Chemical Science

Multifaceted interception of 2-chloro-2-oxoacetic anhydrides: a catalytic asymmetric synthesis of β-lactams†

Li Huang, Wenjun Zhao, Richard J. Staples and William D. Wulff*

Aziridine-2-carboxylic acids will react with oxalyl chloride to give morpholin-2,3,5-trionones, cyclic *N*-carboxyanhydrides or β-lactams depending on the nature of the substituent at the 3-position. All substrates can be diverted to β-lactams upon treatment with a Vilsmeier reagent. The three to four membered ring expansion is stereospecific and proceeds with high yields and diastereoselection. This method provides for an asymmetric synthesis of β-lactams from simple aldehydes *via* a multi-component catalytic asymmetric aziridination reaction.
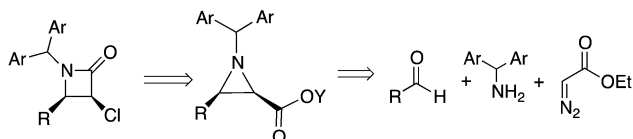
Introduction

It has been 83 years since Fleming's discovery of penicillin and β-lactams are still widely used in combating bacterial infections.[1] The last two decades have seen modifications of the β-lactam ring that have yielded a plethora of pharmacological activities ranging from cholesterol absorption inhibitory activity to anticancer activity.[2] Perhaps as a response to the diverse structures involved, there has been an increase in the development of methods for the synthesis of β-lactams and the last decade has seen an increased emphasis on catalytic asymmetric methods.[3] These methods include CO insertion into aziridines with kinetic resolution of the aziridine,[4] the kinetic resolution of β-lactams,[5] intramolecular C–H insertion reactions of diazoacetamides,[6] the reaction of alkynes with nitrones (Kinugasa reaction),[7] and the amide catalyzed addition of ester enolates to imines.[8] By far the most important method is the addition of imines to ketenes (Staudinger reaction).[9]

We sought to develop a new catalytic asymmetric synthesis of β-lactams that couples our recently developed multi-component

Scheme 1 Synthesis of β-lactams *via* aziridines.

Department of Chemistry, Michigan State University, East Lansing, MI, USA. E-mail: wulff@chemistry.msu.edu; Fax: +1 517-353-1793; Tel: +1 517-355-9715

† Electronic supplementary information (ESI) available: Protocols for procedures and NMR analysis. CCDC reference numbers 884444–884446. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2sc21240d

Scheme 2 Interception of 2-chloro-2-oxoacetic anhydrides.

catalytic asymmetric aziridination of aldehydes, amines and α-diazoesters[10] with a chloride assisted ring expansion of the resultant aziridine-2-carboxylate derivative (Scheme 1). There are two previous reports of the conversion of aziridines to β-lactams *via* a chloride induced ring-expansion of aziridine-2-carboxylic acids.[11,12] In the course of the investigation of this ring-expansion we found that in addition to β-lactams, this reaction can also produce morpholin-2,3,5-triones and cyclic *N*-carboxyanhydrides depending on reaction conditions and on the nature of the substrate (Scheme 2).

Results and discussion

The two previous reports on the chloride induced ring expansion of aziridine-2-carboxylates to β-lactams begin with the conversion of the carboxylic acid to its sodium salt.[11,12] For example, Sharma and coworkers reported that the sodium salt **5** was converted to the β-lactam **6** in 62% yield by treatment with

either oxalyl chloride and triethylamine or with thionyl chloride and sodium hydride (Scheme 3).[12] In attempting to repeat the latter, we found that the β-lactam **6** was produced in 56% yield.[13] However, when we attempted to repeat the reaction of **5** with oxalyl chloride we found that instead the major product had three carbonyl absorptions in the infrared spectrum at 1830, 1780 and 1701 cm^{−1} instead of just one as expected for the β-lactam **6**. In fact, **6** could not be detected in the ^{1}H NMR spectrum of the crude reaction mixture. The major product was assigned the structure **7** and was formed in 34% yield (NMR). The yield of **7** was increased to 82% if the acid **8** was reacted with oxalyl chloride.

Morpholin-2,3,5-triones have only been reported[14] on two previous occasions and both were from the reaction of an α-amino acid with oxalyl chloride. Morpholin-2,3,5-triones are not stable to silica gel and thus **7** could not be brought to a high level of purity. A firmer assignment of structure could be made for the morpholinetrione **11** obtained from the aziridine acid **10** (Scheme 4).[15] Morpholinetrione **11** could be crystallized to give high quality single crystals which were characterized by X-ray diffraction. The related morpholinetriones **12** and **13** could be obtained in the same manner from the proper aziridine-2-carboxylic acid. Two likely mechanisms are the nucleophilic addition of the aziridine nitrogen to the acyl chloride unit to give the aziridinium ion **16** which is then opened by chloride,[11] or the initial opening of the aziridine to give the β-chloroamine **17** which then closes to the morpholinetrione **11**. The reaction of the sodium salt **5** in the presence of Et₃N would be expected to occur *via* the former.

