An Efficient Synthesis of Azetidines with (2-Bromoethyl)sulfonium Triflate

Sven P. Fritz, Juan F. Moya, Matthew G. Unthank, Eoghan M. McGarrigle,* Varinder K. Aggarwal*

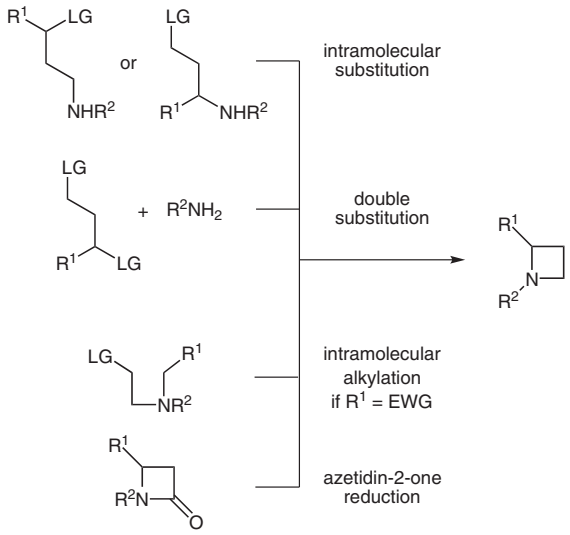
School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, UK
Fax +44(117)9277985; E-mail: v.aggarwal@bristol.ac.uk; E-mail: eoghan.mcgarrigle@bristol.ac.uk

Received: 17.01.2012; Accepted after revision: 19.03.2012

Abstract: Easily accessible arylglycine derivatives were cyclized to azetidines by using commercially available (2-bromoethyl)sulfonium triflate in a simple and mild procedure. The high-yielding reaction has a relatively broad scope and was extended to the synthesis of an oxetane.

Key words: annulations, cyclizations, heterocycles, sulfur, ylides

Azetidines are important N-heterocycles, not only because of their biological importance[1] and their increasing use in medicinal chemistry,[2] but also because they are valuable synthetic intermediates[3] that have found application in asymmetric synthesis.[4] In particular, certain types of azetidines have been used in the modulation and fine-tuning of the pharmacokinetic properties of potentially bioactive molecules.[2] However, because of the inherent ring strain in azetidines, the synthesis of these compounds is not always straightforward.[2a,b,5,6] Scheme 1 shows some approaches commonly used in the syntheses of 2-substituted azetidines; however, these approaches often suffer from limitations in the scope of suitable precursors or in the conditions required for cyclization. New synthetic methods for preparing these heterocycles are therefore needed.

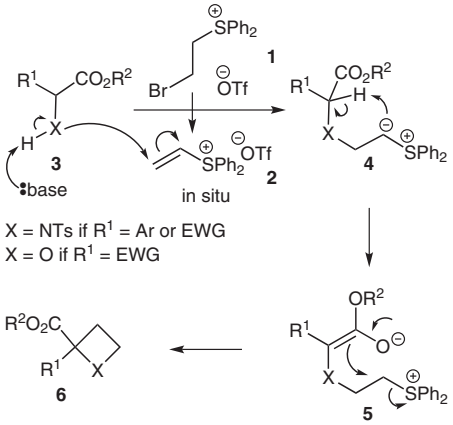


Scheme 1 Methods for the synthesis of 2-substituted azetidines. LG = leaving group; EWG = electron-withdrawing group

SYNTHESIS 2012, 44, 1584–1590
Advanced online publication: 26.04.2012
DOI: 10.1055/s-0031-1290951; Art ID: SS-2012-N0057-OP

We have previously reported on the use of (2-bromoethyl)sulfonium triflate (**1**) in the synthesis of five-, six-, and seven-membered heterocycles.[7,8] We therefore examined the possibility of extending this methodology to the synthesis of strained four-membered heterocycles, such as azetidines.

Scheme 2 shows our proposed annulation reaction mechanism, which is based on an analogous reaction of amino alcohols.[7c] Nucleophilic addition of ester **3** to the vinylsulfonium salt **2**, generated in situ from (2-bromoethyl)sulfonium triflate (**1**) and base, gives the ylide intermediate **4**, which after proton transfer forms enolate **5**. Subsequent intramolecular nucleophilic attack displaces the Ph_2S leaving group to give the four-membered product **6**.[9] Here, we report the successful application of this method in the synthesis of azetidines from readily available amino ester derivatives such as aryl glycines.

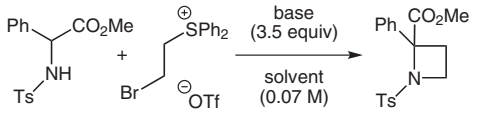


Scheme 2 Proposed mechanism for the formation of four-membered rings; EWG = electron-withdrawing group

Initial investigations showed that the reaction of amino ester **7a**[10] with (2-bromoethyl)sulfonium triflate **1** in dichloromethane containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base gave a good yield of azetidine **8a** (Table 1, entry 1). Heating improved the yield and shortened the reaction time (entry 2). Switching to a higher-boiling solvent led to a slight reduction in yield, due to some decomposition of the salt (entry 3). Other bases were not as effective for this transformation (entries 4–6).

We then explored the scope of this annulation with regard to the choice of substrate (Table 2). A change from a methyl ester to an ethyl ester[11] increased the yield slightly (entry 2), but the use of the bulkier *tert*-butyl ester resulted in no additional improvement (entry 3). The use of a

Table 1 Optimization of the Reaction Conditions



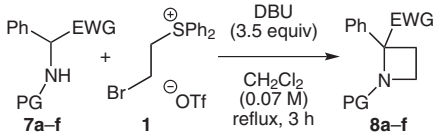
7a 1 8a

Entry	Base	Temp	Solvent	Time (h)	Yield[a] (%)
1	DBU	r.t.	CH_2Cl_2	24	62
2	DBU	reflux	CH_2Cl_2	3	72
3	DBU	reflux	MeCN	1.5	64[b]
4	Et_3N	reflux	CH_2Cl_2	3	trace
5	DIPEA	reflux	CH_2Cl_2	3	trace
6	NaH	r.t.	CH_2Cl_2	3	n.r.

