J|A|C|S
ARTICLES

Hydrogen-Bonding-Promoted Oxidative Addition and Regioselective Arylation of Olefins with Aryl Chlorides

Jiwu Ruan, Jonathan A. Iggo, Neil G. Berry, and Jianliang Xiao*

Department of Chemistry, University of Liverpool, Liverpool L69 7ZD, U.K.

Received September 10, 2010; E-mail: j.xiao@liv.ac.uk

Abstract: The first, general, and highly efficient catalytic system that allows a wide range of activated and unactivated aryl chlorides to couple regioselectively with olefins has been developed. The Heck arylation reaction is likely to be controlled by the oxidative addition of ArCl to Pd(0). Hence, an electron-rich diphosphine, 4-MeO-dppp, was introduced to facilitate the catalysis. Solvent choice is critical, however; only sluggish arylation is observed in DMF or DMSO, whereas the reaction proceeds well in ethylene glycol at 0.1−1 mol % catalyst loadings, displaying excellent regioselectivity. Mechanistic evidence supports that the arylation is turnover-limited by the oxidative addition step and, most importantly, that the oxidative addition is accelerated by ethylene glycol, most likely via hydrogen bonding to the chloride at the transition state as shown by DFT calculations. Ethylene glycol thus plays a double role in the arylation, facilitating oxidative addition and promoting the subsequent dissociation of chloride from Pd(II) to give a cationic Pd(II)−olefin species, which is key to the regioselectivity observed.

Introduction

The palladium-catalyzed Heck arylation of olefins with aryl halides is one of the most important tools for constructing sp^2 C−C bonds in synthetic chemistry[1] and is probably one of the most frequently applied Pd-catalyzed coupling reactions in the fine chemical and pharmaceutical industries.[2] In the vast majority of reported Heck reactions, aryl bromides and iodides are used as substrates, for which very good reactivities and regioselectivities have been demonstrated in the last three decades or so.[1,2]

Aryl chlorides are the cheapest and most widely available aryl halides. As such, several highly efficient catalysts have been developed for the Heck reaction with such substrates.[3] These include palladium complexes bearing electron-rich phosphines,[3a,4] N-heterocyclic carbenes,[5] palladacycles,[5n,6] palladium pincer complexes,[6k,7] and palladium nanoparticles.[1c,8] However, these catalysts can only effectively be applied to neutral or activated olefins, such as styrene and acrylates. When used for electron-

---

(1) For general reviews of Heck reaction, see: (a) Oestreich, M. *The Mizoroki-Heck Reaction*; Wiley: Chichester, U.K., 2009. (b) Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5*, 31. (c) Phan, N. T. S.; Van Der Sluys, M.; Jones, C. W. *Adv. Synth. Catal.* **2006**, *348*, 609. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771. (e) Oestreich, M. *Eur. J. Org. Chem.* **2005**, 783. (f) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds.; Wiley-VCH: New York, 2004; p 217. (g) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: Chichester, U.K., 2004. (h) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533. (i) Larhed, M.; Hallberg, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, p 1133. (j) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (k) Hegedus, L. S. In *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Sausalito, CA, 1999; Chapter 4.6. (l) Crisp, G. T. *Chem. Soc. Rev.* **1998**, *27*, 427.

(2) For applications of Heck reaction, see: (a) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (c) Farina, V. *Adv. Synth. Catal.* **2004**, *346*, 1553. (d) Blaser, H.-U.; Indolese, A.; Naud, F.; Nettekoven, U.; Schnyder, A. *Adv. Synth. Catal.* **2004**, *346*, 1583. (e) Zapf, A.; Beller, M. *Top. Catal.* **2002**, *19*, 101. (f) de Vries, J. G. *Can. J. Chem.* **2001**, *79*, 1086.

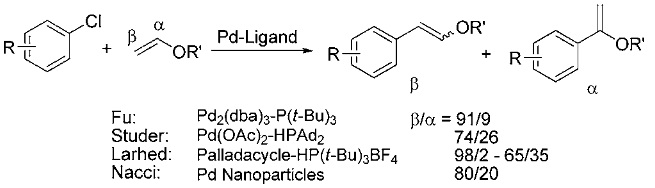
(3) For reviews of Heck reaction of aryl chlorides, see: (a) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555. (b) Bedford, R. B.; Cazin, C. S. J.; Holder, D. *Coord. Chem. Rev.* **2004**, *248*, 2283. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (d) Whitcombe, N. J.; Hii, K. K.; Gibson, S. E. *Tetrahedron* **2001**, *57*, 7449. (e) Riermeier, T. H.; Zapf, A.; Beller, M. *Top. Catal.* **1997**, *4*, 301.

(4) (a) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989. (b) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295. (c) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677. (d) Ehrentraut, A.; Zapf, A.; Beller, M. *Synlett* **2000**, 1589. (e) Littke, A. F.; Fu, G. C. *J. Org. Chem.* **1999**, *64*, 10. (f) Portnoy, M.; Ben-David, Y.; Rousso, I.; Milstein, D. *Organometallics* **1994**, *13*, 3465. (g) Portnoy, M.; Ben-David, Y.; Milstein, D. *Organometallics* **1993**, *12*, 4734. (h) Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995. For reviews on electron-rich phosphines for coupling reactions, see. (i) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338. (j) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (k) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431. Also see ref 3a.

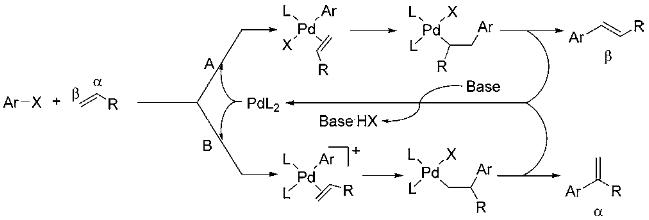
(5) (a) Han, Y.; Huynh, H. V.; Koh, L. L. *J. Organomet. Chem.* **2007**, *692*, 3606. (b) Liu, J.; Zhao, Y.; Zhou, Y.; Li, L.; Zhang, T. Y.; Zhang, H. *Org. Biomol. Chem.* **2003**, *1*, 3227. (c) Selvakumar, K.; Zapf, A.; Beller, M. *Org. Lett.* **2002**, *4*, 3031. (d) César, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Organometallics* **2002**, *21*, 5204. (e) Peris, E.; Loch, J. A.; Mata, J.; Crabtree, R. H. *Chem. Commun.* **2001**, 201. (f) Calò, V.; Nacci, A.; Lopez, L.; Mannarini, N. *Tetrahedron Lett.* **2000**, *41*, 8973. (g) McGuinness, D. S.; Cavell, K. J. *Organometallics* **2000**, *19*, 741. (h) Schwarz, J.; Böhm, V. P. W.; Gardiner, M. G.; Grosche, M.; Herrmann, W. A.; Hieringer, W.; Raudaschl-Sieber, G. *Chem.−Eur. J.* **2000**, *6*, 1773. (i) Böhm, V. P. W.; Herrmann, W. A. *Chem.−Eur. J.* **2000**, *6*, 1017. (j) Herrmann, W. A.; Elison, M.; Fischer, J.; Köcher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed.* **1995**, *34*, 2371. For general reviews on N-heterocyclic carbenes for coupling reactions, see: (k) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523. (l) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440. (m) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366. (n) Herrmann, W. A.; Öfele, K.; von Preysing, D.; Schneider, S. K. *J. Organomet. Chem.* **2003**, *687*, 229.

10.1021/ja1081926

Scheme 1. Examples of Heck Arylation of Enol Ethers with Aryl Chlorides in the Literature[4a,8a,9,10]



Scheme 2. The Two Competing Pathways in the Heck Reaction



rich or deactivated olefins, such as enol ethers and enamides, they are generally less active and, without exception, give rise to a mixture of α- and β-arylated products, in which the β isomer usually dominates (Scheme 1). In 2001, Fu first reported the Pd−P(t-Bu)$_3$ catalyzed Heck arylation of n-butyl vinyl ether by 4-chloroacetophenone, affording a 91/9 mixture of β- and α-arylated products in 82% yield.[4a] Using a Pd−HPAd$_2$ (Ad = adamantyl) catalyst, Studer and co-workers later obtained a mixture of regioisomers having a β/α ratio of 74/26 in the arylation with 4-chlorotoluene.[9] In 2006, Larhed and co-workers applied microwave heating to the arylation of n-butyl vinyl ether with various aryl chlorides by Pd−P(t-Bu)$_3$, obtaining mixtures of β- and α-arylated products in moderate yields.[10] More recently, Calò and Nacci et al. used Pd nanoparticles to catalyze the arylation with chlorobenzene in ionic liquids, but a low yield of 25% of a mixture of products was observed (Scheme 1).[8a] In view of the importance of α-arylated products in chemical and particularly bioactive compound synthesis,[11] access to these olefins in high yield from cheap aryl chlorides would be an important extension of the Heck reaction.

