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Diverse Cyclization Catalyzed by $In(OTf)_3$ for the Convergent Assembly of Substituted Tetrahydrofurans and Tetrahydropyrans

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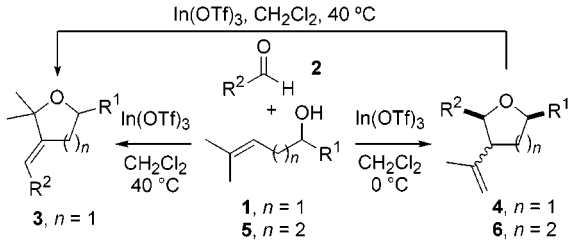
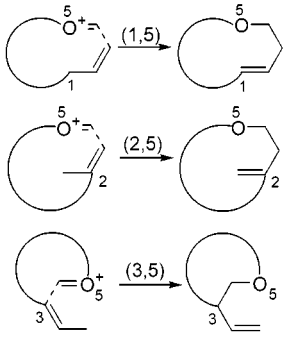
ABSTRACT



A novel $In(OTf)_3$-catalyzed (3,5) oxonium-ene type cyclization for the facile construction of various multisubstituted tetrahydrofurans and tetrahydropyrans was successfully developed. Further mechanistic investigations unveiled an $In(OTf)_3$-catalyzed skeletal reorganization of the tetrahydrofuran to its thermodynamic isomer under thermal conditions.

Substituted tetrahydrofuran and tetrahydropyran motifs find widespread occurrences in a great number of biologically active natural products and therapeutic agents. The development of facile methodologies to access various five- and six-membered cyclic ethers is therefore of great interest in organic synthesis.[1] The intramolecular addition between an oxonium and an alkene provides a convenient avenue to various cyclic ethers. This oxonium-ene type cyclization can be classified into three subtypes based on Mikami's terminology, namely, (1,5), (2,5), and (3,5) (Scheme 1).[2] Cyclization of the (1,5) type has been well studied,[3] and type (2,5) has also been developed by Mikami's group recently.[4] However, the class of (3,5) cyclization is rarely reported,[2] and its synthetic value demands in-depth investigations.

Scheme 1. Classification of Oxonium-Ene Type Cyclization[2]



(1) For reviews, see: (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (b) Bartlett, P. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, Chapter 6. (c) Boivin, T. L. *Tetrahedron* **1987**, *43*, 3309. For some recent examples, see: (d) Trost, B. M.; Sharma, S.; Schmidt, T. *J. Am. Chem. Soc.* **1992**, *114*, 7903. (e) Mikami, K.; Shimizu, M. *Tetrahedron Lett.* **1992**, *33*, 6315. (f) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 249. (g) Yang, J.; Li, C.-J. *Synlett* **1999**, 717. (h) Viswanathan, G. S.; Yang, J.; Li, C.-J. *Org. Lett.* **1999**, *1*, 993. (i) Lolkema, L. D. M.; Hiemstra, H.; Semeyn, C.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7115. (j) Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748. (k) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354. (l) Nakamura, M.; Toganoh, M.; Wang, X. Q.; Yamago, S.; Nakamura, E. *Chem. Lett.* **2000**, 664.

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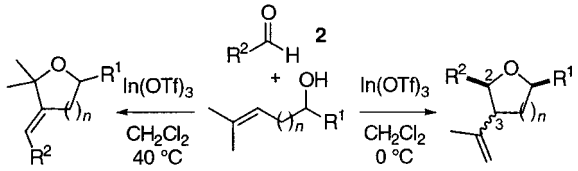
Recently, we disclosed an $In(OTf)_3$-catalyzed tandem protocol for tetrahydrofuran formation.[5] Further investigations directed at clarification of its mechanism unveiled a convergent method for the diverse assembly of various cyclic ethers catalyzed by $In(OTf)_3$.[6] Herein, we report an $In(OTf)_3$-catalyzed (3,5) oxonium-ene type cyclization and a thermodynamically controlled skeletal reorganization of cyclic ether.

