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Synthesis and reactivity of cyclic sulfamidites and sulfamidates

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Contents

1. Introduction

Cyclic sulfamidites and cyclic sulfamidates have served important roles for the synthesis of various products possessing heteroatomic functional groups (Fig. 1). For

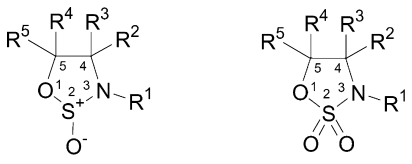

Figure 1. General structure and numbering of five-membered cyclic sulfamidites and sulfamidates.

Keywords: cyclic sulfamidites; cyclic sulfamidates; oxidation; sulfinamides; sulfoxides; antimicrobial agents; amino acids; carbohydrates; glycopeptides; biogenic amines; morpholines.

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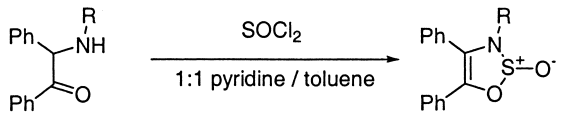
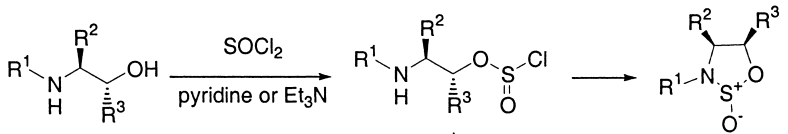


1: R = phenyl
2: R = *m*-tolyl
3: R = *p*-tolyl

4: R = phenyl
5: R = *m*-tolyl
6: R = *p*-tolyl

Figure 2. Five-membered cyclic sulfamidites from α-amino ketones.[16]

as reactive intermediates for organic synthesis is likely to increase sharply, because of the emergence of several new effective methods for their synthesis.[2,12–14] The subject of sulfamidites and sulfamidates has been previously reviewed; moreover, their cyclic analogs have been covered within the context of a review on cyclic sulfate derivatives.[15] Recent developments in their chemistry have prompted a need for a more comprehensive review on the specific subject of cyclic sulfamidites and sulfamidates. In this context, we have focused primarily on the synthesis



7: R^1 = ^{t}Bu, R^2 = H, R^3 = H
8: R^1 = ^{t}Bu, R^2 = H, R^3 = CH_3
9: R^1 = ^{t}Bu, R^2 = CH_3, R^3 = H
10: R^1 = ^{t}Bu, R^2 = H, R^3 = Ph
11: R^1 = ^{t}Bu, R^2 = Ph, R^3 = H
12: R^1 = ^{t}Bu, R^2 = H, R^3 = Ph
13: R^1 = Ph, R^2 = Ph, R^3 = CO_2Et

14: R^1 = ^{t}Bu, R^2 = H, R^3 = H
15: R^1 = ^{t}Bu, R^2 = H, R^3 = CH_3[a]
16: R^1 = ^{t}Bu, R^2 = CH_3, R^3 = H[a]
17: R^1 = ^{t}Bu, R^2 = H, R^3 = Ph[a]
18: R^1 = ^{t}Bu, R^2 = Ph, R^3 = H[a]
19: R^1 = ^{t}Bu, R^2 = H, R^3 = Ph
20: R^1 = Ph, R^2 = Ph, R^3 = CO_2Et

Figure 3. Five-membered cyclic sulfamidites **14–20** from β-amino alcohols **7–13**.[17] [a]Both *cis* and *trans* isomers were formed.

example, cyclic sulfamidites have been used as starting materials for the construction of enantiomerically enriched sulfinamides and sulfoxides,[1,2] as well as antimicrobial agents used in deodorants and shampoos.[3] Cyclic sulfamidites have been points of departure for the construction of enantiopure amino acids,[4,5] carbohydrates[6,7] and glycopeptides[8] as well as isotopically enriched ^{18}F analogs of biogenic amines[9] and the non-competitive *N*-methyl-D-aspartate antagonist MK-801.[10] They have also served as effective reagents for converting epoxides into morpholines.[3,11] Furthermore, the application of these heterocycles methods for their construction, their reactivity, and stereochemical issues concerning their employment.

2. Five-membered cyclic sulfamidites

2.1. Synthesis of five-membered cyclic sulfamidites

A little more than 90 years ago, the treatment of α-keto-β-arylamino-α,β-diphenylethanes **1–3** with thionyl chloride in 1:1 pyridine/toluene produced the corresponding cyclic

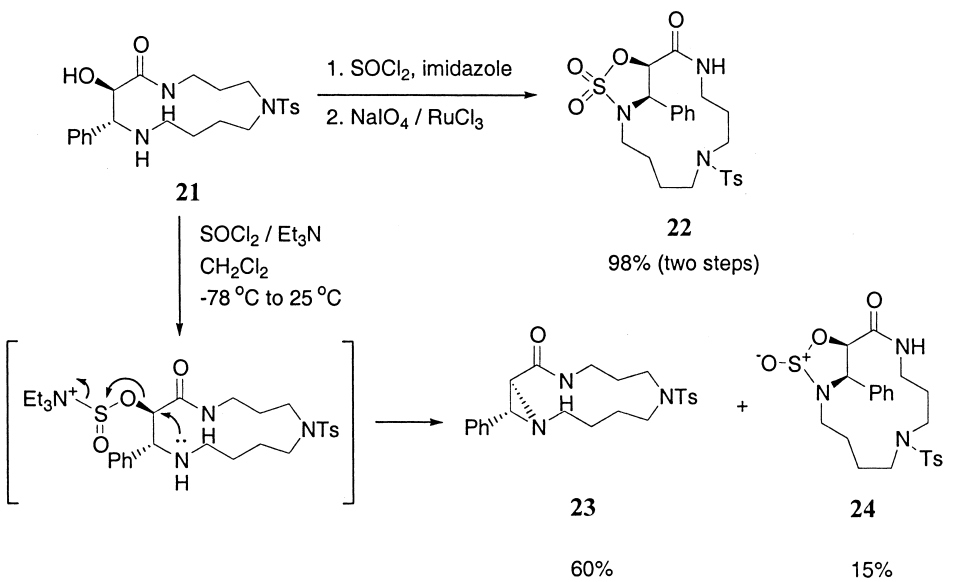


Figure 4. Cyclic sulfamidite **24** from macrocylic β-amino alcohol **21**.[18]

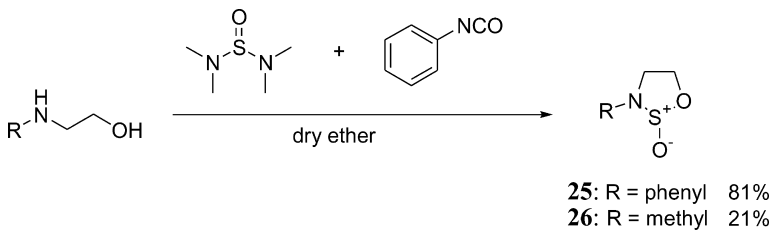


Figure 5. Examples of cyclic sulfamidites from *N*-(alkyl)ethanolamine.[19]

sulfamidites **4**–**6** as yellow solids that were soluble in alcohols and organic solvents and turned a dark emerald-green color when treated with a drop of concentrated sulfuric acid. These compounds were termed 'oxasulphinazoles' and, other than their hydrolysis to the starting amino ketones by boiling with concentrated aqueous KOH, their chemistry remained unexplored for nearly sixty years (Fig. 2).[16] Pursuing a direct synthesis of aziridines, a series of *N*-*tert*-butyl- and *N*-phenyl-β-amino alcohols **7**–**13** were later treated with thionyl chloride and a tertiary amine (triethylamine or pyridine) in a non-polar solvent (hexane or benzene).[17] Anticipating that the amine might displace a chlorosulfite intermediate to form the aziridine, the authors were surprised to isolate products that retained the elements of SO_2 and demonstrated that these conditions produced the corresponding 2-oxo-1,2,3-oxathiazolidines **14**–**20** (Fig. 3).

Many five-membered cyclic sulfamidites have since been prepared from their β-amino alcohol counterparts using similar conditions[2,5,18] which may be improved by the employment of more polar solvents such as acetonitrile and dichloromethane, nucleophilic heterocycles such as imidazole and pyridine, and lower temperatures.[5] For example, employment of imidazole at 0°C yielded quantitatively bicyclic sulfamidite **24** from macrocyclic amino alcohol **21**, which had previously reacted with thionyl chloride and triethylamine in dichloromethane at −78°C, to give only 15% yield of **24**, with competing formation of aziridine **23** in 60% yield (Fig. 4).[18]

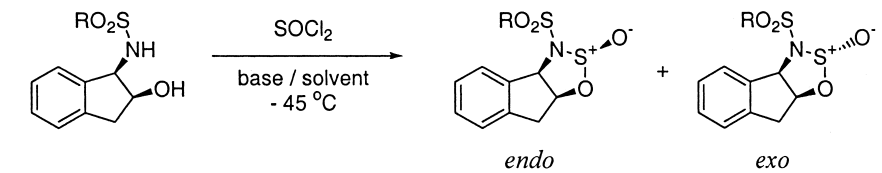
In an alternative approach, 3-phenyl and 3-methyl 1,2,3-oxathiazolidine-2-oxides **25** and **26** were prepared respectively in 81 and 21% yield by treatment of the corresponding *N*-(alkyl)ethanolamine with the adduct formed from *N*,*N*,*N*′,*N*′-tetramethylsulfurous diamine and phenyl isocyanate in ether followed by heating the resulting oily substance at 120–130°C for 10 min (Fig. 5).[19]

The stereochemical outcome at the newly formed chiral sulfur has been controlled in the case of indane *N*-(4-toluenesulfonyl)sulfamidite **29** by varying the combination of base and solvent, such that the *endo*/*exo* ratio was varied from 1:4 to 9:1 on passing from triethylamine in DCM to 2,4,6-collidine in THF.[2] This ratio could be optimized further using the more sterically demanding *N*-(2,4,6-mesitylene)sulfonamide **28** and 3,5-lutidine in THF which provided a 97:3 *endo*/*exo* mixture of diastereomers, such that kilogram quantities of (2*S*,4*R*,5*S*)-*N*-(mesitylenesulfonyl)sulfamidite *endo*-**30** could be synthesized in enantiopure form (Table 1).

2.2. Configurational assignment of five-membered cyclic sulfamidites

The sulfoxide bond exhibits acetylenic-like anisotropy in

Table 1. Diastereoselective formation of sulfamidites **29** and **30**[2]



27: R = 4-tolyl
28: R = 2,4,6-mesityl

29: R = 4-tolyl
30: R = 2,4,6-mesityl

Product	R	Base/solvent	*endo*/*exo*
29	4-Tolyl	TEA/DCM	1:4
29	4-Tolyl	2,4,6-Collidine/THF	9:1
30	2,4,6-Mesityl	3,5-Lutidine/THF	97:3

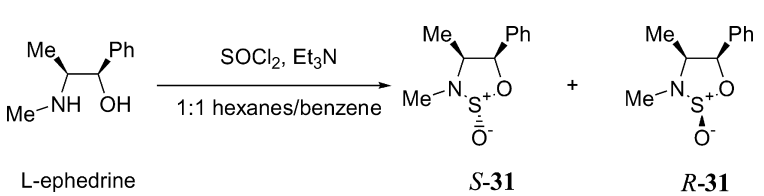


Figure 6. Cyclic sulfamidites from L-ephedrine.[1]

Table 2. ^{1}H NMR signal assignments of sulfamidites 2*R*- and 2*S*-**32**, and sulfamidate **33**

Position	2*R*-**32**, δ_H [int. mult, *J* (Hz)]	2*S*-**32**, δ_H [int. mult, *J* (Hz)]	**33**, δ_H [int. mult, *J* (Hz)]
4	3.51 (1H, dd, 1.4, 7.1)	3.37 (1H, t, 7.9)	3.64 (1H, dd, 4.0, 8.1)
5β	4.41 (1H, dd, 1.4, 9.4)	4.32 (1H, t, 7.9)	4.38 (1H, dd, 1.4, 8.7)
5α	4.75 (1H, dd, 7.1, 9.4)	4.95 (1H, t, 7.9)	4.02 (1H, dd, 8.1, 8.7)
MeO	3.42 (3H, s)	3.57 (3H, s)	3.69 (3H, s)
PhF	7.17–8.17 (13H, m)	7.19–7.77 (13H, m)	7.19–8.22 (13H, m)

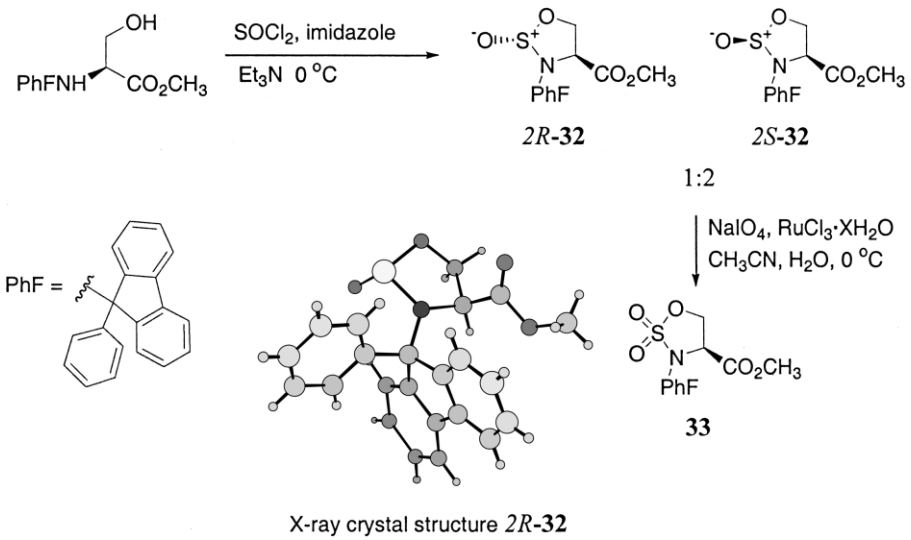


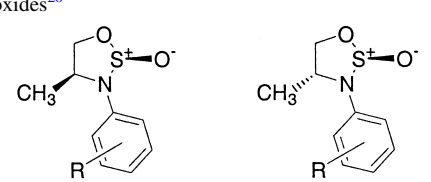
Figure 7. Synthesis and X-ray crystal structure of five-membered cyclic sulfamidites **32**.[5]

the NMR spectra of sulfamidites such that in the five-membered case, ring-substituents which are *cis* to the sulfoxide are deshielded.[17] For example, the major diastereomer *S*-**31**, from treatment of L-ephedrine with thionyl chloride and triethylamine in 1:1 hexanes/benzene at 0°C, exhibited a NMR spectrum in which the signals for the β-methyl-, α-aryl and *N*-methyl-group protons all were more shielded than those exhibited by *R*-**31** (Fig. 6).[1]

In the case of *N*-(PhF)serine sulfamidite **32** [PhF=9-(9-phenylfluorenyl)], diastereoisomers 2*R*-**32** and 2*S*-**32** could be separated by chromatography.[5] The absolute assignment of the configuration at sulfur for the diastereoisomers was made by comparisons of their ^{1}H NMR spectra with that of their oxidation product, sulfamidate **33** (Table 2). The 2*R*-sulfamidite 2*R*-**32** exhibited similar steric as well as anisotropic effects as sulfamidate **33**. For example, in the spectra of 2*R*-**32** and **33**, the C-4 proton appeared as a doublet of doublets as the result of steric interactions between the exocyclic oxygen atom on sulfur and the PhF group which twisted the five-membered ring such that significantly different dihedral angles existed between the C-4 and C-5 protons. By contrast, the C-4 proton in 2*S*-**32** appeared as a triplet, indicative of a conformation with similar dihedral angles between the C-4 proton and each of the C-5 protons. The magnetic anisotropy of the S–O bond shifted downfield the resonances of proximal PhF protons as well as the C-4 proton in the spectra of 2*R*-**32** and **33** relative to the respective signals in the spectrum of 2*S*-**32**. These assignments were confirmed by X-ray crystallographic analysis of 2*R*-**32** (Fig. 7). Single-crystal X-ray analysis showed that the dihedral angle between the C-4 proton and the C-5α proton was 25.4°, and the dihedral angle between the C-4 proton and the C-5β proton was 82.6°. The crystal structure of 2*R*-**32** exhibited a conformation in which the α-proton and the α-acid carbonyl are nearly coplanar (159.5°).

Carbon-13 NMR spectroscopy was used to study 4- and 5-substituted 3-aryl-1,2,3-oxathiazolidine-2-oxides **34**–**52**. The ^{13}C chemical shifts were suggested to depend on ring conformation.[20,21] In the 4-substituted series, the chemical shifts (δ) for the signals of the C-4 carbon were observed upfield for the *trans* diastereomer relative to signals for the *cis* diastereomer. The chemical shifts (δ) for the C-5 carbon

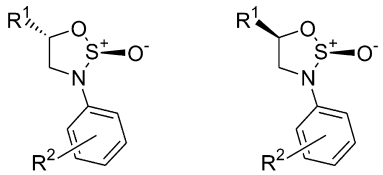
Table 3. Carbon-13 chemical shifts (δ) of 3-aryl-4-methyl-1,2,3-oxathiazolidine-2-oxides[20]



cis *trans*

Compound	R	Chemical shifts (δ)			
		C-4 *cis*	C-4 *trans*	C-5 *cis*	C-5 *trans*
34	H	55.5	52.6	75.8	76.9
35	*p*-Cl	55.6	52.8	75.9	77.0
36	*p*-CH_3	56.2	52.8	75.7	77.2
37	*o*-Cl	58.6	54.3	75.6	77.1
38	*o*-CH_3	61.3	52.8	75.5	77.0

Table 4. Carbon-13 chemical shifts (δ) of 3-aryl-5-alkyl-1,2,3-oxathiazolidine-2-oxides[21]

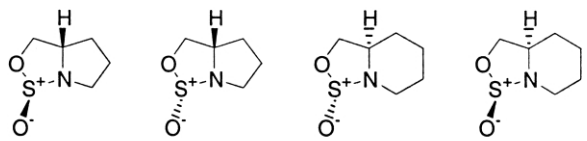


cis *trans*

Compound	R^1	R^2	Chemical shifts (δ)			
			C-4 *cis*	C-4 *trans*	C-5 *cis*	C-5 *trans*
39	CH_3	H	50.6	52.7	83.7	79.3
40	CH_3	*o*-CH_3	53.3	54.9	82.8	79.8
41	CH_3	*m*-CH_3	50.6	52.7	83.6	79.1
42	CH_3	*p*-CH_3	51.0	52.9	83.6	79.3
43	CH_3	*o*-Cl	52.6	54.2	82.8	80.0
44	CH_3	*m*-Cl	50.6	52.8	84.1	79.5
45	CH_3	*p*-Cl	50.8	53.0	83.9	79.6
46	C_2H_5	H	48.8	50.9	88.9	84.3
47	C_2H_5	*o*-CH_3	51.6	53.2	87.9	84.8
48	C_2H_5	*m*-CH_3	48.8	50.9	88.7	84.1
49	C_2H_5	*p*-CH_3	49.2	51.2	88.7	84.2
50	C_2H_5	*o*-Cl	50.8	52.4	87.8	84.8
51	C_2H_5	*m*-Cl	48.8	51.0	89.2	84.5
52	C_2H_5	*p*-Cl	49.0	51.1	89.1	84.5

were observed upfield for the *cis* diastereomer relative to those for the *trans* diastereomer (Table 3).[20] The opposite effect was observed for the 5-substituted series in which C-4 was observed upfield for the *cis* diastereomer and C-5 was observed upfield for the *trans* diastereomer (Table 4).[21]

Assignment of the relative configurations of 5,5- and 5,6-fused ring systems **53** and **54** was in part accomplished by examination of the molar isotropic shifts of ring proton NMR signals upon the addition of Eu(fod)$_3$ which ligates the exocyclic oxygen of the sulfamidite. In both cases, the major diastereomer formed from the reaction of *S*-prolinol and 2*RS*-piperidine-methanol with thionyl chloride in the presence of pyridine, featured the S^+-O^- and ring-fusion C–H bonds in a *trans* relationship (Fig. 8).[22]

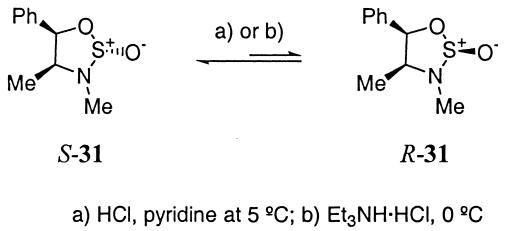


cis-**53** *trans*-**53** *cis*-**54** *trans*-**54**

Figure 8. Conformational analysis using the chiral shift reagent Eu(fod)$_3$ has been performed on fused ring systems **53** and **54**.[22]

2.3. Epimerization of five-membered cyclic sulfamidites

Similar to their sulfoxide,[24] alkyl sulfite[25] and sulfinamide counterparts,[26] cyclic sulfamidites are potentially configurationally labile to epimerization. For example, in a study with sulfamidite *S*-**31** derived from L-ephedrine, after crystallization of the major *S*-diastereomer from ether, the mother liquor was treated with 'a drop of pyridine and a trace of hydrogen chloride gas' to afford a second crop of *S*-**31**.[1] Similarly, triethylammonium chloride, formed during the preparation of **31** from L-ephedrine with thionyl



S-**31** *R*-**31**

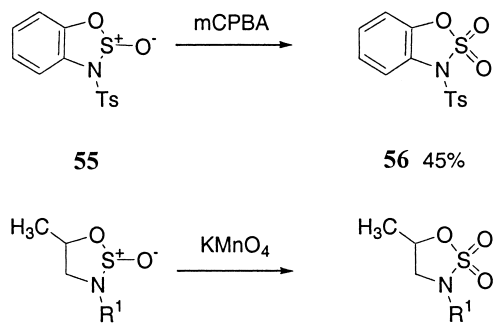
a) HCl, pyridine at 5 ºC; b) $Et_3NH{\cdot}HCl$, 0 ºC

Figure 9. Epimerization of cyclic sulfamidite **31**.[1,23]

chloride and triethylamine in dichloromethane, was used to epimerize the chiral center at sulfur such that 70% yield of pure *S*-**31** could be isolated by crystallization of the epimerizing mixture (Fig. 9).[23]

2.4. Oxidation of cyclic sulfamidites to cyclic sulfamidates

A few oxidants have been used to convert cyclic sulfamidites to cyclic sulfamidates. For example, *m*-chloroperoxybenzoic acid in $CHCl_3$ at ≤10°C oxidized 3-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole 2-oxide **55** to its dioxide **56** in 45% yield.[27] Conversion of 3-aryl-5-methyl-1,2,3-oxathiazolidine-2-oxides **57** and **58** to their sulfamidates was achieved in AcOH by treating with an aq. solution of $KMnO_4$ at 20°C in 43 and 38%, yields respectively (Fig. 10).[28]



