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## Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides

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### Abstract

The direct cross-coupling of two different electrophiles, such as an aryl halide with an alkyl halide, offers many advantages over conventional cross-coupling methods that require a carbon nucleophile. Despite its promise as a versatile synthetic strategy, a limited understanding of the mechanism and origin of cross selectivity has hindered progress in reaction development and design. Herein, we shed light on the mechanism for the nickel-catalyzed cross-electrophile coupling of aryl halides with alkyl halides and demonstrate that the selectivity arises from an unusual catalytic cycle that combines both polar and radical steps to form the new C-C bond.

### Introduction

Following two decades of study, cross-coupling methods such as the Suzuki-Miyaura reaction<sup>1</sup> (Figure 1) revolutionized organic synthesis in academics and industry.<sup>2</sup> These methods couple a carbon nucleophile (R-B(OH)<sub>2</sub>, R-ZnX, etc.) with a carbon electrophile. Of the two substrates, the carbon nucleophile is more difficult to access and less tolerant of functional groups. As a result, there are orders of magnitude more organic halides commercially available than organometallic reagents.<sup>3</sup> These challenges have led to the development of a variety of methods for the synthesis of carbon nucleophiles<sup>4</sup> and the development of C-H functionalization reactions that couple C-H bonds with carbon electrophiles.<sup>5</sup> A less well developed, but potentially powerful solution would be to avoid the difficulties associated with organometallic reagents by directly cross-coupling two different carbon electrophiles (Figure 1).

Recently, we and others have reported catalysts that selectively couple aryl halides with alkyl halides (Figure 1),<sup>6-78</sup> acyl halides with alkyl halides,<sup>9</sup> and  $\alpha,\beta$ -unsaturated ketones with organic halides<sup>10</sup> under reducing conditions. The reactions selectively form cross-product over the di-meric products.<sup>6-7</sup> Unlike the cross-coupling of a nucleophile with an electrophile, where there is an inherent difference in reactivity between the two coupling partners, the origin of selectivity in cross-electrophile coupling reactions was not immediately evident. This lack of understanding has prevented rational improvement of low-yielding reactions and limited development of new cross-electrophile couplings. To enable reliable application of this strategy, we decided to study the mechanism by which iodoarenes are selectively coupled with iodoalkanes and bromoalkanes using bipyridine-nickel catalysis.<sup>6</sup>

Previous studies on the stoichiometric reactivity of organonickel reagents<sup>11</sup> as well as nickel-catalyzed dimerization<sup>12</sup> and electrochemical cross-electrophile coupling

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Associated Content: Supporting Information. Figures S1-S8, experimental details, and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

reactions<sup>8a, 13</sup> have demonstrated several different potential mechanisms for cross-electrophile coupling (Figure 2): (A) *in situ* formation of an organometallic reagent from the reducing agent (e.g., RMnI) with concomitant nucleophile-electrophile cross-coupling;<sup>14</sup> (B) transmetalation between two different nickel centers,<sup>11b, 12a, 15</sup> (C) sequential oxidative addition steps at a single metal center,<sup>8a, 12c, d, 13b, 16</sup> and (D) radical chain reaction.<sup>8a, 11a, 13b</sup>

Using a mixture of stoichiometric and catalytic studies, particularly studies that varied the catalyst concentration, we have collected data that demonstrate how a radical chain mechanism (Figure 2D) can account for the selectivity observed in the cross-coupling of an alkyl halide with an aryl halide. The mechanism blends familiar polar steps found in conventional cross-coupling reactions with elements of free-radical chemistry and explains how the two different electrophiles are selectively activated at different stages of the catalytic cycle.

## Results and Discussion

We began our studies by making several small modifications to our published conditions<sup>6-7</sup> to facilitate mechanistic analysis. For simplicity, we decided to use only one bidentate ligand, 4,4'-di-*tert*-butyl-2,2'-bipyridine (**L**), which provided the best yields and selectivity among several bipyridine and bisphosphine ligands tested (Table 1 and Figure S1). Additionally, we chose to use DMF in place of DMPU because the former is readily available in deuterated form. Finally, we started with a nickel(0) pre-catalyst in some cases so that stoichiometric experiments did not require initial reduction steps. The resulting reaction is still cross-selective, and the yields are comparable to our published conditions (Table 1, entries 1 and 8).<sup>6-7</sup>

With respect to mechanism A (Figure 2A), we had previously reported that tetrakis(dimethylamino)ethylene (TDAE) can replace Mn or Zn, providing about six turnovers.<sup>6-7, 17</sup> This result appears to rule out mechanism A because the hypothetical TDAE-derived carbanion intermediate would not be stable.

