

## Nickel-Catalyzed Reductive Cross-Coupling of Aryl Halides with Alkyl Halides

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While transition-metal (Pd, Ni, Fe)-catalyzed methods to form alkylated aromatic compounds are synthetically important and well-studied,<sup>1,2</sup> most approaches require the use of an organometallic reagent [RB(OH)<sub>2</sub>, RBF<sub>3</sub>K, RZnI, RMgBr] in conjunction with an organohalide. Generally, the organometallic reagents are synthesized from the corresponding abundant organic halides<sup>3</sup> in a separate step. To avoid the handling of air- and moisture-sensitive organometallic reagents, “one-pot” procedures have been developed.<sup>4</sup> Recently, several groups have shown that in some cases the organometallic reagent can be formed in situ by cobalt-catalyzed organozinc synthesis,<sup>5</sup> iron-catalyzed Grignard formation,<sup>6</sup> or direct zinc insertion into the C–X bond in a water/surfactant mixture<sup>7</sup> (Figure 1). These new procedures, while taking a large step toward eliminating the need for preformed organometallic reagents, are focused only on benzyl chlorides,<sup>5</sup> suffer from limited functional-group compatibility,<sup>6</sup> or require a large excess of one of the two organic halides.<sup>7</sup>

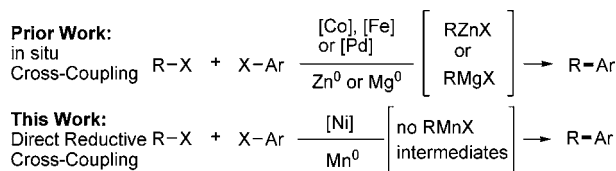
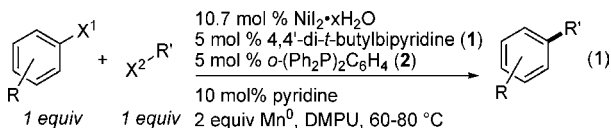


Figure 1. Approaches to the cross-coupling of organohalides.

In contrast to these approaches, direct reductive cross-coupling of aryl halides with alkyl halides—without the intermediacy of a stoichiometric organometallic reagent—has not been studied extensively (Figure 1). We report here a new, general method for performing direct reductive cross-couplings through the action of a dual-ligand nickel catalyst system (eq 1). The reaction proceeds with exceptional functional-group compatibility and generally high yields while requiring only 1 equiv of each coupling partner in a simple benchtop procedure.



The major challenges to the development of this new process were finding a means to observe selectivity for cross-coupling over homocoupling and eliminating the formation of reduction products (presumably produced as a consequence of  $\beta$ -hydride elimination from an alkylnickel species<sup>8</sup>). A combination of four observations enabled us to overcome these challenges (Table 1): (a) a combination of two ligands, 4,4'-di-*tert*-butyl-2,2'-bipyridine (**1**) and 1,2-bis(diphenylphosphino)benzene (**2**), provides results equal to or better than those obtained using **1** only (entries 1–4 and Table S5;<sup>9</sup> up to 20% improvement in yield<sup>10</sup>); (b) reactions conducted in 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)<sup>11</sup> solvent

occurred in higher yields than those conducted in any other solvent tested (Table S3<sup>9</sup>); (c) reactions conducted with added pyridine (5–20 mol %) formed fewer products from  $\beta$ -hydride elimination (entries 1 and 7); and (d) reactions were more selective for the cross-coupled product when at least one of the reactants was an organic iodide (entries 1, 8–10).

