

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 owing 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 BF₃·OEt₂ (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 BF₃·OEt₂ (or other

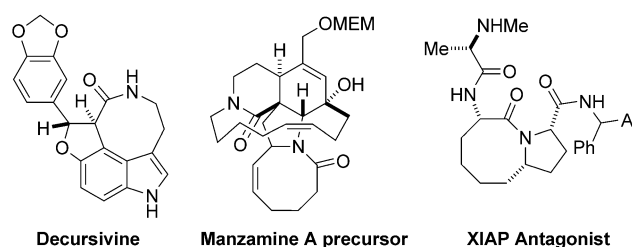
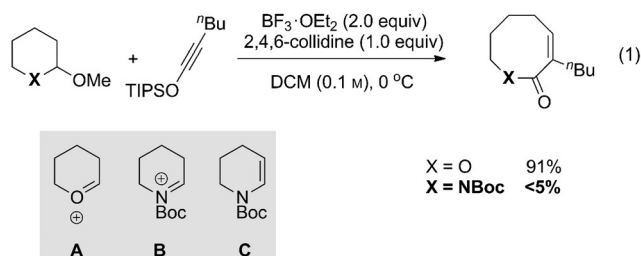


Figure 1. Important molecules that contain medium lactam units.

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).



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, TiCl₄ (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

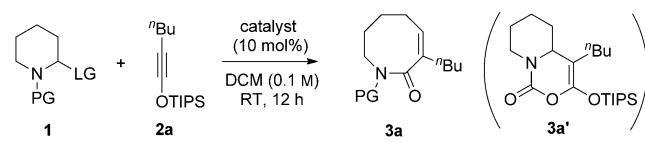
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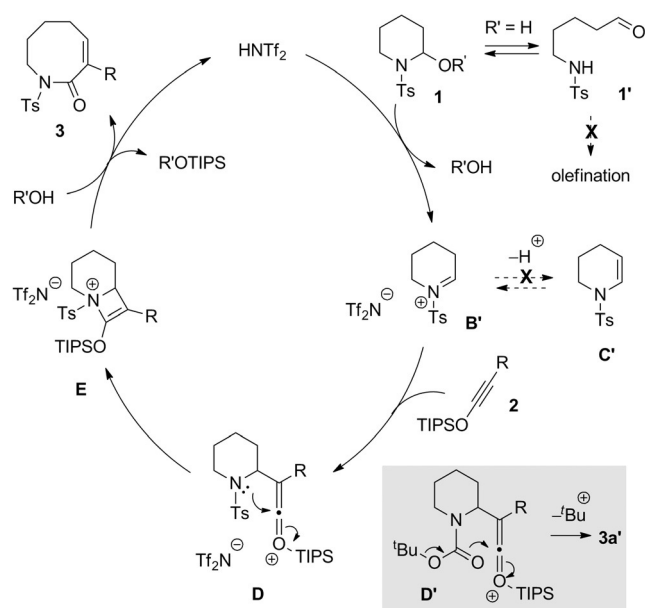
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201504926>.

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 ₂ Me	OMe	TiCl ₄ (2.0 eq) ^[c]	< 10 %
5	Ts	OMe	TiCl ₄ (2.0 eq) ^[c]	89 %
6	Ts	OMe	BF ₃ ·OEt ₂ (2.0 eq) ^[d]	39 %
7 ^[e]	Ts	OMe	PPh ₃ AuSbF 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 CH₂Br₂ as an internal standard. [b] Lewis acids include Cu(OTf)₂, TMSOTf, Sc(OTf)₃, Zn(OTf)₂, FeCl₃, 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 = methanesulfonyl, Ns = 4-nitrobenzenesulfonyl.



Scheme 2. Proposed mechanism.

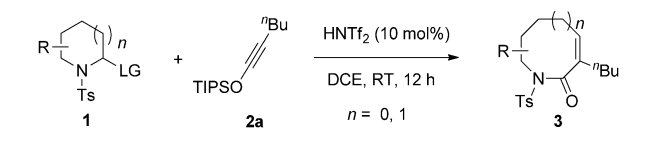
significant improvement (89% yield, entry 5). The structure was unambiguously confirmed by X-ray diffraction (see the Supporting Information). We reasoned that the excellent performance of the Ts group is not only consistent with its low nucleophilicity (vs. Boc), but also a reflection of its strong 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 TiCl₄, 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] HNTf₂ 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	3a	87 %
2	R = Me (1b)	3b	3b	82 %
3	R = allyl (1c)	3c	3c	51 %
4	R = Et (1d)	3d	3d	62 %
5	R = <i>i</i> -Pr (1e)	3e	3e	57 %
6	R = <i>p</i> -MeOC ₆ H ₄ (1f)	3f	3f	77 %
7	R = allyl (1g)	3g	3g	45 %
8	1h	3h	3h	39 % ^[b]
9	R = H (1i)	3i	3i	71 %
10	R = Me (1j)	3j	3j	72 %
11	R = allyl (1k)	3k	3k	70 %
12	1l	3l	3l	47 %

