Organic & Biomolecular Chemistry

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The asymmetric synthesis of terminal aziridines by methylene transfer from sulfonium ylides to imines†

Cite this: DOI: 10.1039/c3ob27271k

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A new ylide-based protocol for the asymmetric aziridination of imines *via* methylene transfer has been developed involving the use of a simple chiral sulfonium salt and an organic strong base. A systematic study identified triisopropylphenyl sulfonylimines as optimal substrates for the process. Unexpectedly, hindered C_2-symmetric sulfonyl salts incorporating bulky ethers at C-2 and C-5 – which had previously been useful in the corresponding epoxidation chemistry – decomposed in these aziridination reactions *via* competing elimination pathways. Under optimised conditions it was found that a simple salt derived from (2*R*,5*R*)-2,5-diisopropyl thiolane could mediate asymmetric methylene transfer to a range of imines with uniformly excellent yields with 19–30% *ee*. Since this is a similar level of enantiomeric excess to that obtained using these same salts in epoxidation chemistry, it was concluded that if more bulky sulfonium salts could be devised which were resistant to decomposition under the reaction conditions, that highly enantioselective aziridine formation by methylene transfer would be possible.

Received 22nd November 2012,
Accepted 3rd April 2013

DOI: 10.1039/c3ob27271k

www.rsc.org/obc

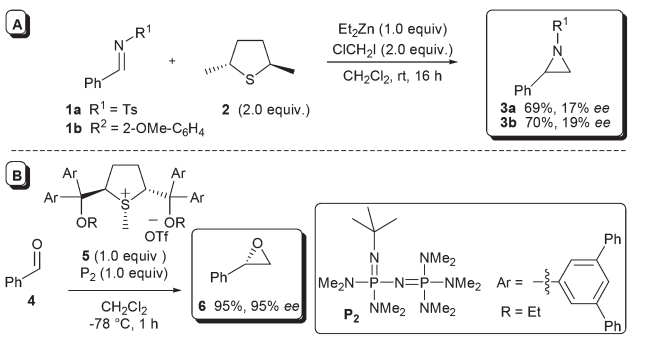
Introduction

Aziridines are 3-membered nitrogen heterocycles of substantial synthetic importance found in a number of pharmaceutically relevant molecules,[1,2] and natural products.[3] Their considerable utility largely derives from ring-strain,[4] which facilitates their participation in highly selective ring-opening reactions with nucleophiles.[5] It is unsurprising therefore, that the catalytic asymmetric synthesis of chiral aziridines from acyclic starting materials has been the subject of intensive research endeavour.[6] Several methodologies have been developed; these can be organised into three general transformation classes: (a) addition (formal or otherwise) of either a nitrene or nitrene-equivalent to alkenes,[6] (b) the reaction between carbenoids and imines[6,7] and (c) the sulfonium ylide-mediated aziridination of imines.[6,8]

The latter class of reaction is an aza-analogue of the highly successful asymmetric Johnson–Corey–Chaykovsky process[8a,b,9,10] and has proven particularly useful for the synthesis of di- and trisubstituted aziridines with excellent levels of enantiocontrol and moderate–good diastereoselectivity.[11] However, as has been the case (until recently) with the epoxidation variant of the process,[12] the sulfonium-ylide based methodologies are bedevilled by an Achilles heel which limits the substrate scope: the catalytic asymmetric synthesis of *terminal aziridines* from methylene transfer to imines is an inefficient and relatively unselective process.

To date a single report has emerged on this subject: Aggarwal *et al.*[12c] demonstrated that the benzaldehyde-derived imines **1a–b** could be converted to the corresponding terminal aziridines **3a–b** in good yields (*ca.* 70%) and 19–20% *ee* under Simmons–Smith type conditions involving the use of 2.0 equivalents of both the chiral sulfide **2** and ICH_2Cl in the presence of stoichiometric amount of diethyl zinc (Scheme 1A).

