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Indium-mediated radical cyclization of iodoalkenes and iodoalkynes with and without allylic and propargylic leaving groups

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Abstract—Upon treatment with In and I_2, mono-substituted alkenes having an iodine substituent at the δ-position of the tether gave the corresponding iodinated cyclic compounds, whereas di- and tri-substituted alkenes gave the corresponding hydroxylated cyclic compounds. Alkenes bearing leaving groups at the allylic position were transformed only to the corresponding vinyl substituted cyclic compounds. On the other hand, alkynes bearing good leaving groups at the propargylic position gave allenic products selectively.

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 the complete removal of the tin species from the reaction mixture.[2] For this reason, there is a requirement for more convenient and useful radical reducing reagents to replace tributyltin hydride.[3] Indium (In)-mediated reactions have gained increasing popularity over the past decade as useful tools in organic synthesis[4] under environmentally benign conditions.[5] The first ionization potential of In is 5.8 eV, and is as low as that of Li and Na. Therefore, it is 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 not apparent.[6] We have already reported the indium-mediated atom-transfer 5-*exo*-cyclization and reductive 5-*exo*-cyclization of iodoalkynes by the combination of In and I_2.[7] Herein we report novel indium-mediated 5-*exo* radical cyclization of iodoalkenes and iodoalkynes with and without allylic and propargylic leaving groups.

First, we studied the radical cyclization reaction of iodoalkene **1a** under various conditions. The results are summarized in Table 1. Compound **1a** was treated with In (2 equiv) and I_2 (1 equiv) in MeOH to give high polar compound **2a**.[8] We first expected to obtain a reductive 5-*exo*-cyclized alkane (**3d**: $R^1 = R^2 = R^3 = H$). Because heterocyclic alkenes, reductive 5-*exo*-cyclized products, were obtained when we treated iodoalkynes under similar conditions.[7] Furthermore, Baba and co-worker's reported that the same iodoalkenes gave the reductive 5-*exo*-cyclized alkanes using $InCl_3$–$NaBH_4$ system.[9] The NMR experiment of compound **2a** revealed that it has a methylene unit and not a methyl substituent. Without additives, compound **2a** remained unchanged. The addition of 1 N hydrochloric acid, the reaction proceeded to give alkyl iodide **3a** as a mixture of stereoisomers (α/β = 8:1) (entry 1). The α/β-stereoselectivity of compound **3d** ($R^1 = R^2 = R^3 = H$) has been explained with molecular mechanics calculations by Beckwith and Page.[10] Our results are in agreement with their findings. In the presence of lithium chloride, this reaction did not occur (entry 2).[9] Sodium hydroxide (1 N) is also effective (entry 3). Under continuous bubbling of air or pure oxygen, this reaction did not proceed.[11] The reaction proceeded more effectively with 1 N sodium hydroxide–hydrogen peroxide or just hydrogen peroxide (entries 4 and 5). The same radical cyclization procedure could be successfully applied to other di- and tri-substituted olefins (**1b** and **c**) (entries 6 and 7). It was surprising that the products were obtained as hydroxylated compounds **3b**

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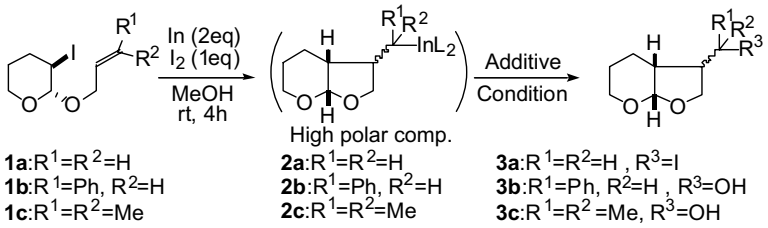
Table 1. 5-*exo*-Radical cyclization of aliphatic iodoalkenes



Entry	1	Condition		Additive (2 equiv)	3[a]	Yield (%)
		Temperature (°C)	Time			
1	**a**	80	18 h	1 N HCl	**a**	63
2	**a**	80	20 h	LiCl	**a**	0
3	**a**	80	18 h	1 N NaOH	**a**	50
4	**a**	Rt	20 min	1 N NaOH, H_2O_2	**a**	73
5	**a**	Rt	20 min	H_2O_2	**a**	75
6	**b**	0	20 min	H_2O_2	**b**	68
7	**c**	0	20 min	H_2O_2	**c**	71

[a] **3a**: ($\alpha/\beta = 8:1$), **3b**: dr (7:5:2:1), **3c**: ($\alpha/\beta = 2:1$).

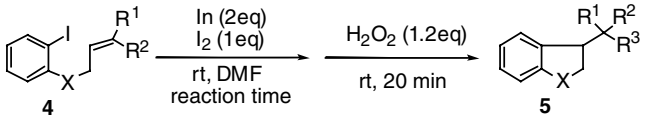
and **c** in good yields, instead of iodinated compounds. The role of hydrogen chloride, sodium hydroxide, sodium hydroxide-hydrogen peroxide, and just hydrogen peroxide is perhaps via coordination to the indium atom in the highly polar compounds **2** to form indium ate complexes (indates), whose In–C bond is expected to be more reactive. The reason why the products from mono-, di-, and tri-substituted olefins were different and the role of the additives are unclear at present.

