

# Indium–Copper-Mediated Barbier–Grignard-Type Alkylation Reaction of Imines in Aqueous Media

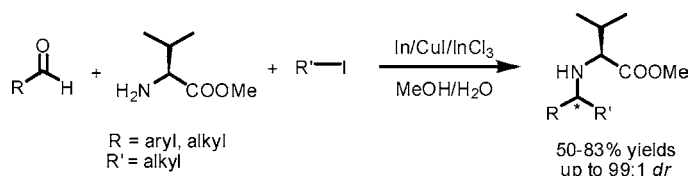
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## ABSTRACT



An efficient system of In/CuI/InCl<sub>3</sub> was developed for Barbier–Grignard-type alkylation reactions of simple imines, using a one-pot condensation of various aldehydes, amines (including aliphatic and chiral version), and alkyl iodides in water or aqueous media. The reactions proceeded efficiently at room temperature to give the desired products in moderate to good yields. Good diastereoselectivities were obtained when using L-valine methyl ester as substrate.

Amines are important compounds which are featured in a wide variety of drugs and natural products. Among the many synthetic methods available for the synthesis of amines, the addition of organometallics to imines provides one of the most straightforward methods to amines.<sup>1,2</sup> Unfortunately, due to the labile nature of imines and moisture-sensitive organometallics, most of these reactions have to be carried out under strictly anhydrous conditions. In recent years, there have been some successes in carrying out metal-mediated allylation reactions with zinc and indium in aqueous media.<sup>3,4</sup> However, the corresponding *alkylation* of imines is more difficult to achieve and has been the target of research by numerous groups.<sup>5–9</sup> Unfortunately, these methods are mainly applicable to more reactive imines such as oxime ethers, hydrazones, and glyoxylate imines.<sup>6,7</sup> The limited scope in these reported systems encourages us to search for new

metal-mediated alkylation reactions of simple imines in aqueous media. Therefore, the development of new metal-mediated alkylation reactions of simple imines in aqueous media remains a challenge for organic chemists. If successful, this method can also be used to replace or substitute Grignard reagents and will greatly aid organic chemists. In this Letter,

(3) Allylation of imines in aqueous media is mostly limited to activated imines, such as sulfonimines, tosyl and aryl hydrazones, glyoxylic oxime ethers, etc. For examples, see: (a) Piao, X.; Jung, J. K.; Knag, H. Y. *Bull. Korean Chem. Soc.* **2007**, 28, 139 and references cited therein. (b) Chan, T. H.; Lu, W. *Tetrahedron Lett.* **1998**, 39, 8605. (c) Lu, W.; Chan, T. H. *J. Org. Chem.* **2000**, 65, 8589. (d) Lu, W.; Chan, T. H. *J. Org. Chem.* **2001**, 66, 3437. (e) Kumur, H. M. S.; Anjaneyulu, S.; Reddy, E. J.; Yadav, J. S. *Tetrahedron Lett.* **2000**, 41, 9311. (f) Ritson, D. J.; Cox, R. J.; Berge, J. *Org. Biomol. Chem.* **2004**, 2, 1921. (g) Bernardi, L.; Cere, V.; Fermoni, C.; Pollicino, S.; Ricci, A. *J. Org. Chem.* **2003**, 68, 3348. (h) Miyabe, H.; Yamaoka, Y.; Naito, T.; Takemoto, Y. *J. Org. Chem.* **2003**, 68, 6745. (i) Miyabe, H.; Yamaoka, Y.; Naito, T.; Takemoto, Y. *J. Org. Chem.* **2004**, 69, 1415.

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(1) For reviews, see: (a) Bloch, R. *Chem. Rev.* **1998**, 98, 1407. (b) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, UK, 1991; Vol. 1, Chapter 1.12, pp 355, and references cited therein. (c) Friestad, G. K. *Tetrahedron* **2001**, 57, 5461. (d) Denmark, S. E.; Nicaise, O. J.-C. *Chem. Commun.* **1996**, 999.

