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Indium/copper-mediated conjugate addition of unactivated alkyl iodides to α,β-unsaturated carbonyl compounds in water

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A B S T R A C T

An efficient method for the conjugate addition of unactivated alkyl iodides to α,β-unsaturated carbonyl compounds using indium/copper in water is described. The reactions proceed more efficiently in water than in organic solvents. In, CuI, and $InCl_3$ are all essential for efficient reaction. Formation of a symmetrical *vic*-diarylalkane is observed when an aryl-substituted alkene is used as substrate.

Conjugate addition of alkyl groups to α,β-unsaturated carbonyl compounds is a versatile synthetic method for the construction of C–C bonds.[1] Among the various methods available, the most commonly employed strategies involve the use of organometallic species such as Grignard reagents (RMgX) or organolithium (RLi) reagents.[2] However, the use of these highly reactive organometallic reagents can lead to undesired side reactions such as hydrolysis, Wurtz coupling, β-elimination of the organometallic reagent, and the reduction of carbonyl compounds. Also, 1,2-addition of the alkyl group to the carbonyl group can compete with the 1,4-conjugate addition reaction. If this reaction could be developed to take place in water[3] without the above-mentioned side reactions, it would greatly aid organic chemists.

The pioneering works by Luche, Li, Naito, and others have shown that it is possible to carry out alkyl additions to conjugated systems in water.[4–6] Unfortunately, in most cases, the use of harsh reaction conditions such as ultrasonication, inert atmospheres, cosolvent systems, and the narrow substrate scope limit their applicability to complex molecule synthesis. Therefore, the development of more general and practical methods for alkyl addition to α,β-unsaturated carbonyl compounds under mild conditions is highly desirable. In previous reports, our group has described indium/copper- and indium/silver-mediated Barbier–Grignard-type alkylation reactions of imines and aldehydes using unactivated alkyl iodides in water.[7] In continuation of our work to develop alkylation reactions in water, herein, we report an efficient method for the conjugate addition of unactivated alkyl iodides to α,β-unsaturated carbonyl compounds (including a chiral version) using indium/copper in water.[8–10] In addition, the formation of symmetrical *vic*-diarylalkanes was observed when aryl-substituted alkenes were used as the substrate.

Initial studies focused on the reaction of α,β-unsaturated ester **1** and cyclohexyl iodide under different reaction conditions.

As shown in Table 1, it was found that the combination of In/CuI/$InCl_3$ (6:3:0.1) was an efficient system for activation of the conjugate addition reaction in water. The reaction proceeded smoothly at room temperature to generate the corresponding adduct **2** in 80% yield (entry 1). It is important to note that, without the use of CuI, the reaction proceeded sluggishly to give the desired product in poor yield (entry 2). Without the addition of $InCl_3$, the yield of the product decreased to 54% (entry 3). In addition, it was found that the use of the metal (i.e., indium) was also indispensable (entry 4). Among the several metals screened, indium proved to be the best for this reaction. The following order was apparent for activation of the conjugate alkylation: In > Zn > Al > Sn. Other copper and silver compounds such as CuBr, CuCl, and AgI were also investigated, but all gave the products in lower yields in comparison to CuI (entries 5–7). It was worthwhile to note that the reactions proceeded more efficiently in water than in organic solvents such as MeOH, THF, CH_2Cl_2, DMF, DMSO, and hexane. Furthermore, the reactions were carried out without an inert atmosphere and ultrasonication was unnecessary.

With optimized reaction conditions in hand, we next applied the reaction system to various α,β-unsaturated carbonyl compounds and alkyl iodides. As illustrated in Table 2, the reactions

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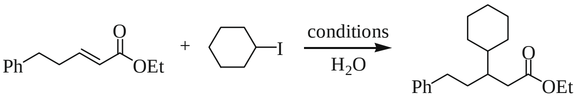
Table 1
Optimization of the reaction conditions[a]



