Synthetic Methods

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Catalytic Ring Expansion of Cyclic Hemiaminals for the Synthesis of Medium-Ring Lactams**

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Abstract: *A mild and efficient intermolecular ring-expansion approach was developed for the synthesis of medium-ring lactams by using siloxy alkynes. Key to success is the suitable combination of a superior catalyst and an exceptional nitrogen-protecting group. Control experiments indicated that the reaction is remarkably selective toward the desired lactam formation, even with many possible non-productive pathways.*

Amide formation is one of the most important reactions in organic chemistry owning to the wide occurrence of amide functionality, for example, in peptides, proteins, synthetic polymers, and various pharmaceuticals and biologically active compounds.[1] As a result, it has been a long-standing pursuit of the synthetic community to achieve efficient and selective methods for this reaction, ideally in a catalytic and waste-free manner.[2–5] Medium-ring lactams, a special class of amides, are important subunits of a wide range of natural compounds, biologically significant molecules, and synthetic intermediates (Figure 1).[6] However, owing to the generally challenging formation of medium rings, particularly eight-membered rings,[7] efficient strategies for medium-ring lactam synthesis remain in high demand.[8–10] Herein, we report a catalytic ring-expansion approach that makes use of *N*-sulfonyliminiums[11] and siloxy alkyne[12–14] for the efficient synthesis of eight-membered lactams.

Recently, we reported a ring-expansion strategy for the efficient synthesis of medium- and large-ring lactones [Eq. (1), X = O].[13b] The reaction is believed to proceed via cyclic oxocarbenium **A**, generated from a cyclic acetal in the presence of $BF_3{\cdot}OEt_2$ (2.0 equiv), which undergoes cycloaddition with a siloxy alkyne followed by ring expansion. While the reaction is generally efficient, the process cannot be rendered catalytic. A decreased loading of $BF_3{\cdot}OEt_2$ (or other Brønsted/Lewis acid catalysts) resulted in significantly lower efficiency. More importantly and disappointingly, direct extension of this approach to medium-ring lactam synthesis was not straightforward. Under identical conditions, the use of a Boc-protected cyclic hemiaminal as a substrate did not produce the desired lactam [Eq (1), X = NBoc, via *N*-acyliminium **B**]. Instead, enamide **C** was observed as the major product and presumably results from the more facile deprotonation of **B** (relative to the desired intermolecular C–C bond formation).

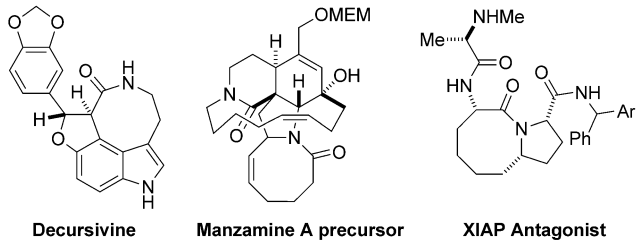
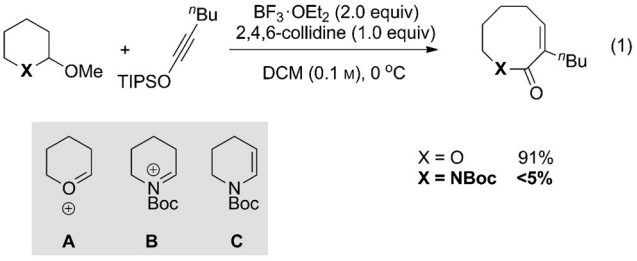


Figure 1. Important molecules that contain medium lactam units.



Despite this initial failure, we spent considerable effort aiming to improve this reaction in view of its significance. For example, various Brønsted and Lewis acids were evaluated in either catalytic or stoichiometric amounts, with or without additives, but the majority of them were ineffective (Table 1, entry 1). Encouragingly, $TiCl_4$ (2.0 equiv) did promote the desired lactam formation, albeit in only 18% yield (entry 2). Other easily cleavable carbamate-based N-protecting groups (PGs), such as Cbz and methoxycarbonyl, did not improve the efficiency (entries 3–4). However, with some of these conditions (entry 1), we were able to detect the formation of a bicyclic product **3a′**, which might result from nucleophilic attack by the carbonyl oxygen of the Boc group on the ketenium moiety in the key intermediate (**D′**; Scheme 2, see below). The results suggested that a protecting group with decreased nucleophilicity might be a solution. To our delight, the use of a *p*-toluenesulfonyl (Ts) group resulted in

