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Published on Web 04/01/2006

Amino Alcohols as Ligands for Nickel-Catalyzed Suzuki Reactions of Unactivated Alkyl Halides, Including Secondary Alkyl Chlorides, with Arylboronic Acids

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Early work in the area of palladium- and nickel-catalyzed cross-coupling focused on reactions of aryl and vinyl electrophiles.[1] More recently, there has been noteworthy progress in employing unactivated *alkyl* electrophiles as coupling partners in certain processes.[2,3] Among cross-coupling methods, the Suzuki reaction is particularly widely used, due in part to the abundance of commercially available arylboronic acids, as well as their attractive stability, nontoxic nature, and functional-group compatibility. The only catalyst that has been reported to be effective for Suzuki couplings of unactivated secondary alkyl halides is based on nickel/bathophenanthroline.[4] This method can be applied to cross-couplings of a range of secondary bromides, secondary iodides, and primary iodides with arylboronic acids (eq 1). Of course, as for many initial discoveries, there are limitations to the scope of this catalyst; for example, primary or secondary alkyl chlorides, primary alkyl bromides, and hindered arylboronic acids cannot be efficiently coupled. Furthermore, with respect to a longer-term objective of achieving asymmetric Suzuki reactions of alkyl halides,[5] the ineffectiveness of 2/9-substituted phenanthrolines (e.g., neocuproine) was a cause for concern.[4,6]

$$\underset{\text{X = Br, I}}{\mathrm{R_{alkyl}{-}X}} \quad \underset{\text{1.2 equiv}}{\mathrm{(HO)_2B{-}R}} \xrightarrow[\text{KO}t\text{-Bu (1.6 equiv)},\ s\text{-butanol},\ 60\ ^\circ\text{C}]{4\%\ \mathrm{Ni(cod)_2},\ 8\%\ \text{bathophenanthroline}} \mathrm{R_{alkyl}{-}R} \quad (1)$$

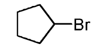
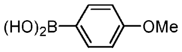
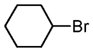
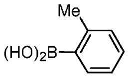
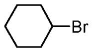
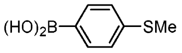
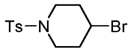
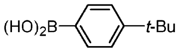
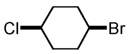
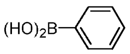
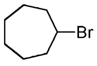
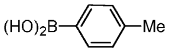
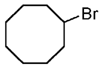
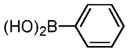
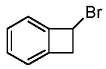
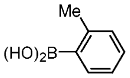
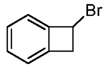
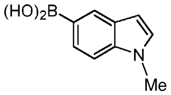
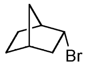
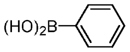
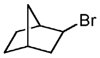
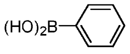
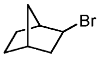
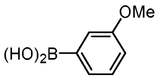
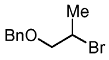
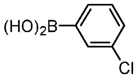
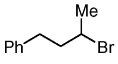
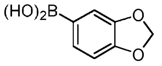
Cognizant of the need for more versatile catalysts for Suzuki reactions of alkyl electrophiles, we have been exploring the possibility of employing ligands other than bipyridine derivatives to these cross-coupling processes. In this report, we describe our discovery that readily available amino alcohols provide catalysts with significantly enhanced scope (eqs 2 and 3), permitting, for example, the first Suzuki reactions of unactivated secondary alkyl chlorides.

$$\underset{\text{X = Br, I}}{\mathrm{R_{alkyl}{-}X}} \quad \underset{\text{1.2 equiv}}{\mathrm{(HO)_2B{-}R}} \xrightarrow[\text{NaHMDS (2 equiv)},\ i\text{-propanol, 60 °C}]{6\%\ \mathrm{NiI_2},\ 6\%\ trans\text{-2-aminocyclohexanol}} \mathrm{R_{alkyl}{-}R} \quad (2)$$

$$\mathrm{R_{alkyl}{-}Cl} \quad \underset{\text{1.5 equiv}}{\mathrm{(HO)_2B{-}R}} \xrightarrow[\text{KHMDS (2 equiv)},\ i\text{-propanol, 60 °C}]{6\%\ \mathrm{NiCl_2 \bullet glyme},\ 12\%\ \text{prolinol}} \mathrm{R_{alkyl}{-}R} \quad (3)$$

