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Efficient Intramolecular Cyclizations of Phenoxyethynyl Diols into Multisubstituted α,β-Unsaturated Lactones

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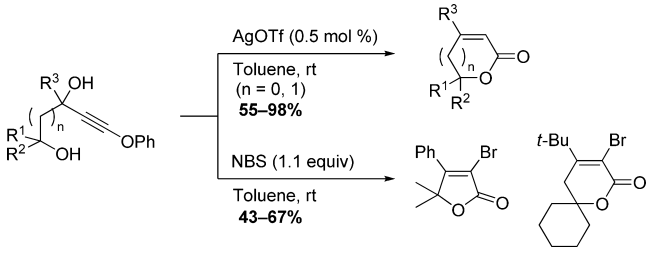
ABSTRACT



AgOTf-catalyzed intramolecular cyclization of phenoxyethynyl diols proceeded under mild conditions to afford the multisubstituted α,β-unsaturated-γ-lactones in 55−98% yields. This method was also applicable to the synthesis of α,β-unsaturated-δ-lactones. A similar cyclization proceeded when AgOTf was replaced with a stoichiometric amount of *N*-bromosuccinimide to furnish the α-bromo-substituted α,β-unsaturated lactones.

α,β-Unsaturated-γ-lactones are constituents of a wide variety of naturally occurring compounds that exhibit a range of biological activities with medicinal and agricultural applicability.[1] The potential importance of such compounds has stimulated the development of a number of synthetic methodologies, especially by employing various transition metals, for developing environmentally benign processes.[2] Recently, considerable attention has been devoted to developing a reliable and efficient γ,γ-disubstituted α,β-unsaturated-γ-lactone preparation protocol, as this scaffold forms part of the structure of the natural bioactive compounds.[3] Some typical examples of transition-metal-catalyzed intramolecular lactone generation methods are summarized in Figure 1: (a) the ring-closing metathesis of **A** using ruthenium catalysts to generate an alkene moiety,[4] (b) the intramolecular cyclization of allenic acids

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and their esters **B** that proceed in the presence of copper and palladium catalysts to furnish quaternary carbon centers,[5] and (c) the construction of oxygen−acyl bonds through the gold-catalyzed cyclization of (*Z*)-enynols **C1** followed by the oxidative cleavage of the exomethylene moiety,[6] and also through the palladium- or rhodium-catalyzed addition of organoboron compounds to 4-hydroxy-2-alkynoates **C2** followed by lactonization.[7] In addition, the cyclization of homopropargyl alcohols **C3** having a silyl or bromo group at the acetylene terminus has been successfully executed using palladium, mercury, and gold catalysts, although with the production of α,β-saturated-γ-lactones.[8]

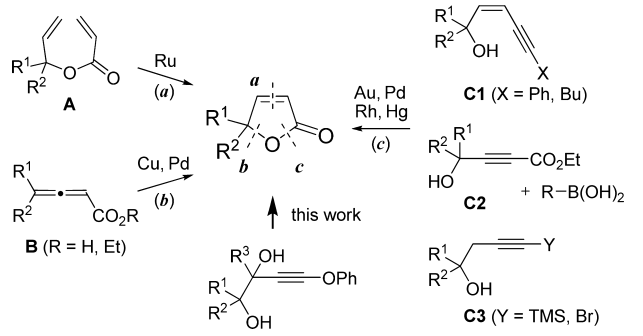
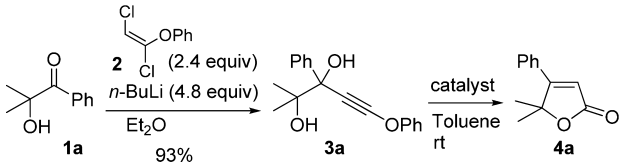


Figure 1. Reported Transition-Metal-Catalyzed Intramolecular Lactone Formation.

