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Two Flavors of PEPPSI-IPr: Activation and Diffusion Control in a Single NHC-Ligated Pd Catalyst?

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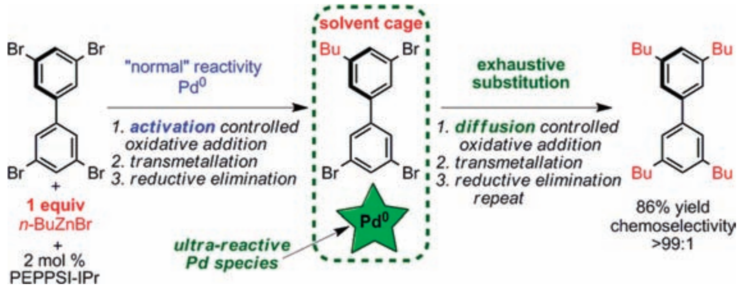
ABSTRACT



Abnormal reactivity has been observed in Negishi, Suzuki−Miyaura, and Kumada−Tamao−Corriu cross-couplings in which PEPPSI-IPr (where PEPPSI stands for pyridine enhanced precatalyst preparation, stabilization, and initiation and IPr refers to the NHC ligand) is employed, implicating the presence of two distinct Pd^0 species in the catalytic cycle. Polybrominated arenes and organometallic reagents react selectively to give the product of exhaustive polysubstitution regardless of the initial reaction stoichiometry. Competition experiments suggest that, after an initial activation controlled oxidative addition, reductive elimination produces an ultrareactive Pd^0 species which consumes all remaining C−Br bonds in the molecule under diffusion control.

The emergence of N-heterocyclic carbenes as ligands in transition metal catalysis has had, and continues to have, a significant effect on synthetic chemistry.[1] Since the first NHC-supported palladium-mediated cross-coupling was disclosed by Herrmann,[2a] this concept has proven to be revolutionary, and almost all standard palladium mediated C−C and C−heteroatom bond forming methodologies have been shown to benefit from this new paradigm. Although many early studies focused on the *in situ* preparation of catalysts,[1] a number of well-defined precatalysts[1,2] have been disclosed. Of special note are the pyridine enhanced precatalyst preparation stabilization and initiation (PEPPSI) catalysts of Organ and co-workers, able to carry out extremely challenging transformations with low catalyst loading.[2f,j,k] Further, the high stability of these precatalysts, which can be purified by simple column chromatography and stored under air, contrasts with some of the phosphine

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(1) For reviews on the use of NHCs in transition metal catalysis, see: (a) Diez-Gonzalez, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612. (b) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768. (c) Glorius, F., Ed.; *N-Heterocyclic Carbenes in Transition-Metal Catalysis*; Springer: Berlin, 2007.

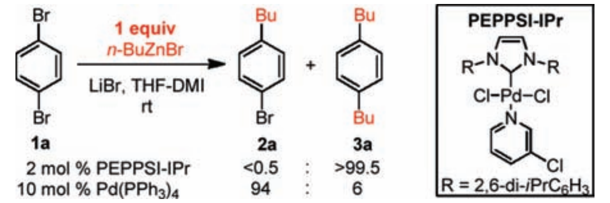
(2) (a) Herrmann, W. A.; Elison, M.; Fischer, J.; Kocher, C.; Artus, G. R. J. *Angew. Chem., Int. Ed.* **1995**, *34*, 2371. (b) Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363. (c) Cesar, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Organometallics* **2002**, *21*, 5204. (d) Navarro, O.; Kelly, R. A.; Nolan, S. P. *J. Am. Chem. Soc.* **2003**, *125*, 16194. (e) Frisch, A. C.; Zapf, A.; Briel, O.; Kayser, B.; Shaikh, N.; Beller, M. *J. Mol. Catal.* **2004**, *214*, 231. (f) Organ, M. G.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. *Chem.—Eur. J.* **2006**, *12*, 4749. (g) Organ, M. G.; Abdel-Hadi, M.; Avola, S.; Hadei, N.; Nasielski, J.; O'Brien, C. J.; Valente, C. *Chem.—Eur. J.* **2007**, *13*, 150. (h) Esposito, O.; Gois, P. M. P.; Lewis, A. K.; de, K.; Caddick, S.; Cloke, F. G. N.; Hitchcock, P. B. *Organometallics* **2008**, *27*, 6411. (i) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440. (j) Wurtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523. (k) Valente, C.; Baglione, S.; Candito, D.; O'Brien, C. J.; Organ, M. G. *Chem. Commun.* **2008**, *6*, 735. (l) Winkelmann, O. H.; Riekstins, A.; Nolan, S. P.; Navarro, O. *Organometallics* **2009**, *28*, 5809. (m) Tennyson, A. G.; Lynch, V. M.; Bielawski, C. W. *J. Am. Chem. Soc.* **2010**, *132*, 9420.

