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Highly Selective Palladium-Catalyzed Oxidative Csp^2–Csp^3 Cross-Coupling of Arylzinc and Alkylindium Reagents through Double Transmetallation

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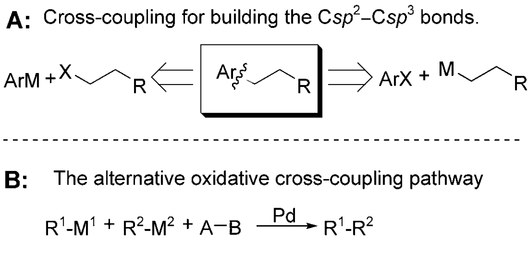
Abstract: Using desyl chloride (2-chloro-1,2-diphenylethanone) as the oxidant, the palladium-catalyzed reaction of arylzinc with alkylindium reagents occurred smoothly in a highly selective manner to afford the products in 57–90% yields. Preliminary kinetic data indicated that alkylindium reagents were highly favored for transmetallation with the alkoxypalladium moiety.

Keywords: alkylindium reagents; arylzinc reagents; cross-coupling reaction; palladium

Introduction

Csp^2–Csp^3 bond formation, especially the Csp^2(aryl)–Csp^3 version, is a valuable tool of unfailing interest in organic synthesis. This transformation could be realized *via* classic methods such as nucleophilic substitution, Friedel–Crafts reaction, etc., or modern methods involving transition metals as catalysts. Scheme 1 A illustrates the latter strategies, in which either ArX or $R_{alkyl}X$ could serve as the electrophile.[1] The ArX option has been explored, in which $R_{alkyl}M$ could be either alkylzinc reagents (Negishi reaction),[2–4] alkylboron reagents (Suzuki reaction)[5] or others. When $R_{alkyl}X$ was the electrophile, the success was more limited due to the difficult oxidative addition of $R_{alkyl}X$ towards metal catalysts, and the fast but deleterious β-H elimination.[6–9] Recently, pioneered by Fu, Organ and Nolan etc., cross-coupling reactions involving $R_{alkyl}X$ were revolutionized by employing electron-rich and sterically hindered phosphine ligands or carbene ligands, and showed good potential in organic synthesis.[7,10–20]

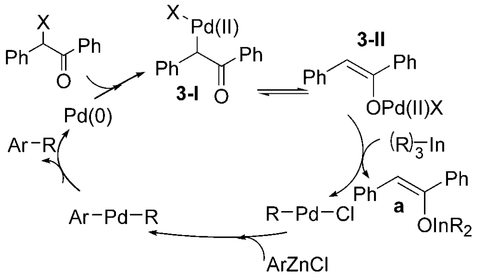


Scheme 1. Strategies for Csp^2–Csp^3 bond formation.

With our strong interest in Csp^3-related coupling reactions, we recently developed an oxidative cross-coupling reaction (shown in Scheme 1B), in which two nucleophiles, prepared readily from inexpensive and abundant organic chlorides, could be coupled together in the presence of an oxidant, A–B. The strategy has been successfully applied in cross-coupling of Csp–Sn reagents and Csp^3–Zn reagents.[21] Herein, we report our extension to make Csp^2–Csp^3 bonds by this strategy, in which arylzinc reagents and alkylindium reagents were successfully cross-coupled with high selectivities under mild conditions.

Results and Discussion

Inspired by previous results, desyl chloride **3** (2-chloro-1,2-diphenylethanone), which had successfully promoted the Csp–Csp^3 oxidative cross-coupling,[21] was chosen as the oxidant. Desyl chloride **3** was expected to add oxidatively to Pd(0) to form *C*-bonded Pd-enolate **3-I**, which could tautomerize possibly to *O*-bonded Pd-enolate **3-II** (Scheme 2). Both the chloride anion and *C*-enolate anion or *O*-enolate anion attached to palladium in **3-I** or **3-II** could serve as leaving groups, and their intrinsic different activities



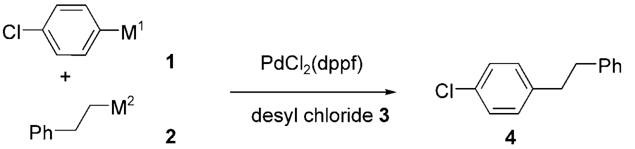
Scheme 2. Proposed mechanism of oxidative cross-coupling reaction between ArZnX and R_3In.

