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Indium Trichloride Mediated Intramolecular Prins-Type Cyclization

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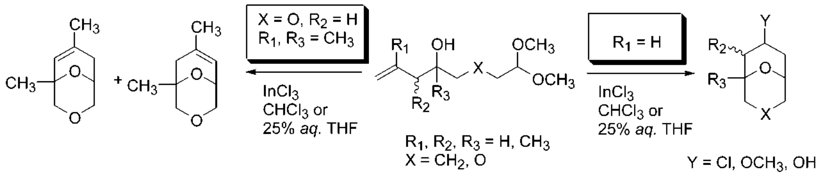
ABSTRACT



Intramolecular Prins-type reactions of compounds having both functionalities of homoallyl alcohol and acetal moiety are described. The intramolecular Prins cyclizations were performed using indium trichloride in chloroform or 25% aqueous THF. Both 9-oxabicyclo[3.3.1]nonane and 3,9-dioxabicyclo[3.3.1]nonane compounds were successfully obtained in moderate yields.

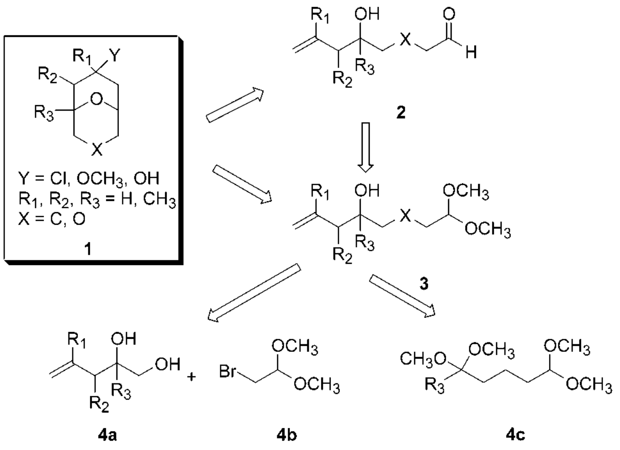
Recently, there has been an increasing interest on coupling of olefins to aldehydes induced by Lewis acid, known as Prins reactions, to generate tetrahydropyran (THP) derivatives.[1] These reactions have been extensively applied to synthesize polyether antibiotics and other complex natural products that contain THP backbones.[2]

To the best of our knowledge, only intermolecular reactions between aldehydes and homoallylic alcohols using Lewis acid has been reported.[1] Herein, we report an intramolecular Prins-type cyclization mediated by indium trichloride to yield bicyclo[3.3.1]nonane compounds.

Previously, we have reported the highly chemoselective deprotection and allylation of acetal and ketal mediated by indium in the presence of allyl bromide in aqueous media.[3,4] On the basis of these results, we prepared some acetal-ketal substrates and employed them in the intramolecular Prins cyclization.

Our synthetic strategy is depicted in Scheme 1. The final product **1** was obtained via intramolecular Prins-type cyclization from olefin-aldehyde **2** or olefin-acetal **3** using

Scheme 1



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(1) (a) Bohlmann, F.; Schulz, H. J.; Riemann, J. *Tetrahedron Lett.* **1964**, 1705−1706. (b) Yang, J.; Viswanathan, G. S.; Li, C-J. *Tetrahedron Lett.* **1999**, *40*, 1627−1630. (c) Viswanathan, G. S.; Yang, J.; Li, C-J. *Org. Lett.* **1999**, *1*, 993−995. (d) Yang, J.; Li, C-J. *Synlett* **1999**, *6*, 717−718. (e) Li, C-J.; Zhang, W-C. *Tetrahedron* **2000**, *56*, 2403−2411. (f) Yang, X- F.; Mague, J. T.; Li, C-J. *J. Org. Chem.* **2001**, *66*, 739−747. (g) Li, J.; Li, C-J. *Tetrahedron Lett.* **2001**, *42*, 793−796.

(2) (a) Blumenkopt, T. A.; Bratz, M.; Castaneda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Chem.* **1990**, *112*, 4386−4399. (b) Blumenkopt, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399−4403.

