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Solvent-Controlled Selective Transformation of 2-Bromomethyl-2-methylaziridines to Functionalized Aziridines and Azetidines

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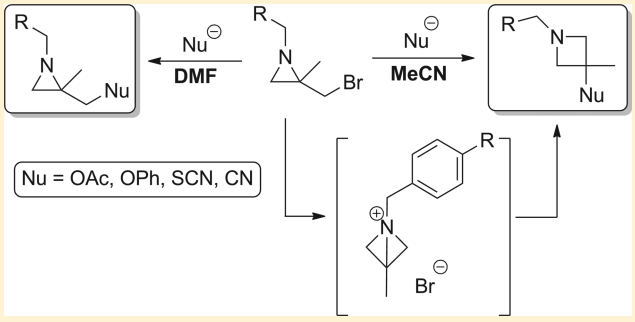
Supporting Information

ABSTRACT: The reactivity of 2-bromomethyl-2-methylaziridines toward oxygen, sulfur, and carbon nucleophiles in different solvent systems was investigated. Remarkably, the choice of the solvent has a profound influence on the reaction outcome, enabling the selective formation of either functionalized aziridines in dimethylformamide (through direct bromide displacement) or azetidines in acetonitrile (through rearrangement via a bicyclic aziridinium intermediate). In addition, the experimentally observed solvent-dependent behavior of 2-bromomethyl-2-methylaziridines was further supported by means of DFT calculations.

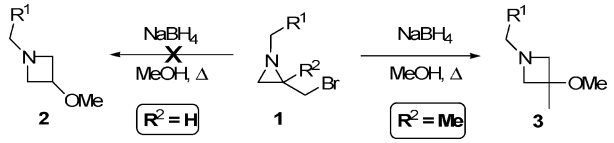


INTRODUCTION

Aziridines display an uncommon combination of reactivity, atom economy and synthetic utility related to the ring strain of this class of nitrogen-containing heterocycles.[1] As a consequence, aziridines are frequently deployed as versatile synthetic intermediates for the preparation of a variety of ring-opened and ring-expanded amines via regio- and stereoselective ring-opening reactions with nucleophiles.[2] Azetidines, the higher homologues of aziridines, have acquired a prominent position in organic chemistry as well. Next to their synthetic relevance,[3] compounds containing an azetidine moiety have been shown to possess a wide range of biological activities.[4] For example, 3-alkoxy- and 3-aryloxyazetidines have been described as G-protein coupled receptor agonists,[5] inhibitors of stearoyl-coenzyme d-9 desaturase[6] and antibacterial agents.[7]

Within the class of 2-substituted, nonactivated aziridines, the use of 2-(bromomethyl)aziridines **1** (R^2 = H) as substrates for ring-opening reactions and nucleophilic substitutions has found great application in synthetic chemistry. In particular, these compounds have been used as suitable synthons for the preparation of cyclopropanes,[8] morpholines,[9] pyrrolizidines,[10] pyrrolidines,[10] 2-imino-1,3-thiazoli(di)nes[11] and piperidine derivatives.[12] In addition, the nucleophilic substitution of bromide in 2-(bromomethyl)aziridines **1** (R^2 = H) with various heteroatom nucleophiles[9,11,13] and carbon nucleophiles[8,14] has provided a convenient access toward a variety of 2-substituted aziridines. Furthermore, it should be stressed that these aziridines **1** (R^2 = H) are not susceptible to a ring expansion process upon heating with $NaBH_4$ in methanol to afford the corresponding 3-methoxyazetidines **2** (Scheme 1).[15] On the other hand, we recently reported that structurally similar 2-bromomethyl-2-methylaziridines **1** (R^2 = Me) readily rearrange into 3-methoxy-3-methylazetidines **3** under the same reaction conditions ($NaBH_4$, MeOH, reflux).[16] In the same paper, a single example of the ring rearrangement of a 2-bromomethyl-2-methylaziridine into the corresponding 3-bromo-3-methylazetidine has been described as well upon heating in acetonitrile for 15 h. The isomerization of 2-(halomethyl)aziridines to 3-haloazetidines has been observed in the literature in only a few exceptional cases,[17] pointing to the peculiar nature of this type of rearrangement.

Scheme 1. Reactivity of 1-Alkyl-2-(bromomethyl)aziridines 1 with Respect to $NaBH_4$ in MeOH



The limited number of reports regarding aziridine to azetidine ring expansions and the mainly unexplored synthetic potential of 2-bromomethyl-2-methylaziridines prompted us to investigate the chemistry of this class of aziridines in more detail. Thus, the present study deals with the reactivity of 2-bromomethyl-2-methylaziridines **1** (R^2 = Me) toward different oxygen, sulfur and carbon nucleophiles in different solvent

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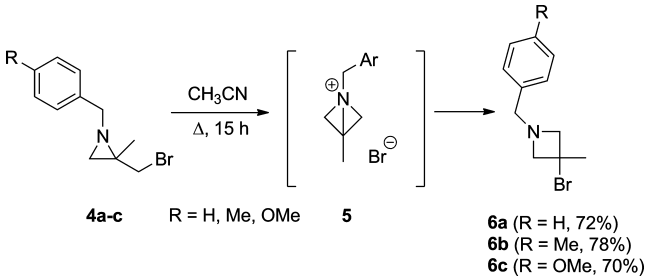
systems, providing an unexpected solvent-mediated synthesis of substituted aziridines and azetidines selectively. The experimentally observed results were further investigated and supported by high-level molecular modeling.

RESULTS AND DISCUSSION

Experimental Results. The synthesis of 2-bromomethyl-2-methylaziridines **4** through $NaBH_4$-mediated reduction of α,β-dibromoaldimines, obtained by bromination and subsequent imination of 2-methylpropenal, has recently been reported.[16] To provide a general access to novel 3-bromoazetidines as versatile synthons, 2-bromomethyl-2-methylaziridines **4a–c** were subjected to heating in acetonitrile at reflux temperature for 15 h. These reactions resulted in the selective formation of 3-bromo-3-methylazetidines **6a–c**, obtained through bromide attack at the more-hindered carbon atom of the intermediate bicyclic aziridinium species **5** (Scheme 2). The broad synthetic

Scheme 2. Transformation of 2-(Bromomethyl)aziridines 4 to 3-Bromoazetidines 6a–c

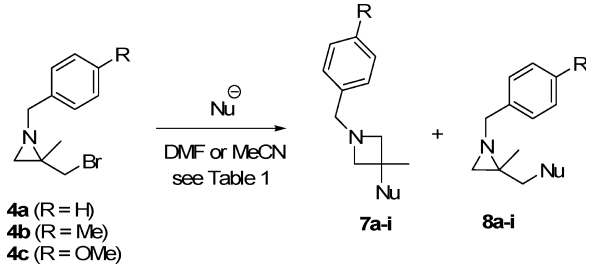


potential of 3-haloazetidines has been demonstrated in the literature in terms of their nucleophilic substitution with different nucleophiles.[18] The intermediacy of bicyclic aziridinium species **5** in this peculiar aziridine to azetidine rearrangement protocol has previously been studied and was confirmed by means of high level molecular modeling calculations.[16] It should be stressed that this thermodynamically-controlled aziridine to azetidine rearrangement has very few precedents in the chemical literature and might provide a window of opportunities for the selective synthesis of novel 3-substituted azetidines.

Thus, the intrinsic reactivity of 2-bromomethyl-2-methylaziridines **4** to undergo a ring rearrangement was further investigated utilizing a variety of different nucleophiles such as thiocyanate, cyanide, phenoxide and acetate to assess the scope of this transformation with respect to carbon and heteroatom nucleophiles.

