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

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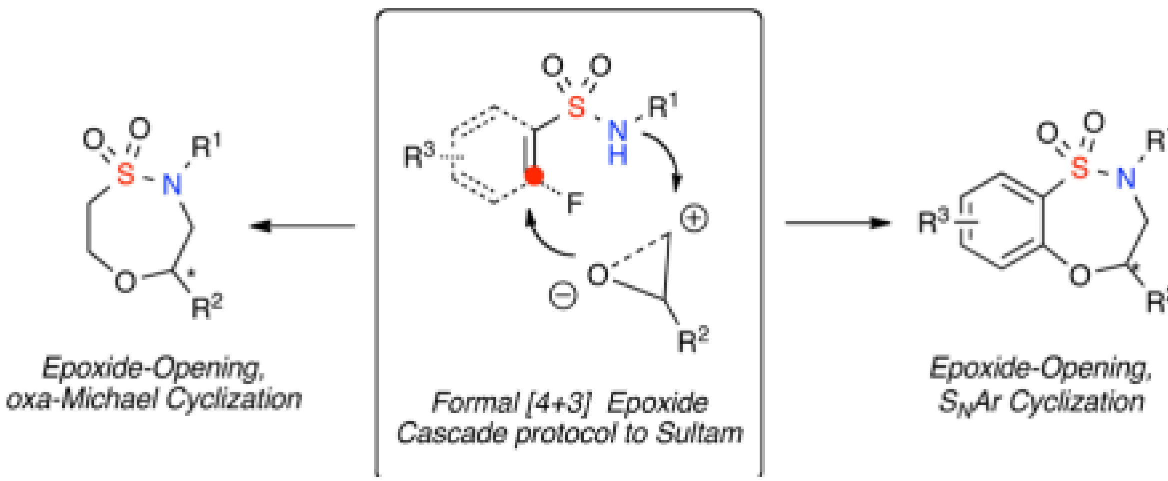
Abstract



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

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

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. Towards the realization of this goal, we herein report the development of a formal [4+3] epoxide cascade protocol which 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 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 α-fluorobenzene-sulfonamides, followed by subsequent S_NAr cyclization to give the corresponding piperazines and 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 both the choice of 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 and crude purity when utilized in the cascade protocol. The utilization of microwave irradiation at 110 °C for 20 minutes 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 using a variety of epoxides and α-fluorobenzenesulfonamides to yield the corresponding sultams **1–9** in good yield and crude purity (Table 1).[18]

During these investigations, it was found that when utilizing *tert*-butyldimethylsilyl (*R*)-(−)-glycidyl ether under the aforementioned reactions 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 (Table 2).[16]

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, $^{2G}OACC_{50}$, 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 3).[19]

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 polar solvent such as THF but not DMF. Using these slightly modified conditions, a variety of vinylsulfonamides were subjected to the epoxy cascade protocol affording the corresponding sultams **17**–**24** in good yield and high crude purity (Table 4).

As demonstrated in the case of α-fluorobenzene sulfonamides (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, entry 2 and 8). Overall, the employment of ambiphilic vinylsulfonamides in comparison to α-fluorobenzene sulfonamides gives rapid access to the corresponding non-benzofused 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Nicolaou KC, Chen JS. Chem Soc Rev 2009;11:2993–3009. [PubMed: 19847336] b) Enders D, Grndal C, Hüttl MRM. Angew Chem Int Ed 2007;46:1570–1581. c) Tietze LF, Beifuss U. Angew Chem Int Ed Engl 1993;32:131–163.
2. (a) Tietze, LF.; Brasche, G.; Gericke, KM., editors. 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. [PubMed: 17480078] (c) Bi HP, Liu XY, Gou FR, Guo LN, Duan XH, Shu XZ, Liang YM. Angew Chem Int Ed 2007;46:7068–7071. (d) Rolfe A, Young K, Hanson PR. Eur J Org Chem 2008:5254–5262.
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. [PubMed: 16967941] (c) Tejedor D, Méndez-Abt G, González-Platas J, Ramirez MA, García-Tellado F. Chem Comm 2009:2368–2370. [PubMed: 19377688] (d) Kozytska MV, Dudley GB. Chem Comm 2005:3047–3049. [PubMed: 15959580]
4. (a) Molecules containing both electrophilic and nucelophilic nodes have been also defined as amphoteric molecules by Yudin, see: a) Hili R, Yudin AK. J Am Chem Soc 2009;131:16404–16406. [PubMed: 19856916] (b) Hili R, Yudin AK. Angew Chem Int Ed 2008;47:4188–4191. (c) Baktharaman S, Hili R, Yudin AK. Aldrichimica Acta 2008;41:109–119.Molecules containing both electrophilic and nucleophilic nodes have also been also defined as amphiphilic molecules, see: (d)

Nakamura H, Shim JG, Yamamoto Y. J Am Chem Soc 1997;119:8113–8114. (e) Nakamura H, Aoyagi K, Shim JG, 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.

