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Lewis acid-catalyzed Prins-type reactions of methylenecyclopropylcarbinols with aldehydes and aldimines

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Abstract—Lewis acid-catalyzed Prins-type reactions of methylenecyclopropylcarbinols with aldehydes and aldimines proceeded smoothly to give the corresponding 3-oxa-bicyclo[3.1.0]hexane units via 5-*exo* cyclization in good to high total yields.

Prins reaction[1] between homoallylic alcohols and aldehydes is a powerful method for the formation of tetrahydrofuran and tetrahydropyran[2] rings, which has also been used for the syntheses of many natural products.[3] Tetrahydrofuran and related subunits are ubiquitous in nature, occurring in a wide range of biologically active substances. Therefore, there has been much interest in the development of methods for the synthesis of these subunits.[4,5] However, Prins-type cyclization has not been so often used for the synthesis of tetrahydrofuran because this cyclization of homoallylic alcohols prefers 6-endocyclic products (tetrahydropyrans) to 5-exocyclic products (tetrahydrofurans).[6] To the best of our knowledge, there are only few examples of synthesizing substituted tetrahydrofurans via Prins-type cyclization from homoallylic or homopropargylic alcohols and aldehydes which utilize a functional group as trimethylsilyl group to stabilize the generated carbocation, resulting in driving 5-*exo* cyclization to tetrahydrofurans instead of 6-endo cyclization to tetrahydropyrans.[7] In recent years, we have paid much attention to the Lewis acid-mediated chemistry of methylenecyclopropanes (MCPs)[8] and found some novel reaction patterns of these substrates, allowing the formation of products distinctly different from those obtained via transition metals catalyzed processes.[9] For example, in the $BF_3{\cdot}OEt_2$-catalyzed reactions of MCPs with aldehydes, we found that indene and THF skeletons can be generated at different temperatures, which we have rationalized to be formed by Prins-type reaction pathways.[10] In the reaction the driving force is attributed to the stabilization of the cyclopropyl ring to the generated carbocation.[11] Recently, we have been involved in the research of another kind of MCPs, namely, 3-hydroxylmethyl substituted MCPs (methylenecyclopropylcarbinols) **1**.[12] To expand the scope of the useful Prins-type cyclization of MCPs, we also set out to examine the reactions of methylenecyclopropylcarbinols **1** which can be thought as a kind of special homoallylic alcohols and may also result in 5-*oxo* cyclization to tetrahydrofuran units for the same reasons.[11] In this Letter, we wish to report the Prins-type cyclization of methylenecyclopropylcarbinols **1** with aldehydes or aldimines to form 5-exocyclic products, 3-oxa-bicyclo[3.1.0]hexane units.

Prins-type cyclization of MCP **1a** with benzaldehyde **2a** was firstly examined in 1,2-dichloroethane (DCE) in the presence of various Lewis acids (10 mol %) to find out the optimal conditions.[13] After several trials and errors, we were pleased to observe that the reaction of **1a** and **2a** in the ratio of 2:1, catalyzed by zinc triflate [$Zn(OTf)_2$, 10 mol %] in DCE (1.0 mL), at room temperature afforded the corresponding products **3a** and **3a′** in 70% and 22% yield, respectively (Scheme 1). It should be noted here that both **3a** (including diastereoisomers of **3a-I** and **3a-II** as an unseparable mixture) and **3a′** (also including diastereoisomers of **3a′-I** and **3a′-II** as an unseparable mixture) are formed as mixtures of 2 diastereoisomers with the ratio of approximately 1:1.[13] The structure of one diastereoisomer of **3a**, **3a-I** was

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Keywords: Lewis acid; Cyclization; Prins reaction; Methylenecyclopropylcarbinols; Aldehydes; Aldimines.

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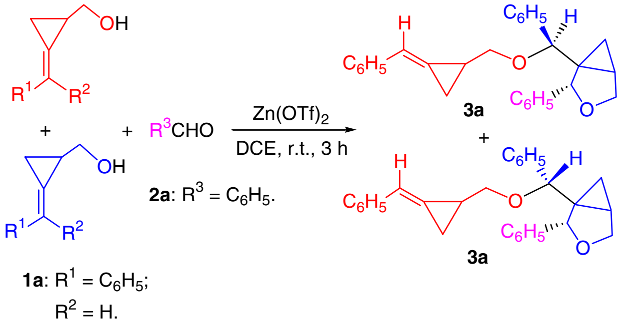
confirmed unambiguously by an X-ray diffraction (Fig. 1).[14] In this reaction all the four diastereoisomers were obtained, which were assigned by ^{1}H NMR spectroscopy. Here we will use **3a-I** and **3a-II** as the examples to display this assignment. It is clear here that the red regions of **3a-I** and **3a-II** are a pair of stereoisomers, which should share the same ^{1}H NMR spectroscopy. Considering the third chiral center in **3a-I** and **3a-II** (**1** and **1′** in **3a-I** and **3a-II**, respectively), we believe here that compounds **3a-I** and **3a-II** should share the similar ^{1}H NMR spectroscopy (Fig. 2).

