# Palladium-Catalyzed R(sp<sup>3</sup>)–Zn/R(sp)–SnBu<sub>3</sub> Oxidative Cross-Coupling

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**Abstract:** A novel bond formation through oxidative cross-coupling with desyl chloride as the oxidant has been investigated. The coupling can be carried out under mild conditions. The Csp<sup>3</sup>-center carbon was involved even in the presence of a  $\beta$ -H, and up to 90% of the desired cross-coupling product was obtained with the secondary Csp<sup>3</sup>-center substrate.

Key words: oxidative cross-coupling, transmetalation, organotin reagents, organozinc reagents, palladium



Scheme 1

## Introduction

The transition-metal-catalyzed cross-coupling reaction is one of the most focused as well as the most fruitful areas for the construction of carbon–carbon and carbon–heteroatom bonds.<sup>1–3</sup> In general, the reaction involves three elementary steps: (1) an oxidative addition of R<sup>1</sup>X (X = I, Br, OTf, etc.) to the metal complexes to form R<sup>1</sup>MX; (2) a transmetalation of R<sup>1</sup>MX with an other organometallic reagent leading to R<sup>1</sup>MR<sup>2</sup>; and (3) a reductive elimination of R<sup>1</sup>MR<sup>2</sup> to form the desired R<sup>1</sup>–R<sup>2</sup> products.<sup>4</sup> In the 1970s, several new cross-coupling reactions were discovered by employing different organometallic reagents (in the transmetalation step), such as Kumada reaction (R<sup>2</sup>Li or R<sup>2</sup>MgX),<sup>5,6</sup> Negishi reaction (R<sup>2</sup>ZnX, etc.),<sup>7,8</sup> Suzuki reaction [R<sup>2</sup>B(OH)<sub>2</sub>],<sup>9</sup> and the Stille reaction (R<sup>2</sup>SnBu<sub>3</sub>),<sup>10</sup>

SYNTHESIS 2008, No. 4, pp 0649–0654 Advanced online publication: 29.10.2007 DOI: 10.1055/s-2007-990863; Art ID: Z17407SS © Georg Thieme Verlag Stuttgart · New York which generally involved ArI or ArBr as the electrophiles. Recently, by employing electron-rich and/or sterically hindered ligands in cross-coupling reactions, another breakthrough was achieved by using R<sup>1</sup>Cl as the electrophile for the above-mentioned cross-couplings.<sup>11–24</sup> It was proved that the electron-rich and/or sterically hindered ligands can facilitate the oxidative addition of ArX and Pd species.<sup>19,20,25–27</sup>

Compared with above-mentioned achievements, moderate attention was given to the reductive elimination. In terms of the influence of electronic property, the use of electron-rich ligands, though accelerating the oxidative addition, will inhibit the reductive elimination.<sup>28</sup> In fact, there are still many problems and challenges in employing Csp<sup>3</sup>-center as one or both coupling partners.<sup>29</sup> The oxidative addition of Rsp<sup>3</sup>–X to transition-metal complexes is slower than others (Rsp–X and Rsp<sup>2</sup>–X); the fast  $\beta$ -H elimination of the formed alkyl–metal complexes will compete with the cross-coupling;<sup>13,29,30</sup> furthermore, according to Hartwig and Espinet's report, the reductive elimination of  $Csp^2-Pd-Csp^3$  is rather slow.<sup>31,32</sup> Due to these problems, it is difficult to promote the oxidative addition and the reactive elimination at the same time. It is noteworthy that Knochel et al. successfully promoted  $Csp^3$ -invovled cross-coupling by employing the Ni catalysts in the presence of olefin ligands or functional groups in the substrates.<sup>33–37</sup> Not long ago, our research group reported a novel oxidative cross-coupling reactions by using desyl chloride as the oxidant,<sup>38</sup> which seems to be able to address some of the above problems. Herein, we would like to report more details regarding this transformation and the further optimized procedures for the palladium-catalyzed  $R(sp^3)$ –Zn/R(sp)–SnBu<sub>3</sub> oxidative cross-coupling (Scheme 1).

## **Scope and Limitations**

One of our research interests lies in the  $\alpha$ -functionalization of carbonyl compounds. We have attempted to use  $\alpha$ halocarbonyl compounds as the electrophiles to couple with other aryl nucleophiles, such as ArB(OH)<sub>2</sub>, ArZnX, etc.; but we unexpectedly observed that the  $\alpha$ -halocarbonyl compounds could promote the palladium-catalyzed homocoupling reactions of the nucleophiles.<sup>39–41</sup> To understand the mechanistic pathway of these homocoupling reactions, we speculated that the  $\alpha$ -halocarbonyl compounds served as an oxidant. After the oxidative addition, the C-bound Pd-enolate generated from the oxidative addition of  $\alpha$ -halocarbonyl compounds and Pd can tautomerize into the O-bound Pd-enolate (ROPdX, Scheme 2), which, containing two leaving groups, could therefore transmetalate twice with the organometallic reagents, and finally led to the homocoupling products. This hypothesis encouraged us to further investigate the possibility of cross-coupling reaction in this approach, of which the key was to find two different organometallic reagents, which can selectively transmetalate with RO–Pd and Pd–X.





