

## Oxidative Cross-Coupling through Double Transmetalation: Surprisingly High Selectivity for Palladium-Catalyzed Cross-Coupling of Alkylzinc and Alkynylstannanes

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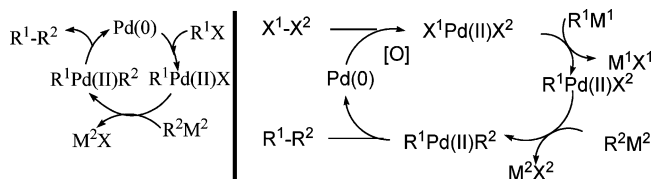
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Palladium-catalyzed cross-coupling reactions have been the center of focus for transition metal chemistry during the past three decades, evolving into one of the most powerful tools for the construction of carbon–carbon and carbon–heteroatom bonds.<sup>1</sup> A general pathway is illustrated in Scheme 1 for many transition metals promoted cross-couplings.<sup>2</sup> This classic pathway typically involves three major fundamental unit reactions: (1) oxidative addition or insertion of the low valent transition metal into the electrophilic carbon–heteroatom bond, (2) transmetalation or displacement of a heteroatom leaving group by the nucleophilic partners, and finally, (3) reductive elimination to form a new C–C or C–heteroatom bond. So far, this classic mode has been extensively studied and widely applied in the coupling of  $sp$ - and  $sp^2$ -hybridized carbon.<sup>3</sup> Cross-coupling has been problematic for  $sp^3$ -hybridized carbon bond formation, and the reasons are multifaceted: (1) slow oxidative addition (O.A.) of  $R_{alkyl}X$ , (2) deleterious  $\beta$ -hydride elimination, and (3) sluggish reductive elimination (R.E.) involving  $C_{sp^3}$ -carbon centers.<sup>4,5</sup> Recently, noteworthy progress has been achieved in Pd-catalyzed  $C_{sp^3}$ – $C_{sp^3}$  bond formation using electron-rich and highly hindered trialkyl phosphines as ligands.<sup>6–16</sup>

Herein, we introduce something different from the traditional cross-couplings by bringing two nucleophilic partners together by a Pd-mediated *oxidative cross-coupling mechanism*, as depicted in Scheme 2. Specifically, the new process would involve successive transmetalation of a divalent palladium species  $X^1$ -Pd(II)- $X^2$  to afford the key intermediate  $R^1$ -Pd(II)- $R^2$ . Reductive elimination of this compound gives rise to the cross-coupled product  $R^1$ - $R^2$ , and a reduced palladium(0) entity. To achieve this, several hurdles have to be overcome. First an appropriate system has to be found to favor the formation of a heterosubstituted intermediate  $R^1$ -Pd(II)- $R^2$ , in preference to the formation of homosubstituted  $R^1$ -Pd(II)- $R^1$  or  $R^2$ -Pd(II)- $R^2$ , which would yield uninspiring homocoupled product  $R^1$ - $R^1$  and  $R^2$ - $R^2$ , respectively. The second challenge, in no small magnitude, is the selection of a suitable oxidizing agent to render a complete catalytic cycle by converting the Pd(0) species into a  $X^1$ Pd(II) $X^2$  to enable the double transmetalation. Toward this end, an essential requirement must be met: this oxidizing agent ( $X^1$ - $X^2$ ) must not react with either of the organometallic agents, with or without Pd catalysis. In this communication, we report a Pd-catalyzed  $C_{sp}$ – $C_{sp^3}$  oxidative cross-coupling<sup>17,18</sup> via the strategy of double transmetalation of organozinc and organotin reagents.

According to the assumption in Scheme 2, the oxidative cross-coupling would be depended on the proper selection of oxidant  $X^1$ - $X^2$ . We envisioned that  $\alpha$ -halocarbonyl compound, for example, 2-chloro-2-phenylacetophenone (desyl chloride), would be a potential candidate, or its proved ability at promoting the homocoupling of type  $C_{sp}$ – $C_{sp}$ ,  $C_{sp^2}$ – $C_{sp^2}$ , and  $C_{sp^3}$ – $C_{sp^3}$ .<sup>19–21</sup> The oxidative addition of desyl chloride to Pd(0) species will form O-bounded Pd enolate chloride.<sup>19</sup> Thus the newly formed Pd species will contain two types of leaving groups: enolate anion and chloride

Scheme 1



anion (Figure 1). In order to achieve the oxidative cross-coupling in Scheme 2, two differentiating metal reagents  $R^1M^1$  and  $R^2M^2$  were needed to obtain the desired heterosubstituted intermediate.

