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Diastereoselective Lewis acid-catalysed [4+2] cycloadditions of 3-alkyl-, 3-aryl- and 3-carboxyl-2*H*-azirines: a route to aziridine containing azabicyclo[4.1.0]heptanes and azatricyclo[2.2.1.0]nonanes

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Abstract—3-Substituted-2*H*-azirines have been employed as 2π components in Lewis acid-catalysed hetero Diels–Alder reactions with a variety of diene systems. A series of Lewis acids were screened for catalytic behaviour in the reaction between Danishefsky's diene and 3-phenyl-2*H*-azirine to give the cycloaddition adduct, and in most cases elevated temperature were required to effect cycloaddition. A noteworthy exception was a $BF_3{\cdot}Et_2O$-catalysed cycloaddition which proceeded in less than 1 h between −70°C and −60°C. The cycloadditions were found to proceed with *endo* selectivity providing a single diastereoisomeric product. Benzyl 2*H*-azirine-3-carboxylates were found to be activated by Lewis acids and participate in *endo* selective cycloadditions at −20°C.

1. Introduction

The hetero Diels–Alder reaction has been established as a powerful synthetic tool for the generation of six-membered heterocycles.[1] For example, the furnishing of nitrogen containing cycloadducts, with their potential for application in the synthesis of alkaloids has proven to be a valuable strategy in organic synthesis. Nevertheless the scope for incorporation of the nitrogen heteroatom as part of the 2π component in the hetero Diels–Alder reaction is limited and usually the C=N moiety is manifested as an iminium ion or an imine bearing electron withdrawing groups.[2]

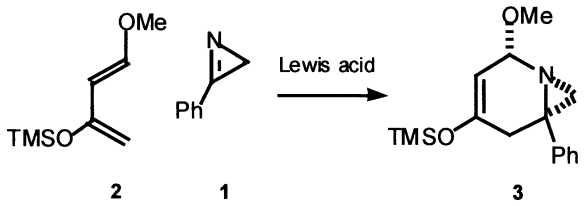
The strained carbon–nitrogen double bond in the 2*H*-azirine system is more reactive than in acyclic imines.[3] There is however, with a few notable exceptions,[4–7] only a few examples illustrating the use of 2*H*-azirines as the dienophile in Diels–Alder reactions. The carbon–nitrogen double bond in azirines is electron rich and while they do participate in reverse electron-demand hetero Diels–Alder reactions,[1] they have previously required the presence of an activating group, such as an ester in the 3-position, to promote their participation in normal electron-demand Diels–Alder reactions. Recently we have shown that this structural requirement can be circumvented through the application of Lewis acids which presumably coordinate to the nitrogen lone pair in the azirine.[8] The products of the Diels–Alder reaction between 2*H*-azirines and buta-1,3-diene systems contain the aziridine functionality, which have become valuable intermediates in the synthesis of biologically interesting derivatives.[9]

Our preliminary study into the activation by boron trifluoride etherate of **1** and subsequent cycloaddition with **2** (Scheme 1) provided results that encouraged us to screen a series of Lewis acids for their potential to effect the desired transformation. It was also desirable to expand the scope of the cycloaddition, both in terms of dienophiles and dienes, and herein is detailed our results from such a study.

2. Results and discussion

2.1. Screening of Lewis acid-catalysts

The reaction of **1**[10] with **2** to produce 1-azabicyclo[4.1.0]-heptene (**3**) was adopted as the model for investigation into the suitability of various Lewis acids as catalysts for these



Scheme 1. The generation of 1-azabicyclo[4.1.0]hept-3-ene **3** via a Lewis acid-catalysed Diels–Alder reaction.

Keywords: azirine; aziridine; hetero Diels–Alder reaction.

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Table 1. Lewis acid-catalysed Diels–Alder reactions of **1** with diene **2**

Entry	Lewis acid[a]	Time (h)	Yield **3** (%)[b]
1	$ZnCl_2$	12	40
2	$YbCl_3$	12	55
3	$CuCl_2$	12	35
4	$ScCl_3$	12	30
5	$BF_3{\cdot}Et_2O$[c]	0.3–0.4	45
6	–	72	0[d]

All reaction were performed in PhMe at 75°C using an equimolar mixture of diene **2** and azirine **1**.
[a] 0.2 equiv. of Lewis acid were used in each entry.
[b] Isolated yield.
[c] Conducted in CH_2Cl_2 at −78 to −60°C.
[d] The starting material was recovered.

cycloadditions (Scheme 1). A series of azaphilic Lewis acids were selected for initial screening,[11] and the results are summarized in Table 1 (entries 1–4). In all cases elevated reaction temperatures were required to effect the cycloaddition and after varying amounts of time adduct **3** were obtained as a single isomer in moderate yields.