The reaction took a different turn with aziridine-2-carboxylic acids in which the 2-position had an additional substituent. These substrates reacted with oxalyl chloride to give the N-

carboxyanhydrides (NCAs) **33–40** (Table 1). A series of substrates were screened with a bis-(3,5-di-*tert*-butylanisyl) methyl group (BUDAM) as the nitrogen substituent since these aziridines can be made with very high enantioselectivities.[16,17] The N-carboxyanhydride **34** has two carbonyl absorptions at 1847 and 1784 cm^{−1} and its structure and relative stereochemistry were determined by X-ray diffraction (Table 1, entry 4). NCAs have had a long history of applications in the synthesis of polypeptides as they are very sensitive to polymerization.[18] Those in Table 1 however are stable to purification by silica gel and this is undoubtedly related to the bulky protecting group on nitrogen.[19] A number of methods have been used to prepare NCAs but most common is the reaction of an α-amino acid with
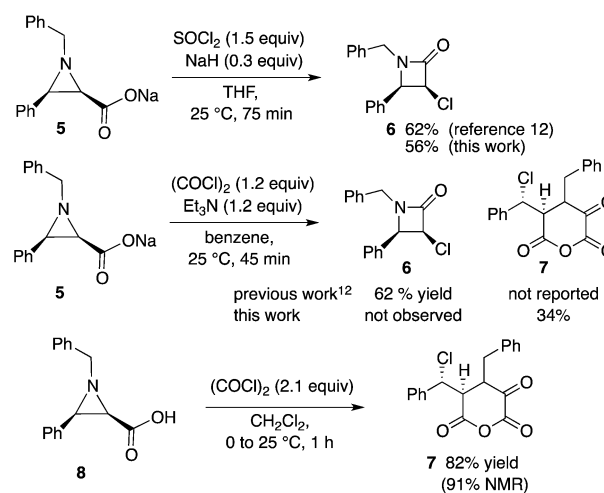
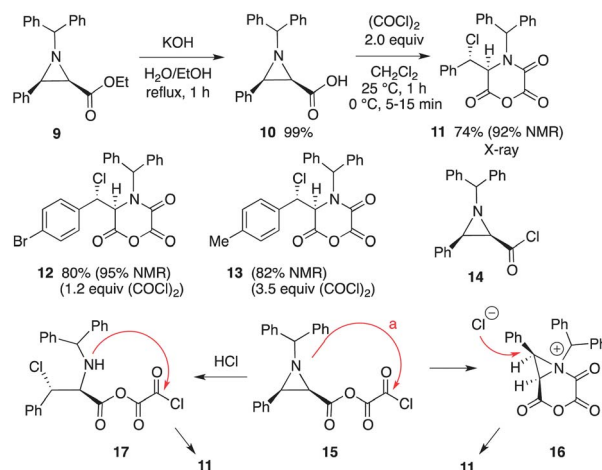**Scheme 3** β-Lactam *vs.* morpholin-2,3,5-trione formation.

Table 1 Reaction of trisubstituted aziridine carboxylic acids with oxalyl chloride[a]

Entry	Aziridine ester	PG[b]	R¹	R²	% Yield (acid)[c]	% Yield (NCA)[d]
1[e]	9	Ph₂CH	C₆H₅	Me	73 (25)	51 (33)
2[e,f]	9	Ph₂CH	C₆H₅	Me	73 (25)	56 (33)
3	9	Ph₂CH	C₆H₅	Me	73 (25)	54 (33)
4	18	BUDAM	C₆H₅	Me	87 (26)	69 (34)
5	19	BUDAM	4-MeC₆H₄	Me	94 (27)	75 (35)
6	20	BUDAM	2-MeC₆H₄	Me	78 (28)	71 (36)
7	21	BUDAM	4-BrC₆H₄	Me	54 (29)	78 (37)
8	22	BUDAM	2-BrC₆H₄	Me	57 (30)	73 (38)
9	23	BUDAM	1-Naphthyl	Me	56 (31)	80 (39)
10	24	BUDAM	4-BrC₆H₄	Et	53 (32)	20 (40)

[a] Alkylation was performed in THF by deprotonation with 2 equiv. LDA at −78 °C followed by addition of methyl or ethyl iodide (3 equiv.). After 1 h at −78 °C, the temperature was increased to ambient. The hydrolysis was performed by refluxing the alkylated ester in THF–EtOH (1 : 1) with 0.8 M aq. KOH (5 equiv.) for 17 h. Formation of the N-carboxyanhydride was effected by reaction of the acid with 2.3 equiv. of (COCl)₂ in CH₂Cl₂ for 5 min at 0 °C and 1 h at 25 °C. [b] BUDAM = [3,5-*t*-Bu₂-4-MeOC₆H₂]₂CH. [c] Isolated yield for 2 steps after purification of the acid by chromatography on silica gel. [d] Isolated yield after purification by chromatography on silica gel. [e] Reaction with (COCl)₂ performed at 25 °C for 2 h. [f] The acid **25** was converted to the sodium salt before reaction with (COCl)₂ (see ESI†).

triphosgene. These are the first examples of NCA synthesis with oxalyl chloride in which one of the carbonyls of the oxalyl chloride is incorporated into the cyclic anhydride.[20] Two mechanisms are possible for NCA formation that mimic those shown in Scheme 4 for morpholinetriones. The reaction of the sodium salt of 25 (Table 1, entry 2) would be expected to be more likely to occur with a mechanism involving initial attack of the aziridine nitrogen on the 1-position of the 2-chloro-2-oxo-acetic anhydride (Scheme 2, path b).

