Homogeneous Catalysis

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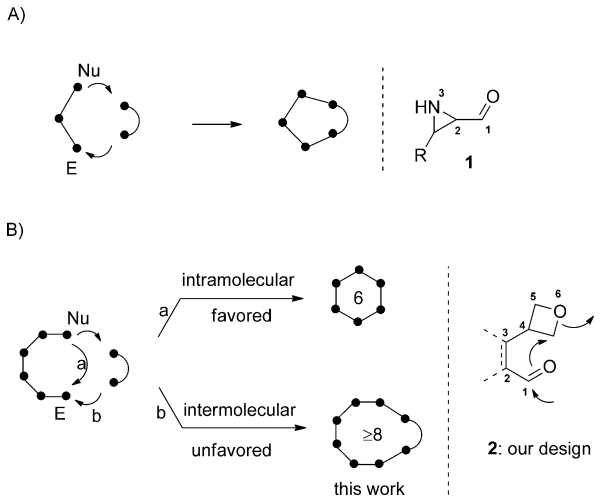
Synthesis of Eight-Membered Lactones: Intermolecular [6+2] Cyclization of Amphoteric Molecules with Siloxy Alkynes**

*Wanxiang Zhao, Zhaobin Wang, and Jianwei Sun**

Medium-sized lactones (8- to 11-membered rings) are important structural motifs that occur in a wide range of biologically active natural products.[1] The efficient synthesis of these medium-sized lactones has attracted considerable attention in organic synthesis.[2–5] Nevertheless, there are only a limited number of methods available, with lactonization and ring-closing metathesis (RCM) being the most popular choices.[2–5] Owing to ring strain and transannular interactions,[6] the formation of medium-sized lactones have proven difficult.[2,7] Although the yields can sometimes be improved under high dilution or slow addition conditions, the results are unpredictable and highly dependent upon the substrates. Thus, there remains a great need for the development of new strategies for the synthesis of medium-sized lactones. Herein we report our design of a new type of amphoteric molecule for the synthesis of eight-membered ring lactones through [6+2] cyclization.

Amphoteric molecules, which bear both nucleophilic and electrophilic moieties, have been demonstrated as a versatile platform for the development of new processes with high bond-forming efficiency and atom economy.[8,9] For example, isocyanides are well-known (1,1)-amphoteric molecules because the terminal carbon atom can be both nucleophilic and electrophilic sites for bond formation.[8] Recently, Yudin and co-workers demonstrated that aziridine aldehydes (**1**; Scheme 1 A) can serve as three-atom "connectors", thus representing a (1,3)-amphoteric system.[9] With this system, they have developed a range of efficient and chemoselective transformations which circumvent using protecting groups.[9] We envisaged that the design of (1,*n*)-amphoteric molecules (where $n > 5$) may provide new opportunities for the formation of medium- and large-sized rings upon cyclization with dipolarophiles. However, the nucleophilic and electrophilic sites in such systems may react in the more favored intramolecular fashion, for example, the formation of a six-membered ring in a (1,6)-amphoteric system (Scheme 1 B, path a), thereby invoking difficulty in designing such systems for intermolecular cyclizations.



Scheme 1. Examples of amphoteric molecules and their reaction topology. A) (1,3)-Amphoteric system (e.g., Yudin's aziridine aldehyde **1**). B) (1,6)-Amphoteric system (our design).

Oxetanes represent a useful structural unit that is less reactive than epoxides and aldehydes, but still prone to ring-opening upon activation.[10–11] We decided to take advantage of such a combination of stability and reactivity to design a new (1,6)-amphoteric system. Our initial design is exemplified in structure **2** (Scheme 1 B), in which an oxetane moiety is connected to an aldehyde group through a two-atom linker. The aldehyde carbon atom (C1) serves as the electrophilic center. Upon attack by a nucleophile, the resulting nucleophilic oxygen atom is expected to initiate an intramolecular ring-opening process and concomitantly generate another nucleophilic oxygen center at the 6-position. Thus, the system is (1,6)-amphoteric overall.

