JOC Article

Indium-Mediated Atom-Transfer and Reductive Radical Cyclizations of Iodoalkynes: Synthesis and Biological Evaluation of HIV-Protease Inhibitors

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Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan, Department of Internal Medicine II, Kumamoto University School of Medicine, Kumamoto, Japan, and Experimental Retrovirology Section, Medicine Branch, Division of Clinical Sciences, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892

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Novel indium-mediated radical cyclization reactions of aliphatic iodoalkynes have been studied. Treatment of iodoalkynes with a catalytic amount of In (0.1 equiv) and I_2 (0.05 equiv) promotes atom-transfer 5-exo cyclization to give five-membered alkenyl iodides. In contrast, reaction with In (2 equiv) and I_2 (1 equiv) yields reductive 5-exo cyclization products via the same 5-exo cyclization. Both processes are most likely initiated by low-valent indium species. To demonstrate versatility of these reactions, optically active HIV protease inhibitors were synthesized by this reductive cyclization method. Among them, several products, which contain a hydroxyethylamine dipeptide isostere as a transition state-mimicking substructure, proved to possess potent activity (IC_{50} = 5−39 nM) against a wide spectrum of HIV strains, including multidrug-resistant variants.

Introduction

The use of radicals in organic synthesis has increased over the last two decades.[1] Tributyltin hydride has played an important role despite its neurotoxicity and the difficulty of complete removal of tin species from the reaction mixture.[2] Therefore, substantial efforts have been invested in the development of more convenient and useful reagents to replace tributyltin hydride.[3] Indium (In)-mediated reactions have gained increasing popularity over the past decade as environmentally benign[4] tools in organic synthesis.[5] Since the first ionization potential of In is 5.8 eV, which is as low as those of Li and Na, it would be easy for In to promote SET (single-electron-transfer) processes. In addition, In is comparatively stable in air and, unlike many metals, has no apparent toxicity.[6] We report herein the indium-mediated atom-transfer 5-exo cyclization (Kharasch-type reaction) and reductive 5-exo cyclization reaction of aliphatic iodoalkynes. In contrast to reductive radical cyclizations,[3,4c] there are few reports on atom-transfer radical cyclizations.[7,8]

We also have synthesized optically active furopyran P_2-ligands that are potent against a variety of HIV strains, including multidrug-resistant variants, by combining optically active hexahydrofuropyran derivatives, synthesized using our indium-mediated reductive cyclization method, and substructural units of previously published HIV protease inhibitors.

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(1) (a) Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072−3082. (b) Hirao, T. *Synlett* **1999**, 175−181. (c) Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **2002**, 674−686.

(2) (a) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH Verlagsgesellschaft mbH: Weinheim, 1996. (b) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Organic Reactions*; John Wiley & Sons: New York, 1996; Vol. 48, pp 301−856.

(3) SmI_2: Curran, D. P.; Totleben, M. J. *J. Am. Chem. Soc.* **1992**, *114*, 6050−6058. PhLi: Bailey, W. F.; Carson, M. W. *J. Org. Chem.* **1998**, *63*, 9960−9967. Et_2Zn: Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 5743−5753. Cobaloxime: Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 5374−5375. Grignard reagent: Inoue, A.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2000**, *2*, 651−653. Cp_2TiCl_2 + Grignard reagent: Nii, S.; Terao, J.; Kambe, N. *J. Org. Chem.* **2000**, *65*, 5291−5297. Cp_2TiCl: Gansäuer, A. *Synlett* **1998**, 801−809. $CrCl_2$: Takai, K.; Matsukawa, N.; Takahashi, A.; Fujii, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 152−155. Mn: Tang, J.; Shinokubo, H.; Oshima, K. *Tetrahedron* **1999**, *55*, 1893−1904. Et_3B + $HGaCl_2$: Mikami, S.; Fujita, K.; Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1853−1855. Et_3B + $Cp_2Zr(H)Cl$: Fujita, K.; Nakamura, T.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2001**, *123*, 3137−3138. H_3PO_2: Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **2000**, 104−105. $Ph_4Si_2H_2$ + Bu_3SnH: Yamazaki, O.; Yamaguchi, K.; Yokoyama, M.; Togo, H. *J. Org. Chem.* **2000**, *65*, 5440−5442. $(TMS)_3SiH$: Chatgilialoglu, C. *Acc. Chem. Res.* **1992**, *25*, 188−194. Cyclohexadienyl-silane: Studer, A.; Amrein, S. *Angew. Chem. Int. Ed.* **2000**, *39*, 3080−3082. Tri-2-furanylgermane: Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **1999**, 1415−1416.

(4) (a) Li, C.-J. *Chem. Rev.* **1993**, *93*, 2023−2035. (b) Li, C.-J. *Tetrahedron* **1996**, *52*, 5643−5668. (c) Paquette, L. A. In *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Anastas, P., Williamson, T., Eds.; Oxford University Press: New York, 1998.

