

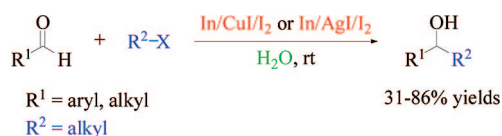
**Indium–Copper and Indium–Silver Mediated Barbier–Grignard-Type Alkylation Reaction of Aldehydes Using Unactivated Alkyl Halides in Water**

Zhi-Liang Shen, Yan-Lin Yeo, and Teck-Peng Loh\*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371

teckpeng@ntu.edu.sg

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An efficient method has been developed for the Barbier–Grignard-type alkylation reaction of aldehydes (including aliphatic version) using unactivated alkyl halides in water in the presence of an In/CuI/I<sub>2</sub> or In/AgI/I<sub>2</sub> system. The reactions proceeded more efficiently in water than in organic solvent. In, CuI or AgI, and I<sub>2</sub> were all essential for the efficient progress of the reactions. A radical-type reaction mechanism was studied and proposed by using 4-pentenal as substrate.

The Barbier–Grignard-type reaction is one of the most important reactions for carbon–carbon bond formations in organic synthesis.<sup>1,2</sup> Classical methods developed for the Barbier–Grignard-type reaction are mainly limited to the use of moisture-sensitive organometallic reagents such as Grignard reagents (RMgX). However, due to the highly reactive nature of Grignard reagents, several undesired byproducts (arose from the hydrolysis, Wurtz coupling, and β-elimination of Grignard reagent, and the reduction of carbonyl compounds) might be generated. Therefore, if the reaction can be developed to carry

out in water<sup>3</sup> with the suppression of such side reactions, it will greatly aid organic chemists.

Until recent decades, the Barbier–Grignard-type allylation,<sup>4</sup> benzylation,<sup>5</sup> arylation,<sup>6</sup> propargylation,<sup>7</sup> and alkynylation<sup>8</sup> reactions have been successfully developed in aqueous media using different metals. However, the most difficult challenge is to develop the Barbier–Grignard-type alkylation reaction of carbonyl compounds in water using unactivated alkyl halides. In 2003, Li and co-workers disclosed their pioneering work to achieve the Barbier–Grignard-type alkylation reaction of aldehydes using alkyl iodides, employing a Zn/CuI/InCl system in aqueous Na<sub>2</sub>C<sub>2</sub>O<sub>4</sub>.<sup>9</sup> The method using expensive reagent InCl was mainly applicable to aromatic aldehydes with an electron-withdrawing group, and the reaction was not applicable to aliphatic aldehydes. In addition, the reaction needed to be performed in Na<sub>2</sub>C<sub>2</sub>O<sub>4</sub> solution, and byproduct generated from pinacol coupling of aldehyde was detected. Therefore, it is still desirable to develop a more efficient and practical method for the Barbier–Grignard-type alkylation reaction of aldehydes using unactivated alkyl halides in water.

Recently, indium has been demonstrated to be an efficient and promising metal to mediate organic reactions in aqueous media.<sup>10</sup> The utilization of indium species as radical initiator via SET (single electron transfer) process in several organic transformations has been reported by Naito et al.<sup>11,12</sup> We envisioned that the generation of water-tolerant neutral free radical would be the key factor for the success of the reaction. Herein, we report an efficient method for the Barbier–Grignard-

