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Synthesis and reactivity of *trans*-2-aryl-3-chloroazetidines

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Abstract—Several *trans*-2-aryl-3-chloroazetidines were synthesized in a stereoselective way by reduction of the corresponding β-lactams, which were formed by a Staudinger reaction using different benzaldimines and chloroketene. The resulting chloroazetidines proved to be excellent building blocks for the synthesis of different 3-substituted azetidines through nucleophilic substitution of the chlorine by different carbon, nitrogen, sulfur and oxygen nucleophiles in good to high yields. Since these substitution reactions took place with retention of stereochemistry, the intermediacy of bicyclic azonio[1.1.0]bicyclobutanes is proposed.

1. Introduction

Within azaheterocyclic chemistry, azetidines are an extraordinary class of strained compounds because of their wide range of known biological activities.[1–4] In the literature, several 3-substituted azetidines with known physiological effects have been reported. 1-Cyclohexyl-3-guanidinylazetidine has an antihypertensive activity,[5] 3-carbamoyl substituted azetidines exhibit a tranquilizing effect on the central nervous system[6] and azetidine-3-carboxylic acid is a known gametocide.[7] In various recent patents, 3,3-difluoroazetidines have been described as therapeutically active and selective inhibitors of the dipeptidyl peptidase-IV enzyme (DPP-IV)[8–12] making them potential drugs for the treatment of type 2 diabetes.[13] Indeed, 3-haloazetidines form an important subclass within the azaheterocycles because of their potential physiological activities and their use as substrates towards the synthesis of 3-substituted azetidine derivatives.

Various reports on the synthesis of 3-haloazetidines can be found in the literature. 2-Aryl-3-bromoazetidinyl-1-tosylates were prepared by electrophile-induced cyclization of *N*-cinnamyl tosylamine with bis(collidine)bromine(I) hexafluorophosphate as electrophile.[14] Furthermore, azetidinyl-3-tosylates and -mesylates are known precursors for 3-haloazetidine formation by substitution reactions,[15–20] and azetidin-3-ols also underwent substitution reactions at the C3 carbon atom upon treatment with triphenylphosphine dibromide or triphenylphosphine in tetrachloromethane towards 3-bromo- and 3-chloroazetidines.[21–23] Another straightforward synthetic method for the synthesis of 3-haloazetidines compromises ring opening of the peculiar and difficultly accessible 1-azabicyclo[1.1.0]butanes. Opening of the bridging 1,3-bond with *p*-toluenesulfonyl chloride,[24–26] hydrogen halides[25,27–29] or acid chlorides[25,30] resulted in a broad group of different 3-haloazetidines. 3-Haloazetidines, such as 1-*tert*-butyl-3-chloroazetidine, have already been used in different reactivity studies with various nucleophiles. Although moderate to good yields were reported, the reaction procedures required long reaction times (up to 11 days) and extreme reaction conditions (heating in steel bombs).[22,31]

In this report, a straightforward and efficient synthesis of *trans*-2-aryl-3-chloroazetidines is disclosed as versatile substrates in organic chemistry. The scope of these synthons for the preparation of a large variety of 3-substituted azetidines was demonstrated by means of different nucleophiles in an efficient and elegant way.

2. Results and discussion

trans-2-Aryl-3-chloroazetidines **4a–g** were prepared by condensation of different aromatic aldehydes **1** with a variety of amines in dichloromethane in the presence of magnesium sulfate as drying agent, and the corresponding aldimines **2** were isolated in excellent yield after reflux for 1 h. In the next step, the latter imines **2** underwent a Staudinger [2+2]-cycloaddition using chloroacetyl chloride as a ketene precursor and 2,6-lutidine as base, affording *trans*-4-aryl-3-chloro-β-lactams **3a–g** (Scheme 1).[32] The stereoselectivity of this reaction was confirmed by literature data regarding the coupling constants of *cis*- and *trans*-3-hydroxy-2-methyl-1-*tert*-butylazetidine between the protons at C3 and C4.[33,34]

Keywords: β-Lactams; Azetidines; Azonio[1.1.0]bicyclobutanes.
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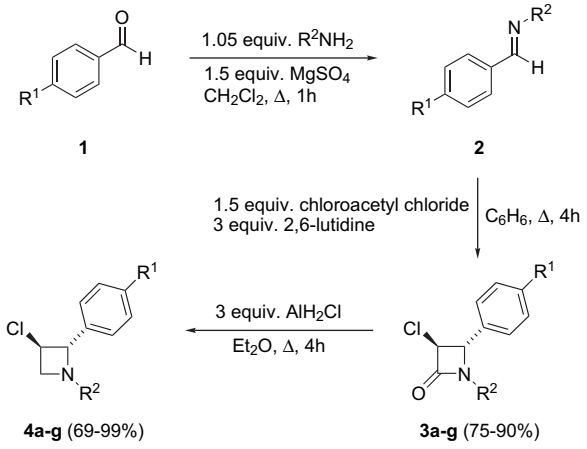
For a cis configuration, coupling constants of 5–6 Hz have been reported, and for a trans configuration a *J*-value of 0–2 Hz.[33,34] All the synthesized β-lactams **3a–g** had a coupling constant of 1.7 or 1.8 Hz between the protons at C3 and C4, indicative of a trans configuration of the chlorine atom with respect to the aromatic substituent (Scheme 1).



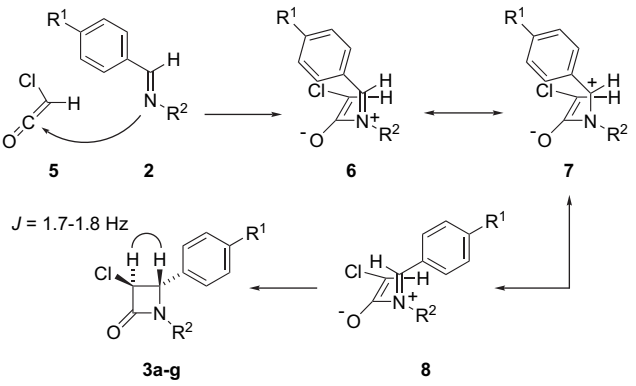
Scheme 1.

The use of monochloroalane has already been proven to be an efficient method for the reduction of β-lactams towards their corresponding azetidines.[35] Also in this case, the use of 3 equiv of monochloroalane in diethyl ether proved to be an efficient method for the stereoselective reduction of the 4-aryl-3-chloroazetidin-2-ones **3a–g**, affording *trans*-2-aryl-3-chloroazetidines **4a–g** in high yield after reflux for 4 h without the formation of undesired ring opening products (Scheme 1, Table 1).

The mechanism of the stereochemical outcome of this Staudinger reaction has been studied thoroughly in the past (Scheme 2).[36] The ketene **5**, formed by dehydrochlorination of the acid chloride with 2,6-lutidine as a base, is attacked by the nitrogen lone pair of the imine **2** at the less hindered side of the ketene with the plane of the imine perpendicular to the ketene. When using *N*-(alkylidene)amines, the formed zwitterionic intermediate **7** undergoes ring closure in the thermodynamic less stable cis isomer in a conrotatory way. In this case however, using aromatic aldimines **2**, isomerization of the imine bond is possible as the positive charge, which occurs during this isomerization, can be stabilized at the benzylic position, allowing rotation of the nitrogen–carbon double bound towards intermediate **8**. Hence, by conrotatory ring closure, the β-lactams **3a–g** are formed in the thermodynamic more stable trans-configuration.[36]

Table 1. Synthesis and yield of 4-aryl-3-chloroazetidin-2-ones **3a–g** and 2-aryl-3-chloroazetidines **4a–g**

Compound	R^1	R^2	Yield of **3** (%)	Yield of **4** (%)
a	H	Allyl	85	73
b	Cl	Allyl	82	80
c	H	Benzyl	75	87
d	Cl	Benzyl	90	69
e	H	*i*Pr	77	83
f	H	cHex	86	79
g	Me	*i*Pr	81	86



Scheme 2.

The retention of the trans configuration of the formed 2-aryl-3-chloroazetidines **4a–g** was confirmed by comparing the coupling constants of the protons at the C2, C3 and C4 carbon atoms with literature data.[37–39] According to the literature, *cis*-3-hydroxy-2-methyl-1-*tert*-butylazetidine has coupling constants of 6.6 and 1.8 Hz between the protons at C3 and C4, whereas *trans*-3-hydroxy-2-methyl-1-*tert*-butylazetidine has coupling constants of 6.7 and 6.4 Hz. The coupling constants between the C2 and C3 protons were about 6 Hz in both cases.[37–39] Upon analysis of the spectral data of azetidines **4a–g**, the coupling constants of the azetidine ring protons were observed to be larger than 5 Hz, indicating the trans-configuration. The proton at the C3 carbon atom was distinguished as a quadruplet-like multiplet in the ^{1}H NMR spectra, which exists of a d×d×d system with similar coupling constants. The protons at the C4 carbon have a triplet like appearance since both coupling constants are about the same size (6.6–7 Hz) (Fig. 1).

Insertion of new functional groups on azetidine rings is a challenging synthetic topic within organic chemistry because of the interesting biological and chemical properties of substituted azetidines. Since no systematic study of nucleophilic substitution reactions of 3-haloazetidines has been performed up to now and the known methods are very laborious, 2-aryl-3-chloroazetidines **4a–g** were treated with different nucleophiles in dimethylsulfoxide (DMSO) and methanol, resulting in several 3-substituted azetidines (Scheme 3). *trans*-2-Aryl-3-chloroazetidines **4a–g** reacted with 4 equiv of sodium azide, potassium cyanide, sodium acetate and potassium thiocyanate, respectively, in dimethylsulfoxide resulting in *trans*-2-aryl-3-azidoazetidines **9a–g**, *trans*-2-aryl-3-cyanoazetidines **9h–j**, *trans*-3-acetoxy-2-arylazetidines **9k–n** and *trans*-2-aryl-3-thiocyanoazetidines **9o–p**, respectively, as substitution products in good yields after overnight heating at 80–120 °C (Table 2).

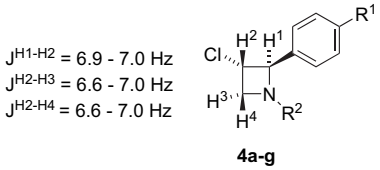
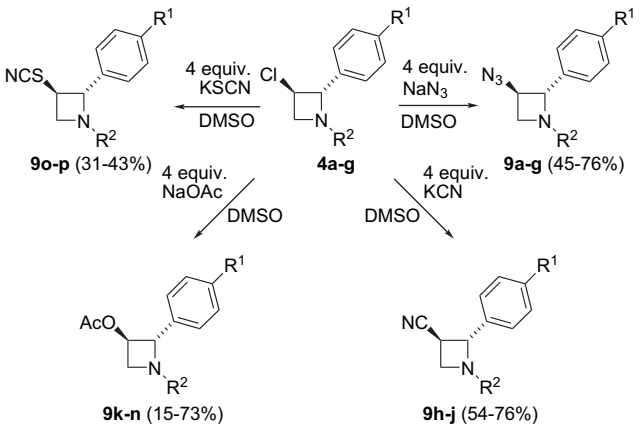


Figure 1.



