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Palladium-Catalyzed Cross-Coupling Reactions of in Situ Generated Allylindium Reagents with Aryl Halides[†]

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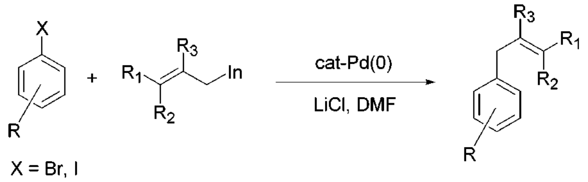
ABSTRACT



In situ generated allylindium reagents from the reaction of 1 equiv of indium with 1.5 equiv of allyl halides could be effective cross-coupling partners in palladium-catalyzed cross-coupling reactions to aryl halides. The best results were obtained with 2% $Pd_2dba_3CHCl_3$ and 16% Ph_3P in the presence of 3 equiv of LiCl in DMF at 100 °C.

The metal-catalyzed cross-coupling reaction of aryl and vinyl halides (or pseudohalides) with organometallics is one of the most straightforward methods for C−C bond formation.[1] The Stille reaction,[2] in which a tin reagent is employed as a coupling partner, belongs to a larger family of palladium- and nickel-catalyzed reactions. These coupling reactions alternatively make use of a variety of transmetalating agents (B, Zn, Mg, Li, Cu, Al, Zr, Si).[3] The use of organostannanes as coupling partners has attracted much attention as a result of their availability and air- and moisture-stability, as well as compatibility with a variety of functional groups. However, the difficulties associated with preparation of regiochemically defined allylstannanes, their tendency to undergo allylic isomerization, tin removal from the product, and tin toxicity represent major limitations associated with the use of allylstannanes as the nucleophilic coupling partners. Although allylstannanes are generally accessible, such procedures are sometimes inadequate and the requisite allylmetals are difficult to obtain. Ideally, allylmetals must be prepared in situ from the reaction of metals with allyl halides. The major advantage of organomagnesium and organolithium compounds as coupling partners is their availability.[3a] However, these reagents show low functional group tolerance. Therefore, the development of new allyl-

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[†] This paper is dedicated to Professor B. M. Trost on the occasion of his 60th birthday.

(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) *Metal-Catalyzed Cross-couplings Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (f) Malleron, J.; Fiaud, J.; Legros, J. *Handbook of Palladium-Catalyzed Organic Reactions*; Academic Press: San Diego, 1997.

(2) (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *The Stille Reaction*; Wiley: New York, 1998. (b) Stille, J. K. *Angew. Chem., Int. Ed. Engl*. **1986**, *25*, 508. (c) Stille, J. K. *Pure Appl. Chem*. **1985**, *57*, 1771. (d) Mitchell, T. N. *Synthesis* **1992**, 803. (e) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React*. **1997**, *50*, 1. (f) Pereyre, M.; Quintard, J.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987.

(3) (a) Geissler, H. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weomheim, 1998; Chapter 2.10. (b) Negishi, E. In *Organozinc Reagents*; Knochel, P., Jones, P., Eds.; Oxford University Press: Oxford, U.K., 1999; Chapter 11. (c) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. (d) Yamamura, M.; Moritani, I.; Murahashi, S. *J. Orgamomet. Chem*. **1975**, *91*, C39. (e) Tamao, K.; Kiso, Y.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc*. **1972**, *94*, 9268. (f) Sekia, A.; Ishikawa, N. *J. Organomet. Chem*. **1976**, *118*, 349. (g) Hatanaka, Y.; Hiyama, T. *Synlett* **1991**, 845. (h) Erdik, E. *Tetrahedron* **1992**, *48*, 9577.

