Published in final edited form as:

Tetrahedron Lett. 2008 ; 49(24): 3888–3890.

Bi(OTf)₃-Catalyzed 5-Exo-Trig Cyclization via Halide Activation

Ryuji Hayashi and Gregory R. Cook*

Department of Chemistry and Molecular Biology, North Dakota State University, Fargo, ND 58105

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 some cases. This suggested that bismuth triflate possesses interesting halophilic properties.

The formation of carbocations¹ from a variety of organohalogen compounds² 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.

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 coworkers reported that catalytic amounts of BiCl₃ catalyzed the Friedel-Crafts reaction of acyl or vinyl chlorides with arenes.⁵ We recently reported the In(III)-catalyzed atom transfer cyclization⁶ and ring-closing Friedel-Craft reaction⁷ 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 reactions⁸ including an interesting BiBr₃-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 InCl₃ in CH₂Cl₂ **1a** decomposed. Interestingly, in the presence of 4Å 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.

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 CH₂Cl₂ (0.5M) at room temperature for 16 hours. Most of the Lewis acids failed to catalyze the reaction. Surprisingly, Lewis acids

* Corresponding author. Tel.: 1-701-231-7413; fax: 1-701-231-1057; e-mail: Gregory.cook@ndsu.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

known to cleave carbon-halide bonds including AlCl_3 , AgSbF_6 , and AgOTf yielded less than 20% (entries 3, 21, 22). From this study, we found $\text{Fe}(\text{ClO}_4)_3$, ZnBr_2 , ZnI_2 , $\text{Bi}(\text{OTf})_3$, InBr , InI , $\text{In}(\text{OTf})_3$, InBr_3 , and InCl_3 (entries 5, 8, 9, 14, 23, 24, 25, 26 and 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 $\text{Bi}(\text{OTf})_3$ (entry 15). ZnBr_2 , ZnI_2 , and $\text{Fe}(\text{ClO}_4)_3$ decomposed the starting material (entries 1, 2, 3). In the presence of 20 mol% InI mostly starting material was observed along with some decomposition (entry 4). When $\text{In}(\text{III})$ salts were employed (InCl_3 , InBr_3 , and $\text{In}(\text{OTf})_3$) in the presence of 4Å molecular sieves, trace amounts of the cyclized product **2b** were seen, however, yields were very poor and mostly decomposition was observed (entries 5, 6, 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 (3Å, 13X, Na^+13Y , or NH_4^+13Y) interfered with catalysis and the starting material was recovered quantitatively (entries 8, 10, 11, 12). On the other hand, employing only 10 mol% of $\text{Bi}(\text{OTf})_3$ with 4Å molecular sieves resulted in successful catalysis of cyclization to yield **2b** in 78% isolated yield. The combination of $\text{Bi}(\text{OTf})_3$ with other types of molecular sieves in this reaction were found to be ineffective (entries 14, 16, 17, 18).

A variety of substrates were tested in the exo-trig cyclization catalyzed by $\text{Bi}(\text{OTf})_3$ and the results are shown in Table 3. In the presence of 10 mol% of $\text{Bi}(\text{OTf})_3$ and 4Å molecular sieves in 0.05M CH_2Cl_2 , the carbocycle **2a**, where both R_1 and R_2 were methyl, was synthesized in 58% 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, 6).

A proposed mechanism is shown in Scheme 3. When treated with a catalytic amount of $\text{Bi}(\text{OTf})_3$ to activate the allylic bromide, substrate **A** undergoes ionization to generate an allyl carbocation. Attack of the nucleophilic alkene produces carbocation intermediate **B** and $\text{Br-Bi}(\text{OTf})_3^-$. 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 decomposition of substrate and/or product.⁷

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

Experimental Procedure

Procedure for Exo-Trig Cyclization (2a)

$\text{Bi}(\text{OTf})_3$ (0.01 mol) was added to a solution of **1a** (0.1 mmol) and 4Å molecular sieves (50 mg) in CH_2Cl_2 (2 mL). The mixture was stirred 16 hours. 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 CH₂Cl₂ (2 mL). The mixture was stirred 16 hours. 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 integration of ¹H-NMR resonances as compared to the internal standard.

Acknowledgements

We are grateful to the National Science Foundation (NSF-CHM-0616485) and the National Institutes of Health (NCRR-P20-RR15566) for financial support of this project. We also thank the NDSU Graduate School for a doctoral dissertation fellowship for RH.

