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Pd-Catalyzed Carbonylative Cross-Coupling Reactions by Triorganoindiums: Highly Efficient Transfer of Organic Groups Attached to Indium under Atmospheric Pressure

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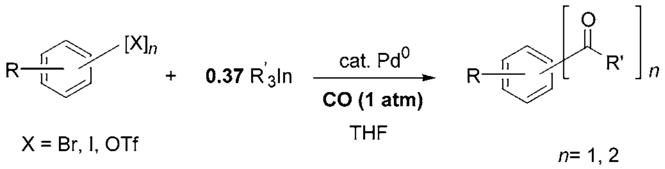
ABSTRACT



A highly atom-efficient synthetic method of unsymmetrical ketones was developed by using trialkyl- and triarylindiums, which could be employed as effective cross-coupling partners in Pd-catalyzed carbonylative cross-coupling reactions with a variety of organic electrophiles. The present method produced unsymmetrical ketones and 1,4-diacylbenzenes in good yields with highly efficient transfer of almost all the organic groups attached to the indium under atmospheric pressure of CO gas in THF at 66 °C.

The palladium-catalyzed carbonylative cross-coupling reaction of organic electrophiles with organometallics is a valuable synthetic method for the preparation of unsymmetrical ketones.[1] However, the utility of this route is limited by the requirements of a high pressure of carbon monoxide, high temperature, the transfer of only one of the organic groups attached to the metal, and β-hydride elimination. For the carbonylative cross-coupling reaction to be useful, it should be highly catalytic, and the reaction conditions and the reagents including the orgarnometallics should be compatible with a variety of functional groups lest the tedious protection−deprotection reactions be necessary. The Stille carbonylative cross-coupling reaction, where tin reagents are employed as a coupling partner, belongs to a representative family of palladium- and nickel-catalyzed carbonylative cross-coupling reactions.[2] These carbonylative cross-coupling reactions alternatively make use of a variety of organometallics (B, Zn, Cu, Al, Si).[3] Although the use of organostannanes as coupling partners in a carbonylative cross-coupling reaction has attracted much attention as a result of their availability and air- and moisture-stability, as well as their

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[1] Reviews: (a) Stille, J. K. *Pure Appl. Chem.* **1985**, *57*, 1771. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, 25, 508. (c) Pereyre, M.; Quintard, J.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: London, UK, 1987. (d) Mitchell, T. N. *Synthesis* **1992**, 803. (e) Ritter, K. *Synthesis* **1993**, 735. (f) Malleron, J.; Fiaud, J.; Legros, J. *Handbook of Palladium-Catalyzed Organic Reactions*; Academic Press: San Diego, CA, 1997. (g) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (h) Diederich, F.; Stang, P. J., Eds. *Metal-Catalyzed Cross-couplings Reactions*; Wiley-VCH: Weinheim, Germany, 1998. (i) Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; Wiley: New York, 1998.

[2] (a) Tanaka, M. *Tetrahedron Lett.* **1979**, *20*, 2601. (b) Cowell, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4193. (c) Tanaka, M. *Synthesis* **1981**, 47. (d) Sheffy, F. K.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 7173. (e) Sheffy, F. K.; Godschalx, J. P.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 4833. (f) Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 6417. (g) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500. (h) Kikukawa, K.; Idemoto, T.; Katayama, A.; Kono, K.; Wada, F.; Matsuda, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1511. (i) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1988**, *110*, 1557. (j) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1991**, *32*, 6449.

