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Multicatalytic Synthesis of Complex Tetrahydrofurans Involving Bismuth(III) Triflate Catalyzed Intramolecular Hydroalkoxylation of Unactivated Olefins

Brendan D. Kelly, Julia M. Allen, Rachel E. Tundel, and Tristan H. Lambert*

Department of Chemistry, Columbia University, New York, New York 10027

tl2240@columbia.edu

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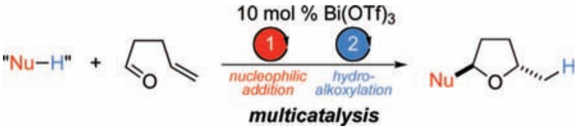
ABSTRACT



A multicatalytic synthesis of complex tetrahydrofurans has been developed involving a $Bi(OTf)_3$-catalyzed nucleophilic addition/hydroalkoxylation sequence. Complex tetrahydrofuranyl products may be formed rapidly in high yield and with good diastereoselectivity. The demonstrated scope of hydroalkoxylation has also been expanded to include substrates bearing useful functional handles including carboxylate ester, olefin, nitrile, and nitro groups.

Extensive reliance on iterative strategies represents perhaps the greatest deficiency in modern synthetic organic chemistry. Indeed, the traditional single-pot/single-transformation approach is maximally inefficient in terms of time and materials and ultimately serves to severely limit overall process yields. Thus it stands to reason that strategies designed to alleviate the need for iterative preparations have the potential to significantly impact the science of chemical synthesis. One such strategy is described by the term multicatalysis,[1] wherein multiple distinct catalytic steps are executed during a single operation, in either a tandem or sequential fashion. Although there has been increasing recognition of the power of multicatalytic synthesis, the number and range of examples disclosed in this area to date is still quite limited.

Recognizing the vast untapped potential that exists in the field of multicatalysis, our group has initiated a program with the broad goals of (1) developing multicatalytic processes for the efficient synthesis of valuable organic architectures and (2) inventing new chemical technologies that enable these processes.[2] As part of this program, we have initiated investigations into the multicatalytic paradigm illustrated in eq 1, aimed at the synthesis of complex heterocycles. Under our general design, we envision the conflation of nucleophilic addition and electrophilic cyclization events to convert simple unsaturated aldehydes or imines of the type **1** into complex cyclic ether or amine products **2** (Scheme 1A). With this framework in mind, we set as our first goal the development of multicatalytic reactions terminated by hydroalkoxylation (Scheme 1B).

The intramolecular hydroalkoxylation of olefins represents a direct and economical strategy to construct complex cyclic ethers from acyclic precursors. Despite the power of this strategy, however, the number of highly efficient methods for effecting hydroalkoxylation of unactivated olefins is rather sparse. Recently, several methods have been advanced that exploit transition metal,[3] Lewis acid,[4] or Brønsted acid[5] agents to catalyze this transformation. Given the reaction design illustrated in eq 1, we felt that the successful

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(1) For selected recent reviews on multicatalytic concepts, see: (a) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754. (b) Lee, J. M.; Na, Y.; Han, H.; Chang, S. *Chem. Soc. Rev.* **2004**, *33*, 302. (c) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001. (d) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (e) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1. (f) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477.

(2) Cernak, T. A.; Lambert, T. H. *J. Am. Chem. Soc.* **2009**. Accepted for publication.