Thin layer chromatography of the reaction mixture always revealed some remaining diene suggesting that the cycloaddition was accompanied by some decomposition of **1**. Due to the electron rich nature of the C=N bond in **1**, elevated reaction temperature coupled with the Lewis acid-mediated activation was necessary to force the normal electron-demand Diels–Alder process to occur. Attempts to effect cycloadditions of these substrates without Lewis acid activation at elevated temperature provided after 72 h only starting materials (entry 6). In contrast, treating a mixture of azirine **1** and diene **2** with $BF_3{\cdot}Et_2O$ at −70°C provided **3** in 45% yield (entry 5), which then proved to be the most potent Lewis acid in the series. In all cases the *endo* isomer **3** was obtained as the sole cycloadduct (Fig. 1).

The structure of bicycle **3** was assigned by NMR spectroscopy and by analogy with similar compounds.[6] Most notably, the COSY spectrum showed couplings between

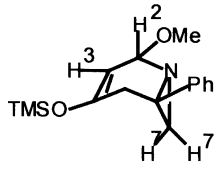


Figure 1. The structure of *endo* Diels–Alder product **3**.

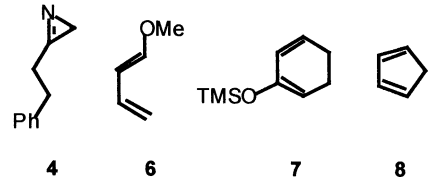


Figure 2. Azirine and diene candidates.

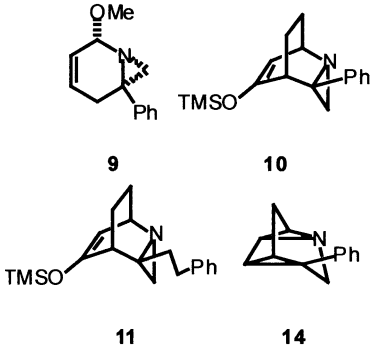


Figure 3. Aziridine cycloadducts **9**–**11** and **14**.

H-2 and H-3, H-2 and H-5_β, and H-5_β and H-7_{exo}, while an interaction between H-5_α and H-7_{endo} was evident in the NOESY spectrum.

2.2. Investigation of the scope of the Diels–Alder reaction

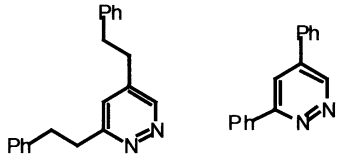
To probe the generality of the Diels–Alder methodology described above dienes **6**–**8** were reacted with azirine **1** and the results are summarized in Table 2 (Fig. 2). Solutions of the 3-phenyl azirine **1** in toluene were treated with a Lewis acid (0.3 equiv.), diene **6** or **7** and then heated to provide the corresponding cycloadducts **9** and **10** in 6–12 h (Table 2, entries 1 and 2, Fig. 3). 3-(2-Phenyl)ethyl azirine **4**[10] was found to participate in a $YbCl_3$ catalysed Diels–Alder reaction at elevated temperature with diene **7** furnishing after 12 h, bridged cycloadduct **11** which was found to be quite unstable, decomposing upon standing at room temperature (Table 2, entry 3).