10.1021/ol1027283

supported catalysts which achieve similar transformations.[3]

During the attempted monobutylation of 1,4-dibromobenzene mediated by PEPPSI-IPr in the presence of 1 equiv of *n*-BuZnBr we unexpectedly observed highly selective *double butylation* (Scheme 1).[2f] In contrast, the corresponding reaction mediated by Pd$(PPh_3)_4$ resulted, as expected, in selective monobutylation of the dibromo starting material.[4]

Scheme 1. Negishi Reaction between 1,4-Dibromobenzene and *n*-BuZnBr

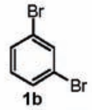
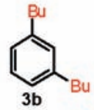
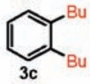
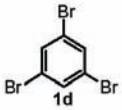
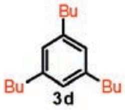
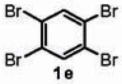
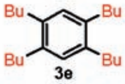
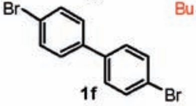
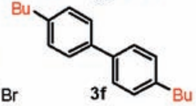
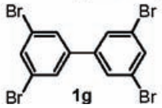
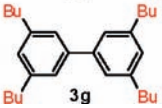


A review of the literature on palladium mediated cross-couplings revealed that a similar observation was made in the context of Suzuki−Miyaura sp^2−sp^2 couplings of dibromoarenes mediated by Pd^0/P*t*-Bu_3.[5] The authors rationalized their observation by proposing diffusion controlled oxidative addition, with the Pd^0 product of reductive elimination rapidly oxidatively adding to the same substrate. This reaction has since been applied to pseudoliving Suzuki−Miyaura polycondensations leading to the synthesis of controlled molecular weight polyarenes and polyheteroarenes for electronic applications, surface grafted and hyperbranched polymers.[6]

By analogy, the result shown in Scheme 1 implies that PEPPSI-IPr has the potential to act as a phosphine-free catalyst in catalyst transfer polycondensations, avoiding the issues associated with the use of phosphine-supported catalysts,[7] with potential applications in the synthesis of commercially important materials.[8] Herein we report our investigation of this phenomenon which not only confirms that it is general but also provides evidence that not all Pd^0 species are created equally; indeed in PEPPSI-IPr mediated cross-couplings it appears that some Pd^0 species react under activation control while others carry out oxidative addition in a diffusion controlled fashion.

When 1,3-dibromobenzene (**1b**) was subjected to PEPPSI-IPr mediated Negishi reaction conditions in the presence of 1 equiv of *n*-BuZnBr, an excellent selectivity of >99:1 for 1,3-dibutylbenzene (**3b**) was observed (entry 1, Table 1). High selectivity for the doubly substituted product was maintained even for the more hindered *ortho* substrate **1c** (97:3, entry 2). Remarkably, tribromobenzene **1d** (entry 3) and even tetrabromobenzene **1e** (entry 4) showed similar behavior, selectively affording the tri- and tetra-butylated products (**3d** and **3e**), respectively. In the case of tetrabromobenzene an unexpected protodebromination side reaction was observed and both tribromobenzene and tributyl benzene were observed as side products, significantly decreasing the yield of the expected product.[9] The selectivity for exhaustive butylation is not limited to simple polybromobenzenes; the same phenomenon was observed when two or even four bromine substituents were positioned at opposite extremes of a biphenyl unit (entries 5 and 6).

