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An Organocatalytic Synthesis of *cis*-*N*-Alkyl- and *N*-Arylaziridine Carboxylates

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Abstract: An extremely mild protocol that employs readily available starting materials, i.e., aldehyde, amine and alkyl diazoacetate, returns structurally diverse *N*-substituted-C-2/3-difunctionalised aziridines in excellent yields and stereoselectivities when pyridinium triflate is incorporated as an organocatalyst. The reaction process is environmentally benign affording water and nitrogen as the only by-products. This racemic protocol paves the way for the development of novel asymmetric organocatalysts capable of generating optically active aziridines.

Keywords: aldehydes; aziridines; diazo compounds; imines; organic catalysis

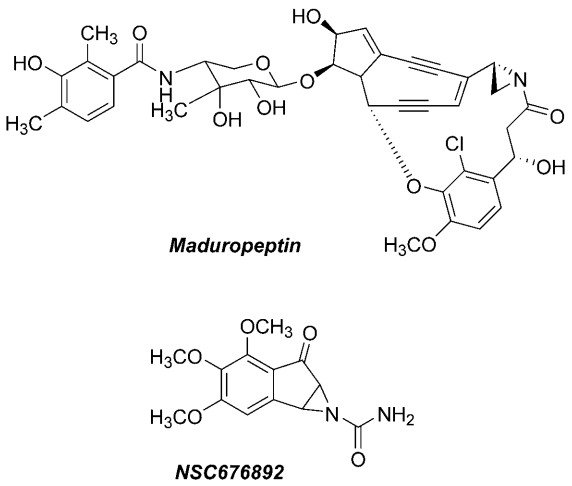
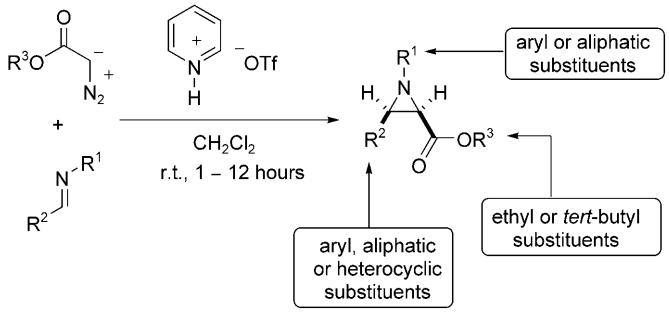


Figure 1. Natural product derived and synthetic aziridines.

Aziridines are important, synthetically versatile 3-membered heterocycles with considerable Baeyer strain.[1] As a consequence, aziridines are relatively reactive and eminently capable of undergoing a plethora of chemical transformations that often afford an assortment of different and useful chemical entities.[2] They have, for example, been used to generate natural and unnatural α- and β-amino acids,[3] azasugars[4] and chiral ligands.[5] Furthermore, aziridines are often found as key bioactive structural elements within natural products, many of which have anticancer and or antibiotic properties, i.e., azinomycin A, maduropeptin[6] (Figure 1), mitomycin C, FK973 and ficellomycin. In addition to the naturally occurring aziridines recounted, there have been numerous and in some cases potentially bioactive synthetic aziridines generated, i.e., NSC676892, a tricyclic, aziridine-containing heterocycle. Thus, as key components of bioactive molecules and as useful precursor species for the development of interesting synthetic intermediates, efficient protocols for aziridine synthesis continue to be an important and very topical research area.[7]

The last 10 years have seen enormous interest in the development and use of organocatalysts capable of mediating C–C and C–X (X = N, O, S) bond formation.[8] During this time a sizeable number of innovative, often optically active and ever more structurally complex organocatalytic systems have been developed and subsequently tested for their ability to mediate reactions that, in many cases, afford increasingly complex reaction products and or synthetic intermediates.[9]

The continued construction of structurally unique organocatalysts is critical if their utility within synthetic chemistry is to be maintained. It is evident, therefore, that new organocatalysts are required to sustain and encourage the impressive developments already achieved. At the same time it is equally important that promising commercial or readily synthes-



Scheme 1. Brönsted acid-derived organocatalytic synthesis of *N*-alkyl- or *N*-arylaziridines.

ised compounds that appear capable but yet uninvestigated or 'dormant' as organocatalysts are examined for their potential to mediate interesting and synthetically useful chemical transformations.

This communication reports our endeavours at utilising heterocyclic salts and, in particular, pyridinium triflate as cheap, commercially available, structurally simple and efficient Brønsted acid organocatalysts. Of the salts tested we demonstrate that pyridinium triflate is a remarkably efficient organocatalyst capable of mediating the synthesis of racemic *N*-alkyl- and *N*-arylaziridines *via* an exceptionally mild reaction protocol, with all of the pyridinium triflate-mediated aziridination reactions tested to date proceeding to completion quickly and efficiently at ambient temperature and with only 1–10 mol% of the salt (Scheme 1).

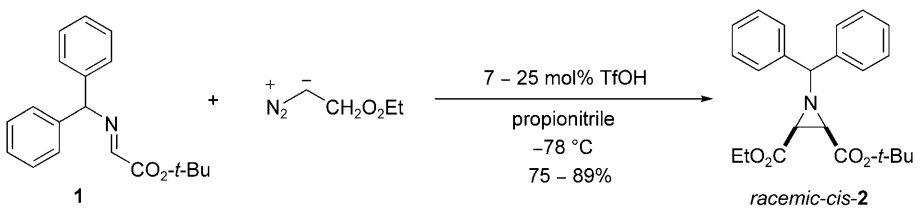
Furthermore, our efficient conversion of *N*-substituted imine starting materials into the corresponding aziridine generates only two by-products; water and nitrogen. Thus utilizing these easily handled, non-hygroscopic salts in conjunction with a wide variety of structurally diverse primary *N*-alkyl- or *N*-arylamines with arylaldehydes, and alkyl diazoacetates, the corresponding *N*-aryl or *N*-alkyl-*cis*-C-2/3-difunctionalized aziridines are afforded in good i.e., 71% to excellent, i.e., 88% yields.

