JOC Note

Highly Efficient Pd-Catalyzed Carbonylative Cross-Coupling Reactions with Tetraorganoindates

Sung Wook Lee, Kooyeon Lee, Dong Seomoon,
Sundae Kim, Hyunseok Kim, Hyun Kim,
Eunkyong Shim, Miae Lee, Seokju Lee,
Misook Kim, and Phil Ho Lee*

*Department of Chemistry, Kangwon National University,
Chunchon 200-701, Republic of Korea*

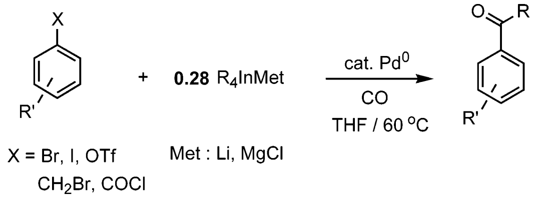
phlee@kangwon.ac.kr

Received March 13, 2004

Abstract: Tetraorganoindates, which were prepared easily from the reaction of 1 equiv of InCl$_3$ with 4 equiv of organometallics, could be employed as effective nucleophilic cross-coupling partners in Pd-catalyzed carbonylative cross-coupling reactions with a variety of organic electrophiles. The present method gave unsymmetrical ketones and 1,4-diacylbenzenes in good yields with highly efficient transfer of almost all the organic groups attached to the indium under a carbon monoxide atmosphere in THF at 60 °C.

Development of efficient methods for C−C bond formation is an important ongoing research theme of organic synthesis. Transition metal-catalyzed cross-coupling reactions of organometallic reagents with electrophilic coupling partners represent one of the most powerful methods to generate C−C bonds.[1] Among these, a reaction using an organoindium reagent has emerged as a favorite due to its reactivity, efficiency, versatility, and chemoselectivity.[2] On the basis of these properties of organoindiums, we reported Pd-catalyzed cross-coupling reactions of allylindiums[3] or allenylindiums,[4] and carbonylative cross-coupling reactions of triorganoindiums[5] with a variety of electrophiles. Also, it was found that a variety of organoindiums acted as nucleophilic coupling partners in transition metal-catalyzed cross-coupling reactions.[6] During the course of this study, we considered the possibility of extending the metal-catalyzed carbonylative cross-coupling reaction[7] using organoindates to overcome previously encountered defects associated with 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. Although organoindates could be easily prepared and their structure elucidated,[8] their application to organic synthesis had not been reported except for 1,4-addition to α,β-unsaturated ketones[9] and cross-coupling reactions.[10] As part of our continued studies directed toward the development of efficient indium-mediated reactions,[11] we describe a successful Pd-catalyzed carbonylative cross-coupling reaction with organoindates (Scheme 1).

SCHEME 1



We first examined the Pd-catalyzed carbonylative cross-coupling reaction of 4-iodotoluene with lithium tetra-*n*-butylindate, which was prepared in situ from the reaction of 1 equiv of indium trichloride with 4 equiv of *n*-butyllithium (Table 1).[8] Of the catalytic systems screened, the best result was obtained with 4 mol % of Pd(PPh$_3$)$_4$ at 60 °C under a balloon containing carbon monoxide, whereupon *n*-butyl 4-methylphenyl ketone (**2**) was produced in 84% yield together with *n*-butyl-4-methylbenzene (**3**) in 6% yield (entry 4). THF was the solvent of choice among several reaction media examined. Although the desired compound **2** was obtained in 18%, 42%, and 72% yields by using 0.07, 0.14 and 0.21 mol of

---

* Address correspondence to this author. Phone: +82 33 250 8493. Fax: +82 33 253 7582.

(1) (a) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985. (b) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G., Abel, E. W., Eds.; Pergamon: Oxford, UK, 1982; Vol. 8, pp 799−938. (c) Farina, V. In *Comprehensive Organometallic Chemistry II*; Wilkinson, G., Stone, F. G., Abel, E. W., Eds.; Pergamon: Oxford, UK, 1995; Vol. 12, pp 161−240. (d) Tsuji. J. *Palladium Reagents and Catalyst*; Wiley: Chichester, UK, 1995; Chapter 4. (e) Diederich, F.; Stang, P. J., Eds. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998. (f) Malleron, J.; Fiaud, J.; Legros, J. *Handbook of Palladium-Catalyzed Organic Reactions*; Academic Press: San Diego, CA, 1997. (g) Negishi, E. *Organopalladium Chemistry*; Wiley-Interscience: New York, 2002; Vols. I and II.

