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Graphical Abstract

Synthesis of 2-Carboxylated Aza-Ring Derivatives through α-Monohalogenation/Ring-Contraction of *N*-Sulfonyl Lactams

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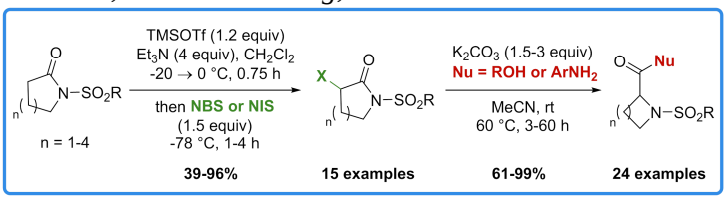

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Synthesis of 2-Carboxylated Aza-Ring Derivatives through α-Monohalogenation/Ring-Contraction of *N*-Sulfonyl Lactams

Fatih Sirindil[a], Solène Miaskiewicz[a], Nicolas Kern[a], Arno Lalaut[a], Anne-Sophie Felten[a], Jean-Marc Weibel[a], Patrick Pale[a]* and Aurélien Blanc[a]*

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ABSTRACT

2-Carboxylated aza-rings have been synthesized in two steps through a highly selective monohalogenation of *N*-sulfonylated lactams of various ring sizes (from 5- to 8-membered rings). The selective monohalogenation of *N*-sulfonyl lactams has been achieved in modest to excellent yields (9 examples, 39-96%) using *N*-halogenosuccinimides via the in situ generation of trimethylsilyl ketene aminal derivatives. The so-obtained α-halogeno *N*-sulfonyl lactams were engaged in a ring opening/ring closing reaction in the presence of various alcohols or anilines under basic conditions affording 2-carboxylated aza-rings, such as azetidine, pyrrolidine or piperidine derivatives in high yields (19 examples, 19-99%).

1. Introduction

N-heterocyclic aminoacids are important natural products found in various organisms, in which they play different roles, either defensive or vital (Figure 1, top). The latter aspect can be illustrated by the azetidine-2-carboxylic acid (AZE) or natural products containing the AZE motif such as mugineic acid family,[1] which exhibits chelating properties for iron and other metals required for organism growth. The former role can be represented with the kainic acid family[2] with their anthelmintic and neuroexcitatory activities. These *N*-heterocyclic aminoacids thus often act as lead structures towards drug discovery (Figure 1, bottom). Recently, they even raised more interest with the emergence of conformationally restricted, but non-flattened and non-aromatic building blocks as alternative scaffolds for drug candidates.[3] However, few routes have been reported to form these functionalized heterocycles, especially for small rings such as azetidines.[4]

For the investigation of metal-catalyzed rearrangements of various heterocycles,[5] we developed rapid, reliable and scalable syntheses of *N*-aryl azetidines[6] and substituted *N*-protected α-carbonylated azetidines from easily available pyrrolidinones.[7] We now report here the generalization of the latter strategy to the formation of *N*-heterocyclic aminoacid derivatives, i.e. azetidine-, pyrrolidine-, piperidine-2-carboxylates. As in our preceding communication,[7] but in a more general way, we expected the formation of α-carbonylated aza-cycles **3** by S_N2 cyclization of α-halogenocarbonyl amide anion intermediates, which could be generated by opening α-halogeno-*N*-sulfonyl lactams **2** with various nucleophiles (Scheme 1). We started from *N*-sulfonylated lactams **1** to favor the nucleophilic attack over proton transfer and to stabilize the intermediate anion.

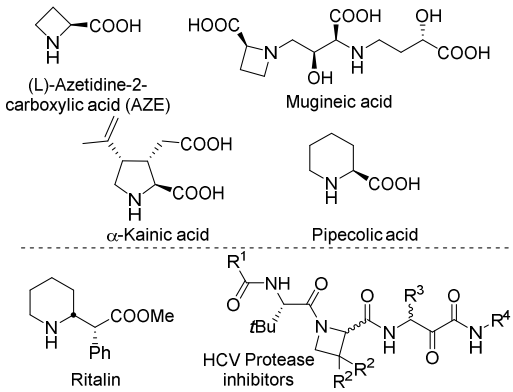
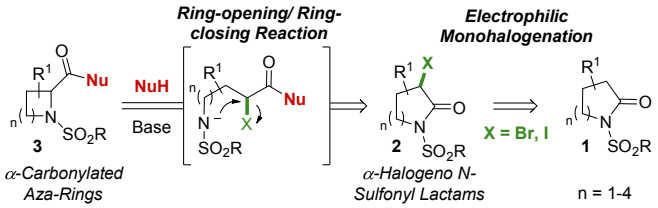


Figure 1. Selected Examples of Azetidine, Pyrrolidine and Piperidine Carboxylic Acids Containing Natural Products and Drugs.



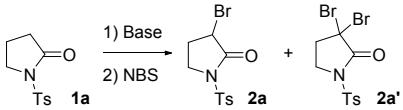
Scheme 1. Retrosynthetic Approach towards 2-Carboxylate Aza-Ring Derivatives from *N*-sulfonyl Lactams.

2. Results and discussion

2.1. α-Monohalogenation of N-Sulfonyl Lactams

The first step of this sequence relies on the selective α-monohalogenation of lactams **1**. Although a priori simple, this step was surprisingly almost unprecedented.[8] With the aim of using common reagents for this transformation, we selected the readily available *N*-tosyl pyrrolidin-2-one **1a** as model substrate and *N*-bromosuccinimide (NBS) as halogen source (Table 1).

Table 1. Screening of Conditions for α-Monobromination of 1-Sulfonylpyrrolidin-2-one **1a** using Various Bases.



Entry	Base (equiv)	Solvent (concn)	**Step 1** temp (°C), time, additive (equiv)	NBS (equiv)	**Step 2** temp (°C), time	Yields[a] **2a**/**2a'** (%)
1	LDA (1.1)	THF (0.2M)	-78, 1 h	1.2	-78, 1 h	60/5[b]
2	LiHMDS (1.1)	THF (0.2M)	-78, 1 h	1.2	-78, 1 h	55/28[c]
3	LiHMDS (1.3)	THF (0.2M)	-78, 1 h	1.2	-78, 1 h	53/23[c]
4	LiHMDS (2.1)	THF (0.2M)	-78, 1 h	1.2	-78, 1 h	37/34[c]
5	LiHMDS (1.6)	THF (0.2M)	-78, 1 h	1.2	-78, 1 h	72/5[d]
6	Et_3N (2.5)	DCM (0.25M)	0, 30 min TMSOTf (1.5) then rt, 1 h	1.5	0, 1 h	70/-
7	Et_3N (2.5)	DCM (0.25M)	0, 30 min TMSOTf (1.5) then rt, 1 h	1.5	0, 1 h	53/-[e]
8	Et_3N (2.5)	DCM (0.25M)	-20, 30 min TMSOTf (1.5) then 0, 45 min	1.5	-78 to -40, 1.5 h	74/-
9	Et_3N (2.5)	DCM (0.25M)	-20, 30 min TMSOTf (1.2) then 0, 45 min	1.5	-78 to -40, 1.5 h	80/-
10	Et_3N (4)	DCM (0.25M)	-20, 30 min TMSOTf (1.2) then 0, 45 min	1.5	-78 to -40, 1.5 h	87/-
11	Et_3N (4)	DCM (0.25M)	-20, 30 min TMSOTf (1.2) then 0, 45 min	1.5	-78 to -40, 1.5 h	89/-[f]

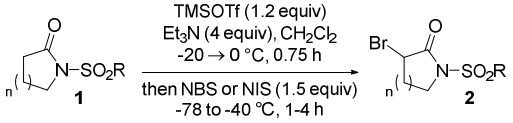
[a] Estimated yield relative to ^1H NMR spectrum of the crude.
[b] The use of LiHMDS (1.1 equiv) gave a cleaner reaction mixture than LDA (entry 2 vs 1).
[c] Along with 15-30% of unreacted starting material.
[d] Reaction was not scalable.
[e] Reaction run on 20 mmol scale.
[f] Reaction run on 100 mmol scale.

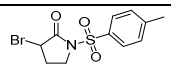
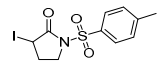
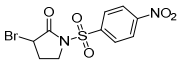
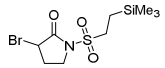
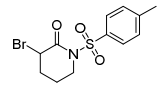
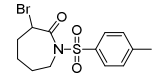
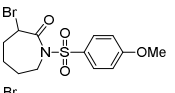
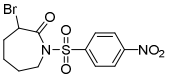
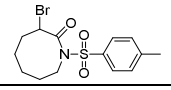
Strong bases, such as LDA or LiHMDS, gave a mixture of mono and dibrominated *N*-tosyl pyrrolidin-2-ones **2a** and **2a'**, even at low temperature (Table 1, entries 1-5). Although the overall yield and ratio of mono and dibrominated product were promising, the use of LDA induced a messier reaction than the use of LiHMDS (Table 1, entry 1 vs 2-3). With the latter, conversion of **1a** remained partial, and its use in excess amounts did not improve this trend while increasing the amount of dibrominated *N*-tosyl pyrrolidin-2-one **2a'** (Table 1, entry 4 vs 2-3). The best compromise between selectivity and conversion could be achieved with 1.6 equiv of LiHMDS, affording a good yield of the monobrominated product **2a**, nevertheless still contaminated by the dibrominated pyrrolidin-2-one **2a'** (Table 1, entry 5). Chromatographical separation of both compounds was clearly unconvenient, and this problem led us to investigate a different approach where the corresponding silyl ketene aminal would be formed and directly trapped by a halogenated electrophile. After a short optimization study, we rewardingly only obtained the monobrominated product **2a** following the sequential action of trimethylsilyl triflate (TMSOTf) and triethylamine (Et_3N) as a mild base followed by low temperature quenching with NBS (Table 1, entries 6-11). In this case, increasing the amount of base while adjusting the amount of TMSOTf allowed a cleaner one-pot process (Table 1, entry 10 vs 8-9). Interestingly, these conditions proved to be suitable to brominate 100 mmol of **1a** (24.9 g) without any loss in efficiency (Table 1, entry 11 vs 10).

We then explored this monobromination reaction with various lactams (Table 2). The use of other halogenation agents was only briefly surveyed since NIS instead of NBS gave lower yields of the corresponding *N*-tosyl 3-iodopyrrolidin-2-one **2b**, but still with a very high selectivity in favor of the monohalogenated derivative (Table 2, entry 2 vs 1). The nature of the *N*-sulfonyl substituent did not significantly affect the reaction (Table 2, entry 3 vs 1), except for the 2-trimethylsilylethylsulfonyl group (SES), probably sensitive to the bromination conditions (Table 2, entry 4 vs 1).

Rewardingly, the reaction proved to be as selective and as efficient with larger ring sized lactams, providing the 6-, 7- and 8-membered α-bromolactams in high yields (Table 2, entries 5-9). Surprisingly, the sulfonyl group nature had some influence on the reaction course with 7-membered lactams, as revealed by the slow reaction rate observed with the *N*-nosyl caprolactam **1h** (Table 2, entry 8 vs 6-7).

