Indium(I)-Mediated Radical Carbon–Carbon Bond-Forming Reaction in Aqueous Media

Masafumi Ueda,[a] Hideto Miyabe,[b] Masafumi Torii,[a] Takahiro Kimura,[a] Okiko Miyata,*[a] Takeaki Naito*[a]

[a] Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658-8558, Japan
Fax +81(78)4417554; fax +81(78)4417642; E-mail: miyata@kobepharma-u.ac.jp; E-mail: taknaito@kobepharma-u.ac.jp

[b] School of Pharmacy, Hyogo University of Health Sciences, Minatojima, Chuo-ku, Kobe 650-8530, Japan

Received 12 March 2010

Abstract: The carbon–carbon bond-forming radical reactions using indium(I) chloride and copper(I) chloride proceeded effectively through a single-electron transfer process in aqueous media.

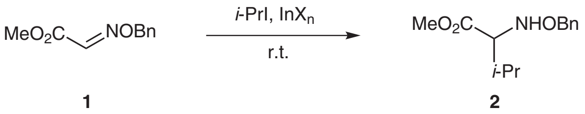
Key words: indium(I) chloride, copper(I) chloride, radical addition, oxime ether, domino reaction, aqueous media

The indium-mediated carbon–carbon bond-forming reactions in aqueous media have been of great importance in organic synthesis.[1–3] Particularly, a low first ionization potential of 5.79 eV makes indium(0) metal attractive for electron-transfer reactions.[2] However, indium-mediated radical reaction has received much less attention,[3–7] although the use of indium has continued to increase in synthetic organic chemistry. Recently, we started to investigate the utility of indium(0) in radical reactions and found that indium(0) has the potential to induce radical reactions as a radical initiator via single electron-transfer process.[4] As a novel related method, indium(0) and iodine mediated reductive radical cyclization of iodoalkenes and iodoalkynes has also been reported by Yanada and Takemoto.[5] Very recently, Loh's group reported an efficient method for the alkylation of imines and nitrones promoted by indium–copper in aqueous media.[8] On the other hand, the utility of indium(I) salts as promoters of radical reactions was much less explored, probably because the second ionization potential for indium is much higher (18.86 eV).[9,10] Therefore, indium(I) halides are only employed for the reactions of a limited number of substrates and the latent reactivities are not disclosed completely so far.[9] Additionally, indium-mediated reactions show considerable potential but current vagaries limit their acceptance.[1a] From synthetic point of view, it is necessary to broaden the scope of indium chemistry by introducing structural diversity on the starting radical acceptors which should open routes to the efficient synthesis of a large amount of compounds.

In this communication, we present an efficient method for promoting the aqueous-medium radical addition to a variety of substrates involving carbon–nitrogen or carbon–carbon double bonds and the α,β-unsaturated analogue by using the suitable combination of indium(I) chloride and copper(I) chloride.[11,12]

We first report the results of an experiment to probe the utility of InCl as a radical initiator. In views of our previous success in promoting radical reaction by indium(0) metal[4a] and of recently reported Loh's work,[8] we began to investigate the reaction of glyoxylic oxime ether **1** with isopropyl iodide under several reaction conditions using

Table 1 Isopropyl Radical Addition to Oxime Ether **1**



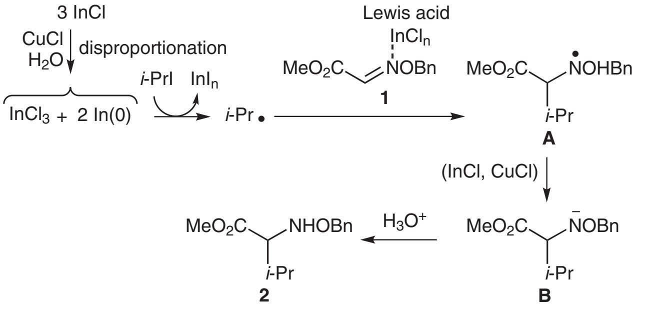
Entry	InX_n	Solvent	Additive	Yield (%)[a]
1[b]	InCl	H_2O–MeOH	none	63
2[b]	InCl	CH_2Cl_2	none	no reaction
3[b]	InBr	H_2O–MeOH	none	trace
4[b]	InI	H_2O–MeOH	none	no reaction
5[c]	InCl	H_2O–MeOH	CuCl	97
6[c]	InCl	CH_2Cl_2	CuCl	no reaction
7[c]	InCl	H_2O–MeOH	CuBr	74
8[c]	InCl	H_2O–MeOH	CuI	65
9[c]	InCl	H_2O–MeOH	$CuCl_2$	50
10[d]	InBr	H_2O-MeOH	CuCl	84
11[d]	InI	H_2O–MeOH	CuCl	18 (74)
12[e]	none	H_2O–MeOH	CuCl	no reaction
13[b]	$InCl_2$	H_2O–MeOH	none	24 (50)
14[c]	$InCl_2$	H_2O–MeOH	CuCl	45 (22)
15[c]	$InCl_3$	H_2O–MeOH	CuCl	no reaction