[a] Isolated yield.
[b] Some decomposition was observed.

nitrile[12] instead of an ester gave a much lower yield (entry 4), possibly as a result of competing elimination of the tosyl group with concomitant formation of an imine. The use of *N*-benzyloxycarbonyl glycine esters was also much less effective in the annulation compared with *N*-tosyl esters (entries 5 and 6). As might be expected from our proposed mechanism, the enantiomerically enriched amines **8a** and **8c** gave racemic products.[13]

Table 2 Optimization of the Substrate Properties

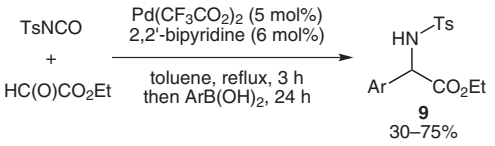


7a–f 1 8a–f

Entry	Product	PG	EWG	Yield[a] (%)
1	**8a**	Ts	CO_2Me	72
2	**8b**	Ts	CO_2Et	82
3	**8c**	Ts	CO_2-*t*-Bu	80
4	**8d**	Ts	CN	32
5	**8e**	Cbz	CO_2Me	38
6	**8f**	Cbz	CO_2-*t*-Bu	n.r.

[a] Isolated yield.

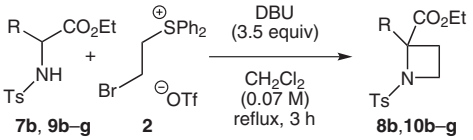
We therefore focused on the use of ethyl esters of *N*-tosyl(2-aryl)glycines.[14] These were easily prepared using the method developed by Lu and co-workers (Scheme 3),[11] in which a simple three-component palladium-catalyzed reaction between ethyl glyoxylate, tosyl isocyanate, and an aryl boronic ester gives the corresponding aryl glycines **9** in moderate-to-good yields.



Scheme 3 Preparation of 2-arylglycine ethyl esters[11]

Table 3 shows the results of the annulation reactions of these aryl glycines. The method was readily extended to electron-rich and electron-deficient aryl substituents (entries 2 and 3, respectively). Sterically bulky (entry 4) or heteroaromatic (entry 5) substituents also gave good yields. Replacing the aryl substituent with a second ester group was also possible, giving azetidine **10f**. However, attempted annulations with alkyl-substituted substrates[15] such as **9g** were unsuccessful (entry 7). Evidently, the acidity of the proton in the position α to the ester is important to the success of the reaction.

Table 3 Substrate Scope of the Annulation Reaction

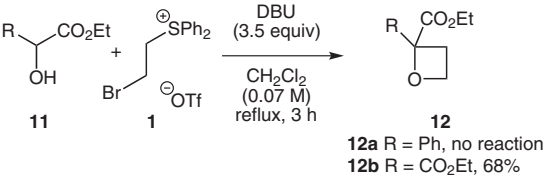


7b, 9b–g 2 8b,10b–g

Entry	R	Product	Yield[a] (%)
1	Ph	**8b**	82
2	4-ClC_6H_4	**10b**	88
3	4-$MeOC_6H_4$	**10c**	62
4	1-naphthyl	**10d**	83
5	3-furyl	**10e**	38
6	CO_2Et	**10f**	78
7	Me	**10g**	n.r.

[a] Isolated yield.

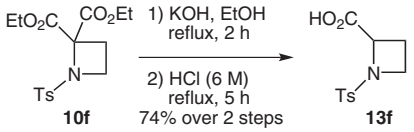
We also attempted to extend the annulation to the synthesis of oxetanes by using α-hydroxy esters. Although initial experiments with the phenyl-substituted ester **11a**[16] were unsuccessful, we found that by increasing the acidity of the α-proton by using diester **11b**[17] the oxetane **12b** was obtainable in good yield (Scheme 4).[18]



11 1

Scheme 4 Exploration of the synthesis of oxetanes

Finally, we report that substrate **10f** can be conveniently decarboxylated to give the monoacid **13f**, which provides access to azetidine-2-carboxylic acids (Scheme 5).[19]



Scheme 5 Monodecarboxylation of **10f** to azetidine-2-carboxylic acid **13f**

In conclusion, we have demonstrated a synthesis of several substituted azetidines and an oxetane in high yields under mild conditions by a simple method starting from readily available materials.

Reactions were performed under a positive pressure of dry N_2 in dry glassware with magnetic stirring. Dry solvents and freshly distilled DBU were transferred by syringe or cannula into the reaction vessels through rubber septa. Reagents of the highest commercial quality available were purchased and used as received, with the exception of DBU, which was distilled from CaH_2. Anhyd solvents (CH_2Cl_2, toluene, and MeCN) were purified on a column of activated alumina (A-2). Flash chromatography was performed on silica gel (Merck Kieselgel 60 F_{254} 230–400 mesh). TLC was performed on aluminum-backed silica plates (0.2 mm, 60 F_{254}), which were visualized by standard techniques: UV fluorescence (254 and 366 nm), I_2 staining, or ninhydrin/heat. The 40–60 °C boiling fraction of PE was used. ^{1}H NMR spectra were recorded at either 300 or 400 MHz on Jeol Delta GX or Eclipse ECP/400 instruments, respectively. ^{13}C NMR spectra were recorded at 75 or 100 MHz using the same instruments. Chemical shifts (δ_H and δ_C) are quoted in parts per million (ppm), referenced to the appropriate NMR solvent peak(s). Low- and high-resolution mass spectra were recorded on a Bruker Daltronics Apex 4e 7.0T FT-MS (ESI) spectrometer. Melting points were measured on a Kofler hotstage melting point apparatus and are uncorrected. Infrared spectra were recorded on the neat compounds using an ATR sampling accessory on a Perkin-Elmer (Spectrum One) FT-IR spectrophotometer. Only strong and selected absorbances (ν_{max}) are reported. Optical rotations were measured using a Perkin-Elmer 241 MC polarimeter.

(2-Bromoethyl)diphenylsulfonium trifluoromethanesulfonate (**1**),[7c] methyl (2*R*)-(tosylamino)(phenyl)acetate **7a**,[10] and (±)-*N*-[cyano(phenyl)methyl]-4-toluenesulfonamide (**7d**)[12] were prepared according to the published procedures.

