

## Communications to the Editor

### Grignard-Type Carbonyl Phenylation in Water and under an Air Atmosphere

Chao-Jun Li\* and Yue Meng

Department of Chemistry, Tulane University  
New Orleans, Louisiana 70118

Received May 17, 2000

Due to the natural abundance of water as well as the inherent advantages of using water as a solvent, recently interest has been growing in studying organic reactions in water. Many reactions that are traditionally carried out in organic solvent can be carried out in water with additional interesting features.<sup>1</sup> Carbon–carbon bond formation is the essence of organic synthesis.<sup>2</sup> One of the most important methods for forming carbon–carbon bonds is through the nucleophilic addition of an organometallic reagent to a carbonyl derivative. Such reactions are exemplified by the Barbier–Grignard type reactions.<sup>3</sup> For carbonyl additions based on organometallic reagents, it is generally accepted that strict anhydrous reaction conditions are required for a smooth reaction.<sup>4</sup>

On the other hand, the significance of performing metal-mediated reactions in water has been recognized recently. Within the last several years, various metals have been developed to mediate Barbier–Grignard type reactions. Recent studies have shown the advantages using aqueous organometallic reactions over those occurring in organic solvent in organic synthesis. For instance, the protection–deprotection processes for certain acidic-hydrogen-containing functional groups can be avoided, which contributes to an overall synthetic efficiency. Water-soluble compounds, such as carbohydrates, can be reacted directly without the need for derivatization, and water-soluble catalyst solutions can be reused for a prolonged period of time which reduces operational cost. However, while the allylation,<sup>5</sup> propargylation,<sup>6</sup> aldol-type reaction,<sup>7</sup> and benzylation of carbonyl compounds<sup>8</sup> has been successful with various metals including magnesium in water,<sup>9</sup> a successful Grignard-type reaction with nonactivated halides in water is yet to be developed.

(1) For general reviews on organic reactions in water, see: Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York 1997. See also: Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149; Li, C. J. *Chem. Rev.* **1993**, *93*, 2023. Li, C. J. *Tetrahedron* **1996**, *52*, 5643. Chan, T. H.; Isaac, M. B. *Pure Appl. Chem.* **1996**, *68*, 919. Lubineau, A.; Auge, J.; Queneau, Y.; Lubineau, A.; Auge, J.; Queneau, Y. *Synthesis* **1994**, 741. *Organic Synthesis in Water*; Grieco, P. A. Ed.; Blackie Academic & Professional: Glasgow, 1998. Cornils, B.; Wiebus, E. *Chemtech* **1995**, 25(1), 33. Hermann, W. A.; Kohlpainter, C. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1524. Kuntz, E. G. *Chemtech* **1987**, *17*(9), 570.

(2) Corey, E. J.; Cheng, X. M. *The Logic of Organic Synthesis*; John Wiley & Sons: New York, 1989.

(3) Kharasch, M. S.; Reinmuth, O. *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: New York, 1954. Barbier, P. *Compt. rend.* **1898**, *128*, 110. Barbier, P. *J. Chem. Soc.* **1899**, 76, Pt. 1, 323. Grignard, V. *Compt. rend.* **1900**, *130*, 1322.

(4) Wakefield, B. J. *Organomagnesium Methods in Organic Synthesis, Best Synthetic Methods series*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Academic Press: San Diego, 1995.

(5) Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Syntheses and Processes*; Anastas, P. A., Williamson, T. C., Eds.; Oxford University Press: Oxford, UK, 1998.

(6) Isaac, M. B.; Chan, T. H. *J. Chem. Soc., Chem. Commun.* **1995**, 1003. Yi, X. H.; Meng, Y.; Hua, X. G.; Li, C. J. *J. Org. Chem.* **1998**, *63*, 7472.

(7) Chan, T. H.; Li, C. J.; Wei, Z. Y. *J. Chem. Soc., Chem. Commun.* **1990**, 505. Shen, Z.; Zhang, J.; Bieber, L. W.; Malvestiti, I.; Storch, E. C. *J. Org. Chem.* **1997**, *62*, 9061. Zou, H.; Yang, M. *Tetrahedron Lett.* **1997**, *38*, 2733.

(8) Bieber, L. W.; Storch, E. C.; Malvestiti, I.; Sila, M. F. *Tetrahedron Lett.* **1998**, *39*, 9393.

(9) Li, C. J.; Zhang, W. C. *J. Am. Chem. Soc.* **1998**, *120*, 9102.