As illustrated in Table 1, NiI_2/*trans*-2-aminocyclohexanol furnishes an active catalyst for Suzuki couplings of unactivated secondary alkyl bromides with arylboronic acids (Table 1).[7] Thus, five-, six-, seven-, and eight-membered carbocycles and heterocycles can be cross-coupled with an array of arylboronic acids, including ortho-substituted[8] and electron-rich substrates (entries 1−7).[9] In addition, bicyclic as well as acyclic secondary alkyl bromides are suitable substrates (entries 8−14). Both *endo*- and *exo*-2-bromonorbornane are converted into the *exo* product (entries 10 and 11), probably due to a radical pathway for oxidative addition. It is noteworthy that the catalyst components (NiI_2 and *trans*-2-aminocyclohexanol) are commercially available and can easily be handled in air (versus air-sensitive $Ni(cod)_2$; eq 1).

Table 1. NiI_2/*trans*-2-Aminocyclohexanol-Catalyzed Suzuki Cross-Couplings of Secondary Alkyl Bromides (reaction conditions: eq 2)

entry	alkyl bromide	arylboronic acid	yield (%)[a]
1			72[b]
2			68
3			70
4			66
5			70[c]
6			84
7			77
8			92
9			92[b]
10			84[d]
11			91[d]
12			68[b,d]
13			85
14			73[b]

[a] Isolated yield (average of two experiments). [b] With 2.0 equiv of the boronic acid used. [c] The starting material was 95:5 cis:trans; the product was 35:65 cis:trans. [d] The *exo* product was formed with >20:1 selectivity.

For alkyl bromides that bear a pendant olefin, a cyclization/cross-coupling sequence can be achieved (eq 4). The diastereoselectivity for these reactions is essentially identical to that obtained in reductive cyclizations of these substrates by Bu_3SnH,[10] an observation consistent with the hypothesis that a radical intermediate is

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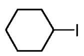
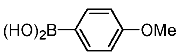
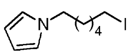
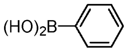
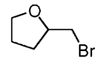
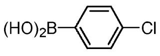
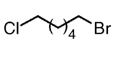
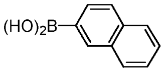
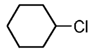
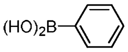
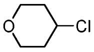
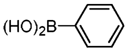
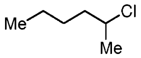
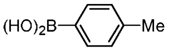
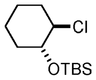
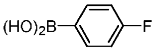
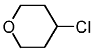
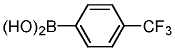
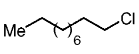
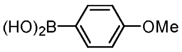
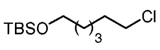
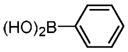
Table 2. NiI_2/*trans*-2-Aminocyclohexanol-Catalyzed Suzuki Cross-Couplings of Secondary Alkyl Iodides, as Well as Primary Alkyl Iodides and Bromides (reaction conditions: eq 2)

entry	alkyl halide	arylboronic acid	yield (%)[a]
1			77[b]
2			97
3			93
4			84[c]

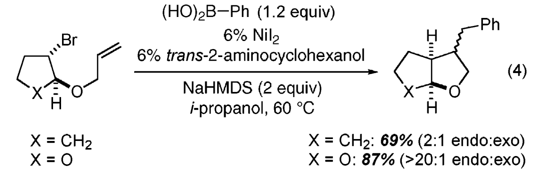
[a] Isolated yield (average of two experiments). [b] With 2.0 equiv of the boronic acid used. [c] With 1.1 equiv of the boronic acid used.

Table 3. $NiCl_2$·Glyme/Prolinol-Catalyzed Suzuki Cross-Couplings of Secondary and Primary Alkyl Chlorides (reaction conditions: eq 3)

entry	alkyl chloride	arylboronic acid	yield (%)[a]
1			80
2			84
3			74
4			46[b]
5			79
6			82[c]
7			87

[a] Isolated yield (average of two experiments). [b] Yield of the trans isomer (yield of the mixture of isomers: 65%, according to GC analysis versus a calibrated standard). The starting material was 95:5 trans:cis; the product was 78:22 trans:cis. [c] With 2.0 equiv of the boronic acid used.

involved in the oxidative-addition step of the nickel-catalyzed processes.[11]



(4)

We were pleased to determine that the NiI_2/*trans*-2-aminocyclohexanol-based method that we had developed for Suzuki reactions of secondary alkyl bromides (Table 1) can be applied without modification to secondary alkyl iodides, primary iodides, and primary bromides (Table 2). The previously described nickel/bathophenanthroline catalyst (eq 1) is ineffective for primary alkyl bromides and displays inferior functional-group compatibility.