***tert*-Butyl (2*R*)-(Tosylamino)(phenyl)acetate (7c)**

A soln of *tert*-butyl (2*R*)-amino(phenyl)acetate (100 mg, 0.48 mmol, 1 equiv) in CH_2Cl_2 (4.8 mL; 0.1 M) was treated with Et_3N (0.18 mL, 1.1 mmol, 2.2 equiv). TsCl (92 mg, 0.48 mmol, 1.0 equiv) was added and the mixture was stirred for 18 h. The reaction was then quenched with sat. aq $NaHCO_3$ (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo to provide a crude product that was purified by flash chromatography [silica gel, EtOAc–PE (3:7)] to give transparent crystals; yield: 142 mg (82%); mp 138–140 °C (CH_2Cl_2–pentane); R_f = 0.5 (EtOAc–PE, 3:7); $[\alpha]_D^{22}$ –78.0 (*c* 0.02, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.17–7.33 (m, 7 H, Ar*H*), 5.75 (d, *J* = 8.0 Hz, 1 H, C*H*), 4.95 (d, *J* = 8.0 Hz, 1 H, N*H*), 2.39 (s, 3 H, ArCH_3), 1.26 (s, 9 H, 3 × CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0 (CO), 143.3 (C), 137.0 (C), 135.9 (C), 129.4 (CH), 128.5 (CH), 128.1 (CH), 127.2 (CH), 126.9 (CH), 83.0 (C), 59.7 (CH), 27.5 (CH_3), 21.4 (ArCH_3).

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{24}NO_4S^+$: 362.1421; found: 362.1425.

Ethyl Esters 7b and 9b–e; General Method

According to the method of Lu and co-workers,[11] a Schlenk tube was charged with toluene (2 mL) then TsOCN (0.71 mmol, 1 equiv), ethyl glyoxylate (0.71 mmol, 1 equiv), $Pd(O_2CCF_3)_2$ (5 mol%), and 2,2′-bipyridine (6 mol%) were added and the mixture was refluxed for 3 h, under argon. The appropriate arylboronic acid (1.42 mmol, 2 equiv) was added and the mixture was refluxed for a further 24 h. The mixture was then cooled to r.t. and diluted with EtOAc (10 mL). The organic layer was washed with brine (10 mL) and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc–PE or EtOAc–pentane).

Ethyl (±)-Phenyl(tosylamino)acetate (7b)

The product was prepared by the general method from phenylboronic acid (173 mg, 1.42 mmol) to give an amorphous white solid; yield: 163 mg (70%); mp 86–88 °C (Lit.[11] 90–91 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.69 (m, 2 H, Ar*H*), 7.21–7.28 (m, 5 H, Ar*H*), 7.18 (m, 2 H, Ar*H*), 5.98 (d, *J* = 8.5 Hz, 1 H, C*H*), 5.06 (d, *J* = 8.5 Hz, 1 H, N*H*), 3.86–4.12 (m, 2 H, CH_2), 2.37 (s, 3 H, ArCH_3), 1.08 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9 (CO), 143.3 (C), 136.8 (C), 135.3 (C), 129.3 (CH), 128.6 (CH), 128.3 (CH), 127.1 (CH), 126.9 (CH), 62.0 (CH_2), 59.3 (CH), 21.3 (CH_3), 13.7 (CH_3).

The spectroscopic data were consistent with those reported in the literature.[11]

Ethyl (±)-(4-Chlorophenyl)(tosylamino)acetate (9b)

The product was prepared by the general method from (4-chlorophenyl)boronic acid (222 mg, 1.42 mmol) to give an amorphous white solid; yield: 172 mg (66%); mp 87–89 °C (Lit.[11] 86–87 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.64 (m, 2 H, Ar*H*), 7.14–7.23 (m, 6 H, Ar*H*), 5.96 (d, *J* = 8.0 Hz, 1 H, C*H*), 5.02 (d, *J* = 8.0 Hz, 1 H, N*H*), 3.90–4.11 (m, 2 H, CH_2), 2.39 (s, 3 H, ArCH_3), 1.09 (t, *J* = 7.1 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5 (CO), 143.6 (C), 136.8 (C), 134.4 (C), 133.9 (C), 129.4 (CH), 128.8 (CH), 128.5 (CH), 127.1 (CH), 62.4 (CH_2), 58.7 (CH), 21.4 (ArCH_3), 13.7 (CH_3).

The spectroscopic data were consistent with those reported in the literature.[11]

Ethyl (±)-(4-Methoxyphenyl)(tosylamino)acetate (9c)

The product was prepared by the general method from (4-methoxyphenyl)boronic acid (222 mg, 1.42 mmol) to give an amorphous white solid; yield: 160 mg (62%); mp 88–90 °C (Lit.[11] 87–89 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.64 (m, 2 H, Ar*H*), 7.12 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.98–7.09 (m, 2 H, Ar*H*), 6.59–6.81 (m, 2 H, Ar*H*), 5.69 (d, *J* = 8.0 Hz, 1 H, C*H*), 4.91 (d, *J* = 8.0 Hz, 1 H, N*H*), 3.79–4.10 (m, 2 H, CH_2), 3.68 (s, 3 H, OCH_3), 2.30 (s, 3 H, ArCH_3), 1.01 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 (CO), 159.7 (C), 143.4 (C), 137.0 (C), 129.4 (CH), 128.3 (CH), 127.5 (CH), 127.2 (CH), 114.1 (C), 62.1 (CH_2), 58.8 (CH), 55.3 (CH_3), 21.4 (ArCH_3), 13.8 (CH_3).

The spectroscopic data were consistent with those reported in the literature.[11]

Ethyl (±)-(2-Naphthyl)(tosylamino)acetate (9d)

The product was prepared by the general method from 2-naphthylboronic acid (222 mg, 1.42 mmol to give an amorphous white solid; yield: 84 mg (31%); mp 111–113 °C (Lit.[11] 115–116 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.82 (m, 1 H, Ar*H*), 7.68–7.76 (m, 2 H, Ar*H*), 7.63–7.68 (m, 1 H, Ar*H*), 7.57–7.63 (m, 2 H, Ar*H*), 7.44–7.52 (m, 2 H, Ar*H*), 7.31 (dd, *J* = 8.5, 2.0 Hz, 1 H,

ArH), 7.04–7.11 (m, 2 H, ArH), 5.81 (d, J = 7.0 Hz, 1 H, CH), 5.22 (d, J = 7.0 Hz, 1 H, NH), 3.95–4.15 (m, 2 H, CH_2), 2.27 (s, 3 H, ArCH_3), 1.11 (t, J = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0 (CO), 143.4 (C), 137.0 (C), 133.0 (C), 133.0 (C), 132.5 (C), 129.3 (CH), 128.7 (CH), 128.0 (CH), 127.5 (CH), 127.1 (CH), 126.7 (CH), 126.5 (CH), 126.4 (CH), 124.4 (CH), 62.3 (CH_2), 59.5 (CH), 21.3 (CH_3), 13.8 (CH_3).