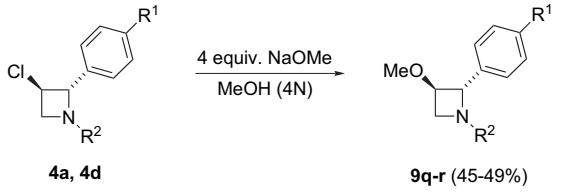
Scheme 3.

Table 2. Substitution reactions of *trans*-2-aryl-3-chloroazetidines **4a–g** towards 3-substituted azetidines **9a–p**

Starting compound **4**	Reagent MX	Temperature (°C)	Reaction time (h)	Isolated compound **9**	Yield (%)
4a	NaN_3	80	22	**9a**	47
4b	NaN_3	90	22	**9b**	62
4c	NaN_3	90	22	**9c**	45
4d	NaN_3	110	22	**9d**	63
4e	NaN_3	80	18	**9e**	62
4f	NaN_3	80	18	**9f**	70
4g	NaN_3	80	18	**9g**	76
4a	KCN	90	22	**9h**	54
4b	KCN	90	46	**9i**	62
4d	KCN	120	22	**9j**	65
4a	NaOAc	90	22	**9k**	52
4b	NaOAc	100	72	**9l**	73
4c	NaOAc	110	22	**9m**	52
4d	NaOAc	125	21	**9n**	15
4a	KSCN	90	22	**9o**	31
4b	KSCN	90	22	**9p**	43

DMSO has proven to be the most suitable solvent for this type of substitution reactions. Treatment of *trans*-2-aryl-3-chloroazetidines **4a–g** with potassium cyanide in acetonitrile or methanol at reflux did not result in substitution, and the starting material was recovered. The required reaction temperature had to be above 80 °C, since a reaction temperature below 80 °C did not result in substitution reactions.

Only for the synthesis of 3-methoxyazetidines **9q–r**, a different solvent had to be chosen. Treatment of *trans*-2-aryl-3-chloroazetidines **4a–d** with 4 equiv of sodium methoxide in methanol (4 N) afforded the corresponding *trans*-2-aryl-3-methoxyazetidines **9q–r** in moderate yields (Scheme 4, Table 3).



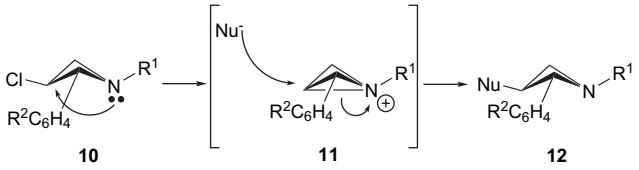
Scheme 4.

The method developed for the stereospecific substitution of *trans*-2-aryl-3-chloroazetidines **4a–d** can be used for a number of different carbon, sulfur, oxygen and nitrogen nucleophiles. In an efficient, straightforward and simple way, several potentially bioactive compounds can be synthesized, which broaden the already significant azetidine chemistry.

Table 3. Reaction of *trans*-2-aryl-3-chloroazetidines **4a** and **4d** with sodium methoxide towards *trans*-2-aryl-3-methoxyazetidines **9q–r**

Starting compound **4**	Temperature (°C)	Reaction time (h)	Isolated compound **9**	Yield (%)
4a	Reflux, Δ	22	**9q**	49
4d	Reflux, Δ	72	**9r**	45

It should be stressed that all substitution reactions took place with retention of stereochemistry, and only trans substituted azetidines were detected in the reaction mixtures. This behaviour can be explained by the formation of a bicyclic azonia[1.1.0]bicyclobutane intermediate **11**, followed by attack of the nucleophile at C3 (Scheme 5). The same intermediate has already been suggested in literature, based on stereospecific retention after hydrolysis and substitution reactions, and ring contraction to aziridinylmethyl derivatives.[40–42] Further investigation of this intermediate by ab initio calculations stated that this bicyclic intermediate is indeed the most stable one, in comparison with other possible intermediates.[43] Moreover, 1-azabicyclo[1.1.0]butanes have been converted into 3-haloazetidines and vice versa via intermediate azonia[1.1.0]bicyclobutane derivatives such as **11**.[44] The fact that thiocyanates **9o–p** are obtained, instead of the corresponding isothiocyanates, after reaction of 3-chloroazetidines **4a–g** with potassium thiocyanate is in accordance with literature data, as in most cases substitution proceeds via attack of the sulfur atom.[45] The preferential attack of the sulfur atom of the thiocyanate nucleophile can be rationalized considering the soft acid character of the intermediate bicyclic azonia[1.1.0]bicyclobutane intermediate **11**.

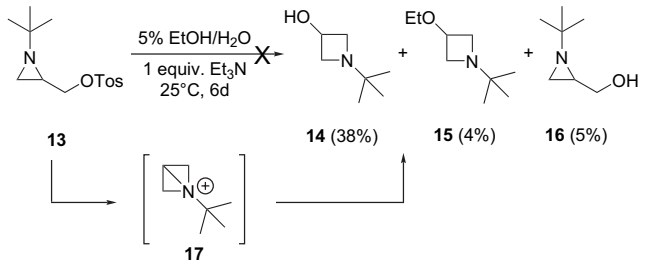


Scheme 5.

trans-2-Aryl-3-chloroazetidines **4a–g** proved to be stable in refluxing methanol for 24 h, and no isomerization to the corresponding isomeric 2-(chloromethyl)aziridines was observed. It should be remarked that upon treatment with nucleophiles the intermediate azonia[1.1.0]bicyclobutanes **11** are opened in a regioselective way at C3 towards 3-substituted azetidines instead of attack at C2 or C4 towards the corresponding aziridine derivatives. However, it has been reported previously that treatment of the analogous *trans*-1-cyclohexyl-3-mesyloxy-2-phenylazetidine with sodium hydroxide resulted in a mixture of the corresponding 3-hydroxyazetidine and both isomers of 1-cyclohexyl-2-(α-hydroxybenzyl)aziridine in a 1:1:1 ratio.[42] The same result, i.e., formation of the corresponding 3-methoxyazetidines and 2-(α-methoxybenzyl)aziridines, was obtained upon treatment of *trans*-1-cyclohexyl-3-mesyloxy-2-phenylazetidine

with sodium methoxide in methanol, which can only be explained by ring opening of the intermediate azonia[1.1.0]-bicyclobutanes at C2. Only when sodium methanethiolate and sodium benzenethiolate were used, no isomerization towards the corresponding aziridines took place.[42]

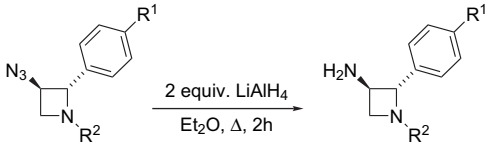
The opposite reactivity has also been reported, i.e., the conversion of a 2-(tosyloxymethyl)aziridine into an azetidine derivative via the intermediacy of an azonia[1.1.0]bicyclobutane salt. These authors described the ring expansion of 1-*tert*-butyl-2-(tosyloxymethyl)aziridine **13** into a mixture of 3-hydroxyazetidine **14** (38%), azetidine **15** (4%) and 2-(hydroxymethyl)aziridine **16** (5%) via the formation of an intermediate bicyclic aziridinium salt **17** after heating for 6 days at 25 °C in 5% EtOH/H_2O in the presence of 1 equiv of Et_3N.[15] As this result seemed to be doubtful in view of our recent study of the reactivity of 2-(bromomethyl)-aziridines, we decided to repeat the solvolysis of aziridine **13**. However, careful repetition of this reaction did not result in the formation of azetidines **14** and **15**, and the starting material was recovered completely (Scheme 6).



Scheme 6.

Although the desired substitution of 3-chloroazetidines **4a–g** was attained by reaction with sodium azide, potassium cyanide, sodium acetate and potassium thiocyanate in DMSO, treatment of *trans*-2-aryl-3-chloroazetidines **4a–g** with sodium bicarbonate, potassium cyanate, potassium fluoride and potassium iodide using the same reaction conditions (overnight heating in DMSO) resulted only in complex reaction mixtures, probably due to the less nucleophilic character of the first three nucleophiles compared to chloride. In the latter case, the higher leaving capacities of iodide in comparison to chloride can be responsible for the failure of the substitutions.

In recent years, 3-aminoazetidines have received a lot of attention because of their antibacterial activities.[46–50] Reduction of *trans*-2-aryl-3-azidoazetidines **9e–g** with 2 equiv of lithium aluminium hydride in ether yielded unprecedented 3-aminoazetidines **18a–c** after reflux for 2 h, which could be purified by performing an acid–base extraction (Scheme 7).

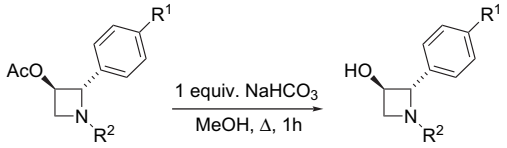


9e R^1= H, R^2= *i*Pr
9f R^1= H, R^2= *c*Hex
9g R^1= Me, R^2= *i*Pr

18a R^1= H, R^2= *i*Pr (70%)
18b R^1= H, R^2= *c*Hex (82%)
18c R^1= Me, R^2= *i*Pr (92%)

Scheme 7.

trans-3-Acetoxy-2-arylazetidines **9k–l** were stable in refluxing methanol, whereas treatment with 1 equiv of sodium bicarbonate in refluxing methanol for 1 h resulted in *trans*-2-arylazetidin-3-ols **19a–b** (Scheme 8). Azetidin-3-ols have been studied intensively in the literature since they form interesting synthons towards azetidinyl tosylates and mesylates.[15,21]



9k R^1= H, R^2= allyl
9l R^1= Cl, R^2= allyl

19a R^1= H, R^2= allyl (47%)
19b R^1= Cl, R^2= allyl (79%)

Scheme 8.

Efforts towards acidic or basic conversion of *trans*-2-aryl-3-cyanoazetidines **9h–j** to the corresponding methyl esters or carboxylic acids as analogues of the gametocide azetidine-3-carboxylic acid[7] by using 2–6 N hydrochloric acid or sulfuric acid in water or methanol only resulted in complex reaction mixtures, while treatment with 6 N aqueous sodium hydroxide yielded the starting compounds **9h–j**.

