined using the ligands shown in Fig. (**1**) [16]. In a typical reaction, a mixture of 4-bromoacetophone **1** (1.0 mmol), *n*-butyl vinyl ether **2** (2.0 mmol), Pd(OAc)$_2$ (2.0 mol%), ligand (4.0 mol%) and Et$_3$N (1.5 mmol) was heated in [bmim][PF$_6$] (1.0 mL) at 115 °C under N$_2$ for 6 h. For comparison, the reaction was also performed with one of the most common monodentate ligands, PPh$_3$ (8.0 mol%). The results are presented in eq 1.

As can be seen, all of the bidentate ligands are capable of promoting the regioselective arylation of **2** with **1**, affording exclusively the α arylated product **3**. This is in line with our previous findings, that is ionic liquids promote the formation of branched olefins by facilitating the ionic pathway **B** [3, 11a-f]. Contrary to one's intuition is, however, the observation that the conversion increases with the increase in the electron deficiency of phosphine; the conversion of the reaction rose from 29% with *p*-MeODPPP to 74% with *p*-CNDPPP. On the basis of previous studies concerning the Heck reaction proceeding *via* the neutral pathway **A**, one might expect a faster rate with Pd-*p*-MeODPPP and Pd-*p*-MeDPPP. Clearly, this is not the case. Still further, using a *p*-OH (σ_p = -0.38) substituted DPPP led to a conversion of 40%, and surprisingly a mixture of regioisomer was obtained, with the branched product accounting for only 37%. Similarly, when using PPh$_3$ as ligand, the reaction becomes less regioselective and slower in comparison with using the *p*-CF$_3$DPPP and *p*-CNDPPP (eq 1). Thus, for the electron-

rich olefin **2**, faster and regioselective arylation is made possible with electron-deficient bidentate phosphines.

The observation above is not an isolated case. In an effort to determine if the chemistry could be extended to other substrates, we investigated the reaction of **1** with four other electron-rich olefins. The results are summarized in Table **1**. As is clear from the table, for all the electron-rich olefins presented here, there is again a significant ligand electronic effect – the more electron-deficient the phosphines, the higher the conversions.

We recently reported the arylation of α-substituted allylic alcohols in ionic liquids [17]. Using the electron-deficient DPPP type ligands, the reaction was again made easier. An example is the arylation of but-1-en-3-ol **9** with 2-bromonaphthalene **8**, shown in Table **2**. As can be seen, a significantly faster reaction along with slightly enhanced regioselectivity was achieved with *p*-CNDPPP and *p*-CF$_3$DPPP. Whilst still unsatisfactory, the regioselectivity observed with *p*-CNDPPP represents the best value for this type of reaction [17].

To shed more light on ligand effects in the Heck reaction, we also examined the arylation of a benchmark electron-deficient olefin, methyl acrylate, as shown in eq 2. In a manner similar to that for eq 1, a reaction mixture of **12** (2.0 mmol), **1** (1.0 mmol), Pd(OAc)$_2$ (2.0 mmol%), ligand (4.0 mol%) and Et$_3$N (1.5 mmol) in [bmim][PF$_6$] (1.0 mL) was heated at 115 °C under N$_2$ for 12 h. The monodentate PPh$_3$ (8 mol%) was again used for the purpose of comparison. The results show that the bidentate ligands are much less effective than PPh$_3$ for the palladium catalysis and as might be expected, electron-rich diphosphines significantly outperform their electron-deficient analogues. As with other Heck reaction of electron-deficient olefins, the regioselectivity is in favor of the linear product **14** regardless of the ligands used. These results highlight the difference in ligand requirement for the Heck reaction of electron-rich *vs* -deficient olefins, and the former is facilitated with electron-deficient, bidentate phosphines.

