Grignard Additions to Cyclic Sulfamidate Imines: Synthesis of N-Substituted Quaternary Sulfamidate Building Blocks

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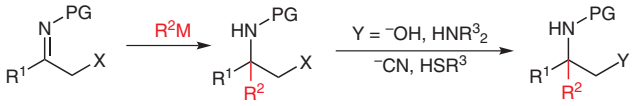
Received 18 January 2010; revised 28 March 2010

Dedicated in memory of Professor Keith Fagnou

Abstract: The addition of Grignard reagents to cyclic sulfamidate imines has been developed as a facile method for the synthesis of N-substituted quaternary sulfamidates. By way of ring opening with an appropriate nucleophile, versatile synthons for 1,2-amino alcohols, 1,2-diamines, and β-amino acids are produced.

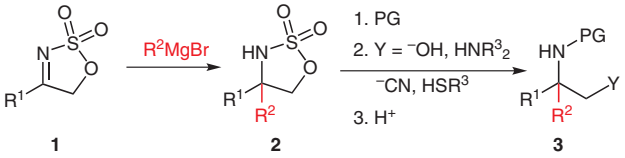
Key words: cyclic imine, Grignard addition, sulfamidate imine, N-substituted quaternary stereocenter

Chiral amines play a fundamental role as building blocks for the synthesis of natural products, drugs, chiral ligands and auxiliaries.[1] Nucleophilic additions of carbon nucleophiles to aldimines and ketimines are powerful methods for the synthesis of chiral nitrogen-substituted tertiary and quaternary stereocenters, respectively (Scheme 1).[2] These amine functional groups, which are synthetically useful on their own, possess greater synthetic value when prepared adjacent to a reactive leaving group or leaving group synthon that could be displaced with nucleophiles such as alkoxides, amines and cyanides to produce 1,2-amino-alcohols, diamines and amino nitriles.[3]



Scheme 1 Addition to imines and α-functionalization

The outcome of nucleophilic addition reaction to imines is often influenced by the presence of enolizable protons, the nature of the imine N-substitution, and the imine *E*/*Z* geometry. Moreover, the utility of the transformation is also affected by the ease with which the imine activating group can be removed after the addition. As part of our efforts to develop methods for the rapid synthesis of chiral amines that can be readily diversified with adjacent heteroatoms, we investigated the potential use of cyclic sulfamidate imines **1**[4] (Scheme 2) in Grignard addition chemistry. The cyclic sulfamidate imine functional group would serve to constrain the imine geometry in addition to activating the imine towards nucleophilic addition. The resultant cyclic sulfamidate products are well known, and have been prepared from amino alcohols and diols,[5] intramolecular amidation[6] and asymmetric intramolecular amidation of sulfamate esters.[7] The advantage of preparing cyclic sulfamidates **2** from their corresponding imines **1** lies in the ability to generate an array of substituted products from a common starting substrate. Once suitably protected, the resulting cyclic sulfamidate could be displaced by a variety of nucleophiles and deprotected under mild acidic conditions.[8] Indeed, the attractiveness of this substrate class has not gone unnoticed: Zhou[4a,b] has demonstrated their use as asymmetric hydrogenation substrates, while Tang[4c] has shown their use as aziridination substrates with sulfur ylides. Blakey has also shown two examples of a seven-membered sulfamidate imine, which was generated by way of a metallonitrene/alkyne metathesis that was trapped in situ with methyl and allyl Grignard reagents.[9]



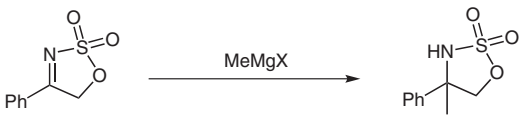
Scheme 2 Addition to cyclic sulfamidate imines

The prerequisite imines **1a** and **1b** were readily prepared in two steps from α-hydroxyacetophenone and acetol, respectively.[6,10] We were pleased to discover that treatment of the cyclic sulfamidate imine **1a** with MeMgCl or MeMgBr at –78 °C afforded the desired addition product, albeit in low HPLC assay yields (31% and 32%, respectively; Table 1, entries 1 and 2).

