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An Efficient Prins Cyclization for Stereoselective Synthesis of Tetrahydropyran from Imines and Homoallyl Alcohols

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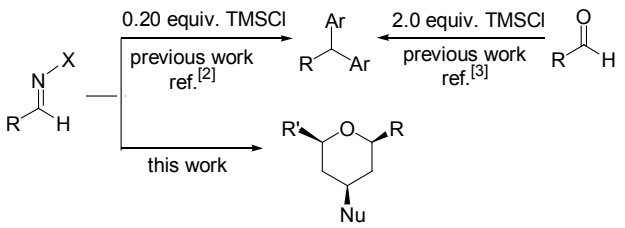
An unprecedented protocol has been developed for the efficient synthesis of substituted tetrahydropyrans via a bismuth-promoted Prins cyclization of imines with homoallyl alcohols. In the presence of 40 mol% $BiCl_3$, a wide variety of imines react smoothly with homoallyl alcohols at room temperature to give the corresponding 4-chlorotetrahydropyran derivatives in good to excellent yields.

Keywords Prins cyclization, tetrahydropyrans, imine, homoallyl alcohol, Lewis acid

Introduction

Various nucleophiles undergo additions to imines by breaking the C—N π bonds but delivering the stronger C—N σ bonds to the final products.[1] In comparison, the transformation of imines has rarely been reported through the complete cleavage of C=N bonds. In the presence of carbon or heteroatom nucleophiles, the C=N bonds of imines can be converted into two σ bonds.[2] Recently, we reported a biarylation of imines or carbonyl compounds with arenes,[2,3] wherein the reactions of imines only need a catalytic amount of Lewis acid (TMSCl), but carbonyl compounds need two-equivalent Lewis acid (TMSCl). Inspired by this study, we investigated the Prins cyclization of imines with homoallyl alcohols for the formation of substituted tetrahydropyrans and developed an efficient synthesis of tetrahydropyrans with a catalytic amount of Lewis acid (Scheme 1).

Scheme 1 Breaking the C=N bonds of imines



It is well known that the Prins cyclization is a powerful method to generate polysubstituted tetrahydropyrans with excellent stereoselectivity.[4] Substituted tetrahydropyran ring system is an important unit because of its presence in many biologically active natural products,[5] such as acutiphycins, oscillatoxins, aplysiatoxins, avermectins, talaromycins and latrunculins. These heterocycles are also frequently utilized in medicinal chemistry.[6] Generally, they are prepared from the Prins cyclization of aldehydes and homoallyl alcohols under Brønsted or Lewis acid promoted conditions.[7] However, many of these classical methods often involve the use of stoichiometric amounts of Lewis acid and poor tolerance of substrates. Our goal was to decrease the amount of Lewis acid and extend the scope of substrates.

Results and Discussion

The Prins cyclization of *N*-tosyl imine (**1a**) with homoallyl alcohol (**2a**) was selected as a model reaction to evaluate the catalytic activity of chlorinated Lewis acid at room temperature. As summarized in Table 1, a number of Lewis acids (40 mol%) were examined in dichloromethane, and to our delight, the best catalytic activity was observed with $BiCl_3$, an inexpensive and environmentally benign Lewis acid,[8] which promoted the reaction to afford tetrahydropyran **3a** in 98% yield. Further efforts to decrease the amount of $BiCl_3$ resulted in a lower yield (Table 1, Entry 7). Moreover, the reaction gave a lower yield when replacing the *p*-toluenesulfonyl group in imine (**1a**) with a phenyl group, a sulfamido group, an acyl group or a sulfinyl group (Table 1, Entries 8—11).

