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Nickel-Catalyzed Efficient and Practical Suzuki−Miyaura Coupling of Alkenyl and Aryl Carbamates with Aryl Boroxines

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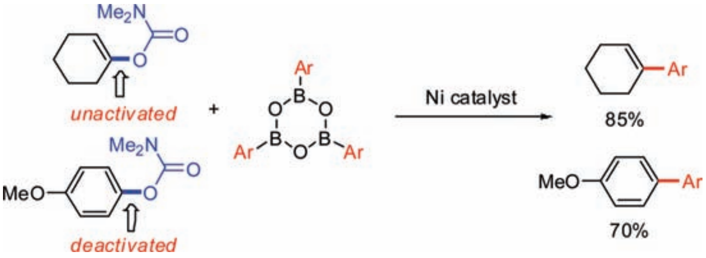
ABSTRACT



Suzuki−Miyaura coupling of unactivated alkenyl carbamates is described to construct polysubstituted olefins. The developed process is also suitable for heteroaromatic and even electron-rich aromatic carbamates.

Suzuki−Miyaura coupling has become one of the most versatile synthetic methods in organic synthesis.[1] The easy availability of boron reagents, broad functional group tolerance, and general applicability of the reaction contributed to its increasing importance in both academic research and industrial production.[2] In the past several decades, significant efforts have been made in catalyst/ligand development, thus expanding the coupling partner from aryl iodide/bromide and triflate to relatively unreactive aryl chloride and tosylate/mesylate.[3] In this context, the identification of a new coupling partner would have significant impact on Suzuki−Miyaura coupling.[4]

Aryl carboxylates, derived from phenols, appeared to be particularly appealing since they are abundant and easily available. Recently, Garg's group and our group have independently developed the nickel-catalyzed Suzuki−Miyaura coupling of aryl carboxylates.[5] The substrate scope of this type of Suzuki−Miyaura coupling could be further extended to activated vinyl acetates.[6] Despite these significant advances, the full potential of this reaction has not been

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(2) (a) Buchwald, S. L.; Martin, R. *Acc. Chem. Res.* **2008**, *41*, 1461. (b) Würtz, S.; Glorius, F. *Acc. Chem. Res.* **2008**, *41*, 1523. (c) Molander, G. A.; Ellis, N. *Acc. Chem. Res.* **2007**, *40*, 275. (d) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240. (e) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (f) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 3565.

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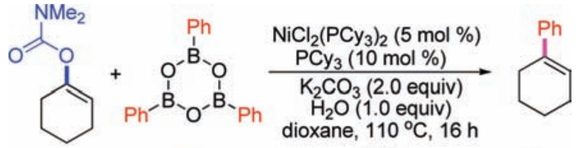
exploited since it suffered from several limitations. First, the catalyst loading was usually high. Second, specific substrates such as naphthyl, activated phenyl, and styryl carboxylates were required to obtain satisfactory results.[5] Unactivated aromatic carboxylate reacted poorly, while vinylic carboxylate has not even been reported to undergo successful reaction by nickel catalysis.[5,6] Thus, we set out to address these issues to make this chemistry more practical. In our continuing efforts in C−O bond activation, we report here the nickel-catalyzed Suzuki−Miyaura coupling of both unactivated alkenyl and phenyl carbamates.[7] The use of carbamate as a protecting group provided further synthetic opportunity due to its well-known ability in directed ortho metalation (DoM) pioneered by Snieckus.[8]

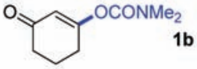
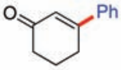
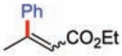
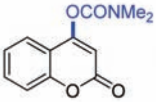
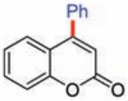
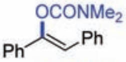
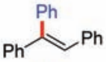
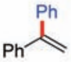
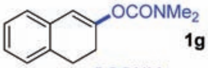
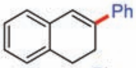
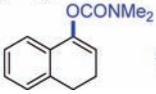
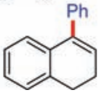
Scheme 1. Cross-Coupling of Unactivated Vinyl Carbamate



1a **2a** 85% **3a**

We initially chose the unactivated alkenyl carboxylate as the substrate, which was readily available and synthetically useful. 1-Cyclohexenyl acetate was first applied to Suzuki−Miyaura coupling. Unfortunately, the desired C−C formation completely failed, with most of the cyclohexanone recovered. Other carboxylates were tested but failed. To our surprise, a change of the protecting group to carbamate resulted in a remarkable improvement of efficiency.[8b,c] *N*,*N*-Dimethyl cyclohexenyl carbamate **1a** engaged in the coupling reaction in a good yield. Further systematic studies indicated that the coupling between carbamate **1a** and phenyl boroxine **2a** ran very smoothly in the presence of $Ni(PCy_3)_2Cl_2$ (5.0 mol %) and PCy_3 (10.0 mol %) as a catalyst, K_2CO_3 (2.0 equiv) as a base, and an adequate amount of water as an additive. The arylated product **3a** was isolated in 85% yield (Scheme 1). This is the first successful example to construct such an arylated olefin from unactivated alkenyl carbamates.

