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Electronic Nature of N-Heterocyclic Carbene Ligands: Effect on the Suzuki Reaction

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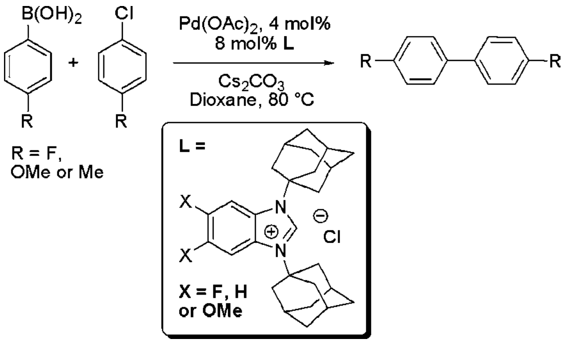
ABSTRACT



Suzuki reactions of aryl chlorides and arylboronic acids with a range of electronically different N-heterocyclic carbene ligands derived from *N*,*N*-diadamantylbenzimidazolium salts are reported. Results indicate that an electron-rich NHC ligand enhances the rate of oxidative addition. However, reductive elimination is unchanged by the electronic nature of the supporting ligand and is primarily affected by the steric environment.

The coupling reaction of organoboron derivatives with aryl-, vinyl-, or alkyl halides, named the Suzuki[1] reaction, has emerged as one of the most important carbon−carbon bond-forming methods in the synthesis of pharmaceutical agents, organic materials, and natural products.[2] The activation of unreactive substrates such as chloroarenes has only recently become reality with the advent of bulky, electron-rich phosphines, introduced by the groups of Beller,[3] Buchwald,[4] and Fu.[5]

In recent years, N-heterocyclic carbenes (NHCs) have emerged as alternatives to phosphines as ligands for a variety of transition metal-catalyzed cross-coupling reactions, including the Suzuki reaction.[6] However, only very recently have NHC ligands reached a level of activity comparable with that of phosphines.[7]

Caddick, Cloke et al. recently published a Suzuki reaction of aryl chlorides with a Pd−NHC catalyst based on the bulky *N*,*N*-di-(2,6-diisopropylphenyl)-imidazoylidene ligand (IPr, **1**, Figure 1) at 40 °C using tetra-*n*-butylammonium bromide as a cocatalyst.[8] Nolan et al. reported an air-stable palladium complex of ligand **1** that coupled aryl chlorides, but high

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[1] Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437.

[2] *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002.

[3] (a) Audreu, M. G.; Zapf, A.; Beller, M. *Chem. Commun.* **2000**, 2475. (b) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153.

[4] (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004,** 43, 1871. (b) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2642. (c) Parrish, C. A.; Buchwald, S. L. *J. Org. Chem.* **2001**, *66*, 3820. (d) Yin, J.; Rainka, M. P.; Zhang, X.-X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1162. (e) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722.

[5] Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *17*, 3387.

[6] Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.

[7] Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201.

[8] Arentsen, K.; Caddick, S.; Cloke, F. G. N.; Herring, A. P.; Hitchcock, P. B. *Tetrahedron Lett.* **2004**, *45*, 3511.

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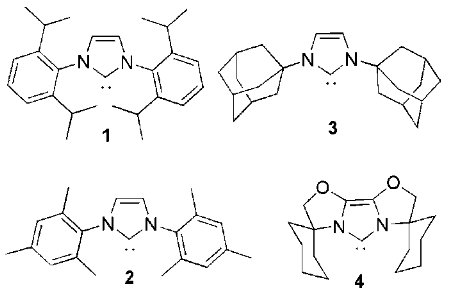
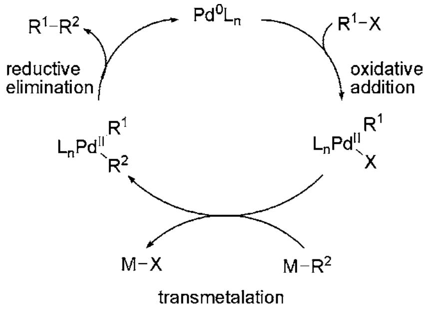


Figure 1. Active NHC ligands for the Suzuki reaction.

Scheme 1. Accepted Mechanism for Palladium-Catalyzed Cross-Coupling Reactions



temperatures were required to achieve acceptable yields.[9] Lebel et al. found that *N*,*N*-di-(2,4,6-trimethylphenyl)-imidazoylidene (IMes, **2**) also functioned as an effective supporting ligand, but again elevated temperatures were required.[10]

Herrmann et al. reported the use of *N*,*N*-diadamantylimidazoylidene (IAd, **3**) in Suzuki reactions at room temperature with aryl chlorides, although ortho-substitued chloroarenes failed to couple.[11] The admantyl groups in IAd are extremely sterically demanding and are believed to be responsible for its activity. Glorius and co-workers similarly reported a Suzuki reaction of aryl chlorides at ambient temperature,[12] including ortho-substituted aryl chlorides and arylboronic acids, with the pentacyclic carbene **4**; the activity of this ligand was attributed to *flexible steric bulk*.