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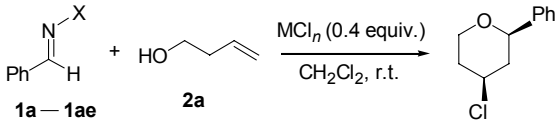
Table 1 Survey of the Lewis acid (MCl_n) and imine *N*-substituents [a]



1a—**1ae** **2a** **3a**

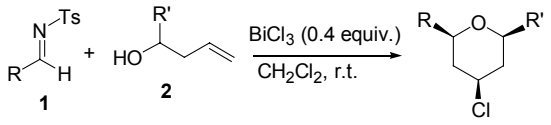
Entry	MCl_n	**1a**—**1ae**, X	Time/h	Yield[d]/%
1	$FeCl_3$	**1a**, Ts	2	87
2	**$BiCl_3$**	**1a, Ts**	**1**	**98**
3	$InCl_3$	**1a**, Ts	24	54
4	$SnCl_3$	**1a**, Ts	24	67
5[b]	$ZnCl_2$	**1a**, Ts	24	80
6	$AlCl_3$	**1a**, Ts	24	30
7[c]	$BiCl_3$	**1a**, Ts	24	81
8	$BiCl_3$	**1ab**, Ph	8	46
9	$BiCl_3$	**1ac**, NHTs	8	53
10	$BiCl_3$	**1ad**, COPh	5	68
11	$BiCl_3$	**1ae**, SO^{t}Bu	2	47

[a] Reaction conditions: imines **1a**—**1ae** (0.2 mmol), homoallyl alcohol **2a** (0.24 mmol), Lewis acid (0.080 mmol), dichloromethane (1.0 mL), room temperature. [b] $ZnCl_2$: 0.60 equiv. (0.12 mmol). [c] $BiCl_3$: 0.34 equiv. (0.068 mmol). [d] Isolated yield.

Encouraged by our preliminary findings, we investigated the substrate scope for the Prins cyclization of imines and homoallyl alcohols. In the presence of 40 mol% $BiCl_3$, a number of aromatic imines bearing either electron-withdrawing groups (Cl, NO_2 and CN) or electron-donating groups (Me and OMe) on the *ortho*-, *meta*- or *para*-positions of the aromatic rings, and aliphatic imines, were transformed into their corresponding 4-chlorotetrahydropyrans at room temperature in good to excellent yields (Table 2, Entries 1—13 and 20). *α*,*β*-Unsaturated imine (**1n**) was also found to be able to serve as a suitable substrate for the Prins cyclization (Table 2, Entries 14 and 17). Next, we examined the reactivity of various homoallyl alcohols toward imines (Table 2, Entries 14—21). A variety of homoallyl alcohols reacted smoothly and produced the corresponding 4-chlorotetrahydropyrans in excellent yields. All the reactions are clean and only *cis*-isomer was obtained in each reaction, its structure being confirmed by contrast with the reported ^{1}H NMR spectra.

The Prins cyclization of imines with homoallyl alcohols was further extended to other nucleophiles (such as $BiBr_3$, thiophenol, arenes). In the presence of 40 mol% $BiBr_3$, the Prins cyclization proceeded smoothly to give the corresponding 4-bromotetrahydropyran (**5a**) in 95% yield (Table 3, Entry 1). When treated with 5 mol% $BiCl_3$, thiophenol, benzene and *p*-xylene all reacted well with imine (**1a**) and homoallyl alcohol (**2a**) to afford the corresponding tetrahydropyran derivatives **5** in good to excellent yields (Table 3, Entries 2—4).

Table 2 Synthesis of 4-chlorotetrahydropyrans from imines, homoallyl alcohols and $BiCl_3$[a]



