Diastereoselective Mannich reactions of pseudo-C$_2$-symmetric glutarimide with activated imines

Tatsuya Ishikawa$^1$, Tomoko Kawasaki-Takasuka$^1$, Toshio Kubota$^2$ and Takashi Yamazaki$^{*1}$

Abstract
As an extension of the boron enolate-based aldol reactions, the oxazolidinone-installed bisimide 1a from 3-(trifluoromethyl)glutaric acid was employed for Mannich reactions with tosylated imines 2 as electrophiles to successfully obtain the corresponding adducts in a stereoselective manner.

Introduction
During these decades, we have been keenly interested in the 3-(trifluoromethyl)glutaric acid derivatives and developed a couple of routes to get successful access to such target molecules with a variety of substituents at the 2-position [1-3]. Previously, the oxazolidinone-installed bisimide 1a was employed for the crossed aldol reactions by the way of boron enolate which allowed the isolation of optically active lactones in good to excellent yields [4,5]. One of the most intriguing features of this protocol is the fact that the enantiomers at the lactone part were readily obtained only by the selection of the tertiary amines employed in the reaction. It is quite apparent that this success is, at least in part, based on its inherent pseudo-C$_2$ symmetric structure [6-8] which enables the formation of plural stereogenic centers by a single operation. These promising results prompted us to extend this aldol protocol to its relative, Mannich reactions [9-13] whose details are reported in this article.

Results and Discussion
On the basis of our previous study [4], the chiral glutarimide 1a was employed as the starting material and optimization of reaction conditions with benzaldehyde-based imines 2 was performed (Table 1). Lithium enolate by the action of LDA to 1a was found to be ineffective as long as the imines with benzyl (2aa) or Boc (2ab) as substituents R were employed (Table 1, entries 1 and 2).
However, the attachment of the stronger electron-withdrawing 4-toluenesulfonyl (Ts) moiety attained efficient activation of the imine 2ac to afford the desired Mannich product 3a in 85% yield as determined by $^{19}$F NMR and in the bracket isolated yields are given, NR: no reaction. $^{19}$F NMR and in the parentheses the sum of the other minor stereoisomers is given. As described above, facile isolation of 3a from unreacted substrate 1a was sometimes required longer reaction times, but worked without any significant problems (Table 2, entries 9–14). As a general trend, LiHMDS tended to afford lower chemical yields because the employment of the phenylalanine-based oxazolidinone as the chiral auxiliary under the same conditions gave similar results as the one obtained from valine (Table 1, entries 8 vs 7), but the steric effect due to the branched structure in the latter affected the reaction to some extent (Table 2, entries 15 and 16). As described above, facile isolation of 3 was sometimes hampered by contamination of the substrate 1a and/or 4-toluenesulfonylamine 5 which is noticed by the absence of isolated yields shown in brackets in Table 2.

The configuration of the major diastereomer of 3a (Table 2, entry 1) was unambiguously determined by X-ray crystallographic analysis (Figure 1) [16].

Based on this information a possible reaction mechanism was formulated as depicted in Scheme 1. It is well-known that

Table 1: Optimization of reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>R</th>
<th>Yield (%)</th>
<th>DS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>LDA</td>
<td>PhCH$_2$</td>
<td>91 (4a)</td>
<td>73:21:6</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>LDA</td>
<td>Boc (2ab)</td>
<td>NR</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>LDA</td>
<td>Ts (2ac)</td>
<td>85 (3a)</td>
<td>69:18:(13)</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>NaHMDS</td>
<td>Ts (2ac)</td>
<td>59 (3a)</td>
<td>38:43:19</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>LiHMDS</td>
<td>Ts (2ac)</td>
<td>80 (3a)</td>
<td>27:62:11</td>
</tr>
<tr>
<td>6$^c$</td>
<td>DCM</td>
<td>DPEA</td>
<td>Ts (2ac)</td>
<td>NR</td>
<td>–</td>
</tr>
<tr>
<td>7$^d$</td>
<td>THF</td>
<td>LDA</td>
<td>Ts (2ac)</td>
<td>96 [75] (3a)</td>
<td>73:17:10</td>
</tr>
<tr>
<td>8$^e$</td>
<td>THF</td>
<td>LDA</td>
<td>Ts (2ac)</td>
<td>91 (4a)</td>
<td>73:21:6</td>
</tr>
</tbody>
</table>

