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Highly Stereoselective Synthesis of β-Lactams Utilizing α-Chloroimines as New and Powerful Chiral Inductors

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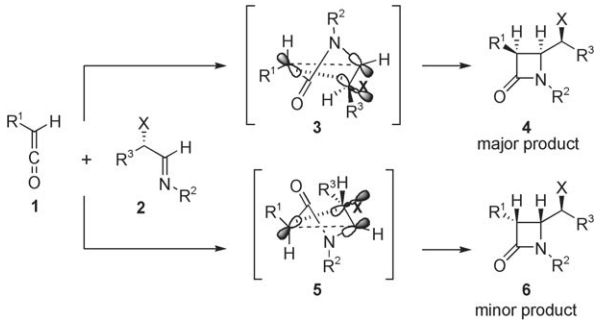
Due to the biological relevance of β-lactams as antibiotics and their usefulness as synthons for further functionalization, the β-lactam skeleton can be considered as one of the most important azaheterocyclic frameworks in organic chemistry.[1] In recent years, the development of chiral approaches (often catalytic methodologies) towards these attractive compounds has become a key issue and challenge in organic synthesis. The Staudinger reaction, in which a ketene and an imine react in a [2+2]-cycloaddition, is generally acknowledged as the method of choice for the asymmetric synthesis of β-lactams.[2] A first approach in this respect consists of the cycloaddition of a chiral ketene,[3] for example, the Evans–Sjögren ketene,[4] and an achiral imine. Alternatively, chirality can be induced by using a chiral imine and an achiral ketene. However, the application of chiral imines derived from chiral amines for the Staudinger synthesis of β-lactams generally results in low levels of diastereoselectivity,[2a] and only in some exceptional cases (e.g. when imines derived from D-glucosamine or D-threonine and cinnamaldehyde are used) high diastereoselectivities (*de* >90) have been reported.[5,6] On the other hand, high stereoselectivities are attained when chiral imines derived from chiral aldehydes (usually α-oxy- or α-aminoaldehyde derived imines) are used.[7,8] Chiral α-alkylimines, derived from chiral α-alkylaldehydes, are known to be unreactive in terms of both chemical reactivity and diastereoselectivity in the Staudinger reaction towards β-lactams.[2a]

The origin of the asymmetric induction in the Staudinger synthesis of β-lactams has been rationalized on the basis of the magnitude of the stereoelectronic effect exerted by the σ*(C–X) orbital (X being an electronegative atom and C a stereogenic carbon atom) over the HOMO in the transition states.[8] The angular disposition between C_3 and the C–X bond in transition state **5** minimizes the steric interaction between R^3 and the forming β-lactam ring, but at the cost of loss of efficiency of the stabilizing interaction between the HOMO and the σ*(C–X) orbital. In the case of transition state **3**, the aforementioned steric interaction does not occur, and therefore the HOMO–σ*(C–X) stabilization takes place more efficiently, favored by the linear arrangement between C_3 and the exocyclic C–X bond. Consequently, the latter transition state **3** has a lower energy and is preferred (Scheme 1).[8]



Scheme 1. AM1-calculated transition states for the asymmetric Staudinger synthesis of β-lactams by Palomo et al.[8]

According to a theoretical study on the hyperconjugative acceptor ability of σ bonds, the σ*(C–X) acceptor abilities increase by at least 30% when X is a halogen atom in comparison with X being an oxygen or a nitrogen atom.[9] In other words, the use of chiral α-chloroimines might lead to higher stereoselectivities compared with those obtained with α-oxy- or α-aminoaldehyde derived imines. However, the

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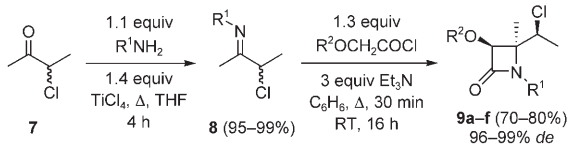
use of chiral α-haloimines for the asymmetric Staudinger synthesis of β-lactams comprises an unexplored field of research up to now. In addition, the presence of a halogenated side chain at C4 in the resulting β-lactams would allow further elaboration towards interesting heterocyclic target compounds.[10]

Herein, α-chloroimines are used for the first time as powerful inductors for the stereoselective synthesis of azetidin-2-ones. This approach is inspired by the mechanistic rationale of the [2+2]-cycloaddition of ketenes and imines derived from α-oxy and α-amino substituted aldehydes,[8] and a predicted higher hyperconjugative acceptor ability of halogens in comparison with both oxygen and nitrogen as the α-heteroatom.[9]

Furthermore, a new approach towards (*S*)-α-chloroaldimines starting from (2*S*)-chloro-1-propanol is disclosed as an improved alternative over known enantioselective α-chlorination procedures for short-chain aldehydes. The latter (*S*)-α-chloroaldimines were applied successfully for the synthesis of novel 4-(1-chloroethyl)-β-lactams in high diastereomeric (84–89%) and enantiomeric excess (90%).