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TABLE 1. Optimization of Reaction Conditions<sup>a</sup>

| entry | conditions                  | yield (%) <sup>b</sup> |
|-------|-----------------------------|------------------------|
| 1     | Mg/CuI/InCl <sub>2</sub>    | 0                      |
| 2     | Sn/CuI/InCl <sub>2</sub>    | 0                      |
| 3     | Cr/CuI/InCl <sub>2</sub>    | 0                      |
| 4     | Ge/CuI/InCl <sub>2</sub>    | 0                      |
| 5     | Mn/CuI/InCl <sub>2</sub>    | 0                      |
| 6     | Fe/CuI/InCl <sub>2</sub>    | trace                  |
| 7     | Al/CuI/InCl <sub>2</sub>    | 48                     |
| 8     | In/CuI/InCl <sub>2</sub>    | 69                     |
| 9     | InCl <sub>2</sub>           | 0                      |
| 10    | In/CuI/InCl                 | 65                     |
| 11    | In/CuI/InBr                 | 41                     |
| 12    | <b>In/CuI/I<sub>2</sub></b> | <b>86</b>              |
| 13    | CuI/I <sub>2</sub>          | 0                      |
| 14    | In/I <sub>2</sub>           | 21                     |
| 15    | In/CuI                      | 31                     |
| 16    | In/CuBr/I <sub>2</sub>      | 63                     |
| 17    | In/CuCl/I <sub>2</sub>      | 58                     |
| 18    | <b>In/AgI/I<sub>2</sub></b> | <b>73</b>              |

<sup>a</sup> The reactions were carried out at rt for 2 days using benzaldehyde (0.5 mmol), cyclohexyl iodide (2.5 mmol), metal (3 mmol), copper iodide (1.5 mmol) or silver iodide (2.5 mmol), additive (0.1 mmol), and water (10 mL). <sup>b</sup> Isolated yield based on aldehyde.

type alkylation reaction of aldehydes by using an In/CuI/I<sub>2</sub> or In/AgI/I<sub>2</sub> system in water.

Initial studies were focused on the Barbier–Grignard-type alkylation reaction of benzaldehyde and cyclohexyl iodide in water employing different metals. The results are summarized in Table 1.

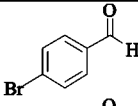

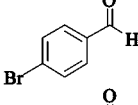

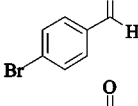

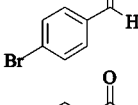

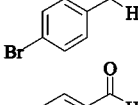

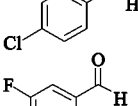

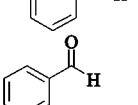

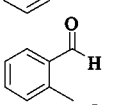

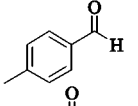

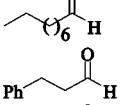

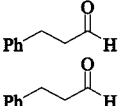

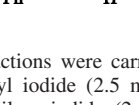

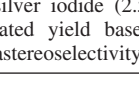

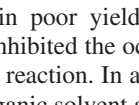

As shown in Table 1, among the several metals screened, indium in conjunction with CuI and InCl<sub>2</sub> afforded 69% yield of the corresponding alkylated product (Table 1, entries 1–8). In addition, it was found that the solo utilization of InCl<sub>2</sub> (without In/CuI) afforded no desired product (Table 1, entry 9). Following an attempt to change the use of InCl<sub>2</sub> to other additives (such as InCl, InBr, and I<sub>2</sub>) showed that the reaction with the use of a combinatorial system of In/CuI/I<sub>2</sub> furnished the corresponding product in the best yield (86%, Table 1, entries 10–12). Since I<sub>2</sub> is the cheapest and easily available reagent compared to other additives, it was chosen as the reaction additive for subsequent reactions.

It is important to note that In, CuI, and I<sub>2</sub> are all essential for the efficient progress of the reaction (Table 1, entries 12–15): (i) without the use of indium, no desired product was obtained; (ii) without employing CuI, the product was obtained in lower yield (21%); (iii) without the addition of I<sub>2</sub>, the corresponding product was generated in relatively poor yield of 31%.

Other copper salts such as CuBr and CuCl were also investigated, but both gave the desired product in lower yields compared to CuI (Table 1, entries 16 and 17). Interestingly, it was found that the same reaction could also proceed efficiently in the presence of the In/AgI/I<sub>2</sub> system to give the desired product in 73% yield (Table 1, entry 18). Therefore, subsequent works involving various aldehydes and alkyl halides were carried out using the optimized reaction conditions of In/CuI/I<sub>2</sub> and In/AgI/I<sub>2</sub> in water.