The yield could be further improved by utilization of MeMgI under identical conditions. A survey of solvents demonstrated the large impact they make on the reaction conversion. Most notably, amongst ethereal solvents, methyl *tert*-butyl ether (MTBE) proved to be far superior to tetrahydrofuran and diethyl ether. Performing the reaction at –22 and 0 °C resulted in improved HPLC yields of 73 and 91%, respectively. Increased amounts of Grignard reagent (2.0 equiv) or substitution of MTBE for dichloromethane under these optimized conditions resulted in a slight decrease in assay yield. Typically, the remaining mass balance in the reactions carried out at low temperature or in diethyl ether and tetrahydrofuran consisted mainly of starting imine. The poor conversion was attributed to competing deprotonation of the starting imine, as

SYNTHESIS 2010, No. 14, pp 2361–2366
Advanced online publication: 05.05.2010
DOI: 10.1055/s-0029-1218778; Art ID: M00310SS

Table 1 Methylmagnesium Halide Addition to Cyclic Sulfamidate Imines



1a **2a**

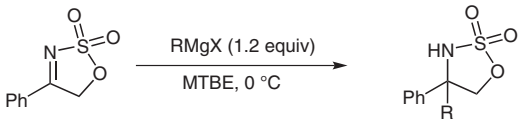
Entry	Solvent	Temp (°C)	Grignard	Equiv	HPLC yield (%)
1	CH_2Cl_2	–78	MeMgCl	1.1	31
2	CH_2Cl_2	–78	MeMgBr	1.1	32
3	CH_2Cl_2	–78	MeMgI	1.1	64
4	toluene	–78	MeMgI	1.1	36
5	THF	–78	MeMgI	1.1	0
6	Et_2O	–78	MeMgI	1.1	21
7	MTBE	–78	MeMgI	1.1	68
8	MTBE	–22	MeMgI	1.1	73
9	MTBE	0	MeMgI	1.2	91
10	CH_2Cl_2	0	MeMgI	1.2	84
11	MTBE	0	MeMgI	2.0	82

evidenced by quenching of the reaction with deuterium oxide. For example, deuterium oxide quench of the reaction between **1a** and MeMgI in tetrahydrofuran at 0 °C provided an 8:1 mixture of mono-deuterated imine **1a** and addition product.

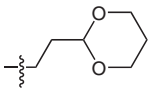
Under the optimized conditions (1.2 equiv Grignard reagent in MTBE at 0 °C), utilization of MeMgBr or MeMgI gave comparable isolated yields of 61 and 67%, respectively (Table 2, entries 1 and 2). As a result of this comparable reactivity, a survey of bromo-Grignard reagents was conducted because of their greater commercial availability in comparison to their iodo-analogues. The reaction proceeded smoothly with the more hindered ethyl and isopropyl Grignard reagents, providing the cyclic sulfamidate products in 84 and 65% yield, respectively. With activated allyl and benzyl Grignard reagents, the addition was also accomplished in good isolated yields (86 and 71%). The acetal-containing Grignard reagent provided the addition product in 69% yield. Interestingly, sp^2 and sp-hybridized carbon nucleophiles such as vinyl, phenyl, and phenyl-ethynyl, reacted poorly (<16% yield). Moreover, no improvement in reactivity was observed upon substitution of PhMgBr for PhMgI. The poor isolated yields for these nucleophiles were also attributed to competing deprotonation of the starting imine substrate. For example, deuterium oxide quench of the reaction described in Table 2, entry 9 provided only mono-deuterated imine **1a**.

We next turned our attention to the cyclic sulfamidate imine derived from acetol **1b**. This imine, like its phenyl counterpart **1a**, reacted smoothly with alkyl Grignard reagents (Me, Et, allyl and benzyl; 65–83% isolated yield, Table 3, entries 1–4). Both sp^2 and sp-hybridized carbon nucleophiles such as phenyl and ethynyl Grignard reagents still reacted poorly (13 and 25% yield, respectively). However, in contrast to imine **1a**, modest yields of addition product could be obtained with vinyl, 4-fluorophenyl and phenylethynyl Grignard reagents (36, 57 and 49% yields, respectively).