1 **2** **3**

Entry	**1**, R	**2**, R'	**3**	Time/h	Yield[b]/%
1	**1a**, Ph	**2a**, H	**3a**	1.0	98
2	**1b**, 2-$NO_2C_6H_4$	**2a**, H	**3b**	2.0	77
3	**1c**, 2-ClC_6H_4	**2a**, H	**3c**	1.5	85
4	**1d**, 2-$MeOC_6H_4$	**2a**, H	**3d**	1.0	95
5	**1e,** 3-$NO_2C_6H_4$	**2a**, H	**3e**	1.5	92
6	**1f**, 4-$NO_2C_6H_4$	**2a**, H	**3f**	2.0	88
7	**1g**, 4-ClC_6H_4	**2a**, H	**3g**	1.5	93
8	**1h**, 4-CNC_6H_4	**2a**, H	**3h**	3.0	98
9	**1i**, 4-MeC_6H_4	**2a**, H	**3i**	1.0	99
10	**1j**, 4-$MeOC_6H_4$	**2a**, H	**3j**	1.0	99
11	**1k**, $PhCH_2$	**2a**, H	**3k**	1.5	68
12	**1l**, cyclohexyl	**2a**, H	**3l**	2.0	73
13	**1m**, Me_2CH	**2a**, H	**3m**	2.0	85
14	**1n**, (*E*)-PhCH=CH	**2a**, H	**3n**	1.0	92
15	**1a**, Ph	**2b**,Ph	**3o**	1.5	99
16	**1a**, Ph	**2c**, Me_2CH	**3p**	2.0	91
17	**1n**, (*E*)-PhCH=CH	**2b**, Ph	**3q**	1.0	93
18	**1d**, 2-$MeOC_6H_4$	**2d**, cyclohexyl	**3r**	2.5	85
19	**1k**, cyclohexy	**2d**, cyclohexyl	**3s**	4.0	87
20	**1n**, 1-naphthyl	**2d**, cyclohexyl	**3t**	3.0	96
21	**1l**, Me_2CH	**2c**, Me_2CH	**3u**	4.0	92

[a] Reaction conditions: imine **1** (0.2 mmol), homoallyl alcohol **2** (0.24 mmol), $BiCl_3$ (0.08 mmol), dichloromethane (1.0 mL), room temperature. [b] Isolated yield.

On the basis of our results and previous relevant mechanistic studies,[9] we proposed the reaction pathway depicted in Scheme 2. We reasoned that a plausible catalytic pathway could be readily initiated via an activation of the imine **1** with the bismuth salt. Its reaction with the homoallyl alcohol **2** affords the intermediate (**6**, **7**, **8**). Intermediate (**6**, **7**, **8**) undergoes cyclization to give tetrahydropyranyl cation **9** that can easily be trapped by nucleophile (Cl^-) to give the final product 4-chlorotetrahydropyran **3**.

Conclusions

In summary, we have developed a highly efficient synthesis of substituted tetrahydropyrans via a bismuth-promoted Prins cyclization of imines with homoallyl alcohols. In the presence of 40 mol% $BiCl_3$, a wide variety of imines react smoothly with homoallyl alcohols to give the corresponding tetrahydropyran derivatives in good to excellent yields. Furthermore, other nucleophiles (such as $BiBr_3$, thiophenol, arenes)

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Scheme 2 proposed reaction pathway

