Formal [4+3] Epoxide Cascade Reaction via a Complementary Ambiphilic Pairing Strategy
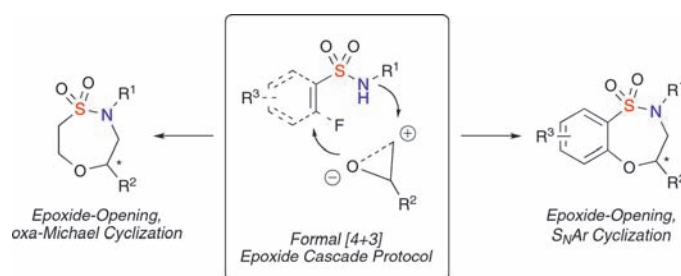
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ABSTRACT

Epoxide-Opening, oxa-Michael Cyclization — *Formal [4+3] Epoxide Cascade Protocol* — *Epoxide-Opening, S$_N$Ar Cyclization*

A formal [4+3] epoxide cascade protocol utilizing ambiphilic sulfonamides and a variety of epoxides (masked ambiphiles) has been developed for the generation of benzothiaoxazepine-1,1′-dioxides and oxathiazepine-1,1′-dioxides. This protocol combines an epoxide ring-opening with either an S$_N$Ar or oxa-Michael cyclization pathway.

The development of cascade reactions, which couple two or more reactions together to produce heterocyclic scaffolds, is an important challenge in drug discovery and natural product synthesis.[1] Cascade or domino reactions are highly efficient pathways that allow for the synthesis of complex molecules from simple substrates and encompass a variety of transformations. Many of these cascade transformations involve the utilization of synthons, which contain either a nucleophilic or an electrophilic site.[2] In contrast, ambiphilic synthons possess

both a nucleophilic and an electrophilic site, making them ideal components for cascade protocols.[3,4] Interest in the utilization of cascade reactions for the synthesis of diverse sultam scaffolds[5] has led us to explore the titled protocol where ambiphilic sulfonamides are combined with an epoxide (a

(1) (a) Nicolaou, K. C.; Chen, J. S. *Chem. Soc. Rev.* **2009**, *38*, 2993–3009. (b) Enders, D.; Grndal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163.

(2) (a) Tietze, L. F.; Brasche, G.; Gericke, K. M., Eds.; *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. (b) Fustero, S.; Jiménez, D.; Sánchez-Roselló, M.; del Pozo, C. *J. Am. Chem. Soc.* **2007**, *129*, 6700–6701. (c) Bi, H.-P.; Liu, X.-Y.; Gou, F.-R.; Guo, L.-N.; Duan, X.-H.; Shu, X.-Z.; Liang, Y.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 7068–7071. (d) Rolfe, A.; Young, K.; Hanson, P. R. *Eur. J. Org. Chem.* **2008**, *31*, 5254–5262.

(3) (a) Bontemps, S.; Gornitzka, H.; Bouhadir, G.; Miqueu, K.; Bourissou, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1611–1614. (b) Bontemps, S.; Bouhadir, G.; Miqueu, K.; Bourissou, D. *J. Am. Chem. Soc.* **2006**, *128*, 12056–12057. (c) Tejedor, D.; Méndez-Abt, G.; González-Platas, J.; Ramirez, M. A.; Garc'a-Tellado, F. *Chem. Commun.* **2009**, 2368–2370. (d) Kozytska, M. V.; Dudley, G. B. *Chem. Commun.* **2005**, 3047–3049.

(4) Molecules containing both electrophilic and nucelophilic nodes also have been defined as amphoteric molecules by Yudin, see: (a) Hili, R.; Yudin, A. K. *J. Am. Chem. Soc.* **2009**, *131*, 16404–16406. (b) Hili, R.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 4188–4191. (c) Baktharaman, S.; Hili, R.; Yudin, A. K. *Aldrichim. Acta* **2008**, *41*, 109–119. Molecules containing both electrophilic and nucleophilic nodes also have been defined as amphiphilic molecules, see: (d) Nakamura, H.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8113–8114. (e) Nakamura, H.; Aoyagi, K.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372–377. (f) Kimura, M.; Tamaki, T.; Nakata, M.; Tohyama, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2008**, *120*, 5887–5889.