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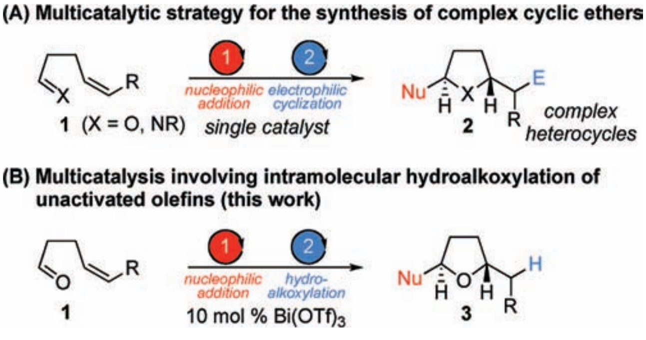
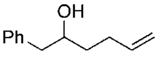
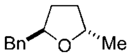
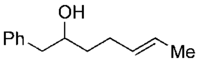
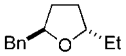
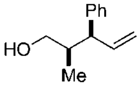
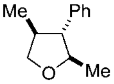
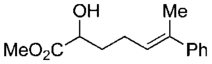
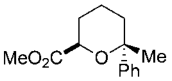
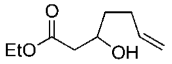
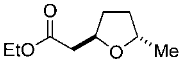
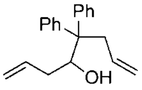
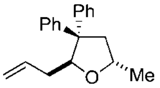
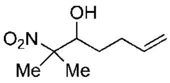
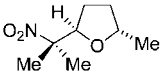
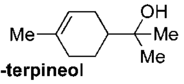
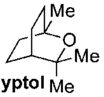
Scheme 1. Multicatalytic Strategies for Heterocycle Synthesis



development of this process would be well attended by the appropriate identification of a Lewis acidic catalyst.

Unfortunately, of the Lewis acidic hydroalkoxylation catalysts that have been reported, we found each of them to be either inconvenient to prepare or poorly efficient. We thus sought to identify a more suitable alternative. Inspired by the reports of Shibasaki[6a] and Rueping[6b] that $Bi(OTf)_3$ is capable of catalyzing the hydrofunctionalization of dienes or styrenyl olefins, respectively, and by the increasing body of work regarding $Bi(OTf)_3$-catalyzed nucleophilic addition reactions,[7] we decided to examine this reagent for its hydroalkoxylation proficiency. Thus, we found that 10 mol % $Bi(OTf)_3$ at 80 °C in DCE effectively catalyzed the conversion of 1-phenyl-5-hexen-2-ol to 2-benzyl-5-methyltetrahydrofuran in 94% yield after only 50 min (Table 1, entry 1). A comparison study revealed that $Bi(OTf)_3$ offers reaction rates superior to those of other metal triflate based hydroalkoxylation catalysts (see Supporting Information).

Table 1. $Bi(OTf)_3$-Catalyzed Intramolecular Hydroalkoxylation of Unactivated Olefins[a]

entry	substrate	product	% yield	*anti:syn*[b]
1			94	2.4:1
2			90[c]	2.4:1
3[d]			83	6.8:1
4			72	1:5
5			80	2.2:1
6			78	4.5:1
7			88	5:1
8[e]	 α-terpineol	 eucalyptol	67	--

[a] Reactions were run in the presence of 10 mol % $Bi(OTf)_3$ at a concentration of 0.2 M in DCE at 80 °C. [b] Diastereomeric ratios were determined by GC or ^{1}H NMR analysis. [c] 2-Benzyl-6-methyltetrahydropyran was also isolated in 5% yield. [d] Reaction run at 70 °C. [e] Reaction run in benzene at 40 °C.

Before progressing to our multicatalytic goal, we decided to examine the substrate scope of the $Bi(OTf)_3$-catalyzed hydroalkoxylation reaction, particularly in the context of the highly functionalized substrates required by our reaction design. Thus, we found that both terminal and internal olefins underwent hydroalkoxylation to furnish tetrahydrofurans in high yield with preference for the *anti* diastereomer (Table 1, entries 1 and 2). Not surprisingly, the presence of additional biasing substituents increased the level of diastereoselection (entry 3). Cyclization to form a pyran also proved possible, as shown in entry 4. Notably, this styrenyl substrate gave rise to a challenging 2,2,6-trisubstituted pyran with good yield and diastereoselectivity. Importantly, we have found that carboxylate ester functionality is well tolerated, thus allowing for the production of cyclic ethers bearing this useful functional handle (entries 4 and 5). Indeed, even a β-hydroxyester substrate was found to undergo facile hydroalkoxylation without any observable elimination of water (entry 5). In addition, we have found that bisolefinic and nitro substrates are well tolerated in this reaction, allowing efficient access to substituted cyclic ether adducts bearing these versatile functional motifs (entries 6 and 7). Finally, although tertiary alcohols tend to be difficult to employ in hydroalkoxylation processes because of their propensity to undergo dehydration, we have found that in certain circumstances this functionality can be successfully employed. Thus, for example, eucalyptol could be prepared in good yield by the treatment of α-terpineol with 10 mol % $Bi(OTf)_3$ in benzene at 40 °C (entry 8).