Table 2. Preparation of α-Halogenated *N*-Sulfonyl Lactams **2**.



Entry	α-Halogenated Lactams		Yields[a] (%)
1		**2a**	89
2		**2b**	59
3		**2c**	83
4		**2d**	61
5		**2e**	86
6		**2f**	90
7		**2g**	83
8		**2h**	39[b]
9		**2i**	96

[a] C = 0.25 mol/L; isolated yield.
[b] 41% of starting material was recovered.

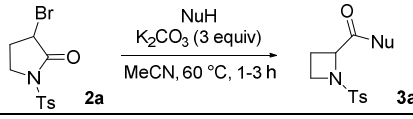
Having in hand a useful and general method for the monohalogenation of lactams, we then explored the second step of the sequence, i.e. the one-pot ring opening–ring closing reaction.

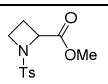
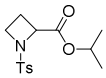
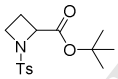
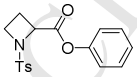
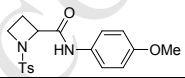
2.2. Ring Contraction of α-Halogenated N-Sulfonyl Lactams

The contraction of α-bromo *N*-tosylpyrrolidinone **2a** was easily performed using 3 equivalents of potassium carbonate in acetonitrile at 60 °C in the presence of various nucleophiles (Table 3). We have already demonstrated that primary alcohols, functionalized or not, readily gave the corresponding α-azetidinyl esters in excellent yields, as for example with methanol (Table 3, entry 1).[7] In contrast, hindered alcohols slowly reacted and the more hindered, the less reactive was the alcohol. Indeed, isopropanol mostly gave degradation products, but the expected ester **3b** could nevertheless be isolated in 19% of yield along with 10% of the corresponding open product (Table 3, entry 2), while *tert*-butanol did not react (Table 3, entry 3). Interestingly, water was able to promote the ring contraction of **2a**, directly affording the corresponding acid derivative **3d** (Table 3, entry 4), but an excess of water was required and the reaction had to be conducted in a 1:1 mixture of MeCN/H_2O to ensure quantitative conversion.

Phenol as well as aniline derivatives could be used as nucleophiles with **2a**, leading to the expected phenyl ester **3e** or amide **3f** in excellent yields (Table 3, entries 5 and 6).

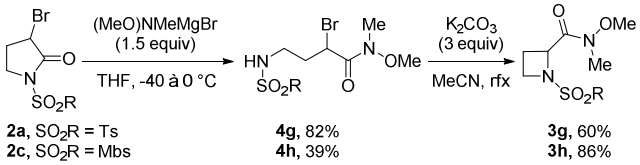
Table 3. Ring-Contraction of α-Bromo *N*-Tosylpyrrolidinone **2a** in the Presence of Nucleophiles.



Entry	Nucleophile (10 equiv)	Azetidine		Yield (%)
1	Methanol		**3a**	96[a]
2	*iso*-Propanol		**3b**	19
3	*tert*-Butanol		**3c**	-[b]
4	H_2O		**3d**	96[c]
5	Phenol		**3e**	81
6	*p*MeO-Aniline		**3f**	90

[a] Performed on 0.05 mol.
[b] The expected **3c** could not be detected, and degradation slowly occurred leading to unidentified by-products.
[c] Reaction run in a mixture of MeCN/H_2O (1/1).

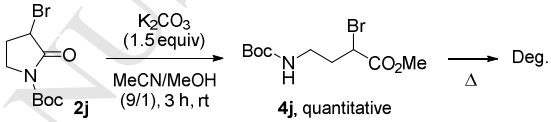
Due to the interesting possibilities this reaction could offer for further transformations, ring contraction with Weinreb amines as nucleophile were envisaged. Unfortunately, the optimized conditions did not allow such amine to react with the bromolactam **2a**. Nevertheless, the Weinreb amido magnesium bromide was nucleophilic enough at low but controlled temperature to give the open products **4**, which could then be cyclized in the presence of potassium carbonate in acetonitrile (Scheme 2). This two-step ring opening-ring closure proved efficient, but overall seemingly less with the *p*-methoxybenzenesulfonyl (Mbs) group at the *N* position (see overall yields for **3h** vs **3g**, respectively 33 vs 42 %). Interestingly, these results confirmed the proposed mechanism (see Scheme 1) with first a ring opening and then an intramolecular SN_2 displacement of the bromine.



2a, SO_2R = Ts — **4g**, 82% — **3g**, 60%
2c, SO_2R = Mbs — **4h**, 39% — **3h**, 86%

Scheme 2. Two-Step Sequence using Anionic Weinreb Amine as Nucleophile.

We also evaluated the more labile Boc protecting group in the ring-contraction reaction. We first prepared the monobrominated *N-tert*-butoxycarbonyl pyrrolidinone **2j** in 53% yield from the commercially available *tert*-butyl 2-oxopyrrolidine-1-carboxylate using reaction conditions of Table 2. Although moderate, this yield is still appreciable given the known lability of Boc groups towards TMSOTf.[9] When submitted to the ring-contraction conditions at room temperature, **2j** quantitatively afforded the opened product **4j** but without any trace of the expected azetidine. Heating the reaction mixture only led to degradation products (Scheme 3).



Scheme 3. Attempt to Ring-Contract α-Bromo *N-tert*-butoxycarbonyl pyrrolidinone **2j**.

The standard ring contraction conditions were then applied to the above prepared lactams **2b-i**, with various nucleophiles (Table 4).

Starting from the *N*-tosyl 3-iodo-2-pyrrolidinone 2**b**, these conditions provided the α-azetidinyl ester **3a** in good yield using methanol as nucleophile, but the reaction was less efficient compared to the 3-bromo-2-pyrrolidinone analog **2a** (Table 4, entry 1 vs Table 3, entry 1). The compatibility of more easily removable *N*-protecting groups than phenylsulfonyl derivatives, was also evaluated in the ring opening/ring closing reaction with the *p*-nosyl (Ns) and 2-trimethylsilylethanesulfonyl (SES), groups. In a satisfactory way, the *N*-nosyl γ-lactam **2c** and *N*-SES **2d** afforded the desired azetidinyl products **3i** and **3j** respectively in excellent yields (Table 4, entries 2-3 vs 1).

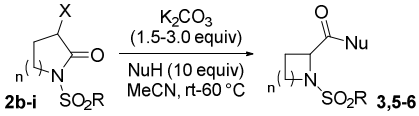
Interestingly, the one-pot ring opening–ring closing reaction was also operational starting from 6- and 7-membered lactams **2e-h**, providing very efficiently the expected proline- or pipecoline-like esters **5** and **6** in the presence of various alcohols. Indeed, the contraction of δ-lactam **2e** led in almost quantitative yields within 4-6 hours to a series of proline ester derivatives **5k-n** employing respectively methanol, ethanol, benzyl alcohol and 3-phenylprop-2-yn-1-ol as nucleophiles (Table 4, entries 4-7).

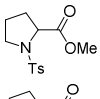
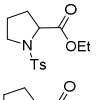
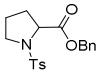
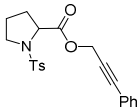
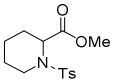
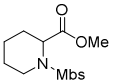
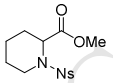
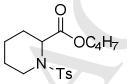
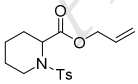
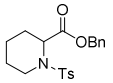
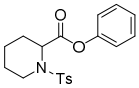
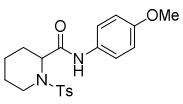
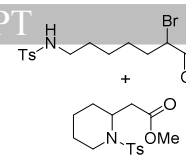
In the 7-membered lactam series, the nature of the *N*-sulfonyl group exhibits again a clear influence on the reaction efficiency (Table 4, entries 8-10). If the tosyl group did not really change the reaction course compared to γ - and δ-lactam series, affording quantitatively **6o** in 6 h (Table 4, entries 8 vs 1 and 4), the *p*-methoxybenzensulfonyl (Mbs) clearly facilitated the reaction, leading to the expected pipecoline derivatives **6p** in only 3 h (Table 4, entries 9). In contrast, the electron-withdrawing *p*-nosyl group significantly increased the reaction time from 6 to 14 h,

presumably by slowing-down the ring-closing step, nevertheless without affecting too much the yield (Table 4, entries 10).

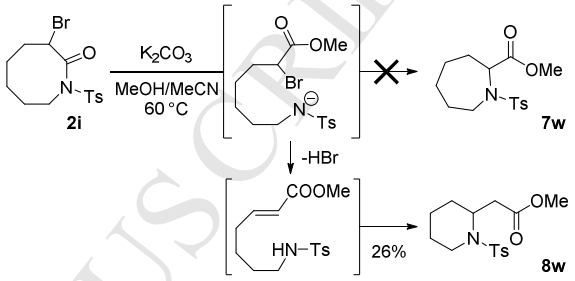
While primary alcohols were perfectly able to promote the contraction of ε-lactam (Table 4, entries 11-13), the use of phenol or aniline derivatives in the contraction of **2f** was far less efficient than in the formation of azetidines from γ-lactam **2a** (Table 4, entries 14-15 vs Table 2, entries 5-6). Indeed, a poor yield of 9% was obtained in the presence of phenol and 48 h of reaction were necessary to reach a modest yield of 57% with *p*-methoxyaniline.

Table 4. Synthesis of α-Methylester Aza-Rings **3**,**5** and **6** from Various *N*-Sulfonyl Lactams **2**.



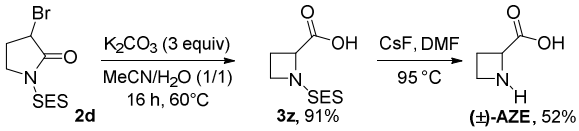
Entry	Lactam	2-Methylester Aza-Rings		Time (h)	Yield (%)
1	**2b**		**3a**	6	61
2	**2c**		**3i**	3	98
3	**2d**		**3j**	3	85
4	**2e**		**5k**	4	98
5	**2e**		**5l**	6	94
6	**2e**		**5m**	6	98
7	**2e**		**5n**	5	99
8	**2f**		**6o**	6	99
9	**2g**		**6p**	3	93
10	**2h**		**6q**	14	85
11	**2f**		**6r**	6	86
12	**2f**		**6s**	18	83
13	**2f**		**6t**	6	97
14	**2f**		**6u**	18	9
15	**2f**		**6v**	48	57
16	**2i**		**4w** + **8w**	18	34 + 26

The largest lactam evaluated, i.e. the 8-membered ring **2i**, also led to a ring-contracted product **8w,** although not the expected one. The latter was almost equally produced together with the open product **4w** (Table 4, entry 16). The newly formed compound could be assigned as the methyl (*N*-tosyl piperidin-2-yl)acetate. Taken together, these results showed that, if the ring opening process readily occurred, the ring closure did not on such long distance (Baldwin rules) and a competitive elimination-Michael addition took place (Scheme 4).



Scheme 4. Competitive Pathway for 8-Membered α -Bromolactam **2i**.