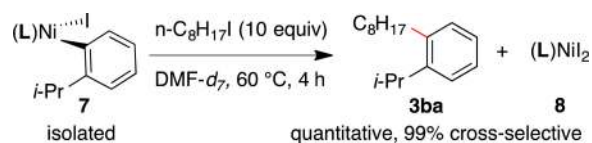
With respect to mechanism B (Figure 2B), we noted that Osakada and Yamamoto had shown that nickel-catalyzed biaryl formation from aryl halides has this mechanism in DMF (as in Figure 2B, but  $R^1=R^2$ ) and that the rate of biaryl formation has a second-order dependence on nickel concentration.<sup>15, 18</sup> If cross-coupled product was obtained by a similar transmetalation mechanism, we hypothesized that the observed selectivity for the formation of product **3aa** over biaryl **4a** should not depend upon the nickel concentration. Thus, a plot of the molar ratio of product/dimer vs. nickel concentration would give a straight, horizontal line. Instead, we observed that selectivity for the cross-coupled product improved significantly at lower nickel concentrations (Figure 3, blue). The amount of alkyl dimer formed was also dependent upon nickel concentration (Figure 3, red).<sup>19</sup> In addition, the reaction of preformed (**L**)Ni(2-tolyl)(I) (**11**) with (**L**)Ni(Et)<sub>2</sub> formed bi-tolyl and 2-ethyltoluene in a 36:1 ratio (Scheme 1). These results are inconsistent with the transmetalation mechanism.

However, the data in Figure 3 are explainable if the rate of biaryl formation has a second-order dependence on nickel concentration and the rate of cross-product formation has about a first-order dependence on nickel concentration ( $[Ni]/[Ni]^2 = 1/[Ni]$ ). In this case, higher concentrations of catalyst would result in more biaryl and lower selectivity, as we observe.

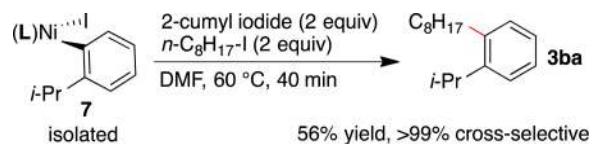
Both mechanisms C and D share the initial oxidative addition of one of the two organic iodides. In order to determine which potential intermediate, (**L**)Ni<sup>II</sup>(Ar)I or (**L**)Ni<sup>II</sup>(Alkyl)I, was formed first, we examined the relative reactivities of iodobenzene (**1a**) and iodoctane

(**2a**) with (**L**)Ni<sup>0</sup>(cod) (**6**). After subjecting **6** to an excess of both **1a** and **2a**, we quenched the reaction mixture with acid and determined both the loss of each organic iodide and the products formed (Table 2). We found that 4.7 times more **1a** than **2a** was consumed in the competition reaction with **6**. These data support the idea of a mechanism in which (**L**)Ni<sup>II</sup>(Ar)I serves as the starting intermediate of the catalytic cycle. However, the oxidative addition may be reversible (Scheme 2),<sup>20</sup> and both arylnickel<sup>8a, 13, 21</sup> and alkylnickel<sup>19, 22</sup> complexes have been reported to react with organic electrophiles.

To differentiate between a mechanism that begins with (**L**)Ni<sup>II</sup>(Ar)I from one that begins with (**L**)Ni<sup>II</sup>(Alkyl)I, we examined both intermediates under relevant reaction conditions. The (**L**)Ni<sup>II</sup>(Alkyl)<sub>2</sub> intermediate that would result from the rapid disproportionation<sup>19</sup> of two (**L**)Ni<sup>II</sup>(Alkyl)I complexes was also investigated. We found that reacting a stable, preformed arylnickel(II) species, (**L**)Ni<sup>II</sup>(2-cumyl)I (**7**), with iodoctane formed the cross-coupled product, 2-octylcumene (**3ba**), in quantitative yield and with the same high selectivity as catalytic reactions (eq 1).<sup>23</sup> Reaction of **7** with a mixture of **2a** and 2-cumyl iodide (**1b**) also formed **3ba** with complete selectivity in 56% yield (eq 2).

