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β-Aminocarbonates in regioselective and ring expansion reactions

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Abstract: The reactivity of β-aminocarbonates as anisotropic electrophiles has been investigated with several phenols. Products distribution shows that the regioselectivity of the anchimerically driven alkylation reaction depends on the nucleophiles. The results suggest that in the presence of nucleophiles that are also good leaving groups, the reaction takes place under thermodynamic control favoring the attack on the most sterically hindered carbon of the cyclic aziridinium intermediate. Furthermore, when an enantiomerically pure pyrrolidine-based carbonate was used, the reaction with phenols proceeds via a bicyclic aziridinium intermediate leading to the stereoselective synthesis of optically active 3-substituted piperidines via ring expansion reaction. These results were confirmed both by NMR spectroscopy and X-ray diffraction analysis.

Keywords: Carbonate chemistry; Anchimeric effect; Ring expansion reaction; Piperidine; Stereoselective reactions.

Introduction

Chlorine-based chemicals are ubiquitous in the chemical industries leading to the production of solvents, catalysts, building blocks, pesticides, herbicides, additives, polymers and drugs.[1] These compounds are easily prepared, very stable and highly reactive especially when the chlorine ion can be released as leaving group, however, they also pose concerns for their environmental and health impact. It is thus not surprising that also several chemical warfare agents (CWA) incorporate the chlorine moiety. Poignant examples are the notorious mustard gases (Yperite) bis(2-chloroethyl)sulfide and bis(2-chloroethyl)ethylamine that, together with their monochloro derivatives, are lethal CWAs owing to their vesicant and noxious properties (Figure 1).[2] Yperites toxicity is strictly related to their reactivity, enhanced by the presence of a chlorine moiety that can be readily eliminated by intramolecular nucleophilic substitution promoted by sulfur/nitrogen anchimeric effect, to form a cyclic episulfonium/aziridinium ion.[2]

Despite their lethal properties, mustard gases have attracted a great interest as versatile electrophiles in inorganic and organic synthesis[3] also employed for the preparation of numerous pharmaceutical intermediates.[4]

Over the years, our research has been focusing on designing smart, safer chemicals by retaining the structural motif encompassing the desired properties while substituting the moiety responsible of the hazard/toxicity of the molecule. In this view the replacement of a chlorine atom by a carbonate moiety via dialkyl carbonate (DAC) chemistry[5] has led to new green synthetic approaches for industrially appealing compounds, i.e., linear and cyclic carbamates,[6] heterocycles,[7] intermediates of cosmetic products and anti-inflammatory drugs.[8]

Recently, it was reported the easy preparation of a new class of organic carbonates named sulfur and nitrogen mustard carbonates (MCs) after their chlorine analogous compounds (Figure 1).[9] MCs reactivity has been investigated with several nucleophiles both in autoclave (180 °C) in absence of any base, as well as in neat (150 °C) in the presence of a catalytic amount of a K_2CO_3 as base. Reaction mechanism and kinetics have confirmed that these compounds retain the anchimeric effect

of their mustard gas analogues, without showing any toxic property. Besides, nitrogen MCs have also been employed in the preparation of new families of azacrowns and polycarbonates.[10]

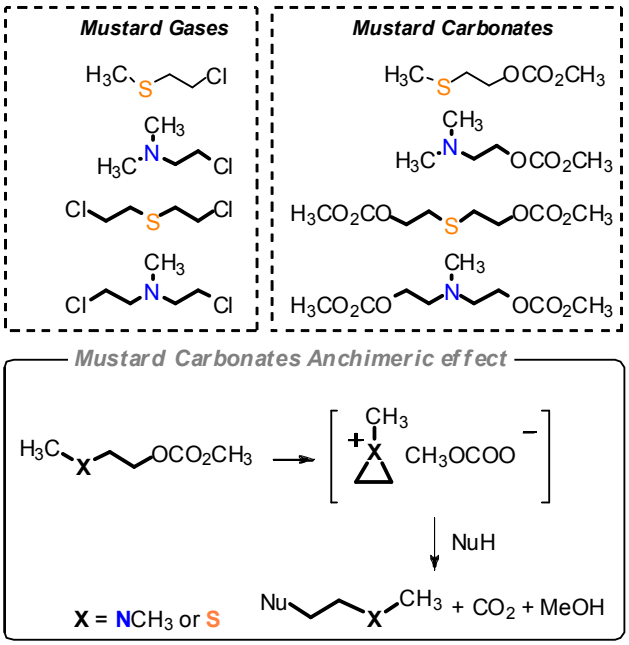


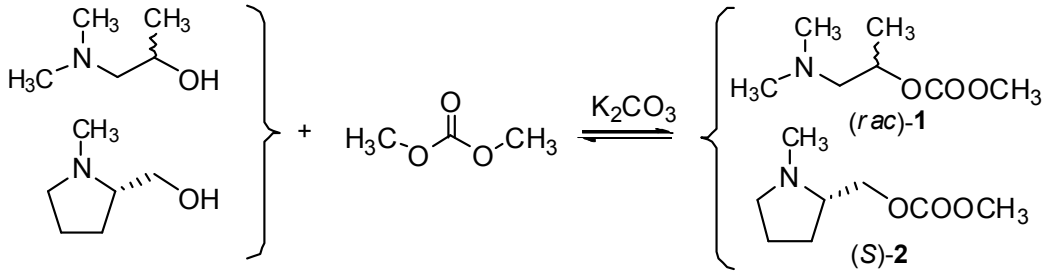
Figure 1. Structure and reactivity of mustard carbonates.

Herein, the reactivity of a new family of nitrogen half-mustard carbonates (HMCs) has been exploited. Parent alcohols of new HMCs have been selected so that the related aziridinium cyclic intermediates would be anisotropic electrophiles. Reactions of novel synthesized HMCs with phenols led to high yielding regioselective, stereoselective and ring expansion reactions for the preparation of optically active 3-substituted piperidines. To the best of our knowledge, the use of DACs chemistry for the functionalization and subsequent ring expansion reactions of prolinols is unprecedented.

Results and Discussion

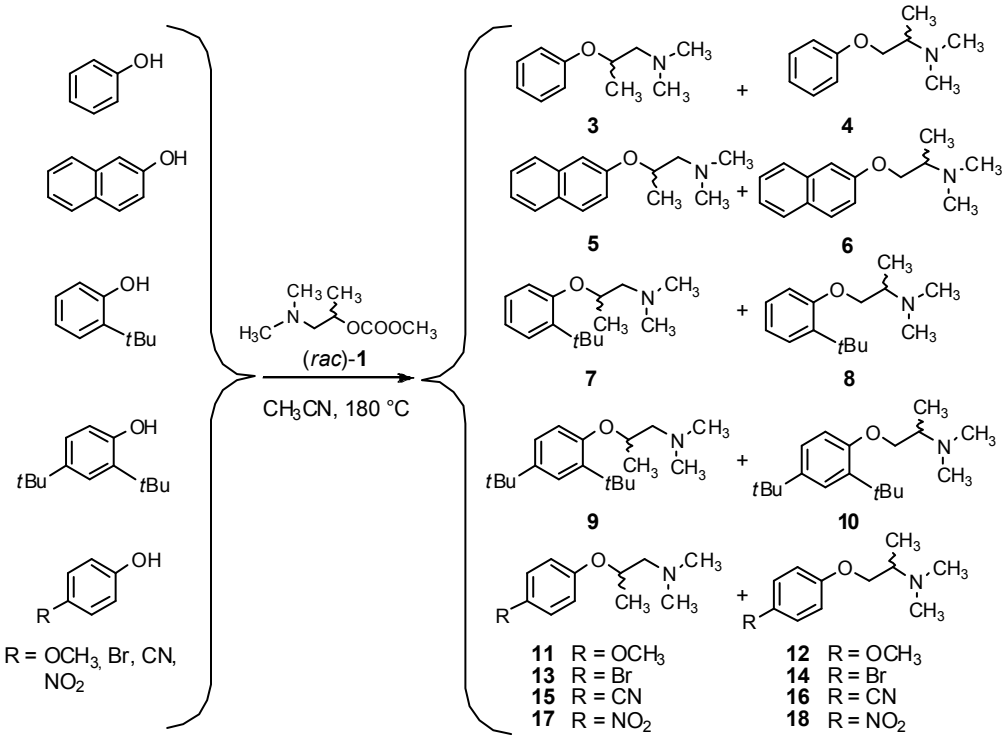
HMCs **1** and **2** have been prepared in good yield by reacting commercially available (*rac*)-1-dimethylamino-2-propanol and (*S*)-1-methyl-2-pyrrolidinemethanol, respectively, with DMC in the presence of K_2CO_3 via a $B_{Ac}2$ mechanism (Scheme 1). HMC **1** was isolated as a racemic mixture