After having explored the scope of this new ring contraction protocol, we then applied it to a short synthesis of **(±)-AZE** natural compound (Scheme 5).[10] The *N*-SES protected free acid AZE derivative **3z** was efficiently obtained in 91% yield starting from the pyrrolidinone **2d** (see Table 2, entry 4) in the presence of water as nucleophile. The SES protecting group was then removed using CsF in DMF at 95 °C affording the (±)-AZE in a reasonable yield of 52%.[11]



Scheme 5. Synthesis of Azetidine-2-Carboxylic Acid **AZE**.

3. Conclusion

Through this work, we have developed a two-step, reliable and scalable synthesis of azetidine-, pyrrolidine- and piperidine-2-carboxylate derivatives. For the first step, we developed a highly selective monobromination of *N*-sulfonylated lactams of various ring sizes (from 5 to 8 membered rings). In the second step, a one-pot ring opening–ring closing reaction was set up starting from the so-formed 5 to 7-membered α-bromolactams, providing very efficiently, sometimes quantitatively, the *N*-sulfonylated heterocyclic esters and amides resulting from a formal ring contraction. We highlighted this two-step sequence with a short synthesis of AZE natural product. This strategy offers an alternative, general and scalable route to various *N*-heterocyclic aminoacids.

4. Experimental section

General Information. Proton (^{1}H NMR) and Carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on 300, 400 or 500 MHz instruments. The chemical shifts are given in part per million (ppm) on the delta scale. The solvent peak was used as reference value: for ^{1}H NMR, $CHCl_3$ = 7.26 ppm; for ^{13}C

NMR, $CHCl_3$= 77.16 ppm. Infrared spectra were recorded neat. Wavelengths of maximum absorbance (ν_{max}) are quoted in wave numbers (cm^{-1}). High resolution mass spectra (HRMS) data were recorded on a microTOF spectrometer equipped with orthogonal electrospray interface (ESI). The parent ions $[M]^{+\cdot}$, $[M+H]^{+}$, $[M+Li]^{+}$ or $[M+Na]^{+}$ are quoted. Analytical thin layer chromatography (TLC) was carried out on silica gel 60 F_{254} plates or basic alumina (63−200 µm) with visualization by ultraviolet light or potassium permanganate dip. Flash column chromatography was carried out using silica gel 60 (40−63 µm) or basic Al_2O_3 (63−200 µm) and the procedure included the subsequent evaporation of solvents *in vacuo*. Reagents and solvents were purified using standard means. Dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN), tetrahydrofuran (THF) and diethyl ether (Et_2O) were dried over activated alumina column (DryStation); triethylamine (Et_3N), pyridine and 1,8-diazabicycloundec-7-ene (DBU) were distilled from KOH. Anhydrous reactions were carried out in flame-dried glassware and under an argon atmosphere. Na_2CO_3, K_2CO_3 and Cs_2CO_3 were dried overnight in an oven at 110 °C. All other chemicals were used as received. All extractive procedures were performed using non-distilled solvents and all aqueous solutions used were saturated unless details are given.

4.1. General Procedure 1 for α-bromination of 1-sulfonylpyrrolidin-, piperidin-, azepan- or azocan-2-ones 1 (GP1):

TMSOTf (2.17 mL, 12 mmol) was added dropwise to a stirred solution of the appropriate 1-sulfonylpyrrolidin-, piperidin-, azepan- or azocan-2-one derivative **1** (10 mmol) and Et_3N (5.60 mL, 40 mmol) in CH_2Cl_2 (40 mL) at -20 °C under argon. The mixture was stirred at -20 °C for 15 min, warmed to 0 °C and stirred for 45 min before being cooled to -78 °C. *N*-Bromosuccinimide (2.67 g, 15 mmol) was added by portions under argon. The mixture was warmed to -40 °C and stirred until completion of the reaction (monitored by TLC; typically 1.5–2 h). Saturated aqueous NH_4Cl (40 mL) was then added at -40 °C, and the resulting yellow solution was warmed to room temperature and stirred for 15 min. Layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (40 mL). The combined organic layers were washed with water (2 x 100 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated. The product was purified by recrystallization including hot filtration (solvent indicated for each compound) or flash chromatography (SiO_2, Cyclohexane/EtOAc) to afford the title compound **2**.

*4.1.1. 3-Bromo-1-tosylpyrrolidin-2-one (**2a**):*

Prepared following the **GP1** in 89 % yield (2.76 g) from 2.39 g of 1-tosylpyrrolidin-2-one,[7] after recrystallization from cyclohexane/EtOAc (3:1). Colorless crystals: mp = 118 °C. TLC R_f = 0.43 (Cyclohexane/EtOAc 40 %), revelator: UV/$KMnO_4$. IR (neat): 2951, 2886, 1734, 1356, 1223, 1168, 1115, 954, 817, 707, 660, 615, 568, 543 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.92 (d, *J* = 8.3 Hz, 2 H), 7.36 (d, *J* = 8.3 Hz, 2 H), 4.34 (dd, *J* = 2.8, 6.7 Hz, 1 H), 4.05−3.84 (m, 2 H), 2.60 (dddd, *J* = 6.7, 7.8, 8.4, 14.4 Hz, 1 H), 2.45 (s, 3 H), 2.30 (dddd, *J* = 2.8, 3.0, 6.2, 14.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 168.5, 145.8, 138.9, 129.9, 128.2, 45.4, 43.4, 29.9, 21.9. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{12}BrNO_3S$ $+Na^+$: 339.9613; found: 339.9579.

*4.1.2. 3,3-Dibromo-1-tosylpyrrolidin-2-one (**2a'**):*

Compound **2a'** was obtained as by-product during the screening of conditions for α-monobromination of 1-sulfonylpyrrolidin-2-one **1a** (Table 1). Colorless crystals: mp = 118 °C. TLC R_f = 0.54 (Cyclohexane/EtOAc 40 %), revelator: UV/$KMnO_4$. IR (neat): 2951, 2886, 1734, 1593, 1482, 1356, 1223, 1168, 1115, 955, 818, 707, 660, 615, 568, 544 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.92 (d, *J* = 8.4 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 2 H), 3.85 (t, *J* = 6.1 Hz, 2 H), 3.00 (t, *J* = 6.1 Hz, 2 H), 2.45 (s, 3 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 164.7, 146.2, 133.0, 130.0, 128.4, 53.6, 44.8, 42.8, 21.9. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{11}Br_2NO_3S$ $+Na^+$: 417.8719; found: 417.8727.

*4.1.3. 3-Iodo-1-tosylpyrrolidin-2-one (**2b**):*

Prepared following the **GP1** in 59 % yield (214 mg) from 241 mg of 1-tosylpyrrolidin-2-one,[7] using *N*-iodosuccinimide (NIS) instead of NBS, after purification by column chromatography on SiO_2 (Cyclohexane/EtOAc). Yellow solid: mp = 130 °C. TLC R_f = 0.30 (Cyclohexane/EtOAc 30 %). IR (neat): 2898, 1722, 1592, 1479, 1432, 1342, 1317, 1293, 1221, 1201, 1183, 1162, 1106, 1081, 1032, 1008, 952, 872, 808, 702, 654, 602, 558, 540, 480 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.92 (d, *J* = 8.2 Hz, 2 H), 7.36 (d, *J* = 8.2 Hz, 2 H), 4.49 (dd, *J* = 1.6, 6.6 Hz, 1 H), 3.94 (ddd, *J* = 1.7, 7.7, 10.1 Hz, 1 H), 3.75 (ddd, *J* = 6.0, 9.4, 10.1 Hz, 1 H), 2.45 (s, 3 H), 2.51−2.42 (m, 1 H), 2.19 (dddd, *J* = 1.7, 1.7, 6.0, 14.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 170.5, 145.8, 133.4, 129.9, 128.3, 46.1, 31.1, 21.9, 18.5. HRMS (HESI): *m/z* $[M + K]^+$ calcd for $C_{11}H_{12}INO_3S$ $+K^+$: 403.9214; found: 403.9231.

*4.1.4. 3-Bromo-1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-one (**2c**):*

Prepared following the **GP1** in 83 % yield (7.03 g) from 6.55 g of 1-((4-nitrophenyl)sulfonyl)pyrrolidin-2-one,[7] after purification by flash chromatography (Cyclohexane/EtOAc 20 % to 60 %). Colorless crystals: mp = 194 °C (Et_2O). TLC R_f = 0.28 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 3113, 2985, 2952, 1743, 1524, 1346, 1313, 1220, 1171, 1119, 1019, 963, 853, 740, 700, 603, 555, 499, 460 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.42 (d, *J* = 9.0 Hz, 2 H), 8.26 (d, *J* = 9.0 Hz, 2 H), 4.37 (dd, *J* = 2.4, 6.5 Hz, 1 H), 4.07 (ddd, *J* = 2.3, 7.8, 10.1 Hz, 1 H), 3.95 (ddd, *J* = 6.4, 8.9, 10.1 Hz, 1 H), 2.65 (dtd, *J* = 6.4, 8.3, 14.6 Hz, 1 H), 2.35 (ddt, *J* = 2.6, 6.4, 14.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 168.7, 151.2, 142.0, 129.7, 124.4, 45.6, 42.7, 29.9. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{10}H_9BrN_2O_6S$ $+Na^+$: 370.9308; found: 370.9313.

*4.1.5. 3-Bromo-1-((2-(trimethylsilyl)ethyl)sulfonyl)pyrrolidin-2-one (**2d**):*

Prepared following the **GP1** in 61 % yield (200 mg) from 250 mg of 1-((2-(trimethylsilyl)ethyl)sulfonyl)pyrrolidin-2-one (See supplementary data), after purification by flash chromatography (Cyclohexane/EtOAc 20 % to 50 %). Colorless oil. TLC R_f = 0.60 (Cyclohexane/EtOAc 50 %), revelator: UV/$KMnO_4$. IR (neat): 2954, 2900, 1726, 1488, 1459, 1418, 1344, 1247, 1214, 1194, 1170, 1150, 1124, 1106, 1075, 956, 895, 830, 787, 746, 714, 690, 638, 621, 583, 571, 511 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 4.48 (dd, *J* = 6.6, 2.4 Hz, 1 H), 4.06–3.84 (m, 2 H), 3.53 (ddd, *J* = 14.4, 13.0, 5.0 Hz, 1 H), 3.31 (ddd, *J* = 14.4, 13.0, 5.1 Hz, 1 H), 2.68 (dddd, *J* = 14.5, 8.6, 7.9, 6.6 Hz, 1 H), 2.38 (ddt, *J* = 14.6, 6.0, 2.5 Hz, 1 H), 1.16–0.91 (m, 2 H), 0.07 (s, 9 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 170.2, 49.3, 45.9, 43.5, 30.1, 9.9, -1.9. HRMS (HESI): *m/z* $[M + K]^+$ calcd for $C_9H_{18}BrNO_3SSi$ $+K^+$: 365.9592; found: 365.9637.