(2) (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (b) Cintas, P. *Synlett* **1995**, 1087. (c) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643. (d) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (e) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149. (f) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16. (g) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015. (h) Pae, A. N.; Cho, Y. S. *Curr. Org. Chem.* **2002**, *6*, 715. (i) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633.

(3) (a) Lee, P. H.; Sung, S.-Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201. (b) Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265.

(4) Lee, K.; Seomoon, D.; Lee, P. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3901.

(5) (a) Lee, P. H.; Lee, S. W.; Lee, K. *Org. Lett.* **2003**, *5*, 1103. (b) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *Synthesis* **2003**, 780.

(6) (a) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267. (b) Gelman, D.; Schumann, H.; Blum, J. *Tetrahedron Lett.* **2000**, *41*, 7555. (c) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155. (d) Hirashita, T.; Yamamura, H.; Kawai, M.; Araki, S. *Chem. Commun.* **2001**, 387. (e) Takami, K.; Yorimitsu, H.; Shnokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, 3, 1997. (f) Pena, M. A.; Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *Chem. Commun.* **2002**, 2246.

(7) (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) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1. (g) Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; Wiley: New York, 1998.

(8) (a) Hoffmann, K.; Weiss, E. *J. Organomet. Chem.* **1972**, *37*, 1. (b) Hoffmann, K.; Weiss, E. *J. Organomet. Chem.* **1973**, *50*, 17. (c) Hoffmann, K.; Weiss, E. *J. Organomet. Chem.* **1973**, *50*, 25.

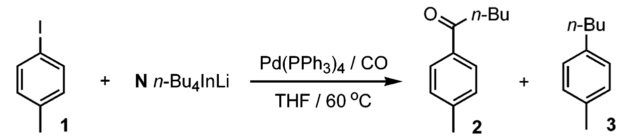
(9) Araki, S.; Shimizu, T.; Jin, S.-J.; Butsugan, Y. *Chem. Commun.* **1991**, 824.

(10) Lee, P. H.; Lee, S. W.; Seomoon, D. *Org. Lett.* **2003**, *5*, 4963.

(11) (a) Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Kim, H.; Kim, S.; Lee, P. H.; Iwasawa, N. *Org. Lett.* **2003**, *5*, 1725. (b) Lee, P. H.; Seomoon, D.; Lee, K.; Heo, Y. *J. Org. Chem.* **2003**, 68, 2510. (c) Lee, K.; Kim, H.; Miura, T.; Kiyota, K.; Kusama, H.; Kim, S.; Iwasawa, N.; Lee, P. H. *J. Am. Chem. Soc.* **2003**, *125*, 9682. (d) Lee, P. H.; Seomoon, D.; Kim, S. D.; Nagaiah, K.; Damle, S. V.; Lee, K. *Synthesis* **2003**, 2189 and references therein.

10.1021/jo0495790 CCC: $27.50

TABLE 1. Optimization of the Pd-Catalyzed Carbonylative Cross-Coupling Reaction



entry	N (mol)	time (h)	theoretical yield (%)[a]	GC ratio **1**	GC ratio **2**	GC ratio **3**	isolated yield (%)[a,b]
1	0.07	1	28	82	18	0	
2	0.14	1	56	58	42	0	
3	0.21	1	83	20	72	3	
4	0.28	1	100	0	91	7	84 (6)[c]
5	0.28	16					69[d] (12,[c] 12[e])
6	0.37[f]	3					89 (2)[e]

[a] Theoretical yield and isolated yield were based on 4-iodotoluene. [b] Reaction performed in the presence of 4 mol % of $Pd(PPh_3)_4$ and N mol of n-Bu_4InLi under a balloon containing CO, unless otherwise noted. [c] 1-*n*-Butyl-4-methylbenzene (**3**). [d] 10 atm of CO. [e] *n*-Butyl-4-methylbenzoate. [f] 0.37 mol of n-Bu_3In was used instead of n-Bu_4InLi.[5a]

tetra-*n*-butylindate, respectively (entries 1−3), the best results were obtained with 0.28 mol of tetra-*n*-butylindate (entry 4). This result shows that all of the *n*-butyl groups attached to the indium were involved in product formation. Under 10 atm pressure of CO, the carbonylative cross-coupling product was formed in 69% yield together with 12% of *n*-butyl-4-methylbenzene (**3**) and 12% of *n*-butyl-4-methylbenzoate, respectively (entry 5). Because 4-methylphenyl *n*-butyl ketone (**2**) was obtained in 89% yield with tri-*n*-butylindium in THF at 66 °C for 3 h,[5] tetra-*n*-butylindate seems to be a more reactive nucleophilic coupling partner than tri-*n*-butylindium in Pd-catalyzed carbonylative cross-coupling reactions (entries 4 and 6).

