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Indium-Mediated Tandem Radical Addition–Cyclization-Trap Reactions in Aqueous Media

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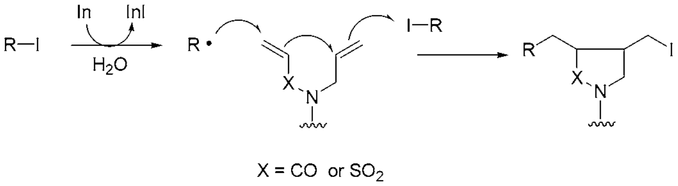
ABSTRACT



Tandem carbon–carbon bond-forming reactions were studied by using indium as a single-electron-transfer radical initiator. The radical addition–cyclization-trap reaction of a substrate having a vinyl sulfonamide group and an olefin moiety proceeded smoothly in aqueous media. The radical addition–cyclization reaction of hydrazone gave the functionalized cyclic products.

Free radical reactions have developed as a powerful method for constructing the carbon−carbon bond in organic synthesis.[1] Particularly, strategies involving tandem radical reaction or radical annulation offer the advantage of multiple carbon−carbon bond formations in a single operation; thus, a number of extensive investigations were reported in recent years.[1,2] However, the aqueous-medium tandem construction of carbon−carbon bonds has not been widely studied, and therefore, tandem radical reactions in aqueous media have been a subject of current interest[3]

The use of water as a solvent has many advantages in organic synthesis from both economical and environmental points of view.[4] Particularly, carbon−carbon bond formation in aqueous media is a challenging problem for synthetic organic chemistry.[5,6] We recently reported the indium-

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(1) (a) Fossey, J.; Lefort, D.; Sorba, J. In *Free Radicals in Organic Chemistry*; Translated by J. Lomas; John Wiley & Sons Inc.: New York, 1995. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (d) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React. (N.Y.)* **1996**, *48*, 301. (e) Curran, D. P.; Porter, N. A.; Giese, B. In *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*; VCH: Weinheim, Germany, 1996. (f) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562. (g) Sibi, M. P.; Porter, N. A. *Acc. Chem. Res.* **1999**, *32*, 163. (h) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1. (i) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: New York, 2001.

(2) For some examples, see: (a) Angoh, A. G.; Clive, D. L. J. *J. Chem. Soc., Chem. Commun.* **1985**, 941. (b) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (c) Feldman, K. S.; Vong, A. K. K. *Tetrahedron Lett.* **1990**, *31*, 823. (d) Tsuritani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2001**, *3*, 2709. (e) Sibi, M. P.; Chen, J.; Rheault, T. R. *Org. Lett.* **2001**, *3*, 3679. (f) Kitagawa, O.; Yamada, Y.; Sugawara, A.; Taguchi, T. *Org. Lett.* **2002**, *4*, 1011. (g) Takasu, K.; Ohsato, H.; Kuroyanagi, J.; Ihara, M. *J. Org. Chem.* **2002**, *67*, 6001. (h) Sibi, M. P.; Miyabe, H. *Org. Lett.* **2002**, *4*, 3435. (i) Demircan, A.; Parsons, P. J. *Eur. J. Org. Chem.* **2003**, 1729.

(3) We have studied the tandem radical addition−cyclization reactions of oxime ether and hydrazone by using triethylborane as a radical initiator. Some of these reactions proceeded even in aqueous media. See: (a) Miyabe, H.; Ueda, M.; Fujii, K.; Nishimura, A.; Naito, T. *J. Org. Chem.* **2003**, *68*, 5618. (b) Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071. (c) Miyabe, H.; Fujii, K.; Tanaka, H.; Naito, T. *Chem. Commun.* **2001**, 831.

(4) Garner, P. P.; Parker, D. T.; Gajewski, J. J.; Lubineau, A.; Ange, J.; Queneau, Y.; Beletskaya, I. P.; Cheprakov, A. V.; Fringuelli, F.; Piermatti, O.; Pizzo, F.; Kobayashi, S. In *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie Academic & Professional: London, UK, 1998.