First, aziridines **4a–c** were treated with 1 equiv of KSCN in acetonitrile at reflux temperature for 2–4 h, furnishing mixtures of 3-methyl-3-thiocyanatoazetidines **7a–c** and 2-methyl-2-(thiocyanatomethyl)aziridines **8a–c**, with azetidines **7a–c** being the major products (ratio **7**/**8** = 50–67/50–33, entry 1–3, Table 1) (Scheme 3). From these mixtures, azetidines

Scheme 3. Transformation of 2-Bromomethyl-2-methylaziridines 4 to Functionalized Azetidines 7 and Aziridines 8



7a–c were isolated in pure form by preparative TLC chromatography on silica gel. Several experiments were performed to optimize the reaction conditions. Surprisingly, when aziridines **4a–c** were treated with 1 equiv of KSCN in DMF at 60–70 °C for 15–20 h aziridines **8a–c** were obtained as the sole reaction products (entry 10–12, Table 1), giving rise to a new and straightforward synthetic methodology for the selective preparation of either aziridines in DMF and azetidines in acetonitrile. Aziridines **8a–c** were then successfully purified by means of column chromatography on silica gel to obtain

Table 1. Transformation of 2-Bromomethyl-2-methylaziridines 4 to Functionalized Azetidines 7 and Aziridines 8

entry	R	Nu	reaction conditions	ratio 7/8[a]	yield 7 or 8
1	H	SCN	1 equiv KSCN, 2 h, Δ, MeCN	50/50	**7a** (45%)
2	Me	SCN	1 equiv KSCN, 3 h, Δ, MeCN	57/43	**7b** (55%)
3	OMe	SCN	1 equiv KSCN, 4 h, Δ, MeCN	67/33	**7c** (65%)
4	Me	CN	2 equiv KCN, 26 h, Δ, MeCN	100/0	**7d** (96%)
5	OMe	CN	2 equiv KCN, 26 h, Δ, MeCN	100/0	**7e** (95%)
6	Me	OPh	2.2 equiv PhOH, 5 equiv K_2CO_3, 20 h, Δ, MeCN	57/43	**7f** (47%)
7	OMe	OPh	2.2 equiv PhOH, 5 equiv K_2CO_3, 24 h, Δ, MeCN	67/33	**7g** (65%)
8	Me	OAc	1.1 equiv NaOAc, 24 h, Δ, MeCN	100/0	**7h** (95%)
9	OMe	OAc	1.1 equiv NaOAc, 22 h, Δ, MeCN	100/0	**7i** (92%)
10	H	SCN	1 equiv KSCN, 15 h, 60–70 °C, DMF	0/100	**8a** (94%)
11	Me	SCN	1 equiv KSCN, 15 h, 60–70 °C, DMF	0/100	**8b** (95%)
12	OMe	SCN	1 equiv KSCN, 20 h, 60–70 °C, DMF	0/100	**8c** (90%)
13	Me	CN	1 equiv KCN, 16 h, 50–60 °C, DMF	0/100	**8d** (85%)
14	OMe	CN	1 equiv KCN, 16 h, 50–60 °C, DMF	0/100	**8e** (89%)
15	Me	OPh	2.2 equiv PhOH, 5 equiv K_2CO_3, 17 h, 50 °C, DMF	10/90	**8f** (85%)
16	OMe	OPh	2.2 equiv PhOH, 5 equiv K_2CO_3, 14 h, 50 °C, DMF	0/100	**8g** (90%)
17	Me	OAc	1.1 equiv NaOAc, 5 days, r.t., DMSO	20/80	**8h** (72%)
18	OMe	OAc	1.1 equiv NaOAc, 3 days, r.t., DMSO	25/75	**8i** (45%)

[a]Determined based on ^{1}H NMR.

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analytically pure samples. Aziridines **8a–c** were susceptible to partial decomposition during the chromatographic purification process.

Bearing in mind the different reactivity profile of aziridines **4** toward KSCN in different solvents (MeCN versus DMF), 2-bromomethyl-2-methylaziridines **4b,c** were then treated with other nucleophiles such as cyanide, phenoxide and acetate both in MeCN and DMF as the solvent medium (Scheme 3, Table 1).

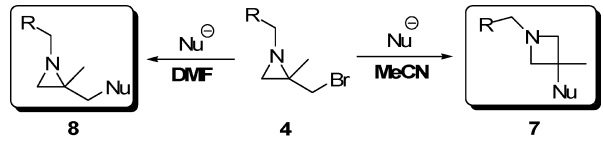
After treatment of aziridines **4b,c** with 2 equiv of KCN in MeCN for 26 h at reflux temperature, only 3-cyano-3-methylazetidines **7d,e** were obtained (entry 4–5, Table 1), whereas the same reaction in DMF gave exclusively 2-cyanomethyl-2-methylaziridines **8d,e** after 16 h at 50–60 °C (entry 13–14, Table 1). As in the case of thiocyanate (Nu = SCN), the reaction outcome was shown to be dictated by the solvent used in these reactions, providing an efficient method for the synthesis of new functionalized aziridines and azetidines in a selective way. Azetidines **7d,e** and aziridines **8d,e** were purified by means of column chromatography on silica gel to provide analytically pure samples.

The reaction of aziridines **4b,c** with 2.2 equiv of phenol and 5 equiv of K_2CO_3 in MeCN for 20–24 h was not so straightforward and gave mixtures of 3-methyl-3-phenoxyazetidines **7f,g** and 2-methyl-2-(phenoxymethyl)aziridines **8f,g**, in which azetidines **7f,g** were present as the major isomers (ratio **7**/**8** = 57–67/43–33, entry 6–7, Table 1). These compounds were separated and isolated by means of column chromatography (SiO_2) to obtain analytically pure samples. On the other hand, treatment of aziridines **4b,c** with 2.2 equiv of phenol and 5 equiv of K_2CO_3 in DMF for 14–17 h at 50 °C provided 2-methyl-2-(phenoxymethyl)aziridines **8f,g** as the major products (entry 15–16, Table 1), and only small amounts (~10%) of azetidine **7f** were observed. However, the purification by silica gel column chromatography did not provide completely pure products due to coelution of an unidentified side product in small quantities (10–15%). Finally, when aziridines **4b,c** were subjected to 1.1 equiv of NaOAc in MeCN for 22–24 h at reflux temperature, 3-acetoxy-3-methylazetidines **7h,i** were produced without traces of the corresponding aziridines (entry 8–9, Table 1). On the other hand, the reaction of the same aziridines **4b,c** with 1.1 equiv of NaOAc in DMF for 16–20 h resulted in complex mixtures, in which the presence of 2-acetoxymethyl-2-methylaziridines **8h,i** (30–40%) as well as 3-acetoxy-3-methylazetidines **7h,i** (10–20%) was acknowledged by means of ^{1}H NMR analysis. It should be mentioned that the reaction with NaOAc provided a unique case of noteworthy amounts of azetidine formation in DMF as the solvent, while in all other cases (except in the case of a small amount of azetidine **7f**) the formation of azetidines using DMF as the solvent was not observed. After several attempts to optimize the reaction conditions in different solvents (DMF and DMSO), at different temperatures (r.t. to 100 °C), and by using additional reagents (such as $AgBF_4$), aziridines **8h,i** were finally obtained as the major compounds (ratio **7**/**8** = 20–25/80–75) after treatment of aziridines **4b,c** with 1.1 equiv of NaOAc in DMSO at room temperature for 3–5 days. Higher temperatures (>30 °C) yielded complete conversion of the starting aziridines **4b,c** only after a few hours, however at the expense of selectivity of this reaction (ratio **7**/**8** = 40–50/60–50). From these mixtures, aziridines **8h,i** could not be isolated in completely pure form by means of column chromatography on silica gel due to coelution of azetidines **7h,i** and small amounts of some side products (10–15%).

The ratio **7**/**8** was determined by spectroscopic analysis (^{1}H NMR) of the crude reaction mixtures. After purification, the structures of the azetidines **7** and aziridines **8** were confirmed by means of different characterization methods (^{1}H NMR, ^{13}C NMR, IR, MS).

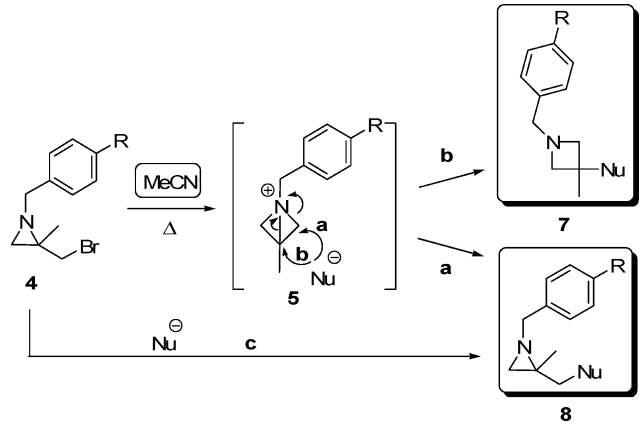
The selective transformation of aziridines **4** toward either azetidines **7** in acetonitrile or aziridines **8** in dimethylformamide (Scheme 4) provides interesting opportunities for further elaboration to valuable azaheterocycles.