Space considerations preclude going into detail on the synthesis of aziridines; a number of excellent reviews[10] and monographs exist.[11] Instead, discussion will be limited to relevant protocols that employ imines as the core starting materials[12] and the problems associated with these protocols. Traditional aziridine synthesis *via* 'imine activation' relies heavily on the application of strong, often metal-based Lewis acids, i.e., $Zn(OTf)_2$, $AlCl_3$ or $TiCl_4$. By means of example, Jørgensen et al.[13] activated *N*-alkylimines using $Zn(OTf)_2$ (10 mol%) and similarly Templeton et al.[14] activated *N*-arylimines with $BF_3{\cdot}OEt_2$ (10 mol%) in a process that allowed, after the addition of EDA, the formation of racemic *cis*- or *cis*/*trans*-mixtures of *N*-alkyl- or *N*-aryl-C-2/3-disubstituted aziridines, respectively, in very poor to good yields, i.e., 2–76%. The low yields can be partially accounted for by the formation of isomeric enamines generated *via* 1,2-aryl or 1,2-hydrogen shifts occurring on the zwitterionic intermediate generated *via* the initial reaction between the alkyl diazoacetate and the *N*-substituted imine.

From a non-metal mediated viewpoint Armstrong et al.[15] reported the synthesis of *trans*-aziridinyl ketones and esters in good, i.e., 62% to excellent, i.e., 97% yields *via* the aziridination of chalcones or acrylates using N–N ylids generated *in situ via* amination of NMO with *O*-(diphenylphosphinyl)hydroxylamine.

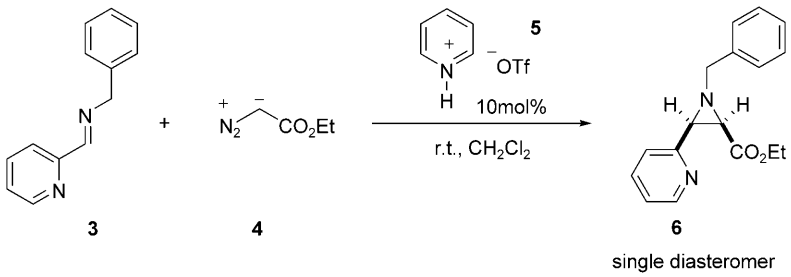
Wulff et al.[16] reported an asymmetric catalyst capable of generating *N*-benzhydryl-C-2/3-disubstituted aziridines from the corresponding *N*-benzhydrylimines using a catalyst derived from either vaulted biaryl ligand (*S*)-VANOL or (*S*)-VAPOL which are transformed prior to application into the corresponding (*S*)-VANOL- or (*S*)-VAPOL-pyroborate complexes.[17] Although the yields (51–77%) and *ee*s (91–98%) of the aziridines are good, the reaction is susceptible to enamine formation, i.e., 1–16%.

In an important contribution Johnston et al. demonstrated that strong protic acids, i.e., TFA (pK_a 0.5) and triflic acid (pK_a −14) catalyse, at a rather high loading (7–25 mol%) the aza-Darzen reaction between *N*-benzhydrylimines and EDA affording mixtures of *cis*-/*trans*-*N*-benzhydryl-C-2/3-disubstituted aziridines in 40–89% yields (Scheme 2).[18] The most notable problems with this protocol are that aldimines generally afforded poor *cis*-/*trans*-aziridine regioselectivities [(60:40)–(90:10) *cis*-/*trans*, respectively] and that aldimines synthesised from cycloalkane, aliphatic or aromatic aldehydes afford the corresponding aziridines in meagre 40–45% yields. Furthermore, although Schiff bases derived from glyoxalate esters, for example, **1** afforded moderate to excellent yields (62–89%, mass balance comprised enamide by-products)



1 *racemic-cis*-**2**

Scheme 2. Triflic acid for the synthesis of aziridine *cis*-**2**.



Scheme 3. Pyridinium triflate as an efficient organocatalyst for the synthesis of racemic aziridine **6**.

and excellent regioisomer ratios (95:5) of racemic *cis*/*trans*-C-2/3-disubstituted aziridines these products, for example, **2** have limited synthetic applications. Further additional drawbacks are evident. Thus, TfOH is relatively expensive and both acids are extremely hygroscopic making them difficult to handle and store, both acids have to be dried and distilled before use, their application on a large and small scale requires that strictly anhydrous solvents/reaction conditions be maintained at all times, if not degradation of the imine occurs, and use of either of these acids requires −78 °C reaction conditions not, as would be preferable, ambient temperature. Furthermore, the use of such strong acid precludes chemistry on substrates that have acid-sensitive functional/protecting groups and, in fact, the chemistry of diazocarbonyl compounds with strong acids is dominated by reports of their instability.[19]

Initiating our programme we sought to obviate the problems recounted with transition metal-based Lewis acids or strong protic acids and probe the ability of readily and/or commercially available heterocyclic salts to act as simple organocatalysts capable of generating aziridines in high yield and in mild reaction conditions. Employing heterocyclic salts confers numerous benefits to our protocol. As stable solids they are easily weighed and handled, are cheap, non-hygroscopic, require 'no immediate to use' drying or crystallisation, are easily removed from the reaction by filtration (plug of alumina) and their mildly acidic nature should allow incorporation of acid-sensitive functional and/or protecting groups.

Focusing on pyridinium triflate (**5**), tosylate and trifluoroacetate, with **3** and diazo ester **4**, we were delighted to observe that at ambient temperature all three salts catalysed (at 10 mol%) the reaction albeit in variable reaction times, i.e., 2, 5 and 48 h, respectively, with triflate **5** being the most efficient affording an unoptimised 83% yield of racemic **6** (Scheme 3).