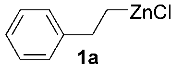
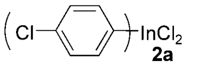
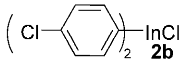
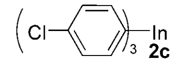
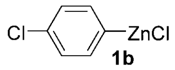
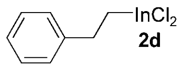
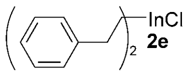
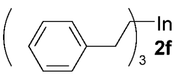
toward organometallic reagents would make a highly selective transmetallation process possible.

LiX has been reported to promote Stille coupling of ArOTf with organostannane reagents.[22] This information along with the success of our previous Csp–Sn and Csp^3–Zn oxidative cross-coupling, encouraged us to employ a tin reagent as a halophilic reagent. Unfortunately, all attempts using Ar–Sn reagents and R_{alkyl}–Zn reagents resulted in poor yields and poor selectivities for cross-coupled products. Satisfactorily, organoindium reagents (R_3In, R = alkyl, alkenyl, alkynyl, aryl), possessing interesting chemical properties including a low first oxidation potential, stability under aqueous conditions and low toxicity,[21,23–33] turned out to be a good option, and the combination of (4-chlorophenyl)zinc(II) chloride **1b** and triphenethylindium **2f** with $PdCl_2(dppf)$ as catalyst displayed a promising result. The cross-coupled product was obtained in 78% yield (Table 1, entry 6). Reactions of **1b** with alkylindium dichloride **2d** or dialkylindium chloride **2e** gave moderate yields (Table 1, entries 4 and 5). On the other hand, reactions of arylindium reagent **2a**, **2b** or **2c** with alkylzinc reagent **1a** all resulted in poor yields (Table 1, entries 1–3).

Encouraged by the preliminary results, we investigated the oxidative cross-coupling using various ligands. The effect of ligand was evaluated in the reaction of **1b** and **2f** in THF at 60 °C (Table 2). Catalyst precursors without added ligands such as $PdCl_2(CH_3CN)_2$, $Pd(dba)_2$ and $Pd(OAc)_2$ gave moderate yields of product **4** together with 19–21% yields of side product **4a** (Table 2, entries 1–3). Monophosphine **L1** and monophosphite **L2** ligands lowered the yields and selectivities of **4** (Table 2, entries 4 and 5). Bidentate phosphine ligand Xantphos gave an even poorer result (Table 2, entry 6). However, DPEphos satisfactorily improved the reaction results to 95% selectivity in 81% yield.

Table 1. Combination of different organometallic reagents for palladium-catalyzed oxidative cross-coupling.[a]

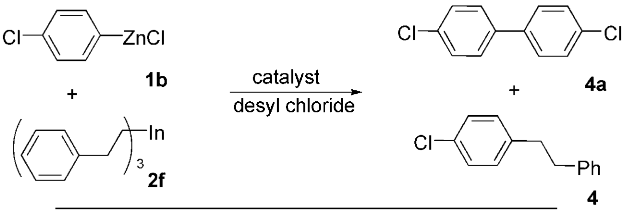


Entry	1	2	Yield[b] [%] 4
1	 **1a**	 **2a**	35
2	**1a**	 **2b**	41
3	**1a**	 **2c**	38
4	 **1b**	 **2d**	53
5	**1b**	 **2e**	55
6	**1b**	 **2f**	78

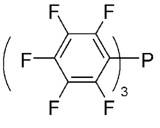
[a] *Reaction conditions:* The reactants **1**, **2**, and **3** (in a ratio of 1.1:1.2:1) were mixed in THF in the presence of 5 mol% $PdCl_2(dppf)$ in 60 °C.

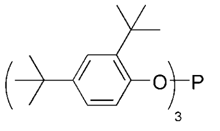
[b] The yield was determined by GC after 5 h using naphthalene as the internal standard.