5. Sultams, the cyclic analogs 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 PR. Org Lett 2008;10:2223–2226. [PubMed: 18447383]
6. (a) Corey EJ, Russey WE, Ortiz de Montellano PR. J Am Chem Soc 1966:4750–4751. [PubMed: 5918046] (b) van Tamelen EE, Willett JD, Clayton RB, Lord KE. J Am Chem 1966:4752–4753. (c) Vilotijevic I, Jamison TF. Angew Chem Int Ed 2009;48:5250–5281. (c) Topczewski JJ, Callahan MP, Neighbors JD, Wiemer DF. J Am Chem Soc 2009;131:14630–14631. [PubMed: 19824722] (d) Neighbors JD, Beutler JA, Wiemer DF. J Org Chem 2005;70:925–931. [PubMed: 15675850]
7. (a) Nicolaou KC, Prasad CVC, Somers PK, Hwang CK. 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 TP, Jamison TF. Org Lett 2003;5:2339–2342. [PubMed: 12816443]
8. (a) Dai LZ, Qi MJ, Shi YL, Liu XG, Shi M. Org Lett 2007;9:3191–3194. [PubMed: 17629294] (b) Tarselli MA, Zuccarello JL, Lee SJ, Gagne MR. Org Lett 2009;11:3490–3492. [PubMed: 19588972]
9. (a) Kwon DW, Cho MS, Kim YH. Synlett 2003;7:959–962. (b) Park HS, Kwon DW, Lee K, Kim YH. Tetrahedron Lett 2008;49:1616–1618.
10. Odedra A, Lush SF, Lui RS. J Org Chem 2007;72:567–573. [PubMed: 17221975]
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 which appeared online on December 24, 2009: Cleator E, Baxter CA, O'Hagan M, O'Riordan TJC, Sheen FJ, Stewart GW. Tetrahedron Lett 2010:1079–1082.
13. (a) Hromatka O, Binder D, Knollmüller M. Monatshfte Für Chemie 1968;99:1062–1067. (b) Hasegawa K, Hirooka S. Bull Soc Chem Jap 1972;45:525–528.
14. (a) Zhou A, Hanson PR. Org Lett 2008;10:2951–2954. [PubMed: 18553974] (b) Zhou A, Rayabarapu D, Hanson PR. Org Lett 2009;11:531–534. [PubMed: 19115841]
15. Rolfe A, Young K, Volp K, Schoenen F, Neuenswander B, Lushington GH, Hanson PR. J Comb Chem 2009;11:732–738.
16. Conventional heating in oil bath required 20–24 hours 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- and a Br at the 2-. Under the standard reaction conditions, the corresponding TBDMS protected epoxide acyclic product was produced as observed by crude ^{1}H 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 DL, Hanson PR. J Org Chem 2004;69:8340–8344. [PubMed: 15549805] (b) Rolfe A, Probst D, Volp KA, Omar I, Flynn D, Hanson PR. J Org Chem 2008;73:8785–8790. [PubMed: 18937412]

