Synthesis of Functionalized Cyclopropanes by MIRC Reactions of Aziridinyl-methylenemalonates.

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Abstract: The synthesis of cyclopropane derivatives via a MIRC reaction of azidirinyl-methylenemalonates is described. In this way it is possible to introduce a hydrogen, a phenylthio, a tributylstannyl and an olefinic function at the cyclopropane ring, that further contains an alkylamino substituent. Addition of CuCN catalyzed Grignard reagents gave the most promising results. The diastereoselectivity was dependent on the aziridine nitrogen substituent and the bulkiness of the reagent.

INTRODUCTION

The intramolecular ring opening of aziridinecarboxamides by a nucleophilic center at the $\gamma$-atom in the carboxamide part was the subject of a previous paper from our laboratories. The required nucleophilic site was generated by removal of a suitable acidic proton leading in general to a highly substituted lactam. To further explore intramolecular ring-opening reactions of functionalized aziridines, the inducing nucleophilic site was positioned at the $\beta$-atom relative to the aziridine-ring. In principle, such a nucleophile can be obtained by a deprotonation process. However, an alternative method was chosen, which was inspired by the work of Kasatkin et al. These authors reported recently the synthesis of cyclopropane dicarboxylates using Michael-reaction Initiated Ring Closure (MIRC) reactions of diethyl (2,3-epoxybutylidene)malonate (Scheme 1).

Application of the MIRC reaction in an analogous manner to activated aziridines could be of interest and could illustrate the potential of aziridinyl-methylenemalonates for the synthesis of functionalized cyclopropanes. However, aziridinyl-methylenemalonates can react with a nucleophile by two distinctly different pathways, as is shown in scheme 2. The desired pathway $a$ involves conjugate addition of the nucleophile followed by opening of the aziridine ring. The alternative pathway $b$ is a direct nucleophilic opening of the three-membered ring. In the proposed scheme 2, the choice of the $N$-activating group may be of great importance for the success of the reaction. Reactions of $\beta$-aziridinyl-$\alpha,\beta$-enoates with organo-copper reagents have been investigated whereby predominantly anti-$S_N2'$ products are produced. In the system which
is proposed for the present investigations, such an $S_N2'$ reaction seems highly improbable because of the strongly activated methylenemalonates and is therefore not further taken into account. The formation of four-membered ring systems instead of three-membered was not observed.

(Nucleophilic attack at the C-2 aziridine carbon is omitted in this scheme.)

**RESULTS AND DISCUSSION**

*Preparation of diethyl aziridinyl-methylenemalonate derivatives.* The required aziridines 3 were prepared as shown in Scheme 3. For this study racemic aziridines were used because the prime interest was the diastereoselectivity during the Michael additions. Direct reduction of 1-tosyl-3-hexyl-aziridine-2-carboxylic acid ethyl ester 1a to the aldehyde 2a followed by condensation with diethyl malonate afforded diethyl aziridinyl-methylenemalonate 3a. 1-Mesyl-3-hexyl-aziridine derivative 3b, 1-tosyl-3-methyl-aziridine 3c, 1-(2-mesityl-sulfonyl)-3-methyl-aziridine 3d and 1-(2-mesitylsulfonyl)-3-hexyl-aziridine 3e were prepared similarly. In the condensation using TiCl$_4$-pyridine, chlorinated side-products were observed as a result of aziridine ring-opening reactions. The degree of chlorination differed among substrates 3, and depended on the 2-substituents and sulfonyl groups (from 0% for 3e to 41% for 3a).

**Scheme 3**

*Reactions of 1-tosyl-aziridine derivative 3a.* Several products can result from these reactions of 3 (vide supra). Compounds 4 and 7 (Scheme 4) are the result of a conjugate reaction. Subsequent cyclization of the initial products 4 and 7 leads to cyclopropanes 5 and 8, respectively. The compounds 6 and 9 are the result of a direct $S_N2$-type opening of the aziridine ring (see pathway $b$ in Scheme 2). The diastereomer ratios of the cyclopropanes 5 and 8 were determined by 400 MHz $^1$H NMR spectroscopy.
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Scheme 4

It was felt that organocuprate reagents should be suitable for selective MIRC reactions because of their high conjugate addition potential. When higher order organocuprates were used (Table 1), dimethyl cyanocuprate gave cyclopropane 5a (entry 1), but, the dibutyl derivative gave a very poor result (entry 2). Three equivalents of reagent were used in these reactions to obtain acceptable yields (entries 1-5). Boron trifluoride etherate has been reported as an effective co-additive for organocuprates, and Bu₂Cu(CN)Li₂BF₃ did indeed

Table 1. Reactions of aziridinyl-methylenemalonate 3a with various nucleophilic reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions</th>
<th>R</th>
<th>Product (yield in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>Me₂Cu(CN)Li₂, Et₂O, -30 °C, 3h</td>
<td>Me</td>
<td>4a (0)</td>
</tr>
<tr>
<td>2</td>
<td>Bu₂Cu(CN)Li₂, Et₂O, -30 °C, 3h</td>
<td>Bu</td>
<td>4b (24)</td>
</tr>
<tr>
<td>3</td>
<td>Bu₂Cu(CN)Li₂ BF₃, Et₂O, -30 °C, 3h</td>
<td>Bu</td>
<td>4b (54)</td>
</tr>
<tr>
<td>4</td>
<td>BuCu(CN)MgBr BF₃, Et₂O, -30 °C, 3h</td>
<td>Bu</td>
<td>4b (29)</td>
</tr>
<tr>
<td>5</td>
<td>BuCu(CN)MgBr BF₃, THF, -30 °C, 3h</td>
<td>Bu</td>
<td>4b (65)</td>
</tr>
<tr>
<td>6</td>
<td>BuMgBr, 10 mol% CuCN, Et₂O, -78 °C - rt, 2h</td>
<td>Bu</td>
<td>4b (0)</td>
</tr>
<tr>
<td>7</td>
<td>(Vinyl)MgBr, 10 mol% CuCN, Et₂O, -78 °C - rt, 4h</td>
<td>Vinyl</td>
<td>4c (31)</td>
</tr>
<tr>
<td>8</td>
<td>Bu₂C=CH-CuMgBr₂ SMe₂, Et₂O, -30 °C, 4h</td>
<td>Bu₂C=CH-</td>
<td>4d (0)</td>
</tr>
<tr>
<td>9</td>
<td>(Bu₃Sn)BuCu(CN)Li₂, Et₂O, -30 °C, 3h</td>
<td>Bu₃Sn</td>
<td>4e (16)</td>
</tr>
<tr>
<td>10</td>
<td>PhSNa, THF, -50 °C, 3h</td>
<td>PhS</td>
<td>4f (64)</td>
</tr>
<tr>
<td>11</td>
<td>K-Selectride, THF, 0 °C, 1h</td>
<td>H</td>
<td>4g (0)</td>
</tr>
</tbody>
</table>

*1:1 Mixture of cis/trans diastereomers. b Total yield of the mixture is shown. 5b:6b = 45:55. cis/trans ratio of 5b, ca. 65:35. The minor diastereomer could not be detected by ¹H NMR spectroscopy. c cis/trans ratio not determined. d cis/trans ratio 90:10. e cis/trans ratio 75:25.
improve the conjugate addition (entry 3). As an alternative butyl-donor, BuCu(CN)MgBrBF3OEt2 was used and it showed high reactivity and isomeric selectivity (entry 4). The cyclopropane derivative 5b was obtained uncontaminated with the S22 reaction products 6b. It is of interest that when tetrahydrofuran was used as solvent, only the conjugate addition product 4b was obtained containing only traces of cyclization product 5b (entry 5).

It was found necessary to carry out the reaction at higher temperatures in order to improve the chemical yield further. But, use of excess of reagents (3 equiv; entries 1-5) does not permit higher reaction temperatures since organocuprate reagents are known to open the aziridine ring at a temperature higher than -20 °C. Therefore a stoichiometric amount of Grignard reagent was added in the CuCN catalyzed reaction (entry 6). This resulted in an excellent yield with high degree of stereoselectivity (85:15). Although the vinyl group could also be introduced, a considerable amount of uncyclized product 4c was observed even after a prolonged reaction time (4h) at room temperature (entry 7). Whilst the stereoselectivity of 5c was surprisingly high (90:10) for this small nucleophile, the diastereomer ratio of 4c could not be determined (it was likely to be low, considering the low diastereoselectivity observed during the methyl introduction in entry 1). It was assumed that a high stereoselectivity for the introduction of an unsaturated function might be achieved with a more sterically hindered group. For this purpose, alkenylcoppermagnesium dibromide was prepared in situ and submitted to the MIRC reaction (entry 8). Although the chemical yield was moderate, a high stereoselectivity was observed (90:10).

Lipshutz et al. reported the direct formation of trialkyltin cuprates from tin hydrides. The alkylstannyl function is of value because of its potential for lithium-transmetalation with stereo-retention. Tributyltin cuprate transferred the tributyltin group in moderate yield (entry 9) with a disappointing stereoselectivity (75:25).

Sodium thiophenoxide, another nucleophilic reagent, gave conjugate addition product 4f only (entry 10), and K-selectride transferred hydride to ultimately give cyclopropane derivative 5g in good yield (entry 11).

Reactions of 1-mesyl-aziridine derivative 3b. The reactions of the aziridine derivative 3b, which carries the methylsulfonyl (mesyl) group as the aziridine-activating group were examined briefly (Table 2).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reaction Conditions a</th>
<th>R</th>
<th>Product (yield in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me2Cu(CN)Li2, Et2O</td>
<td>Me</td>
<td>7a (42) 8a/9a (38)b</td>
</tr>
<tr>
<td>2</td>
<td>Bu2Cu(CN)Li2, Et2O</td>
<td>Bu</td>
<td>7b (40) 8b (16)c</td>
</tr>
<tr>
<td>3</td>
<td>Bu2Cu(CN)Li2 BF3, Et2O</td>
<td>Bu</td>
<td>7b (23) 8b (23)c</td>
</tr>
<tr>
<td>4</td>
<td>Bu2Cu(CN)Li2, THF</td>
<td>Bu</td>
<td>7b (43) 8b (trace)</td>
</tr>
</tbody>
</table>

a -30 °C, 3h. b R = H in 9a, Cis/trans ratio of 8a ca. 55:45. Total yield of the mixture is shown. 8a/9a = 83:17. c The minor diastereomer was not detected by 1H NMR spectroscopy.

The reaction trend of 3b was almost the same as that of 3a. Me2Cu(CN)Li2 showed approximately the same degree of stereoselectivity with 3b (ca. 55:45 ratio; Table 2, entry 1). Surprisingly, a considerable amount of uncyclized product 7a was observed. The cyclopropane 8a was obtained as an inseparable mixture with 9a (R=H). Bu2Cu(CN)Li2 reacted with an almost exclusive stereoselectivity in contrast to the reaction of 3a.
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(Table 1, entry 3, and Table 2, entry 2), and the cyclopropane 8b could be isolated. In contrast to the accelerative effect of BF$_3$ on 3a, the organocuprate boron trifluoride complex did not dramatically change the outcome of the reaction of 3b (entry 3). Although the exclusive formation of one diastereomer 8b was impressive, the stereoselectivity during the reactions of 3b with the butylogancuprate reagents is in the same range as that observed for 3a. The high diastereopurity of 5b was also observed (Table 1, entry 4). In accordance with the solvent effect of THF noted earlier (Table 1, entry 5), THF prevented cyclization (entry 4).