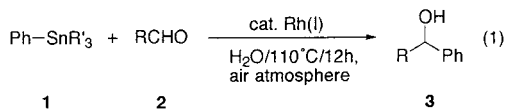
**Table 1.** Rhodium-Catalyzed Reaction of Trimethylphenylstannane with Aldehyde in Water

Entry	RCHO (2)	Product (3)	Yield (%)
1	PhCHO		82
2	p-ClPhCHO		86
3	p-FPhCHO		78
4	m-BrPhCHO		82
5	p-CH3PhCHO		75
6	p-CH3CH2PhCHO		70
7	p-CH3OPhCHO		74
8	p-CNPhCHO		92
9	n-C6H13CHO		52
10	n-C7H15CHO		65
11	HOPhCHO		56

<sup>a</sup> All reactions were carried out in deionized water under an atmosphere of air and at 110 °C (oil bath temperature). Yields were isolated ones after flash chromatography on silica gel. Nearly the same result was obtained when tributylphenyltin was used for entry 1.

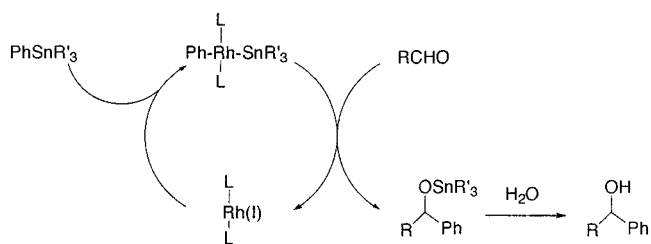
This is largely due to the fact that it requires a highly reactive metal to break a nonactivated carbon–halogen bond (as well as to react with the carbonyl once the organometallic intermediate is formed) and, with a highly reactive metal, various competing side-reactions (such as the reduction of water, the reduction of starting materials, and the hydrolysis of the organometallic intermediate, even if it is successfully generated) will prevail. This seems like an insurmountable dilemma (as judged by the numerous failed attempts of our own) that restricts the further development of aqueous organometallic reactions. Herein we wish to report a design that shows promise in overcoming such a

dilemma, in which the first Grignard-type phenylation of aldehydes in water has been developed. In the presence of a catalytic amount of  $\text{Rh}(\text{COD})_2\text{BF}_4$ ,<sup>10</sup> phenyltin derivatives (trimethyl and tributyl) react effectively with aldehydes in water and under an atmosphere of air to give nucleophilic addition products in high yields (eq 1).



To begin our study, phenyltrimethylstannane was stirred with benzaldehyde and a catalytic amount of a rhodium catalyst (5 mol %) at room temperature in water. No reaction was observed even after several days. However, when the reaction was carried out under refluxing conditions, a smooth reaction occurred to give a clean product overnight as judged by GC-MS and TLC. The GC-MS analysis also indicated the formation of the desired product. Subsequently, isolation and characterization confirmed the structure of the nucleophilic addition product. Various aldehydes were thus converted to the corresponding alcohols similarly (Table 1). The presence of NaF improved the reaction yield slightly. Phenyltributylstannane is equally effective in serving as the nucleophile. Aryl halides (such as chloride, fluoride, and bromide) are inert under the present reaction conditions which imparts chemoselectivity. The presence of electron-withdrawing and potentially reactive cyano and hydroxyl groups did not adversely interfere with the reaction. Aliphatic aldehydes are also effective in reacting with the tin reagent, although the yields of the desired products were slightly lower. Scheme 1 outlines a tentative mechanism in which rhodium serves as a catalyst for the addition. In conclusion, the first successful aqueous Grignard-type phenylation of aldehydes was developed. The scope, mech-

**Scheme 1.** Proposed Mechanism for the Rhodium-Catalyzed Addition of Aryl Stannanes to Aldehydes in Water



anism, and synthetic application of this novel reaction are under investigation.

A typical experimental procedure follows: A mixture of benzaldehyde (106 mg, 1 mmol), phenyltrimethylstannane (241 mg, 1 mmol), sodium fluoride (210 mg, 5 mmol), and bis(1,4-cyclooctadiene)rhodium tetrafluoroborate (20 mg, 5% mol) in 20 mL of deionized water was capped and stirred at 110 °C (oil bath temperature) overnight. Upon cooling, the reaction mixture was extracted with ethyl acetate. The combined organic fractions were dried over  $\text{MgSO}_4$  and concentrated. The residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 5:1) to give 151 mg (82% yield) of diphenylmethanol.

**Acknowledgment.** We are grateful to NSF (CAREER), the NSF-EPA joint program for a sustainable environment, and LEQSF for partial support of our research.

**Supporting Information Available:** Characterization of products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

JA001699B

(10) Hayashi, T.; Ishigedani, M. *J. Am. Chem. Soc.* **2000**, *122*, 976.