The mass spectrum of compound **11** revealed a peak corresponding to a mass of 289 ($[C_{20}H_{20}N_2+H]^-$), in addition to the molecular ion at 314 ($[M+H]^+$), suggesting that a retro Diels–Alder process and subsequent generation of pyridazine **12** was occurring under the mass spectrometry

Table 2. Lewis acid-catalysed Diels–Alder cycloadditions of azirines **1** and **4**

Entry	Diene/azirine	Lewis acid[a]	Temperature (°C)	Time (h)	Product (%)[b]
1	**6/1**	$ZnCl_2$	75	8	**9** (50)
2	**7/1**	$YbCl_3$	90	6	**10** (50)
3	**7/4**	$YbCl_3$	90	12	**11** (36)
4	**8/1**	$BF_3{\cdot}Et_2O$[c]	−78	2	**14** (25)
5	**7/1**	–	90	12	**10** (48)
6	**7/4**	–	90	72	**11** (32)

All reactions were conducted in PhMe using 1 equiv. of diene and azirine.
[a] 0.3 equiv.
[b] Isolated yield.
[c] 0.6 equiv. in CH_2Cl_2.



12 13

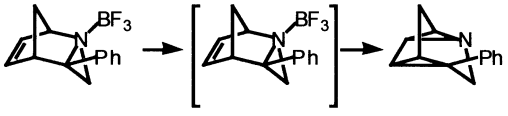
Figure 4. Pyridazines generated via retro Diels–Alder reaction of cycloadducts **10** and **11** followed by ring-opening and cycloaddition of azirines **1** and **4**.

conditions. 2*H*-Azirines are known to undergo ring opening and dimerisation to the corresponding pyridazines[12] and indeed the mass spectrum of **10** also exhibited a peak of 233 corresponding to pyridazine **13** ($[C_{16}H_{12}N_2+H]^+$, Fig. 4).

The cycloaddition of **1** with **8** was unsuccessful at elevated temperature and was attempted using boron trifluoride etherate at −78°C (Table 2, entry 4). After 2–3 h at reduced temperature in the presence of $BF_3{\cdot}Et_2O$ (0.6 equiv.) a compound assigned with the structure **14** was isolated. Lower catalytic amounts of Lewis acid were unsuccessful in providing any product. All spectroscopic data obtained were consistent for the proposed structure of **14**, which can form via a Lewis acid-mediated rearrangement of the Diels–Alder product **13** while still complexed to the boron trifluoride (Scheme 2). Azirines **1** and **4** were also found to react with diene **7** under purely thermal conditions albeit with longer reaction times and reduced yields. (Table 2, compare entries 5 and 6 with 2 and 3, respectively).

2.3. Lewis acid-catalysed Diels–Alder cycloadditions of 3-benzyloxycarbonyl-2*H*-azirine (5)

2*H*-Azirines harbouring an ester substituent in the 3-position undergo thermal Diels–Alder cycloadditions with a variety of dienes.[4–7] There is the potential to utilise the ester carbonyl as a second site of coordination for a Lewis



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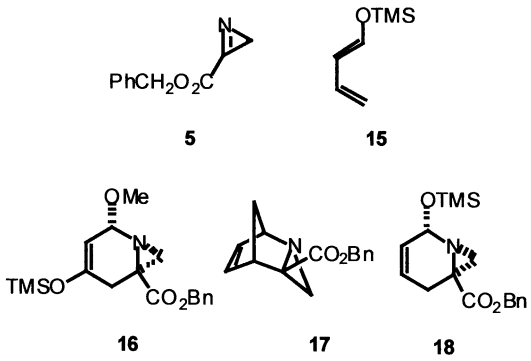
Scheme 2. A proposed mechanism for the rearrangement of **13** into isolated product **14** from the Diels–Alder reaction of azirine **1** with **8**.

Table 3. Diels–Alder reactions of azirine **5**

Entry	Diene	Lewis acid	Temperature (°C)	Time (h)	Product (%)[a]
1	**2**	$YbCl_3$[b]	−20	3	**16** (65)
2	**8**	$ZnCl_2$[c]	−20	12	**17** (32)
3	**15**	$YbCl_3$[b]	−20	4	**18** (52)
4	**2**	–	rt	18	**16** (61)
5	**8**	–	rt	24	**17** (31)
6	**15**	–	rt	18	**18** (30)

All reaction were conducted in Et_2O.
[a] Isolated yield.
[b] 0.3 equiv.
[c] 0.1 equiv.