We recently became interested in the corresponding reactions to form terminal epoxides[13] from aldehydes (a process which was also characterised by poor–moderate levels of enantioselectivity and product yield[12c,14]) and reported the design of novel, highly hindered sulfonium salts such as **5**, which



Scheme 1 (A) The literature protocol for sulfonium ylide-mediated asymmetric aziridination to yield terminal aziridines. (B) Asymmetric epoxidation of benzaldehyde to styrene oxide mediated by sulfonium salt **5**.

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†Electronic supplementary information (ESI) available: All procedures and characterisation data. See DOI: 10.1039/c3ob27271k

proved capable of mediating these reactions in >90% yield and *ee* for the first time (Scheme 1B).[15]

Results and discussion

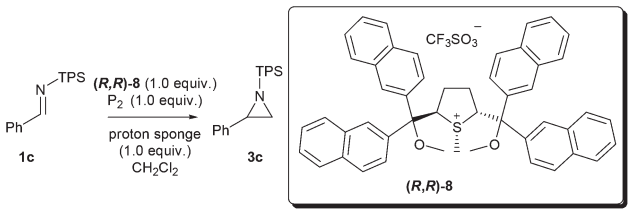
Naturally therefore, our first approach to tackling the problem of asymmetric aziridination reactions centred on the use of sulfonium ions such as **5**. To determine if these general reaction conditions involving the use of a strong organic base such as P_2 would be compatible with aziridine formation, we reacted the *N*-tosyl-imine **1a** with stoichiometric quantities of the achiral sulfonium salt **7** in the presence of proton sponge as an auxiliary base to scavenge any traces of triflic acid associated with the decomposition of **7**. We were pleased to observe clean aziridination of **1** to (***rac***)-**3a** in just 30 min. The more hindered TPS protecting group (*i.e.* imine **1c**) can also be used to generate the corresponding aziridine efficiently, albeit in lower product yield (Scheme 2).

Since this base-mediated aziridination protocol is rapid and furnishes the product in high yield, attention then turned to the question of enantioselectivity. In preliminary experiments, the aziridination of **1c** by the hindered, readily prepared chiral sulfonium salt (***R*,*R***)-**8** (known to be capable of enantioselective terminal epoxidation[15]) was carried out under a range of conditions. A selection this data is presented in Table 1.

Under conditions identical to those outlined in Scheme 2, **3c** was formed in similar yield but only 25% *ee* after 75 min reaction time (entry 1). Somewhat surprisingly, reduction of either the temperature (entry 2) or the reaction concentration (entry 3) led to lower enantioselectivity. In addition, while the reaction at ambient temperature proceeded relatively cleanly, multiple products were observed at lower temperatures and higher dilutions. Careful ^{1}H NMR spectroscopic analysis of the crude material from these reactions indicated that the majority of (***R*,*R***)-**8** had decomposed: subsequent chromatography allowed the identification and isolation of three products derived from (***R*,*R***)-**8** (*i.e.* alkenes **9–10** and allene **11**, Fig. 1).

All three products are characterised by the elimination of methanol and the destruction of at least one (two in the case of **10**) chiral centre. Since all three products are sulfides (as opposed to sulfonium salts) it would appear reasonable to suggest that the low observed product *ee* is due (at least in part) to decomposition of (***R*,*R***)-**8** to methylated sulfonium salt analogues of **9–11** *via* elimination reactions, with subsequent base-mediated methylene transfer to the imine, yielding **9–11**.

Table 1 Asymmetric aziridination involving the chiral salt **8**



Entry	Concentration (M)	Temperature (°C)	Time (h)	Yield[a] (%)	*ee*[b] (%)
1	0.4	rt	1.25	70	25
2	0.08	−78	17	69[c]	15
3	0.01	rt	1.25	n.d.[d]	19

[a] Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [b] Determined by CSP-HPLC. [c] Refers to conversion. [d] Not determined due to the formation of multiple products.