It was worthwhile to note that the same reaction performed in organic solvents, such as CH<sub>2</sub>Cl<sub>2</sub>, hexane, THF, MeOH, CH<sub>3</sub>CN, and DMSO, proceeded sluggishly to give the desired

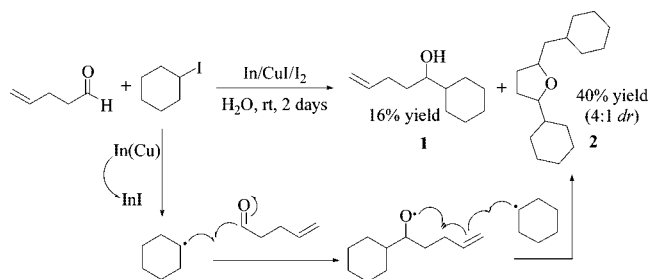
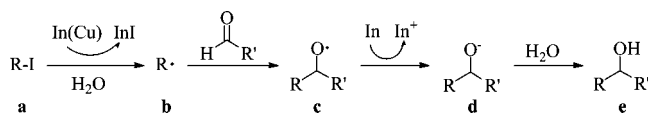
TABLE 2. Barbier–Grignard-Type Alkylation Reaction of Different Aldehydes and Alkyl Halides in Water<sup>a</sup>

| entry | R <sup>1</sup> CHO   | R <sup>2</sup> X  | yield (%) <sup>b</sup> |                       |
|-------|--|---|------------------------|-----------------------|
|       |  |   | In/CuI/I <sub>2</sub>  | In/AgI/I <sub>2</sub> |
| 1     |    |    | 85                     | 79                    |
| 2     |    |    | 56                     | 49                    |
| 3     |    |    | 41                     | 38                    |
| 4     |    |    | 50 <sup>c</sup>        | 31 <sup>d</sup>       |
| 5     |    |    | 52                     | -- <sup>e</sup>       |
| 6     |    |    | 79                     | 76                    |
| 7     |   |   | 53                     | 48                    |
| 8     |  |  | 86                     | 73                    |
| 9     |  |  | 73                     | 67                    |
| 10    |  |  | 74                     | 49                    |
| 11    |  |  | 69                     | 56                    |
| 12    |  |  | 45                     | 42                    |
| 13    |  |  | 66                     | 69                    |
| 14    |  |  | 85                     | 78                    |

<sup>a</sup> The reactions were carried out at rt for 2 days using aldehyde (0.5 mmol), alkyl iodide (2.5 mmol), indium (3 mmol), copper iodide (1.5 mmol) or silver iodide (2.5 mmol), iodine (0.1 mmol), and water (10 mL). <sup>b</sup> Isolated yield based on aldehyde. <sup>c</sup> Diastereoselectivity ratio: 49:51. <sup>d</sup> Diastereoselectivity ratio: 48:52. <sup>e</sup> Not carried out.

products in poor yields. It seemed that the use of organic solvents inhibited the occurrence of the Barbier–Grignard-type alkylation reaction. In addition, it was found that the combination of organic solvent and water as reaction cosolvent also led to decreased yield. The results revealed that water was important for the activation of indium and for scavenging the resulting alkoxide anion.

Encouraged by the above results, we carried out a wide variety of aldehydes and alkyl halides under optimized reaction

**SCHEME 1. Mechanism Study Using 4-Pentenal as Substrate**

**SCHEME 2. Proposed Reaction Mechanism**


conditions using In/Cu/I<sub>2</sub> and In/AgI/I<sub>2</sub> systems in water. The results are summarized in Table 2.