After many attempts, it was found that the combination of Rsp<sup>3</sup>–Zn and Rsp–Sn in the presence of desyl chloride was promising. We thus turned our attention to the investigation of the ligands effects with the results listed in Table 1. We could see from the data in Table 1 that the sterically hindered ligands, such as 15,16,17 and 18 only produced low to moderate amounts of cross-coupling products, that Ph<sub>3</sub>P (14) had almost no selectivity as for the desired cross-coupling, and that the phosphite ligand 19 generated the cross-coupling product in 41% yield. BINAP (12) and BIPHEP (21) also showed low selectivities. The reactions using dppf (13), Xantphos (22), and ligand 20 provided the desired cross-coupling in the yields of 50%, 41% and 18%, respectively. Surprisingly, the catalyst precursor Pd(dba)<sub>2</sub> without extrogenous ligands showed the best result in this oxidative cross-coupling; 87% yield for the Csp–Csp<sup>3</sup> cross-coupling product was obtained (Table 1, entry 12).

 Table 1
 Palladium-Catalyzed Cross-Coupling Oxidized by 3a Using Different Ligands

1 + 2 + 3	Pd(dba) <sub>2</sub> /L THF Ph +	Ph + 10	PhPh		
Entry	Ligand	Yield (%) <sup>a</sup>			
		4	10	11	
1	rac-BINAP 12	4.2	0.1	16	
2	dppf 13	50	trace	28	
3	Ph <sub>3</sub> P <b>14</b>	1.6	19	5.9	
4	<i>t</i> -Bu <sub>3</sub> P <b>15</b>	27	7.5	5.2	
5	P	22	0.6	2.5	
	16				

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#### Table 1 Palladium-Catalyzed Cross-Coupling Oxidized by 3a Using Different Ligands (continued)

1 + 2 + 3 -	Pd(dba) <sub>2</sub> /L THF Ph + Ph	Ph + Ph=	<u>= </u> Ph ] 11	
Entry	Ligand	Yield (%) <sup>a</sup>		
		4	10	11
6		46	0.8	9.3
7	I/ P'Bu <sub>2</sub>	58	3.5	36
8	$ \begin{array}{c} 18 \\ ( 'Bu \longrightarrow O P \\ 3 \\ 19 \\ \end{array} $	41	7.4	8.5
9	$H \\ \downarrow $	18	trace	38
10	MeO PPh <sub>2</sub> MeO PPh <sub>2</sub>	4.2	0.1	28
11	21	41	1.5	50
12	22 none	87	0.7	8.2

<sup>a</sup> Reaction conditions: reactants **1**,**2**, and **3** (1.5:1.5:1) were mixed in THF in the presence of  $5 \mod \text{Pd}(\text{dba})_2$  and  $5 \mod \text{Pd}(\text{dba})_2$ 

Under the guide of the newly developed protocol for Pdcatalyzed oxidative cross-coupling, we investigated the substrate scope under the following reaction conditions: 5 mol% of Pd(dba)<sub>2</sub> and 2.0 equivalents of alkylzinc reagents in THF at 60 °C (Table 2). It was found that besides the 87% yield of the cross-coupling product 4, the reaction of alkynylstannane 32 with alkylzinc reagent 2 generated the cross-coupling product 30 in a high yield of 80% (Table 2, entry 9). After examining the reactions of other alkylzinc reagents containing  $\beta$ -hydrogen, we were pleased to conclude that the  $Pd(dba)_2$  system could work very well with such substrates (Table 2).

Further experiments showed that the transformation can be carried out at room temperature. Alkynylstannane 1, when treated with alkylzinc reagent 2, yielded the crosscoupling product in 92% yield (Scheme 1, Procedure 1). Using the alkylzinc reagent 6, which contains an ester functional group, the desired cross-coupling product was produced in 92% yield in the presence of  $Pd(dba)_2$ 

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



<sup>a</sup> Reaction conditions: reactants Csp<sup>3</sup>–Zn, Csp–Sn and desyl chloride (2:1.2:1) were mixed in THF in the presence of 5 mol%  $Pd(dba)_2$  in 60 °C; isolated yield.