*4.1.6. 3-Bromo-1-tosylpiperidin-2-one (**2e**):*

Prepared following the **GP1** in 86 % yield (621 mg) from 549 mg of 1-tosylpiperidin-2-one (see supplementary data), after purification by column chromatography on silica gel (Cyclohexane/EtOAc 20%). White solid: mp = 130 °C. TLC R_f = 0.39 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 2955, 1690, 1595, 1435, 1387, 1351, 1305, 1277, 1209, 1189, 1157, 1115, 1085, 1053, 1042, 1019, 1001, 973, 895, 880,

825, 810, 754, 690, 655, 623, 590, 565, 534, 477, 460 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.91 (d, *J* = 8.7 Hz, 2 H), 7.32 (d, *J* = 8.7 Hz, 2 H), 4.47 (dd, *J* = 3.3, 4.7 Hz, 1 H), 4.20 (ddd, *J* = 4.7, 4.7, 12.4 Hz, 1 H), 3.81 (ddd, *J* = 4.7, 9.4, 12.4 Hz, 1 H), 2.44 (s, 3 H), 2.38−2.18 (m, 3 H), 1.88−2.05 (m, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 166.1, 145.3, 135.1, 129.5, 128.9, 46.5, 45.3, 30.8, 21.8, 19.9. HRMS (HESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_{14}BrNO_3S$ $+H^+$: 331.9955; found: 331.9966.

*4.1.7. 3-Bromo-1-tosylazepan-2-one (**2f**):*

Prepared following the **GP1** in 90% yield (11.66 g) from 1-(tosyl)azepan-2-one[5e] (10 g) and used as a crude product in the following step. White solid: mp = 102 °C. TLC R_f = 0.52 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 2973, 2934, 2917, 2850, 1703, 1594, 1438, 1351, 1294, 1246, 1162, 1113, 1080, 984, 943, 901, 870, 764, 702, 676, 642, 541 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.85 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 4.69 (dd, *J* = 2.6, 7.3 Hz, 1 H), 4.31 (dd, *J* = 6.7, 16.3 Hz, 1 H), 4.18 (dd, *J* = 9.2, 16.3 Hz, 1 H), 2.43 (s, 3 H), 2.16−2.09 (m, 1 H), 2.08−2.02 (m, 1 H), 2.02−1.92 (m, 2 H), 1.85−1.77 (m, 1 H), 1.77−1.67 (m, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 169.0, 145.0, 136.0, 129.5, 128.7, 51.5, 45.4, 31.8, 29.1, 25.5, 21.8. HRMS (HESI): *m/z* $[M + K]^+$ calcd for $C_{13}H_{16}BrNO_3S$ $+K^+$: 383.9666; found: 383.9682.

*4.1.8. 3-Bromo-1-((4-methoxyphenyl)sulfonyl)azepan-2-one (**2g**):*

Prepared following the **GP1** in 83 % yield (2.11 g) from 2.00 g of 1-((4-methoxyphenyl)sulfonyl)azepan-2-one.[5e] White solid: mp = 135 °C. TLC R_f = 0.56 (Cyclohexane/EtOAc 50 %); revelator: UV/$KMnO_4$. IR (neat): 2943, 1696, 1594, 1496, 1349, 1264, 1161, 1108, 1081, 1017, 904, 832, 803, 756, 715, 679, 648, 589, 547 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.91 (d, *J* = 9.0 Hz, 2 H), 6.97 (d, *J* = 9.0 Hz, 2 H), 4.70 (dd, *J* = 2.8, 7.4 Hz, 1 H), 4.32−4.24 (m, 1 H), 4.21−4.14 (m, 1 H), 3.87 (s, 3 H), 2.16−2.08 (m, 1 H), 2.08−2.01 (m, 1 H), 2.00−1.90 (m, 2 H), 1.84−1.76 (m, 1 H), 1.75−1.65 (m, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 168.9, 163.9, 131.0, 130.2, 114.0, 55.8, 51.6, 45.4, 31.9, 29.0, 25.6. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{16}BrNO_4S$ $+Na^+$: 383.9876; found: 383.9904.

*4.1.9. 3-Bromo-1-((4-nitrophenyl)sulfonyl)azepan-2-one (**2h**):*

Prepared following the **GP1** in 39 % yield (1.41 g) from 1.52 g of 1-((4-nitrophenyl)sulfonyl)azepan-2-one (see supplementary data) after recrystallization from Cyclohexane/EtOAc (3:1). Colorless crystals: mp = 155 °C. TLC R_f = 0.58 (Cyclohexane/EtOAc 50 %); revelator: UV/$KMnO_4$. IR (neat): 3108, 2922, 1717, 1606, 1527, 1351, 1314, 1174, 1143, 1104, 1085, 898, 857, 778, 741, 680, 663, 602, 541, 461 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.37 (d, *J* = 9.0 Hz, 2 H), 8.16 (d, *J* = 9.0 Hz, 2 H), 4.69 (dd, *J* = 2.6, 7.1 Hz, 1 H), 4.41−4.31 (m, 1 H), 4.25−4.15 (m, 1 H), 2.18−2.07 (m, 2 H), 2.07−1.95 (m, 2 H), 1.90−1.82 (m, 1 H), 1.79−1.68 (m, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 169.3, 150.7, 144.5, 130.0, 124.1, 51.0, 45.8, 31.5, 29.2, 25.4. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{13}BrN_2O_5S$ $+Na^+$: 398.9621; found: 398.9663.

*4.1.10. 3-Bromo-1-tosylazocan-2-one (**2i**):*

Prepared following the **GP1** in 96 % yield (896 mg) from 730 mg of 1-tosylazocan-2-one (see supplementary data) after purification by column chromatography (Cyclohexane/EtOAc 20 %). White solid: mp = 136 °C. TLC R_f = 0.32 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 3032, 2924, 2862, 1686, 1595, 1462, 1440, 1375, 1353, 1294, 1274, 1204, 1183, 1111, 1079, 1033, 1017, 877, 828, 811, 783, 705, 670, 647, 598, 557, 539, 476 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.92 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 4.86 (dd, *J* = 4.8, 11.6 Hz, 1 H), 4.53 (dt, *J* = 3.9, 16.3 Hz, 1 H), 3.75 (ddd, *J* = 2.9, 11.9, 16.3 Hz, 1 H), 2.43 (s, 3 H), 2.31−2.13 (m, 2 H), 2.04−1.93 (m, 1 H), 1.89−1.80 (m, 1 H), 1.67−1.45 (m, 4 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 169.6, 145.2, 135.7, 129.4, 129.3, 46.9, 46.5, 39.9, 31.2, 25.4, 24.1, 21.9. HRMS (HESI): *m/z* $[M + K]^+$ calcd for $C_{14}H_{18}BrNO_3S$ $+K^+$: 397.9822; found: 397.9848.

*4.1.11. tert-Butyl 3-bromo-2-oxopyrrolidine-1-carboxylate (**2j**):*

Prepared following the **GP1** in 53% yield (1.14 g) from 1.50 g of commercially available *tert*-butyl 2-oxopyrrolidine-1-carboxylate (CAS 85909-08-6) after purification by column chromatography (Cyclohexane/EtOAc 15 %). White solid: mp = 80 °C. TLC R_f = 0.33 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 2993, 2976, 1741, 1714, 1367, 1303, 1248, 1139, 942, 880, 845, 777, 613 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 4.43 (dd, *J* = 3.0, 6.9 Hz, 1 H), 3.87 (ddd, *J* = 6.6, 8.2, 10.9 Hz, 1 H), 3.84 (ddd, *J* = 3.0, 8.2, 10.9 Hz, 1 H), 2.54 (ddt, *J* = 6.6, 8.2, 14.4 Hz, 1 H), 2.27 (ddt, *J* = 3.0, 6.6, 14.4 Hz, 1 H), 1.54 (s, 9 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 169.3, 149.9, 83.9, 44.4, 44.3, 29.3, 28.0. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_9H_{14}BrNO_3$ $+Na^+$: 286.0049; found: 286.0017.

4.2. General Procedure 2 for conversion of 3-bromo-1-sulfonylpyrrolidin-, piperidin-, azepan- or azocan-2-ones (2) to 1-sulfonylazetidin-, pyrrolidin-, piperidin-2-carboxylic esters (3, 5 or 6) (GP2):

To a stirred solution of the appropriate 3-bromo-1-sulfonylpyrrolidin-, piperidin-, azepan- or azocan-2-one **2** (1 mmol) in MeCN (4.5 mL) were added 10 equivalents of the appropriate alcohol, phenol or aniline (see information for each compound) followed by K_2CO_3 (414 mg, 3 mmol or 207 mg, 1.5 mmol as specified for each compound). The heterogeneous mixture was stirred at 60 °C until completion of the reaction, as monitored by TLC. Filtration through a thin pad of silica gel (eluting with CH_2Cl_2 or MeCN when necessary) followed by concentration and drying under high vacuum (with warming at 50 °C if necessary) afforded the pure compound type **3**,**5** or **6**.

*4.2.1. Methyl 1-tosylazetidine-2-carboxylate (**3a**):*

Prepared following the **GP2** in 96 % yield (12.9 g) from 15.9 g of **2a** and 10 equiv of MeOH after 3 h at 60 °C or in 61 % yield (36.8 mg) from 81.5 mg of **2b** and 10 equiv of MeOH after 6 h stirring at 60 °C. Colorless needles: mp = 105 °C (CH_2Cl_2/hexanes). TLC R_f = 0.37 (Cyclohexane/EtOAc 50 %); revelator: UV/$KMnO_4$. IR (neat): 2953, 1718, 1593, 1432, 1332, 1285, 1202, 1155, 1082, 1047, 847, 680, 585, 548, 497 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.79 (d, *J* = 8.2 Hz, 2 H), 7.35 (d, *J* = 8.2 Hz, 2 H), 4.60 (dd, *J* = 7.9, 9.2 Hz, 1 H), 3.87 (dt, *J* = 7.8, 8.7 Hz, 1 H), 3.74 (ddd, *J* = 4.0, 7.8, 8.7 Hz, 1 H), 3.72 (s, 3 H), 2.45 (s, 3 H), 2.39 (dddd, *J* = 8.1, 8.2, 8.6, 11.4 Hz, 1 H), 2.28 (dddd, *J* = 4.0, 9.0, 9.2, 11.4 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 170.5, 144.3, 133.3, 129.7, 128.3, 60.6, 52.5, 47.8, 21.7, 19.6. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{12}H_{15}NO_4S$ $+Na^+$: 292.0614; found: 292.0587.