Next, we began to test our designed system for the synthesis of medium- and large-sized rings. We initially aimed at developing new [6+2] cyclization processes for the formation of eight-membered rings. After some trials, we were pleased to identify siloxy alkynes[12] as excellent reaction partners for our (1,6)-amphoteric system to form eight-membered lactones. Specifically, the reaction between 2-(oxetan-3-yl)benzaldehyde (**3**) and siloxy alkyne **4**, in the presence of triflimide ($HNTf_2$, 10 mol%) as the catalyst and CH_2Cl_2 as the solvent, proceeds efficiently at room temperature to form the eight-membered lactone **5** in 71% yield upon isolation (Table 1, entry 1). The structure assignment of **5** was based on the X-ray crystallography of its crystalline derivative (see the Supporting Information). Unlike the conventional formation of medium-sized lactones using

[*] W. Zhao, Z. Wang, Prof. Dr. J. Sun
Department of Chemistry
The Hong Kong University of Science and Technology
Clear Water Bay, Kowloon, Hong Kong (China)
E-mail: sunjw@ust.hk

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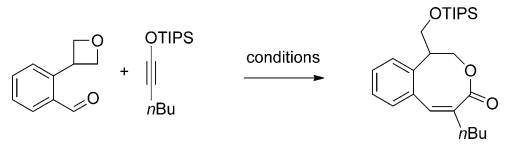
Table 1: Effect of reaction conditions on the 8-membered lactone formation.[a]

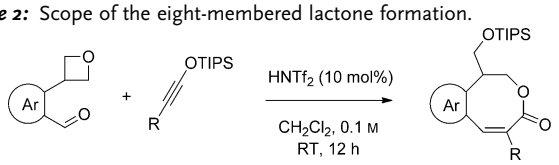


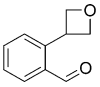
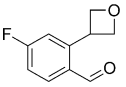
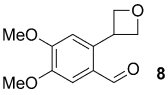
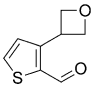
3 4 5

Entry	Catalyst (mol%)	Solvent	Yield [%][b]
1	$HNTf_2$ (10)	CH_2Cl_2	71
2	$AgNTf_2$ (5)	CH_2Cl_2	50
3	AgOTf (5)	CH_2Cl_2	39[c]
4	$AuCl_3$ (5)	CH_2Cl_2	36[c]
5	TfOH (10)	CH_2Cl_2	52
6	*p*-TsOH (10)	CH_2Cl_2	trace
7	MsOH (10)	CH_2Cl_2	trace
8	TFA (10)	CH_2Cl_2	trace
9	$HNTf_2$ (10)	toluene	trace
10	$HNTf_2$ (10)	Et_2O	trace
11	$HNTf_2$ (10)	EtOAc	56
12	$HNTf_2$ (10)	CH_2Cl_2	52[d]

[a] All reactions were performed on a 0.25 mmol scale of **3** with catalyst (5-10 mol%) and **4** (1.2 equiv) in 2.5 mL of solvent (0.1 M) at room temperature for 12 h. [b] Yield of isolated product. [c] Yield determined by NMR spectroscopy using mesitylene as the internal standard. [d] Reaction run at 0.5 M concentration. Ms = methanesulfonyl, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid, TIPS = triisopropylsilyl, Ts = 4-toluenesulfonyl.

Table 2: Scope of the eight-membered lactone formation.



Entry	(1,6)-Amphoteric molecules	R	Yield [%][a]
1	 3	*n*Bu	71
2			62
3		*t*Bu	60
4		*n*Oct	64
5			41
6		Ph	47
7	 7	*n*Bu	70
8			49
9		*t*Bu	87
10		*n*Oct	74
11			51
12			71
13	 8	*n*Bu	47
14		*t*Bu	52
15	 9	*n*Bu	49
16		*t*Bu	53
17		Ph	48

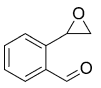
[a] Yield of isolated product.

intramolecular lactonization or RCM strategies, this unusual eight-membered lactone formation is an intermolecular process involving a sequence of several efficient bond-forming/breaking events (see below).[13]

The use of silver triflimide ($AgNTf_2$), which was previously reported to be the catalyst of choice for aldehyde olefination with siloxy alkynes,[14] proved less effective in our lactone formation reaction (Table 1, entry 2). Other Lewis acids, such as AgOTf and $AuCl_3$, did not improve the efficiency. Among all the Brønsted acids evaluated, triflic acid (TfOH) can promote the process, albeit with lower efficiency (entry 5).[15] Other weaker acids, such as MsOH, *p*-TsOH, and TFA, could not promote the desired lactone formation (entries 6–8). In addition, the reaction proceeds less efficiently in other solvents, such as toluene, Et_2O, and EtOAc (entries 9–11). Finally, a decreased yield was obtained when the reaction was run at a higher concentration (entry 12). The observed excellent efficiency with $HNTf_2$ as the catalyst can be explained by its high Brønsted acidity in a polar aprotic solvent combined with the low nucleophilicity of its counterion (Tf_2N^-).[15–17]