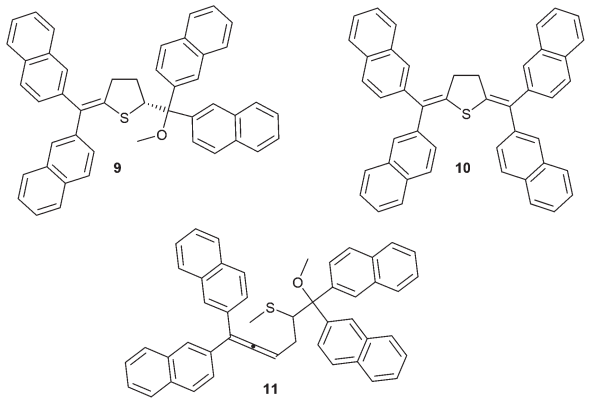
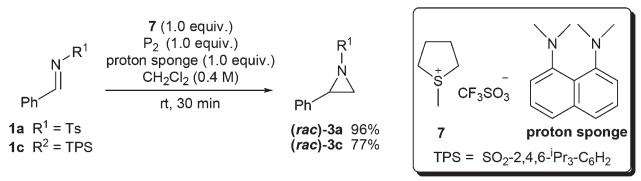


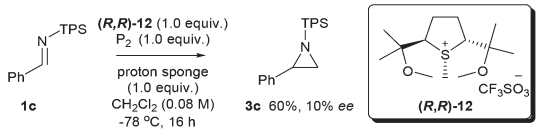
Fig. 1 The isolated decomposition products derived from (***R*,*R***)-**8**.

Since methylene transfer from salts derived from **9–11** would expected to be inefficient from a stereochemical perspective (due to the loss of chiral information during decomposition), low product *ee* results. It is interesting to note that these decomposition pathways *were not a feature of the analogous epoxidation chemistry at any temperature or concentration evaluated*.[15,16]

On the assumption that decomposition could be favourable due to the highly conjugated nature of the alkene products **9–11**, we sought to develop an analogue of (***R*,*R***)-**8** devoid of pendant aromatic substituents. Sulfonium salt (***R*,*R***)-**12** was duly prepared and evaluated in the aziridination of **1c**, resulting in the formation of **3c** in low *ee* (Scheme 3). Again,

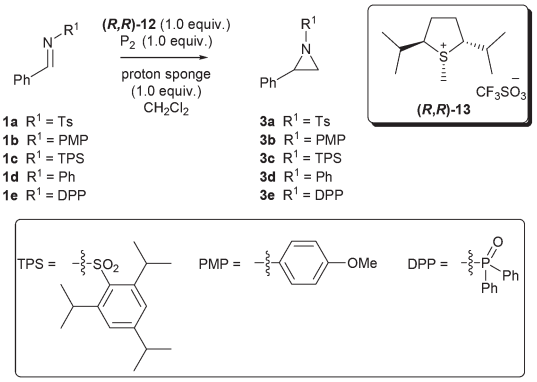


Scheme 2 Initial aziridination experiments using the achiral salt **7**.



Scheme 3 Asymmetric aziridination involving the chiral salt **12**.

Table 2 Asymmetric aziridination involving the chiral salt **(*R*,*R*-13)**



Entry	Imine	Conc. (M)	Temp. (°C)	Time (h)	Yield[a] (%)	*ee*[b] (%)
1	**1a**	0.4	rt	0.5	87	6
2	**1b**	0.4	rt	0.5	8	n.d.
3	**1c**	0.4	rt	0.5	85	14
4	**1d**	0.4	rt	1.5	31	13
5	**1e**	0.4	rt	1.5	70[c]	9
6	**1e**	0.4	−78	16	87[c]	2
7	**1e**	0.4	60	0.5	98[c]	10
8	**1e**	0.08	−78	16.5	96[c]	1
9	**1c**	0.4	−78	17	90	18
10	**1c**	0.08	−78	16	72	22
11[d]	**1c**	0.08	−78	16	94	23
12[d]	**1c**	0.02	−78	17	85	23

[a] Determined by ^{1}H NMR spectroscopy using styrene as an internal standard. [b] Determined by CSP-HPLC. [c] Refers to conversion. [d] In the presence of 3 Å mol. sieves.

^{1}H NMR spectroscopic analysis of the crude material indicated significant catalyst decomposition.