Table 1. Scope of PEPPSI-IPr Mediated Chemoselective Negishi Cross-Coupling[a]

entry	arene	product	ratio[b]	yield[c]
1	 **1b**	 **3b**	>99:1	86%
2	 **1c**	 **3c**	97:3	86%
3	 **1d**	 **3d**	99:1	64%
4	 **1e**	 **3e**	92:8	18%
5	 **1f**	 **3f**	97:3	90%
6	 **1g**	 **3g**	99:1	86%

[a] All reactions were carried out with 1 equiv of *n*-BuZnBr as outlined in Scheme 1. See Supporting Information for further details. [b] Ratios of fully butylated product to other butylated products as determined by GCMS analysis. [c] Yields are defined relative to *n*-BuZnBr and were determined by ^1H NMR analysis of the crude reaction mixture using mesitylene as an internal standard.

These results are consistent with a diffusion controlled oxidative addition process as previously proposed for Fu's catalyst.[5] However, given the recent speculation over the

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(3) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (c) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746. (d) Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38. (e) Fu, G. C. *Acc. Chem. Res.* **2008**, *41*, 1555. (f) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.

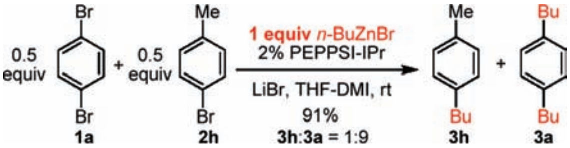
(4) The same result was observed when 2 mol% Pd$(PPh_3)_4$ was employed, but 10 mol% was required in order to give reasonable conversions.

(5) (a) Dong, C.-G.; Hu, Q.-S. *J. Am. Chem. Soc.* **2005**, *127*, 10006. (b) A similar, albeit less selective outcome was observed in the coupling of diiodoarenes mediated by Pd$(PPh_3)_4$. In this case the outcome was rationalized as being due to selective double oxidative addition to the substrate: Sinclair, D. J.; Sherburn, M. S. *J. Org. Chem.* **2005**, *70*, 3730. (c) One example of the double substitution of 1,3-dichlorobenzene by NHC-ligated Pd has been reported in the presence of an excess of the nucleophile: Hartmann, C. E.; Nolan, S. P.; Cazin, C. S. J. *Organometallics* **2009**, *28*, 2915.

(6) (a) Heeney, M.; McCulloch, I. *Tetrahedron Lett.* **2006**, *47*, 5143. (b) Yokoyama, A.; Suzuki, H.; Kubaota, Y.; Ohuchi, K.; Higashimura, H.; Yokozawa, T. *J. Am. Chem. Soc.* **2007**, *129*, 7236. (c) Huang, W.; Su, L.; Bo, Z. *J. Am. Chem. Soc.* **2009**, *131*, 10348. (d) Beryozkina, T.; Boyko, K.; Khanduyeva, N.; Senkovskyy, V.; Horecha, M.; Oertel, U.; Simon, F.; Stamm, M.; Kiriy, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2695.

nature of the active species in PEPPSI-IPr mediated reactions,[10] an alternative hypothesis that PEPPSI-IPr selects for more electron-rich substrates could not be ruled out. Thus, we conducted a simple competition experiment between 4-bromotoluene (**2h**) and 1,4-dibromobenzene (**1a**): if the observed selectivities were electronic in origin we would expect to see consumption of 4-bromotoluene predominantly while diffusion control would be expected to lead to a statistical or near-statistical outcome, as previously reported for $Pd^0/Pt\text{-}Bu_3$.[5] To our surprise neither of these outcomes were observed. Instead, selective conversion of 1,4-dibromobenzene to 1,4-dibutylbenzene (**3a**) took place, indicating that dibromobenzene is the more reactive coupling partner (Scheme 2). It is clear from the high selectivity displayed for **1a** over **2h** not only that the first oxidative addition event is activation controlled but also that the observed polybutylation (Scheme 1 and Table 1) is not the result of selective consumption of more electron-rich substrates.