(5) (a) Kang, S.; Jang, T.-S.; Keum, G.; Kang, S. B.; Han, S.-Y.; Kim, Y. *Org. Lett.* **2000**, *2*, 3615−3617. (b) Yanada, R.; Kaieda, A.; Takemoto, Y. *J. Org. Chem.* **2001**, *66*, 7516−7518 and references therein. (c) Inoue, K.; Sawada, A.; Shibata, I.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 906−907. (d) Miyabe, H.; Ueda, M.; Nishimura, A.; Naito, T. *Org. Lett.* **2002**, *4*, 131−134. (e) Miyabe, H.; Nishimura, A.; Ueda, M.; Naito, T. *Chem. Commun.* **2002**, 1454−1455. (f) Tan, K. T.; Chng, S. S.; Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, *2958*−2963.

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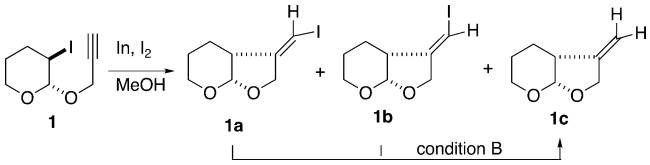
TABLE 1. Radical Cyclization of Iodoalkyne 1[a]



run	condition	In (equiv)	I_2 (equiv)	time (h)	yield (%) 1a	1b	1c	total
1		1	0.0	17	46	4	5	55
2	A	1	0.5	5	76	4	3	83
3		0.1	0.05	32	69	8	3	80
4	B	2	1.0	17	0	0	85	85

[a] Conditions A: **1** (2 mmol), In (2 mmol), I_2 (1 mmol), MeOH (4 mL). Conditions B: **1** (2 mmol), In (4 mmol), I_2 (2 mmol), MeOH (4 mL).

Atom-Transfer Cyclizations and Reductive Cyclizations of Iodoalkynes. We first investigated cyclization reactions of iodoalkyne **1** under various conditions. The results are summarized in Table 1. Iodoalkyne **1** was treated with In (1 equiv) in MeOH at room temperature to give 5-exo cyclized atom-transfer products **1a** (*Z*) and **1b** (*E*) in 50% yield (*Z*:*E* = 11.5:1, run 1). The *Z*-selectivity is in agreement with results reported by Curran et al.[9] They analyzed the formation of (*Z*)- and (*E*)-vinyl iodides with the aid of a Curtin−Hammett kinetic scheme. In the case of compound **1**, high stereoselectivity was observed and the cis-fused products **1a**−**c** were obtained as shown by NMR spectroscopy ($^1H-^1H$ NOESY and NOE spectra). Trans-fused products and 6-endo cyclization products were not observed. It is well-known that In reacts with I_2 in aromatic solvent under reflux to produce In^{1+}, In^{2+}, and In^{3+}.[10] I_2 (0.5 equiv) was therefore added to In (1 equiv) in MeOH (condition A). The reaction proceeded smoothly to yield atom-transfer products **1a** and **1b** in 80% yield within 5 h (19:1, run 2). This atom-transfer-type reaction could be initiated by a catalytic amount of In and I_2. The reaction using In (0.1 equiv) and I_2 (0.05 equiv) gave the expected iodoolefins in 77% yield (**1a**:**1b** = 8.6:1, run 3), but the reaction took a long time.

Next, we used an excess amount of In. In (2 equiv) and I_2 (1 equiv) (condition B) gave only a reductive 5-exo cyclization product **1c** in 85% yield (run 4). Compound **1c** was also obtained from atom-transfer products **1a** and **1b** in 71% yield under condition B. Atom-transfer radical cyclization and reductive radical cyclization reactions were achieved for the first time by only controlling the quantities of In and I_2.

Next, we examined radical cyclizations to various aliphatic iodoalkynes (**2**−**9**) under conditions A and B. As can be seen from Table 2, iodoalkynes **2** and **4**−**6**[11] predominantly gave atom-transfer cyclization products **2a**, **4a**, **5a**, and **6a**[11,12] under conditions A and gave reductive cylization products **2b**, **4b**,[13] **5b**,[14] and **6b**[15] under conditions B (runs 1 and 3−5). Even under conditions A, the use of substrates **3** and **7** bearing an electron-delocalizing phenyl group on the sp carbon resulted in smooth reductive radical cyclization reactions to produce compounds **3b**[16] and **7b** (runs 2 and 6). In general, it is thought that the reduction of vinyl radical intermediates (Scheme 1, **D**) to a vinyl-indium compound (**E**) is slower than the addition of iodine from compound **1** to give atom-transfer cyclization products (**1a** and **1b**) under conditions A. On the other hand, vinylic radicals bearing phenyl groups (electrophilic radicals) might result in subsequent rapid electron transfer to produce a reductive radical cyclization product even under condition A. The atom-transfer cyclization or reductive cyclization may be realized by a subtle balance of reaction rates. We tried this reductive cyclization as an approach to synthesis of bicyclic sugars via radical cyclization (runs 7 and 8). Bicyclic sugars are interesting compounds because of their utility as building blocks for synthesis of natural products and because of their biological activities.[17] The sugar iodides **8** and **9** were prepared from glucal and galactal with propargyl alcohol in the presence of *N*-iodosuccinimide in CH_3CN.[18] Cyclization reactions with indium were carried out under conditions B using compounds **8** and **9**.[19] The reductive cyclization products **8b** and **9b** were obtained in 74 and 75% yields, respectively.