Thus it is likely that the presence of the alkoxy group is the root-cause of the inherent instability of materials such as **8** and **12** in these aziridination processes. Accordingly, we prepared the *bis*-isopropyl substituted sulfonium salt **(*R*,*R*)-13** and reacted it with imines **1a–e** under the base-mediated aziridination conditions (Table 2).

The *N*-tosyl imine proved to be a poor substrate under these conditions (ambient temperature, 0.4 M concentration) from an asymmetric induction standpoint – the aziridine **3a** was formed in good yield and only 6% *ee* (entry 1). Significantly, no evidence of decomposition of the salt **(*R*,*R*)-13** was observed by ^{1}H NMR spectroscopy, only the clean regeneration of the corresponding demethylated sulfide analogue (which could be recovered by column chromatography) was observed. The PMP-protected imine **1b** was found to be relatively unreactive under these conditions (entry 2). The aziridination of the more hindered sulfonylimine **1c** proceeded more selectively: the aziridine **3c** was formed in a modest yet considerably improved 14% *ee* (entry 3). The *N*-phenyl imine **1d** underwent reaction with similar levels of product *ee*, however, as was the case with the PMP-protected analogue **1b** – insufficient activation of the imine by the protecting group proved problematic (entry 4). The use of the diphenylphosphoryl substituent (*i.e.* imine **1e**) resulted in moderate product yield but low enantioselectivity (entry 5).

These experiments indicated that only the TPS- and DPP-substituted imines (*i.e.* **1c** and **1e**) possessed the requisite activity and steric characteristics to be considered as suitable candidates for subsequent optimisation studies. The sensitivity of the aziridination of DPP to both temperate and concentration were next probed: we found that the unusual attenuation of enantioselectivity observed earlier (Table 1) at low temperatures of −78 °C was again a feature (although without catalyst decomposition on this occasion, entry 6), while (surprisingly) increasing the reaction temperature led to a marginal increase in product *ee* (entry 7). It is perhaps noteworthy that in the analogous epoxidation chemistry, improved enantioselectivity at lower temperatures was always observed. Aziridination of **1e** under dilute conditions at low temperature afforded near-racemic product (entry 8).

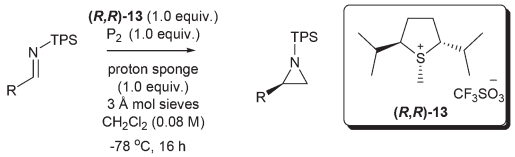
More pleasingly, the hindered TPS-substituted imine **1c** underwent more selective aziridination both when the temperature was decreased (entry 9) and when the concentration was reduced (entry 10). Under these conditions we detected low levels of styrene oxide product – presumably formed from hydrolysis of the imine by adventitious water and subsequent epoxidation mediated by **13** – and therefore we repeated the experiment in the presence of molecular sieves, which resulted in improved product yield (94%) and enantiomeric excess (23% *ee*, entry 11). Further dilution reduced reaction rates and failed to improve the enantioselectivity (entry 12). Thus it is clear from an analysis of the results of these experiments that the TPS protecting group is superior to others evaluated, however the improvement in levels of product enantiomeric excess resulting from the use of this group is marginal.

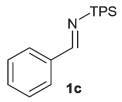
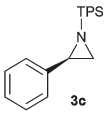
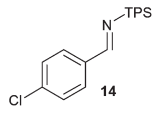
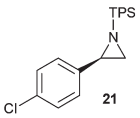
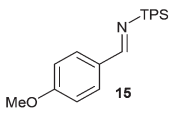
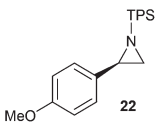
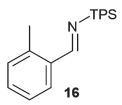
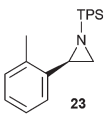
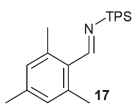
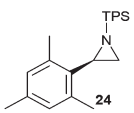
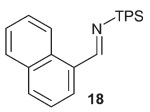
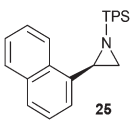
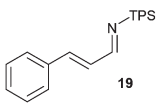
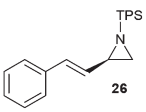
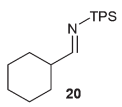
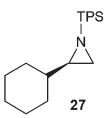
With the optimum conditions in hand, we sought to establish the substrate scope (Table 3). Overall, the scope was found to be quite broad – TPS-substituted imines of various steric and electronic characteristics (aromatic, aliphatic and α,β-unsaturated) could be converted to the corresponding aziridines efficiently in 87–92% isolated yield.