55 **56** 45%

57: R^1 = 2,6-dimethylphenyl **59**: R^1 = 2,6-dimethylphenyl 43%

58: R^1 = 2,6-dichlorophenyl **60**: R^1 = 2,6-dichlorophenyl 38%

Figure 10. Representative examples of oxidations of cyclic sulfamidites to cyclic sulfamidates.[27,28]

These lower yielding oxidants were soon abandoned in favor of the ruthenium tetraoxide/sodium periodate system in acetonitrile/water that had proven effective for converting cyclic sulfites to their corresponding cyclic sulfates.[37] For example, catalytic $RuCl_3{\cdot}H_2O$ with $NaIO_4$ in acetonitrile/water has provided cyclic sulfamidates **33** and **61**–**71** from their corresponding sulfamidites in usually >85% yields (Fig. 11).[4,5,8,29–35] The application of catalytic $RuO_2{\cdot}xH_2O$ with $NaIO_4$ in solvent mixtures such as $CHCl_3/H_2O$, $CH_2Cl_2/CH_3CN/H_2O$ and in EtOAc/H_2O delivered cyclic sulfamidates in notably lower yields (45–78%).[22,38,39] On the other hand, oxidation of sulfamidite **72** from *N*-(trityl)-serine benzyl ester using the catalytic $RuCl_3$ conditions did not provide the corresponding sulfamidate **73**; instead, spontaneous loss of SO_2 was reported to occur with formation of *N*-(trityl)aziridine-2-carboxylates **74** (Fig. 12).[36] Moreover, no oxidation of the sterically hindered 2*S*-isomer of *N*-(PhF)homoserine-derived

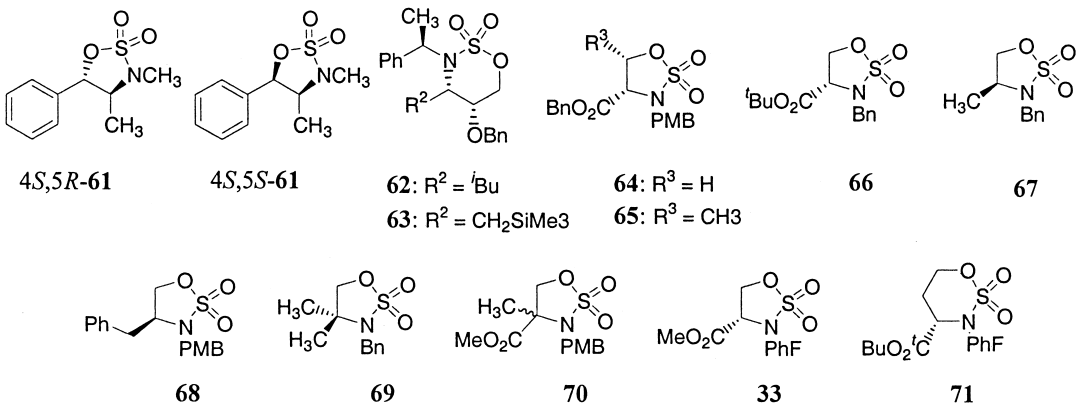


Figure 11. Sulfamidates formed from the corresponding sulfamidites by $RuCl_3{\cdot}H_2O$ oxidation.[4,5,8,29–35]

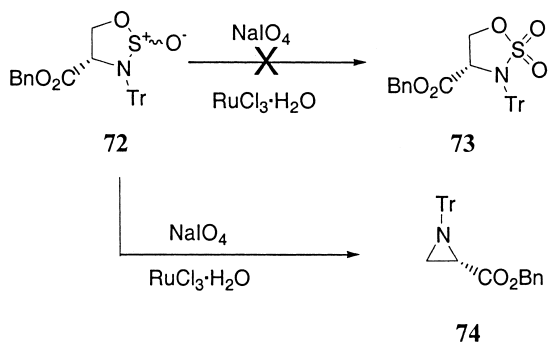


Figure 12. Aziridine **74** formed upon reaction of **72** with $RuCl_3{\cdot}H_2O$ with $NaIO_4$.[36]

six-membered cyclic sulfamidate 2*S*-**102** (Fig. 56) was detected when using the catalytic $RuCl_3$ conditions.[35] These last few examples demonstrate the continuing need for milder and more effective oxidation conditions for converting sulfamidites to sulfamidates.

2.5. Ring-opening of five-membered cyclic sulfamidites with various nucleophiles

The rate of hydrolysis of 3-*tert*-butyl 1,2,3-oxathiazolidine 2-oxide **75** was much higher than that of ethylene sulfite **76** in acid solution at room temperature (Fig. 13).[40] The kinetic behavior of **77** suggested a mechanism in which nitrogen protonation preceded attack of water at sulfur. Furthermore, the tetrabutylammonium salts of bicyclic sulfamidite acids **77**–**79** derived from penicilamine were rapidly hydrolyzed in neutral D_2O (Fig. 13).[41]

In an examination of the reactivity of five-membered cyclic sulfamidites as electrophiles, *S*-(−)-glycidol (80% ee) was converted to enantiomerically enriched sulfamidite **80** which was exposed respectively to NaCN, NaN_3 and BnONa in DMF at 120°C for 6–10 h.[42] In the case of the carbon and nitrogen nucleophiles, ring opening was shown to occur selectively at carbon by GC analysis and the corresponding nitrile **81** and azide **82** were isolated in 80 and 90% yield, respectively (Fig. 14). In the case of the oxygen nucleophile, a mixture of products was obtained in only 24% yield; GC analysis showed benzyl ether **83** was formed as the minor product in a 1:2 ratio with alcohol **84**, presumed to result from attack of alkoxide on sulfur and hydrolysis of the linear sulfamidite intermediate.

Measurement of the enantiomeric purity of azide **82** and nitrile **81** by GC analysis of their respective diastereomeric α-methoxyphenylacetamides indicated that no racemization occurred in the case of the reaction with azide ion; however, cyanide ion (NaCN and LiCN) caused complete racemization presumably via a 1,3-shift mechanism at the product stage (Fig. 15).[42]

In addition, 3-phenyl 1,2,3-oxathiazolidine-2-oxide **25**

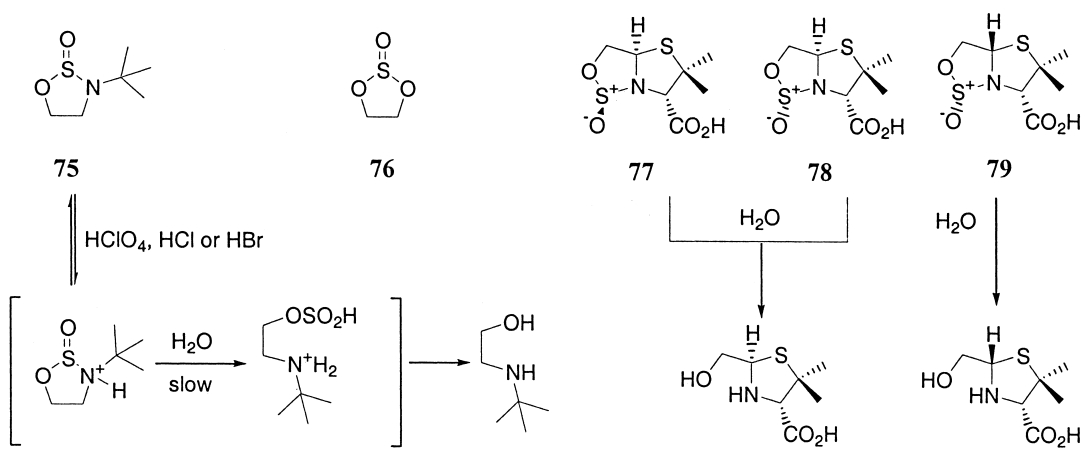


Figure 13. Hydrolysis of cyclic sulfamidites **75**, **77**–**79**.[40,41]

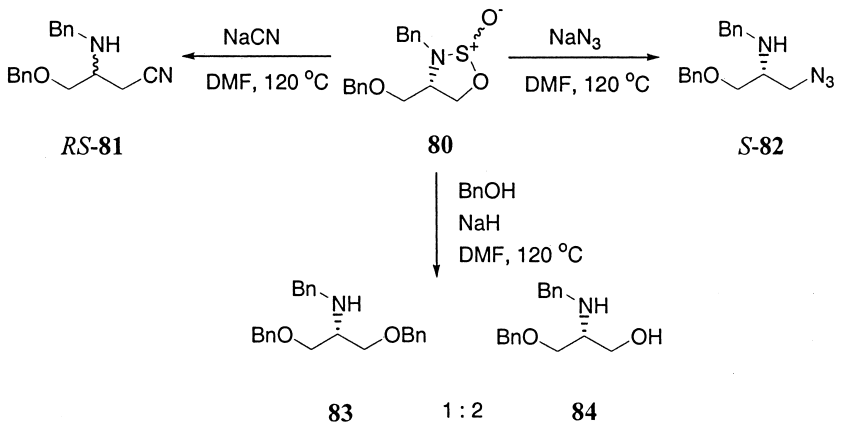


Figure 14. Examples of nucleophilic attack on cyclic sulfamidite **80**.[42]

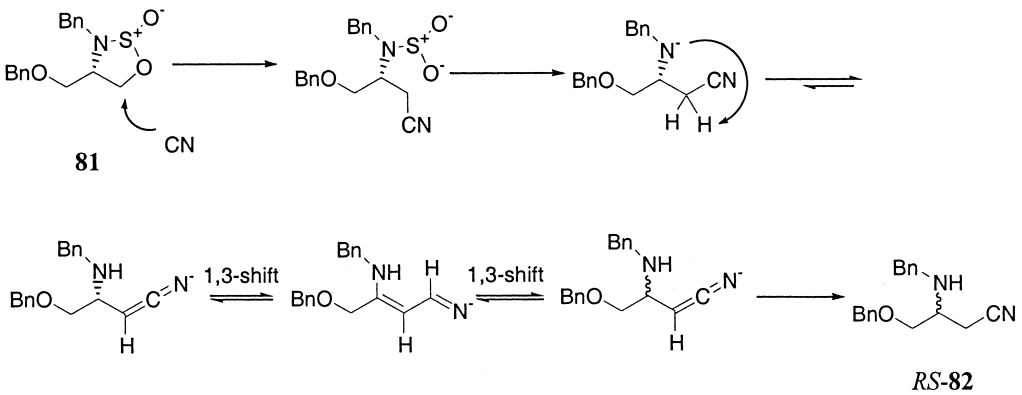


Figure 15. Proposed mechanism for racemization during formation of *RS*-**82**.[42]

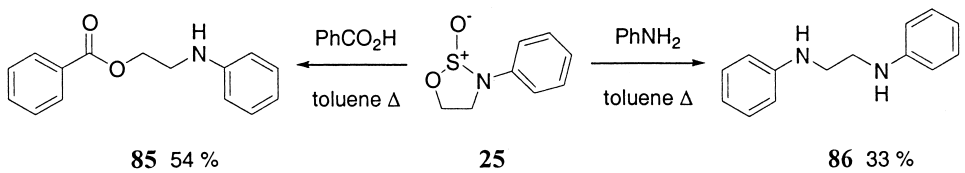


Figure 16. Reaction of sulfamidite **25** with benzoic acid and aniline.[19]

reacted separately with benzoic acid and aniline in xylene at reflux for 7 h to provide β-anilinoethyl benzoate **85** and *N*,*N*-diphenylethylenediamine **86** in 54 and 33% yields, respectively (Fig. 16).[19]

Diastereomerically enriched sulfonamides and enantiomerically enriched sulfoxides have been synthesized by employing L-ephedrine *S*-sulfamidite **31** as a chiral educt. For example, *p*-$CH_3C_6H_4MgBr$ and L-ephedrine *S*-sulfamidite **31** reacted with complete inversion of configuration at sulfur to give sulfinamide **87** in low yield and high diastereomeric purity accompanied by symmetric sulfoxide **88** as a significant byproduct.[1] When PhMgBr was employed, diphenyl sulfoxide **90** was the only isolated product.[23] Coordination of the sulfinamide oxygen and alkoxide anion by magnesium in a seven-membered intermediate (**91**) was suggested to favor addition of a second Grignard reagent to sulfur to produce symmetric sulfoxide which could be diminished by employing tetramethylethylenediamine (TMEDA), albeit with 12% epimerization of the sulfinamide product. Negligible amounts of symmetric sulfoxide and >85, 61 and 41%, respective yields of sulfinamide were obtained when PhLi, MeLi and MeMgBr were employed with TMEDA; however, up to 28% epimer was measured in the sulfinamide products **87**, **89** and **92**. Phenylsulfinamide **89** was isolated, respectively, in 39 and 21% yields with 51 and 82% diastereomeric excess by treatment of cyclic sulfamidite *S*-**31** and with $PhCeCl_2$ and Ph_2CuLi, respectively.[23] Addition of a second organolithium or Grignard reagent to sulfinamides **87**, **89** and **92** furnished a set of enantiomerically enriched sulfoxides with access to either configuration at sulfur by arranging the order of the organometallic additions (Fig. 17).[1,23]

By switching to the more electron deficient and conformationally rigid *N*-mesitylenesulfonyl 1,2,3-oxathiazolidine-2-oxide **30**, organometallic attack on sulfur was directed to proceed with stereoselective S–N bond cleavage to provide sulfinates **93**–**98**,[2] (Fig. 18) instead of the S–O cleavage observed in the synthesis of sulfinamides with ephedrine derived *N*-(methyl)sulfamidite **31**. For example, *tert*-butyl Grignard reagent reacted with **30** in THF at −78°C to provide diastereomerically pure *tert*-butyl sulfite **93** in >95% yield. Subsequent treatment of sulfite **93** with

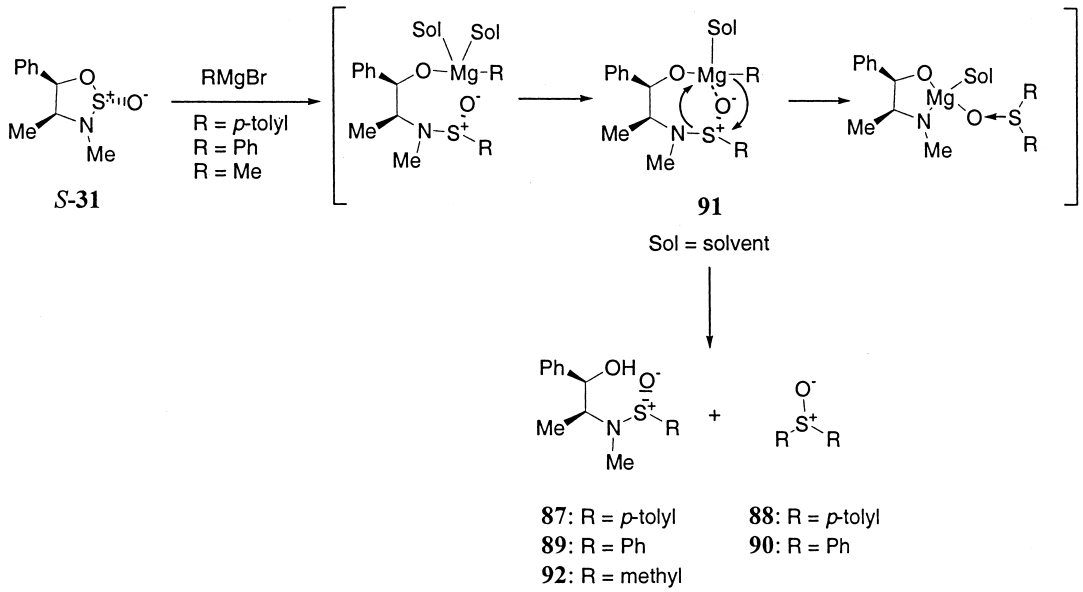


Figure 17. Opening of *S*-**31** with organometallic reagents.[1,23]

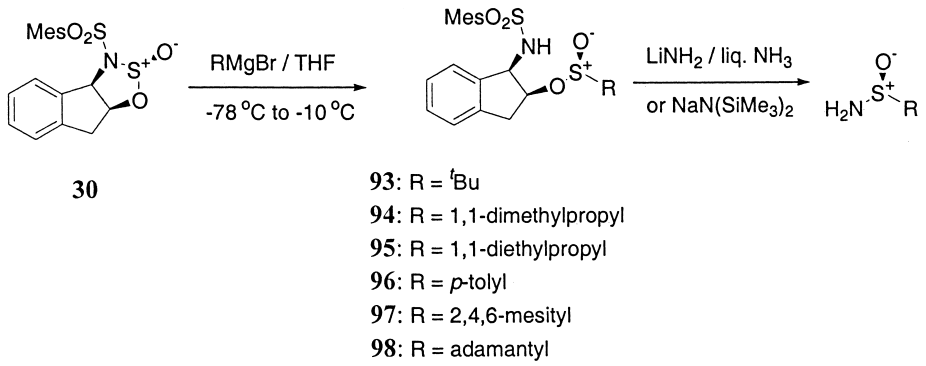


Figure 18. Reaction of **30** with Grignard reagents.[2]

lithium amide in liq. ammonia at −78°C gave enantiopure *tert*-butylsulfinamide in >90% yield with >96% recovery of the starting auxiliary. Application of a series of aryl and tertiary alkyl Grignard reagents in this process furnished enantiopure sulfinamides. In the amination step in the sequence with 4-tolylMgBr, switching from $LiNH_2$/liq. NH_3 to $NaN(SiMe_3)_2$ in THF at −78°C provided 4-tolylsulfinamide in 85% yield with improved enantiomeric purity from 90 to 99% ee.

3. Six-membered cyclic sulfamidites

3.1. Synthesis of six-membered cyclic sulfamidites

By extending the thionyl chloride/tertiary amine/non-polar solvent conditions for making 2-oxo-1,2,3-oxathiazolidines from β-amino alcohols to the case of γ-amino alcohols, the original procedure was shown to convert 3-*t*-butylaminopropanol to the corresponding 2-oxo-1,2,3-tetrahydrooxathiazine **99**.[17] When the base was omitted from this reaction, the γ-amino alcohol was converted to the γ-amino chloride hydrochloride.[43] When the more sterically demanding *N*-(PhF)homoserine *t*-butyl ester **100** was treated under similar conditions ($SOCl_2$, Et_3N, DCM at 0°C), the sulfamidite was not formed; instead, symmetrical sulfite **101** was identified as the major isolated product by high resolution mass spectrometry. Formation of sulfite **101** was avoided and six-membered sulfamidite **102** was isolated in 93% yield as a 4:1 mixture of diastereomers by the addition of excess imidazole to the reaction mixture at higher dilution.[35] In addition, treatment of γ-*N*-(α-methylbenzyl)amino alcohols **103** and **104** with $SOCl_2$ and Et_3N in DCM from −15 to 25°C produced the desired sulfamidites which were oxidized using $RuCl_3$ and $NaIO_4$ to deliver the six-membered cyclic sulfamidates **62** and **63** in 72 and 71% overall yields, respectively (Fig. 19).[32]

3.2. Configurational assignment of six-membered cyclic sulfamidites

The configurational assignments for six-membered *N*-(PhF)sulfamidites **102** were made based on their proton NMR spectra with comparison to six-membered *N*-(PhF)sulfamidate **71**. Sulfamidites **102** and sulfamidate **71** were expected to adopt a chair conformation which has been shown by NMR studies to be the preferred conformation of the related six-membered cyclic sulfates.[17] Small coupling constants between the C-4 and C-5 protons suggested that **102** and **71** adopt conformations with the

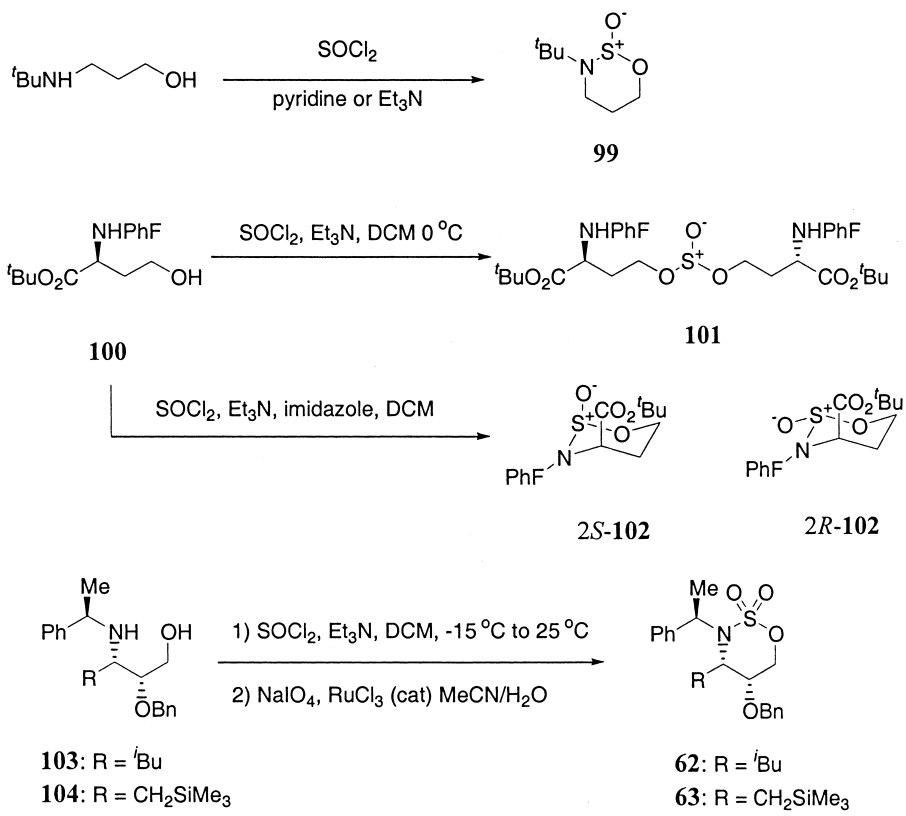


Figure 19. Synthesis of six-membered cyclic sulfamidites with thionyl chloride.[17,32,35]

tert-butyl ester sitting axial, as has been previously observed for related *N*-(PhF)pipecolate *tert*-butyl esters.[44–46] In the proton spectrum of **71**, the anisotropy of the sulfamidate caused the signals for the axial *tert*-butyl ester singlet (1.66 ppm), the C-6 β-proton (4.88 ppm) and the PhF resonances (7.2–8.11 ppm), all to be shifted downfield. In the spectrum of 2*S*-**102**, the presence of the axial sulfoxide oxygen caused a similar down field shift of its *tert*-butyl ester singlet (1.61 ppm) and C-6 β-proton (4.9 ppm). In the spectrum of 2*R*-**102**, only the PhF resonances (7.20–8.27 ppm) were shifted further downfield by the presence of the equatorial sulfoxide oxygen, and the signals for the *tert*-butyl ester singlet (1.40 ppm) and C-6 β-proton (4.37 ppm) remained upfield (Fig. 20).[35]

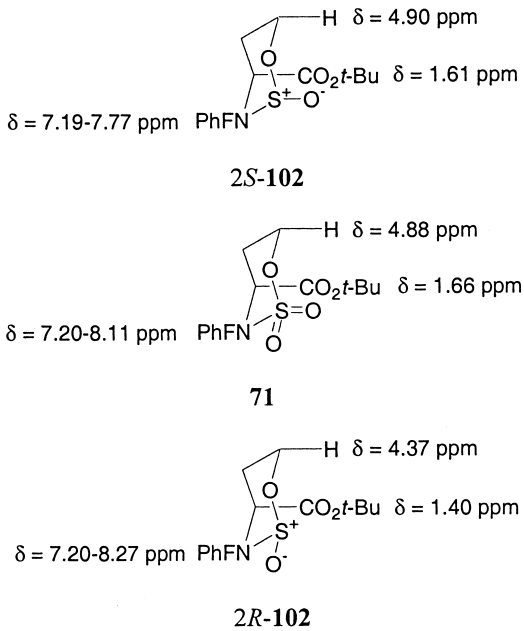


Figure 20. Influence of S–O bond anisotropy on chemical shift in related six-membered sulfamidate and *R*- and *S*- sulfamidites.[35]

4. Five-membered cyclic sulfamidates

4.1. Synthesis of five-membered cyclic sulfamidates

Among the most direct routes to synthesize five-membered cyclic sulfamidates has been treatment of the β-amino alcohol with sulfuryl chloride. This method has been effective for conformationally rigid amino alcohols. For example, 3-(*p*-toluenesulfonyl)-1,2,3-benzoxathiazole 2,2-dioxide **56** was synthesized in 85% yield on treatment of **105** with SO_2Cl_2 and Et_3N in DCM at −78°C followed by warming to 5°C. A series of related analogs **106–111** possessing different aromatic substituents were later prepared by this method.[27] Prolinol reacted under similar conditions to give the sulfamidate **113** in 63% yield; however, this reaction was not successful at higher temperatures.[39] Although attempts to convert D-allosamine derivative **114** into cyclic sulfamidate **115** with sulfuryl chloride failed and starting material was recovered, 1,1′-sulfonyl diimidazole reacted with **114** to provide cyclic sulfamidate **115** in 71% yield after reinstallment of the acetyl group with acetyl chloride.[6,7] Apparently, sodium imidazolate, released from the reaction of **114** with 1,1′-sulfonyl diimidazole, removed nucleophilically the acetyl group during this reaction (Fig. 21).