Scheme 4. Selective Transformation of 2-Bromomethyl-2-methylaziridines 4 to Functionalized Azetidines 7 and Aziridines 8



From a mechanistic point of view, different pathways can be considered to explain the synthesis of functionalized aziridines and azetidines starting from 2-bromomethyl-2-methylaziridines **4**. An overview of possible reactivity profiles of aziridines **4** in MeCN is presented in Scheme 5. Bearing in mind the

Scheme 5. Possible Synthetic Routes for the Formation of Azetidines 7 and Aziridines 8 from Aziridines 4 in MeCN-mediated Reactions



previously reported intermediacy of bicyclic aziridinium ions in the synthesis of 3-methoxy-3-methylazetidines starting from 2-bromomethyl-2-methylaziridines,[16] the nucleophilic attack at the more hindered carbon atom of the strained intermediates **5** (path b, Scheme 5) is considered to be the most plausible route for the formation of 3-substituted azetidines **7** in MeCN, possibly through the less stable nonbridged carbenium ion. This fact is also in accordance with the ring transformation of 2-bromomethyl-2-methylaziridines **4a–c** in MeCN at reflux temperature (Scheme 2). It should be noted that in some cases (entries 1–3, 6, 7, Table 1) the formation of aziridines **8** was observed as well (33–50%). The presence of aziridines **8** in these MeCN-mediated reactions can be attributed to nucleophilic attack at the less-hindered carbon atom of the bicyclic aziridinium ions **5** (path a, Scheme 5), taking into

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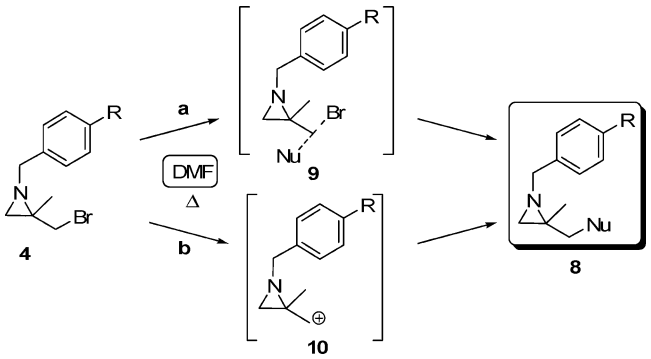
account a few isolated literature examples on the ring opening of strained bicyclic intermediates.[19] However, direct nucleophilic displacement of bromide in 2-bromomethyl-2-methylaziridines **4** by the nucleophile (path c, Scheme 5) will most probably prevail as the pathway toward substituted aziridines **8**.

The proposed mechanistic pathways for the selective formation of aziridines **8** in DMF are depicted in Scheme 6.

Scheme 6. Possible Synthetic Routes for the Formation of Aziridines 8 from Aziridines 4 in DMF-mediated Reactions



Herein, two different routes can be considered, involving either direct displacement of bromide by the approaching nucleophile via a S_N2 protocol (path a, intermediate **9**, Scheme 6) or via the formation of primary carbenium ions **10** (S_N1 mechanism, path b, Scheme 6), which might be stabilized by the nitrogen lone pair through anchimeric assistance. The formation of aziridines **8** via nucleophilic attack at the less-substituted carbon atom of bicyclic aziridinium intermediates **5** (path a, Scheme 5) in DMF should not be completely neglected, although the fact that aziridines **4** do not rearrange into azetidines **6** upon heating in DMF for several hours suggests that no bicyclic aziridinium species **5** are formed in these reactions.

To shed more light on the remarkable preference for the formation of azetidines in MeCN and aziridines in DMF (Schemes 5 and 6), some computational analyses were performed.

Theoretical Rationalization. The solvent-dependent reactivity of different nucleophiles toward 2-bromomethyl-2-methylaziridines was further investigated by means of DFT calculations. The difference in the observed selectivity in DMF and MeCN was unexpected, since both solvents are polar and aprotic, and have very similar dielectric constants (36.71 and 35.94, respectively). However, they have different densities (943.87 and 776.49 kg m^{-3}, respectively), molar volumes (77.442 and 52.870 cm^3 mol^{-1}, respectively), shapes and dipoles. The latter properties of DMF and MeCN can influence the way they solvate ions, and ion solvation is known to be correlated with rate constants of chemical reactions.[20] Free energies of solvation of relevant ions in DMF and MeCN are quite similar, e.g. 251 and 256 kJ mol^{-1} for Br^-, 243 and 248 kJ mol^{-1} for CN^- and 213 and 217 kJ mol^{-1} for SCN^-, respectively,[21] but the difference in close-packing can be crucial for their relative reactivities, i.e. this can influence how free the nucleophiles are to attack and how willing the nucleophuge is to leave. This notion will be investigated with computational methods.

Computational Methodology. The B3LYP/6-31+G(d,p) level of theory was used for geometry optimizations of clusters of ions and solvent molecules.[22] Stationary points were characterized as minima (ground states) *via* frequency calculations. The B3LYP functional has been proven to produce good geometries, but is less accurate for energy calculations.[23] Therefore energies were refined with the MPW1K functional, which has shown its utility for energy calculations.[24] Previous computational studies have demonstrated the necessity of *d* and *f* polarization functions on the sulfur basis set,[25] hence, the MPW1K functional was used in conjunction with the 6-311+G(3df,2p) basis set for sulfur and the 6-31++G(d,p) basis set for all other atoms, since this method was shown to be adequate for calculations on sulfur-containing systems.[24e] All thermal free energy corrections reported were taken from B3LYP/6-31+G(d,p) optimizations at 1 atm and 298 K. All computations were performed with the Gaussian 09 program packages.[26]

Coordination Solvation Energies. As briefly mentioned earlier, a different close-packing of the nucleophiles (CN^- and SCN^-), the nucleophuge Br^- or even the bicyclic aziridinium intermediate **5** by DMF and MeCN could be very important for the relative reactivity of these ions. To investigate the close-packing, the convergence behavior of the energy of coordination solvation was inspected by means of systematically increasing the number of explicit solvent molecules around the ions, and the corresponding coordination solvation energies (CSE's) and coordination solvation free energies (CSG's) were calculated.[24e,f,27] CSG's are known to converge before CSE's, which is merely caused by entropic effects. CSE's are listed in the Supporting Information.

It has recently been reported that rearrangement of 2-bromomethyl-2-methylaziridines **1** (R^2 = Me) with $NaBH_4$ in MeOH toward 3-methoxy-3-methylazetidines **3** (Scheme 1) takes place *via* a bicyclic aziridinium ion.[16] Free energies of activation for the formation of the bicyclic intermediate were found to be reasonable and the bicyclic intermediate was found to be far more stable than its nonbridged counterpart. Therefore, it is likely that the rearrangement of aziridines **4** toward azetidines **7** takes place *via* a bicyclic aziridinium species **5** (Scheme 5).

Coordination of the bicyclic aziridinium species **5** by DMF and MeCN is shown in Figures 1 and 2, respectively. From experimental data, it is clear that this intermediate was formed in MeCN (Table 1) but not in DMF (Table 1). A possible explanation is a better stabilization of intermediate **5** in MeCN than in DMF. From the coordination solvation energies, stabilization of **5** does not seem to cause the difference in reactivity in DMF and MeCN, since coordination at the most accessible places by both solvents gives rise to a stronger coordination with DMF than with MeCN (CSG_{MPW1K} = −49.7 and −34.6 kJ/mol for DMF and MeCN, respectively, Figures 1 and 2). This is understandable, since the DMF oxygen and the MeCN nitrogen interact with the hydrogen atoms of **5**, and oxygen is more electronegative than nitrogen. This can also be seen in the distances between the hydrogen atoms of **5** and both the DMF oxygen atoms (2.29−2.65 Å) and the MeCN nitrogen atoms (2.50−2.84 Å). Moreover, coordination solvation energies for both solvents converge with 3 solvent molecules, thus coordination with more solvent molecules is not expected to make a substantial difference. The close-packing of **5** by DMF could avoid it from getting attacked by a nucleophile to give azetidine **7**, while **5** is more readily available for nucleophilic attack in MeCN.

The difference in observed regioselectivity in DMF and MeCN can alternatively be due to a stronger coordination and

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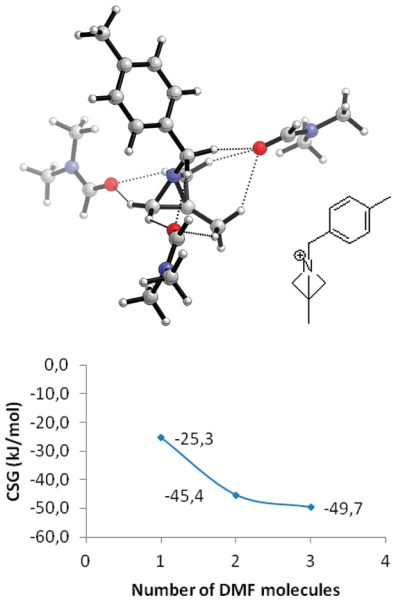

Figure 1. Coordination of the bicyclic aziridinium **5b** by an increasing number of DMF molecules. MPW1K/6-31++G(d,p)//B3LYP/6-31+G(d,p). **5b** with 3 DMF molecules shown in figure. Distances between the hydrogen atoms of **5** and the DMF oxygen atoms are 2.29−2.65 Å.

