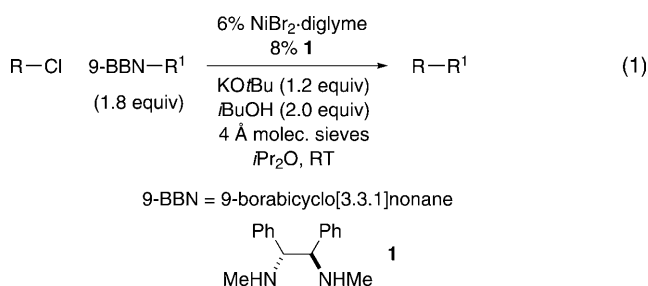


Alkyl–Alkyl Suzuki Cross-Coupling of Unactivated Secondary Alkyl Chlorides**

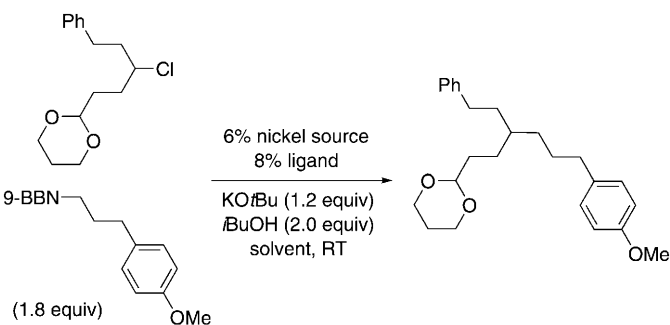
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Among cross-coupling processes that form carbon–carbon bonds, the Suzuki reaction is perhaps the most widely used, owing to considerations such as functional-group tolerance, the accessibility of organoboron coupling partners, and toxicity issues.^[1] Most early investigations of Suzuki cross-coupling focused on reactions of aryl and vinyl electrophiles. Of course, the ability to also couple a wide range of alkyl electrophiles would significantly enhance the utility of Suzuki reactions, and advances toward this goal have been described.^[2,3] Despite this progress, many classes of alkyl–alkyl Suzuki cross-coupling reactions still have not been achieved, including reactions of unactivated secondary alkyl chlorides.^[4,5] Herein, we establish that this family of electrophiles can indeed serve as suitable partners in alkyl–alkyl Suzuki coupling reactions under mild conditions through the use of an appropriate nickel catalyst [Eq. (1)].



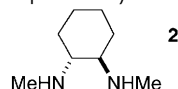
In the case of our previously described method for the alkyl–alkyl Suzuki cross-coupling of secondary bromides and iodides,^[4a] we observed that the corresponding chlorides are much less reactive. For example, the coupling illustrated in entry 1 of Table 1 proceeded in poor yield (9%) when that procedure was applied. Nevertheless, by systematically exam-

Table 1: Effect of reaction parameters on an alkyl–alkyl Suzuki cross-coupling reaction of an unactivated secondary alkyl chloride.



Entry	Nickel source	Ligand	Solvent	Yield [%] ^[a]
1	NiCl ₂ ·glyme	2	dioxane	9
2	NiBr ₂ ·diglyme	2	dioxane	14
3	NiBr ₂ ·diglyme	1	dioxane	43
4	NiBr ₂ ·diglyme	1	<i>i</i> Pr ₂ O	86

[a] Determined by GC with a calibrated internal standard (average of two experiments).



ining the various reaction parameters, we determined that the desired cross-coupling of an unactivated secondary alkyl chloride can in fact be carried out efficiently at room temperature. Specifically, by altering the nickel source (Table 1, entry 1→entry 2), the ligand (entry 2→entry 3), and the solvent (entry 3→entry 4), we developed a method that furnished the target coupling product in good yield (Table 1, entry 4: 86%). Furthermore, all of the catalyst components are commercially available.