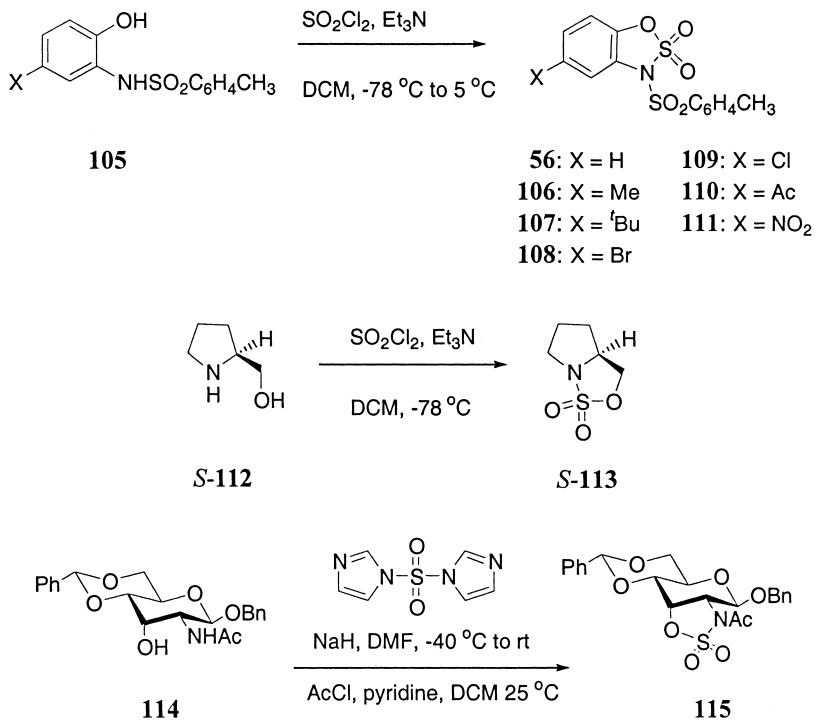


Figure 21. Direct routes for the synthesis of cyclic sulfamidates from β-amino alcohols.[6,7,27,39]

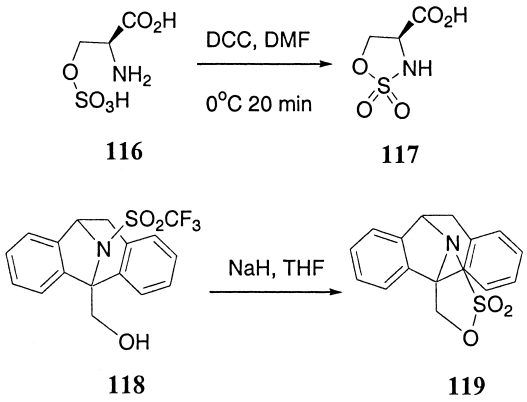


Figure 22. Cyclic sulfamidate formation by intramolecular nuclephilic attack on sulfur.[10,48]

More conformationally flexible amino alcohols tend to react with SO_2Cl_2 to form aziridines and not the desired sulfamidates. For example, *N*-(trityl)serine methyl ester reacted with SO_2Cl_2 and Et_3N in toluene at −50°C to furnish a 90% yield of methyl *N*-(trityl)aziridine-2-carboxylate.[36,47] For this reason, five-membered cyclic sulfamidates have usually been synthesized from β-amino alcohols by a two step process featuring oxidation of a sulfamidite intermediate.

The introduction of the SO_2 moiety into a sulfamidate without oxidation has also been achieved via *O*-sulfate and *N*-trifluoromethanesulfonamido analogs of the starting β-amino alcohol. For example, L-serine *O*-sulfate **116** was shown to react with dicyclohexylcarbodiimide (DCC) in DMF to form the cyclic sulfamidate **117** based on elemental analysis and a change in the IR absorption band for the C–O–S vibration from 775 to 800–810 cm^{-1} on passing from sulfate **116** to product sulfamidate **117**.[48] β-Trifluoromethanesulfonamido alcohol **118** has been converted to cyclic sulfamidate **119** by a process which features nucleophilic attack of alkoxide at sulfur and subsequent loss of trifluoromethyl anion (Fig. 22). This sulfur-based version of the haloform reactions of α-trihalomethylketones has been accomplished using $(n\text{-}Bu)_4N^+F^-$ in acetonitrile at 22°C in 54% yield, as well as NaH in THF which is useful for preparative purposes.[10]

1,2-Diols have been converted to five-membered cyclic sulfamidates by treatment with Burgess-type reagents (250 mol% $Et_3N^+SO_2N^-CO_2R$) in THF with heating.[13] Double sulfonylation was proposed to convert the diol to its bis-sulfamidate **120** which undergoes cyclization via an S_N2 mechanism with departure of the better leaving group (Fig. 23).[13]

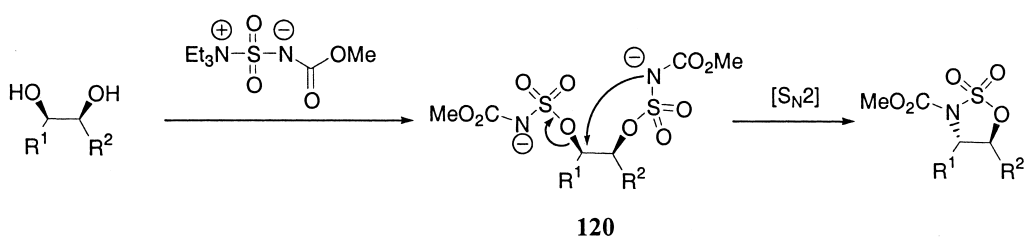
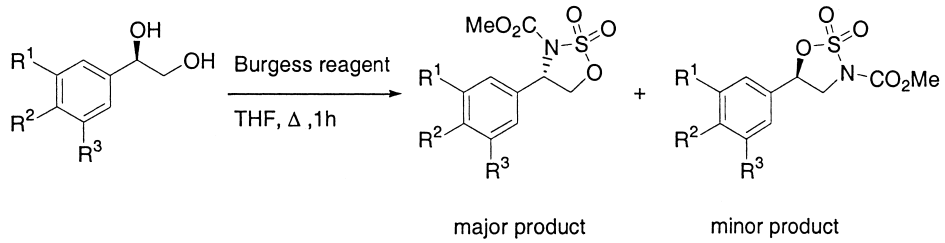


Figure 23. Proposed mechanism for 1,2-diol conversion into cyclic sulfamidate using Burgess reagent.[13]

Table 5. Regioselective synthesis of sulfamidates from diols using Burgess reagent[13]



	R^1	R^2	R^3	Major product	Ratio of regioisomers	Yield (%)
121	H	OMe	H	**128**	>98:2	91
122	H	OAc	H	**129**	95:5	88
123	^{t}Bu	H	^{t}Bu	**130**	95:5	87
124	H	F	H	**131**	95:5	79
125	H	H	H	**132**	93:7	92
126	H	CF_3	H	**133**	85:15	83
127	NO_2	H	H	**134**	55:45	86

α-Aryl diols **121**–**127** were studied initially because they can be practically synthesized in high enantiomeric purity by the asymmetric dihydroxylation of styrenes.[49] Displacement by nitrogen was performed in THF at reflux and shown to occur with high regioselectivity (≥95:5) at the benzylic position when the aromatic substituents were electron donating or neutral; however, a 55:45 ratio of diastereomers was obtained with the electron withdrawing *m*-nitrophenyl analog **127** (Table 5). Selectivity was improved for **127** to 75:25 at the expense of low conversion at room temperature and to 95:5 in the synthesis of β-methyl analog **135** (Fig. 24).[13]

Steric effects alone favored (>98:2) amine substitution at the primary carbon of hexane-1,2-diol to form **136**. Proof that the cyclization proceeded by an S_N2 process with

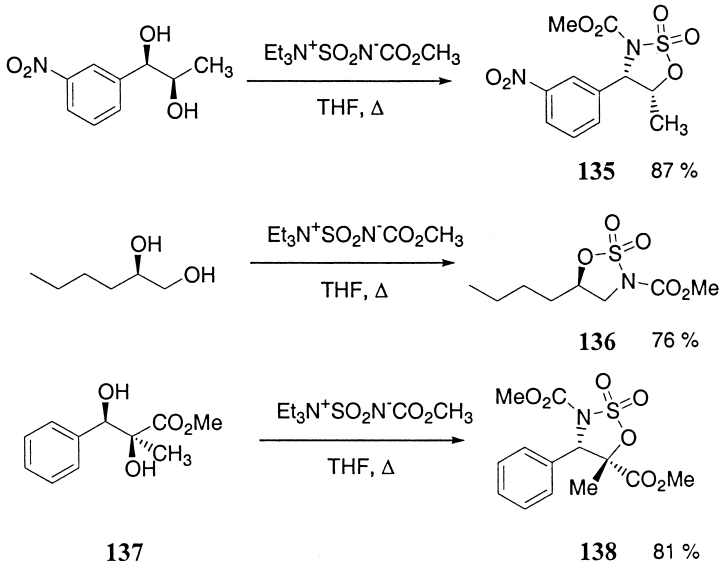


Figure 24. Sulfamidates **135**, **136** and **138** were prepared using Burgess reagent.[13]

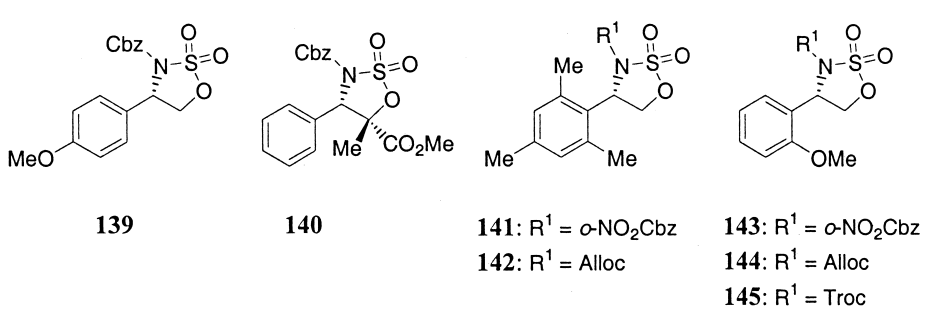


Figure 25. Sulfamidates **139**–**145** from use of *O*-modified Burgess reagents.[13]

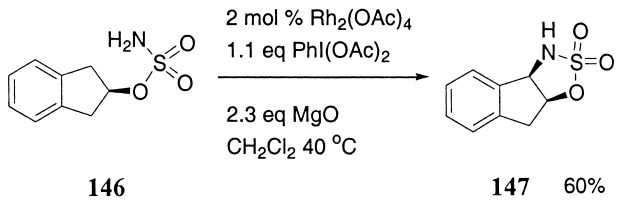


Figure 26. Formation of **147** from rhodium catalyzed intramolecular C–H insertion.[12]

complete stereoinversion was obtained using X-ray crystallographic analysis of sulfamidate **138** prepared from *cis*-diol **137** and chiral HPLC analysis of **138** prepared from enantiomerically enriched diol (Fig. 24).[13]

Although the original Burgess reagent provided only *N*-(methoxycarbonyl)sulfamidates, sulfamidates **139–145** possessing a variety of carbamate analogs [Cbz, *o*-NO_2Cbz, allyl carbamate (Alloc) and 2,2,2-trichloroethyl carbamate (Troc) groups] were effectively synthesized by the application of novel $Et_3N^+SO_2N^-CO_2R$ analogs, prepared by treating chlorosulfonylisocyanate with different alcohols followed by exposure to triethylamine (Fig. 25).[13]

Finally, in cases when the formation of a six-membered sulfamidate was prevented such as in **146**, rhodium catalyzed intramolecular C–H insertion provided five-membered sulfamidate **147** (Fig. 26).[12]

4.2. Nucleophilic ring-opening of five-membered cyclic sulfamidates

4.2.1. Ring-opening of five-membered cyclic sulfamidates with sulfur nucleophiles. Serine-derived sulfamidates **33**, **66** and **70** reacted with thiocyanate ion in DMF at room temperature to give 68–91% yields of *S*-cyanocysteines **148–150**.[4,5,33] In the case of (2*S*)-*N*-PhF-*S*-cyanocysteine methyl ester **148**, conversion to *N*-PhF-L-alanine and comparison of its specific rotation with the literature value was used to estimate enantiomeric purity. Cleavage of the S–C bond with Raney nickel in EtOAc at reflux for 6 h and hydrolysis of the methyl ester with 1N NaOH in ethanol for 1 h gave *N*-PhF-L-alanine in 74% overall yield from **148**. The specific rotation of *N*-PhF-L-alanine and comparison with its literature value demonstrated that the material from sulfamidate opening was significantly enriched with one enantiomer.[5] In addition, D-allosamine-derived sulfamidate **115** reacted with thioacetate ion **151** in DMF at room temperature to provide thioester **152** in 82% yield (Fig. 27).[6,7]

Alkylthiols have not reacted with five-membered cyclic-sulfamidates under neutral conditions; however, they do react usually at the β-carbon under alkaline conditions. For example, *N*-(PhF)serine derived sulfamidate **33** failed to react with propane thiol and DMF at room temperature, yet partially (10%) eliminated to form *N*-PhF-dehydroalanine methyl ester **153** when NaH was added to the reaction mixture.[5] α-Methylserine-derived sulfamidate **70** was converted to *S*-(*p*-methoxybenzyl)cysteine **155** in 94–100% yields on treatment with *p*-methoxybenzylthiol in DMF with Cs_2CO_3 or with 1,1,3,3-tetramethylguanidine at room temperature, as well as with lithium *p*-methoxybenzylthiolate in THF at −78°C.[33] Similarly, sulfamidate **70** reacted with *iso*-pentylthiol and Cs_2CO_3 in DMF to provide *S*-(*iso*-pentyl)cysteine **154** in 95% yield (Fig. 28).[33]

A series of glycosylthiolate ions have been reacted with D-allosamine-, serine- and threonine-derived sulfamidates **115**, **117**, **159** and **161** to furnish a variety of carbohydrate analogs (Fig. 29).[6–8,50] In the case of D-allosamine-derived sulfamidate **115**, treatment with 2,3,4-tri-*O*-acetyl-1-thio-α-L-fucopyranose **156** and NaH in DMF at 0°C produced the desired disaccharide **157** in 61% yield along with the

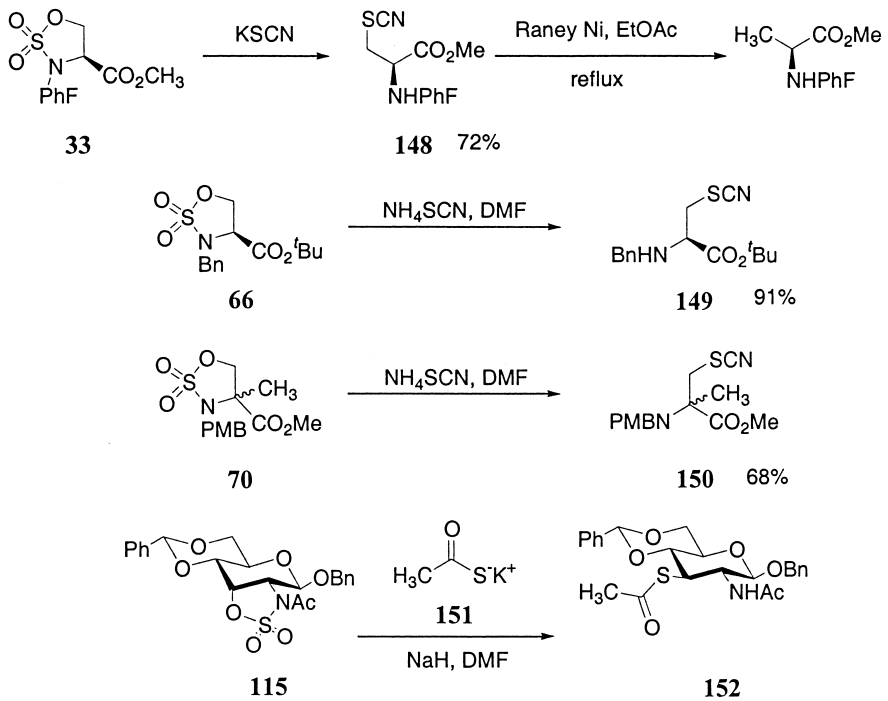


Figure 27. Reaction of sulfamidates **33**, **66** and **70** with thiocyanate ion and **115** with thioacetate.[4–7,33]

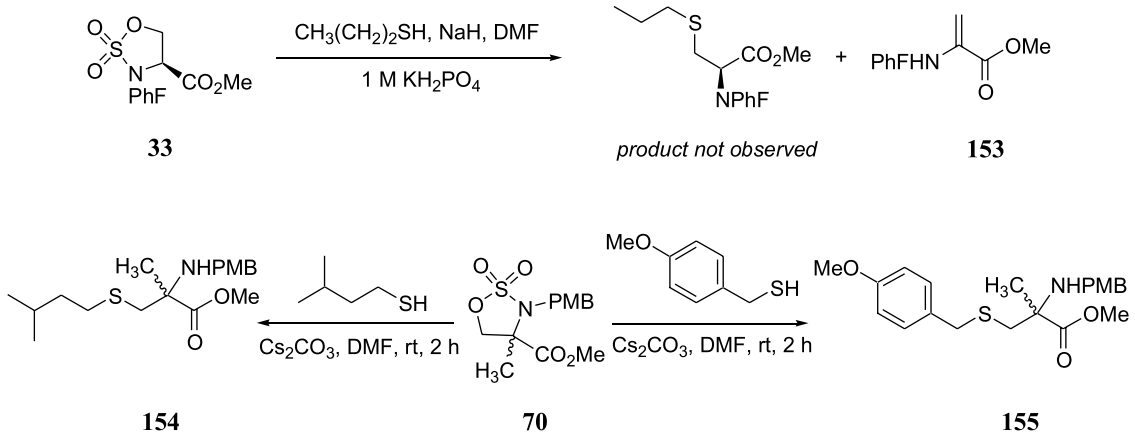


Figure 28. Reaction of sulfamidates **33** and **70** with alkylthiols.[5,33]

deacetylated sulfamidate **158** in 17%.[7] Trisaccharide **160** was later synthesized from sulfamidate **159** using similar conditions (**156**, NaH, DMF, 0°C→room temperature) in 77% yield.[50] Mild reaction conditions (0.5 M aq. $NaHCO_3$, pH 8, 23°C) and minimal functional group protection have provided *S*-linked glycosyl amino acid conjugates **162**, **164** and **166** in 85–90% yields by the addition of 1-thio-β- and α-D-glucose and 1-thio-*N*-acetyl-β-D-glucosamine to serine-derived sulfamidate **117**, followed by hydrolysis of sulfamic acid intermediate with aq. HCl (5 M) at 37°C. The