The unicyclized compounds 4b, 4c, 4f, 7a and 7b were then treated with a catalytic amount of NaOEt in EtOH at room temperature (Scheme 5). The reactions of 4b, 7a and 7b proceeded in excellent yields affording diastereomerically pure cyclized products. Unexpectedly, the yield of the vinylcyclopropane 5c was relatively low. The cyclopropane 5e isolated was dominantly rich of a single isomer, which was reconfirmed by $^{13}$C NMR spectroscopy. This isomer showed a significant N.O.E. between H-2 and H-3, establishing the 2,3-cis-configuration (cis/trans ratio 90:10). The cyclization reactions of 4b, 7a and 7b gave exclusively single isomers. These results indicate that 4b, 7a and 7b are highly rich of one type of diastereomers. Surprisingly, compound 4f derived from 3a and sodium thiophenoxide did not give any cyclization when treated with NaOEt in EtOH.

Reactions of aziridine derivatives 3c, 3d and 3e. In order to investigate further the steric influence of substituents on the reaction of the aziridine rings, reactions of 3a, 3c, 3d and 3e with Grignard reagents in the presence of 10 mol% CuCN were examined (Table 3). When 3-methyl-1-tosyl-aziridine derivative 3c was treated with BuMgBr/CuCN, the cyclopropane derivative 10 was obtained in 51% yield with a stereoselectivity of 85:15. Under the reaction conditions, the aziridine ring-opened compound 11 was also obtained (21% yield). The modest yields obtained from 3e and 3d are possibly due to decomposition of the aziridines since they were consumed totally during the course of the reactions.

When the 1-(mesitylsulfonyl)-3-methyl-aziridine derivative 3d was subjected to the MIRC reaction with the MeMgl/CuCN reagent, a Me group was transferred to give product 12 in 46% yield; the diastereomer ratio was 40:60 (entry 4). This stereoselectivity is not substantially different from that observed for 3a (entry 1). The steric effect of the mesitylsulfonyl group may be reduced by sulfonamide inversion (vide infra). BuMgBr/CuCN similarly gave the desired cyclopropane 13 in 48% yield with high diastereoselectivity (diastereomeric ratio 91:9). In these reactions, no aziridine ring-opened compounds, such as 11, were detected. The modest yields obtained from 3c and 3d are possibly due to decomposition of the aziridines since they were consumed totally during the course of the reactions.

3-Hexyl-1-(mesitylsulfonyl)-aziridine 3e, which bears large substituents on both the aziridine nitrogen and the aziridine C-3 atom, produced a cyclopropane derivative with high stereoselectivity. It is especially noteworthy that the methyl substituted cyclopropane derivative 14 was obtained with an exceptionally high
diastereoselectivity (79:21) considering a methyl transfer had occurred. The diastereoselectivity for the introduction of a butyl group (entry 6) was the same as that found for compound 13.

Table 3. Reactions of aziridinyl-methylene malonates 3c-3e with Grignard reagents catalyzed by CuCN

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aziridine</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Cyclopropane</th>
<th>Yield (%)</th>
<th>Cis/trans ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>Ts</td>
<td>Hex</td>
<td>Me</td>
<td>5a</td>
<td>97</td>
<td>60:40</td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>Ts</td>
<td>Hex</td>
<td>Bu</td>
<td>5b</td>
<td>91</td>
<td>85:15&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>Ts</td>
<td>Me</td>
<td>Bu</td>
<td>10</td>
<td>51</td>
<td>85:15</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>SO&lt;sub&gt;2&lt;/sub&gt;-2,4,6-(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Me</td>
<td>Bu</td>
<td>12</td>
<td>46</td>
<td>40:60</td>
</tr>
<tr>
<td>5</td>
<td>3d</td>
<td>SO&lt;sub&gt;2&lt;/sub&gt;-2,4,6-(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Me</td>
<td>Bu</td>
<td>13</td>
<td>48</td>
<td>91:9</td>
</tr>
<tr>
<td>6</td>
<td>3e</td>
<td>SO&lt;sub&gt;2&lt;/sub&gt;-2,4,6-(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Hex</td>
<td>Me</td>
<td>14</td>
<td>60</td>
<td>79:21</td>
</tr>
<tr>
<td>7</td>
<td>3e</td>
<td>SO&lt;sub&gt;2&lt;/sub&gt;-2,4,6-(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Hex</td>
<td>Bu</td>
<td>15</td>
<td>69</td>
<td>90:10</td>
</tr>
</tbody>
</table>

<sup>a</sup>This is the same experiment as shown in Table 1, entry 6.

Stereochemistry. The <sup>1</sup>H NMR spectra of the diastereomerically pure cyclopropane derivatives 5b, 8a, 8b and 15 unfortunately exhibited a complicate coupling pattern and it has not been possible so far to assign the configurations at the cyclopropane C-3 atom. The coupling constants (J<sub>H<sub>2</sub>, H<sub>3</sub></sub>) of single-diastereomer-rich (90:10) cyclopropanes 5e and 5d was 9.7 Hz. Braun<sup>19</sup> observed coupling constants of 7.5 Hz for trans-vinylicyclopropane and 9.0 Hz for the corresponding cis isomer. Kasatkin et al. observed a 5 Hz coupling for the trans isomer and 8 Hz for the cis isomers (cf. Scheme 1). The vinylicyclopropane 5e was convincingly shown to have a 2,3-cis-configuration by NOE measurement, and the cyclopropane 5d was therefore assigned to have the 2,3-cis-configuration also.

The chemical shift pattern of all major diastereomers of 5b-e, 8a, 8b, 10, 13, 14, and 15 are very similar, which suggests that they all have the same relative configuration about the C-3 atom. Assuming this is valid, we tentatively assigned the relative configuration at the C-3 atom of the major cyclopropane diastereomers as cis, because the C-3 configuration of the vinylicyclopropane 5e was determined to be cis (vide supra). It was anticipated that the consideration of the transition state of the conjugate addition reaction might provide a support for the assignment.

When the N-substituent of the aziridine ring was altered from tosyl to the mesitylsulfonyl group, there was an increase of the degree of the cis/trans ratio (Table 3, compare entries 1, 2, 3 with entries 6, 7, 5 respectively). This effect was not observed when the tosyl group was changed for the mesyl group (Table 2); the degrees of the cis/trans ratio's during the reactions of the two types of N-substituents were observed to be essentially identical. It is very noteworthy that the mesitylsulfonyl group provided the 79:21 cis/trans ratio during the reaction of the aziridine 3e and methylmagnesium iodide (Table 3, entry 6) but the mesyl group produced a 1:1 mixture of the methylcyclopropane derivatives (Table 2, entry 1).

Yamamoto et al. studied the diastereoselectivity of the conjugate addition of organocuprate reagents to γ-alkoxy α,β-unsaturated diester derivatives. They discussed whether a powerful Michael acceptor having a high electron-accepting ability or a reactive copper reagent having a high electron-donating ability is prone to
produce a π-complex (Figure 1). When the γ-t-butyldimethylsilyloxy (TBDMS) containing Michael acceptors (R'=TBDMS; the TBDMS is a "non-chelating" group), reacted with organocopper reagents, the steric bulk difference between R and R' determined the outcome. The electron-deficient nitrogen atom of the aziridines may be assumed to be comparatively non-chelating as is the oxygen atom of the tert-butyldimethylsilyloxy group. If this Yamamoto's approach is applied to the aziridinyl-substituted Michael acceptors described here, the conjugate reactions could occur through the transition state model shown in Figure 2. In this model, the preferred conformation arising from rotation about the single bond between the aziridinyl C-2 atom and the olefinic carbon is incorporated. The model is presented as a Newman projection viewed along this bond. The 1,3-allylic strain theory supports this configuration in which the hydrogen atom on the aziridine C-2 is positioned inside. Another relevant aspect is the relative position of the C-3 substituent and the N-arylsulfonyl group. It is presumed that the steric effect is more influential than the bond-orbital effect. Molecular models show considerable differences of the steric environment around C-3 and sulfonyamide group when this group inverts. The preponderant conformational isomer of 3 with respect to the sulfonyamide group is likely to be the one where the C-3 alkyl group and the N-sulfonyl group are positioned on opposite sides of the aziridine ring and the sulfonyl group covers the upper side of the methylene double bond. The largest group on the aziridine of this isomer is the sulfonyamide group, which is assumed to occupy the anti position in the model with C-3 on the outside position, as shown in Figure 2. In the alternative minor aziridine invertomer, the C-3 alkyl substituent and the N-sulfonyl group are positioned on the same side. Thus, the sulfonyl group does not shield the double bond and the aziridine C-3 substituent is now the largest group and located in an anti position. Nucleophilic attack at the Michael acceptor can take place from both sides of the double bond when there is no shielding effect. Attack from the upper side should produce the 2,3-trans-cyclopropane whereas the 2,3-cis-cyclopropane should result by attack at the alternative lower face. By taking into account that in the preferred conformation (as shown in Figure 2) the upper face is shielded by the N-sulfonyl group, the formation of the cis product is favored.

![Figure 1. Yamamoto's model](image1)

![Figure 2. A model for the preferred conformation of aziridine 3](image2)

Some information about the inversion of the nitrogen atom in these aziridine derivatives was obtained from temperature dependent 1H NMR measurements. At a temperature of -63 °C, the H-3 aziridine ring proton of 3a shows up as two signals in the ratio of 70:30. Although the exact reaction temperature at which the conjugate addition occurs is not clear, this NMR analysis is consistent with the experimental result. Since 30%
of the aziridine 3a seems to possess the conformation with the tosyl group on the side opposite to the unsaturated diester moiety, conjugate addition of nucleophiles can occur equally well from both sides of the double bond leading therefore to the 50:50 ratio. Meanwhile, the other conformer (70%) allows nucleophiles to approach from only one side of the double bond. This results in 85:15 cis/trans ratio observed during the reaction with BuMgBr.