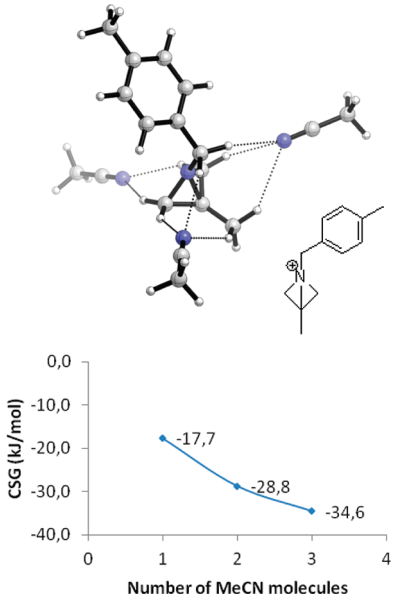

Figure 2. Coordination of the bicyclic aziridinium **5b** by an increasing number of MeCN molecules. MPW1K/6-31++G(d,p)//B3LYP/6-31+G(d,p). **5b** with 3 MeCN molecules shown in figure. Distances between the hydrogen atoms of **5** and the MeCN nitrogen atoms are 2.50−2.84 Å.

better stabilization of the nucleophile by MeCN and hence, a higher probability for the formation of the bicyclic intermediate **5** in MeCN—with subsequent formation of azetidine **7**—over the direct replacement of Br^- by the nucleophile in aziridine **4** and formation of aziridine **8** (Scheme 4). Coordination of the nucleophile CN^- by DMF and MeCN is shown in Figures 3 and 4, respectively. Coordination of CN^- with three explicit DMF or MeCN molecules shows that CN^- is strongly coordinated and thus better stabilized by MeCN than by DMF (CSG_{MPW1K} = −41.0 and −56.3 kJ/mol for DMF and

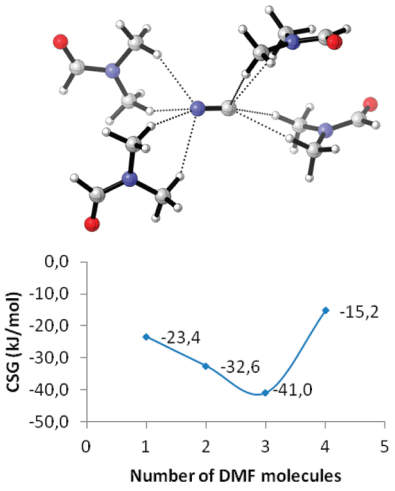

Figure 3. Coordination of CN^- by an increasing number of DMF molecules. MPW1K/6-31++G(d,p)//B3LYP/6-31+G(d,p). CN^- with 4 DMF molecules shown in figure. Distances between the hydrogen atoms of DMF and the CN^- nitrogen and carbon are 2.40−2.67 and 2.57−2.89 Å, respectively.

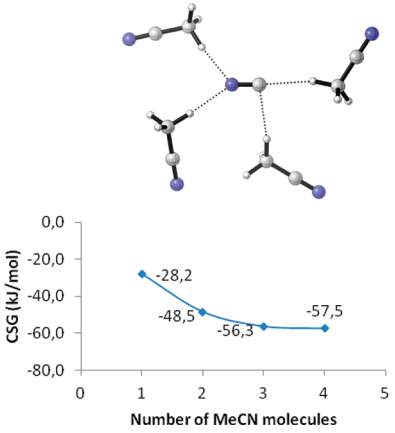

Figure 4. Coordination of CN^- by an increasing number of MeCN molecules. MPW1K/6-31++G(d,p)//B3LYP/6-31+G(d,p). CN^- with 4 MeCN molecules shown in figure. Distances between the hydrogen atoms of MeCN and the CN^- nitrogen and carbon are 2.14−2.17 and 2.36−2.51 Å, respectively.

MeCN, respectively). Furthermore, MeCN molecules can pack more closely than DMF molecules, as seen in the relative distances between the hydrogen atoms of the solvent and the CN^- nitrogen (2.40−2.67 and 2.14−2.17 Å in DMF and MeCN, respectively) and the CN^- carbon (2.57−2.89 and 2.36−2.51 Å in DMF and MeCN, respectively). Coordination solvation energies for DMF and MeCN converge after coordination with three and four molecules, respectively, and two hydrogen atoms of each DMF molecule can coordinate with CN^- while only one hydrogen atom of MeCN coordinates with CN^-, but the bulky DMF methyl groups prevent the DMF molecules from packing closely. The stronger coordination and better stabilization of CN^- by MeCN can point to a lower reactivity, hence allowing the formation of azetidine **7** via formation of the bicyclic intermediate **5**. Since CN^- is less stabilized in DMF, it will be more reactive and hence, nucleophilic substitution in aziridine **4** will lead to aziridine **8**.

In the case of the nucleophile SCN^-, a mixture of both **7** and **8** is experimentally observed. Hence, the difference between the

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coordination solvation of CN^- and SCN^- can illustrate the reasoning behind this experimental observation. Coordination of SCN^- by DMF and MeCN is shown in Figures 5 and 6,

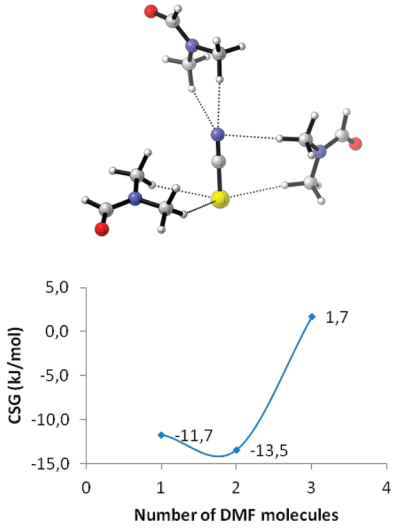

Figure 5. Coordination of SCN^- by an increasing number of DMF molecules. MPW1K/6-31++G(d,p)//B3LYP/6-31+G(d,p). SCN^- with 3 DMF molecules shown in figure. Distances between the hydrogen atoms of DMF and the SCN^- nitrogen and sulfur are 2.40–2.64 and 3.03–3.11 Å, respectively.

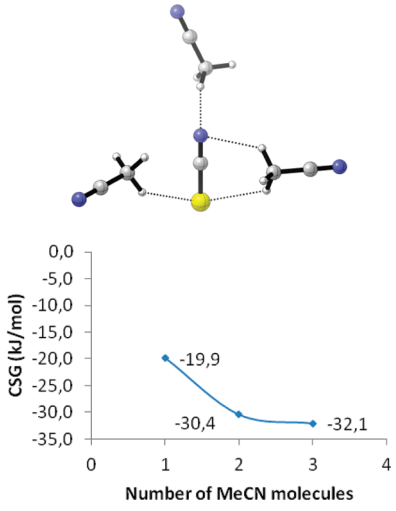

Figure 6. Coordination of SCN^- by an increasing number of MeCN molecules. MPW1K/6-31++G(d,p)//B3LYP/6-31+G(d,p). SCN^- with 3 MeCN molecules shown in figure. Distances between the hydrogen atoms of MeCN and the SCN^- nitrogen and sulfur are 2.22–2.72 and 2.93–3.07 Å, respectively.

respectively. Coordination of SCN^- with two explicit DMF or MeCN molecules shows that SCN^- is strongly coordinated and thus better stabilized in MeCN as the solvent as compared to DMF as the solvent (CSG_{MPW1K} = −13.5 and −30.4 kJ/mol for DMF and MeCN, respectively). Coordination solvation energies for SCN^- with DMF and MeCN converge after coordination with two and three molecules, respectively. However, in this case the packing distances of MeCN and DMF molecules are not strikingly different. On the other hand, MeCN molecules pack more closely to CN^- than to SCN^- (distances between the hydrogen atoms of MeCN and the CN^- and SCN^- nitrogen are 2.14–2.17 and 2.22–2.72 Å, respectively, and distances between the hydrogen atoms of MeCN and the CN^- carbon and SCN^- sulfur are 2.36–2.51 and 2.93–3.07 Å, respectively). This, together with the difference between the coordination solvation energies of CN^- and SCN^- in MeCN (CSG_{MPW1K} = −56.3 and −32.1, respectively) could explain why both the formation of the bicyclic intermediate **5** and nucleophilic substitution in aziridine **4** are possible for SCN^- in MeCN.

