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Suzuki−Miyaura Coupling of NHC−Boranes: A New Addition to the C−C Coupling Toolbox

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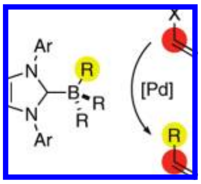
ABSTRACT



Complexes of triaryl- and trialkylboranes with N-heterocyclic carbenes (NHCs) participate in Suzuki−Miyaura cross-coupling reactions and provide coupled products in good yields under base-free conditions. The reaction can be applied to Csp^2−Csp^2 and Csp^2−Csp^3 carbon−carbon bond formation with triflates, iodides, bromides, and chlorides. These results enrich the utility of NHC−borane complexes, which can be added to the toolkit of Suzuki−Miyaura cross-couplings, along with boronic acids and organotrifluoroborates.

Lewis acidic main group elements form Lewis pairs with N-heterocyclic carbenes (NHCs).[1] This offers important opportunities to discover new chemistry of main group elements like boron. Yet, NHC−borane chemistry remains largely unexplored.[2] The importance of boron reagents in organic chemistry[3] encourages closer examination of these structurally attractive compounds.

Tamm[2b] and Stephan[2c] showed that combining bulky borane and NHC components leads to frustrated Lewis pairs that activate hydrogen and ammonia. In contrast, NHC complexes of borane (NHC−BH_3) are very stable compounds. We recently showed that they reduce xanthates through a radical mechanism[4] and halides and sulfonates through ionic or organometallic mechanisms.[5]

In the organometallic transformations, the hydride in NHC−boranes was presumably transferred to palladium.[5]

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(1) (a) Arduengo, A. J., III.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361–363. (b) Herrmann, W. A.; Köcher, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2162–2187. (c) Bourissou, D.; Guerret, O.; Gabbaï, F.; Bertrand, G. *Chem. Rev.* **2000**, *100*, 39–91.

(2) (a) Wang, Y.; Quillian, B.; Wei, P.; Wannere, C. S.; Xie, Y.; King, R. B.; Schaefer, H. F., III.; Schleyer, P. v. R.; Robinson, G. H. *J. Am. Chem. Soc.* **2007**, *129*, 12412–12413. (b) Holschumacher, D.; Bannenberg, T.; Hrib, C. G.; Jones, P. G.; Tamm, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7428–7432. (c) Chase, P. A.; Stephan, D. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7433–7437. (d) Lee, K. S.; Zhugralin, A. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 7253–7255. (e) Wood, T. K.; Piers, W. E.; Keay, B. A.; Parvez, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4009–4012. (f) Matsumoto, T.; Gabbaï, F. P. *Organometallics* **2009**, *28*, 4252–4253.

(3) *Science of Synthesis Organometallics: Boron Compounds*; Kaufmann, D. E., Matteson, D. S., Eds.; Georg Thieme Verlag: Stuttgart-New York, 2004; Vol. 6.

(4) (a) Ueng, S.-H.; Makhlouf Brahmi, M.; Derat, E.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Curran, D. P. *J. Am. Chem. Soc.* **2008**, *130*, 10082–10083. (b) Walton, J. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 1726–1728. (c) Ueng, S.-H.; Solovyev, A.; Yuan, X.; Geib, S. J.; Fensterbank, L.; Lacôte, E.; Malacria, M.; Newcomb, M.; Walton, J. C.; Curran, D. P. *J. Am. Chem. Soc.* **2009**, *131*, 11256–11262.

(5) Chu, Q.; Makhlouf Brahmi, M.; Solovyev, A.; Ueng, S.-H.; Curran, D. P.; Malacria, M.; Fensterbank, L.; Lacôte, E. *Chem.−Eur. J.* **2009**, accepted for publication.

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On the basis of this, we hypothesized that boron−carbon bonds could also be activated by NHC complexation.[6]

Here we report that stable complexes of the common NHC bis-2,6-diisopropylphenyl imidazolylidinene (IPr) with BPh_3 and BEt_3 participate in base-free Suzuki−Miyaura couplings.[7] The findings significantly extend the potential uses of NHC−boranes in organic synthesis; they are in effect a new class of boron reagents amenable to Pd-catalyzed couplings. As such, they complement boranes, boronic acids, and organotrifluoroborates.[8]

To start, we selected complexes **1** and **2** because they were readily available and stable (Figure 1). Triphenyl derivative **1** was chosen to assess aryl−aryl coupling, while triethyl derivative **2** was selected to illustrate alkyl−aryl couplings.