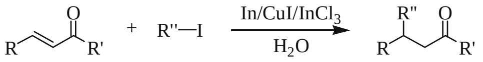
1 2

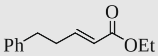
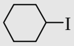
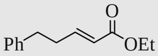
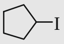
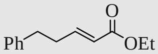
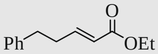
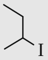
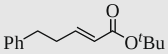
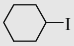
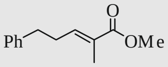
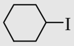
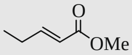
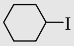
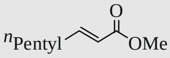
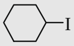
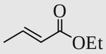
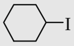
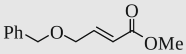
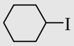
Entry	Conditions	Yield[b] (%)
1	In/CuI/$InCl_3$	80
2	In/$InCl_3$	<20
3	In/CuI	54
4	CuI/$InCl_3$	0
5	In/CuBr/$InCl_3$	68
6	In/CuCl/$InCl_3$	<50
7	In/AgI/$InCl_3$	48

[a] The reactions were carried out at rt for one day using In (3 mmol), CuX (X = Cl, Br, I) or AgI (1.5 mmol), $InCl_3$ (0.05 mmol), α,β-unsaturated ester **1** (0.5 mmol), cyclohexyl iodide (2.5 mmol), and water (10 mL).

[b] Isolated yield.

Table 2
Conjugate addition of alkyl iodides to various α,β-unsaturated esters[a,11]



Entry	α,β-Unsaturated ester	Alkyl iodide	Yield[b] (%)
1			80
2			84
3			70
4			73 (dr 52:48)[c]
5			70
6			75 (dr 31:69)[c]
7			61
8			84
9			76
10			48

[a] The reactions were carried out at rt for one day using In (3 mmol), CuI (1.5 mmol), $InCl_3$ (0.05 mmol), α,β-unsaturated ester (0.5 mmol), alkyl iodide (2.5 mmol), and water (10 mL).

[b] Isolated yield.

[c] Diastereoselectivity was determined by ^1H NMR and ^{13}C NMR analyses.

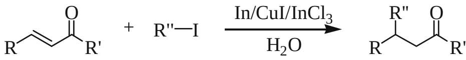
proceeded efficiently in water at ambient temperature. The desired products were obtained in moderate to good yields. In contrast, the reaction between α,β-unsaturated ester **1** and cyclohexyl bromide proceeded sluggishly to give the desired product in poor yield (<20%). The desired product was not obtained when the reaction was carried out using substrate **1** and *tert*-butyl iodide.

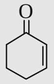
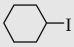
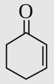
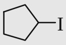
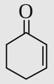
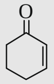
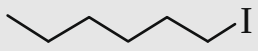
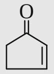
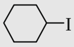
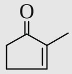
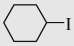
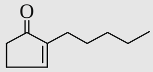
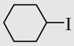
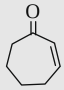
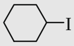
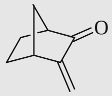
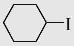
It was gratifying to find that even cyclic enones such as cyclohexenone and cyclopentenone also reacted efficiently with different alkyl iodides to furnish the desired 1,4-addition products in moderate to good yields (Table 3). The formation of 1,2-addition products was not detected.

With the success of the reactions above, we further applied this reaction system to α,β-unsaturated carbonyl compounds with chiral auxiliary groups in the hope of providing an efficient method for the synthesis of chiral carbonyl compounds.

Three typical chiral auxiliaries, (−)-8-phenylmenthol, (*S*)-4-benzyl-2-oxazolidinone, and (1*S*)-(−)-2, 10-camphorsultam were incorporated into α,β-unsaturated carbonyl compounds for asymmetric induction in the conjugate addition reactions. As outlined in Table 4, the conjugate addition of alkyl iodides to α,β-unsaturated carbonyl compounds with chiral auxiliary groups proceeded efficiently in water to afford the desired products in moderate to

Table 3
Conjugate addition of alkyl iodides to various cyclic enones[a,11]



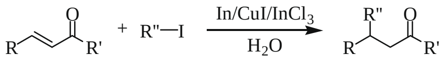
Entry	Enone	Alkyl iodide	Yield[b] (%)
1			85
2			78
3			73
4			45
5			53
6			81 (dr 63:37)[c]
7			83 (dr 53:47)[c]
8			74
9			65

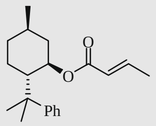
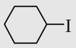
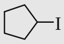
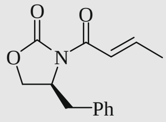
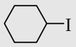
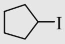
[a] The reactions were carried out at rt for one day using In (3 mmol), CuI (1.5 mmol), $InCl_3$ (0.05 mmol), α,β-unsaturated ketone (0.5 mmol), alkyl iodide (2.5 mmol), and water (10 mL).

