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Palladium-Catalyzed Inter- and Intramolecular Coupling Reactions of Aryl and Vinyl Halides Mediated by Indium

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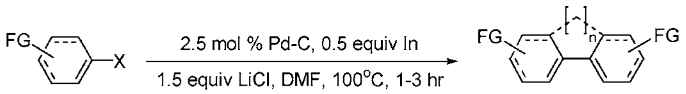
ABSTRACT



FG = H_2N, HO, OHC, Ac, MeO, Cl, Br, alkyl, aryl, heteroaryl

X = Cl, Br, I   n = 1, 2, 3

Treatment of aryl and vinyl halides with 50 mol % of 100 mesh indium, 2.5 mol % of Pd–C, and 1.5 equiv of LiCl under mild conditions (DMF, 100 °C, 1–3 h) could produce coupling products efficiently in good to excellent yields in which the C_{sp2}–C_{sp2} bond was formed. This reagent worked equally well with both intermolecular and intramolecular coupling reactions, producing a variety of biaryls, 1,3-dienes, and cyclic compounds.

The $C_{sp2}-C_{sp2}$ bond formation is one of the most useful reactions in organic synthesis.[1] Traditionally, copper-catalyzed coupling reactions of aryl and vinyl halides have been extensively used for the formation of biaryls and 1,3-dienes.[2] However, the use of high temperatures (neat, >200 °C), poor substrate scope, and the need to use stoichiometric amounts of copper reagents have limited the utility of these reactions in some cases.[2] Ullmann reductive coupling reactions of aryl, heteroaryl, and alkenyl halides proceeded with copper(I) thiophene-2-carboxylate and substrates possessing a coordinating *ortho* substituent at room temperature.[3] Although nickel in the presence of reducing agents such as zinc, LiH, and NaH has been applied in the Ullmann reaction, excess use of reducing agents and additives makes functional group tolerance narrow.[4] Pd-mediated coupling reactions of aryl and vinyl halides reported to date require inconvenient reaction conditions to regenerate Pd(0) species, high temperature, several specific ligands, and additives.[5] Thus, overcoming the harsh conditions typically required for Ullmann

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(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, 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, 1995; Vol. 12, pp 161−240. (d) Tsuji, J. *Palladium Reagents and Catalyst*; Wiley: Chichester, U.K., 1995; Chapter 4. (e) Diederich, F., Stang, P. J., Eds. *Metal-Catalyzed Cross-couplings Reactions*; Wiley-VCH: Weinheim, 1998. (f) Malleron, J.; Fiaud, J.; Legros, J. *Handbook of Palladium-Catalyzed Organic Reactions*; Academic Press: San Diego, 1997. (g) Negishi, E. *Organopalladium Chemistry*; Wiley-Interscience: New York, 2002; Vols. I and II.

(2) (a) Fanta, P. E. *Chem. Rev.* **1946**, *46*, 139. (b) Fanta, P. E. *Synthesis* **1974**, 9. (c) Cohon, T.; Cristea, I. *J. Org. Chem.* **1975**, *40*, 3649. (d) Sainsbury, M. *Tetrahedron* **1980**, *36*, 3327. (e) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977. (f) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2655. (g) Meyers, A. I. *J. Heterocycl. Chem.* **1998**, *35*, 991. (h) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(3) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312.

(4) (a) Semmelhack, M. F.; Helquisy, P. M.; Jones, L. D. *J. Am. Chem. Soc.* **1971**, *93*, 5908. (b) Zembayashi, M.; Tamao, K.; Yoshida, J.-I.; Kumada, M. *Tetrahedron Lett.* **1977**, *18*, 4089. (c) Semmelhack, M. F.; Helquist, P.; Jones, L. D.; Keller, L.; Mendelson, L.; Ryono, L. S.; Smith, J. G.; Stauffer, R. D. *J. Am. Chem. Soc.* **1981**, *103*, 6460. (d) Chao, C. S.; Cheng, C. H.; Chang, C. T. *J. Org. Chem.* **1983**, *48*, 4904. (e) Takagi, K.; Hayama, N.; Sasaki, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1887. (f) Jutand, A.; Mosleh, A. *Synlett* **1993**, 568. (g) Massicot, F.; Schneider, R.; Fort, Y. *J. Chem. Res., Synop.* **1999**, 664.