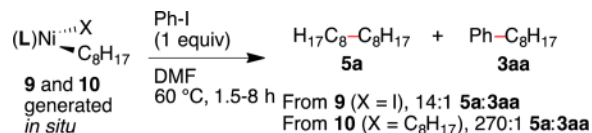


(1)



(2)

In contrast, when preformed (**L**)Ni<sup>II</sup>(octyl)I (**9**) or a mixture of (**L**)Ni<sup>II</sup>(octyl)<sub>2</sub>(**10**) and (**L**)Ni<sup>II</sup>I<sub>2</sub> were reacted with **1a** (eq 3), the alkyl dimer, hexadecane (**5a**), was the major product.<sup>24, 22a</sup> These stoichiometric studies support initial oxidative addition of iodoarene to nickel(0) to form (**L**)Ni<sup>II</sup>(Ar)I.



(3)

The above results are consistent with both mechanisms C and D. In mechanism C, (**L**)Ni<sup>II</sup>(Ar)(X) would have to react with an alkyl halide via an oxidative addition to form (**L**)Ni<sup>IV</sup>(Ar)(Alkyl)X<sub>2</sub>.<sup>25</sup> In mechanism D, (**L**)Ni<sup>II</sup>(Ar)(X) would react with an alkyl radical that originated from an alkyl halide. While oxidative addition of an alkyl halide, as in C,

may<sup>26</sup> or may not<sup>27</sup> involve an alkyl radical intermediate, mechanism D must involve a radical intermediate.

To test for radical intermediates,<sup>28</sup> we next examined reactions with two radical probes, cyclopropylmethyl bromide (**2b**) and an enantioenriched secondary bromide (**2c**).<sup>29</sup> If the alkyl halide is converted to an alkyl radical intermediate, we would expect to observe some amount of rearranged products, **3cb'** and **3ab'** due to the rapid rearrangement of cyclopropylmethyl radicals to homoallylic radicals.<sup>26, 30, 31</sup> Consistent with the presence of a radical intermediate, we observed only the rearranged products **3cb'** and **3ab'** (Scheme 3). Similarly, the observation of ( $\pm$ )-**3ac** without background racemization of **2c** suggests a radical intermediate.<sup>32</sup>

While both mechanisms C and D could involve an alkyl radical intermediate, the two mechanisms differ in the number of nickel centers with which each alkyl radical interacts. In mechanism C, the radical would be generated and consumed at the same nickel center to provide a net oxidative addition, but *in mechanism D, the radical is generated and consumed at different nickel centers*. Only in mechanism D would the apparent radical lifetime (degree of radical clock rearrangement) change with the concentration of the nickel catalyst. A similar strategy was used to probe radical chain reactions previously.<sup>26c-e</sup>

We chose to examine the effect of catalyst concentration on the products formed from the reaction of 5-hexenyl-1-iodide (**2d**) with iodobenzene (**1a**) (Figure 4). The 5-hexenyl radical rearranges to the cyclopentylmethyl radical more slowly than the cyclopropylmethyl radical rearranges to a homoallylic radical, allowing us to observe both the unrearranged (**U**, **3ad** and olefin isomers) and rearranged (**R**, **3ad'**) products under our standard conditions. If mechanism C was operative, we would expect that **U/R** would not change with catalyst concentration. If mechanism D, a radical chain, was operative, then we would expect that **U/R** would increase at higher catalyst concentrations. This is because at higher catalyst concentrations, the radical has less time to rearrange before reacting with another nickel. Under standard conditions, some rearrangement of **2d** to cyclopentylmethyl iodide was observed, but control experiments confirmed that this was not the major source of **R** (**3ad'**). This rearrangement could be minimized by using Mn activated with TMS-Cl (See Supporting Information for details). Figure 4 shows that **U/R** depends upon catalyst concentration, consistent with mechanism D, but not mechanism C.<sup>33, 34</sup>

Taken together, these observations support mechanism D: (1) bipyridine-ligated nickel(0) reacts selectively with aryl iodide over alkyl iodide to form an arylnickel(II) intermediate; (2) stoichiometric reaction of an arylnickel(II) intermediate with iodoalkane forms product without added reductant; (3) reaction of an alkylnickel(II) intermediate with an arylnickel(II) intermediate did not form product; and (4) an alkyl radical is generated in the reaction with a lifetime inversely dependent on catalyst concentration. A proposed catalytic cycle that is consistent with these data is shown in Scheme 4.