[b] Isolated yield.

[c] Diastereoselectivity was determined by ^1H NMR and ^{13}C NMR analyses.

Table 4
Conjugate addition of alkyl iodides to chiral α,β-unsaturated esters and amides[a,11]



Entry	α,β-Unsaturated compound	Alkyl iodide	Yield[b] (%)	dr[c]
1			50	30:70
2			52	34:66
3			51	34:66
4			86	44:56
5			86	41:59
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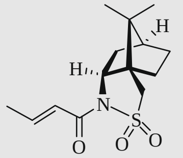
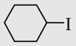
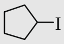
7			60	40:60
8			84	48:52
9			80	38:62

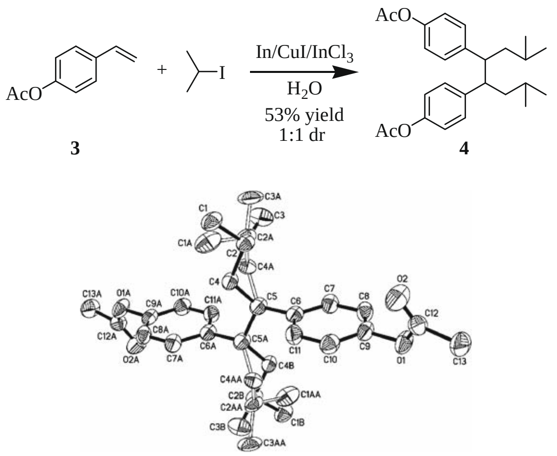
[a] The reactions were carried out at rt for one day using In (3 mmol), CuI (1.5 mmol), InCl$_3$ (0.05 mmol), α,β-unsaturated compound (0.5 mmol), alkyl iodide (2.5 mmol), and water (10 mL).

[b] Isolated yield.

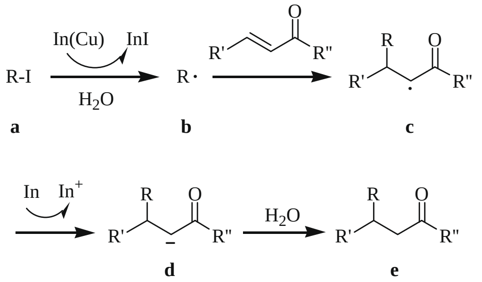
[c] Diastereoselectivity was determined by ^{1}H NMR and ^{13}C NMR analyses.

good yields. However, only poor to moderate diastereoselectivities were achieved.

Of mechanistic interest is the formation of a symmetrical *vic*-diarylalkane when an aryl-substituted alkene was used as the substrate. As shown in Scheme 1, when 4-acetoxystyrene **3** was reacted with 2-iodopropane, alkylative dimerization of **3** exclusively gave symmetrical *vic*-diarylalkane **4** in 53% yield and 1:1 dr. The structure was confirmed by X-ray crystallographic analysis. The reaction most likely proceeds via the addition of an alkyl radical to arylalkene **3** to form a benzyl radical. Dimerization of the thus formed benzyl radical then affords symmetrical *vic*-diarylalkane **4**. This result provides strong support for a radical-type reaction mechanism in this type of addition reaction, including the above-mentioned conjugate addition reactions.



Scheme 1. Formation of symmetrical *vic*-diarylalkane **4** and the X-ray crystallographic structure of **4** (CCDC 694091).



Scheme 2. Proposed reaction mechanism.

A plausible reaction mechanism is proposed (Scheme 2). The reaction is possibly initiated by a single-electron transfer from indium/copper to alkyl iodide **a** to generate an alkyl radical **b**. This radical can attack the α,β-unsaturated carbonyl compound *via* 1,4-conjugate addition to furnish a radical intermediate **c**. Subsequent indium-promoted reduction of intermediate **c** and quenching of the generated anion **d** in the presence of water affords the expected product **e**.