As no information is available regarding the use of chiral α-haloimines for the Staudinger synthesis of β-lactams, the attainability of the concept was first evaluated starting from racemic substrates. Thus, *N*-(2-chloro-1-methylpropylidene)-amines **8**, prepared via condensation of racemic 3-chloro-2-butanone (**7**) and different primary amines in the presence of titanium(IV) chloride in THF,[11] were treated with 1.3 equivalents of benzyloxy- or phenoxyacetyl chloride in refluxing benzene in the presence of three equivalents of triethylamine. After workup, the resulting β-lactams **9** were obtained in an excellent diastereomeric excess (96–100%, determined by ^{1}H NMR and GC), pointing to a strong inducing effect of the α-chloro atom (Scheme 2, Table 1).

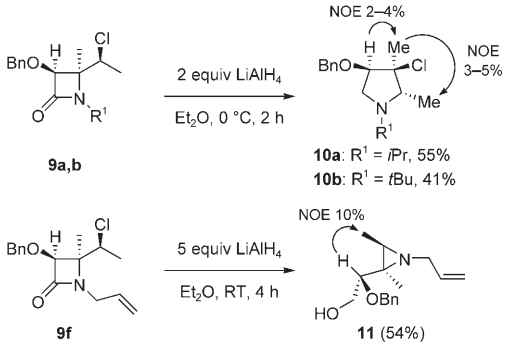


Scheme 2. Diastereoselective synthesis of *rac*-4-(1-chloroethyl)-4-methyl-β-lactams **9**.

Table 1. Diastereoselective synthesis of *rac*-4-(1-chloroethyl)-4-methyl-β-lactams **9a–f**.

Product	R^1	R^2	Yield [%]	*de* [%]
9a	*i*Pr	Bn	75	>99
9b	*t*Bu	Bn	80	>99
9c	cHex	Bn	70	>99
9d	Et	Bn	72	>99
9e	*i*Pr	Ph	76	>99
9f	allyl	Bn	72	96

To confirm the relative configuration of β-lactams **9**, azetidin-2-ones **9a**,**b** were treated with two molar equivalents of lithium aluminum hydride in diethyl ether at 0°C for two hours, affording pyrrolidines **10a**,**b** (Scheme 3) in accordance with the previously described reactivity of 4-(1-chloro-1-methylethyl)-β-lactams towards $LiAlH_4$.[10] Subsequently, NOE experiments performed on the latter pyrrolidines **10** resulted in NOE effects of 2–4% between the C4 proton and the C3 methyl group, and NOE effects of 3–5% between the C2 and C3 methyl substituents (Scheme 3). On the other hand, treatment of β-lactam **9f** (less bulky at nitrogen) with five molar equivalents of $LiAlH_4$ in diethyl ether afforded aziridine **11** after four hours at room temperature (Scheme 3), again in accordance with previously reported transformations of 4-(1-chloro-1-methylethyl)-β-lactams.[10] For aziridine **11**, a distinct NOE effect of 10% between the proton at the α-position of the benzyloxy substituent and the aziridine C3 methyl substituent was measured (Scheme 3), affording strong evidence for the *trans*-relationship of the two methyl substituents on the aziridine ring. Furthermore, the observed $^3J_{CH}$ coupling of 3.5 Hz between the aziridine C2 methyl substituent and the aziridine C3 proton is in accordance with literature data,[12,13] as coupling constants between a *cis*-oriented C2 methyl substituent and a C3 proton are usually between 2 and 4 Hz. On the other hand, this type of coupling constants is barely observable in aziridines with a C2-methyl group and a C3-hydrogen atom in a *trans*-configuration. Based on the observed NOE effects and coupling constants in pyrrolidines **10** and aziridine **11**, the relative stereochemistry of β-lactams **9** could be assigned as depicted in Schemes 2 and 3.