The transition state model shown in Figure 2 indicates that the variation of substituents at the aziridine C-3 position (methyl or hexyl) would probably have only a slight effect on the diastereoselectivity, because the steric environment around the aziridine C-3 is less crowded than that around the nitrogen of the tosylamido group due to the trans-configuration. Nucleophilic approach should be preferred from the bottom side leading to 2,3-cis-cyclopropane (reactions of 3a - e). The size of this C-3 substituent may influence however the ratio of the aziridine invertomers; the smaller the substituent the more this ratio shifts to 1:1, and therefore the size of the C-3 substituent will indirectly affect the shielding of the upper face of the Michael acceptor. The experiments of the substrates 3a and 3c with BuMgBr/CuCN as the reagent showed no significant difference in the cis/trans ratio. The reaction of MeMgI/CuCN with 3d showed a lower diastereoselectivity. Apparently, the sterically hindered mesitylsulfonyl group does not shield the upper side of the unsaturated diester moiety sufficiently to prevent attack by the small nucleophile from the upper face. This result supports the supposition that the conformational preference of this substrate is less outspoken, presumably because the small C-3 substituent (methyl) has only little effect on the ratio of the sulfonamide invertomers (almost 1:1 ratio) and therefore diminishing the shielding over the Michael acceptor. In contrast substrate 3e which has a larger hexyl group at C-3 shows a much higher diastereoselectivity (Table 3, entry 6) in its reaction with the MeMgI/CuCN reagent. Clearly, the preponderant conformational isomer in Figure 2 is now much more predominant due to the steric repulsion between the large mesitylsulfonyl group and the C-3 (hexyl) group when compared with 3c, implying that in 3e the mesitylsulfonyl group exerts an effective shielding effect on the olefinic moiety which results in a high diastereoselectivity. When the more bulky reagent BuMgBr/CuCN is used in these MIRC reactions, invariably excellent diastereoselectivity was achieved (Table 3, entries 2, 3, 5 and 7). This result is readily explained as the sterically demanding reagent will be more sensitive to sterical constraint in the substrate, meaning that the least hindered pathway will be followed in the course of the approach of nucleophiles.

In order to gain further support for the proposed transition state model, cis aziridine derivative 16 was subjected to the MIRC reaction (Scheme 6).

This substrate molecule was conveniently prepared from threonine (see the Experimental Section). Aziridine 16 reacted with BuMgBr/CuCN to yield the cyclopropanedicarboxylate 18 in 24% yield. The $^1H$
NMR chemical shift pattern suggested that the configuration of 18 was 2,3-trans. The uncyclized product 17 was also obtained in a considerable amount (37%). Compound 17 was converted to compound 19 on treatment with NaOEt/EtOH overnight at room temperature. Cyclization under the last-mentioned conditions was followed by a lactamization reaction which was not observed for the trans-aziridine substrates.

The formation of the trans-cyclopropane product 18 can be explained by adopting the same approach as for the trans-aziridine 3. The preferred conformation of 16 leading to the transition state is strongly governed by the 2,3-cis configuration of the C-3 methyl group and the olefinic moiety. This cis relationship forces the N-tosyl group on the side opposite to both the C-3 methyl group and the olefinic moiety. The shielding effect on the Michael acceptor, therefore, will not be as effective as in the substrate 3c. The configuration of the aziridine C-3 of 16 is opposite to that of 3e and inspection of molecular models suggests that the preferred conformation can be pictured as shown in Figure 3, whereby the methyl group is shielding the bottom side. As a consequence the nucleophilic reagent, BuMgBr/CuCN, is primarily directed toward the upper face of the Michael acceptor.

![Figure 3. Newman projection of the preferred conformation of aziridine 16](image)

Reactions with Hetero-Organocuprate Reagents. During the discussion of the results presented in Table 3 (vide supra), it was indicated that more sterically demanding nucleophilic reagents increase the diastereoselectivity of the MIRC reaction. Further elaboration of this observation leads to the suggestion that better diastereoselectivity may be obtained when copper reagents with a large “dummy” volume are employed. Hetero-organocuprates possibly provide such a “dummy” volume. The non-transferable group R’ in RR’CuM with M being Li or MgBr can be residues derived from alcohols, thiols, amines or alkynes. The effect of non-transferable R’ group on the MIRC reaction was investigated. Grignard reagents were used instead of organolithium reagents as the source of the transferable R group because of easier availability.

Initially, methyl transfer was implemented with hetero-organocuprates, but attempts based on a common procedure using preformed MeCu and R’Li did not give cyclopropanes. It is known that the extent of stereoselectivity of organocuprate reagents is influenced by various factors such as the structure of the substrate, solvent, concentration of reagents, presence of salts and the reaction temperature. The sequence of addition was inversed with MeMgBr being added to the preformed R’Cu (Table 4). The R’Cu compounds were conveniently prepared by addition of an ethereal solution of R’Li to an ethereal suspension of Cul. The use of two equivalents of MeMgBr is essential for achieving the desired conjugate addition. The use of only one equivalent of the Grignard reagent resulted in recovery of unchanged 3a (entry 2).
The results shown in Table 4 indicate that indeed the diastereoselectivity of the MIRC reaction improves as the steric bulk of R' increased. The combination of diisopropylamine and diethyl ether (entry 7) resulted in a high reaction yield and a high diastereoselectivity, but a lower chemical yield with higher diastereoselectivity was observed using dimethyl sulfide as solvent (entry 6). The chemical yield and diastereoselectivity was most satisfactory using (-)-terpinen-4-ol (entry 5).

In the set-up of the experiments collected in Table 3, the mesitylsulfonyl group was selected as the second aziridine activating function with the objective to improve the diastereofacial selectivity during the conjugate addition. It was therefore surprising that reactions of 1-(mesitylsulfonyl)-aziridine derivative 3e with hetero-organocuprates involving the use of diisopropylamine and terpinenol resulted in diastereomer ratio's ranging from 67:33 to 80:20. The diastereoselectivity even varied under the same reaction conditions. Although no clear answer is yet available for this observation, the following explanation is proposed.

In the preferred configuration (Figure 2) leading to the transition state where the N-arylsulfonyl group shields the olefinic moiety, the bulky mesitylsulfonyl group of 3e provokes more serious repulsion with the olefinic moiety. The mesitylsulfonyl group, therefore, cannot sustain the anti position and rotates slightly outside to ease the repulsion (Figure 4). This rotation at the same time means the move of the C-3 hexyl group of the aziridine toward the anti position. But when the hexyl group occupies the anti position, there will be much less space for the nucleophilic reagents to form a π-complex from the lower face of the olefinic moiety in Figure 4. Because of this rotation, the voluminous hetero-organocuprates do not experience an energetic advantage during the attack from the lower side of the olefinic moiety. Meanwhile, since one extra equivalent of MeMgBr is present (and required), certain amount of uncomplexed Grignard reagent may well exist in equilibrium with the organocuprate complex. These free species may be able to approach the upper face and the lower face of the Michael acceptor with comparable ease.

### Table 4. Reactions of 3a with hetero-organocuprate reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'H</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>Cis/trans ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuOH</td>
<td>Et₂O</td>
<td>80</td>
<td>81:19</td>
</tr>
<tr>
<td>2</td>
<td>t-BuOH</td>
<td>Et₂O</td>
<td>0*</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Cyclohexanol</td>
<td>Et₂O</td>
<td>95</td>
<td>79:21</td>
</tr>
<tr>
<td>4</td>
<td>DL-Menthol</td>
<td>Et₂O</td>
<td>69</td>
<td>76:24</td>
</tr>
<tr>
<td>5</td>
<td>(-)-Terpinen-4-ol</td>
<td>Et₂O</td>
<td>78</td>
<td>87:13</td>
</tr>
<tr>
<td>6</td>
<td>Diisopropylamine</td>
<td>Me₂S</td>
<td>64</td>
<td>87:13</td>
</tr>
<tr>
<td>7</td>
<td>Diisopropylamine</td>
<td>Et₂O</td>
<td>95</td>
<td>82:18</td>
</tr>
<tr>
<td>8</td>
<td>Dicyclohexylamine</td>
<td>Me₂S</td>
<td>64</td>
<td>84:16</td>
</tr>
<tr>
<td>9</td>
<td>Hexamethylidisilazane</td>
<td>Me₂S</td>
<td>45</td>
<td>87:13</td>
</tr>
</tbody>
</table>

*1.1 eq. MeMgBr was used. 64% of 3a was recovered.*
The occurrence of Michael-reaction Initiated Ring Closure (MIRC) reactions of aziridinyl-methylenemalonates 3 and 16 has been established. A variety of substituents could be introduced onto the resulting cyclopropane dicarboxylic ester derivatives with a highly diastereoselective formation of the cis-isomer (cis:trans ratios ranged from 50:50 to 91:9). Conjugate addition to the methylenemalonate moiety was much more favorable than direct aziridine ring opening due to the presence of the activating malonate system. Grignard reactions catalyzed by CuCN appeared to be the most promising because clean reactions with a high degree of diastereoselectivity were achieved. Even the small methyl group was introduced with a relatively high diastereoselectivity (cis:trans ratio of 87:13).

It is of interest to note that the preference for the formation of the cis-cyclopropane derivatives is opposite to that observed by Kasatkin during the MIRC reaction of the epoxide analogue. This difference can be attributed to the influence of the arylsulfonyl group at the aziridine nitrogen atom on the preferred conformation of the substrate 3 in the transition state. In this conformation, one face of the Michael acceptor is effectively shielded by the N-arylsulfonyl group implying a selective approach of the nucleophilic reagent to the other face of the double bond moiety. For the substrate 16 which has a cis-substituted aziridine ring, the formation of trans-cyclopropane derivatives is predominant. This stereochemical course could be explained similarly by invoking the preferred conformation leading to the transition state.

The results obtained suggest that steric interactions between the nucleophilic reagent and the substituents of the three-membered heterocyclic ring are of importance in governing the stereochemical outcome. Moreover, the stoichiometry and the sequence of addition of hetero-organocuprates play a significant role.

**EXPERIMENTAL SECTION**

Proton and $^{13}$C magnetic resonance spectra were measured on a Bruker AC-100 or a Bruker AM-400 spectrometer. Chemical shift values are reported as $\delta$-values relative to tetramethylsilane as an internal standard. Mass spectra were obtained with a double focussing VG 7070E spectrometer. IR spectra were recorded on a Perkin-Elmer 298 infrared spectrophotometer. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. Recrystallizations were carried out using hexane-EtOAc unless stated otherwise. GLC was conducted with a Hewlett-Packard HP 5890 gas chromatograph, using a capillary column (25m) of HP-1, and nitrogen at 2 ml/min (0.5 atm) as the carrier gas. Commercial n-BuLi solution in hexane (ca. 1.6 M) was purchased from Merck. MeMgBr (3.0 M in Et$_2$O) was purchased from Aldrich Chemical Co. and was diluted with Et$_2$O to make a 1.0 M solution. (Vinyl)MgBr (1.0 M in tetrahydrofuran) was also purchased from Aldrich Chemical Co. tert-Butyl alcohol, hexane and dimethyl sulfide were distilled from calcium hydride, and menthol was recrystallized from pet.-ether (60-80), and other alcohols, cyclohexanol.
and terpineol were simply distilled before use. All amines for hetero-organocuprates, i.e. diisopropylamine, di-tert-butylamine and hexamethyldisilazane were distilled over calcium hydride under Ar prior to use. Diethyl ether was pre-dried over calcium chloride, then distilled from calcium hydride and again from sodium hydride. Tetrahydrofuran was freshly distilled from lithium aluminiumhydride. All other solvents were obtained commercially and used unpurified. Thin-layer chromatography (TLC) was performed on silica gel F-254 plates (thickness 0.25 mm). Spots were visualized with a UV hand lamp, K2Cr2O7 solution in dil.H2SO4 or C12-TDM. Column chromatography was performed using silica 60H (for flash chromatography, Merck, art. nr. 7736) or silica 60 (Merck, art. nr. 7734).