while HMC **2** is an enantiomerically pure compound as confirmed by NMR investigation with optically active shift reagent europium tris[3-(heptafluoropropylhydroxyl methylene)-(+) camphorate].†



Scheme 1. Synthesis of HMCs **1**-**2**.

The reactivity of HMC **1** was then investigated with a generic nucleophile, i.e., phenol (Scheme 2, Table 1). In a typical reaction, phenol and HMC **1**, dissolved into a selected solvent, were allowed to react in an autoclave in the absence of any base at 180 °C. When the reaction was carried out in acetonitrile, the substrate was fully converted in two major products, namely the alkylated derivatives **3** and **4** isolated, both as racemic mixtures, via column chromatography (Table 1).



Scheme 2**.** Synthesis of HMCs **1**-**2**.

In these conditions the reaction showed only a minor regioselectivity towards the product **4** as a result of the preferential attack of the phenol on the less sterically hindered carbon of the cyclic aziridinium intermediate (Scheme 3).

Table 1. Autoclave reactions between phenol and half mustard carbonates **1** in various solvents and at different temperature.[a]

Entry	Solvent	Temp (°C)	P (bar)	t (h)	Conv.[b] (%)	Selectivity[c], (%)	
						3	**4**
1	Acetonitrile	180	10	18	100	40	60
2	Toluene	180	2	74	96	44	56
3	THF	180	19	39	96	41	59
4	Methanol	180	30	20	100[d]	0	0
5	Acetonitrile	120	0	70	84	42	58
6	Acetonitrile	150	5	22	100	40	60
7	Acetonitrile	210	18	6	100	41	59

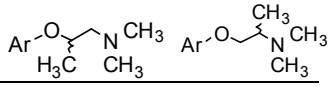
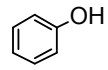
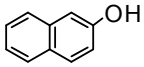
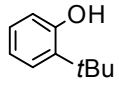
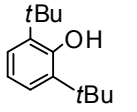
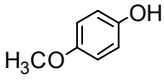
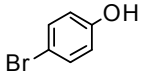
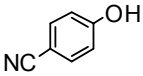
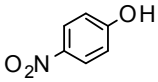
[a] Reaction conditions: PhOH : HMC 3:1 ($C_{HMC\ 1}$ = 3 mg/l); [b] Calculated via GC-MS analysis; [c] Calculated via NMR analysis; [d] 75% of 1-(*N,N*)-dimethylamino propanol-2 and 25% of anisol were detected on GC-MS.

The effects of the solvent and temperature on the products selectivity have been taken into consideration (Table 1). The results show that the reaction rate increases in polar solvents (# 1-3, Table 1). In methanol, however, formation of products **3** and **4** could not be detected, most probably as the result of transesterification of HMC **1** with the solvent. Notably, the reaction regioselectivity is not influenced by changes of polarity of the reaction medium. Furthermore, varying the reaction temperature from 120 to 210 °C (# 5-7, Table 1), a significant increase of the reaction rate was observed, however the regioselectivity remained unaffected.

The influence of different types of catalysts has also been investigated.[†] The presence of weak (K_2CO_3) or strong bases (*t*BuOK, NaH, DBU), as well as, the amphoteric catalyst hydrotalcite KW2000 did not result in any evident change of products distribution. Reactions conducted with both homogenous (CH_3COOH) and heterogeneous (Amberlyst 15) acidic catalysts did not yield the alkylated products **3**-**4**, most probably as they inhibit the formation of the aziridinium intermediate.

The effect of the nucleophile on the products distribution was then investigated; differently substituted phenols were selected considering both steric and electronic factors (Scheme 2, Table 2).

Table 2. Reactivity of HMC **1** with different nucleophiles

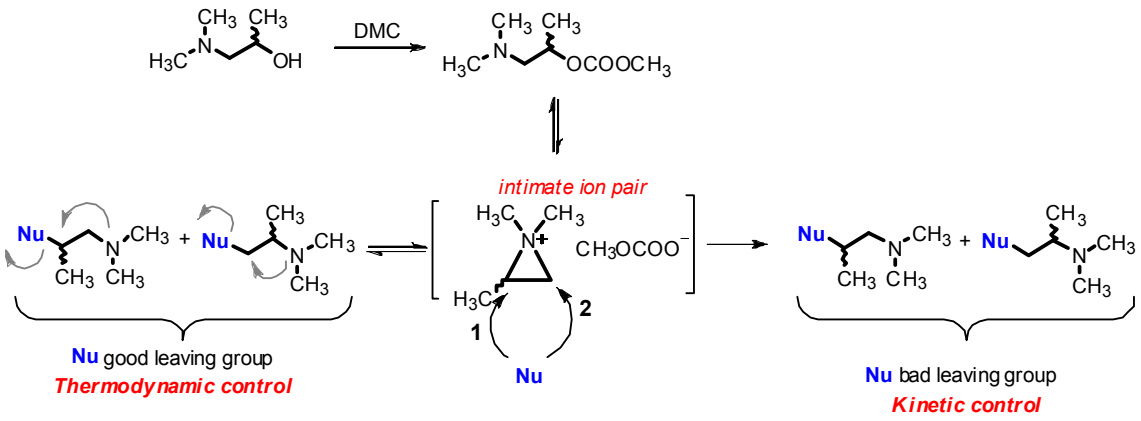
#	Substrate	Conv.[b] %	Selectivity[c] % 	
1		100	40 (28)	60 (60)
2		100	47 (32)	53 (35)
3		100	37 (24)	63 (39)
4		63	39 (20)	61 (40)
5		100	40 (27)	60 (44)
6		100	44 (35)	56 (29)
7		100	85 (85)	15 (14)
8		100	88 (74)	12 (0)

[a] Reaction conditions: ArOH : HMC **1** : 1.2 at 180 °C in CH_3CN; [b] Conversion determined via GC-MS analysis, [c] Calculated via NMR analysis on the crude reaction mixture; isolated yields (%) are given in brackets.

Reaction of HMC **1** with naphthol, mono and di-*tert*-butyl phenol showed a regioselectivity similar to that of phenol. 2,6-Di-*tert*-butyl phenol was the only substrate not completely converted into the alkylated products **9** and **10**, most probably as a result of the substrate steric hindrance.

Interestingly, the presence of strong electron-withdrawing substituents, such as the *p*-cyano and *p*-nitro groups, led to the high regioselective formation of alkylated compounds **15** and **17** derived from the nucleophilic attack on the most sterically hindred site of the cyclic intermediate.

The regioselectivity observed in this reaction can be elucidated according to extensively explored rearrangement of β-amino alcohols via an aziridinium intermediate that usually involves activation of the hydroxy group followed by the addition of nucleophiles.[11] It has been reported that the ratio of the products formed by the nucleophilic attack at either the C-1 or C-2 position of the aziridinium intermediate varies according to the nature of the nucleophiles and the presence of substituents on the nitrogen, but also to the solvents and the temperature of the reaction (Scheme 3).[12]



Scheme 3. Proposed reaction mechanism for the regioselective alkylation of acidic nucleophiles.