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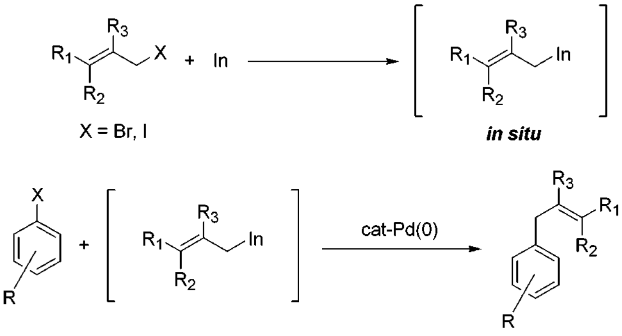
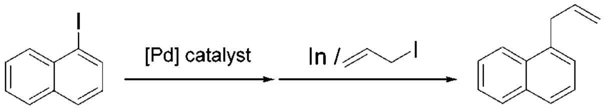
metals as coupling partners was explored to overcome these difficulties. Our interest, both in overcoming the limitations of the Stille reaction and applying indium metal to modern organic synthesis,[4] has led us to investigate the participation of indium organometallics in metal-catalyzed reactions.[5] In this letter, we report the palladium-catalyzed cross-coupling reaction of in situ generated allylindium reagents with aryl halides (Scheme 1).

Scheme 1



First, the catalytic activity of several palladium complexes was examined in the reaction of 1-iodonaphthalene with allylindium,[6] which was in situ generated from the reaction of allyl iodide and indium.[7] The results are summarized in Table 1. Among the catalysts examined, 4% $Pd(PPh_3)_4$ and 2% $Pd_2dba_3CHCl_3$ showed high catalytic activity (entries 6 and 14). Other palladium complexes, such as $PdCl_2$, $Pd(OAc)_2$, $Pd(CH_3CN)_2Cl_2$, and $Pd(PhCN)_2Cl_2$, produced 1-allylnaphthalene in good yields (entries 1−4). Among the ligands examined, triphenylphosphine gave the best results (entry 14). The use of lithium chloride is also critically important for a successful reaction (entry 11).[8] Of the catalytic systems examined, the best results were obtained with 2% $Pd_2dba_3CHCl_3$ and 16% Ph_3P in the presence of 3 equiv of LiCl in DMF at 100 °C under a nitrogen atmosphere (entry 14). Also, allylindium reagent which was in situ generated from the reaction of 1 equiv of indium with 1.5 equiv of allyl iodide gave the best result as a coupling partner. The use of indium in less than 1 equiv and allyl iodide in less than 1.5 equiv resulted in a sluggish reaction and gave lower yields as well as longer reaction times (entries 12 and 13).

Table 1 Catalyst Optimization



entry	catalyst	ligand	time (h)	isolated yield (%)[a]
1	4% $PdCl_2$	Ph_3P	1	86
2	4% $Pd(OAc)_2$	Ph_3P	1	86
3	4% $Pd(CH_3CN)_2Cl_2$	Ph_3P	3	70
4	4% $Pd(PhCN)_2Cl_2$	Ph_3P	1	87
5	4% $Pd(PPh_3)_4$		18	58[b]
6	4% $Pd(PPh_3)_4$		1	91
7	2% $Pd_2dba_3CHCl_3$	$[2,6\text{-}(MeO)_2Ph]_3P$	21	10
8	2% $Pd_2dba_3CHCl_3$	$(o\text{-Tolyl})_3P$	21	11
9	2% $Pd_2dba_3CHCl_3$	Ph_3As	20	11
10	2% $Pd_2dba_3CHCl_3$	$(2\text{-furyl})_3P$	3	75
11	2% $Pd_2dba_3CHCl_3$	Ph_3P	1	0[c]
12	2% $Pd_2dba_3CHCl_3$	Ph_3P	16	46[d]
13	2% $Pd_2dba_3CHCl_3$	Ph_3P	16	50[e]
14	2% $Pd_2dba_3CHCl_3$	Ph_3P	1	93

[a] Reaction performed in the presence of 16% ligand and 3 equiv of LiCl in DMF at 100 °C unless otherwise noted. Allylindium was obtained from the reaction of 1 equiv of indium with 1.5 equiv of allyl iodide unless otherwise noted. [b] THF was used as solvent. [c] LiCl was not used. [d] In:allyl iodide = 0.66:1. [e] In:allyl iodide = 1:1.