As expected, imine **1c** could be converted to **3c** in excellent yield and 23% *ee* (entry 1). It is noteworthy that while this level of asymmetric induction is modest, the protocol represents a small improvement in terms of stereoselectivity and a significant advance from an efficacy standpoint over the previous literature benchmark (*i.e.* considerably higher yields using half the amount of ylide precursor). The more activated imine **14** underwent slightly less selective aziridination (entry 2). The deactivated imine **15** proved a relatively useful substrate (entry 3), while more hindered analogues **16**, **17** and **18** formed **23–25** with comparable enantioselectivity (entries 4–6). We were pleased to observe that both electrophilic α,β-unsaturated- and base-sensitive aliphatic imines were compatible with the methodology – no competing cyclopropanation or self-condensation through enamide ions (respectively) were observed (entries 7–8).

In summary, we have developed a new protocol for the asymmetric aziridination of imines which is marginally more

Table 3 Evaluation of substrate scope



Entry	Substrate	Product	Yield[a] (%)	*ee*[b] (%)
1	 **1c**	 **3c**	91	23
2	 **14**	 **21**	88	18
3	 **15**	 **22**	92	25
4	 **16**	 **23**	87	30
5	 **17**	 **24**	87	25
6	 **18**	 **25**	92	23
7	 **19**	 **26**	92	18
8	 **20**	 **27**	91	20

[a] Isolated yield. [b] Determined by CSP-HPLC.

selective and considerably more efficient than the literature benchmark. Highly hindered sulfonium catalysts bearing an alkoxy group which proved very successful in the corresponding epoxide chemistry were not useful here due to competing elimination reactions which generate less discriminating sulfonium salts *in situ*. The easily prepared and stable salt **(*R*,*R*)-13** was found to be capable of mediating the highly efficient ylide-based synthesis of terminal aziridines (the substrate scope of this class of process was probed for the first time) with either comparable or higher levels of product *ee* to the only previous example in the literature.

It is noteworthy that the degree of enantioinduction observed in this process is marginally higher than that obtained from the use of **13** in the corresponding epoxidation

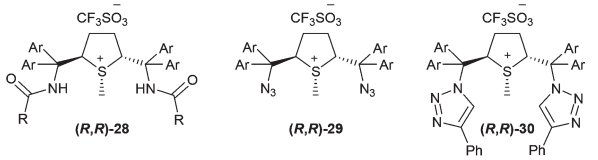


Fig. 2 Unsuccessful candidate structures.

chemistry under optimised conditions (*e.g.* **13** mediated the formation of styrene oxide from benzaldehyde in 80% yield and 18% *ee*[13c]). This leads to the conclusion that the there is nothing inherently problematic with the aziridine substrates in these reactions from a asymmetric induction standpoint, and that if the steric bulk of **(*R*,*R*)-13** could be augmented considerably[17] without the structure decomposing during aziridination, then, as was the case with the epoxidation chemistry (*vide supra*), that excellent enantioselectivity should be possible. As yet we have not been able to devise such a structure. Avenues we have explored thus far (Fig. 2) include candidate materials such as **28–30**, which fail due to base-sensitivity (**28** and **29**) and unselective alkylation (**30**). Efforts to circumvent these difficulties are underway.

