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The utility of indium in aqueous medium radical reactions

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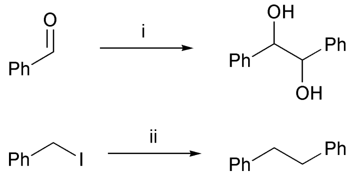
Indium-mediated radical reactions proceed in the absence of toxic tin hydride, providing a new carbon–carbon bond-forming method in aqueous media. Herein, the results of experiments to probe the utility of indium as a radical initiator in reactions in aqueous media are reported. The indium-mediated tandem reactions also proceed smoothly *via* two carbon–carbon bond-forming processes for the preparation of various types of functionalized cyclic compounds.

Introduction

The use of water as a solvent has generated considerable interest from both economical and environmental points of view.[1] Carbon–carbon bond-formation in aqueous media is a particularly challenging problem. In principle, the reactions of strictly neutral species such as uncharged free radicals are not affected by the presence of water.[2] Therefore, employment of a moisture-resistant radical species would eliminate the cumbersome operations involved in conventional ionic reactions.

The indium-mediated carbon–carbon bond-forming reactions in aqueous media have been of great importance in organic synthesis.[3] However, most synthetically useful indium-mediated reactions are mainly limited to allylation of carbonyl compounds and imine derivatives and Reformatsky-type reactions. These allylation reactions would proceed through an allylindium(I) intermediate, which reacts with carbonyl compounds and imine derivatives, and thus, simple alkylation reactions are not investigated.

Reductive carbon–carbon bond formation constitutes one of the fundamental processes. As an important indium-mediated synthetic transformation, several reductive coupling reactions were studied.[4,5] Indium can promote the pinacol coupling of aldehydes or imines[4] and the reductive coupling of alkyl halides or carbonyl compounds (Scheme 1).[5] This mode of reaction could be explained by a single-electron transfer (SET) process, although there is no evidence for such a mechanism.



Scheme 1 *Reagents and conditions*: i, In, H_2O, sonication; ii, In, DMF, reflux.

As a part of our program directed towards the development of aqueous medium radical reactions,[6] we have started to investigate the utility of indium as a radical initiator in aqueous media.[7] The first ionization potential of indium (5.8 eV) is as low as that of lithium and sodium. Therefore, we expected that indium has the potential to induce radical reactions as a radical

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Hideto Miyabe (left) and Takeaki Naito (right)

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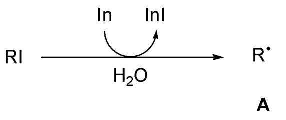
initiator *via* a single-electron transfer process (Scheme 2).[8,9] Detailed herein is a review of our novel indium-mediated radical reactions in aqueous media. As shown below, the indium-mediated radical reactions provide new opportunities for carbon–carbon bond-formation such as alkylation reactions of imines and 1,4-addition to α,β-unsaturated carbonyl compounds.

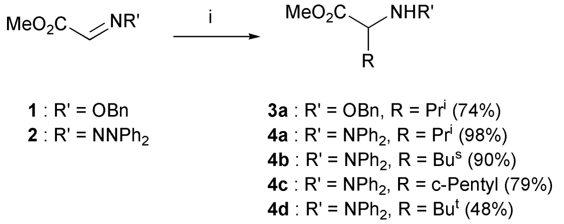


Scheme 2

Alkylation reaction of imines

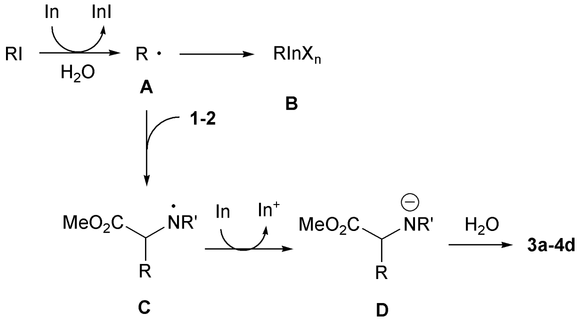
The carbon–nitrogen double bond has emerged as a radical acceptor, and thus several intermolecular radical addition reactions of imines were recently investigated in organic solvents.[10] Our recent studies show that imine derivatives such as oxime ethers, hydrazones, and nitrones are excellent water-resistant radical acceptors for aqueous-medium reactions using triethylborane as a radical initiator.[6]

We first investigated the reaction of glyoxylic oxime ether **1** under several reaction conditions (Scheme 3).[7a] The monophasic reaction of **1** in H_2O–MeOH gave the isopropylated product **3a**, after being stirred for only 0.5 h, without formation of significant byproducts such as a reduced product. It is important to note that practically no reaction of **1** occurred in the absence of water. These results suggest that water would be important for the activation of indium and for proton donation to the resulting amide anion. In the presence of a galvinoxyl free radical as radical scavenger, the reaction did not proceed effectively; and thus, this reaction would proceed *via* a radical mechanism based on a single-electron transfer process from indium.



