

## Suzuki Cross-Couplings of Unactivated Secondary Alkyl Bromides and Iodides

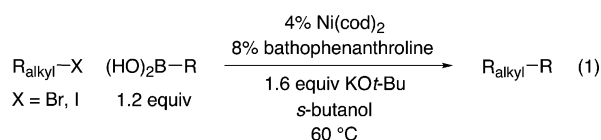
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During the past few decades, nickel- and palladium-catalyzed cross-couplings of aryl and vinyl halides/sulfonates have been developed into very powerful tools for carbon-carbon bond formation.<sup>1</sup> The first indications that such couplings might also be viable for  $\beta$ -hydrogen-containing, unactivated alkyl halides/sulfonates<sup>2</sup> were provided by the pioneering work of Suzuki in 1992<sup>3,4</sup> and a series of investigations by Knochel beginning in 1995,<sup>5,6</sup> which focused on reactions with boron and zinc reagents, respectively. Within the past two years, the pace of progress in the development of methods for cross-coupling alkyl electrophiles has accelerated significantly with reports of reactions with magnesium,<sup>7</sup> tin,<sup>8</sup> silicon,<sup>9</sup> and zirconium<sup>10</sup> reagents.<sup>11</sup> However, these studies only describe couplings of *primary* alkyl halides/sulfonates.

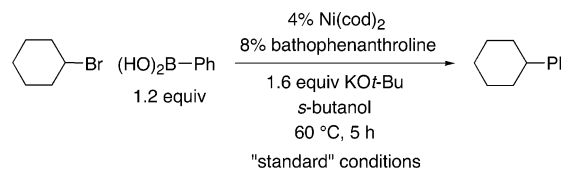
Clearly, to fully exploit the exciting potential of alkyl electrophiles as partners in nickel- or palladium-catalyzed cross-couplings, it is imperative that methods be available to couple more hindered substrates. In 2003, we disclosed the first examples of cross-couplings of unactivated *secondary* alkyl electrophiles, specifically, Negishi reactions of bromides and iodides.<sup>12</sup> More recently, we have turned our attention to Suzuki reactions. Among cross-coupling processes, Suzuki reactions are particularly widely used, due to attractive attributes such as the commercial availability, the air and water stability, and the nontoxic nature of boronic acids.<sup>13</sup> In this communication, we report the first method for achieving Suzuki cross-couplings of unactivated secondary alkyl halides (eq 1).



During our catalyst-development effort, we focused our attention on coupling cyclohexyl bromide with phenylboronic acid. After exploring a wide array of conditions, we determined that 4% Ni(cod)<sub>2</sub>/8% bathophenanthroline/1.6 equiv KOt-Bu in *s*-BuOH at 60 °C furnishes an excellent yield (91%) of the desired Suzuki cross-coupling product (Table 1, entry 1).

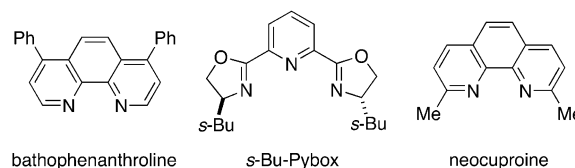
The data in Table 1 illustrate the impact of various parameters on the efficiency of this process. Although Ni(acac)<sub>2</sub> displays some activity (entry 2), other nickel and palladium complexes afford essentially no carbon-carbon bond formation (entries 3–4). *s*-Bu-Pybox, which is useful for Negishi reactions of secondary alkyl halides,<sup>12</sup> is ineffective under these conditions (entry 5), as are an array of phosphine and carbene ligands (e.g., entries 6–7). Phenanthroline itself (entry 8)—but not a more hindered derivative (entry 9)—is a moderately efficient ligand, as are bipyridines (entries 10–11). A decrease in the bathophenanthroline:Ni ratio leads to a decrease in yield (entry 12), and no phenylcyclohexane is observed if bathophenanthroline is omitted (entry 13). Use of KOEt, rather than KOt-Bu, results in slightly less effective coupling (entry 14). To achieve a reasonable reaction rate, heating is required (entry

