ORGANIC
LETTERS

2001
Vol. 3, No. 13
1997−1999

Palladium-Catalyzed Cross-Coupling Reaction of Organoindiums with Aryl Halides in Aqueous Media

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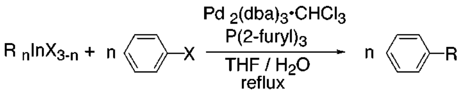
Received April 12, 2001

ABSTRACT



Diaryl-, divinyl-, and dialkylindium proved to be stable in aqueous media and to undergo a palladium-catalyzed cross-coupling reaction with aryl halides in aqueous THF. Treatment of 3-iodophenol with diphenylindium compound, generated from indium trichloride and two equimolar amounts of a phenyl Grignard reagent, in aqueous media under palladium catalysis provided the corresponding coupling product in excellent yield. Divinyl- and diethylindium can be used for the coupling reaction in the presence of water. A wide range of functional groups, including a hydroxy group and a formyl group, are compatible with this reaction.

The palladium-catalyzed cross-coupling reaction is one of the most important methodologies in organic synthesis.[1] The Suzuki−Miyaura coupling of organoboranes with organic halides has attracted much attention because of the low toxicity and easy handling of boron reagents as well as good functional group compatibility under the reaction conditions.[2] On the other hand, the cross-coupling reaction with organoindium compounds has not been widely studied.[3] A recent report[3a,e] shows that triorganoindium can efficiently transfer the three organic groups on the metal. Therefore, studies of this attractive cross-coupling reaction with organoindium are warranted.

There is increasing recognition that organic reactions carried out in water may offer advantages over those in organic solvents.[4] Among them, allylic indium provides a powerful tool for allylation of carbonyl compounds in aqueous media.[5,6] The usefulness of allylindium in water was well illustrated in the synthesis of (+)-3-deoxy-D-glycero-D-*galacto*-nonulosonic acid (KDN), starting from unprotected D-mannose.[7] Here we wish to report the cross-coupling reaction of organoindiums with aryl halides in aqueous media.[8,9] This study disclosed that diaryl-, divinyl-, and dialkylindium species are available in the presence of water, similar to allylic indium.

First, we examined the coupling reaction of triphenylin-

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[1] (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) Heck, R. F. *Palladium Regents in Organic Syntheses*; Academic Press: New York, 1985. (c) Tsuji, J. *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*; Wiley: Chichester, U.K., 1996.

[2] (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A., in ref 1a, Chapter 2.

[3] (a) Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267−1269. (b) Gelman, D.; Schumann, H.; Blum, J. *Tetrahedron Lett.* **2000**, *41*, 7555−7558. (c) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4095−4101. (d) Hirashita, T.; Yamamura, H.; Kawai, M.; Araki, S. *Chem. Commun.* **2001**, 387−388. (e) Pérez, I.; Pérez Sestelo, J.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155−4160.

[4] (a) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997. (b) Grieco, P. A. *Organic Synthesis in Water*; Blackie Academic & Professional: London, 1998. (c) Lubineau, A.; Auge, J. In *Modern Solvents in Organic Synthesis*; Knochel, P., Ed.; Springer-Verlag: Berlin Heidelberg, 1999.

[5] Review on the use of indium in organic synthesis; Cintas, P. *Synlett* **1995**, 1087−1096.

[6] (a) Li, C.-J.; Chan, T.-H. *Tetrahedron Lett.* **1991**, *32*, 7017−7020. (b) Araki, S.; Jin, S.; Idou, Y.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1736−1738.

[7] (a) Chan, T.-H.; Li, C.-J. *J. Chem. Soc., Chem. Commun.* **1992**, 747−748. (b) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023−2035.

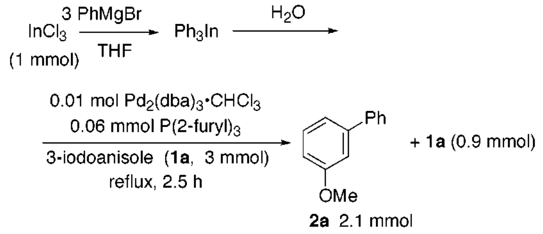
[8] For reviews on transition metal-catalyzed coupling reactions in aqueous media, see refs 4a, Chapter 5.5, and 4c, Chapter 2.

[9] Palladium-catalyzed Ullmann-type reductive coupling reaction of aryl halides was reported: Venkatraman, S.; Li, C.-J. *Org. Lett.* **1999**, *1*, 1133−1135.