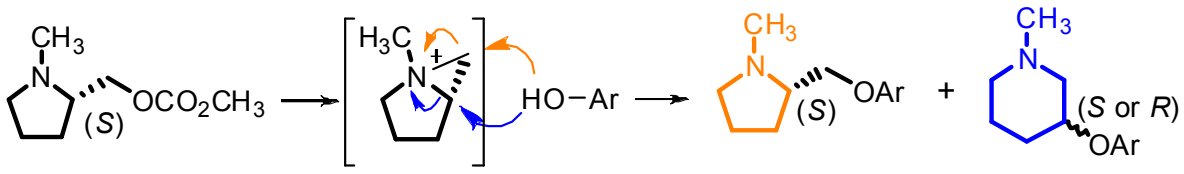
In our case study, the HMC **1** due to its anchimeric effect is able to form the aziridinium intermediate via S_Ni in neutral condition. The cyclic intermediate is trapped in a intimate ion pair together with the methoxycarbonate anion, i.e., the leaving group.[13] In the presence of phenol, or nucleophiles with similar moderate acidity, the alkylated products form under kinetic control as the nucleophiles is not a good leaving group. Thus, the regioselectivity observed (#1-6; Table 1) is justified by the preferential attack on the less sterically hindered C2 carbon.

On the other hand, the presence of a strong electron withdrawing group (#7-8; Table 1) in the nucleophile enhances its ability as leaving group. In this case, the reaction proceeds under thermodynamic control and the attack on the sterically hindered C1 position is favored.

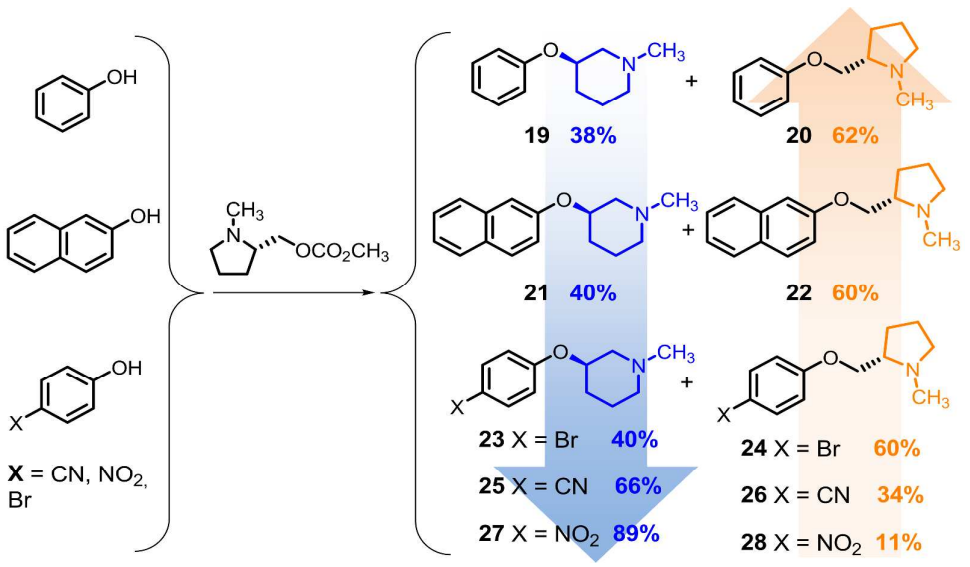
In order to have a further insight on the stereochemistry of the reaction the reactivity of carbonate pyrrolidine HMC **2** derived from the enantiomerically pure (*S*)-parent alcohol was then investigated.

In this case, reaction of a phenol with HMC **2** could lead to three distinct products, i.e., a substituted (*S*)-pyrrolidine and the two enantiomers of the substituted piperidine formed via ring expansion (Scheme 4). In fact, only the nucleophilic attack on the more sterically hindered tertiary carbon of the bicyclic aziridinium intermediates would affect the stereogenic center of the pyrrolidine.

This latter reaction is particularly interesting as might lead to the formation of optically active 3-substituted piperdines that are very common building blocks both in natural and bioactive compounds.[14] Several synthetic approaches to these compounds have been reported in the literature, including hydrogenation of substituted pyridines followed by enantiomeric resolution of their related ammonium salts,[15] enantioselective hydrogenation of tetrahydropyridines,[15] diastereoselective alkylation and reduction of oxazolopiperidines and/or the separation of the diastereomers,[16] cyclization of optically active linear azido sulfonate derivatives after reduction of the azido group[17] and enantioselective ring expansion of prolinols.[18] Over the years, the latter synthetic approach led to the efficient synthesis of several C3-substituted piperidines including 3-halo-, 3-hydroxy-, 3-amino, 3-thio, 3-cyano and 3-arylpiperidines.[19]



Scheme 4. Reaction of HMC **2** with a phenol.



Scheme 5. Reaction of phenols with HMC **2**. Conversion was 100% for all substrates. Products distribution was calculated via NMR analysis on the reaction crude mixture.

In our case study, a substituted phenol was reacted with HMC **2** in 1:1 mol. ratio at 180 °C in acetonitrile. Results, reported in Scheme 5, are consistent with the regioselectivity observed for HMC **1**. Alkylation of less acidic nucleophiles led mainly to substituted pyrrolidines (kinetically controlled reaction). Conversely, more acidic *p*-cyano and *p*-nitro phenol formed preferably the related piperidines as a result of the thermodynamically controlled mechanism.

Products **19-27** have been isolated as pure compounds and both NMR spectroscopy and mass spectrometry have confirmed the proposed structures.[†]

Ring expansion of *N*-alkylated prolinols is generally highly stereoselective, however, to the best of our knowledge this is the first example based on carbonate derivatives. Thus, in order to assess the stereoselectivity of the reaction, an NMR investigation was firstly carried out. In particular, slow addition of europium tris[3-(heptafluoropropylhydroxyl methylene)-(+) camphorate] to a chloroform-*d* solution of piperidines **25** or **27**, isolated as pure compounds, did not lead to any peaks splitting in the spectra, indicating the presence of only one enantiomer, at least within the detection limits of the NMR analysis.

However, having established the enantioselectivity of the ring expansion reaction, the absolute stereochemistry of the product remained yet to be assessed. Luckily, *N*-methyl-3-(4-

cyanophenoxy)piperidine **25** gave single crystals amenable to an X-ray diffraction analysis, which unambiguously proved the *R* configuration of the product.† In the structure (Figure 2), the piperidine ring adopts a chair conformation, with the O1 and C6 substituents occupying the equatorial positions. The angle between normals to the average planes of the piperidine and the phenyl ring is 59.0°.

