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Palladium-Catalyzed Oxidative Carbonylation of Alkyl and Aryl Indium Reagents with CO under Mild Conditions

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Abstract: CO now can react with organoindium reagents. A novel palladium-catalyzed oxidative carbonylation reaction of organoindium reagents by CO gas with desyl chloride as oxidant was developed in supplementation with the classical methods for preparation of carboxylic acid derivatives. Primary, secondary alkyl indium reagents with β-hydrogens and aryl indium reagents were suitable substrates, and the reaction could be carried out at 60 °C under 50 psi CO. Carbonylation of alkyl indium reagents can occur smoothly without additional base. Although the indium reagents were prepared from corresponding Grignard reagents (at low temperature), they displayed full compatibility with various functional groups under the protic reaction conditions. Preliminary mechanistic studies including stoichiometric and catalytic reaction examination provided evidence to support the operation of the mechanism consisted of oxidative addition of deslyl chloride to Pd(0) and quick tautomerization to give a palladium enolate species **II** (ROPdCl), displacement of the enolate group in **II** by R^2OH, followed by CO insertion to give alkoxycarbonyl palladium complex **V**, which undergoes transmetalation with R^1_3In and reductive elimination to afford the product and a Pd(0) species. In this mechanism, the alkoxycarbonyl group was transferred to the palladium center prior to the alkyl group, different from traditional ways initiated from oxidative addition of alkyl halides to a Pd(0) species.

Introduction

Transition metal-catalyzed carbonylation of organic halides with CO gas, pioneered by Heck and co-workers in the 1970s, represents one of the most commonly employed reactions to make carboxylic acids derivatives in the synthesis of high value fine chemicals and complex synthetic intermediates.[1–8] In the past three decades, the scope of substrates has been extended from aryl iodides, triflates, bromides, and benzyl chlorides to less reactive aryl chlorides and aryl arenesulfonaes,[5,9–11] and palladium dominates as catalyst in this area. However, catalytic carbonylations of alkyl halides $R_{alkyl}X$ with CO remain very challenging and are limited to allylic halides and fluorinated alkyl halides (Scheme 1, path A).[12] The particular problems

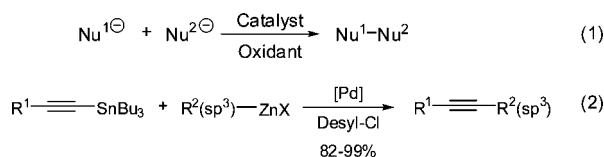**Scheme 1.** Different Approaches toward the Carbonylation
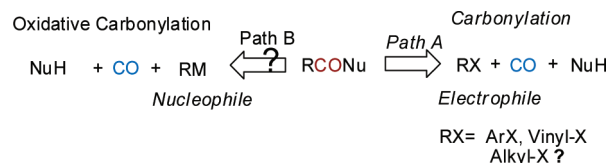
associated with these systems arise mainly from the difficulty in oxidative addition of $R_{alkyl}X$ to the metal center,[13] typically fast and deleterious β-hydride elimination,[13,14] and the inherent weakness of alkyl–metal bonds. The few reports concerning this reaction undergoing classical mechanism initiated by oxidative addition of the alkyl halide are under harsh conditions, either high temperature or high pressure of CO.[12,15–25] In addition,

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Scheme 2. Oxidative Coupling toward Bond Formation

Table 1. Oxidative Carbonylation of Trialkyl-In Reagent without β-Hydrogen[a]

entry	1	ROH	2 (yield [%])	
1	**1a** $n = 1$	MeOH	**2a**	43
2	**1b** $n = 2$	MeOH	**2a**	46
3	**1c** $n = 3$	MeOH	**2a**	99
4	**1c**	EtOH	**2b**	95
5	**1c**	n-BuOH	**2c**	98
6[b]	**1c**	t-BuOH	**2d**	trace

[a] The reactions were conducted with 0.5 mmol of desyl chloride, 0.6 mmol of **1**, and 3 mol % PdCl$_2$(dppf) with respect to desyl chloride in ROH at 60 °C, with a balloon pressure of CO gas. The yield was determined by GC. [b] **2e** was obtained as the major product in 58% isolated yield. **2e**: 2,6-dimethyl-2,6-diphenylheptan-4-one.