*4.2.2. Isopropyl 1-tosylazetidine-2-carboxylate (**3b**):*

Prepared following the **GP2** in 19 % yield (101 mg) from 579 mg of **2a** and 10 equiv of isopropanol, using 3 equiv of K_2CO_3 at 80 °C for 24 h, after purification by flash chromatography (from Cyclohexane/EtOAc 5 % to 40 %). White solid: mp = 95 °C. TLC R_f = 0.39 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 2984, 2935, 2895, 1739, 1597, 1524, 1450, 1377, 1344, 1243, 1195, 1159, 1089, 1049, 998, 948, 931,

906, 813, 802, 786, 710, 661, 600, 547, 497 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.79 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.2 Hz, 2 H), 5.02 (qq, *J* = 6.3, 6.3 Hz, 1 H), 4.57 (dd, *J* = 8.2, 8.7 Hz, 1 H), 3.90 (ddd, *J* = 7.5, 8.7, 8.7 Hz, 1 H), 3.72 (ddd, *J* = 4.2, 7.5, 8.7 Hz, 1 H), 2.44 (s, 3 H), 2.41−2.32 (m, 1 H), 2.32−2.24 (m, 1 H), 1.21 (d, *J* = 6.3 Hz, 3 H), 1.20 (d, *J* = 6.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 169.6, 144.3, 133.8, 129.8, 128.4, 69.3, 61.0, 47.8, 21.8, 19.6. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{19}NO_4S$ $+Na^+$: 320.0927; found: 320.0966.

*4.2.3. 1-Tosylazetidine-2-carboxylic acid (**3d**):*

Prepared following modified **GP2** in 96 % yield (75 mg) from 100 mg of **2a** in a mixture of $MeCN/H_2O$ after 16 h at 60 °C.[12] After completion of reaction, the solvents were removed in vacuo. The residue was then partitioned between EtOAc and HCl aqueous solution (1N). After extraction with EtOAc, the combined organic layers were dried over $MgSO_4$ concentrated and dried under high vacuum to afford the pure compound **3d**. White solid: mp = 137 °C. TLC R_f = 0.20 (EtOAc); revelator: UV/$KMnO_4$. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.74 (br, 1 H), 7.74 (d, *J* = 8.2 Hz, 2 H), 7.39 (d, *J* = 7.9 Hz, 2 H), 4.53 (dd, *J* = 7.8, 9.6 Hz, 1 H), 3.73 (dd, *J* = 6.6, 8.7 Hz, 2 H), 2.53−2.24 (m, 2 H), 2.46 (s, 3 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 173.1, 145.1, 131.2, 130.1, 128.5, 60.6, 47.8, 21.7, 19.8. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{13}NO_4S$ $+Na^+$: 278.0457; found: 278.0427.

*4.2.4. Phenyl 1-tosylazetidine-2-carboxylate (**3e**):*

Prepared following the **GP2** in 81 % yield (135 mg) from 156 mg of **2a** and 10 equiv of phenol after 2 h at 60 °C. The crude product was purified by flash chromatography (from Cyclohexane/EtOAc 10% to 40%). White solid: mp = 103−104 °C (CH_2Cl_2/hexanes). TLC R_f = 0.51 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 3054, 2920, 2868, 1742, 1598, 1586, 1497, 1479, 1451, 1362, 1346, 1291, 1251, 1184, 1161, 1119, 1083, 1007, 887, 808, 748, 691, 662, 616, 580, 541, 431 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.27 (d, *J* = 8.2 Hz, 2 H), 7.65 (d, *J* = 8.2 Hz, 2 H), 7.60–7.52 (m, 2 H), 7.34–7.19 (m, 3 H), 5.15 (dd, *J* = 8.2, 8.2 Hz, 1 H), 4.31 (ddd, *J* = 3.4, 8.2, 10.2 Hz, 1 H), 4.16 (ddd, *J* = 7.4, 8.2, 10.2 Hz, 1 H), 2.87 (dddd, *J* = 3.5, 7.4, 7.5, 13.2 Hz, 1 H), 2.75 (s, 3 H), 2.50 (dddd, *J* = 8.2, 8.2, 8.2, 13.2 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 169.8, 157.5, 145.7, 134.9, 130.0, 129.7, 128.3, 122.5, 116.2, 75.6, 43.5, 26.7, 21.9. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{17}NO_4S$ $+Na^+$: 354.0770; found: 354.0776.

*4.2.5. N-(4-Methoxyphenyl)-1-tosylazetidine-2-carboxamide (**3f**):*

Prepared following the **GP2** in 90 % yield (240 mg) from 156 mg of **2a** and 10 equiv of *p*-anisidine after 16 h at 60 °C. The crude product was dissolved in EtOAc, washed with 1N aqueous HCl, brine and dried over $MgSO_4$. Evaporation of the solvent yielded the pure product. White solid: mp = 160−162 °C. TLC R_f = 0.30 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 3355, 2960, 2916, 2839, 1728, 1598, 1514, 1447, 1339, 1275, 1227, 1155, 1119, 1087, 1027, 996, 908, 830, 809, 754, 657, 583, 546, 494 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.94 (d, *J* = 8.2 Hz, 2 H), 7.35 (d, *J* = 8.2 Hz, 2 H), 6.75 (d, *J* = 9.0 Hz, 2 H), 6.56 (d, *J* = 9.0 Hz, 2 H), 4.04−3.97 (m, 1 H), 3.94 (dd, *J* = 7.9, 11.0 Hz, 1 H), 3.82−3.75 (m, 1 H), 3.72 (s, 3 H), 2.68 (dddd, *J* = 1.3, 6.3, 7.8, 12.6 Hz, 1 H), 2.44 (s, 3 H), 1.91 (dddd, *J* = 8.9, 10.8, 10.8, 12.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 172.4, 153.4, 145.8, 140.6, 135.0, 130.0, 128.3, 115.5, 115.0, 57.1, 55.9, 44.0, 29.1, 21.9. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{20}N_2O_4S$ $+Na^+$: 383.1036; found: 383.1026.

*4.2.6. Methyl 1-((4-nitrophenyl)sulfonyl)azetidine-2-carboxylate (**3i**):*

Prepared following the **GP2** in 98 % yield (288 mg) from 350 mg of **2c** and 10 equiv of MeOH after 3 h stirring at 60 °C. Colorless crystals: mp = 129 °C (CH_2Cl_2/hexanes). TLC R_f = 0.30 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 3107, 2979, 2958, 1744, 1607, 1542, 1441, 1348, 1303, 1238, 1161, 1092, 1045, 1010, 906, 857, 802, 738, 684, 628, 583, 466 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.38 (d, *J* = 8.9 Hz, 2 H), 8.13 (d, *J* = 8.9 Hz, 2 H), 4.89 (dd, *J* = 7.7, 9.4 Hz, 1 H), 4.13 (ddd, *J* = 7.8, 7.8, 9.0 Hz, 1 H), 3.77 (ddd, *J* = 4.5, 7.5, 9.0 Hz, 1 H), 3.72 (s, 3 H), 2.48 (dddd, *J* = 4.5, 9.0, 9.4, 11.3 Hz, 1 H), 2.42 (dddd, *J* = 7.7, 8.6, 9.0, 11.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 170.4, 150.3, 144.2, 129.2, 124.2, 60.9, 52.6, 48.1, 19.4. HRMS (HESI): *m/z* $[M + Li]^+$ calcd for $C_{11}H_{12}N_2O_7S$ $+Li^+$: 323.0323; found: 323.0323.

*4.2.7. Methyl 1-((2-(trimethylsilyl)ethyl)sulfonyl)azetidine-2-carboxylate (**3j**):*

Prepared following the **GP2** in 85 % yield (36 mg) from 50 mg of **2d** and 10 equiv of MeOH after 3 h at 60 °C. Colorless oil. TLC R_f = 0.51 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 2954, 2900, 1746, 1438, 1421, 1326, 1285, 1248, 1212, 1169, 1138, 1074, 1024, 939, 894, 860, 831, 800, 746, 700, 639, 544 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 4.86 (dd, *J* = 9.5, 8.1 Hz, 1 H), 4.17 (td, *J* = 8.8, 7.5 Hz, 1 H), 3.73 (s, 3 H), 3.59 (ddd, *J* = 8.6, 7.4, 4.3 Hz, 1 H), 3.01 (qdd, *J* = 14.1, 12.0, 5.4 Hz, 2 H), 2.49–2.34 (m, 2 H), 1.10–0.95 (m, 2 H), 0.02 (s, 9 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 171.4, 60.2, 52.5, 49.9, 47.1, 19.5, 9.9, -1.8. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{29}NO_4SSi$ $+Na^+$: 279.0961; found: 279.0959.

*4.2.8. Methyl N-tosyl-L-prolinate (**5k**):*

Prepared following the **GP2** in 98 % yield (77.8 mg) from 92.7 mg of **2e** and 10 equiv of MeOH in 4 h at 60 °C. White solid: mp = 79 °C. TLC R_f = 0.14 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.75 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.3 Hz, 2 H), 4.30 (dd, *J* = 4.4, 7.9 Hz, 1 H), 3.71 (s, 3 H), 3.50−3.44 (m, 1 H), 3.35−3.28 (m, 1 H), 2.42 (s, 3 H), 2.08−1.89 (m, 3 H), 1.82−1.70 (m, 1 H); consistent with literature data.[5e] ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 172.7, 143.8, 135.4, 129.8, 127.7, 60.5, 52.5, 48.6, 31.0, 24.8, 21.7; consistent with literature data.[5e]

*4.2.9. Ethyl N-tosylprolinate (**5l**):*

Prepared following the **GP2** in 94 % yield (77 mg) from 91 mg of **2e** and 10 equiv of ethanol after 6 h at 60 °C. Pale yellow solid: mp = 83-85 °C. TLC R_f = 0.19 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 3283, 2983, 2958, 2904, 2871, 2177, 2075, 1975, 1744, 1596, 1495, 1476, 1454, 1401, 1380, 1338, 1312, 1292, 1239, 1201, 1181, 1154, 1136, 1091, 1066, 1023, 1008, 934, 920, 886, 851, 818, 758, 709, 660, 635, 590, 543, 493, 429 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): *δ* = 7.78–7.73 (m, 2 H), 7.30 (d, *J* = 7.9 Hz, 2 H), 4.30–4.26 (m, 1 H), 4.21–4.10 (m, 2 H), 3.50–3.44 (m, 1 H), 3.31 (dt, *J* = 9.6, 7.0 Hz, 1 H), 2.42 (s, 3 H), 2.07–1.90 (m, 3 H), 1.79–1.71 (m, 1 H), 1.25 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 126 MHz): *δ* = 172.2, 143.6, 135.5, 129.7, 127.6, 61.4, 60.6, 48.5, 31.1, 24.7, 21.7, 14.2. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{19}O_4NS$ $+Na^+$: 320.0927; found 320.0927.

*4.2.10. Benzyl N-tosylprolinate (**5m**):*

Prepared following the **GP2** in 98 % yield (98 mg) from 92 mg of **2e** and 10 equiv of benzyl alcohol after 6 h at 60 °C and purification by bulb-to-bulb distillation. Yellow oil. TLC R_f = 0.16 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR

(neat): 3033, 2957, 2924, 2086, 2019, 1746, 1597, 1496, 1454, 1383, 1339, 1304, 1276, 1153, 1091, 1011, 912, 847, 815, 781, 733, 697, 661, 587, 545, 490, 435 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.77–7.72 (m, 2 H), 7.39–7.31 (m, 5 H), 7.28 (d, *J* = 8.1 Hz, 2 H), 5.19–5.11 (m, 2 H), 4.37 (dd, *J* = 8.4, 3.9 Hz, 1 H), 3.50–3.44 (m, 1 H), 3.33 (dt, *J* = 9.3, 7.1 Hz, 1 H), 2.41 (s, 3 H), 2.09–1.88 (m, 3 H), 1.76 (dtt, *J* = 9.7, 7.5, 5.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 172.1, 143.7, 135.7, 135.5, 129.8 , 128.7, 128.5, 128.2, 127.7, 67.1, 60.6, 48.5, 31.1, 24.8, 21.7. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{21}O_4NS$ $+Na^+$: 382.1083; found 382.1064.