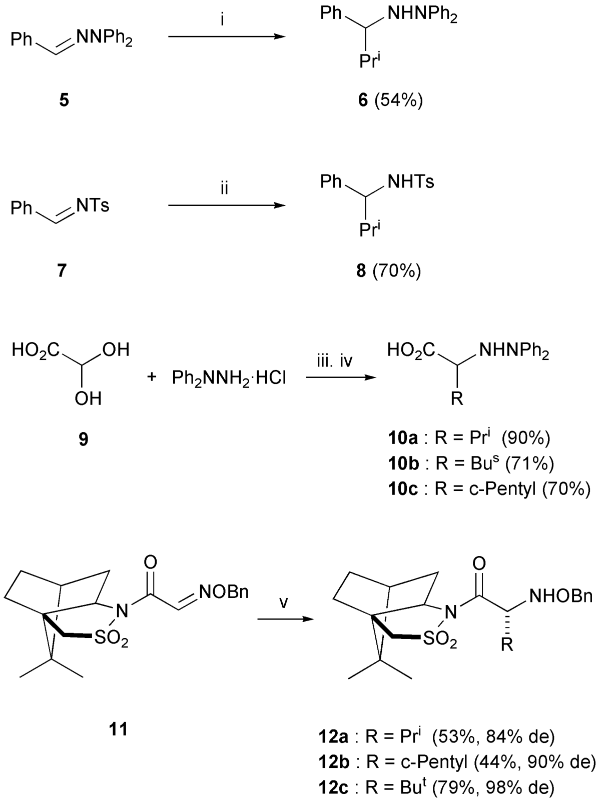
Scheme 3 *Reagents and conditions*: i, RI, In, H_2O–MeOH, 20 °C.

The reaction was initiated by single-electron transfer from indium to RI with generation of an alkyl radical, which then attacked the oxime ether group of **1** to form the aminyl radical **C** (Scheme 4). The process was completed by indium-mediated reduction of the intermediate aminyl radical **C** followed by protonation of the resulting amide anion **D**. However, an alternative mechanistic hypothesis involving the addition of an alkylindium species **B** was not excluded. We also found that the indium-mediated alkyl radical addition to glyoxylic hydrazone **2** is a highly promising approach to the synthesis of α-amino acids. In the case of the aqueous-medium reactions of **2** using triethylborane, the undesired *C*- and *N*-dialkylated products were only obtained as a result of additional *N*-alkylation.[6a] In contrast, the indium-mediated alkyl radical addition to **2** gave selectively the desired *C*-monoalkylated products **4a**–**d** with no detection of dialkylated products. In the indium-mediated radical reactions, indium(0) was oxidized to indium(I). Additionally, indium(I) would be converted to indium(0) and indium(III) as a result of a disproportionation reaction.



Scheme 4

To survey the scope and limitations of the present method, we investigated the alkylation reaction of several imine derivatives. Although the reactivity of hydrazone **5**, derived from benzaldehyde, is not high, the biphasic reaction of **5** in H_2O–CH_2Cl_2 proceeded to give **6** after being stirred for 2 days (Scheme 5). The monophasic reaction of *N*-sulfonylimine **7** in H_2O–MeOH proceeded effectively to give the isopropylated product **8** after being stirred for 1 h.