[a] Isolated yield; yields in parentheses are for the recovered starting material **1**.
[b] Reactions were carried out with *i*-PrI (5 equiv X 2) and InX_n (10 equiv).
[c] Reactions were carried out with *i*-PrI (5 equiv X 2), InX_n (10 equiv), and CuX_n (1 equiv).
[d] Reactions were carried out with *i*-PrI (5 equiv X 2), InX (10 equiv), and CuCl (4 equiv).
[e] Reaction was carried out with *i*-PrI (5 equiv X 2) and CuCl (4 equiv).

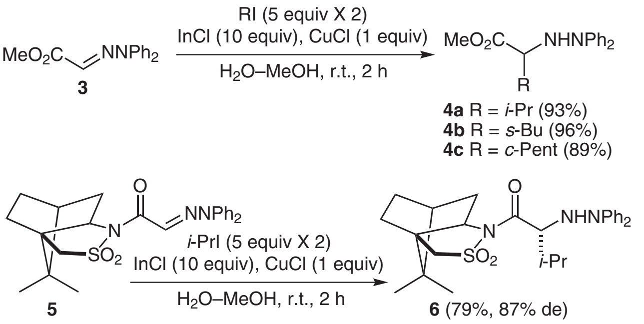
SYNLETT 2010, No. 9, pp 1341–1344
Advanced online publication: 06.05.2010
DOI: 10.1055/s-0029-1219921; Art ID: U01810ST

indium(I) salts.[13] On our initial attempt, the reaction using InCl in H_2O–MeOH gave the desired adduct **2** in 63% yield (Table 1, entry 1). Aqueous solvent was essential to achieve good conversions; when the reaction was carried out in organic solvent such as CH_2Cl_2, no desired product was observed (entry 2). In contrast to InCl, InBr and InI were less effective under the similar reaction conditions (entries 3 and 4). It is important to emphasize that InCl worked well in aqueous media, in spite of a high second ionization potential of indium. Therefore, as one possible reaction pathway, we propose that the first step of the present reaction would be the disproportionation of InCl giving indium(0) metal (Scheme 1).[14] Another role of InCl would be the activation of oxime ether group as Lewis acid.[10] Further experiments showed that the addition of CuCl led to an enhancement in chemical yield (entry 5). The monophasic reaction of **1** in H_2O–MeOH gave the isopropylated product **2** in 97% yield without formation of significant byproducts such as a reduced product. At this stage, the role of CuCl in our reactions was questioned. We assume that one role would involve the activation of InCl or the promotion of disproportionation by redox reaction between indium(I) and copper(I).[15] Other copper(I) salts were also investigated but provided poor results relative to CuCl (entries 7 and 8). The addition of $CuCl_2$ did not affect the chemical efficiency (entry 9). The combination of InBr and CuCl accelerated the reaction with good activity (entry 10), in contrast, the reaction using InBr in the absence of CuCl gave only a trace amount of product (entry 3). It was reported that copper(I) salts promoted radical reactions;[16] thus, we tried the reaction with CuCl in the absence of indium(I) salts, however, no reaction took place (entry 12). More interestingly, $InCl_2$ promoted the reaction to form the product **2** in moderate yields (entries 13 and 14). However, $InCl_3$ did not work (entries 15).[7] On the basis of these results, we concluded that the best conditions are shown in entry 5. As an alkyl radical precursor, primary iodide such as methyl iodide did not work and *tert*-butyl iodide gave a complex mixture. It is important to note that the reaction using InCl and CuCl was suppressed by the addition of a galvinoxyl free radical as radical scavenger. Thus, the present indium(I)-induced reaction proceeded through a radical mechanism based on a single-electron transfer process (Scheme 1), which was analogously proposed by Loh's group under different reaction conditions but with no systematic investigation and discussion involving scavenger experiment.[8]