Scheme 3. Transformations of 4-(1-chloroethyl)-β-lactams 9 into pyrrolidines **10** and aziridine **11**.

Due to these encouraging results, the development of an asymmetric version using chiral α-haloimines was envisaged.

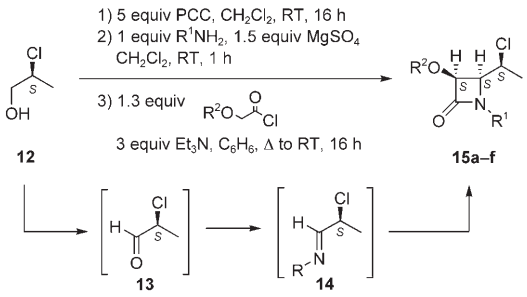
To obtain 4-(1-chloroethyl)azetidin-2-ones, 2-chloropropanal was chosen as a substrate for imination and further lactamization. To date, only two methods leading towards chiral α-chloroaldehydes bearing an α-hydrogen are available in the literature.[14,15] Both approaches are based on the enantioselective organocatalytic α-chlorination of aldehydes, either by means of 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone in the presence of (*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one[14] or by NCS (*N*-chlorosuccinimide) in the pres-

ence of L-prolinamide.[15] The synthesis of chiral 2-chloropropanal has only been described by the second method in low *ee* (75%). As a possible and convenient alternative, the oxidation of chiral 2-chloro-1-propanol, readily available from α-amino acids,[16] towards chiral 2-chloropropanal was examined. Thus, treatment of the commercially available (2*S*)-chloro-1-propanol (**12**) with five equivalents of PCC (pyridinium chlorochromate) in dichloromethane at room temperature afforded the premised (2*S*)-chloropropanal (**13**). Filtration of the reaction mixture over silica gel and subsequent treatment with one equivalent of benzylamine and 1.5 equivalents of $MgSO_4$ yielded (*S*)-*N*-(2-chloropropylidene)benzylamine (**14a**) after one hour at room temperature. Due to the high volatility, **13** was not isolated from the solvent dichloromethane and used in solution for the next step. The imine **14a** appeared to be unstable in pure form at room temperature, as all attempts to purify the compound failed.

It should be noted that the application of Swern oxidation conditions or the use of pyridinium sulfur trioxide in DMSO instead of PCC did not afford the anticipated aldehyde **13**.

Due to the instability, **14a** was used as such in the next step and treated with 1.3 equivalents of benzyloxyacetyl chloride in dichloromethane under Staudinger conditions to afford the corresponding β-lactam **15a**, albeit in a very low overall yield (2%, based on alcohol **12**). However, the diastereomeric excess appeared to be excellent (98% based on ^{1}H NMR and GC), pointing to the very high stereoinduction by α-chloroimines in the Staudinger reaction. In addition, allylamine was used to perform the imination of **13** and subsequent lactamization of the intermediate imine **14b** towards *N*-allylazetidin-2-one **15b**. Again, the latter β-lactam **15b** was obtained in a high diastereomeric excess (98%) but in a low overall yield (3%, based on alcohol **12**). The expected *cis*-diastereoselectivity during β-lactamization towards azetidin-2-ones **15** could be confirmed based on a coupling constant of 5 Hz between the C3 and C4 protons (^{1}H NMR, $CDCl_3$). From these results, it was already clear that the high stereocontrol by the halogen in favor of the *syn*-isomer comprised a useful tool in organic synthesis.

An optimization of the reaction conditions for the synthesis of β-lactams **15** appeared necessary due to the excellent stereoinduction. Whereas the reaction of **14a** with benzyloxyacetyl chloride under Staudinger conditions in benzene at room temperature was unsuccessful, the addition of 1.3 equivalents of benzyloxyacetyl chloride to a refluxing solution of **14a** and triethylamine in benzene afforded the corresponding β-lactam **15a** in a satisfying 27% overall yield (after purification by column chromatography) and 86% diastereomeric excess (Scheme 4). Although lower as compared to the reaction in dichloromethane, the diasteromeric excess of 86% is still very high and comparable to the *de* values obtained when chiral α-oxy- or α-aminoaldehyde derived imines are used in the Staudinger reaction.[2a] The incorporation of a chlorinated side chain in the resulting β-lactams enables further elaboration towards chiral azaheterocyclic target compounds with potential biological interest.[10]



Scheme 4. One-pot synthesis of chiral 4-(1-chloroethyl)-β-lactams **15** from (2*S*)-chloro-1-propanol.

