

## Nickel-Catalyzed Cross-Couplings of Organosilicon Reagents with Unactivated Secondary Alkyl Bromides

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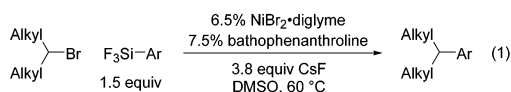
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Recent advances in catalyst development have markedly increased the utility of palladium- and nickel-catalyzed cross-coupling reactions.<sup>1</sup> Nevertheless, very significant challenges remain, including expanding the scope to include couplings of unactivated alkyl halides.<sup>2</sup> The past several years have witnessed noteworthy progress in this regard, largely with respect to reactions of *primary* alkyl electrophiles.<sup>3–9</sup> These studies have played a critical role in dispelling the widespread belief that rapid  $\beta$ -hydride elimination might preclude the development of general methods for cross-coupling alkyl halides.

Unfortunately, primary alkyl halides represent only a fraction of the alkyl halide coupling partners that are of interest to synthetic chemists. Secondary alkyl halides comprise a second, very substantial subset. Due to a variety of issues, including slow oxidative addition and comparatively rapid elimination to an olefin, the cross-coupling of secondary alkyl electrophiles is a relatively difficult challenge. To date, unactivated secondary alkyl halides have only been successfully coupled with organozinc<sup>10</sup> and organoboron<sup>11</sup> compounds, as well as less functional-group-tolerant Grignard reagents.<sup>12</sup>

To exploit the full potential of cross-couplings of alkyl electrophiles, it is critical, as it is for couplings of aryl and vinyl electrophiles, that it be possible to employ a broad spectrum of organometallic reaction partners. Organosilicon compounds have become increasingly popular partners in cross-couplings of aryl and vinyl halides due to attractive features such as ready availability, low toxicity, and high functional-group tolerance.<sup>13,14</sup> Cognizant of these attributes, we decided to pursue the development of a method for coupling unactivated secondary alkyl halides with organosilicon reagents, and in this communication we describe a nickel-based catalyst that accomplishes this objective (eq 1; bathophenanthroline = 4,7-diphenyl-1,10-phenanthroline). To the best of our knowledge, there have been no previous reports of nickel-catalyzed cross-couplings of organosilicon compounds with organic (alkyl, vinyl, or aryl) halides.



The conditions that we have found useful for Negishi (cat. Ni(cod)<sub>2</sub>/*s*-Bu-Pybox)<sup>10</sup> and Suzuki (cat. Ni(cod)<sub>2</sub>/bathophenanthroline; KO*t*-Bu)<sup>11</sup> reactions of secondary alkyl bromides proved to be ineffective for the cross-coupling of cyclohexyl bromide with trifluorophenylsilane (<5% yield).<sup>15</sup> Fortunately, by investigating a variety of reaction parameters, we were able to develop a method that cleanly achieves the desired coupling (Table 1, entry 1).

Entries 2–11 of Table 1 provide information on the impact of several key variables on the efficiency of this new cross-coupling process. As expected, in the absence of NiBr<sub>2</sub>·diglyme, no carbon–

**Table 1.** Effect of Reaction Parameters on the Efficiency of the Cross-Coupling of Cyclohexyl Bromide with Trifluorophenylsilane

entry	change from the standard conditions	yield (%) <sup>a</sup>
1	none	86
2	no NiBr <sub>2</sub> ·diglyme	<5
3	NiBr <sub>2</sub> [instead of NiBr <sub>2</sub> ·diglyme]	74
4	Ni(cod) <sub>2</sub> [instead of NiBr <sub>2</sub> ·diglyme]	63
5	Pd(OAc) <sub>2</sub> or Pd <sub>2</sub> (dba) <sub>3</sub> [instead of NiBr <sub>2</sub> ·diglyme]	<5
6	no bathophenanthroline	<5
7	15% bathophenanthroline	<5
8	1,10-phenanthroline [instead of bathophenanthroline]	70
9	2,2'-bipyridine [instead of bathophenanthroline]	76
10	no CsF	<5
11	KF or TBAF·3H <sub>2</sub> O [instead of CsF]	<5

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

carbon bond formation occurs (entry 2). Replacement of NiBr<sub>2</sub>·diglyme with NiBr<sub>2</sub> (entry 3) or Ni(cod)<sub>2</sub> (entry 4) leads to a modest drop in yield, whereas substitution with a palladium complex (e.g., Pd(OAc)<sub>2</sub> or Pd<sub>2</sub>(dba)<sub>3</sub>) results in a loss of cross-coupling activity (entry 5). The observation that a Ni(II) complex can serve as an effective catalyst for cross-couplings of secondary alkyl electrophiles is quite noteworthy from a practical point of view, since NiBr<sub>2</sub>·diglyme is significantly less expensive than Ni(cod)<sub>2</sub> and, perhaps more importantly, is air-stable.