One practical drawback of our previous procedures for alkyl–alkyl Suzuki reactions of secondary bromides/iodides^[4] was our observation that cross-coupling reactions that were set up without a glove box proceeded in lower yield than reactions conducted in a glove box. When we attempted to employ the method illustrated in entry 4 of Table 1 without a glove box, the product was also obtained in diminished yield. We hypothesized that adventitious water might be the culprit and therefore added powdered 4 Å molecular sieves to the reaction mixture. Indeed, with this modification, we obtained the Suzuki coupling product of the secondary chloride in good yield (83%) without the use of a glove box.

The scope of this new cross-coupling method is fairly broad.^[6] Both cyclic secondary alkyl chlorides (Table 2, entries 1–6), including nitrogen and oxygen heterocycles (entries 5 and 6), and acyclic secondary alkyl chlorides

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[**] Support has been provided by the National Institutes of Health (National Institute of General Medical Sciences, grant R01-GM62871), Eli Lilly (fellowship to Z.L.), the Martin Family Society of Fellows for Sustainability (fellowship to Z.L.), Merck Research Laboratories, and Novartis. We thank Dr. Bunai Saito for preliminary studies and Dr. Jeffrey H. Simpson for assistance with NMR spectroscopy.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201003272>.

Table 2: Alkyl–alkyl Suzuki cross-coupling reactions of unactivated secondary alkyl chlorides [for reaction conditions, see Equation (1)].

Entry	R–Cl	9-BBN–R ¹	Yield [%] ^[a]
1		9-BBN–CH ₂ CH ₂ Ph	80
2		9-BBN–CH ₂ CH ₂ Ph	69 ^[b]
3		9-BBN–CH ₂ CH ₂ Ph	53 ^[b]
4		9-BBN–CH ₂ CH ₂ Ph	67 ^[c]
5		9-BBN–CH ₂ CH ₂ Ph	70
6		9-BBN–CH ₂ CH ₂ Ph	71
7		9-BBN–CH ₂ CH ₂ CH ₂ Ph	72
8		9-BBN–CH ₂ CH ₂ CH ₂ OTBS	64
9		9-BBN–CH ₂ CH ₂ CH ₂ OTIPS	64
10		9-BBN–CH ₂ CH ₂ CH ₂ CH ₂ Me	74
11		9-BBN–CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CO ₂ Et	72
12		9-BBN–CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ CO ₂ Me	81
13		9-BBN–CH ₂ CH ₂ CH ₂ CH ₂ CH ₂ OMe	83

[a] Yield of the isolated product (average of two experiments). [b] Diastereoselectivity: *trans/cis* > 20:1 (relative to the proximal substituent). [c] Diastereoselectivity: β/α 2:1. Cbz = carbobenzyloxy, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

(entries 7–13) are suitable substrates. A variety of functional groups are compatible with the reaction conditions, such as alkyl and silyl ethers (Table 2, entries 2, 6, 8, 9, and 13), alkenes (entry 4), carbamates (entry 5), esters (entries 11 and 12), and acetals (entries 12 and 13).

This method for alkyl–alkyl Suzuki cross-coupling, which we optimized for a new family of substrates (unactivated secondary alkyl chlorides), can be applied without modification to an array of other reaction partners. Thus, secondary alkyl bromides and iodides, both cyclic (including heterocyclic) and acyclic, are suitable electrophiles (Table 3, entries 1–8).^[7] Furthermore, primary alkyl chlorides, bromides, and iodides underwent the Suzuki coupling in good yield (entries 9–11).

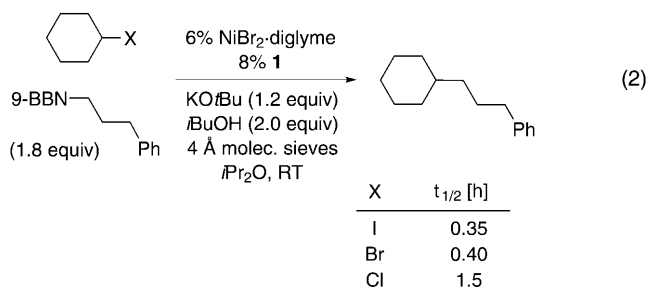
We examined the relative reactivity of cyclohexyl halides in Suzuki cross-coupling reactions with an alkyl borane under this set of conditions [Eq. (2)]. The alkyl iodide and the alkyl

Table 3: Alkyl–alkyl Suzuki cross-coupling reactions of unactivated alkyl halides [for reaction conditions, see Equation (1)].