**trans-2-Formyl-3-hexyl-aziridine derivatives:** The synthesis of trans-2-formyl-3-hexyl-1-(toluene-4-sulfonyl)-aziridine 2a is representative. A hexane solution of diisobutylaluminumhydride (1.0 M, 2.7 mL, 2.7 mmol) was added to a cooled (-78 °C) solution of ethyl trans-3-hexyl-1-(toluene-4-sulfonyl)-aziridine-2-carboxylate 1a (0.80 g, 2.3 mmol) in dichloromethane (11 mL) under Ar. On completion of the addition, the mixture was stirred for a further one hour when a solution of sodium fluoride (0.94 g) in water (0.72 mL) was added. The reaction mixture was allowed to warm slowly to room temperature and the white solid thus obtained was collected. The filtrate was concentrated in vacuo and column chromatography (hexane-EtOAc (4:1)) of the residual oil afforded trans-2-formyl-3-hexyl-1-(toluene-4-sulfonyl)-aziridine 2a (0.60 g, 1.9 mmol) in 84% yield.

**trans-2-Formyl-3-hexyl-1-(toluene-4-sulfonyl)-aziridine (2a).** Oil; IR (CCl4) 2920, 1718, 1450, 1340 cm⁻¹; 1H NMR (CDCl3) δ 0.78-0.98 (m, 3H, CH3CH2), 1.08-1.85 (m, 10H, CH3(CH2)5), 2.46 (s, 3H, C6H4CH3), 3.08 (dd, J = 3.3, 6.7 Hz, 1H, NCHCHO), 3.25-3.45 (m, 1H, HexCHN), 7.38 (d, J = 9.4 Hz, 2H, 3, 5-C6H4), 7.86 (d, J = 9.4 Hz, 2H, 2, 6-C6H4), 9.44 (d, J = 6.6 Hz, 1H, CHO); HRMS (M+I)+; Calcd for C16H24NO3S: 310.14769; Found: 310.14759 amu.

**trans-2-Formyl-3-hexyl-1-methylsulfonyl-aziridine (2b).** 86% yield; 2b was obtained as an oil in a similar manner; 1H NMR (CDCl3) δ 0.78-1.01 (m, 3H, CH3CH2), 1.01-1.92 (m, 10H, CH3(CH2)5), 3.03-3.20 (m+s, 4H, SO2CH3, CH2CHN), 3.22-3.44 (m, 1H, NCHCHO), 9.33 (d, J = 6.7 Hz, 1H, CHO); HRMS (M+I)+; Calcd for C10H20NO3S: 234.11639; Found: 234.11641 amu.

**Ethyl 3-methyl-1-(2,4,6-trimethylbenzenesulfonyl)-aziridin-2-carboxylate.** A stirred cooled (0 °C) solution of ethyl 3-methyl-aziridin-2-carboxylate (0.70 g, 5.4 mmol), Et3N (1.5 mL, 11 mmol) and a small catalytic amount of DMAP in CH2Cl2 (50 mL) maintained under Ar was treated with mesitylenesulfonyl chloride (1.5 g, 6.5 mmol). The mixture was stirred at 0 °C for 30 min and then at room temperature for 2 days, whereon it was treated with saturated aqueous NH4Cl (50 mL) and extracted with CH2Cl2 (3x30 mL). The combined organic extracts were washed with brine, dried (MgSO4) and concentrated in vacuo. Column chromatography (hexane-EtOAc (7:1)) of the residue gave the N-(2,4,6-trimethylbenzenesulfonyl)-aziridine derivative as an oil (0.89 g, 53% yield). IR (CCl4) 2980, 1750, 1600, 1510, 1330, 1240 cm⁻¹; 1H NMR (CDCl3) δ 1.21 (t, J = 7.2 Hz, 3H, OCH2CH3), 1.71 (d, J = 5.9 Hz, 3H, CH2CH3), 2.30 (s, 3H, 4-CH2-C6H2), 2.70 (s, 6H, 2, 6-(CH3)3C6H2), 3.02-3.23 (m, 1H, CH3CHN), 3.32 (d, J = 3.9 Hz, 1H, NCHCO2Et), 4.13 (q, J = 7.1 Hz, 2H, OCH2CH3), 6.94 (s, 2H, 3, 5-C6H2); MS (EI): m/e (relative intensity (%)) 311 (M, 32), 266 (3.0), 238 (7.5), 174 (31), 128 (54), 119 (100), 100 (100).
trans-2-Formyl-3-methyl-1-(2,4,6-trimethylbenzenesulfonyl)-aziridine (2d). 91% yield; 2d was obtained as an oil in a similar manner starting from ethyl 3-methyl-1-(2,4,6-trimethylbenzenesulfonyl)-aziridine-2-carboxylate; IR (CCl4) 2940, 1720, 1600, 1450, 1400, 1330, 1165 cm⁻¹; 1H NMR (CDCl₃) δ 1.51 (d, J = 5.7 Hz, 3H, CH₃CHN), 2.68 (s, 6H, 2, 6-(CH₃)₂C₆H₄), 3.12 (dd, J = 3.8, 6.7 Hz, 1H, NCHCHO), 3.32-3.54 (m, 1H, CH₃CHN), 6.98 (s, 2H, 3, 5-C₆H₄), 9.31 (d, J = 6.7 Hz, 1H, CHO); MS (EI): m/e (relative intensity (%)) 267 (M, 15), 174 (9.7), 119 (100), 84 (45).

Aziridinyl-methylenemalonate derivatives: The following synthesis of diethyl [3-hexyl-1-(toluene-4-sulfonyl)-aziridin-2-ylmethylene]-malonate 3a is representative. Dry THF (15 mL) was placed in a 50-mL flask and kept under Ar at 0 °C; TiCl₄ (0.33 mL, 3.0 mmol) was added with a syringe to give a yellow suspension. Diethyl malonate (0.22 mL, 1.5 mmol) and then 2-formyl-3-hexyl-1-(toluene-4-sulfonyl)-aziridine (0.45 g, 1.5 mmol) each dissolved in dry THF (5 mL) were added and successively, followed by pyridine (0.48 mL, 6.0 mmol) to give a deep red-brown solution. The mixture was stirred at room temperature for 3 days, treated with saturated NH₄Cl aqueous solution (25 mL) and extracted with ether (3x 25 mL). The combined organic layers were washed with brine, dried (MgSO₄) and concentrated in vacuo. Column chromatography (hexane- EtOAc (7:1)) of the residue gave 3a (0.35 g, 7.8 mmol) as an oil (52%).

2-[3-Hexyl-1-(toluene-4-sulfonyl)-aziridin-2-ylmethylene]-malonic acid diethyl ester (3a). IR (CCl₄) 2920, 1730, 1330, 1250, 1160 cm⁻¹; 1H NMR (CDCl₃) δ 0.72-1.0 (m, 3H, CH₃CH₂CH₂), 1.0-1.5 (m, 14H, CH₃(CH₂)₅, 2xOCH₂CH₃), 2.88-3.1 (m, 1H, HexCHN), 3.09 (s, 3H, SO₂CH₃), 3.49 (dd, J = 4.5, 10 Hz, 1H, CH=CH), 4.23+4.33 (2xq, J = 7.1 Hz, 4H, 2xOCH₂CH₃), 6.78 (d, J = 9.6 Hz, 1H, CH=C); HRMS (M+I)+; Calcd for C₁₇H₃₀NO₆S: 376.17938; Found: 376.17939 amu.

2-[3-Methyl-1-(toluene-4-sulfonyl)-aziridin-2-ylmethylene]-malonic acid diethyl ester (3b). 3b was obtained similarly in 62% yield as an oil; IR (CCl₄) 2920, 1730, 1465, 1330, 1150 cm⁻¹; 1H NMR (CDCl₃) δ 0.80-1.05 (m, 3H, CH₂CH₂CH₂), 1.15-1.95 (m, 16H, CH₃(CH₂)₅, 2xOCH₂CH₃), 2.88-3.1 (m, 1H, HexCHN), 3.09 (s, 3H, SO₂CH₃), 3.49 (dd, J = 4.5, 10 Hz, 1H, NCHCH=CH), 4.26 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 4.34 (q, J = 7.3 Hz, 2H, OCH₂CH₃), 6.77 (d, J = 10 Hz, 1H, CH=C); HRMS (M+I)+; Calcd for C₁₇H₃₀NO₆S: 376.17938; Found: 376.17939 amu.

2-[3-Methyl-1-(2,4,6-trimethylbenzenesulfonyl)-aziridin-2-ylmethylene]-malonic acid diethyl ester (3c). Methyl analogue 3e was prepared as above (cf. 3a) from ethyl 3-methyl-aziridin-2-carboxylate via the N-tosyl-aziridine (92% yield), reduction (41% yield) and condensation with diethyl malonate (65% yield). The product was an oil; 1H NMR (CDCl₃) δ 1.20-1.50 (m, 6H, 2xOCH₂CH₃), 1.58 (d, J = 6.0 Hz, 3H, CH₃CHN), 2.44 (s, 3H, CH₃CH₂CH₂), 2.90-3.14 (m, 1H, CH₃CHN), 3.58 (dd, J = 3.9, 9.7 Hz, 1H, NCHCH=C), 4.23+4.33 (2xq, J = 7.1 Hz, 4H, 2xOCH₂CH₃), 6.78 (d, J = 9.6 Hz, 1H, CH=C), 7.31 (d, J = 8.2 Hz, 2H, 3,5-C₆H₄), 7.81 (d, J = 8.2 Hz, 2H, 2,6-C₆H₄).

2-[3-Methyl-1-(2,4,6-trimethylbenzenesulfonyl)-aziridin-2-ylmethylene]-malonic acid diethyl ester (3d). 3-Methyl-1-(mesitylsulfonyl)-aziridine 3d was prepared in the same manner as 3a from 2d by condensation with diethyl malonate (95% yield). oil; IR (CCl₄) 2990, 1720, 1600, 1440, 1370, 1330, 1160 cm⁻¹; 1H NMR δ 1.28+1.33 (2xt, J = 7.1 Hz, 6H, 2xOCH₂CH₃), 1.57 (d, J = 5.8 Hz, 3H, CH₃CHN), 2.30 (s, 3H, 4-CH₃Ph), 2.67 (s, 6H, 2,6-(CH₃)₂Ph), 2.95-3.16 (m, 1H, CH₃CHN), 3.58 (dd, J = 3.9, 9.7 Hz, 1H, NCHCH=CH).
4.22-4.31 (2q, J = 7.1 Hz, 4H, 2x OCH2CH3), 6.78 (d, J = 9.7 Hz, 1H, CH=C), 6.95 (s, 2H, 3,5-Ph); HRMS (M)+; Calcd for C20H27NO6S: 409.1559; Found: 409.1558.