The origin of regioselectivity in the Heck reaction may be accounted for by two competing reaction pathways, as illustrated in Scheme 2.[12,13] The neutral pathway (pathway A, Scheme 2) produces the β product and features the dissociation of a neutral ligand from Pd^{II}. In contrast, the ionic pathway (pathway B), involving halide dissociation instead, yields the α product. Considering the electrophilic nature of cationic Pd^{II}, pathway B is expected to favor electron-rich olefins.[14] Indeed, in competition reactions involving both electron-rich and -deficient olefins, the former preferentially undergoes arylation when the reaction follows the ionic pathway.[15,16] A modified mechanism has recently been proposed by Amatore, Jutand, and co-workers, who showed that the electron-rich isobutyl vinyl ether reacts with [Pd(dppp)(Ph)X] (X = I, OAc) via the cationic species, [Pd(Ph)(dppp)(solvent)]$^+$, affording both α and β products.[17] Their kinetic study led to the suggestion that the succeeding Pd−olefin intermediate, [Pd(Ph)(dppp)(olefin)]$^+$, undergoes reversible 1,2- as well as 2,1-insertion, resulting in α arylation when the concentration of coordinating anions is low but β product when the anion is abundant.[17b]

The α regioselectivity along the ionic pathway is probably a result of the electron-rich olefin being polarized upon coordination to the cationic Pd(II) center, which renders the α carbon positively charged and hence more susceptible to attack by the migrating aryl moiety, as highlighted by the resonance structures shown in Scheme 3 for a vinyl ether.[18] DFT calculations have provided more insight into the mechanism[19] and 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.[19a] Thereotical 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

---

(6) (a) Alacid, E.; Nájera, C. *Adv. Synth. Catal.* **2008**, *350*, 1316. (b) Yan, X.; Liu, Y.; Xi, C. *Appl. Organometal. Chem.* **2008**, *22*, 341. (c) Iyer, S.; Jayanthi, A. *Tetrahedron Lett.* **2001**, *42*, 7877. (d) Gruber, A. S.; Zim, D.; Ebeling, G.; Monteiro, A. L.; Dupont, J. *Org. Lett.* **2000**, *2*, 1287. (e) Iyer, S.; Ramesh, C. *Tetrahedron Lett.* **2000**, *41*, 8981. (f) Herrmann, W. A.; Böhm, V. P. W.; Reisinger, C.-P. *J. Organomet. Chem.* **1999**, *576*, 23. (g) Herrmann, W. A.; Brossmer, C.; Reisinger, C.-P.; Riermeier, T. H.; Öfele, K.; Beller, M. *Chem.*—*Eur. J.* **1997**, *3*, 1357. (h) Herrmann, W. A.; Brossmer, C.; Öfele, K.; Reisinger, C.-P.; Priermeier, T.; Beller, M.; Fischer, H. *Angew. Chem., Int. Ed.* **1995**, *34*, 1844. For general reviews on palladacycles for coupling reactions, see: (i) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512. (j) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527. (k) Bedford, R. B. *Chem. Commun.* **2003**, 1787. (l) Herrmann, W. A.; Böhm, V. P. W. *J. Organomet. Chem.* **1999**, *572*, 141. Also see reference 5n.

(7) (a) Morales-Morales, D.; Redon, R.; Yung, C.; Jensen, C. M. *Chem. Commun.* **2000**, 1619. (b) Ohff, M.; Ohff, A.; van der Boom, M. E.; Milstein, D. *J. Am. Chem. Soc.* **1997**, *119*, 11687. For general reviews on palladium pincer complexes for coupling reactions, see: (c) Serrano-Becerra, J. M.; Morales-Morales, D. *Curr. Org. Synth.* **2009**, *6*, 169. (d) Weck, M.; Jones, C. W. *Inorg. Chem.* **2007**, *46*, 1865. (e) Peris, E.; Crabtree, R. H. *Coord. Chem. Rev.* **2004**, *248*, 2239. (f) Singleton, J. T. *Tetrahedron* **2003**, *59*, 1837. Also see ref 6k.

(8) (a) Calò, V.; Nacci, A.; Monopoli, A.; Cotugno, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 6101. (b) Calò, V.; Nacci, A.; Monopoli, A.; Laera, S.; Cioffi, N. *J. Org. Chem.* **2003**, *68*, 2929. (c) Djakovitch, L.; Köhler, K. *J. Am. Chem. Soc.* **2001**, *123*, 5990. For general reviews on palladium nanoparticles for coupling reactions, see: (d) Prechtl, M. H. G.; Scholten, J. D.; Dupont, J. *Molecules* **2010**, *15*, 3441. (e) Köhler, K.; Kleist, W.; Pröckl, S. S. *Inorg. Chem.* **2007**, *46*, 1876. (f) Astruc, D. *Inorg. Chem.* **2007**, *46*, 1884. (g) de Vries, J. G. *Dalton Trans.* **2006**, 421. Also see ref 1c.

(9) Schnyder, A.; Aemmer, T.; Indolese, A. F.; Pittelkow, U.; Studer, M. *Adv. Synth. Catal.* **2002**, *344*, 495.

(10) Datta, G. K.; von Schenck, H.; Hallberg, A.; Larhed, M. *J. Org. Chem.* **2006**, *71*, 3896.

(11) For examples of the Heck branched products used for bioactive compounds, see: (a) Moral, J. A.; Moon, S.-J.; Rodriguez-Torres, S.; Minehan, T. G. *Org. Lett.* **2009**, *11*, 3734. (b) Arefalk, A.; Wannberg, J.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2006**, *71*, 1265. (c) Harrison, P.; Meek, G. *Tetrahedron Lett.* **2004**, *45*, 9277. (d) Legros, J.-Y.; Primault, G.; Fiaud, J.-C. *Tetrahedron* **2001**, *57*, 2507. (e) Sakagami, H.; Ogasawara, K. *Heterocycles* **2001**, *54*, 43. (f) Wu, J.; Marcoux, J. F.; Davies, I. W.; Reider, P. J. *Tetrahedron Lett.* **2001**, *42*, 159. (g) Wegge, T.; Schwarz, S.; Seitz, G. *Tetrahedron: Asymmetry* **2000**, *11*, 1405. (h) Homan, E. J.; Tulp, M. T. M.; Nilsson, J. E.; Wikström, H. V.; Grol, C. J. *Bioorg. Med. Chem.* **1999**, *7*, 2541. (i) Savelon, L.; Bizot-Espiard, J. G.; Caignard, D. H.; Pfeiffer, B.; Renard, P.; Viaud, M. C.; Guillaumet, G. *Bioorg. Med. Chem.* **1998**, *6*, 1963. Also see refs 1h,2a,b.

(12) (a) Ozawa, F.; Kubo, A.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 1417. (b) Sato, Y.; Sodeoka, M.; Shibasaki, M. *Chem. Lett.* **1990**, 1953.

(13) (a) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2. (b) Daves, G. D., Jr.; Hallberg, A. *Chem. Rev.* **1989**, *89*, 1433.

(14) Hahn, C. *Chem.*—*Eur. J.* **2004**, *10*, 5888.

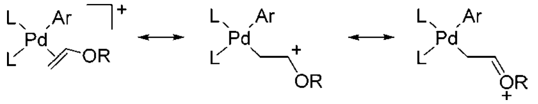
(15) Mo, J.; Xu, L.; Xiao, J. *J. Am. Chem. Soc.* **2005**, *127*, 751.

(16) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1992**, *57*, 3558.

(17) (a) Amatore, C.; Godin, B.; Jutand, A.; Lemaître, F. *Chem.*—*Eur. J.* **2007**, *13*, 2002. (b) Amatore, C.; Godin, B.; Jutand, A.; Lemaître, F. *Organometallics* **2007**, *26*, 1757.

(18) Chen, C.; Luo, S.; Jordan., R. F. *J. Am. Chem. Soc.* **2010**, *132*, 5273.

Scheme 3. Resonance Structures of the Cationic Pd(II) Intermediate



exclusively through only one of the two olefinic carbons, the C4 atom, supporting the representations in Scheme 3.[20]

Extensive studies have been carried out of how to control the regioselectivity and promote α arylation.[10,15,16,21−24] The work of Hallberg and Larhed,[21] Cabri,[16,22] and other researchers[23] revealed that high α/*β* regioselectivity could be obtained under Pd-dppp (dppp =1,3-bis(diphenylphosphino)propane) catalysis by employing aryl triflates or by adding stoichiometric silver or thallium salts when aryl iodides and bromides are chosen. Silver and thallium salts act as halide scavengers, thereby promoting pathway B. Similarly, the lability of the Pd−OTf bond facilitates the formation of the cationic $\mathrm{Pd^{II}}$−olefin species, thus leading to regioselective production of the branched product.[25] It is also apparent from Scheme 2 that a monodentate phosphine ligand would make pathway A more likely, whereas a bidentante ligand such as dppp would promote pathway B. These tactics have also been widely exploited in effecting enantioselective Heck reactions, where the ionic pathway is generally believed to give high enantioselectivities.[1h,26]

High regioselectivity has also been observed by changing the reaction medium. In the past few years, we have shown that α regiocontrol in the coupling of aryl bromides with electron-rich olefins can be readily achieved by using imidazolium ionic liquids as solvents.[15,27] Under these conditions, we believe that the formation of the key cationic $\mathrm{Pd^{II}}$ species in pathway B is favored, thus enhancing selectivity for the α product. Ionic liquids are entirely composed of ions;[28] hence, electrostatic interactions would favor the generation of a $\mathrm{Pd^{II}}$−olefin cation and a halide anion (Scheme 2, pathway B). Consistent with this view, Amatore and Jutand have shown that a high ionic strength favors α arylation.[17] This method, alongside those reported by Hallberg and Larhed,[29,30] Caló,[31] and Alper,[32] enables a highly regioselective Heck reaction without the use of halide scavengers or triflates.[33,34] However, none of these methods are known to allow for efficient and selective α arylation of olefins with aryl chlorides.