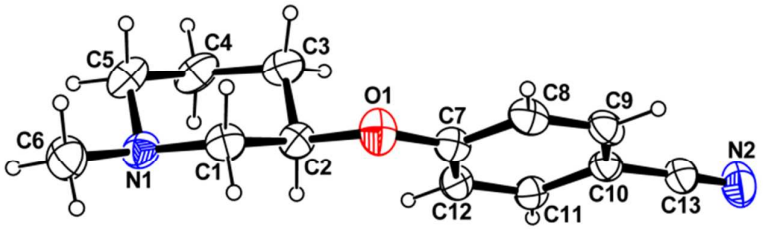
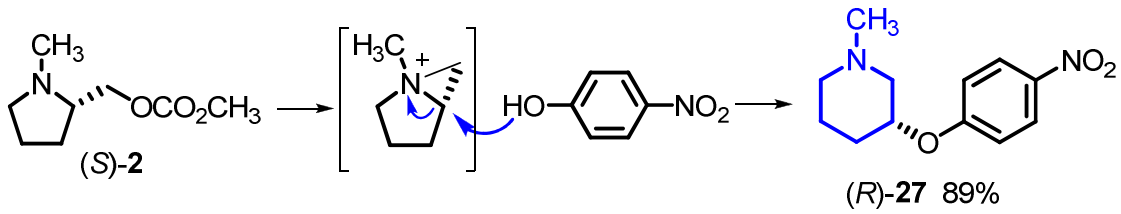


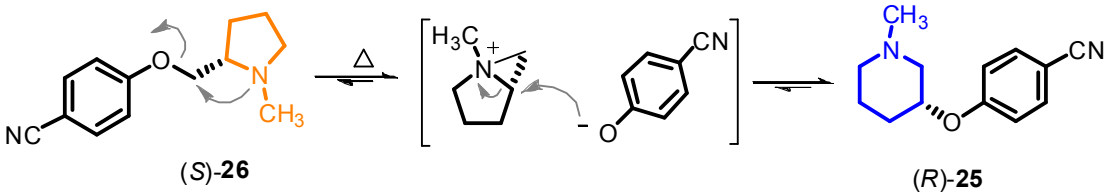
Figure 2. X-Ray diffraction structure of (*R*)-N-methyl-3-(4-cyanophenoxy)piperidine **25**. Anisotropic displacement ellipsoids are drawn at the 30% probability level.

These results confirm that in case of nucleophiles which could be good leaving groups the reaction proceeds under thermodynamic control via a stereoselective ring expansion reaction leading to optically active 3-substituted piperidines (Scheme 6).



Scheme 6. Stereoselective ring-expansion reaction of (*S*)-HMC **2** leading to (*R*)-N-methyl-3-(4-nitrophenoxy)piperidine **27**.

An additional experiment was conducted so to assess the thermodynamic behavior of the ring-expansion reaction when performed in the presence of a nucleophile that can also operate as a good leaving group. Thus, a pure sample of (*S*)-4-((1-methylpyrrolidin-2-yl)methoxy)benzonitrile **26** dissolved in acetonitrile was heated at 180 °C in autoclave. Samples taken at time interval showed an increasing conversion of the substituted (*S*)-pyrrolidine **26** into the related optically active piperidine, i.e., (*R*)-N-methyl-3-(4-cyanophenoxy)piperidine **25** (Scheme 7).† This result is perfectly in accordance with the proposed thermodynamically controlled mechanism.



Scheme 7. Thermodynamic behavior of the ring-expansion reaction: conversion of the substituted (S)-pyrrolidine **26** into the related (*R*)-piperidine **25**.

Conclusions

In summary, alkylation of several substituted phenols via anchimeric effect of nitrogen HMC **1** and **2** has been investigated. A possible mechanism accounting for the reaction regioselectivity has been proposed. Nucleophiles that are also good leaving group attack preferably the most sterically hindered carbon as the products are in equilibrium with the aziridinium cyclic intermediate and this ultimately favors the formation of the most thermodynamically stable compound.

According to the results obtained on the reactivity of HMC **2** with substituted phenols, it was demonstrated that, when the nucleophile attacks the electrophilic site bearing the stereocenter, the anchimerically driven alkylation is also stereoselective with inversion of configuration as demonstrated by the X-ray diffraction analysis.

As a result this synthetic approach can be employed for the synthesis of enantiomerically pure 3-substituted piperidine via ring-expansion reaction of pyrrolidines. This is quite appealing as the piperidine moiety is present in numerous alkaloids, biologically active molecules and therapeutic agents and numerous studies have been devoted to their synthesis especially focusing on the possibility to control the stereoselectivity of this scaffold.[20]

Experimental Section

All reagents were purchased by Sigma Aldrich and used without any further purification. Mass spectra were run on GC-MS Agilent Technologies (GC System 6890N Network, Agilent Technologies Mass Selective Detector 5973, capillary column of silica HP-5). ^{1}H NMR spectra were recorded at 400 MHz on a Bruker Ascend^{TM} 400. The chemical shifts are reported in ppm

from the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm) and regarding the tetramethylsilane (TMS). Data are reported as follows: chemical shift, integration multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, sext = sextet, sept = septet, m = multiplet,) and coupling constants (Hz). ^{13}C NMR spectra were recorded at 100 MHz on a Bruker Ascend^{TM} 400. Chemical shift are reported in ppm from the solvent resonance as internal standard ($CDCl_3$: 77 ppm).

DIP-EI-MS spectra were recorded on a large-scale tandem mass spectrometer (Waters AutoSpec 6F – Organic Synthesis and Mass Spectrometry Lab – University of Mons, Belgium) combining six sectors of E1B1c1E2c2E3B2c3E4 configuration (E stands for electric sector, B for magnetic sector and c for collision cell). General conditions were 8 kV accelerating voltage, 70 eV ionizing electron energy and 200 °C ion source temperature. The PEI samples (1 mg), introduced in small Pyrex capillaries, were directly introduced into the ion source without any external heating. The ions were obtained under electron ionization in positive ion mode (200 μA trap current). The full scan mass spectra were recorded by scanning the field of the first magnetic sector and collecting the ions with an off-axis photomultiplier detector. Accurate mass measurements were acquired using perfluorokerosene (PFK) as the internal standard.

General procedure for the synthesis of nitrogen half mustard carbonates HMC 1 and 2. In a typical experiment, 1-dimethylamino-2-propanol or (*S*)-(-)-1-methyl-2-pyrrolidinemethanol (1.0 eq. mol), DMC (20.0 eq. mol) and dried potassium carbonate (1.0 mol eq.) were placed into a round-bottomed flask equipped with a reflux condenser. While being stirred magnetically, the mixture was heated at the reflux temperature (90 °C) for 43 and 27 hours respectively. The progress of the reactions was monitored by GC-MS until consumption of the starting amino alcohol. The methanol formed as by-product in the transesterification reaction was being removed during the reaction by a Dean-Stark apparatus. The reaction mixture was then cooled, filtered and the solvent evaporated

under vacuum. Half mustard carbonates **1** and **2** were obtained pure and did not need any further purification.

1-(dimethylamino)propan-2-yl methyl carbonate **1**. Brown liquid; 62 % yield (9.64 g). GC-MS Calcd for $C_7H_{15}NO_3$ 161.2 $g{\cdot}mol^{-1}$; Found 161.1 $g{\cdot}mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_7H_{15}NO_3$ 161.1051; Found 161.1049. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, 3H), 2.20 (s, 6H), 2.20 (q, 1H), 2.47 (q, 1H), 3.7 (s, 3H), 4.82 (sext, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 46.0, 54.5, 64.2, 72.7, 155.4 ppm.

(S)-methyl (1-methylpyrrolidin-2-yl)methyl carbonate **2**. Brown liquid; 81 % yield (4.64 g). GC-MS Calcd for $C_8H_{15}NO_3$ 173.2 $g{\cdot}mol^{-1}$; Found 173.1 $g{\cdot}mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_8H_{15}NO_3$ 173.1051; Found 173.1052. ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.52-1.80 (m, 3H), 1.83-1.94 (m, 1H), 2.15-2.23 (m, 1H), 2.35 (s, 3H), 2.40-2.48 (m, 1H), 2.97-3.04 (m, 1H), 3.71 (s, 3H), 3.98-4.05 (m, 1H), 4.06-4.12 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 28.4, 41.4, 54.7, 57.6, 63.7, 70.1, 155.9 ppm.

Reaction of nitrogen half mustard carbonates 1 with different nucleophiles. In a typical experiment, a solution of selected nucleophile (1.0 mol eq.) and HMC **1** (1.2 mol eq.) in 100.0 mL of acetonitrile was placed into a steel autoclave and heated at 180 °C for 5-24 hours under pressure while being stirred. The autoclave was then cooled and vented and the solvent was evaporated under vacuum. The pure products were isolated as pure by column chromatography.