The reaction took yet another turn with the finding that aziridine-2-carboxylic acids with an alkyl substituent in the 3-position give exclusively β-lactams upon reaction with oxalyl chloride (Table 2). No detectable amount of *N*-carboxyanhydrides or morpholinetriones was observed. The reactions of *cis*-substituted aziridines lead to the formation of *cis*-substituted β-lactams with an expected single carbonyl absorption (1755 cm^{-1} for 41) and the relative stereochemistry was confirmed for β-lactam 41 by X-ray diffraction. This reaction can also provide β-bromo-β-lactams with oxalyl bromide but some isomerization


Scheme 4 Morpholin-2,3,5-trione formation.

to the *trans*-β-lactam is observed. The reaction is faster with oxalyl bromide (0 °C, 15 min) giving the *cis*-bromo-lactam 44 in 83% yield along with a 12% yield of the *trans*-isomer 45 but only if an aqueous quench at 0 °C is employed. If the reaction mixture is simply concentrated at 25 °C without an aqueous quench, a 1 : 2 mixture of *cis*–*trans* β-lactams is observed. Extended reaction times or increased temperatures do not enhance the proportion of the *trans*-isomer past 2 : 1. The reaction is stereospecific with oxalyl chloride as the *trans*-cyclohexyl aziridine 55 gives exclusively the trans isomer of the β-chloro-β-lactam 56 (56 : 41 ≥ 100 : 1, Scheme 5) and the corresponding *cis*-cyclohexyl aziridine gives exclusively the *cis* isomer of the β-chloro-β-lactam 41 (41 : 56 ≥ 50 : 1, Table 2). The only example with oxalyl chloride where less than complete diastereoselection was observed was with the *tert*-butyl-β-lactam 51. This was a very slow reaction and after 24 h at 25 °C a 9 : 1 mixture of *cis* and *trans* isomers was formed in 38 and 4% yields, respectively, along with a 46% yield of the acid chloride of the starting aziridine acid.[21,22]

Table 2 Reactions of 3-alkylaziridine carboxylic acids with oxalyl chloride[a]
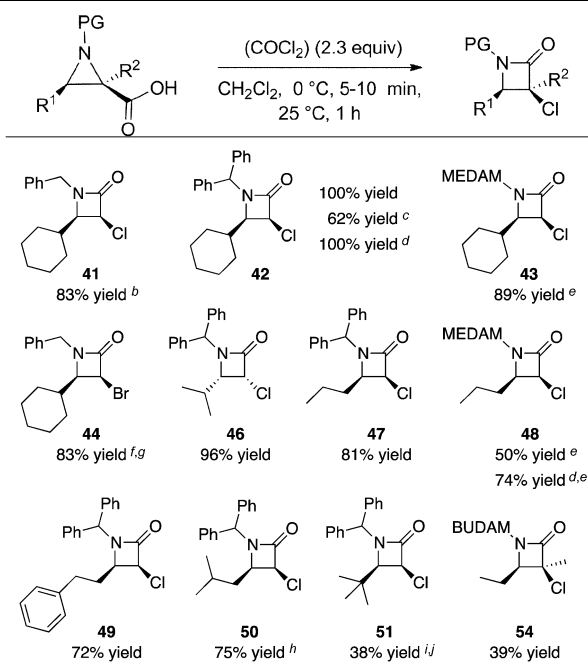
^{a} Unless otherwise specified, all reactions were carried out in CH$_2$Cl$_2$ at 0.1 M in aziridine acid with 2.3 equiv. of (COCl)$_2$ at 0 °C for 5 min and then at 25 °C for 1 h. The solvent was then removed and the product purified by chromatography on silica gel. MEDAM = (3,5-Me$_2$-4-MeOC$_6$H$_2$)$_2$CH, BUDAM = (3,5-t-Bu$_2$-4-MeOC$_6$H$_2$)$_2$CH. Yields are isolated after chromatography on silica gel. ^{b} The ratio of *cis* : *trans* ≥50 : 1. ^{c} SOCl$_2$ (2.0 equiv.) used instead of (COCl)$_2$. ^{d} Vilsmeier reagent (2.3 equiv.) used instead of (COCl)$_2$ (see Table 4). ^{e} The reaction was at 0 °C for 10 min. ^{f} This reaction was carried out with (COBr)$_2$ and also gave a 12% yield of the *trans*-β-lactam 45 (*c*–*t* = 7 : 1). ^{g} The reaction was carried out at 0 °C for 15 min and quenched with sat aq. NaHCO$_3$ at 0 °C. ^{h} Reaction was at 0 °C for 5 min and 25 °C for 30 min. ^{i} Reaction at 25 °C for 24 h and was quenched with sat. aq. NaHCO$_3$ before concentration. ^{j} This reaction also gives a 4% yield (NMR) of *trans*-β-lactam 52 (*c*–*t* = 9 : 1) and a 46% yield of the acid chloride 53 of the aziridine-2-carboxylic acid.
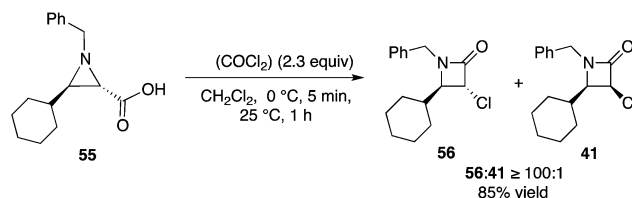
Scheme 5 Ring expansion of *trans*-aziridine 55.
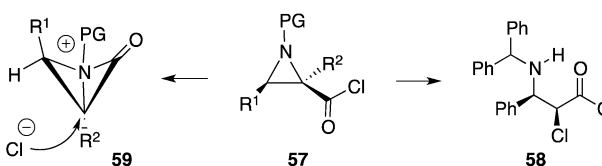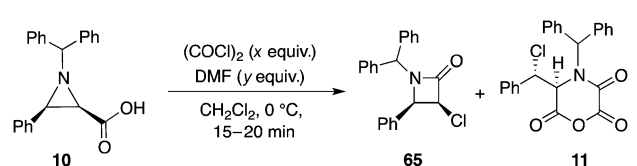