Satisfied that the substrate scope allowed by $Bi(OTf)_3$ catalysis was suitably broad, we next sought to actualize the multicatalytic goal illustrated in Scheme 1B. After much experimentation, we found that complex tetrahydrofurans can be readily assembled by the coupling of a range of silylated nucleophilic partners and aldehydes under the action of 10

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(3) (a) Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536. (b) Ohta, T.; Kataoka, Y.; Miyoshi, A.; Oe, Y.; Furukawa, I.; Ito, Y. *J. Organomet. Chem.* **2007**, *692*, 671. (c) Grant, V. H.; Liu, B. *Tetrahedron Lett.* **2005**, *46*, 1237. (d) Komeyama, K.; Morimoto, T.; Nakayama, Y.; Takaki, K. *Tetrahedron Lett.* **2007**, *48*, 3259. (e) Marotta, E.; Foresti, E.; Marcelli, T.; Peri, F.; Righi, P.; Scardovi, N.; Rosini, G. *Org. Lett.* **2002**, *4*, 4451. (f) Yang, C.-G.; Reich, N. W.; Shi, Z.; He, C. *Org. Lett.* **2005**, *7*, 4553. (g) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966.

(4) (a) Coulombel, L.; Rajzmann, M.; Pons, J.-M.; Olivero, S.; Duñach, E. *Chem. Eur. J.* **2006**, *12*, 6356. (b) Coulombel, L.; Favier, I.; Duñach, E. *Chem. Commun.* **2005**, 2286.

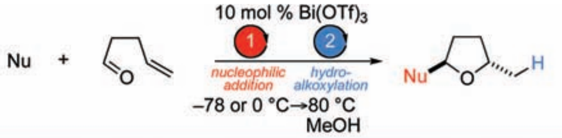
(5) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179.

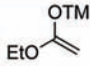
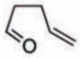
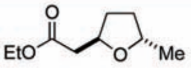
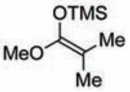
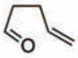
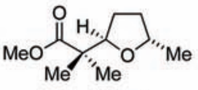
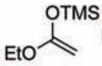
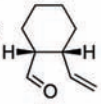
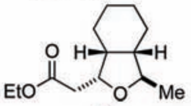
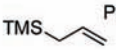
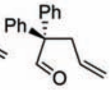
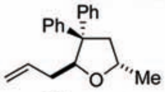
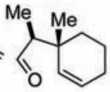
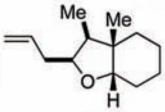
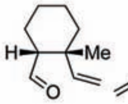
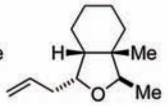
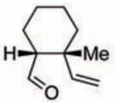
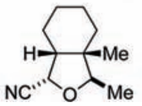
(6) (a) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 1611. (b) Rueping, M.; Nachtsheim, B. J.; Kuenkel, A. *Synlett* **2007**, 1391.

(7) For reviews on the chemistry of $Bi(OTf)_3$, see: (a) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373. (b) Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517.

mol % Bi(OTf)$_3$ at either −78 or 0 °C, followed by heating the reaction mixture to 80 °C with the addition of a small amount of MeOH to cleave the silyl ether intermediate (Table 2). Specifically, we found that Mukaiyama aldol/hydroalkoxylation sequences could be achieved with high efficiency to furnish 2-acetyltetrahydrofurans, a structural motif widely encountered in natural product architectures (entries 1−3). Alternatively, Sakurai addition/hydroalkoxylation proved feasible, providing access to tetrahydrofuranyl products bearing an olefinic functional handle (entries 4−6). Finally, we have found that employment of TMSCN allows for the efficient production of a complex tetrahydrofuranyl nitrile (entry 7).