To the ends of the mechanistic elucidation of our tandem sequence,[5] α-regioselective homoallylic alcohol **1** was made to undergo the cyclization, wherein a solution of **1**, hydrocinnamaldehyde (**2a**), and catalytic amount of $In(OTf)_3$ in CH_2Cl_2 was heated at 40 °C for 14 h. The reaction afforded the desired product **3a**. To our surprise, when the reaction was conducted at 0 °C, the cyclization took a different turn to afford the tetrahydrofuran product **4a** instead, which can be viewed as arising via a (3,5) oxonium-ene type cyclization or an exocyclic Oppolzer's type III cyclization.[7] Temperature appears to function as the key switch in alteration of the reaction pathway. This observation prompted us to carry out mechanistic investigations and to examine the potential of this method for the synthesis of various cyclic ethers. Homoallylic alcohol **1** and the chain elongated homologue **5** were employed as substrates in our studies and were reacted with a variety of aldehydes (Table 1).

Table 1. Convergent Formation of Cyclic Ethers Catalyzed by $In(OTf)_3$[a]



3, $n = 1$ — **1**, $n = 1$; **5**, $n = 2$ — **4**, $n = 1$; **6**, $n = 2$

entry		n	R^1	R^2	T / °C	yield %	2,3-*trans* : *cis*[b]
1	**a**	1	c-C_6H_{11}	$PhCH_2CH_2$	40	65 (**3a**)	–
2	**a**	1	c-C_6H_{11}	$PhCH_2CH_2$	0	95 (**4a**)	65 : 35
3	**b**	1	c-C_6H_{11}	$CH_3(CH_2)_7$	40	81 (**3b**)	–
4	**b**	1	c-C_6H_{11}	$CH_3(CH_2)_7$	0	69 (**4b**)	62 : 38
5	**c**	1	c-C_6H_{11}	Ph	40	97 (**3c**)	–
6	**c**	1	c-C_6H_{11}	Ph	0	72 (**4c**)	80 : 20
7	**d**	1	c-C_6H_{11}	c-C_6H_{11}	40	75 (**3d**)	–
8	**d**	1	c-C_6H_{11}	c-C_6H_{11}	0	77 (**4d**)	87 : 13
9	**a**	2	Me	$PhCH_2CH_2$	40	39 (**6a**)	–
10	**a**	2	Me	$PhCH_2CH_2$	0	88 (**6a**)	95 : 5
11	**b**	2	Me	$CH_3(CH_2)_7$	0	87 (**6b**)	97 : 3
12	**c**	2	Me	Ph	0	77 (**6c**)	92 : 8
13	**e**	2	Me	PhCH=CH	0	89 (**6e**)	90 : 10
14	**f**	2	Me	*p*-CNC_6H_4	0	86 (**6f**)	93 : 7
15	**g**	2	Me		0	63 (**6g**)	99 : 1
16	**h**	2	Me	2-OH-Ph	0	56 (**6h'**)	99 : 1

[a] Strem Chemicals, Inc. [b] Determined by NMR or isolation yield.

All reactions proceeded smoothly to afford various five- and six-membered cyclic ethers. Adjustment of the chain length ($n = 1, 2$) gives rise to different ring sizes of cyclic ethers. In addition, the method exhibits excellent functional tolerance, and a great variety of aldehydes can be employed to furnish the ring backbone with different substituents. It is noteworthy that the path of reaction leading to **3** or **4** can be altered by the choice of different temperature when $n = 1$. However, the reaction of the substrate with $n = 2$ only produced oxonium-ene type cyclization product **6** regardless of the changes in conditions.

The relative stereochemical outcome of the oxonium-ene type cyclizations was determined by NMR studies and single-crystal X-ray diffraction analysis (Figure 1).[8] When $n = 2$,

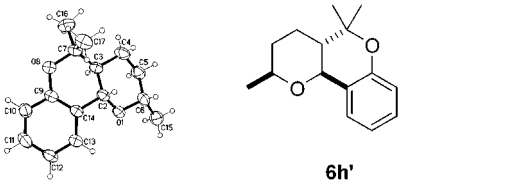


Figure 1. Single-crystal X-ray diffraction analysis of **6h′**.

all examples gave the 2,3-*trans*-2,6-*cis* relative stereochemistry predominantly, exhibiting excellent stereoselectivity. This can be rationalized on the basis of an all-equatorial substitution pattern in a cyclic six-membered chairlike transition state. However, when $n = 1$, the 2,3-*trans*-2,5-*cis* product remains the preferred isomer, albeit in much lower selectivity. This can be accounted for by the relatively nonrigid five-membered transition state (Scheme 2).