Intermolecular lactonizations have also utilized the ruthenium- or palladium-catalyzed cycloaddition of allenyl alcohols and ketones with carbon monoxide.[9] The palladium-catalyzed γ-arylation of α-angelicalactone has also been reported.[10] However, owing to their inherent steric hindrance, the application of these methods to the syntheses of γ,γ-disubstituted α,β-unsaturated-γ-lactones frequently requires a high catalyst loading, furnishes moderate yields, has a narrow substrate scope, and calls for harsh reaction conditions involving elevated temperatures or a prolonged reaction time.

Our ongoing research has focused on the transition-metal-catalyzed rearrangements of propargyl alcohols into α,β-unsaturated carbonyl compounds.[11] These studies have revealed that propargyl alcohols having a phenoxy group at the acetylene terminus undergo rearrangement more rapidly than those with alkyl and aryl groups. This is attributed to the inherent high reactivity of the phenoxyethynyl moiety, which accelerates the 1,3-shift of the hydroxyl groups to the adjacent position of the phenoxy group.[12] It was anticipated that the use of phenoxyethynyl groups would render the alkyne susceptible to attack even by bulky nucleophiles in the intramolecular cyclization. Herein, we report the highly efficient AgOTf-catalyzed intramolecular cyclization of phenoxyethynyl diols **3** having tertiary alcohol moieties under mild conditions to afford γ,γ-disubstituted α,β-unsaturated-γ-lactones **4** in good to excellent yields. Additionally, *N*-bromosuccinimide (NBS) promoted a similar cyclization of **3** to give the corresponding α-bromo derivatives **9**.

Table 1. Screening of Reaction Conditions for the Cyclization of **3a** to **4a**



entry	catalyst	time (h)	yield of **4a** (%)[b]
1[a]	none	6	74
2	$(Ph_3P)AuCl$, AgOTf (0.5 mol % each)	2.5	79
3	AgOTf (0.5 mol %)	0.5	93
4	$AgNTf_2$ (0.5 mol %)	1	90
5	Ag_3PO_4 (0.5 mol %)	4.5	45
6	CF_3CO_2H (10 mol %)	2	78
7	CF_3SO_3H (10 mol %)	1.5	34
8	Me_3SiOTf (10 mol %)	2.5	52
9	PhOH (10 mol %)	3	no reaction

[a] The reaction was conducted under reflux. [b] Isolated yield.

Lithium phenoxyacetylide, generated in situ from dichlorovinyl phenyl ether **2**[13] and *n*-BuLi, reacted with the hydroxyketone **1a** in Et_2O to afford the corresponding diol **3a** in 93% yield. Using **3a** as a substrate, the reaction conditions for the lactonization were evaluated as shown in Table 1. MaGee et al. reported that the intramolecular lactonization of similar substrates, i.e., ethoxyethynyl diols, required a temperature of 150 °C, which suggested

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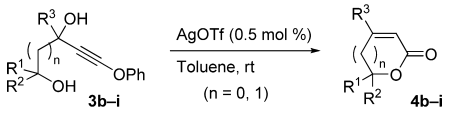
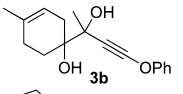
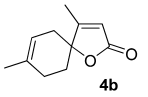
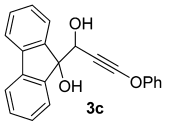
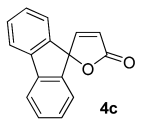
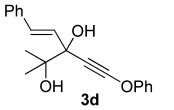
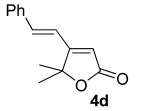
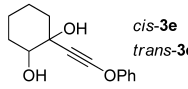
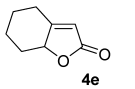
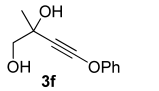
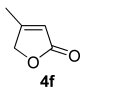
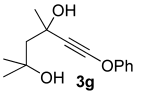
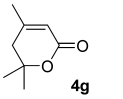
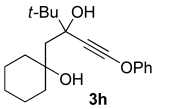
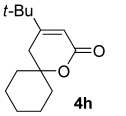
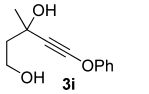
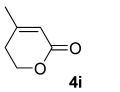
the formation of a ketene intermediate as an initial step.[14] In contrast, the intramolecular cyclization of **3a** proceeded gradually in refluxing toluene (at slightly lower temperature) to give **4a** in 74% yield, along with the same quantity of phenol (entry 1), which suggested that the latter cyclization went on via a different pathway. In order to achieve a milder cyclization temperature, a cationic gold species[15,16] generated from $(Ph_3P)AuCl$ and AgOTf was examined because of its highly alkynophilic nature (entry 2). The reaction was achieved at room temperature with an extremely low catalyst loading of 0.5 mol % each. Moreover, the use of silver catalysts[17] was responsible for the rapid completion of the reaction (entries 3–5). In particular, comparable effects were achieved by using AgOTf or $AgNTf_2$ as the catalyst, although AgOTf was slightly superior. The treatment of **3a** with either protic or Lewis acids enabled the intramolecular cyclization; however, 10 mol % of the acids was required and the yields of **4a** were moderate (entries 6–8). It was found that the released PhOH, which is acidic, did not function as a catalyst (entry 9). Thus, AgOTf was considered as the most suitable catalyst for the intramolecular cyclization of **3a**.