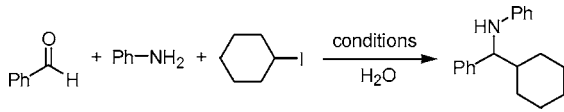
(2) For examples, see: (a) Miyoshi, N.; Ikehara, D.; Kohno, T.; Matsui, A.; Wada, M. *Chem. Lett.* **2005**, 34, 760. (b) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, 128, 9998. (c) Saito, S.; Hatanaka, K.; Yamamoto, H. *Synlett* **2001**, 1859 and references cited therein.

we report an efficient method for the alkylation of a wide variety of imines via a one-pot condensation of aldehyde, amine (including aliphatic and chiral version), and alkyl iodide using indium–copper in aqueous media.

Initial studies were focused on the one-pot reaction of benzaldehyde, aniline, and cyclohexyl iodide under different conditions.

As shown in Table 1, it was found that the combination of In/CuI/InCl<sub>3</sub> was an efficient system for the activation of

**Table 1.** Optimization of Reaction Conditions<sup>a</sup>

		
entry	conditions	yield (%) <sup>b</sup>
1	In/CuI/InCl <sub>3</sub>	97
2	In/InCl <sub>3</sub>	17
3	In/CuI	53
4	CuI/InCl <sub>3</sub>	0
5	In/CuBr/InCl <sub>3</sub>	63
6	In/CuCl/InCl <sub>3</sub>	36

<sup>a</sup> The reaction was carried out at rt for 1 day, using In(6 equiv), CuI (4 equiv), InCl<sub>3</sub> (0.1 equiv), aldehyde (1 equiv), amine (1.2 equiv), alkyl iodide (5 equiv), and water (10 mL). <sup>b</sup> Isolated yield.

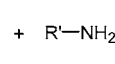


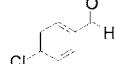


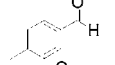


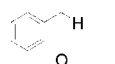


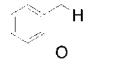
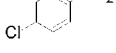

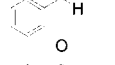





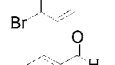


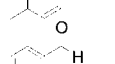
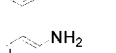

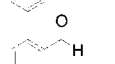


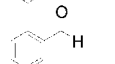
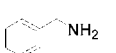

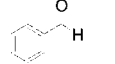
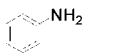

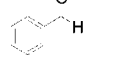


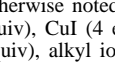
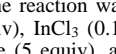

imine alkylation in water, to generate the corresponding product in 97% yield (entry 1). It is important to note that the reaction without the use of CuI gives the desired product only in 17% yield (entry 2, mainly giving imine self-coupling product).<sup>10</sup> In addition, it was observed that the reaction proceeded sluggishly to produce the desired product only in 53% yield without the addition of InCl<sub>3</sub> (entry 3). Moreover, it was found that the use of metal (here indium) is also indispensable for the occurrence of this alkylation reaction. Without it, no desired product was formed (entry 4). Among the several metals screened, indium proved to be the best for this reaction, and the metals exhibited the following order for the activation of the imine alkylation reaction: In > Zn > Al > Sn. Other copper compounds such as CuBr and CuCl were also investigated, but all gave the products in lower yields in comparison with CuI (entries 5–6).

It was worthwhile to note that the same reactions carried out in organic solvents such as MeOH, THF, CH<sub>2</sub>Cl<sub>2</sub>, DMF,

DMSO, and hexane afforded the desired product in much lower yields. With the optimized reaction conditions in hand, we applied this reaction system to various aldehydes, amines, and alkyl iodides.

As shown in Table 2, the one-pot reaction involving various aldehydes, amines, and secondary alkyl iodides<sup>11</sup>

**Table 2.** One-Pot Alkylation Reaction of Imines in Water<sup>a</sup>

entry	aldehyde	amine	alkyl iodide	yield (%) <sup>b</sup>
1				84
2				65
3				99
4				97
5				68 <sup>c</sup>
6				86
7				77 <sup>c,d</sup>
8				70 <sup>c,d</sup>
9				81 <sup>c,d</sup>
10				88
11				65 <sup>c,d</sup>
12				49 <sup>c,d</sup>
13				83 <sup>e</sup>
14				61 <sup>c,d,f</sup>