As suggested by entry 4 of Table 2 and entry 5 of Table 1, Ni/*trans*-2-aminocyclohexanol is significantly more reactive toward alkyl bromides than alkyl chlorides. Nevertheless, this catalyst does exhibit slight activity for Suzuki reactions of alkyl chlorides (e.g., cyclohexyl chloride cross-couples with phenylboronic acid in 7% yield under the conditions described in eq 2). In view of the lack of precedent for Suzuki couplings of unactivated secondary alkyl chlorides, we chose to pursue the development of the first effective catalyst for such processes.

Capitalizing on the ready availability of structurally diverse amino alcohols, we surveyed a variety of ligands and discovered a method that achieves the desired objective (Table 3). Thus, when prolinol, rather than *trans*-2-aminocyclohexanol, is employed as a ligand, nickel-catalyzed Suzuki cross-couplings of unactivated secondary and primary alkyl chlorides proceed in good yield.[12] Acyclic as well as cyclic chlorides are suitable reaction partners, as are electron-poor and electron-rich arylboronic acids.

In conclusion, we have demonstrated that Suzuki cross-coupling reactions of an unprecedented array of unactivated primary and secondary alkyl halides (including challenging alkyl chlorides) can be accomplished through the use of nickel/amino alcohol-based catalysts. Both the nickel precatalyst and the amino alcohols (prolinol and *trans*-2-aminocyclohexanol) are commercially available and air-stable. In view of the remarkable diversity of amino alcohols that are readily accessible, we believe that the door is now open to the rapid development of versatile catalysts for a wide range of cross-coupling processes.

Acknowledgment. We thank Frontier Scientific for boronic acids and CEM for a microwave apparatus. Support has been provided by the National Institutes of Health (NIGMS, R01-GM62871), Merck Research Laboratories (including a postdoctoral fellowship to F.G.-B.), and Novartis. Funding for the MIT Department of Chemistry Instrumentation Facility has been furnished in part by the National Science Foundation (CHE-9808061 and DBI-9729592).

Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) For asymmetric Negishi reactions of alkyl halides, see: (a) Fischer, C.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 4594−4595. (b) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482−10483.

(6) For a review of chiral bipyridine and phenanthroline ligands, see: Chelucci, G.; Thummel, R. P. *Chem. Rev.* **2002**, *102*, 3129−3170.

(7) Notes: (a) The hydrochloride salt of *trans*-2-aminocyclohexanol was employed since that is the form in which it is commonly supplied. (b) In a 10 mmol experiment, the coupling depicted in entry 6 of Table 1 proceeds in 85% yield (1.6 g of product). (c) For cross-couplings of electron-rich arylboronic acids, 2 equiv of the boronic acid was used, due to competitive protodeborylation. (d) The coupling of cyclohexyl bromide with phenylboronic acid can be achieved under microwave conditions under air (57% yield according to GC analysis versus a calibrated internal standard; 80 °C, 250 W, 5 min; not extensively optimized). (e) Reactions of several heteroaryl-, vinyl-, and alkylboronic acids proceeded in relatively poor yield (<30%). We have not yet examined the capacity of other nickel/amino alcohol catalysts to achieve Suzuki cross-couplings of these families of substrates.

(8) For the Suzuki reaction illustrated in entry 2 of Table 1, the Ni/bathophenanthroline catalyst (eq 1) furnishes <5% of the cross-coupling product.

(9) For the cross-coupling depicted in entry 5 of Table 1, we have not detected the formation of any product resulting from reaction of the secondary alkyl chloride.

(10) (a) Pandey, G.; Rao, K. S. S. P.; Palit, D. K.; Mittal, J. P. *J. Org. Chem.* **1998**, *63*, 3968−3978. (b) Hackmann, C.; Schäfer, H. J. *Tetrahedron* **1993**, *49*, 4559−4574. (c) Mayer, S.; Prandi, J.; Bamhaoud, T.; Bakkas, S.; Guillou, O. *Tetrahedron* **1998**, *54*, 8753−8770.

(11) For an earlier discussion, see: Powell, D. A.; Maki, T.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 510−511. Under our standard conditions, alkyl tosylates are essentially unreactive (<10% yield), presumably due to their reluctance to undergo oxidative addition via a radical pathway.

(12) Notes: (a) Future studies will be directed at gaining an understanding of the interplay among various reaction parameters and their impact on the efficiency of these cross-coupling processes. (b) This method is not effective for ortho-substituted arylboronic acids (<30% yield).

JA0613761