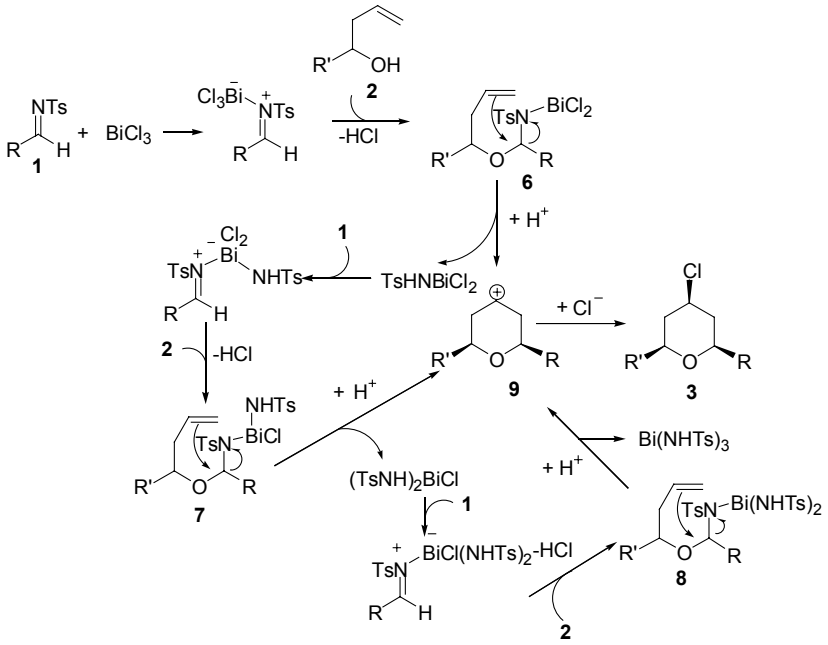
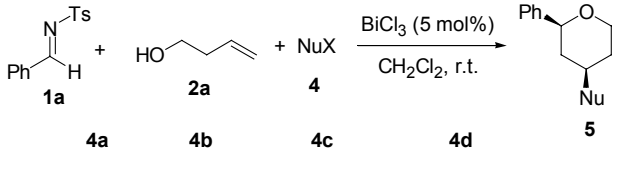
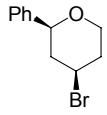
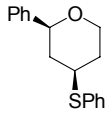
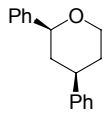
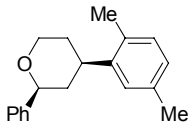


Table 3 Synthesis of structurally diverse tetrahydropyrans from imine **1a**, homoallyl alcohol **2a** and $BiBr_3$, arenes, phenthiol[a]



	4a	**4b**	**4c**	**4d**	
	$BiBr_3$	PhSH	PhMe	*p*-Xylene	
Entry	NuX	Product		Time/h	Yield[e]/%
1[b]	**4a**	 **5a**		1.5	95
2	**4b**	 **5b**		10	84
3[c]	**4c**	 **5c**		24	66
4[d]	**4d**	 **5d**		24	60

[a] Reaction conditions: imines **1a** (0.2 mmol), homoallyl alcohol **2a** (0.24 mmol), $BiCl_3$ (0.010 mmol), dichloromethane (1.0 mL), room temperature. [b] Without $BiCl_3$, $BiBr_3$ 0.08 mmol. [c] Benzene 1.0 mL, without dichloromethane. [d] Xylene 1.0 mL, without dichloromethane. [e] Isolated yield.

are also found to serve as suitable nucleophiles for the Prins cyclization of imine **3a** with homoallyl alcohol **2a**. The attractive features of this protocol to synthesize substituted tetrahydropyrans include catalytic amount of chlorinated Lewis acid, high yield, broad substrate scope, mild reaction conditions, and experimental simplicity.

Experimental

General information

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 FT spectrometer (300 MHz and 75 MHz, respectively) using tetramethylsilane as internal reference. IR spectra were recorded on a Perkin-Elmer 2000 FTIR spectrometer. High resolution mass spectra were recorded on a LC-TOF spectrometer (Micromass). the UV detection was monitored at 254 nm. Compounds **1a**—**1n** and **2b**—**2d** were prepared according to known procedures.[10] The rest of chemicals were purchased from the Sinopharm Chemical Reagent Co., Meryer, Acros, and Alfa Aesar, and used as received.

General procedure for the Prins cyclization of imine, homoallyl alcohol and $BiCl_3$

A mixture of imine **1** (0.20 mmol), homoallyl alcohol **2** (0.24 mmol), $BiCl_3$ (25.2 mg, 0.080 mmol) and CH_2Cl_2 (1.0 mL) was stirred at room temperature. When the reaction did not proceed further as indicated by TLC, the reaction mixture was directly purified by flash column chromatography on silica gel, eluting with petroleum ether/EtOAc (30∶1 to 10∶1, *V*∶*V*), to give product **3** (Table 2).

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