3. Conclusion

Several *trans*-2-aryl-3-chloroazetidines were synthesized in a stereoselective way by reduction of the corresponding β-lactams, which were, on their turn, formed by a Staudinger reaction between different benzaldimines and chloroketene. The formed chloroazetidines were subjected to a variety of substitution reactions with nitrogen, carbon, sulfur and oxygen nucleophiles in DMSO. Since these substitution reactions took place with retention of stereochemistry, the occurrence of a bicyclic azonio[1.1.0]bicyclobutane intermediate is proposed. These substitution reactions resulted in several *trans*-2-aryl-3-substituted azetidines as valuable new compounds with potential biological activities and as substrates for further elaboration towards e.g., 3-amino- and 3-hydroxyazetidines.

4. Experimental

4.1. General

^{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+) with $CDCl_3$ as solvent. Mass spectra were obtained with a mass spectrometer (VARIAN MAT 112), 70 eV using a GC–MS coupling (RSL 200, 20 m glass capillary column, i.d. 0.53 mm, He carrier gas) or AGILENT 1100, 70 eV. IR spectra were measured with a Spectrum One FT-IR spectrophotometer. Melting points were measured using a Büchi B-540 apparatus and are uncorrected. Elemental analysis was performed on a Perkin–Elmer 2400 Elemental Analyzer. Dichloromethane was distilled over calcium hydride, while diethyl ether

and THF were freshly distilled over sodium benzophenone ketyl. Other solvents were used as received from the supplier.

4.1.1. Synthesis of *trans*-4-aryl-3-chloro-β-lactams 3a–g. The synthesis of *trans*-1-allyl-3-chloro-4-phenylazetidin-2-one **3a** is given as a representative example. *N*-(Benzylidene)allylamine (7.23 g, 0.05 mol) was dissolved in benzene (150 ml) and 2,6-lutidine (16.05 g, 0.15 mol, 3 equiv) was added, after which the solution was heated to reflux. Chloroacetylchloride (8.48 g, 0.075 mol, 1.5 equiv) was added dropwise to this refluxing solution. The resulting solution was kept at reflux temperature for 22 h. After cooling, the precipitated 2,6-lutidine hydrochloride was filtered off and the filtrate was washed twice with 1 N hydrochloric acid. Drying over magnesium sulfate, filtration and evaporation of the solvent yielded *trans*-1-allyl-3-chloro-4-phenylazetidin-2-one (10.85 g, 49 mmol, 97%). Although the obtained β-lactams were pure enough for direct use in the next step, further purification was performed by flash chromatography on silica gel.

4.1.1.1. *trans*-1-Allyl-3-chloro-4-phenylazetidin-2-one 3a. Yield 85%, light yellow oil. Hexane/EtOAc 3:1, R_f=0.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.41 (1H, d×d×d, J=15.5 Hz, J=7.2 Hz, J=0.8 Hz, NC(*H*)H), 4.21 (1H, d×d×t, J=15.5 Hz, J=5.0 Hz, J=1.6 Hz, NC(H)*H*), 4.54 (1H, d×d, J=1.8 Hz, J=0.8 Hz, C*H*C_6H_5), 4.58 (1H, d, J=1.8 Hz, CHCl), 5.08–5.21 (2H, m, CH=CH_2), 5.66–5.78 (1H, m, C*H*=CH_2), 7.28–7.47 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 43.54 (CH_2N), 63.06 (*C*HC_6H_5), 65.73 (CHCl), 119.53 (CH=*C*H_2), 126.63, 129.28 and 129.49 (C*C*$_5H_5$), 130.30 (*C*H=CH_2), 134.83 (*C*C_5H_5), 163.84 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1772. MS (70 eV): *m*/*z* (%): 224/2 (M^++1, 100), 186 (45). Anal. Calcd for $C_{12}H_{12}ClNO$ (%): C, 65.02; H, 5.46; N, 6.32. Found (%): C, 65.28; H, 5.22; N, 6.44.

4.1.1.2. *trans*-1-Allyl-3-chloro-4-(4-chlorophenyl)azetidin-2-one 3b. Yield 82%, light yellow oil. Hexane/EtOAc 3:1, R_f=0.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.39 (1H, d×d, J=15.6 Hz, J=7.3 Hz, NC(*H*)H), 4.10–4.20 (1H, m, NC(H)*H*), 4.50–4.52 (2H, m, CHCl and C*H*C_6H_4Cl), 5.09–5.22 (2H, m, CH=CH_2), 5.65–5.79 (1H, m, C*H*=CH_2), 7.23–7.40 (4H, m, C_6H_4Cl). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 43.72 (CH_2N), 63.22 and 65.11 (*C*HC_6H_4Cl and CHCl), 119.88 (CH=*C*H_2), 128.08 and 129.61 (C*C*$_4H_4CCl$), 130.29 (*C*H=CH_2), 130.99 and 135.51 (*C*C_4H_4*C*Cl), 163.50 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1774. MS (70 eV): *m*/*z* (%): 258/6 (M^++1, 100), 116 (37). Anal. Calcd for $C_{12}H_{11}Cl_2NO$ (%): C, 56.27; H, 4.33; N, 5.47. Found (%): C, 56.08; H, 4.51; N, 5.39.

4.1.1.3. *trans*-1-Benzyl-3-chloro-4-phenylazetidin-2-one 3c. Yield 75%, light yellow oil. Hexane/EtOAc 3:1, R_f=0.32. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (1H, d, J=15.1 Hz, C(*H*)HC_6H_5), 4.38 and 4.55 (2×1H, 2×d, J=1.8 Hz, CHCl and C*H*C_6H_5), 4.86 (1H, d, J=15.1 Hz, C(H)*H*C_6H_5), 7.10–7.42 (10H, m, $CH_2C_6H_5$ and CHC_6H_5). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 44.90 (*C*$H_2C_6H_5$), 63.19 and 65.26 (CHCl and *C*HC_6H_5), 126.65, 128.05, 128.42, 128.89, 129.24 and 129.43 (2×C*C*$_5H_5$), 134.30 and 134.68 (2×*C*C_5H_5), 163.61 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1777. MS (70 eV): *m*/*z* (%): 274/2 (M^++1, 100), 91 (14). Anal. Calcd for $C_{16}H_{14}ClNO$ (%): C, 70.72; H, 5.19; N, 5.15. Found (%): C, 70.94; H, 5.29; N, 5.01.

4.1.1.4. *trans*-1-Benzyl-3-chloro-4-(4-chlorophenyl)-azetidin-2-one 3d. Yield 90%, light yellow oil. Hexane/EtOAc 3:1, R_f=0.44. Mp: 83 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.84 (1H, d, J=15.0 Hz, C(*H*)HC_6H_5), 4.35 (1H, d, J=1.7 Hz, CHCl), 4.52 (1H, d×d, J=1.7 Hz, J=0.7 Hz, C*H*C_6H_4Cl), 4.84 (1H, d, J=15.0 Hz, C(H)*H*C_6H_5), 7.29–7.38 (9H, m, $CH_2C_6H_5$ and CHC_6H_4Cl). ^{13}C NMR (75 MHz, $CDCl_3$): δ 45.04 (*C*$H_2C_6H_5$), 63.15 and 64.61 (CHCl and *C*HC_6H_4Cl), 128.01, 128.18, 128.45, 128.97 and 129.47 (C*C*$_4H_4CCl$ and C*C*$_5H_5$), 133.28, 134.07 and 135.34 (*C*C_4H_4*C*Cl and *C*C_5H_5), 163.40 (C=O). IR (KBr, cm^{-1}): $\nu_{C=O}$=1765. MS (70 eV): *m*/*z* (%): 310/08/06 (M^++1, 100). Anal. Calcd for $C_{16}H_{13}Cl_2NO$ (%): C, 62.76; H, 4.28; N, 4.57. Found (%): C, 62.91; H, 4.18; N, 4.74.

4.1.1.5. *trans*-3-Chloro-1-isopropyl-4-phenylazetidin-2-one 3e. Yield 77%, light yellow oil. Hexane/EtOAc 3:2, R_f=0.64. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.07 and 1.31 (2×3H, 2×d, J=6.9 Hz, CH(C*H*$_3$)$_2$), 3.75 (1H, septet, J=6.9 Hz, C*H*(CH_3)$_2$), 4.46 and 4.53 (2×1H, 2×d, J=1.7 Hz, NCH and CHCl), 7.35–7.47 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 19.80 and 20.74 (CH(*C*H_3)$_2$), 45.63 (*C*H(CH$_3$)$_2$), 62.23 and 64.75 (NCH and CHCl), 126.42, 128.86 and 129.08 (C*C*$_5H_5$), 136.24 (*C*C_5H_5), 163.13 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1765. MS (70 eV): *m*/*z* (%): no M^+, 139 (57), 137 (100), 102 (46). Anal. Calcd for $C_{12}H_{14}ClNO$ (%): C, 64.43; H, 6.31; N, 6.26. Found (%): C, 64.21; H, 6.43; N, 6.34.

4.1.1.6. *trans*-3-Chloro-1-cyclohexyl-4-phenylazetidin-2-one 3f. Yield 86%, light yellow oil. Hexane/EtOAc 3:2, R_f=0.65. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.96–2.04 (10H, m, $(CH_2)_5$), 3.33–3.45 (1H, m, NCH), 4.44 and 4.54 (2×1H, 2×d, J=1.7 Hz, NCH and CHCl), 7.34–7.46 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 24.95, 25.01, 30.21, 31.15 and 32.80 ((CH_2)$_5$), 53.75 (NCH), 62.85 and 65.15 (NCH and CHCl), 126.95, 129.20 and 129.31 (C*C*$_5H_5$), 136.71 (*C*C_5H_5), 163.82 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1769. MS (70 eV): no M^+, 140/38 (100). Anal. Calcd for $C_{15}H_{18}ClNO$ (%): C, 68.30; H, 6.88; N, 5.31. Found (%): C, 68.51; H, 7.01; N, 5.19.