With the optimal conditions in hand, we next carried out the reactions of various methylenecyclopropylcarbinols **1** (0.6 mmol) with aldehydes **2** (0.3 mmol) under catalysis of Zn(OTf)$_2$ (10 mol %). All reactions proceeded smoothly to give the expected products **3** and **3′** in good to high total yields, with product **3** as the major one in almost all cases (Table 1). Substituents on substrates **1** and **2**, whether they are electron-rich or -poor ones, did not significantly affect the reaction. Alkyl-substituted aldehyde **2g** also can complete the transformation to give the corresponding products **3m** and **3m′** in good total yields (Table 1, entry 12). It should also be noted here that both **3** and **3′** represent a pair of diastereoisomers formed in a ratio of about 1:1.[13] The X-ray crystal structure of one diastereoisomer



Scheme 1. Optimized reaction conditions of MCP **1a** with benzaldehyde **2a**.

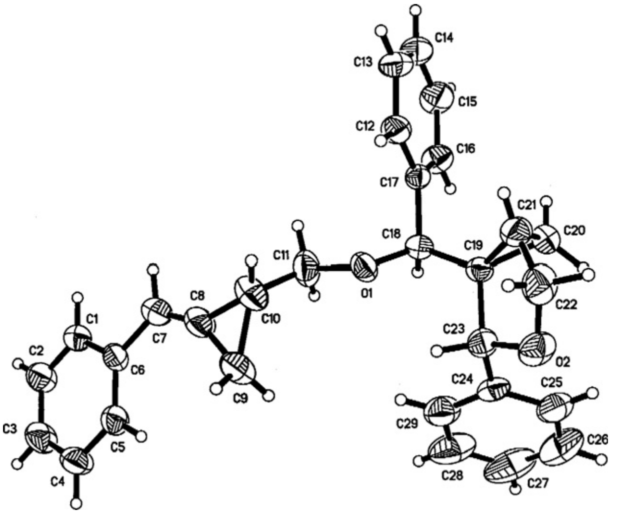


Figure 1. ORTEP drawing of **3a-I**.

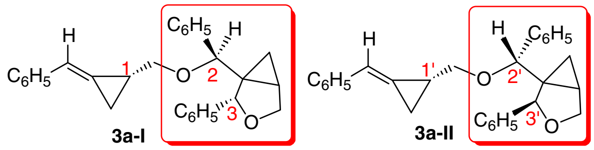
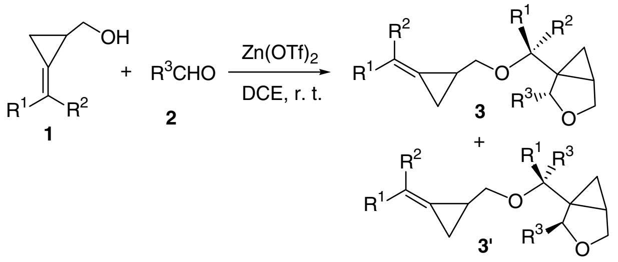


Figure 2.

Table 1. Reactions of methylenecyclopropylcarbinols **1** with aldehydes **2** catalyzed by Zn(OTf)$_2$



Entry	**1** (R^1/R^2)	**2** (R^3)	Time (h)	Yields[a](%)	
				3[b]	**3′**[b]
1	**1a** (C_6H_5/H)	**2b** (4-ClC_6H_4)	24	**3b**, 67	**3b′**, 30
2	**1a**	**2c** (4-BrC_6H_4)	24	**3c**,57	**3c′**, 20
3	**1a**	**2d** (4-MeC_6H_4)	3	**3d**, 59	**3d′**, 19
4	**1a**	**2e** (3-MeC_6H_4)	3	**3e**, 57	**3e′**, 24
5	**1a**	**2f** (4-MeOC_6H_4)	3	**3f**, 54	**3f′**, 20
6	**1b** (4-MeC_6H_4/H)	**2b**	24	**3g**, 61	**3g′**, 26
7	**1b**	**2d**	2	**3h**, 58	**3h′**, 22
8	**1c** (4-ClC_6H_4/H)	**2d**	24	**3i**, 53	**3i′**, 28
9	**1d** (4-BrC_6H_4/H)	**2d**	24	**3j**, 54	**3j′**, 21
10	**1d**	**2e**	24	**3k**, 56	**3k′**, 15
11	**1e** (H/C_6H_5)	**2a** (C_6H_5)	24	**3l**, 10	**3l′**, 56
12	**1a**	**g** ($C_6H_5CH_2CH_2$)	24	**3m**, 53	**3m′**, 23

[a] Isolated yields.