Next, the reactivity of diverse phenoxyethynyl diols **3** was examined using 0.5 mol % of AgOTf in toluene at room temperature (Table 2). The intramolecular cyclizations of **3b**–**f**[18] proceeded smoothly within 60 min to give the α,β-unsaturated-γ-lactones **4b**–**f** in 50–98% yields (entries 1–6), which included the products (**4b**, **4d**–**f**) with alkyl and styryl groups at the β-position, as well as **4c** with no substituent at the β-position. The formation of the sterically hindered spiro compounds **4b** and **4c** in high yields is another advantage of this method (entries 1 and 2). Interestingly, the diastereomers (*cis*- and *trans*-**3e**) were found to have different reactivities (entries 4 and 5). In the case of **3f**, the combined catalyst of $(Ph_3P)AuCl$ and AgOTf exhibited better performance than AgOTf alone to give **4f** in 79% yield. Moreover, AgOTf-catalyzed intramolecular cyclizations could be extended to the syntheses of α,β-unsaturated-δ-lactones **4g**–**i** (entries 7–9).

A plausible mechanism for AgOTf-catalyzed intramolecular cyclization of **3** is proposed in Scheme 1. The phenoxyethynyl group is an electron-rich moiety, as evident from its resonance form **3′**,[12] and readily coordinates to the silver cation to generate the electrophilic oxonium intermediate **5**, which is susceptible to the nucleophilic attack by even sterically hindered tertiary alcohol (**5**→**6**). Subsequently, the donation of a lone pair on the ethereal oxygen atom results in the generation of the transient

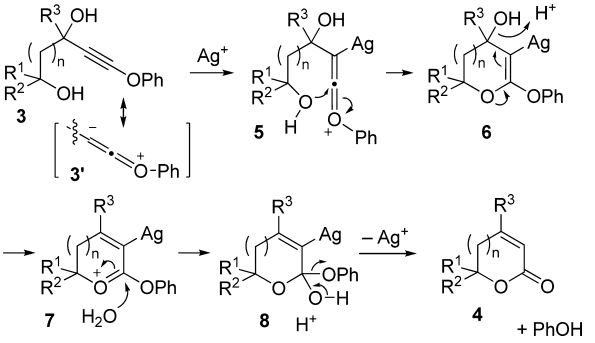
Table 2. AgOTf-Catalyzed Intramolecular Cyclization of **3b**–**i** into **4b**–**i**



entry	substrate, **3**	product, **4**	time	yield[a]
1	 **3b**	 **4b**	40 min	98%
2	 **3c**	 **4c**	50 min	89%
3	 **3d**	 **4d**	50 min	55%
4	 *cis*-**3e**	 **4e**	60 min	82%
5	*trans*-**3e**		60 min	50%
6	 **3f**	 **4f**	30 min	61% (79%)[b]
7	 **3g**	 **4g**	40 min	84%
8	 **3h**	 **4h**	40 min	96%
9	 **3i**	 **4i**	30 min	77%

[a] Isolated yield. [b] Using $(Ph_3P)AuCl$–AgOTf (0.5 mol % each) instead of AgOTf.