Table 2 Grignard Addition to Cyclic Phenyl Sulfamidate Imines

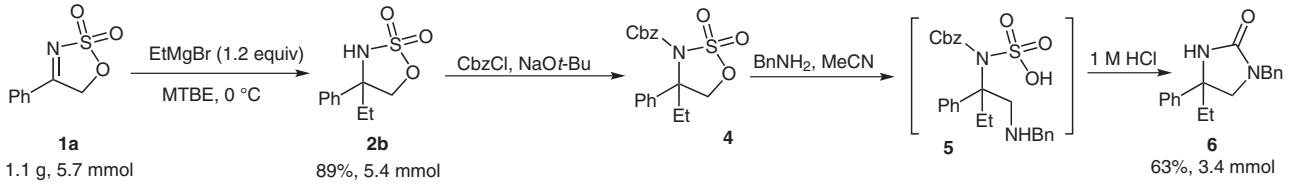


1a **2**

Entry	Product	R	X	Grignard solvent	Isolated yield (%)
1	**2a**	Me	Br	Et_2O	61
2	**2a**	Me	I	Et_2O	67
3	**2b**	Et	Br	Et_2O	84
4	**2c**	*i*-Pr	Br	THF	68
5	**2d**	allyl	Br	Et_2O	86
6	**2e**	Bn	Br	THF	71
7	**2f**		Br	THF	69
8	**2g**	vinyl	Br	THF	16
9	**2h**	Ph	Br	THF	–
10	**2h**	Ph	I	THF	–
11	**2i**	PhC≡C	Br	THF	–

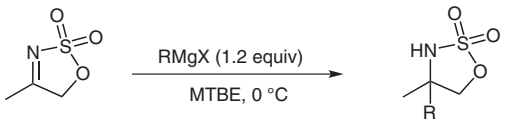
The reaction proved to be amenable to modest scale-up; when the reaction was performed on a 1.1 gram (5.7 mmol) scale with imine **1a** and ethyl magnesium bromide, the addition product **2b** was obtained in comparable yield (89%) to that obtained on a 0.25 mmol scale (84%). To further demonstrate the known utility of cyclic sulfamidates,[4,8] **2b** was protected as the benzylcarbamate **4** under standard conditions (Scheme 3). Compound **4** was then ring opened with benzylamine to give intermediate **5**, which, upon acidification, underwent desulfonylation and cyclization to provide the protected urea **6** in 63% yield over three steps.

In conclusion, the addition of Grignard reagents to cyclic sulfamidate imines has been developed as a method for the preparation of cyclic sulfamidates bearing N-substituted quaternary stereocenters. The products are versatile intermediates for a variety of substitution reactions, allowing for the rapid synthesis of a diverse array of compounds.



Scheme 3 Addition and ring opening on increased scale

Table 3 Grignard Addition to Cyclic Methyl Sulfamidate Imines



1b **2**

Entry	Product	R	Grignard solvent	Isolated yield (%)
1	**2j**	Me	Et_2O	81
2	**2k**	Et	Et_2O	83
3	**2l**	allyl	Et_2O	82
4	**2m**	Bn	THF	65
5	**2n**	vinyl	THF	36
6	**2a**	Ph	THF	13
7	**2o**	4-FC_6H_4	Et_2O	57
8	**2p**	HC≡C	THF	25
9	**2q**	PhC≡C	THF	49

All solvents and Grignard reagents were commercially available and were used without further purification. Flash column chromatography was carried out on silica gel (60 Å, 230–400 mesh) and was performed with reagent grade solvents. ^{1}H NMR and ^{13}C NMR spectroscopic data were obtained with a Bruker Avance 400 spectrometer. HRMS were recorded with an Agilent 6169A spectrometer. Melting points were determined by thermal gravimetric analysis.

Grignard Addition to Imine 1a; General Procedure

A round-bottom flask was charged with imine **1a** (50 mg, 0.25 mmol) and purged with N_2. MTBE was added and the reaction was cooled to 0 °C. Grignard reagent (0.30 mmol, 1.2 equiv) was added dropwise and the solution was stirred at 0 °C for the time indicated. The reaction was quenched with 0.5 M HCl (2 mL), extracted with EtOAc (10 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was then purified by silica gel chromatography.