To demonstrate the efficiency and scope of the present method, we applied this catalytic system to a variety of allyl halides and aryl halides. For the allyl halides as coupling partners, the presence of various alkyl substituents at the α and γ positions did not exhibit a significant effect on either the reaction rates or product yields. The results are summarized in Table 2. Under the optimized conditions, **7** was treated with allyl bromide and indium to produce **16** in 87% yield (entry 3). The reaction of **7** with crotyl bromide (cis:trans = 1:5) in the presence of indium yielded a 1:3.2 mixture of α (cis:trans = 1.5:1, **17**) and γ products (**18**), but the product resulting from γ attack predominates (entry 4). Treatment of **7** with prenylindium gave the desired product **19** in 88% yield (entry 5). The reaction of **7** with in situ generated geranylindium from indium and geranyl bromide gave cross-coupling product **20** (cis:trans = 1:2) in 71% yield (entry 6). In the case of 3-bromocyclohexene, the desired products were obtained in good to excellent yields (entries 7, 10, and 17). For a vast number of aryl iodides, the presence of various substituents, e.g., *n*-butyl (entry 7), acetyl (entries 8 and 9), ketal (entry 10), ethoxycarbonyl (entries 11−13), and nitro (entries 14−18), on the aromatic ring did not show a significant effect on efficiency of the reactions. It should

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(4) (a) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643. (b) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (c) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023. (d) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149. (e) Normera, R.; Miyazaki, S.-I.; Matsuda, H. *J. Am. Chem. Soc.* **1992**, *114*, 2378. (f) Perez, I.; Sestelo, J.; Sarandeses, L. *Org. Lett.* **1999**, *1*, 1267. (g) Perez, I.; Sestelo, J.; Maestro, M. A.; Moourino, A.; Sarandeses, L.-A. J. *Org. Chem.* **1998**, *63*, 10074. (h) Cintas, P. *Synlett* **1995**, 1087. (i) Babu, G.; Perumal, P. T. *Aldrichimica Acta*. **2000**, *33*, 16. (j) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015. (k) Gelman, D.; Schumann, H.; Blum, J. *Tetrahedron Lett.* **2000**, *41*, 7555. (l) Aanwar, U.; Grigg, R.; Rasparini, M.; Savic, V.; Sridharan, V. *Chem. Commun.* **2000**, 645. (m) Anwar, U.; Grigg, R.; Sridharan, V. *Chem. Commun.* **2000**, 933. (n) Hirashita, T.; Yamamura, H.; Kawai, M.; Araki, S. *Chem. Commun.* **2000**, 387. (o) Takami, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997. (p) Perez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155.

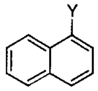
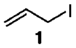
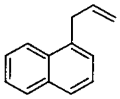
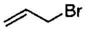
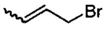
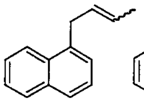
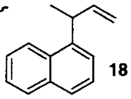
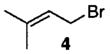
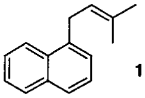
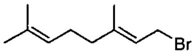
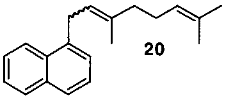
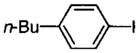
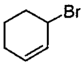
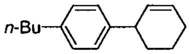
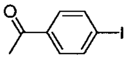
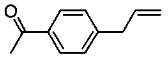
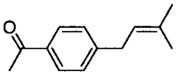
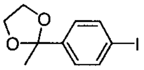
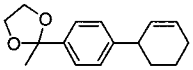
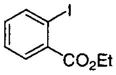
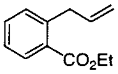
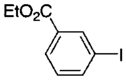
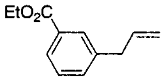
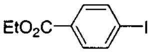
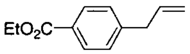
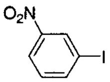
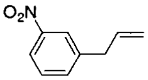
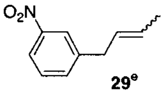
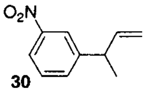
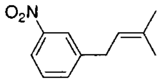
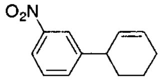
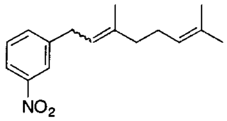
(5) (a) Lee, P. H.; Bang, K.; Lee, K.; Lee, C.-H.; Chang, S. *Tetrahedron Lett.* **2000**, *41*, 7521. (b) Lee, P. H.; Ahn, H.; Lee, K.; Sung, S.-Y.; Kim, S. *Tetrahedron Lett.* **2001**, *42*, 37.