Table 2. Ligands effects in the oxidative cross-coupling reactions.[a]



Entry	Catalyst	Yield[b] [%] 4	4a
1	$PdCl_2(CH_3CN)_2$	61	19
2	$Pd(dba)_2$	60	21
3	$Pd(OAc)_2$	68	20
4	$PdCl_2(CH_3CN)_2$ + L1	49	30
5	$PdCl_2(CH_3CN)_2$ + L2	55	23
6	$PdCl_2(CH_3CN)_2$ + XantPhos	39	18
7	$PdCl_2(CH_3CN)_2$ + DPEphos	81	4

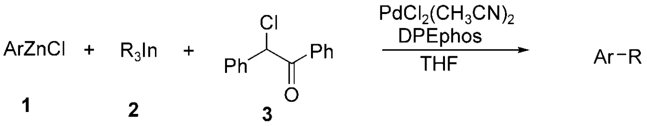

L1

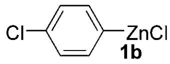
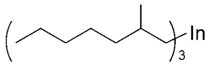
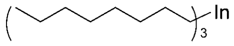
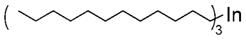
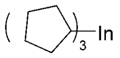
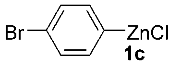
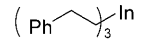
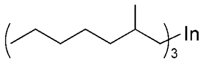
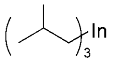
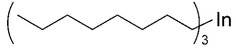
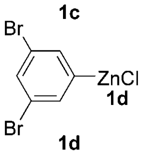
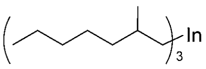
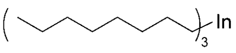
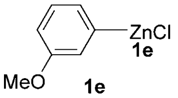
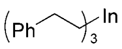
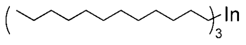

L2

[a] *Reaction conditions:* The reactants **1b**, **2f**, and **3** (in a ratio of 1.1:1.2:1) were mixed in THF in the presence of 5 mol% catalyst in 60 °C.

[b] The yield was determined by GC after 5 h using naphthalene as the internal standard.

Table 3. Palladium-catalyzed oxidative cross-coupling reactions.[a]



Entry	ArZnCl	R$_3$In	Yield[b] [%] Ar−R	
1	 **1b**		**5**	75
2	**1b**		**6**	66
3	**1b**		**7**	90
4	**1b**		**8**	57
5	 **1c**		**9**	77
6	**1c**		**10**	85
7	**1c**		**11**	70
8	**1c**		**12**	81
9	 **1d**		**13**	84
10	**1d**		**14**	82
11	 **1e**		**15**	90
12	**1e**		**16**	81

[a] *Reaction conditions:* The reactants **1**, **2**, and **3** (in a ratio of 1.1:1.1:1) were mixed in THF in the presence of 5 mol% $PdCl_2(CH_3CN)_2$ and DPEphos in 60 °C except for entries 5–10 which were run at room temperature.

[b] The yield was determined by NMR in 5 h using dibromomethane as the internal standard.

The substrate scope of this reaction was further explored under the optimized conditions (Table 3). Both primary and secondary alkylindium reagents reacted smoothly, and it was noteworthy that bromo and chloro substituents on the arylzinc reagents were well tolerated (Table 3, entries 1–10). In all reactions, Csp^2–Csp^3 cross-couplings were achieved selectively with less than 5% homo-coupling products. Moreover, (t-Bu)$_2$RIn (R = $PhCH_2CH_2$–), in place of trialkylindium reagents R_3In, provided good selectivity and yield as well (83%).

To gain some understanding of the mechanism, the entire catalytic process of the reaction between (3-methoxyphenyl)zinc(II) chloride **1e** and triphenylethanylindium **2f** was monitored by *in-situ* IR and GC. The depletion of desyl chloride **3** and formation of product **15** and a new species assigned as R′OInR$_2$ **a** (compared to authentic sample, see Supporting Information) were clearly observed. The kinetic profiles are listed in Figure 1A. Rate constants k_{obs} of the

