ORGANIC
LETTERS

XXXX
Vol. XX, No. XX
000–000

Tertiary Amine-Triggered Cascade S_N2/Cycloaddition: An Efficient Construction of Complex Azaheterocycles under Mild Conditions

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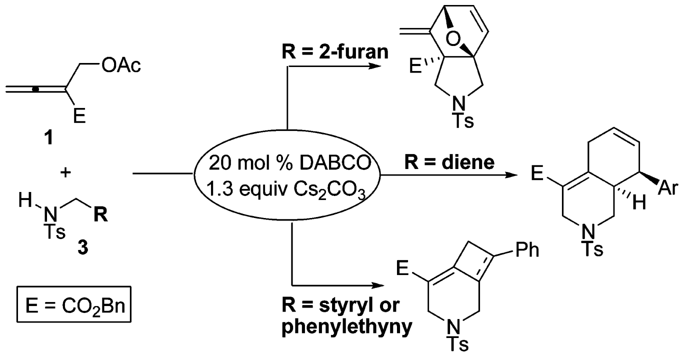
Received August 20, 2012

ABSTRACT



In this paper, an amine-triggered cascade S_N2/cycloaddtion sequence between 2-(acetoxymethyl)buta-2,3-dienoate 1 and various π-system functionalized tosylamides 3 has been reported, which provides a facile method for stereoselective construction of structurally diverse azaheterocycles.

The development of new reactions that increase molecular complexity in an economical[1] and green[2] fashion is a paramount goal of modern chemical synthesis. Cascade reactions represent one of the most efficient techniques for this goal, which combine multiple transformations in one pot, thereby eliminating the need for separate workup and isolation steps.[3] In the majority of cases, the functionality produced from the first step renders the subsequent step possible, which can allow for a rapid increase in molecular complexity. Herein, we report a new cascade reaction under mild conditions for facile construction of complex azaheterocycles from readily available starting materials **1** and **3** (Scheme 1).

In our laboratory, we are interested in exploring allenoate **1**, which can be readily converted into intermediate **A** with the interaction of a phosphine catalyst (Scheme 1).[4] We have demonstrated that **A** is a potential biselectrophile for $(4 + n)$ annulations with various 1,*n*-bisnucleophiles.

Surprisingly, a formal S_N2-substituted product **2** was isolated in 76% yield when *N*-butyl-tosylamide was tested (Scheme 1). This result led us to propose that the remaining allenic moiety in **2** might offer an additional chance to

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(1) (a) Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197. (b) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40. (c) Trost, B. M. *Science* **1991**, *254*, 1471. (d) Trost, B. M. *Angew. Chem., Int. Ed.* **1995**, *34*, 259.

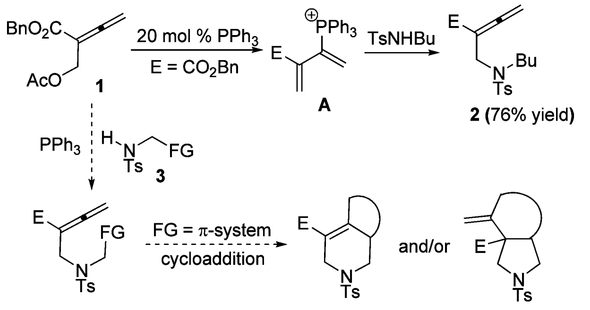
(2) (a) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University: New York, 1998. (b) Hjeresen, D. L.; Schutt, D. L; Boese, J. M. *J. Chem. Educ.* **2000**, *77*, 1543. (c) Ryan, M. A.; Tinnesand, M., Eds. *Introduction to Green Chemistry*; American Chemical Society: Washington, DC, 2002.

(3) For selected reviews, see: (a) Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Chemistry*; Wiley-VCH: Weinheim, 2006. (b) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (d) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993.