We examined the reaction scope using our standard reaction conditions (Table 1, entry 1). As shown in Table 2, a range of (1,6)-amphoteric molecules, such as those having aryl linkers substituted with electron-withdrawing and electron-donating groups, as well as those with a thiophene linker, can all participate successfully in the [6+2] cyclization process to form the desired eight-membered lactone products. With regard to the substitutions on the siloxy alkynes, it is noteworthy that the increased steric hindrance does not result in a significant decrease in efficiency (entries 2, 3, and 9). Aryl substitution on the siloxy alkynes is tolerated (entries 6 and 17). Finally, the TIPS-protected primary alcohol is retained under our standard protocol (entry 12), thus illustrating functional group compatibility of the reaction conditions with the silyl protecting groups.

Although the use of an aryl linker between the oxetane and aldehyde moieties proved successful, molecules having a $C(sp^3)$–$C(sp^3)$ linker give low yields for these [6+2] cyclization reactions. It is also worth noting that the substitution of an oxirane (e.g., **6**) for the oxetane moiety does not carry a similar intermolecular reaction pattern with siloxy alkynes. Instead, when subjected to our standard reaction conditions, aldehyde **6** undergoes a known intermolecular homocyclization between the oxirane and the aldehyde functionalities,[18] and no desired lactone product is observed. This observation can be explained by the higher reactivity (lower stability) of the oxirane relative to that of the oxetane functionality.



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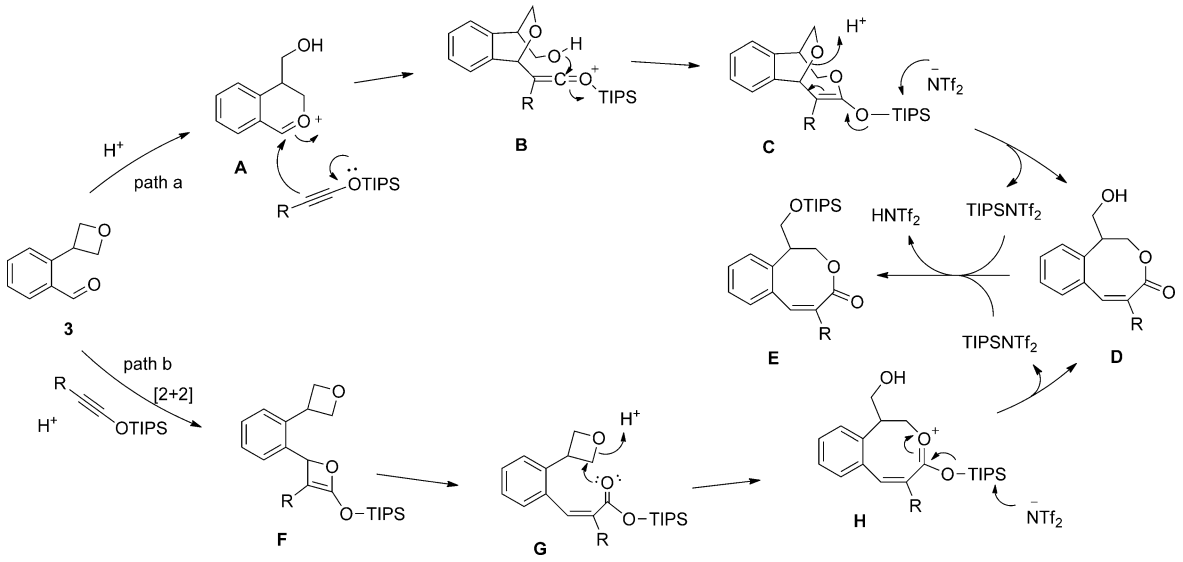
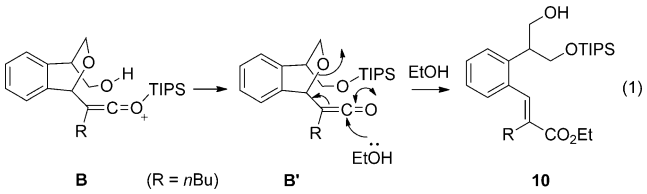
With regard to the reaction mechanism, we have proposed two possible pathways (Scheme 2). In path a, the reaction begins with the oxetane ring-opening to form the oxonium intermediate **A**[19] with subsequent attack of the electron-rich alkyne to give the ketenium intermediate **B**. Furthermore, 8-exo-dig cyclization forms cyclic silyl ketene acetal **C**. Next, **C** undergoes a ring-opening step to form **D**, which is silylated to deliver the observed eight-membered lactone **E**. Alternatively, as shown in path b, a [2+2] cycloaddition between the