10.1021/ol015975i CCC: $20.00

dium with aryl iodide in aqueous THF. Triphenylindium (1.0 mmol) was prepared in situ by mixing three equimolar amounts of phenylmagnesium bromide with indium trichloride for 30 min (Scheme 1). Water (1 mL), 3-iodoanisole (**1a**, 3.0 mmol), and palladium−trifurylphosphine complex[10] were sequentially added to a THF solution of triphenylindium at 25 °C. The whole mixture was then heated at reflux for 2.5 h. Usual workup and silica gel column purification provided 2.1 mmol of the cross-coupling product **2a**, and 0.9 mmol of **1a** was recovered. Therefore, two, at least, of the three phenyl groups attached to the indium could survive in aqueous THF at reflux and could be employed for the coupling reaction.[11] The NMR experiment revealed that triphenylindium is transformed into diphenylindium hydroxide[12] by the addition of water.[13]

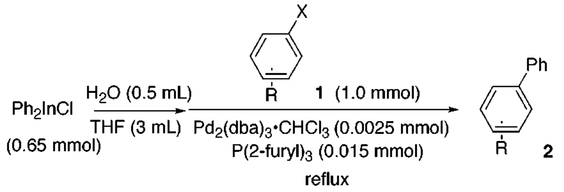
Scheme 1



According to the above fact, we set up a standard procedure for the coupling reaction of arylindium with aryl halide in an aqueous medium as follows. Two equimolar amounts of phenylmagnesium bromide were added to a THF solution of indium trichloride to prepare diphenylindium chloride (0.65 mmol). Water was then added to the reaction mixture. Aryl halide (1.0 mmol) was treated with the diphenylindium hydroxide[14] in the presence of palladium catalyst[15] at reflux[16] to provide the corresponding coupling product. The results are summarized in Table 1.

The reaction with aryl iodides was quite satisfactory (entries 1−6 and 11). Ester and nitro moieties were untouched under the reaction conditions. Interestingly, 3-iodophenol (**1e**) and 2-iodobenzyl alcohol (**1f**), which have reactive hydrogen, underwent the coupling reaction with ease. Unfortunately, the use of 4-iodoanilines **1g** and **1h** resulted in moderate conversion under the standard conditions. Treatment of 4-iodobenzoic acid (**1i**) with the phenylindium compound in the presence of $NaHCO_3$ provided the corresponding product in 40% yield.[17] However, treatment of **1i** with 2.2 equiv of monophenylindium species in the presence of $NaHCO_3$ in aqueous THF yielded the coupling product in 90% yield (entry 10).

Table 1. Coupling Reaction of Diphenylindium Compounds with Aryl Halides



entry	1	X	R	time/h	yield/%
1	**1a**	I	3-OCH_3	3	100
2	**1b**	I	4-CO_2-*n*-C_4H_9	1	99
3	**1c**	I	4-NO_2	1	96
4	**1d**	I	2-NO_2	1	95
5	**1e**	I	3-OH	1	95
6	**1f**	I	2-CH_2OH	2	88
7	**1g**	I	4-NH_2	2.5	50
8	**1h**	I	4-$N(CH_3)_2$	2	49
9	**1i**	I	4-CO_2H	3	40^{a}
10	**1i**	I	4-CO_2H	4	$90^{a,b}$
11	**1j**	2-iodopyridine		5	100
12	**1k**	Br	3-CN	3.5	90
13	**1l**	Br	2-CHO	2	100
14	**1m**	Br	4-$COCH_3$	2.5	63
15	**1n**	Br	4-OCH_3	2.5	6
16	**1o**	Br	4-CH_2OH	3	6
17	**1p**	OTf	H	4	0

[a] The product was isolated as the allyl ester after the carboxylic acid was treated with allyl bromide in the presence of K_2CO_3 in DMF at 25 °C. $NaHCO_3$ (5.0 mmol) was used as an additive. [b] $PhInCl_2$ (2.2 mmol) was used instead of 0.65 mmol of Ph_2InCl.

The catalytic system also proved to be highly efficient for electron-deficient aryl bromides (entries 12 and 13). For example, treatment of 2-bromobenzaldehyde (**1l**) with the diphenylindium species under palladium catalysis yielded 2-biphenylcarbaldehyde (**2l**) quantitatively. However, a poor yield was obtained for 4-bromoanisole (**1n**), which is consistent with the general trend that electron-rich aryl bromide is less reactive than electron-deficient aryl bromide. In contrast to the literature,[3a,e] aryl triflate **1p** did not undergo coupling.