For completeness, coordination of Br^- by DMF and MeCN is shown in Figures 7 and 8, respectively. Like CN^-, Br^- is

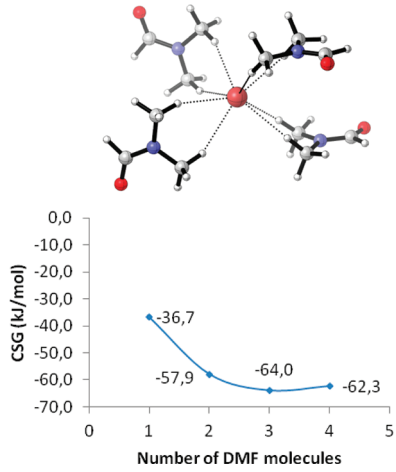

Figure 7. Coordination of Br^- by an increasing number of DMF molecules. MPW1K/6-31++G(d,p)//B3LYP/6-31+G(d,p). Br^- with 4 DMF molecules shown in figure. Distances between the hydrogen atoms of DMF and Br^- are 2.76–2.87 Å.

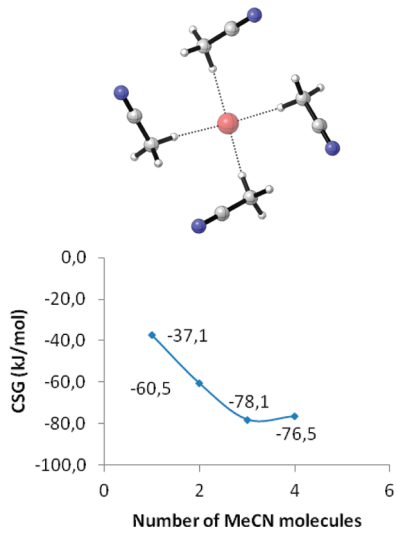

Figure 8. Coordination of Br^- by an increasing number of MeCN molecules. MPW1K/6-31++G(d,p)//B3LYP/6-31+G(d,p). Br^- with 4 MeCN molecules shown in figure. Distances between the hydrogen atoms of MeCN and Br^- are 2.60 Å.

strongly coordinated and thus better stabilized by MeCN than by DMF (CSG_{MPW1K} = −64.0 and −78.1 kJ/mol for three explicit DMF and MeCN molecules, respectively). The stronger coordination of Br^- by MeCN can improve its leaving group capacity and thus help in the formation of the bicyclic intermediate **5**.

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Thus, stabilization of **5** does not seem to cause the difference in reactivity in DMF and MeCN but the close-packing of **5** by DMF could avoid it from getting attacked by a nucleophile. Furthermore, the stronger coordination and better stabilization of CN^- by MeCN can point to a lower reactivity, hence allowing the formation of azetidine **7** via formation of the bicyclic intermediate **5**. Since CN^- is less stabilized in DMF, it will be more reactive, and hence, nucleophilic substitution of aziridine **4** will lead to aziridine **8**. The weaker coordination of SCN^- by MeCN, compared to CN^-, could explain why both the formation of the bicyclic intermediate **5** and nucleophilic substitution in the aziridine **4** are possible for SCN^- in MeCN. Finally, the stronger coordination of Br^- by MeCN can improve its leaving group capacity and thus help in the formation of the bicyclic intermediate **5**.

In summary, the reactivity of 2-bromomethyl-2-methylaziridines **4** with regard to different carbon, oxygen and sulfur nucleophiles was investigated, providing an efficient strategy toward the selective synthesis of a large variety of functionalized aziridines and azetidines. The reaction outcome was proven to be controlled by the choice of the solvent, showing DMF to be a suitable solvent for the synthesis of the corresponding aziridines **8** and MeCN for the synthesis of the corresponding azetidines **7** as major compounds via strained bicyclic intermediates. To account for the experimentally observed results, DFT calculations were employed to elucidate the extraordinary preference for the formation of azetidines in MeCN and aziridines in DMF.

EXPERIMENTAL PART

General. ^{1}H NMR spectra were recorded at 300 MHz with $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 75 MHz with $CDCl_3$ as solvent. Mass spectra were recorded using either a direct inlet system (electron spray, 4000 V) or LC-MS coupling (UV detector). IR spectra were recorded on a FT-IR spectrometer. All compounds were analyzed in neat form with an ATR (Attenuated Total Reflectance) accessory. Dichloromethane was distilled over calcium hydride, while diethyl ether and THF were distilled from sodium and sodium benzophenone ketyl before use.

Synthesis of 3-Bromo-3-methylazetidines 6a,c. As a representative example, the synthesis of 1-benzyl-3-bromo-3-methylazetidine **6a** is described here. 1-Benzyl-2-bromomethyl-2-methylaziridine **4a** (1.20 g, 5 mmol) was dissolved in acetonitrile (30 mL), and the mixture was heated at reflux temperature for 15 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent in vacuo afforded 1-benzyl-3-bromo-3-methylazetidine **6a** (0.86 g, 72%), which was purified by silica gel column chromatography (petroleum ether/ethyl acetate 7/1) to obtain an analytically pure sample.

1-Benzyl-3-bromo-3-methylazetidine ***6a.*** Yellow oil; R_f = 0.30 (petroleum ether/ethyl acetate 7/1); Yield, 72%; isolated yield, 62% (after purification); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (3H, *s*), 3.52 (2H, *d*, *J* = 9.1 Hz), 3.69 (2H, *d*, *J* = 9.1 Hz), 3.71 (2H, *s*), 7.21−7.33 (5H, *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 31.6 (CH_3), 51.9 (C), 63.2 (CH_2), 70.9 (2× CH_2), 127.3 (2× CH), 128.5 (3× CH), 137.8 (C); IR (neat, cm^{-1}) ν_{max} = 2924, 2844, 1495, 1453, 1362, 1245, 1208, 1181, 746, 696; MS *m*/*z* (%) 240/2 (M^+ + 1, 100).

3-Bromo-1-(4-methoxybenzyl)-3-methylazetidine ***6c.*** Yellow oil; R_f = 0.22 (petroleum ether/ethyl acetate 7/1); Yield, 70%; isolated yield, 59% (after purification); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99 (3H, *s*), 3.49 (2H, *d*, *J* = 9.1 Hz), 3.67 (2H, *d*, *J* = 9.1 Hz), 3.64 (2H, *s*), 3.79 (3H, *s*), 6.83−6.86 and 7.18−7.20 (4H, 2 × *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 31.6 (CH_3), 52.0 (C), 55.3 (CH_3), 62.6 (CH_2), 70.7 (2× CH_2), 113.8 (2× CH), 129.7 (2× CH), 129.1 (C), 158.9 (C); IR (neat, cm^{-1}) ν_{max} = 2930, 2835, 1612, 1511, 1243, 1171, 1034, 819, 738, 696; MS *m*/*z* (%) 240/2 (M^+ + 1, 100).

Synthesis of 3-Methyl-3-thiocyanatoazetidines 7a−c. As a representative example, the synthesis of 1-(4-methoxybenzyl)-3-methyl-3-thiocyanatoazetidine **7c** is described here. 2-Bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine **4c** (1.35 g, 5 mmol) was dissolved in acetonitrile (30 mL), after which KSCN (0.49 g, 1 equiv) was added and the mixture was heated at reflux temperature for 4 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 1-(4-methoxybenzyl)-3-methyl-3-thiocyanatoazetidine **7c** and 2-methyl-2-(thiocyanatomethyl)aziridine **8c** (**7c**/**8c** = ratio 67/33), from which 1-(4-methoxybenzyl)-3-methyl-3-thiocyanatoazetidine **7c** (0.94 g, 65%) was isolated in pure form by preparative thin layer chromatography on silica gel (hexane/ethyl acetate/triethylamine 1/1/0.01) to obtain an analytically pure sample.

1-Benzyl-3-methyl-3-thiocyanatoazetidine ***7a.*** Yellow oil; R_f = 0.20 (hexane/ethyl acetate/triethylamine 1/1/0.01); Yield, 45%; isolated yield, 36% (after purification); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.79 (3H, *s*), 3.35 (2H, *d*, *J* = 8.8 Hz), 3.47 (2H, *d*, *J* = 8.8 Hz), 3.69 (2H, *s*), 7.24−7.35 (5H, *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 26.4 (CH_3), 47.5 (C), 62.5 (CH_2), 66.3 (2× CH_2), 111.5 (C), 127.5 (CH), 128.5 (2× CH), 128.6 (2× CH), 137.2 (C); IR (neat, cm^{-1}) ν_{SCN} = 2151; MS *m*/*z* (%) 219 (M^+ + 1, 100).

3-Methyl-1-(4-methybenzyl)-3-thiocyanatoazetidine ***7b.*** Yellow oil; R_f = 0.22 (hexane/ethyl acetate/triethylamine 1/1/0.01); Yield, 55%; isolated yield, 47% (after purification); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (3H, *s*), 2.33 (3H, *s*), 3.33 (2H, *d*, *J* = 8.8 Hz), 3.46 (2H, *d*, *J* = 8.8 Hz), 3.64 (2H, *s*), 7.11−7.18 (4H, *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.2 (CH_3), 26.4 (CH_3), 47.5 (C), 62.3 (CH_2), 66.2 (2× CH_2), 111.5 (C), 128.5 (2× CH), 129.2 (2× CH), 134.1 (C), 137.1 (C); IR (neat, cm^{-1}) ν_{SCN} = 2151; MS *m*/*z* (%) 233 (M^+ + 1, 100).