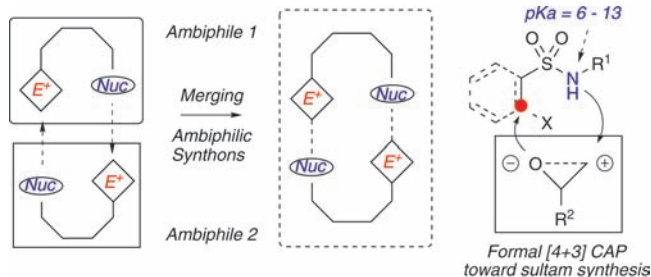masked ambiphile), in a cascade reaction termed complementary ambiphile pairing (CAP) (Figure 1).


Figure 1. Generation of sultam hetrocycles utilizing complementary ampbiphile pairing (CAP).

Epoxide cascade reactions have been known for over a half-century and have played a key role in the synthesis of polycyclic natural products.[6] Despite the wide application of epoxide cascade reactions in natural product synthesis, application in the synthesis of complex small heterocycles has been utilized to a lesser degree. Epoxide cascades can utilize a variety of organic acids,[7] or metal catalysts, to promote the cyclization. These include Au(I) cyclization with alkynes and allenes,[8] SmI_2 opening−iodocyclization,[9] and cobalt-mediated cycloadditions.[10] Notably absent from the literature are methods which combine epoxide ring-opening pathways with other pathways in a domino cascade. Toward the realization of this goal, we herein report the development of a formal [4+3] epoxide cascade protocol that combines an epoxide ring-opening with either an S_NAr or oxa-Michael cyclization pathway for the generation of benzothiaoxazepine-1,1′-dioxides and oxathiazepine-1,1′-dioxides (Figure 2).

Reports of the cyclization of an in situ generated epoxide-derived alkoxide via an intramolecular S_NAr cyclization have been limited. Albanese and co-workers first reported the
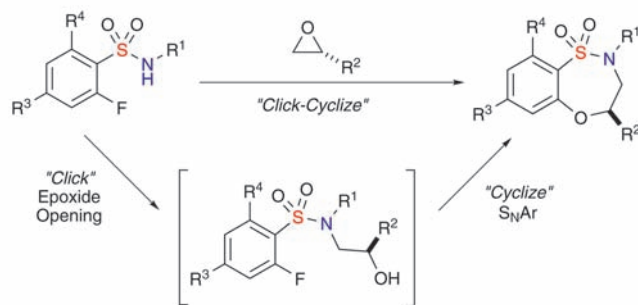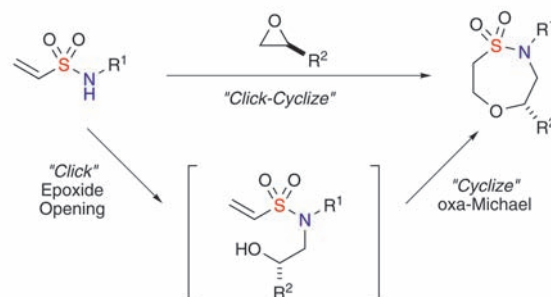

Figure 2. Epoxide cascade protocols for the synthesis of sultams.

synthesis of piperazines utilizing an epoxide-opening, S_NAr protocol.[11] More recently, a key report by Cleator and co-workers at Merck demonstrated the ring-opening of epoxides with o-fluorobenzenesulfonamides, followed by subsequent S_NAr cyclization to give the corresponding sultams.[12] Reports of intramolecular Michael cyclizations with vinylsulfonamides have been utilized in seminal work by Knollmüller and Hirooka,[13] to more recent applications in the area of diversity-oriented synthesis (DOS) strategies using a "Click, Click, Cyclize" approach.[14] However, the opening of an epoxide and subsequent cyclization via oxa-Michael is not known.