[b] Almost all of the diastereoisomers of **3** and **3′** with the diastereoselectivity of 1:1.

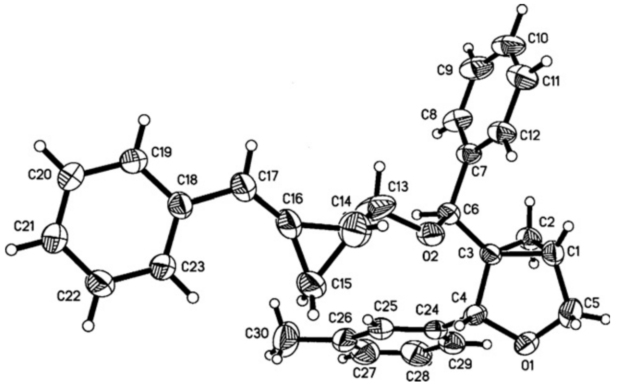


Figure 3. ORTEP drawing of **3e-I**.

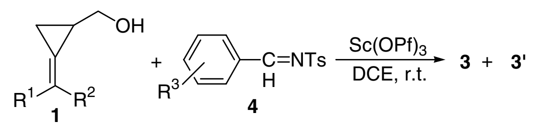
of products **3e**, **3e-I**, was obtained to further verify the structure of the products (Fig. 3).[15]

Reactions of methylenecyclopropylcarbinols **1** with *N*-tosyl imines were also examined and it was found that Lewis acid $Sc(OPf)_3$ ($OPf = C_8F_{17}SO_3$) showed the best activity in this case. As can be seen from Table 2, all reactions proceeded smoothly also to give products **3** and **3′** in good to high total yields with products **3** as the major one in almost all cases.

When *N*-phenyl imine was used as the substrate, the reaction became sluggish and only lower yield of the ring-closure product **6** was obtained for the reaction of methylenecyclopropylcarbinol **1a** with *N*-phenyl imine **5** (Scheme 2).

A plausible mechanism for this Prins-type cyclization reaction of MCPs **1** with aldehydes **2** or aldimines **4** or **5** is proposed as below: the reaction of **1** with the Lewis acid activated aldehydes or *N*-tosyl imines generates intermediate **A**, which will give the corresponding oxocarbenium ion **B** *if XH is labile to liberate in the presence of Lewis acid* (*X* = O *or NTs in this case*). Intermediate **B** undergoes 5-*oxo* Prins-type cyclization reaction with the double bond of **1** to give intermediates **C** and **C′**. It is obvious that intermediate **C** would be the major intermediate due to the relatively less steric hindrance between the sterically bulkier groups R^1 and R^3. Addition of another molecule **1** to intermediates **C** and **C′** furnishes products **3** and **3′**, respectively (Scheme 3). It appears to be the driving force for this Prins-type cyclization via 5-*exo* pattern because the carbocation formed in intermediates **C** and **C′** are greatly stabilized by the cyclopropyl ring and one aromatic ring (R^1 or R^2).[11] In the case of X = NPh, in which *XH is not a good leaving group* (*X* = *NPh in this case*), the Lewis acid activated *N*-phenyl aldimine will alternatively add to the double bond of **1** to afford intermediate **D**. Ring-closure of intermediate **D** by intramolecular attack of the OH group will furnish product **6**.[12d] It should be noted here that the leaving ability of the corresponding XH group dramatically affect the reaction pattern. In other words, if XH is a good leaving group, intermediate **B** will be easily formed which will give intermediates **C** and **C′** via 5-*exo* cyclization with the double bond of **1**, while XH is a bad leaving group, intermediate **D** will be facile to obtain via electrophilic addition of the Lewis acid activated imines to the double bond of **1** (Scheme 3).

