

## Cross-Couplings of Unactivated Secondary Alkyl Halides: Room-Temperature Nickel-Catalyzed Negishi Reactions of Alkyl Bromides and Iodides

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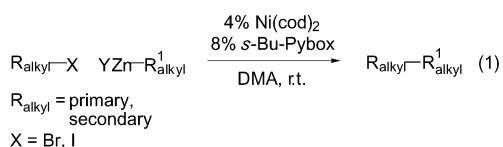
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Palladium- and nickel-catalyzed cross-coupling reactions are widely used tools for constructing carbon–carbon bonds.<sup>1</sup> To date, most studies of these processes have focused on forming C<sub>sp</sub><sup>2</sup>–C<sub>sp</sub><sup>2</sup> (particularly biaryl) bonds. Unfortunately, there has been considerably less progress in developing effective cross-coupling catalysts for generating C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>3</sup> bonds.<sup>2</sup> The availability of general methods for building the latter set of bonds would no doubt have a significant impact on synthetic organic chemistry.

The primary obstacles to constructing C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>3</sup> bonds via metal-catalyzed cross-couplings of alkyl electrophiles with alkylmetals are believed to generally arise from the electrophile. Thus, this reaction partner can be reluctant to oxidatively add to palladium or nickel (Figure 1). Furthermore, even if oxidative addition does occur, β-hydride elimination from intermediate **A** can be facile, relative to the desired sequence of transmetalation and reductive elimination.

Recently, several groups have described advances in addressing the challenge of achieving efficient nickel- and palladium-catalyzed C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>3</sup> bond formation.<sup>3,4,5</sup> Unfortunately, the methods have only been shown to be applicable to reactions of *primary* alkyl electrophiles. Clearly, the full potential of such metal-catalyzed cross-coupling processes will only be realized when more hindered electrophiles can also be employed as reaction partners.<sup>6</sup> In this communication, we report our progress toward achieving this objective, specifically, a simple nickel catalyst that accomplishes room-temperature Negishi couplings of unactivated secondary alkyl bromides and iodides (eq 1; DMA = *N,N*-dimethylacetamide).



We chose to focus our initial studies on the Negishi reaction in part because alkylzinc reagents are highly functional-group tolerant and can be generated under very mild conditions.<sup>7</sup> Specifically, we decided to examine the cross-coupling of isopropyl bromide with *n*-nonylzinc bromide (Table 1). After considerable effort, we established that 4% Ni(cod)<sub>2</sub>/8% *s*-Bu-Pybox in DMA effects this C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>3</sup> bond formation in excellent yield at room temperature (91%; entry 1).<sup>8</sup>

Table 1 illustrates the impact of a variety of reaction parameters on the course of the cross-coupling process. In the absence of Ni(cod)<sub>2</sub> (entry 2), or in the presence of other metal complexes (entries 3–4), coupling is either ineffective or less effective than with Ni(cod)<sub>2</sub>. Pybox ligands that bear larger or smaller R<sup>1</sup> groups than *s*-Bu-Pybox furnish lower yields of the desired product (entries 5–8). A range of non-Pybox ligands, including those with utility in couplings of *primary* alkyl electrophiles, are ineffective (entries 9–13).<sup>9</sup> Furthermore, a decrease in the quantity of *s*-Bu-Pybox leads to a decrease in the efficiency of carbon–carbon bond formation

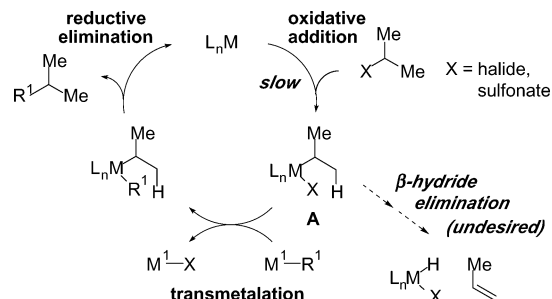
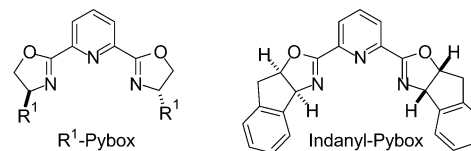


Figure 1. Generalized pathway for metal-catalyzed cross-coupling of an alkyl electrophile.