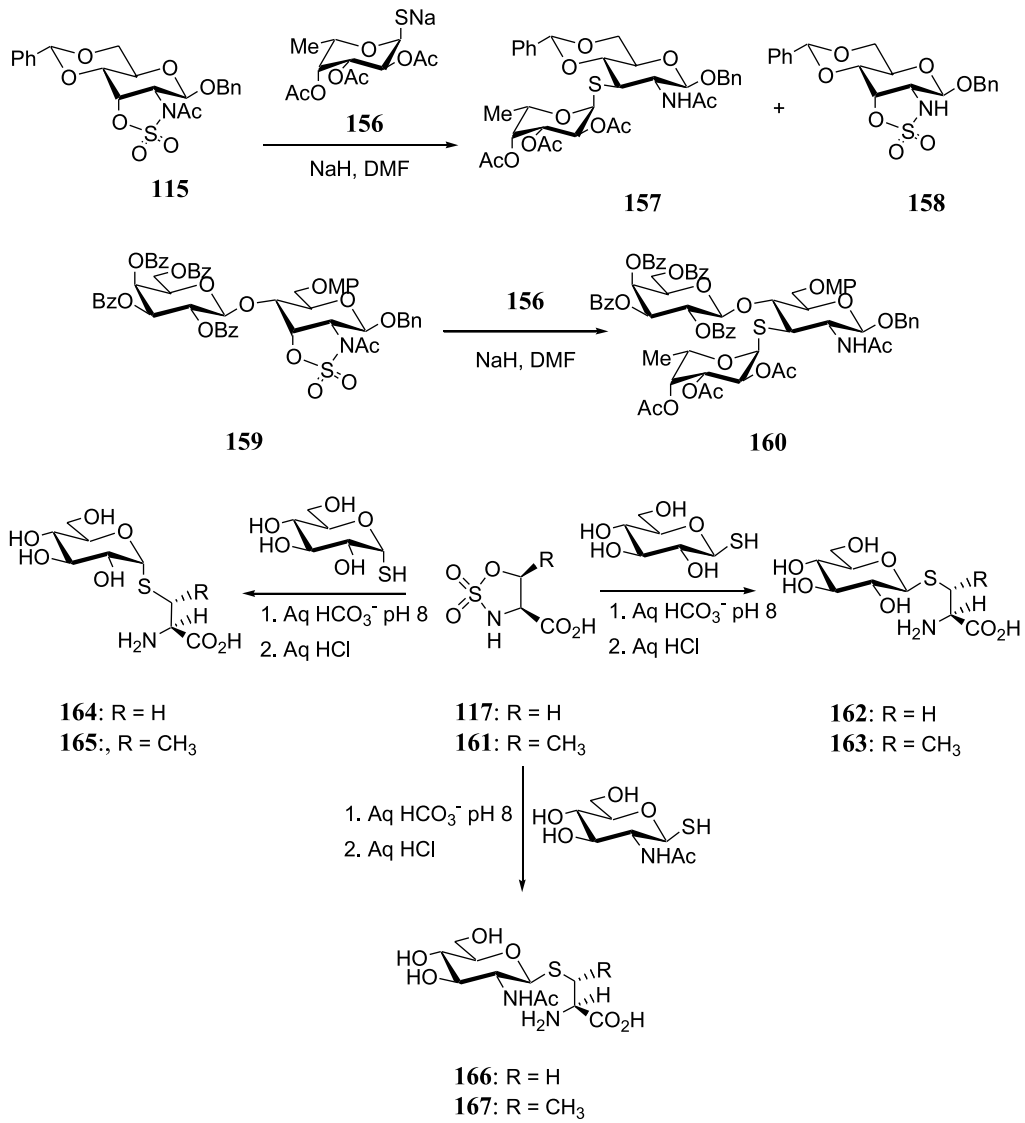


Figure 29. Products from reactions of D-allosamine-, serine- and threonine-derived sulfamidates with glycosylthiolate ions.[6–8,50]

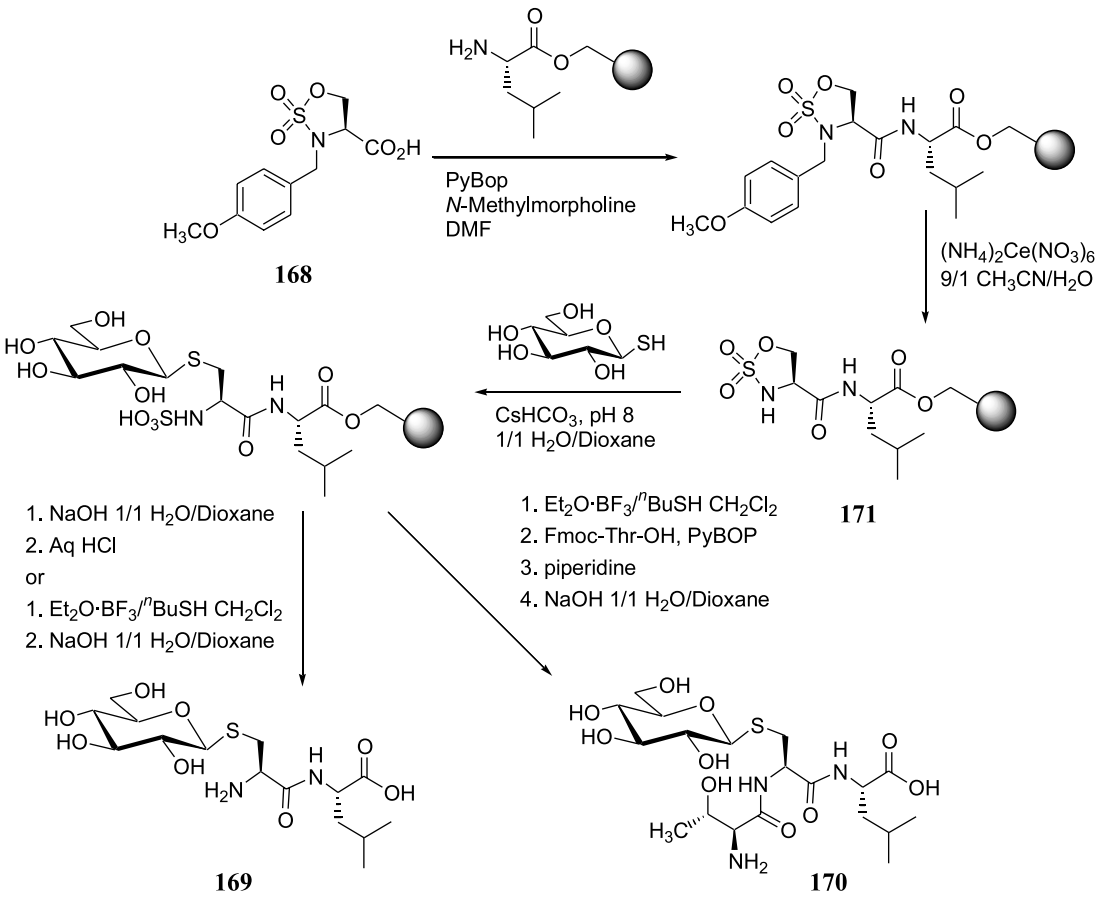


Figure 30. Synthesis of glycopeptide analogs **169** and **170** on solid-phase.[8]

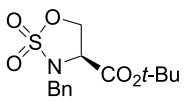
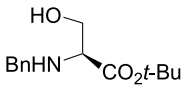
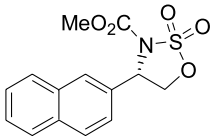
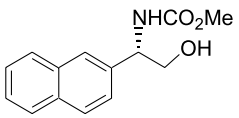
same reactions with threonine-derived sulfamidate **161** provided low yield (10%) of product and *allo*-threonine was the major product from competing hydrolysis. Augmentation of the yield was accomplished by employing excess 1-thio sugar, increasing concentration of the reactants, switching to $CsHCO_3$ (1.5 M, pH 8) and heating to 37°C. These improved conditions provided the thio-threonine conjugates **163** and **167**, both in 60% yield from 1-thio-β-D-glucose and 1-thio-*N*-acetyl-β-D-glucosamine, respectively and a 40% yield of **165** from 1-thio-α-D-glucose. Steric interactions were suggested to account for the difficulty in making the α-thio conjugate from sulfamidate **161**. Conjugates **162**–**167**, all were claimed to be of ≥97% diastereomeric purity after proton NMR analysis because no minor isomeric components were detected (Fig. 29).[8]

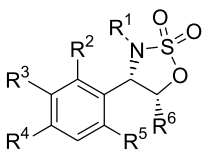
Applying *N*-(*p*-methoxybenzyl)serine sulfamidate **168** in solid-phase glycopeptide synthesis on a polystyrene resin modified with poly(ethylene glycol) (3000–4000 MW PEG), *S*-β-D-glucopyranosyl-L-cysteinyl-leucine **169** and threoninyl-*S*-β-D-glucopyranosyl-L-cysteinyl-leucine **170**, both were synthesized in high purity from a sequence featuring attack of resin-bound dipeptide sulfamidate **171** with 1-thio-β-D-glucose using the cesium bicarbonate conditions in 1:1 dioxane/water. The hydrolysis of the *N*-sulfate intermediate and resin cleavage were pursued in two ways. Sodium hydroxide in 1:1 dioxane/water liberated the glyco-peptide *N*-sulfate which was hydrolyzed in solution with aq. HCl. Alternatively, Lewis acid catalyzed hydrolysis of the resin-bound *N*-sulfate was performed with boron trifluoride etherate and *n*-butanethiol in dichloromethane prior to removal of glyco-peptide **169** from the resin with NaOH. Glyco-peptide **169** of similar purity was obtained from both cases, the later offering potential to extend the peptide chain as demonstrated in the synthesis of glycopeptide **170**, by a subsequent coupling of *N*(Fmoc)-threonine prior to resin cleavage.[8] Alternative methods for cleaving *N*-sulfates which do not employ protic nor Lewis acids may allow this protocol to be extended to di- and polysaccharides which possess glycosidic linkages that are sensitive to such conditions (Fig. 30).

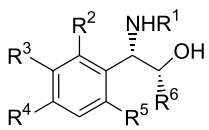
4.2.2. Ring-opening of five-membered cyclic sulfamidates with oxygen nucleophiles. Hydrolysis of sulfamidate **66** to *N*-(benzyl)serine *tert*-butyl ester **174** was achieved with 2 M aq. HCl in dioxane (v:v 1/1) at 0–20°C after 14 h in 63% yield.[4] Similar conditions (4 M HCl in dioxane) were later shown to convert *N*-(alkyloxycarbonyl)sulfamidates **135**, **139**, **172**, **173**, **143**–**145** to the corresponding β-aryl-β-carbamato-alcohols **175**–**181** in ≥90% yields (Table 6).[13]

On the other hand, 3-*N*-toluenesulfonyl-1,2,3-benzoxathiazole 2,2-dioxide **56** did not react with HCl in EtOH as ascertained by scanning at 330–220 nm and by TLC. Selective attack of the endocyclic sulfonyl group of 3-*N*-toluenesulfonyl-1,2,3-benzoxathiazole 2,2-dioxide **56** by NaOH in aq. CH_3CN caused S–N bond cleavage to deliver the sulfamido sulfate **182** which on hydrolysis gave

Table 6. Examples of formation of β-aryl-β-carbamato-alcohols from *N*-(alkyloxycarbonyl)sulfamidates using HCl in dioxane[4,13]

Starting material	Product	*t* (h)	Yield (%)
 **66**	 **174**	14	63
 **172**	 **175**	10	94





	R^1	R^2	R^3	R^4	R^5	R^6			
173	$MeCO_2$	Me	H	Me	Me	H	**176**	30	95
135	$MeCO_2$	H	NO_2	H	H	Me	**177**	12	92
139	Cbz	H	H	OMe	H	H	**178**	2	92
143	*o*-NO_2-CBz	H	H	H	OMe	H	**179**	26	95
144	Alloc	H	H	H	OMe	H	**180**	24	93
145	Troc	H	H	H	OMe	H	**181**	16	90

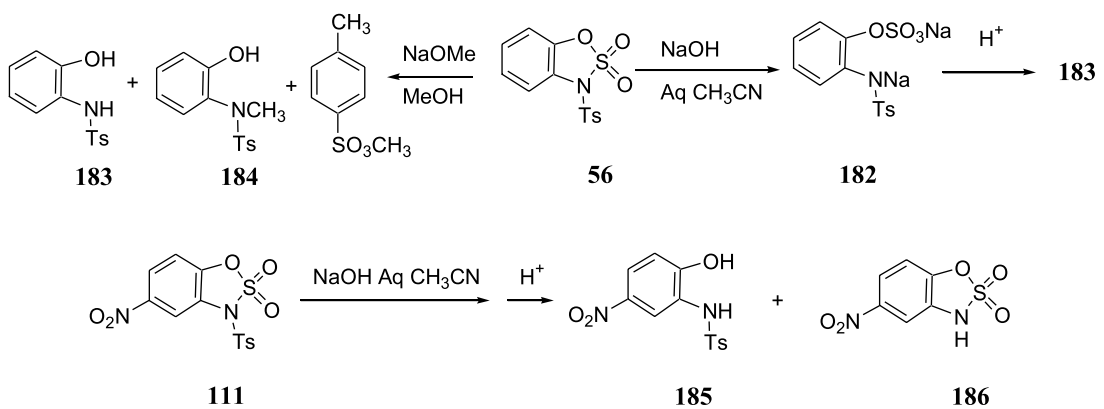


Figure 31. Nucleophilic opening of **56** and **111** using of NaOH and NaOMe.[27,51]

sulfonamide **183**.[27] 5-Nitro analog **111** reacted similarly with NaOH in aq. acetonitrile to afford 92% yield of sulfonamide **185** and 6% yield of N-deprotected sulfamidate **186**.[51] On the contrary, NaOMe produced mixtures from attack of both the endo- and exocyclic sulfonyl groups of 3-*N*-toluenesulfonyl-1,2,3-benzoxathiazole 2,2-dioxide **56** which resulted in formation of sulfonamide **183** and its *N*-methyl analog **184** from in situ N-alkylation with methyl tosylate generated from attack at the exocyclic sulfonamide (Fig. 31).[27]

Prolinol-derived sulfamidate *S*-**113** was selectively ring-opened at carbon by using a catalytic drop of trifluoroacetic acid in methanol at reflux for 2 days.[39] Hydrolysis of the resulting sulfamic acid intermediate with NaOH at 90°C was

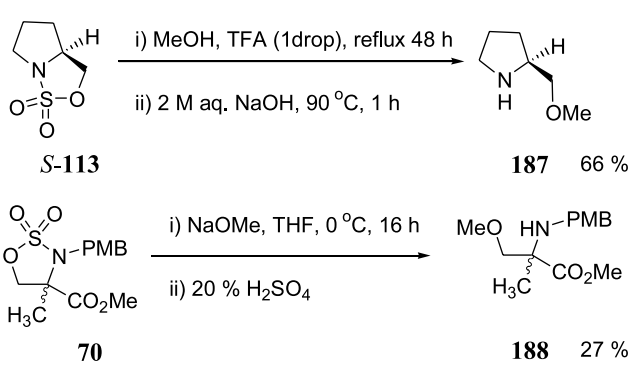


Figure 32. Methyl ether formation from ring opening of cyclic sulfamidates **70** and *S*-**113**.[33,39]

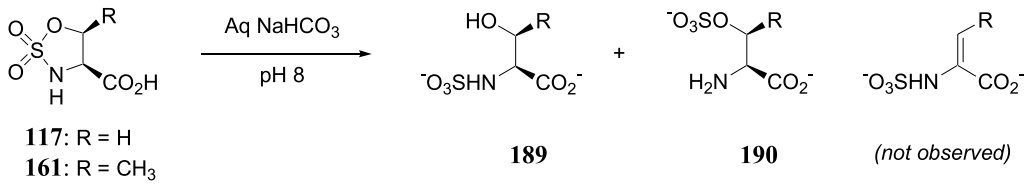


Figure 33. Ring-opening of **117** and **161** in D_2O under basic conditions.[8]

reported to give 2-(*S*)-(methoxymethyl)pyrrolidine **187** in 66% yield. Attempts with NaOMe were unsuccessful;[39] however, difficulty in hydrolyzing the sodium sulfamate intermediate with NaOH at 90°C have been suggested to account for failure to produce methyl ether **187**.[52] α-Methylserine-derived sulfamidate **70** was converted to methyl ether **188** on treatment with NaOMe in THF at 0°C albeit in 27% yield (Fig. 32).[33]

The ring-opening of serine- and threonine-derived sulfamidates **117** and **161** in D_2O, made alkaline (pH 8) with sodium bicarbonate, was studied by proton NMR at room temperature.[8] Sulfamidates **117** and **161**, both had half lives of 20 h under these conditions that decomposed the starting materials by nucleophilic attack at sulfur forming a mixture of the corresponding sulfamic acid **189** and sulfate ester **190**. No products from elimination nor attack at the β-carbon were observed (Fig. 33).

Ring-opening with substitution at carbon has been achieved with weakly basic oxygen nucleophiles. For example, D-allosamine derived sulfamidate **115** reacted with NaOAc in DMF at 40°C for 48 h to provide a 47% yield of the corresponding acetate **191**.[7] Alaninol derived sulfamidate **192** was opened with $(Et_4N)_2CO_3$ to presumably form the carbonic acid **193** (detected by HPLC), which after acid hydrolysis gave back the starting material, alcohol **194** in 93% yield.[9] Sodium *o*-methoxyphenolate reacted in DMF with a series of sulfamidates **195**–**197** to provide, after acidic hydrolysis of the sulfamic acid intermediate, the corresponding aryl ethers **198**–**200** in 47–82% yields.[53] Bicyclic sulfamidate (−)-**22** was displaced with $NaNO_2$ after heating in DMF at 70°C for 15 h. The intermediate nitrite was cleaved during acidic work-up with AcOH to furnish the corresponding macrocyclic alcohol **201**, a key intermediate in the synthesis of (−)-(2*R*,3*S*)-3-hydroxycelacinnine (Fig. 34).[18]

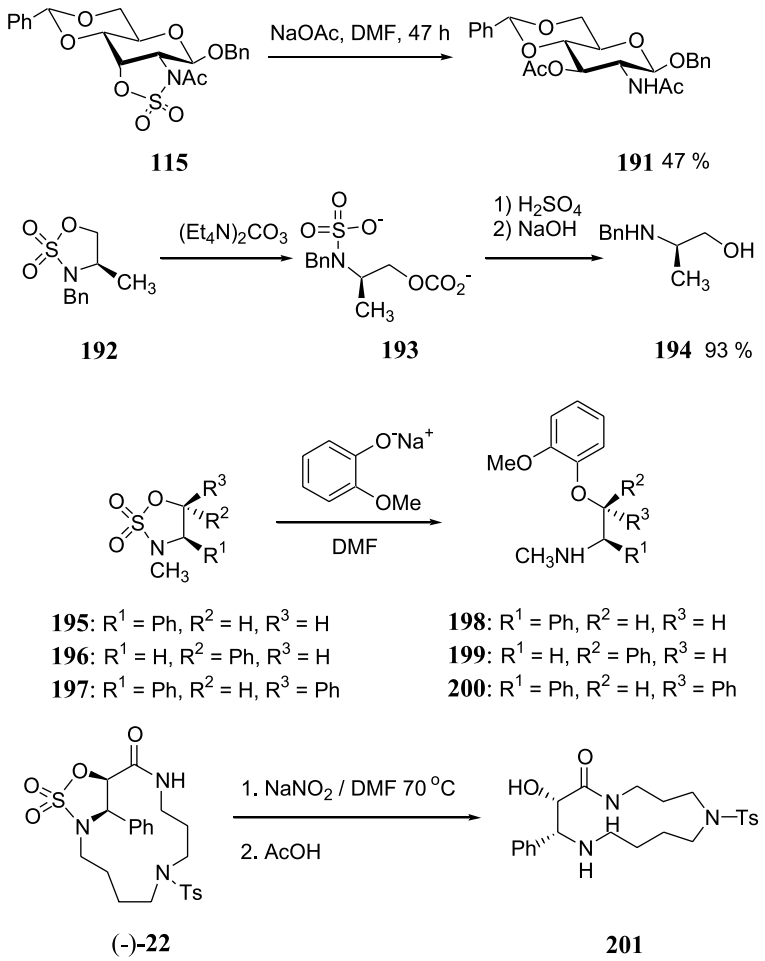
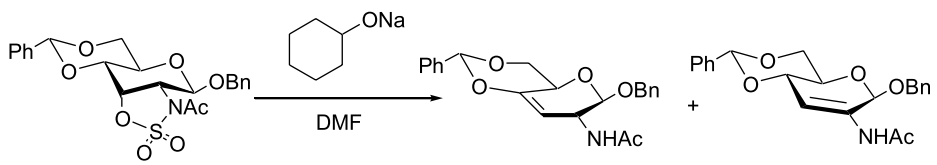


Figure 34. Examples of reaction of sulfamidates with weakly basic oxygen nucleophiles.[7,9,18,53]



115 **202** **203**

Figure 35. Elimination products from the reaction of **115** with sodium cyclohexanolate.[7]

Stronger bases have often caused elimination of the sulfamidate. For example, D-allosamine derived sulfamidate **115** reacted with sodium cyclohexanolate in DMF at 20°C for 3 h to provide a 51% yield of a 1:0.8 mix of allylic amine **202** and enamine **203** (Fig. 35).[7] Similarly, cyclic-sulfamidate **33** derived from *N*-(PhF)serine methyl ester was converted quantitatively to *N*-PhF-dehydroalanine methyl ester **153** using NaOMe in DME at room temperature (Fig. 28).[5]

4.2.3. Ring-opening of five-membered cyclic sulfamidates with nitrogen nucleophiles. Cyclic-sulfamidates react effectively with azide ion to provide β-amino azides in high yield under milder conditions than those used to open the related five-membered cyclic-sulfamidites. For example, β-azido alanines **204**–**206** were isolated in ≥90% yields from treatment of their serine-derived sulfamidate counterparts **66**, **33** and **70** with NaN_3 in a polar solvent (DMF or 1:1 acetone/water) at room temperature.[4,5,33] Under similar conditions (NaN_3, DMF), D-allosamine and phenylalaninol derived sulfamidates **115** and **68** reacted respectively to furnish the corresponding azido sugar **207** and β-amino azide **208** in 79 and 92% yield.[6,7,31] Heating was required to open 4,4-dimethyl and 4,4,5-trimethyl sulfamidates **69** and **211** with NaN_3 in DMF to furnish azides **209** and **210** in 70 and 68% yield,[54] respectively (Fig. 36).

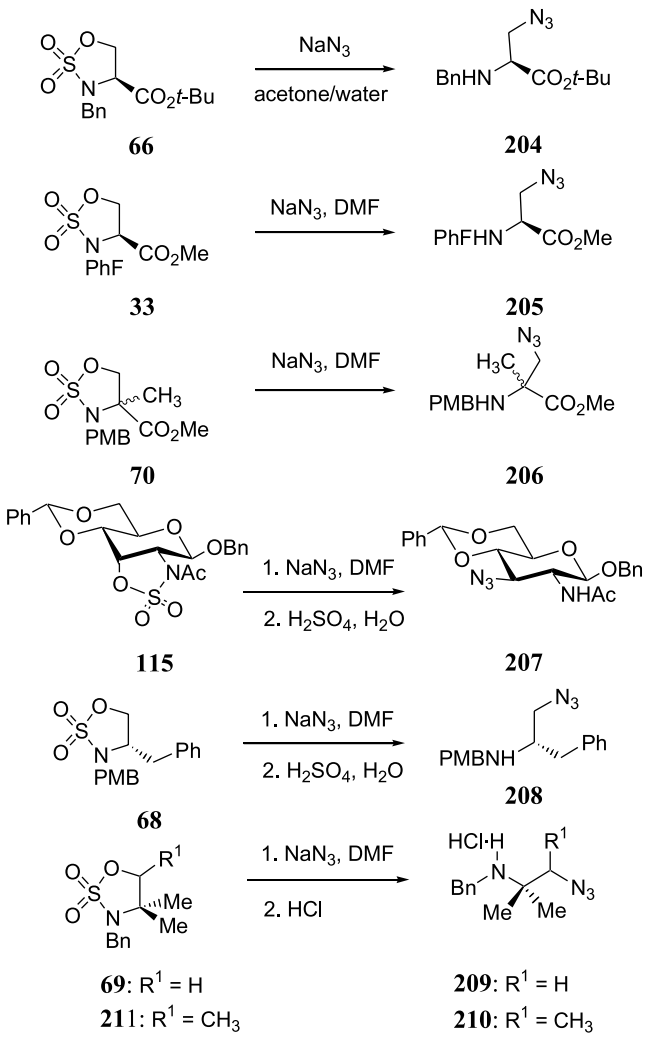


Figure 36. Opening of five-membered cyclic sulfamidates with NaN_3.[4–7,31,33,54]

Azole-alanines **213**–**216** were produced in 55–85% yield on reaction of pyrazole and imidazole with serine-derived sulfamidates without additional base in polar solvents (CH_3CN, DME, DMF) on heating (60–80°C).[4,5,55] By employing $CsCO_3$ in DMF, pyrazole and imidazole were reacted with α-methylserine-derived sulfamidate **70** and 4,4,-dimethylsulfamidate **69** at room temperature and 100°C respectively to give azoles **216** and **217** in 74 and 72% yields (Fig. 37).[33,54] Triethylamine did not promote the same reaction with 4,4- dimethylsulfamidate **69**.