We recently reported that by using the Pd-dppp catalyst and a hydrogen bond donor additive, such as $[\mathrm{HNEt_3}][\mathrm{BF_4}]$, regioselective α arylation of olefins with aryl bromides can be effected in a common solvent, such as DMF.[35] The hydrogen bond donor is essential, probably promoting the dissociation of bromide from [Pd(dppp)(Ph)Br] and thus the formation of the cationic Pd−olefin intermediate in Scheme 2. We were delighted to find that under these conditions, the benchmark electron-rich olefin *n*-butyl vinyl ether can be α arylated, for the first time, with aryl chlorides (Scheme 4a).[35] A similar reaction of aryl chlorides was also demonstrated in neat water by Larhed and co-workers[36] using an electron-rich alkyl diphosphine, 1,3-bis(diisopropylphosphino)propane (dippp) (Scheme 4b).[4g] However, these two catalytic systems only work for a few activated aryl chlorides, i.e., those bearing electon-withdrawing substituents. For those that are unactivated, i.e., electron-neutral or -rich, the catalysts were ineffective. The inefficiency of dppp may be a result of its inability to promote the oxidative addition of ArCl to Pd(0), while that of dippp probably stems from the formation of catalytically inactive $[\mathrm{Pd(dippp)Cl_2}]$.[4g,36] In addi-

---

(19) For DFT studies, see: (a) Deeth, R. J.; Smith, A.; Brown, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7144. (b) von Schenck, H.; Åkermark, B.; Svensson, M. *J. Am. Chem. Soc.* **2003**, *125*, 3503. (c) Hii, K. K.; Claridge, T. D. W.; Brown, J. M.; Smith, A.; Deeth, R. J. *Helv. Chim. Acta* **2001**, *84*, 3043. (d) Deeth, R. J.; Smith, A.; Hii, K. K.; Brown, J. M. *Tetrahedron Lett.* **1998**, *39*, 3229. (e) Albert, K.; Gisdakis, P.; Rosch, N. *Organometallics* **1998**, *17*, 1608.

(20) Henriksen, S. T.; Norrby, P.-O.; Kaukoranta, P.; Andersson, P. G. *J. Am. Chem. Soc.* **2008**, *130*, 10414.

(21) (a) Arefalk, A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2005**, *70*, 938. (b) Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639. (c) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2003**, *125*, 3430. (d) Bengston, A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 5854. (e) Nilsson, P.; Larhed, M.; Hallberg, A. *J. Am. Chem. Soc.* **2001**, *123*, 8217. (f) Olofsson, K.; Sahlin, H.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 544. (g) Vallin, K. S. A.; Larhed, M.; Johansson, K.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 4537. (h) Olofsson, K.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7235. (i) Olofsson, K.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **1998**, *63*, 5076. (j) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 7858. (k) Larhed, M.; Hallberg, A. *J. Org. Chem.* **1996**, *61*, 9582.

(22) (a) Cabri, W.; Candiani, I.; Bedeschi, A.; Santi, R. *J. Org. Chem.* **1993**, *58*, 7421. (b) Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi, R. *J. Org. Chem.* **1992**, *57*, 1481.

(23) (a) Hansen, A. L.; Skrydstrup, T. *Org. Lett.* **2005**, *7*, 5585. (b) Hansen, A. L.; Skrydstrup, T. *J. Org. Chem.* **2005**, *70*, 5997. (c) Tu, T.; Hou, X.-L.; Dai, L.-X. *Org. Lett.* **2003**, *5*, 3651. (d) Barcia, J. C.; Cruces, J.; Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron Lett.* **2002**, *43*, 5141. (e) Ludwig, M.; Strömberg, S.; Svensson, M.; Åkermark, B. *Organometallics* **1999**, *18*, 970.

(24) For other examples of regioselective Heck reaction of electron-rich olefins, see: (a) Calò, V.; Nacci, A.; Monopoli, A.; Ferola, V. *J. Org. Chem.* **2007**, *72*, 2596. (b) Fall, Y.; Berthiol, F.; Doucet, H.; Santelli, M. *Synthesis* **2007**, 1683. (c) Calò, V.; Nacci, A.; Monopoli, A. *Eur. J. Org. Chem.* **2006**, 3791. (d) Svennebring, A.; Nilsson, P.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 3345. (e) Bouquillon, S.; Ganchegui, B.; Estrine, B.; Hénin, F.; Muzart, J. *J. Organomet. Chem.* **2001**, *634*, 153.

(25) (a) Jutand, A. *Eur. J. Inorg. Chem.* **2003**, 2017. (b) Brown, J. M.; Hii, K. K. *Angew. Chem., Int. Ed.* **1996**, *35*, 657. (c) Jutand, A.; Mosleh, A. *Organometallics* **1995**, *14*, 1810.

(26) Intramolecular coordination of an olefin may facilitate the dissociation of a halide anion from palladium to form the cationic palladium intermediate (Scheme 2): Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488.

(27) (a) Mo, J.; Xu, L.; Ruan, J.; Liu, S.; Xiao, J. *Chem. Commun.* **2006**, 3591. (b) Hyder, Z.; Mo, J.; Xiao, J. *Adv. Synth. Catal.* **2006**, *348*, 1699. (c) Xu, L.; Chen, W.; Ross, J.; Xiao, J. *Org. Lett.* **2001**, *3*, 295. For a recent review, see: (d) Liu, S.; Xiao, J. *J. Mol. Catal. A: Chem.* **2007**, *270*, 1.

(28) For reviews, see: (a) Jain, N.; Kumar, A.; Chauhan, S.; Chauhan, S. M. S. *Tetrahedron* **2005**, *61*, 1015. (b) Welton, T. *Coord. Chem. Rev.* **2004**, *248*, 2459. (c) Wilkes, J. S. *J. Mol. Catal. A: Chem.* **2004**, *214*, 11. (d) Cole-Hamilton, D. J. *Science* **2003**, *299*, 1702. (e) Dupont, J.; de Souza, R. F.; Suarez, P. A. Z. *Chem. Rev.* **2002**, *102*, 3367. (f) Olivier-Bourbigou, H.; Magna, L. *J. Mol. Catal. A: Chem.* **2002**, *182−183*, 419. (g) Zhao, D.; Wu, M.; Kou, Y.; Min, E. *Catal. Today* **2002**, *74*, 157. (h) Tzschucke, C. C.; Markert, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3964. (i) Zhao, H.; Malhotra, S. V. *Aldrichim. Acta* **2002**, *35*, 75. (j) Sheldon, R. *Chem. Commun.* **2001**, 2399. (k) Gordon, C. M. *Appl. Catal., A* **2001**, *222*, 101. (l) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772.

(29) Vallin, K. S. A.; Emilsson, P.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2002**, *67*, 6243.

(30) The arylation can also be performed in a DMF−water mixture: Vallin, K. S. A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2001**, *66*, 4340. This paper also shows that the regioselective Heck reaction is feasible by using a mixture of DMF and MeOH.

(31) Caló, V.; Nacci, A.; Monopoli, A.; Detomaso, A.; Iliade, P. *Organometallics* **2003**, *22*, 4193.

(32) Park, S. B.; Alper, H. *Chem. Commun.* **2004**, 1306.

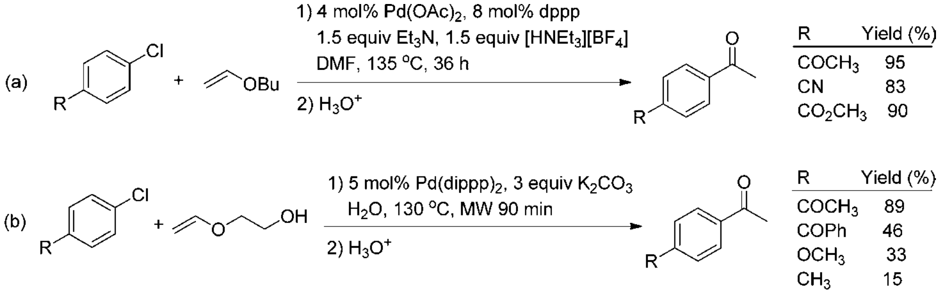
(33) For *β* arylation in ionic liquid, see ref 24c and references therein.

(34) Opposite regioselectivities have been observed when the reaction is run in poly(ethylene glycol): Chandrasekhar, S.; Narsihmulu, Ch.; Sultana, S. S.; Reddy, N. R. *Org. Lett.* **2002**, *4*, 4399.

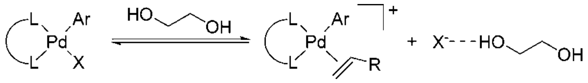
(35) Mo, J.; Xiao, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 4152.

(36) Arvela, R. K.; Pasquini, S.; Larhed, M. *J. Org. Chem.* **2007**, *72*, 6390.