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mediated alkylation reactions of imines and electron-deficient olefins in aqueous media.[7] In these studies, we proposed a mechanistic hypothesis involving addition of a radical species.[8,9] However, an alternative mechanistic hypothesis involving the addition of an alkylindium species was not excluded. As a part of our program directed toward the development of aqueous-medium radical reactions,[10] we now report indium-mediated tandem carbon−carbon bond-forming reactions in aqueous media. In this study, we also expected that the tandem reactions would lead to informative suggestions regarding the reaction mechanism of indium-mediated alkylation reactions.

As a preliminary study, we investigated the indium-mediated reaction of substrates having two different radical acceptors. At first, the tandem addition−cyclization-trap reaction of substrate **1** having acrylate and olefin moieties was examined (Scheme 1). To a suspension of **1** in H_2O were added *i*-PrI (2 × 5 equiv) and indium (2 equiv), and then the reaction mixture was stirred at 20 °C for 2 h. As expected, the reaction proceeded smoothly to give the desired cyclic product **2a** in 63% yield as a trans/cis mixture in 3.2:1 ratio, along with 13% yield of the addition product **3a** (Table 1, entry 1).[11] The biphasic reaction in $H_2O-CH_2Cl_2$ (4:1, v/v) proceeded slowly to give **2a** in 63% yield after being stirred at 20 °C for 20 h (entry 2). Thus, a highly concentrated organic phase without CH_2Cl_2 should be advantageous for indium-mediated atom-transfer reactions. A cyclopentyl radical worked well under similar reaction conditions to give the cyclic product **2b** in 65% yield, although a bulky *tert*-butyl radical was less effective under the present reaction conditions (entries 3−5).

Scheme 1. Indium-Mediated Tandem Reaction of Substrate **1**

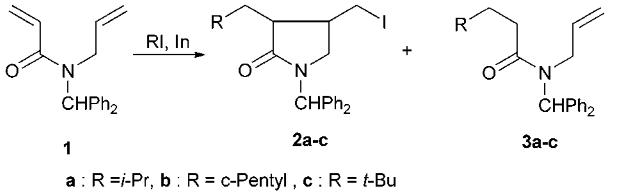


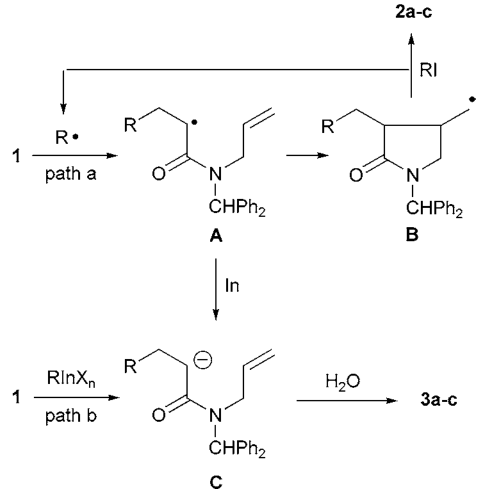
Table 1. Indium-Mediated Tandem Reaction of Substrate **1**

entry	RI	solvent	time (h)	yield (%)[a]	
				2a−c[b]	**3a−c**
1[c]	*i*-PrI	H_2O	2	63 (3.2:1)	13
2[d]	*i*-PrI	$H_2O-CH_2Cl_2$ (4:1)	20	63 (4.7:1)	21
3[c]	c-Pentyl I	H_2O	2	65 (4.0:1)	9
4[c]	*t*-BuI	H_2O	2	38 (3.6:1)	19
5[d]	*t*-BuI	$H_2O-CH_2Cl_2$ (4:1)	20	38 (3.2:1)	26

[a] Isolated yields. [b] Ratio in parentheses is for trans:cis selectivity of **2a−c**. The trans:cis selectivities were determined by ^1H NMR analysis. [c] Reactions were carried out with RI (2 × 5 equiv) and In (2 equiv) in H_2O at 20 °C. [d] Reactions were carried out with RI (10 equiv) and In (3 equiv) in $H_2O-CH_2Cl_2$ (4:1, v/v) at 20 °C.

The preferential formation of cyclic products **2a−c** could be obviously explained by a radical mechanism (Scheme 2).

