Stereoelectronic Factors in Diastereoselective Alkenenitrile Alkylations

Matthew Kartzman

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STEREOELECTRONIC FACTORS IN DIASTEREOSELECTIVE ALKENENITRILE ALKYLATIONS

A Thesis
Submitted to the Bayer School of Natural and Environmental Sciences

Duquesne University

In partial fulfillment of the requirements for
the degree of Master of Science

By
Matthew Kartzman

August 2014
STEREOELECTRONIC FACTORS IN DIASTEREOSELECTIVE ALKENENITRILE ALKYLATIONS

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ABSTRACT

STEREOELECTRONIC FACTORS IN DIASTEREOSELECTIVE ALKENENITRILE ALKYLATIONS

By

Matthew Kartzman

August 2014

Thesis supervised by Jeffrey Evanseck

Alkylations of alkoxy-substituted alkenenitriles exert an unusual diastereoselectivity. A series of alkylations were computed with alkyl halides, alkyl benzoate derivatives, and alkyl carbonates. Diastereoselectivity depends on the nature of the electrophile, but the trend is difficult to correlate with specific structural features. Density functional theory (DFT) has been applied to compute transition structures using Gaussian 09 to address the reasons for the observed diastereoselectivities. Stereoselective ratios can be explained by comparing the transition structures energies, and it is found that the α-carbon of the metalated nitrile experiences torsional strain with the stereocenter β-carbon. Torsional strain is a result of a gauche orientation of two alkyl groups. The methoxy oxygen atom and the electrophile alkyl cation, as well as the alkyl cation clashing with the carbon
backbone of the nucleophile influence stereoselectivity. This thesis work allows for an improved understanding and synthetic methodology for the alkylations of acyclic metalated nitriles.
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Asymmetric induction is a key concept in asymmetric synthesis.\(^1\) It refers to the preference of one enantiomer or diastereomer being preferred over another due to chiral features in the substrate, reagent, catalyst, or environment.\(^2\) To better understand asymmetric induction, it can be divided into three types.\(^3\) The first is known as *internal* asymmetric induction, where the chiral information is already present in the starting material. The second is *relayed* asymmetric induction, in which a chiral auxiliary is introduced into the starting material in a separate step and removed later. The third is known as *external* asymmetric induction, where a chiral catalyst or ligand is used to control stereoselectivity.

Internal asymmetric induction has been utilized in Mukaiyama aldol addition. For example, Evans et al. used the Felkin-Anh model\(^4\) for 1,2-asymmetric induction and Evans’ own model\(^5\) for 1,3-asymmetric induction.\(^6\) Adding an alkyl substituent to the \(\alpha\)-position of the starting aldehyde and adding a heteroatomic substituent to the \(\beta\)-position (1, Scheme 1) can control the stereoselectivity of this aldol addition. When the aldehyde is *anti*-substituted, the Felkin product (2) dominates, and both models enforce this prediction. When the aldehyde is *syn*-substituted, selectivity is dependent on the size of the enolsilane alkyl substituent (R). The Felkin product (2) is preferred when the substituent is large, and the anti-Felkin product (3) is preferred when it is small. In this case, the Felkin-Anh model only applies when R is large, and the Evans model prevails otherwise.
**Scheme 1.** Lewis Acid Promoted Aldol Reactions of Enolsilanes with \( \alpha \)-Methyl-\( \beta \)-alkoxy Aldehydes

\[
\begin{align*}
\text{H} & \quad \text{OP} \\
\text{Me} & \quad \text{IrPr} \\
1 \\
P & \text{PMB or TBS}
\end{align*}
\]

Fleming’s group has previously studied alkylations of cyclic metalated nitriles.\(^7\) Stereoselective alkylations can be accomplished by using cyclic alkenenitriles. In one example (Scheme 2), 4-(\( \text{tert} \)-butyl)cyclohexane-1-carbonitrile (4) is alkylated with methyl iodide to give 2.6:1 equatorial stereoselectivity (6). Electrophilic attack from the more accessible side of the nucleophilic carbon avoids mild steric strain with axial protons. Furthermore, brominating 4 to create 7, then adding \( \text{i-PrMgBr} \) creates the magnesiated nitrile 8. Adding MeI to the reaction mixture results in exclusive equatorial methylation (9). This can be attributed to the preference of magnesiated nitriles to be \( C \)-metalated.

**Scheme 2.** Stereoselective Alkylation of \( C \)- and \( N \)-Metalated Nitriles
Alkylations of acyclic metalated nitriles are more challenging. This is partly due to the fact that unlike cyclic nitriles, all of the single bonds on the reactive center are able to rotate freely, changing the conformation of the molecule. However, this conformation can be partly constrained by having sterically demanding substituents on its flexible backbone. One specific strategy is to utilize the concept of internal 1,2-asymmetric induction. By including a trisubstituted alkene at C-4 and vicinal substituents at C-2 and C-3, the conformational mobility of lithiated alkenenitriles such as 10 can be restricted (Scheme 3). Torsional strain between R¹ and the methyl group on C-3 in 11' causes the 2-3 bond to rotate so that the methyl group is closer to the less sterically demanding nitrile group. Electrophilic attack from the more accessible side of 11'' creates 12 with essentially one diastereomer. One example of this is the alkylation of 10a with iPrI to create 12a with a single diastereomer.