1-(4-Methoxybenzyl)-3-methyl-3-thiocyanatoazetidine ***7c.*** Yellow oil; R_f = 0.18 (hexane/ethyl acetate/triethylamine 1/1/0.01); Yield, 65%; isolated yield, 52% (after purification); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.78 (3H, *s*), 3.32 (2H, *d*, *J* = 9.4 Hz), 3.44 (2H, *d*, *J* = 9.4 Hz), 3.62 (2H, *s*), 3.80 (3H, *s*), 6.84−6.87 and 7.18−7.20 (4H, 2 × *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 26.4 (CH_3), 47.5 (C), 55.4 (CH_3), 61.9 (CH_2), 66.1 (2× CH_2), 111.5 (C), 113.9 (2× CH), 129.2 (C), 129.8 (2× CH), 159.0 (C); IR (neat, cm^{-1}) ν_{SCN} = 2151; MS *m*/*z* (%) 249 (M^+ + 1, 100); HRMS *m*/*z* (ESI) calculated for $C_{13}H_{16}N_2OS$ $[MH]^+$ 249.1062, found 249.1059.

Synthesis of 2-Methyl-2-(thiocyanatomethyl)aziridines 8a−c. As a representative example, the synthesis of 2-methyl-1-(4-methylbenzyl)-2-(thiocyanatomethyl)aziridine **8b** is described here. 2-Bromomethyl-2-methyl-1-(4-methylbenzyl)aziridine **4b** (1.27 g, 5 mmol) was dissolved in DMF (30 mL), after which KSCN (0.49 g, 1 equiv) was added and the mixture was stirred at 60−70 °C for 15 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-methyl-1-(4-methylbenzyl)-2-(thiocyanatomethyl)aziridine **8b** (0.91 g, 95%), which was purified by silica gel column chromatography (hexane/ethyl acetate/triethylamine 1/1/0.1) to obtain an analytically pure sample. It should be mentioned that aziridines **8a−c** showed to be rather unstable on silica gel column during the purification process.

1-Benzyl-2-methyl-2-(thiocyanatomethyl)aziridine ***8a.*** Light yellow oil; R_f = 0.43 (hexane/ethyl acetate/triethylamine 1/1/0.1); Yield, 94%; isolated yield, 41% (after purification); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (1H and 3H, *s*), 2.08 (1H, *s*), 3.02 (H, *d*, *J* = 12.9 Hz), 3.14 (H, *d*, *J* = 12.9 Hz), 3.53 (H, *d*, *J* = 13.8 Hz), 3.78 (H, *d*, *J* = 13.8 Hz), 7.26−7.35 (5H, *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.0 (CH_3), 38.8 (C), 40.3 (CH_2), 45.1 (CH_2), 57.1 (CH_2), 113.1 (C),

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127.2 (CH), 128.0 (2× CH), 128.6 (2× CH), 139.3 (C); IR (neat, cm^{-1}) ν_{SCN} = 2152; MS *m/z* (%) 219 (M^+ + 1, 100); HRMS *m/z* (ESI) calculated for $C_{12}H_{14}N_2S$ $[MH]^+$ 219.0956, found 219.0952.

2-Methyl-1-(4-methylbenzyl)-2-(thiocyanatomethyl)aziridine ***8b***. Light yellow oil; R_f = 0.44 (hexane/ethyl acetate/triethylamine 1/1/0.1); Yield, 95%; isolated yield, 64% (after purification); ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (1H and 3H, *s*), 2.05 (1H, *s*), 2.34 (3H, *s*), 3.02 (H, *d*, *J* = 12.7 Hz), 3.13 (H, *d*, *J* = 12.7 Hz), 3.49 (H, *d*, *J* = 13.2 Hz), 3.73 (H, *d*, *J* = 13.2 Hz), 7.13−7.24 (4H, *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.0 (CH_3), 21.2 (CH_3), 38.8 (C), 40.2 (CH_2), 45.2 (CH_2), 56.8 (CH_2), 113.1 (C), 127.9 (2× CH), 129.2 (2× CH), 136.3 (C), 136.8 (C); IR (neat, cm^{-1}) ν_{SCN} = 2151; MS *m/z* (%) 233 (M^+ + 1, 100); HRMS *m/z* (ESI) calculated for $C_{13}H_{16}N_2S$ $[MH]^+$ 233.1112, found 233.1110.

1-(4-Methoxybenzyl)-2-methyl-2-(thiocyanatomethyl)aziridine ***8c***. Light yellow oil; R_f = 0.36 (hexane/ethyl acetate/triethylamine 1/1/0.1); Yield, 90%; isolated yield, 37% (after purification); ^1H NMR (300 MHz, $CDCl_3$) δ 1.46 (1H and 3H, *s*), 2.04 (1H, *s*), 3.00 (H, *d*, *J* = 12.9 Hz), 3.12 (H, *d*, *J* = 12.9 Hz), 3.45 (H, *d*, *J* = 13.2 Hz), 3.71 (H, *d*, *J* = 13.2 Hz), 3.81 (3H, *s*), 6.86−6.89 and 7.25−7.28 (4H, 2 × *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.0 (CH_3), 38.8 (C), 40.2 (CH_2), 45.2 (CH_2), 55.4 (CH_3), 56.5 (CH_2), 113.1 (C), 114.0 (2× CH), 129.2 (2× CH), 131.4 (C), 158.8 (C); IR (neat, cm^{-1}) ν_{SCN} = 2153; MS *m/z* (%) 249 (M^+ + 1, 100); HRMS *m/z* (ESI) calculated for $C_{13}H_{16}N_2OS$ $[MH]^+$ 249,1062, found 249.1058.

Synthesis of Azetidine-3-carbonitriles 7d,e. As a representative example, the synthesis of 1-(4-methoxybenzyl)-3-methylazetidine-3-carbonitrile **7e** is described here. 2-Bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine **4c** (1.35 g, 5 mmol) was dissolved in acetonitrile (30 mL), after which KCN (0.64 g, 2 equiv) was added in small portions and the mixture was heated at reflux temperature for 26 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-(4-methoxybenzyl)-3-methylazetidine-3-carbonitrile **7e** (0.96 g, 95%), which was purified by silica gel column chromatography (dichloromethane/methanol 10/1) to obtain an analytically pure sample.

3-Methyl-1-(4-methylbenzyl)azetidine-3-carbonitrile ***7d***. Yellow oil; R_f = 0.28 (dichloromethane); Yield, 96%; isolated yield, 88% (after purification); ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (3H, *s*), 2.33 (3H, *s*), 3.19 (2H, *d*, *J* = 6.9 Hz), 3.48 (2H, *d*, *J* = 6.9 Hz), 3.58 (2H, *s*), 7.04−7.24 (4H, *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.2 (CH_3), 22.9 (CH_3), 27.1 (C), 62.5 (CH_2), 63.4 (2× CH_2), 123.5 (C), 128.4 (2× CH), 129.2 (2× CH), 133.9 (C), 137.1 (C); IR (neat, cm^{-1}) ν_{CN} = 2238; MS *m/z* (%) 201 (M^+ + 1, 100); HRMS *m/z* (ESI) calculated for $C_{13}H_{16}N_2$ $[MH]^+$ 201.1392, found 201.1389.

1-(4-Methoxybenzyl)-3-methylazetidine-3-carbonitrile ***7e***. Yellow oil; R_f = 0.60 (dichloromethane/methanol 10/1); Yield, 95%; isolated yield, 89% (after purification); ^1H NMR (300 MHz, $CDCl_3$) δ 1.64 (3H, *s*), 3.18 (2H, *d*, *J* = 7.2 Hz), 3.48 (2H, *d*, *J* = 7.2 Hz), 3.56 (2H, *s*), 3.80 (3H, *s*), 6.84−6.87 and 7.16−7.19 (4H, 2 × *m*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7 (CH_3), 27.0 (C), 55.3 (CH_3), 62.1 (CH_2), 63.2 (2× CH_2), 113.8 (2× CH), 123.4 (C), 128.9 (C), 129.6 (2× CH), 158.9 (C); IR (neat, cm^{-1}) ν_{CN} = 2238; MS *m/z* (%) 217 (M^+ + 1, 100); HRMS *m/z* (ESI) calculated for $C_{13}H_{16}N_2O$ $[MH]^+$ 217.1341, found 217.1340.