Initial investigation into the proposed epoxide cascade focused on the development of orthogonal reaction conditions that would initiate the ring-opening of the corresponding epoxide, followed by intramolecular S_NAr cyclization to yield the desired sultam in a one-pot, domino process.[15] It was found that the choice of both solvent and base was key to the overall reaction process with dioxane essential for the initial epoxide ring-opening step, and DMF for the S_NAr ring-closing step of the cascade. After screening a wide variety of bases, anhydrous Cs_2CO_3 produced the best overall yield

(5) Sultams, the cyclic analogues of sulfonamides, although not found in nature, represent a subclass of relatively unexplored molecular space for the discovery of new therapeutic drugs. Recent reports have demonstrated that sultams possess a broad spectrum of biological activity. For an extensive list of biological sultams and methods for synthesis see: Jimenez-Hopkins, M.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 2223–2226.

(6) (a) Corey, E. J.; Russey, W. E.; Ortiz de Montellano, P. R. *J. Am. Chem. Soc.* **1966**, *88*, 4750–4751. (b) van Tamelen, E. E.; Willett, J. D.; Clayton, R. B.; Lord, K. E. *J. Am. Chem. Soc.* **1966**, *88*, 4752–4753. (c) Vilotijevic, I.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5250–5281. (d) Topczewski, J. J.; Callahan, M. P.; Neighbors, J. D.; Wiemer, D. F. *J. Am. Chem. Soc.* **2009**, *131*, 14630–14631. (e) Neighbors, J. D.; Beutler, J. A.; Wiemer, D. F. *J. Org. Chem.* **2005**, *70*, 925–931.

(7) (a) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C. K. *J. Am. Chem. Soc.* **1989**, *111*, 5335–5340. (b) Morimoto, Y.; Nishikawa, Y.; Ueba, C.; Tanaka, T. *Angew. Chem.* **2006**, *118*, 824–826. (c) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158–8159. (d) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339–2342.

(8) (a) Dai, L.-Z.; Qi, M.-J.; Shi, Y.-L.; Liu, X.-G.; Shi, M. *Org. Lett.* **2007**, *9*, 3191–3194. (b) Tarselli, M. A.; Zuccarello, J. L.; Lee, S. J.; Gagne, M. R. *Org. Lett.* **2009**, *11*, 3490–3492.

(9) (a) Kwon, D. W.; Cho, M. S.; Kim, Y. H. *Synlett* **2003**, *7*, 959–962. (b) Park, H. S.; Kwon, D. W.; Lee, K.; Kim, Y. H. *Tetrahedron. Lett.* **2008**, *49*, 1616–1618.

(10) Odedra, A.; Lush, S.-F.; Lui, R.-S. *J. Org. Chem.* **2007**, *72*, 567–573.

(11) (a) Albanese, D.; Landini, D.; Penso, M. *Chem. Commun.* **1999**, 2095–2096. (b) Albanese, D.; Landini, D.; Lupi, V.; Penso, M. *Ind. Eng. Chem. Res.* **2003**, *42*, 680–686.

(12) After the submission of this paper for review, we became aware of the following report that appeared online on December 24, 2009:Cleator, E.; Baxter, C. A.; O'Hagan, M.; O'Riordan, T. J. C.; Sheen, F. J.; Stewart, G. W. *Tetrahedron Lett.* **2010**, 1079–1082.

(13) (a) Hromatka, O.; Binder, D.; Knollmüller, M. *Monatsh. Chem.* **1968**, *99*, 1062–1067. (b) Hasegawa, K.; Hirooka, S. *Bull. Soc. Chem. Jpn.* **1972**, *45*, 525–528.

and crude purity when utilized in the cascade protocol. The utilization of microwave irradiation at 110 °C for 20 min was essential to obtain both high yields and crude purity in addition to a significant decrease in reaction times.[16,17] After optimization of reaction conditions for the synthesis of sultam **1**, the substrate scope was investigated with use of a variety of epoxides and *o*-fluorobenzenesulfonamides to yield the corresponding sultams **1−9** in good yield and crude purity (Table 1).[18]