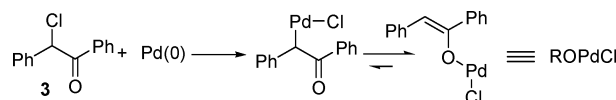


Figure 1

Our initial attempts at identifying an appropriate pair of organometallic reagents are listed in Table 1. The reactions of alkylzinc (**1a**) with Si-, Zn-, and B-reagents provided low selectivity for the desired product. The reactions of alkynylzinc reagent (**2a**) with alkylboronic (**1b**) and alkylsilicate reagent (**1c**) favored the formation of diyne (**6**), in 87% and 63% yield, respectively. We were very delighted to find that a combination of organozinc **1a** and organotin **2b** displayed promising result for the coupling of  $C_{sp}$  and  $C_{sp^3}$  centers, in which cross-coupling product **4** was obtained in 67% yield in the presence of  $PdCl_2(dppf)$ , while only 26% of both homocoupling products of  $C_{sp}$ – $C_{sp}$  and  $C_{sp^3}$ – $C_{sp^3}$  was observed (Table 1, entry 2).

We then investigated the ligand effect on this oxidative cross-coupling, and the results were listed in the Supporting Information.

Table 1. The Combination of Different Organometallic Reagents for Palladium-Catalyzed Oxidative Cross-Coupling<sup>a</sup>

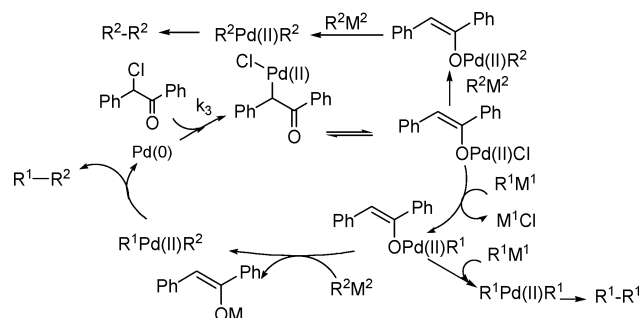
Entry	$R^1$ - $M^1$	$R^2$ - $M^2$	Yield(%) <sup>b</sup>		
			4a	5	6
1			3	12	0
2			67	12	14
3			42	1	54
4			41	15	49
5			0	3	87
6			24	10	63

<sup>a</sup> Reaction condition: The reactants of **1, 2**, and **3** (the ratio of 2:1.2:1) was mixed in THF in the presence of 2.5 mol %  $PdCl_2(dppf)$  in 60 °C.  
<sup>b</sup> The yield was detected by GC in 5 h using naphthalene as the internal standard.  
<sup>c</sup> The reagents were prepared in situ by mixing the corresponding Grignard reagent and tributyl borate and tetraethyl orthosilicate, respectively.

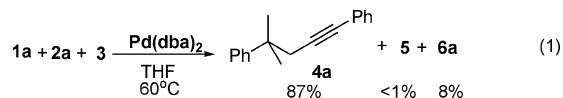
**Table 2.** Palladium-Catalyzed Oxidative Cross-Coupling<sup>a</sup>

Entry	2	1	Yield <sup>a</sup> (%)
1	Ph—C≡C—SnBu <sub>3</sub>	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ZnCl	91
2		<i>n</i> -C <sub>12</sub> H <sub>25</sub> ZnCl	94
3		Ph—CH <sub>2</sub> —ZnCl	93
4		BrZn—CH <sub>2</sub> —CH <sub>2</sub> —COOEt	92
5		<i>n</i> -C <sub>4</sub> H <sub>9</sub> ZnCl	76
6	<i>n</i> -C <sub>5</sub> H <sub>11</sub> —C≡C—SnBu <sub>3</sub>	<i>n</i> -C <sub>8</sub> H <sub>17</sub> ZnCl	77
7		<i>n</i> -C <sub>12</sub> H <sub>25</sub> ZnCl	95
8		Ph—CH <sub>2</sub> —ZnCl	94
9		Ph—C(CH <sub>3</sub> ) <sub>2</sub> —ZnCl	80
10		<i>n</i> -C <sub>4</sub> H <sub>9</sub> ZnCl	67

<sup>a</sup> Reaction condition: The reactants of **1**, **2**, and **3** (the ratio of 2:1.2:1) was mixed in THF in the presence of 2.5 mol % Pd(dba)<sub>2</sub> in 60 °C; isolated yield.