Next, we investigated the use of other organoindiums such as vinyl-, ethyl-, methyl-, and (1-octynyl)indium compounds. The availability of the organo group for the coupling reaction in the presence of water was examined by ^{13}C NMR experiments. Trivinyl- and triethylindium were found to lose one of the three organo groups, forming divinyl- and

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(10) The palladium catalyst was prepared from $Pd_2(dba)_3$•$CHCl_3$ (0.01 mmol) and trifurylphosphine (0.06 mmol) in THF (1 mL).

(11) Without water, 2.82 mmol of **2a** was obtained.

(12) It is not clear that diphenyindium hydroxide was formed. Tetraphenylindoxane or other oligomeric forms might be produced. However, throughout this text, we describe the compound as diphenyindium hydroxide for convenience.

(13) See Supporting Information.

(14) We also checked the formation of diphenylindium hydroxide from diphenylindium chloride on exposure to water. See Supporting Information.

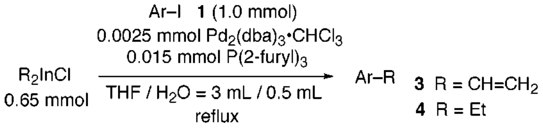
(15) Trifurylphosphine was the best among the ligands examined. Three equimolar amounts of phosphine to palladium were necessary. The use of one, two, or four equimolar amounts of trifurylphosphine gave **2a** in 56%, 71%, or 65% yield, respectively, in the reaction of **1a** with diphenylindium.

(16) The reaction was sluggish when performed at ambient temperature. Treatment of **1a** with diphenylindium at 25 °C for 24 h provided **2a** in 14% yield.

(17) Addition of $NaHCO_3$ was essential to reproduce the yield of the coupling product. It is worth noting that other reactions shown in Table 1 did not require any bases. The effect of a base in the case of **1i** is not clear at this stage.

diethylindium species, respectively.[13] Thus, the reaction of divinyl- and diethylindium compounds with aryl iodide was examined in analogy with the diphenylindium species, and satisfactory results were obtained (Table 2). The NMR measurement of trimethylindium revealed that trimethylindium is stable in water. However, cross-coupling with **1a** led to recovery of the starting material. Methylated product was obtained in 3% yield. Upon treatment of tri(1-octynyl)indium with water, the signals of the carbons that indicated the presence of octynylindium disappeared. 1-Octyne was detected instead. Complete decomposition of tri(1-octynyl)indium was suggested. The reaction of tri(1-octynyl)indium could not afford the product at all in the coupling reaction with **1a** in aqueous media.

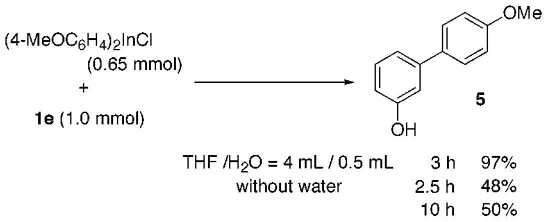
Table 2. Coupling Reaction of Divinyl- and Diethylindium Compounds with Aryl Iodides



substrate	R	time/h	product	yield/%
1a	CH=CH$_2$	3	**3a**	96
1b	CH=CH$_2$	2	**3b**	94
1c	CH=CH$_2$	2	**3c**	96
1e	CH=CH$_2$	2	**3e**	75
1f	CH=CH$_2$	2	**3f**	65
1c	Et	4	**4c**	92

In contrast to the results in aqueous THF, addition of water was effective for the reaction of bis(4-methoxyphenyl)indium chloride with **1e**. Treatment of **1e** with bis(4-methoxyphenyl)indium chloride for 3 h in refluxing aqueous THF yielded **5** in 97% yield (Scheme 2). In contrast, a 48% isolated yield of **5** was obtained in THF itself. To investigate the effect of water, several other cosolvents were examined. Addition of dioxane, methanol, or DMF, instead of water, furnished **5** in 52%, 61%, or 99% yield, respectively, in the reaction of **1e** with bis(4-methoxyphenyl)indium. A polar cosolvent tends to promote the coupling reaction. Further investigation is necessary to explain the solvent effect.

Scheme 2



In summary, we have reported the cross-coupling reaction of organoindiums in aqueous media. It is also disclosed through this work that the reaction showed a wide range of chemoselectivity.

Acknowledgment. Financial support by Grants-in-Aid for Scientific Research (Nos. 09450341 and 10208208) from the Ministry of Education, Culture, Sports, Science and Technology, Japan, is acknowledged. H.Y. thanks JSPS for financial support.

Supporting Information Available: Detailed experimental procedures and characterization of organoindium compounds by ^{13}C NMR experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

OL015975I