Indium-Mediated Intermolecular Alkyl Radical Addition to Electron-Deficient C=N Bond and C=C Bond in Water

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The intermolecular alkyl radical addition to imine derivatives was studied in aqueous media by using indium as a single-electron-transfer radical initiator. The one-pot reaction based on radical addition to glyoxylic hydrazone provided a convenient method for preparing the α -amino acids. The indium-mediated radical addition to an electron-deficient C=C bond also proceeded effectively to provide the new carbon–carbon bond-forming method in aqueous media.

Indium-mediated carbon–carbon bond-forming reactions in aqueous media have been of great importance from both economical and environmental points of view. Recently, numerous and useful indium-mediated allylation reactions of carbonyl compounds have been reported.¹ However, the corresponding reaction of imine derivatives has not been widely studied because of the lower electrophilicity of carbon–nitrogen double bond. Therefore, the development of indium-mediated reactions of imines in aqueous media has been a subject of current interest. Chan's group reported the first studies on the indium-mediated allylation reactions proceeded through an allylindium(I) intermediate, which reacts with the *N*-sulfonylimines, and thus, simple alkylation

reactions were not investigated. As a part of our program directed toward the development of reactions of imines in aqueous media,^{3,4} we now report the indium-mediated alkylation reactions of imine derivatives based on the alkyl radical addition to carbon–nitrogen double bond.

The carbon–nitrogen double bond has emerged as a radical acceptor, and thus several intermolecular radical addition reactions of imines were recently investigated in organic solvents.^{5–7} Our recent studies show that imine derivatives such as oxime ethers, hydrazones, and nitrones are excellent water-resistant radical acceptors for the aqueous-medium reactions using triethylborane as a radical initiator.^{3a}

On the basis of these results, we newly investigated the intermolecular radical addition to imine derivatives by using indium as a new radical initiator.^{8,9} As a preliminary experi-

⁽¹⁾ For a recent review, see: Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. For some examples of indium-mediated reaction, see: (a) Yang, Y.; Chan, T. H. *J. Am. Chem. Soc.* **2000**, *122*, 402. (b) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228. (c) Paquette, L. A.; Rothhaar, R. R. *J. Org. Chem.* **1999**, *64*, 217. (d) Woo, S.; Sqires, N.; Fallis, A. G. *Org. Lett.* **1999**, *1*, 573. (e) Engstrom, G.; Morelli, M.; Palomo, C.; Mitzel, T. *Tetrahedron Lett.* **1999**, *40*, 5967. (f) Loh, T.-P.; Zhou, J. R. *Tetrahedron Lett.* **1999**, *40*, 9115.

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^{(3) (}a) Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, *65*, 5043. (b) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071. We recently reported that *N*-sulfonylimines have shown the excellent reactivity toward nucleophilic carbon radical. See: (c) Miyabe, H.; Ueda, M.; Naito, T. *Chem. Commun.* **2000**, 2059.

⁽⁴⁾ For some selected examples, see: (a) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604. (b) Nakamura, T.; Yorimitsu, H.: Shinokubo, H.: Oshima, K. *Synlett* **1998**, 1351. (c) Kita, Y.; Nambu, H.; Ramesh, N. G.; Anikumar, G.; Matsugi, M. *Org. Lett.* **2001**, *3*, 1157.

⁽⁵⁾ For a recent review, see: Friestad, G. K. Tetrahedron 2001, 57, 5461.

ment, the substrates of choice were the glyoxylic oxime ether **1** and glyoxylic hydrazone **3** since they have shown excellent reactivity toward nucleophilic carbon radicals in our previous work on triethylborane-induced radical reactions.^{3a} Additionally, we also expected that the direct comparison of indiummediated reactions with triethylborane-induced reactions would lead to informative and instructive suggestions regarding indium as a single-electron-transfer radical initiator.

We first investigated the reaction of glyoxylic oxime ether **1** under several reaction conditions (Scheme 1). To a biphasic



solution of **1** and *i*-PrI (5 equiv) in $H_2O-CH_2Cl_2$ (4:1, v/v) was added indium (7 equiv), and then the reaction mixture

(6) For some examples, see: (a) Hart, D. J.; Seely, F. L. J. Am. Chem. Soc. 1988, 110, 1631. (b) Kim, S.; Lee, I. Y.; Yoon, J.-Y.; Oh, D. H. J. Am. Chem. Soc. 1996, 118, 5138. (c) Kim, S.; Yoon, J.-Y. J. Am. Chem. Soc. 1997, 119, 5982. (d) Ryu, I.; Kuriyama, H.; Minakata, S.; Komatsu, M.; Yoon, J.-Y.; Kim, S. J. Am. Chem. Soc. 1999, 121, 12190. (e) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. Synlett 1998, 780. (f) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. J. Org. Chem. 1999, 64, 9189. (h) Friestad, G. K.; Qin, J. J. Am. Chem. Soc. 2000, 122, 8329. For some examples of our studies, see: (i) Friestad, G. K.; Qin, J. J. Am. Chem. Soc. 2001, 123, 9922 (j) Miyabe, H.; Ushiro, C.; Naito, T. Chem. Commun. 1997, 1789. (k) Miyabe, H.; Sibata, R.; Ushiro, C.; Naito, T. J. Org. Chem. 1999, 64, 2174. (m) Miyabe, H.; Fujishima, Y.; Naito, T. J. Org. Chem. 1999, 64, 2174. (m) Miyabe, H.; Yamakawa, K.; Naito, T. J. Org. Chem. 2000, 65, 176.