Scheme 2. Plausible reaction mechanisms.

alkyne and aldehyde **3** forms oxetene **F**,[20] which undergoes ring-opening to give the α,β-unsaturated ester **G**.[21] Upon activation of the oxetane by the acid catalyst, an 8-exo-tet cyclization step gives the same intermediate **D** via **H**. We have made alkene **G** (R = H) separately and subjected it to our reaction conditions. The corresponding eight-membered lactone **E** (R = H) was obtained (see the Supporting Information), thus suggesting that **G** can be a viable intermediate. However, for path a, we were able to isolate the ester **10** by quenching the reaction with EtOH at partial conversion [Eq. (1)], and it is likely formed from the intermediate **B** by



a silyl shift and ethanol addition to the ketene **B′**. When the product **E** is subject to EtOH in the presence of $HNTf_2$ compound **10** is not formed.

In summary, we have designed a new type of (1,6)-amphoteric molecule by appropriate positioning of the oxetane and aldehyde functional groups within a molecule. Enabled by this design, we have successfully demonstrated an efficient [6+2] cyclization process between these (1,6)-amphoteric molecules and siloxy alkynes to form a range of eight-membered lactones. Unlike the conventional intramolecular approaches, such as lactonization and ring-closing metathesis, our method represents the first intermolecular reaction for the eight-membered lactone synthesis. Preliminary mechanistic analysis suggests that this unusual process involves a sequence of several selective ring-opening/ring-closing events with concomitant bond formation and cleavage. This approach is now added to the limited number of strategies available for the elaboration of medium-sized lactones. The development of other useful processes employing these new amphoteric molecules is underway.

Experimental Section

General procedure: The aldehyde (0.2 mmol), the siloxy alkyne (0.24 mmol), and anhydrous CH_2Cl_2 (2.0 mL) were added to an oven-dried 4 mL vial was added under N_2. Next, $HNTf_2$ (0.1 g mL^{-1} in CH_2Cl_2, 56 μL, 0.02 mmol) was added via syringe at room temperature. The reaction mixture was stirred at the same temperature and monitored by thin layer chromatography. Upon completion (ca. 12 h), the reaction was quenched with saturated $NaHCO_3$ aqueous solution (10 mL) and diluted with CH_2Cl_2 (2 mL). The organic layer was separated and washed with H_2O (3 × 10 mL) and brine (3 × 10 mL), dried over $MgSO_4$, filtered, and concentrated. The desired product was purified by flash chromatography on silica gel.

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[1] For a review, see: a) G. Rousseau, *Tetrahedron* **1995**, *51*, 2777–2849; For other examples of natural products containing medium-ring lactones, see: b) S. Sang, X. Cheng, H. Fu, D. Shieh, N. Bai, K. Lapsley, R. E. Stark, R. T. Rosen, C. Ho, *Tetrahedron Lett.* **2002**, *43*, 2547–2549; c) M. Tsoukatou, H. Siapi, C. Vagias, V. Roussis, *J. Nat. Prod.* **2003**, *66*, 444–446; d) A. Bermejo, J. R. Tormo, N. Cabedo, E. Estornell, B. Figadere, D. Cortes, *J. Med. Chem.* **1998**, *41*, 5158–5166.

[2] For reviews on the formation of medium- and large-sized lactones, see: a) A. Parenty, X. Moreau, J.-M. Campagne, *Chem. Rev.* **2006**, *106*, 911–939; b) I. Shiina, *Chem. Rev.* **2007**, *107*, 239–273.