Intermolecular coupling reactions of alkyl iodide with electron-deficient olefins are well-known. To confirm the presence of radical intermediate **D** (Scheme 1), we investigated In-mediated cyclization of **1** in the presence of electron-deficient olefins such as α,β-unsaturated

(6) (a) Nakajima, M.; Takahashi, H.; Sasaki, M.; Kobayashi, Y.; Ohno, Y.; Usami, M. *Teratog., Carcinog., Mutagen.* **2000**, *20*, 219−227. (b) Nakajima, M.; Sasaki, M.; Kobayashi, Y.; Ohno, Y.; Usami, M. *Teratog., Carcinog., Mutagen.* **1999**, *19*, 205−209.

(7) (a) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1998**, *63*, 8604−8605. (b) Chakraborty, A.; Marek, I. *Chem. Commun.* **1999**, 2375−2376. (c) Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 11041−11047.

(8) Atom-transfer cyclization reactions with Bu_3SnH have been reported. (a) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489−2490. (b) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265−6276.

(9) Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1989**, *111*, 6265−6276.

(10) (a) Freeland, B. H.; Tuck, D. G. *Inorg. Chem.* **1976**, *15*, 475−476. In reacts with I_2 in a refluxing aromatic solvent to form InI_3. A solution of InI_3 reacts with excess In under reflux with 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 is formed. (b) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 8214−8219.

(11) Haaima, G.; Hanton, L. R.; Lynch, M.-J.; Mawson, S. D.; Routledge, A.; Weavers, R. T. *Tetrahedron* **1994**, *50*, 2161−2174.

(12) Haaima, G.; Lynch, M.-J.; Routledge, A.; Weavers, R. T. *Tetrahedron* **1993**, *49*, 4229−4252.

(13) Okuma, K.; Kamahori, Y.; Tsubakihara, K.; Yoshihara, K.; Tanaka, Y.; Shioji, K. *J. Org. Chem.* **2002**, *67*, 7355−7360.

(14) Trost, B. M.; Marrs, C. M. *J. Am. Chem. Soc.* **1993**, *115*, 6636−6645.

(15) Haaima, G.; Lynch, M.-J.; Routledge, A.; Weavers, R. T. *Tetrahedron* **1991**, *47*, 5203−5214.

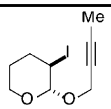
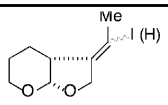
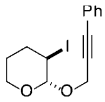
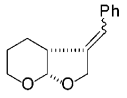
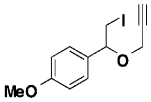
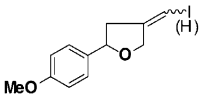
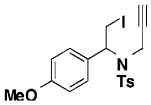
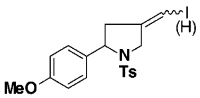
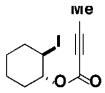
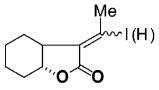
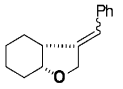
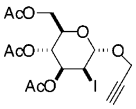
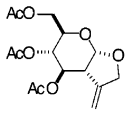
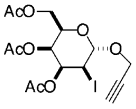
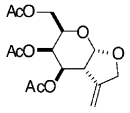
(16) Torii, S.; Inokuchi, T.; Yukawa, T. *J. Org. Chem.* **1985**, *50*, 5875−5877.

(17) Recently, bicyclic sugars have been prepared extensively with Bu_3SnH. (a) Ferrier, R. J.; Petersen, P. M. *Tetrahedron* **1990**, *46*, 1−11. (b) De Mesmaeker, A.; Hoffman, P.; Winkler, T.; Waldner, *Synlett* **1990**, 201−204. (c) Moufid, N.; Chapleur, Y.; Mayon, P. *J. Chem. Soc., Perkin Trans. 1* **1992**, 991−998. (d) Lesueur, C.; Nouguier, R.; Bertrand, M. P.; Hoffmann, P.; De Masmaeker, *Tetrahedron* **1994**, *50*, 5369−5380. (e) Mayer, S.; Prandi, J.; Bamhaoud, T.; Bakkas, S.; Guillou, O. *Tetrahedron* **1998**, *54*, 8753−8770. (f) Yamazaki, O.; Yamaguchi, K.; Yokoyama, M.; Togo, H. *J. Org. Chem.* **2000**, *65*, 5440−5442.