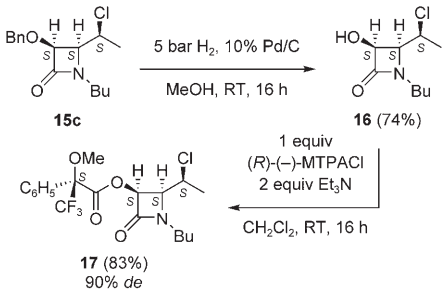
Table 2. Stereoselective synthesis of 4-(1-chloroethyl)azetidin-2-ones **15a–f**.

Product	R^1	R^2	Overall yield [%][a]	*de* [%]
15a	Bn	Bn	27	86
15b	Allyl	Bn	31	85
15c	Bu	Bn	30	88
15d	*i*Bu	Bn	43	84
15e	*i*Pr	Bn	19	89
15f	Bu	Me	6	80

[a] Yields after column chromatography and with respect to alcohol **12**.

The generality of this methodology was demonstrated by the one-pot synthesis of different 3-benzyloxy-4-(1-chloroethyl)azetidin-2-ones **15a–e** in acceptable overall yields (19–43% after purification by column chromatography) and high diastereomeric excesses of 84–89% (Scheme 4, Table 2). It should be noted that the overall yields of 19–43% were obtained after purification by column chromatography on silica gel in order to obtain analytically pure samples. The crude overall yields of these β-lactams **15** were considerably higher (32–61%). Only for the synthesis of 3-methoxyazetidin-2-one (**15f**), a lower overall yield (6% after purification) was obtained.

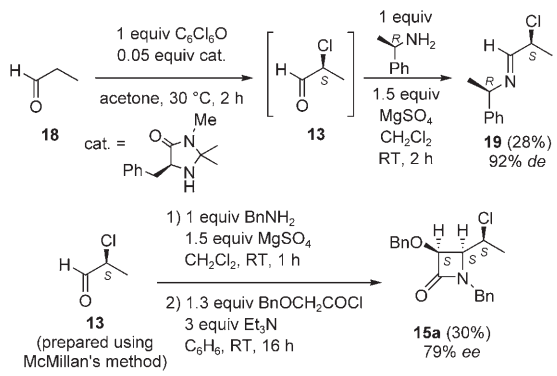
To determine the enantiomeric excess of the β-lactams **15**, which can be influenced by the stability of the intermediate α-chloroimines **14** towards racemization upon imine–enamine tautomerism, the coupling of β-lactam **15c**, after *O*-debenzylation, with a chiral acid chloride was envisaged. Hydrogenolysis of the benzyloxy group of azetidin-2-one **15c** in methanol at room temperature, followed by esterification of the resulting 3-hydroxy-β-lactam **16** with one equivalent of (*R*)-α-methoxy-α-trifluoromethyl phenylacetic acid chloride in dichloromethane at room temperature, afforded the corresponding 3-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)-β-lactam (**17**; Scheme 5) in at least 90% diastereomeric excess. This conclusion was based on the presence of 3 isomers upon GC-analysis, that is, the (3*S*,4*S*,4′*S*)-isomer (93%), the (3*R*,4*R*,4′*R*)-isomer (3%) and the (3*R*,4*R*,4′*S*)-isomer (3%). Thus, it can be concluded that the starting β-lactam **15c** was prepared in an enantiomeric excess of 90%. The high diastereomeric excess points to the fact that little epimerization of the intermediate α-chloroaldehyde **13** or α-chloroimines **14** occurs during the three-step sequence lead-



Scheme 5. Synthesis of 3-(3,3,3-trifluoro-2-methoxy-2-phenylpropanoyloxy)-β-lactam (**17**) starting from azetidin-2-one (**15c**).

ing to β-lactams **15**. These data provide the first information on the stability of chiral α-chloroaldimines under these reaction conditions.