The mechanism in Scheme 4 begins with selective oxidative addition of an aryl iodide to nickel(0). The resulting arylnickel(II) species appears to be the resting state of the catalyst<sup>35</sup> and reacts with an alkyl radical to form a diorganonickel(III) intermediate.<sup>36</sup> Reductive elimination of the cross-product generates a reactive nickel(I) species that can react with the alkyl iodide to generate a nickel(II) diiodide and regenerate an alkyl radical.<sup>37</sup> Finally, the nickel(II) diiodide is reduced by the manganese reductant to regenerate nickel(0) intermediate **6**.<sup>12c</sup>

Although we have not studied initiation in detail, we propose that either Mn<sup>11b</sup> or (L)Ni<sup>II</sup>(Ar)I<sup>38</sup> could participate. For the nickel-mediated mechanism, see Scheme 5. When

sufficient alkyl radicals are present, a radical-chain mechanism dominates (B). At low radical concentration, self initiation could occur by halogen-atom abstraction by  $(\mathbf{L})\text{Ni}^{\text{II}}(\text{Ph})\text{I}$  according to the general mechanism found in atom-transfer radical addition reactions (A).<sup>38</sup> The resulting  $(\mathbf{L})\text{Ni}^{\text{III}}(\text{Ar})\text{I}_2$  complex could extrude Ar-I to form  $(\mathbf{L})\text{Ni}^{\text{II}}\text{I}$ , which is a proposed on-cycle intermediate.<sup>39</sup> If this step is reversible, the observed inverse dependence of the rate of product formation on aryl halide concentration<sup>7</sup> could be explained as competitive inhibition.

The second selectivity-determining step, generation of an alkyl radical, is part of a radical chain reaction embedded in the catalytic cycle (Scheme 4, radical hemisphere). This type of radical-chain mechanism was first proposed by Hegedus for the stoichiometric reaction of preformed allylnickel(II) reagents with organic halides,<sup>11a</sup> and Durandetti<sup>8a</sup> and Devaud<sup>13b</sup> later suggested it may play a role in electrochemically driven cross-electrophile coupling. However, later studies by Hegedus and Kochi favored a variation on mechanism B involving transmetalation between a transient nickel(III) species and the starting allylnickel(II) complex,<sup>11b, 12a</sup> and Durandetti noted that both mechanisms C and D could be operative. Our study on selectivity as a function of nickel concentration (Figure 3) and the reported low selectivity of nickel(I) in oxidative addition<sup>37</sup> argue against the later Hegedus mechanism, but we cannot rule out reversible formation of an unstable  $(\mathbf{L})\text{Ni}^{\text{III}}(\text{alkyl})\text{X}_2$  intermediate.<sup>39-40</sup> Our study on radical lifetime as a function of nickel concentration (Figure 4) appears to rule out mechanism C.

The selectivity for cross-coupled product results from two different steps: (1) selective oxidative addition of iodoarene over iodoalkane and (2) selective formation of an alkyl radical over an aryl radical (Scheme 4). Biaryl and bialkyl formation appears to arise from competing mechanisms, perhaps involving disproportionation of organonickel intermediates<sup>15, 18</sup> or radical recombination. Besides the improved selectivity that can be achieved at lower catalyst concentration (Figure 3), ligands that disfavor disproportionation could be advantageous. These results are also consistent with our observations that highly reactive alkyl halides, such as benzyl bromide, or poorly reactive aryl halides, such as iodomesitylene, produce low yields of cross-coupled product. In these cases, formation of an allylnickel(II) intermediate would be faster than formation of the key arylnickel(II) intermediate, resulting in low cross-selectivity and yield. Application of this new mechanistic understanding to the rational improvement of difficult cross-electrophile coupling reactions is ongoing, as are further studies to better understand the observed ligand effects (Table 1).