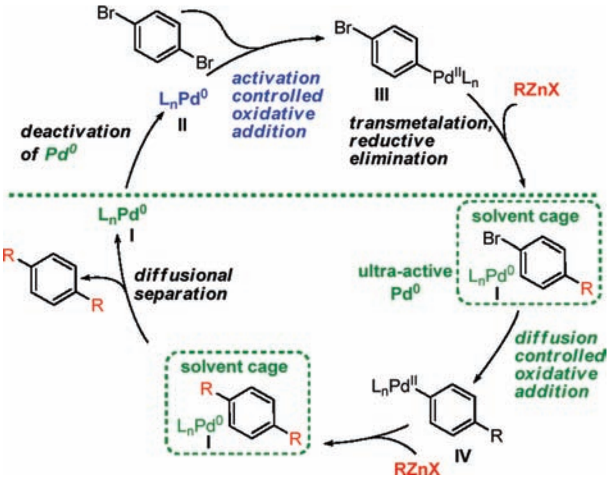
Scheme 2. Competitive Negishi Cross-Coupling of 1,4-Bromotoluene and 1,4-Dibromobenzene



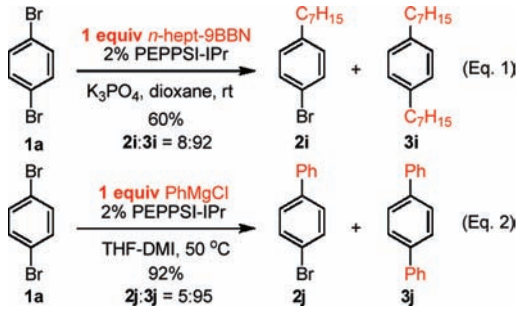
In order to rationalize our observations we propose that at least *two distinct Pd^0 species* carry out oxidative addition in these reaction systems (Scheme 3). The dominant Pd^0 species in the bulk, **II**, appears to react under activation control to give “normal” selectivity, whereas a second Pd^0 species, **I**, which results from reductive elimination, reacts under diffusion control (Scheme 3). Although there has long been a debate in the field of phosphine supported palladium catalysis as to the nature of the species which undergoes oxidative addition to the halo arene,[11] to our knowledge this is the first time that multiple active Pd^0 species have been required to explain the observed outcome of *a single* cross-coupling reaction.[12]

A recently published DFT study on the Negishi reaction between EtZnBr and EtBr mediated by PEPPSI-IPr identified the initial product of reductive elimination to be a Pd^0-ZnBr_2 adduct in which a persistent Pd−Zn interaction is present.[13] We postulated that this may correspond to hyper-reactive Pd^0 species **I** (Scheme 3). If a Pd−Zn interaction was responsible for activation of the Pd^0 center, the effect would be expected to disappear when other coupling methods are used in which Zn is absent. Accordingly we investigated the Suzuki−Miyaura coupling of *n*-heptyl-9BBN with 1,4-dibromobenzene (Scheme 4, eq 1) mediated by PEPPSI-IPr.[2j]

Scheme 3. Proposed Catalytic Cycle Operating under Both Activation and Diffusion Control



Scheme 4. Suzuki−Miyaura (Eq 1) and Kumada−Tamao−Corriu (Eq 2) Couplings of 1,4-Dibromobenzene



In this case the selective production of the dialkylated product was also observed indicating that this unusual behavior is not limited to Negishi couplings with alkyl zincates.[14] Further, the Kumada−Tamao−Corriu coupling of phenyl magnesium bromide (Scheme 4, eq 2) also led selectively to the difunctionalized product.[2g] These results indicate that this unusual behavior is not limited to sp^3-sp^2 couplings but is actually a general property of the PEPPSI-IPr precatalyst.

Having determined the exhaustive substitution of polybrominated arenes to be a general property of PEPPSI-IPr mediated cross-couplings, we briefly investigated the analogous reactions of other di(pseudo)halo benzenes (Table 2). In the case of 1,4-diiodobenzene, exhaustive butylation was

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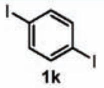
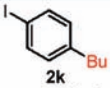
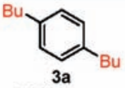
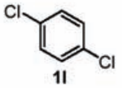
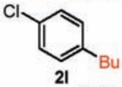
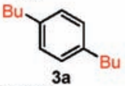
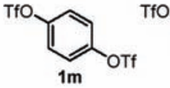
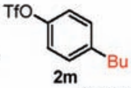
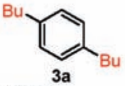
(7) (a) Goodson, F.; Wallow, T. I.; Novak, B. M. *Macromolecules* **1998**, *31*, 2047. (b) Jayakannan, M.; Lou, X.; Van Dongen, J. L. J.; Janssen, R. A. J. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 1454. (c) Sakamoto, J.; Rehahn, M.; Wegner, G.; Schlüter, A. T. *Macromol. Rapid Commun.* **2009**, *30*, 653.