The spectroscopic data were consistent with those reported in the literature.[11]

Ethyl (±)-(3-Furyl)(tosylamino)acetate (9e)
The product was prepared by the general method from 3-furylboronic acid (159 mg, 1.42 mmol) as an amorphous yellow–white solid of sufficient purity for use in the next step; yield: 92 mg (40%); mp 68–70 °C; R_f = 0.25 (EtOAc–pentane, 2:8).

FTIR (neat): 3288, 3092, 2956, 1744, 1366 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, J = 8.3 Hz, 2 H, ArH), 7.07–7.29 (m, 3 H, ArH), 6.08–6.33 (m, 2 H, ArH), 5.56 (d, J = 8.5 Hz, 1 H, CH), 5.09 (d, J = 8.5 Hz, 1 H, NH), 3.87–4.24 (m, 2 H, CH_2), 2.32 (s, 3 H, ArCH_3), 1.07 (t, J = 7.2 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9 (CO), 147.7 (C), 143.5 (C), 143.0 (CH), 136.9 (C), 129.5 (CH), 127.1 (CH), 110.5 (CH), 109.1 (CH), 62.5 (CH_2), 53.6 (CH), 21.5 (CH_3), 13.8 (CH_3).

MS (ESI$^+$): m/z (%) = 341.1 (100) $[M + NH_4]^+$, 324.1 (10), $[M + H]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{15}H_{17}NNaO_5S^+$: 346.0724; found: 346.0719.

Diethyl (Tosylamino)malonate (9f)
Diethyl aminomalonate (211 mg, 1 mmol, 1 equiv) was treated with TsCl (210 mg, 1.1 mmol, 1.1 equiv) and Et_3N (0.42 mL, 3.0 mmol, 3.0 equiv) in CH_2Cl_2 (0.1 M) for 15 h at r.t. The reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by flash chromatography [EtOAc–pentane (2:8)] to give a gummy white solid; yield: 205 mg (62%); mp 60–62 °C (CH_2Cl_2–pentane); R_f = 0.4 (EtOAc–pentane, 2:8).

FTIR (neat): 3276, 2944, 1748, 1339 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, J = 8.5 Hz, 2 H, ArH), 7.22 (d, J = 8.5 Hz, 2 H, ArH), 5.74 (d, J = 7.0 Hz, 1 H, CH), 4.58 (d, J = 8.5 Hz, 1 H, NH), 4.06 (dq, J = 11.0, 7.0 Hz, 2 H, 2 × CHH), 4.03 (dq, J = 11.0, 7.0 Hz, 2 H, 2 × CHH), 2.34 (s, 3 H, ArCH_3), 1.12 (t, J = 7.0 Hz, 6 H, 2 × CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5 (C), 143.8 (C), 136.4 (C), 129.5 (CH), 127.2 (CH), 62.7 (CH_2), 58.6 (CH), 21.4 (ArCH_3), 13.7 (CH_3).

MS (ESI): m/z = 330 $[M + H]^+$.

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{14}H_{19}NNaO_6S$: 352.0837; found: 352.0825.

Azetidines: General Method
(2-Bromoethyl)sulfonium triflate (**1**; 93 mg, 0.21 mmol, 1.25 equiv) was added to a soln of the appropriate *N*-protected arylglycine ester (0.167 mmol, 1 equiv) in CH_2Cl_2 (2.3 mL, 0.07 M). DBU (87 μL, 0.58 mmol, 3.5 equiv) was added to the stirred soln, and the mixture was refluxed for 3 h. The mixture was then cooled to r.t. and the reaction was quenched with sat. aq $NaHCO_3$ (5 mL). The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The product was purified by flash chromatography (silica gel, EtOAc–PE or EtOAc–pentane).

Methyl (±)-2-Phenyl-1-tosylazetidine-2-carboxylate (8a)
The racemic product was prepared according to the general method from methyl (2*R*)-phenyl(tosylamino)acetate (100 mg, 0.31 mmol) to give the racemic product as a clear oil; yield: 74 mg (72%); R_f = 0.5 (EtOAc–PE, 3:7); $[\alpha]_D^{20}$ 0.0 (*c* 1.0, $CHCl_3$).

FTIR (neat): 3272, 3092, 2959, 1741, 1331 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.63 (m, 2 H, ArH), 7.39–7.46 (m, 2 H, ArH), 7.30–7.38 (m, 3 H, ArH), 7.21–7.28 (m, 2 H, ArH), 4.20 (ddd, J = 9.2, 7.0, 7.0 Hz, 1 H, CHH), 3.86 (ddd, J = 9.2, 7.0, 4.9 Hz, 1 H, CHH), 3.73 (s, 3 H, $COCH_3$), 2.94 (ddd, J = 11.2, 9.2, 4.9 Hz, 1 H, CHH), 2.55 (ddd, J = 11.2, 9.2, 7.0 Hz, 1 H, CHH), 2.42 (s, 3 H, ArCH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9 (CO), 143.3 (C), 139.0 (C), 136.4 (C), 129.3 (CH), 128.3 (CH), 128.0 (CH), 127.4 (CH), 126.0 (CH), 77.2 (C), 52.8 (CH_3), 47.4 (CH_2), 29.6 (CH_2), 21.5 (CH_3).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{18}H_{19}NNaO_4S^+$: 368.0927; found: 368.0926.

Ethyl (±)-2-Phenyl-1-tosylazetidine-2-carboxylate (8b)
The product was prepared according to the general method from ethyl phenyl(tosylamino)acetate (57 mg, 0.17 mmol, 1 equiv) to give a clear oil; yield: 50 mg (82%) R_f = 0.3 (EtOAc–pentane, 2:8).

FTIR (neat): 3265, 2968, 1724, 1336, 1156 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.62 (m, 2 H, ArH), 7.40–7.47 (m, 2 H, ArH), 7.29–7.39 (m, 3 H, ArH), 7.21–7.26 (m, 2 H, ArH), 4.13–4.30 (m, 3 H, CH_2 and CHH), 3.83 (ddd, J = 9.0, 7.0, 5.0 Hz, 1 H, CHH), 2.91 (ddd, J = 11.0, 9.0, 5.0 Hz, 1 H, CHH), 2.58 (ddd, J = 11.0, 9.0, 7.0 Hz, 1 H, CHH), 2.41 (s, 3 H, ArCH_3), 1.28 (t, J = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6 (C), 143.2 (C), 139.1 (C), 136.7 (C), 129.3 (CH), 128.2 (CH), 128.0 (CH), 127.3 (CH), 126.2 (CH), 77.4 (C), 62.1 (OCH_2), 47.3 (CH_2), 29.2 (CH_2), 21.4 (ArCH_3), 13.9 (CH_3).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{19}H_{21}NNaO_4S$: 382.1083; found: 382.1083.