Synthesis of 2-Cyanomethyl-2-methylaziridines 8d,e. As a representative example, the synthesis of 2-cyanomethyl-2-methyl-1-(4-methylbenzyl)aziridine **8d** is described here. 2-Bromomethyl-2-methyl-1-(4-methylbenzyl)aziridine **4b** (1.27 g, 5 mmol) was dissolved in DMF (30 mL), after which KCN (0.33 g, 1 equiv) was added and the mixture was stirred at 50−60 °C for 16 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 2-cyanomethyl-2-methyl-1-(4-methylbenzyl)aziridine **8d** (0.85 g, 85%), which was purified by silica gel column chromatography (hexane/ethyl acetate 1/1) to obtain an analytically pure sample. It should be mentioned that aziridines **8d,e** showed to be rather unstable on silica gel column during the purification process.

2-Cyanomethyl-2-methyl-1-(4-methylbenzyl)aziridine ***8d***. Yellow oil; R_f = 0.29 (hexane/ethyl acetate 1/1); Yield, 85%; isolated yield, 36% (after purification); ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (1H, *s*), 1.43 (3H, *s*), 1.96 (1H, *s*), 2.33 (3H, *s*), 2.40 (H, *d*, *J* = 16.8 Hz), 2.49 (H, *d*, *J* = 16.8 Hz), 3.52 (H, *d*, *J* = 13.8 Hz), 3.69 (H, *d*, *J* = 13.8 Hz), 7.13−7.25 (4H, *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.8 (CH_3), 21.2 (CH_3), 29.4 (CH_2), 36.7 (C), 39.4 (CH_2), 56.7 (CH_2), 117.8 (C), 127.7 (2× CH), 129.3 (2× CH), 136.4 (C), 136.8 (C); IR (neat, cm^{-1}) ν_{CN} = 2250; MS *m/z* (%) 201 (M^+ + 1, 100); HRMS *m/z* (ESI) calculated for $C_{13}H_{16}N_2$ $[MH]^+$ 201.1392, found 201.1386.

2-Cyanomethyl-1-(4-methoxybenzyl)-2-methylaziridine ***8e***. Yellow oil; R_f = 0.21 (hexane/ethyl acetate 1/1); Yield, 89%; isolated yield, 42% (after purification); ^1H NMR (300 MHz, $CDCl_3$) δ 1.39 (1H, *s*), 1.44 (3H, *s*), 1.96 (1H, *s*), 2.41 (H, *d*, *J* = 17.1 Hz), 2.49 (H, *d*, *J* = 17.1 Hz), 3.49 (H, *d*, *J* = 13.5 Hz), 3.68 (H, *d*, *J* = 13.5 Hz), 3.81 (3H, *s*), 6.86−6.90 and 7.26−7.28 (4H, 2 × *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 14.8 (CH_3), 29.4 (CH_2), 36.7 (C), 39.4 (CH_2), 55.4 (CH_3), 56.4 (CH_2), 114.0 (2× CH), 117.8 (C), 128.9 (2× CH), 131.5 (C), 158.8 (C); IR (neat, cm^{-1}) ν_{CN} = 2249; MS *m/z* (%) 217 (M^+ + 1, 100); HRMS *m/z* (ESI) calculated for $C_{13}H_{16}N_2O$ $[MH]^+$ 217.1341, found 217.1344.

Synthesis of 3-Methyl-3-phenoxyazetidines 7f,g. As a representative example, the synthesis of 1-(4-methoxybenzyl)-3-methyl-3-phenoxyazetidine **7g** is described here. 2-Bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine **4c** (1.35 g, 5 mmol) was added to a mixture of phenol (1.04 g, 2.2 equiv) and K_2CO_3 (3.46 g, 5 equiv) dissolved in acetonitrile (30 mL), and the resulting suspension was heated at reflux temperature for 24 h. The reaction mixture was cooled to room temperature, poured into a NaOH solution (30 mL, 0.5M) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 1-(4-methoxybenzyl)-3-methyl-3-phenoxyazetidine **7g** and 1-(4-methoxybenzyl)-2-methyl-2-(phenoxymethyl)aziridine **8g** (**7g**/**8g** = ratio 67/33), from which 1-(4-methoxybenzyl)-3-methyl-3-phenoxyazetidine **7g** (0.93 g, 65%) was isolated in pure form by silica gel column chromatography (petroleum ether/ethyl acetate 4/1).

3-Methyl-1-(4-methylbenzyl)-3-phenoxyazetidine ***7f***. Yellow oil; R_f = 0.25 (petroleum ether/ethyl acetate 4/1); Yield, 47%; isolated yield, 37% (after purification); ^1H NMR (300 MHz, $CDCl_3$) δ 1.60 (3H, *s*), 2.33 (3H, *s*), 3.29 (2H, *d*, *J* = 8.3 Hz), 3.55 (2H, *d*, *J* = 8.3 Hz), 3.66 (2H, *s*), 6.67−6.70, 6.91−6.95 and 7.11−7.31 (9H, 3 × *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.2 (CH_3), 22.0 (CH_3), 63.4 (CH_2), 66.3 (2× CH_2), 73.6 (C), 116.8 (2 × CH), 120.9 (CH), 128.5 (2× CH), 129.1 (2× CH), 129.5 (2× CH), 136.8 (C), 137.0 (C), 155.3 (C); IR (neat, cm^{-1}) ν_{max} = 2927, 2838, 1599, 1587, 1514, 1494, 1456, 1241, 1223, 1170, 1034, 959, 803, 752, 692; MS *m/z* (%) 268 (M^+ + 1, 100); HRMS *m/z* (ESI) calculated for $C_{18}H_{21}NO$ $[MH]^+$ 268.1701, found 268.1698.

1-(4-Methoxybenzyl)-3-methyl-3-phenoxyazetidine ***7g***. Yellow oil; R_f = 0.07 (petroleum ether/ethyl acetate 4/1); Yield, 65%; isolated yield, 42% (after purification); ^1H NMR (300 MHz, $CDCl_3$) δ 1.67 (3H, *s*), 3.28 (2H, *d*, *J* = 8.3 Hz), 3.53 (2H, *d*, *J* = 8.3 Hz), 3.63 (2H, *s*), 3.79 (3H, *s*), 6.67−6.70, 6.84−6.95 and 7.20−7.26 (9H, 3 × *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 22.0 (CH_3), 55.3 (CH_3), 63.0 (CH_2), 66.2 (2× CH_2), 73.6 (C), 113.8 (2× CH), 116.8 (2× CH), 121.0 (CH), 129.5 (2× CH), 129.8 (2× CH), 130.2 (C), 155.3 (C), 158.9 (C); IR (neat, cm^{-1}) ν_{max} = 2932, 2834, 2364, 1611, 1586, 1511, 1493, 1242, 1223, 1204, 1171, 1034, 958, 818, 752, 693; MS *m/z* (%) 284 (M^+ + 1, 100); HRMS *m/z* (ESI) calculated for $C_{18}H_{21}NO_2$ $[MH]^+$ 284.1651, found 284.1645.

Synthesis of 2-Methyl-2-(phenoxymethyl)aziridines 8f,g. As a representative example, the synthesis of 1-(4-methoxybenzyl)-2-methyl-2-(phenoxymethyl)aziridine **8g** is described here. 2-Bromomethyl-1-(4-methoxybenzyl)-2-methylaziridine **4c** (1.35 g, 5 mmol) was added to a mixture of phenol (1.04 g, 2.2 equiv) and K_2CO_3 (3.46

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g, 5 equiv) in DMF (30 mL), and the resulting suspension was heated at 50 °C for 14 h. The reaction mixture was cooled to room temperature, poured into a NaOH solution (30 mL, 0.5M) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 1-(4-methoxybenzyl)-2-methyl-2-(phenoxymethyl)aziridine **8g** (1.27 g, 76%), which was purified by silica gel column chromatography (petroleum ether/ethyl acetate 4/1) to obtain an analytically pure sample.

2-Methyl-1-(4-methylbenzyl)-2-(phenoxymethyl)aziridine ***8f***. Yellow oil; R_f = 0.17 (petroleum ether/ethyl acetate 4/1); Yield, 85%; isolated yield, 70% (after purification); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (1H, *s*), 1.44 (3H, *s*), 2.00 (1H, *s*), 2.34 (3H, *s*), 3.60 (H, *d*, *J* = 14.0 Hz), 3.73 (H, *d*, *J* = 14.0 Hz), 3.75 (H, *d*, *J* = 9.8 Hz), 3.90 (H, *d*, *J* = 9.8 Hz), 6.88−6.96 and 7.11−7.30 (9H, 2 × *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 13.0 (CH_3), 21.2 (CH_3), 38.9 (CH_2), 39.2 (C), 56.3 (CH_2), 75.8 (CH_2), 114.7 (2× CH), 120.8 (CH), 127.7 (2× CH), 129.1 (2× CH), 129.5 (2× CH), 136.4 (C), 137.0 (C), 159.1 (C); IR (neat, cm^{-1}) ν_{max} = 3030, 2922, 1599, 1586, 1495, 1456, 1241, 1171, 1034, 1020, 798, 752, 691; MS *m*/*z* (%) 268 (M^+ + 1, 100); HRMS *m*/*z* (ESI) calculated for $C_{18}H_{21}NO$ $[MH]^+$ 268.1701, found 268.1689.