Ryu et al. have developed an atom transfer carbonylation method,[26–29] in which alkyl iodide was converted to acyl iodide via a radical mechanism to achieve the carbonylations in the presence of palladium catalyst under irradiation.[30,31]

One of our research interests lies in coupling two nucleophiles together in the presence of a proper catalyst and a co-oxidant (oxidative coupling, Scheme 2, eq 1). We have recently reported the Pd-mediated oxidative cross-coupling of Csp–Sn and Csp^3–Zn using desyl chloride (2-chloro-1,2-diphenylethone) as the oxidant (Scheme 2, eq 2).[32] Inspired by the above work, we designed a novel type of carbonylation reaction conceptually involving the following key steps: (1) formation of intermediate XPd(II)CONu through the reaction of CO and a nucleophile with Pd(II)-species generated from an oxidant and Pd(0)-species; (2) transmetalation of R$_{alkyl}$–M to the Pd-intermediate to afford the key intermediate R$_{alkyl}$–Pd(II)CONu, which could avoid the difficult oxidative addition of alkyl halide over Pd(0) species; and (3) reductive elimination to provide the final product R$_{alkyl}$CONu with concomitant releasing of the reduced palladium(0)-species. CO is known to be good π-acceptor ligand, so the final reductive elimination should be fast and the competitive β-hydride elimination could possibly be suppressed.

Apparently, to realize the proposal, several practical issues must be finely addressed. These primarily include the identification of a catalytic system that would strongly promote the formation of the desired intermediate R$_{alkyl}$–Pd(II)–CONu while at the same time effectively suppressing the competing reaction channels involving homosubstituted R$_{alkyl}$–Pd(II)–R$_{alkyl}$ and R$_{alkyl}$COPd(II)–R$_{alkyl}$; and the selection of a suitable oxidant that could promptly convert Pd(0) back to Pd(II) for further transmetalation and render the entire process catalytic,[33–37] and that would not interfere with the reactivity of all other steps in the catalytic cycle. Described herein is our recent discovery of such a system that is capable of catalyzing the oxidative

carbonylations of a broad spectrum of organoindium reagents with CO gas under very mild conditions.
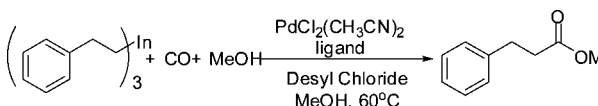
Result and Discussion

Oxidative Carbonylation of Alkyl Indium Reagents. We first set out to seek the appropriate oxidant and alkyl organometallic species R$_{alkyl}$–M. Our previous work demonstrated that desyl chloride efficiently promoted Pd-catalyzed Csp–Csp^3 oxidative cross-coupling reactions;[32] we therefore surmised it to be a promising candidate here. Carbonylations are usually carried out in protic solvents, such as MeOH and EtOH. Thus, a reasonable R$_{alkyl}$–M should exhibit a high level of tolerance toward these protic reaction media. Organoindium reagents (R$_3$In, R = alkyl, alkenyl, alkynyl, aryl), which recently have attracted much attention for their versatile chemistry and stability in aqueous/protic conditions,[38–48] emerge as a possible R$_{alkyl}$–M precursor. Thus, we decided to focus on investigating the feasibility of oxidative carbonylations of organoindiums with CO gas using desyl chloride as oxidant.