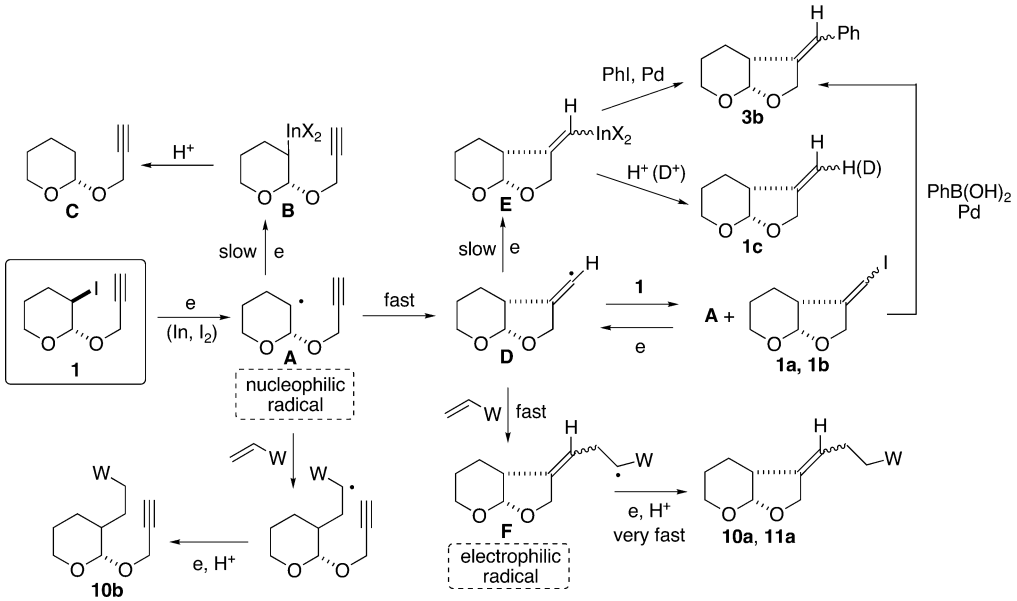
(18) α-Isomers **8** and **9** were obtained predominantly (**8**: 75% yield, α: β = 13:1; **9**: 74% yield, α: β = 14:1). (a) Audin, C.; Lancelin, J.-M.; Beau, J.-M. *Tetrahedron Lett.* **1988**, *29*, 3691−3694. (b) De Mesmaeker, A.; Hoffmann, P.; Ernst, B. *Tetrahedron Lett.* **1989**, *30*, 57−60.

(19) Cyclization products **8b** and **9b** were probably deacetylated by $InX_n(OMe)_{3-n}$. Thus, reacetylation with acetic anhydride and (dimethylamino)pyridine in THF was done.

TABLE 2. Radical Cyclizations of Various Iodoalkynes 2−9

Run	Substrate	Time (h)	Condition	Solvent	Product	Yield (%) Atom-transfer **a**	(*E*/*Z* ratio) Reductive **b**
1	**2** 	5	A	MeOH	**2a** 	60 (1 : 3.6)	0
		5	B	MeOH	**2b**	0	65 (1 : 1)
2	**3** 	8	A	MeOH	**3b** 	0	73 (8.1 : 1)
3	**4** 	18	A	MeOH	**4a** 	67 (1 : 1.3)	0
		48	B	DMF	**4b**	0	86
4	**5** 	18	A	MeOH	**5a** 	70 (1 : 1.5)	8
		48	B	DMF	**5b**	0	82
5	**6** 	24	A	DMF	**6a** 	41 (1 : 3.4)	0
		48	B	DMF	**6b**	0	21 (1.3 : 1)
6	**7** 	30	A	MeOH	**7b** 	0	57 (2 : 1)
7	**8** 	20	B	DMF	**8b** 	0	74
8	**9** 	20	B	DMF	**9b** 	0	75

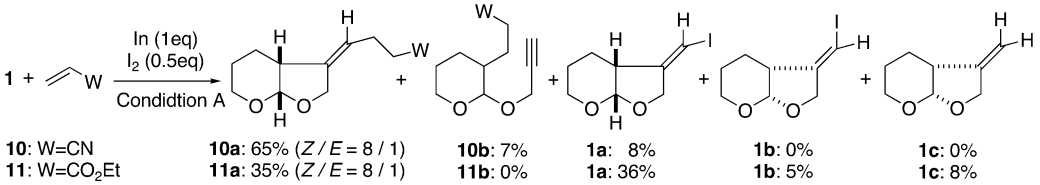
SCHEME 1. Mechanism of Indium-Mediated Radical Cyclization Reaction



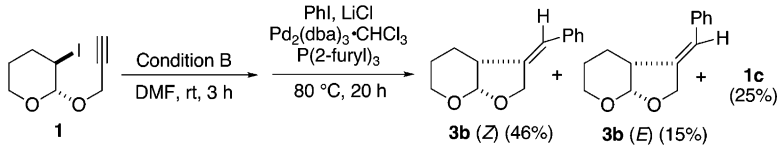
nitrile and ester in a protic solvent, MeOH (Scheme 2). When **1** was subjected to conditions A with acrylonitrile or ethyl acrylate (2 equiv), the desired compounds **10a** or **11a** were obtained in 65 and 35% yields, respectively, with or without compounds **10b**, **1a**, **1b**, and **1c**.