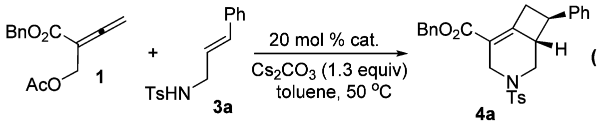
(4) (a) Zhang, Q.; Yang, L.; Tong, X. *J. Am. Chem. Soc.* **2010**, *132*, 2550. (b) Li, C.; Zhang, Q.; Tong, X. *Chem. Commun.* **2010**, *46*, 7828. (c) Li, K.; Hu, J.; Tong, X. *Chem. Commun.* **2012**, *48*, 2900.

10.1021/ol302329b

Scheme 1. Design Plan for Cascade Reaction



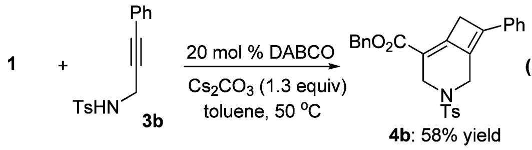
develop a cascade reaction when tosylamide **3**, bearing a proper functionalized group (FG), was instead employed (Scheme 1). Indeed, the chemistry of allenes has been recognized as an integral part of modern synthetic methods.[5] The higher reactivity of this type of cumulated system, compared to that of alkenes and alkynes, offers unique opportunities for the invention of new reactions. In this context, thermally and photochemically induced allene cycloadditions have been well developed for the preparation of natural and non-natural products of interest.[6] With these considerations in mind, we thus envisioned that π-system functionalized tosylamide **3** might be able to initiate a cascade reaction: catalytic S_N2-type substitution followed by intramolecular cycloaddition of an allenoate and a π-system (Scheme 1).



(1)

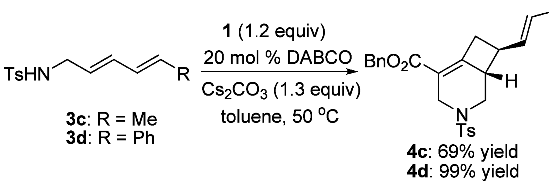
cat. = PPh$_3$: 76% yield
cat. = DABCO: 99% yield

We initially employed tosylamide **3a** to verify the postulation outlined in Scheme 1. The reaction of **1** and **3a**, with the use of PPh$_3$ (20 mol %) as the catalyst and Cs$_2$CO$_3$ (1.3 equiv) as the base in toluene solvent at 50 °C, delivered the desired bicyclo[4.2.0]oct-1-ene **4a** in 76% yield, in which only the terminal C−C double bond of allene participated in [2 + 2] cycloaddition (eq 1).[7] Further optimization of the conditions disclosed that DABCO is a better catalyst for this cascade reaction, enabling **4a** to be obtained in 99% yield under otherwise identical conditions (eq 1).[8] It is worth noting that the corresponding S_N2-substituted compound was not observed at all, strongly implying that the subsequent [2 + 2] cycloaddition might be a fast step.



(2)

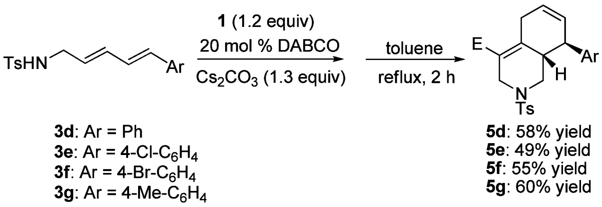
This amine-triggered S_N2/[2 + 2] cycloaddition sequential reaction can be extended to alkyne-functionalized substrate **3b**. Indeed, the DABCO-catalyzed reaction of **1** and **3b** occurs smoothly to afford bicyclo[4.2.0]octa-1,6-diene **4b** in 58% yield (eq 2).[7]



(3)

The success of [2 + 2] cycloaddition inspired us to explore the possibility of a Diels−Alder reaction with the use of diene-functionalized tosylamide as the substrate. Somewhat surprisingly, [2 + 2] cycloaddition products **4c** and **4d** were still isolated in yields of 69% and 99%, respectively, when compounds **3c** and **3d** were employed (eq 3).