[3] For examples of RCM approaches to the synthesis of medium-sized lactones, see: a) A. K. Chatterjee, J. P. Morgan, M. Scholl,

R. H. Grubbs, *J. Am. Chem. Soc.* **2000**, *122*, 3783 – 3784; b) K. R. Buszek, N. Sato, Y. Jeong, *Tetrahedron Lett.* **2002**, *43*, 181 – 184; c) T. Takahashi, H. Watanabe, T. Kitahara, *Heterocycles* **2002**, *58*, 99 – 104; d) Y. Baba, G. Saha, S. Nakao, C. Iwata, T. Tanaka, T. Ibuka, H. Ohishi, Y. Takemoto, *J. Org. Chem.* **2001**, *66*, 81 – 88; e) C. O. Kangani, A. M. Brückner, D. P. Curran, *Org. Lett.* **2005**, *7*, 379 – 382; f) P. Davoli, A. Spaggiari, L. Castagnetti, F. Prati, *Org. Biomol. Chem.* **2004**, *2*, 38 – 47; g) R. V. Anand, S. Baktharaman, V. K. Singh, *J. Org. Chem.* **2003**, *68*, 3356 – 3359; h) M. K. Gurjar, R. Nagaprasad, C. V. Ramana, *Tetrahedron Lett.* **2003**, *44*, 2873 – 2875; i) E. Diez, D. J. Dixon, S. V. Ley, A. Polara, F. Rodriguez, *Synlett* **2003**, 1186 – 1188; j) D. Liu, S. A. Kozmin, *Org. Lett.* **2002**, *4*, 3005 – 3007; k) A. Fürstner, K. Radkowski, C. Wirtz, R. Goddard, C. W. Lehmann, R. Mynott, *J. Am. Chem. Soc.* **2002**, *124*, 7061 – 7069; l) J. I. Aird, A. N. Hulme, J. W. White, *Org. Lett.* **2007**, *9*, 631 – 634; m) N. Brown, G. Gao, M. Minatoya, B. Xie, D. VanderVelde, G. H. Lushingto, J. H. Perchellet, E. M. Perchellet, K. R. Crow, K. R. Buszek, *J. Comb. Chem.* **2008**, *10*, 628 – 631.

[4] For examples of lactonization approaches to the synthesis of medium-sized lactones, see: a) T. Tabuchi, K. Kawamura, J. Inanaga, M. Yamaguchi, *Tetrahedron Lett.* **1986**, *27*, 3889 – 3890; b) B. Simonot, G. Rousseau, *J. Org. Chem.* **1993**, *58*, 4 – 5; c) K. R. Buszek, N. Sato, Y. Jeong, *J. Am. Chem. Soc.* **1994**, *116*, 5511 – 5512; d) A. N. Hulme, G. E. Howells, *Tetrahedron Lett.* **1997**, *38*, 8245 – 8248; e) I. Shiina, M. Kubota, H. Oshiumi, M. Hashizume, *J. Org. Chem.* **2004**, *69*, 1822 – 1830; f) I. Shiina, M. Hashizume, Y. Yamai, H. Oshiumi, T. Shimazaki, Y. Takasuna, R. Ibuka, *Chem. Eur. J.* **2005**, *11*, 6601 – 6608; g) E. Metay, E. Léonel, J. Nédélec, *Synth. Commun.* **2008**, *38*, 889 – 904; h) J. D. White, C. M. Lincoln, J. Yang, W. H. C. Martin, D. B. Chan, *J. Org. Chem.* **2008**, *73*, 4139 – 4150; i) J. Pietruszka, A. C. M. Rieche, *Adv. Synth. Catal.* **2008**, *350*, 1407 – 1412.

[5] For alternative approaches to the synthesis of medium-sized lactones, see: a) D. M. Tapiolas, M. Roman, W. Fenical, T. J. Stout, J. Clardy, *J. Am. Chem. Soc.* **1991**, *113*, 4682 – 4683; b) S. Inoue, Y. Iwabuchi, H. Irie, S. Hatakeyama, *Synlett* **1998**, 735 – 736; c) Ref. [1d]; d) H. Ohi, S. Inoue, Y. Iwabuchi, H. Irie, S. Hatakeyama, *Synlett* **1999**, 1757 – 1759; e) R. A. Pilli, M. M. Victor, *Tetrahedron Lett.* **2002**, *43*, 2815 – 2818; f) E. A. Anderson, J. E. P. Davidson, J. R. Harrison, P. T. O'Sullivan, J. W. Burton, I. Collins, A. B. Holmes, *Tetrahedron Lett.* **2002**, *58*, 1943 – 1971; g) P. T. O'Sullivan, W. Buhr, M. A. M. Fuhry, J. R. Harrison, J. E. Davies, N. Feeder, D. R. Marshall, J. W. Burton, A. B. Holmes, *J. Am. Chem. Soc.* **2004**, *126*, 2194 – 2207.