So why are electron-deficient, bidentate ligands better for the Heck reaction of electron-rich olefins? The use of a bidentate ligand to promote the ionic pathway **B** has long been established [3, 10-15, 17]. However, the electronic effects of such ligands have rarely been investigated and those
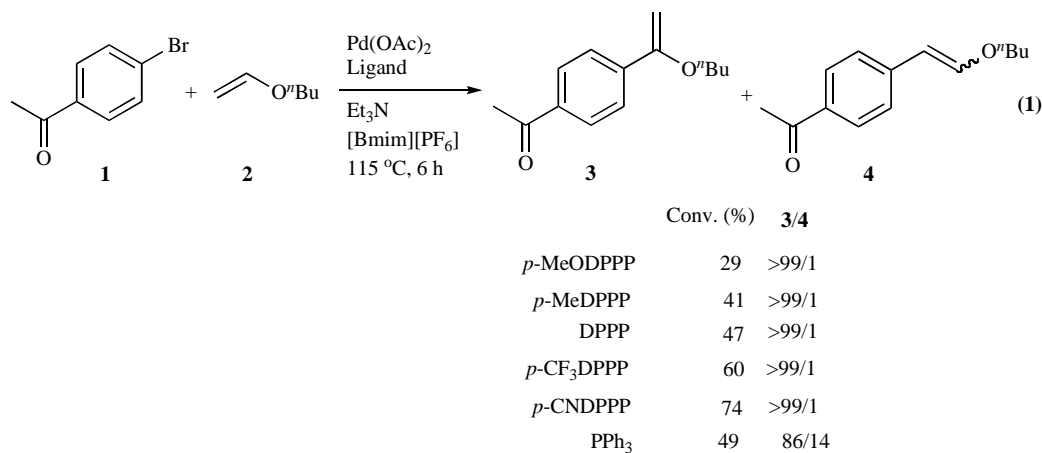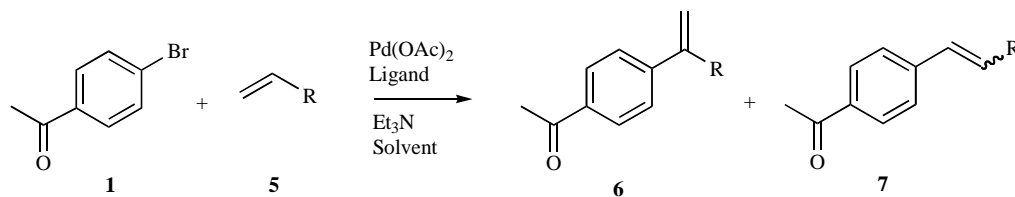

	Conv. (%)	3/4
p-MeODPPP	29	>99/1
p-MeDPPP	41	>99/1
DPPP	47	>99/1
p-CF$_3$DPPP	60	>99/1
p-CNDPPP	74	>99/1
PPh$_3$	49	86/14

Table 1. **Arylation of Electron-Rich Olefins with 4-Bromoacetophenone Catalyzed by Pd-diphosphine**[a]

R	Ligands	Conversion (%)[f]	6/7[f]
N(Me)C(O)Me[b]	p-CNDPPP	40	>99
	p-CF_3DPPP	34	>99
	DPPP	28	>99
	p-MeDPPP	20	>99
	p-MeODPPP	15	>99
CH_2Si(Me)_3[c]	p-CNDPPP	90	93/7
	p-CF_3DPPP	72	94/6
	DPPP	44	94/6
	p-MeDPPP	21	94/6
	p-MeODPPP	15	94/6
CH_2OH[d]	p-CNDPPP	88	>99
	p-CF_3DPPP	69	>99
	DPPP	56	>99
	p-MeDPPP	39	>99
	p-MeODPPP	31	>99
(CH_2)_2OH[e]	p-CNDPPP	93	74/26
	p-CF_3DPPP	89	74/26
	DPPP	84	74/26
	p-MeDPPP	82	75/25
	p-MeODPPP	77	75/25

[a]Reaction conditions: **1** (1.0 mmol), Et_3N (1.5 mmol), Pd(OAc)_2 (2.0 mol%), ligand (4.0 mol%), at 115 °C, N_2.
[b]**5** (1.1 mmol), [bmim][PF_6] (0.5 mL)-DMSO (0.5 mL), 24 h.
[c]**5** (2.0 mmol), [bmim][PF_6] (1.0 mL), 24 h.
[d]**5** (1.5 mmol), [bmim][PF_6] (0.5 mL)-DMSO (0.5 mL), 10 h.
[e]Pd(OAc)_2 (1.0 mol%), **5** (2.0 mmol), [bmim][PF_6] (0.5 mL)-DMSO (0.5 mL), 6 h.
[f]Determined by ¹H NMR.