As shown in Table 2, the Barbier–Grignard-type alkylation reaction of different aldehydes and alkyl halides proceeded smoothly in water to generate the corresponding products in moderate to good yields. In contrast to the reported system,<sup>9</sup> it was noteworthy that even aliphatic aldehydes (hydrocinnamaldehyde and nonyl aldehyde) could also react efficiently with alkyl iodides to furnish the alkylated products in moderate to good yields (Table 2, entries 11–14). However, with regard to alkyl bromide, the reaction involving 4-bromobenzaldehyde and cyclohexyl bromide proceeded sluggishly to give the desired product in poor yield (<11%).

In order to investigate the reaction mechanism, we continued to apply the reaction system to 4-pentenal. As shown in Scheme 1, aside from the generation of expected alkylation product **1**, the formation of a furan-type product **2** has also been observed in the reaction of 4-pentenal with cyclohexyl iodide. It provided powerful evidence for a radical-type reaction mechanism. According to this observation, a plausible reaction mechanism has been proposed as shown in Scheme 2.

As illustrated in Scheme 2, the reaction was initiated by a single-electron transfer from indium–copper (or indium–silver) to alkyl iodide **a** to generate an alkyl radical **b**, then it attacked the aldehyde to furnish a radical intermediate **c**. Subsequent indium-promoted reduction of intermediate **c** and the quenching

of the generated alkoxide anion **d** in the presence of water afforded the desired product **e**.

In summary, we have developed an efficient method for the Barbier–Grignard-type alkylation reaction of different aldehydes using unactivated alkyl halides in water. This method is practical, and it works with a wide variety of aldehydes including aliphatic aldehydes. The mild reaction conditions, moderate to good yields, and the simplicity of the reaction procedure make this method attractive for scale-up purposes. Further investigations regarding the development of an asymmetric version of Barbier–Grignard-type alkylation reaction of aldehydes in water are currently in progress.

**Experimental Section**

**General Procedure for the Barbier–Grignard-Type Alkylation Reaction of Benzaldehyde in Water.** Water (10 mL), benzaldehyde (0.053 g, 0.5 mmol), and I<sub>2</sub> (0.0253 g, 0.1 mmol) were added to a 10 mL round-bottomed flask. After stirring for several minutes, then indium (0.344 g, 3 mmol) and copper iodide (0.286 g, 1.5 mmol) or silver iodide (0.587 g, 2.5 mmol) were added sequentially to the flask. After stirring for 10 min, cyclohexyl iodide (0.53 g, 2.5 mmol) was introduced into the reaction system, and it was stirred vigorously at room temperature for 2 days. After reaction, 2 mL of aqueous HCl (1 M) was added to the flask, then it was extracted with diethyl ether (20 mL × 3), washed with brine, dried over sodium sulfate, filtered, and evaporated to give the oil residue. It was subjected to silica gel column chromatography using ethyl acetate and hexane as eluent to afford the desired product as colorless oil: *R*<sub>f</sub> = 0.28 (ethyl acetate/hexane, 1:8); FTIR (NaCl, neat)  $\nu$  3440 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  0.84–1.29 (m, 5H), 1.34–1.38 (m, 1H), 1.53–1.77 (m, 4H), 1.95–2.00 (m, 2H), 4.33 (d, *J* = 7.14 Hz, 1H), 7.22–7.34 (m, 5H) ppm; <sup>13</sup>C NMR (75.4 MHz, CDCl<sub>3</sub>)  $\delta$  143.6 (C), 128.1 (CH × 2), 127.3 (CH), 126.6 (CH × 2), 79.3 (CH), 44.9 (CH), 29.3 (CH<sub>2</sub>), 28.8 (CH<sub>2</sub>), 26.4 (CH<sub>2</sub>), 26.1 (CH<sub>2</sub>), 26.0 (CH<sub>2</sub>) ppm; HRMS (EI, *m/z*) [*M*]<sup>+</sup>, calcd for C<sub>13</sub>H<sub>18</sub>O 190.1358, found 190.1346.

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**Supporting Information Available:** Compound characterization data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, and HRMS) and copies of <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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