Primary and secondary amines have generally reacted effectively with five-membered cyclic-sulfamidates at room temperature in a polar solvent (DCM, CH_3CN, DMF) to furnish good yields of the corresponding diamines.[4,55,56] Solvent appeared to influence yield dramatically in the reaction of pyrrolidine to α-methyl-serine-derived sulfamidate **70** in the presence of Cs_2CO_3 at room temperature, such that the yield of diamine went from 25 to 96% on switching from DMF to acetonitrile.[33] In the case of the bulkier amine **218**, heating the reaction mixture with serine-derived sulfamidate **219** at 60°C in CH_3CN was necessary to obtain a 50% yield of tertiary amine product **220**.[56] Steric bulk also influenced attack on 4,4-dimethyl-sulfamidate **69** which reacted with neat *n*-Bu, *s*-Bu and *t*-amyl amines at reflux to render **221**–**223** in 71, 70 and 41% yields, respectively.[54] When lithium *iso*-pentylamide was reacted with α-methylserine-derived sulfamidate **70** in THF at −78°C, β-lactam **224** was produced in 60% yield via nucleophilic attack at the β-carbon and lactam cyclization.[33] A series of secondary amines reacted with prolinol-derived sulfamidate *S*-**113** under acidic conditions (catalytic trifluoroacetic acid) in chloroform at reflux for 24 h to furnish the diamines **225**–**228**, after hydrolysis of the sulfamic acid intermediate with NaOH at 90°C and a final distillation, in 45–62% overall yields.[39] In addition, 3-(2,6-dimethylphenyl)-4-methyl-1,2,3-oxathiazolidine-2,2-dioxide **59** was opened with ethanolic dimethylamine in a steel bomb heated at 120–125°C for 3 h giving, in 92%

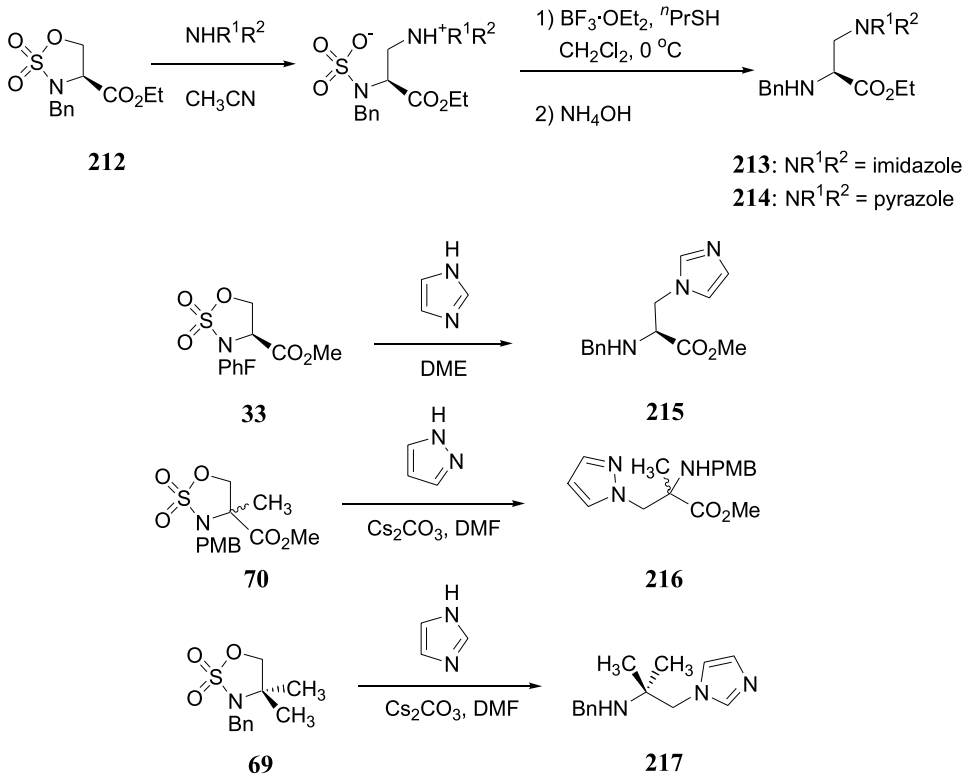


Figure 37. Synthesis of β-azol-alanines.[4,5,33,54,55]

yield, sulfamic acid salt **229**, which was hydrolyzed to diamine **230** using aq. HCl at 60°C in 93% yield (Fig. 38).[28]

Methyl and *tert*-butyl amines both opened the ring of 3-*N*-toluenesulfonyl-1,2,3-benzoxathiazole 2,2-dioxide **56** to furnish sulfamido sulfamidates **231** and **232** in 89 and 44% yield;[27] however, nitro analog **111** was *N*-deprotected by benzyl and *tert*-butyl amines affording cyclic sulfamidate **186** in 86 and 53% yield, respectively (Fig. 39).[51] Although the corresponding *tert*-butyl sulfonamide was not reported to have been isolated from the later reaction with **111**, *N*-benzyl-sulfonamide was isolated in 88% yield from the former.[51] Pyridine failed to react with nitro analog **111** in acetonitrile.

N-(PhF)Serine-derived sulfamidate **33** (Fig. 28) was shown by NMR spectroscopy to eliminate and form *N*-PhF-dehydroalanine methyl ester **153** on treatment with diethylamine at room temperature in <10, 50 and 100% yields, respectively, as solvent was changed from DME to CH_3CN to DMF.[5]

The enantiomeric purity of the products from ring opening of serine-derived sulfamidate **211** with pyrazole and piperidine was evaluated after conversion to diastereomeric amides using respectively (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride and (−)-menthyl chloroformate. A comparison of the diastereomeric amides with material prepared from racemic serine using proton NMR spectroscopy led the authors to conclude that 'no apparent racemization occurred in the course of both the ring opening and the hydrolysis reactions involved in the preparation of the diamine products **214** and **233**.[55] Similarly, (2*S*)-methyl 3-(1-imidazol)-2-[*N*-(PhF)amino]propionate **234** was concluded to be of >97% enantiomeric purity by conversion to diastereomeric amides **235** upon ester hydrolysis and coupling to L- and D-phenylalanine methyl ester, and subsequent measurement of the diastereotopic methyl ester singlets at 3.71 and 3.76 ppm in $CDCl_3$ by 400 MHz ^1H NMR spectroscopy (Fig. 40).[5]

4.2.4. Ring-opening of five-membered cyclic sulfamidates with carbon nucleophiles. Cyanide ion (NaCN) reacts effectively with serine- and phenylalaninol-derived sulfamidates **66**, **70** and **68** in DMF at room temperature to furnish 82–100% yields of their nitrile counterparts **236**–**238**.[4,31,33] The more sterically bulky 4,4-dimethyl and 4,4,5-trimethyl sulfamidates **69** and **209** reacted under such conditions for 1 h to give, after *N*-sulfate hydrolysis with HCl, nitrile **239** and **240** in 59 and 22% respective yields (Fig. 41).[54]

Prolinol-, valinol- and alaninol-derived cyclic sulfamidates *R*-**113**, **247** and **67** have also reacted with more basic carbon nucleophiles in low to moderate yields, after *N*-sulfate hydrolysis. Although PhLi was claimed to react unsuccessfully with prolinol-derived sulfamidate *S*-**113**,[39] a later report showed that 3,4-dimethoxyphenyl-, phenyl- and 2-thienyl-lithium reagents, all reacted with its enantiomeric sulfamidate *R*-**113** in THF at −78°C to furnish the sulfamic acid salts as hygroscopic solids that were hydrolyzed with 2N aq. HCl at reflux to furnish pyrrolidines **244**–**246** in 38–62% yields.[52] The earlier reported failure to produce 2-benzylpyrrolidine **245** from *S*-**113** was suggested to be the result of difficulty in cleaving the sulfamic acid salt using NaOH at 90°C.[52] Treatment of valinol-derived sulfamidate **247** with dibromomethyllithium at −100°C in 3:2:1 THF/Et_2O/hexanes with slow warming to room temperature, followed by hydrolysis with 1N H_2SO_4, furnished

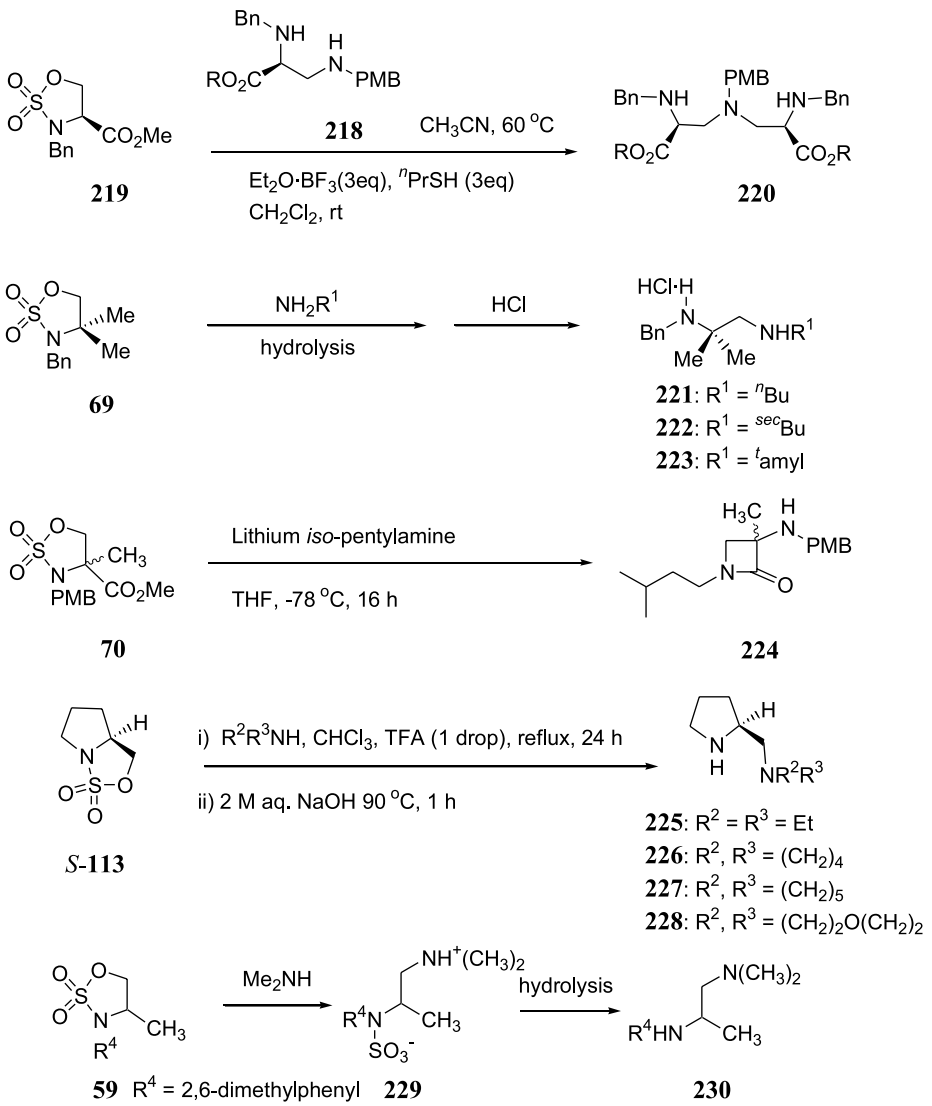


Figure 38. Representative reactions of a variety of amines with five-membered cyclic sulfamidates.[28,33,39,54,56]

3-benzylamino-1,1-dibromo-4-methylpentane **248** as a crystalline solid in 62% overall yield that could be stored at 0°C.[38] Alaninol-derived sulfamidate **67** was converted to 4-benzylaminopentane nitrile **249** in 66% yield upon treatment with lithiated acetonitrile at −78°C, warming to room temperature, and hydrolysis with H_2SO_4; however, application of the same conditions to prolinol-derived sulfamidate *S*-**113** gave a mixture of products.[34] Attempts to react **67** with *n*-BuLi and PhLi also gave multiple products, presumably due to competing C- and S-attack.[34] Sulfamidate **67** did react successfully with lithiated 1,3-dithiane and lithium di(*n*-butyl)cuprate at −20°C to furnish amines **250** and **251** in 51 and 23% yields, respectively after hydrolysis (Fig. 42).[34]

Opening of serine-derived cyclic-sulfamidates with carbon

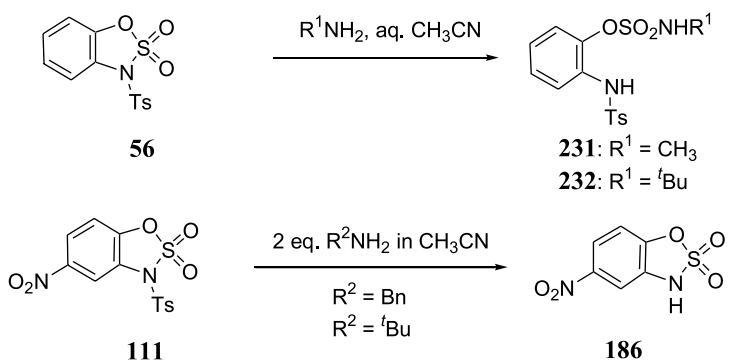


Figure 39. Reaction of cyclic sulfamidates **56** and **111** with amines.[27,51]

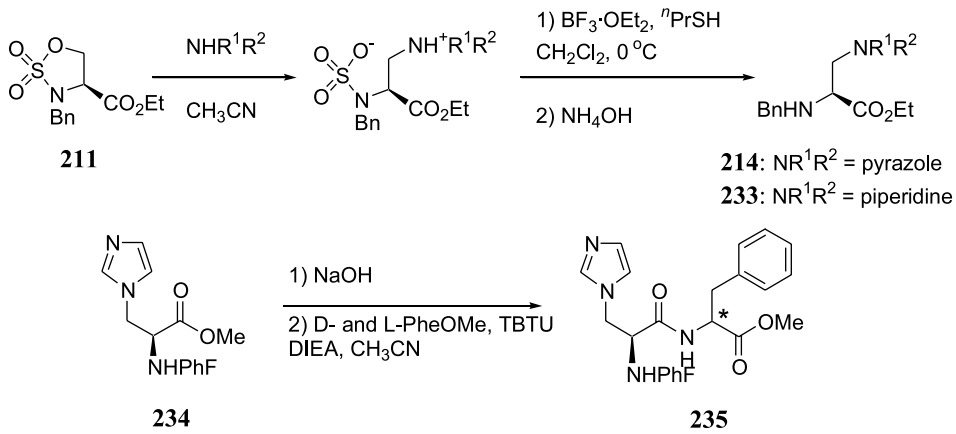


Figure 40. Enantiomeric purity studies of sulfamidate opening products.[5,55]

nucleophiles other than cyanide has been generally unsuccessful.[4,5,33] For example, attempts to react selectively at the β-carbon of α-methyl serine-derived sulfamidate **70** with alkyllithiums and Grignard reagents gave complicated mixtures due to competitive attack of the ester carbonyl, and starting material was recovered from attempts with copper catalyzed Grignard reagents, higher-order cuprates, zincates, deprotonated malonates and silyl enol ethers.[33] When *N*-(PhF)serine-derived sulfamidate **33** was reacted with β-keto esters, β-keto ketones, dimethyl malonate and nitroethane in the presence of NaH in DME, followed by heating at 60°C, and hydrolysis of the reaction mixture with 1 M KH_2PO_4, amino acid derivatives **253**–**259** were isolated in good yields after chromatography (Fig. 43).[5] Low specific rotation values were recorded for many products derived from **253**–**259** and suggested the possibility of racemization because *N*-(PhF)-α-amino carboxylates characteristically exhibit high specific rotations.

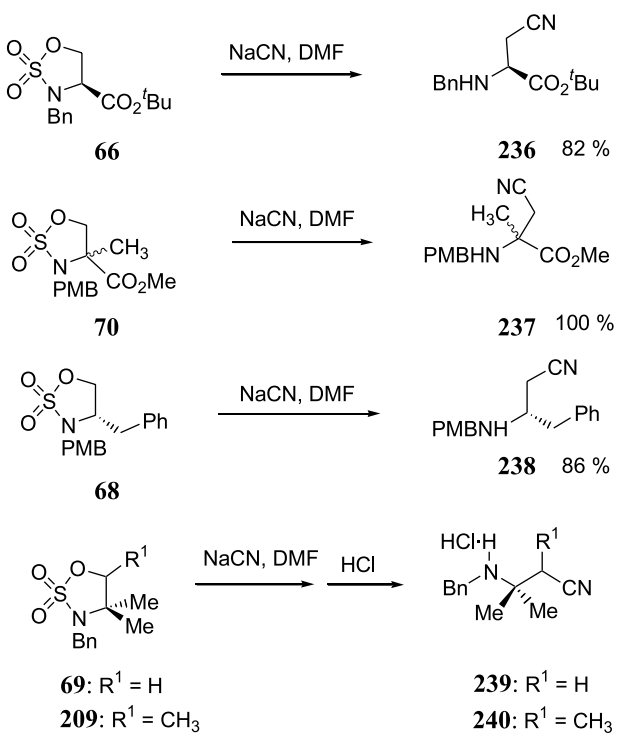


Figure 41. Opening of cyclic sulfamidates using NaCN.[4,31,33,54]

Moreover, conversion of β-keto ester **255** into *cis*-*N*-(Boc)-5-methylprolyl-(*S*)- and (*R*)-α-methylbenzylamides *R*- and *S*-**260** and analysis of the diastereomeric methyl doublets in their ^{1}H NMR spectra indicated that they were of only 10% diastereomeric excess (Fig. 44). Consequently, α-deprotonation and rapid β-elimination of cyclic-sulfamidate **33** was demonstrated to form dehydroalanine **252** which was shown to serve as a Michael acceptor for the formation of racemic β-keto ester.[5] The formation of *N*-(PhF)dehydroalanine **252** was suggested to be favored because the α-proton and β-hydroxyl group from serine were constrained in a nearly coplanar geometry with orbital overlap facilitating β-elimination (Fig. 43).[5]

Although γ-acyl pyroglutamate **261** was furnished on treatment of *N*-(benzyl)serine-derived sulfamidate **66** with diethyl malonate and sodium in THF/HMPA, dehydroalanine product was also encountered in this synthesis, suggesting that pyroglutamate **261** was of suspect enantiomeric purity because it may result from a similar elimination/Michael addition reaction (Fig. 45).[4] In addition, sulfamidate **263**, obtained from *N*-(benzyl)threonine methyl ester, reacted with lithium di(*n*-butyl)cuprate at −20°C to furnish a 3:1 mixture of diastereomers **264** in 40% yield (Fig. 45).[34] Because nucleophilic attack at the β-carbon of threonine-derived sulfamidate **263** would be expected to occur by an S_N2 process with complete inversion of configuration, the formation of a diastereomeric mixture suggests that a similar elimination/Michael addition mechanism may be at play during this cuprate addition.