Scheme 2. Synthesis of Compounds **5d**−**g** via a Two-Step Procedure



Interestingly, **4d** was found to undergo a rearrangement reaction in refluxing toluene, offering **5d** in 58% isolated yield as a single isomer (Scheme 2). It should be noted that the overall yield of **5d** would dramatically drop to 21% when the rearrangement step was directly conducted by heating just after the completion of S_N2/[2 + 2] cycloaddition. Probably, the presence of DABCO and salts might impose some negative effects on the subsequent rearrangement. This two-step procedure is also applicable to substrates **3e**−**f**, offering the rearrangement products **5e**−**f** in moderate overall yields (Scheme 2). However, **4c** was

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[5] For books, see: (a) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, 1984. (b) Landor, S. R. *The Chemistry of the Allenes*; Academic: London, 1982. (c) Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, 2004. For selected reviews, see: (d) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (e) Bandini, M. *Chem. Soc. Rev.* **2011**, *40*, 1358. (f) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954.

[6] For selected reviews, see: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Soc. Rev.* **2010**, *39*, 783. (b) Dolbier, W. R., Jr. *Acc. Chem. Res.* **1991**, *24*, 63. (c) Back, T. G.; Clary, K. N.; Gao, D. *Chem. Rev.* **2010**, *110*, 4498. (d) Yu, S.; Ma, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3074.

[7] For representive intramolecular [2 + 2] cycloaddtion of allene under thermal conditions, see: (a) Padwa, A.; Meske, M.; Murphree, S. S.; Watterson, S. H.; Ni, Z. *J. Am. Chem. Soc.* **1995**, *117*, 7071. (b) Hansen, T. V.; Skattebøl, L.; Stenstrøm, Y. *Tetrahedron* **2003**, *59*, 3461. (c) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Redondo, M. C.; Torres, M. R. *Chem.—Eur. J.* **2006**, *12*, 1539. (d) Ohno, H.; Mizutani, T.; Kadoh, Y.; Aso, A.; Miyamura, K.; Fujii, N.; Tanaka, T. *J. Org. Chem.* **2007**, *72*, 4378. (e) Mukai, C.; Hara, Y.; Miyashita, Y.; Inagaki, F. *J. Org. Chem.* **2007**, *72*, 4454. (f) Jiang, X.; Ma, S. *Tetrahedron* **2007**, *63*, 7589. (g) Oh, C. H.; Gupta, A. K.; Park, D. I.; Kim, N. *Chem. Commun.* **2005**, 5670.

[8] Without the catalyst, the reaction was sluggish and the yield of **4a** was 7% even when the reaction time was elongated to 48 h.

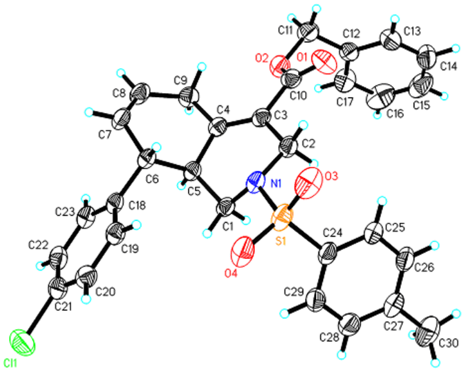
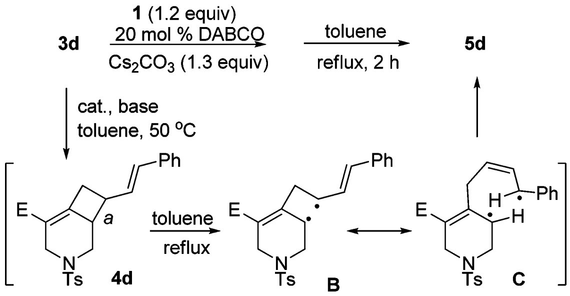


Figure 1. X-ray crystal structures of **5e**. Thermal ellipsoids are set at 50% probability.

recovered in 91% yield even upon exposure to refluxing toluene for 24 h.

The relative stereochemistry of **5e** was unambiguously determined by single crystal X-ray diffraction analysis (Figure 1). The stereochemistry of other compounds was tentatively assigned by comparing the ^{1}H NMR spectra with those of **5e**.