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Lewis acid. The compound **2** was obtained by deacetalization from **3**, which was generated through the coupling of homoallyl alcohol **4a** with bromoacetaldehyde dimethyl acetal **4b** or the chemoselective allylation of acetal-ketal compound **4c**. The diol **4a** was prepared by allylation of acetol or glycoaldehyde dimer with various allyl bromides. The precursors developed for intramolecular Prins-type cyclization reaction are shown in Figure 1.[5]

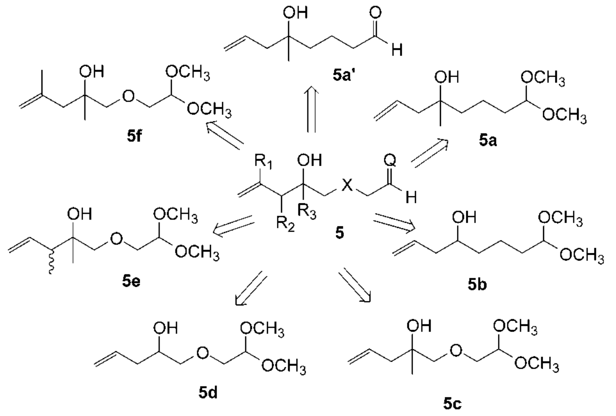


Figure 1.

First, intramolecular Prins-type cyclizations of the compounds having both functionalities of homoallylic alcohol and acetal moiety were performed using indium trichloride in chloroform. The bicyclo[3.3.1]nonane products were successfully obtained as a single diastereomer, and the results are demonstrated in Scheme 2. Indium trichloride as Lewis acid was the first choice as it tolerates moisture and is routinely used in Prins reactions. To optimize the reaction condition, the amount of indium trichloride was varied from 1 to 3 equiv in the reaction of 2,2-dimethoxyethyl 2-hydroxy-2-methyl-4-pentenyl ether (**5c**). As a result, the highest yield was observed when 3 equiv of indium trichloride was used (Table 1).

Scheme 2

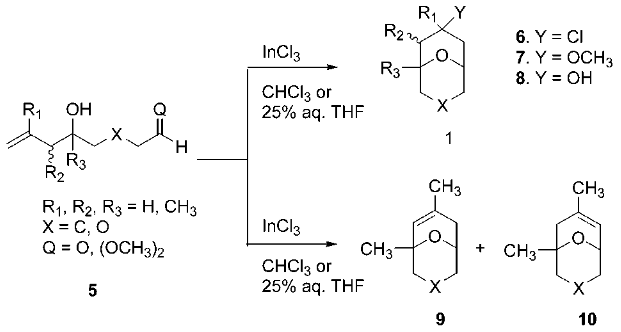
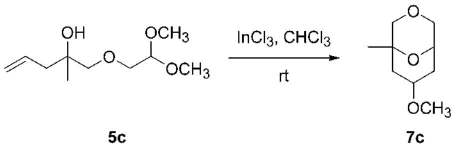


Table 1. Optimization of the Intramolecular Prins Reaction



entry	$InCl_3$ (equiv)	time (h)	yield (%)
1	1.0	20	13
2	2.0	20	43
3	3.0	5	56

The homoallyl alcohols having acetal moieties could be deacetalized in situ and cyclized. As a solvent, chloroform was considered to be more effective than methylene chloride because the former contains acidic impurities.

When 8,8-dimethoxy-4-methyloct-1-en-4-ol (**5a**) was treated with indium trichloride in freshly distilled chloroform under nitrogen atmosphere, no reaction occurred. This indicates that the moisture in the reaction system can induce the deacetalization reaction.

When HPLC grade chloroform was used as a solvent in the open air at ambient temperature, after 4 h the reaction was completed to give 3-chloro-1-methyl-9-oxabicyclo[3.3.1] nonane (**6a**).

When we used H_2O or 25% aqueous THF, no reaction occurred. By elevating the temperature to reflux condition, a hydroxy group was introduced to the generated carbocation to give 7-hydroxy-1-methyl-3,9-dioxabicyclo[3.3.1]nonane (**8a**) in 46% yield.

The results of sequential deacetalization−Prins cyclization−nucleophilic addition or elimination reaction are summarized in Tables 2 and 3, respectively. In the case of X = CH_2, (entries 1, 2, and 4 in Table 2), 3-chloro-substituted bicyclo[3.3.1]nonane compounds **6a** and **6b** were obtained in chloroform. However, in entries 6, 8, and 10 (X = O), 3-methoxy-substituted bicyclo[3.3.1]nonane compounds **7c**, **7d**, and **7e** were produced under the same reaction conditions.