4.1.1.7. *trans*-3-Chloro-1-isopropyl-4-(4-methylphenyl)-azetidin-2-one 3g. Yield 81%, light yellow oil. Hexane/EtOAc 3:2, R_f=0.53. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.06 and 1.30 (2×3H, 2×d, J=6.6 Hz, CH(C*H*$_3$)$_2$), 2.38 (3H, s, C_qCH3), 3.74 (1H, septet, J=6.6 Hz, C*H*(CH$_3$)$_2$), 4.44 and 4.49 (2×1H, 2×d, J=1.7 Hz, NCH and CHCl), 7.23–7.25 (2×2H, 2×d, J=9.0 Hz, C_6H_4). ^{13}C NMR (68 MHz, $CDCl_3$): δ 20.09, 21.08 and 21.22 (CH(*C*H_3)$_2$ and C_q*C*H3), 45.80 (*C*H(CH$_3$)$_2$), 62.53 and 64.92 (NCH and CHCl), 126.63 and 129.79 (C*C*$_cH_4$C), 133.48 and 139.37 (*C*C_4H_5*C*), 163.57 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1769. MS (70 eV): *m*/*z* (%): 238/6 (M^+, 1), 154/2 (100), 118 (44), 117 (82), 115 (75), 91 (58), 70 (42). Anal. Calcd for $C_{13}H_{16}ClNO$ (%): C, 65.68; H, 6.78; N, 5.89. Found (%): C, 65.49; H, 6.86; N, 6.02.

4.1.2. Synthesis of *trans*-2-aryl-3-chloroazetidines 4a–g. The reduction of *trans*-1-allyl-3-chloro-4-phenylazetidin-2-one **3a** to *trans*-2-aryl-3-chloroazetidine **4a** is given as a representative example. To a solution of aluminium(III) chloride (12.13 g, 0.09 mol, 3 equiv) in dry diethyl ether (150 ml) was added carefully lithium aluminium hydride (3.44 g, 0.09 mol, 3 equiv) at 0 °C. This reaction mixture was stirred at 0 °C for 10 min, and subsequently refluxed for 30 min. *trans*-1-Allyl-3-chloro-4-phenylazetidin-2-one (6.64 g, 0.03 mol) in dry diethyl ether (100 ml) was added slowly and after addition was complete, reflux was maintained for 4 h. The reaction was cooled and water (200 ml) was added carefully. The aqueous phase was extracted with dichloromethane and dried over magnesium sulfate. After filtration and evaporation of the solvent and further purification by flash chromatography on silica gel, *trans*-2-aryl-3-chloroazetidine (4.57 g, 0.022 mol, 73%) was obtained as a light yellow oil.

4.1.2.1. *trans*-1-Allyl-3-chloro-2-phenylazetidine 4a. Yield 73%, light yellow oil. Hexane/EtOAc 4:1, R_f=0.40. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.97–3.01 (1H, m, C(*H*)HCHCl), 3.06 (1H, d×d, *J*=13.4 Hz, *J*=6.9 Hz, C(*H*)HCH=CH_2), 3.32 (1H, d×d×t, *J*=13.4 Hz, *J*=5.5 Hz, *J*=1.4 Hz, C(H)*H*CH=CH_2), 3.83–3.89 (1H, m, C(H)*H*CHCl), 4.05–4.12 (2H, m, CHCl and C*H*C_6H_5), 5.02–5.20 (2H, m, CH=CH_2), 5.65–5.80 (1H, m, C*H*=CH_2), 7.19–7.44 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.69 (*C*HC_6H_5), 60.80 (*C*H_2CHCl), 61.10 (*C*H_2CH=CH_2), 78.72 (CHCl), 117.66 (CH=*C*H_2), 126.59, 128.05 and 128.45 (C*C*$_5H_5$), 133.81 (*C*H=CH_2), 139.55 (*C*C_5H_5). MS (70 eV): *m*/*z* (%): 210/8 (M^++1, 100). Anal. Calcd for $C_{12}H_{14}ClN$ (%): C, 69.39; H, 6.79; N, 6.74. Found (%): C, 69.11; H, 6.95; N, 6.70.

4.1.2.2. *trans*-1-Allyl-3-chloro-2-(4-chlorophenyl)azetidine 4b. Yield 80%, light yellow oil. Hexane/EtOAc 4:1, R_f=0.60. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.98–3.03 (1H, m, C(*H*)HCHCl), 3.07 (1H, d×d, *J*=13.4 Hz, *J*=6.9 Hz, C(*H*)HCH=CH_2), 3.29 (1H, d×d×t, *J*=13.4 Hz, *J*=5.6 Hz, *J*=1.0 Hz, C(H)*H*CH=CH_2), 3.84–3.88 (1H, m, C(H)*H*CHCl), 4.00–4.07 (2H, m, C*H*C_6H_4Cl and CHCl), 5.03–5.21 (2H, m, CH=CH_2), 5.64–5.77 (1H, m, C*H*=CH_2), 7.29–7.39 (4H, m, C_6H_4Cl). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.71 (CHCl), 60.80 (*C*H_2CHCl), 61.09 (*C*H_2CH=CH_2), 78.72 (*C*HC_6H_4Cl), 117.94 (CH=*C*H_2), 127.99 and 128.66 (C*C*$_4H_4$CCl), 133.70 (*C*H=CH_2), 133.82 and 138.19 (*C*C_4H_4*C*Cl). MS (70 eV): *m*/*z* (%): 246/4/2 (M^++1, 50), 116 (23). Anal. Calcd for $C_{12}H_{13}Cl_2N$ (%): C, 59.52; H, 5.41; N, 5.78. Found (%): C, 59.68; H, 5.36; N, 5.71.

4.1.2.3. *trans*-1-Benzyl-3-chloro-2-phenylazetidine 4c. Yield 87%, light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00 (1H, t, *J*=7.2 Hz, C(*H*)HCHCl), 3.47 (1H, d, *J*=12.9 Hz, C(*H*)HC_6H_5), 3.71–3.75 (1H, m, C(H)*H*CHCl), 3.89 (1H, d, *J*=12.9 Hz, C(H)*H*C_6H_5), 4.03–4.10 (1H, m, CHCl), 4.16 (1H, d, *J*=6.9 Hz, C*H*C_6H_5), 7.22–7.33 (10H, m, $CH_2C_6H_5$ and CHC_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.92 (CHCl), 60.86 (*C*H_2CHCl), 61.93 (*C*$H_2C_6H_5$), 78.52 (*C*HC_6H_5), 126.56, 127.20, 128.05, 128.28, 128.45 and 128.63 (2×C*C*$_5H_5$), 137.29 and 139.37 (2×*C*C_5H_5). MS (70 eV): *m*/*z* (%): 260/58 (M^++1, 23), 120 (100), 91 (36). Anal. Calcd for $C_{16}H_{16}ClN$ (%): C, 74.55; H, 6.26; N, 5.43. Found (%): C, 74.70; H, 6.38; N, 5.31.

4.1.2.4. *trans*-1-Benzyl-3-chloro-2-(4-chlorophenyl)-azetidine 4d. Yield 69%, light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.97–3.02 (1H, m, C(*H*)HCHCl), 3.48 (1H, d, *J*=12.7 Hz, C(*H*)HC_6H_5), 3.67–3.75 (1H, m, C(H)*H*CHCl), 3.82 (1H, d, *J*=12.7 Hz, C(H)*H*C_6H_5), 3.97–4.03 (1H, m, CHCl), 4.10 (1H, d, *J*=6.6 Hz, C*H*C_6H_4Cl), 7.22–7.37 (9H, m, $CH_2C_6H_5$ and CHC_6H_4Cl). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.81 (CHCl), 60.80 (*C*$H_2C_6H_5$), 61.88 (CH_2N), 77.84 (*C*HC_6H_4Cl), 127.27, 127.90, 128.13, 128.30 and 128.60 (C*C*$_4H_4$CCl and C*C*$_5H_5$), 133.73, 137.02 and 137.90 (*C*C_4H_4*C*Cl and *C*C_5H_5). MS (70 eV): *m*/*z* (%): 120 (100), 91 (38). Anal. Calcd for $C_{16}H_{15}Cl_2N$ (%): C, 65.77; H, 5.17; N, 4.79. Found (%): C, 65.89; H, 5.36; N, 4.61.

4.1.2.5. *trans*-3-Chloro-1-isopropyl-2-phenylazetidine 4e. Yield 83%, light yellow oil. ^{1}H NMR (270 MHz, C_6D_6): δ 0.60 and 0.77 (2×3H, 2×d, *J*=6.0 Hz, CH(CH_3)$_2$), 2.24 (1H, septet, *J*=6.0 Hz, C*H*(CH_3)$_2$), 2.74 (1H, d×d, *J*=6.6 Hz, *J*=6.6 Hz, NC*H*(H)), 3.51 (1H, d×d×d, *J*=6.6 Hz, *J*=6.6 Hz, *J*=1.0 Hz, NCH(*H*)), 3.79 (1H, q, *J*=6.6 Hz, CHCl), 3.93 (1H, d, *J*=6.6 Hz, NC*H*C_6H_5), 7.06–7.20 and 7.42–7.45 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, C_6D_6): δ 20.09 and 20.84 (CH(*C*H_3)$_2$), 52.99 (CHCl), 59.64 and 59.93 (*C*H(CH_3)$_2$ and NCH_2), 78.83 (N*C*HC_6H_5), 126.95–128.62 (NCHC*C*$_5H_5$), 141.96 (NCH*C*C_5H_5). MS (70 eV): *m*/*z* (%): 211/09 (M^+, 27), 196/4 ($M-Me^+$, 25), 132 (100). Anal. Calcd for $C_{12}H_{16}ClN$ (%): C, 68.73; H, 7.69; N, 6.68. Found (%): C, 68.89; H, 7.60; N, 6.82.

4.1.2.6. *trans*-3-Chloro-1-cyclohexyl-2-phenylazetidine 4f. Yield 79%, light yellow oil. ^{1}H NMR (270 MHz, C_6D_6): δ 0.75–1.57 (10H, m, (CH_2)$_5$), 2.00–2.04 (1H, m, NCH), 2.79 (1H, d×d, *J*=7.0 Hz, *J*=7.0 Hz, NC*H*(H)), 3.59 (1H, d×d, *J*=7.0 Hz, *J*=7.0 Hz, NCH(*H*)), 3.85 (1H, q, *J*=7.0 Hz, CHCl), 3.99 (1H, d, *J*=7.0 Hz, NC*H*C_6H_5), 7.07–7.20 and 7.45–7.48 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 24.29, 24.37, 25.77, 30.03 and 30.87 ((CH_2)$_5$), 52.90 (CHCl), 59.44 (NCH_2), 67.94 (NCH), 78.62 (N*C*HC_6H_5), 126.66, 127.87 and 128.34 (NCHC*C*$_5H_5$), 141.15 (NCH*C*C_5H_5). MS (70 eV): *m*/*z* (%): 252/0 (M+H^+, 100). Anal. Calcd for $C_{15}H_{20}ClN$ (%): C, 72.13; H, 8.07; N, 5.61. Found (%): C, 72.28; H, 8.22; N, 5.80.