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

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

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- [1] a) V. R. Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471–479; b) J. W. Bode, *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 765–775; c) T. Cupido, J. Tulla-Puche, J. Spengler, F. Albericio, *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 768–783; d) J. M. Humphrey, A. R. Chamberlin, *Chem. Rev.* **1997**, *97*, 2243–2266.
- [2] Reviews on the use of stoichiometric coupling reagents: a) S.-Y. Han, Y.-A. Kim, *Tetrahedron* **2004**, *60*, 2447–2467; b) C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827–10852; c) E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606–631.
- [3] Representative examples of catalytic amide bond formation with organic catalysts: a) K. Ishihara, S. Ohara, H. Yamamoto, *J. Org. Chem.* **1996**, *61*, 4196–4197; b) Y. Furuya, K. Ishihara, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 11240–11241; c) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797; d) J. W. Bode, S. S. Sohn, *J. Am. Chem. Soc.* **2007**, *129*, 13798–13799; e) R. M. Al-Zoubi, O. Marion, D. G. Hall, *Angew. Chem. Int. Ed.* **2008**, *47*, 2876–2879; *Angew. Chem.* **2008**, *120*, 2918–2921.
- [4] Representative reviews and examples of catalytic amide bond formation with metal catalysts: a) W.-J. Yoo, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 13064–13065; b) C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790–792; c) J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2007**, *46*, 8460–8463; *Angew. Chem.* **2007**, *119*, 8612–8615; d) L. U. Nordström, H. Vogt, R. Madsen, *J. Am. Chem. Soc.* **2008**, *130*, 17672–17673; e) A. Brennfürer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133; *Angew. Chem.* **2009**, *121*, 4176–4196; f) B. Kang, Z. Fu, S. H. Hong, *J. Am. Chem. Soc.* **2013**, *135*, 11704–11707; g) N. A. Stephenson, J. Zhu, S. H. Gellman, S. S. Stahl, *J. Am. Chem. Soc.* **2009**, *131*, 10003–10008; h) P. Hermange, A. T. Lindhardt, R. H. Taaning, K. Bjerglund, D. Lupp, T. Skrydstrup, *J. Am. Chem. Soc.* **2011**, *133*, 6061–6071; i) B. Li, Y. Park, S. Chang, *J. Am. Chem. Soc.* **2014**, *136*, 1125–1131; j) T. Xu, H. Alper, *J. Am. Chem. Soc.* **2014**, *136*, 16970–16973; k) L. Huang, M. Arndt, K. Gooßen, H. Heydt, L. J. Gooßen, *Chem. Rev.* **2015**, *115*, 2596–2697; l) K. Dong, X. Fang, R. Jackstell, G. Laurenczy, Y. Li, M. Beller, *J. Am. Chem. Soc.* **2015**, *137*, 6053–6058.
- [5] Alternative approaches to amide formation: a) N. Shanguan, S. Katukojvala, R. Greenberg, L. J. Williams, *J. Am. Chem. Soc.* **2003**, *125*, 7754–7755; b) J. W. Bode, R. M. Fox, K. D. Baucom, *Angew. Chem. Int. Ed.* **2006**, *45*, 1248–1252; *Angew. Chem.* **2006**, *118*, 1270–1274; c) N. Carrillo, E. A. Davalos, J. A. Russak, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 1452–1453; d) X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2008**, *130*, 5446–5448; e) B. Shen, D. M. Makley, J. N. Johnston, *Nature* **2010**, *465*, 1027–1033.
- [6] Manzamine A precursor (6a), decursivine (6b), XIAP antagonist (6c): a) U. K. Pandit, B. C. Borer, H. Bieräugel, *Pure Appl. Chem.* **1996**, *68*, 659–662; b) H. Zhang, S. Qiu, P. Tamez, G. T. Tan, Z. Aydogmus, N. V. Hung, N. M. Cuong, C. Angerhofer, D. D. Soejarto, J. M. Pezzuto, H. H. S. Fong, *Pharm. Biol.* **2002**, *40*, 221–224; c) H. Sun, Z. Nikolovska-Coleska, J. Lu, J. L. Meagher, C.-Y. Yang, S. Qiu, Y. Tomita, Y. Ueda, S. Jiang, K. Krajewski, P. P. Roller, J. A. Stuckey, S. Wang, *J. Am. Chem. Soc.* **2007**, *129*, 15279–15294.
- [7] a) G. Illuminati, L. Mandolini, *Acc. Chem. Res.* **1981**, *14*, 95–102; b) G. A. Molander, *Acc. Chem. Res.* **1998**, *31*, 603–609; c) L. Yet, *Chem. Rev.* **2000**, *100*, 2963–3007.