(Scheme 1, Procedure 2). With a secondary alkylzinc reagent **8**, the desired Csp–Csp<sup>3</sup> product was obtained in a noticeable 93% yield (Scheme 1, Procedure 3).

The proposed mechanism is shown in Scheme 3. The oxidative addition of desyl chloride **3** to the Pd(0)-species generates C-bound Pd-enolate **I**, which then tautomerizes to O-bound Pd-enolate **II**. The intermediate **II** contains a chloride anion and an enolate anion, which can serve as leaving groups. Thus, we speculated that the enolate **II** (RO–Pd–Cl) could transmetalate twice respectively with alkylzinc and tin reagents, which can generate the intermediate V. The reductive elimination of V yields the desired cross-coupling product. The transmetalations of RO–Pd–Cl with a Csp<sup>3</sup>–Zn and Csp–Sn reagents are noteworthy, for alkylzinc reagents could transmetalate with either RO–Pd or Pd–Cl bonds. To achieve high selectivity for the Csp–Csp<sup>3</sup> cross-coupling product, the alkylzinc reagents should only transmetalate one of RO–Pd or Pd–Cl bonds. In kinetic experimentations, we observed the formation of enolate IV with in situ IR monitoring (ReactIR 4000), and found that this rate equaled the decreasing rate of desyl chloride **3**. This result clearly indicated that the alkylzinc reagents could selectively transmetalate with RO–Pd.

In conclusion, we have explored a novel approach to the cross-coupling reactions. In the presence of desyl chloride as the oxidant, alkylzinc reagents and alkynylstannanes, two different nucleophiles can be coupled together in high yield and selectivities. The alkylzinc reagents can contain a  $\beta$ -H, and the secondary alkylzinc reagent can be smoothly coupled in high yield at room temperature.

#### Procedures

Three typical procedures are described for the oxidative cross-coupling transformation.

All reactions and manipulations were performed in a N<sub>2</sub>-filled glove-box or using standard Schlenk techniques; column chromatography was performed using EM silica gel 60 (200–300 mesh). <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on Mercury 300 spectrometer. GC-MS spectra were recorded on a Varian GC-MS 3900-2100T spectrometer. All <sup>1</sup>H NMR experiments were reported in parts per million (ppm) downfield of TMS. All <sup>13</sup>C NMR spectra were obtained with <sup>1</sup>H decoupling and reported in ppm. Gas chromatographic analyses were preformed on Varian GC 2000 gas chromatography instrument with an FID detector and naphthalene was employed as internal standard.

All common reagents were prepared in the laboratory or obtained from commercial suppliers and were purified following standard procedure. Organotins were prepared by reaction of the corresponding Grignard reagents with Bu<sub>3</sub>SnCl, and purified by distillation under reduce pressure.<sup>42</sup> Pd(dba)<sub>2</sub> was prepared following general methods.<sup>43</sup> THF was dried and distilled from sodium/benzophenone ketyl under N<sub>2</sub>. All alkylzincs, except the (4-ethoxy-4-oxobutyl)zinc(II) bromide (**6**), were prepared from RMgX and anhyd ZnCl<sub>2</sub>.<sup>44</sup> Anhyd ZnCl<sub>2</sub> was obtained by refluxing the commercial ZnCl<sub>2</sub> with SOCl<sub>2</sub> for one or two days.



#### Scheme 3

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#### Palladium-Catalyzed Oxidative Coupling; 1-(4-Methyl-4-phenylpent-1-ynyl)benzene (4); Procedure 1

Conditions A: A dried 10 mL Schlenk flask equipped with a rubber septum and a magnetic stirring bar was charged with anhyd ZnCl<sub>2</sub> (312.8 mg, 2.3 mmol) and THF (2 mL). The solution was cooled in an ice bath at 0 °C while (2-methyl-2-phenylpropyl)magnesium chloride (3.0 mL, 0.5 M, 1.5 mmol) was added dropwise over 10 min. The resulting mixture was stirred for 2 h at r.t. To this zinc reagent solution were added tributyl(phenylethynyl)stannane (1; 470.0 mg, 1.2 mmol), desyl chloride (3; 230.7 mg, 1.0 mmol), and Pd(dba)<sub>2</sub> (28.7 mg, 5 mol% Pd). The mixture was stirred at 60 °C for 2 h and then poured into aq 1 M KF (50 mL). The aqueous layer was extracted with Et<sub>2</sub>O (100 mL), and the organic layer was washed repeatedly with aq KF until there was no precipitation between the two phases. The organic extracts was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated by rotary evaporation. After flash column chromatography, product 4 was obtained as a light yellow oil (203.6 mg, 87%).

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.41–7.38 (m, 2 H), 7.30–7.23 (m, 4 H), 7.20–7.16 (m, 4 H), 2.62 (s, 2 H), 1.42 (s, 6 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 147.7, 130.7, 127.3, 126.7, 125.1, 124.9, 123.2, 87.4, 81.7, 37.2, 33.9, 27.4.