It is interesting to note that a polycyclic compound **6h′** was obtained when salicylaldehyde (**2h**) was employed in the reaction. This observation suggests that the oxonium-ene type cyclization proceeds in a stepwise manner by way

(2) For a review, see: Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021.

(3) For a review, see: (a) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. For examples, see: (b) Blumenlopf, T. A.; Look, G. C.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 4399.

(4) Ohmura, H.; Smyth, G. D.; Mikami, K. *J. Org. Chem.* **1999**, *64*, 6056.

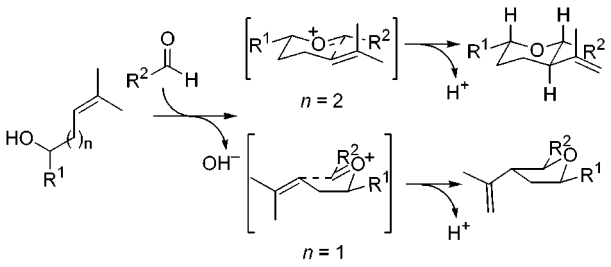
(5) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc.* **2001**, *123*, 2450.

(6) For recent reviews, see: (a) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015. (b) Babu, G.; Perumal, P. T. *Aldrichimica Acta* **2000**, *33*, 16. (c) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149. For examples on the synthetic application of $In(OTf)_3$, see: (d) Trost, B. M.; Chan, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 2326. (e) Loh, T.-P.; Chua, G.-L.; Vittal, J. J.; Wong, M.-W. *Chem. Commun.* **1998**, 861. (f) Prajapati, D.; Laskar, D. D.; Sandhu, J. S. *Tetrahedron Lett.* **2000**, *41*, 8639. (g) Ali, T.; Chauhan, K. K.; Frost, C. G. *Tetrahedron Lett.* **1999**, *40*, 5621. (h) Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743. (i) Gadhwal, S.; Sandhu, J. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2827.

(7) These two pathways are not mechanistically distinct. For reviews, see: (a) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl* **1978**, *17*, 476. (b) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vol. 2, pp 527−661.

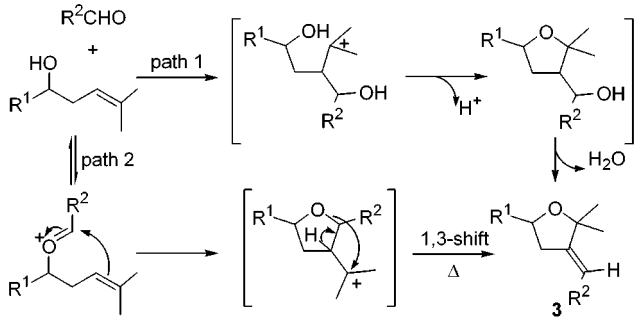
(8) X-ray data for **6h′**: $C_{15}H_{20}O_2$; fw = 232.31; triclinic; space group *P*-1; $a = 8.9084(7)$, $b = 10.0653(8)$, $c = 14.7694(11)$ Å; $V = 1287.45(17)$ Å^3; $Z = 4$; $R_1 = 0.0566$, $wR_2 = 0.1213$, GOF = 1.005 for 7428 observations with $I > 2\sigma(I)$.

Scheme 2. Stereochemical Outcome of (3,5) Oxonium-Ene Type Cyclization



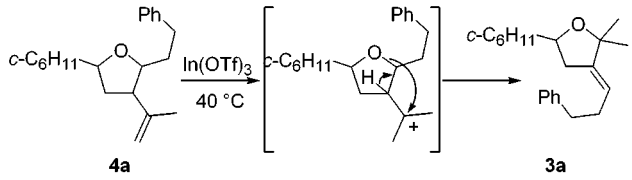
of an intermediate carbocation.[9] In relation to this observation, two reaction pathways appear to be equally viable in accounting for the formation of tetrahydrofuran **3**.[5] One is the Lewis acid catalyzed nucleophilic addition of an alkene to the carbonyl functionality with subsequent cyclization. The other is an oxonium-ene type cyclization to afford a carbocation intermediate, prior to rapid 1,3-shift,[10] rearranging to the thermodynamic product **3** under thermal condition (Scheme 3).

