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Enantiopure 1,4-Benzoxazines via 1,2-Cyclic Sulfamidates. Synthesis of Levofloxacin

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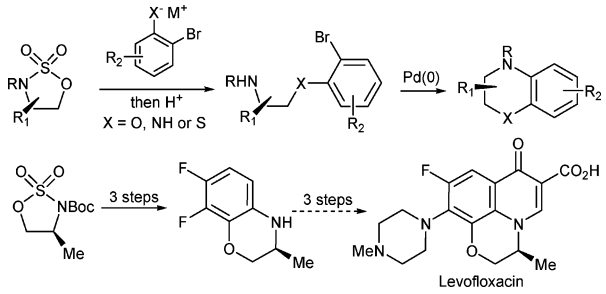
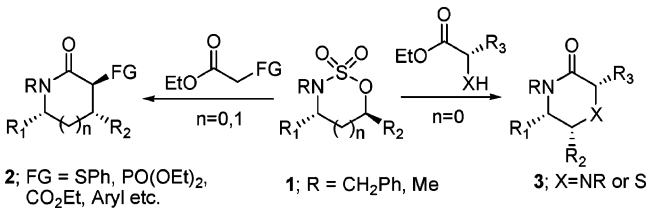
ABSTRACT



1,2-Cyclic sulfamidates undergo efficient and regiospecific nucleophilic cleavage with 2-bromophenols (and related anilines and thiophenols), followed by Pd(0)-mediated amination to provide an entry to substituted and enantiomerically pure 1,4-benzoxazines (and quinoxalines and 1,4-benzothiazines). This chemistry provides a short and efficient entry to (3*S*)-3-methyl-1,4-benzoxazine 19, a late stage intermediate in the synthesis of levofloxacin.

1,2- and 1,3-cyclic sulfamidates **1**, which are readily available from substituted and often enantiopure 1,2- and 1,3-aminoalcohols, are synthetically versatile electrophiles displaying a reactivity profile analogous to activated aziridines and azetidines, respectively. Nucleophilic cleavage, which is highly selective for the C−O bond, occurs in a stereospecific manner (S_N2), and the resulting *N*-sulfate is readily hydrolyzed to the final product under mildly acidic conditions.[1] Cyclic sulfamidates are readily exploitable in a number of ways, and we have developed efficient and flexible entries to a range of enantiomerically pure *N*-heterocyclic structures as illustrated in Scheme 1.[2] Of particular value is the nucleophilic cleavage of 1,2- and 1,3-cyclic sulfamidates with α-functionalized ester enolates which provides an entry to substituted pyrrolidinones and piperidinones **2**.

Scheme 1. Cyclic Sulfamidates as Precursors to N-Heterocycles



The scope of this methodology has been defined both in terms of *N*-heterocyclic methodologies[2b,d] and via efficient, asymmetric routes to biologically active targets, such as the antidepressant (−)-paroxetine[2f] and natural products (+)-

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(1) For a review on the synthesis and reactivity of cyclic sulfamidates, see: Meléndez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *59*, 2581−2616. Six-ring cyclic sulfamidates, where nitrogen is part of an aziridine ring system, undergo nucleophilic cleavage preferentially at the C−N bond to afford substituted seven-ring cyclic sulfamidates: (a) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481−2483. (b) Duran, F. J.; Ghini, A. A.; Dauban, P.; Dodd, R. H.; Burton, G. *J. Org. Chem.* **2005**, *70*, 8613−8616.

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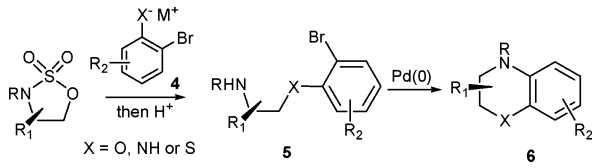
laccarin[2f] and (−)-aphanorphine.[2c,e] Heteroatom-based nucleophiles (α-amino or thio esters) react with 1,2-cyclic sulfamidates to give thiomorpholinones and piperazinones **3** in a stereospecific manner.[2a]

In this paper, we describe a new application of heteroatom nucleophiles to provide an efficient and convergent two-step protocol for the synthesis of substituted and enantiopure 1,4-benzoxazines and related benzofused heterocycles.[3,4]