4-Methyl-4-phenyl[1,2,3]oxathiazolidine 2,2-Dioxide (2a)

Reaction time: 6.5 h. Flash chromatography (hexanes–EtOAc, 10→40%).

Yield: 61% with MeMgBr, 67% with MeMgI; white solid; mp 82 °C; R_f = 0.3 (hexanes–EtOAc, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (m, 4 H), 7.36 (m, 1 H), 4.64 (d, *J* = 8.8 Hz, 1 H), 4.61 (s, 1 H), 4.58 (d, *J* = 8.8 Hz, 1 H), 1.82 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 129.2, 128.6, 125.0, 80.3, 65.4, 27.5.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 236.0352; found: 236.0353.

4-Ethyl-4-phenyl[1,2,3]oxathiazolidine 2,2-Dioxide (2b)

Reaction time: 2 h. Flash chromatography (hexanes–EtOAc, 5→25%).

Yield: 84%; white solid; mp 90 °C; R_f = 0.4 (hexanes–EtOAc, 4:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (m, 2 H), 7.33 (m, 3 H), 4.67 (d, *J* = 8.8 Hz, 1 H), 4.63 (s, 1 H), 4.62 (d, *J* = 8.8 Hz, 1 H), 2.18 (dq, *J* = 14.0, 7.6 Hz, 1 H), 2.04 (dq, *J* = 14.0, 7.6 Hz, 1 H), 0.82 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.5, 129.0, 128.4, 125.3, 79.5, 68.9, 33.1, 8.2.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 250.0508; found: 250.0510.

4-Isopropyl-4-phenyl[1,2,3]oxathiazolidine 2,2-Dioxide (2c)

Reaction time: 5 h. Flash chromatography (hexanes–EtOAc, 5→45%).

Yield: 65%; white solid; mp 122 °C; R_f = 0.4 (hexanes–EtOAc, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (m, 2 H), 7.31 (m, 1 H), 7.29 (m, 2 H), 4.78 (d, *J* = 8.8 Hz, 1 H), 4.66 (d, *J* = 8.8 Hz, 1 H), 4.57 (s, 1 H), 2.34 (qq, *J* = 6.8, 6.8 Hz, 1 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.78 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 128.7, 128.3, 126.0, 78.0, 71.4, 36.4, 17.5, 16.9.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 264.0665; found: 264.0667.

4-Allyl-4-phenyl[1,2,3]oxathiazolidine 2,2-Dioxide (2d)

Reaction time: 3 h. Flash chromatography (hexanes–EtOAc, 5→35%).

Yield: 86%; white solid; mp 85 °C; R_f = 0.4 (hexanes–EtOAc, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (m, 5 H), 5.48 (m, 1 H), 5.28 (d, *J* = 10.0 Hz, 1 H), 5.24 (d, *J* = 17.2 Hz, 1 H), 4.77 (s, 1 H), 4.69 (d, *J* = 8.8 Hz, 1 H), 4.56 (d, *J* = 8.8 Hz, 1 H), 2.88 (dd, *J* = 14.0, 8.0 Hz, 1 H), 2.82 (dd, *J* = 14.0, 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.7, 130.6, 129.1, 128.6, 125.2, 122.3, 78.1, 67.2, 44.4.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 262.0508; found: 262.0510.

4-Benzyl-4-phenyl[1,2,3]oxathiazolidine 2,2-Dioxide (2e)

Reaction time: 4.5 h. Flash chromatography (hexanes–EtOAc, 5→35%).

Yield: 71%; white solid; mp 140 °C; R_f = 0.4 (hexanes–EtOAc, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 3 H), 7.19 (m, 3 H), 7.07 (m, 2 H), 6.77 (m, 2 H), 4.85 (d, *J* = 8.8 Hz, 1 H), 4.67 (s, 1 H), 4.61 (d, *J* = 8.8 Hz, 1 H), 3.42 (d, *J* = 13.6 Hz, 1 H), 3.34 (d, *J* = 13.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.1, 133.5, 130.5, 128.9, 128.6, 128.5, 127.6, 125.3, 78.0, 68.4, 45.6.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 312.0665; found: 312.0669.