Table 1. One-Pot Epoxide, S_NAr Cascade Utilizing α-Fluorobenzenesulfonamides

entry	R¹	R²	R³	yield, %
1	(CH₂)₃CH₃	CH₂OBn	6-F	73
2	(CH₂)₃CH₃	(CH₂)₂CH=CH₂	6-F	71
3	4-F-Ph(CH₂)₂	CH₂OPh	6-F	71
4	4-OMe-Bn	(CH₂)₂CH=CH₂	6-F	69
5	(R)-CH(CH₃)Ph	(R)-CH₂CO₂(CH₂)₂CH₃	6-F	76
6	(CH₂)₃CH₃	CH₂OBn	3-Br	65
7	Allyl	CH₂O(CH₂)₃CH₃	5-Cl	74
8	(CH₂)₃CH₃	CH₂OPh	3-Br	78
9	2-OMe-Bn	CH₂O(CH₂)₃CH₃	5-Cl	74

During these investigations, it was found that when utilizing *tert*-butyldimethylsilyl (R)-(−)-glycidyl ether under the aforementioned reaction conditions, the corresponding hydroxy-sultam **11** was isolated. This presumably occurs when the in situ-generated fluoride ion deprotects the corresponding TBDMS-protected sultam **10** yielding the free hydroxy sultam **11** in good yield (Scheme 1).[16]

Scheme 1. Proposed Mechanism for the Generation of Sultam **11**
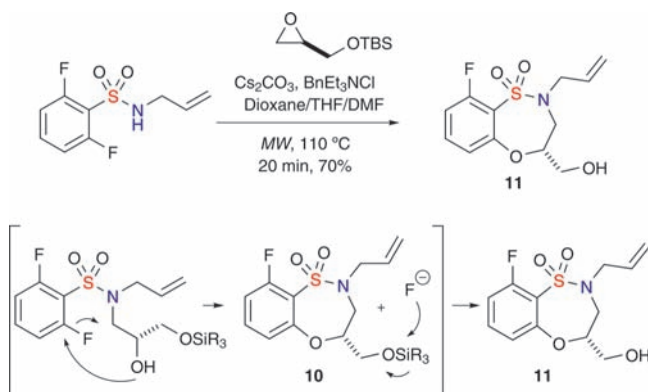
With sultam **11** in hand, facile derivatization of the free hydroxy was achieved via ester formation with a variety of

acids. In this case, an oligomer coupling reagent, ²GOACC₅₀, derived from ring-opening metathesis polymerization (ROMP) was utilized to yield the corresponding sultam esters **12−16** in high yield and purity without the need for conventional purification (Table 2).[19]

Table 2. S_NAr Intramolecular Mitsunobu Route to Benzothiaoxazepine-1,1-dioxides
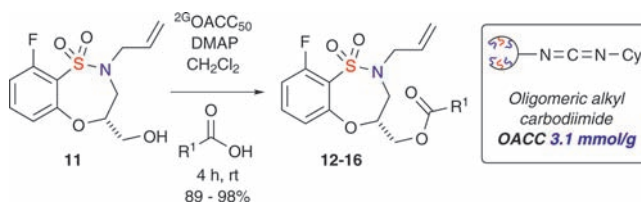
entry	R¹	yield, %	purity,[a] %
1	3-MePh	94	>95
2	3-OMePh	94	>95
3	3,4-MePh	96	>95
4	CH₂CN	89	>95
5	CH₂SPh	98	>95

[a] Crude purity determined by ¹H NMR.

We have previously shown that vinylsulfonamides undergo oxa- and aza-Michael additions to afford the corresponding oxathiazepine-1,1′-dioxides and oxathiazocine-1,1-dioxides.[10] Therefore, the utilization of vinylsulfonamides in the aforementioned epoxy cascade reaction was investigated. In this case, it was envisioned that following the opening of an epoxide with a vinylsulfonamide, the in situ-generated hydroxy group would spontaneously undergo a oxa-Michael cyclization reaction to the corresponding sultam in a one-pot cascade protocol.