4.2.5. Ring-opening of five-membered cyclic sulfamidates with halogen nucleophiles. Several examples of the ring-opening of five-membered cyclic-sulfamidates with fluoride ion have been reported to yield a variety of β-amino fluorides. In particular, sulfamidates have been used to make ^{18}F-labeled compounds as biological tools for imaging with use of Positron Emission Tomography (PET). The application of the nucleophilic displacement to introduce fluoride at the final synthesis step is particularly desirable because of the relatively short (110-min) half-life of the ^{18}F nucleus. In this application, treatment of sulfamidates 4*S*,5*R*-**61** and 4*S*,5*S*-**61** with a 1:4 KF/CaF_2 mix in dry acetonitrile in the presence of Kryptofix[2.2.2]® at 80°C gave, after aq. H_2SO_4 work-up, (1*R*,2*S*)-(−)-1-fluoro-1-deoxyephedrine 1*R*,2*S*-**265** and (1*S*,2*S*)-(+)-1-fluoro-1-deoxypseudoephedrine

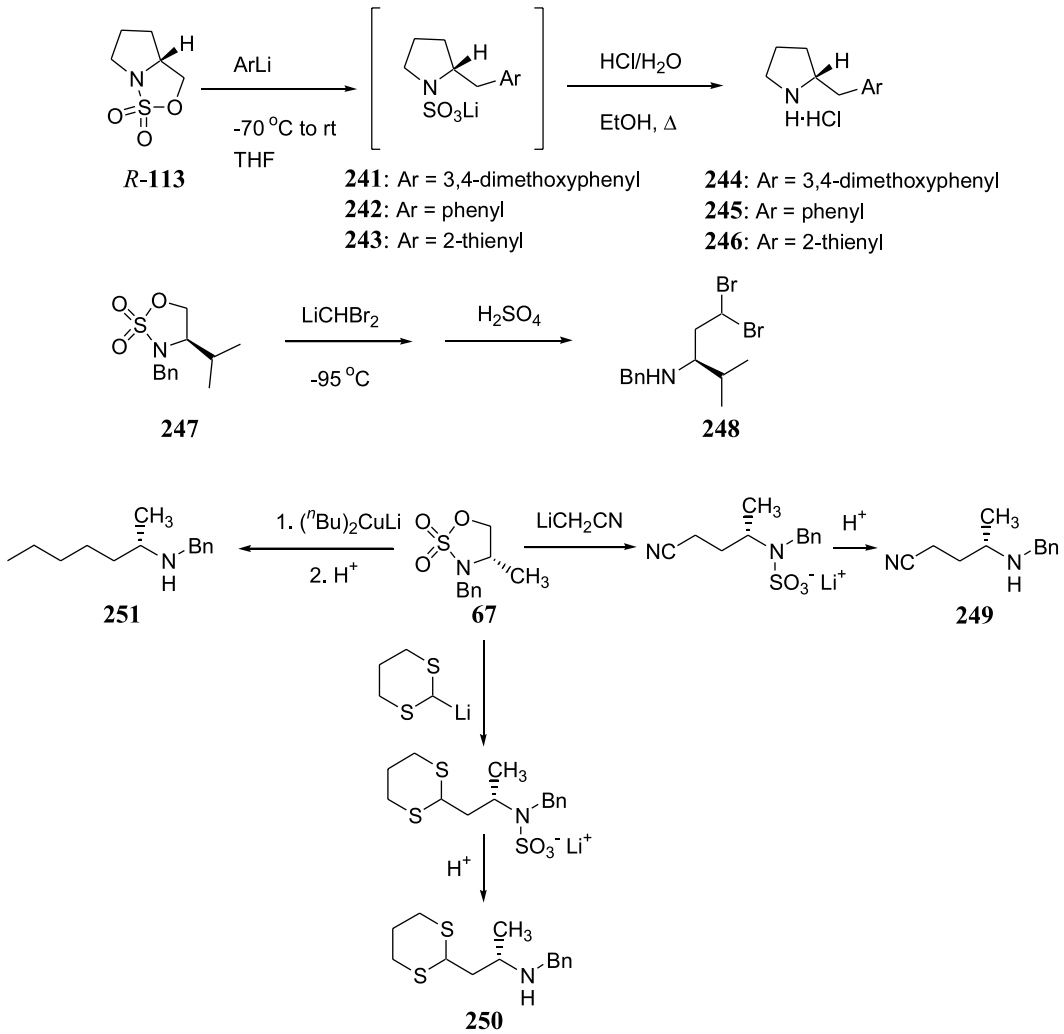


Figure 42. Representative reactions of cyclic sulfamidates with carbon nucleophiles.[34,38,39,52]

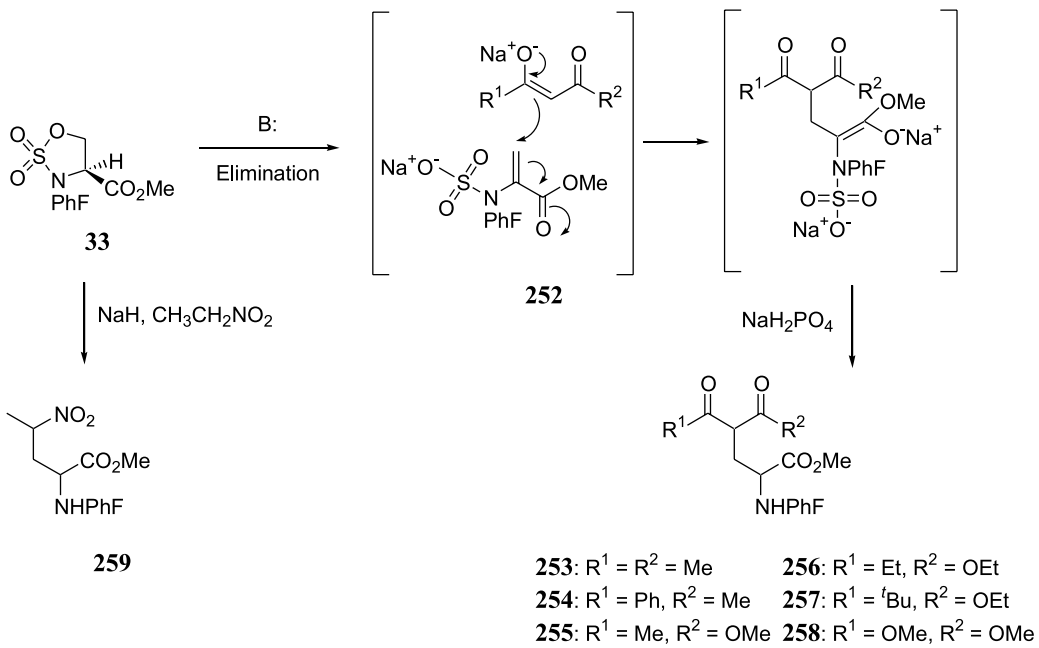
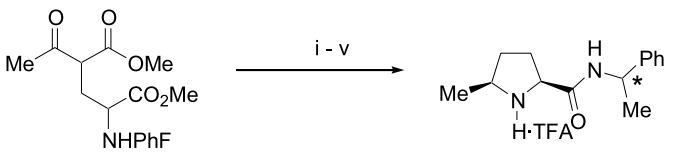


Figure 43. Proposed mechanism for the ring opening of sulfamidate **33** using β-keto esters, β-keto ketones, dimethyl malonate and nitroethane.[5]



i) 1) NaOH, EtOH, reflux, 2) MeI, K_2CO_3, CH_3CN; ii) H_2, Pd/C, MeOH, $(Boc)_2O$; iii) $KOSiMe_3$, Et_2O
iv) 10 % TFA, CH_2Cl_2; v) 1) *R*- and *S*-$PhCH(CH_3)NH_2$, TBTU, CH_3CN, 2) 10 % TFA, CH_2Cl_2

Figure 44. Diastereomeric studies of *R*- and *S*-**260**, which were obtained from **255**.[5]

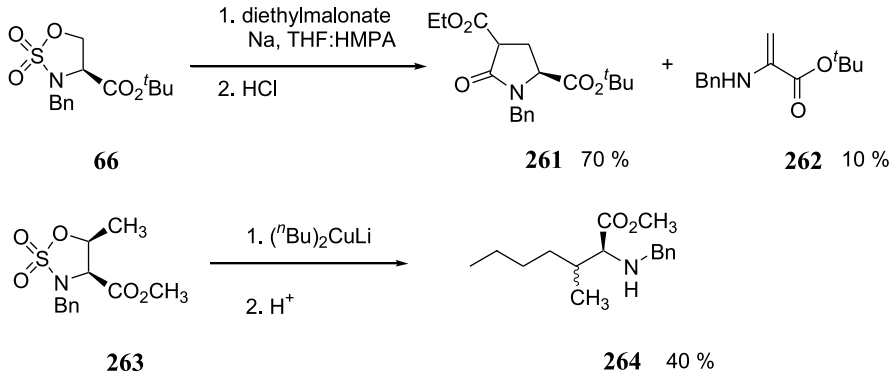


Figure 45. Reaction of serine and threonine derived sulfamidates **66** and **263** with carbon nucleophiles.[4,34]

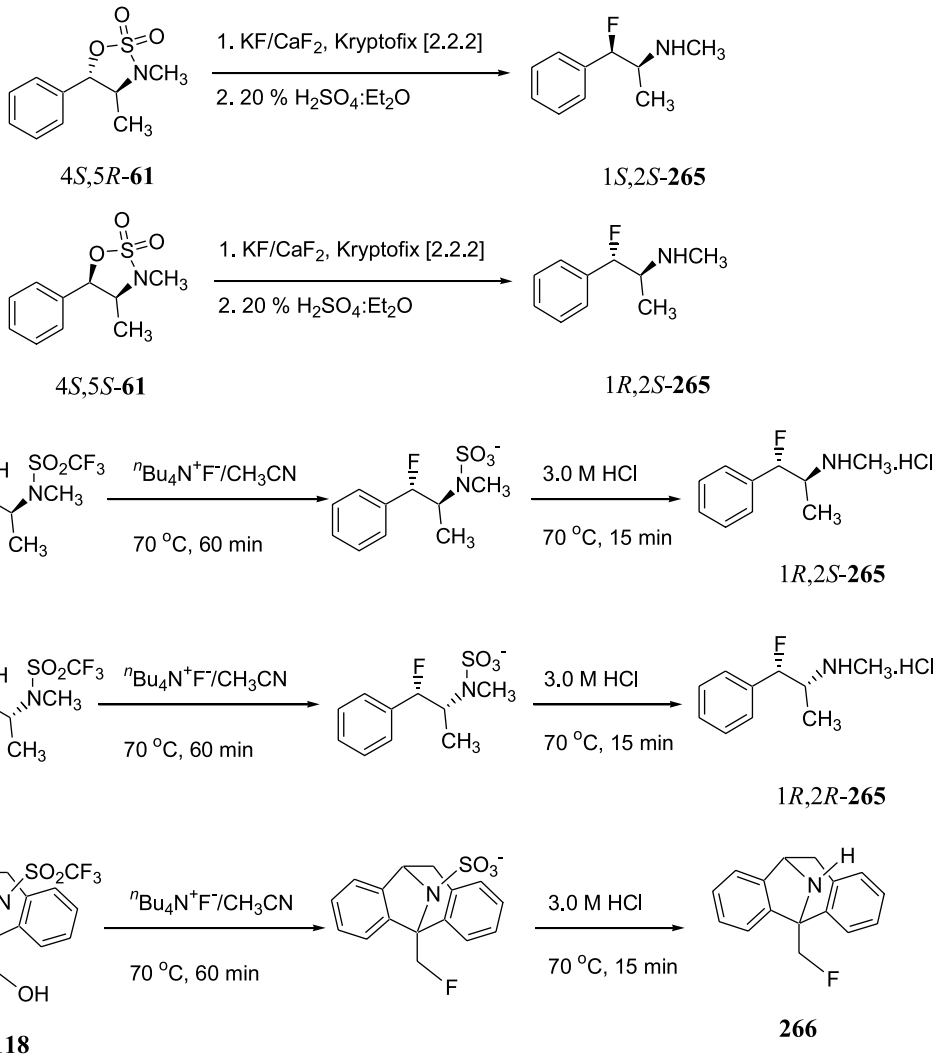


Figure 46. Examples of ring-opening of cyclic sulfamidates using fluoride ion.[10,30,57]

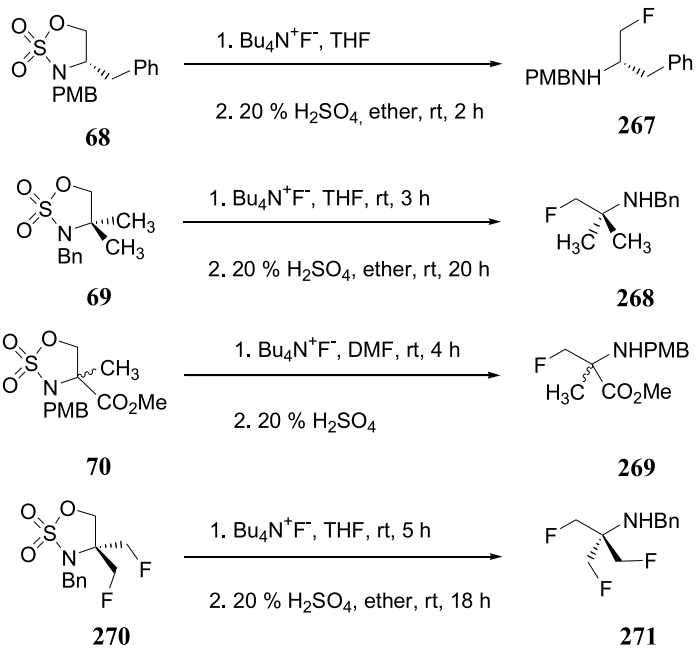


Figure 47. Opening of cyclic sulfamidates using TBAF.[9,29,33]

1*S*,2*S*-**265** in 54 and 63% respective yields.[30] When high specific, no carrier-added [^{18}F]fluoride ion, prepared from irradiation of [^{18}O]H_2O,[57] was used as fluoride source, this stereospecific reaction furnished product in high radiochemical yield.[30] Alternatively, a one-pot procedure featuring in-situ generation and ring-opening of the cyclic-sulfamidate was achieved by treating *N*-trifluorosulfonamide analogs of (−)-ephedrine and (−)-pseudoephedrine with *n*-$Bu_4N^+F^-$ in acetonitrile at 70°C and gave after aq. HCl work-up, the respective fluorides 1*R*,2*S*-**265** and 1*R*,2*R*-**265** in 45 and 30% yields.[10] Using this same one-pot process, the fluorinate version of the non-competitive *N*-methyl-D-aspartate antagonist MK-801 **266** was also synthesized in 71% yield (Fig. 46).[10]

Tetrabutylammonium fluoride has been commonly used to open sulfamidates, such as those derived from *N*-(*p*-methoxybenzyl)phenylalanininol **68**, *N*-benzyl-2-amino-2-methyl-1-propanol **69**[9,29] and α-methyl-*N*-(*p*-methoxybenzyl)serine methyl ester **70**,[33] which at room temperature in THF and DMF as polar solvent gave the corresponding fluorides **267**–**269** in 61–77% yields, typically after acidic hydrolysis of the sulfamic acid intermediate and purification on silica gel. Similarly, *N*-benzyl-tri(fluoromethyl)methylamine **271** was synthesized in 92% yield on ring opening of the corresponding sulfamidate **270** with *n*-$Bu_4N^+F^-$ in THF at room temperature (Fig. 47).[29]

On the other hand, attempts to ring open the cyclic-sulfamidate derived from *N*-(PhF)serine methyl ester **33** with *n*-$Bu_4N^+F^-$ in DME at room temperature failed to provide the corresponding fluoride; instead, *N*-PhF-dehydroalanine methyl ester **153** was detected as the major product.[5] Similarly, 4,4,5-trimethylsulfamidate **209** was observed by ^{1}H NMR spectroscopy to eliminate to benzyl-(1,1-dimethyallyl)-amine **272** on treatment with TBAF in CD_3CN at 80°C (Fig. 48).[54]

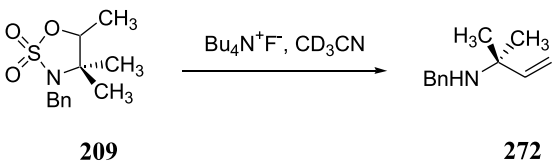


Figure 48. Elimination from the reaction of **209** with TBAF.[54]

4.3. *N*-Deprotection and protection of cyclic sulfamidates

Several nucleophiles can remove *N*-acyl and sulfonyl residues from sulfamidates such as **56** and **111**. For example, sodium imidazolate attacked rapidly the *N*-acetyl group of D-allosamine derived sulfamidate **115** in THF to furnish its deacetylation product sulfamidate **158** in 94% yield (Fig. 29).[7] 3-*N*-Toluenesulfonyl-1,2,3-benzoxathiazole 2,2-dioxide **56** was *N*-deprotected to cyclic sulfamidate **273** and toluenesulfonyl fluoride in 93 and 87% yields respectively, using KF in aq. acetonitrile;[27] its 5-nitro analog **111** reacted similarly to provide a 81% yield of cyclic sulfamidate **185** (Fig. 49).[51] 5-Nitro 3-*N*-toluenesulfonyl-1,2,3-benzoxathiazole 2,2-dioxide **111** was also *N*-deprotected in 53–86% yields by the action of imidazole, azide ion, benzyl and *tert*-butyl amines in acetonitrile (Fig. 39).[51]

Reactions on the nitrogen substituent of 3-*N*-toluenesulfonyl-1,2,3-benzoxathiazole 2,2-dioxide **56** have been

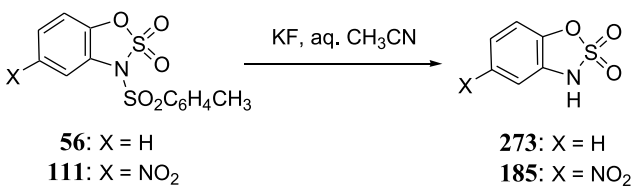


Figure 49. Removal of *N*-tosyl group from sulfamidates **56** and **111** using KF.[27,51]

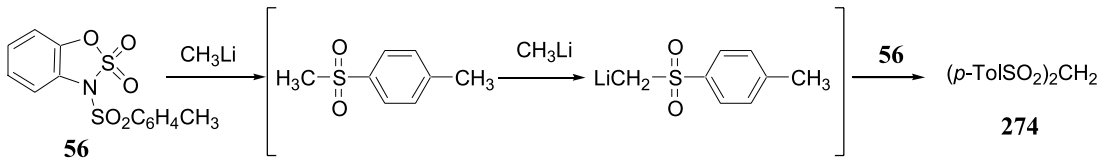


Figure 50. Methyllithium reacts with **56** to give bis-(*p*-tolylsulfonyl)methane.[27]

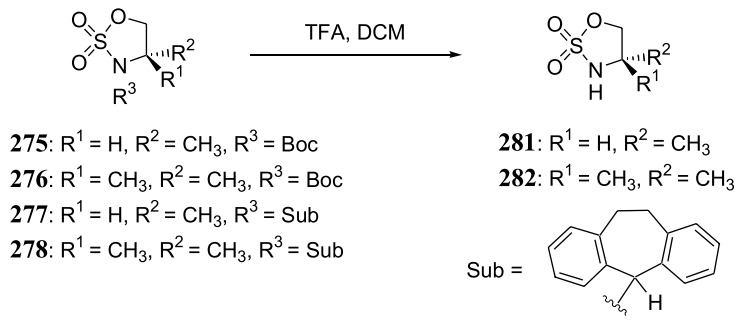


Figure 51. Removal of Boc and Sub groups from cyclic sulfamidates **275**–**278**.[58]

observed with methyllithium and phenyllithium; however, the *N*-deprotected sulfamidate was not recovered. Bis-(*p*-tolylsulfonyl)methane **274** was isolated with MeLi in 49% yield, presumably by attack of the exocyclic sulfonyl group to form *p*-tolyl methyl sulfone which after deprotonation served to attack a second molecule of **56** (Fig. 50).[27] Phenyllithium reacted with **56** to give *p*-tolyl phenyl sulfone in 78% yield.

N-*tert*-Butyloxycarbonyl and *N*-(5-dibenzosuberyl) five-membered cyclic sulfamidates **275**–**278** possessing 4-methyl and 4,4-dimethyl substituents were *N*-deprotected in 73–90% yields by trifluoroacetic acid in dichloromethane (Fig. 51).[58]

N-Alkylation of 1,2,3-benzoxathiazole 2,2-dioxide **273** (Fig. 49) was accomplished in 48% yield with NaH and MeI in THF at 0°C.[27] Using 5 mol% of $BnBu_3NCl$ as catalyst, 4-methyl and 4,4-dimethyl sulfamidates **281** and **282** were alkylated in 76 and 93% respective yields with BnBr in aq. NaOH/DCM at room temperature.[58] With less reactive electrophiles, the Mitsunobu reaction proved the most effective means for *N*-alkylation with sulfamidates **281** and **282**. For example, 3-phenylpropanol reacted with **281** and **282** in the presence of diisopropyl azodicarboxylate and triphenylphosphine in acetonitrile or THF to furnish *N*-(phenylpropanyl)sulfamidates **284** and **285**, respectively, in 43 and 89% yields (Fig. 52).[58]

N-Acylation of six- and seven-membered sulfamidates **286**–**289** has been achieved with CbzCl using sodium *t*-butoxide and triethylamine as base respectively to produce **290**–**293** (Fig. 53).[12,14]

The one pot construction of 2-substituted morpholines from heating 1,2,3-oxathiazolidine-2,2-dioxide with alkyl substituted epoxides and NaOH at 50°C in MeOH involves initial *N*-alkylation with epoxide ring-opening followed by intramolecular nucleophilic attack by the resulting alkoxide onto the sulfamidate.[59] Thienyloxymethylmorpholines **294**–**300** were synthesized in 38–53% yields by this process in DMSO and later evaluated as potential antidepressant drugs (Fig. 54).[11] Similarly, *N*-alkylation of 3-phenyl-1,2,3-thiazolidine-2-oxide **25** by a second

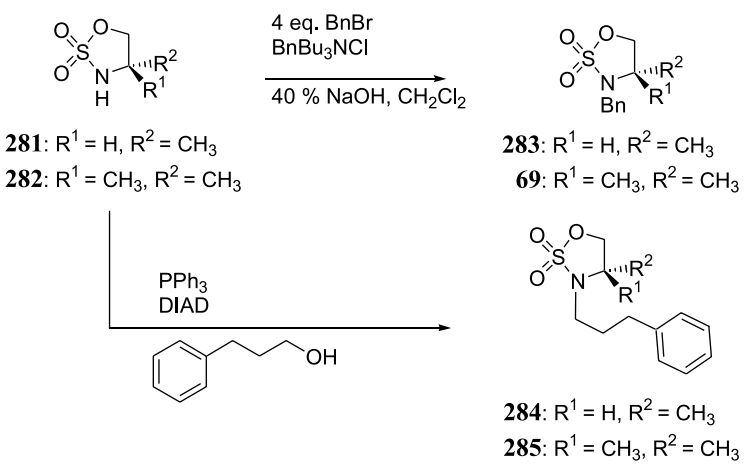


Figure 52. *N*-Alkylation of cyclic sulfamidates **281** and **282**.[58]

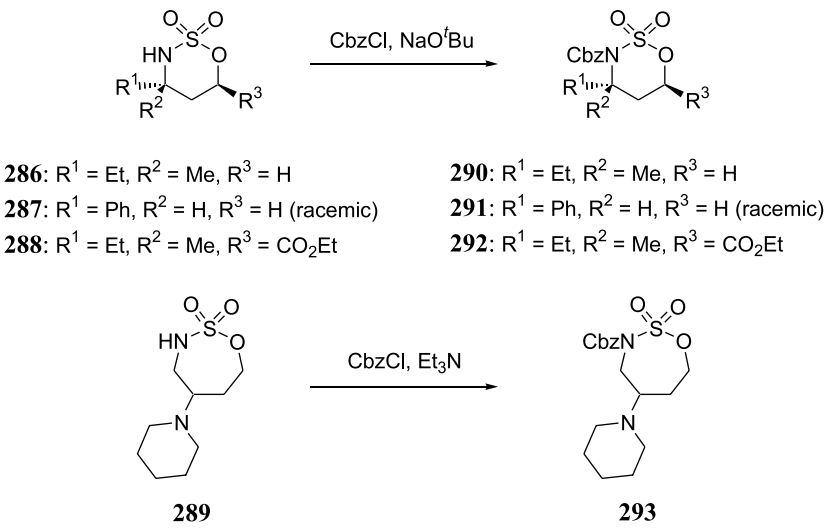


Figure 53. *N*-Acylation of six- and seven-membered sulfamidates.[12,14]

molecule of this cyclic sulfamidite is likely the first step in the formation of *N*,*N*′-diphenylpiperazine in 6% yield from thermolysis at reflux in xylene (Fig. 54).[19]

4.4. Hydrolysis of the sulfamic acid

Protic and Lewis acid conditions have been employed in the hydrolysis of the sulfamic acid intermediate generated from nucleophilic opening of sulfamidate. Protic acids, such as HCl,[12,14,27,52] H_2SO_4[6,7,9,29,31,33,34,38,53] and NaH_2PO_4[5,35,60] have been commonly employed in the hydrolysis step. The NaH_2PO_4 conditions feature a weaker (pK_a 7.2) acid and have been used after reactions with *N*-(PhF)sulfamidates.[5,35,60] In general, the sulfamic acid-containing reaction mixture may be evaporated to dryness, dissolved in an organic solvent and treated with the mineral acid, or alternatively, directly partitioned between an organic solvent (Et_2O, EtOAc, EtOH or DCM) and an aq. solution of the mineral acid. Representative systems include: 20% aq. H_2SO_4/Et_2O; 2N aq. HCl/EtOH; 1 M NaH_2PO_4/DME. The mechanism of the reaction of sulfamic acids with aq. mineral acid has been reviewed and proceeds by attack of water at sulfur prior to S–N bond cleavage.[15]