Furthermore, we carried out palladium-catalyzed cross-coupling reaction (Oshima's reaction)[21] in order to confirm that vinyl indium intermediate **E** is generated from compound **1** (Scheme 3). After treatment of compound **1** under conditions B in DMF, iodobenzene (0.9 equiv),

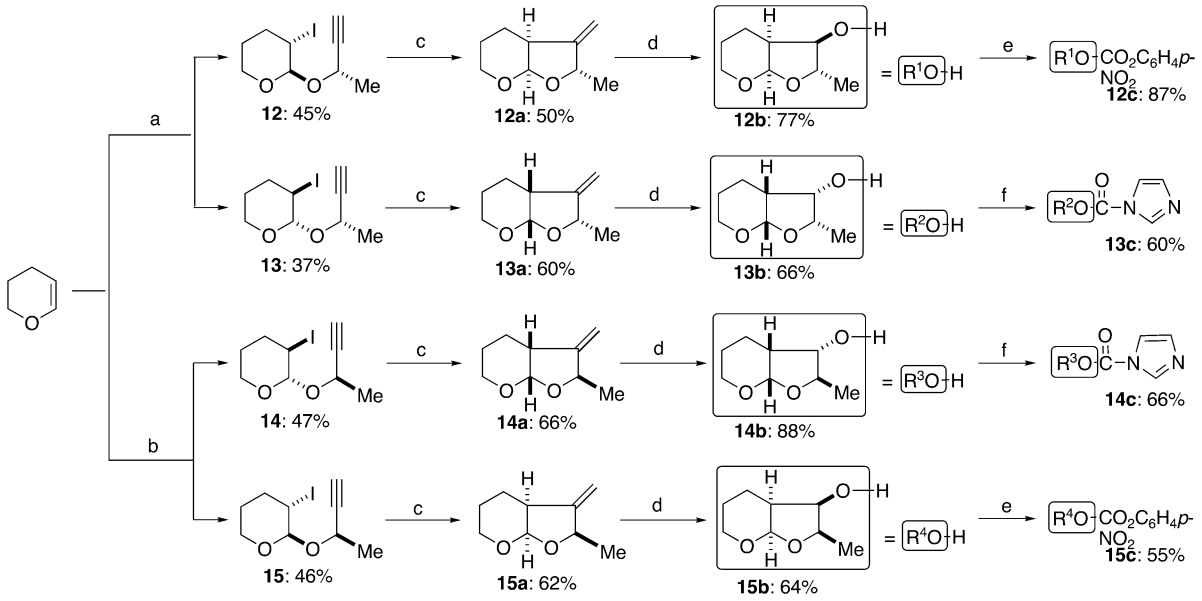
SCHEME 2. Intermolecular 1,4-Addition to Electron-Deficient Olefins



SCHEME 3. Application to Oshima's Reaction



SCHEME 4. Synthesis of Optically Active Bicyclic Ligands[a]



[a] Conditions: (a) *N*-Iodosuccinimide, (*S*)-(−)-3-butyn-2-ol, CH_2Cl_2, 0 °C-rt. (b) *N*-Iodosuccinimide, (*R*)-(+)-3-butyn-2-ol, CH_2Cl_2, 0 °C−rt. (c) In, I_2, MeOH, rt. (d) (1) O_3, MeOH, rt; (2) $NaBH_4$, rt. (e) 4-Nitrophenyl chloroformate, Et_3N, CH_2Cl_2, rt. (f) 1,1′-Carbonyldiimidazole, KOH (cat), toluene.

palladium−trifurylphosphine complex, prepared from $Pd_2(dba)_3$•$CHCl_3$ (0.02 equiv) and trifurylphosphine (0.12 equiv) in THF, and lithium chloride[22] (3 equiv) were added to the reaction mixture. Then, the reaction mixture was heated at 80 °C for 20 h to provide the corresponding coupling products **3b** in 61% yield (*Z*:*E* = 3:1) accompanied with the reductive cyclization product **1c** (25% yield). The geometrical chemistry of compounds **3b** (*Z* and *E*) was determined by NOE experiments of ^{1}H NMR. The results showed the presence of vinyl indium intermediate **E**.

On the basis of the above-described results, we propose the following reaction mechanism (Scheme 1). Treatment of compound **1** with low-valent indium (In, In^{1+}, and/or In^{2+}), produced by In and I_2 in MeOH, provides alkyl radical **A** (nucleophilic radical). In general, it is not easy for radical **A** to be reduced to compound **C** through alkyl indium intermediate **B**.[23] Alkyl radical **A** smoothly undergoes a radical cyclization reaction to produce vinyl radical **D**. This radical is readily reduced to vinyl indium compound **E**[24] when there are enough low-valent indium species. Protonation of **E** produces **1C**, whereas the Oshima reaction of **E** produces **3b**. When there is only a small amount of reducing agent, radical **D** abstracts the iodine radical from compound **1** to produce vinyl iodides **1a** and **1b** and to reproduce alkyl radical **A**. In the presence of α,β-unsaturated compounds, intermolecular addition of radical **D** to the activated olefins occurred to give radical **F** (electrophilic radical). Sequential addition of one electron and one proton proceeded smoothly to give