Experimental

General

Proton nuclear magnetic resonance spectra were recorded on a Bruker Avance 400 or 600 MHz spectrometer in $CDCl_3$ referenced relative to residual $CHCl_3$ (δ = 7.26 ppm) or DMSO-d_6 referenced relative to residual DMSO-d_6 (δ = 2.50 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instruments (100 or 150 MHz) with total proton decoupling. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer Spectrum One spectrophotometer. Flash chromatography was carried out using silica gel, particle size 0.04–0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualised by UV irradiation, $KMnO_4$, phosphomolybdic acid, or anisaldehyde staining. Specific rotation measurements were made on a Rudolph research analytical Autopol IV instrument, and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Anhydrous THF was distilled over sodium–benzophenone ketyl radical before use. Methylene chloride, toluene and triethylamine were distilled from calcium hydride. All reactions were carried out under a protective argon atmosphere. Analytical CSP-HPLC was performed on Daicel CHIRALCEL OJ-H (4.6 mm × 25 cm) and CHIRALPAK AD-H (4.6 mm × 25 cm). Solid reagents for all catalysed reactions were weighed using a Precisa balance, series 320XR, model XR125SM-FR (readability 0.01 mg/0.1 mg). For all known compounds the spectral characteristics were in agreement with those reported in the literature. (2*R*,5*R*)-2,5-Diisopropyl-thiolane was prepared according to a literature procedure.[13c] Imines *N*-benzylidene-4-methoxybenzenamine (**1b**),[18] *N*-(benzylidene)-4-methylbenzenesulfonamide (**1a**),[19] *P*,*P*-diphenyl-*N*-(phenylmethylene)phosphinic

amide (**1e**)[20] and *N*-phenyl benzaldehyde imine (**1d**)[21] were prepared according to literature procedures. The spectroscopic data of the aforementioned compounds were consistent with those previously reported.

General procedure A: synthesis of imines (1c and 14–20)

An oven dried round bottomed flask was charged with 2,4,6-triisopropylbenzenesulfonamide (1 equiv.), fitted with a septum and placed under an atmosphere of argon (balloon). CH_2Cl_2 was then added *via* syringe followed by triethylamine (3 equiv.) and the appropriate aldehyde (1 equiv.). The resulting solution was cooled to 0 °C. Titanium(IV) chloride (0.5 equiv.) in CH_2Cl_2 was then added dropwise to the cooled solution and the resulting solution was allowed to stir for 1 h at this temperature. The reaction mixture was filtered through Celite and washed with CH_2Cl_2. The filtrate was concentrated *in vacuo* and the resulting solid was suspended in toluene and then filtered. The filtrate was then concentrated under reduced pressure to afford the desired imine which was purified as required.

Representative example: synthesis of (*R*)-2-phenyl-1-(2,4,6-triisopropylbenzenesulfonyl)aziridine (3c)

An oven dried round bottomed flask containing a magnetic stirring bar and (2*R*,5*R*)-**13** (21.36 mg, 0.063 mmol) was charged with proton sponge (13.60 mg, 0.063 mmol), **1c** (23.58 mg, 0.063 mmol) and activated 3 Å molecular sieves. The flask was placed under vacuum for 1 h and then immediately flushed with argon, fitted with a rubber septum and placed under an atmosphere of argon (balloon). Freshly distilled CH_2Cl_2 (0.79 cm^3 – stored over activated 3 Å molecular sieves) and styrene (7.3 μL, 0.063 mmol), was then added sequentially *via* syringe. The resulting solution was cooled to −78 °C. P_2 base (2.0 M in THF, 31.7 μL, 0.063 mmol) was then added dropwise. After 16 h, the crude material was purified by column chromatography (8 : 2 hexane–CH_2Cl_2) to furnish the desired aziridine **3c** as a white solid (22.20 mg, 91%, 23% *ee*). M.p. 82–84 °C. $[\alpha]_{20}^{D}$ = −7.9 (*c* 0.16, CH_2Cl_2, 23% *ee*). CSP-HPLC: Chiralpak AD-H (4.6 mm × 25 cm), hexane–IPA: 9.5/0.5, 0.5 mL min^{-1}, RT, UV detection at 220 nm, retention times: 10.0 min (minor enantiomer) and 12.2 (major enantiomer). δ_H (400 MHz, $CDCl_3$): 1.23–1.28 (m, 18H), 2.37 (d, *J* 4.4, 1H), 2.90 (septet, *J* 6.9, 1H), 3.04 (d, *J* 7.2, 1H), 3.80 (dd, *J* 4.4, 7.2, 1H), 4.40 (septet, *J* 6.8, 2H), 7.17 (s, 2H), 7.18–7.21 (m, 2H), 7.26–7.32 (m, 3H). δ_C (100 MHz, $CDCl_3$): 23.7, 24.9, 25.1, 29.9, 34.4, 36.3, 40.7, 124.0, 126.6, 128.3, 128.6, 131.4 (q), 135.8 (q), 151.4 (q), 153.7 (q). ν (cm^{-1}): 694, 758, 1151, 1313, 1462, 1562, 1602, 2869, 2929, 2957. HRMS (EI): $[M]^+$ Calcd for $C_{23}H_{31}NO_2S$ 385.2076; found 385.2061.