*4.2.11. 3-Phenylprop-2-yn-1-yl N-tosylprolinate (**5n**):*

Prepared following the **GP2** in 99 % yield (116 mg) from 101 mg of **2e** and 10 equiv of 3-phenylprop-2-yn-1-ol after 5 h at 60 °C and purification by bulb-to-bulb distillation. Yellow oil. TLC R_f = 0.29 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 3060, 2954, 2875, 2225, 1752, 1597, 1571, 1443, 1380, 1338, 1305, 1268, 1153, 1092, 1070, 1024, 1005, 991, 954, 918, 848, 815, 757, 734, 706, 691, 662, 590, 545, 525, 426 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.80–7.76 (m, 2 H), 7.48–7.43 (m, 2 H), 7.37–7.28 (m, 5 H), 4.94 (d, *J* = 1.0 Hz, 2 H), 4.39 (dd, *J* = 8.0, 4.5 Hz, 1 H), 3.49 (ddd, *J* = 9.6, 7.4, 4.7 Hz, 1 H), 3.34 (dt, *J* = 9.6, 7.2 Hz, 1 H), 2.41 (s, 3 H), 2.12–1.94 (m, 3 H), 1.84–1.75 (m, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.6, 143.8, 135.4, 132.0, 129.8, 129.0, 128.5, 127.7, 122.2, 87.0, 82.6, 60.4, 53.8, 48.5, 31.0, 24.8, 21.7. HRMS (HESI): *m/z* $[M + K]^+$ calcd for $C_{21}H_{21}O_4NS$ $+K^+$: 422.0823; found 422.0837.

*4.2.12. Methyl 1-tosylpiperidine-2-carboxylate (**6o**):*

Prepared following the **GP2** in 99 % yield (10.1 g) from 10.6 g of **2f** in 3 h at 60 °C. White solid: mp = 70 °C. TLC R_f = 0.39 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 3036, 2984, 2947, 2857, 1727, 1595, 1493, 1448, 1431, 1336, 1283, 1243, 1218, 1181, 1152, 1127, 1107, 1092, 1057, 989, 939, 925, 841, 810, 733, 659, 584, 562, 537, 509 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.67 (d, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 4.75 (dd, *J* = 2.3, 6.0 Hz, 1 H), 3.76 (ddd, *J* = 2.4, 3.0, 12.5 Hz, 1 H), 3.54 (s, 3 H), 3.21 (ddd, *J* = 3.0, 12.5, 12.5 Hz, 1 H), 2.42 (s, 3 H), 2.11 (ddddd, *J* = 2.5, 2.5, 2.5, 2.5, 13.6 Hz, 1 H), 1.74 (dddd, *J* = 3.3, 5.8, 13.3, 13.6 Hz, 1 H), 1.69−1.60 (m, 2 H), 1.45 (ddddd, *J* = 3.7, 4.7, 13.0, 13.0, 13.5 Hz, 1 H), 1.28 (ddddd, *J* = 3.7, 3.7, 12.9, 13.7, 13.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 171.3, 143.2, 137.0, 129.5, 127.3, 55.1, 52.1, 42.7, 27.9, 24.7, 21.6, 20.1. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{19}NO_4S$ $+Na^+$: 320.0927; found: 320.0937.

*4.2.13. Methyl 1-((4-methoxyphenyl)sulfonyl)piperidine-2-carboxylate (**6p**):*

Prepared following the **GP2** in 93 % yield (1.60 g) from 1.99 g of **2g** in 4 h at 60 °C. White solid: mp = 87 °C. TLC R_f = 0.39 (Cyclohexane/EtOAc 40 %); revelator: UV/$KMnO_4$. IR (neat): 2945, 1728, 1594, 1498, 1440, 1338, 1297, 1261, 1155, 1109, 1093, 1053, 1026, 987, 921, 832, 803, 755, 700, 584, 559, 488 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.71 (d, *J* = 8.9 Hz, 2 H), 6.94 (d, *J* = 8.9 Hz, 2 H), 4.72 (dd, *J* = 2.0, 5.4 Hz, 1 H), 3.85 (s, 3 H), 3.72 (ddd, *J* = 2.9, 3.9, 12.7 Hz, 1 H), 3.55 (s, 3 H), 3.19 (ddd, *J* = 2.9, 12.7, 12.7 Hz, 1 H), 2.14−2.06 (m, 1 H), 1.78−1.68 (m, 1 H), 1.68−1.58 (m, 1 H), 1.52−1.41 (m, 2 H), 1.33−1.21 (m, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 171.4, 162.8, 131.7, 129.4, 114.0, 55.7, 55.1, 52.1, 42.6, 27.9, 24.8, 20.2. HRMS (HESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{19}NO_5S$ $+H^+$: 314.1057; found: 314.1059.

*4.2.14. Methyl 1-((4-nitrophenyl)sulfonyl)piperidine-2-carboxylate (**6q**):*

Prepared following the **GP2** in 85 % yield (547 mg) from 735 mg of **2h** in 2 h at 60 °C. White solid: mp = 126 °C. TLC R_f = 0.60 (Pentane/Et_2O 50 %); revelator: UV/$KMnO_4$. IR (neat): 2953, 1737, 1605, 1528, 1443, 1341, 1277, 1241, 1156, 1090, 1056, 990, 943, 841, 742, 684, 609, 577, 462 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 8.33 (d, *J* = 8.9 Hz, 2 H), 7.96 (d, *J* = 8.9 Hz, 2 H), 4.80 (dd, *J* = 1.7, 5.1 Hz, 1 H), 3.82 (ddd, *J* = 2.3, 3.0, 12.0 Hz, 1 H), 3.56 (s, 3 H), 3.14 (td, *J* = 3.0, 12.7 Hz, 1 H), 2.24−2.17 (m, 1 H), 1.84−1.76 (m, 1 H), 1.75−1.67 (m, 1 H), 1.61−1.50 (m, 2 H), 1.31−1.19 (m, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 170.8, 150.0, 145.8, 128.5, 124.2, 55.6, 52.4, 43.1, 28.1, 25.0, 20.2. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{13}H_{16}N_2O_6S$ $+Na^+$: 351.0621; found: 351.0654.

*4.2.15. Butyl 1-tosylpiperidine-2-carboxylate (**6r**):*

Prepared following the **GP2** in 86 % yield (137 mg) from 162 mg of **2f** and 10 equiv of butanol after 6 h at 60 °C and purification by flash chromatography (from Cyclohexane/EtOAc 10%). Colorless oil. TLC R_f = 0.36 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 3308, 2956, 2868, 2203, 2147, 2019, 1732, 1597, 1495, 1453, 1378, 1337, 1303, 1245, 1175, 1154, 1110, 1092, 1056, 1036, 1018, 959, 932, 919, 885, 870, 842, 814, 726, 654, 582, 544, 509, 476, 415, cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.69–7.65 (m, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 4.77–4.71 (m, 1 H), 3.99 (dt, *J* = 10.8, 6.7 Hz, 1 H), 3.90 (dt, *J* = 10.8, 6.7 Hz, 1 H), 3.76 (dddt, *J* = 12.6, 4.8, 2.4, 1.2 Hz, 1 H), 3.21 (td, *J* = 12.7, 3.0 Hz, 1 H), 2.41 (s, 3 H), 2.12 (dtt, *J* = 13.6, 3.5, 1.8 Hz, 1 H), 1.75 (tdd, *J* = 13.7, 6.0, 3.7 Hz, 1 H), 1.69–1.59 (m, 2 H), 1.54–1.43 (m, 2 H), 1.36–1.22 (m, 4 H), 0.91 (t, *J* = 7.4 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 171.0, 143.2, 137.3, 129.5, 127.4, 65.1, 55.2, 42.7, 30.6, 28.1, 24.9, 21.7, 20.2, 19.2, 13.8. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{25}O_4NS$ $+Na^+$: 362.1397; found 362.1419.

*4.2.16. Allyl 1-tosylpiperidine-2-carboxylate (**6s**):*

Prepared following the **GP2** in 83 % yield (117 mg) from 152 mg of **2f** and 10 equiv of allyl alcohol after 18 h at 60 °C and purification by flash chromatography (from Cyclohexane/EtOAc 5% to 20%). Colorless oil. TLC R_f = 0.22 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 2942, 2860, 2069, 1739, 1649, 1597, 1494, 1446, 1380, 1337, 1302, 1242, 1171, 1153, 1130, 1110, 1092, 1055, 1036, 1018, 982, 944, 873, 840, 814, 728, 654, 580, 547, 507, 476, 413 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.72–7.61 (m, 2 H), 7.32–7.22 (m, 2 H), 5.85–5.72 (m, 1 H), 5.30–5.16 (m, 2 H), 4.77 (dd, *J* = 6.1, 2.4 Hz, 1 H), 4.48 (ddt, *J* = 13.0, 5.7, 1.4 Hz, 1 H), 4.40 (ddt, *J* = 13.1, 5.8, 1.5 Hz, 1 H), 3.81–3.69 (m, 1 H), 3.22 (td, *J* = 12.8, 3.0 Hz, 1 H), 2.41 (s, 3 H), 2.16–2.09 (m, 1 H), 1.75 (tdd, *J* = 13.7, 6.0, 3.6 Hz, 1 H), 1.70–1.59 (m, 2 H), 1.47 (tdd, *J* = 14.3, 10.9, 7.5 Hz, 1 H), 1.30 (tt, *J* = 13.6, 3.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 170.6, 143.2, 137.2, 131.7, 129.6, 127.4, 118.8, 65.7, 55.1, 42.7, 28.0, 24.8, 21.7, 20.2. HRMS (HESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{21}O_4NS$ $+H^+$: 324.1264; found 324.1266.