(20) (a) Shono, T.; Nishiguchi, I.; Sasaki, M. *J. Am. Chem. Soc.* **1978**, *100*, 4314−4315. (b) Luche, J. L.; Allavena, C. *Tetrahedron Lett.* **1988**, *29*, 5369−5372. (c) Blanchard, P.; Da Silva, A. D.; El Kortbi, M. S.; Fourrey, J.-L.; Robert-Géro, M. *J. Org. Chem.* **1993**, *58*, 6517−6519. (d) Takai, K.; Ueda, T.; Ikeda, N.; Moriwake, T. *J. Org. Chem.* **1996**, *61*, 7990−7991.

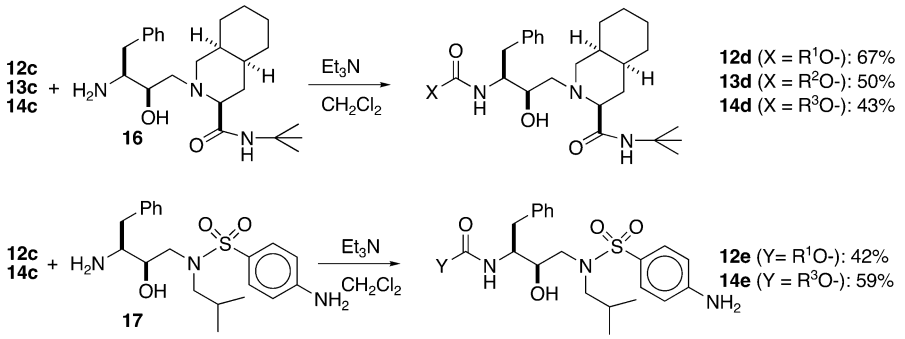
(21) Takaki, K.; Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K. *Org. Lett.* **2001**, *3*, 1997−1999.

(22) Hirashita, T.; Hayashi, Y.; Mitsui, K.; Araki, S. *J. Org. Chem.* **2003**, *68*, 1309−1313.

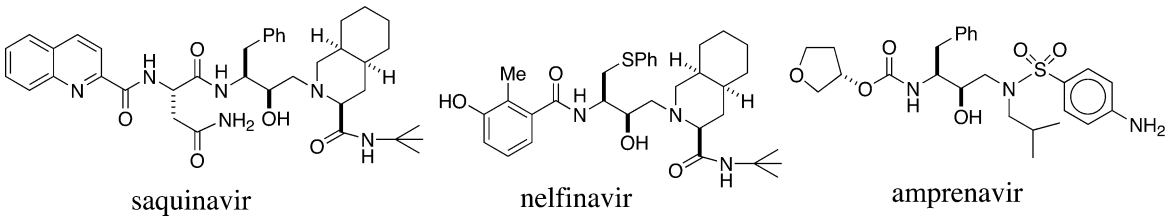
(23) (a) Nuget, W. A.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1988**, *110*, 8561−8562. (b) Curran, D. P.; Fevig, T. L.; Totleben, M. J. *Synlett* **1990**, 773−774.

(24) Quenching with DCl in MeOD under Conditions B yielded the deuterated compound **1c** (89% D, *Z*:*E* = 19:1).

SCHEME 5. Synthesis of Various Inhibitors with Bicyclic Ethers as P_2 Ligands



SCHEME 6. Structures of Saquinavir, Nelfinavir, and Amprenavir



heterocyclic compounds **10a** and **11a** in moderate yields. The reduction of an alkenyl radical **D** to an alkenyl indium compound **E** is slower than 1,4-addition of the radical **D** to α,β-unsaturated compounds. However, one-electron transfer to the resulting radical **F** having electron-withdrawing groups proceeds faster than addition to a different unsaturated bond.

Synthesis of Optically Active HIV Protease Inhibitors and Biological Evaluation. Ghosh et al.[25] reported that stereochemically defined hexahydrofuropyrans play a crucial role as the replacement of asparagine side chain of Ro 31−8959-based HIV protease inhibitors.[26] They also reported that a fused bicyclic ligand with oxygens properly positioned could effectively form a hydrogen bond to the NH of Asp 29 and 30 residues corresponding to the quinardic amide−asparagine amide fragment of the Ro 31−8959 inhibitor.[27]