N,N-dimethyl-2-phenoxypropan-1-amine **3**. Reaction time 18 h. The pure compound was obtained in 28% (96 mg) yield as a brown oil by column chromatography on silica gel using diethyl ether : methanol (9 : 1) as elution mixture. GC-MS Calcd for $C_{11}H_{17}NO$ 179.3 $g{\cdot}mol^{-1}$; Found 179.1 $g{\cdot}mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{11}H_{17}NO$ 179.1310; Found 179.1310. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (d, 3H), 2.34 (s, 6H), 2.42-2.49 (m, 1H), 2.64-2.71 (m, 1H), 4.53 (sext, 1H), 6.92-6.96 (m, 3H), 7.26-7.32 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 46.2, 64.8, 72.0, 116.0, 120.7, 129.5, 157.8 ppm.

N,N-dimethyl-1-phenoxypropan-2-amine **4.** The pure compound was obtained in 60 % (204 mg) as a brown oil by column chromatography on silica gel using diethyl ether : methanol (9 : 1) as elution mixture. GC-MS Calcd for $C_{11}H_{17}NO$ 179.3 $g{\cdot}mol^{-1}$; Found 179.1 $g{\cdot}mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{11}H_{17}NO$ 179.1310; Found 179.1310. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (d, 3H), 2.40 (s, 6H), 3.00 (sext, 1H), 3.85-3.91 (m, 1H), 4.05-4.10 (m, 1H), 6.93-6.98 (m, 3H), 7.28-7.33 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 41.5, 58.4, 69.8, 114.6, 120.7, 129.4, 158.9 ppm.

N,N-dimethyl-2-(naphthalen-2-yloxy)propan-1-amine **5**. The pure compound was obtained in 32% (138 mg) yield as a brown oil by column chromatography on silica gel using diethyl ether : methanol (9 : 1) as elution mixture. GC-MS Calcd for $C_{15}H_{19}NO$ 229,3 $g{\cdot}mol^{-1}$; Found 229.1 $g{\cdot}mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{19}NO$ 229,1466; Found 229.1470. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, 3H), 2.29 (s, 6H), 2.42-2.48 (m, 1H), 2.63-2.70 (m, 1H), 4.63 (sext, 1H), 7.05-7.13 (m, 2H), 7.21-7.29 (m, 1H), 7.31-7.39 (m, 1H), 7.60-7.71 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 46.1, 64.6, 72.0, 108.6, 119.8, 123.6, 126.3, 126.7, 127.6, 129.0, 129.5, 134.6, 155.6 ppm.

N,N-dimethyl-1-(naphthalen-2-yloxy)propan-2-amine **6**. The pure compound was obtained in 32% (138 mg) yield as a brown oil by column chromatography on silica gel using diethyl ether : methanol (9 : 1) as elution mixture. GC-MS Calcd for $C_{15}H_{19}NO$ 229.3 $g \cdot mol^{-1}$; Found 229.1 $g \cdot mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{19}NO$ 229,1466; Found 229.1468. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (d,3H), 2.36 (s, 6H), 3.02 (sext, 1H), 3.90-3.96 (m, 1H), 4.08-4.14 (m, 1H), 7.05-7.10 (m, 2H), 7.22-7.30 (m, 1H), 7.32-7.40 (m, 1H), 7.62-7.72 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 41.5, 58.5, 69.7, 106.7, 119.0, 123.6, 126.4, 126.7, 127.6, 129.0, 129.4, 134.5, 156.8 ppm.

2-(2-(tert-butyl)phenoxy)-N,N-dimethylpropan-1-amine **7**. 24 % yield (105 mg) as a brown oil by column chromatography on silica gel using diethyl ether as elution mixture. GC-MS Calcd for $C_{15}H_{25}NO$ 235.37 $g \cdot mol^{-1}$; Found 235.2 $g \cdot mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{25}NO$ 235.1936; Found 235.1936. ^1H-NMR (400 MHz, $CDCl_3$): δ = 1.27-1.31 (m, 12H); 2.25 (s, 6H); 2.44-2.62 (m, 2H); 4.54-4.61 (m, 1H); 6.75-6.83 (m, 2H); 7.05-7.09 (m, 1H); 7.20-7.22 (m, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 17.5, 28.9, 33.8, 45.3, 63.9, 69.9, 111.2, 118.8, 125.8, 125.8, 137.4, 154.9 ppm.

1-(2-(tert-butyl)phenoxy)-N,N-dimethylpropan-2-amine ***8***. 39 % yield (172 mg) as a brown oil by column chromatography on silica gel using diethyl ether as elution mixture. GC-MS Calcd for $C_{15}H_{25}NO$ 235.37 $g \cdot mol^{-1}$; Found 235.2 $g \cdot mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{25}NO$ 235.1936; Found 235.1927. ^1H-NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, 3H); 1.32 (s, 9H); 2.31 (s, 6H); 2.93-3.01 (m, 1H); 3.77-4.06 (m, 2H); 6.80-6.84 (m, 2H); 7.08-7.13 (m, 1H); 7.21-7.23 (m, 1H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 13.2, 29.9, 34.8, 41.6, 58.8, 70.2, 112.0, 120.4, 126.7, 127.0, 138.1, 157.6 ppm.

2-(2,6-di-tert-butylphenoxy)-N,N-dimethylpropan-1-amine **9**. The pure compound was obtained in 18 % yield (98 mg) as a brown oil by column chromatography on silica gel using hexane : diethyl ether (1 : 1) as elution mixture. GC-MS Calcd for $C_{19}H_{33}NO$ 291.5 $g{\cdot}mol^{-1}$; Found 291.3 $g{\cdot}mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{19}H_{33}NO$ 291.2562; Found 291.2566. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, 3H), 1.33 (s, 18H), 2.22 (s, 6H), 2.47 (d, 2H), 4.40 (sext, 1H), 6.80-6.85 (m, 1H), 7.08-7.12 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7, 32.2, 35.7, 46.6, 65.0, 76.8, 121.6, 126.0, 143.2, 154.8 ppm.

1-(2,6-di-tert-butylphenoxy)-N,N-dimethylpropan-2-amine **10**. The pure compound was obtained in 38 % yield (205 mg) as a brown oil by column chromatography on silica gel using hexane : diethyl ether (1:1) as elution mixture. GC-MS Calcd for $C_{19}H_{33}NO$ 291.5 $g{\cdot}mol^{-1}$; Found 291.2 $g{\cdot}mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{19}H_{33}NO$ 291.2562; Found 291.2567. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, 3H), 1.36 (s, 18H), 2.25 (s, 6H), 3.10 (sext, 1H), 3.64-3.69 (m, 1H) 3.73-3.79 (m, 1H), 6.87-6.93 (m, 1H), 7.18-7.20 (m, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 32.1, 35.7, 41.6, 58.7, 77.4, 122.8, 126.7, 143.7, 158.1 ppm.

2-(4-methoxyphenoxy)-N,N-dimethylpropan-1-amine **11**. The pure compound was obtained in 27% (107 mg) yield as a brown oil by column chromatography on silica gel using diethyl ether : methanol (9 : 1) as elution mixture. GC-MS Calcd for $C_{12}H_{19}NO_2$ 209.3 $g{\cdot}mol^{-1}$; Found 209.2 $g{\cdot}mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{12}H_{19}NO_2$ 209.1426; Found 209.1416. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18 (d, 3H), 2.26 (s, 6H) 2.32-2.39 (m, 1H), 2.54-2.60 (m, 1H), 3.69 (s, 3H), 4.34 (sext, 1H), 6.71-6.83 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.5, 46.2, 55.7, 64.8, 73.1, 114.6, 117.6, 151.8, 154.0

1-(4-methoxyphenoxy)-N,N-dimethylpropan-2-amine **12**. The pure compound was obtained in 44% (107 mg) yield as a brown oil by column chromatography on silica gel using diethyl ether :

methanol (9 : 1) as elution mixture. GC-MS Calcd for $C_{12}H_{19}NO_2$ 209.3 g·mol^{-1}; Found 209.2 g·mol^{-1}. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{12}H_{19}NO_2$ 209.1414; Found 209.1416. ^{1}H NMR (400 MHz, $CDCl_3$): 1.07 (d,3H), 2.20 (s, 6H), 2.90 (sext, 1H), 3.70 (s, 1H), 3.71-3.76 (m, 1H), 3.90-3.96 (m, 1H), 6.72-6.82 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.3, 41.5, 55.7, 58.5, 70.6, 114.6, 115.6, 153.1, 153.9 ppm.