**Table 2.** **Arylation of But-1-en-3-ol with 2-Bromonaphthalene**[a]
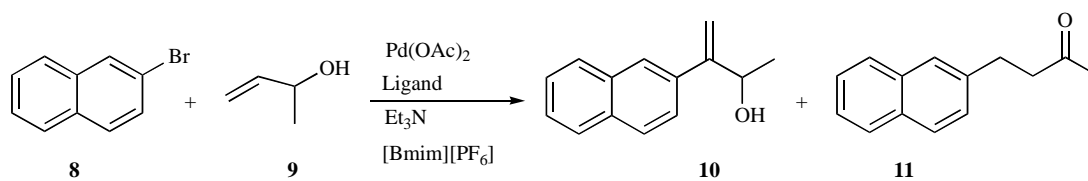
Ligand	Conversion (%)[b]	10/11[b,d]
p-CNDPPP	78[c]	75/25
p-CF_3DPPP	94 (67[c])	70/30
DPPP	80	70/30
p-MeDPPP	69	69/31
p-MeODPPP	43	68/32

[a]Reaction conditions: **8** (1.0 mmol), **9** (1.2 mmol), Et_3N (1.5 mmol), Pd(OAc)_2 (1.0 mol%), ligand (2.0 mol%), in [bmim][PF_6] (1.0 mL), at 115 °C for 8 h under N_2.
[b]Determined by ¹H NMR.
[c]2 h reaction time.
[d]In some cases, product **11** includes <3% of the original alcohol.

$$(2)$$
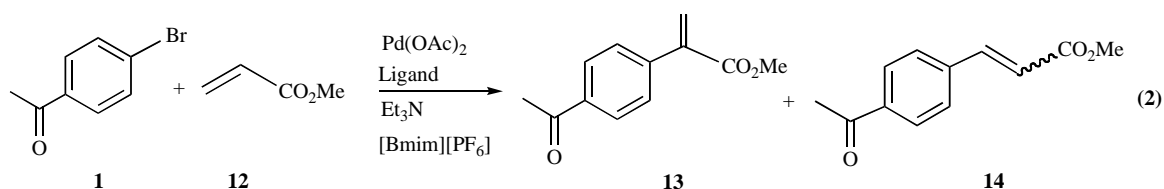
	Conv. (%)	**13/14**
p-MeODPPP	26	<1/99
p-MeDPPP	35	<1/99
DPPP	13	<1/99
p-CF₃DPPP	5.2	<1/99
p-CNDPPP	4.0	<1/99
PPh₃	100	<1/99

observed here are not immediately clear. Previous studies including our own suggest that the ionic pathway is rate-limited by the insertion step when using aryl iodides and bromides and there may be a pre-equilibrium between the neutral $[Pd(Ar)XL_2]$ and the ionic $[Pd(Ar)(olefin)L_2]^+$ species (Pathway **B**, Scheme **1**) [3, 11c, 18]. Assuming this to be the case, one may partly attribute the higher rates associated with the electron-deficient DPPP analogues to a reduced olefin insertion barrier. In a previous DFT calculation using a model Pd-diimine catalyst depicted below, it was shown that electron-withdrawing groups on the diimine ligand lower the insertion barrier and render the Pd(II)-olefin intermediate more stable [12d].
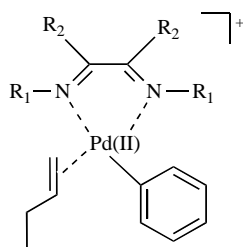
Focusing on the insertion step, we carried out similar calculations on three catalytic species bearing the real ligands, $[Pd(MeOCH=CH_2)(Ph)L_2]^+$ (L_2 = DPPP, *p*-CNDPPP and *p*-MeODPPP) (Fig. (**2**)). The calculations were carried out using density functional theory at the B3LYP/6-31* level as implemented in PCGAMESS [19, 20]. These revealed that
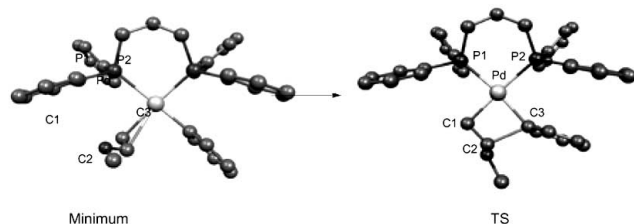