*4.2.17. Benzyl 1-tosylpiperidine-2-carboxylate (**6t**):*

Prepared following the **GP2** in 97 % yield (106 mg) from 101 mg of **2f** and 10 equiv of benzyl alcohol after 6 h at 60 °C and purification by bulb-to-bulb distillation. Yellowish oil. TLC R_f = 0.38 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 3032, 2944, 2860, 1990, 1739, 1597, 1496, 1454, 1375, 1337, 1302, 1261, 1241, 1184, 1154, 1109, 1091, 1055, 1035, 1018, 965, 943, 919, 862, 813, 726, 696, 654, 578, 543, 507, 475 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ = 7.67–7.61 (m, 2 H), 7.39–7.30 (m, 3 H), 7.26–7.23 (m, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 5.05 (d, *J* = 12.2 Hz, 1 H), 4.93 (d, *J* = 12.2 Hz, 1 H), 4.82–4.77 (m, 1

H), 3.79–3.71 (m, 1 H), 3.21 (td, *J* = 12.8, 3.0 Hz, 1 H), 2.40 (s, 3 H), 2.17–2.10 (m, 1 H), 1.76 (tdd, *J* = 13.7, 6.0, 3.6 Hz, 1 H), 1.63 (ddq, *J* = 16.5, 11.0, 3.5 Hz, 2 H), 1.54–1.42 (m, 1 H), 1.30–1.18 (m, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 170.8, 143.2, 137.1, 135.6, 129.5, 128.7, 128.5, 128.2, 127.4, 66.9, 55.2, 42.7, 28.0, 24.8, 21.7, 20.2. HRMS (HESI): *m/z* $[M + K]^+$ calcd for $C_{20}H_{23}O_4NS + K^+$: 412.0943; found 412.0943.

*4.2.18. Phenyl 1-tosylpiperidine-2-carboxylate (**6u**):*

Prepared following the **GP2** in 9 % yield (14 mg) from 136 mg of **2f** and 10 equiv of phenol after 18 h at 60 °C and purification by bulb-to-bulb distillation. White solid: mp = 60-62 °C. TLC R_f = 0.23 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 3065, 2944, 2859, 1994, 1955, 1763, 1591, 1491, 1454, 1401, 1379, 1337, 1303, 1261, 1238, 1186, 1153, 1108, 1091, 1070, 1053, 1034, 1018, 955, 930, 919, 873, 846, 814, 783, 745, 724, 688, 654, 589, 575, 543, 512, 494, 476, 414 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.75–7.70 (m, 2 H), 7.37–7.31 (m, 2 H), 7.25 (d, *J* = 6.4 Hz, 2 H), 7.23–7.19 (m, 1 H), 6.94–6.90 (m, 2 H), 4.98 (dd, *J* = 6.0, 2.3 Hz, 1 H), 3.81 (dddt, *J* = 12.9, 5.1, 2.6, 1.2 Hz, 1 H), 3.32 (td, *J* = 12.6, 3.1 Hz, 1 H), 2.38 (s, 3 H), 2.35–2.27 (m, 1 H), 1.89 (tdd, *J* = 13.6, 6.0, 3.7 Hz, 1 H), 1.80–1.74 (m, 1 H), 1.73–1.67 (m, 1 H), 1.62–1.51 (m, 1 H), 1.44 (qt, *J* = 13.3, 3.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 169.5, 150.3, 143.4, 137.1, 129.7, 129.5, 127.4, 126.2, 121.3, 55.2, 42.8, 28.1, 24.9, 21.6, 20.3. HRMS (HESI): *m/z* $[M + Na]^+$ calcd for $C_{19}H_{21}O_4NS + Na^+$: 382.1083; found 382.1090.

*4.2.19. N-(4-Methoxyphenyl)-1-tosylpiperidine-2-carboxamide (**6v**):*

Prepared following the **GP2** in 57 % yield (111 mg) from 176 mg of **2f** and 10 equiv of *p*-anisidine after 48 h at 60 °C and purification by flash chromatography (from Cyclohexane/EtOAc 5% to 30%). Brown solid: mp = 57-60 °C. TLC R_f = 0.15 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 3384, 2932, 2856, 2832, 2257, 2104, 2019, 1925, 1696, 1595, 1510, 1454, 1382, 1344, 1324, 1307, 1293, 1232, 1185, 1161, 1139, 1109, 1076, 1032, 975, 949, 907, 869, 813, 762, 717, 705, 691, 665, 621, 593, 574, 542, 438, 413 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.92–7.87 (m, 2 H), 7.34–7.28 (m, 2 H), 6.77–6.70 (m, 2 H), 6.45–6.39 (m, 2 H), 4.75–4.66 (m, 1 H), 4.55 (s, 1 H), 4.09 (d, *J* = 10.5 Hz, 1 H), 3.72 (s, 3 H), 3.53 (dd, *J* = 15.8, 11.4 Hz, 1 H), 2.42 (s, 3 H), 2.11–1.96 (m, 3 H), 1.86–1.75 (m, 1 H), 1.72–1.61 (m, 1 H), 1.52 (dddd, *J* = 13.2, 12.0, 10.6, 2.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 174.0, 152.4, 145.0, 140.0, 136.3, 129.5, 128.6, 115.2, 114.4, 58.2, 55.9, 45.9, 31.4, 28.8, 27.4, 21.8. HRMS (HESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{24}O_4N_2S + H^+$: 389.1530; found 389.1488.

*4.2.20. Methyl 2-(1-tosylpiperidin-2-yl)acetate (**8w**):*

Obtained by following the **GP2** in 26 % yield (52.7 mg) from 236 mg of **2i** in 16 h. Colorless oil. TLC R_f = 0.23 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 2945, 2864, 1733, 1598, 1438, 1384, 1354, 1336, 1287, 1264, 1217, 1151, 1092, 928, 814, 732, 710, 694, 650, 589, 548 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.70 (d, *J* = 8.2 Hz, 2 H), 7.27 (d, *J* = 8.2 Hz, 2 H), 4.52 (dddd, *J* = 2.5, 2.5, 5.6, 9.3 Hz, 1 H), 3.79 (ddd, *J* = 2.2, 4.4, 13.8 Hz, 1 H), 3.63 (s, 3 H), 2.93 (ddd, *J* = 2.2, 12.9, 13.8 Hz, 1 H), 2.62 (dd, *J* = 9.3, 14.9 Hz, 1 H), 2.50 (dd, *J* = 5.6, 14.9 Hz, 1 H), 2.41 (s, 3 H), 1.58−1.45 (m, 5 H), 1.37−1.25 (m, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 171.4, 143.2, 138.2, 129.8, 127.1, 52.0, 49.8, 41.1, 35.0, 27.8, 24.7, 21.6, 18.4. HRMS (HESI): *m/z* $[M + K]^+$ calcd for $C_{15}H_{21}NO_4S + K^+$: 350.0823; found: 350.0807.

*4.2.21. Methyl 2-bromo-7-((4-methylphenyl)sulfonamido)heptanoate (**4w**):*

Obtained by following the **GP2** in 34 % yield (86.2 mg) from 236 mg of **2i** in 16 h. Colorless oil. TLC R_f = 0.19 (Cyclohexane/EtOAc 30 %); revelator: UV/$KMnO_4$. IR (neat): 3285, 2938, 2862, 1738, 1598, 1495, 1435, 1323, 1305, 1288, 1152, 1092, 1019, 911, 814, 730, 660, 571, 549 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.74 (d, *J* = 8.2 Hz, 2 H), 7.31 (d, *J* = 8.2 Hz, 2 H), 4.59−4.54 (m, 1 H), 4.16 (dd, *J* = 6.4, 7.9 Hz, 1 H), 3.77 (s, 3 H), 2.92 (ddd, *J* = 6.8, 6.8, 6.8 Hz, 2 H), 2.43 (s, 3 H), 2.05−1.85 (m, 2 H), 1.49−1.43 (m, 2 H), 1.43−1.35 (m, 1 H), 1.34−1.25 (m, 3 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 170.4, 143.6, 137.0, 129.9, 127.2, 53.1, 45.5, 43.0, 34.7, 29.4, 26.8, 25.8, 21.7. HRMS (HESI): *m/z* $[M + K]^+$ calcd for $C_{15}H_{22}BrNO_4S + K^+$: 430.0084; found: 430.0032.

*4.2.22. Methyl 2-bromo-4-((tert-butoxycarbonyl)amino)butanoate (**4j**):*

Obtained quantitatively by following the **GP2** after 3 h at 45 °C from **2j**. Colorless oil. TLC R_f = 0.59 (Cyclohexane/EtOAc 50 %); revelator: UV/$KMnO_4$. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.64 (br, 1 H), 4.31 (dd, *J* = 8.3, 6.1 Hz, 1 H), 3.79 (s, 3 H), 3.40–3.17 (m, 2 H), 2.32 (dq, *J* = 13.6, 6.7 Hz, 1 H), 2.14 (ddt, *J* = 14.5, 8.3, 6.0 Hz, 1 H), 1.44 (s, 9 H).

*4.2.23. 1-((2-(Trimethylsilyl)ethyl)sulfonyl)azetidine-2-carboxylic acid (**3z**):*

Prepared following the modified **GP2** in 91 % yield (37 mg) from 50 mg of **2d** in a mixture of MeCN/H_2O after 16 h at 60 °C.[13] After completion of the reaction, the solvents were removed in vacuo. The residue was then partitioned between EtOAc and HCl aqueous solution (1N). After extraction with EtOAc, the combined organic layers were dried over $MgSO_4$, concentrated and dried under high vacuum to afford the pure compound **3z**. White solid: mp = 76 °C TLC R_f = 0.36 (EtOAc/MeOH 50 %); revelator: UV/$KMnO_4$. IR (neat): 3544, 3456, 3406, 2953, 2898, 1723, 1634, 1613, 1591, 1551, 1420, 1327, 1247, 1136, 1110, 1092, 944, 895, 859, 831, 755, 738, 701, 671, 630, 591, 549, 521 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.85 (br, 1 H), 4.78 (t, *J* = 8.7 Hz, 1 H), 3.99 (q, *J* = 8.2 Hz, 1 H), 3.66 (td, *J* = 7.6, 4.8 Hz, 1 H), 3.00 (qdd, *J* = 14.0, 10.1, 7.3 Hz, 2 H), 2.49–2.37 (m, 2 H), 1.00 (tt, *J* = 10.2, 7.6 Hz, 2 H), 0.02 (s, 9 H). ^{13}C NMR ($CDCl_3$, 500 MHz): δ = 178.5, 63.2, 49.6, 49.4, 21.9, 11.4, 0.0. HRMS (HESI): *m/z* $[M + K]^+$ calcd for $C_9H_{19}NO_4SSi + K^+$: 304.0436; found: 304.0449.