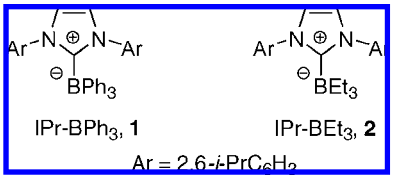


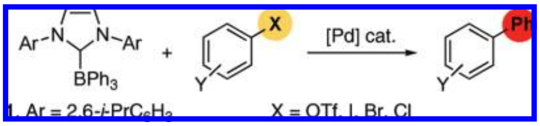
Figure 1. Structures of NHC−borane complexes used in this work with formal charges indicated.

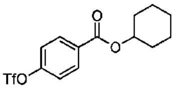
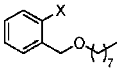
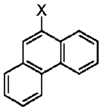
The reagents were assembled by deprotonation of the corresponding imidazolium hydrochloride salt to generate the IPr carbene,[9] followed by addition of the boranes (see Supporting Information). Complexation of the boranes to the carbene was evidenced by large upfield shifts in the ^{11}B NMR spectra (from 86 ppm in BPh_3 to −0.9 ppm in **1** and from 70 ppm in BEt_3 to −13.2 ppm in **2**).

The palladium-catalyzed sp^2−sp^2 C−C couplings with IPr−borane **1** are summarized in Table 1. In a typical experiment, the triflate of cyclohexyl 4-hydroxybenzoate was heated at 60 °C in wet THF together with 6 mol % of $PdCl_2(dppf)$ for 1 h. Full conversion to the corresponding biaryl was achieved (Table 1, entry 1). Wet solvents (10% vol.) were required to ensure reproducible results. In addition, no base was required for the reaction, in contrast to the usual Suzuki−Miyaura conditions.

A control experiment with uncomplexed BPh_3 showed that no reaction took place under the same conditions (entry 2). Clearly, the carbene plays a crucial role. In addition, no reaction occurred when the catalyst was omitted (entry 3).

Table 1. Results for sp^2−sp^2 Coupling: Aryl Transfer



entry	RX	equiv	K_2CO_3 (equiv)	yield (%)
1		1[a]	-	>99
2		1[a,b]	-	S. M.
3		1[c]	-	S. M.
4		0.34[a]	3	96
5	 I[d]	1	-	80
6		0.34	3	71
7	Br[e]	1	-	>99
8		0.34	3	60
9	Cl[f]	1	-	81
10		0.34	3	54
11	 I[d]	1	-	66
12		0.34	3	63
13	Br[e]	1	-	85
14		0.34	3	64
15	Cl[f]	1	-	90
16		0.34	3	80

[a] Conditions: $PdCl_2(dppf)$ (6 mol %), THF−H_2O, 60 °C, 1 h. [b] Reaction was run with BPh_3 instead of **1**. [c] No palladium complex was added. [d] Conditions: $PdCl_2(dppf)$ (6 mol %), THF−H_2O, 60 °C, 8 h. [e] Conditions: $Pd(OAc)_2$ (5 mol %), XPhos (10 mol %), toluene−H_2O (10:1), 80 °C, 24 h. [f] Conditions: $Pd(OAc)_2$ (10 mol %), RuPhos (20 mol %), toluene−H_2O (10:1), 80 °C, 24 h.

We next investigated the possibility of transferring more than one phenyl group from **1**. Reaction of 0.34 equiv of **1** with the triflate of cyclohexyl 4-hydroxybenzoate in the absence of base did not give coupled product in high yield. However, the yield increased to 96% when 3 equiv of K_2CO_3 was added (entry 4).

Iodides (entries 5−6 and 11−12), bromides (entries 7−8 and 13−14), and chlorides (entries 9−10 and 15−16) were also suitable partners for cross coupling. For Br and Cl, we used the preferred ligands for Suzuki−Miyaura couplings (XPhos[10] for Br and RuPhos[11] for Cl). In each case, a single phenyl group was transferred in good yield without base, and all three phenyl groups were transferred when base was added.

To extend the method to sp^2−sp^3 couplings, we probed the transfer of ethyl groups from triethylborane complex **2** (IPr−BEt_3) with triflates and halides. These results are summarized in Table 2.