(6) In ref 7, triallylindium could not prepared by the reaction of excess allylmagnesium bromide with indium(III) trihalide or indium(I) iodide. It is stated that allyl In(I) is formed by reaction of allyl iodide and indium in water but that in DMF at least two allylindium compounds were formed, one of which is the same as the compound formed in aqueous media.

(7) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1989**, *111*, 3228 and references therein.

(8) Although LiBr or LiI has an effect similar to that of LiCl, we used LiCl due to molecular weight and price.

Table 2. Results of Cross-Coupling Reactions

entry	aryl halide	allyl halide	product	time(h)	isolated yield(%)
1	 Y = I (**7**)	 **1**	 **16**	1	93
2	Br (**8**)			3	88
3	**7**	 **2**	**16**	11	87
4	**7**	 **3**	**17**[a]   **18**	24	86(1:3.2)[b]
5	**7**	 **4**	 **19**	25	88
6	**7**	 **5**	 **20**	24	71(1:2)[c]
7	 **9**	 **6**	 **21**	3	70
8	 **10**	**1**	 **22**	1	88
9	**10**	**4**	 **23**	8	72
10	 **11**	**6**	 **24**	3	89
11	 **12**	**1**	 **25**	1	96
12	 **13**	**1**	 **26**	2	84(7)[d]
13	 **14**	**1**	 **27**	2	84
14	 **15**	**1**	 **28**	3	94
15	**15**	**3**	 **29**[e]  **30**	9	89(1:1.2)[f]
16	**15**	**4**	 **31**	9	88
17	**15**	**6**	 **32**	9	81
18	**15**	**5**	 **33**	9	88(1:2)[c]

[a] Diastereomeric ratio of **17**: cis:trans = 1.5:1. [b] **17**(α):**18**(γ) ratio. [c] cis:trans ratio. [d] Ethyl benzoate. [e] Diastereomeric ratio of **29**: cis:trans = 1.5:1. [f] **29**(α):**30**(γ) ratio.

be mentioned that 4-iodoacetophenone, having a labile keto group toward allylindium, provided the desired products in good yields (entries 8 and 9). In the case of ethyl iodobenzoate, both the yield and the selectivity are almost independent of the electronic and steric effect (entries 11−13). The yields of the cross-coupling products were increased for aryl iodides possessing an electron-withdrawing substituent. These results may be understood on the basis of the fact that an electron-withdrawing group on aryl halides generally enhances the rate of oxidative addition of this substrate to the palladium center.[3c] The reaction of 4-iodoanisole possessing an electron-donating substituent with allylindium did not produce the desired product. Aryl iodide was more reactive than aryl bromide, giving a higher yield of cross-coupling product (entries 1 and 2).

Although the mechanism of the reaction of in situ generated allylindiums with aryl halides is not clear at the moment, we assume that allylindium plays a similar role to that of Li or Mg reagents. The elucidation of the detailed reaction mechanism must wait further study.

In conclusion, we have demonstrated for the first time in this letter that in situ generated allylindium reagents from the reaction of indium with allyl halides could be effective cross-coupling partners in palladium-catalyzed cross-coupling reactions of aryl halides. The present method complements the existing synthetic methods due to some advantageous properties of allylindium reagents over allylstannanes such as availability, ease of preparation and handling, high reactivity and selectivity, operational simplicity, and low toxicity.

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Supporting Information Available: Experimental procedure and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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