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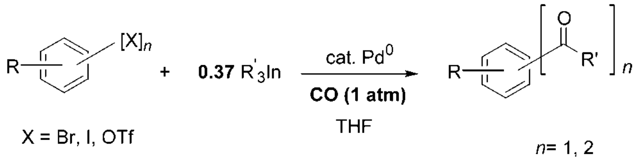
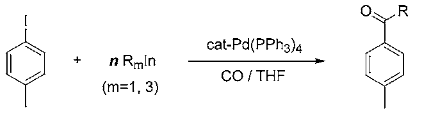
compatibility with a variety of functional groups, the difficulties associated with tin removal from the product, tin toxicity, high temperature, and especially *excessive use of organic groups attached to the Sn* represent major limitations.[1i] Our interest, both in overcoming the limitations of carbonylative cross-coupling reactions and in applying indium metal to modern organic synthesis,[4] has led us to investigate the participation of indium organometallics in metal-catalyzed carbonylative cross-coupling reactions.[5] As part of our continued studies directed toward the development of efficient indium-mediated reactions,[6] we describe a successful experiment with trialkyl- and triarylindium (Scheme 1).

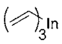
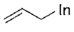
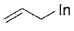
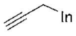
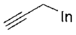
Scheme 1



The catalytic activity of several Pd complexes was initially examined in the reaction of 1-iodotoluene with tri-*n*-butylindium, which was generated in situ from the reaction of 1 equiv of indium trichloride with 3 equiv of *n*-butyllithium.[5b,d] The results are summarized in Table 1. Of the optimized conditions screened, the best results were obtained with 0.37 equiv of tri-*n*-butylindium and 4 mol % of Pd(PPh_3)$_4$ in THF at 66 °C under atmospheric pressure of CO gas, and *n*-butyl *p*-tolyl ketone was produced in 89% yield (Table 1, entry 5). Also, the desired product was obtained in 26% and 59% yields by using 0.12 and 0. 24 equiv of tri-*n*-butylindium, respectively (entries 3 and 4). This result means that all of the *n*-butyl groups attached to the indium were clearly entered into the product. Surprisingly, however, there was no carbonylative cross-coupling product formed under high pressure (5 and 20 atm) of CO gas (entries 6 and 7). Although we tried to obtain unsymmetric ketones by using allylindium[5g,i] and propargylindium[5h] generated in situ from indium and allyl halide or proparyl halide, the desired compound was not produced even under high pressure of CO gas (entries 11−14).

Table 1. Reaction Optimization



entry	*n*	R_mIn	pressure of CO	temp(°C)	time(h)	isolated yield(%)[a]
1	0.37	Me_3In	1	66	4	71
2	0.37	Me_3In	20	66	4	33
3	0.12	*n*-Bu_3In	1	66	3	26
4	0.24	*n*-Bu_3In	1	66	3	59
5	0.37	*n*-Bu_3In	1	66	3	89(2)[b]
6	0.37	*n*-Bu_3In	5	25	5	0
7	0.37	*n*-Bu_3In	20	25	11	0
8	0.37	Ph_3In	1	66	4	79(5)[c]
9	0.37	Ph_3In	20	66	4	36
10	0.37		1	66	24	0
11	1.1		1	25	1	0
12	1.1		20	66	4	0
13	1.1		1	66	1	0
14	1.1		1	25	1	0

[a] Reaction performed in the presence of 4 mol % of Pd(PPh_3)$_4$ and *n* equiv of R_mIn in THF at 66 °C under atmospheric pressure of CO gas, unless otherwise noted. [b] *n*-Butyl 4-methylbenzoate. [c] Benzophenone.

To demonstrate the efficiency and scope of the present method, we applied this catalytic system to a variety of trialkyl- and triarylindiums and organic electrophiles. For the trialkylindiums as coupling partners, various alkyl groups (methyl, butyl, isopropyl, isobutyl, and *sec*-butyl) exhibited little effects either on the reaction rates or on product yields. The results are summarized in Table 2. Under the optimized conditions, the treatment of iodobenzene with 0.37 equiv of tri-*n*-butylindium gave *n*-butyl phenyl ketone (**1**) in 87% yield (Table 2, entry 1). 4-Iodotoluene reacted with triisobutylindium and tri-*sec*-butylindium to produce the desired compounds **5** and **6** in 73% and 74% yields, respectively (entries 5 and 6). Reaction of 4-iodotoluene with triphenylindium gave phenyl *p*-tolyl ketone (**7**) in 79% yield (entry 7).