Notes and references

1 V. H. Dahanukar and I. Zavialov, *Curr. Opin. Drug Discovery Dev.*, 2002, **5**, 918.
2 Representative Tamiflu syntheses: (*a*) S. Abrecht, M. C. Federspiel, H. Estermann, R. Fischer, M. Karpf, H.-J. Mair, T. Oberhauser, G. Rimmler, R. Trussardi and U. Zutter, *Chimia*, 2007, **61**, 93; (*b*) Y. Fukuta, T. Mita, N. Fukuda, M. Kanai and M. Shibasaki, *J. Am. Chem. Soc.*, 2006, **128**, 6312; (*c*) T. Mita, N. Fukuda, F. X. Roca, M. Kanai and M. Shibasaki, *Org. Lett.*, 2007, **9**, 259; (*d*) N. Satoh, T. Akiba, S. Yokoshima and T. Fukuyama, *Angew. Chem., Int. Ed.*, 2007, **46**, 5734; (*e*) B. M. Trost and T. Zhang, *Angew. Chem., Int. Ed.*, 2008, **47**, 1.
3 P. A. S. Lowden, in *Aziridines and Epoxides in Organic Synthesis*, ed. A. K. Yudin, Wiley-VCH, Weinheim, 2006, ch. 11.
4 W. H. Pearson, B. W. Lian and S. C. Bergmeier, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Elsevier, Oxford, 1996, vol. 1A.
5 (*a*) R. S. Atkinson, *Tetrahedron*, 1999, **55**, 1519; (*b*) B. Zwanenburg, *Pure Appl. Chem.*, 1999, **71**, 423; (*c*) D. Tanner, *Angew. Chem., Int. Ed.*, 1994, **33**, 599; (*d*) X. E. Hu, *Tetrahedron*, 2004, **60**, 2701; (*e*) A. Padwa, in *Comprehensive Heterocyclic Chemistry III*, ed. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Oxford, 2008, ch. 1.
6 For a comprehensive recent review see: H. Pellissier, *Tetrahedron*, 2010, **66**, 1509.
7 Selected recent organocatalytic examples: (*a*) T. Hashimoto, N. Uchiyama and K. Maruoka, *J. Am. Chem. Soc.*, 2008, **130**, 14380; (*b*) Y. Zhang, Z. Lu and W. D. Wulff, *Synlett*, 2009, 2715; (*c*) T. Akiyama, T. Suzuki and K. Mori, *Org. Lett.*, 2009, **11**, 2445; (*d*) A. A. Desai and W. D. Wulff, *J. Am. Chem. Soc.*, 2010, **132**, 13100; (*e*) T. Hashimoto, H. Nakatsu, K. Yamamoto and K. Maruoka, *J. Am. Chem. Soc.*, 2011, **133**, 9730.
8 Recent reviews: (*a*) V. K. Aggarwal, E. M. McGarrigle and M. A. Shaw, in *Science of Synthesis*, ed. G. A. Molander, Thieme, 2010, vol. 37, p. 311; (*b*) E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches and V. K. Aggarwal, *Chem. Rev.*, 2007, **107**, 5841; (*c*) J. R. Fulton, V. K. Aggarwal and J. de Vicente, *Eur. J. Org. Chem.*, 2005, 1479.
9 (*a*) A. W. Johnson and R. B. LaCount, *J. Am. Chem. Soc.*, 1961, **83**, 417; (*b*) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, **84**, 867; (*c*) V. Franzen and H.-E. Driesen, *Chem. Ber.*, 1963, **96**, 1881; (*d*) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.
10 (*a*) A.-H. Li, L.-X. Dai and V. K. Aggarwal, *Chem. Rev.*, 1997, **97**, 2341; (*b*) V. K. Aggarwal and J. Richardson, *Chem. Commun.*, 2003, 2644; (*c*) V. K. Aggarwal and C. L. Winn, *Acc. Chem. Res.*, 2004, **37**, 611; (*d*) V. K. Aggarwal, M. Crimmin and S. Riches, in *Science of Synthesis*, ed. C. Forsyth, Thieme, 2008, vol. 37, p. 321.
11 Representative references: (*a*) T. Saito, M. Sakairi and D. Akiba, *Tetrahedron Lett.*, 2001, **42**, 5451; (*b*) V. K. Aggarwal, R. A. Stenson, R. V. H. Jones, R. Fieldhouse and J. Blacker, *Tetrahedron Lett.*, 2001, **42**, 1587; (*c*) V. K. Aggarwal, M. Ferrara, C. J. O'Brien, A. Thompson, R. V. H. Jones and