We applied the indium-mediated reductive cyclization to the synthesis of optically active hexahydrofuropyran derivatives as HIV protease inhibitors with novel P_2-pharmacophores (Schemes 4 and 5). As shown in Scheme 4, the reaction of dihydropyran with *N*-iodosuccinimide and (*S*)- or (*R*)-3-butyn-2-ol gave optically active iodo ethers **12**−**15** in good yields. Radical cyclizations of **12**−**15** with In and I_2 under conditions B afforded the bicyclic acetals **12a**−**15a** (50−66%). Ozonolytic cleavage followed by the reduction of the resulting ketones with sodium borohydride in methanol at −78 °C furnished stereoselectively the optically active endo alcohols **12b**−**15b** in 64−88% yields. The stereochemical assignments of these alcohols **12b**−**15b** were determined by NOE experiments of ^{1}H NMR. The reaction of hexahydrofuropyran ligands **12b** and **15b** with 4-nitrophenyl chloroformate and triethylamine in methylene chloride afforded the active carbonates **12c** and **15c** in good yields. The compounds **13c** and **14c** could not be obtained by the same reaction. We therefore used 1,1′-carbonyldiimidazole instead of 4-nitrophenyl chloroformate. The ligands **13b** and **14b** with 1,1′-carbodiimidazole and potassium hydroxide in toluene afforded the active carbonates **13c** and **14c** in good yields.

Novel optically active hydroxyethylamine isosteres **12d**−**14d** bearing decahydroisoquinoline unit **16**[28,29] and **12e** and **14e** bearing sulfonamide unit **17**[30] were synthesized according to Ghosh's methods[31] (42−67% yields).

TABLE 3. Anti-HIV Activities, Cytotoxicities, and HIV Protease Inhibitory Activities of the Synthetic Compounds

run	compd	IC_{50} (nM)[a]	CC_{50} (μM)[b]	SI[c]
1	**12d**	39 ± 15	36.4 ± 3.5	930
2	**13d**	6 ± 2	32.9 ± 3.3	5480
3	**14d**	5 ± 3	27.8 ± 2.1	5560
4	**12e**	26 ± 4	30.3 ± 4.9	1170
5	**14e**	30 ± 10	40.0 ± 5.2	1330
6	saquinavir	17 ± 3	11 ± 3	650
7	amprenavir	36 ± 11	>100	>2780

[a] IC_{50} values are based on the inhibition of HIV-induced cytopathogenicity in MT-2 cells. [b] CC_{50} values are based on the reduction of the viability of mock-infected MT-2 cells (±1 standard deviation). All values represent the means from at least three independent experiments. [c] Selectivity index (SI) is shown as CC_{50}/IC_{50}.

(25) Ghosh, A. K.; Kincaid, J. F.; Walters, D. E.; Chen, Y.; Chaudhuri, N. C.; Thompson, W. J.; Culberson, C.; Fitzgerald, P. M. D.; Lee, H. Y.; McKee, S. P.; Munson, P. M.; Duong, T. T.; Darke, P. L.; Zugay, J. A.; Schleif, W. A.; Axe., M. G.; Lin, J.; Huff, J. R. *J. Med. Chem.* **1996**, *39*, 3278−3290.

(26) Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. V.; Craig, J. C.; Duncan, I. B.; Galpin, S. A.; Handa, B. K.; Kay, J.; Krohn, A.; Lambert, R. W.; Merrett, J. H.; Mills, J. S.; Parkes, K. E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L.; Thomas, G. J.; Machin, P. J. *Science* **1990**, *248*, 358−361.

(27) (a) Ghosh, A. K.; Thompson, W. J.; Holloway, M. K.; Mckee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 2300−2310. (b) Thompson, W. J.; Ghosh, A. K.; Holloway, M. K.; Lee, H. Y.; Munson, P. M.; Schwering, J. E.; Wai, J. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Am. Chem. Soc.* **1993**, *115*, 801−803.

(28) Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. V.; Craig, J. C.; Duncan, I. B.; Galpin, S. A.; Handa, B. K.; Kay, J.; Krohn, A.; Lambert, R. W.; Merrett, J. H.; Mills, J. S.; Parkes, K. E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L.; Thomas, G. J.; Machin, P. J. *Science* **1990**, *248*, 358−361.

TABLE 4. Anti-HIV Activities of the Synthetic Compounds against HIV-1 Clinical Isolates

			IC_{50} (nM) (fold change)[a] MDR[b]		
run	compd	$HIV_{ERS104pre}$	HIV_{TM}	HIV_{MM}	HIV_{JSL}
1	**12d**	230 ± 30	>1000 (>4 x)	>1000 (>4 x)	NT
2	**13d**	24 ± 0.1	>1000 (>42 x)	>1000 (>42 x)	NT
3	**14d**	33 ± 5	>1000 (>32 x)	>1000 (>32 x)	NT
4	**12e**	24 ± 4	240 ± 190 (10 x)	100 ± 80 (5 x)	290 ± 70 (12 x)
5	**14e**	34 ± 13	260 ± 190 (8 x)	340 ± 20 (10 x)	410 ± 80 (11 x)
6	saquinavir	19 ± 4	230 ± 20 (12 x)	320 ± 2 (17 x)	550 ± 160 (29 x)
7	amprenavir	20 ± 3	480 ± 120 (24 x)	530 ± 80 (27 x)	800 ± 70 (40 x)

[a] IC_{50} values are based on inhibition of HIV p24 antigen expression in PBMC. All values represent the means from at least three independent experiments. Data without standard deviations are derived from the value for one experiment. [b] Amino acid substitutions in the protease-encoding region are shown in Supporting Information.