[6] G. Illuminati, L. Mandolini, *Acc. Chem. Res.* **1981**, *14*, 95 – 102.

[7] For a recent example demonstrating the particular difficulty in the formation of medium-sized lactones, see: A. Lumbroso, N. Abermil, B. Breit, *Chem. Sci.* **2012**, *3*, 789 – 793.

[8] A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300 – 3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168 – 3210.

[9] a) R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2006**, *128*, 14772 – 14773; b) R. Hili, A. K. Yudin, *Angew. Chem. Int. Ed.* **2008**, *47*, 4188 – 44191; c) R. Hili, A. K. Yudin, *J. Am. Chem. Soc.* **2009**, *131*, 16404 – 16406; d) R. Hili, V. Rai, A. K. Yudin, *J. Am. Chem. Soc.* **2010**, *132*, 2889 – 2891; e) B. H. Rotstein, V. Rai, R. Hili, A. K. Yudin, *Nat. Protoc.* **2010**, *5*, 1813 – 1822; f) S. Baktharaman, N. A. Afagh, A. Vandersteen, A. K. Yudin, *Org. Lett.* **2010**, *12*, 240 – 243; g) N. Assem, A. Natarajan, A. K. Yudin, *J. Am. Chem. Soc.* **2010**, *132*, 10986 – 10987; h) Z. He, A. K. Yudin, *Angew. Chem.* **2010**, *122*, 1651 – 1654; *Angew. Chem. Int. Ed.* **2010**, *49*, 1607 – 1610; i) N. A. Afagh, A. K. Yudin, *Angew. Chem.* **2010**, *122*, 270 – 320; *Angew. Chem. Int. Ed.* **2010**, *49*, 262 – 310; j) L. L. W. Cheung, Z. He, S. M. Decker, A. K. Yudin, *Angew. Chem.* **2011**, *123*, 12002 – 12006; *Angew. Chem. Int. Ed.* **2011**, *50*, 11798 – 11802.

[10] For excellent reviews of oxetanes in organic synthesis and medicinal chemistry, see: a) J. A. Burkhard, G. Wuitschik, M. Rogers-Evans, K. Müller, E. M. Carreira, *Angew. Chem.* **2010**, *122*, 9236 – 9251; *Angew. Chem. Int. Ed.* **2010**, *49*, 9052 – 9067; b) G. Wuitschik, E. M. Carreira, B. Wagner, H. Fischer, I. Parrilla, F. Schuler, M. Rogers-Evans, K. Müller, *J. Med. Chem.* **2010**, *53*, 3227 – 3246.

[11] For examples of acid-promoted ring-opening reactions of oxetanes, see: a) M. Mizuno, M. Kanai, A. Iida, K. Tomioka, *Tetrahedron* **1997**, *53*, 10699 – 10708; b) T. Bach, K. Kather, O. Kramer, *J. Org. Chem.* **1998**, *63*, 1910 – 1918; c) M. M.-C. Lo, G. C. Fu, *Tetrahedron* **2001**, *57*, 2621 – 2634; d) F. Bertolini, S. Crotti, V. D. Bussolo, F. Macchia, M. Pineschi, *J. Org. Chem.* **2008**, *73*, 8998 – 9007; e) R. Loy, E. N. Jacobsen, *J. Am. Chem. Soc.* **2009**, *131*, 2786 – 2787; f) J. A. Burkhard, B. H. Tchitchanov, E. M. Carreira, *Angew. Chem.* **2011**, *123*, 5491 – 5494; *Angew. Chem. Int. Ed.* **2011**, *50*, 5379 – 5382; g) D. Rix, R. Ballesteros-Garrido, W. Zeghida, C. Besnard, J. Lacour, *Angew. Chem.* **2011**, *123*, 7446 – 7449; *Angew. Chem. Int. Ed.* **2011**, *50*, 7308 – 7311.