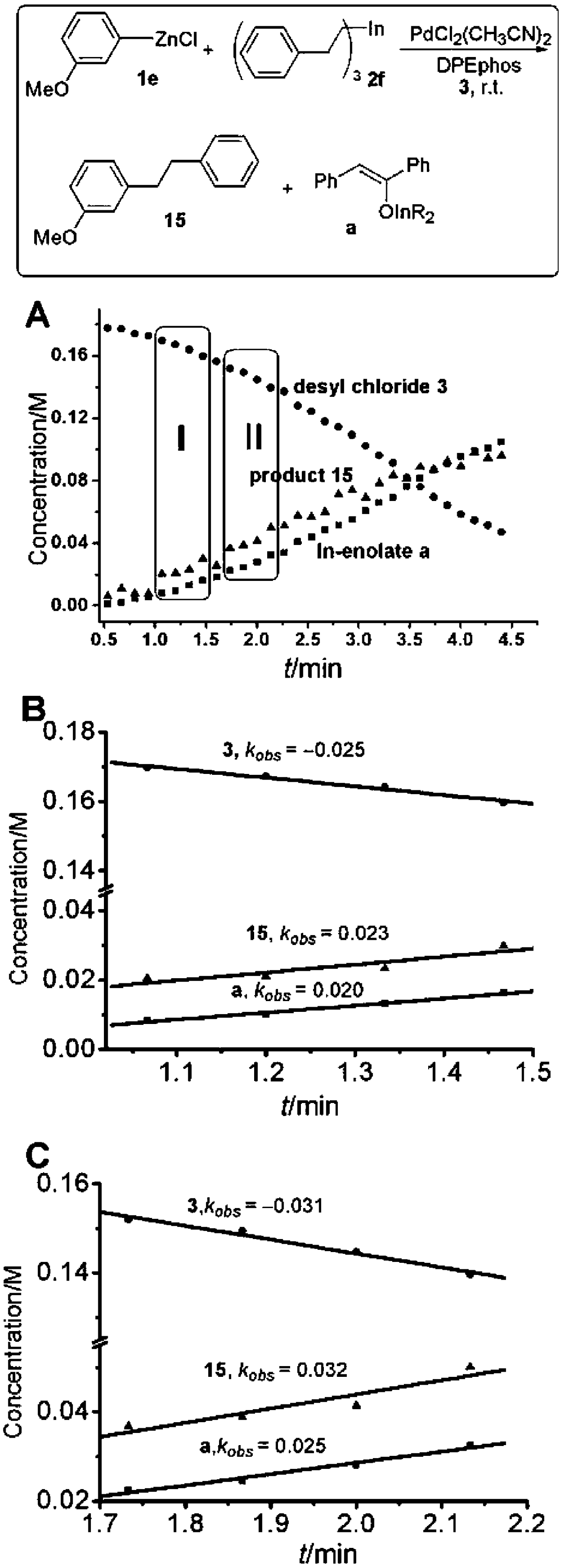


Figure 1. A: The kinetic profiles of desyl chloride **3**, In-enolate **a** and product **15**, which were collected by ReactIR calibrated by GC (In-enolate was calibrated according to 1,2-diphenylethanone). **B:** Linear fitting of period **I**; **C:** Linear fitting of period **II**.

three compounds were calculated through a linear fit in the 1.0–1.5 min (Figure 1B) and 1.7–2.2 min regions, respectively (Figure 1C). In both periods, the k_{obs} of desyl chloride 3, product **15** and In-enolate **a** were in the same order of magnitude, and even the numerical values were very close, indicating that **3**, **a** and **15** were associated in the same catalytic cycle. Thus it was reasonable to suppose that the enolate part of **3** was directly converted to **a** in the reaction system, implying selective transmetallation between R_3In and the *O*-enolate anion OR′ attached to Pd(II).

Therefore, a plausible mechanism of this reaction was proposed as shown in Scheme 2.

Oxidative addition of desyl chloride to a Pd(0) species generated *C*-bound Pd-enolate chloride **3-I**, which could tautomerize possibly to *O*-bonded Pd-enolate chloride **3-II** (R′OPdCl). Then the trialkylindium reagents selectively transmetallate with the OR′ group of **3-II** and release R′OInR$_2$ (*vide supra*). The second transmetallation between ArZn with R–Pd–Cl would form the key intermediate R–Pd–Ar, and the final reductive elimination would result in the desired cross-coupled product, and regenerate the catalytic specie.[34]

Conclusions

In conclusion, Csp^2–Csp^3 oxidative coupling was realized for the first time and nucleophilic arylzinc reagents and alkylindium reagents were cross-coupled with good selectivities and yields using PdCl$_2$(CH$_3$CN)$_2$ as catalyst precursor and DPEphos as ligand. Preliminary kinetic studies were conducted and a mechanism for the reaction was proposed. Currently, desyl chloride was used as the stoichiometric oxidant in this transformation, which was not atom economic. Other oxidants of lower molecular weight, some of which have been used in homocoupling of arylboronic acids, would make this reaction greener.[35,36] Oxidative cross-coupling employing lower molecular weight oxidants including O_2 or air are under investigation in this laboratory and will be reported in due course.