The initial screening experiments employed 2-methyl-2-phenylpropylindium(III) chloride **1a** (Table 1, $n = 1$), which was readily generated from the corresponding Grignard reagent and InCl$_3$. The indium reagent in alcoholic solvent was mixed with desyl chloride and then allowed to react with balloon pressure of CO gas in the presence of a catalytic amount (3 mol %) of PdCl$_2$(dppf). Under this condition, low conversion of desyl chloride was observed, and the desired product was detected only in 43% yield. Employment of a dialkyl indium

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Table 2. Optimization of the Ligand, the Base, and the Pressure of CO[a]

entry	ligand	pressure	yield [%][b] **4a**
1[c]	PPh3	150 psi	35
2	BINAP	150 psi	57
3	BIPHEP	150 psi	70
4	C3-Tunephos	150 psi	76
5	Synphos	150 psi	97
6	Synphos	50 psi	96
7	Synphos	15 psi	50
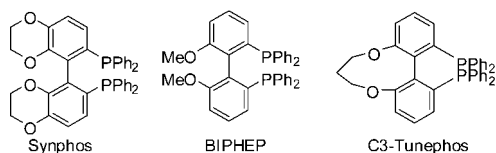
[a] The reactions were conducted with 0.6 mmol of **3**, 0.5 mmol of desyl chloride, 3 mol % PdCl2(CH3CN)2, and 4 mol % ligand with respect to desyl chloride. [b] The yields were determined by GC in 24 h using naphthalene as the internal standard. [c] PdCl2(PPh3)2 (3 mol %) was used.

reagent **1b** ($n = 2$) showed basically no improvement with 46% product detected. To our delight, the oxidative carbonylation of tris(2-methyl-2-phenylpropy)indium **1c** could be accomplished in essentially quantitative yield at 60 °C (Table 1, entry 3). The reaction worked equally well in ethanol and *n*-butanol, with the corresponding product formed in 95% and 98% yield, respectively (Table 1, entries 4 and 5). However, when *t*-BuOH was used as solvent and nucleophile, the product was dialkyl ketone (58%) instead of the *t*-butyl ester (Table 1, entry 6). To examine whether amide could be produced from this method, the oxidative carbonylation of **1c** was carried out with 10 equiv of PhNH2 in THF at 60 °C (eq 3). The reaction provided the corresponding amide **2f** in 95% yield.
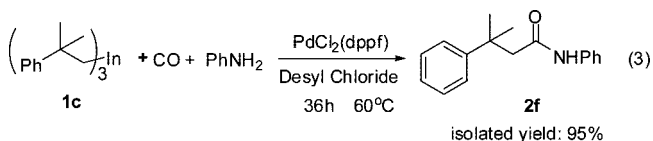
Encouraged by these results, we next turned to examine the reactions of alkyl indium reagents containing *β*-hydrogens. To facilitate CO insertion, CO pressure was raised to 150 psi. However, PdCl2(dppf), highly efficient for the oxidative carbonylation of **1c**, was found not suitable for the reaction involving triphenethylindium **3**. Only trace product was detected by GC. The reaction catalyzed by PdCl2(PPh3)2 provided a notable improvement, giving the product in 35% yield. Employment of other bidentate ligands, such as BINAP, BIPHEP, and C3-Tunephos, further enhanced the yields, but in a moderate way (22−41% increase, see Table 2, entries 2−4). Remarkably, utilizing Synphos as the ligand delivered the product in 97% yield. More refined investigations on the dependence of yield on CO pressure revealed that almost the same yield (96%) could be obtained under a considerably lower pressure, that is, 50 psi (Table 2, entry 6), whereas when CO pressure was lowered to 15 psi, only 50% desired product was formed (Table 2, entry 7).

Table 3. Oxidative Carbonylation of Different Alkyl Indiums[a]