Application of boron trifluoride as a Lewis acid in the presence of a nucleophilic thiol has allowed sulfamic acid cleavage without aqueous solvent.[55] For example, sulfamic acid intermediates **301**–**306**, produced from amine openings of sulfamidate **212** from *N*-(benzyl)serine ethyl ester, were converted to diamines **233**, **213**, **214**, **307**–**309** using $BF_3{\cdot}Et_2O$ and *n*-PrSH in DCM at 0°C (Fig. 55).[55] Attempts to perform the hydrolysis with aqueous mineral acids produced multiple products, presumably because of the reactivity of the ester function.[55] Similar conditions

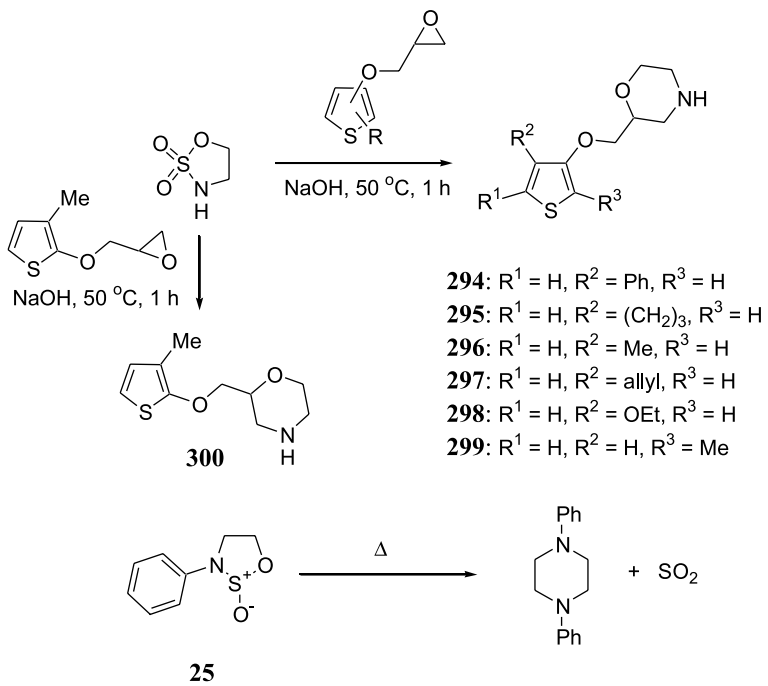


Figure 54. Synthesis of 2-substituted morpholines **294**–**300** and *N*,*N*′-diphenyl-piperazine.[11,19]

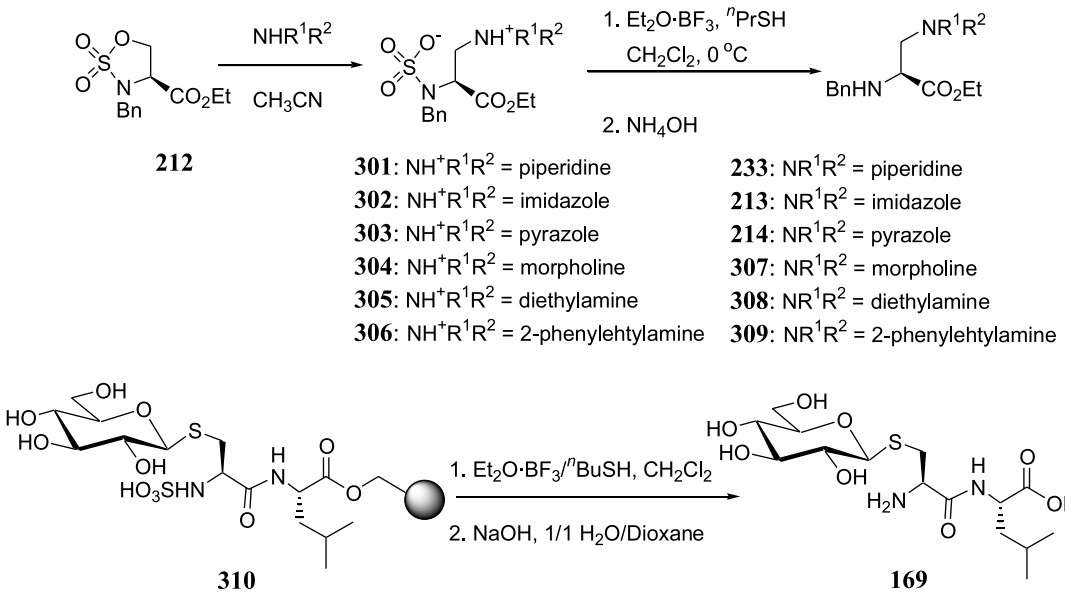


Figure 55. Hydrolysis of sulfamic acids using $BF_3{\cdot}Et_2O$ and *n*-PrSH.[8,55]

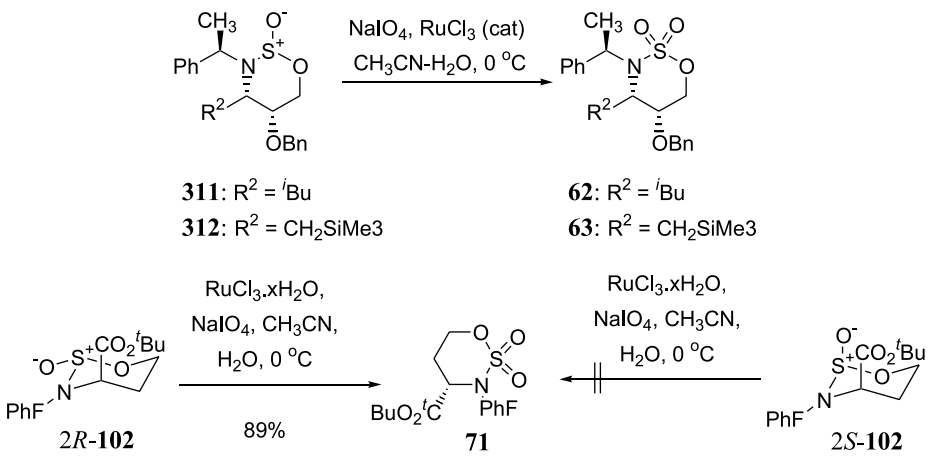


Figure 56. Synthesis of six-membered cyclic sulfamidates **62**, **63** and **71**.[32,35]

($BF_3{\cdot}Et_2O$ and *n*-BuSH in DCM at room temperature) have also been used to convert resin-bound sulfamic acid **310** to the corresponding amine **169** of high purity (Fig. 55).[8]

A suspect procedure that has generated considerable discussion involves treatment of the sulfamic acid intermediate with aq. 2N NaOH and heating to 90°C for 1 h,[39] because ordinary sulfamic acids have been suggested to be stable to dilute aq. base.[61] This procedure was reported to be successful after ring opening of prolinol-derived sulfamidate **239** with MeOH or alkyl amines in $CHCl_3$ containing a drop of trifluoroacetic acid; however, the application of excess amine (2.5–10 equiv.) and protic nucleophiles like MeOH in $CHCl_3$ containing catalytic TFA was later shown to effect sulfamic acid hydrolysis.[52,55] Thus, the NaOH treatment may have likely had no effect on these reaction mixtures. Moreover, the conflicting reports on the reactivity of *R*- and *S*-prolinol-derived sulfamidate **113** with organometallic reagents may be due to the inability of the NaOH conditions to effect hydrolysis of the sulfamic acid in the case when no reactivity was reported with the former,[39] because 38–62% yields of substitution products were isolated from the later after hydrolysis of the sulfamic acid with 2N HCl in EtOH.[52]

5. Six-membered cyclic sulfamidates

5.1. Synthesis of six-membered cyclic sulfamidates

As mentioned, six-membered cyclic sulfamidates **62**, **63**

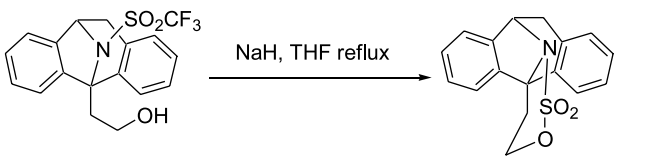
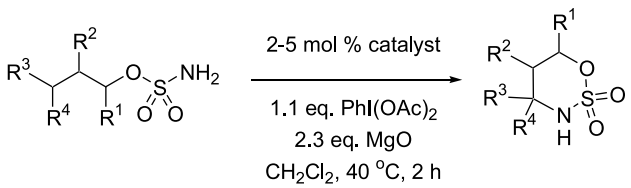
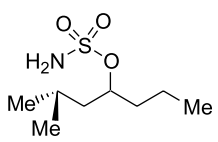
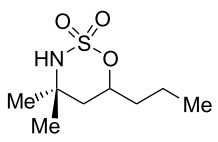
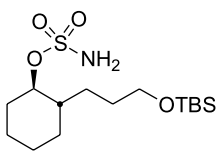
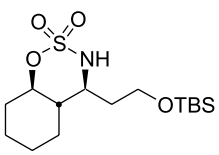
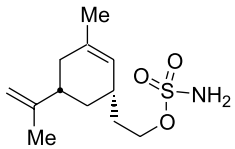
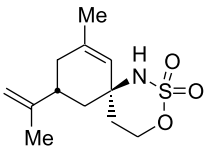
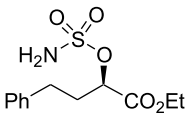
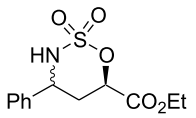
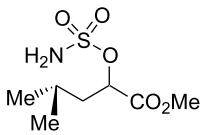
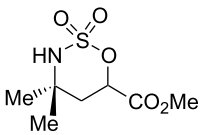
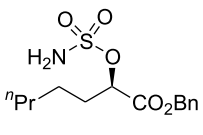
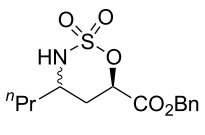
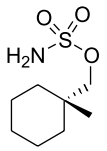
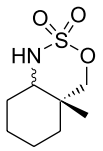
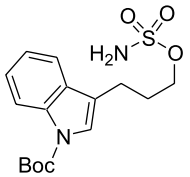
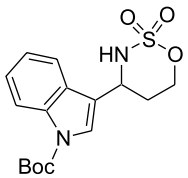


Figure 57. Synthesis of six-membered cyclic sulfamidate **314**.[10]

and **71** have been synthesized by oxidation of their corresponding sulfamidites **311**, **312** and 2*R*-**102**.[32,35] Oxidation of the major (2*R*,4*S*)-*N*-(PhF)sulfamidite 2*R*-**102** with catalytic ruthenium trichloride and sodium periodate in acetonitrile and water at 0°C afforded sulfamidate **71** in 89% yield. On the other hand, treatment of the minor (2*S*,4*S*)-sulfamidite 2*S*-**102** under the same conditions gave no oxidation product **71** and the starting material was recovered unchanged, presumably because the $S^{+}-O^{-}$ group sits in an axial position and access of the oxidant to the sulfur was blocked by the equatorial PhF group (Fig. 56).[35]

Table 7. Six-membered cyclic sulfamidate synthesis by oxidative cyclization of sulfamate esters[12]



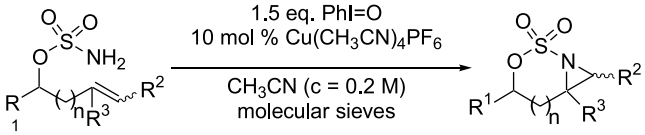
Catalyst=$Rh_2(OAc)_4$		Catalyst=$Rh_2(Oct)_4$	
Substrate	Product (% Yield)[a]	Substrate	Product (% Yield)[a]
 **315**	 **323** (90)	 **320**	 **328** (75)
 **316**	 **324** (80)	 **321**	 **329** (91, 13:1 syn/anti)
 **317**	 **325** (86)	 **322**	 **330** (78, 4:1 syn/anti)
 **318**	 **326** (85, 8:1 cis/trans)		
 **319**	 **327** (78)		

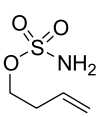
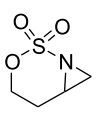
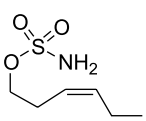
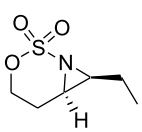
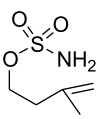
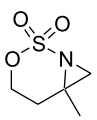
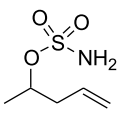
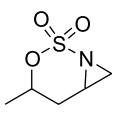
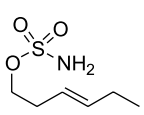
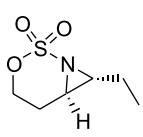
Six-membered cyclic sulfamidate **314** was synthesized by treatment of the *N*-trifluorosulfonamide **313** with NaH in THF at reflux (Fig. 57).[10]

Intramolecular amination of saturated C–H bonds has provided a series of six-membered cyclic sulfamidates from primary and secondary alcohols (Table 7, Fig. 26).[12] Condensation of the alcohol and sulfamoyl chloride ($ClSO_2NH_2$) with pyridine in dichloromethane furnished the respective sulfamates **315**–**322** and **146** in 65–75% yield. Selective γ-C–H insertion, to provide the 2,2-dioxo-tetrahydro-1,2,3-oxathiazines **323**–**330** and **147**, was accomplished in 75–90% yield using $PhI(OAc)_2$, MgO and a rhodium catalyst (2 mol% of $Rh_2(OAc)_4$ or $Rh_2(oct)_4$) in CH_2Cl_2 at 40°C. This reaction, which was suggested to proceed by a chair-like transition state, had a 4 to >20:1 preference for the 1,3-*syn*-diastereomer when the alcohol was situated near a chiral center. In the case of conformationally rigid substrate **316** the insertion reaction proceeded stereospecifically, and could be used to generate quarternary stereocenters.

Intramolecular aziridination of olefins has provided a series of 6,3-fused bicyclic sulfamidates **336**–**340**, from various homoallylic alcohols.[14] The unsaturated sulfamates **331**–**335** were synthesized in 80–95% yields on treatment of the alcohol with 200 mol% of $ClSO_2NH_2$ in dimethylacetamide.[62] Aziridination was then performed using 10 mol% of $Cu(CH_3CN)_4PF_6$ and PhI=O in acetonitrile (c=0.2 M) containing molecular sieves. This one pot procedure proved better yielding when isolation of the iminoiodinane intermediate was avoided, such that 3,6-fused sulfamidates **336**–**340** were obtained in 53–94% yields. Although no facial selectivity was observed in the aziridination of the olefin, the geometry of the starting olefin was retained in the aziridine products (Table 8).

Table 8. Intramolecular copper-catalyzed olefin aminations[62]



Substrate	Product (% Yield)	Substrate	Product (% Yield)
 **331**	 **336** (69)	 **334**	 **339** (80)
 **332**	 **337** (53)	 **335**	 **340** (72)
 **333**	 **338** (94)		

5.2. Nucleophilic ring-opening of six-membered cyclic sulfamidates

5.2.1. Ring-opening of six-membered cyclic sulfamidates with sulfur nucleophiles. Thiophenol failed to react with *N*-(PhF)homoserine sulfamidate **71** in acetonitrile at 75°C for 30 h and starting material was recovered. Sodium thiophenolate reacted with sulfamidate **71** in DMF at 60°C to provide *S*-phenylhomocysteine **341** in 56% yield.[35] With the more electron deficient, less sterically bulky six-membered *N*-(Cbz)sulfamidate **291**, thiophenol reacted efficiently using K_2CO_3 in acetonitrile providing thioether **342** in 95% yield.[12] 6,3-Bicyclic sulfamidate **336** was shown to react with PhSH in the presence of $BF_3{\cdot}Et_2O$ in chloroform at 0°C to provide seven-membered cyclic sulfamidate **343** in 52% yield from nucleophilic attack at the ring-fusion carbon with cleavage of the S–N bond. Relief of ring strain has been suggested to account for the unusual reactivity of bicyclic sulfamidate **336** which undergoes nucleophilic attack with displacement of nitrogen instead of substitution at the oxygen-bearing carbon (Fig. 58).[14]

Potassium thiocyanate reacted with **71** in acetonitrile at 75°C to give 68% yield of *S*-cyanohomocysteine **344**

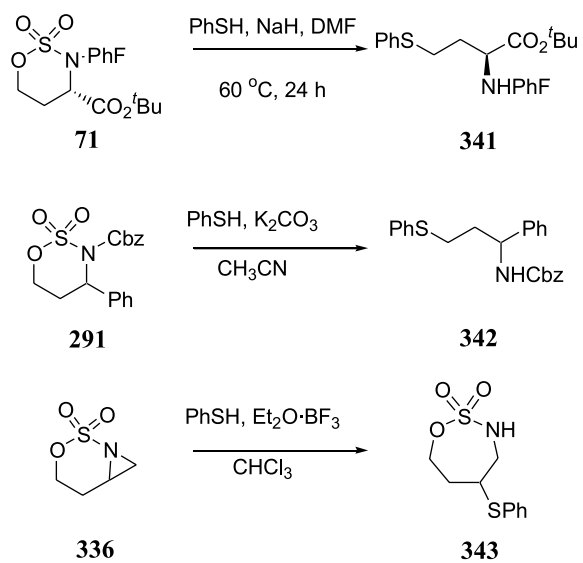


Figure 58. Reaction of six-membered cyclic sulfamidates with thiophenol.[12,14,35]

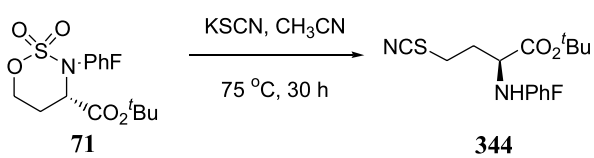


Figure 59. Reaction of **71** with KSCN.[35]

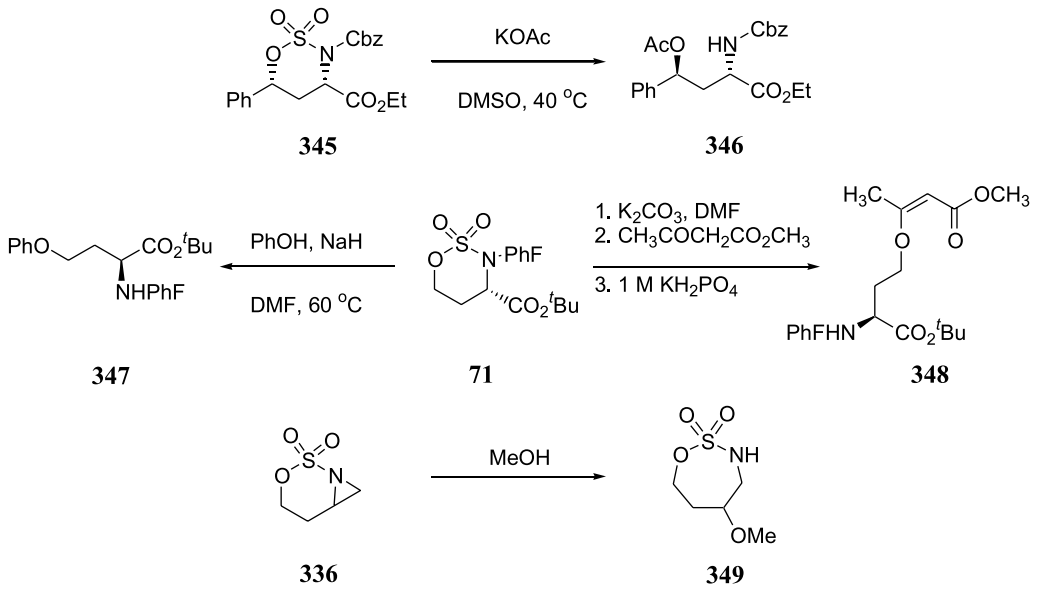


Figure 60. Reaction of six-membered cyclic sulfamidates with oxygen nucleophiles.

(Fig. 59).[35] Attempts to open sulfamidate **71** with benzylthiolate ion failed to provide the corresponding *S*-benzylhomocysteine and analysis of the crude reaction mixture indicated sulfamidate decomposition.[35] Preliminary results thus indicate that attack on the γ-carbon of six-membered cyclic-sulfamidates with sulfur nucleophiles varied with the pK_a of the corresponding thiol such that better yields of thioether were obtained using the conjugate bases of more acidic thiols. This may be due to competitive attack on sulfur by the more alkaline nucleophiles.