Scheme 4. α-Arylation of Enol Ethers with Aryl Chlorides Reported in the Literature[35,36]



Scheme 5. Possible Effect of EG on the Formation of the Key Cationic Pd(II) Species



tion, like most other alkyl phosphines which are usually liquid- and air-sensitive, dippp is not easy to handle. Apart from these two catalytic systems, no other catalyst is known to be effective for α-selective Heck reaction of ArCl.

More recently, we disclosed that when carried out in alcohols such as ethylene glycol (EG),[37] the arylation of electron-rich olefins with aryl bromides catalyzed by Pd-dppp is fast, affording up to 1.5×10^4 h^{-1} turnover frequency (TOF) and 3.8×10^5 turnover number (TON),[37d] and exclusively α-regioselective.[37,38] The promoting effect of the protic solvent can be attributed, as in the case of the [HNEt$_3$][BF$_4$],[35] to the equilibrium shown in Scheme 5 being shifted by hydrogen bonding to favor the cationic Pd(II) complex,[39,40] Since the Heck reaction of ArX (X = I, Br, OTf) is likely to be turnover-limited by the olefin insertion step when proceeding via the pathway B,[4f,17] a higher equilibrium concentration of the Pd−olefin cation is expected to give rise to a faster overall rate.

Alcohols are known to act as receptors for halide anions,[41] and EG is a particularly good hydrogen bond donor, as judged by its high E_T^N value of 0.790.[40,42] An illuminating example is that tetraalkylammonium halides show no ionic association when dissolved in ethylene glycol. In contrast, there is evidence for ionic association for such salts in acetonitrile and DMF,[43] in which the Heck reaction of ArBr with vinyl ethers leads to mixtures of α- and β-arylation products.[15,16,22]

These studies point to a strategy for addressing the issue of aryl chlorides in α selective arylation. First, an electron rich ligand is necessary, since the overall Heck reaction is almost certainly turnover-limited by the oxidative addition of ArCl to Pd(0).[3,44,45] Second, the ligand should be bidentate, and third the reaction medium should be highly ionizing. The latter two conditions are necessary in order to channel the arylation into the ionic pathway, without which the arylation would stop at the [Pd(dppp)(Ph)Cl] intermediate or yield both regioiosmers,[17b] even if the oxidative addition occurred. Bearing in mind the success with dppp in controlling the α regioselectivity in arylation with ArBr, an electron-rich, dppp-like ligand would be a good starting point. We report herein that by combining such a diphosphine with palladium in EG, a wide range of aryl chlorides can indeed be coupled with electron-rich olefins, in a highly α-regioselective manner.

Results and Discussion

Identification of Catalytic System. We started the investigation by examining the coupling of a deactivated aryl chloride, 4-chloroanisole **1c**, with *n*-butyl vinyl ether **2a**. Since palladium in combination with dppp in EG has been shown to be highly effective for various ArBr coupling with **2a**,[37] we initially focused on exploring conditions using this readily available ligand. The results are given in Table 1. As can be seen, when performed in EG with Pd(OAc)$_2$-dppp (4 mol % Pd) as catalyst and using Et$_3$N as base for 24 h, the arylation afforded **3c** in 35% yield following acidic hydrolysis of the Heck product (Table 1, entry 1); a similar yield was obtained with Cy$_2$NMe, and no β-arylated product was detected by NMR in the reaction. Surprisingly, the yield increased significantly, up to 85%, when an inorganic base was used (entries 2−6), with the best yield being observed with KOH (entry 4). This is remarkable, as few arylphosphines are known to be able to effect the Heck reaction of an electron-rich aryl chloride, such as **1c**.[3] In sharp contrast, when other solvents (entries 7−13) or ligands (entries 15−26), regardless of being mono or bidentate, were used, much lower

---

(37) (a) Hyder, Z.; Ruan, J.; Xiao, J. *Chem.—Eur. J.* **2008**, *14*, 5555. (b) Xu, D.; Liu, Z.; Tang, W.; Xu, L.; Hyder, Z.; Xiao, J. *Tetrahedron Lett.* **2008**, *49*, 6104. (c) McConville, M.; Blacker, J.; Xiao, J. *Synthesis* **2010**, 349. (d) Liu, M.; Hyder, Z.; Sun, Y.; Tang, W.; Xu, L.; Xiao, J. *Org. Biomol. Chem.* **2010**, *8*, 2012.

(38) (a) He, T.; Tao, X.; Wu, X.; Cai, L.; Pikeb, V. W. *Synthesis* **2008**, 887. Using alcohol as additives, see: (b) Ohrai, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 11737.

(39) EG may hydrogen bond to the halide anions via only one of its hydroxyl groups (see the section on DFT calculations); but chelation is also possible: Barcza, L.; Pope, M. T. *J. Phys. Chem.* **1974**, *78*, 168.

(40) Ethylene glycol is an excellent hydrogen bond donor: Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, 2003.

(41) (a) Smith, D. K. *Org. Biomol. Chem.* **2003**, *1*, 3874. (b) Llinares, J. M.; Powell, D.; Bowman-James, K. *Coord. Chem. Rev.* **2003**, *240*, 57. (c) Aullón, G.; Bellamy, D.; Brammer, L.; Bruton, E. A.; Orpen, A. G. *Chem. Commun.* **1998**, 653.

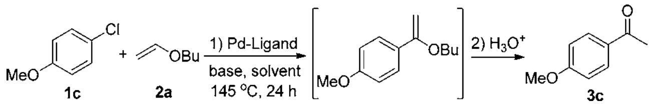
(42) The hydrogen bonding equilibria of alcohols and other hydrogen bond donors with Cl$^-$ have been measured. For instance, methanol interacts with Cl$^-$, forming a 1:1 complex with an association constant *K* of 6.5 in sulfolane at 30 °C. In the case of phenol, a better hydrogen bond donor, *K* increased to 160. See: Lam, S. Y.; Louis, C.; Benoit, R. L. *J. Am. Chem. Soc.* **1976**, *98*, 1156.

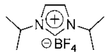
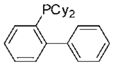
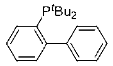
(43) DeSieno, R. P.; Greco, P. W.; Mamajek, R. C. *J. Phys. Chem.* **1971**, *75*, 1722.

(44) (a) Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8141. (b) Barrios-Landeros, F.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 6944. (c) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749. (d) Herrmann, W. A.; Broβmer, C.; Priermeier, T.; Öfele, K. *J. Organomet. Chem.* **1994**, *481*, 97. (e) Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665.

(45) For DFT studies, see: (a) Surawatanawong, P.; Fan, Y.; Hall, M. B. *J. Organomet. Chem.* **2008**, *693*, 1552. (b) Ahlquist, M.; Norrby, P.-O. *Organometallics* **2007**, *26*, 550. (c) Lam, K. C.; Marder, T. B.; Lin, Z. *Organometallics* **2007**, *26*, 758. (d) Ahlquist, M.; Fristrup, P.; Tanner, D.; Norrby, P.-O. *Organometallics* **2006**, *25*, 2066. (e) Kozuch, S.; Amatore, C.; Jutand, A.; Shaik, S. *Organometallics* **2005**, *24*, 2319. (f) Senn, H. M.; Ziegler, T. *Organometallics* **2004**, *23*, 2980.

Table 1. Screening Conditions for Heck Arylation of *n*-Butyl Vinyl Ether (**2a**) with 4-Chloroanisole (**1c**)[a]



entry	ligand	base	solvent	yield (%)[b]
1	dppp	Et_3N	EG	35
2	dppp	K_2CO_3	EG	73
3	dppp	Cs_2CO_3	EG	70
4	dppp	KOH	EG	85
5	dppp	NaOH	EG	82
6	dppp	NaOAc	EG	55
7	dppp	Et_3N	DMF	<2
8	dppp	Cy_2NMe	DMF	5
9	dppp	K_2CO_3	DMF	8
10	dppp	KOH	DMF	<2
11	dppp	Et_3N/HBD[c]	DMF	10
12	dppp	KOH	DMSO	<2
13	dppp	KOH	Toluene	<2
14	/	KOH	EG	0
15[d]	PPh_3	KOH	EG	<2
16[d]	PCy_3	KOH	EG	5
17[d]	$P(Ad)_2Bu$	KOH	EG	3
18[d,e]	P^tBu_3	KOH	EG	45
19[f]		KOH	EG	<2
20		KOH	EG	<2
21		KOH	EG	<2
22	dppe	KOH	EG	38
23	dppb	KOH	EG	32
24	dppf	KOH	EG	<2
25	BINAP	KOH	EG	<2
26	Xantphos	KOH	EG	<2

[a] Reaction conditions: 1) **1c** (1 mmol), **2a** (3 mmol), $Pd(OAc)_2$ (4 mol %), ligand (6 mol %), base (1.5 mmol), solvent (4 mL), 145 °C or reflux, 24 h; 2) 3 M HCl, r.t., 1 h. [b] Isolated yields of ketone. [c] HBD = 1.5 equiv of $[H_2N^iPr_2][BF_4]$. [d] 12 mol % ligand used. [e] 8% linear product and 30% anisole formed. [f] 8 mol % ligand used.

yields were recorded, showing the importance of both EG and a dppp type ligand to successful arylation with ArCl. In particular, the hydrogen bond donor $[H_2N^iPr_2][BF_4]$, which we had previously shown to be highly effective for ArBr,[35] led to a yield of only ca. 10% in DMF with ArCl (entry 11), and although Fu's P^tBu_3 afforded **3c** in 45% yield in EG, significant dechlorination was observed (entry 18). As may be expected, no reaction occurred without ligand (entry 14).