***tert*-Butyl (±)-2-Phenyl-1-tosylazetidine-2-carboxylate (8c)**
The racemic product was prepared according to the general method from *tert*-butyl (2*R*)-phenyl(tosylamino)acetate (43.0 mg, 0.12 mmol, 1 equiv) to give a clear oil; yield: 37 mg (80%); R_f = 0.15 (EtOAc–PE, 3:7); $[\alpha]_D^{23}$ 0.0 (*c* 0.11, $CHCl_3$).

FTIR (neat): 3260, 2961, 1721, 1339, 1152 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54–7.63 (m, 2 H, ArH), 7.38–7.46 (m, 2 H, ArH), 7.27–7.37 (m, 3 H, ArH), 7.17–7.25 (m, 2 H, ArH), 4.27 (ddd, J = 9.1, 6.9, 6.9 Hz, 1 H, NCHH), 3.70 (ddd, J = 9.1, 6.9, 4.8 Hz, 1 H, NCHH), 2.83 (ddd, J = 11.2, 9.1, 4.8 Hz, 1 H, CHH), 2.61 (ddd, J = 11.2, 9.1, 6.9 Hz, 1 H, CHH), 2.40 (s, 3 H, $ArCH_3$) 1.55 (s, 9 H, 3 × CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0 (CO), 143.0 (C), 139.4 (C), 137.5 (C), 129.3 (CH), 128.0 (CH), 127.8 (CH), 127.1 (CH), 126.5 (CH), 83.0 (C), 77.8 (C), 47.1 (CH_2), 28.7 (CH_2), 27.8 (CH_3), 21.4 ($ArCH_3$).

HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{21}H_{25}NaNO_4S^+$: 410.1410; found: 410.1397.

(±)-2-Phenyl-1-tosylazetidine-2-carbonitrile (8d)
The product was prepared according to the general method from phenyl(tosylamino)acetonitrile (30.0 mg, 0.10 mmol, 1 equiv) to give a clear oil; yield: 10.5 mg (32%); R_f = 0.3 (EtOAc–PE, 2:8).

FTIR (neat): 3253, 3011, 2981, 1742, 1330, 1155 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.2 Hz, 2 H, ArH), 7.62–7.69 (m, 2 H, ArH), 7.37–7.48 (m, 3 H, ArH), 7.33 (d, J = 7.9 Hz, 2 H, ArH), 4.10 (ddd, J = 8.5, 8.5, 7.0 Hz, 1 H, NCHH), 3.98 (ddd, J = 8.5, 7.0, 4.0 Hz, 1 H, NCHH), 2.83 (ddd, J = 11.0, 8.5, 4.0

Hz, 1 H, C*H*H), 2.66 (ddd, *J* = 11.0, 8.5, 8.5 Hz, 1 H, C*H*H), 2.45 (s, 3 H, $ArCH_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6 (C), 136.6 (C), 129.63 (C), 129.57 (CH), 129.0 (CH), 128.4 (CH), 128.1 (CH), 125.6 (CH), 117.2 (CN), 66.0 (C), 47.0 (CH_2), 33.6 (CH_2), 21.6 ($ArCH_3$).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{16}N_2NaO_2S^+$: 335.0825; found: 335.0832.

Ethyl (±)-2-(4-Chlorophenyl)-1-tosylazetidine-2-carboxylate (10b)

The product was prepared according to the general method from ethyl (4-chlorophenyl)(tosylamino)acetate (61 mg, 0.17 mmol, 1 equiv) to give a clear oil; yield: 58 mg (88%); R_f = 0.4 (EtOAc–pentane, 2:8).

FTIR (neat): 3212, 2986, 1729, 1339, 1156 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.63 (m, 2 H, ArH), 7.22–7.42 (m, 6 H, ArH), 4.21 (m, 3 H, OCH_2 and NC*H*H), 3.83 (ddd, *J* = 9.0, 7.0, 5.0 Hz, 1 H, NC*H*H), 2.89 (ddd, *J* = 11.0, 9.0, 5.0 Hz, 1 H, C*H*H), 2.52 (ddd, *J* = 11.0, 9.0, 7.0 Hz, 1 H, C*H*H), 2.42 (s, 3 H, $ArCH_3$), 1.27 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 (CO), 143.5 (C), 137.9 (C), 136.6 (C), 134.0 (C), 129.4 (CH), 128.3 (CH), 127.7 (CH), 127.3 (CH), 77.1 (C), 62.3 (CH_2) 47.4 (CH_2), 29.2 (CH_2), 21.5 ($ArCH_3$), 13.8 (CH_3).

MS(ESI^+): *m/z* = 418.1 $[M + Na, {}^{37}Cl]^+$, 416.1 $[M + Na, {}^{35}Cl]^+$.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{20}ClNaNO_4S^+$: 416.0692; found: 416.0694.

Ethyl (±)-2-(4-Methoxyphenyl)-1-tosylazetidine-2-carboxylate (10c)

The product was prepared according to the general method from ethyl (4-methoxyphenyl)(tosylamino)acetate (62 mg, 0.17 mmol, 1 equiv) to give a clear oil; yield: 41 mg (62%); R_f = 0.17 (EtOAc–pentane, 2:8).

FTIR (neat): 2979, 1731, 1339, 1157 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.59 (m, 2 H, Ar*H*), 7.30–7.40 (m, 2 H, Ar*H*), 7.22 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.80–6.92 (m, 2 H, Ar*H*), 4.09–4.35 (m, 3 H, OCH_2 and C*H*H), 3.73–3.92 (m, 4 H, OCH_3 and C*H*H), 2.85 (ddd, *J* = 11.5, 9.0, 5.0 Hz, 1 H, C*H*H), 2.60 (ddd, *J* = 11.5, 9.0, 7.0 Hz, 1 H, C*H*H), 2.41 (s, 3 H, $ArCH_3$), 1.28 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (CO), 159.3 (C), 143.1 (C), 136.9 (C), 130.8 (C), 129.2 (CH), 127.8 (CH), 127.3 (CH), 113.6 (CH), 76.6 (C), 62.0 (CH_2), 55.3 (OCH_3), 47.1 (CH_2), 29.1 (CH_2), 21.5 ($ArCH_3$), 13.9 (CH_3).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{20}H_{23}NNaO_5S^+$: 412.1195; found: 412.1189.