Reactions with triflates were carried out in wet toluene at 80 °C with $Pd(OAc)_2$/XPhos (Table 2, entries 1−2, conditions A). 2-Iodobenzyl heptyl ether gave the expected coupling product in 65% yield with $PdCl_2(dppf)$ (Conditions

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(6) For an NHC-activated opening of oxiranes by organoaluminum reagents, see: Zhou, H.; Campbell, E. J.; Nguyen, S. T. *Org. Lett.* **2001**, *3*, 2229–2231.

(7) (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568.

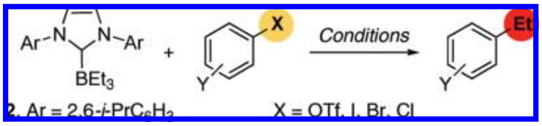
(8) Organotrifluoroborates are more stable than boronic acids but are believed to hydrolyze to the boronates under the coupling conditions. See: (a) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275–286. (b) Darses, S.; Genêt, J.-P. *Chem. Rev.* **2008**, *108*, 288–325. For another approach using modified boronic acids, see: (c) Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2007**, *129*, 6716–6717. (d) Knapp, D. M.; Gillis, E. P.; Burke, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 6961–6963. (e) Yamamoto, Y.; Takizawa, M.; Yu, X.-Q.; Miyaura, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 928–931.

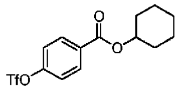
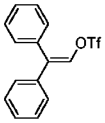
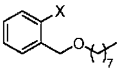
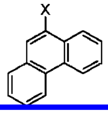
(9) IPr is commercially available. Nonetheless, the IPr used in this work was prepared in our laboratories.

(10) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653–6655.

(11) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028–13032.

Table 2. Results for sp^2-sp^3 Coupling: Ethyl Transfer under Base-Free Conditions



entry	substrate		conditions[a]	yield (%)
1			A	99
2			A	99
3		I	B	65[b]
4		I	C	83[b]
5		Br	A	97
6		Br	D	94
7		Cl	E	90
8		Cl	F	76
9		I	B	83
10		Br	A	87
11		Cl	F	99

[a] Conditions (1 equiv of **2** was used). A: $Pd(OAc)_2$ (5 mol %), XPhos (10 mol %), toluene−H_2O (10:1), 80 °C, 24 h. B: $PdCl_2(dppf)$ (6 mol %), THF−H_2O, 60 °C, 8 h. C: $PdCl_2(dppf)$ (6 mol %), THF−H_2O, MW, 110 °C, 15 min. D: $Pd(OAc)_2$ (5 mol %), XPhos (10 mol %), toluene−H_2O (10:1), MW, 140 °C, 30 min. E: $Pd(OAc)_2$ (10 mol %), RuPhos (20 mol %), toluene−H_2O (10:1), 80 °C, 24 h. F: $Pd(OAc)_2$ (10 mol %), RuPhos (20 mol %), toluene−H_2O (10:1), MW, 140 °C, 30 min. [b] NMR yield. Remaining starting material could not be separated from product.

B, entry 3), while iodo-phenanthrene gave 83% of the desired biaryl (entry 9). Microwave heating could also be employed, slightly improving the yield obtained from the ether-substituted aryl iodide (Conditions C, entry 4).

Coupling of the bromide substrates required switching to the more active $Pd(OAc)_2$/XPhos ligand system (Conditions A and D, entries 5−6 and 10), while $Pd(OAc)_2$/RuPhos was used for the chloride (Conditions E and F, entries 7−8 and 11). Overall, microwave heating gave similar yield to conventional heating, yet the reaction times were considerably shortened.

As before, all reactions worked under base-free conditions. In contrast, proton NMR spectra of a crude product suggested that no more than one ethyl group per carbene complex **2** was transferred.[12]

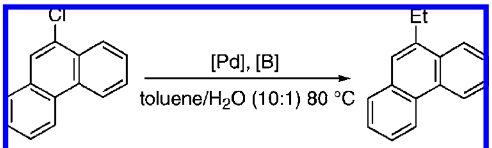
These new results raise two mechanistic issues in the context of the accepted mechanisms for the Suzuki−Miyaura reaction: (1) why is the base sometimes not needed? And (2) is the carbene−boron bond inert, or is the carbene instead transferred to palladium to form an active NHC−Pd catalyst?