## Conclusions

These studies demonstrate how the combination of conventional two-electron steps with single-electron radical chain steps can enable new selectivity and reactivity in catalysis, a nascent area that has recently been reviewed.<sup>41</sup> Although radical intermediates are routinely invoked for nickel-catalyzed cross-coupling reactions, with the exception of Hu's recent report,<sup>36, 42</sup> they are generally suggested to recombine with the same nickel complex that formed them via a rebound-type mechanism.<sup>22c, 43</sup> Given the subtle differences between the rebound and radical chain mechanisms and our results, other cross-coupling reactions that use nickel catalysts to couple organometallic reagents with alkyl halides may also proceed through a similar radical chain mechanism.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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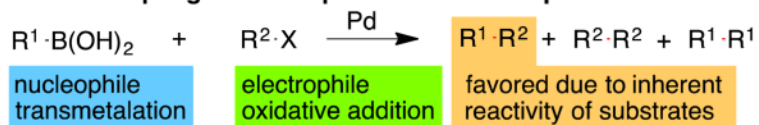
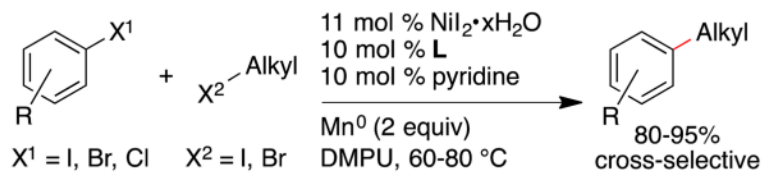
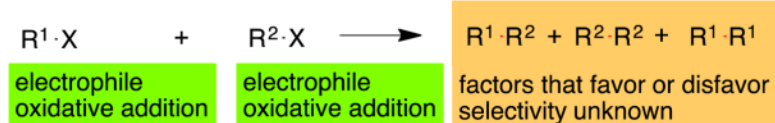
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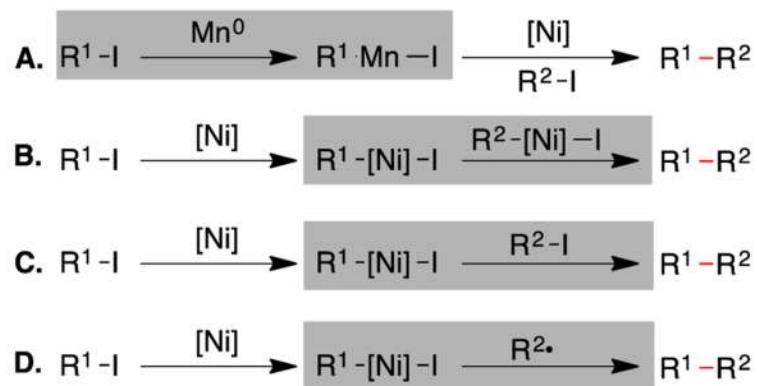
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33. A reviewer suggested, correctly, that a radical-chain oxidative addition to form (L)Ni<sup>IV</sup>(Ar)(Alkyl)X<sub>2</sub> would also be consistent with our results. While we cannot rule out this possibility, it would require that reductive elimination from (L)Ni<sup>III</sup>(Ar)(Alkyl)X be slower than its reaction with alkyl-X. Decomposition of diorganonickel(III) complexes is reported to be rapid, see the following endnote.
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35. Two points argue that arylnickel(II) is the resting state of the catalyst: (1) reaction mixtures are red, consistent with the presence of arylnickel(II), but not (L)Ni<sup>0</sup> (purple) or (L)Ni<sup>II</sup>I<sub>2</sub> (light green); (2) acid-quenched aliquots of the reaction in Table 1, entry 1 showed the presence of arene (48% of catalyst loading) during periods of product formation, but not at the end of the reaction (8% of catalyst loading), consistent with an arylnickel intermediate being present during the reaction but not at the end (Figure S3).
36. Breitenfeld J, Ruiz J, Wodrich MD, Hu X. *J Am Chem Soc.* 2013; 135:12004–1201. [PubMed: 23865460]

37. Yakhvarov DG, Budnikova YH, Sinyashin OG. *Russ Chem Bull.* 2003; 52:567–569.
38. van de Kuil LA, Grove DM, Gossage RA, Zwikker JW, Jenneskens LW, Drenth W, van Koten G. *Organometallics.* 1997; 16:4985–4994.
39. Higgs AT, Zinn PJ, Simmons SJ, Sanford MS. *Organometallics.* 2009; 28:6142–6144.
40. Grove DM, Van Koten G, Zoet R, Murrall NW, Welch AJ. *J Am Chem Soc.* 1983; 105:1379–1380.
41. (a) Jahn U. *Top Curr Chem.* 2012; 320:121–451. [PubMed: 22025066] (b) Jahn U. *Top Curr Chem.* 2012; 320:191–322. [PubMed: 22143610] (c) Jahn U. *Top Curr Chem.* 2012; 320:323–451. [PubMed: 22143611]
42. For radical intermediates in Pd-catalyzed coupling, see: Manolikakes G, Knochel P. *Angew Chem, Int Ed.* 2009; 48:205–209.
43. (a) Lin X, Phillips D. *J Org Chem.* 2008; 73:3680–3688. [PubMed: 18410144] (b) Lin X, Sun J, Xi Y, Lin D. *Organometallics.* 2011; 30:3284–3292. (c) Li Z, Jiang YY, Fu Y. *Chem –Eur J.* 2012; 18:4345–4357. [PubMed: 22374716]