$^{a}$All yields were determined by $^{19}$F NMR and in the bracket isolated yields are given. NR: no reaction. $^{b}$Diastereoselectivities (DS) were determined by $^{19}$F NMR and in the parentheses the sum of the other minor stereoisomers is given. $^{c}$TiCl$_4$ (3.0 equiv) was used as a Lewis acid. $^{e}$The reaction was continued for 6 h. $^{f}$Substrate 1b with the phenylglycine-derived oxazolidinone part was employed instead of 1a.
Table 2: Scope and limitation of the present Mannich reactions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>R</th>
<th>Time (h)</th>
<th>Yield(^a) (%)</th>
<th>Product</th>
<th>DS(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>Ph (2ac)</td>
<td>3.0</td>
<td>96 [75]</td>
<td>3a</td>
<td>73:17:(10)</td>
</tr>
<tr>
<td>2</td>
<td>LiHMDS</td>
<td>Ph (2ac)</td>
<td>6.0</td>
<td>96[74]</td>
<td>3a</td>
<td>27:63:(10)</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>4-BrC(_6)H(_4)- (2bc)</td>
<td>6.0</td>
<td>93 [91]</td>
<td>3b</td>
<td>62:17:(21)</td>
</tr>
<tr>
<td>4</td>
<td>LiHMDS</td>
<td>4-BrC(_6)H(_4)- (2bc)</td>
<td>6.0</td>
<td>84 [62]</td>
<td>3b</td>
<td>26:61:(13)</td>
</tr>
<tr>
<td>5</td>
<td>LDA</td>
<td>4-O(_2)NC(_6)H(_4)- (2cc)</td>
<td>6.0</td>
<td>quant [92]</td>
<td>3c</td>
<td>65:13:(22)</td>
</tr>
<tr>
<td>6</td>
<td>LiHMDS</td>
<td>4-O(_2)NC(_6)H(_4)- (2cc)</td>
<td>6.0</td>
<td>64 [45]</td>
<td>3c</td>
<td>49:44:(7)</td>
</tr>
<tr>
<td>7</td>
<td>LDA</td>
<td>3-FC(_6)H(_4)- (2dc)</td>
<td>6.0</td>
<td>89 [78]</td>
<td>3d</td>
<td>81:6:(13)</td>
</tr>
<tr>
<td>8</td>
<td>LiHMDS</td>
<td>3-FC(_6)H(_4)- (2dc)</td>
<td>6.0</td>
<td>84 [72]</td>
<td>3d</td>
<td>33:51:(16)</td>
</tr>
<tr>
<td>9</td>
<td>LDA</td>
<td>2-furyl- (2ec)</td>
<td>8.0</td>
<td>95 [55]</td>
<td>3e</td>
<td>51:22:(27)</td>
</tr>
<tr>
<td>10</td>
<td>LiHMDS</td>
<td>2-furyl- (2ec)</td>
<td>6.0</td>
<td>48</td>
<td>3e</td>
<td>28:57:(15)</td>
</tr>
<tr>
<td>11</td>
<td>LDA</td>
<td>4-Me(_6)H(_4)- (2fc)</td>
<td>8.0</td>
<td>quant [66]</td>
<td>3f</td>
<td>51:16:(33)</td>
</tr>
<tr>
<td>12</td>
<td>LiHMDS</td>
<td>4-Me(_6)H(_4)- (2fc)</td>
<td>6.0</td>
<td>51</td>
<td>3f</td>
<td>28:64:(8)</td>
</tr>
<tr>
<td>13</td>
<td>LDA</td>
<td>4-MeOC(_6)H(_4)- (2gc)</td>
<td>6.0</td>
<td>86</td>
<td>3g</td>
<td>34:31:(35)</td>
</tr>
<tr>
<td>14</td>
<td>LiHMDS</td>
<td>4-MeOC(_6)H(_4)- (2gc)</td>
<td>6.0</td>
<td>26</td>
<td>3g</td>
<td>38:29:(33)</td>
</tr>
<tr>
<td>15</td>
<td>LDA</td>
<td>iPr (2ie)</td>
<td>6.0</td>
<td>93</td>
<td>3h</td>
<td>39:36:(25)</td>
</tr>
<tr>
<td>16</td>
<td>LDA</td>
<td>iPr (2ie)</td>
<td>6.0</td>
<td>23</td>
<td>3i</td>
<td>37:17:(46)</td>
</tr>
</tbody>
</table>