As previously mentioned, only two methods for the preparation of chiral α-haloaldehydes are available in the literature. The enantioselective organocatalytic chlorination of propanal by means of NCS in the presence of L-prolinamide has been described to afford (*R*)-2-chloropropanal in an *ee* of 75%.[15] The asymmetric chlorination of propanal by 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone in the presence of (5*S*)-benzyl-2,2,3-trimethylimidazolidin-4-one, however, has not been described so far (the McMillan method has been applied for higher aldehydes, for example, octanal, 3-phenylpropanal).[14] In order to compare both approaches with the newly developed methodology, the α-chlorination of propanal by means of one equivalent of 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dienone (C_6Cl_6O) in the presence of 5 mol% of (5*S*)-benzyl-2,2,3-trimethylimidazolidin-4-one was evaluated. In this way, **13** was obtained after 2 h at −30 °C in acetone (Scheme 6). To evaluate the chiral purity of aldehyde **13**, condensation with (*R*)-α-methylbenzylamine[17] was performed by means of standard reaction conditions in dichloromethane towards the corresponding imine **19** (Scheme 6). The latter imine was obtained in a diastereomeric excess of 92% (based on ^{1}H NMR and GC), which corresponds well with the *ee* values reported for the enantioselective chlorination of other aldehydes using the same methodology (91–95%).[14] (2*S*)-Chloropropanal **13** was then



Scheme 6. Synthesis of β-lactam **15a** starting from propanal 18.

further transformed into β-lactam **15a** in 79% *ee* (GC) applying the one-pot reaction conditions as described above. The observed decrease in *ee* (from 92% to 79%) during the Staudinger reaction is in correspondence with the observations made for the synthesis of β-lactam **15c**, which was obtained in an *ee* of 90% starting from an enantiomerically pure substrate.

From these results, it can be concluded that the new method for the stereoselective preparation of 4-(1-chloroethyl)-β-lactams **15** starting from (2*S*)-chloro-1-propanol provides an improved alternative in terms of enantiomeric excess as compared to the synthesis starting from propanal via known organocatalytic α-chlorination procedures. For higher aldehydes, the known α-chlorination procedures remain an attractive approach in this respect.

In continuation of the successful use of chiral α-oxy and α-amino substituted aldehydes for the stereoselective synthesis of β-lactams,[8] the application of chiral α-chloroimines can be considered as an additional tool useful for the stereoselective synthesis of 4-(1-chloroalkyl)-β-lactams in a convenient way. The latter azetidin-2-ones have been demonstrated previously to be suitable synthons for the preparation of other azaheterocyclic compounds such as aziridines and pyrrolidines.[10]

In conclusion, it has been demonstrated for the first time that α-haloimines are powerful inductors for the stereoselective Staudinger synthesis of β-lactams. In particular, a new and efficient one-pot approach towards chiral azetidin-2-ones has been developed starting from (2*S*)-chloro-1-propanol, affording novel β-lactams in high diastereomeric (80–89%) and enantiomeric excess (90%). In this case, the oxidation of (2*S*)-chloro-1-propanol towards (2*S*)-chloropropanal constitutes an improved alternative over known enantioselective α-chlorination procedures. Furthermore, the first data on the stability of chiral α-chloroimines were provided, pointing to the observation that the latter compounds are relatively stable towards epimerization under Staudinger reaction conditions.

Experimental Section

^{1}H NMR spectra were recorded at 270 MHz (JEOL JNM-EX 270) or at 300 MHz (JEOL ECLIPSE+) with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 68 MHz (JEOL JNM-EX 270) or at 75 MHz (JEOL ECLIPSE+) in $CDCl_3$. Mass spectra were obtained with a mass spectrometer (70 eV) using a GC-MS coupling (20 m glass capillary column, i.d. 0.53 mm, He carrier gas) or were recorded using a direct inlet system (70 eV). Elemental analyses were performed with a PerkinElmer Series II CHNS/O Analyzer 2400. Dichloromethane was dried over calcium hydride, while diethyl ether and THF were dried by distillation over sodium/benzophenone. All other solvents were used as received from the supplier.

General procedure for the synthesis of 4-(1-chloroethyl)-4-methylazetidin-2-ones 9: To a refluxing solution of imine **8** (10 mmol) and triethylamine (30 mmol) in benzene (50 mL) was added dropwise a solution of acid chloride (13 mmol) in benzene (50 mL). The resulting mixture was heated under reflux for 30 min and stirred at room temperature for 16 h. The reaction mixture was then diluted with chloroform (100 mL) and washed with a saturated solution of sodium bicarbonate (150 mL) and

brine (150 mL). Drying ($MgSO_4$) and evaporation of the solvent afforded the crude **9**, which was purified by means of column chromatography on silica gel (hexane/EtOAc).