Among the compounds synthesized by using our method, **12d**−**14d** each have a decahydroisoquinoline unit, which is present in saquinavir[30,32] and nelfinavir,[33] at the $P_{1'}$−$P_{2'}$ position (Scheme 6). Compounds **12e** and **14e** also each have a sulfonamide unit, which is present in amprenavir,[34] at the $P_{1'}$−$P_{2'}$ position.

The anti-HIV activity of compounds **12d**−**14d**, **12e**, and **14e** was determined on the basis of inhibition of HIV-1-induced cytopathogenicity in MT-2 cells (described in Supporting Information).[35] Compounds **13d** and **14d** showed potent anti-HIV activity (Table 3, runs 2 and 3). They proved to be more potent than saquinavir (run 6) and amprenavir (run 7), which have currently been used clinically. It was noted that compounds **12d**−**14d**, **12e**, and **14e** (runs 1−5) exhibited greater selectivity indices (SIs) than saquinavir (run 6).

Next, we determined the anti-HIV activity of compounds **12d**−**14d**, **12e**, and **14e** against multidrug-resistant (MDR) strains as measured by the inhibition of HIV p24 antigen expression in peripheral blood mononuclear cells (PBMC) (described in Supporting Information).[35] The efficacy against $HIV_{ERS104pre}$ and three MDR strains of compounds **12e** and **14e** was similar to that of saquinavir and amprenavir (Table 4, runs 4−7).

Conclusion

In summary, we have found a novel indium-mediated atom-transfer radical cyclization reaction using a catalytic amount of In with I_2 and reductive radical cyclization reaction using an excess amount of In and I_2 without the use of a radical initiator such as AIBN or Et_3B/O_2. The protocol described above provides a new methodology for multibond formation and enables division of geometrical isomers. Novel HIV protease inhibitors, **12d**−**14d**, **12e**, and **14e**, were synthesized using the indium-mediated reductive radical cyclization method. They all inhibited HIV-induced cytopathogenicity in MT-2 cells and were all as effective as saquinavir and amprenavir against MDR strains. The present results will be useful for developing new attractive aspects of indium chemistry.

Experimental Section

General. Indium-Mediated Atom-Transfer Cyclization of Iodoalkyne (1) (condition A). The mixture of iodoalkyne **1** (2 mmol), In (2 mmol), and I_2 (1 mmol) in MeOH (4 mL) was stirred for 5 h at room temperature under nitrogen. MeOH was evaporated, and the residue was filtered with Celite using chloroform as an eluent. The filtrate was concentrated. The residue was purified by flash silica gel column chromatography to afford compound **1a** (404 mg, 76%), **1b** (21 mg, 4%), and **1c** (8 mg, 3%).

Indium-Mediated Reductive Radical Cyclization of Iodoalkyne (1) (condition B). The mixture of iodoalkyne **1** (2 mmol), In (4 mmol), and I_2 (2 mmol) in MeOH (4 mL) was stirred for 17 h at room temperature under nitrogen. MeOH was evaporated, and the residue was filtered with Celite using chloroform as an eluent. The filtrate was concentrated. The residue was purified by flash silica gel column chromatography to afford compound **1c** (238 mg, 85%) as an yellow oil.

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

JO035482M

(29) Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656−3664.

(30) Ghosh, A. K.; Kincaid, J. F.; Cho, W.; Walters, D. E.; Krishnan, K.; Hussain, K. A.; Koo, Y.; Cho, H.; Rudall, C.; Holland, L.; Buthod, J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 687−690.

(31) Kaldor, S. W.; Kalish, V. J.; Davies, J. F., II; Shetty, B. V.; Fritz, J. E.; Appelt, K.; Burgess, J. A.; Campanale, K. M.; Chirgadze, N. Y.; Clawson, D. K.; Dressman, B. A.; Hatch, S. D.; Khalil, D. A.; Kosa, M. B.; Lubbehusen, P. P.; Muesing, M. A.; Patick, A. K.; Reich, S. H.; Su, K. S.; Tatlock, J. H. *J. Med. Chem.* **1997**, *40*, 3979−3985.

(32) Ghosh, A. K.; Thompson, W. J.; McKee, S. P.; Duong, T. T.; Lyle, T. A.; Chen, J. C.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 292−294.

(33) Martin, J. A.; Redshaw, S. Eur. Pat. Appl. EP 432,695, June 19, 1991.

(34) Ghosh, A. K.; Thompson, W. J.; Holloway, M. K.; Mckee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 2300−2310.

(35) Koh, Y.; Nakata, H.; Maeda, K.; Ogata, H.; Bilcer, G.; Devasamudram, T.; Kincaid, J. F.; Boross, P.; Wang, Y. F.; Tie, Y.; Volarath, P.; Gaddis, L.; Harrison, R. W.; Weber, I. T.; Ghosh, A. K.; Mitsuya, H. *Antimicrob. Agents Chemother.* **2003**, *47*, 3123−3129.