Table 2. Bi(OTf)$_3$-Catalyzed Multicatalytic Synthesis of Complex Tetrahydrofurans[a]



entry	Nu	substrate	product	% yield	dr[b]
1				76	2.2:1
2				84	5.9:1
3				76	7.4:1: 0.1:0.01
4				78	4.5:1
5				70	4:1
6				75	10.7:1: 0.3:0.1
7[c]	TMSCN			68	9.1:1.8: 1.4:1.0

[a] Reactions were run in the presence of 10 mol % Bi(OTf)$_3$ at a concentration of 0.2 M in DCE; MeOH (1.5 equiv) was added before the hydroalkoxylation event. [b] Diastereomeric ratios were determined by GC or ^{1}H NMR analysis. [c] Hydroalkoxylation performed at 120 °C in a sealed vial.

Congruent with the findings of Spencer[8] and Hartwig,[5] we have found that the reactivity of Bi(OTf)$_3$ mirrors that of triflic acid, supporting the notion that the hydroalkoxylation activity of Bi(OTf)$_3$ is due to the low-level release of triflic acid. To support this claim, we have found that triflic acid catalyzes hydroalkoxylation with efficiency similar to that of Bi(OTf)$_3$ (see Supporting Information). In addition, we presume TMSOTf, generated from Bi(OTf)$_3$ and the silyl nucleophile, is the true operative catalyst for the nucleophilic addition step as proposed by Carreira.[9] Thus, we suggest the overall mechanistic picture shown in Figure 1, whereby a single reagent, Bi(OTf)$_3$, serves as precatalyst for two distinct catalytic transformations in a single pot. Given the moisture sensitivity of TfOH and TMSOTf and the constrasting moisture stability of Bi(OTf)$_3$, we suggest the present protocol also offers a significant practical advantage of convenience and operational simplicity.

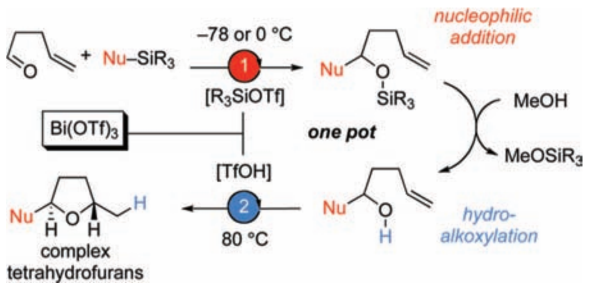


Figure 1. Mechanistic picture of multicatalytic tetrahydrofuran synthesis.

To conclude, we have developed a new multicatalytic synthesis of complex tetrahydrofuran products that capitalizes on the dual activities of Bi(OTf)$_3$. To facilitate this chemistry, we have demonstrated the capacity of Bi(OTf)$_3$ to effectively catalyze the intramolecular hydroalkoxylation of unactivated olefins. In doing so we have also significantly expanded the substrate scope of such hydroalkoxylation reactions to include substrates possessing a range of useful functionality. Currently, the development of related multicatalytic concepts is ongoing in our laboratories.

Acknowledgment. We are grateful to Pfizer for an unrestricted research grant and to Columbia University for funding. We would like to thank Prof. Jim Leighton (Columbia University) for a helpful discussion and the Sames Group (Columbia University) for use of their instrumentation.

Supporting Information Available: Experimental procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] (a) Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem. Eur. J.* **2004**, *10*, 484. (b) See ref 4.

[9] Carreira, E. M.; Singer, R. A. *Tetrahedron Lett.* **1994**, *35*, 4323.