Table 1. Cross-Coupling between **1** and Phenyl Boroxines[a]

entry	Ar-OCONMe2		product		yield(%)
1		**1b**		**3b**	80
2		**1c**		**3c**	67[b]
3		**1d**		**3d**	90
4		**1e**		**3e**	85
5		**1f**		**3f**	79
6		**1g**		**3g**	92
7		**1h**		**3h**	93

[a] All the reactions were carried out on the scale of 0.25 mmol of **1**, 0.30 mmol of **2a**, 0.0125 mmol of $Ni(PCy_3)_2Cl_2$, 0.025 mmol of PCy_3, 0.50 mmol of K_2CO_3, and 0.25 mmol of H_2O in 5 mL of dioxane at 110 °C for 16 h. [b] *E*:*Z* = 5:1.

To explore the substrate scope, we investigated different alkenyl carbamates. Obviously, starting from activated α,β-unsaturated cyclic ketone **1b**, the desired cross-coupling product was afforded in an excellent yield. Both linear and cyclic α,β-unsaturated esters **1c** and **1d** were also suitable substrates, and the desired arylated products **3c** and **3d** were isolated in good to excellent yields (Table 1). Both 1-stilbenyl carbamate **1e** and 1-styryl carbamate **1f** were further submitted, and the corresponding cross-coupling also occurred smoothly. It is important to note that, unlike vinyl acetates, both carbamates located at the 1- or 2-position of the styrene

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(3) (a) Bohm, V. P. W.; Weskamp, T.; Gstottmayr, C. W. K.; Herrmann, W. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1602. (b) Herrmann, W. A.; Elison, M.; Fischer, J.; Kocher, C. G.; Artus, R. J. *Angew. Chem., Int. Ed.* **1995**, *34*, 2371. (c) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (d) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473. (e) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (f) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (g) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818. (h) Tang, Z.-Y.; Hu, Q.-S. *J. Am. Chem. Soc.* **2004**, *126*, 3058. (i) So, C. M.; Lau, C. P.; Kwong, F. Y. *Angew. Chem., Int. Ed.* **2008**, *47*, 8059. (j) Zhang, L.; Wu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12250. (k) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619. (l) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 4114. (m) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440.

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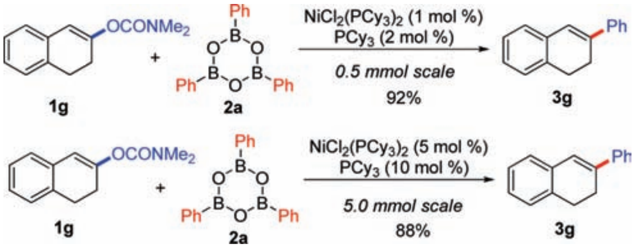
(7) During the preparation of this manuscript, contributions from the groups of Garg and Snieckus appeared: (a) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748. (b) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750.

(8) (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (b) Sengupta, S.; Leite, M.; Raslan, D. S.; Quesnelle, C.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 4066. (c) Yoshikai, N.; Matsuda, H.; Nakamura, E. *J. Am. Chem. Soc.* **2009**, *131*, 9590.

Scheme 2. Cross-Coupling at Lower Catalyst Loading and Larger Scale



derivatives are suitable substrates.[6] Notably, such cross-coupling took place well in the presence of 1.0 mol % of catalyst loading without a decrease in the efficiency (Scheme 2). To explore the application of such transformations, this cross-coupling was scaled up to 5.0 mmol without a decrease of the efficiency.

