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Bi(OTf)$_3$-catalyzed 5-*exo*-trig cyclization via halide activation

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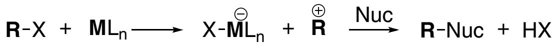
Abstract

Lewis acid activation of allyl halides utilizing Bi(OTf)$_3$ resulted in cationic cyclization of alkenes with high efficiency. While other Lewis acids could catalyze this process with highly substituted alkenes, bismuth salts demonstrated unique reactivity in come cases. This suggested that bismuth triflate possesses interesting halophilic properties.

1. Introduction

The formation of carbocations[1] from a variety of organohalogen compounds[2] by Lewis acid activation is an important process in the field of organic chemistry. The trapping of in situ generated cations by nucleophiles (Scheme 1) is a useful synthetic strategy if the reactions can be well controlled.[3] Weak nucleophiles can readily take part in such processes.

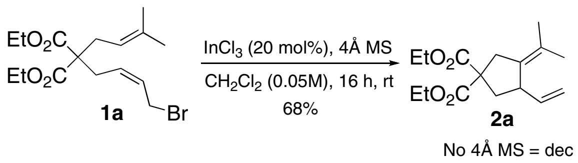


$$\mathbf{R}\text{-X} + \mathbf{ML}_n \longrightarrow \text{X-}\overset{\ominus}{\mathbf{M}}\mathbf{L}_n + \overset{\oplus}{\mathbf{R}} \xrightarrow{\text{Nuc}} \mathbf{R}\text{-Nuc} + \text{HX}$$

Scheme 1.

There are a number of examples of halide activation by Lewis or Brønsted acids to generate carbocations. Typically Lewis acids such as Ag(I), B(III), Ti(IV), Al(III), and Sn(IV) are used to cleave carbon–halide bonds.[4] However, major limitations for this chemistry are that the conditions are often severe and the use of stoichiometric amount of Lewis acids is often required. Strongly acidic byproducts (e.g., HCl, HBr) can poison Lewis acids and perturb their catalytic turnover. Thus, reactions driven by *catalytic halide activation* by Lewis acids are rare. Recently, Hua and co-workers reported that catalytic amounts of BiCl$_3$ catalyzed the Friedel–Crafts reaction of acyl or vinyl chlorides with arenes.[5] We recently reported the In(III)-catalyzed atom transfer cyclization[6] and ring-closing Friedel–Craft reaction[7] proceeding via efficient and mild activation of allylic bromides. During our investigation of these cationic processes we discovered that Bi(OTf)$_3$ was also able to activate allylic halides catalytically with high efficiency. Bismuth Lewis acids are intriguing and have been known to catalyze a variety of reactions[8] including an interesting BiBr$_3$-catalyzed silyl-Prins reaction. Herein, we disclose another application driven by Lewis acid catalyzed halide activation.[9]

Similar to our atom transfer cyclization of alkynes and allyl bromides, we envisioned that the dimethyl substituted alkene-allylic bromide substrate **1a** (Scheme 2) would also undergo a similar process.[6] However, in the presence of 20 mol % of InCl$_3$ in CH$_2$Cl$_2$ **1a** decomposed. Interestingly, in the presence of 4 Å molecular sieves, the diene product **2** was obtained via proton elimination cleanly in 68% isolated yield. We believe that molecular sieves in this reaction play the role of a neutral base to trap HBr after the reaction takes place.



Scheme 2.

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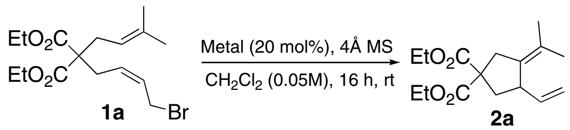
We next turned our attention to screening a variety of metals for the cyclization to determine which catalysts would be capable of effecting the reaction in substoichiometric amounts (Table 1). Thus **1a** was treated with 20 mol % of Lewis acids in CH_2Cl_2 (0.5 M) at room temperature for 16 h. Most of the Lewis acids failed to catalyze the reaction. Surprisingly, Lewis acids known to cleave carbon–halide bonds including $AlCl_3$, $AgSbF_6$, and AgOTf yielded less than 20% (entries 3, 21, and 22). From this study, we found $Fe(ClO_4)_3$, $ZnBr_2$, ZnI_2, $Bi(OTf)_3$, InBr, InI, $In(OTf)_3$, $InBr_3$, and $InCl_3$ (entries 5, 8, 9, 14, and 23–27) demonstrated promising catalytic ability for this reaction.