Conventional Lewis acid-mediated protocols often afford stereoisomeric mixtures of *cis*-/*trans*-aziridines as well as unwanted enamides (*vida supra*). Utilising **3**, **4** and **5** the unpurified reaction mixture containing *rac*-**6** was scrutinised using ^{1}H NMR (400 MHz) for the formation of *cis*- and *trans*-**6**. Typical $J_{2,3}$ values reported for *cis*- and *trans*-aziridines are 7 ± 0.5 Hz[20] and 3 ± 0.5 Hz,[21] respectively. We were delighted to observe the formation of *only* one aziridine stereoisomer with a $J_{2,3}$ of 6.8 Hz indicating exclusive formation of the *cis*-**6** stereoisomer. Proof of the *cis*-relationship between the C-2/3-substituents was sought. X-ray analysis conclusively proved our assignment, using $J_{2,3}$ values, that *cis*-**6** was correct (Figure 2).[22]

Synthesising **7a–c** to **10a–c** (Figure 3), we investigated their ability to mediate the reaction outlined in Scheme 3. Interestingly, quinuclidine (sp^3-nitrogen)

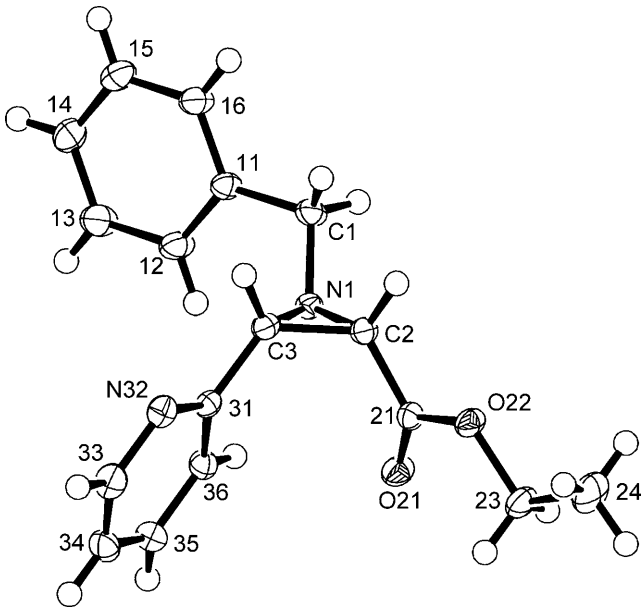


Figure 2. X-ray crystal structure of racemic *cis*-**6**.

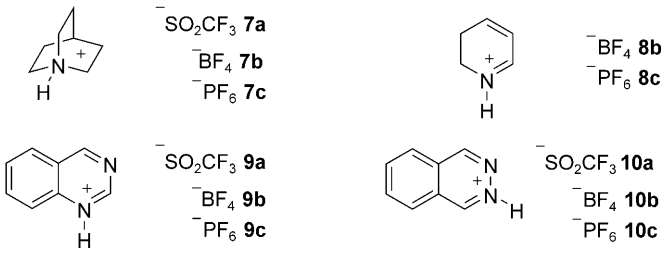


Figure 3. sp^3 and sp^2-nitrogen containing heterocyclic salts.

salts **7a–c** mediated the reaction in 4–12 h and returned *cis*-**6** in 33%, 45% and 68% yields, respectively. On the other hand catalysts **8a**, **b**, **9a**, **b** and **10a**, **b** afforded, generally, higher yields of *cis*-**6**, i.e., 77–83%. Catalyst **9c** afforded no product and **10c** afforded *cis*-**6** in a reduced 10% yield. The poor performance of **9c** and **10c** was attributed to their low solubility in dichloromethane. In significantly slower reaction times (12 h) the monotriflate salts of DBN and TMG afforded *cis*-**6** in 72% and 78% yields, respectively.

The reaction in Scheme 3 was repeated to confirm the importance of **5** to act, presumably, as a catalyst. Initially in the absence of **5** a deuterated chloroform solution of **3** and **4** was shaken in an NMR tube (3 h). Subsequent ^{1}H NMR (400 MHz) analysis confirmed no reaction had occurred. Subsequent addition of **5** (10 mol%) followed within one minute by ^{1}H NMR analysis confirmed two new doublets ($J_{2,3}=6.8$ Hz) at 2.7 ppm and 3.2 ppm had formed; clearly indicating that rapid formation of *cis*-**6** only occurs when catalyst **5** is added to the reaction.

Using **3**, **4** and **5** (10 mol%), the reaction in Scheme 3 was repeated at −78 and −40 °C, there was no reaction. At −20° the reaction was significantly slower (24 h) than the reaction at 0 °C which afforded a 53% yield of racemic *cis*-**6**. This yield is, however, significantly lower than the 83% yield afforded when the reaction was conducted at ambient temperature.

Having established that heterocyclic salts and in particular pyridinium triflate are viable catalysts for *N*-alkylaziridine synthesis, we elected, using **5** and the protocol in Scheme 3, to screen solvents with disparate polarities for their effect, if any, on the *cis*-/*trans*-stereochemistry and yields of racemic **6**. The aziridination reaction was largely unaffected by the solvent employed, thus ethanol (μ5.8, entry 4, Table 1) and pentane (μ0, entry 5) both afforded racemic *cis*-**6** in, essentially, identical yields, i.e., 69% and 68%, respectively. It is known that the use of polar solvents in Lewis acid-mediated aziridinations promotes enamine formation. Gratifyingly, the solvent study demonstrated that utilising a diverse array of polar, apolar or non-polar solvents there was little evidence for enamine formation.

Table 1. Solvent study for the synthesis of racemic *cis*-**6**.

Entry	Solvent	Yield of *cis*-**6**
1	Dichloromethane	82%
2	Toluene	76%
3	Chloroform	70%
4	Ethanol	69%
5	Pentane	68%
6	Ethyl acetate	68%
7	Propionitrile	66%
8	Isopropyl alcohol	65%
9	Ether	57%
10	Tetrahydrofuran	56%
11	*tert*-Butyl methyl ether	48%
12	Pyridine	0%

In an effort to expand the structural diversity of the aziridines created and explore the scope of the reaction a series of *N*-alkyl- and *N*-arylimines was synthesised. Utilising these Schiff bases, ethyl or *tert*-butyl diazoacetate and **5** (10 mol%) we observed the formation of aziridines **11–31** (Table 2) in good (71%) to excellent yields (88%). These preliminary results indicate that a catalytic quantity of **5** efficiently mediates the high yielding synthesis of structurally diverse *N*-alkyl- and *N*-arylaziridines.