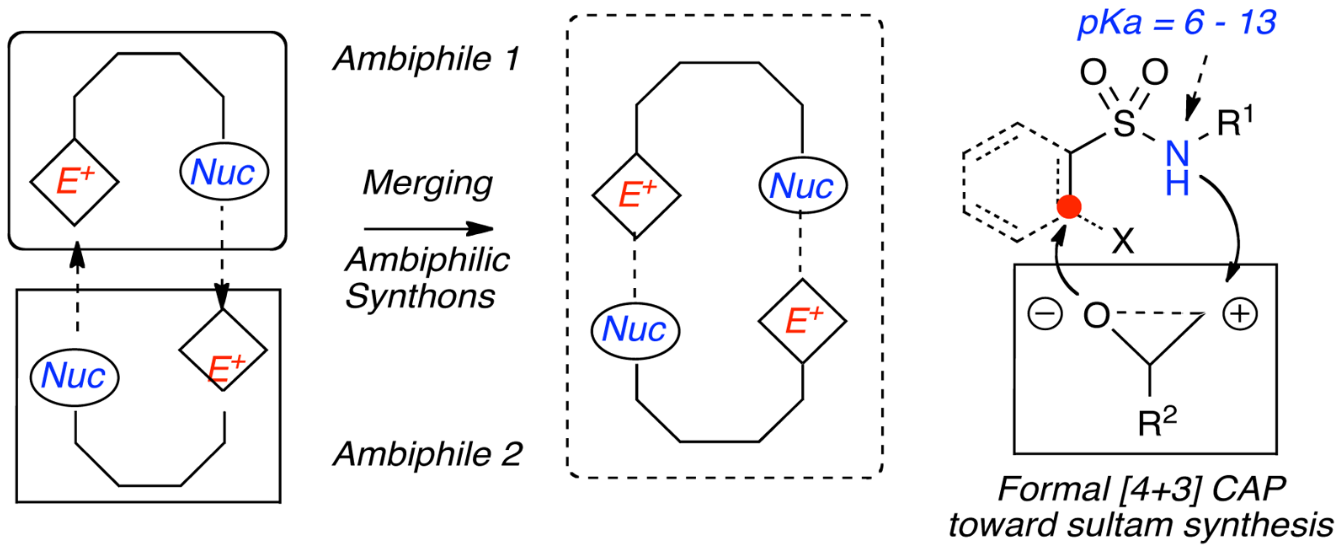


Figure 1.
Generation of sultam hetrocycles utilizing complementary ampbiphile pairing (CAP)

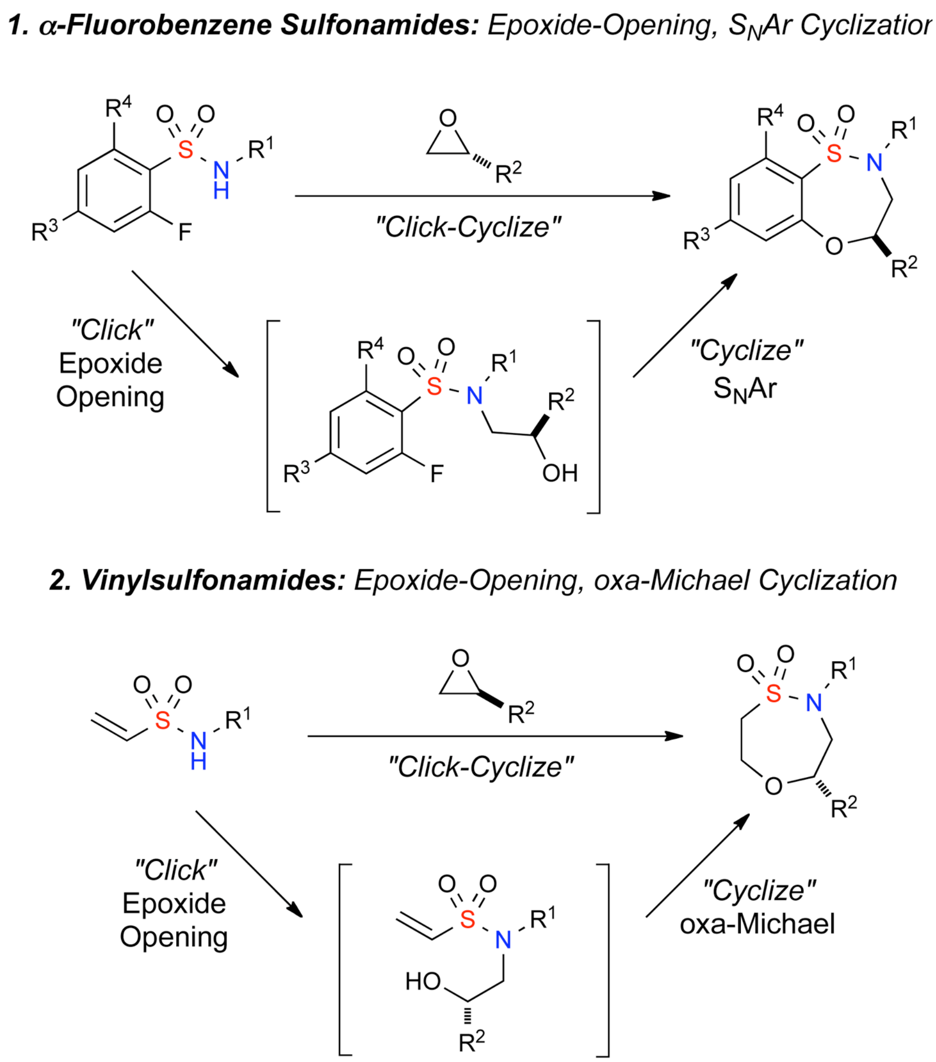
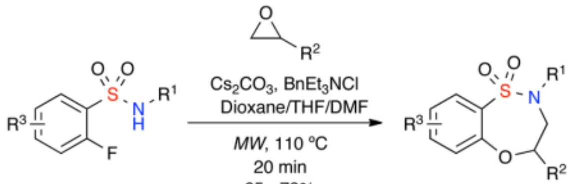