2-[3-Hexyl-1-(2,4,6-trimethylbenzenesulfonyl)-aziridin-2-ylmethylene]-malonic acid diethyl ester (3e). 3-Hexyl-1-(mesitylenesulfonyl)-aziridine 3e was prepared in the manner of 3d from ethyl 3-hexyl-aziridin-2-carboxylate via the N-mesityl-aziridine (83% yield), reduction (59% yield) and condensation with diethyl malonate (97% yield) as an oil; IR (CCl4) 2930, 1730, 1600, 1465, 1380, 1330, 1245, 1160 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85-0.97 (m, 3H, CH₃CHaCH₂), 1.15-1.50 (m, 14H, 2x OCHaCH₃, CH₃(CH₂)₄CH₂), 1.60-1.85 (m, 2H, CH₂CHN), 2.30 (s, 3H, 4-CH₃C₆H₄), 2.68 (s, 6H, 2, 6-(CH₃)₂C₆H₄), 2.95-3.12 (m, 1H, HexCHN), 3.54 (dd, J = 3.8, 10 Hz, 1H, NCHCH=C), 4.28 (dq, J = 6.4, 7.1 Hz, 4H, 2x OCH2CH₃), 6.95 (s, 2H, 3, 5-C₆H₂), 7.01 (d, J = 10 Hz, 1H, CH=C); HRMS (M)+; Calcd for C₂₅H₃₇NO₆S: 479.2342; Found: 479.2337 amu.

Reaction with Higher-Order Alkylcopper Reagents. A stirred, cooled (-78 °C) solution of 3 equiv of the copper reagents in ether or THF (10 mL), was treated with a solution of 3a or 3b (0.80 retool) in ether (or THF; 5 mL). The mixture was allowed to warm to -30 °C, and stirring was continued at this temperature for 3h, when it was poured into a 3:1 mixture of saturated NH₄Cl aqueous solution and 25% ammonia solution (100 mL). The usual workup procedure followed by column chromatography (hexane-EtOAc), afforded the products.

The alkylcopper reagents were prepared as follows. Me₂Cu(CN)Li₂: An ether solution of MeLi (1.6M, 3.0 mL, 4.8 mmol) was added slowly to a precooled (-78 °C) suspension of CuCN (0.22 g, 2.4 retool) in ether (or THF; 10 mL). The mixture was allowed to warm to 0 °C, and then after 10 rain, was cooled to -78 °C. Bu₂Cu(CN)Li₂: A procedure similar to that above, except for the use of BuLi (a 1.6M hexane solution) instead of MeLi. The preparation was carried out at -50 °C instead of 0 °C. Bu₂Cu(CN)Li₂·BF₃·BF₃Et₂O (0.65 mL, 2.4 mmol) was added to Bu₂Cu(CN)Li₂ (prepared as described above) at -78 °C, and the mixture was stirred for 5 min.

Reaction with Butylmagnesiocuprate BF₃ Reagents. BuMgBr (1.6M, 1.3 mL, 2.0 mmol) in ether (or THF) was added by syringe to a stirred, cooled (-78 °C) slurry of CuCN (0.18 g, 2.0 mmol) in dry ether (or THF; 10 mL), and the mixture was allowed to warm to 0 °C. BF₃Et₂O (0.54 mL, 2.0 mmol) was added to the above mixture at -78 °C, which was then stirred for 5 min. A solution of diethyl aziridinyl-methylenemalonate 3a (0.30 g, 0.67 mmol) in dry ether (or THF; 5 mL) was then added dropwise to the above reagent and the reaction mixture was then allowed to -10 °C (or -30 °C in the case of THF solution). Stirring was continued for 2h (or 3h in the case of THF solution) at the respective temperatures. The reaction mixture was poured into a 3:1 mixture of saturated NH₄Cl aqueous solution and 25% ammonia solution (100 mL), processed as usual and subjected to column chromatography (hexane-EtOAc (7:1)) to give the products.

Reaction with Grignard Reagents Catalyzed by CuCN. A stirred, cooled (-78 °C) mixture of diethyl aziridinyl-methylenemalonate 3 (0.67 mmol) and CuCN (0.006 g, 0.067 mmol) in the required solvents (15 mL) was treated with a Grignard reagent (0.73 mmol), and after 15 min, the mixture was allowed to warm to room temperature over 3h. Saturated aqueous NH₄Cl solution (50 mL) was added, and the usual workup procedure followed by column chromatography (hexane-EtOAc) gave the products described.
Synthesis of functionalized cyclopropanes

**Reaction with Alkenylcupratemagnesium bromide/dimethylsulfide reagent.** A reported method was used as follows: The dimethyl sulfide complex of cuprous bromide (0.14 g, 0.67 mmol) was placed in a 50-mL flask maintained under argon. Dimethyl sulfide (0.67 mL) and ether (0.84 mL) were then added separately, and the resulting solution was cooled to -45 °C. The stirred mixture was treated with an ethereal solution of butylmagnesium bromide (1.0 M, 0.74 mL, 0.74 mmol), and after 1.5 h, with 1-hexyne (0.084 mL, 0.74 mmol). The mixture was allowed to warm to -23 °C, and was stirred at this temperature for 2.25 h. The resulting dark green solution was cooled to -50 °C, and treated with a solution in ether (3 mL) of diethyl aziridinyl-methylenemalonate 3a (0.30 g, 0.67 mmol). The mixture was allowed to warm to -30 °C, stirred at this temperature for 2 h, and then at 0 °C for 2 h. The mixture was treated with saturated aqueous NH₄Cl solution and 25% aqueous ammonia (3:1, 25 mL), processed as usual, and column chromatography (hexane-EtOAc (10:1)) of the crude material gave the product (0.20 g).

**Reaction with Tributyltin Cuprate.** The reported method was used as follows: n-BuLi (1.6 M in hexane, 0.94 mL, 1.5 mmol) was added to a stirred, cooled (-78 °C) slurry of CuCN (0.067 g, 0.75 mmol) in ether (10 mL). The mixture was allowed to warm slowly to -50 °C, recooled to -78 °C, whereon n-Bu₃SnH (0.40 mL, 1.5 mmol) was added by syringe. Stirring was continued for 15 min, when diethyl aziridinyl-methylenemalonate 3a (0.30 g, 0.67 mmol) dissolved in ether (5 mL) was added. This mixture was allowed to warm to -30 °C over 1 h, stirred at this temperature for 3 h and then treated with a 3:1 mixture of saturated aqueous NH₄Cl and 25% aqueous ammonia (25 mL). The usual processing followed by column chromatography (hexane-EtOAc (10:1 to 7:1)) gave 4e (0.08 g, 16%) and 5e (0.15 g, 30%).

**Reaction with Sodium Thiophenoxide.** A solution of thiophenol (0.073 mL, 0.74 mmol) in THF (2 mL) was added to a stirred, cooled (0 °C) suspension of sodium hydride (0.018 g, 0.74 mmol) in THF (10 mL). The mixture was set aside for 30 min, cooled to -78 °C and treated with a solution of diethyl aziridinyl-methylenemalonate 3a (0.30 g, 0.67 mmol) in THF (5 mL). After 10 min, the mixture was allowed to warm to 0 °C when stirring was continued for 2.5 h prior to the addition of saturated aqueous NH₄Cl solution (25 mL). The reaction mixture was extracted with ether (3 x 20 mL), the combined organic extracts washed with brine, dried (MgSO₄), and concentrated in vacuo. Column chromatography (hexane-EtOAc (5:1)) of the residue, gave 4f (0.24 g, 64%).

**Reaction with K-Selectride.** A solution of diethyl aziridinyl-methylenemalonate 3a (0.33 g, 0.73 mmol) in dry THF (7 mL) was added to a stirred, cooled (-78 °C) solution of K-Selectride (1.0 M, 0.80 mL, 0.80 mmol) in THF. The reaction mixture was stirred for 15 min at -78 °C, allowed to warm to 0 °C over 1.5 h, and after a further 1 h at this temperature, was treated successively with a 10% NaOH aqueous solution (0.3 mL) and 35% H₂O₂ (3 mL), and set aside to attain room temperature, whereon it was poured into water. The mixture was extracted with ether (3 x 10 mL), and the combined organic extracts washed successively with saturated aqueous NaHCO₃ solution, brine, dried (MgSO₄), filtered, and concentrated in vacuo. Column chromatography (hexane-EtOAc (3:1)) of the residue afforded cyclopropane 5g (0.26 g, 79%) as an oil.

**Syntheses of 5 from 4 and 8 from 7.** Synthesis of 5b from 4b is representative. A stirred solution of aziridine 4b (0.19 g, 0.37 mmol) in EtOH (6 mL) maintained under argon, was treated with a few drops of a solution (1.3 M) of sodium ethoxide, set aside overnight at room temperature and then concentrated in vacuo. Column chromatography (hexane-EtOAc (7:1)) of the residue yielded cyclopropane 5b (0.18 g, 95%) as an oil.

The following were obtained in a similar manner:
3-Methyl-2-[1-(toluene-4-sulfonylamino)-heptyl]-cyclopropane-1,1-dicarboxylic acid diethyl ester (5a). Oil; IR (CCl₄) 3260, 2925, 1465, 1300, 1165 cm⁻¹;¹ H NMR (CDCl₃) δ 0.81-0.86 (m, 3H, CH₃CH₂CH₂), 1.00-1.44 (m, 18H, CH₃(CH₂)₄CHH, CHCH₃, 2xOCH₂CH₃), 1.45-1.84 (m, 3H, CH₃CHCH, CH₃(CH₂)₄CHH), 2.39-2.42 (2x, 3H, C₆H₄CH₃), 2.95-3.12 (m, 0.5H, CHN), 3.57-3.65 (m, 0.5H, CHN), 4.08-4.24 (m, 4H, 2xOCH₂CH₃), 4.90 (d, J = 8.0 Hz, 0.5H, NH), 4.96 (d, J = 8.4 Hz, 0.5H, NH), 7.24-7.32 (m, 2H, 3, 5-C₆H₄), 7.72+7.84 (2x, d, J = 8.0 Hz, 2H, 2, 6-C₆H₄);¹³C NMR (CDCl₃) δ 9.0, 12.8, 14.0, 14.1, 21.4, 22.4, 24.7, 25.0, 28.9, 29.1, 31.5, 35.3, 35.6, 35.8, 37.0, 38.5, 40.1, 50.4, 52.7, 61.1, 61.4, 61.5, 61.6, 126.8, 127.1, 129.4, 129.5, 136.4, 139.1, 143.0, 143.1, 166.7, 167.8, 168.2, 170.3; HRMS (M⁺); Calcd for C₂₄H₃₈NO₆: 468.24199; Found: 468.24207 amu.