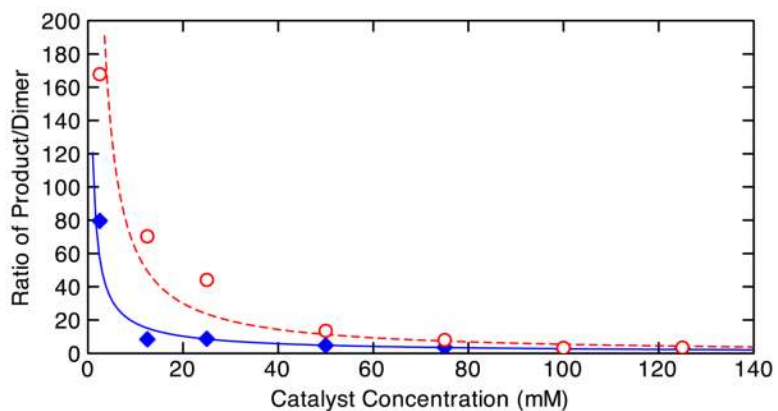
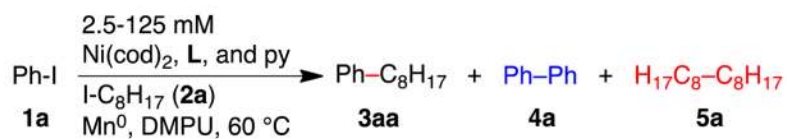


**Cross-Coupling of Nucleophiles with Electrophiles****Cross-Electrophile Coupling – This Work****Figure 1.**

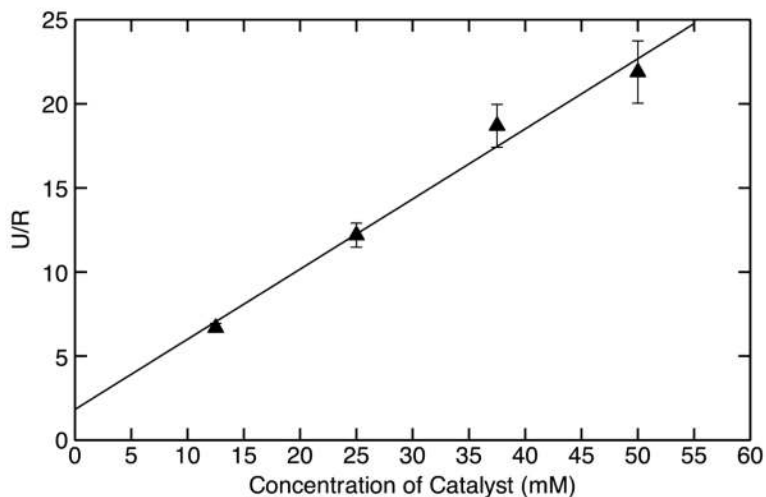
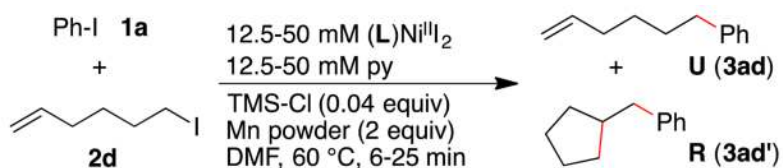
Comparison of the selectivity models of conventional cross-coupling and the studied cross-electrophile coupling. **L** = 1:1 4,4'-di-*tert*-butyl-2,2'-bipyridine:1,2-bis(diphenylphosphino)benzene, 4,4'-di-MeO-2,2'-bipyridine, or 1,10-phenanthroline.



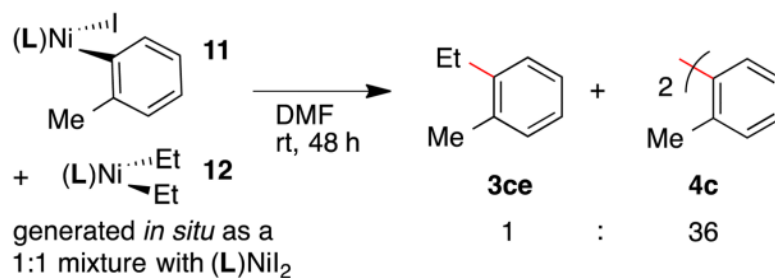
**Figure 2.** Potential mechanisms for cross-electrophile coupling: (A) *in situ* formation of an organometallic reagent ( $R^1MnI$ ) followed by cross-coupling; (B) transmetalation between two organonickel species; (C) sequential oxidative additions at a single nickel center; (D) radical chain reaction.  $R^1$  and  $R^2$  could be either alkyl or aryl.