entry	R3In	product		yield[%]
1	(Ph⌒⌒)3In	Ph⌒⌒COOBu-*n*	**4b**	90[b]
2	(⌒⌒⌒⌒)3In	⌒⌒⌒⌒COOBu-*n*	**5**	76[c]
3	(⌒⌒⌒)3In	⌒⌒⌒COOBu-*n*	**6**	72[c]
4	(⌒⌒⌒⌒)3In	⌒⌒⌒⌒COOBu-*n*	**7**	95[c]
5	(MeO-C6H4⌒)3In	MeO-C6H4⌒COOBu-*n*	**8**	83[c]
6	(Cl-C6H4⌒)3In	Cl-C6H4⌒COOBu-*n*	**9**	66[b]
7	(Ph-O⌒⌒⌒)3In	Ph-O⌒⌒⌒COOBu-*n*	**10**	83[c]
8	(C6H11⌒)3In	C6H11⌒COOBu-*n*	**11**	90[c]
9	(⌒⌒)3In	⌒⌒COOBu-*n*	**12**	60[d]
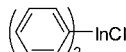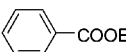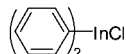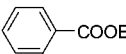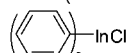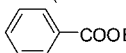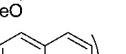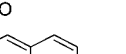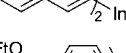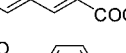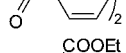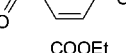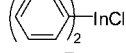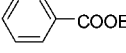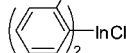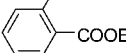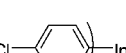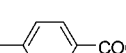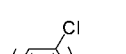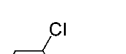
[a] The reactions were conducted with 0.6 mmol of trialkyl indium, 0.5 mmol of desyl chloride, 3 mol % PdCl2(CH3CN)2, and 4 mol % Synphos with respect to desyl chloride in *n*-BuOH, unless otherwise stated. [b] The yields were determined by NMR in 24 h using dibromomethane as the internal standard. [c] Isolated yield. [d] The reaction was conducted with 5 mol % PdCl2(PPh3)2, and the yield was determined by GC in 36 h using naphthalene as the internal standard.

The performance of Pd-Synphos catalyst was then examined over a range of trialkyl indium reagents containing *β*-hydrogens under 50 psi of CO gas in *n*-BuOH, and the yields were found to be generally good to excellent (Table 3). It is noteworthy that even a secondary alkyl group was capable of undergoing oxidative carbonylation in high yield (Table 3, entries 8 and 9). In all of these cases, corresponding Csp^3–Csp^3 homocoupling or Csp^3–CO–Csp^3 byproduct was determined by GC to be less than 5%.

Carbonylation of Aryl Indium Reagents. Without further optimization, the process was extended to aryl indium reagents to probe its scope and limitations, and the results were compiled in Table 4. Unlike trialkyl indium reagents, diaryl indium chlo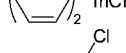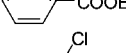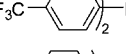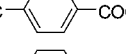rides could undergo the oxidative carbonylation catalyzed by PdCl2(dppf) smoothly to furnish the corresponding products in good to excellent yields when triethylamine as base was added. Diaryl indium reagents bearing electron-withdrawing or electron-donating substituents could afford the product in high yields (Table 4, entries 3, 5, 8, and 10). Only when bromo group was included in the substrates, the yields were a bit reduced (Table 4, entries 11 and 12). On the other hand, substrates bearing an *ortho*-substituent gave lower yields (Table 4, entries 2, 9, and 10), probably due to the steric hindrance. Notably, various functional groups, such as ester, fluoro, chloro, and even bromo substituents, were tolerated under these conditions, indicating that the methodology could provide potential for further transformation of the products.

Mechanistic Studies of the Oxidative Carbonylation Reaction. Two mechanisms of this oxidative carbonylation reaction were proposed on the basis of reported studies and our