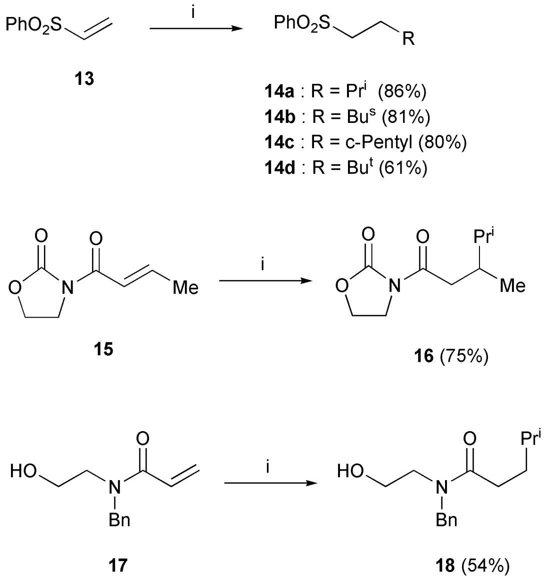


Scheme 5 *Reagents and conditions*: i, Pr^iI, In, H_2O–CH_2Cl_2, 20 °C; ii, Pr^iI, In, H_2O–MeOH, 20 °C; iii, Ph_2NN_2·HCl, MeOH, 20 °C; iv, RI, In, H_2O–MeOH, 20 °C; v, RI, In, H_2O, 20 °C.

Another remarkable feature of this reaction is that employment of a water-resistant radical species successfully integrated a multi-step chemical reaction into a one-pot three-component reaction, thus providing a convenient method for preparing the α-amino acids **10a**–**d** from glyoxylic acid **9**. We next investigated the asymmetric synthesis of α-amino acids by using indium as a single-electron transfer radical initiator.[7b] The treatment of **11** with alkyl iodide and indium in H_2O gave the desired products **12a**–**c**. Modest chemical yield and good diastereoselectivity were obtained in reaction with isopropyl and cyclopentyl radicals. The nucleophilic *tert*-butyl radical worked well to give 79% yield of the desired product **12c** with 98% de.

Radical addition to electron-deficient C=C bond

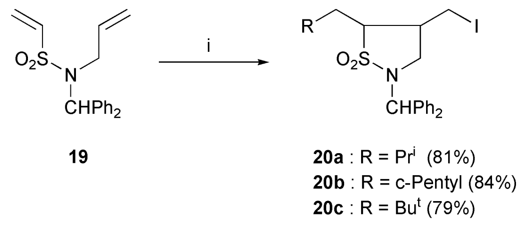
To test the utility of indium as a single-electron transfer radical initiator, we next investigated the indium-mediated alkyl radical addition to compounds **13**, **15**, and **17** having electron-deficient C=C bond (Scheme 6).[7a] The indium-mediated radical addition



Scheme 6 *Reagents and conditions*: i, RI, In, H_2O–MeOH, 20 °C.

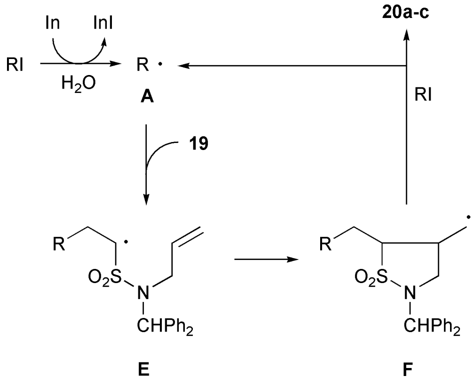
to phenyl vinyl sulfone **13** gave good yields of the desired products **14a–d** in aqueous media. The α,β-unsaturated carbonyl compound **15** also worked well under similar reaction conditions. Additionally, radical 1,4-addition to **17** having the hydroxyl group proceeded effectively to provide a new carbon–carbon bond-forming method in aqueous media. In agreement with the general advantages of radical over anionic reactions, the present radical method would be useful because of the exceptional tolerance of functional groups.

Strategies involving tandem radical reaction offer the advantage of multiple carbon–carbon bond formations in a single operation. 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. We next investigated indium-mediated tandem carbon–carbon bond-forming reactions of substrate **19** having two different radical acceptors (Scheme 7).[7c] The tandem addition–cyclization–trap reaction of **19** with RI in H_2O gave the cyclic products **20a–c** in good yields without the formation of other by-products.



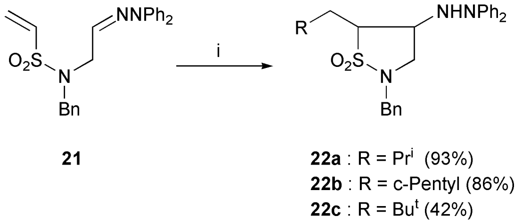
Scheme 7 *Reagents and conditions*: i, RI, In, H_2O, 20 °C.