The reason for methoxy group introduction instead of chlorine is not clear at the moment; however, the alkoxy group might facilitate the chelation with indium chloride.

When 25% aqueous THF was used, 3-hydroxy-substituted bicyclo[3.3.1]nonane compounds **8a**, **8b**, **8c**, and **8e** were afforded in 43−80% yields. In contrast to entry 7, compound **8d** (entry 9) was obtained in low yield under the same reaction conditions. In the case of entries 10 and 11, which have one more stereogenic center (R_2 = CH_3, Table 2), diastereomeric mixtures are obtained in a 1:1 ratio.

Interestingly, in entry 5 of Table 2, when homoallylic alcohol **5b** was treated with 3 equiv of indium trichloride in

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(3) Kwon, J. S.; Lee, J. G.; Pae, A. N.; Choi, K. I.; Koh, H. Y.; Kim, Y.; Cho, Y. S. *Bull. Korean Chem. Soc.* **2000**, *21*, 453−454.

(4) Kwon, J. S.; Pae, A. N.; Choi, K. I.; Koh, H. Y.; Kim, Y.; Cho, Y. S. *Tetrahedron Lett.* **2001**, *42*, 1957−1959.

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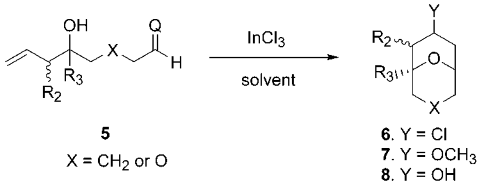
Table 2. Intramolecular Prins-Type Cyclization

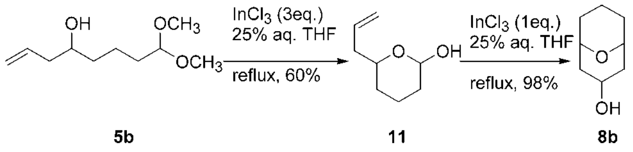


entry	substrate	Q	R_2	R_3	X	Y	solvent	temp (°C)	time (h)	yield (%)
1	**5a′**	O	H	CH_3	CH_2	Cl	CH_2Cl_2	0	6	**6a** (60)
2	**5a**	$(OCH_3)_2$	H	CH_3	CH_2	Cl	$CHCl_3$	rt	8	**6a** (64)
3	**5a**	$(OCH_3)_2$	H	CH_3	CH_2	OH	aq THF	reflux	22	**8a** (46)
4	**5b**	$(OCH_3)_2$	H	H	CH_2	Cl	$CHCl_3$	rt	5	**6b** (52)
5	**5b**	$(OCH_3)_2$	H	H	CH_2	OH	aq THF	reflux	37	**8b** (59)
6	**5c**	$(OCH_3)_2$	H	CH_3	O	OCH_3	$CHCl_3$	rt	5	**7c** (55)
7	**5c**	$(OCH_3)_2$	H	CH_3	O	OH	aq THF	reflux	22	**8c** (80)
8	**5d**	$(OCH_3)_2$	H	H	O	OCH_3	$CHCl_3$	rt	22	**7d** (54)
9	**5d**	$(OCH_3)_2$	H	H	O	OH	aq THF	reflux	22	**8d** (10)
10	**5e**	$(OCH_3)_2$	CH_3	CH_3	O	OCH_3	$CHCl_3$	rt	8	**7e** (30)
11	**5e**	$(OCH_3)_2$	CH_3	CH_3	O	OH	aq THF	reflux	24	**8e** (43)

25% aqueous THF under reflux for 17 h, only an intermediate 6-allyl 2-hydroxy tetrahydropyran **11**[1a] was isolated in 60% yield.

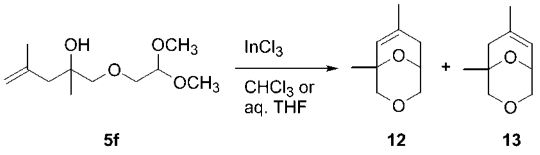
This intermediate was further reacted with 1.0 equiv of indium trichloride. After 20 h, 3-hydroxy-9-oxabicyclo[3.3.1]-nonane (**8b**) was produced in 98% yield, as shown in Scheme 3.