Scheme 6 Incorporation of chloride.

The β-lactams presumably result from either attack of the nitrogen on the proximal carbonyl in intermediate **1** (Scheme 2, path c) or, after collapse of **1** to the acid chloride **57**, on the acyl chloride carbonyl (Scheme 6). The resulting bicyclic acylaziridinium ion **59** can account for the stereoselectivity observed in the β-lactams and evidence has previously been provided for this intermediate.[11,23] It is also possible, but perhaps less likely, that the normal penchant[24] for aziridine-2-carboxylate esters of the type **9** to undergo nucleophilic opening at C-3 is reversed for the corresponding acid chloride **57** which gives the β-lactam *via* **58**.[25] While the β-lactam **51** may have been formed *via* an acid chloride, evidence suggests that this may not be the case for the β-lactam **42**. Reaction of the corresponding acid with Vilsmeier reagent does appear to generate an acid chloride as an intermediate, however, this species can not be detected as an intermediate in the reaction with (COCl)₂ thus suggesting that **42** arises from intermediate **1** *via* path c in Scheme 2 (see ESI†).

The formation of acid chlorides from acids and oxalyl chloride is known to be catalyzed by DMF (Scheme 7).[26] This suggests that a competition can be set up to test the relative rates of DMF and aziridine carboxylic acids towards oxalyl chloride. As the data in Table 3 shows, the amount of morpholinetrione **11** steadily drops as increasing amounts of DMF is employed from 92% with no added DMF to 6% yield with 4 equiv. of DMF. Even with a 1 : 1 ratio of **10** to DMF, a 28% yield of morpholinetrione **11** is formed indicating that the acid can compete with DMF for oxalyl chloride. When the Vilsmeier reagent **61** is generated separately and then added to the acid, only the β-lactam **65** is observed as expected (83% yield) since formation of **11** is no longer possible (entries 6 and 7).

It is presumed that the β-lactam **65** is formed from the reaction of acid **10** with the Vilsmeier reagent **61** *via* the intermediacy of the acid chloride **14** (Scheme 4). Indeed, **14** can be isolated (57% yield) from the reaction in entry 6 of Table 3, if after a reaction time of 1 minute, the crude reaction mixture is directly loaded without concentration onto a silica gel column. The question is then how is the acid chloride **14** converted to the β-lactam **65**. It is observed that when the reaction mixture in entry 6 of Table 3 is concentrated at 25 °C on a rotary evaporator after 20 min at 0 °C, the β-lactam **65** is isolated in 83% yield. In contrast, the acid chloride **14** is relatively stable in CD₂Cl₂ solution: after 24 h at 25 °C there is 72% of **14** remaining, a 5% yield of β-lactam **65** and 23% conversion to other compounds. Heating a sample of **14** in CH₂Cl₂ at 80 °C for 1 h resulted in an 8 : 1 mixture of **14** : **65** with several unknown side-products. The preparation of the Vilsmeier reagent does lead to the generation of HCl, however, attempts to effect the conversion of the acid chloride **14** to β-lactam **65** by treatment with either dry HCl or HOTF in the presence or absence of a chloride source in CH₂Cl₂ followed by concentration gives only a low yield (6–20%) of **65** after 15–240 min at 25 °C.

However, treatment of purified acid chloride **14** with 2.3 equiv. Vilsmeier reagent **61** at 0 °C for 20 min followed by concentration gives a 68% isolated yield of the lactam **65**. To account for the observed facilitation of the conversion of the acid chloride **14** to the β-lactam **65** by the Vilsmeier reagent **61** one can invoke an equilibrium of **14** and **61** with adduct **66** (Scheme 8).[27] An unfavorable equilibrium at normal concentrations would be shifted in the forward direction to **66** as the concentration is increased which could trigger the formation of

Table 3 Reactions of 3-phenylaziridine **10** with (COCl)₂ in the presence of DMF[a]

| Entry	Vilsmeier reagent 61[b]	(COCl)₂ x equiv.	DMF y equiv.	% Yield 65[c]	% Yield 11[c]
1	None	2.0	0	0	92
2	None	2.0	0.1	nd	69
3	None	2.0	1.0	7	28
4	None	2.0	2.0	20	18
5	None	2.0	4.0	47	6
6	2.3 equiv.	—	—	83 (82)	0
7	4.6 equiv.	—	—	83 (83)	0

[a] The reaction was carried out by treatment of a 0.1 M solution of **10** (0.1 mmol) in CH₂Cl₂ with DMF (y equiv.) at 25 °C followed by (COCl)₂ (x equiv.) at 0 °C for 15 min. nd = not detected. [b] The pre-formed Vilsmeier reagent was prepared by reacting (COCl)₂ with 1.24 equiv. of DMF in CH₂Cl₂ at 25 °C for 20 min. [c] The yield was determined from the ¹H NMR spectrum of the crude reaction mixture with the aid of Ph₃CH as internal standard. Yields in parentheses are isolated yields after chromatography on silica gel.