Ethyl (±)-2-(2-Naphthyl)-1-tosylazetidine-2-carboxylate (10d)

The product was prepared according to the general method from ethyl (2-naphthyl)(tosylamino)acetate (65 mg, 0.17 mmol, 1 equiv) to give a clear oil; yield: 58 mg (83%); R_f = 0.2 (EtOAc–pentane, 2:8).

FTIR (neat): 2979, 1732, 1339, 1157 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.86 (m, 3 H, Ar*H*), 7.69–7.77 (m, 1 H, Ar*H*), 7.56–7.63 (m. Ar*H*), 2 H, 7.43–7.53 (m, 3 H, Ar*H*), 7.18 (dd, *J* = 8.5, 0.5 Hz, 2 H, Ar*H*), 4.15–4.43 (m, 3 H, OCH_2 and CH*H*), 3.92 (ddd, *J* = 9.0, 7.0, 5.0 Hz, 1 H, C*H*H), 2.99 (ddd, *J* = 11.0, 9.0, 5.0 Hz, 1 H, C*H*H), 2.64 (ddd, *J* = 11.0, 9.0, 7.0 Hz, 1 H, C*H*H), 2.38 (s, 3 H, $ArCH_3$), 1.30 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6 (CO), 143.3 (C), 136.8 (C), 136.4 (C), 132.8 (C), 131.0 (C), 129.3 (CH), 128.3 (CH), 128.0 (CH), 127.5 (CH), 127.3 (CH), 126.4 (CH), 126.2 (CH), 125.3 (CH), 124.1 (CH), 77.3 (C), 62.2 (CH_2), 47.5 (CH_2), 29.2 (CH_2), 21.4 ($ArCH_3$), 13.9 (CH_3).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{23}NNaO_4S^+$: 432.1230; found: 432.1240.

Ethyl (±)-2-(3-Furyl)-1-tosylazetidine-2-carboxylate (10e)

The product was prepared according to the general method from ethyl (3-furyl)(tosylamino)acetate (45 mg, 0.14 mmol, 1 equiv) to give a clear oil; yield: 19 mg (38%); R_f = 0.2 (EtOAc–pentane, 2:8).

FTIR (neat): 3279, 2927, 1721, 1683, 1321 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.39 (m, 2 H, Ar*H*), 7.20 (dd, *J* = 2.0, 0.5 Hz, 1 H, Ar*H*), 7.11 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 6.47 (dd, *J* = 3.5, 0.5 Hz, 1 H, Ar*H*), 6.29 (dd, *J* = 3.5, 2.0 Hz, 1 H, Ar*H*), 4.20–4.30 (m, 2 H, CH_2), 3.93–4.02 (m, 1 H, C*H*H), 3.85–3.92 (m, 1 H, C*H*H), 2.72–2.84 (m, 1 H, C*H*H), 2.61–2.70 (m, 1 H, C*H*H), 2.32 (s, 3 H, CH_3), 1.27 (t, *J* = 7.0 H Hz, 3 H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4 (C), 142.9 (C), 142.6 (C), 129.3 (CH), 129.2 (CH), 127.3 (CH), 127.1 (C), 110.8 (CH), 110.7 (CH), 70.4 (C), 62.2 (CH_2), 46.9 (CH_2), 27.3 (CH_2), 21.4 ($ArCH_3$), 14.0 (CH_3).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{19}NNaO_5S^+$: 372.0876; found: 372.0871.

Diethyl 1-Tosylazetidine-2,2-dicarboxylate (10f)

The product was prepared according to the general method from diethyl (tosylamino)malonate (56 mg, 0.17 mmol, 1 equiv) to give a clear oil; yield: 47 mg (78%); R_f = 0.25 (EtOAc–pentane, 2:8).

FTIR (neat): 2982, 1737, 1340, 1159 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.21 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 4.22 (q, *J* = 7.0 Hz, 4 H, 2 × CH_2), 3.97 (t, *J* = 7.5 Hz, 2 H, CH_2), 2.55 (t, *J* = 7.5 Hz, 2 H, CH_2), 2.34 (s, 3 H, $ArCH_3$), 1.24 (t, *J* = 7.0 Hz, 6 H, 2 × CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3 (CO), 143.4 (C), 137.9 (C), 129.2 (CH), 127.4 (CH), 62.3 (CH_2), 47.5 (NCH_2), 24.4 (CH_2), 21.5 ($ArCH_3$), 13.9 (CH_3).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{16}H_{21}NNaO_6S$: 378.0984; found: 378.0982.

1-Benzyl 2-Methyl (±)-2-phenylazetidine-1,2-dicarboxylate (8e)

The product was prepared according to the general method from methyl [(benzyloxycarbonyl)amino](phenyl)acetate (51 mg, 0.17 mmol, 1 equiv; prepared by the method of Kashima et al.[20]) to give a clear oil; yield: 21 mg (38%).

FTIR (neat): 3337, 3034, 2946, 1702, 1509, 1354, 1215 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.52 (m, 10 H, ArH), 5.40 (d, *J* = 12.0 Hz, 1 H, C*H*HPh), 5.30 (d, *J* = 12.0 Hz, 1 H, C*H*HPh) 4.30 (ddd, *J* = 11.0, 9.0, 3.5 Hz, 1 H, NC*H*H), 4.16 (ddd, *J* = 11.0, 6.5, 4.0 Hz, 1 H, NC*H*H), 3.71 (s, 3 H, OCH_3), 2.76 (ddd, *J* = 14.0, 6.5, 3.5 Hz, 1 H, C*H*H), 2.03 (ddd, *J* = 14.0, 9.0, 4.0 Hz, 1 H, C*H*H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.9 (CO), 152.7 (CO), 142.6 (C), 136.3 (C), 128.4 (CH), 128.4 (CH), 128.1 (CH), 128.0 (CH), 127.5 (CH), 125.6 (CH), 69.2 (CH_2), 64.4 (CH_2), 63.3 (C), 52.8 (CH_3), 32.0 (CH_2).

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{19}NNaO_4$: 348.1205; found: 348.1206.