Worthy of particular note, the unoptimised yields of **11–31** are generally superior to those reported using Lewis,[13,14] trifluoroacetic or trifluoromethanesulfonic acids.[18] Furthermore, the tolerance of our aziridination reaction to *N*-substituent variation is impressive for, e.g., *N*-allylaziridine **11**, *N*-octylaziridine **12**, *N*-*tert*-butylaziridine **13**, *N*-benzhydrylaziridines **14–16**, *N*-triphenylmethylaziridine **17**, *N*-benzylaziridine **18**, and *N*-arylaziridines **19–31**. Substituting EDA for *tert*-butyl diazoacetate afforded *cis*-**18** in an 82% yield, a yield comparable to that afforded when **4** was utilised *cf.* **6**, 83%. Thus the reaction does not appear to be adversely affected by the incorporation of a sterically encumbered, large *tert*-butyl group within the alkyl diazoacetate component of the reaction. The ability to utilise glyoxalate ester-derived imines for the synthesis of **16** has been established. Furthermore, the ability to append heteroaromatic substituents on the C_3-aziridine ring component, for example, **11–14**, **17–21** has particular appeal, as has the synthesis of *N*-sterically encumbered heteroaromatic species, for example, **17**.

On the other hand, addition of **5** (10 mol%) to a dichloromethane solution of the starting material imine for *N*-arylaziridine **19** and *tert*-butyl diazoacetate resulted in *rapid* evolution of nitrogen gas (~5 min, the reaction rate with EDA was similar), consumption of the starting materials and concomitant formation of *cis*-**19** (using ^{1}H NMR no evidence for *trans*-**19** could be found) in an 87% yield. We decided to probe the possibility of generating *N*-arylaziridines appended with a variety of *N*-aryl substituents. Gratifyingly, our organocatalytic protocol afforded *N*-arylaziridines appended with single, i.e., **19**, **22–31** and multiple electron-rich substitents, i.e., **20** as well as aziridine **21**, derived from the aziridination of the imine generated from condensing 2-pyridinecarbaldehyde and 2-amino-4-nitrophenol.

Focussing on C-3 aryl substituents we demonstrated that a series of diverse functional groups are readily incorporated, e.g., halogens **23–28**, strongly electron-withdrawing substituents, e.g., **31**, as well as weakly

Table 2. *N*-Alkyl- and *N*-arylaziridines synthesised using **5**.

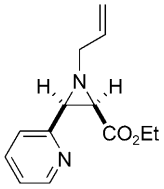
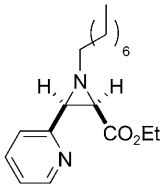
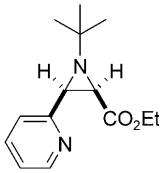
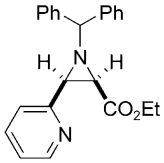
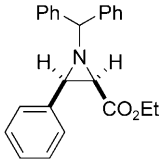
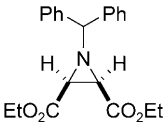
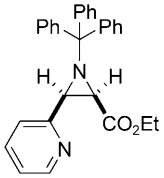
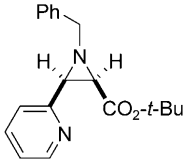
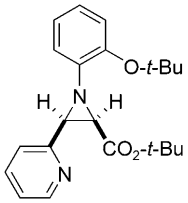
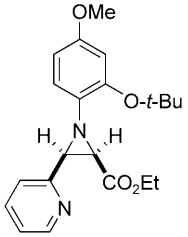
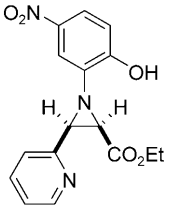
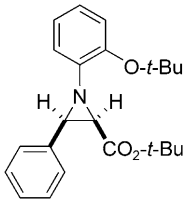
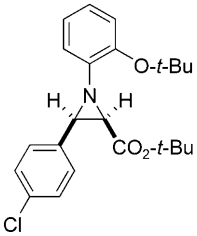
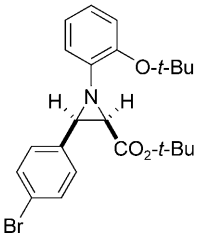
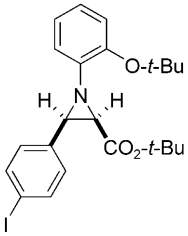
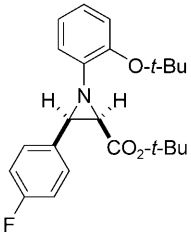
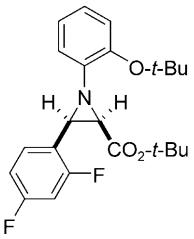
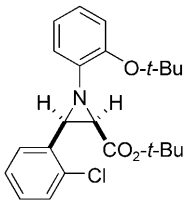
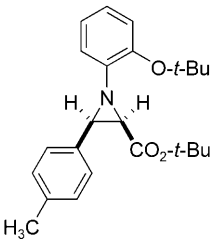
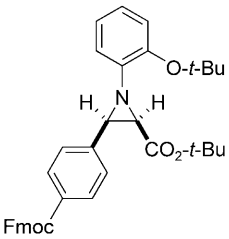
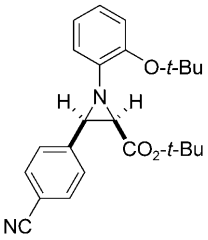
No. and Yield	Aziridine	No. and Yield	Aziridine
11, 92%		**12**, 90%	
13, 86%		**14**, 80%	
15, 74%		**16**, 86%	
17, 78%		**18**, 82%	
19, 97%		**20**, 94%	
21, 79%		**22**, 71%	
23, 76%		**24**, 75%	
25, 79%		**26**, 92%	

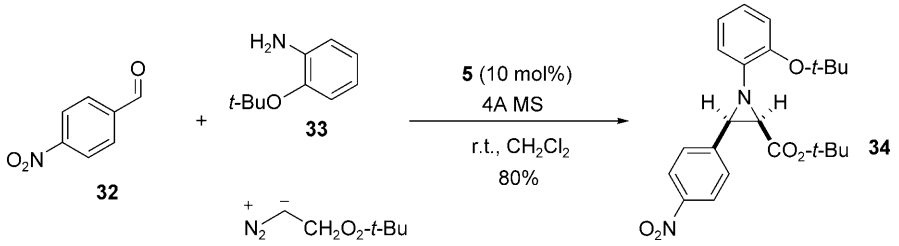
Table 2. (Continued)

No. and Yield	Aziridine	No. and Yield	Aziridine
27, 99%		**28**, 79%	
29, 77%		**30**, 95%	
30, 91%		–	–