The screening above indicates that Pd-dppp in EG affords the most promising catalyst for the arylation with ArCl. At 4 mol % Pd, however, the catalyst loading is too high and the reaction time tends to be long. We therefore decided to vary the electronic property of dppp in the hope to accelerate the oxidative addition of **1c** to Pd-dppp, a step most likely limiting the arylation turnover as aforementioned. Figure 1 shows the new ligands synthesized by following similar literature procedures.[21b]

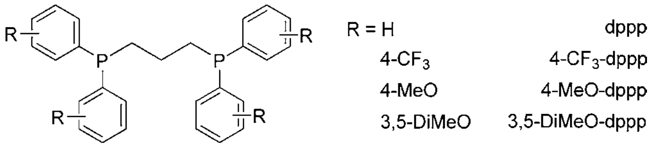


Figure 1. Dppp and its derivatives used in this study.

With these ligands in hand, we undertook further screening, quickly establishing that the more electron-rich dppp analogues are indeed more effective in enabling the palladium-catalyzed coupling of **1c** and **2a** (Table 2). Most delightfully, a high isolated yield of 88% was obtained in 10 h at a palladium loading of 1 mol % when 4-MeO-dppp was used as ligand, with no β product detected by NMR. Consistent with oxidative addition being rate-determining, the electron-deficient 4-CF_3-dppp led to insignificant yields. The lower yield with 3,5-DiMeO-dppp may be electronic or steric in origin. In the case of ArBr substrates, where oxidative addition is less likely to control the turnover, both experiment and computation have shown that electron-deficient ligands actually accelerate the arylation.[46,47] It is worth noting that the viability of 4-MeO-dppp is manifested only when EG is present. Thus, when the

---

(46) von Schenck, H.; Åkermark, B.; Svensson, M. *Organometallics* **2002**, *21*, 2248.

(47) Liu, S.; Saidi, O.; Berry, N.; Ruan, J.; Pettman, A.; Thomson, N.; Xiao, J. *Lett. Org. Chem.* **2009**, *6*, 60.

Table 2. Heck Arylation of **2a** with **1c** Using dppp-type Ligands[a]

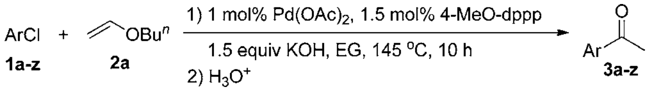
entry	$Pd(OAc)_2$ (mol %)	ligand	reaction time (h)	yield (%)[b]
1	4	4-CF_3-dppp	24	5
2	4	dppp	24	85
3	4	4-MeO-dppp	24	90
4	4	3,5-DiMeO-dppp	24	90
5	1	4-CF_3-dppp	10	<2
6	1	dppp	10	40
7	1	4-MeO-dppp	10	88
8	1	3,5-DiMeO-dppp	10	70

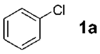
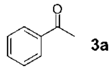
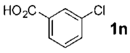
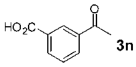
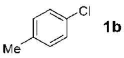
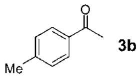
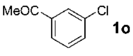
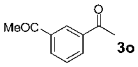
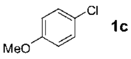
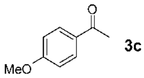
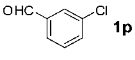
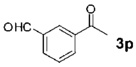
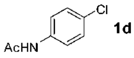
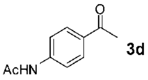
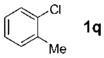
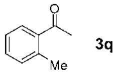
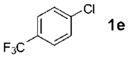
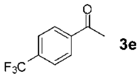
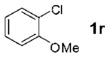
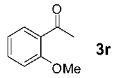
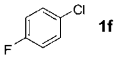
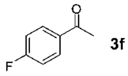
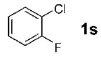
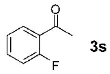
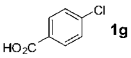
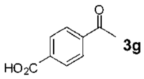
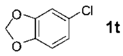
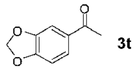
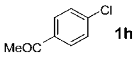
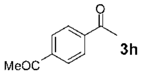
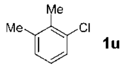
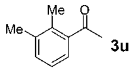
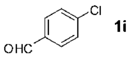
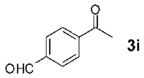
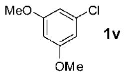
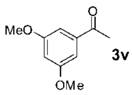
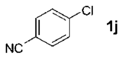
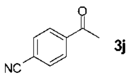
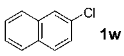
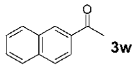
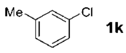
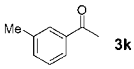
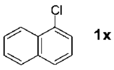
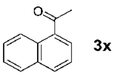
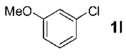
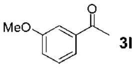
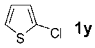
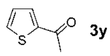
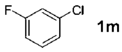
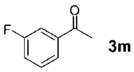
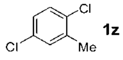
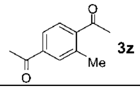
[a] Reaction conditions: (1) **1c** (1 mmol), **2a** (3 mmol), $Pd(OAc)_2$: ligand = 1:1.5, KOH (1.5 mmol), EG (4 mL), 145 °C; (2) 3 M HCl, r.t., 1 h. [b] Isolated yields of ketone.

solvent was switched to DMF or DMSO, the desired ketone product could hardly be detected under conditions otherwise identical to those employed for entry 7 (Table 2), showing that the ligand and solvent are both critical to successful arylation.

α Arylation with ArCl in EG. Using 4-MeO-dppp as ligand for palladium and the conditions shown in Table 2 (entry 7), we then extended the arylation to aryl chlorides **1a**−**z**. The results are shown in Table 3. As can be seen, the reactions afforded good to excellent yields of ketones **3a**−**z**, tolerating activated, unactivated, para-, meta- as well as ortho-substituted aryl chlorides, with all the reactions giving the α-arylation products. We note that none of the previous catalysts are known to be capable of dealing with aryl chlorides of this diversity in the regioselective Heck arylation.[3−10,35,36] Of particular note is that we encountered no problem with aryl chlorides bearing very electron-rich substituents (entries 20−22), and those bearing very electron-deficient groups also led to good yields (entries 5 and 10). Of further interest is the reaction of 3- and 4-chlorobenzoic acid with **2a**, affording the corresponding acetyl benzoic acid in decent yield (entries 7 and 14). To the best of our knowledge, this is the first time a carboxylic acid halide

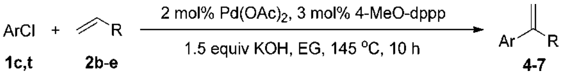
Table 3. Heck Coupling of ArCl **1a**−**z** with **2a**[a]

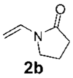
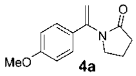
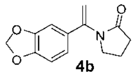
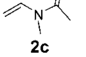
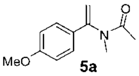
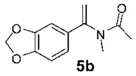
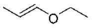
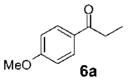
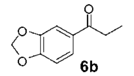
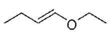
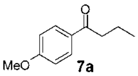
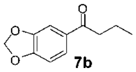


entry	ArCl	product	yield (%)[b]	entry	ArCl	product	yield (%)[b]
1			83	14[c,d]			70
2			87	15[c,e]			86
3			88	16[c,e]			72
4[c]			71	17[c]			76
5			70	18[c]			86
6			80	19[c]			72
7[d]			72	20			90
8[e]			90	21[c]			82
9[e]			80	22			89
10[c,e]			73	23			85
11			82	24[c]			80
12			88	25			75
13			76	26[f]			68

[a] Reaction conditions: (1) **1** (1 mmol), **2a** (3 mmol), $Pd(OAc)_2$ (1 mol %), 4-MeO-dppp (1.5 mol %), KOH (1.5 mmol), ethylene glycol (4 mL), 145 °C, 10 h; (2) 3 M HCl, r.t., 1 h. [b] Isolated yields of ketones. [c] 16 h reaction time. [d] 2.5 equiv of KOH used as base. [e] 1.5 equiv of Et_3N used as base. [f] **2a** (4 mmol), $Pd(OAc)_2$ (2 mol %), 4-MeO-dppp (3 mol %), 16 h.