4-(2-[1,3]Dioxan-2-ylethyl)-4-phenyl[1,2,3]oxathiazolidine 2,2-Dioxide (2f)

Reaction time: 3 h. Flash chromatography (hexanes–EtOAc, 10→50%).

Yield: 69%; light-yellow oil; R_f = 0.2 (hexanes–EtOAc, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 4 H), 7.29 (m, 1 H), 6.44 (s, 1 H), 4.53 (m, 3 H), 4.10 (dd, *J* = 10.8, 4.8 Hz, 2 H), 3.74 (dd, *J* = 12.0, 12.0 Hz, 2 H), 2.37 (m, 1 H), 2.12 (m, 2 H), 1.61 (m, 1 H), 1.48 (m, 1 H), 1.33 (d, *J* = 12.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6, 129.0, 128.1, 125.5, 100.4, 79.2, 68.0, 67.0, 67.0, 33.4, 29.1, 25.4.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 336.0876; found: 336.0880.

4-Phenyl-4-vinyl[1,2,3]oxathiazolidine 2,2-Dioxide (2g)

Reaction time: 4 h. Flash chromatography (hexanes–EtOAc, 10→60%).

Yield:16%; brown oil; R_f = 0.4 (hexanes–EtOAc, 5:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (m, 5 H), 6.14 (dd, *J* = 15.6, 8.8 Hz, 1 H), 5.47 (d, *J* = 8.8 Hz, 1 H), 5.44 (d, *J* = 15.6 Hz, 1 H), 4.75 (s, 2 H), 4.67 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 137.3, 129.2, 129.0, 126.0, 118.8, 78.3, 69.0.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 248.0352; found: 248.0348.

Grignard Addition to Imine 1b; General Procedure

A round-bottom flask was charged with imine **1b** (50 mg, 0.38 mmol) and purged with N_2. MTBE was added and the reaction was cooled to 0 °C. Grignard reagent (0.45 mmol, 1.2 equiv) was added dropwise and the mixture was stirred at 0 °C for the time indicated. The reaction was quenched with 0.5 M HCl (2 mL), extracted with EtOAc (10 mL), washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was then purified by silica gel chromatography.

4,4-Dimethyl[1,2,3]oxathiazolidine 2,2-Dioxide (2j)

Reaction time: 6.5 h. Flash chromatography (hexanes–EtOAc, 10→60%).

Yield: 81%; white solid; R_f = 0.2 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.26 (s, 2 H), 4.18 (s, 1 H), 1.47 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 81.0, 60.3, 26.0.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 174.0195; found: 174.0200.

4-Ethyl-4-methyl[1,2,3]oxathiazolidine 2,2-Dioxide (2k)

Reaction time: 7 h. Flash chromatography (hexanes–EtOAc, 10→55%).

Yield: 83%; pale-yellow oil; R_f = 0.3 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.29 (d, *J* = 8.8 Hz, 1 H), 4.23 (d, *J* = 8.8 Hz, 1 H), 4.18 (s, 1 H), 1.81 (dq, *J* = 14.0, 7.2 Hz, 1 H), 1.66 (dq, *J* = 14.0, 7.2 Hz, 1 H), 1.42 (s, 3 H), 0.98 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.5, 63.4, 31.8, 23.3, 8.1.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 188.0352; found: 188.0353.

4-Allyl-4-methyl[1,2,3]oxathiazolidine 2,2-Dioxide (2l)

Reaction time: 5 h. Flash chromatography (hexanes–EtOAc, 5→30%).

Yield: 82%; colorless oil; R_f = 0.5 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (m, 1 H), 5.24 (d, *J* = 9.6 Hz, 1 H), 5.21 (d, *J* = 17.2 Hz, 1 H), 4.67 (s, 1 H), 4.34 (d, *J* = 8.8 Hz, 1 H), 4.20 (d, *J* = 8.8 Hz, 1 H), 2.52 (dd, *J* = 14.0, 8.0 Hz, 1 H), 2.38 (dd, *J* = 14.0, 8.0 Hz, 1 H), 1.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 130.7, 121.2, 78.5, 62.1, 42.9, 23.9.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 200.0352; found: 200.0350.