In the absence of bathophenanthroline (Table 1, entry 6) or in the presence of a 2.3:1 ratio of bathophenanthroline:Ni (entry 7), no cyclohexylbenzene is produced. Ligands that are structurally related to bathophenanthroline, such as 1,10-phenanthroline (entry 8) and 2,2'-bipyridine (entry 9), can be employed, although the yields are slightly lower. In the absence of CsF (entry 10) or in the presence of other fluoride sources (e.g., KF or TBAF; entry 11), essentially no coupling occurs.<sup>16,17</sup>

As illustrated in Table 2, NiBr<sub>2</sub>·diglyme/bathophenanthroline can be applied to cross-couplings of an array of cyclic and acyclic secondary alkyl bromides.<sup>18–20</sup> Carbon–carbon bond formation proceeds smoothly in the presence of a variety of functional groups, including ethers (entry 7), imides (entry 9), ketones (entry 10), and carbamates (entry 11). Furthermore, alkyl bromides are selectively coupled in preference to aryl (entry 12) and alkyl (entry 13) chlorides. An electronically and sterically diverse set of trifluoroarylsilanes are suitable coupling partners.

We were pleased to determine that this method can also be applied to cross-couplings of secondary alkyl iodides (Table 3, entry 1), primary alkyl bromides (entry 2), and primary alkyl iodides (entry 3). These examples establish the compatibility of functional

**Table 2.** Nickel-Catalyzed Cross-Couplings of Secondary Alkyl Bromides with Trifluoroarylsilanes (eq 1)

entry	R <sub>alkyl</sub> -Br	F <sub>3</sub> Si-Ar	yield (%) <sup>a</sup>
1			80
2			62
3			66 <sup>b</sup>
4			70 <sup>c</sup>
5			65
6			80
7			71
8			68 <sup>d</sup>
9			70 <sup>d</sup>
10			82
11			63
12			72
13			60 <sup>e</sup>

<sup>a</sup> Isolated yield, average of two runs. <sup>b</sup> Starting material: exo/endo = 96/4; product: exo/endo = 94/6. <sup>c</sup> Starting material: exo/endo = 6/94; product: exo/endo = 95/5. <sup>d</sup> 9% NiBr<sub>2</sub>·diglyme, 10% bathophenanthroline. <sup>e</sup> Starting material: cis/trans = 95/5; product: cis/trans = 55/45.

**Table 3.** Nickel-Catalyzed Cross-Couplings of Alkyl Halides with Trifluoroarylsilanes

entry	R <sub>alkyl</sub> -X	F <sub>3</sub> Si-Ar	yield (%) <sup>a</sup>
1			60 <sup>b</sup>
2			80
3			73

<sup>a</sup> Isolated yield, average of two runs. For the reaction conditions, see eq 1. <sup>b</sup> 9% NiBr<sub>2</sub>·diglyme, 10% bathophenanthroline, the starting material and the product are exclusively the exo isomer.

groups such as lactones, acetals, and nitriles with the reaction conditions.

In summary, we have developed the first metal-catalyzed cross-couplings of organosilicon compounds with secondary alkyl halides. Two noteworthy features of the method are its high functional-group compatibility and the air stability of the catalyst components. Primary alkyl halides can also be coupled by this catalyst. Additional efforts to expand the scope of metal-catalyzed cross-coupling reactions of alkyl electrophiles are underway.

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

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- (15) Furthermore, the method that we have described for cross-couplings of organosilicon compounds with primary alkyl halides (catalytic PdBr<sub>2</sub>/P(*t*-Bu)<sub>2</sub>Me; TBAF; THF, rt)(ref 7) is ineffective (<5% yield).
- (16) Presumably, the fluoride ion binds to trifluorophenylsilane to generate a hypervalent silicate that efficiently transfers the phenyl group from silicon to nickel. For a discussion, see ref 13.
- (17) Notes: (a) The stoichiometry of CsF is important: smaller and larger amounts lead to lower yields. (b) Other Lewis bases (e.g., KOSiMe<sub>3</sub>, NaOH, NaOEt, and KO<sup>t</sup>-Bu) are ineffective. (c) Addition of 1 equiv of water results in a substantial decrease in yield.
- (18) Trifluoroarylsilanes are easily prepared from trichloroarylsilanes under a variety of conditions. For example, see: Damrauer, R.; Simon, R. A.; Kanner, B. *Organometallics* **1988**, *7*, 1161–1164 and references therein.
- (19) Notes: (a) On a 10 mmol scale (1.65 g of product), the coupling depicted in entry 12 of Table 2 proceeds in 68% yield. (b) The only identifiable byproduct is the biaryl (typically <5% yield). (c) Among the silanes that we have examined to date, the trifluoroarylsilanes are uniquely effective (<10% yield for the coupling of PhSi(OMe)<sub>3</sub>, PhSiCl<sub>2</sub>, PhSiF<sub>2</sub>Me, PhSiMe<sub>2</sub>OH, or PhSi(-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>-)Me with Cy-Br). (d) These conditions have not proved to be suitable (<10% yield) for couplings of: primary or secondary alkyl chlorides or tosylates, secondary alkyl halides that bear an electron-withdrawing group in the α or β position, and trifluoroalkenylsilanes.
- (20) We believe that these reactions proceed via alkyl radicals that combine with nickel to form alkylnickel intermediates.

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