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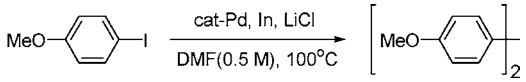
reaction and a simple and general procedure for the coupling reactions of aryl and vinyl halides has remained elusive. Described herein is the novel Pd-catalyzed coupling reaction of aryl and vinyl halides mediated by indium.

The activity of several Pd complexes and In was initially examined in coupling reactions of 4-iodoanisole (Table 1).

Table 1. Optimization of Coupling Reactions of 4-Iodoanisole[a]



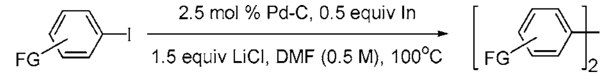
entry	cat-Pd	conversion	time (h)	GC yield[b] (%)
1	Pd(PPh$_3$)$_4$	100	2.5	94
2	Pd(OAc)$_2$	100	1	95
3	Pd$_2$dba$_3$CHCl$_3$	100	1	93
4	(π-ally)$_2$Pd$_2$Cl$_2$	100	1	96
5[c]	Pd(OAc)$_2$	100	1	96
6	Pd−C	100	1	95
7	Pd−C	87	40	31[d]
8[e]	Pd−C	0	40	0
9[f]	Pd−C	23	24	20
10[g]	**Pd−C**	**100**	**2.5**	**98**
11[g,h]	Pd−C	100	4	72

[a] Reaction performed in the presence of 2.5 mol % of Pd catalyst, 1.0 equiv of 100 mesh In, and 1.5 equiv of LiCl in DMF (0.5 M). [b] GC yields were obtained on the basis of an internal standard (dodecane). [c] 50 mol % of trifurylphosphine was used as ligand. [d] Reaction performed at 34 °C. [e] In was not used. [f] 10 mol % of In was used. [g] 50 mol % of In was used. [h] 1 mol % of Pd/C was used.

Of the catalytic systems screened, the best results were obtained with 2.5 mol % of Pd−C and 50 mol % 100 mesh indium in the presence of 1.5 equiv of LiCl in DMF (0.5 M) at 100 °C for 2.5 h under a nitrogen atmosphere, producing 4,4′-dimethoxy-1,1′-biphenyl in quantitative yield (98%) (entry 10). Control experiments revealed that no coupling reaction was observed in the absence of 100 mesh indium and Pd−C (entry 8). Although coupling reactions of alkyl and aryl iodides in the presence of small slices of indium (DMF, reflux, 8−15 h) produced bialkyls and biaryls,[6] treatment of 4-iodoanisole with 1 equiv of 100 mesh indium in DMF (0.25 M) gave only anisole in 98% yield. The use of stoichiometric amounts of indium accelerated the coupling reaction (entry 6), and 10 mol % of indium resulted in sluggish reaction and gave lower yields for 24 h (entry 9). One hundred mesh indium afforded better results than InI and InCl.[7] The rate of coupling reactions was decreased and reduction product (anisole) was produced without LiCl. DMF was the best solvent among several reaction media (DMF, THF, PhCH$_3$, CH$_3$CN, THF−H$_2$O, and DMF−H$_2$O) that were screened.

To demonstrate the efficiency and scope of the present methods, we applied cat-Pd and In to a variety of aryl and vinyl halides. Both electron-rich (entries 3−7) and electron-deficient (entries 1−2 and 8−17) aryl halides were suitable substrates for these reactions to provide the corresponding biaryls in good to excellent yields; the rates and yields of reactions were comparable except 1-naphthyl bromide (16 h, entry 2). The results are summarized in Table 2. Under the optimized conditions, 4-iodophenol and ethyl 4-iodobenzoate gave coupling products in 87% and 88% yield, respectively (entries 7 and 8). Aldehyde and keto groups are tolerated on the aryl iodide components (entries 12 and 13). Treatment of 4-chloro-1-iodobenzene with cat-Pd and In in the presence of LiCl gave 4,4′-dichloro-1,1′-biaryl in 91% yield (entry 14). Heteroatoms turned out to be compatible with the employed reaction conditions (entries 15−17). The coupling reaction of 3-iodopyridine afforded 3,3′-dipyridyl in 89% yield (entry 17).