Table 4. Oxidative Carbonylation of Aryl Indium Reagents[a]

$$\text{Ar}_2\text{InCl} + \text{EtOH} + \text{CO} \xrightarrow[\substack{\text{Desyl chloride} \\ \text{Et}_3\text{N, 60 °C, 24h}}]{\text{PdCl}_2(\text{dppf})} \text{ArCOOEt}$$

| entry	Ar₂InCl	product		yield(%)
1	(C₆H₅)₂InCl	C₆H₅—COOEt	13	83[b]
2	(o-CH₃C₆H₄)₂InCl	(o-CH₃C₆H₄)—COOEt	14	72[b]
3	(m-MeO-C₆H₄)₂InCl	(m-MeO-C₆H₄)—COOEt	15	90[b]
4	(2-naphthyl)₂InCl	(2-naphthyl)—COOEt	16	89[c]
5	(p-EtO₂C-C₆H₄)₂InCl	**25**	(p-EtO₂C-C₆H₄)—COOEt	**17** 95[c]
6	(o-EtOOC-C₆H₄)₂InCl	**26**	(o-EtOOC-C₆H₄)—COOEt	**18** 96[c]
7	(o-F-C₆H₄)₂InCl	**27**	(o-F-C₆H₄)—COOEt	**19** 95[b]
8	(p-Cl-C₆H₄)₂InCl	**28**	Cl—C₆H₄—COOEt	**20** 95[b]
9	(o-Cl-C₆H₄)₂InCl	**29**	(o-Cl-C₆H₄)—COOEt	**21** 81[b]
10	(F₃C, Cl-C₆H₃)₂InCl	**30**	F₃C—(Cl-C₆H₃)—COOEt	**22** 83[c]
11	(Br-C₆H₄)₂InCl	**31**	Br—C₆H₄—COOEt	**23** 65[c]
12	(3,5-Br₂C₆H₃)₂InCl	**32**	(3,5-Br₂C₆H₃)—COOEt	**24** 77[c]

[a] The reactions were carried out with 0.6 mmol of diaryl indium, 0.5 mmol of desyl chloride, 1.0 mmol of Et₃N, and 5 mol % PdCl₂(dppf) in EtOH with a balloon pressure of CO gas. [b] The yield was determined by NMR in 24 h using dibromomethane as the internal standard. [c] Isolated yield.

own experimental evidence (Scheme 3).[10,49–56] Path A involves oxidative addition of desyl chloride to Pd(0) and quick tautomerization to give a palladium enolate species **II**, followed by transmetalation of R^1_3In with the enolate group and migratory insertion of CO to form an acyl palladium complex, which reacts

further with a R^2OH and a base to liberate R^1COOR^2 via reductive elimination from intermediate **IV**. The alternative path to A is displacement of the enolate group in **II** by R^2OH with concomitant release of 1,2-diphenylethanone **33**, followed by CO insertion to give alkoxycarbonyl palladium complex **V**, which undergoes transmetalation with R^1_3In and reductive elimination to afford the product and a Pd(0) species.

To probe the feasibility of path A, we attempted to synthesize intermediate **III** by mixing Pd(dab)₂/PPh₃, desyl chloride, and trialkyl indium **1c** together under balloon pressure of CO in dry THF. Yet it turned out that only 2,6-dimethyl-2,6-diphenylheptan-4-one was produced in 62% yield (by GC) [eq 4], which contradicted with the good selectivity of the carbonylation product over the diketone side product in our reaction system.[57]