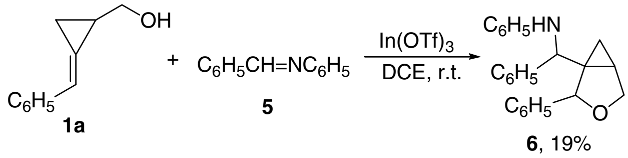
Table 2. $Sc(OPf)_3$-catalyzed reactions of methylenecyclopropylcarbinols **1** with *N*-tosyl aldimines



Entry	**1** (R^1/R^2)	**4** (R^3)	Yields[a](%)	
			3[b]	**3′**[b]
1	**1a** (C_6H_5/H)	**4a** (4-Cl)	**3b**, 59	**3b′**, 27
2	**1a**	**4b** (4-Br)	**3c**, 58	**3c′**, 26
3	**1a**	**4c** (4-Me)	**3d**, 58	**3d′**, 20
4	**1a**	**4d** (3-Me)	**3e**, 56	**3e′**, 37
5	**1a**	**4e** (4-MeO)	**3f**, 53	**3f′**, 30
6	**1b** (4-MeC_6H_4/H)	**4a**	**3g**, 65	**3g′**, 24
7	**1b**	**4c**	**3h**, 47	**3h′**, 18
8	**1e** (H/C_6H_5)	**4** (H)	—	**3I′**, 67

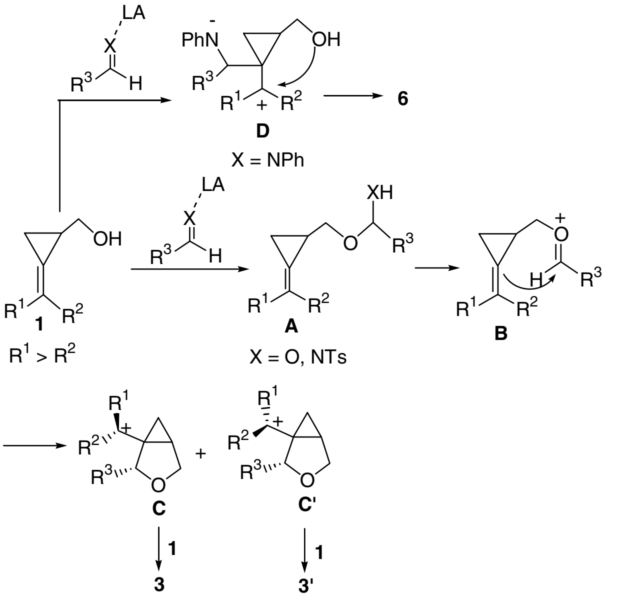
[a] Isolated yields.

[b] Almost all of the diastereoisomers of **3** and **3′** with the diastereoselectivity of 1:1.



Scheme 2.

In conclusion, we have identified an efficient Lewis acid-catalyzed two-component, three-molecular Prins-type reactions of methylenecyclopropylcarbinols **1** with aldehydes **2** or aldimines **4** to furnish the corresponding products **3** and **3′** bearing 3-oxa-bicyclo[3.1.0]hexane units. Stabilization of the cyclopropyl ring to the generated carbocation in the reaction is supposed as the



Scheme 3. Proposed mechanism for the formation of **3**, **3′** and **6**.

driving force for the 5-*exo* cyclization to tetrahydrofuran-related rings. Efforts are underway to further elucidate the reaction mechanism and to understand the scope and limitations of this process.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.146.

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13. See Supporting data for the details.
14. The crystal data of **3a-I** have been deposited in CCDC with number 600930. Empirical formula: $C_{29}H_{28}O_2$; formula weight: 408.51; crystal color, habit: colorless, prismatic; crystal system: triclinic; lattice type: primitive; lattice parameters: $a = 10.0854(11)$ Å, $b = 10.3264(12)$ Å, $c = 12.6482(15)$ Å, $\alpha = 75.413(2)°$, $\beta = 67.988(2)°$, $\gamma = 88.881(2)°$, $V = 1177.8(2)$ Å^3; space group: $P\bar{1}$; $Z = 2$; $D_{\text{calc}} = 1.152$ g/cm^3; $F_{000} = 436$; diffractometer: Rigaku AFC7R; residuals: R; Rw: 0.0542, 0.0935.
15. The crystal data of **3e-I** have been deposited in CCDC with number 606430. Empirical formula: $C_{30}H_{30}O_2$; formula weight: 422.54; crystal color, habit: colorless, prismatic; crystal system: triclinic; lattice type: primitive; lattice parameters: $a = 9.9900(15)$ Å, $b = 10.7440(17)$ Å, $c = 12.6400(19)$ Å, $\alpha = 101.891(3)°$, $\beta = 112.918(3)°$, $\gamma = 92.793(2)°$, $V = 1210.2(3)$ Å^3; space group: $P\bar{1}$; $Z = 2$; $D_{\text{calc}} = 1.160$ g/cm^3; $F_{000} = 452$; diffractometer: Rigaku AFC7R; residuals: R; Rw: 0.0707, 0.1798.