This chemistry capitalizes on the highly efficient cleavage of 1,2-cyclic sulfamidates with readily available 2-bromophenolate nucleophiles (**4**; X = O),[5] allowing direct access to adducts **5** (after *N*-sulfate hydrolysis) which afford the target heterocycles **6** under Pd(0)-mediated Buchwald−Hartwig amination conditions (Scheme 2).[6]

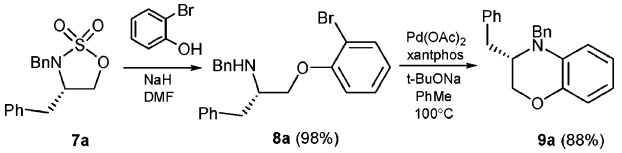
Scheme 2. Tandem Ring-Opening/Pd(0)-Mediated Amination



The scope of this methodology is reported as is its application to a concise, high-yielding, and asymmetric entry to the potent antibiotic drug levofloxacin. In addition, the use of nucleophiles based on 2-bromoaniline (**4**; X = NH) and 2-bromothiophenol (**4**; X = S) provides direct access to substituted and enantiomerically pure quinoxaline and 1,4-benzothiazine variants, respectively.[7]

Using a structurally representative range of substituted 1,2- and 1,3-cyclic sulfamidates **7a**−**e**,[2a,b,d] we have found that nucleophilic cleavage with the sodium anion of 2-bromophenol (2 equiv) generally occurs between room temperature and 60 °C (in DMF) to deliver the corresponding adducts (**8a**−**e**) in high yield (88−99%) (Scheme 3 and Table 1).

Scheme 3. Synthesis of (3*S*)-3-Benzyl-1,4-benzoxazine **9a**[a]

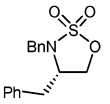
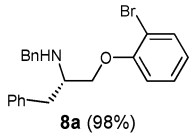
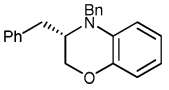
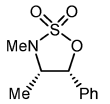
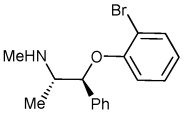
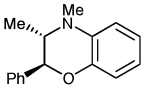
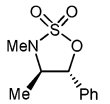
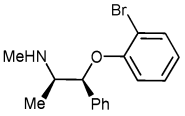
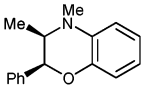
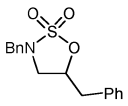
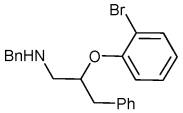
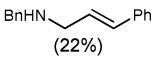
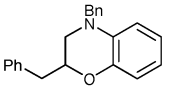
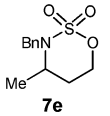
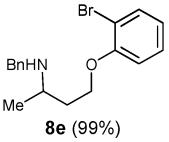
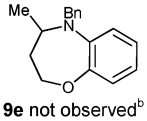


[a] For other examples based on these procedures, see Table 1.

The only exception was cyclic sulfamidate **7d**, a substrate which is sensitive to β-elimination,[2d] which afforded 22% of *N*-benzyl cinnamylamine in addition to the desired adduct **8d** (in 57% yield). The efficient S_N2 nature of the initial nucleophilic displacement step is clearly demonstrated by comparing entries 2 and 3 (leading to **8b** and **8c**) in which none of the alternative diastereomer was detectable.

Pd(0)-catalyzed cyclization of phenylalanine-derived adduct **8a** was investigated using a range of ligands under

Table 1. Synthesis of 2- and 3-Substituted and 2,3-Disubstituted 1,4-Benzoxazines

	sulfamidate	addition product (yield)[a]	heterocycle (yield)[a]
1	 **7a**	 **8a** (98%)	 **9a** (88%)
2	 **7b**	 **8b** (97%)	 **9b** (65%)
3	 **7c**	 **8c** (88%)	 **9c** (79%)
4	 **7d**	 **8d** (57%)[b]  (22%)	 **9d** (76%)
5	 **7e**	 **8e** (99%)	 **9e** not observed[b]

[a] Isolated yield. [b]C−Br reduction and polymerization occurred.