\(^a\)All yields were determined by \(^19\)F NMR and in the bracket the isolated yields are given. \(^b\)Diastereoselectivities (DS) were determined by \(^19\)F NMR for the crude mixture and in the parentheses the sum of the other minor stereoisomers is given.

oxazolidinone-derived imides in general construct bidentate chelation when they are converted to the corresponding metal enolates [17]. The subsequent reactions occur so as to avoid unfavorable steric repulsive interaction with the oxazolidinone substituent, the iPr group in our case (Int-a). The selection of the two enantiotopic enolates should be explained on the basis of the Cieplak effect [18,19] for the enolate conformation with the allylic hydrogen possessing the same plane for making the steric bias minimum (Int-b) [20,21]. The most important argument for this effect is the stabilization of the forming electron-deficient Σ^*\(≠\)σ orbital in the transition state by the electron donation from the neighboring orbital. In our case, possible electron donation is expected either by the σC-C in TS(pro-R,si) or σC-CF\(_3\) in TS(pro-R,re). Because the former orbital is more electron-rich, imines as electrophiles should approach from the si face of the pro-R enolate (E: an appropriate electrophile in Scheme 1). The same orbital interaction would be operative when the electrophile came closer from the re face of the
**Scheme 1:** Explanation of the construction of the main stereoisomers.

pro-S enolate which suffered from the existence of the sterically demanding iPr group. As a result, the major reaction pathway was considered to follow the transition state $\text{TS(pro-R,si)}$ where the $\text{si}$ face of imines seemed to match favorably with a construction of the least sterically demanding conformation, leading to formation of the obtained diastereisomer $3a$.

**Conclusion**

As shown above, the oxazolidinone-installed imide from 3-(trifluoromethyl)glutaric acid $1a$ was found to afford the corresponding adducts $3$ in good to excellent chemical yields in a stereoselective fashion when its enolate was subjected to a solution containing tosylated imines $2$ as electrophiles. Further work is going on in this laboratory to utilize the thus obtained adducts $3$ and the results will be reported in due course.

**Supporting Information**

**Supporting Information File 1**

Experimental procedures, characterization data, copies of $^1$H and $^{13}$C NMR spectra for the new compounds, and crystallographic analysis data are available. [http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-13-244-S1.pdf]

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15. Because of their close Rf values, after evaporation of the volatiles from
   the chromatographically separated fractions containing these two
   compounds 3 and 5, this diastereomer mixture was dissolved in an
   appropriate amount of CH2Cl2 where hexane was added slowly to
   precipitate the sulfonamide 5.

16. CCDC 1575731 contains the supplementary crystallographic data for
   the major diastereomer of 3a. All data can be acquired free of charge
   from The Cambridge Crystallographic Data Centre via
   http://www.ccdc.cam.ac.uk/data_request/cif.

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