Table 4 Reactions of 3-arylaziridine carboxylic acids with Vilsmeier reagent **61**[a]

6 74% yield	**65** 83% yield	**69** 76% yield	**70** 60% yield[b]
71 85% yield[b]	**72** 69% yield	**73** 22% yield[b,c]	
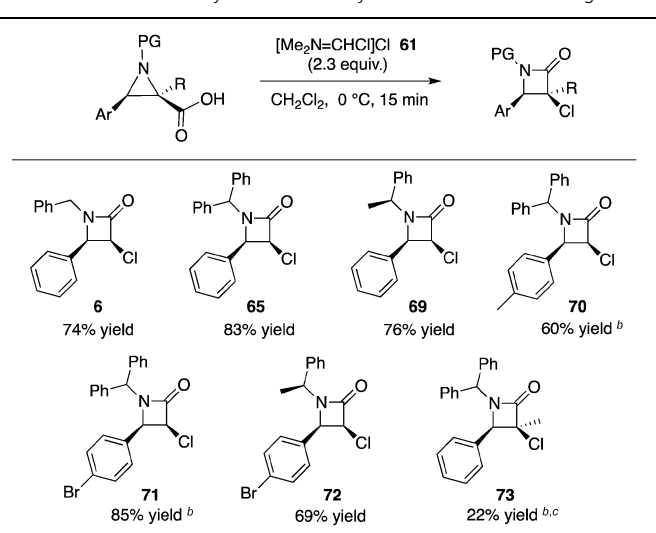
[a] Unless otherwise specified, all reactions were carried out in CH₂Cl₂ at 0.05 M in aziridine acid with 2.3 equiv. of Vilsmeier reagent **61**, prepared as described in Table 3, for 15 min at 0 °C. The solvent was removed and the product purified by chromatography on silica gel. Yields are isolated after chromatography on silica gel. [b] Reaction at 0 °C for 1 h. [c] Reaction with 4.6 equiv. **61**.

Chemical Science
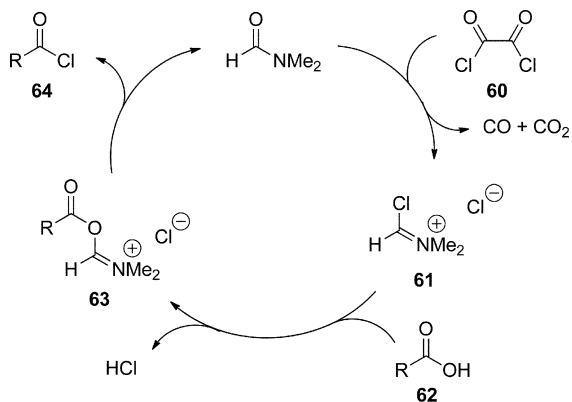

Scheme 7 Catalysis by DMF.
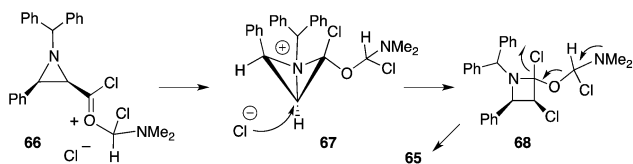
Scheme 8 Assisted ring expansion with Vilsmeier reagent.
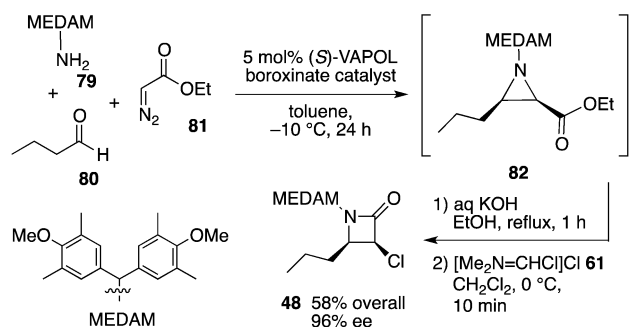
Scheme 9 Sequential multi-component aziridination/β-lactam formation from aldehydes.

the aziridinium ion **67** and then chloride opening to give **68** which collapses to the β-lactam **65**. Aziridinium ion **67** would be expected to be less strained than **59** (Scheme 6) due to the absence of an sp^2 carbon in the 3-membered ring.