2-{{1-[3-Hexyl-1-(toluene-4-sulfonyl)-aziridin-2-yl]-pentyl}-malonic acid diethyl ester (4b). Oil; IR (CCl₄) 2920, 1730, 1460, 1330, 1160 cm⁻¹;¹ H NMR (CDCl₃) δ 0.74-1.04 (m, 6H, 2xCH₃CH₂CH₂), 1.04-1.7 (m, 21H, BuCH, 2xOCH₂CH₃, CH₃(CH₂)₃), 1.7-2.1 (m, 2H, CH₂CH₂CHN), 2.43 (s, 3H, C₆H₄CH₃), 2.5-2.75 (m, 1H, HexCHN), 2.95 (dd, J = 5, 10 Hz, IH, NCHCHBu), 3.28 (d, J = 3.9 Hz, 1H, CH(CO₂Et)₂), 4.12 (q, J = 7.0 Hz, 2H, OCH₂CH₃), 4.20 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 7.30 (d, J = 8.3 Hz, 2H, 3, 5-C₆H₄), 7.85 (d, J = 8.3 Hz, 2H, 2, 6-C₆H₄); HRMS (M); Calcd for C₂₇H₄₃NO₆S: 509.2811; Found: 509.2811 amu.

3-Butyl-2-[1-(toluene-4-sulfonylamino)-heptyl]-cyclopropane-1,1-dicarboxylic acid diethyl ester. The mixture of (5b) and (6b); oil; ¹H NMR (CDCl₃) δ 0.81-0.93 (m, 6H, 2xCH₃CH₂CH₂), 1.0-1.40 (m, 20H, CH₃(CH₂)₂CH₂CH, CH₃(CH₂)₅, 2xOCH₂CH₃), 1.44-1.80 (m, 4H, CH₂CH₂CHCH), 2.41 (s, 3H, C₆H₄CH₃), 2.50-2.68 (m, 0.55H, CHN), 3.21-3.27 (m, 0.5H, CHN), 2.95-3.06 (m, <0.10H, CHN), 3.65-3.74 (m, 0.30H, CHN), 4.11-4.24 (m, 3H, OCH₂CH₃, OCHHCH₃), 4.29 (q, J = 7.2 Hz, 1H, OCHHCH₃), 4.54-4.59 (m, 0.35H, NH), 5.00 (d, J = 8.0 Hz, 0.5H, NH), 6.48 (d, J = 11 Hz, 0.5H, CH=C), 7.24-7.31 (m, 2H, 3, 5-C₆H₄), 7.70-7.78 (m, 2H, 2, 6-C₆H₄).

The single isomer (5b); oil; IR (CCl₄) 3260, 2920, 1730, 1455, 1320, 1230 cm⁻¹;¹ H NMR (CDCl₃) δ 0.70-0.95 (m, 6H, 2xCH₃CH₂CH₂), 0.95-1.40 (m, 20H, CH₃(CH₂)₂CH₂CH, CH₃(CH₂)₃, 2xOCH₂CH₃), 1.44-1.80 (m, 4H, CH₂CH₂CHCH), 2.41 (s, 3H, C₆H₄CH₃), 1.60-1.75 (m, 2H, CHCHBu), 2.41 (s, 3H, CH₃CH₃), 3.50-3.85 (m, 1H, CHN), 4.16+4.18 (2x, J = 7.1 Hz, 4H, 2xOCH₂CH₃), 4.56 (d, J = 7.9 Hz, 1H, NH), 7.27 (d, J = 8.3 Hz, 2H, 3, 5-C₆H₄), 7.75 (d, J = 8.3 Hz, 2H, 2, 6-C₆H₄);¹³C NMR (CDCl₃) δ 14.0, 21.4, 22.4, 23.2, 23.9, 29.2, 29.7, 31.0, 31.3, 31.6, 35.2, 35.4, 36.7, 50.4, 61.1, 61.6, 126.9, 129.5, 138.9, 143.1, 167.0, 170.3; HRMS (M⁺); Calcd for C₂₇H₄₃NO₆S: 509.2811; Found: 509.2811 amu.

2-[[3-Hexyl-1-(toluene-4-sulfonyl)-aziridin-2-yl]-2-propenyl]-malonic acid diethyl ester (4c). Oil; IR (CCl₄) 2920, 1730, 1455, 1330, 1160 cm⁻¹;¹ H NMR (CDCl₃) δ 0.81-0.95 (m, 6H, 2xCH₃CH₂CH₂), 0.95-1.40 (m, 20H, CH₃(CH₂)₄CH₂, CH₃(CH₂)₃, 2xOCH₂CH₃), 1.50-1.60 (m, 2H, CH₂CH₂CHCH), 1.60-1.75 (m, 2H, CHCHBu), 2.41 (s, 3H, CH₃CH₃), 3.50-3.85 (m, 1H, CHN), 4.16+4.18 (2x, J = 7.1 Hz, 4H, 2xOCH₂CH₃), 4.56 (d, J = 7.9 Hz, 1H, NH), 7.27 (d, J = 8.3 Hz, 2H, 3, 5-C₆H₄), 7.75 (d, J = 8.3 Hz, 2H, 2, 6-C₆H₄);¹³C NMR (CDCl₃) δ 14.0, 21.4, 22.4, 23.2, 23.9, 29.2, 29.7, 31.0, 31.3, 31.6, 35.2, 35.4, 36.7, 50.4, 61.1, 61.6, 126.9, 129.5, 138.9, 143.1, 167.0, 170.3; HRMS (M⁺); Calcd for C₂₅H₃₈NO₆S: 480.24187 amu.

2-[[Toluene-4-sulfonylamino]-heptyl]-3-vinyl-cyclopropane-1,1-dicarboxylic acid diethyl ester (5c). Oil; IR (CCl₄) 3260, 2920, 1720, 1455, 1320, 1230 cm⁻¹;¹ H NMR (CDCl₃) δ 0.83-0.94 (m, 3H, CH₃(CH₂)₂CH₂), 1.10-1.30 (m, 14H, CH₃(CH₂)₂CH₂, 2x OCH₂CH₃), 1.50-1.60 (m, 2H, CH(CH₂)₂CH₂), 1.88 (dd,
Synthesis of functionalized cyclopropanes

2-(2-Butyl-1-enyl)-3-[1-(toluene-4-sulfonylamino)-heptyl]-cyclopropane-1,1-dicarboxylic acid diethyl ester (5d). Oil; IR (CCl₄) 2920, 2850, 1720, 1455, 1320 cm⁻¹; ¹H NMR (CDCl₃) δ 6.28-9.25 (m, 9H, 3xCH₂CH₂CH₂), 1.12-1.33 (m, 22H, CH₃(CH₂)₄, 2xCH₂(CH₂)₃, 2xOCH₂CH₃), 1.50-1.75 (m, 2H, CH₂CHN), 1.78 (dd, J = 9.7, 10 Hz, 1H, H-2), 1.82-2.05 (m, 4H, CH=C(CH₂)₂), 2.41 (s, 3H, C₆H₄CH₃), 2.50 (dd, J = 9.5, 9.7 Hz, 1H, H-3), 3.75-3.84 (m, 0.90H, CH₂NH), 4.06-4.22 (m, 4H, 2xOCH₂CH₃), 3.00-3.10 (m, 0.10H, CH₂NH), 4.49 (d, J = 6.8 Hz, 0.12H, NH), 4.65 (d, J = 6.8 Hz, 0.88H, NH), 4.84 (d, J = 9.5 Hz, 1H, CH=C), 7.24 (d, J = 8.4 Hz, 2H, 3, 5-C₆H₄), 7.73 (d, J = 8.4 Hz, 0.2H, 2, 6-C₆H₄); HRMS (M⁺)⁺; Calcd for C₃₃H₅₃NO₆S: 592.3672; Found: 592.3670 amu.

2-{3-Hexyl-1-(toluene-4-sulfonyl)-aziridin-2-yl}-[tri-butylstanny]-methy]-malonic acid diethyl ester (4e). Oil; IR (CCl₄) 2920, 2850, 1720, 1455, 1320 cm⁻¹; ¹H NMR (CDCl₃) δ 0.72-1.05 (m, 12H, 4xCH₂CH₂CH₂), 1.05-2.10 (m, 34H, CH₃(CH₂)₅, 3xCH₃(CH₂)₅, 2xOCH₂CH₃), 2.12-2.35 (m, 1H, CH₂Sn), 2.43 (s, 3H, C₆H₄CH₃), 2.51-2.74 (m, 1H, HexCHN), 2.94 (d, J = 6, 9 Hz, 1H, CH₂N), 3.29 (d, J = 6 Hz, 1H, CH(CO₂Et)₂), 4.12+4.19 (2xq, J = 7 Hz, 4H, 2xOCH₂CH₃), 7.30 (d, J = 8 Hz, 2H, 3, 5-C₆H₄), 7.85 (d, J = 8 Hz, 2H, 2, 6-C₆H₄).
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35.7, 53.7, 61.6, 127.1, 129.6, 138.4, 143.3, 167.7, 169.4; HRMS (M+I)+; Calcd for C_{23}H_{35}NO_6S: 454.22634; Found: 454.22612 amu; Anal. Calcd for C_{23}H_{35}NO_6S: C, 60.90; H, 7.78; N, 3.09; S, 7.07. Found: C, 60.78; H, 7.86; N, 2.99; S, 6.84.

2-[1-(3-Hexyl-1-methylsulfonyl-aziridin-2-yl)-ethyl]-malonic acid diethyl ester (7a). Oil; IR (CCl4) 2920, 1725, 1444, 1366, 1318 cm⁻¹; ¹H NMR δ 0.78-1.02 (m, 3H, CH₃CH₂CH₂), 1.09-1.6 (m, 18H, CH₃(CH₂)₉CH₂, 2xOCH₂CH₃), 1.6-1.9 (m, 1H, CH₃(CH₂)₈CHH), 2.48-2.65 (m, 1H, HexCH₂CH₂), 2.78 (dd, J = 4.4, 8.4 Hz, 1H, NCHCH₂CH₂), 3.14 (s, 3H, SO₂CH₃), 3.59 (d, J = 4.8 Hz, 1H, CH(CO₂Et)₂), 4.22+4.25 (2xq, J = 7.2 Hz, 4H, 2xOCH₂CH₂); HRMS (M+I)+; Calcd for C_{23}H_{35}NO_6S: 392.21063 amu.

2-[1-(Methylsulfonylamino)-heptyl]-3-methyl-cyclopropane-1,1-dicarboxylic acid diethyl ester (8a). The mixture with the aziridine-protonated compound (9a); oil; IR (CCl₄) 3260, 2920, 1730, 1455, 1340, 1150 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85-0.90 (m, 3H, CH₃(CH₂)₃), 1.11-1.6 (m, 18H, CH₃(CH₂)₉, 2xOCH₂CH₃), 1.71-1.96 (m, 2H), 2.16 (dd, J = 7.2, 7.2 Hz, 0.5H), 2.5-2.6 (m, 0.14H), 2.90+2.98 (2s, 0.5H), 3.12-3.16 (m, 0.5H), 3.40-3.49 (m, 0.07H), 3.50-3.51 (m, 0.07H), 3.66-3.80 (m, 0.5H), 4.14-4.31 (m, 4H), 4.69 (d, J = 8.0 Hz, 0.3H), 4.80 (d, J = 8.4 Hz, 0.5H), 5.02+5.08 (2xd, J = 8 Hz, 0.07H), 6.9 (d, J = 8 Hz, 0.04H), 7.04 (dd, J = 8 Hz, 0.04H).