Table 2. Coupling Reactions of Aryl Halides



entry	aryl halides	product	time (h)	yield[a] (%)
1	1-I-Naph	(1-Naph)$_2$	2.5	87 (96)
2	1-Br-Naph	(1-Naph)$_2$	16	90 (97)[b]
3	4-n-Bu-Ph-I	(4-n-Bu-Ph)$_2$	2.5	85 (95)
4	4-MeO-Ph-I	(4-n-MeO-Ph)$_2$	2.5	91 (98)
5	3-MeO-Ph-I	(3-n-MeO-Ph)$_2$	2.5	86 (94)
6	2-MeO-Ph-I	(2-n-MeO-Ph)$_2$	3	81 (84)[c]
7	4-HO-Ph-I	(4-n-HO-Ph)$_2$	2.5	87 (97)
8	4-Et$_2$OC-Ph-I	(4-Et$_2$OC-Ph)$_2$	2	88 (95)
9	3-Et$_2$OC-Ph-I	(3-Et$_2$OC-Ph)$_2$	2.5	86 (95)
10	4-F$_3$C-Ph-I	(4-CF$_3$-Ph)$_2$	2	92 (94)
11	2-F$_3$C-Ph-I	(2-CF$_3$-Ph)$_2$	2.5	85 (93)
12	4-OHC-Ph-I	(4-OHC-Ph)$_2$	3	87 (95)[d]
13	4-Ac-Ph-I	(4-Ac-Ph)$_2$	2.5	88 (95)
14	4-Cl-Ph-I	(4-Cl-Ph)$_2$	2	91 (98)
15	2-I-C$_4$H$_3$S	(2-I-C$_4$H$_3$S)$_2$	1.5	92 (97)
16	2-I-Py	(2-I-Py)$_2$	1.5	86 (96)
17	3-I-Py	(3-I-Py)$_2$	3	89 (95)

[a] Isolated yield. The numbers of parentheses indicate NMR yields obtained on the basis of an internal standard (dodecane). [b] 2.5 mol % of (π-allyl)$_2$Pd$_2$Cl$_2$ and 1 equiv of In were used. [c] 5 mol % of (π-allyl)$_2$Pd$_2$Cl$_2$ was used. Anisole was detected in 16% yield in GC. [d] 5 mol % of Pd−C was used. Benzaldehyde was detected in 5% yield in GC.

Extension of this coupling reaction to vinyl bromides has yielded promising results (Table 3). 2-Bromo-1-octene reacted with cat-Pd and In in the presence of LiCl to give 2,3-di-n-hexyl-1,3-butadiene in 92% yield in DMF for 2 h (entry 1). α-Bromo- and α-chlorostyrene produced 2,3-diphenyl-1,3-butadiene in 93% and 89% yields for 2 h, respectively (entries 2 and 3). p-Bromo-α-bromostyrene

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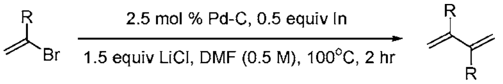
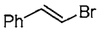
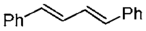
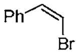
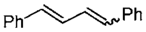
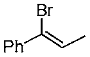
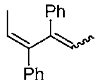
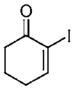
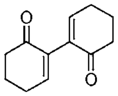
(5) (a) Clark, F. R. S.; Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 1* **1975**, 121. (b) Bamfield, P.; Quan, P. M. *Synthesis* **1978**, 537. (c) Uchiyama, M.; Suzuki, T.; Yamazaki, Y. *Chem. Lett.* **1983**, 1165. (d) Grigg, R.; Stevenson, P.; Worakun, T. *Tetrahedron* **1988**, *44*, 2049. (e) Penalva, V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron Lett.* **1998**, *39*, 2559. (f) Hassan, J.; Penalva, V.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron* **1998**, *54*, 13793. (g) Venkatraman, S.; Li, C.-J. *Org. Lett.* **1999**, *1*, 1133. (h) Hennings, D. D.; Iwama, T.; Rawal, V. H. *Org. Lett.* **1999**, *1*, 1205. (i) Mukhopadhyay, S.; Rothenberg, G.; Gitis, D.; Sasson, Y. *Org. Lett.* **2000**, *2*, 211. (j) Lin, G.-Q.; Hong, R. *J. Org. Chem.* **2001**, *66*, 2877.

(6) Ranu, B. C.; Dutta, P.; Sarkar, A. *Tetrahedron Lett.* **1998**, *39*, 9557.