Next, we examined the stoichiometric reaction between desyl chloride and Pd(dba)₂/PPh₃ in MeOH under balloon pressure of CO, and a methoxycarbonylpalladium(II) complex **34**, corresponding to **V** in path B, was selectively produced in 47% isolated yield with 52% conversion of desyl chloride (by GC) [eq 5]. The structure of complex **34** was confirmed by ¹³C NMR and ¹H NMR as compared to the data reported in literature.[50] The other product was 1,2-diphenylethanone **33**, the yield of which (52% by GC) consisted of the conversion of desyl chloride as well. When complex **34** was treated with trialkyl indium reagent **1c** in MeOH under balloon pressure of CO at room temperature, 48% carbonylation product was obtained [eq 6].
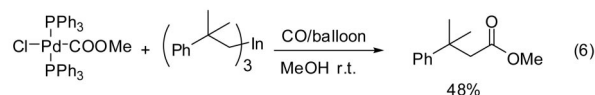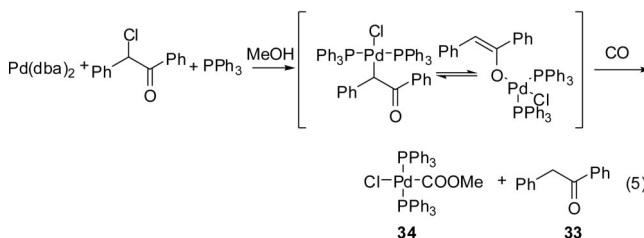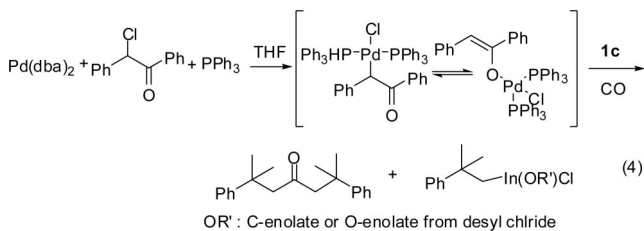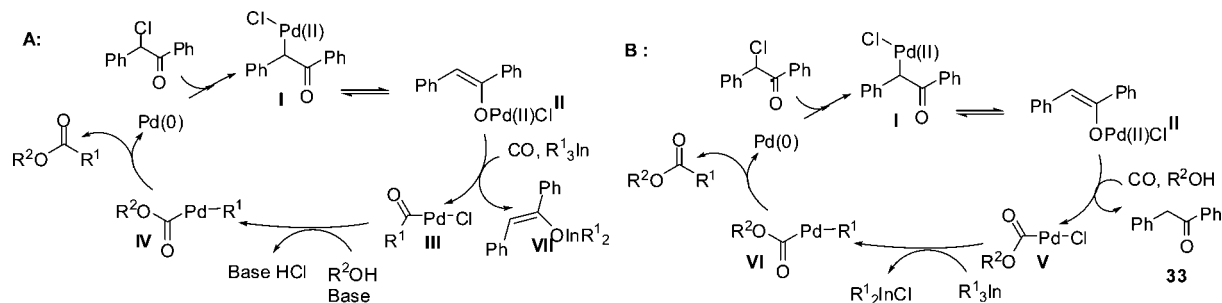

Therefore, we suggested path B to be the route involved in the catalytic oxidative carbonylations. In this cycle, the alkyl group was transferred to the metal center after the alkoxycarbonyl group, and the subsequent reductive elimination was presumed to be accelerated by CO. Thus, the possibility of β-hydride elimination was reduced as compared to traditional ways in which the alkyl group was transferred to the Pd center in the first oxidative addition step. We restrained ourselves at this point from a more detailed mechanistic discussion as the topic of carbonylation pathways is still under active debate,[49,56,58–61]

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(57) For further discussions about experimental evidence opposing path A, see the Supporting Information.

Scheme 3. Speculated Reaction Pathways of the Oxidative Carbonylation

and as there seems to be an appreciable mechanistic difference between the oxidative carbonylations and others.

Conclusion

In summary, we have developed a novel palladium-catalyzed oxidative carbonylation protocol for a broad range of alkyl (primary and secondary) and aryl indium reagents under mild conditions. The methodology avoided the difficult oxidative addition of alkyl halides over Pd(0) species and successfully inhibited the competitive β-hydride elimination. Preliminary experiments supported the proposed mechanism B. Furthermore, although the indium reagents were prepared from corresponding Grignard reagents, they displayed full compatibility with various functional groups under the protic reaction conditions, while Grignard reagents preclude their involvement in such reactions in many cases because of the high activity and basicity. Therefore, the methodology could be of utility in the synthesis of fine chemicals and pharmaceuticals. Further mechanistic studies are ongoing in our laboratory and will be reported in due course.