(7) For reviews on radical reactions, see: (a) Sibi, M. P.; Porter, N. A. Acc. Chem. Res. 1999, 32, 163. (b) Renaud, P.; Gerster, M. Angew. Chem., Int. Ed. 1998, 37, 2563. (c) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. Org. React. (N.Y.) 1996, 48, 301. (d) Curran, D. P.; Porter, N. A.; Giese, B. In Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications; VCH: Weinheim, 1996.

(8) Indium(I) iodide mediated radical cyclization was recently studied. See: (a) Cook, G. R.; Erickson, S.; Hvinden, M. 221th ACS National Meeting, San Diego, April 1–5, 2001. Indium as a reducing agent, see: (b) Moody, C. J.; Pitts, M. R. Synlett **1998**, 1028. (c) Ranu, B. C.; Guchhait, S. K.; Sarkar, A. Chem. Commun. **1998**, 2113. (d) Ranu, B. C.; Dutta, P.; Sarkar, A. J. Chem. Soc., Perkin Trans. 1 **1999**, 40, 3937. (f) Yadav, J. S.; Bandyopadhyay, A.; Reddy, B. V. S. Tetrahedron Lett. **2001**, 42, 6385. Indium-mediated coupling reactions, see: (g) Araki, S.; Butsugan, Y. Bull. Chem. Soc. Jpn. **1991**, 64, 727. (h) Ranu, B. C.; Dutta, P.; Sarkar, A. Tetrahedron Lett. **1998**, 39, 9557. The use of indium trichloride, see: (i) Inoue, K.; Yasuda, M.; Shibata, I.; Baba, A. Tetrahedron Lett. **2000**, 41, 113. (j) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. Tetrahedron Lett. **2001**, 42, 4661.

(9) For the radical reaction using zinc as a radical initiator in water, see:
(a) Petrier, C.; Dupuy, C.; Luche, J. L. *Tetrahedron Lett.* **1986**, *27*, 3149.
(b) Giese, B.; Damm, W.; Roth, M.; Zehnder, M. *Synlett* **1992**, 441. (c) Erdmann, P.; Schäfer, J.; Springer, R.; Zeitz, H.-G.; Giese, B. *Helv. Chim. Acta* **1992**, *75*, 638.

was stirred at 20 °C for 22 h.¹⁰ As expected, glyoxylic oxime ether **1** exhibits a good reactivity to give the desired isopropylated product **2** in 76% yield without formation of significant by-products such as a reduced product (Table 1,

Table 1.	Indium-Mediated	Reaction	of Glyoxyli	c Oxime	Ether
1					

entry	solvent	time (h)	yield (%)
1 ^a	H ₂ O-CH ₂ Cl ₂ 4:1	22	76
2 ^{<i>a</i>}	CH_2Cl_2	24	no reaction
3^{b}	H ₂ O-MeOH 2:1	0.5	74
4 ^c	H ₂ O-MeOH 2:1	0.5	no reaction

^{*a*} Reactions were carried out with *i*-PrI (5 equiv) and indium (7 equiv). ^{*b*} Reaction was carried out with *i*-PrI (4 equiv \times 2) and indium (7 equiv). ^{*c*} Reaction was carried out with galvinoxyl free radical (2 equiv), *i*-PrI (4 equiv \times 2), and indium (7 equiv).

entry 1). It is important to note that practically no reaction of 1 occurred in the absence of water (entry 2). These results suggest that water would be important for the activation of indium and for the proton-donor to the resulting amide anion. In the case of monophasic reaction in $H_2O-MeOH$, the formation of isopropylated product 2 was observed after being stirred for only 0.5 h (entry 3).¹¹ In the presence of galvinoxyl free radical as a radical scavenger, the reaction did not proceed effectively (entry 4); thus, this reaction would proceed via the radical mechanism based on the singleelectron transfer (SET) process from indium. However, an alternative mechanistic hypothesis involving addition of alkylindium species to the C=N bond would not be rigorously excluded, because it is possible that galvinoxyl free radical inhibited the non-radical reaction by scavenging radicals during the formation of the alkylindium species. In general, free radical synthetic methods largely rely on toxic organotin chemistry; therefore, the development of tin-free reactions including SET processes or atom-transfer and group-transfer processes has been of great importance in radical chemistry.12 However, this indium-mediated reaction of 1 was slightly slower than the triethylborane-induced reaction of **1** in aqueous media shown in our recent report.^{3a}