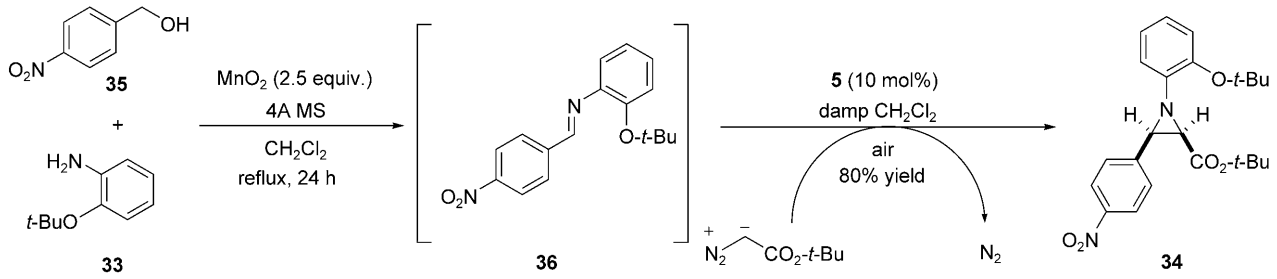
electron-donating groups, e.g., **29**. An unprotected hydroxy group on 4-hydroxybenzaldehyde was not tolerated, simple *O*-protection of the phenol as the corresponding *O*-Fmoc derivative allowed the corresponding *N*-arylaziridine **30** to be efficiently generated in an 85% yield (Table 2).

Synthesising aziridines directly from aldehydes and amines has significant experimental advantages over imine isolating, multi-step procedures. Investigating the possibility of simplifying our aziridination procedure, we reacted one equivalent each of 4-nitrobenzaldehyde (**32**) and 2-*tert*-butoxyaniline (**33**) in DCM (with 4 Å molecular sieves) the resulting imine was subsequently reacted with **4** in the presence of **5** (10 mol%). Racemic *cis*-**6** was afforded in an 82% yield. In our quest to reduce the number of reaction/isolation steps still further, we pondered the possibility of generating racemic *cis*-**34** by mixing all three starting materials *that is,* **4**, **32** and **33** together in the presence of **5** (10 mol%). Gratifyingly, racemic *cis*-**34** was afforded in an excellent 80% yield (Scheme 4).

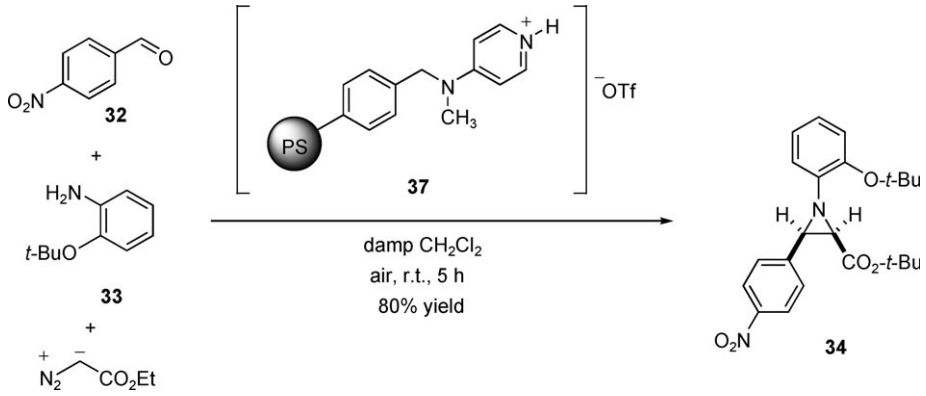
Further exemplification of the scope and potential of our organocatalytic aziridination protocol was sought. The ability to incorporate an *alcohol* in place of an aldehyde would be of significant utility for the synthesis of aziridines. Transforming alcohol and amine core starting materials into *N*-arylaziridines *via* a more efficient two-stage three-component reaction process was deemed worthy of investigation. Taylor et al. reported a one-pot synthesis of imines using alcohols, amines and manganese dioxide.[23] Undertaking the synthesis of *cis*-**34** we synthesised *N*-arylimine **36** from amine **33**, alcohol **35** and manganese dioxide, we filtered off the excess oxidant and subsequently added **5** (10 mol%) and **4**. Even though no special precautions were taken to exclude either water or air



Scheme 4. *cis*-**34** *via* a one-pot three-component process.



Scheme 5. Synthesis of *cis*-**34** *via* an oxidation/imine/aziridination reaction process.



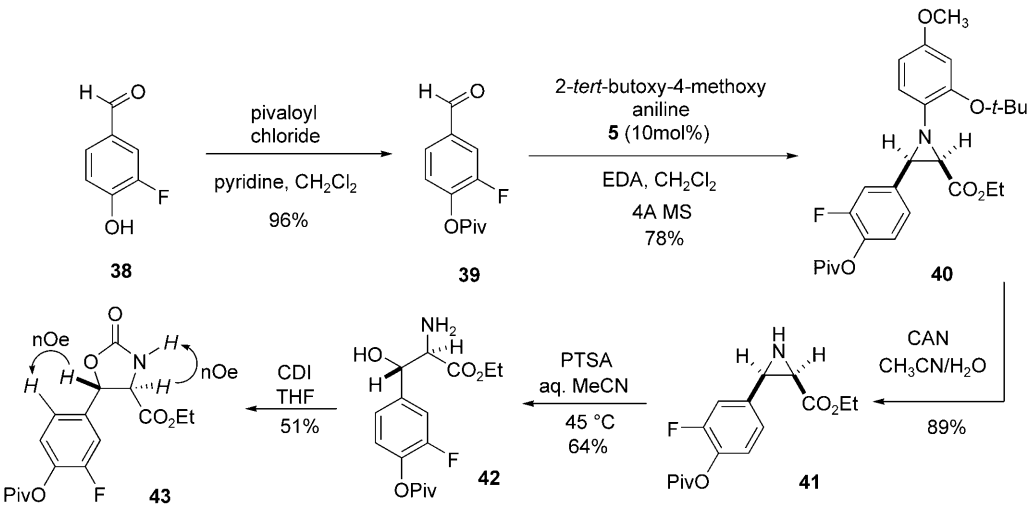
Scheme 6. One-pot synthesis of *cis*-**34** using polymer **37**.