This ring expansion for the 3-phenyl-2-carboxylic acid **10** mediated by Vilsmeier reagent **61** is general for a number of 3-arylaziridine carboxylic acids (Table 4). The 3-chloro-4-aryl-β-lactams are obtained as the *cis*-diastereomer with no evidence for isomerization in any example. The β-lactams **69** and **72** are prepared from aziridines that can be made in highly matched double-stereodifferentiation with VAPOL and VANOL bor-oxinate catalyst.[28] It is to be noted that the ring expansion of aziridine-2-carboxylic acids is much more efficient with Vils-meier reagent **61** than it is with thionyl chloride. The yields for β-lactam **6** are 74% with Vilsmeier reagent (Table 4) and 56% with thionyl chloride (Scheme 3). The yields for β-lactam **42** are 100% and 62% in the same comparison (Table 2).
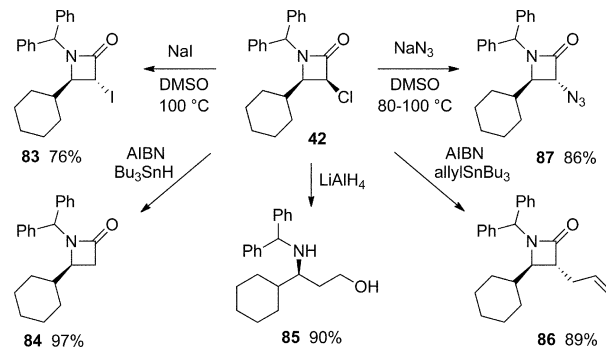
Scheme 10 Transformation of β-lactam **42**.

We have recently developed a multi-component catalytic asymmetric synthesis of aziridines from an amine, an aldehyde and ethyl diazoacetate.[10] For example, the aziridine **82**, can be prepared in 90% isolated yield and 96% ee from butanal with 5 mol% of a boroxinate catalyst prepared from VAPOL and B(OPh)$_3$ (Scheme 9). We have now found that β-lactam **48** can be made from butanal in 58% overall yield where no unit operation except the last is a purification. The overall yield of **48** for the three steps when both intermediates are purified is 41%. Thus the present method provides for a convenient and direct cata-lytic asymmetric access to β-lactams from aldehydes.

The synthetic utility of the 3-chloro-2-azetidinones was probed with the cyclohexyl β-lactam **42** with a benzhydryl protecting group (Scheme 10). Clean inversion was observed upon reaction with sodium iodide in DMSO. The chlorine could be reduced in near quantitative yield with tributyltin hydride to give β-lactam **84** and the 1,3-amino alcohol **85** could be obtained in 90% yield by reduction with LAH. A free radical introduction of an allyl group occurs with diaster-eoselective control to give only the *trans*-β-lactam **86** in 89% yield. Finally, the chlorine substituent can be replaced with an azide group in 86% yield with complete inversion of stereo-chemistry. The introduction of a nitrogen substituent in the 3-position by S$_N$2 substitution of a halide is a known but little used process.[29] Thus the method described here should provide direct access to highly optically enriched β-lactams from simple aldehydes, amines and ethyl diazoacetate *via* aziridine intermediates.

Conclusions

We have reported here the first examples where the reaction of an α-amino acid in the form of an aziridine-2-carboxylic acid can give either morpholin-2,3,5-triones, cyclic N-carboxyanhy-drides or β-lactams *via* ring-expansion of the aziridine. Thus six, five and four membered rings can be obtained from reactions that incorporate two, one or zero carbons from oxalyl chloride. With proper control of reagents and conditions, all substrates can be controlled to give β-lactams and coupled with the multi-component aziridination of aldehydes with amines and ethyl diazoacetate, a new and efficient catalytic asymmetric access to β-lactams is developed.

Experimental section

Multi-component catalytic asymmetric aziridination of butanal

To a 25 mL flame-dried Schlenck flask equipped with a stir bar and filled with N_2 was added (S)-VAPOL (13.7 mg, 0.025 mmol), B(OPh)$_3$ (21.8 mg, 0.075 mmol) and amine **79** (149.7 mg, 0.5 mmol). Dry toluene (1 mL) was added under an N_2 atmosphere to dissolve the reagents. The reaction mixture was stirred at room temperature for 1 h. Then 4 Å molecular sieves (150 mg, freshly flame-dried) were added. After the reaction mixture was cooled to −10 °C, butanal **80** (47.0 μL, 0.522 mmol, 1.04 equiv.) was added followed by the addition of ethyl diazoacetate (EDA) **81** (125 μL, 1.00 mmol, 2.00 equiv.). The resulting mixture was stirred for 24 h at −10 °C. The reaction was diluted by addition of hexane (6 mL). The reaction mixture was then filtered through a Celite pad to a 100 mL round bottom flask. The reaction flask was rinsed with EtOAc (3 mL × 3) and the rinse was filtered through the same Celite pad. The resulting solution was then concentrated in vacuo followed by exposure to high vacuum (0.05 mm Hg) for 1 h to afford the crude aziridine **82** as a viscous yellow oil.

Hydrolysis

To the solution of the crude aziridine **82** in ethanol (2 mL) was added a solution of KOH (140.3 mg, 2.50 mmol, 5.00 equiv.) in H_2O (2 mL). The resulting mixture was refluxed for 1 h and then cooled to rt. Then aq. citric acid (2 N, 2.5 mL) and ether (10 mL) were added. The organic layer was separated and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and filtered. The filtrate was concentrated to afford the crude aziridine acid as a yellow foamy solid.