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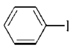
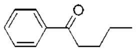
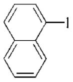
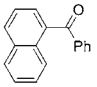
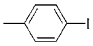
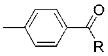
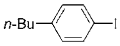
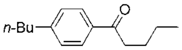
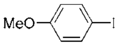
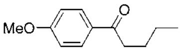
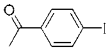
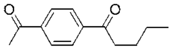
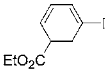
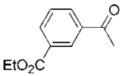
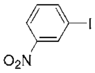
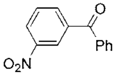
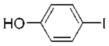
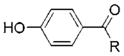
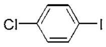
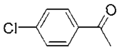
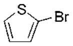
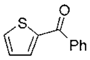
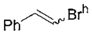
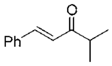
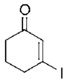
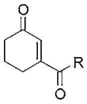
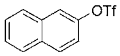
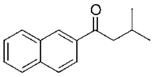
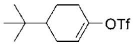
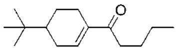
(5) (a) Nomura, R.; Miyazaki, S.-I.; Matsuda, H. *J. Am. Chem. Soc.* **1992**, *114*, 2738. (b) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267. (c) Gelman, D.; Schumann, H.; Blum, J. *Tetrahedron Lett.* **2000**, *41*, 7555. (d) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155. (e) Hirashita, T.; Yamamura, H.; Kawai, M.; Araki, S. *Chem. Commun.* **2001**, 387. (f) Takami, K.; Yorimitsu, H.; Shnokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997. (g) Lee, P. H.; Sung, S.-Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201. (h) Lee, K.; Seomoon, D.; Lee, P. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3901. (i) Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265. (j) Pena, M. A.; Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *Chem. Commun.* **2002**, 2246.

(6) a) Lee, P. H.; Bang, K.; Lee, K.; Lee, C.-H.; Chang, S. *Tetrahedron Lett.* **2000**, *41*, 7521. (b) Lee, P. H.; Bang, K.; Ahn, H.; Lee, K. *Bull. Korean Chem. Soc.* **2001**, *22*, 1385. (c) Lee, P. H.; Seomoon, D.; Lee, K. *Bull. Korean Chem. Soc.* **2001**, *22*, 1380. (d) Lee, K.; Lee, P. H.; Sung, S.-Y.; Chang, S. *J. Org. Chem.* **2001**, 66, 8646. (e) Lee, P. H.; Lee, K.; Kim, S. *Org. Lett.* **2001**, *3*, 3205. (f) Lee, P. H.; Lee, K.; Chang, S. *Synth. Commun.* **2001**, *31*, 3189. (g) Lee, P. H.; Ahn, H.; Lee, K.; Sung, S.-Y.; Kim, S. *Tetrahedron Lett.* **2001**, *42*, 37. (h) Lee, P. H.; Bang, K.; Lee, K.; Sung, S.-Y.; Chang, S. *Synth. Commun.* **2001**, *31*, 3781. (i) Lee, P. H.; Sung, S.-Y.; Lee, K.; Chang, S. *Synlett* **2002**, 146. (j) Bang, K.; Lee, K.; Park, Y. K.; Lee, P. H. *Bull. Korean Chem. Soc.* **2002**, *23*, 1272. (k) Iwasawa, N.; Miura, T.; Kiyota, K.; Kusami, H.; Lee, K.; Lee, P. H. *Org. Lett.* **2002**, *4*, 4463.

Table 2. Pd-Catalyzed Carbonylative Cross-Coupling Reactions of R$_3$In with Organic Electrophiles