(no dry solvents were used and the reaction was performed in a screw-top vial) we were delighted to isolate *cis*-**34**, a precursor to chloramphenicol, in an overall 80% yield. The fact that no precautions to protect the reaction against air or water during the highly efficient synthesis of *cis*-**34** indicates the robust nature of our aziridination protocol (Scheme 5).

The use of a polymer-bound Brønsted acid would confer several benefits to our protocol; these include an easier work-up of the reaction, i.e., simple filtration removes **37** and the potential for recycling **37**. We were delighted that a straightforward synthesis of **37** [addition of TfOH (1 equiv.) to polystyrene-immobilised DMAP in DCM at 0 °C] allowed the generation of *cis*-**34** in a pleasing 80% yield (Scheme 6).

The racemic synthesis of fluorinated tyrosine **42**, an important component of the potent antibiotic fluorobalhimycin, was undertaken.[24] Commercially available 3-fluoro-4-hydroxybenzaldehyde **38** was transformed into the corresponding *O*-pivaloyl derivative **39** *via* reaction with pivaloyl chloride and pyridine. The subsequent transformation of **39** into racemic *cis*-aziridine **40** was performed in a one-pot reaction (75% over the 2 steps from **38**, Scheme 7) by reacting **39** with EDA in the presence of **5** (10 mol%) and 2-*tert*-butoxy-4-methoxyaniline. Gratifyingly, racemic *cis*-aziridine **40** ($J_{2,3}$ = 6.6 Hz) was afforded in an unopitimised 78% yield. Subsequent oxidation using CAN efficiently cleaved the electron-rich *N*-aryl group affording the desired NH-aziridine **41** in an 89% yield. Reaction of **41** with PTSA in aqueous acetonitrile at 40 °C mediated the hydrolytic ring-opening of the aziridine affording racemic *anti*-β-hydroxy-α-amino acid **42** in a 64% yield. Confirmation of the *anti*-stereoselectivity in the ring opening of the aziridine was sought. Reacting β-hydroxy-α-amino ester **42** with CDI in THF afforded oxazolidin-2-one **43**. Analysis of the ^{1}H NMR spectrum of **43** confirmed the *trans* relationship of the C-4/5 protons ($J_{4,5}$ = 5.1 Hz) which is in close agreement to *J* values reported for similar oxazolidin-2-ones.[25] Further evidence for the *trans*-relationship of the C-2/3-substituents on **43** was gathered *via* an nOe study. A correlation was observed beween the C-2 hydrogen and the *ortho*-hydrogens on the aryl ring and between the C-3 hydrogen and the hydrogen on the NH group. No correlation was observed between the C-2/3 hydrogens (Scheme 7).

In summary, an efficient organocatalytic racemic synthesis of structurally diverse *N*-alkyl- and *N*-arylaziridines has been developed with the protocol suited to a wide range of N-substituents. Worthy of particular note, our aziridination reaction is environmentally benign generating only water and N_2 by-products. Furthermore, using an *in situ* tandem oxidation protocol we demonstrate the feasibility and efficiency of taking alcohols through to aziridines *via* a one-pot reaction that does not require aldehyde isola-



Scheme 7. Synthesis of *rac*-**42** from aldehyde **38**.

tion and can be conducted without the exclusion of water or air. Exemplifying our protocol, the first racemic synthesis of 3-fluoro-β-hydroxytyrosine is reported in four steps.

Although the use of asymmetric heterocyclic salts has not, to date, returned optically active aziridines we are currently investigating this aspect of our reaction and our preliminary racemic results pave the way for an asymmetric variant of our reaction to be developed. The results of these studies will be published in due course.

Experimental Section

Typical Procedure

To a stirred solution of 4-nitrobenzyl alcohol (**35**, 766 mg, 5.0 mmol), 2-*tert*-butoxyaniline (**33**, 785 mg, 4.75 mmol) and 4 Å molecular sieves (*ca.* 1 g) in DCM (125 mL) was added activated manganese dioxide (625 mg, 7.5 mmol, 1.5 equiv., Aldrich 21,764-6) and the mixture heated at reflux. A second equivalent of manganese dioxide (435 mg, 5 mmol) was added to the reaction after one hour and the resulting mixture stirred and refluxed overnight. Spent and excess manganese dioxide was removed by filtration through Celite and then washed with DCM (3×25 mL). The combined DCM fractions were concentrated under vacuum affording **36** as a pale yellow oil; yield: 95%.

(*E*)-2-*tert*-Butoxy-*N*-(4-nitrophenylmethylene)phenylamine (**36**, 78 mg, 0.26 mmol) and pyridinium triflate (**5**, 6 mg, 0.026 mmol, 10 mol%) were dissolved in dichloromethane (1 mL). The reaction mixture was stirred at room temperature for 2 min. *tert*-Butyl diazoacetate (0.038 mL, 0.28 mmol, 1.1 equiv.) was added (flurry of bubbles observed, N_2 evolved) and the resulting solution stirred at ambient temperature for 5 h. Subsequent TLC analysis (eluent, hexane: diethyl ether, 4:1) indicated complete consumption of **36**. Removal of the solvent under vacuum afforded a brown semi-solid. Purification of the reaction mixture *via* flash column chromatography (SiO_2, elution with hexane/diethyl ether, 4:1) afforded a yellow solid; yield: 90 mg (84%). Subsequent analysis indicated this to be **34**; mp 117.4–119.3 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.17 (d, *J* = 8.75 Hz, 2H), 7.69 (d, *J* = 8.88 Hz, 2H), 7.02–6.98 (m, 1H), 6.95–6.90 (m, 3H), 3.50 (d, *J* = 6.76 Hz, 1H), 3.11 (d, *J* = 6.77 Hz, 1H), 1.32 (s, 9H), 1.19 (s, 9H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ = 166.5, 148.2, 147.6, 145.6, 143.2, 129.2, 123.7, 123.3, 123.2, 123.1, 120.9, 82.1, 80.6, 47.9, 46.9, 28.9, 28.0; IR (film): ν = 2978, 2933, 1743, 1716, 1603, 1520, 1490, 1451, 1392, 1367, 1344, 1262, 1224, 1160, 1111, 1048, 888, 854, 753 cm^{-1}; MS (EI)$^+$: *m/z* = 412.1 (100%) [M]$^+$; HR-MS (EI)$^+$: m/z = 412.1998, exact mass calculated for $[C_{23}H_{28}N_2O_5]^+$: 412.1993.