Fig. (2). Structures of $[Pd(MeOCH=CH_2)(Ph)(DPPP)]^+$ minimum (left) and transition state (right) obtained from DFT (B3LYP/6-31*) calculations with hydrogen atoms omitted for clarity. Selected bond lengths (Å): Minimum: Pd-P1, 2.460; Pd-P2, 2.358; Pd-C1, 2.323; Pd-C2, 2.653; Pd-C3, 2.077; C1-C2, 1.374; C2-C3, 3.091. Transition state: Pd-P1, 2.308; Pd-P2, 2.448; Pd-C1, 2.107; Pd-C3, 2.209; C1-C2, 1.437; C2-C3, 2.109.

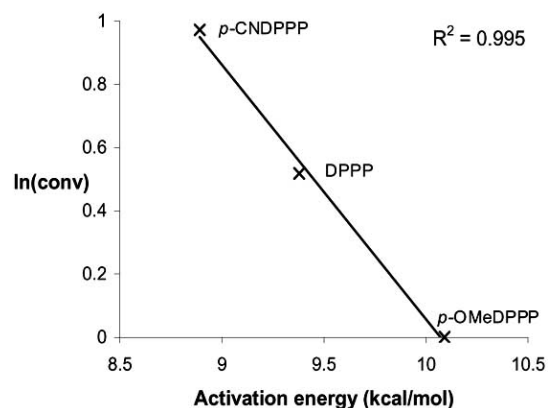there is indeed a good correlation between the conversion and activation energy (Fig. (**3**)).

Fig. (3). Correlation of conversion with olefin insertion barrier [ln(conv) = ln (conversion with respect to that obtained with *p*-OMeDPPP)].

In comparison with DPPP, the electron-deficient *p*-CNDPPP lowers the insertion barrier whilst the electron-rich *p*–MeODPPP does the opposite. This lowering of the insertion barrier could stem from an easier rotation of the olefin from the out-of-plane to in-plane coordination due to reduced π back donation from Pd(II) to the olefin, and from an enhanced positive charge on the coordinated olefin, which is expected to facilitate the intramolecular nucleophilic attack by the aryl group [12, 21].

In summary, the results presented in this study establish that, contrary to the Heck reaction proceeding *via* the neutral pathway **A** that benefits from electron-rich monodentate ligands, the Heck reaction of electron-rich olefins characterized by the ionic pathway **B** necessitates electron-deficient, bidentate phosphines.

ACKNOWLEDGEMENTS

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[16]   *General procedure for the Heck arylation in ionic liquid*: An oven-dried carousel reaction tube containing a stirrer bar was charged with 4-bromoacetophone **1** (1.0 mmol), Pd(OAc)$_2$ (0.02 mmol), ligand (0.04 mmol), and [bmim][PF$_6$] (1 mL) under nitrogen at room temperature. After the mixture was degassed three times, *n*-butyl vinyl ether **2** (2.0 mmol) and Et$_3$N (1.5 mmol) were injected sequentially. The mixture was stirred and heated at 115 °C under N$_2$ for 6 h. After cooled to room temperature, a small sample was taken for NMR analysis. All of the products have previously been fully characterised, and for the purpose of comparison of conversions, the aim of this study, ^{1}H NMR was found to be sufficient, as the products generally contained only trace undesired products.[11c]

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[20]   The 6-31G* basis set was used for all atoms except Pd. Relativistic effects for Pd were addressed by using SBKJC effective core potential (ECP) together with the SBKJC basis set. Geometry optimizations were performed with no symmetry restrictions. Vibrational frequency calculations at B3LYP/6-31G* level of theory were used to derive zero-point-energy and entropy contributions at 413.15K using unscaled frequencies. Energy minima were confirmed by no imaginary frequencies. Transition states were confirmed by only one imaginary frequency with associated atomic motion consistent with the mechanism. The free energy G(gas) has been calculated as follows: G(gas) = H(gas) – TS(gas), H(gas) = H(SCF) + ZPE. G(gas) = free energy in gas phase, H(gas) = enthalpy in gas phase, T = Temperature, 413.15K, S(gas) = entropy in gas phase, H(SCF) = self consistent field energy, ZPE = zero point energy assuming harmonic oscillator approximation. Structures were visualized using Molekel.

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