1-(4-Methoxybenzyl)-2-methyl-2-(phenoxymethyl)aziridine ***8g***. Yellow oil; R_f = 0.31 (petroleum ether/ethyl acetate 4/1); Yield, 90%; isolated yield, 76% (after purification); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41 (1H, *s*), 1.45 (3H, *s*), 2.00 (1H, *s*), 3.56 (H, *d*, *J* = 13.8 Hz), 3.71 (H, *d*, *J* = 13.8 Hz), 3.76 (H, *d*, *J* = 9.4 Hz), 3.81 (3H, *s*), 3.89 (H, *d*, *J* = 9.4 Hz), 6.84−6.96 and 7.24−7.33 (9H, 2 × *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 13.0 (CH_3), 38.9 (CH_2), 39.2 (C), 55.4 (CH_3), 56.0 (CH_2), 75.9 (CH_2), 113.9 (2× CH), 114.8 (2× CH), 120.8 (CH), 128.9 (2× CH), 129.5 (2× CH), 132.2 (C), 158.6 (C), 159.1 (C); IR (neat, cm^{-1}) ν_{max} = 3038, 2930, 2835, 1599, 1586, 1511, 1496, 1463, 1300, 1241, 1172, 1033, 819, 753, 691; MS *m*/*z* (%) 284 (M^+ + 1, 100); HRMS *m*/*z* (ESI) calculated for $C_{18}H_{21}NO_2$ $[MH]^+$ 284.1651, found 284.1659.

Synthesis of 3-Acetoxy-3-methylazetidines 7h,i. As a representative example, the synthesis of 3-acetoxy-3-methyl-1-(4-methylbenzyl)azetidine **7h** is described here. 2-Bromomethyl-2-methyl-1-(4-methylbenzyl)aziridine **4b** (1.27 g, 5 mmol) was dissolved in acetonitrile (30 mL), after which NaOAc (0.45 g, 1.1 equiv) was added and the mixture was heated at reflux temperature for 24 h. The reaction mixture was cooled to room temperature, poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded 3-acetoxy-1-(4-methylbenzyl)-3-methylazetidine **7h** (1.10 g, 87%), which was purified by silica gel column chromatography (petroleum ether/ethyl acetate 4/1) to obtain an analytically pure sample.

3-Acetoxy-3-methyl-1-(4-methylbenzyl)azetidine ***7h***. Yellow oil; R_f = 0.11 (petroleum ether/ethyl acetate 4/1); Yield, 95%; isolated yield, 87% (after purification); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (3H, *s*), 2.01 (3H, *s*), 2.32 (3H, *s*), 3.13 (2H, *d*, *J* = 9.1 Hz), 3.46 (2H, *d*, *J* = 9.1 Hz), 3.61 (2H, *s*), 7.09−7.17 (4H, *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.2 (CH_3), 21.6 (CH_3), 22.7 (CH_3), 63.3 (CH_2), 65.8 (2× CH_2), 74.3 (C), 128.5 (2× CH), 129.1 (2× CH), 135.0 (C), 136.8 (C), 169.7 (C); IR (neat, cm^{-1}) ν_{CO} = 1737; MS *m*/*z* (%) 234 (M^+ + 1, 100); HRMS *m*/*z* (ESI) calculated for $C_{14}H_{19}NO_2$ $[MH]^+$ 234.1494, found 234.1490.

3-Acetoxy-1-(4-methoxybenzyl)-3-methylazetidine ***7i***. Yellow oil; R_f = 0.06 (hexane/ethyl acetate 2/1); Yield, 92%; isolated yield, 84% (after purification); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.64 (3H, *s*), 2.02 (3H, *s*), 3.12 (2H, *d*, *J* = 9.4 Hz), 3.45 (2H, *d*, *J* = 9.4 Hz), 3.59 (2H, *s*), 3.79 (3H, *s*), 6.83−6.86 and 7.17−7.20 (4H, 2 × *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 21.6 (CH_3), 22.6 (CH_3), 55.3 (CH_3), 62.9 (CH_2), 65.6 (2× CH_2), 74.2 (C), 113.8 (2× CH), 129.7 (2× CH), 130.0 (C), 158.8 (C), 169.8 (C); IR (neat, cm^{-1}) ν_{CO} = 1736; MS *m*/*z* (%) 250 (M^+ + 1, 100); HRMS *m*/*z* (ESI) calculated for $C_{14}H_{19}NO_3$ $[MH]^+$ 250.1443, found 250.1444.

Synthesis of 2-Acetoxymethyl-2-methylaziridines 8h,i. As a representative example, the synthesis of 2-acetoxymethyl-2-methyl-1-(4-methylbenzyl)aziridine **8h** is described here. 2-Bromomethyl-2-methyl-1-(4-methylbenzyl)aziridine **4b** (1.27 g, 5 mmol) was dissolved in DMSO (30 mL), after which NaOAc (0.45 g, 1.1 equiv) was added and the mixture was stirred at room temperature for 5 days. The reaction mixture was poured into water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with H_2O (2 × 15 mL) and brine (20 mL). Drying ($MgSO_4$), filtration of the drying agent and evaporation of the solvent afforded a mixture of 3-acetoxy-3-methyl-1-(4-methylbenzyl)azetidine **7h** and 2-acetoxymethyl-2-methyl-1-(4-methylbenzyl)aziridine **8h** (**7h**/**8h** = ratio 20/80), from which 2-acetoxymethyl-2-methyl-1-(4-methylbenzyl)-aziridine **8h** could not be isolated in completely pure form by silica gel column chromatography (petroleum ether/ethyl acetate 4/1). No accurate elemental analyses or HRMS analyses could be performed on 2-(acetoxymethyl)aziridines.

2-Acetoxymethyl-2-methyl-1-(4-methylbenzyl)aziridine ***8h***. Yellow oil; R_f = 0.22 (petroleum ether/ethyl acetate 4/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, *s*), 1.35 (1H, *s*), 1.95 (1H, *s*), 2.07 (3H, *s*), 2.33 (3H, *s*), 3.64 (2H, *s*), 3.89 (H, *d*, *J* = 11.3 Hz), 4.01 (H, *d*, *J* = 11.3 Hz), 7.12−7.15 and 7.25−7.27 (4H, 2 × *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 12.9 (CH_3), 21.0 (CH_3), 21.2 (CH_3), 38.3 (C), 38.6 (CH_2), 56.3 (CH_2), 71.9 (CH_2), 127.6 (2× CH), 129.1 (2× CH), 136.4 (C), 136.9 (C), 171.1 (C); IR (neat, cm^{-1}) ν_{CO} = 1737; MS *m*/*z* (%) 234 (M^+ + 1, 100).

2-Acetoxymethyl-1-(4-methoxybenzyl)-2-methylaziridine ***8i***. Yellow oil; R_f = 0.21 (petroleum ether/ethyl acetate 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, *s*), 1.34 (1H, *s*), 1.94 (1H, *s*), 2.07 (3H, *s*), 3.61 (2H, *s*), 3.80 (3H, *s*), 3.88 (H, *d*, *J* = 11.3 Hz), 4.00 (H, *d*, *J* = 11.3 Hz), 6.85−6.88 and 7.26−7.31 (4H, 2 × *m*); ^{13}C NMR (75 MHz, ref = $CDCl_3$) δ 12.9 (CH_3), 21.0 (CH_3), 38.3 (C), 38.5 (CH_2), 55.4 (CH_3), 56.0 (CH_2), 71.8 (CH_2), 113.8 (2× CH), 128.8 (2× CH), 132.1 (C), 158.6 (C), 171.1 (C); IR (neat, cm^{-1}) ν_{CO} = 1736; MS *m*/*z* (%) 250 (M^+ + 1, 100).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Spectra (^{1}H and ^{13}C NMR) of **6a**, **6c**, **7a−i**, **8a−i**. Cartesian coordinates and energy of the optimized geometries (B3LYP/6-31+G(d,p)) for coordination of the bicyclic aziridinium **5**, CN^-, SCN^- and Br^- by an increasing number of DMF or MeCN molecules. Coordination solvation energies (CSE's) (MPW1K/6-31++G(d,p)//B3LYP/6-31+G(d,p)) for coordination of the bicyclic aziridinium ions **5**, CN^-, SCN^- and Br^- by an increasing number of DMF or MeCN molecules. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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