Figure 2.
Epoxide cascade protocols for the synthesis of sultams

Table 1

One-pot epoxide, S_NAr cascade utilizing α-fluorobenzenesulfonamides



entry	R^1	R^2	R^3	yield
1	$(CH_2)_3CH_3$	CH_2OBn	6-F	73
2	$(CH_2)_3CH_3$	$(CH_2)_2CH{=}CH_2$	6-F	71
3	4-F-Ph$(CH_2)_2$	CH_2OPh	6-F	71
4	4-OMe-Bn	$(CH_2)_2CH{=}CH_2$	6-F	69
5	(*R*)-$CH(CH_3)Ph$	(*R*)-$CH_2CO_2(CH_2)_2CH_3$	6-F	76
6	$(CH_2)_3CH_3$	CH_2OBn	3-Br	65
7	Allyl	$CH_2O(CH_2)_3CH_3$	5-Cl	74
8	$(CH_2)_3CH_3$	CH_2OPh	3-Br	78
9	2-OMe-Bn	$CH_2O(CH_2)_3CH_3$	5-Cl	74

Table 2

Proposed mechanism for the generation of Sultam **11**

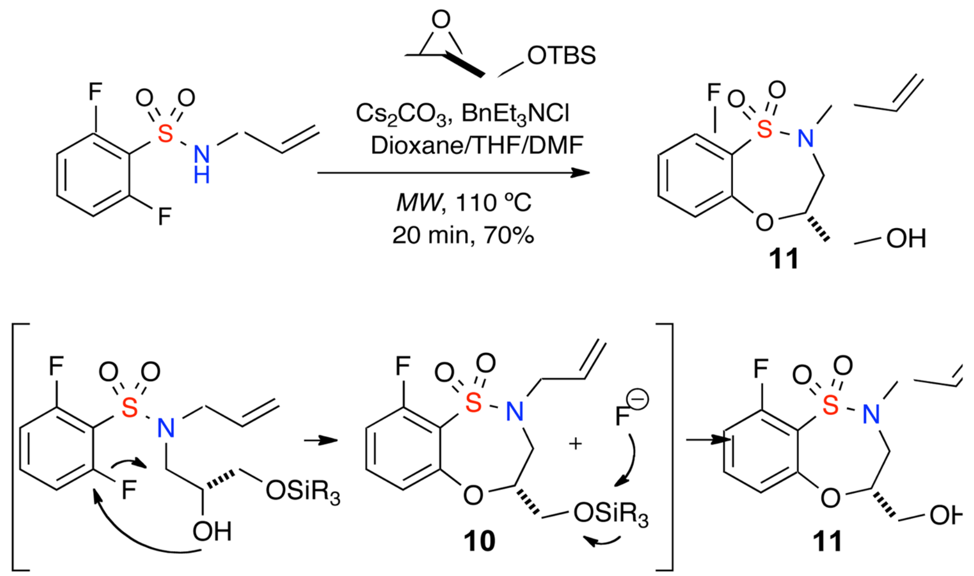


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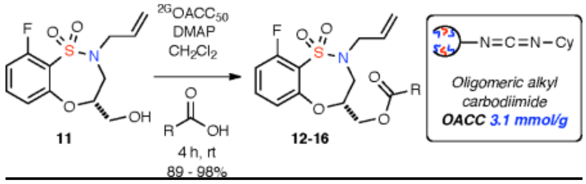
Table 3

S_NAr – intramolecular Mitsunobu route to benzothiaoxazepine-1,1-dioxides

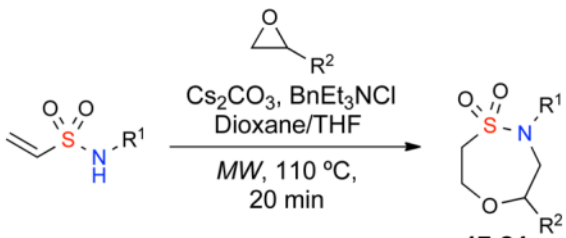


entry	R^1	yield	purity[a]
1	3-MePh	94	>95%
2	3-OMePh	94	>95%
3	3,4-MePh	96	>95%
4	CH_2CN	89	>95%
5	CH_2SPh	98	>95%

[a]Crude Purity determined by ^{1}H NMR

Table 4

One-pot epoxy cascade S_NAr cyclization utilizing vinylsulfonamides



entry	R^1	R^2	yield
1	Allyl	CH_2OBn	65
2	Allyl	(*S*)-CH_2OBn	63
3	$(CH_2)_3CH_3$	CH_2OBn	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_2OPh	53
8	(*R*)-$CH(CH_3)Ph$	(*R*)-$CH_2CO_2(CH_2)_2CH_3$	60