Ring-expansion

To a flame-dried round bottom flask equipped with a stir bar and filled with N_2 was added dry DMF (147.5 μL, 1.9 mmol, 3.8 equiv.) and dry CH$_2$Cl$_2$ (1 mL). The flask was fitted with a rubber septum and a nitrogen balloon. Then (COCl)$_2$ (131 μL, 1.53 mmol, 3.06 equiv.) was added dropwise to the reaction flask with stirring and the Vilsmeier salt precipitated out as a white solid. The mixture was stirred for 20 min at room temperature and cooled to 0 °C. A solution of the crude aziridine acid in dry CH$_2$Cl$_2$ (5 mL) was added dropwise to the reaction flask containing the Vilsmeier salt (1.53 mmol, 3.06 equiv.) over 5 min. The reaction mixture was stirred for 10 min at 0 °C and concentrated to afford a foamy crude product. The yield of lactam **48** was 59% (over three steps) as determined from the ^{1}H NMR spectrum of the crude reaction mixture in CDCl$_3$ with the aid of Ph$_3$CH as an internal standard. The product was purified by column chromatography (silica gel, 25 × 210 mm, hexane : CH$_2$Cl$_2$: ethyl acetate 8 : 8 : 1) to afford β-lactam **48** (124 mg, 0.29 mmol) as a colorless semi-solid in 58% isolated yield (over three steps); The optical purity was determined to be 96% ee by HPLC analysis (Chiralcel OD-H column, 98 : 2 hexane–2-propanol at 222 nm, flow-rate 1.0 mL min^{-1}); retention times:

R_t = 7.06 min (major enantiomer, **48**) and R_t = 11.73 min (minor enantiomer, ent-**48**). R_f = 0.25 (hexane : CH$_2$Cl$_2$: ethyl acetate 8 : 8 : 1). Spectral data for **48**: ^{1}H NMR (500 MHz, CDCl$_3$) δ0.80 (t, 3H, J = 7.2 Hz), 1.04–1.16 (m, 1H), 1.24–1.36 (m, 1H), 1.42–1.50 (m, 1H), 1.68–1.76 (m, 1H), 2.241 (s, 6H), 2.242 (s, 6H), 3.63–3.68 (m, 1H), 3.70 (s, 3H), 3.71 (s, 3H), 4.83 (d, J = 5.5 Hz, 1H), 5.70 (s, 1H), 6.82 (s, 2H), 6.85 (s, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 13.65, 16.19, 16.20, 18.90, 31.43, 57.39, 59.01, 59.62, 59.63, 60.19, 128.13, 128.95, 130.84, 131.06, 132.92, 133.82, 156.44, 156.60, 163.99; IR (thin film) 2934(w), 1767(s), 1485(w), 1221(w) cm^{-1}; HRMS calcd for C$_{25}$H$_{33}$NO$_3$Cl (M + H, ESI$^+$) m/z 430.2149, meas. 430.2141; $[\alpha]_D^{20}$ −13.7° (c 1.0, CH$_2$Cl$_2$) on 96% ee material.

Notes and references

1 S. A. Testero, J. F. Fisher and S. Mobashery, β-Lactam Antibiotics, in Burger's Medicinal Chemistry, Drug Discovery and Development, ed. D. J. Abraham and D. P. Rotella, Wiley-VCH, Hoboken, NJ, 7th edn, 2010, vol. 7, pp. 259–404.
2 P. D. Mehta, N. P. S. Sengar and A. K. Pathak, Eur. J. Med. Chem., 2010, 45, 5541–5560, and references therein.
3 (a) S. France, A. Weatherwax, A. E. Taggi and T. Lectka, Acc. Chem. Res., 2004, 37, 592–600; (b) A. Fu and T. T. Tidwell, Tetrahedron, 2008, 64, 10465–10496; (c) A. Brandi, S. Cicchi and F. M. Cordero, Chem. Rev., 2008, 108, 3988–4035; (d) D. H. Paull, A. Weatherwax and T. Lectka, Tetrahedron, 2009, 65, 6771–6803.
4 S. Calet, F. Urso and H. Alper, J. Am. Chem. Soc., 1989, 111, 931–934.
5 (a) X. Yang, V. D. Bumbu and V. B. Birman, Org. Lett., 2011, 13, 4755–4757; (b) V. D. Bumbu and V. B. Birman, J. Am. Chem. Soc., 2011, 133, 13902–13905.
6 (a) M. P. Doyle and A. V. Kalinin, Synlett, 1995, 1075–1076; (b) For a review, see: P. M. P. Gois and C. A. M. Afonso, Eur. J. Org. Chem., 2004, 3773–3788.
7 (a) M. Miura, M. Enna, K. Okuro and M. Nomura, J. Org. Chem., 1995, 60, 4999–5004; (b) M. M. C. Lo and G. C. Fu, J. Am. Chem. Soc., 2002, 124, 4572–4573; (c) R. Pal, S. C. Ghosh, K. Chandra and A. Basak, Synlett, 2007, 2321–2330; (d) T. Saito, T. Kikuchi, H. Tanabe, J. Yahiro and T. Otani, Tetrahedron Lett., 2009, 50, 4969–4972.
8 (a) H. Fujieda, M. Kanai, T. Kambara, A. Iida and K. Tomioka, J. Am. Chem. Soc., 1997, 119, 2060–2061; (b) T. Kambara and K. Tomioka, Chem. Pharm. Bull., 2000, 48, 1577–1580.
9 For representative examples, see: (a) A. E. Taggi, A. M. Hafez, H. Wack, B. Young, W. J. Drury III and W. T. Lectka, J. Am. Chem. Soc., 2000, 122, 7831–7832; (b) B. L. Hodous and G. C. Fu, J. Am. Chem. Soc., 2002, 124, 1578–1579; (c) E. C. Lee, B. L. Hodius, E. Bergin, C. Shih and G. C. Fu, J. Am. Chem. Soc., 2005, 127, 11586–11587; (d) S. France,