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

entry	change from the standard conditions	yield (%) <sup>a</sup>
1	none	91
2	no Ni(cod) <sub>2</sub>	<5
3	NiBr <sub>2</sub>	44
4	Pd(OAc) <sub>2</sub> or Pd <sub>2</sub> (dba) <sub>3</sub>	<5
5	<i>t</i> -Bu-Pybox	<5
6	<i>i</i> -Pr-Pybox	71
7	Ph-Pybox	80
8	Indanyl-Pybox	42
9	PPh <sub>3</sub>	<5
10	P( <i>t</i> -Bu) <sub>3</sub>	<5
11	P( <i>t</i> -Bu) <sub>2</sub> Me	<5
12	PCy(1-pyrrolidinyl) <sub>2</sub>	<5
13	1,3-bis(1-adamantyl)imidazol-2-ylidene	<5
14	4% <i>s</i> -Bu-Pybox	62
15	no <i>s</i> -Bu-Pybox	<5
16	2% Ni(cod) <sub>2</sub> , 4% <i>s</i> -Bu-Pybox	80
17	1.2 equiv BrZn- <i>n</i> -nonyl	70

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



(entries 1, 14, and 15). Finally, the Negishi cross-coupling proceeds in somewhat diminished, but still useful, yield when less catalyst (entry 16) or less alkylzinc reagent (entry 17) is employed.

The standard procedure (4% Ni(cod)<sub>2</sub>/8% *s*-Bu-Pybox) can be applied to room-temperature Negishi reactions of not only acyclic (Table 1, entry 1) but also cyclic secondary alkyl bromides (Table 2, entries 1–3). Importantly, in addition to bromides, secondary alkyl iodides can be cross-coupled with this catalyst (entries 4–6). As illustrated in Table 2, the reaction conditions are compatible

**Table 2.** Negishi Cross-Couplings of Secondary Alkyl Bromides and Iodides with Alkylzinc Reagents (eq 1; 1.6 equiv of Alkylzinc Reagent)

entry	R <sub>alkyl</sub> -X	YZn-R <sub>alkyl</sub> <sup>1</sup>	yield (%)
1			66
2			62
3			68
4			62
5			78
6			88

All yields are isolated yields (average of two runs).

**Table 3.** Negishi Cross-Couplings of Primary Alkyl Bromides and Iodides with Alkylzinc Reagents (eq 1; 1.6 equiv of Alkylzinc Reagent)

entry	R <sub>alkyl</sub> -X	YZn-R <sub>alkyl</sub> <sup>1</sup>	yield (%)
1			65
2			74
3			73

All yields are isolated yields (average of two runs).

with functional groups such as sulfonamides, ethers, acetals, esters, and amides.<sup>10</sup>

Ni(cod)<sub>2</sub>/*s*-Bu-Pybox can also be employed as a catalyst for Negishi cross-couplings of primary alkyl halides (Table 3), reacting even with very hindered neopentyl iodide (entry 3). These examples provide further evidence for the high functional-group tolerance of the method (e.g., imides and ketones).

In conclusion, we have established that Ni(cod)<sub>2</sub>/*s*-Bu-Pybox catalyzes Negishi reactions of an array of functionalized alkyl bromides and iodides at room temperature. To the best of our knowledge, this is the first nickel- or palladium-catalyzed method for cross-coupling unactivated,  $\beta$ -hydrogen-containing, secondary alkyl halides. Due to the potential impact on synthetic chemistry, we are continuing our efforts to develop effective catalysts for a

wide range of coupling reactions of alkyl electrophiles, as well as initiating mechanistic studies of these 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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- (8) We observe essentially no *n*-dodecane (<0.5%), indicating that the isopropylnickel complex is not undergoing  $\beta$ -hydride elimination to generate an *n*-propylnickel complex.
- (9) We speculate that the chelating nature of Pybox ligands may disfavor  $\beta$ -hydride elimination, which requires a vacant coordination site.
- (10) Notes: (a) The standard coupling conditions can also be applied to Negishi reactions of activated alkyl halides. For example, *n*-nonylZnBr couples with allyl bromide, benzyl bromide, and benzyl chloride in 60, 89, and 100% yields (by GC, versus a calibrated internal standard), respectively. (b) The use of secondary organozinc reagents leads to lower yields (<30%). (c) Alkyl chlorides, alkyl tosylates, and tertiary alkyl bromides/iodides are not suitable coupling partners under the standard conditions.

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