The formation of cyclic products **20a–c** could be explained by a radical mechanism (Scheme 8). The alkyl radical, generated from RI and indium, attacked the electrophilic C=C bond of **19** to form the intermediate sulfonamide-stabilized radical **E**. The cyclic products **20a–c** were obtained *via* the intramolecular reaction of radical **E** with the olefin moiety followed by iodine atom-transfer reaction from RI to the intermediate primary radical **F**. The intermolecular reactions of imines **1**, **2**, **5**, **7**, and **11** or electron-deficient olefins **13**, **15**, and **17** required a large amount of indium (7 or 10 equivalents) for the successful reaction. Therefore, it is important to note that the present tandem radical reactions proceeded in the presence of only 2 equivalents of indium, because the tandem radical reaction is assumed to proceed *via* a catalytic radical cycle. However, the reaction of **19** with Pr^{i}I in the presence of a catalytic amount of indium (0.2 equivalents) did not complete, probably due to the formation of a lump of indium in the aqueous medium. 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.



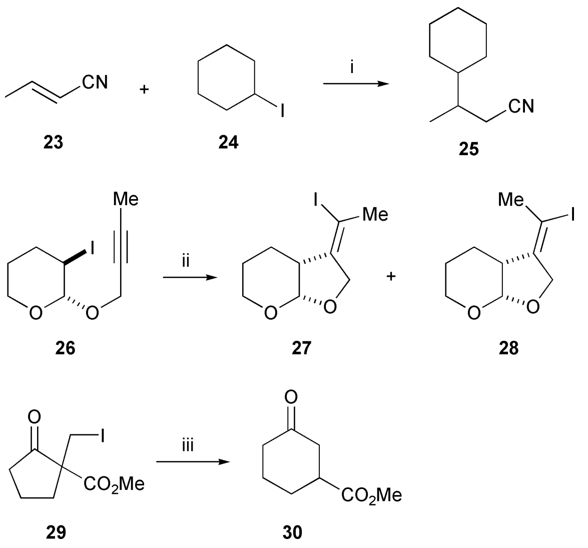
Scheme 8

As a part of our program directed toward the development of tandem reaction of imines,[6d] we finally investigated tandem radical addition–cyclization of hydrazone **21** connected with the vinyl sulfonamide group (Scheme 9). As expected, the reaction proceeded smoothly to give the alkylated products **22a–c** without the formation of simple addition products.



Scheme 9 *Reagents and conditions*: i, RI, In, H_2O–MeOH, 20 °C.

Recently, the related indium-mediated radical reactions have been widely studied (Scheme 10). Indium(I) iodide-mediated radical cyclization was first reported by Cook's group.[8] The indium-mediated 1,4-addition of alkyl radicals to **23** was investigated by using 1-ethylpiperidinium hypophosphite (EPHP) as a hydrogen source in aqueous media.[9a] The atom-transfer radical cyclization of **26** and reductive radical cyclization were studied by using indium and iodine.[9b] Indium-mediated alkyl radical addition to dehydroamino acid deriv-



Scheme 10 *Reagents and conditions*: i, In, 1-ethylpiperidinium hypophosphite (EPHP), cetyltrimethylammonium bromide (CTAB), 4,4′-azo-bis(4-cyanovaleric acid) (ABCVA), H_2O; ii, In, I_2, MeOH; iii, In, *tert*-amyl alcohol, H_2O.

atives was also reported.[9c] The indium-mediated radical ring-expansion reaction of α-halomethyl cyclic β-ketoester **29** was achieved in aqueous alcohol.[9d] In recent years, the development of carbon–carbon bond-forming radical reactions using indium as a radical initiator has been a subject of much interest. Indium shows high synthetic potential to induce radical reactions.

Conclusions and future prospects

In conclusion, we have shown successful radical reactions using indium as a single-electron transfer (SET) radical initiator in aqueous media. In addition to previously reported aqueous medium radical reactions,[2,6] the indium-mediated reactions show a broader utility as moisture-resistant radical species for the construction of carbon–carbon bonds in aqueous media. We have covered carbon–carbon bond formations based on indium-mediated radical reactions which, in contrast to triethylborane as a radical initiator, exhibits low heterophilicity. Thus, indium is a suitable reagent for mediating carbon–carbon bond formation reactions as it can tolerate oxygen and nitrogen functionalities. Furthermore, indium does not readily form corresponding oxides when exposed to air. The indium-mediated radical reaction will be particularly useful 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. This domain offers opportunities for further exploration with intriguing possibilities in aqueous medium radical reactions.

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