4-Benzyl-4-methyl[1,2,3]oxathiazolidine 2,2-Dioxide (2m)

Reaction time: 5 h. Flash chromatography (hexanes–EtOAc, 0→35%).

Yield: 65%; colorless oil; R_f = 0.4 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 3 H), 7.27 (d, *J* = 7.0 Hz, 2 H), 4.58 (s, 1 H), 4.50 (d, *J* = 8.8 Hz, 1 H), 4.29 (d, *J* = 8.8 Hz, 1 H), 3.21 (d, *J* = 13.6 Hz, 1 H), 2.91 (d, *J* = 13.6 Hz, 1 H), 1.41 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.7, 130.6, 128.7, 127.5, 79.1, 63.1, 44.3, 23.6.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 250.0508; found: 250.0508.

4-Methyl-4-vinyl[1,2,3]oxathiazolidine 2,2-Dioxide (2n)

Reaction time: 6.5 h. Flash chromatography (hexanes–EtOAc, 15→50%).

Yield:36%; colorless oil; R_f = 0.3 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.90 (dd, *J* = 17.2, 10.8 Hz, 1 H), 5.46 (d, *J* = 17.2 Hz, 1 H), 5.33 (d, *J* = 10.8 Hz, 1 H), 4.60 (s, 1 H), 4.38 (d, *J* = 8.8 Hz, 1 H), 4.30 (d, *J* = 8.8 Hz, 1 H), 1.55 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 117.4, 79.0, 63.5, 24.1.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 186.0195; found: 186.0194.

4-Methyl-4-phenyl[1,2,3]oxathiazolidine 2,2-Dioxide (2a)

Reaction time: 7 h. Flash chromatography (hexanes–EtOAc, 0→30%).

Yield:13%; colorless oil.

4-(4-Fluorophenyl)-4-methyl[1,2,3]oxathiazolidine 2,2-Dioxide (2o)

Reaction time: 6 h. Flash chromatography (hexanes–EtOAc, 0→40%).

Yield: 57%; colorless oil; R_f = 0.3 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 2 H), 7.07 (m, 2 H), 4.98 (s, 1 H), 4.61 (d, *J* = 8.8 Hz, 1 H), 4.55 (d, *J* = 8.8 Hz, 1 H), 1.78 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.5 (d, *J* = 246.0 Hz), 137.0 (d, *J* = 3.0 Hz), 127.0 (d, *J* = 8.0 Hz), 115.9 (d, *J* = 22.0 Hz), 80.3, 65.0, 27.4.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 254.0258; found: 254.0261.

4-Ethynyl-4-methyl[1,2,3]oxathiazolidine 2,2-Dioxide (2p)

Reaction time: 7 h. Flash chromatography (hexanes–EtOAc, 15→50%).

Yield: 25%; colorless oil; R_f = 0.3 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78 (s, 1 H), 4.60 (d, *J* = 8.4 Hz, 1 H), 4.36 (d, *J* = 8.4 Hz, 1 H), 2.64 (s, 1 H), 1.72 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 81.4, 79.1, 74.9, 56.2, 26.7.

HRMS-ESI: *m*/*z* [M + Na]$^+$ calcd: 184.0039; found: 184.0041.

4-Methyl-4-phenylethynyl[1,2,3]oxathiazolidine 2,2-Dioxide (2q)

Reaction time: 6 h. Flash chromatography (hexanes–EtOAc, 0→35%).

Yield: 49%; colorless oil; R_f = 0.50 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (m, 2 H), 7.34 (m, 3 H), 4.96 (s, 1 H), 4.44 (d, *J* = 8.4 Hz, 1 H), 3.67 (d, *J* = 8.4 Hz, 1 H), 1.80 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.7, 129.3, 128.3, 120.7, 86.3, 85.8, 79.3, 56.9, 26.8.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd: 260.0352; found: 260.0355.