***cis*-3-Benzyloxy-4-(1-chloroethyl)-1-isopropyl-4-methylazetidin-2-one (9a)**: 75% yield, white crystals, m.p. 69.0–70.3°C; TLC R_f = 0.27 (hexane/EtOAc 4:1); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.35, 1.44 (2×d, J=6.6 Hz, 2×3H), 1.43 (s, 3H), 1.53 (d, J=6.6 Hz, 3H), 3.59 (septet, J=6.6 Hz, 1H), 4.23 (s, 1H), 4.46 (q, J=6.6 Hz, 1H), 4.69 (d, J=11.9 Hz, 1H), 4.93 (d, J=11.9 Hz, 1H), 7.29–7.36 ppm (m, 5H); ^{13}C NMR (68 MHz, $CDCl_3$): δ = 15.9, 21.4, 21.7, 21.8, 45.9, 63.0, 66.4, 72.8, 87.1,127.7, 127.9, 128.5, 137.1, 166.2 ppm. IR (NaCl): ν=1735 cm^{-1} (C=O); MS (70 eV): m/z (%): no M^+, 227 (34), 143 (74), 128 (35), 57 (100); elemental analysis calcd (%) for $C_{16}H_{22}ClNO_2$: C 64.97, H 7.50, N 4.74; found: C 65.19, H 7.78, N 4.53.

General method for the synthesis of (3*S*,4*S*)-3-alkoxy-4-((1*S*)-1-chloroethyl)azetidin-2-ones 15: As a representative example, the synthesis of (3*S*,4*S*)-1-benzyl-3-benzyloxy-4-((1*S*)-1-chloroethyl)azetidin-2-one (**15a**) is described. Pyridinium chlorochromate (26.5 mmol) was added to a solution of (2*S*)-chloro-1-propanol (**12**; 5.3 mmol) in dry dichloromethane (200 mL). The reaction mixture was stirred overnight (16 h), filtered over silica gel and the filter cake was washed two times with dichloromethane (25 mL). Benzylamine (5.3 mmol) and $MgSO_4$ (8.0 mmol) were added to the combined organic fractions and the resulting mixture was stirred at room temperature for 1.5 h. After filtration of the drying agent, the solvent was evaporated under reduced pressure until approximately 10 mL of reaction mixture remained in the flask. Then, benzene was added (100 mL), and the residual dichloromethane was evaporated under reduced pressure. Subsequently, a solution of benzyloxyacetyl chloride (6.8 mmol) in benzene (10 mL) was added dropwise to the refluxing solution in benzene. After complete addition, the reaction mixture was stirred overnight (16 h) at room temperature. Subsequently, the reaction mixture was poured into water (100 mL) and extracted with dichloromethane (2×10 mL). After evaporation of the solvent, the crude reaction mixture was purified by column chromatography on silica gel, affording pure (3*S*,4*S*)-1-benzyl-3-benzyloxy-4-((1*S*)-1-chloroethyl)azetidin-2-one **15a** in 27% overall yield.

(3*S*,4*S*)-1-Benzyl-3-benzyloxy-4-((1*S*)-1-chloroethyl)azetidin-2-one (15a): 27% overall yield, white crystals, m.p. 92°C; TLC R_f = 0.1 (hexane/EtOAc 9:1); $[\alpha]_D^{20}$=−10 (c=1 in CH_2Cl_2), *de*: 86%; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49 (d, J=6.6 Hz, 3H), 3.60 (d×d, J=9.9 Hz, J=5.0 Hz, 1H), 4.33 (d×q, J=9.9 Hz, J=6.6 Hz, 1H), 4.38 (d, J=14.9 Hz, 1H), 4.59 (d, J=5.0 Hz, 1H), 4.71 (d, J=11.9 Hz, 1H), 4.86 (d, J=14.9 Hz, 1H), 4.95 (d, J=11.9 Hz, 1H), 7.25–7.38 ppm (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 45.1, 58.5, 62.3, 72.9, 80.9, 127.8, 127.9, 128.1, 128.5, 128.6, 128.8, 135.6, 136.8, 167.9 ppm; IR (NaCl): ν= 1759 cm^{-1} (C=O); MS (70 eV): m/z (%): 330/2 (100) [M^++H]; elemental analysis calcd (%) for $C_{19}H_{20}ClNO_2$: C 69.19, H 6.11, N 4.25; found: C 69.32; H 6.01; N 4.40.

Acknowledgements

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