Table 1. Optimized Reaction Conditions<sup>a</sup>

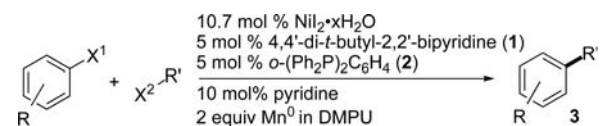
Entry	Deviation from Standard Conditions	Yield (%) <sup>b</sup>
1	none	88
2	10 mol % <b>1</b> in place of a mixture of <b>1</b> and <b>2</b>	83
3	10 mol % <b>2</b> in place of a mixture of <b>1</b> and <b>2</b>	19
4	5 mol % <b>1</b> in place of a mixture of <b>1</b> and <b>2</b>	81
5	no ligands added	6
6	no Mn <sup>0</sup> added	<1
7	pyridine omitted	67
8	Br–C <sub>8</sub> H <sub>17</sub> in place of I–C <sub>8</sub> H <sub>17</sub>	85
9	Br–Ph in place of I–Ph	77
10	Br–C <sub>8</sub> H <sub>17</sub> and Br–Ph in place of I–C <sub>8</sub> H <sub>17</sub> and I–Ph	65
11	TDAE in place of Mn <sup>0</sup> , 2.5 equiv of I–C <sub>8</sub> H <sub>17</sub>	57

<sup>a</sup> Organohalides (0.5 mmol each), 0.054 mmol of NiL<sub>2</sub>·xH<sub>2</sub>O, 0.025 mmol of **1**, 0.025 mmol of **2**, 0.05 mmol of pyridine, 1 mmol of Mn<sup>0</sup> powder, and 2 mL of DMPU were heated for up to 24 h. <sup>b</sup> Corrected GC yield.

The results in Table 2 demonstrate that this reaction has a high degree of functional-group tolerance.<sup>8</sup> Electrophilic functionality, such as a methyl ketone (entry 4),<sup>12</sup> an aryl nitrile (entry 5), an ethyl ester (entry 10), or a pinacol boronate ester (entry 6), is well-tolerated. The last is important because few cross-coupling reactions are orthogonal to the Suzuki reaction, except the Sonogashira coupling of terminal alkynes with haloarenes.<sup>13</sup> Reactions of substrates containing relatively acidic protons, such as those found in an unprotected hydroxyl or a primary carbamate (entries 8, 11, 12), occur in good yield, avoiding the need for protection/deprotection sequences. However, protected amines often alleviate the difficulty in handling free amines, and two of the most-used protecting groups, *t*-butoxycarbonyl (Boc, entry 11) and benzyloxycarbonyl (Cbz, entry 12), are tolerated by the new coupling process.

Nitrogen heterocycles, which are pervasive in medicinal chemistry, often present a significant challenge to metal-catalyzed reactions, but here the acylated 5-bromoindole coupled with iodoctane in high yield (entry 9). However, reactions starting with unprotected indole, imidazole, and pyridine substrates to date have not produced the coupled products in acceptable yields. Steric hindrance on the arene or alkane is reasonably tolerated (entries 7, 14–16).

Even coupling of secondary alkyl bromides<sup>2</sup> occurred in high yield (entry 16). The selectivity for formation of 2-phenylheptane

**Table 2.** Substrate Scope of the Nickel-Catalyzed Reductive Coupling<sup>a</sup>

Entry	Product	X <sup>1</sup>	X <sup>2</sup>	T (°C)	Yield (%) <sup>b</sup>	
1	R = H	<b>3a</b>	I	I	80	77
2	R = OMe	<b>3b</b>	I	I	80	75
3	R = CF <sub>3</sub>	<b>3c</b>	I	I	80	75
4	R = C(O)Me	<b>3d</b>	I	I	80	69
5	R = CN	<b>3e</b>	I	I	80	55
6	R =	<b>3f</b>	Br	I	60	82
7		<b>3g</b>	Br	I	80	82
8		<b>3h</b>	I	I	80	78
9 <sup>c</sup>		<b>3i</b>	Br	I	60	77
10	Y = CH <sub>2</sub> CO <sub>2</sub> Et	<b>3j</b>	I	Br	80	77
11	Y = CH <sub>2</sub> NHBoc	<b>3k</b>	I	Br	60	85
12	Y = CH <sub>2</sub> NHCbz	<b>3l</b>	I	Br	60	65
13 <sup>d</sup>	Y = CH=CMe <sub>2</sub>	<b>3m</b>	I	Br	60	64
14		<b>3n</b>	I	Br	80	75
15		<b>3o</b>	I	I	80	38
16 <sup>d,e,f</sup>		<b>3p</b>	I	Br	60	88 <sup>g</sup>