In our studies on the reactivity of several imine derivatives, we have found that the indium-mediated alkyl radical addition to glyoxylic hydrazone **3** is a highly promising approach to the synthesis of α -amino acids (Scheme 2 and Table 2). In the case of the aqueous-medium reactions of **3**



Table 2.	Alkyl Radical Addition to Glyoxylic Hydrazone 2 ^a				
entry	RX	product	yield (%)		
1	<i>i</i> -PrI	4a	98		
2	<i>i</i> -PrBr	4a	no reaction		
3	s-BuI	4b	90		
4	<i>c</i> -pentyl I	4 c	79		
5	t-BuI	4d	48		
6	EtI	4e	no reaction		

 a Reactions were carried out with RX (5 equiv \times 2), indium (7 equiv), and H_2O in MeOH at 20 °C for 1 h.

using triethylborane, the undesired *C*- and *N*-dialkylated products **5** were only obtained as a result of the additional *N*-alkylation.^{3a} In contrast, the indium-mediated alkyl radical addition to **3** gave selectively the desired *C*-monoalkylated products **4** with no detection of dialkylated products **5**. Not only a secondary alkyl but also the *tert*-butyl radical worked well to give **4a**-**d** in good yields after being stirred for 1 h (entries 1–5). However, the alkyl bromide such as *i*-PrBr and a less reactive primary ethyl iodide did not work (entries 2 and 6).

Integration of multi-step chemical reactions into one-pot reactions is of great significance as an environmentally benign method.¹³ We next extended the indium-mediated reaction to the one-pot synthesis of α -amino acid derivatives (Scheme 3). Condensation of 2-hydroxy-2-methoxyacetic



acid methyl ester **6** with *N*,*N*-diphenylhydrazine hydrochloride proceeded smoothly in MeOH to give **3** after being stirred at 20 °C for 2 h. Subsequently, alkyl iodide, In, and H₂O were added to the reaction vessel to afford good yields of α -amino acid derivatives **4a**-**c**.

To survey the scope and limitations of the present method, we investigated the alkylation reaction of imines 7 and 9



prepared from benzaldehyde (Scheme 4). Although the reactivity of hydrazone **7** is not high, the biphasic reaction of **9** in $H_2O-CH_2Cl_2$ (4:1, v/v) proceeded to give **10** in 54% yield after being stirred for 2 days. The monophasic reaction of *N*-sulfonylimine **9** in $H_2O-MeOH$ (2:1, v/v) proceeded effectively to give the desired isopropylated product **10** in 70% yield accompanied with 29% of TsNH₂ as a hydrolysis product after being stirred for only 1 h.^{3c}

To test the utility of indium as a single-electron transfer radical initiator, we next investigated the indium-mediated alkyl radical addition to electron-deficient C=C bond (Scheme 5). To a solution of phenyl vinyl sulfone **11** and



RI (5 equiv) in MeOH were added indium (7 equiv) and H_2O , and then the reaction mixture was stirred at 20 °C for 30 min. As expected, **11** exhibits a good reactivity to give the desired alkylated products **12a**-**d** in good yields with no detection of by-products such as a reduced product. The reaction would proceed via the single-electron transfer process from indium as shown in Scheme 5.

In conclusion, we have shown a new method for synthesis of α -amino acid derivatives based on the indium-mediated radical reaction of glyoxylic hydrazone. Since the known examples of indium-mediated carbon—carbon bond-forming reactions in aqueous media are mainly limited to allylation reactions, it is noteworthy that the newly found reaction involves the alkylation of imine derivatives. Additionally, the indium-mediated carbon—carbon bond-forming reactions

⁽¹⁰⁾ As a comparison, the triethylborane-induced reaction of 1 was usually run by using a large amount of alkyl iodides (more than 30 equiv) to suppress the competitive reaction with ethyl radical generated from triethylborane. See ref 3a.

⁽¹¹⁾ See Supporting Information for detail on the experimental procedures.

⁽¹²⁾ We previously reported the radical reaction based on an iodine atom transfer process. See: Miyabe, H.; Ueda, M.; Yoshioka, N.; Naito, T. *Synlett* **1999**, 465.

⁽¹³⁾ We previously investigated the one-pot reactions via radical addition to oxime ethers. See: (a) Miyabe, H.; Ueda, M.; Yoshioka, N.; Yamakawa, K.; Naito, T. *Tetrahedron* **2000**, *56*, 2413. (b) Miyabe, H.; Yamakawa, K.; Yoshioka, N.; Naito, T. *Tetrahedron* **1999**, *55*, 11209. (c) Miyabe, H.; Yoshioka, N.; Ueda, M.; Naito, T. J. Chem. Soc., Perkin Trans. 1 **1998**, 3659.

based on the radical addition to electron-deficient C=C bond also proceeded smoothly in aqueous media.

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Supporting Information Available: General experimental procedures and characterization data for obtained compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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