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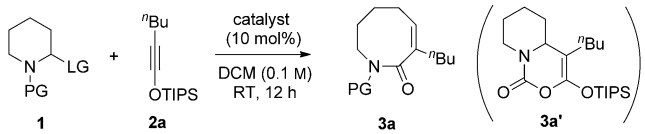
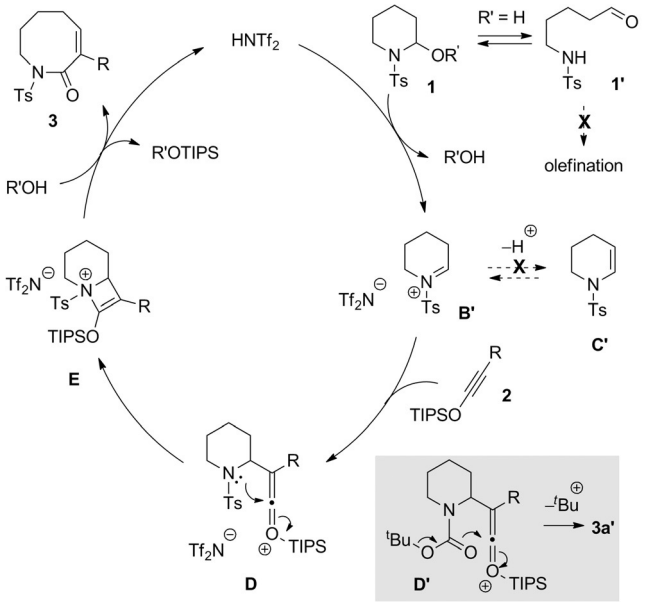
Table 1: Reaction optimization.



Entry	PG	LG	Catalyst	Yield (**3a**)[a]
1	Boc	OMe	$HNTf_2$ or Lewis acids[b]	<10%
2	Boc	OMe	$TiCl_4$ (2.0 eq)[c]	18%
3	Cbz	OMe	$TiCl_4$ (2.0 eq)[c]	<10%
4	CO_2Me	OMe	$TiCl_4$ (2.0 eq)[c]	<10%
5	Ts	OMe	$TiCl_4$ (2.0 eq)[c]	89%
6	Ts	OMe	$BF_3{\cdot}OEt_2$ (2.0 eq)[d]	39%
7[e]	Ts	OMe	PPh^3AuSbF_6	<10%
8[e]	Ts	OMe	$Cu(OTf)_2$	<10%
9[e]	Ts	OMe	$Zn(OTf)_2$	10%
10[e]	Ts	OMe	$AgNTf_2$	43%
11[e]	Ts	OMe	$HNTf_2$	74%
12[e]	Ms	OMe	$HNTf_2$	22%
13[e]	Ns	OMe	$HNTf_2$	<10%
14[e]	Ts	OH	$HNTf_2$	84%
15[e]	**Ts**	**OAc**	**$HNTf_2$**	**96%**

[a] Yield based on ^1H NMR with CH_2Br_2 as an internal standard. [b] Lewis acids include $Cu(OTf)_2$, TMSOTf, $Sc(OTf)_3$, $Zn(OTf)_2$, $FeCl_3$, and $In(OTf)_3$. **3a′** was observed. [c] Run with the additive 2,4,6-collidine (1.0 equiv) for 2 h, −78 °C→rt. [d] Run with additive 2,4,6-collidine (1.0 equiv) at 0 °C for 2 h. [e] Dichloroethane (DCE) as solvent. Ts = tosyl = toluene-4-sulfonyl, Ms = mesyl = methanesulfony, Ns = 4-nitrobenzenesulfonyl.