**Table 1.** Impact of Reaction Parameters on the Efficiency of a Suzuki Cross-Coupling of a Secondary Alkyl Bromide



entry	deviation from the "standard" conditions <sup>b</sup>	yield (%) <sup>a</sup>
1	none	91
2	Ni(acac) <sub>2</sub> [instead of Ni(cod) <sub>2</sub> ]	24
3	NiBr <sub>2</sub> [instead of Ni(cod) <sub>2</sub> ]	<3
4	Pd(OAc) <sub>2</sub> or Pd <sub>2</sub> (dba) <sub>3</sub> [instead of Ni(cod) <sub>2</sub> ]	<3
5	<i>s</i> -Bu-Pybox [instead of BP]	<3
6	PPh <sub>3</sub> or P( <i>t</i> -Bu) <sub>2</sub> Me [instead of BP]	<3
7	1,3-bis(1-adamantyl)imidazol-2-ylidene [instead of BP]	<3
8	1,10-phenanthroline [instead of BP]	65
9	neocuproine [instead of BP]	<3
10	bpy [instead of BP]	43
11	4,4'-dimethoxy-2,2'-bipyridine [instead of BP]	57
12	4% bathophenanthroline [instead of 8%]	49
13	no bathophenanthroline	<3
14	KOEt [instead of KOt-Bu]	83
15	r.t.	8
16	2% Ni(cod) <sub>2</sub> , 4% BP [instead of 4% Ni(cod) <sub>2</sub> , 8% BP]	76

<sup>a</sup> Yield according to GC, versus a calibrated internal standard (average of two runs). <sup>b</sup> BP = bathophenanthroline.



15). Finally, use of a lower catalyst loading leads to a modestly lower yield (entry 16).<sup>14</sup>

Our optimized procedure can be applied directly to Suzuki cross-couplings of a range of secondary alkyl bromides (Table 2).<sup>15</sup> Both electron-rich (entries 3–4) and electron-poor (entries 5–6) arylboronic acids can be coupled, along with certain heteroarylboronic acids (entries 7–8). Interestingly, for the substrates illustrated in entry 9, the reaction occurs selectively at the secondary C<sub>sp</sub><sup>3</sup>-Br, rather than the Ar-Cl, bond.

The method that we have developed for cross-coupling alkyl bromides can also be employed for Suzuki reactions of alkyl iodides (Table 3).<sup>16</sup> Thus, without re-optimizing the conditions, we have determined that 4% Ni(cod)<sub>2</sub>/8% bathophenanthroline catalyzes couplings of secondary (entries 1–2) and primary (entries 3–4) alkyl iodides with aryl- and alkenylboronic acids in satisfactory yield.

In conclusion, we have developed a catalyst system that achieves the first Suzuki reactions of unactivated secondary alkyl bromides and iodides. The ability to couple readily available, easy-to-handle boronic acids is an attractive feature of this process. We anticipate

**Table 2.** Suzuki Cross-Couplings of Unactivated Secondary Alkyl Bromides (eq 1)

entry	R <sub>alkyl</sub> -Br	(HO) <sub>2</sub> B-R	yield (%)
1			74 <sup>a</sup>
2			71 <sup>a</sup>
3			90
4			68
5			44
6			63 <sup>b</sup>
7			63
8			67
9			75

<sup>a</sup>The exo product is formed. <sup>b</sup>The trans product is formed.

**Table 3.** Suzuki Cross-Couplings of Unactivated Alkyl Iodides (eq 1)

entry	R <sub>alkyl</sub> -I	(HO) <sub>2</sub> B-R	yield (%)
1			62
2			65
3			75
4			63

that the capacity to employ alkyl electrophiles as coupling partners will markedly increase the already exceptional utility of cross-coupling reactions, and our current efforts are therefore focused on developing highly versatile catalysts for a range of processes.

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**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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- (14) The addition of water (1.0 equiv) leads to a 74% yield of phenylcyclohexane.
- (15) Notes: (a) For each entry, a single regio- and stereoisomer (>50:1) is observed (see the Supporting Information). Our current hypothesis is that a radical intermediate may be involved. (b) Under our standard conditions, primary and tertiary alkyl bromides, alkylboronic acids, and ortho-substituted arylboronic acids are not suitable substrates.
- (16) Notes: (a) Under our standard conditions, alkyl chlorides and tertiary alkyl iodides are not suitable substrates. (b) Reactions of functionalized alkyl electrophiles proceed in lower yield.

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