CBz-Protection, Nucleophilic Ring-Opening and Cyclization

A round-bottom flask was charged with a solution of *t*-BuONa (0.79 g, 8.2 mmol, 1.5 equiv) in DME (38 mL) and purged with N_2. Cyclic sulfamidate **2b** (1.24 g, 5.4 mmol) was added and the reaction was stirred for 1.5 h. Benzyl chloroformate (2.0 mL, 14.0 mmol, 2.5 equiv) was then added and the reaction was stirred for 17 h. The reaction was quenched with H_2O (15 mL) and extracted with EtOAc. The organic phase was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography (hexanes–EtOAc, 5→30%) to provide Cbz-protected cyclic sulfamidate [R_f = 0.6 (hexanes–EtOAc, 7:3)].

A round-bottom flask was charged with protected cyclic sulfamidate **4** (5.4 mmol), MeCN (25 mL) and purged with N_2. Benzylamine (0.89 mL, 8.2 mmol, 1.5 equiv) was added and the reaction was heated to 80 °C and stirred for 28 h. The reaction was cooled, diluted with EtOAc (20 mL), 1 M HCl (20 mL) was added and the mixture was stirred at r.t. for 2 h. The organic layer was separated, washed with 1 M NaOH (25 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel chromatography.

1-Benzyl-4-ethyl-4-phenylimidazolidin-2-one (6)

Flash chromatography (hexanes–EtOAc, 30→80%).

Yield: 0.94 g (3.35 mmol, 63%); white solid; mp 111 °C; R_f = 0.30 (hexanes–EtOAc, 3:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (m, 10 H), 5.39 (s, 1 H), 4.59 (d, *J* = 14.8 Hz, 1 H), 4.28 (d, *J* = 14.8 Hz, 1 H), 3.42 (d, *J* = 8.8 Hz, 1 H), 3.39 (d, *J* = 8.8 Hz, 1 H), 1.89 (m, 2 H), 0.80 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 144.6, 137.0, 128.7, 128.6, 128.4, 128.2, 128.0, 127.5, 127.2, 127.0, 124.9, 60.6, 57.6, 47.3, 34.3, 8.1.

HRMS-ESI: *m/z* [M + Na]$^+$ calcd: 281.1648; found: 281.1656.

Acknowledgment

The authors thank Louis-Charles Campeau, Carmela Molinaro and David Powell for helpful discussions.

References

(1) (a) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689. (b) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127.

(2) For reviews, see: (a) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569. (b) Ferraris, D. *Tetrahedron* **2007**, *63*, 9581. (c) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541. (d) Connon, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 3909. (e) Kang, S. H.; Kang, S. Y.; Lee, H.-S.; Buglass, A. J. *Chem. Rev.* **2005**, *105*, 4537. (f) Alvaro, G.; Savoia, D. *Synlett* **2002**, 651. (g) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (h) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. For selected recent examples, see: (i) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968. (j) Kattuboina, A.; Kaur, P.; Nguyen, T.; Li, G. *Tetrahedron Lett.* **2008**, *49*, 3722. (k) Fu, P.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2008**, *130*, 5530. (l) Notte, G. T.; Leighton, J. L. *J. Am. Chem. Soc.* **2008**, *130*, 6676. (m) Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2008**, *73*, 940. (n) Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 500. (o) Lauzon, C.; Charette, A. B. *Org. Lett.* **2006**, *8*, 2743. (p) Shen, K.-H.; Yao, C.-F. *J. Org. Chem.* **2006**, *71*, 3980. (q) Nishimura, T.; Yasuhara, Y.; Hayashi, T. *Org. Lett.* **2006**, *8*, 979. (r) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687. (s) Basra, S.; Fennie, M. W.; Kozlowski, M. C. *Org. Lett.* **2006**, *8*, 2659. (t) Sugimoto, H.; Nakamura, S.; Hattori, M.; Ozeki, S.; Shibata, N.; Toru, T. *Tetrahedron Lett.* **2005**, *46*, 8941. (u) Kizirian, J.-C.; Cabello, N.; Rinchard, L.; Caille, J.-C.; Alexakis, A. *Tetrahedron* **2005**, *61*, 8939. (v) Coté, A.; Boezio, A. A.; Charette, A. B. *Angew. Chem. Int. Ed.* **2004**, *43*, 6525.