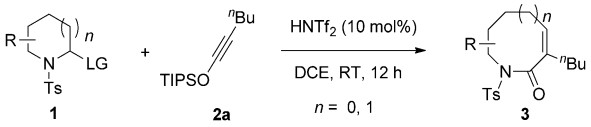
Scheme 2. Proposed mechanism.

significant improvement (89% yield, entry 5). The structure was unambiguously confirmed by X-ray diffraction (see the Supporting Information). We reasoned that the excellent performance of the Ts group is not only consistent with its low nucleophilicity (vs. Boc), but also a reflection of its strong electron-withdrawing ability, which would be expected to enhance the electrophilicity of the iminium (**B′**), thereby facilitating the intermolecular C–C bond formation (vs. deprotonation).

Although the reaction is efficient with two equivalents of $TiCl_4$, decreasing its loading to a catalytic amount resulted in disappointingly low yield. Aiming at achieving truly catalytic amide formation, which might be more amenable to large-scale synthetic applications, we re-evaluated other Lewis and Brønsted acids. While most gave either no desired product or low yield (entries 6–10),[15] $HNTf_2$ was found to provide good efficiency at 10 mol% loading (74% yield, entry 11).[16,17] Other sulfonyl-based protecting groups (Ms and Ns) did not improve the efficiency (entries 12–13). Further evaluation of other leaving groups (LGs) indicated that both OH and OAc exhibited good performance, with the latter being superior (96% NMR yield, entry 15).

Next, we examined the reaction scope (Table 2). Under the established standard catalytic conditions, a range of cyclic hemiaminals bearing different substituents at different positions can participate in the ring-expansion reaction to afford the corresponding enlarged lactams in moderate to good yields. It is worth mentioning that although OAc is a relatively better leaving group than OH (Table 1), substrates with the latter are easier to prepare by direct lactam reduction (an additional acylation step is required to give those with OAc), so they are better represented in the scope study. Seven-membered lactams can also be formed from the correspond-

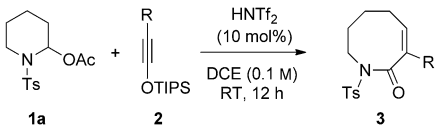
Table 2: Scope with regard to the hemiaminal.



Entry	Hemiaminal	Product	**3**	Yield[a]
1	R = **H** (LG = OAc **1a**)		**3a**	87%
2	Me (**1b**)		**3b**	82%
3	allyl (**1c**)		**3c**	51%
4	R = Et (**1d**)		**3d**	62%
5	^{i}Pr (**1e**)		**3e**	57%
6	*p*-$MeOC_6H_4$ (**1f**)		**3f**	77%
7	allyl (**1g**)		**3g**	45%
8	**1h**		**3h**	39%[b]
9	R = H (**1i**)		**3i**	71%
10	Me (**1j**)		**3j**	72%
11	allyl (**1k**)		**3k**	70%
12	**1l**		**3l**	47%

[a] Yield of isolated product. [b] Purified twice by using a silica gel column and preparative thin-layer chromatography.

Table 3: Scope with regard to the alkyne.



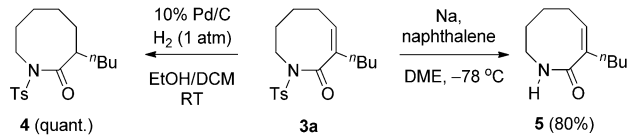
1a 2 3

Entry	R	Product	Yield[a]
1	*n*-Octyl	**3m**	74%
2	Ph	**3n**	57%
3	TIPSO	**3o**	75%
4		**3p**	83%

[a] Yield of isolated product.

ing five-membered cyclic hemiaminals (Table 2, entries 9–12).[18] Siloxy alkynes with different substituents are also suitable reaction partners (Table 3). It is worth noting that although the TBS group is removed under the acidic conditions (**3l**), the bulkier triisopropylsilyl (TIPS) group is well tolerated (**3o**). Furthermore, our ring-expansion method does not require the use of high dilution or slow addition of substrates, thus making it amenable to large-scale applications.

To further demonstrate the potential utility of our process, we also carried out product derivatizations (Scheme 1). The α,β-unsaturated medium lactam **3a** can be hydrogenated (Pd/C, H_2) to give saturated lactam **4** with excellent efficiency. The Ts protecting group can be efficiently removed to form free amide **5**.