<sup>a</sup> As in Table 1, footnote a, but on a 1 mmol scale. <sup>b</sup> Isolated yield of purified product. Average of two runs. <sup>c</sup> Only bipyridine **1** (0.10 mmol) was used. <sup>d</sup> Longer reaction times (26–37 h) were required. <sup>e</sup> Using 1.2 equiv of 2-bromoheptane (technical grade). <sup>f</sup> **3p**/branched isomer/linear isomer selectivity = 89:7:4. <sup>g</sup> A 95:5 mixture of **3p** and 3-phenylheptane was obtained.

over 1-phenylheptane and other branched isomers was high. Formation of the isomeric *n*-alkyl and branched products from secondary alkyl halides in cross-coupling reactions is known to occur<sup>14</sup> but is minimized in our new procedure.

The previously reported couplings of alkyl halides with aryl halides appear to involve the formation of discrete organometallic reactants, such as alkyl–ZnI<sup>5,7</sup> or alkyl–MgBr.<sup>6</sup> Several pieces of evidence argue against an analogous mechanism invoking the intermediacy of an RMnX species in our new nickel-catalyzed process: (1) consistent with literature precedent,<sup>15</sup> direct insertion of Mn<sup>0</sup> does not occur on a time scale that is competitive with the reaction (Tables S1 and S2<sup>9</sup>); (2) use of a nonmetallic reducing agent, 1,1,2,2-tetrakis(dimethylamino)ethylene (TDAE),<sup>16</sup> in place of Mn<sup>0</sup> produces an appreciable amount of product (Table 1, entry 11); (3) the reaction tolerates electrophilic functionality<sup>12</sup> and acidic protons (Table 2); and (4) reactions run using an anhydrous source of nickel [Ni(cod)<sub>2</sub>] form the same high yield of product as reactions run with a nickel hydrate (0.4 equiv of H<sub>2</sub>O). Instead, we propose that the reaction proceeds by initial reduction of [Ni<sup>II</sup>] to [Ni<sup>0</sup>],

oxidative addition of organic halide to form [Ni<sup>II</sup>](R)(X), reduction to [Ni<sup>I</sup>](R), oxidative addition of another organic halide to form [Ni<sup>III</sup>](R)(R')(X), reductive elimination of product (R–R') to form [Ni<sup>I</sup>](X), and reduction of [Ni<sup>I</sup>](X) back to [Ni<sup>0</sup>]. This is analogous to the mechanisms proposed<sup>17</sup> for nickel- or cobalt-catalyzed reductive homocoupling<sup>18</sup> and cross-coupling<sup>19</sup> reactions of aryl halides.

The role of ligand **2** remains unclear at the moment. Reactions conducted with a 1:1:1 Ni/**1**/**2** ratio did not consume starting material, and reactions catalyzed by a combination of NiI<sub>2</sub> and **2** alone provided poor yields of the cross-coupling product (Table 1, entry 3). These data imply direct participation of two distinct catalysts in this reaction.<sup>20</sup> Further investigation of this two-ligand synergistic effect, as well as work to reveal the origin of the observed cross-coupling selectivity, is ongoing. Regardless, this nickel-catalyzed reductive cross-coupling of alkyl halides with aryl halides represents an operationally simple, high-yielding method to form cross-coupled products directly from organic halides.

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

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- (8) See Table S4 in the Supporting Information for detailed data on the amounts of homocoupling and reduction products for the reactions in Table 2.
- (9) See the Supporting Information.
- (10) Excess nickel was employed in all of the reactions because excess ligand was found to slightly diminish the yield (see page S3 in the Supporting Information).
- (11) Anhydrous-grade DMPU is available from Aldrich for a similar price to DMF, and removal in workup requires only filtration through silica gel.
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