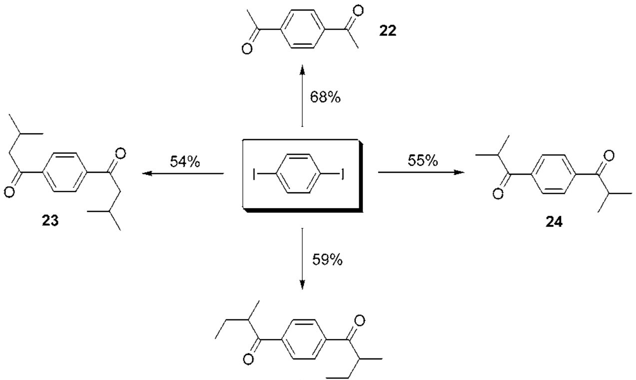
entry	organic electrophile	**0.37** R$_3$In	product		isolated yield(%)[a]
1		*n*-Bu$_3$In		**1**	87
2		Ph$_3$In		**2**	68(18)[b]
3		Me$_3$In		**3**	71
4		*n*-Bu$_3$In		**4**	89(2)[c]
5		*iso*-Bu$_3$In		**5**	73
6		*sec*-Bu$_3$In		**6**	74(4)[d]
7		Ph$_3$In		**7**	79(5)[b]
8		*n*-Bu$_3$In		**8**	77(2)[e]
9		*n*-Bu$_3$In		**9**	77
10		*n*-Bu$_3$In		**10**	79(16)[f]
11		Me$_3$In		**11**	63
12		Ph$_3$In		**12**	72
13		*n*-Bu$_3$In[g]		**13**	64
14		*iso*-Bu$_3$In[g]		**14**	61
15		Me$_3$In		**15**	76
16		Ph$_3$In		**16**	61(9)[b]
17		*iso*-Pr$_3$In		**17**	63(13)[i]
18		Me$_3$In		**18**	76
19		Ph$_3$In		**19**	63(10)[j]
20		*iso*-Bu$_3$In		**20**	67
21		*n*-Bu$_3$In		**21**	80(9)[k]

[a] Reaction performed in the presence of 4 mol % of Pd(PPh$_3$)$_4$ and 0.37 equiv of R$_3$In in THF at 66 °C under atmospheric pressure of CO gas, unless otherwise noted. [b] Benzophenone. [c] *n*-Butyl 4-methylbenzoate. [d] 4-*sec*-Butyl methylbenzene. [e] *n*-Butyl 4-butylbenzoate. [f] 4-*n*-Butylacetophenone. [g] 0.73 equiv of *n*-Bu$_3$In was used. [h] Cis:trans 1:4. [i] Isopropyl *trans*-cinnamate. [j] 4-Phenyl-2-cyclohexen-1-one. [k] 1-*n*-Butyl-4-*tert*-butylcyclohexene.

All of the reactions proceeded clearly with just 0.37 equiv of indium reagents under atmospheric pressure of CO gas. However, in the case of tri-*tert*-butylindium, trivinylindium, and triphenylethynylindium, the ketone compounds were not obtained. For a vast number of aryl iodides as organic electrophiles, the presence of various substituents, e.g., methyl (entries 3−7), *n*-butyl (entry 8), methoxy (entry 9), acetyl (entry 10), ester (entry 11), nitro (entry 12), and chloride (entry 15), on the aromatic ring showed little effect on efficiency of the carbonylative cross-coupling reactions. 4-Iodoacetophenone provided the desired product **10** in 79% yield (entry 10) together with 4-*n*-butylacetophenone in 16% yield. Varying the electron demand of the substituents on the arene did not diminish the efficiency of the present method (entries 8−9 and 11−12). Especially, 4-iodoanisole possessing the methoxy group as a strong electron-donating group underwent carbonylative cross-coupling reactions to produce *n*-butyl 4-methoxyphenyl ketone in 77% yield (entry 9). The reaction of 4-iodophenol having the hydroxy group with 0.73 equiv of tri-*n*-butylindium produced the desired product **13** (entry 13). This result means that tri-*n*-butylindium acts as a base before playing its role as a nucleophilic coupling partner. 4-Chloroiodobenzene was subjected to a carbonylative coupling reaction to produce selectively 4-chloroacetophenone (**15**) in 76% yield (entry 15). Heteroatoms turned out to be compatible with the employed reaction conditions (entry 16). Treatment of β-bromostyrene with 0.37 equiv of triisopropylindium afforded α,β-unsaturated ketone **17** in 63% yield (entry 17). The reaction worked equally well with vinyl iodide having an oxo group without protection (entries 18 and 19). In the case of aryl and vinyl triflate, the desired products **20** and **21** were obtained in 67% and 80% yields, respectively (entries 20 and 21).