Thus, the recurrent theme in NHC ligand design has been to adjust the steric environment around the metal center. The electronic nature of the carbene ligand and how it might affect the overall performance of the Pd−NHC catalyst has received almost no attention at all. Batey et al. reported a single example of an NHC-carbene bearing an electron-withdrawing carbonyl substituent on the ring nitrogen atom; a Pd complex of this carbene was shown to be a competent catalyst in the Sonogashira reaction.[13] However, no mechanistic studies or comparison with similar ligands have appeared as yet. Moreover, investigations of the electronic properties of the central palladium atom, which is ultimately responsible for the chemistry taking place, are virtually nonexistent for the Pd−NHC catalysts.

The accepted mechanism for Pd-catalyzed cross-coupling reactions (Scheme 1) involves three discrete steps: oxidative addition, transmetalation, and finally reductive elimination. For facile oxidative insertion into the strong carbon−chlorine bond of aryl chlorides, an electron-rich ligand is needed. Whether the active species for this step is a mono- or diligated palladium complex is still under debate.[14] The steric bulk of the ligand is believed to aid the reductive elimination of the product concomitant with the regeneration of the catalyst; however, if the ligand is too sterically demanding, the rate of oxidative addition can be adversely affected.[14b]

It is clear that a subtle balance between steric and electronic factors has to be achieved for a highly active catalyst system to be created.

In an attempt to provide an answer to the role of electronic effects in Pd−NHC-mediated couplings, we decided to synthesize a range of NHC ligands (Figure 2) and explore their activity in Suzuki couplings of aryl chlorides.

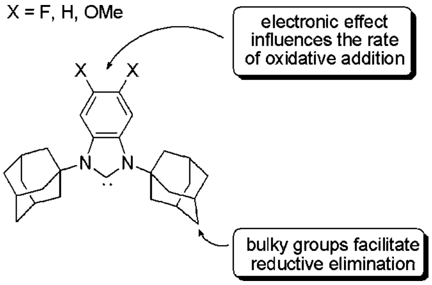


Figure 2. Proposed tunable benzimidazolidine NHC ligands.

Even though benzimidazolidines have received scant attention as NHC ligands,[15] they provide a suitable platform for tuning the electron density on the carbene carbon. Introducing electronically different substituents at positions 5 and 6 would remotely alter the electronic character of the palladium metal center without any steric interference from the substituent itself. At the same time, the presence of *N*-adamantyl groups ensures the required steric bulk for facile reductive elimination is in place.

Synthesis of the NHC precursor benzimidazolium salts followed a protocol developed by Diver and co-workers.[16] A Buchwald−Hartwig amination of the required 1,2-dibromoarene (**5**−**7**) with excess 1-adamantylamine and sodium *tert*-butoxide followed by cyclization with ethyl orthofor-

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[9] Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 3171.

[10] Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046.

[11] Gstöttmayr, C. W. K.; Böhm, V. P. W.; Herdtweck, E.; Grosche, M.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1363.

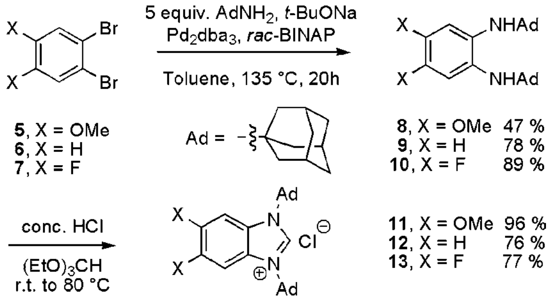
[12] (a) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690. (b) Altenhoff, G.; Goddard, R.; Lehmann, C.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15196.

[13] Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411.

[14] (a) Christmann, U.; Vilar, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 366. (b) Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 5749.

[15] (a) Metallinos, C.; Barrett, F. B.; Chaytor, J. L.; Heska, M. E. A. *Org. Lett.* **2004**, *6*, 3641. (b) Perry, M. C.; Burgess, K. *Tetrahedron: Asymmetry* **2003**, *14*, 951.

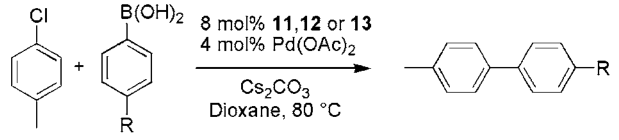
Scheme 2. Benzimdazolium Salt Synthesis

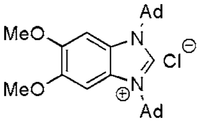
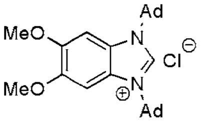
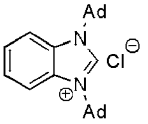
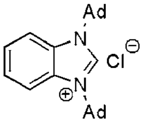
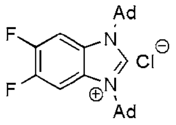
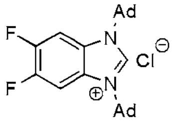


mate/HCl yielded the benzimidazolium chlorides (**11**−**13**) in good yields in two steps (Scheme 2).

