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Indium-mediated atom-transfer cyclizations and reductive cyclizations

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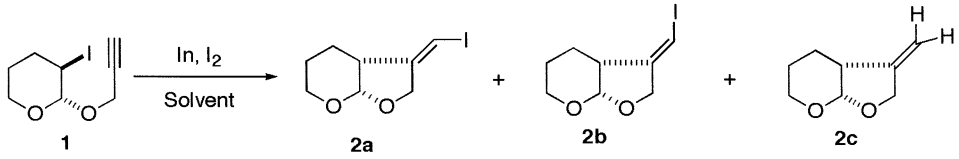
Abstract—Novel indium-mediated reactions have been studied. Treatment of iodoalkyne with In (0.5 equiv.) and I_2 (0.5 equiv.) in MeOH promotes the atom-transfer 5-*exo*-cyclization. In contrast, the reaction with In (2 equiv.) and I_2 (1 equiv.) gives rise to a reductive 5-*exo*-cyclized product.

The first ionization potential of indium (In) (5.8 eV) is as low as that of Li and Na. Therefore, it might be easy for In to promote SET (single electron transfer) processes. In addition, In is comparatively stable in air, and the toxicity observed in many metals is little known in In.[1] For these reasons, In is one of the most notable metals at present, and its usefulness in organic synthesis has been studied[2] in terms of green chemistry.[3] The use of radicals in organic synthesis has increased within the last two decades.[4] During the recent development of radical methodology, tributyltin hydride has played an important role despite its toxicity and the difficulty of the complete removal of the tin species in the reaction mixture. For this reason, new reductive radical reactions to replace tributyltin hydride have been investigated. In contrast to the reductive radical cyclizations,[5] there are some reports on atom-transfer radical cyclization.[6,7] Here we report a novel indium-mediated atom-

Table 1. Radical cyclization of iodoalkyne **1**



Run	In (equiv.)	I_2 (equiv.)	Condition	Solvent	Time (h)	Yield (%)		
						2a	**2b**	**2c**
1	1.0	0.0		MeOH	17	46	4	5
2	**0.5**	**0.5**	**A**	**MeOH**	**17**	**77**	**5**	**0**
3	1.0	0.5		MeOH	17	66	5	1
4	1.0	1.0		MeOH	3	75	5	6
5	1.0	0.5		$EtOH/H_2O = 1/1$	17	65	5	7
6	1.0	0.5		THF	17	53	6	10
7	1.0	0.5		H_2O	22	22	13	2
8	**2.0**	**1.0**	**B**	**MeOH**	**17**	**0**	**0**	**85**
9	InI (0.5 equiv.)	InI_3 (0.5 equiv.)		MeOH	7	67	5	4
10		InI (2 equiv.)		MeOH	7	4	5	55
11		InI_3 (2 equiv.)		MeOH	8	No reaction		

Keywords: indium; iodine; radical; atom-transfer cyclization; reductive cyclization.

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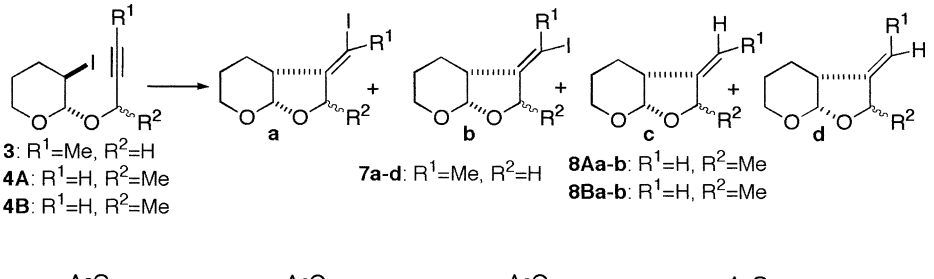
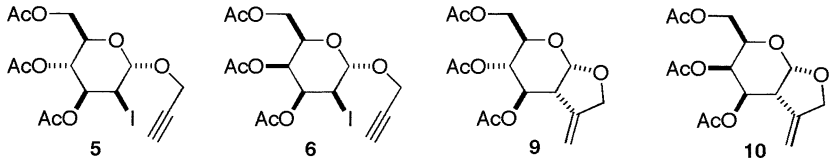
transfer 5-*exo*-cyclization (Kharasch-type reaction) of iodoalkynes to heterocyclic iodoalkenes (condition A) and to tandem radical addition reaction with electron-deficient olefin. Furthermore, we also developed a novel indium-mediated reductive 5-*exo*-cyclization of iodoalkynes to heterocyclic alkenes (condition B). Our report herein would be a novel example regarding in as much as only a change in the quantity of the reagents (In and I_2) can provide different products under the same conditions. We first investigated the cyclization reaction of iodoalkyne **1** in expectation of good results by importing several conditions. Iodoalkyne **1** was treated with 1 equiv of In in MeOH at room temperature to give atom-transfer products **2a** and **2b** in 50% yield accompanied with the starting material (ca. 20%) (Table 1, run 1). Then treatment of compound **1** with In (0.5 equiv.) and I_2 (0.5 equiv.) in MeOH (condition A) afforded atom-transfer 5-*exo*-cyclized products **2a** and **2b** as major products (run 2). This reaction was studied under several conditions (runs 3–7). After all, condition A was the best for atom-transfer 5-*exo*-cyclization. On the other hand, the reaction with compound **1**, In (2 equiv.), and I_2 (1 equiv.) (condition B) gave only a reductive cyclization product **2c** in 85% yield (run 8). Compound **2c** was also obtained in 71% yield from atom-transfer products **2a** and **2b** under condition B. These atom-transfer or reductive cyclization reactions did not occur when bromoalkyne was used instead of iodoalkyne **1** (recovery of the starting material, 86%). Next, we examined the use of commercially available InI and InI_3 (runs 9–11). The result of run 9 was the same as that of run 4. The active species based on chemical equations, for example InI_2, might be produced.[8] The results of runs 8 and 10 were also the same. They gave the reductive cyclization product predominantly. InI_3 could not promote atom-transfer cyclization of compound **1** (run 11).