To survey the scope and limitations of the present method, we next investigated the reaction of hydrazones **3** and **5** (Scheme 2).[17] Under analogous reaction conditions using InCl–CuCl system, the reaction of **3** with isopropyl radical was facile to give product **4a** in 93% yield. The *sec*-butyl and cyclopentyl iodides worked well. Good diastereoselectivity was observed in the reaction of hydrazone **5**, although its reaction was slightly less effective, which was attributed to the greater steric bulk. In general all reactions found here took place effectively as in the case of In(0)-mediated reaction.[4]



Scheme 1 Proposed reaction pathway from **1** to **2**



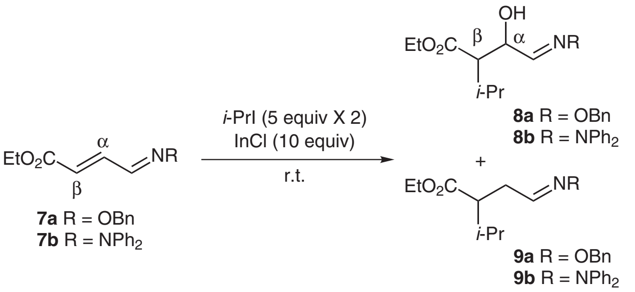
Scheme 2 Alkyl radical addition to hydrazones **3** and **5**

Further application of InCl–CuCl system into the α,β-unsaturated imines **7a** and **7b** led us very interesting result as follows. Treatment of conjugated oxime ether **7a** with isopropyl iodide in the presence of InCl and CuCl in H_2O–EtOH gave regioselectively β-addition product **9a** in 58% yield (Table 2, entry 1). Interestingly, lacking of CuCl gave a mixture of two products **8a** and **9a** in 18% and 22% yields, respectively, with 4% yield recovery of **7a** (entry 2). The former product **8a** is β-isopropyl and α-hydroxy adduct.[17c] When H_2O–Et_2O was employed as a solvent, two products **8a** and **9a** were produced more efficiently in 40% and 38% yields, respectively (entry 3). In order to explain the origin of hydroxy group on adduct **8a**, oxygen saturated ether was employed as H_2O–Et_2O system, but both alkyl adduct **9a** and hydroxylated alkyl adduct **8a** were formed in less yields indicating that too much amount of oxygen retards the reaction (entries 4 and 5). As an alternative solvent system, H_2O–CH_2Cl_2 combination in the absence of CuCl gave both products **8a** and **9a** in better yields (entry 6). The corresponding conjugated hydrazone **7b** worked well to afford isopropyl adduct **9b** in moderate yield with a trace amount of hydroxylated alkyl adduct **8b** under InCl–CuCl conditions in H_2O–Et_2O or H_2O–EtOH (entries 7 and 8).

Reaction pathway from conjugated oxime ether **7a** to isopropyl adduct **9a** is reasonably explained through two step process of SET via a carbanion intermediate **D**, while the pathway from **7a** to β-isopropyl and α-hydroxy adduct **8a** is not clear but proposed as shown in Scheme 3.

To gain further insight into the utility of InCl–CuCl system, we next examined the reaction of several radical acceptors which were employed in our previous studies

Table 2 Isopropyl Radical Reaction to α,β-Unsaturated Imines **7a** and **7b**[a]



Entry	Substrate	Solvent	Additive (1 equiv)	Time (h)	Yield of **8a**,**b**[b] (%)[c]	Yield of **9a**,**b** (%)[c]
1	**7a**	H_2O–EtOH	CuCl	3	–	58
2	**7a**	H_2O–EtOH	none	5	18	22[d]
3	**7a**	H_2O–Et_2O	CuCl	7	40	38
4	**7a**	H_2O–Et_2O[e]	none	5	28	22[d]
5[f]	**7a**	H_2O–Et_2O[e]	none	6	19	10[d]
6	**7a**	H_2O–CH_2Cl_2	none	24	30	47
7	**7b**	H_2O–Et_2O	CuCl	5	trace	50[d]
8	**7b**	H_2O–EtOH	CuCl	5	trace	61

[a] Reactions were carried out with *i*-PrI (5 equiv X 2) and InCl (10 equiv) under air atmosphere.