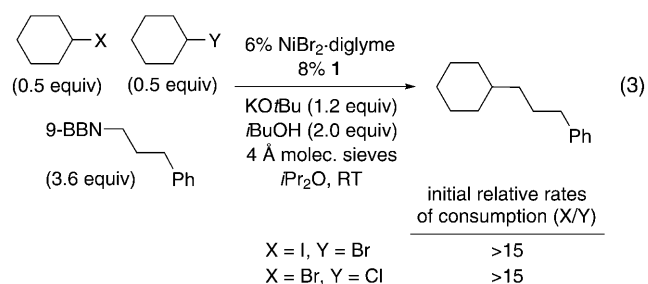
Entry	R–X	9-BBN–R ¹	Yield [%] ^[a]
1		9-BBN–CH ₂ CH ₂ Ph	X = Br: 75
2		9-BBN–CH ₂ CH ₂ Ph	X = I: 75
3		9-BBN–CH ₂ CH ₂ Ph	X = Br: 65
4		9-BBN–CH ₂ CH ₂ Ph	X = I: 64
5		9-BBN–CH ₂ CH ₂ Ph	X = Br: 74
6		9-BBN–CH ₂ CH ₂ Ph	X = I: 76
7		9-BBN–CH ₂ CH ₂ CH ₂ CH ₂ CO ₂ Et	X = Br: 75
8		9-BBN–CH ₂ CH ₂ CH ₂ CH ₂ CO ₂ Et	X = I: 76
9		9-BBN–CH ₂ CH ₂ CH ₂ CH ₂ Ph	63
10		9-BBN–CH ₂ CH ₂ CH ₂ CH ₂ Ph	70
11		9-BBN–CH ₂ CH ₂ CH ₂ CH ₂ Ph	78

[a] Yield of the isolated product (average of two experiments). Ts = *p*-toluenesulfonyl.

bromide underwent cross-coupling at comparable rates, whereas the alkyl chloride reacted more slowly.



Interestingly, in competition experiments between pairs of cyclohexyl electrophiles, the catalyst differentiated effectively between alkyl halides [Eq. (3)].^[8] Collectively, these data are consistent with oxidative addition not being the turnover-limiting step of the catalytic cycle in the case of cyclohexyl iodide and bromide.^[9]



We determined that, for the reaction of cyclohexyl bromide, the rate law is first-order in the catalyst (NiBr₂·diglyme/ligand **1**), first-order in the alkyl borane, and zeroth-order in the electrophile. These data are also consistent with oxidative addition not being the turnover-limiting

step for this Suzuki reaction of cyclohexyl bromide. In contrast, for cyclohexyl chloride, the rate of cross-coupling is dependent on the concentration of the electrophile.

In conclusion, we have developed the first alkyl–alkyl Suzuki reaction of unactivated secondary alkyl chlorides. Carbon–carbon bond formation occurs under mild conditions (at room temperature) with the aid of commercially available catalyst components. This method, although developed for the cross-coupling of unactivated secondary chlorides, has proved to be versatile: without modification, it can be applied to Suzuki reactions of secondary and primary alkyl bromides and iodides, as well as primary alkyl chlorides. Mechanistic investigations suggest that oxidative addition is not the turnover-limiting step of the catalytic cycle for unactivated secondary alkyl iodides and bromides, whereas it may be (partially) for the corresponding alkyl chlorides. Additional mechanistic and catalyst-development studies of a wide array of alkyl–alkyl cross-coupling reactions are under way.