2-(4-bromophenoxy)-N,N-dimethylpropan-1-amine **13**. The pure compound was obtained in 35% (178 mg) yield as a brown oil by column chromatography on silica gel using Et_2O : CH_3OH (9 : 1) as elution mixture. GC-MS Calcd for $C_{11}H_{16}BrNO$ 258.15 g·mol^{-1}; Found 258.1 g·mol^{-1}. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{11}H_{16}BrNO$ 257.0415; Found 257.0417. ^{1}H NMR (400 MHz, $CDCl_3$): 1.20 (d,3H), 2.27 (s, 6H), 2.37-2.44 (m, 1H), 2.57-2.64 (m, 1H), 4.45 (sext, 1H), 3.90-3.96 (m, 1H), 6.71-6.76 (m, 2H), 7.27-7.31 (m,2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 46.2, 64.7, 72.5, 112.8, 117.8, 132.3, 156.9 ppm.

1-(4-bromophenoxy)-N,N-dimethylpropan-2-amine **14**. The pure compound was obtained in 29% (145 mg) yield as a brown oil by column chromatography on silica gel using Et_2O : CH_3OH (9 : 1) as elution mixture. GC-MS Calcd for $C_{11}H_{16}BrNO$ 258.15 g·mol^{-1}; Found 257.9 g·mol^{-1}. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{11}H_{16}BrNO$; Found 257.0413. ^{1}H NMR (400 MHz, $CDCl_3$): 1.05 (d,3H), 2.28 (s, 6H), 2.88 (sext, 1H), 3.70-3.76 (s, 1H), 3.89-3.95 (m, 1H), 6.70-6.75 (m, 2H), 7.27-7.31 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2, 40.5, 57.3, 69.2, 111.9, 115.4, 131.2, 157.0 ppm.

4-(1-(dimethylamino)propan-2-yloxy)benzonitrile **15**. Reaction time 7 h. The pure compound was obtained in 85% (545 mg) yield as a brown oil by column chromatography on silica gel using diethyl ether : methanol (9 : 1) as elution mixture. GC-MS Calcd for $C_{12}H_{16}N_2O$ 204.3 g·mol^{-1} ; Found 204.1 g·mol^{-1}. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{12}H_{16}N_2O$ 204.1267; Found 204.1262. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, 3H), 2.24 (s, 6H), 2.35-2.42 (m, 1H), 2.56-2.63 (m, 1H), 4.51

(sext, 1H), 6.86-6.92 (m, 2H), 7.46-7.52 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1, 46.2, 64.5, 72.7, 103.7, 116.2, 119.3, 134.0, 161.3 ppm

4-(2-(dimethylamino)propoxy)benzonitrile **16**. The pure compound was obtained in 14% (88 mg) yield as a brown oil by column chromatography on silica gel using diethyl ether : methanol (9 : 1) as elution mixture. GC-MS Calcd for $C_{12}H_{16}N_2O$ 204.3 $g{\cdot}mol^{-1}$; Found 204.1 $g{\cdot}mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{12}H_{16}N_2O$ 204.1267; Found 204.1266. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (d, 3H), 2.28 (s, 6H), 2.92 (sext, 1H), 3.78-3.83 (m, 1H), 3.97-4.02 (m, 1H), 6.86-6.92 (m, 2H), 7.47-7.53 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 41.4, 58.1, 70.3, 104.0, 115.3, 119.2, 133.9, 162.2 ppm.

N,N-dimethyl-2-(4-nitrophenoxy)propan-1-amine **17**. The pure compound was obtained in 74% (312 mg) yield as a brown oil by column chromatography on silica gel using diethyl ether : methanol (2 : 1) as elution mixture. GC-MS Calcd for $C_{11}H_{16}N_2O_3$ 224.3 $g{\cdot}mol^{-1}$; Found 224.2 $g{\cdot}mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{11}H_{16}N_2O_3$ 224.1161; Found 224.1163. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (d, 3H), 2.28 (s, 6H), 2.42-2.48 (m, 1H), 2.62-2.69 (m, 1H), 4.61 (sext, 1H), 6.88-6.93 (m, 2H), 8.10-8.14 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1, 46.2, 64.5, 73.2, 115.4, 125.9, 141.2, 163.2 ppm.

Reaction of nitrogen half mustard carbonates 2 with different nucleophiles. In a typical experiment, a solution of selected nucleophile (1.0 mol eq.) and HMC **2** (1.0 mol eq.) in 100.0 mL of acetonitrile was placed into a steel autoclave and heated at 180 °C for 5-24 hours under pressure while being stirred. The autoclave was then cooled and vented and the solvent was evaporated under vacuum. The pure products were isolated as pure by column chromatography.

(R)-1-methyl-3-phenoxypiperidine **19**. The pure compound was obtained in 32% (114 mg) yield as a brown oil by column chromatography on silica gel using methanol as elution mixture. GC-MS Calcd for $C_{12}H_{17}NO$ 191.3 $g \cdot mol^{-1}$; Found 191.1 $g \cdot mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{12}H_{17}NO$ 191.1310; Found 191.1309. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35-1.48 (m, 1H), 1.50-1.64 (m, 1H), 1.72-1.82 (m, 1H), 1.89-1.99 (m, 1H), 2.02-2.18 (m, 2H), 2.25 (s, 3H), 2.51-2.60 (m, 1H), 2.84-2.93 (m, 1H), 2.28-4.37 (m, 1H),2.81-6.90 (m, 3H), 7.14-7.23 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0, 29.2, 46.4, 55.5, 59.8, 72.6, 116.0, 120.9, 129.5, 157.6 ppm.

(S)-1-methyl-2-(phenoxymethyl)pyrrolidine **20**. The pure compound was obtained in 46% (164 mg) yield as a brown oil by column chromatography on silica gel using methanol as elution mixture. GC-MS Calcd for $C_{12}H_{17}NO$ 191.3 $g \cdot mol^{-1}$; Found 191.1 $g \cdot mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{12}H_{17}NO$ 191.1310; Found 191.1313. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.70-1.93 (m, 3H), 2.00-2.10 (m, 1H), 2.28-2.37 (m, 1H), 2.51 (s, 3H), 2.64-2.72 (m, 1H), 3.10-3.18 (m, 1H), 3.88-3.93 (m, 1H), 4.00-4.05 (m, 1H), 6.91-7.00 (m, 3H), 7.26-7.34 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0, 28.8, 41.6, 57.7, 64.4, 70.7, 114.5, 120.7, 129.4, 159.0 ppm.