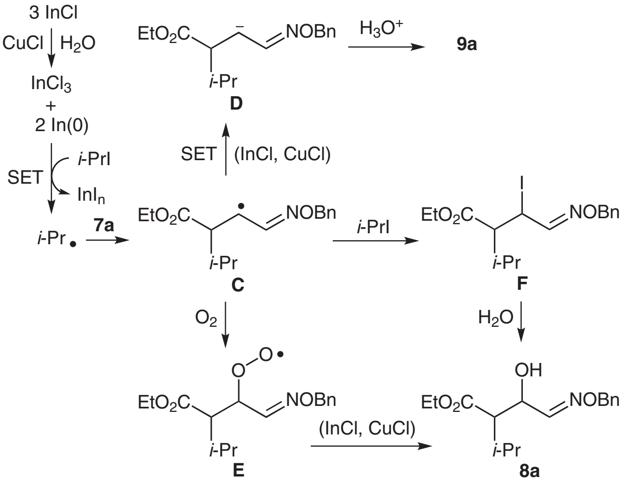
[b] Obtained as 3.7–2.3:1 ratio of *anti*/*syn* isomers.

[c] Isolated yields.

[d] A small amount of substrate was recovered.

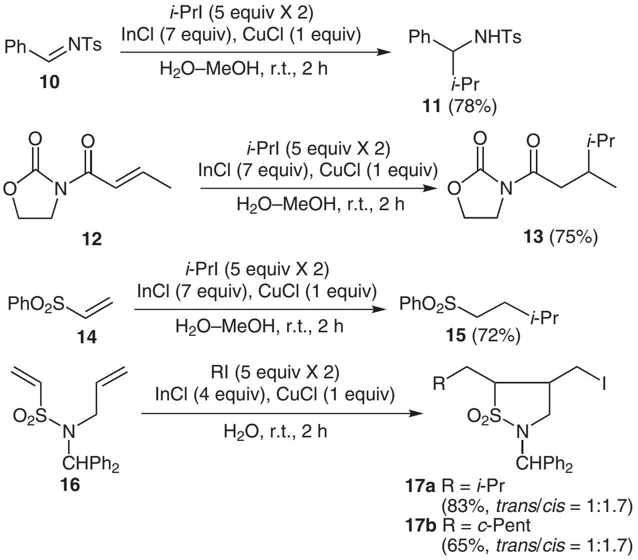
[e] Pretreatment of Et_2O with O_2 gas.

[f] Reaction was carried out under O_2 gas.



Scheme 3 Proposed reaction pathway from **7a** to **8a** and **9a**

(Scheme 4).[4,18,19] Reaction of *N*-Ts imine **10** proceeded smoothly to give the desired product **11** in good yield.[18] Next, radical addition to electron-deficient C=C bond was investigated. Radical 1,4-addition to **12** proceeded effectively to provide a new carbon–carbon bond-forming method in aqueous media. Phenyl vinyl sulfone **14** also worked well without significant polymerization. The InCl–CuCl system was successfully applied to the domino radical addition–cyclization–trapping reaction of **16**.[19]



Scheme 4 Radical addition to various substrates **10**, **12**, **14**, and **16**

In conclusion, we have disclosed an efficient InCl–CuCl system promoting the radical reactions in aqueous media which are amenable to green chemistry. In conjunction with Loh's group works,[8] our found InCl–CuCl-mediated reaction is proved to be quite general and applicable to a substrate of wide scope, because it does not require the use of moisture-sensitive irritant tin hydride and any special precautions such as drying, degassing, and purification of solvents.

Acknowledgment

This work was supported in part by Grant-in-Aid for Young Scientists (B) (M.U.), for Scientific Research (C) (H.M.), for Scientific Research (B) (T.N.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. Our thanks are also directed to the Science Research Promotion Fund of the Japan Private School Promotion Foundation for a research grant.