(3) (a) Kotti, S. R. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101. (b) Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1. (c) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, *37*, 2580. (d) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, **1997**. (e) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

(4) (a) Wang, Y.-Q.; Yu, C.-B.; Wang, D.-W.; Wang, X.-B.; Zhou, Y.-G. *Org. Lett.* **2008**, *10*, 2071. (b) Zhou, Y.-G.; Wang, Y.-Q.; Yu, C.-B. CN-101423504, **2009**. (c) Zhu, B.-H.; Zheng, J.-C.; Yu, C.-B.; Sun, X.-L.; Zhou, Y.-G.; Shen, Q.; Tang, Y. *Org. Lett.* **2010**, *12*, 504.

(5) (a) Ni, C.; Liu, J.; Zhang, L.; Hu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 786. (b) Rönnholm, P.; Södergren, M.; Hilmersson, G. *Org. Lett.* **2007**, *9*, 3781. (c) Bower, J. F.; Švenda, J.; Williams, A. J.; Charmant, J. P. H.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Lett.* **2004**, *6*, 4727. (d) Nicolaou, K. C.; Snyder, S. A.; Longbottom, D. A.; Nalbandian, A. Z.; Huang, X. *Chem. Eur. J.* **2004**, *10*, 5581. (e) Williams, A. J.; Chakthong, S.; Gray, D.; Lawrence, R. M.; Gallagher, T. *Org. Lett.* **2003**, *5*, 811. (f) Cohen, S. B.; Halcomb, R. L. *J. Am. Chem. Soc.* **2002**, *124*, 2534. (g) Nicolaou, K. C.; Huang, X.; Snyder, S. A.; Rao, P. B.; Bella, M.; Reddy, M. V. *Angew. Chem. Int. Ed.* **2002**, *41*, 834. (h) Posakony, J. J.; Tewson, T. J. *Synthesis* **2002**, 766. (i) Posakony, J. J.; Grierson, J. R.; Tewson, T. J. *J. Org. Chem.* **2002**, *67*, 5164. (j) Cohen, S. B.; Halcomb, R. L. *Org. Lett.* **2001**, *3*, 405. (k) Atfani, M.; Wei, L.; Lubell, W. D. *Org. Lett.* **2001**, *3*, 2965. (l) Wei, L.; Lubell, W. D. *Can. J. Chem.* **2001**, *79*, 94. (m) Wei, L.; Lubell, W. D. *Org. Lett.* **2000**, *2*, 2595.

(6) (a) Toumieux, S.; Compain, P.; Martin, O. R.; Selkti, M. *Org. Lett.* **2006**, *8*, 4493. (b) Wehn, P. M.; Du Bois, J. *Org. Lett.* **2005**, *7*, 4685. (c) Fiori, K. W.; Fleming, J. J.; Du Bois, J. *Angew. Chem. Int. Ed.* **2004**, *43*, 4349. (d) Fleming, J. J.; Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 2028. (e) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935.

(7) (a) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem. Int. Ed.* **2002**, *41*, 3465. (b) Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Che, C.-M. *J. Org. Chem.* **2004**, *69*, 3610. (c) Zhang, J.; Chan, P. W. H.; Che, C.-M. *Tetrahedron Lett.* **2005**, *46*, 5403. (d) Fruit, C.; Müller, P. *Tetrahedron: Asymmetry* **2004**, *15*, 1019.

(8) (a) Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 3283. (b) Meléndez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *59*, 2581. (c) Posakony, J. J.; Tewson, T. J. *Synthesis* **2002**, 859. (d) Boulton, L. T.; Stock, H. T.; Raphy, J.; Horwell, D. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1421.

(9) Thornton, A. R.; Blakey, S. B. *J. Am. Chem. Soc.* **2008**, *130*, 5020.

(10) (a) Okada, M.; Iwashita, S.; Koizumi, N. *Tetrahedron Lett.* **2000**, *41*, 7047. (b) Kamal, A.; Sattur, P. B. *Synthesis* **1981**, 272.