Scheme 1. Plausible Mechanism for AgOTf-Catalyzed Intramolecular Cyclization of **3**



(14) Liang, L.; Ramaseshan, M.; MaGee, D. I. *Tetrahedron* **1993**, *49*, 2159–2168.

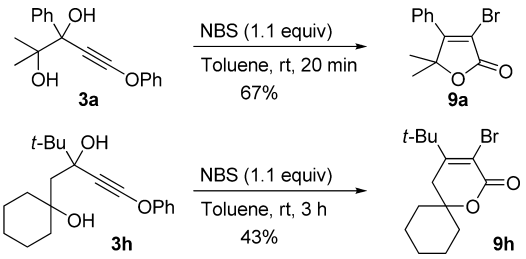
(15) We discovered the cationic gold(I)-catalyzed intramolecular cyclization of 3-alkyne-1,2-diols. However, the use of AgOTf alone did not promote a similar cyclization; see: (a) Egi, M.; Azechi, K.; Akai, S. *Org. Lett.* **2009**, *11*, 5002–5005. For other cyclizations of that type, see: (b) Hashmi, A. S. K.; Bührle, M.; Wölfle, M.; Rudolph, M.; Wieteck, M.; Rominger, F.; Frey, W. *Chem.—Eur. J.* **2010**, *16*, 9846–9854.

(16) For recent reviews on gold catalysis, see: (a) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448–2462. (b) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766–1775.

(17) For a review on silver catalysis, see: Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-García, I. *Chem. Rev.* **2008**, *108*, 3174–3198.

(18) The reaction of the hydroxycarbonyl compounds **1** (1.0 equiv) with *i*-PrMgCl (1.0 equiv) and lithium phenoxyacetylide (1.0 equiv) in THF provided an efficient alternative route to the synthesis of the phenoxyethynyl diols **3**. See the Supporting Information.

Scheme 2. NBS-Mediated Cyclization of **3** into **9**



oxonium cation and water (**6**→**7**). Then, **7** reacts with water to give the intermediate **8** releasing a proton and finally provides the corresponding lactone **4** along with the regeneration of the Ag(I) species for further cyclization.

Based on the above encouraging results, the bromonium-ion-mediated intramolecular cyclization of phenoxyethynyl diols **3** was also evaluated.[19,20] Here, the use of NBS instead of AgOTf brought about the intramolecular cyclization of **3a** and **3h** to provide the α-bromo lactones **9a** and **9h** in 67% and 43% yields, respectively (Scheme 2); the bromo group of these compounds should facilitate further installation of a wide variety of functional groups at the α-position.

In conclusion, this study illustrates the feasibility of phenoxyethynyl diols **3** as useful substrates for intramolecular lactonizations. The reactions proceeded in the presence of 0.5 mol % of AgOTf to afford a variety of multisubstituted α,*β*-unsaturated-*γ*- and *δ*-lactones **4**.[21] The advantages of this method include a rapid reaction (< 60 min) at room temperature and good-to-excellent yields. Moreover, the NBS-mediated cyclization of **3** provided the α-bromo lactones **9**. Further investigation of the practical extension of this method and elucidation of the reaction mechanism are in progress in our laboratory.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) In the past decade, there has been an explosive increase in interest in electrophilic heteroatom cyclizations. For reviews, see: (a) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *Chem.—Eur. J.* **2012**, *18*, 5460–5489. (b) Godoi, B.; Schumacher, R. F.; Zeni, G. *Chem. Rev.* **2011**, *111*, 2937–2980. (c) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. *Aldrichimica Acta* **2011**, *44*, 27–40.

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(21) **Typical Experimental Procedure.** Under a nitrogen atmosphere, AgOTf (1.0 mg, 0.0039 mmol) was added to a solution of the phenoxyethynyl diol **3a** (217 mg, 0.78 mmol) in toluene (2.0 mL, 0.4 M) at room temperature. The reaction mixture was stirred for 30 min and then filtered through a pad of Celite. The filtrate was evaporated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexane/EtOAc = 5:1) to give the unsaturated lactone **4a** (133 mg, 93%).

The authors declare no competing financial interest.