5 15

16 17 18

Figure 5. Azirine **5**, diene **17** and aziridine cycloadducts **16**–**18**.

acid to further activate the [4+2] process. To examine this, solutions of azirine **5**[5] in Et_2O were treated with either $YbCl_3$ or $ZnCl_2$ and dienes **2**, **8** or **15** at −20°C providing in a matter of a few hours the corresponding cycloadducts **16**–**18** in moderate to fair yields, and in all cases the *endo* isomer was the only detectable diastereomer (Table 3, entries 1–3, Fig. 5). For purposes of comparison these cycloadditions were also conducted at room temperature in the absence of Lewis acid. The reactions proceeded smoothly with similar yields but took between two and four times longer to go to completion, indicating the beneficial influence of the Lewis acids (compare entries 4–6 with 1–3, respectively).

We have shown that through the application of Lewis acid-catalysts, 2*H*-azirines with or without activating substituents in the 3-position, will participate in normal electron-demand Diels–Alder reactions. Through this study and our initial investigation we have extended the existing chemistry, concerning thermal cycloadditions of 3-carboxylated azirines, to include 2*H*-azirines harbouring a greater variety of 3-substituent. Efforts are being made to apply this chemistry for the synthesis of complex nitrogen containing compounds, the results of which will be discussed elsewhere.

3. Experimental[13]

3.1. Method 1: general procedure for screening of Lewis acids

3.1.1. 2-Methoxy-4-trimethylsilyloxy-6-phenyl-1-azabicyclo[4.1.0]hept-3-ene (3). To a solution of azirine **1** (23 mg, 0.19 mmol) in PhMe (3 mL) at ambient temperature, was added the Lewis acid (0.2 equiv.). After ca. 5 min a solution of **2** (33 mg, 0.2 mmol) in PhMe (1 mL) was added and the reaction mixture was heated to 75°C. The reaction temperature was maintained until TLC indicated the absence of **1**. Once cooled, the reaction mixture was washed with aq. $NaHCO_3$ (2×4 mL). The combined aqueous phases were extracted with CH_2Cl_2 (2×5 mL) and then the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was dissolved in CH_2Cl_2 (1 mL) and passed through a Pasteur pipette filled with basic alumina (7:1 pentane/ethyl acetate) to yield **3** as a yellow oil. R_f=0.70 (pentane/EtOAc 7:1); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.23 (m, 5H), 5.07 (br s, 1H), 4.66 (d,

J=1.5 Hz, 1H), 3.68 (s, 3H), 2.56 (d, J=17.3 Hz, 1H), 2.52 (d, J=17.5 Hz, 1H), 2.24 (s, 1H), 1.69 (s, 1H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 128.8, 128.3, 126.7, 125.9, 99.9, 88.1, 56.1, 40.0, 32.1, 31.3, 0.00; IR (neat) 2100, 1696, 1395, 1265, 1073, 913 cm^{-1}; HRMS calculated for $C_{16}H_{23}O_2NSi$ $[M+H]^+$: 290.1576, found 290.1581.

3.2. Method 2: boron trifluoride etherate-catalysed reaction

3.2.1. Aziridine 3. To a solution of azirine **1** (23 mg, 0.19 mmol) in CH_2Cl_2 (3 mL) at −78°C was added a solution of **2** (33 mg, 0.19 mmol) in CH_2Cl_2 (1 mL). After ca. 3 min to the reaction mixture was added boron $BF_3{\cdot}Et_2O$ (5 μL, 0.04 mmol). The reaction mixture was stirred at −78°C for 0.3 h at which time no azirine was visible by TLC. The reaction mixture was then added to sat. aq. $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2×4 mL) and the combined organic layers were dried ($MgSO_4$) and evaporated. The residue was dissolved in dichloromethane (1 mL) Purification as above gave **3** (24 mg, 45%) as a yellow oil. This sample of cycloadduct was identical by proton and carbon NMR spectroscopy to that prepared in method 1.