(2) (a) Williams, A. J.; Chakthong, S.; Gray, D.; Lawrence, R. M.; Gallagher, T. *Org. Lett.* **2003**, *5*, 811−814. (b) Bower, J. F.; Švenda, J.; Williams, A. J.; Charmant, J. P. H.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Lett.* **2004**, *6*, 4727−4730. (c) Bower, J. F.; Szeto, P.; Gallagher, T. *Chem. Commun.* **2005**, 5793−5795. (d) Bower, J. F.; Chakthong, S.; Švenda, J.; Williams, A. J.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Biomol. Chem.* **2006**, *4*, 1868−1877. (e) Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Biomol. Chem.* **2007**, *5*, 143−150. (f) Bower, J. F.; Riis-Johannessen, T.; Szeto, P.; Whitehead, A. J.; Gallagher, T. *Chem. Commun.* **2007**, 728−730.

(3) For a recent review covering the synthesis and biological importance of 1,4-benzoxazines, see: Ilaš, J.; Anderluh, P. Š.; Dolenc, M. S.; Kikelj, D. *Tetrahedron* **2005**, *61*, 7325−7348.

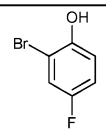
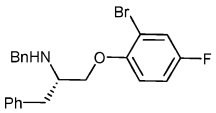
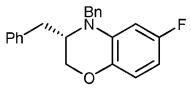
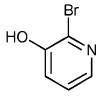
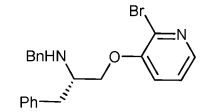
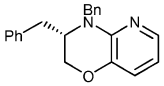
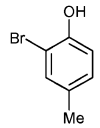
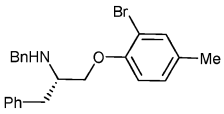
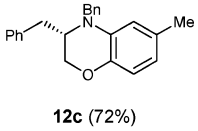
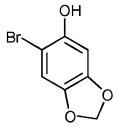
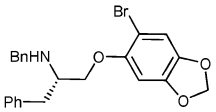
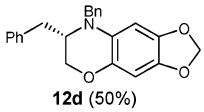
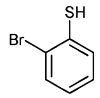
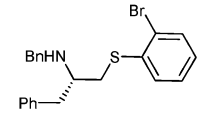
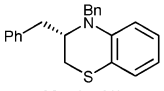
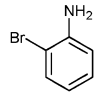
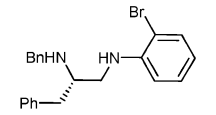
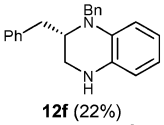
(4) For recent approaches to 1,4-benzoxazines and related heterocyclic scaffolds, see: (a) Wolfer, J.; Bekele, T.; Abraham, C. J.; Dogo-Isonagie, C.; Lectka, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 7398−7400. (b) Xu, D.; Chiaroni, A.; Fleury, M.-B.; Largeron, M. *J. Org. Chem.* **2006**, *71*, 6374−6381. (c) Feng, G.; Wu, J.; Dai, W.-M. *Tetrahedron* **2006**, *62*, 4635−4642. (d) Shinkevich, E. Y.; Novikov, M. S.; Khlebnikov, A. F. *Synthesis* **2007**, 225−230.

(5) Openings of 1,2-cyclic sulfamidates with 2-methoxyphenolate have previously been reported in 47−82% isolated yield: Okuda, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 4585−4586.

(6) For a review on Pd-catalyzed amination, see: (a) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. For a previous approach to benzoxazines using Ni(0)-mediated intramolecular amination of aryl chlorides, see: (b) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett.* **2003**, *5*, 2311−2314. For an example using Pd(0)-mediated intramolecular amination of an aryl chloride, see: (c) Omar-Amrani, R.; Schneider, R.; Fort, Y. *Synthesis* **2004**, 2527−2534.

(7) For a previous synthesis of a quinoxalinone via intramolecular Pd(0)-mediated amination of an aryl iodide, see: Kitagawa, O.; Takahashi, M.; Yoshikawa, M.; Taguchi, T. *J. Am. Chem. Soc.* **2005**, *127*, 3676−3677.