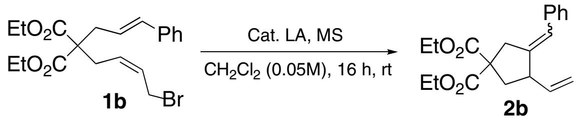
We next examined the phenyl-substituted substrate **1b** utilizing several of the most promising Lewis acid catalysts (Table 2). Again, we were surprised to find that none of the catalysts tested resulted in success with the exception of $Bi(OTf)_3$ (entry 15). $ZnBr_2$, ZnI_2, and $Fe(ClO_4)_3$ decomposed the starting material (entries 1–3). In the presence of 20 mol % InI mostly starting material was observed along with some decomposition (entry 4). When In(III) salts were employed ($InCl_3$, $InBr_3$, and $In(OTf)_3$) in the presence of 4 Å molecular sieves, trace amounts of the cyclized product **2b** were seen; however, yields were very poor and mostly decomposition was observed (entries 5, 6, and 9). In the absence of molecular sieves the starting material also decomposed (entry 7). The combination of $InCl_3$ with other types of molecular sieves was also tested; however, all of them (3 Å, 13X, Na^+13Y, or NH_4^+13Y) interfered with catalysis, and the starting material was recovered quantitatively (entries 8, and 10–12). On the other hand, employing only 10 mol % of $Bi(OTf)_3$ with 4 Å molecular sieves resulted in successful catalysis of cyclization to yield **2b** in 78% isolated yield. The combination of $Bi(OTf)_3$ with other types of molecular sieves in this reaction was found to be ineffective (entries 14, and 16–18).

Table 1
Lewis acid screen



Entry	Metal	Yield	Entry	Metal	Yield
1	MgI_2	SM	21	$AgSbF_6$	18%
2	$Mg(OTf)_2$	SM	22	AgOTf	20%
3	$AlCl_3$	8%	**23**	**InBr**	**63%**
4	$Sc(OTf)_3$	SM	**24**	**InI**	**81%**
5	**$Fe(ClO_4)_3$**	**63%**	**25**	**$In(OTf)_3$**	**66%**
6	$CuCl_2$	Trace	**26**	**$InBr_3$**	**71%**
7	$Cu(OTf)_2$	SM	**27**	**$InCl_3$**	**68%**
8	**$ZnBr_2$**	**91%**	28	$Sn(OTf)_2$	Trace
9	**ZnI_2**	**86%**	29	$Ho(OTf)_3$	SM
10	$Zn(OTf)_2$	SM + dec	30	$Lu(OTf)_3$	SM
11	$TiCl_4$	SM	31	$WO_2(OH)_2$	SM
12	Cp_2ZrCl_2	SM	32	IrCl(oct)	SM
13	$Zr(OC_3H_7)_4$	SM	33	$PtCl_2$	SM
14	**$Bi(OTf)_3$**	**58%**	34	$Au(PPh_3)Cl$	SM
15	Grubbs II	SM	35	AuCl	SM and dec
16	Wilkinson's	SM	36	$NaAuBr_4$	SM and dec
17	$[RhCl(C_2H_4)_2]_2$	SM	37	$La(OTf)_3$	SM
18	$Pd_2(dba)_3$ + dppf	SM	38	$Eu(OTf)_3$	SM
19	$Pd_2(dba)_3$	SM	39	$YbCl_3$	SM
20	$PdCl_2$	SM	40	$Yb(OTf)_3$	SM

Table 2
Phenyl-substituted substrates

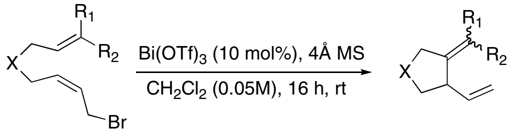


Entry	LA	MS	Yield
1	$ZnBr_2$ (20 mol %)	4 Å	dec
2	ZnI_2 (20 mol %)	4 Å	dec
3	$Fe(ClO_4)_3$ (20 mol %)	4 Å	dec
4	InI (20 mol %)	4 Å	SM and dec
5	$In(OTf)_3$ (20 mol %)	4 Å	Trace and dec
6	$InBr_3$ (20 mol %)	4 Å	Trace and dec
7	$InCl_3$ (20 mol %)	None	dec
8	$InCl_3$ (20 mol %)	3 Å	SM
9	$InCl_3$ (20 mol %)	4 Å	SM and dec
10	$InCl_3$ (20 mol %)	13X	SM
11	$InCl_3$ (20 mol %)	Na^+13Y	SM
12	$InCl_3$ (20 mol %)	NH_4^+13Y	SM
13	$Bi(OTf)_3$ (10 mol %)	None	dec
14	$Bi(OTf)_3$ (10 mol %)	3 Å	SM
15	**$Bi(OTf)_3$ (10 mol %)**	**4Å**	**78%**[a]
16	$Bi(OTf)_3$ (10 mol %)	13X	SM
17	$Bi(OTf)_3$ (10 mol %)	Na^+13Y	SM
18	$Bi(OTf)_3$ (10 mol %)	NH_4^+13Y	SM

[a] NMR yield (internal standard), *E*/*Z* = 5:1.