3.2.2. 2-Methoxy-6-phenyl-1-azabicyclo[4.1.0]hept-3-ene (9). To a solution of **1** (25 mg, 0.21 mmol) in PhMe (4 mL) at ambient temperature was added anhydrous $ZnCl_2$ (5.7 mg, 0.042 mmol). After ca. 5 min a solution of **6** (18 mg, 0.21 mmol) in PhMe (1 mL) was added. After work up and purification as described in method 1, **9** was afforded as a yellow oil (21 mg, 50%). R_f=0.66 (pentane/EtOAc 7:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49–7.19 (m, 5H), 5.73–5.69 (m, 1H), 5.47 (m, 1H), 4.82 (br s, 1H), 3.59 (s, 3H), 2.85 (dd, J=6.4, 18.2 Hz, 1H), 2.37 (dd, J=2.1, 18.2 Hz, 1H), 2.17 (s, 1H), 1.63 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.7, 130.9, 130.3, 129.5, 124.8, 86.8, 56.6, 31.4, 30.1, 27.5; IR (neat) 2098, 1450, 1259 cm^{-1}; MS (CI, NH_3): m/z (%) 202 (100) $[M+H]^+$; HRMS calculated for $C_{13}H_{16}ON$ $[M+H]^+$: 202.1232, found 202.1235.

3.2.3. 4-Phenyl-6-trimethylsilyloxy-2-azatricyclo[3.2.2.0]-non-6-ene (10). Aziridine **10** (38 mg, 50%) was prepared from **1** and **7** as an yellow oil as described for **9**. R_f=0.53 (pentane/EtOAc 7:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41–7.13 (m, 5H), 5.83 (d, J=10.7 Hz, 1H), 4.01 (dd, J=4.9, 11.9 Hz, 1H), 2.28–2.32 (m, 3H), 2.01–1.97 (m, 1H), 1.89–1.62 (m, 2H), 1.41 (br s, 1H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 133.5, 130.1, 129.9, 128.7, 120.6, 73.7, 37.9, 32.3, 25.4, 19.5, 0.0; IR (neat) 2102, 1693, 1249 cm^{-1}; MS (CI +): m/z (%) 286 (100) $[M+H]^+$, 233 (20) $[C_{16}H_{12}N_2+H]^+$; HRMS calculated for $C_{17}H_{23}SiON$ $[M+H]^+$: 286.1627, found 286.1634.

3.2.4. 4-(2-Phenylethyl)-6-trimethylsilyloxy-2-azatricyclo-[3.2.2.0]non-6-ene (11). Aziridine **11** (11 mg, 34%) was prepared from **4** and **7** as an yellow oil as described for **9**. R_f=0.58 (pentane/EtOAc 7:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.01 (m, 5H), 5.82 (d, J=10.1 Hz, 1H), 4.01 (dd, J=4.9, 11.8 Hz, 1H), 2.85–2.01 (m, 9H), 1.98 (s, 1H), 1.31 (s, 1H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 141.3, 129.4, 129.1, 129.0, 128.8, 126.7, 74.1, 37.2, 36.8, 35.5, 32.5, 25.4, 22.5, 0.0; IR (neat) 2103, 1687, 1496, 1454, 1251, 1137 cm^{-1}; MS (CI +): m/z (%)=314 (5) $[M+H]^+$, 289 (100) $[C_{20}H_{20}N_2+H]^+$, 169 (35) $[C_9H_{16}OSi+H]^+$; HRMS calculated for $C_{19}H_{28}NOSi$ $[M+H]^+$: 314.1940, found 314.1927.

3.2.5. Amine 14. To a solution of **1** (77 mg, 0.66 mmol) in CH_2Cl_2 (2 mL) at −78°C was added **8** (163 μL, 1.98 mmol) and $BF_3{\cdot}Et_2O$ (83 μL, 0.66 mmol). After 2 h at −78°C the reaction mixture was quenched with sat. aq. NH_4Cl (4 mL), extracted with Et_2O (3×4 mL), dried ($MgSO_4$) and evaporated. Purification by flash chromatography (pentane/Et_2O 25:1→10:1) provided **14** (30 mg, 25%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.26 (m, 3H), 7.13–7.08 (m, 2H), 3.89 (br s, 1H), 3.76 (d, J=12.0 Hz, 1H), 3.46 (br s, 1H), 3.41 (d, J=12.0 Hz, 1H), 2.57 (dd, J=3.2, 5.9 Hz, 1H), 2.34–2.31 (m, 2H), 2.25–2.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 137.2, 128.9, 127.5, 126.2, 51.6, 50.0, 47.3, 42.7, 33.5, 28.2, 23.8; IR (neat) 1450, 1128, 977, 912, 755 cm^{-1}; MS (CI, NH_3): m/z (%) 184 (100) $[M+H]^+$; HRMS calculated for $C_{13}H_{13}N$ $[M+H]^+$: 184.1123, found 184.1125.