4.1.2.7. *trans*-3-Chloro-1-isopropyl-2-(4-methylphenyl)-azetidine 4g. Yield 86%, light yellow oil. ^{1}H NMR (270 MHz, C_6D_6): δ 0.64 and 0.78 (2×3H, 2×d, *J*=6.3 Hz, CH(CH_3)$_2$), 2.11 (3H, S, C_qCH_3), 2.26 (1H, septet, *J*=6.3 Hz, C*H*(CH_3)$_2$), 2.75 (1H, d×d, *J*=7.0 Hz, *J*=7.0 Hz, NC*H*(H)), 3.53 (1H, d×d, *J*=7.0 Hz, *J*=7.0 Hz, NCH(*H*)), 3.83 (1H, q, *J*=7.0 Hz, CHCl), 3.94 (1H, d, *J*=7.0 Hz, NC*H*C_6H_4), 7.00 and 7.37 (2×2H, 2×d, *J*=7.9 Hz, C_6H_4). ^{13}C NMR (68 MHz, $CHCl_3$): δ 20.09 and 20.79 (CH(*C*H_3)$_2$), 21.11 (C_qCH_3), 52.56 (CHCl), 59.68 (*C*H(CH_3)$_2$ and NCH_2), 78.58 (N*C*HC_6H_5), 126.61 and 129.04 (NCHCC_4H_4C), 137.32 and 138.47 (NCH*C*C_4H_4*C*). MS (70 eV): *m*/*z* (%): 225/3 (M^+, 22), 210/08 ($M-Me^+$, 22), 146 (100). Anal. Calcd for $C_{13}H_{18}ClN$ (%): C, 69.79; H, 8.11; N, 6.26. Found (%): C, 69.62; H, 8.19; N, 6.11.

4.1.3. Synthesis of 3-substituted azetidines 9a–p. The transformation of *trans*-3-chloro-2-phenylazetidine **4a** into *trans*-3-azido-2-phenylazetidine **9a** is given as a representative example of substitution reactions of 3-chloroazetidines. *trans*-3-Chloro-2-phenylazetidine (1 g, 4.8 mmol) was dissolved in DMSO (40 ml). To this solution, sodium azide (1.25 g, 19.28 mmol, 4 equiv) was added carefully. This mixture was stirred overnight at 80 °C. After cooling, the reaction mixture was poured into water (40 ml) and the mixture was extracted with diethyl ether. The combined organic extracts were washed with water and brine. After drying over magnesium sulfate and evaporation of the solvent, crude *trans*-3-azido-2-phenylazetidine (1 g, 4.7 mmol, 98%) was obtained. Further purification was performed by flash chromatography on silica gel, yielding *trans*-3-azido-2-phenylazetidine (0.48 g, 2.3 mmol, 47%).

The same procedure was executed with potassium cyanide, sodium acetate and potassium thiocyanate. The reaction times and temperatures for the other derivatives are listed in Section 2.

Caution: All reactions with sodium azide were performed behind a safety shield. No (violent) decomposition of the organic azides was observed throughout.

4.1.3.1. *trans*-1-Allyl-3-azido-2-phenylazetidine 9a. Yield 47%, light yellow oil. Hexane/EtOAc 7:1, R_f=0.18. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.78–2.82 (1H, m, C(*H*)HCHN$_3$), 3.00 (1H, d×d, *J*=13.2 Hz, *J*=6.9 Hz, C(*H*)HCH=CH$_2$), 3.30 (1H, d×d, *J*=13.2 Hz, *J*=5.5 Hz, C(H)*H*CH=CH$_2$), 3.67–3.77 (2H, m, C(H)*H*CHN$_3$ and CHN$_3$), 3.92 (1H, d, *J*=5.6 Hz, C*H*C$_6$H$_5$), 5.04–5.20 (2H, m, CH=C*H*$_2$), 5.67–5.80 (1H, m, C*H*=CH$_2$), 7.22–7.43 (5H, m, C$_6$H$_5$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.54 (*C*H$_2$CHN$_3$), 58.34 (CHN$_3$), 60.75 (*C*H$_2$CH=CH$_2$), 74.97 (*C*HC$_6$H$_5$), 117.63 (CH=*C*H$_2$), 126.69, 127.95 and 128.55 (C*C*$_5$H$_5$), 133.93 (*C*H=CH$_2$), 139.99 (*C*C$_5$H$_5$). IR (NaCl, cm^{-1}): ν_{N3}=2101. MS (70 eV): *m*/*z* (%): 215 (M$^+$+1, 23). Anal. Calcd for $C_{12}H_{14}N_4$ (%): C, 67.27; H, 6.59; N, 26.15. Found (%): C, 67.49; H, 6.71; N, 26.40.

4.1.3.2. *trans*-1-Allyl-3-azido-2-(4-chlorophenyl)azetidine 9b. Yield 62%, light yellow oil. Hexane/EtOAc 3:1, R_f=0.33. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.78–2.85 (1H, m, C(*H*)HCHN$_3$), 3.02 (1H, d×d, *J*=13.2 Hz, *J*=6.7 Hz, C(*H*)HCH=CH$_2$), 3.26 (1H, d×d, *J*=13.2 Hz, *J*=5.8 Hz, C(H)*H*CH=CH$_2$), 3.66–3.74 (2H, m, CHN$_3$ and C(H)*H*CCN$_3$), 3.88 (1H, d, *J*=5.5 Hz, C*H*C$_6$H$_4$Cl), 5.04–5.25 (2H, m, CH=C*H*$_2$), 5.65–5.78 (1H, m, C*H*=CH$_2$), 7.31–7.39 (4H, m, C$_6$*H*$_4$Cl). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.52 (*C*H$_2$CHN$_3$), 58.45 (CHN$_3$), 60.71 (*C*H$_2$CH=CH$_2$), 74.36 (*C*HC$_6$H$_4$Cl), 117.82 (CH=*C*H$_2$), 128.08 and 128.76 (C*C*$_4$H$_4$CCl), 133.76 (*C*H=CH$_2$), 133.76 and 138.59 (*C*C$_4$H$_4$*C*Cl). IR (NaCl, cm^{-1}): ν_{N3}=2103. MS (70 eV): *m*/*z* (%): 251/49 (M$^+$+1, 100). Anal. Calcd for $C_{12}H_{13}ClN_4$ (%): C, 57.95; H, 5.27; N, 22.53. Found (%): C, 57.66; H, 5.42; N, 22.69.

4.1.3.3. *trans*-3-Azido-1-benzyl-2-phenylazetidine 9c. Yield 45%, light yellow oil. Hexane/EtOAc 5:1, R_f=0.53. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.80 (1H, t, *J*=6.9 Hz, C(*H*)HCHN$_3$), 3.42 (1H, d, *J*=12.8 Hz, C(*H*)HC$_6$H$_5$), 3.55–3.60 (1H, m, C(H)*H*CHN$_3$), 3.67–3.76 (1H, m, CHN$_3$), 3.88 (1H, d, *J*=12.8 Hz, C(H)*H*C$_6$H$_5$), 4.01 (1H, d, *J*=6.6 Hz, C*H*C$_6$H$_5$), 7.18–7.47 (10H, m, CH$_2$C$_6$*H*$_5$ and CHC$_6$*H*$_5$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.42 (*C*H$_2$CHN$_3$), 58.48 (CHN$_3$), 61.39 (*C*H$_2$C$_6$H$_5$), 74.63 (*C*HC$_6$H$_5$), 126.59, 127.15, 127.90, 128.25, 128.51 and 128.63 (2×C*C*$_5$H$_5$), 137.32 and 138.80 (2×*C*C$_5$H$_5$). IR (NaCl, cm^{-1}): ν_{N3}=2102. MS (70 eV): *m*/*z* (%): 265 (M$^+$+1, 22), 120 (100) and 91(20). Anal. Calcd for $C_{16}H_{16}N_4$ (%): C, 72.70; H, 6.10; N, 21.20. Found (%): C, 72.96; H, 6.01; N, 21.02.

4.1.3.4. *trans*-3-Azido-1-benzyl-2-(4-chlorophenyl)-azetidine 9d. Yield 63%, light yellow oil. Hexane/EtOAc 3:2, R_f=0.76. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.81–2.85 (1H, m, C(*H*)HCHN$_3$), 3.45 (1H, d, *J*=12.8 Hz, C(*H*)HC$_6$H$_5$), 3.58–3.63 (1H, m, C(H)*H*CHN$_3$), 3.66–3.73 (1H, m, CHN$_3$), 3.83 (1H, d, *J*=12.8 Hz, C(H)*H*C$_6$H$_5$), 3.98 (1H, d, *J*=6.6 Hz, C*H*C$_6$H$_4$Cl), 7.21–7.42 (9H, m, CH$_2$C$_6$*H*$_5$ and CHC$_6$*H*$_4$Cl). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.52 (*C*H$_2$CHN$_3$), 58.64 (CHN$_3$), 61.48 (*C*H$_2$C$_6$H$_5$), 74.14 (*C*HC$_6$H$_4$Cl), 127.34, 128.02, 128.36 and 128.73 (C*C*$_4$H$_4$CCl and C*C*$_5$H$_5$), 133.67, 137.09 and 138.36 (*C*C$_4$H$_4$*C*Cl and *C*C$_5$H$_5$). IR (NaCl, cm^{-1}): ν_{N3}=2102. MS (70 eV): *m*/*z* (%): 120 (100), 91 (18). Anal. Calcd for $C_{16}H_{15}ClN_4$ (%): C, 64.32; H, 5.06; N, 18.75. Found (%): C, 64.13; H, 5.24; N, 18.60.

4.1.3.5. *trans*-3-Azido-1-isopropyl-2-phenylazetidine 9e. Yield 62%, light yellow oil. Hexane/EtOAc 3:1, R_f=0.3. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.72 and 0.77 (2×3H, 2×d, *J*=6.3 Hz, CH(C*H*$_3$)$_2$), 2.48 (1H, septet, *J*=6.3 Hz, C*H*(CH$_3$)$_2$), 2.76 (1H, t, *J*=7.0 Hz, NC*H*(H)), 3.61 (1H, q, *J*=7.0 Hz, CHN$_3$), 3.68 (1H, q, *J*=7.0 Hz, NCH(*H*)), 3.87 (1H, d, *J*=7.0 Hz, NC*H*C$_6$H$_5$), 7.22–7.40 and 7.43–7.47 (5H, m, C$_6$H$_5$). ^{13}C NMR (68 MHz, $CDCl_3$): δ 20.04 and 20.75 (CH(*C*H$_3$)$_2$), 55.40 (NCH$_2$), 57.68 (CHN$_3$), 59.23 (*C*H(CH$_3$)$_2$), 74.77 (N*C*HC$_6$H$_5$), 126.74, 127.71 and 128.62 (NCHC*C*$_5$H$_5$), 141.79 (NCH*C*C$_5$H$_5$). IR (NaCl, cm^{-1}): ν_{N3}=2106. MS (70 eV): *m*/*z* (%): 201 (M−Me$^+$, 25), 173 (M−N$_3$−Me$^+$, 48) 161 (100), 119 (69), 91 (100). Anal. Calcd for $C_{12}H_{16}N_4$ (%): C, 66.64; H, 7.46; N, 25.90. Found (%): C, 66.91; H, 7.59; N, 25.78.