Next, we tried the cyclization of iodoalkynes **3–6** under condition A or B. The results are summarized in Table 2. Iodoalkynes **3** and **4** gave iodoolefins **7a**, **7b**, **8Aa**, **8Ab**, **8Ba**, and **8Bb** in good yields under condition A. On the other hand, under condition B, iodoolefin **3** gave only reductive cyclization products **7c** and **7d** in moderate yields. Bicyclic sugars are interesting compounds because of their utility as a building block for synthesis of natural products and their biological activities.[9] The sugar iodides **5** and **6** were prepared from glucal and galactal with propargyl alcohol in the presence of *N*-iodosuccinimide in CH_3CN.[10] Using compounds **5** and **6**, the radical cyclization reaction mediated by indium species was carried out under condition B.[11] The reductive cyclization products **9** and **10** were obtained in good yields. The produced 5-*exo*-cyclized bicyclic sugars have *cis*-fused rings. *trans*-Fused products and 6-*endo*-cyclization products were not observed. The atom-transfer cyclization under condition A or reductive cyclization under condition B may be realized by a subtle balance of the quantity of the active species.

We next investigated intermolecular radical addition[12] of radical intermediate to an α,β-unsaturated nitrile, electron-deficient olefin in order to clarify the reaction mechanism (Scheme 1). When compound **1** was sub-

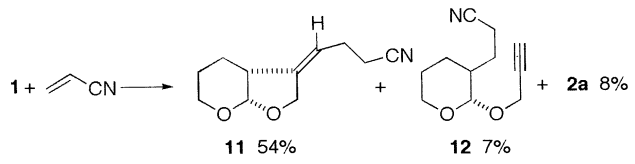
Table 2. Radical cyclizations of iodoalkynes **3–6**





Run	Starting material	Condition	Time (h)	Product	Yield (%)			
					a	**b**	**c**	**d**
1	**3**	A	5	**7**	47	13	0	0
2	**3**	B	27	**7**	0	0	28	28
3	**4A**[a]	A	8	**8A**	41	36	0	0
4	**4B**[a]	A	8	**8B**	66	11	0	0
5	**5**	B	17	**9**		74		
6	**6**	B	17	**10**		75		

[a] Compounds **4A** and **4B** are separable diastereoisomers.



Scheme 1.

jected to condition A in the presence of acrylonitrile (2 equiv.), 5-*exo*-cyclized nitrile **11** was obtained in 54% yield accompanied with compounds **12** and **2a**. This indium-mediated sequential radical cyclization and cross-coupling reaction provide a new methodology.

On the basis of these facts, we propose the following reaction mechanism (Scheme 2). First, indium species (In, In^+ and/or In^{2+}) would induce atom-transfer radical cyclization of iodoalkyne **1** to provide vinyl radical **13**. When there is little reducing agent, radical **13** abstracts the iodine radical from compound **1** to produce vinyl iodides **2a** and **2b**. When there are enough low valent indium species, they would be effective to reduce vinyl radical **13** to provide reductive cyclization product **2c** after protonation to the anionic compound.[13] In the presence of α,β-unsaturated nitrile, intermolecular addition of radical **13** to acrylonitrile occurred. Sequential addition of one electron and a proton gave heterocyclic nitrile **11** in moderate yield.

In summary, we have found a novel indium-mediated[14] atom-transfer cyclization and reductive cyclization of iodoalkynes[15] without the use of conventional radical initiators such as AIBN, Et_3B/O_2, etc. In- and I_2-mediated sequential generation and utilization of radical species is the essential factors in the cross-coupling reaction of iodoalkyne and aryl boronic acid or electron-deficient olefin. This protocol provides a new methodology for multibond formation. The present results will develop a new attractive aspect of indium chemistry.