MS (EI): *m*/*z* = 234.0, 119.0, 91.1, 77.2, 63.0.

HRMS (EI): *m/z* calcd for C<sub>18</sub>H<sub>18</sub>: 234.1409; found: 234.1380.

*Conditions* **B**: The procedure was the same as given for conditions A except that the reaction was carried out at r.t. with 1.5 equiv alkylzinc reagent and the yield was 92% (GC).

#### Palladium-Catalyzed Oxidative Coupling; Ethyl 6-Phenylhex-5-ynoate (7); Procedure 2

A dried 10 mL Schlenk flask equipped with a rubber septum and a magnetic stirring bar was evacuated and refilled with N2 three times. The flask was charged with Zn dust (126.7 mg, 1.95 mmol) and I<sub>2</sub> (22.5 mg, 0.089 mmol). Anhyd DMA (5 mL) was added to the flask via a syringe. The mixture was stirred at r.t. for a few min until the color of I<sub>2</sub> had disappeared. Then ethyl 4-bromopentanoate (5; 240.0 mg, 1.23 mmol) was added via a syringe and the mixture was stirred for 3 h at 80 °C to produce a solution of the zinc reagent and a suspension of excess zinc dust. The solution was allowed to cool to r.t. and tributyl(phenylethynyl)stannane (1; 235.0 mg, 0.60 mmol), desyl chloride (3; 115.8 mg, 0.50 mmol), Pd(dba)<sub>2</sub> (14.3 mg, 5 mol% Pd), and THF (2 mL) were added. The mixture was then stirred for 5 h at r.t. The resulting mixture was diluted with Et<sub>2</sub>O (100 mL) and washed with aq 1 M KF repeatedly until there was no precipitation between the two phases. The organic phase was combined and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated by rotary evaporation. A 92% yield was determined by <sup>1</sup>H NMR spectroscopy (dibromomethane as the internal standard).45

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.40–7.38 (m, 2 H), 7.28–7.26 (m, 3 H), 4.14 (q, *J* = 10.6 Hz, 2 H), 2.52–2.46 (m, 4 H), 1.98–1.88 (m, 2 H), 1.26 (t, *J* = 6.9 Hz, 3 H).

MS (EI): *m*/*z* = 216.0, 188.0, 174.0, 143.2, 128.0.

### Palladium-Catalyzed Oxidative Coupling; 1-(2-Cyclohexylethynyl)benzene (9); Procedure 3

A dried 100 mL Schlenk flask equipped with a magnetic stirring bar was charged with anhyd  $ZnCl_2$  (1.36 g, 10 mmol). The flask was evacuated and heated with a heat gun for 10 min, flushed three times with N<sub>2</sub>, and then allowed to cool to r.t. THF (20 mL) was added to the flask. Then the mixture was cooled to -25 °C and cyclohexylmagnesium chloride (5.9 mL, 0.85 M, 5.0 mmol) was added dropwise via a syringe at -25 °C. A white precipitate was formed immediately. The mixture was kept at -25 °C for an additional 1 h before immersing in an ice-water bath. Afterwards the temperature was allowed to slowly increase to r.t. After 3 h, tributyl(phenylethynyl)stannane (1; 460 mg; 1.2 mmol), desyl chloride (3; 230 mg, 1.0 mmol), and Pd(dba)<sub>2</sub> (27.5 mg, 5 mol% Pd) were added and the mixture was stirred for 5 h at r.t. After that, aq 1 M KF (50 mL) was added to the flask and the mixture was stirred for 2 h. The resulting mixture was extracted with Et<sub>2</sub>O (3 × 50 mL). The organic phase was combined and dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated by rotary evaporation. The GC yield of the product **9** was estimated to be 93% (naphthalene as the internal standard). The product was purified by column chromatography [eluent: petroleum ether (bp 30–60 °C)]; yield: 154.8 mg (84%).

<sup>1</sup>H NMR (300 MHz,  $CDCl_3$ ):  $\delta$  = 7.35–7.27 (m, 2 H), 7.24–7.17 (m, 3 H), 2.60–2.40 (m, 1 H), 1.90–1.75 (m, 2 H), 1.74–1.60 (m, 2 H), 1.58–1.38 (m, 3 H), 1.36–1.21 (m, 3 H).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ = 131.8, 128.4, 127.6, 94.7, 80.4, 32.9, 29.9, 26.2, 25.1.

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- (45) The desired cross-coupling product was mixed with 1,2diphenylethanone, which was formed from the Zn-enolate IV. Efforts to completely separate the two compounds were unsuccessful.