References and Notes

(1) For reviews, see: (a) Rowlands, G. J. *Tetrahedron* **2010**, *66*, 1593. (b) Rowlands, G. J. *Tetrahedron* **2009**, *65*, 8603. (c) Perchyonok, V. T.; Lykakis, I. N. *Curr. Org. Chem.* **2009**, *13*, 573. (d) Kargbo, R. B.; Cook, G. R. *Curr. Org. Chem.* **2007**, *11*, 1287. (e) Herrerías, C. I.; Yao, X. Q.; Li, Z. P.; Li, C. J. *Chem. Rev.* **2007**, *107*, 2546. (f) Li, C. J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68. (g) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095. (h) Nair, V.; Ros, S.; Jayan, C. N.; Pillia, B. S. *Tetrahedron* **2004**, *60*, 1959. (i) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (j) Li, C. J. *Acc. Chem. Res.* **2002**, *35*, 533. (k) Li, C. J. *Green Chem.* **2002**, *4*, 1. (l) Maher, J. P. *Annu. Rep. Prog. Chem., Sect. A* **2001**, *97*, 49. (m) Yuang, Y. F.; Cao, Z.; Hu, A. G.; Wang, J. T. *Chin. J. Org. Chem.* **2000**, *20*, 269. (n) Liao, L. A.; Li, Z. M. *Chin. J. Org. Chem.* **2000**, *20*, 306. (o) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149. (p) Li, C.-J.

Tetrahedron **1996**, *52*, 5643. (q) Cintas, P. *Synlett* **1995**, 1087. (r) Lubineau, A.; Angé, J.; Queneau, Y. *Synthesis* **1994**, 741. (s) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023.

(2) (a) Auge, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739. (b) Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739. (c) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633. (d) Ranu, B. C. *Eur. J. Org. Chem.* **2000**, 2347. (e) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015.

(3) (a) Qin, Y.-Y.; Yang, Y.-Y.; Qiu, X.-L.; Qing, F.-L. *Synthesis* **2006**, 1475. (b) Takami, K.; Mikami, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Tetrahedron* **2003**, *59*, 6627. (c) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 906.

(4) For a review, see: (a) Miyabe, H.; Naito, T. *Org. Biomol. Chem.* **2004**, *2*, 1267. Our previous studies, see: (b) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Tetrahedron* **2004**, *60*, 4227. (c) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131. (d) Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun.* **2002**, 1454.

(5) (a) Yanada, R.; Takemoto, Y. *J. Synth. Org. Chem.* **2009**, *67*, 239. (b) Yanada, R.; Obika, S.; Nishimori, N.; Yamauchi, M.; Takemoto, Y. *Tetrahedron Lett.* **2004**, *45*, 2331. (c) Yanada, R.; Koh, Y.; Nishimori, N.; Matsumura, A.; Obika, S.; Mitsuya, H.; Fujii, N.; Takemoto, Y. *J. Org. Chem.* **2004**, *69*, 2417. (d) Yanada, R.; Nishimori, N.; Matsumura, A.; Fujii, N.; Takemoto, Y. *Tetrahedron Lett.* **2002**, *43*, 4585.

(6) Recently, the related indium(0)-mediated radical reactions were reported, see: (a) Sugi, M.; Sakuma, D.; Togo, H. *J. Org. Chem.* **2003**, *68*, 7629. (b) Jang, D. O.; Cho, D. H. *Synlett* **2002**, 631. (c) Huang, T.; Keh, C. C. K.; Li, C.-J. *Chem. Commun.* **2002**, 2440.

(7) The use of indium(III) chloride in atom-transfer cyclization, see: Cook, G. R.; Hayashi, R. *Org. Lett.* **2006**, *8*, 1045.

(8) (a) Yang, Y.-S.; Shen, Z.-L.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 1209. (b) Shen, Z. L.; Cheong, H. L.; Loh, T. P. *Chem. Eur. J.* **2008**, *14*, 1875. (c) Shen, Z. L.; Yeo, Y. L.; Loh, T. P. *J. Org. Chem.* **2008**, *73*, 3922. (d) Shen, Z.-L.; Loh, T.-P. *Org. Lett.* **2007**, *9*, 5413.