M. H. Shah, A. Weatherwax, H. Wack, J. P. Roth and T. Lectka, *J. Am. Chem. Soc.*, 2005, **127**, 1206; (*e*) Y. Huang and M. A. Calter, *Tetrahedron Lett.*, 2007, **48**, 1657–1659; (*f*) Y.-R. Zhang, L. He, X. Wu, P.-L. Shao and S. Ye, *Org. Lett.*, 2008, **10**, 277–280; (*g*) M. He and J. W. Bode, *J. Am. Chem. Soc.*, 2008, **130**, 418–419; (*h*) N. Duguet, C. D. Campbell, A. M. Z. Slawin and A. D. Smith, *Org. Biomol. Chem.*, 2008, **6**, 1108–1113; (*i*) M. J. Bodner, R. M. Phelan and C. A. Townsend, *Org. Lett.*, 2009, **11**, 3606–3609.

10 A. K. Gupta, M. Mukherjee and W. D. Wulff, *Org. Lett.*, 2011, **13**, 5866–5869.

11 (*a*) J. A. Deyrup and S. C. Clough, *J. Am. Chem. Soc.*, 1969, **91**, 4590–4591; (*b*) J. A. Deyrup and S. C. Clough, *J. Org. Chem.*, 1974, **39**, 902–907.

12 S. D. Sharma, S. Kanwar and S. Rajpoot, *J. Heterocyclic Chem.*, 2006, **43**, 11–19.

13 The spectral data reported for β-lactam **6** (ref. 12) does not match those that we have obtained for this compound (*vide infra*) nor does it match that previously reported for this compound: Y. Dejaegher, B. Denholf, C. V. Stevens and N. De Kimpe, *Synthesis*, 2005, 193–198.

14 (*a*) R. Bentley, A. H. Cook, J. A. Elvidge and G. J. Shaw, *J. Chem. Soc.*, 1949, 2351–2357; (*b*) W. R. Hearn and R. E. Worthington, *J. Org. Chem.*, 1967, **32**, 4072–4074.

15 Y. Zhang, A. Desai, Z. Lu, G. Hu, Z. Ding and W. D. Wulff, *Chem.–Eur. J.*, 2008, **14**, 3785–3803.

16 Y. Zhang, Z. Lu, A. Desai and W. D. Wulff, *Org. Lett.*, 2008, **8**, 5429–5432.

17 A. Patwardan, V. R. Pulgam, Y. Zhang and W. D. Wulff, *Angew. Chem., Int. Ed.*, 2005, **44**, 6169–6172.

18 H. R. Kricheldorf, *Angew. Chem., Int. Ed.*, 2006, **45**, 5752–5784.

19 T. B. Sim and H. Rapoport, *J. Org. Chem.*, 1999, **64**, 2532–2536.

20 Oxalyl chloride has been used to generate acid chlorides in NCA formation, see: (*a*) D. Konopinska and I. Z. Siemlon, *Angew. Chem., Int. Ed. Engl.*, 1967, **6**, 248; (*b*) S. Mobashery and M. Johnston, *J. Org. Chem.*, 1985, **50**, 2200–2202.

21 The acid chloride **53** (precursor to **61**) could be isolated by chromatography on silica gel in 22% yield.

22 Concentration of the crude reaction mixture and storage for 3 months at 25 °C gave the *cis*-β-lactam **51** in 68% yield and the corresponding *trans*-β-lactam **52** in 15% yield.

23 For citations to the literature of the related α-lactams, see: R. V. Hoffman, Z. Zhao, A. Costales and D. Clarke, *J. Org. Chem.*, 2002, **67**, 5284–5294.

24 (*a*) X. E. Hu, *Tetrahedron*, 2004, **60**, 2701–2743; (*b*) P. Lu, *Tetrahedron*, 2010, **66**, 2549–2560.

25 R. Naidu, *PCT Int. Appl.*, WO 2005082875 A2 20050909, 2005.

26 (*a*) H. H. Bosshard, R. Mory, M. Schmid and Hch. Zollinger, *Helv. Chim. Acta*, 1959, **42**, 1653–1658; (*b*) For a recent example, see: B. Lunelli, *Tetrahedron Lett.*, 2007, **48**, 3595–3597.

27 The Vilsmeier reagent could also add to the nitrogen leading to an activated ring-opening of the type **57** to **58**. This is considered less likely since HCl did not facilitate the conversion of acid chloride **14** to β-lactam **65** as the Vilsmeier reagent did.

28 L. Huang, Y. Zhang, R. J. Staples, R. H. Huang and W. D. Wulff, *Chem.–Eur. J.*, 2012, **18**, 5302–5313.

29 (*a*) M. D. Bachi and O. Goldberg, *J. Chem. Soc., Chem. Commun.*, 1972, 319–320; (*b*) F. H. van der Steen and G. van Koten, *Tetrahedron*, 1991, **47**, 7503–7524.