In summary, we have developed an efficient method for the conjugate addition of alkyl iodides to α,β-unsaturated carbonyl compounds using indium/copper in water at room temperature. This method works with a wide variety of α,β-unsaturated carbonyl compounds. The mild reaction conditions, moderate to good yields, and the simplicity of the reaction procedure make this method an attractive alternative to conventional methods using highly reactive organometallic reagents in anhydrous conditions.

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Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.079.

References and notes

1. For reviews, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992; (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829; (c) Christoffers, J. *Synlett* **2001**, 723; (d) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171; (e) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033; (f) Sibi, M. P.; Liu, M. *Enantiomer* **1999**, *4*, 575; (g) Leonard, J.; Diez-Barra, E.; Merino, S. *Eur. J. Org. Chem.* **1998**, 2051; (h) Little, R. D.; Masjedizadeh, M. R.; Wallquist, O.; McLoughlin, J. I. *Org. React.* **1995**, *47*, 315; (i) Zhang, W. *Tetrahedron* **2001**, *57*, 7237; (j) Srikanth, G. S. C.; Castle, S. L. *Tetrahedron* **2005**, *61*, 10377; (k) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263.
2. For reviews, see: (a) Alexakis, A.; Benhaim, C. *Eur. J. Org. Chem.* **2002**, 3221; (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771; (c) Woodward, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 5560.
3. Organic reactions in water, for reviews, see: (a) Herrerías, C. I.; Yao, X. Q.; Li, Z. P.; Li, C. J. *Chem. Rev.* **2007**, *107*, 2546; (b) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015; (c) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16; (d) Loh, T. P. In *Science of Synthesis*; Yamamoto, H., Ed.; Georg Thieme Verlag: New York, 2004; p 413; (e) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149; (f) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095; (g) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023; (h) Li, C. J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68; (i) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563; (j) Kobayashi, S.; Manabe, A. K. *Acc. Chem. Res.* **2002**, *35*, 209; (k) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751; (l) Li, C. J. *Acc. Chem. Res.* **2002**, *35*, 533; (m) Li, C. J. *Green Chem.* **2002**, *4*, 1.
4. For zinc/copper-mediated alkyl addition to various conjugated systems, see: (a) Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149; (b) Luche, J. L.; Allavena, C. *Tetrahedron Lett.* **1988**, *29*, 5369; (c) Dupuy, C.; Petrier, C.; Sarandeses, L. A.; Luche, J. L. *Synth. Commun.* **1991**, *21*, 643; (d) Giese, B.; Damm, W.; Roth, M.; Zehnder, M. *Synlett* **1992**, 441; (e) Erdmann, P.; Schafer, J.; Springer, R.; Zeitz, H. G.; Giese, B. *Helv. Chim. Acta* **1992**, *75*, 638; (f) Luche, J. L.; Allavena, C.; Petrier, C.; Dupuy, C. *Tetrahedron Lett.* **1988**, *29*, 5373;

(g) Pietrusiewicz, K. M.; Zablocka, M. *Tetrahedron Lett.* **1988**, *29*, 937; (h) Roth, M.; Damm, W.; Giese, B. *Tetrahedron Lett.* **1996**, *37*, 351; (i) Suarez, R. M.; Sestelo, J. P.; Sarandeses, L. A. *Synlett* **2002**, 1435; (j) Suarez, R. M.; Sestelo, J. P.; Sarandeses, L. A. *Chem.-Eur. J.* **2003**, *9*, 4179; (k) Fleming, F. F.; Gudipati, S. *Org. Lett.* **2006**, *8*, 1557; (l) Fleming, F. F.; Gudipati, S.; Aitken, J. A. *J. Org. Chem.* **2007**, *73*, 6961.