(8) (a) Koller, G.; Falk, B.; Weller, C.; Giles, M.; McCulloch, I. W.I.P.O. Patent 2005/014691 A2, Feb. 17, 2005. (b) Heeney, M.; Zhang, W.; Duffy, W. ; McCulloch, I.; Koller, G. W.I.P.O. Patent 2007/059838, May 31, 2007.

(9) Unfortunately, this protodehalogenation side reaction dominates in the case of hexabromobenzene leading to a complex mixture of protodebrominated starting material and polybutylated products.

(10) Manolikakes, G.; Knochel, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 205.

Table 2. PEPPSI-IPr Mediated Negishi Cross-Coupling of 1,4-Dihaloarenes[a]

entry	arene	product(s)	yield[b]
1	 **1k**	 **2k**  **3a** **2k**:**3a** = <5:95[c]	71%
2	 **1l**	 **2l**  **3a** **2l**:**3a** = 65:35[c]	85%
3	 **1m**	 **2m**  **3a** **2m**:**3a** = 91:9[c]	53%

[a] All reactions were carried out with 1 equiv of *n*-BuZnBr as outlined in Scheme 1. See Supporting Information for further details. [b] Yields of **2**+**3** are defined relative to *n*-BuZnBr and were determined by ^{1}H NMR analysis of the crude reaction mixture using mesitylene as an internal standard. [c] Ratios of **2**:**3** were determined by ^{1}H NMR analysis.

once again observed (Table 2, entry 1). However, in the case of dichlorobenzene **1l** (entry 2) and ditriflate **1m** (entry 3) "normal" selectivity for the monobutylated product is restored. This is reasonable since significantly higher activation barriers are associated with oxidative addition to Ar−Cl and Ar−OTf bonds, and this increase in barrier height could be expected to turn the diffusive separation of Pd^0 species **I** and the product of reductive elimination (Scheme 3) into the preferred pathway.

In conclusion, we have observed the extremely selective polyfunctionalization of polybromo aromatic compounds mediated by PEPPSI-IPr which appears to be the result of the diffusion controlled reactivity of the Pd^0 produced during reductive elimination. Despite this high reactivity the system still exhibits activation controlled behavior in the initial encounter of Pd^0 with the substrate in bulk solution leading us to propose that these Pd^0 species displaying distinctly different reactivity are distinct entities. Although we have yet to identify the origin of this duality of behavior, one possibility is deactivation of the unicoordinate Pd^0−NHC species (**I**) produced during reductive elimination by recoordination of the "throwaway" pyridine ligand to give a less reactive dicoordinate Pd^0 species (**II**).[15] Our results suggest that PEPPSI-IPr mediated polycondensations can be expected to proceed by a catalyst-transfer chain-growth mechanism with concomitant benefits in terms of product control. Despite the success of phosphine supported catalysts in metal mediated polycondensations[16] drawbacks have been documented.[7] Based on our results we propose that PEPPSI-type catalysts have significant potential benefits in the synthesis of functional polymers including the reduction in catalyst loading, the potential to mount the kinetically stable Pd−NHC unit on solid support,[17] and the addition of sp^3−sp^2 and sp^3−sp^3 coupling procedures, in which PEPPSI-IPr is particularly competent, to the polymer chemists tool box.

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Supporting Information Available: Detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1027283

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(12) An alternative explanation in which diffusion controlled, irreversible recapture of the Pd^0 through π-complex formation by the product following reductive elimination but prior to oxidative addition is qualitatively different but functionally equivalent to diffusion controlled oxidative addition as we propose, and these pathways cannot be differentiated here.

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(14) The reaction between 1,4-dibromobenzene and *n*-heptylzincbromide gave the same outcome as that reported in Scheme 1 for *n*-BuZnBr.

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