Experimental Section

Oxidative Carbonylations of Alkyl Indium Reagents. To a 10 mL vial in a glovebox was mixed the corresponding organoindium reagent (0.6 mmol), which was generated freshly from Grignard reagents and InCl$_3$, with *n*-butanol (2.5 mL), desyl chloride (115 mg, 0.5 mmol), and PdCl$_2$(CH$_3$CN)$_2$ (3.9 mg, 0.015 mmol, 3 mol %). Synphos ligand (10 mg, 0.016 mmol) was then added to the above mixture. The vial was placed into an autoclave. Following evacuation and replacement with CO (three cycles), the autoclave was closed and heated to the desired reaction temperature (60 °C). After 24 h, the reaction was cooled to room temperature. The reaction mixture was diluted with ether (50 mL), washed with saturated NH$_4$Cl (2 × 20 mL), and the aqueous phase was extracted with ether (2 × 20 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The crude product was then purified by column chromatography. Butyl 3-phenylpropanoate,[62] as an example of the products, was obtained in 90% yield. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35−7.22 (m, 2H), 7.22−7.12 (m, 3H), 4.07 (t, J = 6.5 Hz, 2H), 2.95 (t, J = 7.7 Hz, 2H), 2.62 (t, J = 7.7 Hz, 2H), 1.65−1.45 (m, 2H), 1.43−1.20 (m, 2H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.2, 140.8, 128.7, 128.5, 126.5, 64.6, 36.2, 31.3, 30.9, 19.4, 13.9.

General Procedure Producing Aryl Indium Reagents.[63] To a 5 mL flask were added LiCl (46.6 mg, 1.1 mmol) and *i*-PrMgCl (1.1 mL, 1.0 M, 1.1 mmol). The mixture was stirred at room temperature for 12 h. At −15 °C, the resulted solution was added in one portion to a 15 mL Schlenk flask, which was charged with aryl halide (1.0 mmol). The solution was stirred for 1 h at −15 °C, and after that InCl$_3$ (1.1 mL, 1.0 M in THF, 0.55 mmol) was added dropwise to the flask. Afterward, the temperature was allowed to slowly increase to room temperature, and the mixture was stirred for an additional 2 h.

The substrates **25−32** were prepared using the procedure mentioned above.

Oxidative Carbonylations of Aryl Indium Reagents. The solvent (THF) of aryl indium reagents was removed under vacuum before desyl chloride (115 mg, 0.5 mmol) and PdCl$_2$dppf (18.3 mg, 0.025 mmol, 5 mol %) were added to the Schlenk flask. A CO balloon was then charged to the flask, and ethanol (2.5 mL) was added. The mixture was heated to the desired reaction temperature (60 °C). After 24 h, the reaction was cooled to room temperature. The reaction mixture was diluted with ether (50 mL), washed with saturated NH$_4$Cl (2 × 20 mL), and the aqueous phase was extracted with ether (2 × 20 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pressure. The crude product was then purified by column chromatography. Diethyl terephthalate,[6] as an example of the products, was obtained in 95% yield with a colorless oil. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.10 (s, 4H), 4.40 (q, J = 7.4 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 161.3, 129.6, 124.9, 56.8, 9.7.

Synthesis of *trans*-[PdCl(COOMe)(PPh$_3$)$_2$[50] (24). To a 25 mL Schlenk flask were added Pd(dba)$_2$ (114.6 mg, 0.2 mmol), triphenyl phosphine (235.0 mg, 0.8 mmol), and methanol (5 mL), and the mixture was stirred for 4 h at room temperature. Next, desyl chloride (46.0 mg, 0.2 mmol) was added and a CO balloon was charged to the flask. After being heated at 60 °C for 5 h, the mixture was cooled to room temperature. The orange suspension was filtered to obtain a solid, which was washed by methanol and hexane (five times) and dried at room temperature under vacuum to give 67 mg (46% yield) of an off-white solid. It was identified by comparison with the NMR spectra of the known sample. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.82−7.69 (m, 12H), 7.46−7.28 (m, 18H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 184.9, 135.0, 134.9, 132.0, 131.7, 131.4, 130.6, 128.5, 52.4, 1.268. ^{31}P NMR (CDCl$_3$) 16.6 ppm.

Supporting Information Available: Spectroscopic data and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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