Scheme 2. Indium-Mediated Tandem Addition−Cyclization-Trap Reaction



The indium-mediated reaction was initiated by single-electron transfer (SET) to RI with generation of an alkyl radical, which then attacked the electrophilic acrylate moiety of **1** to form the carbonyl-stabilized radical **A** (path a). The cyclic products **2a−c** were obtained via the intramolecular reaction of radical **A** with the olefin moiety followed by iodine atom-transfer reaction from RI to the intermediate primary radical **B**. Although there are many examples of anions adding to

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(5) For a recent review, see: (a) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. (b) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633.

(6) For selected examples of aqueous-medium radical reactions, 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. (d) Nambu, H.; Hata, K.; Matsugi, M.; Kita, Y. *Chem. Commun.* **2002**, 1082.

(7) For our indium-mediated radical reactions, see: (a) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131. (b) Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun.* **2002**, 1454.

(8) Recently, three related indium-mediated radical reactions were reported. See: (a) Huang, T.; Keh, C. C. K.; Li, C.-J. *Chem. Commun.* **2002**, 2440. (b) Yanada, R.; Nishimori, N.; Matsumura, A.; Fujii, N.; Takemoto, Y. *Tetrahedron Lett.* **2002**, *43*, 4585. (c) Jang, D. O.; Cho, D. H. *Synlett* **2002**, 631.

(9) Indium(I) iodide-mediated radical cyclization was recently studied. See: (a) Cook, G. R.; Erickson, S.; Hvinden, M. *Abstracts of Papers*, 221st National Meeting of the American Chemical Society, San Diego, CA, April 1−5, 2001; American Chemical Society: Washington, DC, 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**, 1139. (e) Reddy, G. V.; Rao, G. V.; Iyengar, D. S. *Tetrahedron Lett.* **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.

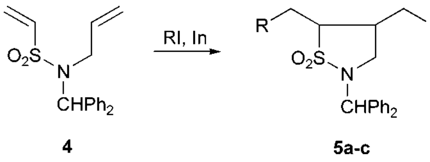
(10) For our reactions of imines in aqueous media, see: (a) Miyabe, H.; Ueda, M.; Naito, T. *J. Org. Chem.* **2000**, *65*, 5043. (b) Miyabe, H.; Ueda, M.; Naito, T. *Chem. Commun.* **2000**, 2059. (c) Miyabe, H.; Yamaoka, Y.; Naito, T.; Takemoto, Y. *J. Org. Chem.* **2003**, *68*, 6745.

(11) The configuration of major and minor products **2a**, **5a**, and **7a** was determined by these NOESY spectra. See the Supporting Information.

isolated double bonds, these reactions have been limited to lithium-mediated reactions.[12] Thus, the formation of cyclic products **2a**−**c** from a carbanion **C** would be excluded. In contrast, the formation of the addition products **3a**−**c** could be explained by either a radical mechanism (path a) or an ionic mechanism (path b) via carbanion **C**. As for the formation of compounds **3a**−**c**, the indium-mediated reduction of the compounds **2a**−**c** and the subsequent ring-opening reaction could be proposed as an alternative pathway. To study the reversibility in this reaction, the compound **2a** was treated with indium under similar reaction conditions. However, the formation of compound **3a** was not observed and compound **2a** was recovered, probably due to low reactivity of the primary alkyl iodide moiety of **2a** toward indium. A similar trend was observed in our previous study.[7a] The primary alkyl iodides such as ethyl iodide did not work in indium-mediated radical reactions. Therefore, the alternative pathway giving compounds **3a**−**c** from compounds **2a**−**c** would be excluded. Trans selectivity in the formation of the cyclized products **2a**−**c** is coincident with the case of the thiyl radical addition−cyclization of analogous substrates.[13] One possible explanation is that cyclized radical **B** would be equilibrated with the precursor radical **A** and therefore temporarily formed *cis*-**B** would be transformed to more stable *trans*-**B**, which would give preferably the trans isomer. In the indium-mediated radical reactions, indium(0) was oxidized to indium(I), which then would be converted to indium(0) and indium(III) as a result of a disproportionation reaction.