Received: May 30, 2010

Published online: August 16, 2010

Keywords: alkyl halides · boron · cross-coupling · homogeneous catalysis · nickel

- [1] For leading references, see: a) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; b) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-i. Negishi), Wiley-Interscience, New York, **2002**; c) *Cross-Coupling Reactions: A Practical Guide, Topics in Current Chemistry Series 219* (Ed.: N. Miyaura), Springer, New York, **2002**.
- [2] a) For a pioneering study of Suzuki reactions of primary alkyl electrophiles, see: T. Ishiyama, S. Abe, N. Miyaura, A. Suzuki, *Chem. Lett.* **1992**, 691–694; b) for a review of cross-coupling reactions of secondary alkyl electrophiles, see: A. Rudolph, M. Lautens, *Angew. Chem.* **2009**, *121*, 2694–2708; *Angew. Chem. Int. Ed.* **2009**, *48*, 2656–2670.
- [3] For examples of applications of alkyl–alkyl Suzuki cross-coupling reactions in the total synthesis of natural products, see: a) K. A. Keaton, A. J. Phillips, *Org. Lett.* **2007**, *9*, 2717–2719; b) N. D. Griggs, A. J. Phillips, *Org. Lett.* **2008**, *10*, 4955–4957.
- [4] For alkyl–alkyl Suzuki reactions of unactivated secondary alkyl bromides and/or iodides, see: a) B. Saito, G. C. Fu, *J. Am. Chem. Soc.* **2007**, *129*, 9602–9603; b) B. Saito, G. C. Fu, *J. Am. Chem. Soc.* **2008**, *130*, 6694–6695.
- [5] For alkyl–aryl Suzuki reactions of unactivated secondary alkyl iodides, bromides, and chlorides at 60 °C, see: F. González-Bobes, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 5360–5361; see also: J. Zhou, G. C. Fu, *J. Am. Chem. Soc.* **2004**, *126*, 1340–1341.
- [6] Additional details about the reaction: 1) In the absence of $\text{NiBr}_2 \cdot \text{diglyme}$ or ligand **1**, essentially none of the desired product was formed (< 1 %). 2) On a gram scale, the Suzuki reaction in entry 1 of Table 2 proceeded in 79 % yield (yield of the isolated product, average of two experiments). 3) Under our standard conditions, secondary alkyl boranes, primary alkyl boronate esters, primary alkyl boronic acids, and primary alkyl trifluoroborates did not undergo cross-coupling in good yield. 4) By ^{11}B NMR spectroscopy, we determined that the potassium alkoxide reacts with the alkyl-9-BBN reagent to form a tetravalent boron complex. This interaction not only activates the trialkyl borane reagent, but also attenuates the Brønsted basicity of the reaction mixture. 5) On a 1 mmol scale in a microwave (60 °C for 3.5 h), the cross-coupling reaction in entry 1 of Table 2 proceeded in 74 % yield. 6) When $t\text{BuOMe}$ or Et_2O was used as the solvent in place of $i\text{Pr}_2\text{O}$, product yields were slightly lower, whereas the use of THF led to a greatly diminished yield.
- [7] Under our standard conditions, attempts to cross-couple an unactivated tertiary chloride, bromide, and iodide led to essentially none of the desired products.
- [8] High selectivity ($\text{I} > \text{Br} > \text{Cl}$) is often observed in oxidative addition/abstraction processes that proceed through an inner-sphere electron-transfer pathway; see, for example: S. L. Scott, J. H. Espenson, Z. Zhu, *J. Am. Chem. Soc.* **1993**, *115*, 1789–1797.
- [9] For mechanistic proposals for nickel-catalyzed Negishi reactions of alkyl electrophiles, see: a) G. D. Jones, J. L. Martin, C. McFarland, O. R. Allen, R. E. Hall, A. D. Haley, R. J. Brandon, T. Konovalova, P. J. Desrochers, P. Pulay, D. A. Vicić, *J. Am. Chem. Soc.* **2006**, *128*, 13175–13183; b) X. Lin, D. L. Phillips, *J. Org. Chem.* **2008**, *73*, 3680–3688.