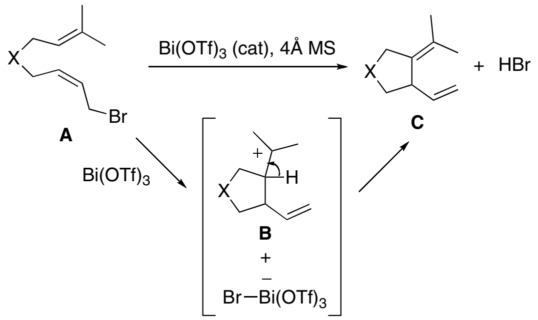
A variety of substrates were tested in the *exo*-trig cyclization catalyzed by $Bi(OTf)_3$, and the results are shown in Table 3. In the presence of 10 mol % of $Bi(OTf)_3$ and 4 Å molecular sieves in 0.05 M CH_2Cl_2, carbocycle **2a**, where both R_1 and R_2 were methyl, was synthesized in 58%

Table 3
Substrate modification



Entry	R_1	R_2	X	Yield	Prod
1	Me	Me	$C(CO_2Et)_2$	58%[a]	**2a**
2	Me	Me	NSO_2Ph	60%[b]	**3a**
3	Me	Me	O	dec	
4	H	Ph	$C(CO_2Et)_2$	78%[c]	**2b**
5	H	Me	$C(CO_2Et)_2$	SM	
6	H	H	$C(CO_2Et)_2$	SM	

[a] Isolated yield.
[b] NMR yield (internal standard).
[c] NMR yield (*E*/*Z* = 5:1).



Scheme 3. Proposed mechanism.

isolated yield (entry 1). Nitrogen heterocycle **3a** was produced in 60% yield (entry 2). If X was oxygen, the starting material decomposed (entry 3). Alkene substitution was also varied with mixed results. In the case of phenyl substituted alkene, **2b** was obtained in 78% yield (entry 4). However, with alkyl disubstituted alkene or terminal alkene, the substrate was recovered unreacted (entries 5 and 6).

A proposed mechanism is shown in Scheme 3. When treated with a catalytic amount of $Bi(OTf)_3$ to activate the allylic bromide, substrate **A** undergoes ionization to generate an allyl carbocation. Attack of the nucleophilic alkene produces carbocation intermediate **B** and $Br–Bi(OTf)_3^-$. Importantly, the stabilization of the carbocation in **B** is critical for this reaction. Stabilization is optimal with *gem*-dimethyl or phenyl substitution. Elimination of proton then yields the 1,3-diene product **C** and HBr as a byproduct. Molecular sieves serve to trap the HBr and prevent the decomposition of substrate and/or product.[7]

In conclusion, a $Bi(OTf)_3$ catalyzed *exo*-trig cyclization via halide activation was demonstrated. The choice of molecular sieves was critical as only 4 Å molecular sieves were effective in this particular reaction. Screening of Lewis acis showed that Zn(II), Fe(III), In(I), In(III), and Bi(III) catalysts were capable of activating the allylic halide; however, $Bi(OTf)_3$ was optimal for the phenyl substituted alkene. Further investigation into the unique role of bismuth Lewis acids is currently underway.

2. Experimental procedure

Procedure for exo-trig cyclization (**2a**): $Bi(OTf)_3$ (0.01 mol) was added to a solution of **1a** (0.1 mmol) and 4 Å molecular sieves (50 mg) in CH_2Cl_2 (2 mL). The mixture was stirred 16 h. Upon completion, the mixture was directly loaded onto a silica gel column and eluted with 95:5 hexane/EtOAc to obtain pure cyclized product **2a**.

General procedure for exo-trig cyclization (**2b**, **3a**): $Bi(OTf)_3$ (0.01 mol) was added to the solution of allyl bromide (0.1 mmol) and 4 Å molecular sieves (50 mg) in CH_2Cl_2 (2 mL). The mixture was stirred 16 h. Upon completion, the mixture was filtered through a short plug of silica gel with EtOAc (10 mL). Solvent was removed under reduced pressure and an internal standard (1,2,3-trimethoxybenzene, 0.1 mmol) was added. Yield was obtained by the integration of ^1H NMR resonances as compared to the internal standard.

Acknowledgments

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