5.2.2. Ring-opening of six-membered cyclic sulfamidates with oxygen nucleophiles. Potassium acetate reacted with *N*-(Cbz)sulfamidate **345** in DMF at 40°C to give acetate **346** in 86% yield.[12] Sodium phenolate reacted with six-membered *N*-(PhF)homoserine derived sulfamidate **71** in DMF at 60°C to provide *O*-phenylhomoserine **347** in 56% yield.[35] Methyl acetoacetate reacted with potassium carbonate and **71** in DMF to provide, after hydrolysis with 1 M KH_2PO_4 and chromatography enol ether **348** in 65% yield. The formation of enol ether **348** was verified by its conversion to the trifluoroacetate of homoserine on treatment with trifluoroacetic acid in CH_3CN/H_2O.[63] Alternatively, the related *O*-alkylhomoserine could not be isolated from treatment of **71** with methoxide; instead, cursory analyses of the reaction mixture indicated decomposition of sulfamidate **71**. The remarkable reactivity of bicyclic sulfamidate **336** was further demonstrated by its solvolysis in methanol which produced seven-membered sulfamidate ether **349** in 69% yield (Fig. 60).[14]

5.2.3. Ring-opening of six-membered cyclic sulfamidates with nitrogen nucleophiles. As observed with the five-membered sulfamidates, azide ion reacts effectively with the six-membered sulfamidate analogs. For example, six-membered *N*-PhF- and *N*-Cbz-sulfamidates **71** and **345** have been respectively ring-opened with sodium azide in DMF at 60°C and in DMSO at room temperature to furnish azides **351** and **352** in 83 and 96% yields.[12,35] Sterically hindered, 3-benzyl-5,5-dimethyl-1,2,3-oxathiazolidine-2,2-dioxide **350** reacted with NaN_3 in DMF at 100°C to furnish 52% yield of azide **353**.[54] Bicyclic sulfamidate **336** was converted to seven-membered sulfamidate **354** in 79% yield using trimethylsilylazide and tetrabutylammonium fluoride in THF (Fig. 61).[14]

Nitrogen protection with $(Boc)_2O$ in pyridine followed by ring opening of cyclic sulfamidate **355** with NaN_3 in DMF gave 92% yield of the corresponding azide **356**. Orthogonally protected β-carbamato azide **356** has served as a key intermediate in the total synthesis of the bromopyrrole alkaloid manzacidin A **357** (Fig. 62).[64]

To open *N*-(PhF)homoserine-derived sulfamidate **71**, imidazole and morpholine were initially employed with

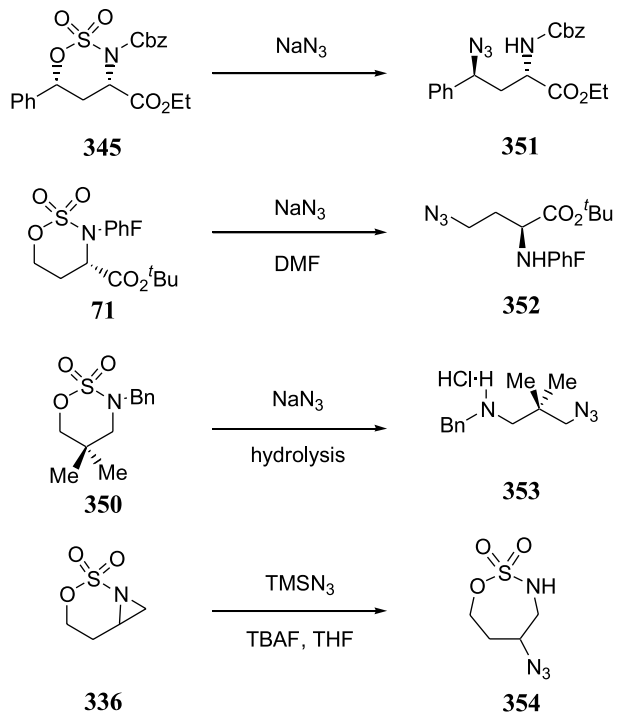


Figure 61. Reaction of cyclic sulfamidates with azide ion.[12,14,35,54]

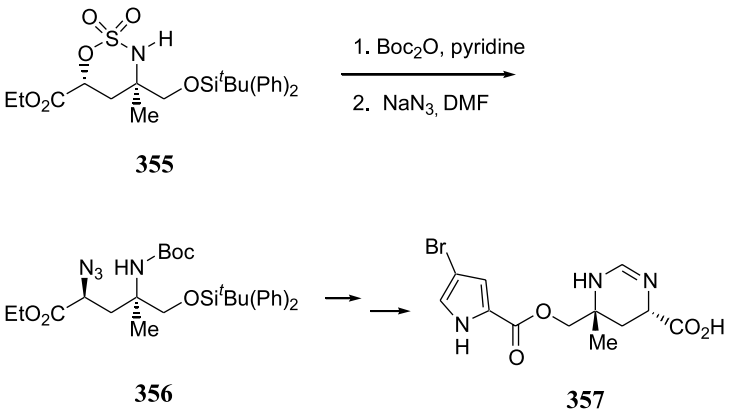


Figure 62. Nucleophilic opening of sulfamidate **355** is a key step in the synthesis of manzacidin A **357**.[64]

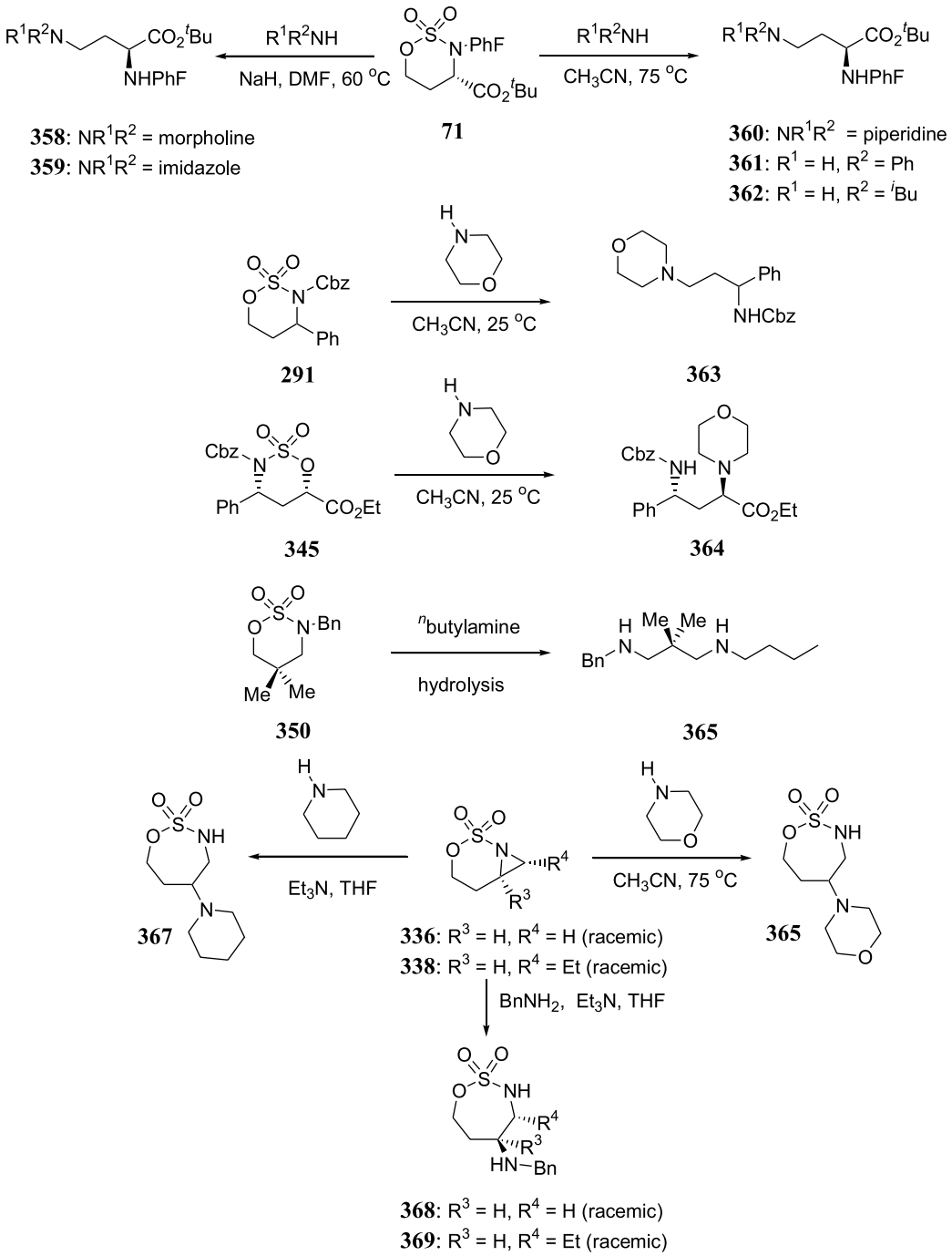


Figure 63. Opening of cyclic sulfamidates with nitrogen nucleophiles.[12,14,35,54]

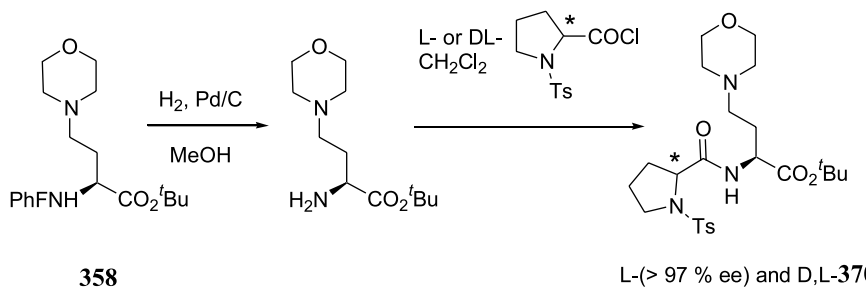


Figure 64. Enantiomeric purity study of morpholine adduct **358**.[35]

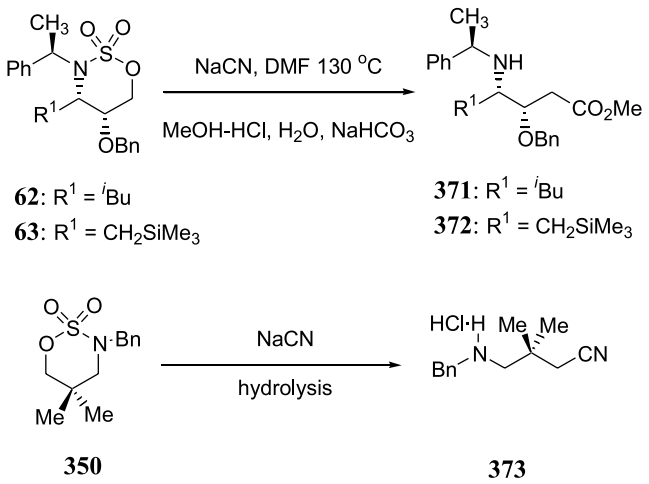


Figure 65. Opening of cyclic sulfamidates using cyanide ion.[32,54]

NaH in DMF at 60°C and furnished α,γ-diamino esters **358** and **359** in 50 and 85% yields.[35] Higher yields (65–95%) and cleaner products were later obtained in the absence of NaH when amines (imidazole, morpholine, piperidine, *i*-butylamine and aniline) were heated with **71** in acetonitrile at 70°C for 30 h. The more reactive *N*-(Cbz)sulfamidates **291** and **345** reacted respectively with morpholine in acetonitrile at room temperature and in DMSO at 40°C to afford diamines **363** and **364** in 88 and 80% yields.[12] *N*-Benzyl 5,5-dimethylsulfamide **350** was unchanged after heating in neat *sec*-butyl amine at reflux for 8 days; in contrast, the less bulky *n*-butylamine reacted under similar conditions to give 61% yield of diamine **365**.[54] Bicyclic sulfamidate **336** reacted with morpholine in acetonitrile at 75°C to afford the seven-membered cyclic sulfamidate **366** in 55% yield.[14] By using triethylamine in THF, improved yields were obtained in the attack of pyrrolidine and benzylamine at the ring-fusion carbon of bicyclic sulfamidates **336** and **338** to furnish seven-membered cyclic sulfamidates **367**–**369** in 80–86% yields (Fig. 63).[14]

The enantiomeric purity of morpholine adduct **358**, obtained from conditions in the presence of NaH, was examined after its conversion to L- and DL–*N*-(toluenesulfonyl)prolylamides **370** by hydrogenolytic cleavage of the PhF group and acylation with L- and DL-prolyl chloride and Et_3N in CH_2Cl_2 for 1 h.[35] After aqueous washes and evaporation of the organic phase, the diastereomic *tert*-butyl ester signals at 1.48 and 1.57 ppm were measured in C_6D_6 at 400 MHz which demonstrated amide L-**370** to be of >97% diastereomeric purity (Fig. 64). Hence, γ-substituted α-*N*-(PhF)amino esters and their deprotection products, all are presumed to be of >97% enantiomeric purity.

5.2.4. Ring-opening of six-membered cyclic sulfamidates with carbon nucleophiles. Sodium cyanide was used to open six-membered sulfamidates **62**, **63** and **350** in DMF at 100–130°C.[32,54] With the former two, concurrent hydrolysis of the sulfamic acids and nitrile functions with MeOH·HCl provided methyl esters **371** and **372** in 67 and 65% yields, respectively (Fig. 65). *N*-Benzyl 5,5-dimethylsulfamidate **350** was opened at the neopentyl carbon using cyanide ion in DMF at 100°C to obtain **373** in 44% yield (Fig. 65).[54]

N-(PhF)homoserine derived sulfamidate **71** reacted with a premixed solution of ethyl pivaloylacetate and NaH in DME followed by heating at reflux for 72 h. Hydrolysis of the sulfamic acid and chromatography furnished β-ketoester **374**, which on hydrolysis and decarboxylation with sodium hydroxide in ethanol at reflux provided (2*S*)-*tert*-butyl 7,7-dimethyl-6-oxo-4(ethyloxycarbonyl)-2-[*N*-(PhF)amino]-octanoate **375** in 19% overall yield (Fig. 66).[63]

5.2.5. Ring-opening of six-membered cyclic sulfamidates with halogen nucleophiles. In the synthesis of *N*-methyl-D-aspartate receptor antagonists, nucleophilic ring opening of six-membered sulfamidate **314** was reported to proceed by heating with tetrabutylammonium fluoride in CH_3CN at 70°C to furnish both the displacement product dibenzo[*a*,*d*]cycloalkenimine **376** and vinyl elimination product **377** (Fig. 67).[65]

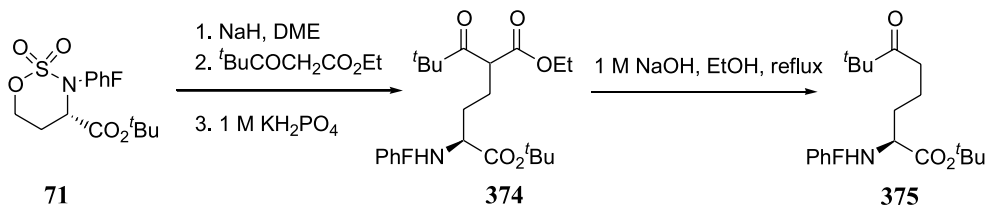
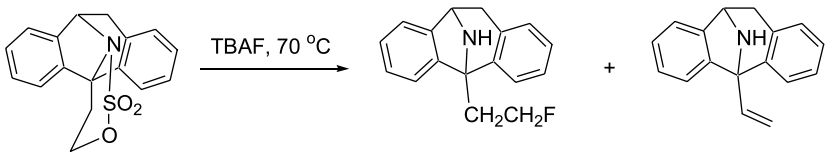
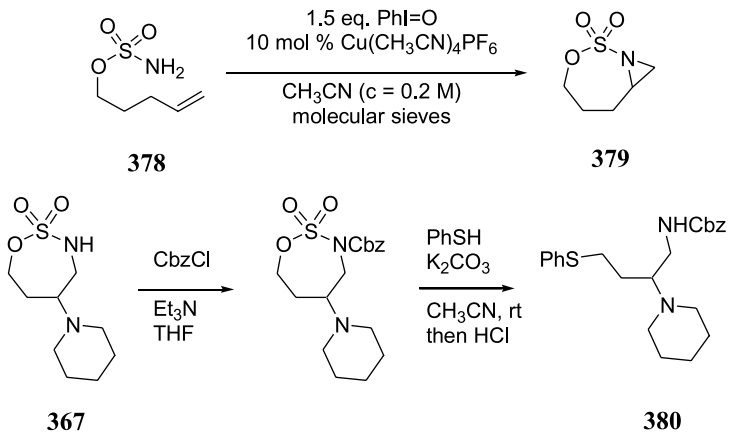


Figure 66. C-alkylation of **71** with β-ketoester **375**.[63]



314 **376** **377**

Figure 67. Reaction of cyclic sulfamidate **314** with TBAF.[65]



378 **379** **367** **380**

Figure 68. Synthesis and ring opening of seven-membered cyclic sulfamidates.[14]

6. Seven-membered cyclic sulfamidates

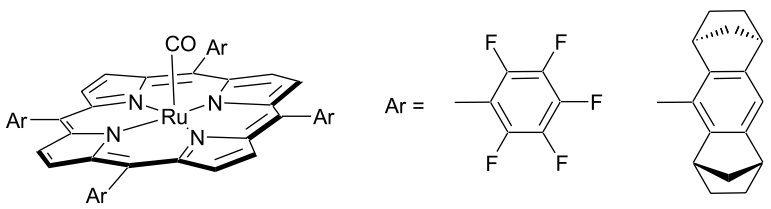
As mentioned above, nucleophilic attack of 6,3-fused bicyclic sulfamidate **336** with thiophenol, methanol, azide and amines, all furnished the corresponding seven-membered cyclic sulfamidates **343**, **348**, **354**, **366**–**368**.[14] Furthermore, intramolecular aziridation of sulfamidate **378**, derived from 4-pentene-1-ol, using catalytic $Cu(CH_3CN)_4$-PF_6 and PhI═O in acetonitrile furnish 3,7-fused sulfamidate **379** in 50% yield. Ring opening of piperidino sulfamidate **367** was achieved, after *N*-acylation with benzyloxychloroformate and triethylamine in THF, by nucleophilic attack with thiophenol and potassium carbonate in acetonitrile to afford, after hydrolysis of the sulfamic acid with aq. HCl, diamino thioether **380** in 42% overall yield (Fig. 68).[14]

7. Concluding remarks

Their ability to serve in selective activation and judicious protection of heteroatomic functional groups makes cyclic sulfamidites and sulfamidates important precursors for the synthesis of alkyl chains bearing sulfur, nitrogen and oxygen functionality. In general, cyclic sulfamidites have proven to be less reactive compared to their sulfamidate counterparts. Alkaline carbon nucleophiles generally add to cyclic sulfamidites at sulfur to furnish sulfonamides and sulfoxides contingent on nitrogen substitution, yet the less basic cyanide ion attacked on the oxygen bearing carbon to provide amino nitrile. In displacements of oxygen in ring-opening reactions at C-5 of cyclic sulfamidites and sulfamidates, nucleophiles such as CN^-, RCO_2^-, N_3^-, F^-, RS^-, the conjugate bases of relatively strong acids reacted better than more alkaline nucleophiles such as organometallic reagents and alkoxides which often caused an elimination reaction. New conditions for adding carbon nucleophiles at C-5 have shown some promise; moreover, attempts to explore the reactivity of carbon nucleophiles with enantiomerically enriched sulfamidites and sulfamidates have revealed their potential configurational lability.

A wide variety of chemically and biologically important molecules have been prepared from cyclic sulfamidites and cyclic sulfamidates. Furthermore, increased application of cyclic sulfamidates in organic synthesis is expected because of the recent introduction of novel methods for their synthesis from common alcohols and diols. Moreover, intramolecular aziridation of remote olefins has given access to fused 6,3-and 7,3-systems possessing a bridging cyclic sulfamidate function such that nucleophiles may be added to the oxygen- and one of the two nitrogen-bearing carbons in order to furnish multi-substituted alkyl amines. In light of these new methods for their preparation and because they have been effectively employed as electrophiles in both solution-phase and solid-phase protocols, cyclic sulfamidates are well suited for application in combinatorial processes for generating molecular diversity. After summarizing the past hundred years of cyclic sulfamidite and cyclic sulfamidate chemistry in this review, we are confident that such useful building blocks will continue to demonstrate their effectiveness in versatile applications in the future.

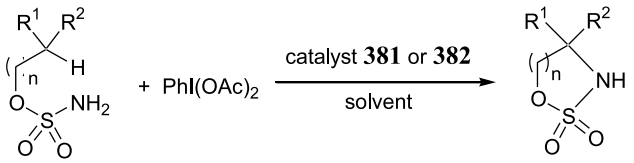
During preparation of the review, diastereo- and enantioselective amidation of saturated C–H bonds was achieved using electron-deficient ruthenium porphyrin catalysts **381** and **382** to provide five- and six-membered cyclic sulfamidates (Fig. 69, Table 9).[66] As observed in Rh-catalyzed intramolecular C–H insertions, six-membered



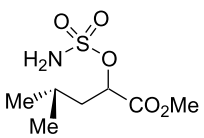
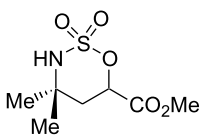
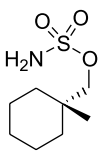
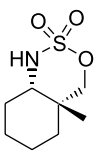
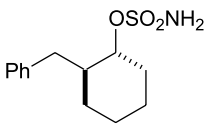
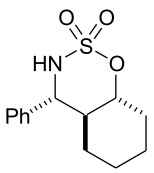
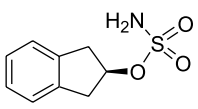
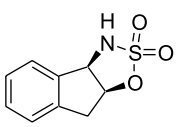
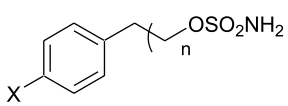
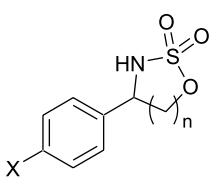
381 **382**

Figure 69. Electon-deficient ruthenium porphyrin catalysts employed in stereoselective cyclic sulfamidate syntheses.[66]

Table 9. Ru-catalyzed intramolecular amidation of sulfamate esters[12,66]



n = 1, 2

Substrate	Product	Catalyst	Solvent (°C)	Yield (%)	*ee* (%)
 **317**	 **325**	**381**	CH_2Cl_2 (40°C)	76	
 **318**	 **326**	**381**	CH_2Cl_2 (40°C)	88	
 **387**	 **392**	**381**	CH_2Cl_2 (40°C)	88	
 **146**	 **147**	**382**	C_6H_6 (80°C)	53	81
		**382**	C_6H_6 (5°C)	39	82
383; X=H, *n*=1	**388**; X=H, *n*=1	**382**	C_6H_6 (80°C)	43	82
		382	C_6H_6 (5°C)	35	87
384; X=H, *n*=2	**389**; X=H, *n*=2	**382**	C_6H_6 (80°C)	63	79
		382	C_6H_6 (5°C)	48	84
385; X=F, *n*=1	**390**; X=F, *n*=1	**382**	C_6H_6 (80°C)	40	80
		382	C_6H_6 (5°C)	20	83
386; X=Br, *n*=1	**391**; X=Br, *n*=1	**382**	C_6H_6 (80°C)	46	78
		382	C_6H_6 (5°C)	31	86

cyclic sulfamidates were isolated unless their formation was prevented as in the cases of **146**, **383**, **385** and **386** which furnished five-membered cyclic sulfamidates **147**, **388**, **390** and **391** in 52–61% yields. With catalyst **381** and $PhI(OAc)_2$, best yields were obtained using Al_2O_3 as inorganic base and DCM as solvent. Higher catalyst efficiency (>300 turnovers) and better diastereoselectivity were observed in the intramolecular amidation with **318** as substrate, which was converted to **326** as a pure *cis*-isomer when Ru-catalyst **381** was employed instead of the 8:1 *cis*/*trans* mixture obtained from the $Rh_2(OAc)_4$ catalyzed reaction. Catalyst **381** also proved more effective and gave higher yields of cyclic sulfamidate than related Fe- and Mn-catalysts as well as other Ru-catalysts possessing non-porphyrin ligands.

Enantioselective intramolecular C–H insertion was achieved on treating substrate with chiral ruthenium porphyrin catalyst **382**, $PhI(OAc)_2$ and Al_2O_3 (in a 1:0.1:1.4:2.5 ratio) in benzene. Product of higher enantiomeric purity (up top 87% ee) was generally obtained when the reaction was performed at 5°C albeit in lower yield. In the case of **147**, the (1*R*,2*S*)-diastereomer was obtained using the (1*S*,4*R*,5*R*,8*S*)-catalyst **382**, as verified by X-ray crystallography. Preliminary attempts to identify the intermediates of the amidation reaction suggested that a bis(imido) species [Ru-(porphyrin)$(NSO_2(OR))_2$] may be involved in this effective approach for converting achiral linear precursors into enantiomerically enriched cyclic sulfamidates.

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Rosa E. Meléndez was born and received her elementary education in El Salvador and in 1990 moved with her family and settled in Nova Scotia, Canada. She received her B.Sc. in 1995 from Saint Mary's University where she performed undergraduate research under the guidance of Professor Michael J. Zaworotko. She completed her graduate studies under the direction of Professor Andrew D. Hamilton and obtained her M.Sc. from the University of Pittsburgh in 1997 and her PhD from Yale University in 2001 for the application of concepts in molecular recognition to self-assembly and organogelation. Presently she is a postdoctoral fellow of the 'Fonds de recherche sur la nature et les technologies' of Québec, in the laboratory of Professor William D. Lubell at the Université de Montréal, Canada. Her current work is in the area of peptide mimicry, in particular the synthesis and conformational studies of azapeptides.

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