Acknowledgements

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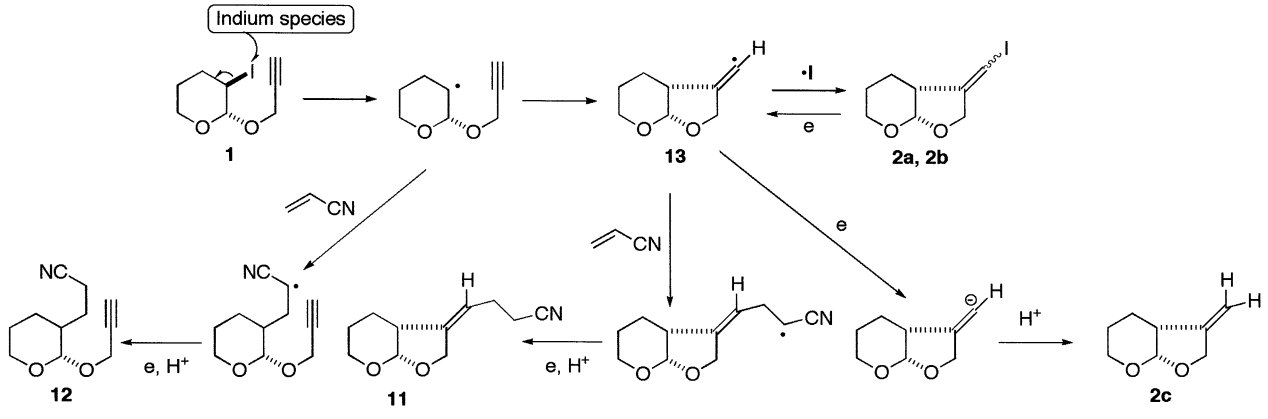

Scheme 2. Plausible mechanism.

986–987; (l) Gansäuer, A. *Synlett* **1998**, 801–809. For $CrCl_2$, see: (m) Takai, K.; Matsukawa, N.; Takahashi, A.; Fujii, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 152–155. For Mn, see: (n) Tang, J.; Shinokubo, H.; Oshima, K. *Tetrahedron* **1999**, *55*, 1893–1904. For Et_3B+$HGaCl_2$, see: (o) Mikami, S.; Fujita, K.; Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1853–1855. For Et_3B+$Cp_2Zr(H)Cl$, see: (p) Fujita, K.; Nakamura, T.; Yoeimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 3137–3138. For H_3PO_2, see: (q) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **2000**, 104–105. For $Ph_4Si_2H_2$+Bu_3SnH, see: (r) Yamazaki, O.; Yamaguchi, K.; Yokoyama, M.; Togo, H. *J. Org. Chem.* **2000**, *65*, 5440–5442. For $(TMS)_3SiH$, see: (s) Chatgilia, C. *Acc. Chem. Res.* **1992**, *25*, 188–194. For cyclohexadienylsilane, see: (t) Studer, A; Amrein, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3080–3082. For tri-2-furanylgermane, see: (u) Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **1999**, 1415–1416.

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8. (a) Freeland, B. H.; Tuck, D. G. *Inorg. Chem.* **1976**, *15*, 475–476. It is well-known that In reacts with I_2 in aromatic solvent under reflux to produce In^+, In^{2+}, and/or In^{3+}. In reacts with I_2 in refluxing aromatic solvent to form InI_3. Solution of InI_3 reacts with excess In under reflux with the gradual precipitation of pure highly crystalline InI_2. On treatment of InI_2 with diethyl ether or other Lewis bases, the insoluble InI is precipitated and the corresponding InI_3–Lewis base adduct formed. (b) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 8214–8219.
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10. α-Isomers **5** and **6** were obtained predominantly (**5**: 75% yield, α:β = 13:1, **6**: 74% yield, α:β = 14:1). See: (a) Audin, C.; Lancelin, J.-M.; Beau, J.-M. *Tetrahedron Lett.* **1988**, *29*, 3691–3694; (b) De Mesmaeker, A.; Hoffmann, P.; Ernst, B. *Tetrahedron Lett.* **1989**, *30*, 57–60.
11. The cyclization products **9** and **10** were deacetylated probably by $InX_n(OMe)_{3-n}$. So reacetylation with acetic anhydride and dimethylaminopyridine in THF has been done.
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13. The cyclization reaction in MeOD under condition B provided the labelled products of **2c**.
14. Recently, Baba et al. reported indium hydride ($InHCl_2$) generated from $NaBH_4$ and $InCl_3$ as a convenient alternative radical reagent to tributyltin hydride. See: Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 906–907.
15. The radical cyclization of iodoalkenes has been now in progress. The interesting results are obtained. We will write as soon as possible about the results.