Table 4. Heck Coupling of ArCl **1c** and **1t** with Olefins **2b**−**e**[a]



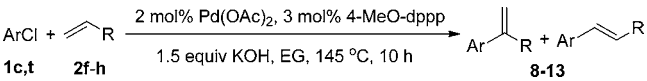
entry	ArCl	olefin	product	yield (%)[b]
1	**1c**	 **2b**	 **4a**	70
2	**1t**		 **4b**	71
3	**1c**	 **2c**	 **5a**	68
4	**1t**		 **5b**	72
5[c]	**1c**	 **2d**	 **6a**	73
6[c]	**1t**		 **6b**	75
7[c]	**1c**	 **2e**	 **7a**	70
8[c]	**1t**		 **7b**	72

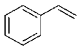
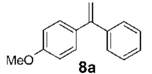
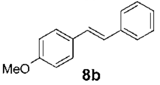
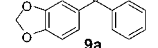
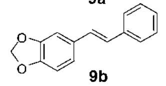
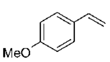
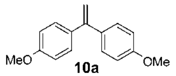
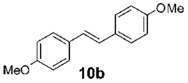
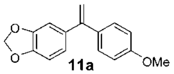
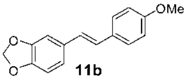
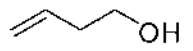
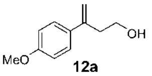
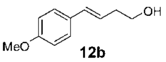
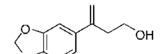
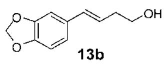
[a] Reaction conditions: **1** (1 mmol), **2** (3 mmol), Pd(OAc)$_2$ (2 mol %), 4-MeO-dppp (3 mol %), KOH (1.5 mmol), ethylene glycol (4 mL), 145 °C, 10 h. [b] Isolated yields. [c] Products were obtained after hydrolysis with 3 M HCl at r.t. for 1 h.

substrate has been shown to be viable in the Heck arylation reaction of aryl chlorides. The dichloride substrate **1z** also coupled, furnishing a diketone product when 2 mol % catalyst and 4 equiv olefin were used (entry 26). In the reactions with ArCl that contains the base-sensitive acetyl, formyl, or nitrile group (entries 8−10, 15−16), NEt$_3$ was shown to be a better base than KOH; the latter led to side reactions being observed and consequently lower yields of products.

With the success in *n*-butyl vinyl ether **2a**, we then turned our attention to other electron-rich olefins **2b**−**e**. These olefins have been α arylated with ArBr previously;[15,16,21b,23b,c,35,37a,48] but none is known to couple with an ArCl. To demonstrate the viability of the catalytic system, two typical electron-rich ArCl **1c** and **1t** were selected to couple with **2b**−**e**. As can be seen from the results shown in Table 4, all the reactions afforded good yields of the α-arylation products. In comparison with **2a**, however, these four olefins led to slightly lower yields, probably due to increased steric bulk in the olefins. In addition, *N*-vinylacetamide failed to give any detectable arylation product, probably due to decomposition of the substrate under the reaction conditions. In contrast, it undergoes successful α arylation with aryl bromides and tosylates, as shown by Skrydstrup and others.[11c,23a,b,49]

Table 5. Heck Coupling of ArCl **1c** and **1t** with Olefins **2f**−**h**[a]



entry	ArCl	olefin	product and yield[b]
1	**1c**	 **2f**	 **8a**  **8b** 78% (**8a**/**8b**=60/40)
2	**1t**		 **9a**  **9b** 80% (**9a**/**9b**=47/53)
3	**1c**	 **2g**	 **10a**  **10b** 80% (**10a**/**10b**=90/10)
4	**1t**		 **11a**  **11b** 82% (**11a**/**11b**=60/40)
5	**1c**	 **2h**	 **12a**  **12b** 75% (**12a**/**12b**=80/20)
6	**1t**		 **13a**  **13b** 78% (**13a**/**13b**=78/22)

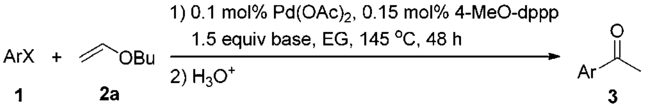
[a] Reaction conditions: **1** (1 mmol), **2f** or **2g** (1.5 mmol), or **2h** (3 mmol), Pd(OAc)$_2$ (2 mol %), 4-MeO-dppp (3 mol %), KOH (1.5 mmol), ethylene glycol (4 mL), 145 °C, 10 h. [b] Isolated yields of both isomers, which were separated except for **12a**,**b** and **13a**,**b** which were isolated as mixtures.

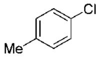
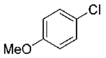
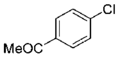
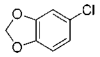
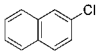
To expand further the scope of the catalysis, unactivated olefins, i.e., olefins without a heteroatom adjacent to the C═C double bond, were explored next. The olefins **2f**−**h** were chosen and tested against the chlorides **1c** and **1t**. As shown in Table 5, all the olefins were arylated. With the relatively more electron-rich **2h**, α-arylated homoallylic alcohols were predominately produced. The regioselectivity is similar to that observed when the homoallylic alcohol was arylated with ArBr in an ionic liquid−DMSO mixture.[27a] In contrast, the styrenes **2f** and **2g** gave rise to a mixture of regioisomers, with the α/*β* ratio varying with the electronic properties of both the olefin and aryl chloride. In particular, when 4-methoxystyrene **2g** was coupled with 4-chloroanisole **1c**, the products were obtained in a surprising α/*β* ratio of 90/10 (entry 3), providing a convenient means for

---

(48) Andappan, M. M. S.; Nilsson, P.; von Schenck, H.; Larhed, M. *J. Org. Chem.* **2004**, *69*, 5212.
(49) Gøgsig, T. M.; Lindhardt, A. T.; Dekhane, M.; Grouleff, J.; Skrydstrup, T. *Chem.*−*Eur. J.* **2009**, *15*, 5950.

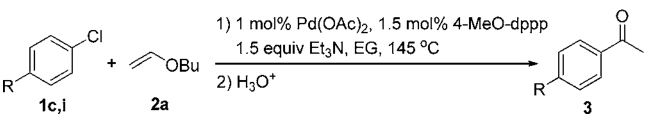
Table 6. Heck Arylation of **2a** with **1** at Low Catalyst Loading[a]



entry	ArX	base	TON
1		KOH	800
2		KOH	780
3		Et_3N	960
4		KOH	900
5		KOH	1000

[a] Reaction conditions: (1) **1** (1 mmol), **2a** (3 mmol), $Pd(OAc)_2$ (0.1 mol %), 4-MeO-dppp (0.15 mol %), base (1.5 mmol), EG (4 mL), 145 °C, 48 h; (2) 3 M HCl, r.t., 1 h. TON was calculated according to the conversion of ArX (no other products were detected).

Table 7. Effects of Chloride Anion on the Heck Arylation of **2a** with **1c**,**i**[a]



entry	R	NBu_4Cl (mmol)	initial rate (× 10^{-7} M·s^{-1})[b]
1	OCH_3	none	7.4
2	OCH_3	1	8.0
3	CHO	none	225
4	CHO	1	244

[a] Reaction conditions: (1) **1c** or **1i** (1 mmol), **2a** (3 mmol), $Pd(OAc)_2$ (1 mol %), 4-MeO-dppp (1.5 mol %), Et_3N (1.5 mmol), NBu_4Cl (0 or 1 mmol), EG (4 mL), 145 °C; (2) 3 M HCl, r.t., 1 h. [b] The initial rates were based on conversions <10%.

synthesizing 1,1-diarylalkene derivatives, which are useful precursors for the synthesis of biologically active compounds.[50] No (*Z*)-configured olefins were detected for all the β-arylation products. We note that with all the existing literature methods, it is the β-arylation products that are normally afforded when styrenes are arylated.[1,3] The high α selectivity observed in the case of **1c** and **2g** may stem from an increased nucleophilicity at the migrating Ar group and an increased positive charge at the α carbon of the styrene in the cationic Pd−olefin intermediate (Scheme 2).

From a practical viewpoint, it is highly desirable to minimize catalyst loading, although in the Heck reaction of aryl chlorides, rarely can one employ <1 mol % palladium for reactions using electron-rich olefins or unactivated aryl chlorides.[4a,e,5c,g,i,6b,c,e,7a] With this in mind, we examined the Heck arylation of *n*-butyl vinyl ether (**2a**) with chlorobenzene derivatives under a lower catalyst loading. As shown in Table 6, TON up to 1000 can be achieved by using 0.1 mol % $Pd(OAc)_2$ in EG. To the best of our knowledge, this is the highest TON ever obtained for the Heck arylation of electron-rich olefins with aryl chloride substrates, showing the potential of the current catalytic system for industrial applications.