With the salts **11**−**13** in hand, we submitted them to the Suzuki reaction using conditions developed by Lebel.[10] First, we were interested in whether there would be a difference in reactivity when 4-chlorotoluene was coupled with electron-rich and electron-deficient boronic acids (Table 1). Results suggest that the transmetalation and reductive elimination steps are unaffected by the electronic nature of the carbene ligand. Electron-deficient ligands are believed to accelerate the reductive elimination step.[2] However, reactions conducted with the most electron-deficient ligand **13** consistently yielded the lowest amount of product, while the most electron-rich ligand **11** was found to give the highest yields. These results indirectly corroborate the theory that the reductive elimination step is primarily governed by the steric nature of the NHC ligand.

Table 1. Suzuki Cross-Coupling Reactions with Electronically Different Boronic Acids[a]

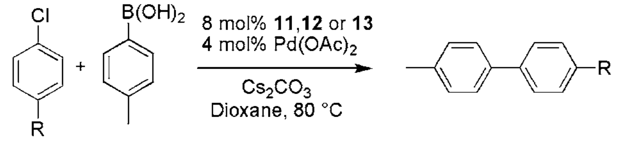


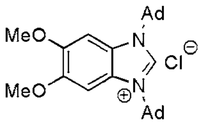
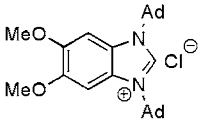
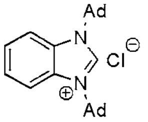
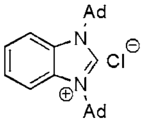
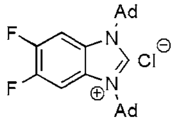
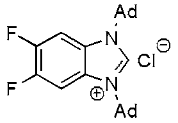
entry	ligand	R	yield (%)[b]
1		OMe	94
2		F	91
3		OMe	100 (98)
4		F	76
5		OMe	72
6		F	81

[a] Reaction conditions: 0.5 mmol of 4-chlorotoluene, 0.75 mmol of arylboronic acid, 1 mmol of Cs_2CO_3, in duplicate. [b] GC yield against a calibrated internal standard (undecane). Isolated yields in parentheses.

Next, we investigated whether the electronic nature of the aryl halide had an effect on the cross-coupling reaction with ligands **11**−**13**. The results (Table 2) demonstrate that ligand **11**, the most electron rich, yielded the most cross-coupling product, followed, respectively, by **12** and **13**, the most electron deficient.

Table 2. Suzuki Cross-Coupling Reactions with Electronically Different Aryl Chlorides[a]



entry	ligand	R	yield (%)[b]
1		OMe	83
2		F	100 (97)
3		OMe	72
4		F	100
5		OMe	53
6		F	89

[a] Reaction conditions: 0.5 mmol of aryl chloride, 0.75 mmol of p-tolyl boronic acid, 1 mmol of Cs_2CO_3, in duplicate. [b] GC yield against calibrated internal standard (undecane). Isolated yields in parentheses.

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(16) (a) Rivas, F. M.; Riaz, U.; Diver, S. T. *Tetrahedron: Asymmetry* **2000**, *11*, 1703. (b) Rivas, F. M.; Riaz, U.; Giessert, A.; Smulik, J. A.; Diver, S. T. *Org. Lett.* **2001**, *3*, 2673.

Assuming that oxidative addition is the rate-determining step and its rate is increased by an electron-rich metal center,[2] these results can be explained by assuming that rate of oxidative addition of the palladium complexes is in the order **11** > **12** > **13**, which is in agreement with the current mechanistic theories detailed above.

In conclusion, the studies on the Pd−NHC-catalyzed Suzuki reaction presented here help further clarify the mechanistic picture of the overall process. The oxidative addition is primarily affected by the electronic nature of the palladium metal center, while the reductive elimination step is not unduly affected by the electronic nature of the supporting ligand but by the steric environment it imparts.

These results imply that NHC ligand design should focus on creating an electron-rich carbene ligand with a carefully selected steric environment. The topography created by the neighboring N-substituents must not retard the oxidative addition but be sufficient to ensure rapid elimination of the product and thus turnover of the catalysts.[17]

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Note Added after ASAP Publication. Erroneous values were listed for the isolated yields of 4-methyl-4′-methoxybiphenyl and 4-fluoro-4′-methylbiphenyl in the Supporting Information (p S6) published ASAP April 9, 2005; the corrected version was published April 13, 2005.

Supporting Information Available: Procedures for the preparation and full characterization of compounds **8**−**13** and a representive procedure for the coupling reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] We are currently involved in computation studies that we hope will allow rationale design of the NHC carbene ligand. These studies will be published in due course.