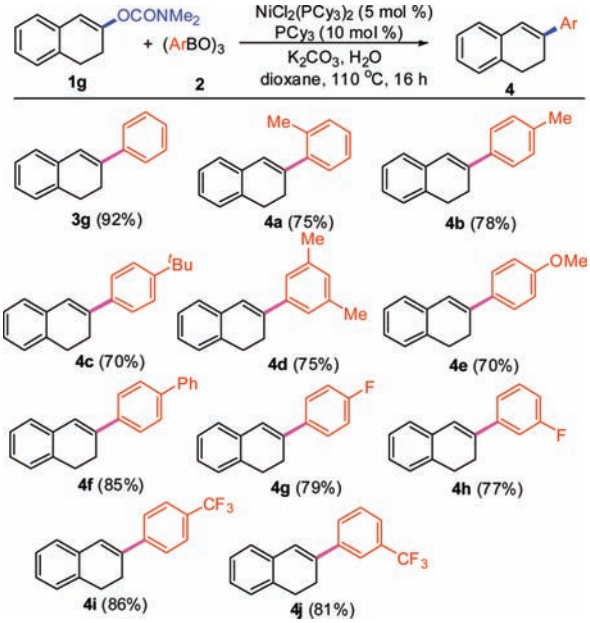


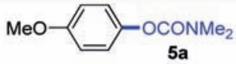
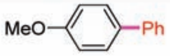
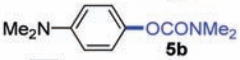
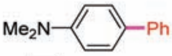
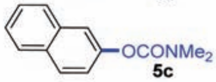
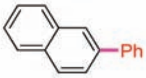
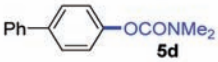
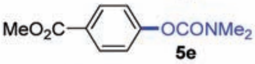
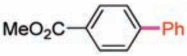
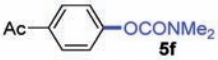
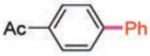
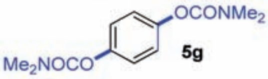
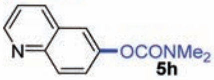
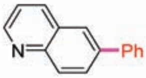
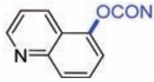
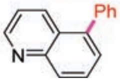
Figure 1. Ni-catalyzed coupling products of various boroxines **2**.

The reactions of different substituted aryl boroxines with slightly unreactive alkenyl carbamate **1g** were subsequently investigated (Figure 1). Sterically hindered *ortho*-methyl phenyl boroxine did not affect the yield. Electron-withdrawing and electron-donating groups on the phenyl boroxine had no impact on the efficiencies. Various functional groups such as methoxy and fluoro groups were compatible with such mild conditions, which provided an opportunity for further functionalization of the products with various methods.[4,9]

With this developed efficient method, we further investigated the electron-rich aromatic system, which was more challenging in Suzuki–Miyaura coupling due to the deactivation by the electron-donating substituents (Table 2). To our satisfaction, with a carbamate as a leaving group, the cross-coupling took place smoothly with phenylboroxine as a nucleophile in good efficiency, regardless of whether a methoxyl or a *N*,*N*-dimethylamino group was equipped under our developed condition (entries 1 and 2). Undoubtedly, activated aromatic substrates such as 2-naphthyl carbamate and phenyl carbamates with electron-withdrawing groups gave better results (entries 3–6). With the *p*-resorcinol derived dicarbamate, double arylation was also observed, and terphenyl was produced in one step in good yield (entry 7). Although generally pyridinyl and quinolyl derivatives tend to deactivate the catalytic reactivity of nickel complexes, our system was also suitable for such substrates, and the desired products were produced in good yields (entries 8 and 9).

Table 2. Ni-Catalyzed Cross-Coupling of Various Aryl Carbamates **5** with **2a**[a]

$$\underset{\mathbf{5}}{\text{Ar–OCONMe}_2} + \underset{\mathbf{2a}}{(\text{PhBO})_3} \xrightarrow[\substack{K_2CO_3,\ H_2O \\ \text{dioxane, 110 °C, 16 h}}]{\substack{NiCl_2(PCy_3)_2\ (5\ mol\ \%) \\ PCy_3\ (10\ mol\ \%)}} \underset{\mathbf{6}}{\text{Ar–Ph}}$$

entry	Ar-OCONMe2	product	yield(%)
1	 **5a**		**6a** (70)
2	 **5b**		**6b** (62)
3	 **5c**		**6c** (94)
4	 **5d**		**6d** (74)
5	 **5e**		**6e** (78)
6	 **5f**		**6f** (85)
7	 **5g**		**6d** (65)
8	 **5h**		**6g** (78)
9	 **5i**		**6h** (80)

[a] All the reactions were carried out in the scale of 0.25 mmol of **5**, 0.30 mmol of **2a**, 0.0125 mmol of $Ni(PCy_3)_2Cl_2$ and 0.025 mmol of PCy_3, 0.50 mmol of K_2CO_3, and 0.25 mmol of H_2O in 5 mL of dioxane at 110 °C for 16 h.

In summary, we demonstrated the Suzuki–Miyaura coupling of alkenyl carbamates with aryl boroxines to construct polysubstituted olefins. Such cross-coupling was also suitable for even electron-rich aryl carbamates. Lower catalyst loading, easy scaling-up, and a wide range of substrate scope

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make this process applicable to produce complex molecules. Further exploration of its synthetic utility and mechanistic investigation is currently underway.

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Supporting Information Available: Brief experimental details and other spectral data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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