Mechanistic Observations. As aforementioned, the arylation under question is likely to be rate-limited by the oxidative addition of ArCl to Pd(0). To gain more insight into the arylation mechanism in EG, several experiments were carried out. We first examined the effect of chloride anion on the Heck arylation of *n*-butyl vinyl ether (**2a**) with 4-substituted chlorobenzenes (**1c**,**i**). If oxidative addition is the turnover-determining step, introduction of halide anions into the reaction should have an insignificant effect on the arylation rate, unless a subsequent step in the catalytic cycle has an energy barrier close to the oxidative addtion. As shown in Table 7, in both cases the added chloride anion did not inhibit the reaction, which in fact went slightly faster in the presence of the chloride salt,[51] indirectly supporting the assertion above. In sharp contrast, the arylation with aryl bromides and iodides in *nonprotic* solvents, such as DMF and imidazolium ionic liquids, is dramatically retarded when halide anion is added.[35,22b] In these later cases, the arylation is probably controlled by the olefin insertion step and hence is expected to suffer from halide coordination, which decreases the concentration of the Pd−olefin cation.[4f,15,17] In kinetic studies of [Pd(dppp)(Ph)X] reacting with isobutyl vinyl ether in DMF, the reaction rate is also found to be inversely proportional to the concentration of added iodide ion.[17b]

In EG, the equilibrium in Scheme 5 lies probably far to the right, favoring the cationic Pd−olefin intermediate.[37a] Chloride anions, when added, are likely to be well solvated by the medium, via hydrogen bonding with EG molecules, and hence have little effect on the equilibrium.[40−42] As mentioned previously, the ions of tetraalkylammonium halides are not associated in EG, due to EG hydrogen bonding with the halide anions.[43] The strength of interaction of halide anions with EG may be further judged from the standard molar Gibbs free energy of transporting single chloride anions from water to EG, $\Delta G = 9.0$ kJ/mol. For comparison, chloride ion transfer to DMSO and DMF costs $\Delta G = 40.3$ and 48.3 kJ/mol, respectively, indicating, unsurprisingly, much less favorable interactions of chloride anions with these two solvents.[52]

We next studied the effect of olefin concentration on the initial rate of Heck arylation of **2a** with **1c**. The results are summarized in Table 8. As can be seen, the reaction rates remained essentially the same when the concentration of olefin was varied, suggesting that the olefin insertion step is unlikely to dictate the turnover rate of the arylation cycle. Note that the initial rates in Table 8 are different from those in Table 7 due to the bases used being different.

To probe further the mechanism, we studied the effect of para substituents of ArCl on the arylation of **2a** with ArCl (**1**). Based on the initial rate measurements, a Hammett plot using the σ constants is obtained, revealing a positive ρ value of 2.1 (Figure 2). This indicates the building up of negative charge at the transition state and thus is consistent with an oxidative addition-, rather than olefin insertion-, controlled reaction,

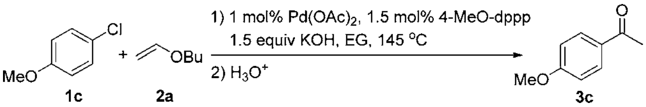
---

(50) (a) Barda, D. A.; Wang, Z.-Q.; Britton, T. C.; Henry, S. S.; Jagdmann, G. E.; Coleman, D. S.; Johnson, M. P.; Andis, S. L.; Schoepp, D. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3099. (b) Faul, M. M.; Ratz, A. M.; Sullivan, K. A.; Trankle, W. G.; Winneroski, L. L. *J. Org. Chem.* **2001**, *66*, 5772. (c) Nussbaumer, P.; Dorfstatter, G.; Grassberger, M. A.; Leitner, I.; Meingassner, J. G.; Thirring, K.; Stutz, A. *J. Med. Chem.* **1993**, *36*, 2115. (d) Waespe, H. K. Eur. Pat. Appl. EP0278915 (A2), 1988.

(51) Chloride anion additives are known to accelerate the Heck reaction catalyzed by Pd−PPh_3; see: Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc.* **1991**, *113*, 8375.

(52) Marcus, Y. *Pure Appl. Chem.* **1983**, *55*, 977.

Table 8. Effect of Olefin Concentration on the Initial Rate of Heck Arylation of **2a** with **1c**[a]



entry	olefin (equiv)	initial rate ($\times 10^{-6}$ M$\cdot$s^{-1})[b]
1	1	8.0
2	2	8.3
3	3	8.4
4	4	8.0

[a] Reaction conditions: (1) **1c** (1 mmol), **2a** (1−4 mmol), Pd(OAc)$_2$ (1 mol %), 4-MeO-dppp (1.5 mol %), KOH (1.5 mmol), EG (4 mL), 145 °C; (2) 3 M HCl, r.t., 1 h. [b] The initial rates were based on conversions <10%.

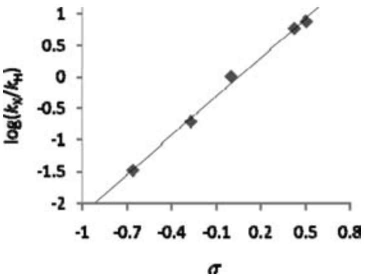


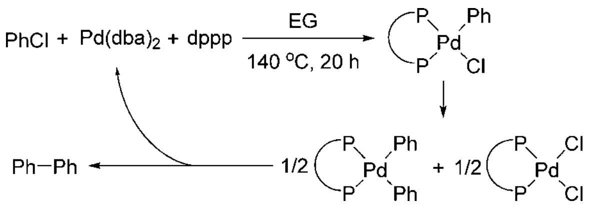
Figure 2. Plot of log(k_X/k_H) vs Hammett substituent constant σ for the arylation of **2a** with ArCl (see the Supporting Information for experimental details).

probably with a concerted or a S$_N$Ar-type transition state.[1b,45,53,54] Judging from Scheme 3, one would actually expect the olefin insertion to benefit from electron-donating substituents on the migrating aryl moiety.[19a] This ρ value is significantly smaller than that (5.2) determined by Milstein[44e] using Pd-dippp in dioxane and the σ^- constant but is similar to those measured for ArI[55] and ArOTf;[25c] this may suggest an easier oxidative addition step in EG.[1b]

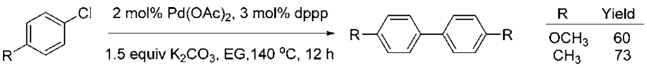
The investigations above are in agreement with the arylation with ArCl being controlled by the oxidative addition of ArCl. The success of the current catalytic system may then be traced to the use of an electron-rich ligand, 4-MeO-dppp. However, ligands are not the decisive factor in the success of our catalytic system. As mentioned above, without EG as solvent, neither Pd-dppp nor Pd-4-MeO-dppp afforded a significant amount of product. This raises questions of fundamental importance: is the oxidative addition of ArCl to Pd(0) accelerated by EG and, if so, how?

In order to discover if choice of solvent might affect the oxidative addition step, we reacted Pd(dba)$_2$ (0.1 mmol) with chlorobenzene (1.0 mmol) in the presence of dppp (0.11 mmol) in EG. The major product identified by NMR was [PdCl$_2$(dppp)] and biphenyl (ca. 22% yield) (Scheme 6). This result is consistent with an initial oxidative addition reaction to give [PdCl(Ph)(dppp)], which disproportionates, yielding [PdCl$_2$(dppp)] and [Pd(Ph)$_2$(dppp)] as shown in Scheme 6; the latter then gives rise to the biphenyl and Pd(0)-dppp, which can react again with PhCl. However, catalytically inactive [PdCl$_2$(dppp)] is produced in each catalytic cycle, limiting the maximum biphenyl yield to ca. 0.2 mmol, i.e., 20% [active palladium avaliable = 0.1 mmol × (1 + 1/2 + 1/4 + 1/8 + ...)]. Similar reactions have been previously observed when heating [PdCl(Ph)(dippp)].[4f] In contrast, little biphenyl was detected when the reaction of Scheme 6 was carried out in DMF or DMSO under the same conditions, indicative of no or little oxidative addition taking place in these solvents. In a related study by Herrmann, heating Pd(dba)$_2$ and dppp in neat chlorobenzene at 140 °C only led to a very low yield of [PdCl(Ph)(dppp)].[44d]

Scheme 6. Oxidative Addition of PhCl to Pd(0) in EG



Scheme 7. Catalytic Homocoupling of ArCl in EG



The reaction in Scheme 6 becomes catalytic when performed in the presence of base. Thus, when 4-chloroanisole or 4-chlorotoluene was subjected to homocoupling in EG with K$_2$CO$_3$ added, the corresponding biaryl was isolated in ca. 60−70% yield (Scheme 7).[56] Most likely, reduction of [PdCl$_2$(dppp)] with EG occurs in the presence of K$_2$CO$_3$, which neutralizes the HCl formed. These results suggest that oxidative addition of ArCl to palladium occurs readily in EG but do not explain how.

DFT Calculations. To gain further insight into the oxidative addition step, we carried out DFT calculations by using B3LYP functional[57] on the reaction of [Pd(dppp)] with PhCl, assuming that the Pd(0) species is in situ generated from Pd(OAc)$_2$ and dppp.[58] The transition state of the reaction in vacuo was located and is shown in Figure 3 (**TS1**). This appears to be a concerted transition state,[1b,45,54] with Pd interacting with both C$_{ipso}$ and Cl, and resembles those calculated for aryl halides using different Pd(0)−diphosphine complexes.[45a,c,e,f] An interesting feature of these transition states is the large angle between the planes defined by PdPP and PdXC$_{ipso,}$[45a,c,e,f] which is 59.98° in the this case.

A similar calculation was then conducted for the reaction in methanol, using the PCM continuum solvation model.[59] Comparing the calculated structures in vacuo and in MeOH shows

---

(53) For the mechanism of classical S$_N$Ar reactions, see: (a) Smith, M. B.; March, J. *Advanced Organic Chemistry*, 6th ed.; Wiley-Interscience: Hoboken, NJ, 2007; Chapter 13. (b) Buncel, E.; Dust, J. M.; Terrier, F. *Chem. Rev.* **1995**, *95*, 2261.

(54) Concerted mechanism has also be suggested: (a) Jakt, M.; Johannissen, L.; Rzepa, H. S.; Widdowson, D. A.; Wilhelm, R. *J. Chem. Soc., Perkin Trans. 2* **2002**, 576. (b) Sundermann, A.; Uzan, O.; Martin., J. M. L. *Chem.−Eur. J.* **2001**, *7*, 1703. (c) Amatore, C.; Pflüger, F. *Organometallics* **1990**, *9*, 2276 In this mechanism, charge separation at the transition state appears to be moderate.