Next, we applied this 5-*exo*-radical cyclization procedure induced In and I_2 to mono- and tri-substituted aromatic iodoalkenes (Table 2). Various reaction conditions were examined because the radical cyclization of aromatic compounds only proceeded slowly. We focused on the radical cyclization reactions in solvents other than MeOH. When DMF was used, this reaction proceeded smoothly. As expected, mono-substituted aromatic olefins **4a** and **c** gave heteroaromatic iodoalkanes **5a** and **c** in good yields after treatment with hydrogen peroxide (entries 1 and 3). On the other hand, tri-substituted olefins **4b** and **d** gave heteroaromatic tertiary hydroxy alkanes **5b** and **d** in high yields (entries 2 and 4). The product **5c** is a model compound of a CBI (enhanced and simplified analogue of the CC-1065 and Duocarmycin) precursor, which Boger et al. has recently synthesized.[12]

Next we applied this radical cyclization procedure to the iodoalkenes **6a**–**e** bearing leaving groups at the allylic position: Table 3 shows the results. All compounds **6a**–**e** gave the same 5-*exo*-reductive radical cyclization product **7** in good yield through perhaps an E1cb like mechanism (entries 1–5). The α and β ratio of the vinyl substituent of compound **7** is 5:1. This reaction proceeded cleanly without any byproducts.

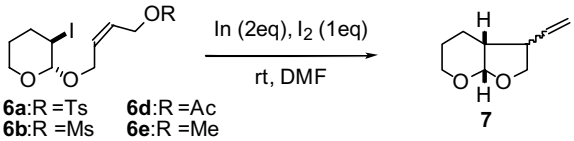
Table 4 shows the results of the radical cyclization of iodoalkenes **8a**–**e** bearing leaving groups at the propargylic positions. In general, the leaving group ability is quite closely related to the pK_a of the group.[13] The radical cyclization of compounds **8a** and **b**, which have good leaving groups, gave the same allene **9** in good yields (entries 1 and 2). On the other hand, the

Table 2. 5-*exo*-Radical cyclization of aromatic iodoalkenes



Entry	4	X	R^1	R^2	Reaction time (h)	5	R^3	Yield (%)
1	**a**	O	H	H	4	**a**	I	87
2	**b**	O	Me	Me	5	**b**	OH	78
3	**c**	*N*-Boc	H	H	4	**c**	I	70
4	**d**	*N*-Boc	Me	Me	7	**d**	OH	80

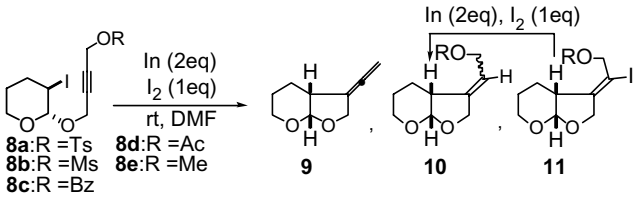
Table 3. Radical cyclization of iodoalkenes bearing leaving groups



Entry	6	Reaction time (h)	7[a] Yield (%)
1	**a**	6	75
2	**b**	6	73
3	**c**	12	70
4	**d**	8	79
5	**e**	6	70

[a] $\alpha/\beta = 5:1$.

Table 4. Radical cyclization of iodoalkynes bearing leaving groups



Entry	8	pK_a (in H_2O)	Reaction time (h)	Yield (%)			
				9	10	11[d]	Total
1	**a**	TsOH = −2.7	5	73	0	0	73
2	**b**	MsOH = −1.9	5	77	0	0	77
3	**c**	BzOH = 4.2	5	0	**c** 62[a]	**c** 10	72
4	**d**	AcOH = 4.8	5	0	**d** 44[b]	**d** 26	70
5	**e**	MeOH = 15.5	6	0	**e** 75[c]	0	75

[a] $E/Z = 1.5:1$.
[b] $E/Z = 1.5:1$.
[c] $E/Z = 3.0:1$.
[d] Only Z.

iodoalkynes **8c–e**, with poor leaving groups, gave olefinic compounds **10c–e**, and vinyl iodides **11c–e** (entries 3–5). Compound **11** can be transformed to compound **10** by further reductive deiodination with In (2 equiv) and I_2 (1 equiv). Overall, iodoalkynes bearing good leaving groups at the propargylic position gave allenic compound **9**, and those bearing less good leaving groups gave olefinic compounds **10**.

In summary, we have demonstrated 5-*exo*-radical cyclizations of alkenes with In and I_2 without the use of radical initiators such as AIBN. Mono-substituted alkenes selectively gave iodinated heterocyclic compounds, and di- or tri-substituted alkenes gave hydroxylated heterocyclic compounds in good yields. This is a simple, selective and effective method to obtain iodo- or hydroxy-cyclic alkanes from alkenes having an iodine substituent at the δ-position of the tether. The mechanisms of these reactions are currently under examination. Alkenes bearing leaving groups were transformed to vinyl substituted cyclic compounds. On the other hand, alkynes bearing propargylic leaving groups gave allenic or olefinic compounds selectively depending on the leaving group ability. These 5-*exo*-radical cyclizations of haloalkenes with In and I_2 have significant synthetic potential.

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