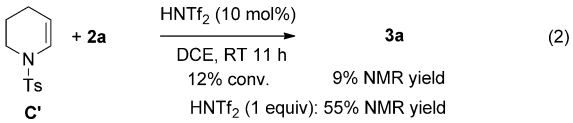


4 (quant.) **3a** **5** (80%)

Scheme 1. Product derivatization.

A mechanism is proposed in Scheme 2. The reaction begins with activation of the hemiaminal (**1**) by $HNTf_2$ to generate *N*-sulfonyliminium **B′**. Subsequent nucleophilic attack by siloxy alkyne forms ketenium **D**, which cyclizes through nitrogen attack to give azetidinium **E**, rather than undergoing the oxygen attack observed with **D′** (which bears a Boc group). Further ring expansion, together with desilylation, furnishes lactam **3** and regenerates the catalyst $HNTf_2$.

To gain further insight into the mechanism, we carried out some control experiments. First, enamide **C′** was prepared and subjected to the standard conditions, but the reaction showed very low conversion and the desired lactam **3a** was formed in low yield [Eq (2)]. The use of one equivalent of $HNTf_2$ could improve the yield (55%). To further mimic the standard reaction, in which the leaving unit (R′OH) is present, we then added AcOH (1 equiv, corresponding to the OAc leaving group in **1a**) to the above reaction [Eq (3)]. While the conversion is complete, the yield of **3a** was not improved. Moreover, the dimerization product **6** was observed, presumably also with oligomers as the remainder of the mass balance. These results, combined with the good efficiency observed with the standard reaction (no formation of **6**), may suggest that **B′** is a viable intermediate but its conversion to enamide **C′** by reversible deprotonation is not heavily involved in our standard method. The deprotonation of **B′** is probably inhibited by relatively fast nucleophilic attack by the siloxy alkyne as a result of the strong electron-withdrawing ability of the Ts group.



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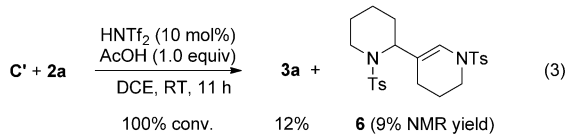
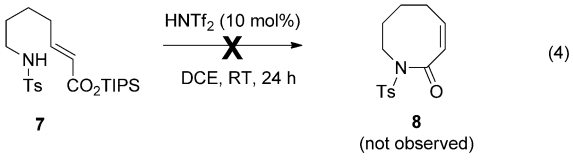


(3)

The possibility of other pathways was also examined. For example, the hemiaminal substrate may be in equilibrium with aldehyde **1′** (particularly with the OH leaving group or with adventitious water present). The reaction might then proceed through carbonyl olefination with siloxy alkynes to form an α,β-unsaturated TIPS ester (similar to **7**), followed by 8-membered-ring closing.[19] However, the reaction with **7** under the standard conditions did not form the desired lactam **8** [Eq (4)]. Furthermore, the ketenium **D** may undergo hydration to form a cyclic TIPS ester (similar to **9**). However, ester **9** did not lead to production of the 8-membered lactam **8** [Eq (5)]. Overall, it is remarkable that the reaction proceeds



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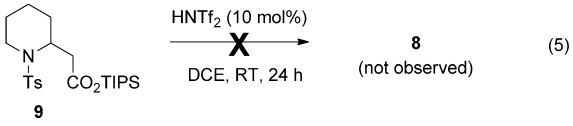

(5)

in such an efficient and selective manner in spite of these potential non-productive side pathways at different stages, and this result highlights the proper choice of the N-protecting group and the suitability of the conditions.

In summary, an efficient catalytic ring-expansion approach for medium-ring lactam synthesis was developed. This also represents a new reaction between siloxy alkynes and *N*-acyliminiums (or analogues), both of which are versatile species in organic synthesis. With the proper choice of the superior Brønsted acid catalyst $HNTf_2$ and the exceptional Ts protecting group, this efficient process, which overcomes the propensity to take multiple side pathways, proceeds specifically to form the desired medium lactams. The lactam products are useful precursors to other medium-ring nitrogen-containing heterocycles.

Keywords: alkynes · lactams · medium-ring compounds · ring expansion · triflimide

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