(9) The use of indium(I) salts has been less explored except for allylation, see: (a) Ranu, B. C.; Mandal, T. *Tetrahedron Lett.* **2006**, *47*, 2859. (b) Babu, S. A.; Yasuda, M.; Shibata, I.; Baba, A. *J. Org. Chem.* **2005**, *70*, 10408. (c) Peppe, C. R.; das Chagas, P. *Synlett* **2004**, 1187. (d) Ranu, B. C.; Mandal, T. *J. Org. Chem.* **2004**, *69*, 5793. (e) Ranu, B. C.; Das, A. *Tetrahedron Lett.* **2004**, *45*, 6875. (f) Ranu, B. C.; Mandal, T. *Synlett* **2004**, 1239. (g) Ranu, B. C.; Mandal, T.; Samanta, S. *Org. Lett.* **2003**, *5*, 1439. (h) do R. Barros, O. S.; Lang, E. S.; de Oliveira, C. A. F.; Peppe, C.; Zeni, G. *Tetrahedron Lett.* **2002**, *43*, 7921. (i) Nóbrega, J. A.; Gonçalves, S. M. C.; Peppe, C. *Tetrahedron Lett.* **2001**, *42*, 4745. (j) Nóbrega, J. A. S.; Gonçalves, M. C.; Peppe, C. *Tetrahedron Lett.* **2000**, *41*, 5779.

(10) The use of indium(I) salts as Lewis acid for activation of functional groups, see: (a) Mahesh, M.; Murphy, J. A.; Wessel, H. P. *J. Org. Chem.* **2005**, *70*, 4118. (b) Keh, C. C.; Wei, K. C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 4062.

(11) For reviews on radical reactions, see: (a) In *Radicals in Organic Synthesis*, Vol. 1 and 2; Renaud, P.; Sibi, M. P., Eds.; Wiley-VCH: Weinheim, **2001**. (b) Sibi, M. P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* **2003**, *103*, 3263. (c) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461. (d) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140.

(12) Radical reactions in aqueous media, see: (a) Yamazaki, O.; Togo, H.; Nogami, G.; Yokoyama, M. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2519. (b) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604. (c) Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **1998**, 1351. (d) Kita, Y.; Nambu, H.; Ramesh, N. G.; Anikumar, G.; Matsugi, M. *Org. Lett.* **2001**, *3*, 1157.

(13) **General Procedure for the Reaction of Oxime Ether 1**
To a microtube containing oxime ether **1** (50 mg, 0.26 mmol), *i*-PrI (1.3 mL, 1.3 mmol), indium salt (2.6 mmol), copper salt (0.26 mmol), and MeOH (0.2 mL) H_2O was added dropwise (0.4 mL) at r.t. After the reaction mixture was vigorously stirred at the same temperature for 1 h, *i*-PrI (1.3 mL, 1.3 mmol) was added to the reaction mixture. After being vigorously stirred at the same temperature for 1 h, the reaction mixture was diluted with aq 36% potassium sodium (+)-tartrate and then extracted with EtOAc. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by preparative TLC (hexane–EtOAc, 4:1) afforded the adduct **2**[4b] in the yields shown in Table 1.

(14) Disproportionation of InX, see: Peppe, C.; Tuck, D. G.; Victoriano, L. *J. Chem. Soc., Dalton Trans.* **1982**, 2165.

(15) Redox reaction in the InCl–$SnCl_2$ system, see: Beck, H. P.; Wilhelm, D.; Hartl-Gunselmann, A. *Z. Anorg. Allg. Chem.* **1991**, *602*, 65.

(16) CuCl-mediated radical reactions, see: (a) Nagashima, H.; Wakamatsu, H.; Itoh, K.; Tomo, Y.; Tsuji, J. *Tetrahedron Lett.* **1983**, *24*, 2395. (b) Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 2133.

(17) (a) Ueda, M.; Miyabe, H.; Nishimura, A.; Sugino, H.; Naito, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2857. (b) Ueda, M.; Miyabe, H.; Sugino, H.; Naito, T. *Org. Biomol. Chem.* **2005**, *3*, 1124. (c) Ueda, M.; Miyabe, H.; Kimura, T.; Kondoh, E.; Naito, T.; Miyata, O. *Org. Lett.* **2009**, *11*, 4632.

(18) Miyabe, H.; Ueda, M.; Naito, T. *Chem. Commun.* **2000**, 2059.

(19) Ueda, M.; Miyabe, H.; Nishimura, A.; Miyata, O.; Takemoto, Y.; Naito, T. *Org. Lett.* **2003**, *5*, 3835.