The aforementioned S_NAr results showed that the utilization of dioxane was essential for quantitative epoxide opening at 110 °C under microwave irradiation. Additionally, the oxa-Michael cyclization reaction proceeds efficiently in a polar solvent such as THF but not DMF. With use of these slightly modified conditions, a variety of vinylsulfonamides were

(14) (a) Zhou, A.; Hanson, P. R. *Org. Lett.* **2008**, *10*, 2951–2954. (b) Zhou, A.; Rayabarapu, D.; Hanson, P. R. *Org. Lett.* **2009**, *11*, 531–534.

(15) Rolfe, A.; Young, K.; Volp, K.; Schoenen, F.; Neuenswander, B.; Lushington, G. H.; Hanson, P. R. *J. Comb. Chem.* **2009**, *11*, 732–738.

(16) Conventional heating in an oil bath required 20−24 h at 150 °C to afford the desired product, although yields were on average 10−20% lower.
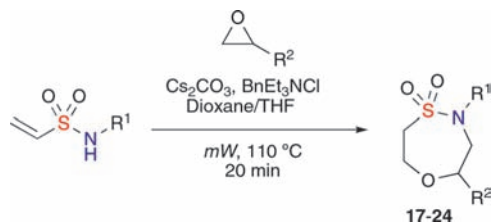
(17) 2-Fluorobenzenesulfonamides bearing additional halogen functionality on the benzene ring were designed for diversification at a later stage in library format. No reduction in yield or reaction rates for the epoxide cascade protocol was observed when these were not present in the starting material.

(18) The control experiment was carried out utilizing *N*-allyl-2-bromobenzenesulfonamide whereby the fluorine at the 2- and 6-position was replaced by H at the 6-position and a Br at the 2-position. Under the standard reaction conditions, the corresponding TBDMS protected epoxide acyclic product was produced as observed by crude ¹H NMR, indicating the TBDMS group was not removed under the reaction conditions producing the corresponding free OH group.

(19) (a) Zhang, M.; Vedantham, P.; Flynn, D. L.; Hanson, P. R. *J. Org. Chem.* **2004**, *69*, 8340–8344. (b) Rolfe, A.; Probst, D.; Volp, K. A.; Omar, I.; Flynn, D.; Hanson, P. R. *J. Org. Chem.* **2008**, *73*, 8785–8790.

subjected to the epoxy cascade protocol affording the corresponding sultams **17−24** in good yield and high crude purity (Table 3).

Table 3. One-Pot Epoxy Cascade S_NAr Cyclization Utilizing Vinylsulfonamides

entry	R^1	R^2	yield, %
1	allyl	CH$_2$OBn	65
2	allyl	(S)-CH$_2$OBn	63
3	(CH$_2$)$_3$CH$_3$	CH$_2$OBn	58
4	Bn	4-Me-PhOCH$_2$	62
5	allyl	4-Me-PhOCH$_2$	57
6	cyclopentyl	4-Me-PhOCH$_2$	55
7	propargyl	CH$_2$OPh	53
8	(R)-CH(CH$_3$)Ph	(R)-CH$_2$CO$_2$ (CH$_2$)$_2$CH$_3$	60

As demonstrated in the case of *o*-fluorobenzenesulfon-amide (Table 1), the reaction conditions were tolerant to a variety of vinylsulfonamides and epoxides, allowing for the incorporation of functional handles and stereogenic centers into the molecule (Table 3, entries 2 and 8). Overall, the employment of ambiphilic vinylsulfonamides in combination with *o*-fluorobenzenesulfonamides gives rapid access to the corresponding nonbenzofused oxathiazepine-1,1′-dioxide derivatives.

In conclusion, we report the development of a facile, one-pot epoxide cascade protocol for the synthesis of benzothiaoxazepine-1,1′-dioxides and oxathiazepine-1,1′-dioxides from ambiphilic sulfonamides. Epoxide ring-opening followed by either intramolecular S_NAr cyclization or intramolecular oxa-Michael cyclization yields these heterocycles. In both cases, a variety of epoxides and sulfonamides were utilized to demonstrate substrate scope and utility of the method. Ongoing efforts aimed at the investigation of additional CAP strategies continue and will be reported in due course.

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

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