**Figure 3.** Change of the molar ratio of **3aa/5a** (red circles) and **3aa/4a** (blue diamonds) with catalyst concentration, suggesting product and dimers arise from different mechanisms. Exponential fits: solid blue line:  $f(x) = 121.05x^{-0.824}$ ,  $R^2 = 0.94$ ; dashed red line:  $f(x) = 723.81x^{-1.063}$ ,  $R^2 = 0.92$ .

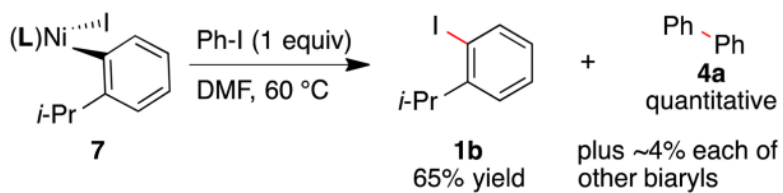


**Figure 4.** Ratio of **U** (**3ad**, includes olefin isomers) to **R** (**3ad'**) formed in reactions at different catalyst concentrations, showing that the degree of rearrangement, a measure of the radical lifetime, depends upon nickel concentration. The data shown are for 50-100% conversion to avoid fluctuations in active catalyst concentration at the beginning of the reaction. Error bars are SD of the data used for the plot. Linear fit:  $f(x) = 0.417x + 1.83$ ;  $R^2 = 0.984$ . The same experiment run with unactivated Mn gave the same conclusion, but the reactions had longer induction periods (Figure S2).

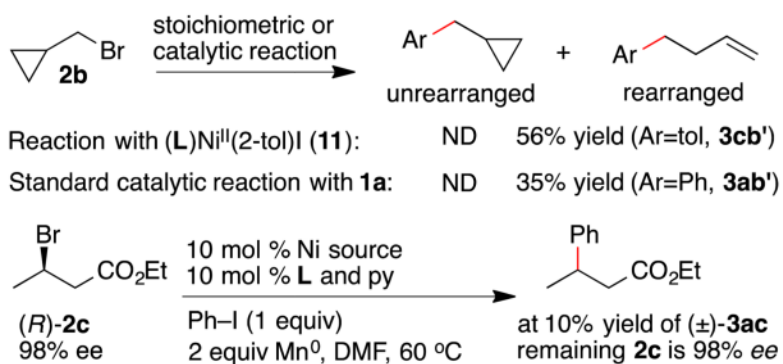


**Scheme 1. Formation of Biaryl From the Reaction of Arylnickel with Alkylnickel<sup>a</sup>**

<sup>a</sup> Ratio of organic products determined by GC analysis. See Supporting Information for full details. The corresponding reaction with  $(\text{L})\text{Ni}(\text{Et})\text{I}$  could not be run because this intermediate could only be generated at low concentration with an excess of Et-I, *vide infra*.