(55) Fauvarque, J.-F.; Pflüger, F.; Troupel, M. *J. Organomet. Chem.* **1981**, *208*, 419.

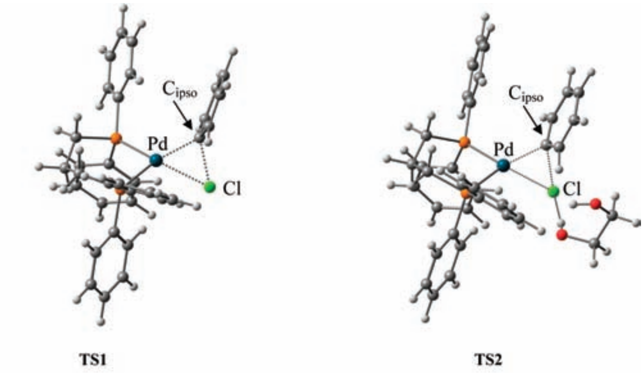
(56) The homocoupling of aryl bromides or iodides in 3-pentanol by palladium catalysis has recently been reported, but it is inefficient for aryl chlorides: Zeng, M.; Du, Y.; Shao, L.; Qi, C.; Zhang, X. *J. Org. Chem.* **2010**, *75*, 2005.

(57) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.

(58) Generation of Pd(0)−diphosphine from Pd(0)−bisdiphosphine can be an energy-cost process: Shaw, B. L.; Perera, S. D. *Chem. Commun.* **1998**, 1863. Also see ref 45f.

(59) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999.

(60) http://www.chemcraftprog.com/.



	Distances (Å)				Angles (°)		
	Pd-C$_{ipso}$	C$_{ipso}$-Cl	Pd-Cl	Cl-HO	Pd-C$_{ipso}$-Cl	C$_{ipso}$-Cl-Pd	Cl-Pd-C$_{ipso}$
TS1	2.124	2.115	2.613	-	76.10	52.11	51.79
TS2	2.070	2.228	2.832	2.30	82.34	46.42	51.24

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. Molecules rendered using Chemcraft.[60]

a root-mean-square deviation of only 0.218 Å in bond distances between the two structures (all atoms). The main difference between the two structures is the angle between the planes defined by PdPP and PdClC$_{ipso}$ increasing from 59.98° in vacuo to 72.55° in MeOH, reflecting possible interactions of the departing chloride with the medium. The Pd−C$_{ipso}$ distance shortened to 2.091 Å while the C$_{ipso}$−Cl and Pd−Cl distances elongated to 2.143 Å and 2.784 Å, respectively. Most interestingly, the energy of the transition state in methanol is significantly lower. Indeed, the transition state in this polar protic solvent is 7.16 kcal/mol lower in energy than the analogous transition state in vacuo. A much longer C$_{ipso}$−Cl and Pd−Cl distance at the transition state was found by Ziegler for the oxidative addition of PhCl to [Pd(dmpe)] (dmpe = $Me_2PCH_2CH_2PMe_2$) in THF, indicating a dissociative process in the reaction.[45f]

In line with Ziegler's results[45f] and the Hammett plot (Figure 2), significant charge separation was found at the transition state. The calculated atomic charges on the PhCl moiety are −0.42 in vacuo and −0.49 in MeOH, while the partial atomic charges on the chloride atom are −0.29 (vacuum) and −0.38 (methanol). In comparison, the charge on the chloride at the ground state is almost zero (−0.009). With the significant negative charge developed at the chloride, solvents capable of hydrogen bonding with the chloride are expected to stabilize the transition state.

A further calculation indeed shows that EG interacts with the chloride, significantly lowering the energy barrier by 13.03 kal/mol relative to that in vacuo. The calculation was carried out by introducing one EG molecule. As can be seen from Figure 3 (**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. This is significantly shorter than the sum (2.95 Å) of van der Waals radii of H and Cl, falling in the category of "short" H···Cl interactions.[41c] As with the results above, shortening of the Pd−C$_{ipso}$ distance and elongation of the C$_{ipso}$−Cl and Pd−Cl were also observed. The PdClC$_{ipso}$ plane becomes closer to being perpendicular to that of PdPP; this minimizes steric interactions with the dppp phenyl rings. The energy barrier with one EG involved is considerably lower than that obtained with the continuous MeOH medium, suggesting that hydrogen bonding may play a more important role in stabilizing the transition state than is captured by the continuum solvation model.

The DFT studies thus established that the oxidative addition of ArCl to Pd(0) is indeed facilitated in an alcohol medium, and this can be traced to hydrogen bonding between the alcohol and the departing chloride, which lowers the energy barrier of the trasnsition state. Although oxidative addition reactions proceeding via the S_N2 mechanism are known to be promoted by polar aprotic solvents,[44c,61] which function to solvate the leaving anions,[62] we are not aware of examples of oxidative addition of organohalides that are accelerated by hydrogen bond donors. However, solvents of this nature have long been known to "exert an electrophilic pull on the departing anions in much the same way that heavy metal ions (Ag^+, Hg^{2+}) catalyze nucleophilic substitution reactions of haloalkanes".[40] Indeed, as indicated earlier, numerous examples are known of O−H···Cl^- hydrogen bonding,[41] including O−H···Cl−M interactions, where the chloride bonds to a metal,[41c] resembling the TS involving EG above. In the classic S_NAr reaction that bears similarities to the concerted mechanism under question, suggestions have been made of N−H hydrogen bonding to fluoride, facilitating its leaving.[63] Furthermore, H···Cl hydrogen bonding has been exploited to facilitate C−Cl bond breaking in stoichiometric,[64] organo-catalytic,[65] and enzymatic reactions.[66]

Conclusion

We have developed the first, general, and highly efficient catalytic system that allows a wide range of activated and unactivated aryl chlorides to couple, α-regioselectively, with electron-rich olefins. Further advantages of the protocol include a ligand that is easy to synthesize and handle, and an inexpensive, readily available solvent of low toxicity. While the Heck reaction has been extensively studied for over four decades, α arylation of electron-rich olefins with aryl chlorides remained largely elusive until now. The efficacy of the current catalysis arises from the use of an electron-rich diphosphine ligand 4-MeO-dppp and an alcohol solvent EG, with the latter playing the more important role. Experimental and computational studies provide evidence which indicates that the arylation is controlled by the oxidative addition step and that the success of our system is due to acceleration of this step by a specific hydrogen bonding interaction between a solvent molecule and the chloride of ArCl at the transition state.

EG also plays a second role in the regioselective arylation, viz. promotion of the dissociation of chloride anions from the [PdCl(Ar)(dppp)] to give the $[Pd(Ar)(olefin)(dppp)]^+$ intermediate. Without the formation of this cationic Pd(II) species, the arylation is expected to give rise to a mixture of α- and *β*-arylation products, at a slow rate. Most likely, this promotion stems from the strong ionizing power of EG and its ability to

---

(61) Rendina, L. M.; Puddephatt, R. J. *Chem. Rev.* **1997**, *97*, 1735.

(62) Hayaki, S.; Yokogawa, D.; Sato, H.; Sakaki, S. *Chem. Phys. Lett.* **2008**, *458*, 329.

(63) (a) Crampton, M. R. In *Organic Reaction Mechanisms-2004*; Knipe, A. C., Ed.; Wiley: Chichester, U.K., 2008, Chapter 5. (b) Forlani, L. *J. Phys. Org. Chem.* **1999**, *12*, 417.

(64) Stanger, K. J.; Lee, J.-J.; Smith, B. D. *J. Org. Chem.* **2007**, *72*, 9663.

(65) (a) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198. (b) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404. (c) Almerindo, G. I.; Pliego, J. R., Jr. *Chem. Phys. Lett.* **2006**, *423*, 459. (d) Pliego, J. R., Jr. *J. Mol. Catal. A: Chem.* **2005**, *239*, 228.

(66) (a) Soriano, A.; Silla, E.; Tuñón, I.; Ruiz-López, M. F. *J. Am. Chem. Soc.* **2005**, *127*, 1946. (b) Devi-Kesavan, L. S.; Gao, J. *J. Am. Chem. Soc.* **2003**, *125*, 1532.

solvate the resulting chloride anions through hydrogen bonding (Scheme 5). Given the ample evidence recorded in the literature,[40−42] showing that alcohols hydrogen bond to chlorides as free ions or when bonded to metal or carbon atoms, it is surprising that hydrogen bonding has not previously been intentionally exploited to facilitate metal-catalyzed reactions of organohalides and the derivatives, including the Heck arylation studied in this contribution.

Acknowledgment. We thank the EPSRC (EP/F000316 and EP/C005643/1) for support and dedicate this paper to Professor Albert S. C. Chan on the occasion of his 60th birthday. This paper is also dedicated to Professor Richard Heck on the occasion of his, together with Professors Ei-ichi Negishi and Akira Suzuki, winning of the 2010 Nobel Prize in Chemistry, which was announced while the manuscript was being refereed.

Supporting Information Available: Experimental procedures and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

JA1081926