R. Fieldhouse, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1635; (*d*) V. K. Aggarwal, E. Alonso, G. Fang, M. Ferrara, G. Hynd and M. Porcelloni, *Angew. Chem., Int. Ed.*, 2001, **40**, 1433; (*e*) V. K. Aggarwal and J.-L. Vasse, *Org. Lett.*, 2003, **5**, 3987; (*f*) Y. Gui, S. Shen, H.-Y. Wang, Z.-Y. Li and Z.-Z. Huang, *Chem. Lett.*, 2007, 1436.

12 (*a*) B. R. Bellenie and J. M. Goodman, *Chem. Commun.*, 2004, 1076; (*b*) V. K. Aggarwal, A. Ali and M. P. Coogan, *J. Org. Chem.*, 1997, **62**, 8628; (*c*) V. K. Aggarwal, M. P. Coogan, R. A. Stenson, R. V. H. Jones, R. Fieldhouse and J. Blacker, *Eur. J. Org. Chem.*, 2002, 319.

13 (*a*) S. A. Kavanagh, A. Piccinini, E. M. Fleming and S. J. Connon, *Org. Biomol. Chem.*, 2008, **6**, 1339; (*b*) S. A. Kavanagh and S. J. Connon, *Tetrahedron: Asymmetry*, 2008, **19**, 1414; (*c*) A. Piccinini, S. A. Kavanagh, P. B. Connon and S. J. Connon, *Org. Lett.*, 2010, **12**, 608; (*d*) S. A. Kavanagh, A. Piccinini and S. J. Connon, *Adv. Synth. Catal.*, 2010, **352**, 2089.

14 (*a*) B. M. Trost and R. F. Hammen, *J. Am. Chem. Soc.*, 1973, **95**, 962; (*b*) L. Breau and T. Durst, *Tetrahedron: Asymmetry*, 1991, **2**, 367.

15 A. Piccinini, S. A. Kavanagh and S. J. Connon, *Chem. Commun.*, 2012, **48**, 7814.

16 For mechanistic rationales for the formation of **9–11** see the ESI.†

17 The bis-*tert* butyl analogue of **13** is known (ref. 13*c*), but is difficult to prepare in appreciable quantities for screening studies.

18 R. E. Grote and E. R. Jarvo, *Org. Lett.*, 2009, **11**, 485.

19 C. Palomo, M. Oiarbide, R. Halder, A. Laso and R. López, *Angew. Chem., Int. Ed.*, 2006, **45**, 117.

20 W. B. Jennings and C. J. Lovely, *Tetrahedron*, 1991, **47**, 5561.

21 R. I. Kureshy, K. J. Prathap, S. Agarwal, N. H. Khan, S. H. R. Abdi and R. V. Jasra, *Eur. J. Org. Chem.*, 2008, 3118.