The next substrate of choice was the sulfonamide **4**, since phenyl vinyl sulfone has shown excellent reactivity as an electron-deficient olefin in our previous work on indium-mediated intermolecular reactions (Scheme 3).[7a] As expected, sulfonamide **4** exhibited good reactivity to give moderate and good yields of the desired cyclic products **5a**−**c** without the formation of other byproducts. The indium-mediated tandem reaction of **4** with *i*-PrI in H_2O gave selectively the cyclic product **5a** in 81% yield as a trans/cis mixture in 1:1.4 ratio, with no detection of simple addition product (Table 2, entry 1).

Scheme 3. Indium-Mediated Tandem Reaction of Substrate **4**



a : R = *i*-Pr, **b** : R = c-Pentyl , **c** : R = *t*-Bu

Thus, indium was found to be a highly promising radical initiator in aqueous media. In the case of the biphasic reaction in $H_2O-CH_2Cl_2$, the cyclic product **5a** was obtained in 42% yield after being stirred for 48 h (entry 2). Other alkyl radicals such as cyclopentyl and *tert*-butyl radicals worked well under similar reaction conditions, allowing facile incorporation of structural variety (entries 3 and 4). These results indicate that the electrophilic vinyl sulfonamide group of **4** has excellent reactivity toward nucleophilic carbon radicals and the intermediate sulfonamide-stabilized radical shows a strongly electrophilic nature, which easily reacted with the vinyl group. Additionally, the overall difference in steric and stereoelectronic factors between sulfonamides and carboxamides also would be important for cyclization as shown in the related studies on intramolecular reactions of sulfonamides.[14,15] Compared with the case of the carboxamide **1**, cis-products **5a**−**c** were major isomers though this different behavior of these two types of amides cannot be easily explained at the moment.

Table 2. Indium-Mediated Tandem Reaction of Substrate **4**

entry	RI	solvent	time (h)	yield (%)[a]
1[b]	*i*-PrI	H_2O	4	81 (1:1.4)
2[c]	*i*-PrI	$H_2O-CH_2Cl_2$ (4:1)	48	42 (1:1.1)
3[b]	*c*-pentyl I	H_2O	4	84 (1:1.3)
4[b]	*t*-BuI	H_2O	4	79 (1:2.0)

[a] Isolated yields. Ratio in parentheses is for trans:cis selectivities which were determined by ^1H NMR analysis. [b] Reactions were carried out with RI (2 × 5 equiv) and In (2 equiv) in H_2O at 20 °C. [c] Reaction was carried out with RI (2 × 5 equiv) and In (2 × 2 equiv) in $H_2O-CH_2Cl_2$ (4:1, v/v) at 20 °C.

As shown in our previous studies,[7] the intermolecular reactions of imines and electron-deficient olefins required a large amount of indium (7 or 10 equiv) for the successful reaction. Therefore, it is important to note that the present tandem radical reactions proceeded in the presence of only 2 equiv of indium, because the tandem radical reaction is assumed to proceed via catalytic radical cycle. However, the reaction of **4** with *i*-PrI in a catalytic amount of indium (0.2 equiv) did not complete, probably due to the formation of a lump of indium in the aqueous media, to give the cyclic product **5a** in 14% yield, accompanied by starting material **4**. Additionally, a remarkable feature of this reaction is the concomitant construction of two carbon−carbon bonds and a carbon−iodine bond via a tandem process, providing an effective and convenient method for the synthesis of highly functionalized cyclic compounds.

As a part of our program directed toward the development of tandem reaction of imines,[3] we finally investigated tandem radical addition−cyclization of hydrazone **6** connected with the vinyl sulfonamide group (Scheme 4).