Scheme 3. Proposal for the Diradical-Involved Rearrangement



The chemical outcome of this rearrangement can be explained by the proposed mechanism shown in Scheme 3 (with **4d** as the substrate). Compound **4d** might be able to undergo thermally induced selective homocleavage of the *a*-bond of cyclobutane to produce diradical intermediate **B** which is believed to coexist with its resonant **C**.[9] For intermediate **C**, the phenyl group and cyclohexane moiety should be in opposite directions in order to minimize their steric hindrances. As a result, product **5d** with a trans-configuration would be formed after recombination of the two radicals.

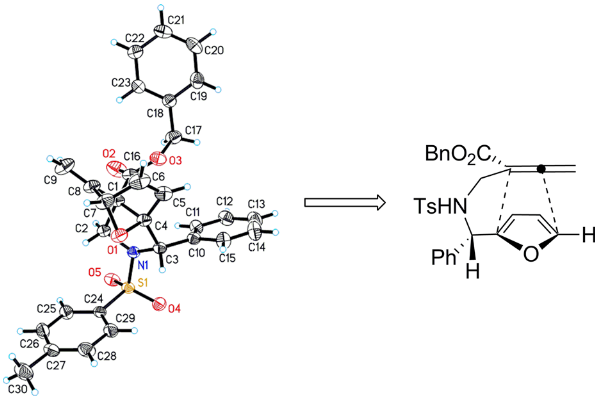
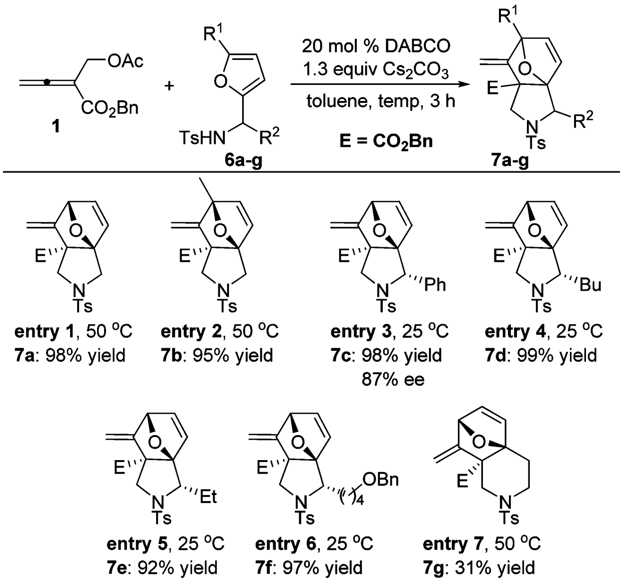


Figure 2. X-ray crystal structure of **7c** (left) and transition state for [4 + 2] cycloaddition (right). Thermal ellipsoids are set at 50% probability.

Scheme 4. Scope of Cascade S$_N$2/[4 + 2] Cycloaddition[a]



[a] Reaction conditions: **1** (0.24 mmol), **6** (0.2 mmol), DABCO (20 mol %), Cs$_2$CO$_3$ (1.3 equiv), toluene (2.0 mL), 3 h, under Ar. All yields reported are those of isolated products.

While the anticipated Diels–Alder reaction was not observed in the cases of diene-functionalized tosylamides **3c–g**, we next wanted to extend the chemistry to the furan-functionalized analogue considering that furan has been proven to be an excellent diene in Diels–Alder reactions.[10] Fortunately, tosylamide **6a** was found to react well with **1** under the optimized conditions, offering oxatricycle **7a** in almost quantitative yield (Scheme 4, entry 1). In contrast to [2 + 2] cycloaddition, the internal C–C double bond of allene participated in the [4 + 2] cycloaddition process selectively. Introduction of a methyl group into the 5-position of furan had no negative effect on the

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(9) (a) Jung, M. E.; Nishimura, N.; Novack, A. R. *J. Am. Chem. Soc.* **2005**, *127*, 11206. (b) Jung, M. E.; Nishimura, N. *J. Am. Chem. Soc.* **1999**, *121*, 3529. (c) Dolbier, W. R., Jr.; Mancini, G. J. *Tetrahedron Lett.* **1975**, *16*, 2141. (d) Dolbier, W. R., Jr.; Piedrahita, C. A.; Al-Sader, B. H. *Tetrahedron Lett.* **1979**, *20*, 2957. (e) Jung, M. E.; Murakami, M. *Org. Lett.* **2007**, *9*, 461.