(7) The use of 1 equiv of InI and InCl gave the desired product in trace and 40% yields, respectively.

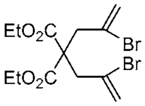
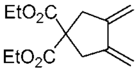
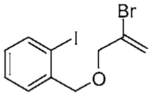
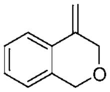
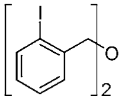
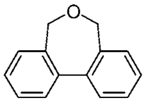
Table 3. Coupling Reactions of Vinyl Halides



entry	R	yield^a (%)	entry	vinyl halide	product	yield^a (%)
1	*n*-Hex	92	11			91
2	Ph	93				
3	Ph	89^b	12			81^d
4	4-MeO-Ph	87				
5	3-H_2N-Ph	79^c	13			71^e
6	3-HO-Ph	72^c				
7	2-Cl-Ph	89				
8	4-F_3C-Ph	88	14			85
9	4-Br-Ph	88				
10	4-Py	89^c				

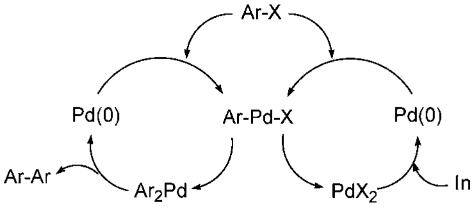
[a] Isolated yield. [b] α-Chlorostyrene was used. [c] Reduction product was isolated in 3% yield. [d] Ratio of *trans,trans* and *trans,cis* product = 1.2:1. Reaction time: 12 h. [e] Ratio of *cis,cis* and *cis,trans* product = 1.7:1. Reaction time: 6 h.

Table 4. Intramolecular Vinyl and Aryl Coupling Reactions

entry	aryl halides	product	time (h)	yield^a (%)
1			2	69
2			2	91
3			3	77^b

[a] Isolated yield. Reaction performed in the presence of 2.5 mol % of Pd—C, 50 mol % In and 1.5 equiv of LiCl in DMF (0.5 M) at 100 °C. [b] 0.05 M in DMF.

Scheme 1. Proposed Catalytic Cycle



selectively afforded 2,3-di(*p*-bromophenyl)-1,3-butadiene, which is the coupling product of vinyl halide, in 88% yield under the present conditions (entry 9). This result implies that vinyl bromide is more reactive than aryl bromide in coupling reactions. *trans*-*β*-Bromostyrene produced *trans*,*trans*-1,4-diphenyl-1,3-butadiene in 91% yield (entry 11). 2-Iodo-2-cyclohexen-1-one was treated with cat-Pd, In, and LiCl to give the desired product in 85% yield (entry 14).

Intramolecular vinyl and aryl coupling reactions proceeded smoothly to produce five to seven-membered rings in good yields under the present conditions (Table 4). Intramolecular coupling reaction of vinyl bromide produced 1,3-diene in 69% yield (entry 1). 2-Bromoallyl *o*-iodobenzyl ether in which aryl iodide and vinyl bromide were tethered was cyclized to give the desired product in 91% yield (entry 2). Symmetrical seven-membered-ring biaryl was obtained in 77% yield using cat-Pd, In, and LiCl in DMF (0.05 M) for 3 h at 100 °C (entry 3).

Although the mechanism of the coupling reactions has not been established, we believe that this transformation most likely proceeded via a direct electron transfer from indium to palladium(II) which completed the catalytic cycle (Scheme 1). In addition, potential for single electron transfer to generate radical or arylindium species can be considered.

In conclusion, we have demonstrated that treatment of aryl and vinyl halides with 50 mol % of 100 mesh indium, 2.5 mol % of Pd—C, and 1.5 equiv of LiCl under mild conditions (DMF, 100 °C, 1—3 h) could produce coupling products efficiently in good to excellent yields in which $C_{sp2}-C_{sp2}$ bond was formed. This reagent worked equally well with both intermolecular and intramolecular coupling reactions, producing a variety of biaryls, 1,3-dienes, and cyclic compounds.

Acknowledgment. This work was supported by the CMDS at KAIST and Grant No. R02-2003-000-10023-0 of the Basic Research Program of the KOSEF. The NMR and mass data were obtained from the central instrumental facility in Kangwon National University.

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

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