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References

[1] J. B. Sweeney, *Chem. Soc. Rev.* **2002**, *31*, 247.
[2] X. Eric Hu, *Tetrahedron* **2004**, *60*, 2701.
[3] B. Zwanenburg, P. T. Holte, *Top. Curr. Chem.* **2001**, *216*, 93.
[4] a) D. Tanner, *Angew. Chem.* **1994**, *106*, 625; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 599; b) T. K. Chakraborty, S. Jaiprakash, *Tetrahedron Lett.* **1997**, *38*, 8899; c) G. J. Joly, K. Peeters, H. Mao, T. Brossette, G. J. Hoornaert, F. Compernolle, *Tetrahedron Lett.* **2000**, *41*, 2223.
[5] P. Somfai, *Latvijas Kimijas Zurnals* **1999**, 59.
[6] K. Komano, S. Shimamura, M. Inoue, M. Hirama, *J. Am. Chem. Soc.* **2007**, *129*, 14184.
[7] W. McCoull, F. A. Davis, *Synthesis* **2000**, 1347.

[8] a) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; b) H. Pellissier, *Tetrahedron* **2007**, *63*, 9267; c) P. I. Dalko, L. Moisan, *Angew. Chem.* **2004**, *116*, 5248; *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; d) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726.

[9] a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; b) H. Kotsuki, H. Ikishima, A. Okuyama, *Heterocycles* **2008**, *75*, 757; c) W. R. Roush, J. L. Methot, *Adv. Synth. Catal.* **2004**, *346*, 1035; d) Q. Tao, G. Tang, K. Lin, Y.-F. Zhao, *Chirality* **2008**, *20*, 838; e) M. Shi, X.-G. Liu, *Org. Lett.* **2008**, *10*, 1043; f) S. H. McCooey, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367; g) N. Dahlin, A. Bøgevig, H. Adolfsson, *Adv. Synth. Catal.* **2004**, *346*, 1101.

[10] a) H. M. Osborn, J. B. Sweeney, *Tetrahedron: Asymmetry* **1997**, *8*, 1693; b) G. S. Singh, M. D'hooghe, N. De Kimpe, *Chem. Rev.* **2007**, *107*, 2080; c) V. H. Dahanukar, I. A. Zavialov, *Curr. Opin. Drug. Discovery and Development*, **2002**, *5*, 918.

[11] V. K. Aggarwal, D. M. Badine, V. A. Moorthie, in: *Aziridines and Epoxides in Organic Synthesis*, (Ed.: A. K. Yudin), Wiley-VCH, Weinheim, **2006**, pp 1–35.

[12] a) A. Takahiko, S. Tohru, M. Keiji, *Org. Lett.* **2009**, *11*, 2445; b) Z. Lu, Y. Zhang, W. D. Wulff, *J. Am. Chem. Soc.* **2007**, *129*, 7185; c) A. Mazumdar, Z. Xue, M. F. Mayer, *Synlett* **2007**, 2025; d) Y. Deng, Y. R. Lee, C. A. Newman, W. D. Wulff, *Eur. J. Org. Chem.* **2007**, 2068; e) S. Zhu, Y. Liao, S. Zhu, *Synlett* **2005**, 1429; f) S.-H. Lee, I.-W. Song, *Bull. Korean Chem. Soc.* **2005**, *26*, 223; g) A. F. Khlebnikov, M. S. Novikov, R. R. Kostikov, *Russ. Chem. Rev.* **2005**, *74*, 171; h) B. Vanderhoydonck, C. V. Stevens, *Synthesis* **2004**, 722; i) Y. Li, P. W. H. Chan, N.-Y. Zhu, C.-M. Che, H.-L. Kwong, *Organometallics* **2004**, *23*, 54; j) M. Redlich, H. H. Hossain, *Tetrahedron Lett.* **2004**, *45*, 8987; k) J. S. Yadav, B. V. S. Reddy, M. S. Rao, P. N. Reddy, *Tetrahedron Lett.* **2003**, *44*, 5275; l) W. Sun, C.-G. Xia, H.-W. Wang, *Tetrahedron Lett.* **2003**, *44*, 2409; m) T. Akiyama, S. Ogi, K. Fuchibe, *Tetrahedron Lett.* **2003**, *44*, 4011; n) J. R. Krumper, M. Gerisch, J. M. Suh, R. J. Bergman, T. D. Tilley, *J. Org. Chem.* **2003**, *68*, 9705; o) D. Morales, J. Pérez, L. Riera, V. Riera, R. Corzo-Suárez, S. García-Granda, D. Miguel, *Organometallics* **2002**, *21*, 1540; p) M. V. Spanedda, B. Crousse, S. Narizuka, D. Bonnet-Delpon, J.-P. Bégué, *Collect. Czech. Chem. Commun.* **2002**, *67*, 1359; q) M. F. Mayer, Q. Wang, M. M. Hossain, *J. Organomet. Chem.* **2001**, *630*, 78; r) C. Loncaric, W. D. Wulff, *Org. Lett.* **2001**, *3*, 3675; s) V. K. Aggarwal, M. Ferrara, C. J. O'Brien, A. Thompson, R. V. H. Jones, R. J. Fieldhouse, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1635; t) M. P. Doyle, W. Hu, D. J. Timmons, *Org. Lett.* **2001**, *3*, 933; u) S.-H. Lee, T.-D. Han, K. Yu, K. H. Ahn, *Bull. Korean Chem. Soc.* **2001**, *22*, 449; v) B. Crousse, S. Narizuka, D. Bonnet-Delpon, J.-P. Bégué, *Synlett* **2001**, 679; w) J. C. Antilla, W. D. Wulff, *Angew. Chem.* **2000**, *112*, 4692; *Angew. Chem. Int. Ed.* **2000**, *39*, 4518; x) S. Sengupta, S. Mondal, *Tetrahedron Lett.* **2000**, ***41***, 6245; y) T. Kubo, S. Sakaguchi, Y. Ishii, *Chem. Commun.* **2000**, 625; z) J. C. Antilla, W. D. Wulff, *J. Am. Chem. Soc.* **1999**, *121*, 5099; aa) W. Xie, J. Fang, J. Li, P. G. Wang, *Tetrahedron* **1999**, *55*, 12929; ab) K. Juhl, R. G. Hazell, K. A. J. Jørgensen, *J. Chem. Soc. Perkin Trans. 1* **1999**, 2293; ac) J. H. Espenson, *Chem. Commun.* **1999**, 479; ad) M. F. Mayer, M. M. Hossain, *J. Org. Chem.* **1998**, *63*, 6839; ae) S. Nagayama, S. Kobayashi, *Chem. Lett.* **1998**, 685; af) K. G. Rasmussen, K. Juhl, R. G. Hazell, K. A. J. Jørgensen, *Chem. Soc. Perkin Trans. 2* **1998**, 1347; ag) H.-J. Ha J.-M. Suh, K.-H. Kang, Y.-G. Ahn, O. Han, *Tetrahedron* **1998**, *54*, 851; ah) J. M. Mohan, B. S. Uphade, V. R. Choudhary, T. Ravindranathan, A. Sudalai, *Chem. Commun.* **1997**, 1429; ai) T. B. Gunnoe, P. S. White, J. L. Templeton, L. Casarrubios, *J. Am. Chem. Soc.* **1997**, *119*, 3171; aj) V. K. Aggarwal, A. Thompson, R. V. H. Jones, M. C. H. Standen, *J. Org. Chem.* **1996**, *61*, 8368; ak) Z. Zhu, J. H. Espenson, *J. Am. Chem. Soc.* **1996**, *118*, 9901; al) K. G. Rasmussen, K. A. J. Jørgensen, *J. Chem. Soc. Chem. Commun.* **1995**, 1401; am) Z. Zhu, J. H. Espenson, *J. Org. Chem.* **1995**, *60*, 7090; an) K. B. Hansen, N. S. Finney, E. N. Jacobsen, *Angew. Chem.* **1995**, *107*, 750; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 676; ao) M. Moran, G. Bernardinelli, P. Müller, *Helv. Chim. Acta* **1995**, *78*, 2048; ap) P. Baret, H. Buffet, J.-L. Pierre, *Bull. Soc. Chim. Fr.* **1972**, 2493; aq) T. Hashimoto, N. Uchiyama, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 14380; ar) T. Akiyama, T. Suzuki, K. Mori, *Org. Lett.* **2009**, *11*, 2445; as) X. Zeng, Z. Zeng, Z. Zu, M. Lu, G. Zhong, *Org. Lett.* **2009**, *11*, 3026.