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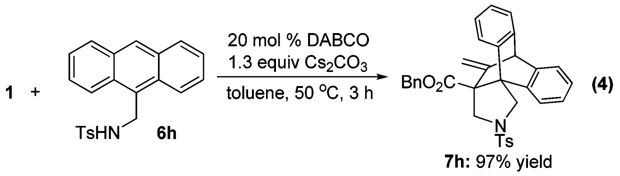
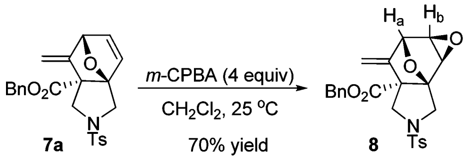
reaction, and the corresponding product **7b** was obtained in 95% yield (Scheme 4, entry 2). In this case, three quaternary stereocenters were successfully established. Substrate **6c**, with a tethered phenyl group, gave **7c** in 96% yield with a 6:1 diastereoselectivity (Scheme 4, entry 3). However, reducing the reaction temperature to 25 °C significantly improved the diastereoselectivity, rendering **7c** as a single isomer. The [4 + 2] cycloaddition could smoothly occur at a lower temperature likely due to the Thorpe–Ingold effect[11] imposed by the tethered phenyl group. As a result, **7c** with 87% ee was obtained in 98% yield when **6c** with 85% ee was reacted at 25 °C. Similarly, the reaction of the substrate with an alkyl group at tether, such as **6d**, **6e**, and **6f**, afforded the corresponding products as a single isomer in high yields (Scheme 4, entries 4–6). The structure of **7c** was unambiguously established by X-ray analysis, which clearly disclosed that the subsequent Diels–Alder reaction proceeded in an *endo*-fashion (Figure 2).[12] The reaction of substrate **6g** with an extended carbon tether was found to be worse, offering **7g** only in 31% yield (Scheme 4, entry 7).



(4)

Interestingly, anthracene-functionalized tosylamide **6h** also proceeded under these conditions, producing compound **7h** in 97% yield (eq 4).

The products of the cascade reaction possess olefins, which might be available for further transformations. For example, the endocyclic olefin of **7a** can be selectively epoxidated using common *m*-CPBA epoxidation conditions while the exo-one is untouched, providing epoxide product **8** in 70% isolated yield (eq 5).[13]



(5)

In summary, we have developed an efficient S_N2/cycloaddtion cascade reaction of allenoate **1** with various π-system functionalized tosylamides in the presence of a catalytic amount of DABCO, which provides a facile access to important classes of azaheterocycles. The reaction features readily available starting materials and mild reaction conditions. More importantly, this cascade reaction increases molecular complexity by forming three σ-bonds and up to three rings, as well as quaternary centers. Additional investigations of the synthetic transformation are currently underway in our laboratory.

Acknowledgment. The financial support from NSFC (No. 21002025), the Fundamental Research Funds for the Central Universities, Shanghai Rising-Star Program (11QA1401700), and Specialized Research Fund for the Doctoral Program of Higher Education (20100074120014) is highly appreciated.

Supporting Information Available. Experimental procedures and copies of NMR spectra for all new products and X-ray crystallographic data for **5e** and **7c** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For reviews, see: (a) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735. (b) Sammes, P. G.; Weller, D. J. *Synthesis* **1995**, 1205. (c) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117. (d) Bunz, U. H. F. *Top. Curr. Chem.* **1999**, *201*, 131.

(12) (a) Ismail, Z. M.; Hoffmann, H. M. R. *J. Org. Chem.* **1981**, *46*, 3549. (b) Lohse, A. G.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 3430. (c) Henderson, J. R.; Chesterman, J. P.; Parvez, M.; Keay, B. A. *J. Org. Chem.* **2010**, *75*, 988 and references therein.

(13) The bridged H_a is a singlet, indicating that the corresponding $J_{H_a\text{-}H_b}$ value is really small. Thus, the relative stereochemistry between H_a and H_b could be assigned to be syn.

The authors declare no competing financial interest.