**Scheme 3**

Interestingly, the surprisingly high selectivity toward cross-coupling came from the system using simple Pd(dba)<sub>2</sub> as the catalyst precursor without exogenous phosphine ligands. Using this catalyst, the desired cross-coupling product **4a** was obtained in 87% yield, while the extent of C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>3</sup> homocoupling was less than 1%, and the C<sub>sp</sub>–C<sub>sp</sub> homocoupling was 8% (eq 1).



The substrate scope of the Zn–Sn oxidative cross-coupling reaction was examined and the results are summarized in Table 2. High selectivity of C<sub>sp</sub>–C<sub>sp</sub><sup>3</sup> cross-coupling products were achieved for all tested substrates in Table 2, and the homocoupling byproduct, either C<sub>sp</sub>–C<sub>sp</sub> or C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>3</sup>, was less than 5%. It is interesting to note that the current catalytic system tolerates the presence of β-H well. Excellent yields were obtained when long chain alkyl zinc reagents (*n*-C<sub>12</sub>H<sub>25</sub>ZnCl and *n*-C<sub>8</sub>H<sub>17</sub>ZnCl) were employed as the substrates (Table 2, entries 1, 3, 6, and 8). Functional groups, such as phenyl and carbonyl group, could be tolerated in this system (Table 2, entries 4, 5, and 9). When a short-chain alkyl zinc reagent, such as *n*-C<sub>4</sub>H<sub>9</sub>ZnCl, was employed as the substrate, fairly good yields (76% and 67%) of cross-coupling products were obtained, while the corresponding diynes homocoupling were still less than 5%.

A possible mechanism for the oxidative cross-coupling is proposed in Scheme 3. The oxidative addition of desyl chloride to Pd(0) generates the C-bound Pd enolate chloride, which undergoes tautomerization into O-bound Pd enolate chloride. The ensuing double transmetalation with zinc and tin reagents on the Pd(II)

species produces the C<sub>sp</sub>–Pd–C<sub>sp</sub><sup>3</sup> intermediate. The final reductive elimination yields the desired cross-coupling product. Theoretically, two homocoupled products (C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>3</sup> and C<sub>sp</sub>–C<sub>sp</sub>) could be formed at 25% each along with 50% of the heterocoupled product under a nonselective situation. The observed high selectivity toward C<sub>sp</sub>–C<sub>sp</sub><sup>3</sup> cross-coupling may be a reflection of either the different rates of transmetalation by the organozinc and organostannanes with ROPdCl (R = stilbenyloxy), or the favorable reductive elimination for the heterosubstituted intermediate (R<sup>1</sup>PdR<sup>2</sup>). Preliminary kinetic studies (see Supporting Information) by in situ IR reveals that the rate of formation of R<sup>1</sup>–R<sup>2</sup> is faster than that of R<sup>1</sup>–R<sup>1</sup> and R<sup>2</sup>–R<sup>2</sup>. In addition, we identified the formation of ROZnCl (R = stilbenyloxy), and found that its rate of formation is almost equal to that of the consumption of desyl chloride and the formation of cross-coupling product R<sup>1</sup>–R<sup>2</sup> (see Supporting Information, this tends to implicate the rate-limiting nature of the transmetalation step to form R<sup>1</sup>PdR<sup>2</sup>.<sup>2</sup> However, given the multiple possibilities of Pd(II) species within the reaction system, the underlying reasons for the selectivity still remain to be elucidated.

In conclusion, useful selectivity can be achieved for palladium catalyzed oxidative cross-couplings, with the appropriate combination of organometallic partners. High selectivity and yields for the C<sub>sp</sub>–C<sub>sp</sub><sup>3</sup> cross-coupling were obtained using Pd(dba)<sub>2</sub> as the catalyst precursor. This may present a new mode for carbon–carbon bond formation. Many aspects regarding other oxidative cross-couplings, such as the bond formation of C<sub>sp</sub><sup>2</sup>–C<sub>sp</sub><sup>3</sup>, C<sub>sp</sub><sup>2</sup>–C<sub>sp</sub><sup>2</sup>, and C<sub>sp</sub><sup>1</sup>–C<sub>sp</sub><sup>3</sup>, others combinations of organometallic reagents, and kinetic studies of transmetalation and reductive elimination, are under investigation in our laboratory.

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**Supporting Information Available:** Ligand effects, kinetic studies, spectroscopic data, GC–MS, experiments details, and ligand effects. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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