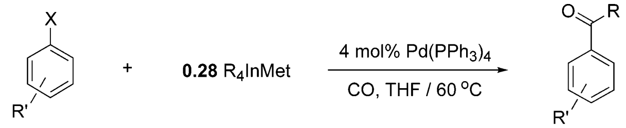
The scope of the carbonylative cross-coupling reaction with respect to the ligand on tetraorganoindates was examined (Table 2). A variety of alkyl groups such as methyl, butyl, isopropyl, isobutyl, *sec*-butyl, and phenyl exhibited little effect, either on the reaction rates or on product yields for the tetraorganoindates as nucleophilic coupling partners. Under the optimized conditions, subjecting 4-iodotoluene to 0.28 mol of tetraisopropylindate and tetraisobutylindate afforded 4-methylphenyl isopropyl ketone (**5**) and 4-methylphenyl isobutyl ketone (**6**) in 80% and 70% yields, respectively (entries 2 and 3). Although tetra-*tert*-butylindate did not react with 4-iodotoluene, tetra-*sec*-butylindate gave the desired product in 68% yield (entries 4 and 5). In the case of tetravinylindate, 4-vinyltoluene, which was the cross-coupling product, was obtained in 92% yield (entry 6). Reaction of 4-iodotoluene with tetraphenylindate afforded 4-methylphenyl phenyl ketone (**9**) in 72% yield (entry 8). All of the reactions proceeded cleanly with just 0.28 mol of organoindates under a balloon containing CO. On the basis of these results, the substituent effect on the electrophilic coupling partners was investigated. Aryl iodides having electron-withdrawing groups such as ethoxycarbonyl and halogen and triflate of 2-naphthol underwent the carbonylative cross-coupling reaction (entries 10, 12, and 15). Also, electron-donating groups such as methyl, methoxy, and hydroxy substituents produced the desired product in good yields (entries 1−4, 8, 9, and 11). Heterocyclic aryl ketones were also obtained under the standard reaction conditions (entries 16 and 17). Treatment of β-bromostyrene with 0.28 equiv of tetra-*sec*-butylindate gave the α,β-enone **19** in 63% yield (entry 18). Next, we examined the reactivity of benzyl bromide to expand the utility of organoindates in Pd-catalyzed carbonylative cross-coupling reactions. Although tetraorganoindates seem to be more reactive than triorganoindiums, the Pd-catalyzed carbonylative cross-coupling product **20** is obtained in 75% yield without nucleophilic substitution (entry 19). Treatment of 0.28 mol of tetraphenylindate with benzoyl chloride in the presence of Pd(0) led to the formation of benzil (**21**) in 73% yield (entry 20). Results in Table 2 suggest that organoindates react faster than organoindiums, by comparison with data using organoindiums.[5a] The present method was also successfully tested in reactions leading to di-*p*-acylbenzenes. Reactions of 0.84 mol of organoindate with 1,4-diiodobenzene under these optimum conditions afforded good yields of the desired products (entries 13 and 14). Dimerized compounds of aryl halide and cross-coupling products were produced as byproducts in Pd-catalyzed carbonylative cross-coupling reactions.

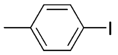
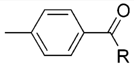
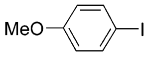
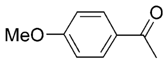
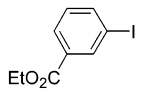
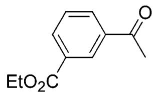
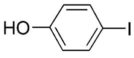
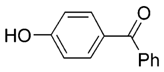
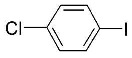
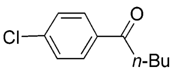
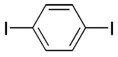
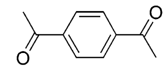
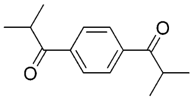
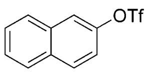
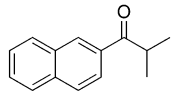
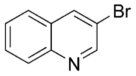
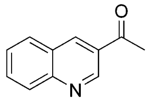
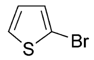
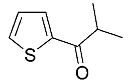
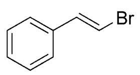
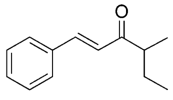
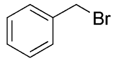
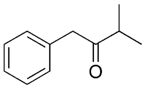
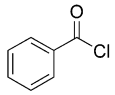
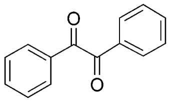
In summary, we have shown that tetraorganoindates can be directly employed in Pd-catalyzed carbonylative cross-coupling reactions with a variety of organic electrophiles such as aryl and vinyl halide, aryl triflate, benzyl bromide, and benzoyl chloride. In these reactions, tetraorganoindates containing methyl and primary and secondary alkyl and aryl groups transferred the four organic groups to electrophiles producing unsymmetrical ketones and 1,4-diacylbenzenes in good yields. Although Sn and other metals were used as nucleophilic coupling partners in Pd-catalyzed carbonylative cross-coupling reactions, the present method complements the existing synthetic methods owing to some advantageous properties such as availability, ease of preparation and handling, high reactivity, operational simplicity of organoindate reagents, and mild reaction conditions.