(R)-1-methyl-3-(naphthalen-2-yloxy)piperidine **21**. The pure compound was obtained in 23% (141 mg) yield as a brown oil by column chromatography on silica gel using Et_2O: CH_3OH 8:2 as elution mixture. GC-MS Calcd for $C_{15}H_{19}NO$ 241.3 $g \cdot mol^{-1}$; Found 241.2 $g \cdot mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{19}NO$ 241.1466; Found 241.1461. ^1H-NMR (400 MHz, $CDCl_3$): δ = 1.60-2.33 (m, 7H); 2.41 (s, 3H); 2.72-2.76 (m, 1H); 3.10-3.13 (m, 1H); 4.61-4.66 (m, 1H); 7.17-7.28 (m, 2H); 7.33-7.37 (m, 1H); 7.43-7.47 (m, 1H); 7.72-7.80 (m, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 22.7, 29.0, 46.2, 55.4, 59.4, 72.2, 108.6, 119.5, 123.7, 126.3, 126.3, 126.8, 127.6, 129.0, 129.5, 134.5, 155.2 ppm.

(S)-1-methyl-2-((naphthalen-2-yloxy)methyl)pyrrolidine **22**. The pure compound was obtained in 35% (219 mg) yield as a brown oil by column chromatography on silica gel using Et_2O : CH_3OH 8:2 as elution mixture. GC-MS Calcd for $C_{15}H_{19}NO$ 241.3 $g.mol^{-1}$; Found 241.2 $g.mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{15}H_{19}NO$ 241.1466 found 241.1462. ^{1}H-NMR (400 MHz, $CDCl_3$): δ =1.65-2.05 (m, 4H); 2.26-2.32 (m, 1H); 2.48 (s, 3H); 2.67-2.70 (m, 1H); 3.09-3.13 (m, 1H); 3.94-3.98 (m, 1H); 4.06-4.10 (m, 1H); 7.07-7.11 (m, 2H); 7.23-7.27 (m, 1H); 7.33-7.37 (m, 1H); 7.63-7.67 (m, 3H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 22.9, 28.6, 41.5, 57.7, 64.6, 70.4, 106.7, 118.9, 123.6, 126.4, 126.8, 127.6, 134.5, 156.8 ppm.

(R)-3-(4-bromophenoxy)-1-methylpiperidine **23**. The pure compound was obtained in 37% (262 mg) yield as a brown oil by column chromatography on silica gel using methanol as elution mixture. GC-MS Calcd for $C_{12}H_{16}BrNO$ 270.2 $g.mol^{-1}$; Found 270.0 $g.mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{12}H_{16}BrNO$ 271.0394; Found 271.0395. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36-1.47 (m, 1H), 1.52-1.64 (m, 1H), 1.72-1.82 (m, 1H), 1.86-1.95 (m, 1H), 2.05-2.19 (m, 2H), 2.25 (s, 3H), 2.50-2.60 (m, 1H), 2.80-2.89 (m, 1H), 4.24-4.32 (m, 1H), 6.73-6.77 (m, 2H), 7.26-7.30 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.8, 29.0, 46.3, 55.4, 59.5, 72.9, 113.0, 117.7, 132.3, 156.6 ppm.

(S)-2-((4-bromophenoxy)methyl)-1-methylpyrrolidine **24**. The pure compound was obtained in 54% (374 mg) yield as a brown oil by column chromatography on silica gel using methanol as elution mixture. GC-MS Calcd for $C_{12}H_{16}BrNO$ 270.2 $g.mol^{-1}$; Found 270.0 $g.mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{12}H_{16}BrNO$ 271.0400; Found 271.0394. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.59-1.85 (m, 3H), 1.89-2.00 (m, 1H), 2.19-2.28 (m, 1H), 2.41 (s, 3H), 2.55-2.62 (m, 1H), 3.02-3.08 (m, 1H), 3.75-3.81 (m, 1H), 3.86-3.91 (m, 1H), 6.70-6.74 (m, 2H), 7.26-7.32 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.0, 28.6, 41.7, 57.7, 64.3, 71.0, 112.9, 116.3, 132.2, 158.1 ppm.

(R)-N-methyl-3-(4-cyanophenoxy)piperidine **25**. The pure compound was obtained in 56% (318 mg) yield as a brown oil by column chromatography on silica gel using methanol as elution mixture. GC-MS Calcd for $C_{13}H_{16}N_2O$ 216.3 g.mol^{-1}; Found 216.0 g·mol^{-1}. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{13}H_{16}N_2O$ 216.1262; Found 216.1265. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.49-1.63 (m, 1H), 1.63-1.77 (m, 1H), 1.85-1.93 (m, 1H), 1.95-2.06 (m, 1H), 2.18-2.36 (m, 2H), 2.36 (s, 3H), 2.60-2.69 (m, 2H), 2.88-2.96 (s, 1H), 4.46-4.56 (m, 1H), 6.97-7.03 (m, 2H), 7.56-7.62 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6, 28.8, 46.3, 55.3, 59.2, 72.8, 103.9, 116.1, 119.2, 134.1, 161.0 ppm.

(S)-4-((1-methylpyrrolidin-2-yl)methoxy)benzonitrile **26**. The pure compound was obtained in 23% (132 mg) yield as a brown oil by column chromatography on silica gel using methanol as elution mixture. GC-MS Calcd for $C_{13}H_{16}N_2O$ 216.3 g.mol^{-1}; Found 216.2 g·mol^{-1}. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{13}H_{16}N_2O$ 216.1262; Found 216.1267. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.58-1.82 (m, 3H), 1.89-2.03 (m, 1H), 2.20-2.29 (m, 1H), 2.40 (s, 3H), 2.57-2.63 (m, 1H), 3.00-3.09 (m, 1H), 3.82-3.88 (m, 1H), 3.90-3.97 (m, 1H), 6.85-6.92 (m, 2H), 7.47-7.53 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1, 28.6, 41.7, 57.7, 64.1, 71.1, 104.0, 115.2, 119.3, 134.0, 162.3 ppm.

(R)-1-methyl-3-(4-nitrophenoxy)piperidine **27**. The pure compound was obtained in 89% (558 mg) yield as a brown oil by column chromatography on silica gel using methanol as elution mixture. GC-MS Calcd for $C_{12}H_{16}N_2O_3$ 236.3 g.mol^{-1}; Found 236.0 g·mol^{-1}. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{12}H_{16}N_2O_3$ 236.1160; Found 236.1158. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51-1.66 (m, 1H), 1.66-1.78 (m, 1H), 1.85-1.94 (m, 1H), 1.98-2.08 (m, 1H), 2.20-2.37 (m, 2H), 2.37 (s, 3H), 2.59-2.69 (m, 1H), 2.89-2.99 (m, 1H), 4.51-4.61 (m, 1H), 6.97-7.04 (m, 2H), 8.17-8.23 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6, 28.8, 46.2, 55.2, 59.1, 73.1, 115.3, 126.0, 141.4, 162.8 ppm.

(S)-1-methyl-2-((4-nitrophenoxy)methyl)pyrrolidine **28**. The pure compound was obtained in 3% (17 mg) yield as a brown oil by column chromatography on silica gel using methanol as elution mixture. GC-MS Calcd for $C_{12}H_{16}N_2O_3$ 236.3 $g.mol^{-1}$; Found 236.0 $g.mol^{-1}$. HRMS (EI) m/z: $[M]^+$ Calcd for $C_{12}H_{16}N_2O_3$ 236.1160; Found 236.1154. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.60-1.85 (m, 3H), 1.93-2.04 (m, 1H), 2.23-2.32 (m, 1H), 2.43 (s, 3H), 2.60-2.70 (m, 1H), 3.03-3.11 (m, 1H), 3.89-3.94 (m, 1H), 3.96-4.03 (m, 1H), 6.87-6.94 (m, 2H), 8.09-8.16 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.1, 28.6, 41.7, 57.7, 64.0, 71.5, 114.5, 125.9, 141.5, 164.0 ppm.

Supporting Information†

The Supporting Information is available free of charge on the ACS Publications website and it includes experimental details, compound characterization, and NMR spectra (PDF); X-ray data for compound **25** (CIF).

References

(1) Tundo, P. *Pure Appl. Chem.* **2012**, *84*,411-423.