Table 2. Synthetic Scope: O-, N-, and S-Based Nucleophiles

	nucleophile	addition product (yield)[a]	heterocycle (yield)[a]
1	 **10a**	 **11a** (98%)	 **12a** (86%)
2	 **10b**	 **11b** (98%)	 **12b** (79%)
3	 **10c**	 **11c** (99%)	 **12c** (72%)
4	 **10d**	 **11d** (83%)	 **12d** (50%) (+ 9% of **11d**)
5	 **10e**	 **11e** (100%)	 **12e** (89%)
6	 **10f**	 **11f** (56%)	 **12f** (22%) (+ 25% of **11f**)

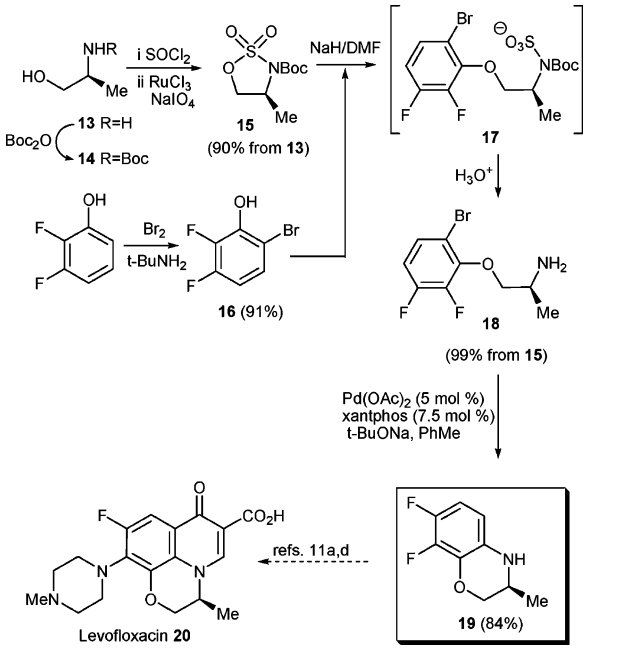
[a] Isolated yield.

standard conditions (*t*-BuONa, PhMe, 5 mol % of $Pd(OAc)_2$, 100 °C), and of those screened, xantphos (7.5 mol %) was most efficient affording benzoxazine **9a** in 88% yield.[8] These conditions have successfully been applied to adducts **8b**−**d** to deliver the target heterocycles **9b**−**d** in good to excellent yield. A representative example based on the conversion of **7a** to **9a** is shown in Scheme 3, and other substrates are summarized in Table 1 (full details are given in the Supporting Information). Unfortunately, the annulation adduct **8e** derived from 1,3-cyclic sulfamidate **7e** did not cyclize (to form **9e**), and only reduction and polymerization were observed.[9]

Using the phenylalanine-derived cyclic sulfamidate **7a**, a more comprehensive assessment of the scope of the nucleophilic component and the subsequent Pd-catalyzed cyclization involved in this process has been conducted (Table 2). Phenolates are generally well tolerated, and a range of both electron-poor (including **10a** and 3-hydroxypyridine **10b**) and electron-rich (**10c** and **10d**[10]) nucleophiles are highly efficient in this process. The subsequent Pd-catalyzed arylation step occurs in moderate to excellent yield leading to **12a**−**d**; the most difficult substrates were those which possess electron-donating substituents on the aromatic (e.g., **11d** → **12d**), and in such cases, cyclization was both slower and less efficient.

Extension of this two-step protocol also allows access to thio and aza variants **12e** and **12f**. Cyclic sulfamidate **7a** reacted efficiently with 2-bromothiophenol **10e** to deliver **11e** in quantitative yield. Cyclization of this species was facile and afforded benzothiazine **12e** in 89% yield. Opening of **7a** with the anion of aniline **10f** was less efficient, possibly due to competing elimination, and adduct **11f** was isolated in 56% yield. Cyclization of **11f** was also slow, and quinoxaline **12f** was isolated in only 22% yield (30% based on recovered **11f**). Obviously this process requires further optimization, but the results shown in Table 2 clearly demonstrate the breadth and potential applicability of this chemistry.

Scheme 4. Synthesis of Benzoxazine **19** and Formal Synthesis of Levofloxacin



The blockbuster antibiotic levofloxacin **20** (2006 sales of US $1.41 billion) provides an appropriate focus for this methodology. The major challenge associated with developing an asymmetric entry to **20** resides in identifying efficient routes to the key chiral benzoxazine core **19**, and in this regard, several approaches have been reported.[11] We have achieved this goal through the union of alanine-derived cyclic sulfamidate **15** and 6-bromo-2,3-difluorophenol **16** (Scheme 4).