Scheme 3



Unexpectedly, in the case of 2,2-dimethoxyethyl-2,4-dimethyl-2-hydroxy pentenyl ether **5f,** which has a substituent at the vinyl group, elimination instead of electrophilic capture after the cyclization occurred to give two isomers **12** and **13** in 1:1 ratio using chloroform or 25% aqueous THF, as shown in Table 3. This might be due to the stabilization of generated carbocation by methyl group.

Table 3. Intramolecular Prins-Type Cyclization and Elimination Reaction



entry	solvent	temp (°C)	time (h)	ratio (**12**:**13**)	yield (%)
1	$CHCl_3$	rt	10	1:1	48
2	aq THF	reflux	18	1:1.3	46

To determine the configuration of the products, NOE experiment for **7c** as a typical example was performed. The results are depicted in Figure 2. Irradiation of the methyl group at the ring junction gave 0.67% and 0.65% NOE enhancement of H_{2a} and H_{2e}, respectively.

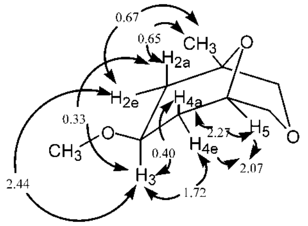
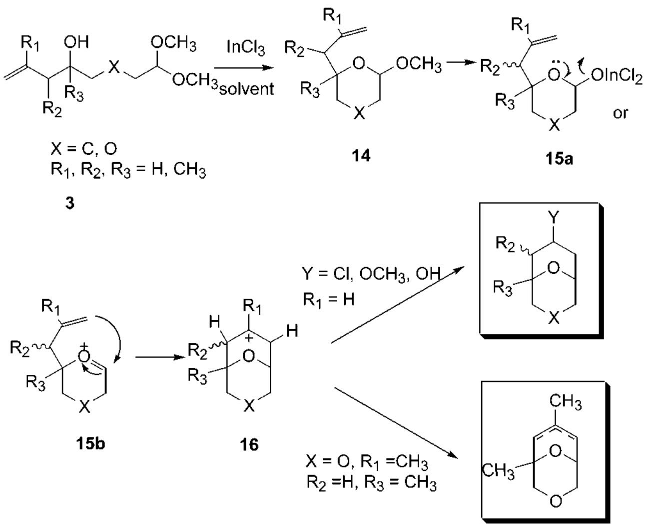


Figure 2. Selected NOE effects on **7c**.

Irradiation of H_5 proton showed 2.27% and 2.07% enhancement of H_{4a} and H_{4e}, respectively, which means that **7c** could have a chairlike conformation. A boatlike conformation is not consistent with the observed NOE effect. Irradiation of the H_3 proton resulted in a strong NOE effect on H_{2e} and H_{4e} (2.44% and 1.72%) and much less effect on H_{2a} and H_{4a} (0.33% and 0.40%). These results confirmed that H_3 takes an axial position.

The proposed mechanism can be deduced as follows (Scheme 4): The reaction seems to proceed by methoxy tetrahydropyran **14** via $InCl_3$-mediated ionization of acetal to the oxocarbenium ion and intramolecular trapping by the alcohol, followed by hydrolysis to give hemiacetal **15a** in aqueous THF or oxonium ion **15b** in chloroform, and

Scheme 4



subsequent Prins cyclization to give intermediate **16**.[6] Thus, a variety of nucleophile could attack carbocation **16** to afford 3-substituted bicyclo[3.3.1]nonanes.

On the other hand, in the case of the reaction with the compound having substituents at the vinyl group, elimination occurred at the carbocation neighboring position, resulting two unsaturated isomers.

In conclusion, indium trichloride could be considered as an effective Lewis acid for producing 3-substituted bicyclo[3.3.1]nonane backbones in moderate to high yields. The 3-chloro-, 3-methoxy-, or 3-hydroxy-substituted compounds could be obtained by controlling the reaction conditions, such as solvents and reaction temperature. These products were generated through sequential deacetalization, intramolecular Prins cyclization, and nucleophilic addition reaction in one pot.

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

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