[13] K. G. Rasmussen, K. A. Jørgensen, *J. Chem. Soc. Perkin Trans. 1* **1997**, 1287.

[14] L. Casarrubios, J. A. Pérez, M. Brookhart, J. L. Templeton, *J. Org. Chem.* **1996**, *61*, 8358.

[15] A. Armstrong, C. A. Baxter, S. G. Lamont, A. R. Pape, R. Wincewicz, *Org. Lett.* **2007**, *9*, 351.

[16] J. C. Antilla, W. D. Wulff, *Angew. Chem.* **2000**, *112*, 4692; *Angew. Chem. Int. Ed.* **2000**, *39*, 4518.

[17] Y. Zhang, A. Desai, Z. Lu, Z. Ding, W. D. Williams, *Chem. Eur. J.* **2008**, *14*, 3785.

[18] A. L. Williams, J. N. Johnston, *J. Am. Chem. Soc.* **2004**, *126*, 1612.

[19] *Diazo compounds: properties and synthesis* (Eds.: M. Regitz, G. Maas), Orlando, London, Academic Press, **1986**.

[20] K. G. Rasmussen, K. A. Jørgensen, *J. Chem. Soc. Chem. Commun.* **1995**, 1401.

[21] W. Xie, J. Fang, J. Li, P. G. Wang, *Tetrahedron* **1999**, *55*, 12929.

[22] Crystal data for compound *cis*-**6**: $C_{17}H_{18}N_2O_2$, M = 282.3. Orthorhombic, space group $P2_12_12_1$ (no. 19), a = 7.5305(5), b = 10.8160(6), c = 18.2893(9) Å, V = 1489.66(14) Å^3. Z = 4, $\rho_{calc.}$ = 1.259 g cm^{-3}, F(000) = 600, T = 140(1) K, μ(Mo-Kα) = 0.83 cm^{-1}, λ(Mo-Kα) = 0.71069 Å. Colourless plate crystal. Intensity data measured on an Oxford Diffraction Xcalibur-3 CCD diffractometer (Mo-Kα radiation, graphite monochromator). 4334 unique reflections (R_{int} = 0.044) to θ_{max} = 30°; 4218 'observed' with $I > 2\sigma_I$. Data processed using the CrysAlis-CCD and -RED[26] programmes. Structure determined by direct methods in SHELXS[27] and refined in SHELXL.[27] Non-hydrogen atoms were refined ani-

sotropically. Hydrogen atoms in idealised positions with Uiso values riding. At conclusion, $wR_2 = 0.099$ and $R_1 = 0.045$ for all 4334 reflections; for 'observed' data only, $R_1 = 0.043$. Flack x = −0.9(10); absolute configuration not certain.CCDC 609715 contains the supplementary crystallographic data for product *cis*-**6** in this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

[23] L. Blackburn, R. J. K. Taylor, *Org. Lett.* **2001**, *3*, 1637.

[24] S. Weist, B. Bister, O. Puk D. Bischoff, S. Pelzer, G. J. Nicholson, W. Wohlleben, G. Jung, R. D. Süssmuth, *Angew. Chem.* **2002**, *114*, 3531; *Angew. Chem. Int. Ed.* **2002**, *41*, 3383.

[25] T. Manaka, S-I. Nagayama, W. Desadee, N. Yajima, T. Kumamoto, T. Watanabe, T. Ishikawa, M. Kawahata, K. Yamaguchi, *Helv. Chim. Acta* **2007**, *90*, 128–142.

[26] *Programmes CrysAlis-CCD and -RED*, Oxford Diffraction Ltd., Abingdon, UK, **2005**.

[27] G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112.