5. For zinc- or indium-mediated conjugate addition of alkyl halides to more reactive conjugated systems such as α-phthalimidoacrylate derivatives and phenyl vinyl sulfone, see: (a) Huang, T.; Keh, C. C. K.; Li, C. J. *Chem. Commun.* **2002**, 2440; (b) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131.
6. Recently, Jang and co-workers demonstrated that alkyl addition to α,β-unsaturated carbonyl compounds could be achieved using In, EPHP (1-ethylpiperidinium hypophosphite), CTAB (cetyltrimethylammonium bromide) and ABCVA (4,4′-azobis(4-cyanovaleric acid)) at 80 °C in aqueous media under an argon atmosphere. See: Jang, D. O.; Cho, D. H. *Synlett* **2002**, 631.
7. (a) Shen, Z. L.; Cheong, H. L.; Loh, T. P. *Chem.-Eur. J.* **2008**, *14*, 1875; (b) Shen, Z. L.; Loh, T. P. *Org. Lett.* **2007**, *9*, 5413; (c) Shen, Z. L.; Yeo, Y. L.; Loh, T. P. *J. Org. Chem.* **2008**, *73*, 3922.
8. For reviews concerning the use of indium compounds in organic synthesis, see: (a) Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739; (b) Auge, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739; (c) Cintas, P. *Synlett* **1995**, 1087; (d) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633; (e) Nair, V.; Ros, S.; Jayan, C. N.; Pillai, B. S. *Tetrahedron* **2004**, *60*, 1959; (f) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347.
9. Indium-mediated radical reactions in aqueous media, for a review, see: (a) Miyabe, H.; Naito, T. *Org. Biomol. Chem.* **2004**, *2*, 1267; For examples, see: (b) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* **2004**, *60*, 4227; (c) Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun.* **2002**, 1454; (d) Sugi, M.; Sakuma, D.; Togo, H. *J. Org. Chem.* **2003**, *68*, 7629; (e) Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett.* **2003**, *5*, 3835; (f) Kang, S.; Jang, T. S.; Keum, G.; Kang, S. B.; Han, S. Y.; Kim, Y. *Org. Lett.* **2000**, *2*, 3615.
10. Indium-mediated radical reactions in organic solvents, for examples, see: (a) Yanada, R.; Nishimori, N.; Matsumura, A.; Fujii, N.; Takemoto, Y. *Tetrahedron Lett.* **2002**, *43*, 4585; (b) Yanada, R.; Obika, S.; Nishimori, N.; Yamauchi, M.; Takemotoa, Y. *Tetrahedron Lett.* **2004**, *45*, 2331; (c) Bhatti, N. H.; Salter, M. M. *Tetrahedron Lett.* **2004**, *45*, 8379; (d) Ranu, B. C.; Mandal, T. *Tetrahedron Lett.* **2007**, *47*, 2859; (e) Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsuya, H.; Fujii, N.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 2417; (f) Miura, K.; Tomita, M.; Ichikawa, J.; Hosomi, A. *Org. Lett.* **2008**, *10*, 133.
11. *General procedure for the conjugate addition of cyclohexyl iodide to α,β-unsaturated carbonyl compound* ***1****:* To a 10 mL round-bottomed flask were added water (10 mL), α,β-unsaturated carbonyl compound **1** (0.1021 g, 0.5 mmol), and $InCl_3$ (0.011 g, 0.05 mmol). After stirring for several minutes, indium (0.344 g, 3 mmol), copper iodide (0.286 g, 1.5 mmol), and cyclohexyl iodide (0.525 g, 2.5 mmol) were added sequentially. The reaction mixture was stirred vigorously at room temperature for one day. After completion, the reaction mixture was extracted using diethyl ether (20 mL × 3), and the combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated in *vacuo* to give the crude product. Silica gel column chromatography using ethyl acetate and hexane as eluent afforded the desired product **2**, 0.115 g (80% yield) as a colorless oil. $R_f = 0.57$ (ethyl acetate/hexane = 1/8); FTIR (NaCl, neat) ν 1732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96–1.44 (m, 6H), 1.24 (t, $J = 7.15$ Hz, 3H), 1.47–1.90 (m, 8H), 2.22 (dd, $J = 15.04, 7.48$ Hz, 1H), 2.37 (dd, $J = 15.09, 6.16$ Hz, 1H), 2.56–2.62 (m, 2H), 4.12 (q, $J = 7.17$ Hz, 2H), 7.16–7.29 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9 (C), 142.6 (C), 128.3 (CH × 4), 125.7 (CH), 60.2 (CH_2), 40.6 (CH), 40.3 (CH), 36.5 (CH_2), 33.8 (CH_2), 33.4 (CH_2), 29.9 (CH_2), 29.2 (CH_2), 26.8 (CH_2), 26.7 (CH_2), 26.7 (CH_2), 14.3 (CH_3) ppm; HRMS (EI, *m/z*) [M]$^+$, calcd for $C_{19}H_{28}O_2$ 288.2089, found 288.2051.