4.1.3.6. *trans*-3-Azido-1-cyclohexyl-2-phenylazetidine 9f. Yield 70%, light yellow oil. Hexane/EtOAc 3:1, R_f=0.3. ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.68–1.77 (10H, m, (C*H*$_2$)$_5$), 2.11–2.21 (1H, m, NCH), 2.77 (1H, t, *J*=7.0 Hz, NC*H*(H)), 3.61 (1H, q, *J*=7.0 Hz, CHN$_3$), 3.69 (1H, q, *J*=7.0 Hz, NCH(*H*)), 3.90 (1H, d, *J*=7.0 Hz, NC*H*C$_6$H$_5$), 7.23–7.36 and 7.40–7.46 (5H, m, C$_6$H$_5$). ^{13}C NMR (68 MHz, $CDCl_3$): δ 24.35, 24.40, 25.84, 30.08 and 30.94 ((CH$_2$)$_5$), 55.08 (NCH$_2$), 58.17 (CHN$_3$), 67.53 (NCH), 74.64 (N*C*HC$_6$H$_5$), 126.65, 127.65 and 128.39 (NCHC*C*$_5$H$_5$), 141.88 (NCH*C*C$_5$H$_5$). IR (NaCl, cm^{-1}): ν_{N3}=2101. MS (70 eV): *m*/*z* (%): 257 (M+H$^+$, 100).

4.1.3.7. *trans*-3-Aazido-1-isopropyl-2-(4-methylphenyl)azetidine 9g. Yield 76%, light yellow oil. ^{1}H NMR (300 MHz, C$_6$D$_6$): δ 0.72 and 0.98 (2×3H, 2×d, *J*=6.3 Hz, CH(C*H*$_3$)$_2$), 2.33 (3H, S, C$_q$C*H*$_3$), 2.45 (1H, septet, *J*=6.3 Hz, C*H*(CH$_3$)$_2$), 2.74 (1H, t, *J*=7.0 Hz, NC*H*(H)),

3.69 (1H, q, J=7.0 Hz, J=7.0 Hz, NCH(*H*)), 3.83 (1H, q, J=7.0 Hz, CHN_3), 3.84 (1H, d, J=7.0 Hz, NC*H*C_6H_4), 7.15 and 7.34 (2×2H, 2×d, J=8.3 Hz, C_6H_4). ^{13}C NMR (75 MHz, $CHCl_3$): δ 20.07 and 20.79 (CH(*C*H_3)$_2$), 21.13 (C_qCH_3), 55.36 (NCH_2), 57.77 (CHN_3), 59.30 (*C*H(CH$_3$)$_2$), 74.68 (N*C*HC_6H_4), 126.70 and 129.14 (NCH*C*$_4$H$_4$C), 137.36 and 138.87 (NCH*C*C$_4$H$_4$*C*). IR (NaCl, cm^{-1}): ν_{N3}=2105. MS (70 eV): *m*/*z* (%): No M$^+$, 175 (100), 133 (65), 105 (83). Anal. Calcd for $C_{13}H_{18}N_4$ (%): C, 67.80; H, 7.88; N, 24.33. Found (%): C, 67.98; H, 7.70; N, 24.47.

4.1.3.8. *trans*-1-Allyl-3-cyano-2-phenylazetidine 9h. Yield 54%, light yellow oil. Hexane/EtOAc 5:1, R_f=0.36. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95–3.09 (3H, m, C(*H*)HCH=CH_2, CHC≡N and C(*H*)HCHC≡N), 3.27 (1H, d×d×t, J=13.4 Hz, J=5.5 Hz, J=1.4 Hz, C(H)*H*CH=CH_2), 3.65–3.70 (1H, m, C(H)*H*CHC≡N), 4.21 (1H, d, J=8.0 Hz, C*H*C_6H_5), 5.04–5.25 (2H, m, CH=C*H*$_2$), 5.62–5.77 (1H, m, C*H*=CH_2), 7.22–7.48 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.51 (*C*HC≡N), 53.50 (*C*H_2CHC≡N), 60.17 (*C*H_2CH=CH_2), 71.93 (*C*HC_6H_5), 118.05 (CH=*C*H_2), 118.97 (C≡N), 126.57, 128.56 and 128.68 (C*C*$_5$H$_5$), 133.15 (*C*H=CH_2), 139.25 (*C*C_5H_5). IR (NaCl, cm^{-1}): $\nu_{C\equiv N}$=2241. MS (70 eV): *m*/*z* (%): 176 (25). Anal. Calcd for $C_{13}H_{14}N_2$ (%): C, 78.75; H, 7.12; N, 14.13. Found (%): C, 78.61; H, 7.01; N, 14.29.

4.1.3.9. *trans*-1-Allyl-2-(4-chlorophenyl)-3-cyanoazetidine 9i. Yield 62%, light yellow oil. Hexane/EtOAc 3:1, R_f=0.3. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.93–3.06 (2H, m, CHC≡N and C(*H*)HCH=CH_2), 3.10 (1H, d×d, J=9.2 Hz, J=6.5 Hz, C(*H*)HCHC≡N), 3.24 (1H, d×d×t, J=13.5 Hz, J=5.6 Hz, J=1.5 Hz, C(H)*H*CH=CH_2), 3.67–3.72 (1H, m, C(H)*H*CHC≡N), 4.19 (1H, d, J=8.3 Hz, C*H*C_6H_4Cl), 5.02–5.22 (2H, m, CH=C*H*$_2$), 5.61–5.77 (1H, m, C*H*=CH_2), 7.27–7.47 (4H, m, C_6H_4Cl). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.62 (*C*HC≡N), 53.45 (*C*H_2CHC≡N), 60.19 (*C*H_2CH=CH_2), 71.23 (*C*HC_6H_4Cl), 118.33 (CH=*C*H_2), 118.77 (C≡N), 128.01 and 128.89 (C*C*$_4$H$_4$CCl), 133.15 (*C*H=CH_2), 134.65 and 137.78 (*C*C$_4$H$_4$*C*Cl). IR (NaCl, cm^{-1}): $\nu_{C\equiv N}$=2242. MS (70 eV): *m*/*z* (%): 235/3 (M$^+$+1, 66). Anal. Calcd for $C_{13}H_{13}ClN_2$ (%): C, 67.10; H, 5.63; N, 15.23. Found (%): C, 67.30; H, 5.54; N, 15.39.

4.1.3.10. *trans*-1-Benzyl-2-(4-chlorophenyl)-3-cyanoazetidine 9j. Yield 65%, light yellow oil. Hexane/EtOAc 3:1, R_f=0.43. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.92–3.01 (1H, m, CHC≡N), 3.12 (1H, d×d, J=9.2 Hz, J=6.4 Hz, C(*H*)HCHC≡N), 3.49 (1H, d, J=12.9 Hz, C(*H*)HC_6H_5), 3.56–3.61 (1H, m, C(H)*H*CHC≡N), 3.81 (1H, d, J=12.9 Hz, C(H)*H*C_6H_5), 4.28 (1H, d, J=8.3 Hz, C*H*C_6H_4Cl), 7.22–7.42 (9H, m, $CH_2C_6H_5$ and CHC_6H_4Cl). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.83 (*C*HC≡N), 53.55 (*C*H_2CHC≡N), 61.10 (*C*H_2C$_6$H$_5$), 71.18 (*C*HC_6H_4Cl), 118.72 (C≡N), 127.57, 127.98, 128.47, 128.68 and 128.92 (C*C*$_4$H$_4$CCl and C*C*$_5$H$_5$), 134.44, 136.27 and 137.54 (*C*C$_4$H$_4$*C*Cl and *C*C$_5$H$_5$). IR (NaCl, cm^{-1}): $\nu_{C\equiv N}$=2242. MS (70 eV): *m*/*z* (%): 120 (100), 91 (40). Anal. Calcd for $C_{17}H_{15}ClN_2$ (%): C, 72.21; H, 5.35; N, 9.91. Found (%): C, 72.36; H, 5.48; N, 9.73.

4.1.3.11. *trans*-3-Acetoxy-1-allyl-2-phenylazetidine 9k. Yield 52%, light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.05 (3H, s, CH_3C=O), 2.75–2.80 (1H, m, C(*H*)HCHO), 3.05 (1H, d×d, J=13.4 Hz, J=6.9 Hz, C(*H*)HCH=CH_2), 3.33 (1H, d×d×t, J=13.4 Hz, J=5.6 Hz, J=1.4 Hz, C(H)*H*CH=CH_2), 3.85 (1H, d×d×d, J=7.3 Hz, J=6.5 Hz, J=1.1 Hz, C(H)*H*CHO), 3.99 (1H, d, J=6.3 Hz, C*H*C_6H_5), 4.83–4.90 (1H, m, CHOC=O), 5.03–5.29 (2H, m, CH=C*H*$_2$), 5.68–5.80 (1H, m, C*H*=CH_2), 7.25–7.47 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.73 (CH_3), 57.91 (*C*H_2CHO), 61.03 (*C*H_2CH=CH_2), 70.68 (*C*HOC=O), 74.62 (*C*HC_6H_5), 117.52 (CH=*C*H_2), 127.11, 127.84 and 128.34 (C*C*$_5$H$_5$), 134.04 (*C*H=CH_2), 139.86 (*C*C_5H_5), 170.00 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1745. MS (70 eV): *m*/*z* (%): 232 (M$^+$+1, 89), 190 (83) and 172 (84). Anal. Calcd for $C_{14}H_{17}NO_2$ (%): C, 72.70; H, 7.41; N, 6.06. Found (%): C, 72.91; H, 7.26; N, 5.94.