Inorganic bases are thought to play a key part in Suzuki couplings by promoting the transmetalation step via the ate complexes directly from the boron reagent or after formation of an oxo-Pd species.[13] The boron atoms in **1** and **2** are already tetravalent and sp^3-hybridized. Though neutral, these complexes have a formal negative charge on boron, just like ate complexes. So we speculate that the first aryl or alkyl group transmetalates directly from these complexes to palladium. In support of this, control experiments showed that both complexes are inert to heating at reflux in toluene with water and base.

The boron product of the first Suzuki coupling is presumably IPr−BR_2X, where X is halogen or OTf. We have isolated related complexes where R = H,[5] and we know that they are not stable to heating with water. From this, we can speculate that base and water convert the first-formed boron product to IPr−BR_2OH. In the complex where R = Ph, this intermediate might provoke transfer of a second phenyl group and later a third (perhaps via IPr−$BPh(OH)_2$).

Nolan has introduced NHCs as ligands for Suzuki−Miyaura couplings of difficult substrates.[14] Thus, we wondered whether a *carbene* exchange from boron to palladium was essential to the reactivity.

Scheme 1. Probing the Role of the NHC−Borane with 9-Chlorophenanthrene



entry	[Pd]	[B]	result
1	**IPr**$Pd(OAc)_2$	**IPr**-BEt_3 **2**	90% prod
2	**IPr**$Pd(OAc)_2$	BEt_3	12% prod
3	$Pd(OAc)_2$	**IPr**-BEt_3 **2**	73% prod
4	$Pd(OAc)_2$	BEt_3/K_2CO_3	90% S. M.

To assess this issue further, the behavior of 9-chlorophenanthrene was examined in more detail (Scheme 1). The reaction of independently prepared IPr•$Pd(OAc)_2$[15] and NHC−borane **2** without base in a 10:1 toluene−water mixture at 80 °C gave 9-ethylphenanthrene in 90% yield (entry 1). When the boron reagent was switched to triethylborane, the yield of 9-ethylphenanthrene dropped sharply to 12%, and much of the starting chloride was recovered

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(12) We rapidly screened other carbene−borane complexes. Triazole-derived NHC−boranes failed to give any conversion with the aryl bromide. A benzimidazole carbene gave only 21% of desired product after one day (61% recovered S. M.), where the more sterically demanding **2** gave 97% yield under the same conditions (Table 2, entry 4). It appears from this preliminary survey that a good balance between steric hindrance and electronic effects on the NHC is critical to the reaction.

(13) Tsuji, J. *Palladium Reagents and Catalysts*, 2nd ed.; John Wiley & Sons: Chichester, 2004; pp 288−312 and references cited therein. (b) Braga, A. A. C.; Morgon, N. H.; Ujaque, G.; Maseras, F. *J. Am. Chem. Soc.* **2005**, *127*, 9298–9307. (c) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461–470.

(14) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440–1449.

(15) Viciu, M. S.; Stevens, E. D.; Petersen, J. L.; Nolan, S. P. *Organometallics* **2004**, *23*, 3752–3755.

(entry 2). A similar reaction with $Pd(OAc)_2$ and NHC−borane **2** delivered 73% of the coupled product (entry 3). Finally, a control experiment with $Pd(OAc)_2$ and Et_3B with base essentially led to recovered starting material (entry 4).

Suzuki−Miyaura couplings with aryl chlorides occur in high yields only if activating ligands are used to accelerate the otherwise slow oxidative addition step.[16] Indeed, the control experiment in entry 4 confirms that the activating IPr ligand is essential. In comparing the other permutations, the IPr ligand is optionally present on the palladium (compare entries 1 and 3) but must be present on the boron (compare entry 2 with entries 1 and 3).[17]

The successful coupling in entry 3 is an especially interesting result because the catalyst was not introduced with an activating ligand. This suggests that some of the IPr ligand migrated from boron to palladium to provide an active catalyst for insertion that is similar or identical to the catalyst in entry 1.

In conclusion, NHC−boron complexes are efficient nucleophilic transmetalating partners which should be added to the toolkit of Suzuki−Miyaura cross couplings, along with boronic acids and organotrifluoroborates. Finally, the present report extends the scope of NHC−borane reactivity. The door is open for their further use in other ionic C−C bond forming processes.

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

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(16) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., de Meijere, A., Eds.; Wiley Interscience: New York, 2002; Vol. 1, p 132.

(17) The little conversion we observed with Et_3B and $(IPr)Pd(OAc)_2$ may be due to some addition of water or acetate to triethylborane, but this ground reaction is not an efficient enough process to explain the high yields observed when NHC−boranes were employed.