Diethyl Oxetane-2,2-dicarboxylate (12b)

Diethyl hydroxymalonate (60 mg, 0.34 mmol, 1 equiv; prepared according to the method of Cohen et al.[16]) was dissolved in CH_2Cl_2 (4.5 mL, 0.07 M). (2-Bromoethyl)sulfonium triflate (**1**; 185 mg, 0.42 mmol, 1.25 equiv) and DBU (175 µL, 1.16 mmol, 3.5 equiv) were added sequentially and the mixture was refluxed for 3 h. Workup according to the general procedure to give a clear oil; yield: 47 mg (68%); R_f = 0.5 (EtOAc–pentane, 2:8).

FTIR (neat): 3337, 2946, 1701, 1509, 1366 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.67 (t, *J* = 8.0 Hz, 2 H, CH_2), 4.31 (q, *J* = 7.0 Hz, 4 H, OCH_2CH_3), 3.09 (t, *J* = 8.0 Hz, 2 H, CH_2), 1.31 (t, *J* = 7.0 Hz, 6 H, 2 × CH_3).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 168.7 (CO), 84.4 (C), 67.9 (CH_2), 62.1 (CH_2), 28.4 (CH_2), 14.0 (CH_3).

MS (ESI^+): *m/z* = 225.1 $[M + Na]^+$, 203.1 $[M + H]^+$.

HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_9H_{14}NaO_5^+$: 225.0735; found: 225.0733.

(±)-1-Tosylazetidine-2-carboxylic Acid (13f)

A 2 M soln of KOH in EtOH (4 mL) was added to diethyl 1-tosylazetidine-2,2-dicarboxylate (**10f**; 100 mg, 0.28 mmol, 1 equiv) and the mixture was refluxed for 2 h with vigorous stirring, then cooled. The resulting mixture was acidified with 2 M aq HCl and extracted with EtOAc (3 × 30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. (LC/MS at this stage showed complete conversion into the dicarboxylic acid.) The resulting crude mixture was treated with 6 M aq HCl (4 mL), refluxed with stirring for 5 h, and cooled to r.t. H_2O was added (10 mL) and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo to give a white coating on the flask; yield: 53 mg (74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.5 Hz, 2 H, ArH), 7.33 (d, *J* = 8.5 Hz, 2 H, ArH), 4.34–4.50 (m, 1 H, CH), 4.18 (ddd, *J* = 11.5, 9.5, 5.5 Hz, 1 H, NC*H*H), 3.81–3.97 (m, 1 H, NC*H*H), 2.64–2.79 (m, 1 H, C*H*H), 2.43 (s, 3 H, $ArCH_3$), 2.28 (dddd, *J* = 13.0, 11.5, 11.5, 9.0 Hz, 1 H, C*H*H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1 (COOH), 144.4 (C), 135.8 (C), 130.1 (CH), 127.4 (CH), 66.2 (CH_2), 51.9 (CH), 31.5 (CH_2), 21.7 ($ArCH_3$).

The spectroscopic data were consistent with those reported in the literature.[21]

Acknowledgment

S.P.F. thanks the Engineering and Physical Sciences Research Council (EPSRC) for a scholarship. J.F.M. thanks the Junta de Andalucía (C.E.I.y C.) for a predoctoral fellowship. V.K.A. thanks the Royal Society for a Wolfson Research Merit Award, the EPSRC for a Senior Research Fellowship, and Merck for research support.

References

(1) For azetidine iminosugars, see: (a) Lenagh-Snow, G. M. J.; Araujo, N.; Jenkinson, S. F.; Rutherford, C.; Nakagawa, S.; Kato, A.; Yu, C.-Y.; Weymouth-Wilson, A. C.; Fleet, G. W. J. *Org. Lett.* **2011**, *13*, 5834. For total syntheses, see: (b) Kinoshita, E.; Yamakoshi, J.; Kikuchi, M. *Biosci., Biotechnol., Biochem.* **1993**, *57*, 1107. (c) Takemoto, T.; Nomoto, K.; Fushiya, S.; Ouchi, R.; Kusano, G.; Hikino, H.; Takagi, S.; Matsuura, Y.; Kakudo, M. *Proc. Jpn. Acad., Ser. B* **1978**, *54*, 469.

(2) (a) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3524. (b) Burkhard, J. A.; Guérot, C.; Knust, H.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 66. For recent examples of thrombin inhibitors, see: (c) Ericksson, B. I.; Carlsson, S.; Halvarsson, M.; Risberg, B.; Mattsson, C. *Thromb. Haemostasis* **1997**, *78*, 1404. (d) Kirk, I. WO 00/41716, **2000**.

(3) (a) Ghorai, M. K.; Kumar, A.; Das, K. *Org. Lett.* **2007**, *9*, 5441. (b) Van Brabandt, W.; Van Landeghem, R.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 1105. (c) Vargas-Sanchez, M.; Couty, F.; Evano, G.; Prim, D.; Marrot, J. *Org. Lett.* **2005**, *7*, 5861. (d) Banide, E.; de Talancé, V. L.; Schmidt, G.; Lubin, H.; Comesse, S.; Dechoux, L.; Hamon, L.; Kadouri-Puchot, C. *Eur. J. Org. Chem.* **2007**, 4517. (e) Almens, J.; Foubelo, F.; Yus, M. *Tetrahedron* **1994**, *50*, 5775.

(4) (a) Zi, G. F.; Liu, R. C.; Bai, X. M.; Zhang, Z. B. *Appl. Organomet. Chem.* **2008**, *22*, 671. (b) Couty, F.; Prim, D. *Tetrahedron: Asymmetry* **2002**, *13*, 2619. (c) Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **2001**, *12*, 605. (d) Hermsen, P. J.; Cremers, J. G. O.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **2001**, *42*, 4243. (e) Doyle, M. P.; Davies, S. B.; Hu, W. *Chem. Commun.* **2000**, 867. (f) Starmans, W. A. J.; Walgers, R. W. A.; Thijs, L.; de Gelder, R.; Smits, J. M. M.; Zwanenburg, B. *Tetrahedron* **1998**, *54*, 4991.

(5) For a recent example, see: Medjahdi, M.; González-Gámez, J. C.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2009**, *74*, 7859.

(6) For reviews on synthetic methods for azetidines, see: (a) Couty, F.; Evano, G. *Synlett* **2009**, 3053. (b) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988.