4.1.3.12. *trans*-3-Acetoxy-1-allyl-2-(4-chlorophenyl)-azetidine 9l. Yield 73%, light yellow oil. Hexane/EtOAc 5:2, R_f=0.48. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04 (3H, s, CH_3C=O), 2.80–2.84 (1H, m, C(*H*)HCHO), 3.09 (1H, d×d, J=13.2 Hz, J=6.9 Hz, C(*H*)HCH=CH_2), 3.29 (1H, d×d, J=13.2 Hz, J=6.1 Hz, C(H)*H*CH=CH_2), 3.83–3.88 (1H, m, C(H)*H*CHO), 3.97 (1H, d, J=6.3 Hz, C*H*C_6H_4Cl), 4.83–4.90 (1H, m, CHOC=O), 5.14–5.20 (2H, m, CH=C*H*$_2$), 5.65–5.78 (1H, m, C*H*=CH_2), 7.26–7.42 (4H, m, C_6H_4Cl). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.73 (CH_3), 57.61 (*C*H_2CHO), 60.94 (*C*H_2CH=CH_2), 70.52 (*C*HOC=O), 74.14 (*C*HC_6H_4Cl), 117.90 (CH=*C*H_2), 128.51 and 128.59 (C*C*$_4$H$_4$CCl), 133.61 (*C*H=CH_2), 133.72 and 138.27 (*C*C$_4$H$_4$*C*Cl), 169.98 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1746. MS (70 eV): *m*/*z* (%): 268/6 (M$^+$+1, 100). Anal. Calcd for $C_{14}H_{16}ClNO_2$ (%): C, 63.28; H, 6.07; N, 5.27. Found (%): C, 63.40; H, 6.10; N, 5.16.

4.1.3.13. *trans*-3-Acetoxy-1-benzyl-2-phenylazetidine 9m. Yield 52%, light yellow oil. Hexane/EtOAc 5:2, R_f=0.59. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.03 (3H, s, CH_3C=O), 2.77–2.82 (1H, m, C(*H*)HCHO), 3.49 (1H, d, J=13.1 Hz, C(*H*)HC_6H_5), 3.73–3.78 (1H, m, C(H)*H*CHO), 3.91 (1H, d, J=13.1 Hz, C(H)*H*C_6H_5), 4.08 (1H, d, J=5.0 Hz, C*H*C_6H_5), 4.87–4.91 (1H, m, CHOC=O), 7.19–7.48 (10H, m, $CH_2C_6H_5$ and CHC_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.78 (CH_3), 57.90 (*C*H_2CHO), 61.62 (*C*H_2C$_6$H$_5$), 70.97 (*C*HOC=O), 74.34 (*C*HC_6H_5), 127.09, 127.87, 128.25, 128.34, 128.50 and 128.74 (2×C*C*$_5$H$_5$), 137.46 and 139.69 (2×*C*C$_5$H$_5$), 169.99 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1744. MS (70 eV): *m*/*z* (%): 282 (M$^+$+1, 12), 120 (100) and 91(20). Anal. Calcd for $C_{18}H_{19}NO_2$ (%): C, 76.84; H, 6.81; N, 4.98. Found (%): C, 76.99; H, 6.70; N, 4.88.

4.1.3.14. *trans*-3-Acetoxy-1-benzyl-2-(4-chlorophenyl)-azetidine 9n. Yield 15%, light yellow oil. Hexane/EtOAc 10:3, R_f=0.43. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04 (3H, s, CH_3C=O), 2.29–2.84 (1H, m, C(*H*)HCHO), 3.50 (1H, d, J=12.9 Hz, C(*H*)HC_6H_5), 3.74 (1H, t, J=6.3 Hz, C(H)*H*CHO), 3.86 (1H, d, J=12.9 Hz, C(*H*)HC_6H_5), 4.02 (1H, d, J=6.1 Hz, C*H*C_6H_4Cl), 4.79–4.85 (1H, m, CHOC=O), 7.22–7.42 (9H, m, $CH_2C_6H_5$ and CHC_6H_4Cl). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.75

(CH_3), 57.74 (CH_2CHO), 61.67 ($CH_2C_6H_5$), 70.95 (CHOC=O), 71.49 (CHC_6H_4Cl), 127.21, 127.99, 128.28, 128.44 and 128.71 (CC_4H_4CCl and CC_5H_5), 137.29, 138.34 and 169.96 (CC_4H_4CCl and CC_5H_5), 184.16 (C=O). IR (NaCl, cm^{-1}): $\nu_{C=O}$=1745. MS (70 eV): *m/z* (%): 318/6 (M^++1, 14), 120 (100).

4.1.3.15. *trans*-1-Allyl-2-phenyl-3-thiocyanoazetidine 9o. Yield 31%, light yellow oil. Hexane/EtOAc 2:1, R_f=0.48. ^1H NMR (300 MHz, $CDCl_3$): δ 3.08 (1H, d×d, *J*=13.3 Hz, *J*=6.6 Hz, C(*H*)HCH=CH_2), 3.11–3.16 (1H, m, C(*H*)HCHSC≡N), 3.32 (1H, d×d, *J*=13.3 Hz, *J*=5.5 Hz, C(H)*H*CH=CH_2), 3.37–3.44 (1H, m, CHSC≡N), 3.85–3.90 (1H, m, C(H)*H*CHSC≡N), 4.18 (1H, d, *J*=7.7 Hz, C*H*C_6H_5), 5.06–5.38 (2H, m, CH=C*H*$_2$), 5.65–5.80 (1H, m, C*H*=CH_2), 7.25–7.48 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 42.88 (*C*HSC≡N), 57.80 (CH_2CHSC≡N), 60.58 (CH_2CH=CH_2), 75.94 (CHC_6H_5), 110.57 (CH=CH_2), 118.18 (SC≡N), 126.84, 128.60 and 128.80 (CC_5H_5), 133.65 (*C*H=CH_2), 139.24 (CC_5H_5). IR (NaCl, cm^{-1}): $\nu_{C\equiv N}$=2156. MS (70 eV): *m/z* (%): 231 (M^++1, 100). Anal. Calcd for $C_{13}H_{14}N_2S$ (%): C, 67.79; H, 6.13; N, 12.16. Found (%): C, 67.96; H, 6.30; N, 12.05.

4.1.3.16. *trans*-1-Allyl-2-(4-chlorophenyl)-3-thiocyanoazetidine 9p. Yield 43%, light yellow oil. Hexane/EtOAc 10:3, R_f=0.45. ^1H NMR (300 MHz, $CDCl_3$): δ 3.12 (1H, d×d, *J*=13.2 Hz, *J*=6.6 Hz, C(*H*)HCH=CH_2), 3.11–3.17 (1H, m, C(*H*)HCHSC≡N), 3.28 (1H, d×d×t, *J*=13.2 Hz, *J*=5.8 Hz, *J*=1.4 Hz, C(H)*H*CH=CH_2), 3.32–3.40 (1H, m, CHSC≡N), 3.85–3.90 (1H, m, C(H)*H*CHSC≡N), 4.16 (1H, d, *J*=7.4 Hz, C*H*C_6H_4Cl), 5.05–5.24 (2H, m, CH=C*H*$_2$), 5.63–5.77 (1H, m, C*H*=CH_2), 7.26–7.43 (4H, m, C_6H_4Cl). ^{13}C NMR (75 MHz, $CDCl_3$): δ 42.87 (*C*HSC≡N), 57.60 (CH_2CHSC≡N), 60.41 (CH_2CH=CH_2), 75.20 (CHC_6H_4Cl), 118.22 (CH=CH_2), 128.10 and 128.89 (CC_4H_4CCl), 133.38 (*C*H=CH_2), 110.21 and 134.27 (CC_4H_4CCl), 137.74 (SC≡N). IR (NaCl, cm^{-1}): $\nu_{C\equiv N}$=2157. MS (70 eV): *m/z* (%): 267/5 (M^++1, 100). Anal. Calcd for $C_{13}H_{13}ClN_2S$ (%): C, 58.97; H, 4.95; N, 10.58. Found (%): C, 59.19; H, 4.74; N, 10.50.

4.1.4. Synthesis of 3-methoxyazetidines 9q–r. The reaction of *trans*-1-allyl-3-chloro-2-phenylazetidine **4a** to afford *trans*-1-allyl-3-methoxy-2-phenylazetidine **9q** is given as a representative example for the substitution reactions of the 3-chloroazetidines with sodium methoxide. Sodium methoxide (4 N) (5 ml, 20 mmol, 4 equiv) in methanol was added to *trans*-3-chloro-2-phenylazetidine (1 g, 4.8 mmol) and the resulting mixture was refluxed overnight (22 h). After cooling, water (10 ml) was added and the mixture was extracted with diethyl ether and dried over magnesium sulfate. After evaporation of the solvent in vacuo, *trans*-3-methoxy-2-phenylazetidine (0.69 g, 3.4 mmol, 71%) was obtained. After flash chromatography (Hexane/EtOAc 3:2) on silica gel, pure *trans*-3-methoxy-2-phenylazetidine (0.48 g, 2.35 mmol, 49%) was isolated.

4.1.4.1. *trans*-1-Allyl-3-methoxy-2-phenylazetidine 9q. Yield 49%, light yellow oil. Hexane/EtOAc 3:2, R_f=0.48. ^1H NMR (300 MHz, $CDCl_3$): δ 2.73 (1H, t, *J*=6.3 Hz, C(*H*)HCHO), 3.01 (1H, d×d, *J*=13.3 Hz, *J*=7.0 Hz, C(*H*)HCH=CH_2), 3.23 (3H, s, OCH_3), 3.24–3.32 (1H, m, C(H)*H*CH=CH_2), 3.70 (1H, t, *J*=6.3 Hz, C(H)*H*CHO), 3.79–3.83 (1H, m, CHO), 3.86 (1H, d, *J*=5.5 Hz, C*H*C_6H_5), 5.00–5.20 (2H, m, CH=C*H*$_2$), 5.67–5.80 (1H, m, C*H*=CH_2), 7.22–7.48 (5H, m, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.35 (OCH_3), 56.62 (CH_2CCHO), 59.95 (CH_2CH=CH_2), 75.35 (CHC_6H_5), 77.00 (*C*HO), 116.06 (CH=CH_2), 125.84, 126.30 and 127.17 (CC_5H_5), 133.28 (*C*H=CH_2), 140.12 (CC_5H_5). MS (70 eV): *m/z* (%): 204 (M^++1, 100). Anal. Calcd for $C_{13}H_{17}NO$ (%): C, 76.81; H, 8.43; N, 6.89. Found (%): C, 76.96; H, 8.56; N, 6.80.