[12] For examples of cyclization reactions employing siloxy alkynes, see: a) C. J. Kowalski, G. S. Lal, *J. Am. Chem. Soc.* **1988**, *110*, 3693 – 3695; b) M. P. Schramm, D. S. Reddy, S. A. Kozmin, *Angew. Chem.* **2001**, *113*, 4404 – 4407; *Angew. Chem. Int. Ed.* **2001**, *40*, 4274 – 4277; c) J. Sun, S. A. Kozmin, *J. Am. Chem. Soc.* **2005**, *127*, 13512 – 13513; d) T. B. Clark, K. A. Woerpel, *Org. Lett.* **2006**, *8*, 4109 – 4112; e) M. Movassaghi, M. D. Hill, O. K. Ahmad, *J. Am. Chem. Soc.* **2007**, *129*, 10096 – 10097; f) E. C. Minnihan, S. L. Colletti, F. D. Toste, H. C. Shen, *J. Org. Chem.* **2007**, *72*, 6287 – 6289; g) X. Qi, J. M. Ready, *Angew. Chem.* **2008**, *120*, 7176 – 7178; *Angew. Chem. Int. Ed.* **2008**, *47*, 7068 – 7070; h) W. F. Austin, Y. Zhang, R. L. Danheiser, *Tetrahedron* **2008**, *64*, 915 – 925.

[13] To the best of our knowledge, there have been no previous reports on intermolecular reactions for the formation of eight-membered lactones.

[14] J. Sun, V. A. Keller, S. T. Meyer, S. A. Kozmin, *Adv. Synth. Catal.* **2010**, *352*, 839 – 842.

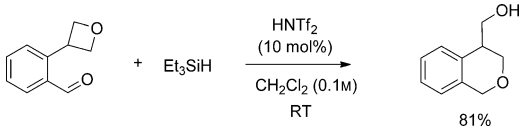
[15] The acidity of TfOH was found to be lower than that of $HNTf_2$ in the gas phase (Ref. [16a]), but the trend in protic solvents is reversed (Ref. [16b]), see: a) I. A. Koppel, R. W. Taft, F. Anvia, S. Zhu, L. Hu, K. Sung, D. D. DesMarteau, L. M. Yagupolskii, Y. L. Yagupolskii, N. V. Ignat'ev, N. V. Kondratenko, A. Y. Volkonskii, V. M. Vlasov, R. Notario, P. Maria, *J. Am. Chem. Soc.* **1994**, *116*, 3047 – 3057; b) J. Foropoulos, D. D. DesMarteau, *Inorg. Chem.* **1984**, *23*, 3720 – 3723.

[16] For a review on $HNTf_2$ in organic synthesis, see: a) K. Takasu, *Synlett* **2009**, 1905 – 1914; b) J. Sun, *Triflimide* in *Encyclopedia of Reagents for Organic Synthesis*, Wiley, Hoboken, **2010**, DOI: 10.1002/047084289X.rn01222.

[17] For some examples demonstrating the superiority of $HNTf_2$ over other acids, see: a) Ref. [12c]; b) K. Inanaga, K. Takasu, M. Ihara, *J. Am. Chem. Soc.* **2005**, *127*, 3668 – 3669; c) K. Ishihara, K. Nakano, *J. Am. Chem. Soc.* **2007**, *129*, 8930 – 8931.

[18] This process forms a cyclic acetal product, and is a known process: P. Krasik, M. Bohemier-Bernard, Q. Yu, *Synlett* **2005**, 854 – 856.

[19] As suggested by one of the referees, Et_3SiH was used as the nucleophile and the following product was obtained.



[20] Oxetene adducts formed from a [2+2] cycloaddition reaction between an alkyne and an aldehyde or ketone have been

previously observed. For some examples, see: a) W. J. Middleton, *J. Org. Chem.* **1965**, *30*, 1307; b) L. E. Friedrich, J. D. Bower, *J. Am. Chem. Soc.* **1973**, *95*, 6869 – 6870; c) K. Aikawa, Y. Hioki, N. Shimizu, K. Mikami, *J. Am. Chem. Soc.* **2011**, *133*, 20092 – 20095.

[21] The alkene configuration of the electrocyclic ring-opening process is controlled by torquoselectivity; a) W. R. Dolbier, Jr., H. Koroniak, K. N. Houk, C. Sheu, *Acc. Chem. Res.* **1996**, *29*, 471 – 477, and references therein; b) T. Yoshikawa, S. Mori, M. Shindo, *J. Am. Chem. Soc.* **2009**, *131*, 2092 – 2093, and references therein; For an example of dramatic catalyst dependence for torquoselectivity, see: c) N. Shindoh, K. Kitaura, Y. Takemoto, K. Takasu, *J. Am. Chem. Soc.* **2011**, *133*, 8470 – 8473.