- [8] U. Nubbemeyer, *Top. Curr. Chem.* **2001**, *216*, 125–196.
- [9] Examples of amide formation in the synthesis of eight-membered lactams, including non-catalytic (a–d) and three excellent catalytic (e–g) reactions: a) S. Kim, G. H. Joe, J. Y. Do, *J. Am. Chem. Soc.* **1993**, *115*, 3328–3329; b) P. A. Evans, A. B. Holmes, I. Collins, P. R. Raithby, K. Russell, *J. Chem. Soc. Chem. Commun.* **1995**, 2325–2326; c) F. Homsí, G. Rousseau, *J. Org. Chem.* **1998**, *63*, 5255–5258; d) J. E. Forsee, J. Aubé, *J. Org. Chem.* **1999**, *64*, 4381–4385; e) A. Klapars, S. Parris, K. W. Anderson, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 3529–3533; f) R. T. Yu, R. K. Friedman, T. Rovis, *J. Am. Chem. Soc.* **2009**, *131*, 13250–13251; g) S. Wu, R. Zeng, C. Fu, Y. Yu, X. Zhang, S. Ma, *Chem. Sci.* **2015**, *6*, 2275–2282.
- [10] Synthesis of eight-membered lactams without amide bond formation, typically with moderate efficiency and/or high dilution: a) S. Fustero, M. Sánchez-Roselló, D. Jiménez, J. F. Sanz-Cervera, C. del Pozo, J. L. Aceña, *J. Org. Chem.* **2006**, *71*, 2706–2714; b) L. Yang, G. Deng, D.-X. Wang, Z.-T. Huang, J.-P. Zhu, M.-X. Wang, *Org. Lett.* **2007**, *9*, 1387–1390; c) B. You, K. Hamer, W. Lewis, J. Dowden, *Chem. Commun.* **2013**, 49, 795–797; d) P. J. Gritsch, C. Leitner, M. Pfaffenbach, T. Gaich, *Angew. Chem. Int. Ed.* **2014**, *53*, 1208–1217; *Angew. Chem.* **2014**, *126*, 1230–1239; e) S. S. Scully, S.-L. Zheng, B. K. Wagner, S. L. Schreiber, *Org. Lett.* **2015**, *17*, 418–421.
- [11] *N*-Sulfonyliminiums are *N*-acyliminium analogues. Reviews: a) W. N. Speckamp, M. J. Moolenaar, *Tetrahedron* **2000**, *56*, 3817–3856; b) P.-Q. Huang, *Synlett* **2006**, 1133–1149; c) A. Yazici, S. G. Pyne, *Synthesis* **2009**, 339–368; d) A. Yazici, S. G. Pyne, *Synthesis* **2009**, 513–541.
- [12] Review on siloxy alkynes: a) M. Shindo, *Tetrahedron* **2007**, *63*, 10–36; b) H. Qian, W. Zhao, J. Sun, *Chem. Rec.* **2014**, *14*, 1070–1085.
- [13] a) W. Zhao, Z. Wang, J. Sun, *Angew. Chem. Int. Ed.* **2012**, *51*, 6209–6213; *Angew. Chem.* **2012**, *124*, 6313–6317; b) W. Zhao, Z. Li, J. Sun, *J. Am. Chem. Soc.* **2013**, *135*, 4680–4683.
- [14] An example of the intramolecular formation of large (not medium) lactams by using alkoxy alkynes at low concentration: X. Y. Mak, R. P. Ciccolini, J. M. Robinson, J. W. Tester, R. L. Danheiser, *J. Org. Chem.* **2009**, *74*, 9381–9387.
- [15] During the optimization process, dichloroethane (DCE) was employed at some point with the option to raise reaction temperature. Nevertheless, it was finally found to be the solvent of choice at room temperature.
- [16] Reviews on HNTf₂: a) K. Takasu, *Synlett* **2009**, 1905–1914; b) J. Sun, *Triflimide in Encyclopedia of Reagents for Organic Synthesis*, Wiley, **2010**, DOI: 10.1002/047084289X.rn01222.
- [17] Dalla and co-workers pioneered excellent studies on HNTf₂-catalyzed nucleophilic additions to *N*-acyliminiums: a) R. B. Othman, T. Bousquet, M. Othman, V. Dalla, *Org. Lett.* **2005**, *7*, 5335–5337; b) M.-J. Tranchant, C. Moine, R. B. Othman, T. Bousquet, M. Othman, V. Dalla, *Tetrahedron Lett.* **2006**, *47*, 4477–4480; c) A. Devineau, G. Pousse, C. Taillier, J. Blanchet, J. Rouden, V. Dalla, *Adv. Synth. Catal.* **2010**, *352*, 2881–2886; d) M. Saber, S. Comesse, V. Dalla, P. Netchitailo, A. Daich, *Synlett* **2011**, 2425–2429.
- [18] We also tried to prepare substrates with larger ring sizes, but the hemiaminals with an OH leaving group (precursors to substrates with other leaving groups) were not successfully obtained owing to facile ring-opening to form the acyclic aldehydes (e.g., analogues of **1'**; see Scheme 2).
- [19] J. Sun, V. A. Keller, S. T. Meyer, S. A. Kozmin, *Adv. Synth. Catal.* **2010**, *352*, 839–842.

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