4.1.4.2. *trans*-1-Benzyl-2-(4-chlorophenyl)-3-methoxyazetidine 9r. Yield 45%, light yellow oil. Hexane/EtOAc 5:2, R_f=0.33. ^1H NMR (300 MHz, $CDCl_3$): δ 2.73–2.77 (1H, m, C(*H*)HCHO), 3.21 (3H, s, OCH_3), 3.46 (1H, d, *J*=12.8 Hz, C(*H*)HC_6H_5), 3.59–3.60 (1H, m, C(H)*H*CHO), 3.70–3.76 (1H, m, CHO), 3.82 (1H, d, *J*=12.8 Hz, C(H)HC_6H_5), 3.92 (1H, d, *J*=5.8 Hz, C*H*C_6H_4Cl), 7.18–7.41 (9H, m, C_6H_5 and C_6H_4Cl). ^{13}C NMR (75 MHz, ref=$CDCl_3$): δ 56.73 (OCH_3), 57.97 (CH_2CHO), 61.92 ($CH_2C_6H_5$), 75.69 (CHC_6H_4Cl), 78.67 (CHO), 127.24, 128.37, 128.46, 128.63 and 128.87 (CC_4H_4CCl and CC_5H_5), 133.22, 137.88 and 139.87 (CC_4H_4CCl and CC_5H_5). MS (70 eV): *m/z* (%): 290/88 (M^++1, 20), 120 (100). Anal. Calcd for $C_{17}H_{18}ClNO$ (%): C, 70.95; H, 6.30; N, 4.87. Found (%): C, 70.79; H, 6.45; N, 4.99.

4.1.5. Synthesis of *trans*-3-amino-2-arylazetidines 18a–c. The synthesis of *trans*-3-amino-1-isopropyl-2-phenylazetidine **18a** is described as a representative example.

To *trans*-3-azido-1-isopropyl-2-phenylazetidine (1 g, 4.6 mmol) in diethyl ether (10 ml) at 0 °C was added lithium aluminium hydride (0.35 g, 9.2 mmol, 2 equiv). This reaction mixture was refluxed for 2 h and after cooling, water was added until all remaining lithium aluminium hydride had decomposed. The resulting suspension was poured into water and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were dried (magnesium sulfate) and, after filtration and evaporation of the solvent in vacuo, *trans*-3-amino-1-isopropyl-2-phenylazetidine (0.62 g 3.22 mmol, 70%) was obtained. Purification was performed by an acid–base extraction.

4.1.5.1. *trans*-3-Amino-1-isopropyl-2-phenylazetidine 18a. Yield 70%, yellow oil. ^1H NMR (270 MHz, $CDCl_3$): δ 0.71 and 0.98 (2×3H, 2×d, *J*=6.3 Hz, CH(CH_3)$_2$), 1.66 (2H, br s, NH_2), 2.32 (1H, septet, *J*=6.3 Hz, C*H*(CH_3)$_2$), 2.48 (1H, t, *J*=7.0 Hz, NC*H*(H)), 3.18 (1H, q, *J*=7.0 Hz CHNH_2), 3.43 (1H, d, *J*=7.0 Hz, NC*H*C_6H_5), 3.76 (1H, q, *J*=7.0 Hz, NCH(*H*)), 7.21–7.48 (5H, m, C_6H_5). ^{13}C NMR (68 MHz, $CDCl_3$): δ 20.31 and 21.02 (CH(CH_3)$_2$), 52.96 (CHNH_2), 59.62 (*C*H(CH_3)$_2$), 60.07 (NCH_2), 80.88 (N*C*HC_6H_5), 126.57, 127.08 and 128.19 (NCHCC_5H_5), 142.98 (NCH*C*C_5H_5). IR (NaCl, cm^{-1}): ν_{NH_2}=3379, 3306. MS (70 eV): *m/z* (%): 147 (M−*i*Pr^+, 48), 106 (56). Anal. Calcd for $C_{12}H_{18}N_2$ (%): C, 75.74; H, 9.53; N, 14.72. Found (%): C, 75.99; H, 9.27; N, 14.94.

4.1.5.2. *trans*-3-Amino-1-cyclohexyl-2-phenylazetidine 18b. Yield 82%, yellow oil. ^1H NMR (270 MHz, $CDCl_3$): δ 0.95–1.97 (10H, m, (CH_2)$_5$), 2.00–2.12 (1H, m,

NCH), 2.48 (1H, t, J=7.0 Hz, NCH(H)), 3.18 (1H, q, J=7.0 Hz, CHNH$_2$), 3.45 (1H, d, J=7.0 Hz, NCHC$_6$H$_5$), 3.76 (1H, q, J=7.0 Hz, NCH(H)), 7.21–7.45 (5H, m, C$_6$H$_5$). ^{13}C NMR (68 MHz, CDCl$_3$): δ 24.49, 24.56, 25.93, 30.33 and 31.25 ((CH$_2$)$_5$), 53.58 (CHNH$_2$), 59.75 (NCH$_2$), 68.10 (NCH), 80.90 (NCHC$_6$H$_5$), 126.54, 127.10 and 128.21 (NCHCC_5H$_5$), 143.11 (NCHCC_5H$_5$). IR (NaCl, cm^{-1}): ν_{NH_2}=3379, 3307. MS (70 eV): m/z (%): 231 (M+H$^+$, 72), 112 (100). Anal. Calcd for C$_{15}$H$_{22}$N$_2$ (%): C, 78.21; H, 9.63; N, 12.16. Found (%): C, 78.47; H, 9.41; N, 12.32.

4.1.5.3. *trans*-3-Amino-1-isopropyl-2-(4-methylphenyl)-azetidine 18c. Yield 92%, yellow oil. ^{1}H NMR (270 MHz, CDCl$_3$): δ 0.71 and 0.97 (2×3H, 2×d, J=6.3 Hz, CH(CH_3)$_2$), 2.32 (3H, S, C$_q$CH_3), 2.41 (1H, septet, J=6.3 Hz, CH(CH$_3$)$_2$), 2.41 (1H, t, J=7.0 Hz, NCH(H)), 3.14 (1H, q, J=7.0 Hz, CHNH$_2$), 3.37 (1H, d, J=7.0 Hz, NCHC$_6$H$_4$), 3.73 (1H, t, J=7.0 Hz, J=7.0 Hz, NCH(H)), 7.12 and 7.32 (2×2H, 2×d, J=7.9 Hz, C$_6$H$_4$). ^{13}C NMR (68 MHz, CHCl$_3$): δ 20.34 and 21.08 (CH(CH_3)$_2$) and (C$_q$CH_3), 53.06 (CHNH$_2$), 59.68 (CH(CH$_3$)$_2$), 60.02 (NCH$_2$), 80.86 (NCHC$_6$H$_4$), 126.56 and 128.91 (NCHCC_4H$_4$C), 136.62 and 140.11 (NCHCC_4H$_4$C). IR (NaCl, cm^{-1}): ν_{NH_2}=3376. MS (70 eV): m/z (%): No M$^+$, 175 (M−NH$_2$−Me$^+$100), 133 (66), 106 (93), 84 (66). Anal. Calcd for C$_{13}$H$_{20}$N$_2$ (%): C, 76.42; H, 9.87; N, 13.71. Found (%): C, 76.66; H, 9.71; N, 13.79.

4.1.6. Synthesis of *trans*-2-arylazetidin-3-ols 19a–b. The hydrolysis of 3-acetoxy-1-allyl-2-phenylazetidine **9k** to 1-allyl-2-phenylazetidin-3-ol **19a** is described as a representative example. 3-Acetoxy-1-allyl-2-phenylazetidine **9k** (0.2 g, 0.87 mmol) was dissolved in methanol (30 ml). To this solution, sodium bicarbonate (1.89 g, 0.87 mmol, 1 equiv) was added. The resulting mixture was refluxed for 1 h. At the end of the reaction, water was added to the mixture, after which extraction was performed with diethyl ether. After drying on magnesium sulfate, filtration and evaporation of the solvent, crude 1-allyl-2-phenylazetidin-3-ol **19a** (0.28 g, 0.78 mmol, 89%, purity 95%) was obtained. Flash chromatography yielded pure 1-allyl-2-phenylazetidin-3-ol (0.15 g, 0.41 mmol, 47%).

4.1.6.1. *trans*-1-Allyl-2-phenylazetidin-3-ol 19a. Yield 47%, light yellow oil. Hexane/EtOAc 3:2, R_f=0.15. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.63–2.68 (1H, m, C(H)HCHOH), 2.95 (1H, d×d, J=13.1 Hz, J=6.9 Hz, C(H)HCH=CH$_2$), 3.23 (1H, d×d, J=13.1 Hz, J=5.9 Hz, C(H)HCH=CH$_2$), 3.56–3.60 (1H, m, C(H)HCHOH), 3.73 (1H, d, J=6.6 Hz, CHC$_6$H$_5$), 4.01–4.07 (1H, m, CHOH), 4.98–5.13 (2H, m, CH=CH_2), 5.59–5.72 (1H, m, CH=CH$_2$), 7.21–7.32 (5H, m, C$_6H_5$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 60.06 (CH_2CHOH), 61.23 (CH_2CH=CH$_2$), 69.84 (CHOH), 78.69 (CHC$_6$H$_5$), 117.67 (CH=CH_2), 126.91, 127.60 and 128.36 (CC$_5$H$_5$), 133.99 (CH=CH$_2$), 140.33 (CC$_5$H$_5$). IR (NaCl, cm^{-1}): ν_{OH}=3367, MS (70 eV): m/z (%): 190 (M$^+$+1, 100). Anal. Calcd for C$_{12}$H$_{15}$NO (%): C, 76.16; H, 7.99; N, 7.40. Found (%): C, 76.25; H, 7.50; N, 8.54.

4.1.6.2. *trans*-1-Allyl-2-(4-chlorophenyl)azetidin-3-ol 19b. Yield 79%, light yellow oil. ^{1}H NMR (300 MHz, CDCl$_3$): δ 2.68–2.73 (1H, m, C(H)HCHOH), 3.01 (1H, d×d, J=13.2 Hz, J=6.9 Hz, C(H)HCH=CH$_2$), 3.23 (1H, d×d, J=13.2 Hz, J=5.8 Hz, C(H)HCH=CH$_2$), 3.66–3.70 (1H, m, C(H)HCHOH), 3.73 (1H, d, J=6.1 Hz, CHC$_6$H$_4$Cl), 4.03–4.09 (1H, m, CHOH), 5.00–5.21 (2H, m, CH=CH_2), 5.62–5.75 (1H, m, CH=CH$_2$), 7.26–7.33 (4H, m, C$_6H_4$Cl). ^{13}C NMR (75 MHz, CDCl$_3$): δ 60.11 (CH_2CHOH), 60.12 (CH_2CH=CH$_2$), 70.10 (CHOH), 77.96 (CHC$_6$H$_4$Cl), 117.84 (CH=CH_2), 128.24 and 128.51 (CC$_4$H$_4$CCl), 133.29 (CC_4H$_4$CCl), 133.81 (CH=CH$_2$), 138.89 (CC$_4$H$_4$CCl). IR (NaCl, cm^{-1}): ν_{OH}=3343. MS (70 eV): m/z (%): 226/4 (M$^+$+1, 100). Anal. Calcd for C$_{12}$H$_{14}$ClNO (%): C, 64.43; H, 6.31; N, 6.26. Found (%): C, 64.65; H, 6.43; N, 6.12.

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