3.2.6. Benzyl-2-methoxy-4-trimethylsilyloxy-1-azabicyclo-[4.1.0]hept-3-ene-6-carboxylate (16). To a solution of benzyl ester azirine **5** (28 mg, 0.16 mmol) in Et_2O (6 mL) at −20°C was added $YbCl_3$ (11 mg, 0.04 mmol) and after 5 min, **2** (27 mg, 0.16 mmol) in Et_2O (1 mL). The reaction temperature was maintained at −20°C. After 3 h at this temperature TLC indicated the absence of the starting materials. The reaction mixture was washed with sat. aq. $NaHCO_3$, dried ($MgSO_4$) and evaporated. Dissolution of the crude product in CH_2Cl_2 (1 mL) and filtration through a Pasteur pipette filled with alumina (pentane/EtOAc 2:1) followed by evaporation provided **16** as an orange oil (35 mg, 65%). R_f=0.82 (pentane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.25 (m, 5H), 5.28 (d, J=10.6 Hz, 1H), 5.18 (d, J=10.6 Hz, 1H), 5.01 (br s, 1H), 4.59 (br s, 1H), 3.67 (s, 3H), 2.86 (d, J=18.1 Hz, 1H), 2.61 (d, J=18.1 Hz, 1H), 2.17 (s, 1H), 2.12 (s, 1H), 0.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 148.7, 136.4, 128.9, 128.8, 99.9, 88.4, 67.3, 39.1, 29.3, 27.3, 0.0; IR (neat) 2107, 1737, 1456, 1255, 1191 cm^{-1}; MS (CI +): m/z (%)= 348 (100), $[M+H]^+$; HRMS calculated for $C_{18}H_{25}O_4NSi$ $[M+H]^+$: 348.1631, found 348.1634.

3.2.7. Benzyl-2-azatricyclo[3.2.1.0]oct-6-ene-4-carboxylate (17). Aziridine **17** (10 mg, 32%) was prepared from **5** and **8** as a yellow oil as described for **16**. R_f=0.23 (pentane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.31 (m, 5H), 6.24 (ddd, J=1.8, 3.6, 5.3 Hz, 1H), 5.59 (dd, J=2.4, 5.3 Hz, 1H), 5.34 (d, J=12.4 Hz, 1H), 5.17 (d, J=12.4 Hz, 1H), 4.17 (br s, 1H), 3.58 (m, 1H), 2.44 (d, J=3.0 Hz, 1H), 2.11 (dt, J=2.0, 8.0 Hz, 1H), 1.74 (dd, J=3.0, 8.0 Hz, 1H), 1.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 137.1, 134.4, 129.7, 129.4, 129.3, 129.2, 67.8, 67.2, 61.6, 45.2, 44.1, 43.8; IR (neat) 2109, 1725, 1454, 1236, 1091 cm^{-1}; MS (CI +): m/z (%)=242 (70), $[M+H]^+$, 210 (70), 194 (45); HRMS calculated for $C_{15}H_{15}O_2N$ $[M+H]^+$: 242.1181, found 242.1181.

3.2.8. Benzyl-2-trimethylsilyloxy-1-azabicyclo[4.1.0]hept-3-ene-6-carboxylate (18). Aziridine **18** (32 mg, 52%) was

prepared from **5** and **15** as described for **16**. R_f=0.66 (pentane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30–7.11 (m, 5H), 5.56–5.51 (m, 1H), 5.29–5.24 (m, 1H), 5.11 (br s, 1H), 5.05 (d, J=9.8 Hz, 1H), 5.01 (d, J=9.8 Hz, 1H), 2.55 (d, J=18.5 Hz, 1H), 2.42 (dd, J=6.3, 18.5 Hz, 1H), 1.96 (s, 2H), 0.00 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 136.6, 129.1, 128.6, 128.3, 126.6, 123.5, 79.5, 66.7, 38.5, 28.8, 21.5, 0.0; IR (neat) 2109, 1731, 1456, 1251, 1160, 1072 cm^{-1}; MS (CI +): m/z (%)=318 (100), $[M+H]^+$; HRMS calculated for $C_{17}H_{23}O_3NSi$ $[M+H]^+$: 318.1519, found 318.1522.

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