<sup>a</sup> Unless otherwise noted, the reaction was carried out at rt for 1 day, using In(6 equiv), CuI (4 equiv), InCl<sub>3</sub> (0.1 equiv), aldehyde (1 equiv), amine (1.2 equiv), alkyl iodide (5 equiv), and water (10 mL). <sup>b</sup> Isolated yield. <sup>c</sup> Using MeOH:H<sub>2</sub>O = 1:1. <sup>d</sup> Using 2 equiv of amine. <sup>e</sup> Diastereoselectivity ratio: 50:50. <sup>f</sup> Diastereoselectivity ratio: 60:40.

proceeded efficiently in water at ambient temperature to generate the corresponding alkylation products in moderate to excellent yields. It was gratifying to find that even aliphatic amines such as benzylamine could also react efficiently with different aldehydes and secondary alkyl iodides to furnish the desired products in moderate to good yields (entries 7–9, 11, 12, and 14).

(11) For primary iodide and tertiary iodide, the one-pot reactions of benzaldehyde, aniline, and *n*-hexyl iodide or *tert*-butyl iodide proceeded sluggishly under optimized conditions to give the desired products in very low yields.

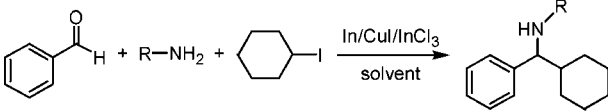
(7) For reviews, see: (a) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140 and references cited therein. (b) Miyabe, H.; Naito, T. *Org. Biomol. Chem.* **2004**, *2*, 1267. For examples, see: (c) Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, *65*, 5043. (d) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* **2004**, *60*, 4227. (e) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131. (f) Miyabe, H.; Ueda, M.; Naito, T. *Chem. Commun.* **2000**, 2059. (g) Ueda, M.; Miyabe, H.; Nishimura, A.; Sugino, H.; Naito, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2857. (h) Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun.* **2002**, 1454. (i) Ueda, M.; Miyabe, H.; Sugino, H.; Naito, T. *Org. Biomol. Chem.* **2005**, *3*, 1124.

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(9) For the alkylation of aldehydes in aqueous media, see: Keh, C. C. K.; Wei, C. M.; Li, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 4062.

(10) Kalyanam, N.; Rao, G. V. *Tetrahedron Lett.* **1993**, *34*, 1647.

**Table 3.** One-Pot Alkylation Reaction of Imines with Various Chiral Amines<sup>a</sup>

				
entry	amine	solvent	yield (%) <sup>b</sup>	dr
1		MeOH:H <sub>2</sub> O (1:1)	65 <sup>c</sup>	92:8
2		MeOH:H <sub>2</sub> O (1:1)	77	92:8
3		H <sub>2</sub> O	60	90:10
4		MeOH	<30	-- <sup>d</sup>
5		MeOH:H <sub>2</sub> O (1:1)	62	50:50
6		MeOH:H <sub>2</sub> O (1:1)	77	50:50
7		MeOH:H <sub>2</sub> O (1:1)	46	50:50
8		MeOH:H <sub>2</sub> O (1:1)	72	78:22

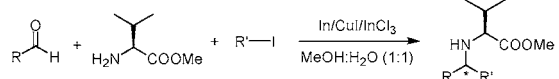
<sup>a</sup> Unless otherwise noted, the reaction was carried out at rt for 1 day, using In (6 equiv), CuI (4 equiv), InCl<sub>3</sub> (1 equiv), aldehyde (1 equiv), amine (2 equiv), alkyl iodide (5 equiv), MeOH (5 mL), and H<sub>2</sub>O (5 mL). <sup>b</sup> Isolated yield. <sup>c</sup> Using InCl<sub>3</sub> (0.1 equiv). <sup>d</sup> Not determined.

With the possibility of using aliphatic amines such as benzylamine for this one-pot reaction in water, we continued to apply this reaction system to chiral amines in the hope of providing a new method for the synthesis of enantiomerically enriched amino compounds.

As indicated in Table 3, using L-valine methyl ester as substrate, it was found that the one-pot reaction proceeded more efficiently in a mixture of MeOH and H<sub>2</sub>O (1:1) than in water or MeOH, to give the desired product in good yields and diastereoselectivities (77% yield, 92:8 dr, entries 2–4). In addition, it was observed that the utilization of 1 equiv of InCl<sub>3</sub> helped to increase the reaction yield from 65% to 77% (entries 1 and 2). When the optimized reaction conditions were extended to other chiral amines, in all cases the reactions proceeded efficiently to furnish the desired products in moderate to good yields and lower diastereoselectivities (entries 5–8). Therefore, L-valine methyl ester was used as a chiral amine in subsequent reactions with various aldehydes and secondary alkyl iodides.