(8) Other ligands screened included BINAP which gave **9a** in 76% yield and Verkade's TTPU ligand (Urgaonkar, S.; Xu, J. H.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8416−8423) which gave **9a** in 86% yield.

(9) An example of a successful Pd-catalyzed cyclization to form a related seven-ring system has been reported.[6c]

(10) For the preparation of **10d**, see: Novak, Z.; Timar, G.; Kotschy, A. *Tetrahedron* **2003**, *59*, 7509−7513.

Commercially available alaninol **13** was *N*-Boc protected under standard conditions to give **14**, which was then converted to cyclic sulfamidate **15** in 90% yield over three steps.[12] Reaction of **15** (in DMF) with the sodium anion of phenol **16** (1.2 equiv) (prepared by bromination of commercially available 2,3-difluorophenol in 91% yield[13]) led to smooth nucleophilic cleavage to afford the intermediate *N*-sulfate **17**. In this case, direct and concomitant removal of *both* the *N*-sulfate and *N*-Boc moieties was achieved by employing 10% H_2SO_4 in *p*-dioxane for the hydrolysis step which afforded cyclization precursor **18** in 99% overall yield from **15**. Cyclization of **15** (5 mol % of $Pd(OAc)_2$, 7.5 mol % of xantphos, *t*-BuONa, PhMe, 100 °C) then cleanly afforded the key benzoxazine intermediate **19** in 84% yield {$[\alpha]_D^{20}$ −9.1 (*c* 1.3, $CHCl_3$); lit. $[\alpha]_D^{23}$ −7.8 (*c* 0.7, $CHCl_3$)[11b]}. This sequence is highly efficient affording benzoxazine **19** in 74% overall yield over six steps. Conversion of this intermediate in three steps to levofloxacin **20** has previously been reported.[11a,d]

In summary, we have demonstrated an efficient and modular two-step protocol for the coupling of 1,2-cyclic sulfamidates with readily available 2-bromophenols as a means of accessing substituted and enantioenriched 1,4-benzoxazines and have shown that analogous chemistry is equally applicable to the synthesis of quinoxaline and 1,4-benzothiazine scaffolds. This methodology provides a direct and high-yielding entry to the drug levofloxacin, and its fundamental simplicity—the use of readily available nucleophilic and electrophilic components—makes it well suited to further applications within both academic and industrial settings.

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Supporting Information Available: Full experimental details, compound characterization data, and copies of ^1H and ^{13}C NMR are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For selected previous synthetic studies on **20**, see: (a) Hayakawa, I.; Atarashi, S.; Imamura, M.; Yokohama, S.; Higashihashi, N.; Sakano K.; Ohshima, M. US patent, 1986, *5*,053,407. (b) Atarashi, S.; Yokohama, S.; Yamazaki, K.; Sakano, K.; Imamura, M.; Hayakawa, I. *Chem. Pharm. Bull.* **1987**, *35*, 1896−1902. (c) Sakano, K.; Yokohoma, S.; Hayakawa, I.; Atarashi, S.; Kadoya, S. *Agric. Biol. Chem.* **1987**, *51*, 1265−1270. (d) Mitscher, L. A.; Sharma, P. N.; Chu, D. T. W.; Shen, L. L.; Pernet, A. G. *J. Med. Chem.* **1987**, *30*, 2283−2286. (e) Atarashi, S.; Tsurumi, H.; Fujiwara, T.; Hayakawa, I. *J. Heterocycl. Chem.* **1991**, *28*, 329−331. (f) Kang, S. B.; Ahn, E. J.; Kim, Y.; Kim, Y. H. *Tetrahedron Lett.* **1996**, *37*, 9317−9320. (g) Satoh, K.; Inenaga, M.; Kanai, K. *Tetrahedron: Asymmetry* **1998**, *9*, 2657−2662. (h) Adrio, J.; Carretero, J. C.; Ruano, J. L. G.; Pallarés, A.; Vicioso, M. *Heterocycles* **1999**, *51*, 1563−1572.

(12) Tewson has previously reported the synthesis of cyclic sulfamidate **15** in 78% yield from **14**: Posakony, J. J.; Grierson, J. R.; Tewson, T. J. *J. Org. Chem.* **2002**, *67*, 5164−5169.

(13) Pearson, D. E.; Wysong, R. D.; Breder, C. V. *J. Org. Chem.* **1967**, *32*, 2358−2360.