(7) For the direct use of (2-bromoethyl)sulfonium triflate in annulation reactions, see: (a) McGarrigle, E. M.; Fritz, S. P.; Favereau, L.; Yar, M.; Aggarwal, V. K. *Org. Lett.* **2011**, *13*, 3060. (b) Fritz, S. P.; Mumtaz, A.; Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Eur. J. Org. Chem.* **2011**, 3156. (c) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Org. Lett.* **2009**, *11*, 257.

(8) For related work on the applications of vinyl sulfonium salts in synthesis, see: (a) Yar, M.; Fritz, S. P.; McGarrigle, E. M.; Aggarwal, V. K. *Eur. J. Org. Chem.* **2012**, 160. (b) Chen, J. R.; An, J.; Chang, N. J.; Song, L. D.; Jin, Y. Q.; Ma, Y.; Xiao, W. J. *Chem. Commun.* **2011**, *47*, 1869. (c) Yar, M.; McGarrigle, E. M.; Unthank, M. G.; Aggarwal, V. K. *Chem.–Asian J.* **2011**, *6*, 372. (d) Xie, C. S.; Han, D. Y.; Hu, Y.; Liu, J. H.; Xie, T. A. *Tetrahedron Lett.* **2010**, *51*, 5238. (e) Maeda, R.; Ooyama, K.; Anno, R.; Shiosaki, M.; Azema, T.; Hanamoto, T. *Org. Lett.* **2010**, *12*, 2548. (f) Catalán-Muñoz, S.; Müller, C. A.; Ley, S. V. *Eur. J. Org. Chem.* **2010**, 183. (g) Bornholdt, J.; Felding, J.; Kristensen, J. L. *J. Org. Chem.* **2010**, *75*, 7454. (h) Xie, C. S.; Han, D. Y.; Liu, J. H.; Xie, T. *Synlett* **2009**, 3155. (i) Unthank, M. G.; Tavassoli, B.; Aggarwal, V. K. *Org. Lett.* **2008**, *10*, 1501. (j) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3784. (k) Kokotos, C. G.; McGarrigle, E. M.; Aggarwal, V. K. *Synlett* **2008**, 2191. (l) Hansch, M.; Illa, O.; McGarrigle, E. M.; Aggarwal, V. K. *Chem.–Asian J.* **2008**, *3*, 1657. (m) Unthank, M. G.; Hussain, N.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2006**, *45*, 7066. (n) Yamanaka, H.; Matsuo, J.; Kawana, A.; Mukaiyama, T. *ARKIVOC* **2004**, *(iii)*, 42. (o) Yamanaka, H.; Matsuo, J.; Kawana, A.; Mukaiyama, T. *Chem. Lett.* **2003**, *32*, 626. (p) Matsuo, J.; Yamanaka, H.; Kawana, A.; Mukaiyama, T. *Chem. Lett.* **2003**, *32*, 392. (q) Kim, K. H.; Jimenez, L. S. *Tetrahedron: Asymmetry* **2001**, *12*, 999. (r) Yar, M.; McGarrigle, E. M.; Aggarwal, V. K. In *Encyclopaedia of Reagents for Organic Synthesis;* Paquette, L. A.; Crich, D.; Fuchs, P. L.; Molander, G. A., Eds.; Wiley: Hoboken, **2012**, in press, DOI: 10.1002/047084289X. (s) Fritz, S. P. *Synlett* **2012**, *23*, 480.

(9) Note that in the case of the diester-substituted azetidine and oxetane, it is not clear whether the heteroatom or the enolate is the nucleophile in the conjugate addition to salt **2**.

(10) Tanaka, M.; Kurosaki, Y.; Washio, T.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2007**, *48*, 8799.

(11) Lu, X. Y.; Dai, H. X.; Yang, M. *Adv. Synth. Catal.* **2008**, *350*, 249.

(12) Das, B.; Balasubramanyam, P.; Krishnaiah, M.; Veeranjaneyulu, B.; Reddy, G. C. *Synthesis* **2009**, 3467.

(13) In contrast, however, Kawabata has reported an interesting memory-of-chirality effect in a related intramolecular allylation reaction, see: (a) Moriyama, K.; Sakai, H.; Kawabata, T. *Org. Lett.* **2008**, *10*, 3883. (b) Kawabata, T.; Moriyama, K.; Kawakami, S.; Tsubaki, K. *J. Am. Chem. Soc.* **2008**, *130*, 4153. (c) Kawabata, T.; Matsuda, S.; Kawakami, S.; Monguchi, D.; Moriyama, K. *J. Am. Chem. Soc.* **2006**, *128*, 15394.

(14) Although the conventional approach is the Strecker synthesis, many other methods are available. For reviews, see: (a) Sansano, J. M.; Najera, C. *Chem. Rev.* **2007**, *107*, 4584. (b) Williams, R. M.; Hendrix, J. A. *Chem. Rev.* **1992**, *92*, 889.

(15) Zareef, M.; Iqbal, R.; De Dominguez, N. G.; Rodrigues, J.; Zaidi, J. H.; Arfan, M.; Supuran, C. T. *J. Enzym. Inhib. Med. Chem.* **2007**, *22*, 301.

(16) This compound is commercially available and can be found by searching on the CAS Registry Number [774-40-3].

(17) Cohen, S. G.; Khedouri, E. *J. Am. Chem. Soc.* **1961**, *83*, 4228.

(18) For descriptions of the importance of oxetanes, see: (a) Rogers-Evans, M.; Burkhard, J. A.; Wuitschik, G.; Muller, K.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 9052. (b) Carreira, E. M.; Wuitschik, G.; Wagner, B.; Fischer, H.; Parrilla, I.; Schuler, F.; Rogers-Evans, M.; Muller, K. *J. Med. Chem.* **2010**, *53*, 3227.

(19) (a) Azetidine-2-carboxylic acid is the four-membered-ring analogue of the amino acid proline and causes protein misconstruction when used to replace proline. For its first isolation, see: Fowden, L. *Nature* **1955**, *176*, 347. (b) For previous syntheses, see ref. 6b and: Couty, F.; Evano, G.; Vargas-Sanchez, M.; Bouzas, G. *J. Org. Chem.* **2005**, *70*, 9028; and references therein.

(20) Kashima, C.; Tsuruoka, S.; Mizuhara, S. *Tetrahedron* **1998**, *54*, 14679.

(21) Zwanenburg, B.; Starmans, W. A. J.; Thijs, L. *Tetrahedron* **1998**, *54*, 629.