Scheme 3. Postulated Reaction Pathways Leading to **3**



To verify the above postulated mechanism, additional experiments were carried out. The corresponding benzoate ester of the homoallylic alcohol **1** was subjected to the same reaction condition and found to give only recovered starting material. This observation appears to contradict the earlier proposed existence of a Lewis acid catalyzed nucleophilic addition of an alkene to the carbonyl functionality (path 1). Thus, our efforts turn to verification of the existence of a thermodynamically controlled 1,3-shift (path 2). A mixture of **4a** and $In(OTf)_3$ was heated to reflux in CH_2Cl_2 for 12 h, and **3a** was obtained in 92% yield. However, if this experiment was carried out in the presence of 0.5 equiv of

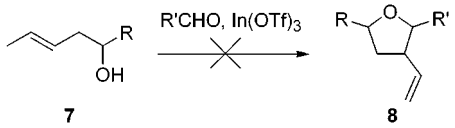
Scheme 4. Conversion of **4a** to **3a**



2,6-di-*tert*-butyl-4-methylpyridine, **4a** was fully recovered (Scheme 4). This observation indicates that a complex protic acid is plausibly formed in the reaction system, which catalyzed the in situ generation of a carbocation, triggering the postulated thermodynamic 1,3-shift.[11] This postulate was further confirmed by the fact that trifluoromethanesulfonic acid[12] also catalyzes the same rearrangement from **4a** to **3a**. The relationship between temperature and the path of reaction to **3** and **4** can be attributed to that of thermodynamic and kinetic control, respectively.

The scope of this oxonium-ene type cyclization was also investigated. It was found that no desired tetrahydrofuran product **8** was obtained when monosubstituted homoallylic alcohol **7** was subjected to the same reaction conditions (Scheme 5).[13] This indicates that disubstitution at the external

Scheme 5. Studies on the Scope of Cyclization



end of the double bond is essential to this oxonium-ene type cyclization.[7b]

In summary, the exploration of the novel Lewis acid $In(OTf)_3$ led to the establishment of a convergent approach to various cyclic ethers via a (3,5) oxonium-ene type cyclization in our laboratory. Further investigations revealed that increasing the reaction temperature from 0 to 40 °C can convert the kinetic product **4** to the thermodynamic isomer **3** via a 1,3-shift, which appears to account for the temperature-dependent reaction pathway. However, this rearrangement is currently limited to the skeletal reorganization of tetrahydrofurans but not the tetrahydropyrans counterpart. Together with our previous reported tetrahydrofuran formations,[5] we successfully developed an $In(OTf)_3$-catalyzed cyclization method for the facile assembly of various substituted cyclic ethers, which offers new opportunities for diversity-based synthesis.[14] Further studies along this line are currently in progress.

(9) For examples of stepwise Lewis acid catalyzed ene reactions, see: (a) Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555. (b) Snider, B. B.; Ron, E. *J. Am. Chem. Soc.* **1985**, *107*, 8160.

(10) For a review, see: (a) Wovkulich, P. M. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: London, 1991; Vol. 1, pp 843−899. For some examples of 1,3-shift, see: (b) Bhupathy, M.; Cohen, T. *J. Am. Chem. Soc.* **1983**, *105*, 6978. (c) Thies, R. W.; Daruwala, K. P. *J. Org. Chem.* **1987**, *52*, 3798.

(11) (a) Cloninger, M. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 1092. (b) Olah, G. A.; Prakash, G. K. S.; Sommer, J. *Superacids*; Wiley: New York, 1985. (c) Farcasiu, D.; Marino, G.; Miller, G.; Kastrup, R. V. *J. Am. Chem. Soc.* **1989**, *111*, 7210.

(12) Only freshly opened TfOH (within 7 days) was found to give the desired product, thus rendering TfOH an inconvenient catalyst to use.

(13) Yang, X.-F.; Mague, J.-T.; Li, C.-J. *J. Org. Chem.* **2001**, *66*, 739.

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Supporting Information Available: Complete experimental details, including characterization data for all new compounds and X-ray crystal data for **6h′** (cif format). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For reviews, see: (a) Arya, P.; Chou, D. T. H.; Beak, M.-G. *Angew. Chem., Int. Ed.* **2001**, *40*, 339. (b) Liu, D. R.; Schultz, P. G. *Angew. Chem., Int. Ed.* **1999**, *38*, 36. (c) Schreiber, S. L. *Science* **2000**, *287*, 1964. (d) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.