The pure cyclopropane (8a); Oil; IR (CCl₄) 3300, 2920, 1723, 1455, 1320, 1150 cm⁻¹; ¹H NMR (CDCl₃) δ 0.79-1.03 (m, 3H, CH₃CH₂CH₂), 1.19-1.61 (m, 19H, CH₃CH₂, CH₃(CH₂)₉, 2xOCH₂CH₃), 1.61-1.93 (m, 2H, CH₃CHCH₂), 3.00 (s, 3H, SO₂CH₃), 3.6-3.88 (m, 1H, CHN), 4.06-4.33 (m, 4H, 2xOCH₂CH₃), 4.47 (d, J = 8.0 Hz, 1H, NH).

2-[1-(3-Hexyl-1-methylsulfonyl-aziridin-2-yl)-pentyl]-malonic acid diethyl ester (7b). Oil; IR (CCl₄) 2920, 1735, 1600, 1465, 1325, 1150 cm⁻¹; ¹H NMR (CDCl₃) δ 0.80-0.90 (m, 3H, CH₃(CH₂)₉), 1.10-1.84 (m, 22H, CH₃(CH₂)₈CH₂, BuCH, CH₃(CH₂)₉, 2xOCH₂CH₃), 1.84-2.24 (m, 1H, CHHCH₂CH₂), 2.5-2.7 (m, 1H, CH₂CH₂CH₂), 2.84 (dd, J = 4.0, 8.2 Hz, 1H, NCHCH₂Bu), 3.14 (s, 3H, SO₂CH₃), 3.64 (d, J = 4.1 Hz, 1H, CH(CO₂Et)₂), 4.22+4.24 (2xq, J = 7.1 Hz, 4H, 2xOCH₂CH₃); HRMS (M+I)+; Calcd for C_{21}H_{40}NO_6S: 434.25772 amu.

3-Butyl-2-[1-(methylsulfonylamino)-heptyl]-cyclopropane-1,1-dicarboxylic acid diethyl ester (8b). Oil; IR (CCl₄) 3270, 2920, 1720, 1460, 1325, 1220 cm⁻¹; ¹H NMR (CDCl₃) δ 0.75-0.93 (m, 6H, 2xCH₂CH₂CH₂), 1.21-1.64 (m, 20H, CH₃(CH₂)₉, CH₃(CH₂)₉, 2xOCH₂CH₃), 1.64-1.90 (m, 4H, CH₂CH₂CH₂, CHCH₂Bu), 2.99 (s, 3H, SO₂CH₃), 3.6-3.95 (m, 1H, CHN), 4.18-4.20 (2xq, J = 7.1 Hz, 4H, 2xOCH₂CH₃), 4.53 (d, J = 8.1 Hz, 1H, NH); HRMS (M+I)+; Calcd for C_{21}H_{40}NO_6S: 434.25772 amu.

3-Butyl-2-[1-(toluene-4-sulfonylamino)-ethyl]-cyclopropane-1,1-dicarboxylic acid diethyl ester (10). Oil; Rf = 0.21 (hexane:EtOAc = 3:1), column chromatography was conducted using hexane-EtOAc (7:1) as eluent; ¹H NMR (CDCl₃) δ 0.83-0.91 (m, 3H, CH₃CH₃(CH₂)₉), 1.09-1.39 (m, 14H, CH₂(CH₂)₈CH₃, CH₂CH₂, 2xOCH₂CH₃), 1.57-1.80 (m, 3H, CH₃(CH₂)₉CHHCH₂, BuCHCH₂), 2.41 (s, 3H, C₆H₄CH₃), 3.00-3.08 (m, 0.15H, CH(NH)), 3.50-3.58 (m, 0.85H, C₆H₄CH₃), 4.09-4.23 (m, 4H, 2xOCH₂CH₃), 4.79 (d, J = 7.8 Hz, 0.85H, NH), 4.92 (d, J = 7.8 Hz, 0.15H, NH), 7.29 (d, J = 8.4 Hz, 2H, 3, 5-C₆H₄), 7.76 (d, J = 8.4 Hz, 2H, 2, 6-C₆H₄). MS (CI): m/e (relative intensity (%)) 440 (M+I)+ (1.0), 394 (19.8), 284 (28.7), 269 (41.3), 241 (20.4), 195 (14.6), 183 (10.7), 155 (19.9).
3-Methyl-2-[1-(2,4,6-trimethylbenzenesulfonylamino)-ethyl]-cyclopropane-1,1-dicarboxylic acid diethyl ester (12). Purification by flash column chromatography using hexane-EtOAc (5:1) as eluent gave 12 (0.13 g, 46%) as an oil; IR (CCl₄) 3300, 2980, 1720, 1455, 1370, 1325, 1210 cm⁻¹; ¹H NMR (CDCl₃) δ 0.78 (d, J = 6.3 Hz, 1.8H, 3-CH₃), 0.96 (d, J = 6.7 Hz, 1.2H, 3-CH₃), 1.13 (d, J = 6.7 Hz, 1.8H, CH₂CHNH), 1.18-1.29 (m, 7.2H, CH₃CHNH, 2x OCH₂CH₃), 1.39-1.46 (m, 0.6H, H-3), 1.61-1.68 (m, 1H, H-2, H-3), 1.78-1.81 (m, 0.4H, H-2), 2.29+2.30 (2s, 3H, 4-(CH₃)₂C₆H₂), 2.64+2.66+2.69 (3s, 6H, 2, 6-(CH₂)₂C₆H₂), 2.98-3.04 (m, 0.6H, CH₂NH), 3.48-3.52 (m, 0.4H, CH₂NH), 4.04-4.22 (m, 4H, 2x OCH₂CH₃), 4.78 (d, J = 8.3 Hz, 0.4H, NH), 4.97 (d, J = 8.6 Hz, 0.6H, NH), 6.94+6.97 (2s, 2H, 3, 5-C₆H₂). HRMS (M)⁺; Calcd for C₂₁H₃₁NO₆S: 425.1872; Found: 425.1875 amu.

3-Butyl-2-[1-(2,4,6-trimethylbenzenesulfnylamino)-ethyl]-cyclopropane-1,1-dicarboxylic acid diethyl ester (13). Purification by flash column chromatography using hexane-EtOAc (7:1) as eluent gave 13 (0.15 g, 48%) as an oil; IR (CCl₄) 3300, 2960, 1720, 1450, 1370, 1320, 1250, 1215 cm⁻¹; ¹H NMR (CDCl₃) δ 0.84 (t, J = 7.2 Hz, 3H, CH₃CH₂CH₂), 1.09-1.35 (m, 15H, 2x OCH₂CH₃, CH₃(CH₂)₃CH, CH₂CHNH), 1.57-1.62 (m, 1H, H-3), 1.68-1.73 (m, 1H, H-2), 2.28+2.30 (2s, 3H, 4-(CH₂)₂C₆H₂), 2.64+2.65 (2s, 6H, 2, 6-(CH₂)₂C₆H₂), 2.98-3.01 (m, 0.09H, CH₂NH), 3.55-3.62 (m, 0.91H, CH₂NH), 4.10-4.23 (m, 4H, 2x OCH₂CH₃), 4.52 (d, J = 8.3 Hz, 0.1H, NH), 4.67 (br s, 0.09H, NH), 6.94+6.96 (2s, 2H, 3, 5-C₆H₂). HRMS (M)⁺; Calcd for C₂₄H₃₇NO₆S: 467.2342; Found: 467.2339 amu.

3-Methyl-2-[1-(2,4,6-trimethylbenzenesulfonylamino)-heptyl]-cyclopropane-1,1-dicarboxylic acid diethyl ester (14). Purification by flash column chromatography using hexane-EtOAc (7:1) as eluent gave 14 (0.20 g, 60%) as an oil; IR (CCl₄) 3300, 2920, 1725, 1455, 1405, 1370, 1320, 1215 cm⁻¹; ¹H NMR (CDCl₃) δ 0.74 (d, J = 6.6 Hz, 0.63H, CH₂CH), 0.83 (t, J = 7.0 Hz, 3H, CH₃CH₂CH₂), 0.98 (d, J = 6.6 Hz, 2.37H, CH₂CH), 1.04-1.28 (m, 14H, 2x OCH₂CH₃, CH₃(CH₂)₄CH₂), 1.32-1.37 (m, 0.42H, CH₂CH), 1.53-1.83 (m, 3.58H, CH₂CH₂, H-2, H-3), 2.28+2.29 (2s, 3H, 4-(CH₂)₂C₆H₂), 2.64 (s, 4.6H, 2, 6-(CH₂)₂C₆H₂), 2.67 (s, 1.4H, 2, 6-(CH₂)₂C₆H₂), 2.98-3.04 (m, 0.21H, CH₂NH), 3.61-3.68 (m, 0.79H, CH₂NH), 4.09-4.24 (m, 4H, 2x OCH₂CH₃), 4.49 (d, J = 8.0 Hz, 0.79H, NH), 4.57 (d, J = 9.0 Hz, 0.21H, NH), 6.93 (s, 1.58H, 3, 5-C₆H₂), 6.97 (s, 0.42H, 3, 5-C₆H₂); HRMS (M)⁺; Calcd for C₂₆H₄₁NO₆S: 495.2655; Found: 495.2654 amu.

3-Butyl-2-[1-(2,4,6-trimethylbenzenesulfonylamino)-heptyl]-cyclopropane-1,1-dicarboxylic acid diethyl ester (15). Purification by flash column chromatography using hexane-EtOAc (10:1) as eluent gave 15 (0.25 g, 69%) as an oil; IR (CCl₄) 3310, 2920, 1720, 1450, 1370, 1320, 1160 cm⁻¹; ¹H NMR (CDCl₃) δ 0.81-0.86 (m, 6H, 2x CH₂CH₂CH₂), 1.06-1.30 (m, 20H, CH₃(CH₂)₄CH₂, CH₃(CH₂)₃CHCH, 2x OCH₂CH₃), 1.48-1.52 (m, 2H, CH₃(CH₂)₄CH₂), 1.65-1.72 (m, 2H, H-2, H-3), 2.28+2.29 (2s, 3H, 4-(CH₂)₂C₆H₂), 2.64+2.66 (2s, 6H, 2, 6-(CH₂)₂C₆H₂), 2.96 (m, 0.10H, CH₂NH), 3.70-3.75 (m, 0.90H, CH₂NH), 4.12-4.21 (m, 4H, 2x OCH₂CH₃), 4.49 (d, J = 8.0 Hz, 0.90H, NH), 4.58 (d, J = 8.0 Hz, 0.10H, NH), 6.93+6.94 (2s, 2H, 3, 5-C₆H₂); ¹³C NMR (CDCl₃) δ 14.0, 20.8, 22.4, 23.0, 23.1, 24.0, 29.2, 31.0, 31.3, 31.6, 35.3, 35.5, 36.7, 50.3, 61.1, 61.6, 131.9, 136.2, 138.4, 141.8, 167.0, 170.7; HRMS (M)⁺; Calcd for C₂₉H₄₇NO₆S: 537.3124; Found: 537.3125 amu.