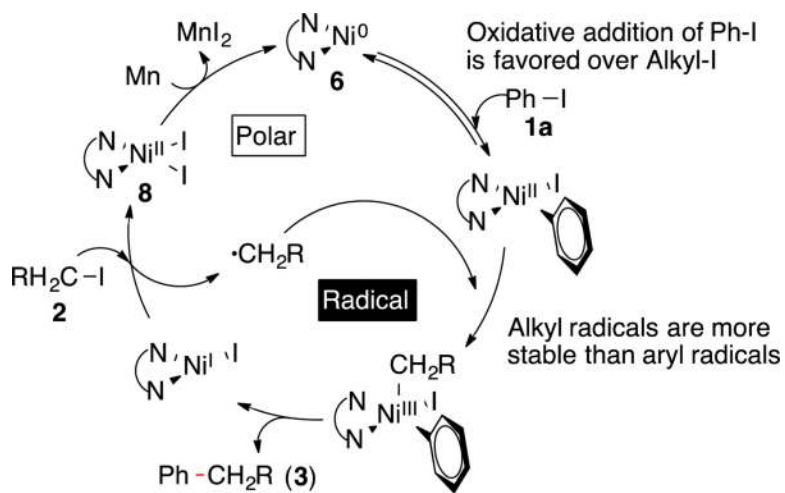


Scheme 2. Apparent Reversibility of Oxidative Addition



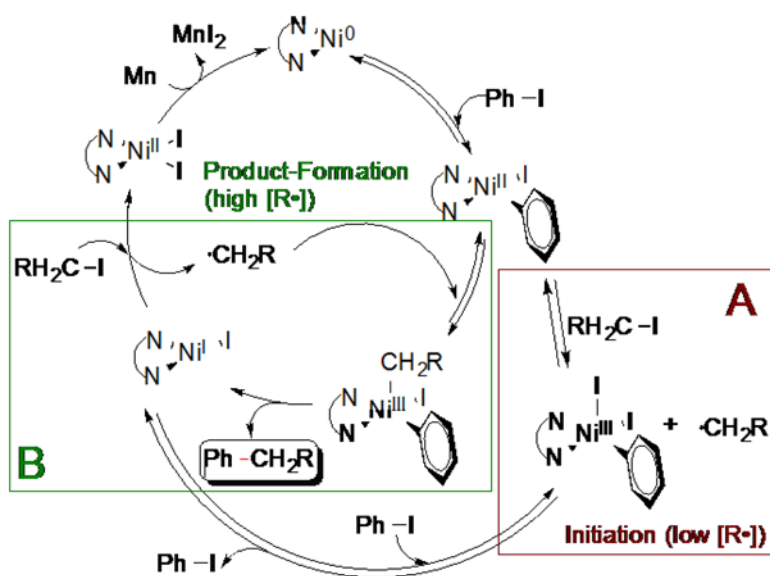
**Scheme 3. Radical Clock Experiments<sup>a</sup>**

<sup>a</sup> ND = none detected. Catalytic reaction as in Table 1, entry 1.



**Scheme 4. Proposed Mechanism for Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides**





Scheme 5. Hypothesis for Self Initiation

**Table 1**  
**Reaction Conditions Used for Mechanistic Studies<sup>a</sup>**

entry	Ligand	yield 3 (%)	ratio 3:(4+5)
1	4,4'-di- <i>tert</i> -butyl-2,2'-bipyridine(L)	60(62)	3:1
2	4,4'-dimethyl-2,2'-bipyridine	55	2:1
3	2,2'-bipyridine	52	2.7:1 <sup>b</sup>
4	4,4'-dimethoxy-2,2'-bipyridine	40	0.9:1
5	5,5'-bis(trifluoromethyl)-2,2'-bipyridine	39	0.9:1
6	1,2-bis(diphenylphosphino)ethane	16	2.2:1 <sup>b</sup>
7	1,2-bis(diphenylphosphino)benzene	27	1.7:1 <sup>b</sup>
g <sup>c</sup>	4,4'-di- <i>tert</i> -butyl-2,2'-bipyridine (L)	(87)	16:1

<sup>a</sup> Reaction of iodobenzene (**1a**) with iodoctane (**2a**) to form octylbenzene (**3aa**), see Supporting Information for procedure. Yields and ratios are from raw GC area% (A%) data, which has proven useful in comparing reactions. Yields in parenthesis are calibrated GC yields.

<sup>b</sup> Larger amounts of olefin, alkane, and arene side products (>25 A%) diminished yield.

<sup>c</sup> 2-Iodocumene (**1b**) was used in place of iodobenzene to form product **3ba**, 2-octylcumene.

Table 2

Selectivity in Oxidative Addition to (L)Ni<sup>0</sup>(cod)<sup>a</sup>

PhI <b>1a</b> + H <sub>17</sub> C <sub>8</sub> I <b>2a</b> + (L)Ni <sup>0</sup> (cod) <b>6</b>		1. DMF, rt 2. NaHSO <sub>4</sub> (aq)		PhH + Ph-Ph + Ph-C <sub>8</sub> H <sub>17</sub> + H <sub>34</sub> C <sub>16</sub>			
				<b>4a</b>	<b>3aa</b>	<b>5a</b>	
substrate	total conv. (%) <sup>b</sup>	to or (%) <sup>c</sup>	Alkyl-H Ph-H	to <b>4a</b> (%) <sup>c</sup>	to <b>3aa</b> (%) <sup>c</sup>	to <b>5a</b> (%) <sup>c</sup>	
Ph-I	89	49		21	13	NA	
H <sub>17</sub> C <sub>8</sub> -I	19	0		NA	51	45	

<sup>a</sup> A 1:1 mixture of **1a:2a** was added to a DMF solution of **6**. Samples were analyzed by GC. Reported values are an average of data using between 2 and 40 equiv each of **1a** and **2a** to **6**. See Supporting Information for full experimental details.

<sup>b</sup> Conversion with respect to amount of **6**.

<sup>c</sup> Yield with respect to amount of **6**. NA = not applicable.