Experimental Section

Typical Experimental Procedure. To a solution of $InCl_3$ (30.5 mg, 0.138 mmol) in THF (1 mL) at −78 °C was added *n*-BuLi (0.55 mmol, 1.55 M in hexane) under the nitrogen atmosphere. After 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_4InLi (0.138 mmol, ∼0.l38 M in dry THF) was subsequently 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 with balloon was established. The reaction mixture was warmed to 60 °C over 40 min and refluxed under atmospheric pressure of CO gas for 0.5 h at 60 °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 organic phases 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 4-methylphenyl ketone (**2**) (74.0 mg, 84%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, $J = 8.11$ Hz, 2H), 7.25 (d, $J = 7.79$ Hz, 2H), 2.94 (t, $J = 7.45$ Hz, 2H), 2.41 (s, 3H), 1.67−1.75 (m, 2H), 1.38−1.43 (m, 2H), 0.93−0.97 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

TABLE 2. Pd-Catalyzed Carbonylative Cross-Coupling Reactions of R_4InMet with Electrophiles



entry	electrophiles	R_4InMet	product		time(h)	isolated yield(%)[a]
1		Me_4InLi		**4**	1.0	85(15)[b]
2		*iso*-$Pr_4InMgCl$	**5**		1.0	80(9)[c]
3		*iso*-$Bu_4InMgBr$	**6**		1.0	70
4		*sec*-$Bu_4InMgCl$	**7**		1.0	68
5		*tert*-$Bu_4InMgBr$			24	0
6		$(CH_2{=}CH)_4InMgBr$			1.0	0(92)[d]
7		$(Ph{-}C{\equiv}C)_4InLi$	**8**		1.5	38(33)[e]
8		$Ph_4InMgCl$	**9**		1.0	72(2)[f]
9		Me_4InLi		**10**	1.5	71
10		Me_4InLi		**11**	2.0	61
11		$Ph_4InMgCl$		**12**	2.0	65(21)[g]
12		*n*-Bu_4InLi		**13**	4.0	72(15)[h]
13		Me_4InLi		**14**		57[i]
14		*iso*-$Pr_4InMgCl$		**15**		60[i]
15		*iso*-$Pr_4InMgCl$		**16**	2.0	58(12)[j]
16		Me_4InLi		**17**	2.0	80
17		*iso*-$Pr_4InMgCl$		**18**	2.0	80
18		*sec*-$Bu_4InMgCl$		**19**	6.0	63
19		*iso*-$Pr_4InMgCl$		**20**	6.0	75
20		$Ph_4InMgCl$		**21**	2.0	73(27)[k]

[a] Reaction performed in the presence of 4 mol % of $Pd(PPh_3)_4$ and 0.28 mol of R_4InMet under a balloon containing CO, unless otherwise noted. Isolated yield was based on electrophiles. [b] 1,4-Dimethylbenzene. [c] 4-Isopropyltoluene. [d] 4-Methylstyrene. [e] 4-(Methylphenyl)phenylacetylene. [f] 4,4′-Dimethylbiphenyl. [g] 4-Phenylphenol. [h] 4,4-Dichlorobiphenyl. [i] 0.84 mol of Indate gave the best result. [j] 2-Isopropylnaphthalene. [k] Biphenyl.

200.3, 143.6, 134.6, 129.2, 128.2, 38.3, 26.6, 22.5, 21.6, 14.0; IR (film) 1676, 1607 cm^{-1}; HRMS (EI) for $C_{12}H_{16}O$ [M$^+$] calcd 176.1201, found 176.1202.

Acknowledgment. This work was supported by Grant No. R02-2003-000-10023-0 of the Basic Research Program of the Korea Science & Engineering Foundation and the CMDS at KAIST. We thank Professor T. Livinghouse of Montana State University for helpful discussions and proof reading of the manuscript.

Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0495790