Experimental Section

All reactions and manipulations were performed in a nitrogen-filled glove-box or using standard Schlenk techniques. Column chromatography was performed using EM silica gel 60 (230–400 mesh). ^{1}H NMR and ^{13}C NMR were recorded on a Mercury 300 MHz spectrometer. GC-mass spectra were recorded on a Varian GC-MS 3900–2100T. All ^{1}H NMR experiments are reported in parts per million (ppm) downfield of TMS. All ^{13}C NMR spectra are reported in ppm and were obtained with ^{1}H decoupling. Gas chromatographic analysis were preformed on a Varian GC 3900 gas chromatography instrument with an FID detector and naphthalene was added as internal standard. The IR spectra were recorded using a ReactIR 4000 from Mettler-Toledo AutoChem fitted with a silicon-tipped (SiComp) probe. Data manipulation was carried out using the iC IR software, version 1.5.105.0.

All common reagents were prepared in our lab or obtained from commercial suppliers and were purified following general procedures. All ligands were obtained from Solvias AG and Strem Chemicals and used without further purification. THF were dried and distilled from sodium/benzophenone ketyl under nitrogen.

Preparation of the Alkylindium Reagents

All of the organoindium reagents were prepared from reactions of the corresponding Grignard reagents with indium(III) chloride.

Di-*tert*-butyl(phenethyl)indium[37]: To a 10-mL Schlenk flask was added indium(III) chloride (220.0 mg, 1 mmol) and THF (1 mL). The solution was cooled to 0 °C and *tert*-butylmagnesium chloride (2.0 mL, 1 M) was added dropwise to the flask. The mixture was stirred for 2 h and then phenethylmagnesium chloride (1.0 mL, 1 mmol) was added dropwise. After that, the resultant solution was allowed to slowly warm to the room temperature and was stirred for additional 2 h.

Preparation of the Arylzinc Reagents

The arylzinc reagents **1a**, **1e** were prepared from the corresponding Grignard reagent with zinc chloride.

(4-Chlorophenyl)zinc(II) chloride[38] (1b): To a 25-mL Schlenk flask were added 1-bromo-4-chlorobenzene (191.4 mg, 1 mmol) and THF (2 mL). The mixture was cooled to −78 °C. After that, *n*-BuLi (0.4 mL, 2.5 M, 1 mmol) was added to the mixture dropwise. The resultant solution was stirred for 1 h at −78 °C. Then, ZnCl$_2$ (2.0 mL, 1.0 M in THF, 2.0 mmol) was added dropwise to the flask. Afterwards the mixturee was allowed to slowly warm to room temperature and stirred for additional 2 h.

(4-Bromophenyl)zinc(II) chloride[39](1c): To a diethyl ether (4.5 mL) and THF (4.5 mL) solution of 1,4-dibromobenzene (236.0 mg, 1 mmol) was slowly added *n*-BuLi (0.4 mL, 2.5 M, 1 mmol) at −78 °C. The resultant solution was stirred at −78 °C for 1 h. After that, ZnCl$_2$ (2.0 mL, 1.0 M in THF, 2.0 mmol) was added dropwise to the flask. Afterwards the mixture was allowed to slowly warm to the room temperature and stirred for additional 2 h.

(3,5-Dibromophenyl)zinc(II) chloride[40] (1d): To a THF (10 mL) solution of 1,3,5-tribromobenzene (314.8 mg, 1 mmol) was slowly added *n*-BuLi (0.4 mL, 2.5 M, 1 mmol) at −78 °C . The resultant solution was stirred at −78 °C for 1 h. After that, ZnCl$_2$ (2.0 mL, 1.0 M in THF, 2.0 mmol) was added dropwise to the flask. Afterwards the mixture was allowed to slowly warm to the room temperature and stirred for additional 2 h.

General Procedure for the Cross Coupling Reaction

Under the protection of nitrogen gas, to a 10-mL Schlenk flask were added desyl chloride (230.7 mg, 1 mmol), PdCl$_2$CH$_3$CN$_2$ (12.9 mg, 0.05 mmol, 5 mol% Pd) and DPEphos (32.3 mg, 0.06 mmol, 6 mol% Pd). To the flask, the arylzinc reagent (1.1 mol) and the alkylindium reagent (1.1 mmol) were added by syringe. Then the solution was warmed to 60 °C (the reaction temperature with arylzinc reagents **1c** and **1d** is room temperature). 5 h later, the reaction mixture was quenched by saturated NH_4Cl solution and extracted by ether. The organic layer was dried over sodium sulfate, filtered, and concentrated. Purification of product was accomplished by silica gel chromatography. The characterization data are available in the Supporting Information file.

Acknowledgements

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