References

1. a) Olah GA, Reddy P, Prakash S. Chem Rev 1992;92:69. b) Arnett EM, Molter KE. Acc Chem Res 1985;18:339. c) Kropp PJ. Acc Chem Res 1984;17:131. d) Brown HC. Acc Chem Res 1983;16:432. e) Olah GA, Prakash GKS. Acc Chem Res 1983;16:440. f) Hehre WJ. Acc Chem Res 1975;8:369.
2. a) Batail P, Fourmigué M. Chem Rev 2004;104:5379. [PubMed: 15535654] b) Alonso F, Beletskaya IP, Yus M. Chem Rev 2002;102:4009. [PubMed: 12428984]
3. a) Richard JP, Amyes TL, Toteva MM. Acc Chem Res 2001;34:981. [PubMed: 11747416] b) Kraus GA, Hon Y, Thomas PJ, Laramay S, Liras S, Hanson J. Chem Rev 1989;89:1591. c) Grob CA. Acc Chem Res 1983;16:426.
4. a) Olah GA, Klumpp DA. Acc Chem Res 2004;37:211. [PubMed: 15096058] b) Beak P. Acc Chem Res 1976;9:230. c) Olah GA. Acc Chem Res 1976;9:41.
5. Sun H, Hua R, Chen S, Yin Y. Adv Synth Catal 2006;348:1919.
6. Cook GR, Hayashi R. Org Lett 2006;8:1045. [PubMed: 16524264]
7. Hayashi R, Cook GR. Org Lett 2007;9:1311. [PubMed: 17346056]
8. a) Desmurs JR, Labrouillière M, Le Roux C, Gaspard H, Laporterie A, Dubac J. Tetrahedron Lett 1997;51:8871. b) Desmurs JR, Labrouillière M, Le Roux C, Gaspard H, Laporterie A, Dubac J. Tetrahedron Lett 1997;51:8874. Suzuki, H.; Matano, Y., editors. Organobismuth Chemistry. Elsevier; Amsterdam: 2001. d) Olah GA, Prahash SGK, Sommer J. Science 1979;206:13. [PubMed: 17812427] e) Gaspard-Iloughmane H, Le Roux C. Eur J Org Chem 2004:2517.
9. Lian Y, Hinkle RJ. J Org Chem 2006;71:7071. [PubMed: 16930067]

Scheme 1.

Scheme 2.

Scheme 3.
Proposed Mechanism

Table 1

Lewis Acid Screen

Entry	Metal	Yield
1	MgI	SM
2	MgOTf	SM
3	AlCl_3	8 %
4	$\text{Sc}(\text{OTf})_3$	SM
5	$\text{Fe}(\text{ClO}_4)_3$	63 %
6	CuCl_2	trace
7	$\text{Cu}(\text{OTf})_2$	SM
8	ZnBr_2	91 %
9	ZnI_2	86 %
10	$\text{Zn}(\text{OTf})_2$	SM + dec
11	TiCl_4	SM
12	ZrCl_2Cp_2	SM
13	$\text{Zr}(\text{OC}_3\text{H}_7)_4$	SM
14	$\text{Bi}(\text{OTf})_3$	58 %
15	Grubbs II	SM
16	Wilkinson's	SM
17	$[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$	SM
18	$\text{Pd}(\text{dppf})$	SM
19	$\text{Pd}(\text{dba})$	SM
20	PdCl_2	SM
21	AgSbF_6	18 %
22	AgOTf	20 %
23	InBr	63 %
24	InI	81 %
25	$\text{In}(\text{OTf})_3$	66 %
26	InBr_3	71 %
27	InCl_3	68 %
28	$\text{Sn}(\text{OTf})_2$	trace
29	$\text{Ho}(\text{OTf})_3$	SM
30	$\text{Lu}(\text{OTf})_3$	SM
31	$\text{WO}_2(\text{OH})_2$	SM
32	$\text{IrCl}(\text{oct})$	SM
33	PtCl_2	SM
34	$\text{Au}(\text{PPh}_3)\text{Cl}$	SM
35	AuCl	SM and dec
36	NaAuBr_4	SM and dec
37	$\text{La}(\text{OTf})_3$	SM
38	$\text{Eu}(\text{OTf})_3$	SM
39	YbCl_3	SM
40	$\text{Yb}(\text{OTf})_3$	SM

Table 2

Phenyl-substituted Substrates

Entry	LA	MS	Yield
1	ZnBr_2 (20 mol%)	4Å	dec
2	ZnI_2 (20 mol%)	4Å	dec
3	$\text{Fe}(\text{ClO}_4)_3$ (20 mol%)	4Å	dec
4	InI (20 mol%)	4Å	SM and dec
5	$\text{In}(\text{OTf})_3$ (20 mol%)	4Å	trace and dec
6	InBr_3 (20 mol%)	4Å	trace and dec
7	InCl_3 (20 mol%)	none	dec
8	InCl_3 (20 mol%)	3Å	SM
9	InCl_3 (20 mol%)	4Å	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	$\text{Bi}(\text{OTf})_3$ (10 mol%)	none	dec
14	$\text{Bi}(\text{OTf})_3$ (10 mol%)	3Å	SM
15	$\text{Bi}(\text{OTf})_3$ (10 mol%)	4Å	78%^a
16	$\text{Bi}(\text{OTf})_3$ (10 mol%)	13X	SM
17	$\text{Bi}(\text{OTf})_3$ (10 mol%)	Na^+13Y	SM
18	$\text{Bi}(\text{OTf})_3$ (10 mol%)	NH_4^+13Y	SM

^a NMR yield (internal standard), E/Z=5:1

Table 3

Substrate Modification

Entry	R ₁	R ₂	X	Yield	Prod
1	Me	Me	C(CO ₂ Et) ₂	58 % ^a	2a
2	Me	Me	NSO ₂ Ph	60 % ^b	3a
3	Me	Me	O	dec	
4	H	Ph	C(CO ₂ Et) ₂	78 % ^c	2b
5	H	Me	C(CO ₂ Et) ₂	SM	
6	H	H	C(CO ₂ Et) ₂	SM	

^a Isolated yield.

^b NMR yield (internal standard).

^c NMR yield (E/Z=5:1)