As shown in Table 4, the one-pot reaction employing various aldehydes and alkyl iodides condensed efficiently with L-valine methyl ester to generate the desired products in moderate to good yields and good diastereoselectivities. It is worthy to note that even aliphatic aldehydes (hydrocinnamaldehyde and nonyl aldehyde, entries 5, 6, 10, 11, 15, and 16) are also good substrates for this reaction. In all cases, the reactions proceeded efficiently in aqueous media to give the desired products in good yields and enantioselectivities.

**Table 4.** One-Pot Alkylation Reaction of Imines with L-Valine Methyl Ester<sup>a</sup>

				
entry	aldehyde	alkyl iodide	yield (%) <sup>b</sup>	dr
1			77	92:8
2			63	88:12
3			80	93:7
4			58	92:8
5			81	83:17
6			66	87:13
7			52	93:7
8			50	93:7
9			66	93:7
10			72	82:18
11			72	84:16
12			54	99:1
13			57	92:8
14			83	91:9
15			71	77:23
16			69	84:16

<sup>a</sup> The reaction was carried out at rt for 1 day, using In (6 equiv), CuI (4 equiv), InCl<sub>3</sub> (1 equiv), aldehyde (1 equiv), amine (2 equiv), alkyl iodide (5 equiv), MeOH (5 mL), and H<sub>2</sub>O (5 mL). <sup>b</sup> Isolated yield.

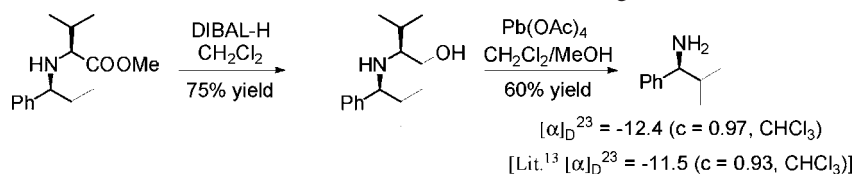
The chiral auxiliary can be easily removed by reported procedures (DIBAL-H reduction followed by Pb(OAc)<sub>4</sub>- or H<sub>5</sub>IO<sub>6</sub>-mediated oxidative cleavage of the corresponding amino alcohol) to afford the optically active amines.<sup>12</sup> With use of this method, the absolute configuration of the product was determined as shown in Scheme 1.

A plausible reaction mechanism is proposed (Scheme 2). The reaction was initiated by a single-electron transfer from

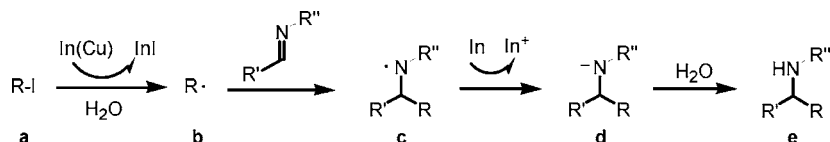
(12) (a) Loh, T. P.; Chen, S. L. *Org. Lett.* **2002**, *4*, 3647. (b) Lee, C. L. K.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2965.

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**Scheme 1.** Determination of Absolute Configuration



**Scheme 2.** Proposed Reaction Mechanism



indium–copper to alkyl iodide **a** to generate an alkyl radical **b**. This radical attacked the imine to furnish a radical intermediate **c**. Subsequent indium-promoted reduction of intermediate **c** and the quenching of the generated amino 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 imines using a one-pot condensation of various aldehydes, amines, and secondary alkyl iodides in water or aqueous media. This method is practical and it works with a wide variety of aldehydes, amines, and secondary alkyl iodides. The mild reaction conditions, moderate to good yields, good to excellent diastereoselectivities, and the simplicity of the

reaction procedure make this method attractive for scale-up purposes.

**Acknowledgment.** We gratefully acknowledge Nanyang Technological University, Ministry of Education (No. M45110000) and A\* STAR (No. M47110000) for the funding of this research.

**Supporting Information Available:** Additional experimental procedures and spectral data for reaction products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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