Methyl (2S, 3S)-3-methyl-1-(toluene-4-sulfonyl)-aziridin-2-carboxylate. Methyl (2S, 3S)-3-methyl-1-trityl-aziridin-2-carboxylate (3.2 g, 8.9 mmol) which was prepared according to a literature method ²⁴ was dissolved in 14 mL of chloroform and methanol (1:1 v/v). To this solution was added 7 mL of trifluoroacetic acid under ice cooling. The mixture was stirred for 3h in an ice bath and then concentrated in vacuo.
Evaporation with newly added ether was repeated several times to remove trifluoroacetic acid as completely as possible. The residue was dissolved in ether again and 3-methyl-aziridine-2-carboxylate trifluoroacetate was extracted with water (3x 30 mL). To the aqueous extract was added sodium hydrogencarbonate (3.5 g, 0.042 mol) and 30 mL of ethyl acetate. Tosyl chloride (1.7 g, 8.9 mmol) was added to the mixture under vigorous stirring in an ice bath. After stirring overnight at room temperature, the ethyl acetate layer was separated from the aqueous layer which was extracted with another portion of ethyl acetate again. The combined organic layers were washed with brine, dried over MgSO₄, and concentrated. The crude product thus obtained was purified by column chromatography (silica, hexane-EtOAc (3:1)) to give 1.2 g (50%) of methyl l-tosyl-aziridinecarboxylate: oil; IR (CCl₄) 2960, 1750, 1440, 1410, 1340, 1280, 1200, 1160 cm⁻¹; ¹H NMR (CDCl₃) δ 1.32 (d, J = 5.6 Hz, 3H, CH₃CHN), 2.45 (s, 3H, C₆H₄CH₃), 3.10 (dq, J = 5.6, 7.4 Hz, 1H, CH₃CHN), 3.39 (d, J = 7.4 Hz, 1H, CH₃), 7.34 (d, J = 8.1 Hz, 2H, 3, 5-C₆H₄), 7.85 (d, J = 8.4 Hz, 2H, 2, 6-C₆H₄); ¹³C NMR (CDCl₃) δ 12.2, 21.7, 40.1, 41.2, 52.6, 128.0, 129.8, 134.4, 145.0, 166.3.

(2S, 3S)-2-Formyl-3-methyl-l-(toluene-4-sulfonyl)-aziridine. A hexane solution of diisobutylaluminum-hydride (1.0M, 5.4 mL, 5.4 mmol) was added to a dichloromethane solution (22 mL) of methyl cis-3-methyl-l-(toluene-4-sulfonyl)-aziridine-2-carboxylate (1.2 g, 4.5 mmol) at -78 °C under Ar. After completion of the addition, the mixture was stirred for one hour and sodium fluoride (1.9 g) and water (1.3 mL) were added. The reaction mixture was then warmed slowly to room temperature and the white solid thus formed was collected. The filtrate was concentrated in vacuo and column chromatography (hexane-EtOAc (2:1)) of the residual oil afforded cis-2-formyl-3-methyl-l-(toluene-4-sulfonyl)-aziridine (0.88 g, 3.7 mmol) in 82% yield also as an oil. IR (CCl₄) 2920, 1730, 1440, 1400, 1340, 1215, 1160 cm⁻¹; IH NMR (CDCl₃) δ 1.39 (d, J = 5.6 Hz, 3H, CH₃CHN), 2.46 (s, 3H, CH₃C₆H₄), 3.12-3.27 (m, 2H, H-2, H-3), 7.36 (d, J = 8.0 Hz, 2H, 3, 5-C₆H₄), 7.84 (d, J = 8.0 Hz, 2H, 2, 6-C₆H₄), 9.31 (d, J = 5.4 Hz, 1H, CHO); ¹³C NMR (CDCl₃) δ 12.9, 21.5, 40.6, 46.4, 127.8, 129.8, 145.1, 195.3.

(2R, 3S)-2-[3-Methyl-l-(toluene-4-sulfonyl)-aziridin-2-ylmethylene]-malonic acid diethyl ester (16). Diethyl cis-3-methyl-aziridinylmethylene-malonate was prepared from cis-2-formyl-3-methyl-1-tosyl-aziridine according to the standard method. After column chromatography (silica-gel, hexane-EtOAc (5:1)), the aziridine 16 (1.2 g, 85%) was obtained as an oil. IR (CCl₄) 2920, 1730, 1440, 1400, 1340, 1215, 1160 cm⁻¹; ¹H NMR (CDCl₃) δ 1.21-1.43 (m, 9H, CH₃CHN, 2x OCH₂CH₃), 2.45 (s, 3H, CH₃C₆H₄), 3.15 (dq, J = 5.9, 7.4 Hz, 1H, CH₃CHN), 3.70 (dd, J = 7.4, 8.4 Hz, 1H, NCHCH=C), 4.23 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 4.34 (q, J = 7.1 Hz, 2H, OCH₂CH₃), 6.61 (d, J = 8.4 Hz, 1H, CH=C), 7.34 (d, J = 8.1 Hz, 2H, 3, 5-C₆H₄), 7.81 (d, J = 8.2 Hz, 2H, 2, 6-C₆H₄); ¹³C NMR (CDCl₃) δ 13.0, 13.9, 14.0, 21.5, 41.4, 41.7, 61.6, 61.7, 127.7, 129.7, 132.6, 134.7, 140.6, 144.7, 162.7, 163.7.

3-Butyl-2-[1-(LS)-(toluene-4-sulfonylamino)-ethyl]-cyclopropane-1,1-dicarboxylic acid diethyl ester (18). Oil; Column chromatography, with hexane-EtOAc (7:1) as eluent; IR (CCl₄) 3300, 2920, 1720, 1550, 1370, 1300, 1250, 1210 cm⁻¹; ¹H NMR (CDCl₃) δ 0.85 (t, J = 6.4 Hz, 3H, CH₂CH₂CH₂), 1.08 (d, J = 6.4 Hz, 3H, CH₃CHN), 1.10-1.41 (m, 12H, (CH₂)₃CH₃, 2x OCH₂CH₂), 1.76-1.81 (m, 2H, H-2, H-3), 2.41 (s, 3H, CH₃CH₃), 3.13-3.18 (m, 1H, CH₂), 4.07-4.27 (m, 4H, 2x OCH₂CH₂), 4.83 (d, J = 6.8 Hz, 1H, NH₂), 7.27 (d, J = 8.4 Hz, 2H, 3, 5-C₆H₄), 7.72 (d, J = 8.4 Hz, 2H, 2, 6-C₆H₄); ¹³C NMR (CDCl₃) δ 13.9, 14.0, 14.2, 21.1, 21.5, 22.3, 27.4, 30.7, 31.5, 38.6, 40.1, 48.9, 61.5, 62.0, 127.0, 129.6, 138.7, 143.1, 168.0, 168.2.
6-Butyl-4-methyl-2-oxo-3-(toluene-4-sulfonyl)-3-aza-bicyclo[3.1.0]hexane-1-carboxylic acid ethyl ester (19). A stirred solution of 17 (0.10 g, 0.23 mmol) in EtOH (7 mL), maintained under argon, was treated with a few drops of 1.3 M ethanolic solution of NaOEt, set aside overnight at room temperature, and concentrated in vacuo. Flash column chromatography (hexane-EtOAc (7:1)) of the residue gave 19 (0.06 g, 66%) as an oil; IR (CCl4) 2960, 1740, 1720, 1370, 1330, 1255, 1170 cm⁻¹; ¹H NMR (CDCl₃) δ 0.79 (t, J = 7.3 Hz, 3H, CH₂CH₂CH₃), 1.01-1.30 (m, 9H, (CH₂)₃CH₃, OCH₂CH₃), 1.63 (d, J = 6.4 Hz, 3H, CH₂CH₂CH₃), 2.02-2.07 (m, 1H, CH₂), 2.14 (d, J = 8.4 Hz, 1H, H-5), 2.42 (s, 3H, C₆H₄CH₃), 4.16-4.23 (m, 3H, OCH₂CH₃, CH₃CHN), 7.31 (d, J = 8.4 Hz, 2H, 3, 5-C₆H₄), 7.95 (d, J = 8.4 Hz, 2H, 2, 6-C₆H₄); ¹³C NMR (CDCl₃) δ 13.8, 14.1, 21.6, 21.8, 21.8, 22.1, 23.0, 30.8, 33.3, 34.2, 52.3, 61.8, 128.7, 129.4, 135.6, 145.2, 165.9, 167.9.

Reactions with Hetero-Organocuprates, Standard procedure: An etherial or dimethyl sulfide (DMS) solution (5 mL) of a lithium alkoxide or lithium amide (obtained by treatment of the corresponding alcohol or amine (0.74 mmol) with MeLi (0.46 mL; 0.74 mmol) at 0 °C) was added to a stirred, cooled (-50 °C) suspension (or solution) of CuI (0.14 g, 0.74 mmol) in ether or DMS (5 mL). The mixture was allowed to warm to -30 °C and maintained at this temperature for 30 min, whereon it was cooled to -78 °C and treated with the appropriate Grignard reagent (1.0 M in ether, 1.4 mmol) followed immediately by addition of a solution of the aziridine 3a (0.30 g, 0.67 mmol) in ether (or DMS; 5 mL). After a further period of 15 min at -78 °C, the mixture was allowed to attain room temperature over 3h. With alkoxide hetero-cuprates, the reaction mixture was treated with saturated aqueous NH₄Cl solution (50 mL), whereas with amide hetero-cuprates, the reaction was quenched by addition of 5% aqueous H₂SO₄ (50 mL). The resultant mixtures were treated with ether (50 mL), filtered through “hyflo”, the inorganic material washed with ether, and the combined ether layers washed (3 x 100 mL) with a saturated aqueous NH₄Cl solution - 25% aqueous ammonia mixture (3:1), brine, dried (MgSO₄) and concentrated in vacuo. Flash column chromatography (hexane-EtOAc (7:1)) of the residue gave cyclopropane 5a.

REFERENCES AND NOTES

# References
18. Upon introduction of the tosyl group to 3-alkyl-aziridine esters using tosyl chloride, chloride opened the N-tosyl aziridine esters to a considerable extent after prolonged stirring (2 days). On the other hand, introduction of the mesitylsulfonyl group required stirring for 2 days. This process did not cause aziridine ring opening by chloride. These findings suggest that the mesitylenesulfonyl group activates the aziridine less than the tosyl group does. This might explain the absence of aziridine ring-opened products, such as 11, in the reaction of 3d.

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