4.3. Preparation of 2-carboxylated aza-ring derivatives by two-step sequence using anionic Weinreb amine.

*4.3.1. N-methoxy-N-methyl 2-bromo-4-((4-methylphenyl)sulfonamido)butanamide (**4g**):*

To a stirred solution of *N,O*-dimethylhydroxylamine hydrochloride salt (1.4 mmol) in dry THF (2 mL) was added isopropyl magnesium chloride (2.83 mmol) at -20 °C. After stirring for 15 min, the mixture was transferred via cannula to a cold solution (-40 °C) of **2a** (300 mg, 0.94 mmol) in dry THF (8 mL). The resulting mixture was then warmed to 0 °C and stirred for 1.5 h at this temperature. The reaction mixture was quenched with an aqueous solution of NH_4Cl (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (Cyclohexane/EtOAc 40%) to afford **4g** (290 mg) in 82 % yield. Colorless oil. TLC R_f = 0.22 (Cyclohexane/EtOAc 50 %); revelator: UV/$KMnO_4$. IR (neat): 3251, 2939, 2873, 1645, 1422, 1324, 1154, 1092, 990, 660, 549 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500

MHz): δ = 7.72 (d, *J* = 8.2 Hz, 2 H), 7.30 (d, *J* = 8.2 Hz, 2 H), 5.03 (dd, *J* = 5.8, 5.9 Hz, 1 H), 4.93 (dd, *J* = 6.8, 6.9 Hz, 1 H), 3.81 (s, 3 H), 3.25−3.20 (bs, 3 H), 3.06 (dt, *J* = 5.8, 6.9 Hz, 1 H), 2.42 (s, 3 H), 2.31 (ddt, *J* = 5.9, 7.0, 14.7 Hz, 1 H), 2.15 (ddt, *J* = 5.8, 6.8, 14.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ = 169.6, 143.6, 136.5, 129.8, 127.1, 61.8, 41.1, 39.1, 34.1, 32.6, 21.6. HRMS (HESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{19}BrN_2O_4S$ +Na^+: 401.0141; found: 401.0151.

*4.3.2. N-Methoxy-N-methyl 1-tosylazetidine-2-carboxamide (**3g**):*

To a stirred solution of **4g** (300 mg, 0.79 mmol) in MeCN (4 mL) was added K_2CO_3 (2.37 mmol). The heterogeneous mixture was refluxed until completion of the reaction, as monitored by TLC. Filtration through a thin pad of silica gel (eluting with MeCN) followed by concentration and drying under high vacuum afforded the pure compound **3g** (120 mg) in 60% yield. White solid: mp = 97 °C. TLC R_f = 0.12 (Cyclohexane/EtOAc 50 %); revelator: UV/$KMnO_4$. IR (neat): 2992, 2975, 2951, 2885, 1667, 1599, 1434, 1339, 1155, 1093, 1035, 997, 972, 866, 811, 703, 666, 545 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.84 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 5.15 (dd, *J* = 8.0, 9.0 Hz, 1 H), 3.99 (ddd, *J* = 7.4, 7.4, 8.6 Hz, 1 H), 3.72 (s, 3 H), 3.73−3.65 (m, 1 H), 3.19 (s, 3 H), 2.43 (s, 3 H), 2.40−2.27 (m, 2 H). ^{13}C NMR ($CDCl_3$, 500 MHz): δ = 170.3, 143.9, 134.6, 129.6, 128.2, 61.4, 59.6, 47.8, 32.5, 21.7, 19.8. HRMS (HESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}N_2O_4S$ +Na^+: 321.0879; found: 321.0885.

*4.3.3. N-methoxy-N-methyl 2-bromo-4-((4-methoxyphenyl)sulfonamido)butanamide (**4h**):*

To a stirred solution of *N*,*O*-dimethylhydroxylamine hydrochloride salt (9.28 mmol) in dry THF (10 mL) was added isopropyl magnesium chloride (17.94 mmol) at -20 °C. After stirring for 15 min, the mixture was transferred via cannula to a cold solution (-40 °C) of **2c** (2.00 g, 5.98 mmol) in dry THF (20 mL). The resulting mixture was then warmed to 0 °C and stirred for 2 h at this temperature. The reaction was quenched with aqueous NH_4Cl (30 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (Cyclohexane/EtOAc 20 to 50%) to afford **4h** (920 mg) in 39 % yield. Colorless oil. TLC R_f = 0.29 (Cyclohexane/EtOAc 50 %); revelator: UV/$KMnO_4$. IR (neat): 3570, 3250, 2941, 2842, 1646, 1595, 1578, 1497, 1459, 1440, 1391, 1324, 1302, 1257, 1148, 1111, 1093, 1022, 989, 940, 833, 802, 768, 666, 628, 556, 486 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.78 (d, *J* = 9.0 Hz, 2 H), 6.98 (d, *J* = 9.0 Hz, 2 H), 4.93 (dd, *J* = 7.0, 7.0 Hz, 1 H), 4.78 (dd, *J* = 6.3, 6.3 Hz, 1 H), 3.87 (s, 3 H), 3.82 (s, 3 H), 3.23 (s, 3 H), 3.10−3.03 (m, 2 H), 2.31 (dtd, *J* = 5.9, 7.4, 14.6 Hz, 1 H), 2.15 (ddt, *J* = 5.7, 7.1, 14.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 500 MHz): δ = 169.6, 163.0, 131.0, 129.3, 114.4, 61.8, 55.7, 41.1, 39.1, 34.0, 32.6. HRMS (HESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{19}BrN_2O_5S$ +H^+: 395.0271; found: 395.0273.

*4.3.4. N-Methoxy-N-methyl 1-((4-methoxyphenyl)sulfonyl)azetidine-2-carboxamide (**3h**):*

To a stirred solution of **4h** (920 mg, 2.33 mmol) in MeCN (11 mL) was added K_2CO_3 (6.99 mmol). The heterogeneous mixture was refluxed until completion of the reaction, as monitored by TLC. Filtration through a thin pad of silica gel (eluting with MeCN) followed by concentration and drying under high vacuum afforded the pure compound **3h** (630 mg) in 86% yield. Colorless crystals: mp = 78 °C. TLC R_f = 0.09 (Cyclohexane/EtOAc 50 %); revelator: UV/$KMnO_4$. IR (neat): 2972, 2943, 2897, 2842, 1672, 1594, 1497, 1461, 1442, 1341, 1303, 1258, 1151, 1093, 1025, 997, 837, 803, 674, 606, 559 cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.90 (d, *J* = 8.9 Hz, 2 H), 6.99 (d, *J* = 8.9 Hz, 2 H), 5.14 (dd, *J* = 8.3, 8.3 Hz, 1 H), 3.98 (ddd, *J* = 8.0, 8.2, 8.6 Hz, 1 H), 3.86 (s, 3 H), 3.71 (s, 3 H), 3.65 (ddd, *J* = 4.8, 7.8, 8.0 Hz, 1 H), 3.17 (s, 3 H), 2.26−2.38 (m, 2 H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.3, 163.3, 130.3, 129.2, 114.1, 61.7, 59.5, 55.6, 47.7, 32.5, 19.8. HRMS (HESI): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{18}N_2O_5S$ +Na^+: 337.0829; found: 337.0248.

*(±)-Azetidine-2-carboxylic acid (**(±)-AZE**):*[13]

To a stirred solution of **3z** (30 mg, 0.113 mmol) in dry DMF (2 mL) was added cesium fluoride (0.34 mmol). The mixture was stirred at 95 °C for 48 h. The solvent was removed in vacuo. The solid residue was extracted with $CHCl_3$ (3 x 1 mL). The combined organic layers were concentrated in vacuo. The residue was purified by flash chromatography (MeOH/EtOAc 20 to 50%) to afford **(±)-AZE** (6 mg) in 52 % yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.90 (dd, *J* = 9.3, 5.7 Hz, 1 H), 1.49−1.43 (m, 2 H), 2.60−2.72 (m, 1 H), 2.49−2.33 (m, 1 H).

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at …

References and notes

1. (a) Takemoto, T., Nomoto, K., Fushiya, S., Ouchi, R., Kusano, G., Hikino, H., Takagi, S., Matsuura, Y.; Kakudo, M. *Proc. Jpn. Acad.* **1978**, *54*B, 469. (b) Nomoto, K., Yoshioka, H., Arima, M., Fushiya, S., Takagi, S.; Takemoto, T. *Chimia* **1981**, *35*, 249. (c) For a crystal structure, see: Mino, Y; Ishida, T.; Ota, N.; Inoue, M.; Nomoto, K.; Takemoto, T.; Tanaka, H.; Sugiura, Y. *J. Am. Chem. Soc.* **1983**, *105*, 4671.
2. (a) Hashimoto, K.; Shirahama, H. *J. Syn. Org. Chem. Jpn.* **1989**, *47*, 212. (b) Hashimoto, K.; Shirahama, H. *Trends Org. Chem.* **1991**, *2*, 1.
3. Non-aromatic scaffolds drug design: (a) Mann, A. In *The Practice of Medicinal Chemistry*, 3rd ed., Wermuth, C. G., Ed.; Elsevier: Amsterdam, **2008**, 363. (b) Marson, C. M. *Chem. Soc. Rev.* **2011**, *40*, 5514. (c) Hu, X.-G.; Hunter, L. Beilstein *J. Org. Chem.* **2013**, *9*, 2696. (d) Lovering, F. *Med. Chem. Commun.* **2013**, *4*, 515.
4. (a) Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29. (b) Couty, F.; Evano, G.; Prim, D. *Mini-Rev. Org. Chem.* **2004**, *1*, 133. (c) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988.
5. (a) Kern, N.; Blanc, A.; Weibel, J.-M.; Pale, P. *Chem. Comm.* **2011**, *47*, 6665. (b) Kern, N.; Blanc, A.; Miaskewicz, S.; Robinette, M.; Weibel, J.-M.; Pale, P. *J. Org. Chem.* **2012**, *77*, 4323. (c) Kern, N.; Hoffmann, M.; Blanc, A.; Weibel, J.-M.; Pale, P. *Org. Lett.* **2013**, *15*, 836. (d) Miaskiewicz, S.; Weibel, J.-M.; Pale, P.; Blanc, A. *Org. Lett.* **2016**, *18*, 844. (e) Miaskiewicz, S.; Gaillard, B.; Kern, N.; Weibel, J.-M.; Pale, P.; Blanc, A. *Angew. Chem. Int. Ed.* **2016**, *55*, 9088.
6. Kern, N.; Hoffmann, M.; Weibel, J.-M.; Pale, P.; Blanc, A. *Tetrahedron* **2014**, *70*, 5519.
7. Kern, N.; Felten, A-S.; Weibel, J.-M.; Pale, P.; Blanc, A. *Org. Lett* **2014**, *16*, 6104.
8. To the best of our knowledge, a single example has been reported on acyclic compounds; see: (a) Otaka, A.; Mitsuyama, E.; Kinoshita, T.; Tamamura, H.; Fujii, N. *J. Org. Chem.* **2000**, *65*, 4888. It is noteworthy that monobromination of cyclic ynamide could not be achieved cleanly using strong bases, see: (b) Tlais, S. F.; Danheiser, R. L. *J. Am. Chem. Soc.* **2014**, 136, 15489.
9. Bastiaans, H. M. M.; van der Baan, J. L.; Ottenheijm, H. C. J. J. Org. Chem. **1997**, *62*, 3880.

10. For a review on Aze synthesis, see: Couty, F.; Evano, G. *Org. Prep. Proced. Int.* **2006**, *38*, 427.
11. Matzanke, N.; Gregg, R. J; Weinreb, S. M. *J. Org. Chem.* **1997**, *62*, 1920.
12. Biswas, T.; Mukherjee, J. P.; Chattopadhyay, S. K. *Tetrahedron: Asymmetry* **2012**, *23*, 1416.
13. Bouazaoui, M.; Martinez, J.; Cavelier, F. *Eur. J. Org. Chem.* **2009**, 2729.