The radical reaction of **6** does not proceed via catalytic radical cycle such as iodine atom-transfer reaction; thus, a

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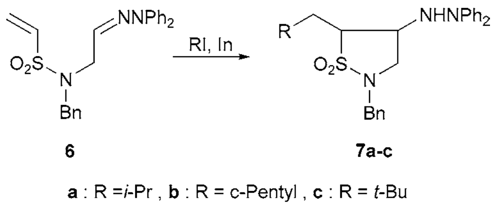
(12) For selected examples see: (a) Bailey, W. F.; Carson, M. W. *J. Org. Chem.* **1998**, *63*, 361. (b) Barluenga, J.; Sanz, R.; Fañanás, F. J. *Tetrahedron Lett.* **1997**, *38*, 2763. (c) Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981. (d) Coldham, I.; Hufton, R. *Tetrahedron Lett.* **1995**, *36*, 2157.

(13) Naito, T.; Honda, Y.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 19.

(14) For the cyclization of radicals generated from α-halomethylsulfonamides, see: Leit, S. M.; Paquette, L. A. *J. Org. Chem.* **1999**, *64*, 9225.

(15) (a) Greig, I. R.; Tozer, M. J.; Wright, P. T. *Org. Lett.* **2001**, *3*, 369. (b) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170.

Scheme 4. Indium-Mediated Tandem Reaction of Hydrazone **6**



large amount of indium was required for the successful reaction (Scheme 5).[16] The tandem reaction of hydrazone **6** with an isopropyl radical was carried out in $H_2O-MeOH$ for 5 h by using *i*-PrI (2 × 5 equiv) and indium (10 equiv). As expected, the reaction proceeded smoothly to give the isopropylated product **7a** in 93% yield as a trans/cis mixture in a 1:1.2 ratio, without the formation of the simple addition product (Table 3, entry 1). The biphasic reaction of **6** in $H_2O-CH_2Cl_2$ also proceeded effectively to afford a 94% yield of **7a** (entry 2). A cyclopentyl radical and a bulky *tert*-butyl radical worked well to give the cyclic products **7b** and **7c** in 86% and 42% yields, respectively (entries 3 and 4). The stereochemical outcome in the cyclization of hydrazone **6** is almost the same as the case of olefin **4** in which cis products were the major products.

Scheme 5. Possible Reaction Pathway

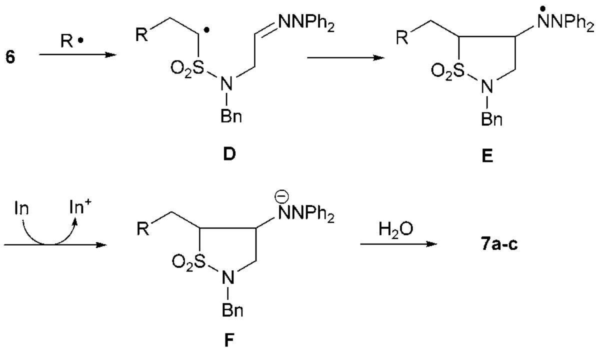


Table 3. Indium-Mediated Tandem Reaction of Hydrazone **6**[a]

entry	RI	solvent	time (h)	yield (%)[b]
1	*i*-PrI	$H_2O-MeOH$ (2:1)	5	93 (1:1.2)
2	*i*-PrI	$H_2O-CH_2Cl_2$ (4:1)	24	94 (1:1.2)
3	*c*-pentyl I	$H_2O-MeOH$ (2:1)	5	86 (1:1.1)
4	*t*-BuI	$H_2O-MeOH$ (2:1)	5	42 (1:1.6)

[a] Reactions were carried out with RI (2 × 5 equiv) and In (10 equiv) at 20 °C. [b] Isolated yields. Ratio in parentheses is for trans:cis selectivities which were determined by ^{1}H NMR analysis.

A favorable experimental feature of indium-mediated radical reactions is that the reactions proceed in the absence of toxic tin hydride, providing the carbon−carbon bond-forming method in aqueous media. Additionally, the indium-mediated reactions disclosed a broader utility of aqueous-medium tandem reaction for the preparation of various types of highly functionalized cyclic compounds.

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Supporting Information Available: Experimental procedures, characterization data for compounds **2a**, **3a**, **5a**, and **7a**, and ^{1}H NMR spectra of compounds **2a**−**c**, **5a**−**c**, and **7a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] Sturino, C. F.; Fallis, A. G. *J. Org. Chem.* **1994**, *59*, 6514.