(2) Wang, Q.-Q.; Begum, R. A.; Day, V. W.; Bowman-James, K. *Org. Biomol. Chem.* **2012**, *10*, 8786−8793. (b) Ghabili, K.; Agutter, P. S.; Ghanei, M.; Ansarin, K.; Panahi, Y.; Shoja, *Crit. Rev. Toxicol.* **2011**, *41*, 384−403. (c) Tang, F. R.; Loke, W. K. *Crit. Rev. Toxicol.* **2012**, *42*, 688−702.

(3) (a) Wang, Q.-Q.; Ara Begum, R.; Day, V. W.; Bowman-James, K. *Inorg. Chem.* **2012**, *51*, 760−762. (b) Erdem, O. F.; Silakov, A.; Reijerse, E.; Lubitz, W.; Kaur-Ghumaan, S.; Huang, P.; Ott, S.; Stein, M.; Schwartz, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 1439−1443. (c) Dub, P. A.; Scott, B. L.; Gordon, J. C. *Organometallics* **2015**, *34*, 4464−4479. (d) Choi, J.-H.; Schloerer, N. E.; Berger, J.; Prechtl, M. H. *Dalton Trans.* **2014**, *43*, 290−299.

(4) (a) Wang, L.; Wen, Y.; Liu, J.; Zhou, J.; Li, C.; Wei, C. *Org. Biomol. Chem.* **2011**, *9*, 2648−2653. (b) Papaconstantinou, I. C.; Fousteris, M. A.; Koutsourea, A. I.; Pairas, G. N.; Papageorgiou, A. D.; Nikolaropoulos, S. S. *Anti-Cancer Drugs* **2013**, *24*, 52−65.

(5) Aricò, F.; Tundo, P. *Russ. Chem Rev.* **2010**, *79*, 479-489.

~~(6)~~ (a) Grego, S.; Aricò, F.; Tundo, P. *Pure Appl. Chem*. **2012**, *84*, 695−705. (b) Mc Elroy1, C. R.; Aricò, F.; Benetollo, F.; Tundo, P. *Pure Appl. Chem.* **2012***, 84*, 707–719.

(7) (a) Aricò, F.; Evaristo, S.; Tundo, P. *Green Chem.* **2015**, *17*, 1176−1185. (a) Aricò, F.; Tundo, P.; Maranzana, A.; Tonachini, G. *ChemSusChem* **2012**, *5*, 1578−1586. (b) Selva, M.; Marques, C. A.; Tundo, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1323−1328.

(8) (a) Aricò, F.; Chiurato, M.; Peltier, J.; Tundo, P. *Eur. J. Org. Chem.* **2012**, 3223−3228. (b) Aricò, F.; Tundo, P. *Pure Appl. Chem.* **2016**, *88*, 3–16.

(9) (a) Aricò, F.; Udrea, I.; Crisma, M.; Tundo, P. *ChemPlusChem* **2015**, *80*, 471−474. (b) Venkataraman, S.; Ng, V. W. L.; Coady, D. J.; Horn, H. W. Jones, G. O.; Fung, T. S.; Sardon, H.; Waymouth, R. M.; Hedrick, J. L.; Yang. Y. Y. *J. Am. Chem. Soc.* **2015**, *137*, 13851−13860.

(10) (a) Métro, T.-X.; Duthion, B.; Pardo, D. G.; Cossy, J. *Chem. Soc. Rev.* **2010**, *39*, 89–102. (b) Dolfen, J.; Yadav, N. N.; De Kimpe, N.; D'hooghe, M.; Hab, H.-J. *Adv. Synth. Catal.* **2016**, *358*, 3485 – 3511. (c) Catak, S.; D'hooghe, M.; De Kimpe, N.; Waroquier, M.; Van Speybroeck, V. *J. Org. Chem.* **2010**, *75*, 885–896. (d) Catak, S.; D'hooghe, M.; Verstraelen, T.; Hemelsoet, K.; Van Nieuwenhove, A.; Ha, H.-J.; Waroquier, M.; De Kimpe, N.; Van Speybroeck, V.; *J. Org. Chem.* **2010**, 75, 4530 – 4541.

(11) (a) Yun, S. Y.; Catak, S.; Lee, W. K.; D'hooghe, M.; De Kimpe, N. *Chem. Commun.* **2009**, 2508–2510; (b) D'hooghe, M.; Catak, S.; Stankovic´, S.; Waroquier, M.; Kim, Y.; Ha, H.-J. Van Speybroeck, V.; De Kimpe, N. *Eur. J. Org. Chem.* **2010**, 4920–4931. (c) Quinodoz, P.; Drouillat, B.; Wright, K.; Marrot, J.; Couty, F. *J. Org. Chem.* **2016**, 81, 2899–2910.

(12) Shiner, V. J.; Fisher, R. D. *J. Am. Chem. Soc.* **1971**, *93*, 2553-2554.

(13) (a) De Kimpe, N.; Boelens, M. *J. Chem. Soc. Chem. Commun.* **1993**, 916-918. (b) de Kimpe, N.; Boelens, M.; Piqueur, J.; Baele. J. *Tetrahedron Lett.* **1994**, *35*, 1925-1928. (c) Viegas, C., Jr.; Bolzani, V. S.; Furlan, M.; Barreiro, E. J.; Young, M. C. M.; Tomazela, D.; Eberlin, M. N. *J. Nat. Prod.* **2004**, *67*, 908−910. (d) Boja, P.; Won, S. W.; Suh, D. H.; Chu, J.; Park, W. K.; Lim, H. J. *Korean Chem. Soc.* **2006**, *27*, 1371−1376. (e) Castro, N. G.; Costa, R. S.; Pimentel, L. S. B.; Danuello, A.; Romeiro, N. C.; Viegas, C., Jr.; Barreiro, E. J.; Fraga, C. A. M.; Bolzani, V. S.; Rocha, M. S. *Eur. J. Pharmacol.* **2008**, 580, 339−349.

(14) Grayson, N. A.; Bowen, W. D.; Rice, K. C. *Heterocycles* **1992**, *34*, 2281 –2292.

(15) (a) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431 –4439; (b) Amat, M.; Brunaccini, E.; Checa, B.; Pèrez, M.; Llor, N.; Bosch, J. *Org. Lett.* **2009**, *11*, 4370 – 4373; (c) Nakamura, Y.; Burke, A. M.; Kotani, S.; Ziller, J. W.; Rychnovsky, S. D. *Org. Lett.* **2010**, *12*, 72– 75.

(16) (a) Takahata, H.; Inose, K.; Araya, N.; Momose, T. *Heterocycles* **1994**, *38*, 1961 –1964; (b) Takahata, H.; Kubota, M.; Takahashi, S.; Momose, T. *Tetrahedron: Asymmetry* **1996**, *7*, 3047 –3054; (c) Takahata, H.; Kubota, M.; Ikota, N. *J. Org. Chem*. **1999**, *64*, 8594 –8601.
(17) (a) De Kimpe, N.; Boelens, M.; Piqueur, J.; Baele, J. *Tetrahedron Lett.* **1994**, *35*, 1925-1928. (b) Cochi, A.; Pardo, D. G.; Cossy, J. Eur. *J. Org. Chem.* **2012**, 2023–2040. (c) Rioton, S.; Orliac, A.; Antoun, Z.; Bidault, R.; Pardo, D. G.; Cossy J. *Org. Lett.* **2015**, *17*, 2916−2919; (d) Déchamps, I.; Pardo, D. G.; Cossy, J. *Eur. J. Org. Chem.* **2007**, 4224–4234.
(18) Pardo, D. G.; Cossy, J. *Chem. Eur. J.* **2014**, 20, 4516 – 452.
(19) Kandepedu, N.; Abrunhosa-Thomasa, I.; Troin, Y. *Org. Chem. Front.* **2017**, *4*, 1655-1704.

Table of contents