With these results in hand, we applied the present method to dihalogenated aromatic compounds to obtain diacylbenzenes, which can be used effectively in materials and dendrimer sciences. Reaction of 1,4-diiodobenzene with 1.1 equiv of trimethylindium produced 1,4-diacetylbenzene (**22**) and 4-methyl acetophenone in 68% and 25% yields, respectively. We were pleased to observe that treatment of 1,4-diiodobenzene with 1.1 equiv of triisopropylindium and tri-*sec*-butylindium gave the desired 1,4-diacylbenzenes **24** and **25** in 55% and 59% yields, respectively (Scheme 2).

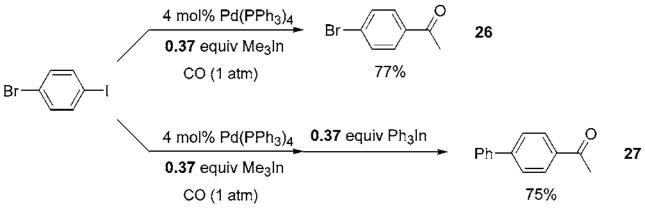
Scheme 2[a]



[a] Reaction conditions: 4 mol % of Pd(PPh$_3$)$_4$, 1.1 equiv of R$_3$In, CO (1 atm).

Reaction of 4-bromoiodobenzene with 0.37 equiv of trimethylindium gave selectively 4-bromoacetophenone (**26**) in 77% yield. On the basis of these results, unsymmetrical ketone **27** was chemoselectively and regioselectively prepared in one pot from 4-bromoiodobenzene in 75% yield through successive Pd-catalyzed carbonylative cross-coupling reaction followed by Pd-catalyzed cross-coupling reaction under atmospheric pressure of CO gas (Scheme 3).

Scheme 3



In conclusion, we have demonstrated that triorganoindium compounds could be employed as effective cross-coupling partners in Pd-catalyzed carbonylative cross-coupling reactions with a variety of organic electrophiles. Moreover, it was found that almost all the organic groups (alkyl and aryl groups) except alkenyl, allyl, and propargyl groups in triorganoindium were also efficiently transferred into product, producing unsymmetrical ketones and 1,4-diacylbenzenes in good yields. The present method complements the existing synthetic methods owing to some advantageous properties of In reagents over Sn and other metals—advantages such as availability, ease of preparation and handling, high reactivity, operational simplicity, low toxicity, and mild reaction conditions. This result would immediately pave the way for more opportunities in searching highly atom-efficient new carbonylative cross-coupling reactions.

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(7) **General Experimental Procedure.** To a solution of $InCl_3$ (40.5 mg, 0.183 mmol) in THF (1 mL) at −78 °C was added *n*-BuLi (0.55 mmol, 1.39 M in hexane) under the nitrogen atmosphere. The mixture was stirred for 30 min, the cooling bath was removed, and the reaction mixture was warmed to room temperature over 30 min. A solution of *n*-Bu_3In (0.18 mmol, ~0.l8 M in dry THF) was added to a mixture of $Pd(PPh_3)_4$ (23.1 mg, 4 mol %) and 4-iodotoluene (109.0 mg, 0.5 mmol) in THF (1 mL) under the nitrogen atmosphere. The resulting mixture was bubbled with CO gas for 5 min at room temperature to flush out nitrogen, then a positive CO pressure was established. The reaction mixture was warmed to 66 °C over 40 min and refluxed under atmospheric pressure of CO gas for 3 h at 66 °C. After being cooled to room temperature, the reaction mixture was quenched with $NaHCO_3$ (saturated aqueous). The aqueous layer was extracted with ether (3 × 20 mL), and the combined organics were washed with water and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc:hexane 1:50) to give *n*-butyl *p*-tolyl ketone (78.2 mg, 89%).