**Scheme 3. Diastereoselective Alkylation of Acyclic Nitriles**

Another study by Fleming examines alkylation of benzyl-substituted alkenenitrile 13a (Table 1). This idea was proposed after the alkylation of the analogous oxonitrile resulted in low stereoselectivity. Unlike the oxonitrile which has a doubly deprotonated intermediate, the intermediate 14a is only singly
deprotonated. Alkylation of 14a with MeI proceeds through transition state 15aa via an S$_N$2 mechanism to result in product 16aa with 6.5:1 selectivity. Next, the analogous methyloxy-substituted alkenenitrile 13b was tested, and resulted in 16ba with 8.5:1 selectivity. The slight increase of stereoselectivity has been attributed to the steric differences in –OBn and –OMe. Alkylations of 13a were then screened with a wide range of electrophiles. Two of those are $n$-propyl iodide and isopropyl iodide, which gave 1:0 and 2.3:1 stereoselectivity, respectively.

Table 1. Alkylations of 13

<table>
<thead>
<tr>
<th>Nucleophile</th>
<th>Electrophile</th>
<th>Product</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>13a</td>
<td>MeI</td>
<td>16aa</td>
<td>6.5:1</td>
</tr>
<tr>
<td>13b</td>
<td>MeI</td>
<td>16ba</td>
<td>8.5:1</td>
</tr>
<tr>
<td>13a</td>
<td>–I</td>
<td>16ab</td>
<td>1:0</td>
</tr>
<tr>
<td>13a</td>
<td>–I</td>
<td>16ac</td>
<td>2.3:1</td>
</tr>
</tbody>
</table>
Some of the reasons for the stereoselectivities of these reactions are not immediately clear. To further investigate these reactions, computational chemistry can be put to use. It can be an effective way to investigate any steric and electronic factors that may be controlling stereoselectivity, and also to predict whether a reaction would be stereoselective.

**COMPUTATIONAL METHODS**

Calculations were done in the Gaussian 09 application.\textsuperscript{10} The M06-2X hybrid functional developed by Truhlar\textsuperscript{11} and the 6-311++G(2d,p) basis set\textsuperscript{12} were used for the geometry optimizations and subsequent frequency calculations. The M06 suite of density functionals has been shown to give more accurate approximations of energy values and structures than older density functionals.\textsuperscript{13} The functionals in this suite are meta-GGA functionals, which include the second derivative of the electron density. The polarizable continuum model (PCM), which has been excessively tested,\textsuperscript{14} was used to model solvent effects. Tetrahydrofuran (THF) with a dielectric constant of 7.58 was used as the implicit solvent in all calculations.

**RESULTS AND DISCUSSION**

The transition structures of the reactions shown in Table 1 have been computed. In order to save time and computational resources, some modifications were made to the original reactions. Alkyl chlorides were substituted for the alkyl iodides used in the experiments since split-valence basis sets for chlorine are available and relatively well tested as compared to those for iodine.\textsuperscript{15} Also, 13b was
used as the nucleophile for all the calculations since the alkyl group extension is not expected to contribute to the observed diastereoselectivity and it has six less heavy atoms than 13a. It was found that for each transition structure, many different structures resulted due to the conformational freedom. Once all the structures were optimized, the energy values were noted and compared. The difference in activation enthalpy ($\Delta\Delta H$) is calculated as follows: $\Delta\Delta H = H - H_{\text{min}}$ where $H$ is the calculated enthalpy value for a given structure and $H_{\text{min}}$ is the enthalpy of the lowest energy structure found for a transition state. The hypothesis is that torsional strain that results from a gauche orientation of the two alkyl groups is the defining factor of selectivity. The goal was to find the lowest energy structures of 15bx' and 15bx'' (Table 1 in analogy to 16) so that it can be observed whether the energy values follow a similar trend to the diastereoselectivities from experiment.

A naming system has been applied to the several structures that resulted from the calculations. The letters S and A stand for syn and anti, respectively. Also, the prime symbol (') is used if there is a third orientation of a certain variable. The first letter refers to the relative positions of the two alkyl groups. The second letter references the position of the ethyl group relative to the methoxy group. The third letter represents the rotation of the ethyl group. Finally, the fourth letter represents the attack direction of the electrophile relative to the position of the 1-methoxyvinyl group. Structure AASA of 15ba'' is shown in Figure 1 as an example. The first letter is A representing the alkyl groups oriented in an anti conformation. The ethyl group is positioned on the opposite side of the methoxy group hence the second letter A. The ethyl group is rotated towards the 1-methoxyvinyl group, which is noted by the
third letter S. The fourth letter A signifies the electrophile approaching from the opposite side from the 1-methoxyvinyl group.

**Figure 1.** Structure 15ba” AASA

The geometry optimizations of 15ba produced 24 total transition structures (Table 2). Twelve structures were of the diastereomer 15ba’, while the other 12 were of 15ba”. It should be noted that the number 2 represents structures where the Li cation is bifurcated between the methoxy O and the nitrile N, which were found to be disfavored. The two lowest energy structures for 15ba’ and 15ba” and the second lowest energy structure for 15ba’ are shown in Figure 2. Both 15ba’ AAAS and 15ba” AAAA avoid torsional strain of the two alkyl groups which are in an *anti* position. The higher energy of 15ba’ AAAS can be attributed to steric strain between the methyl cation and the methoxy group. 15ba’ SAAA has torsional strain
between the two alkyl groups (3C-1C-2C-6C dihedral angle of 52.8°), making it higher in energy than the other two structures.

Table 2. Structures and Energies of 15ba

<table>
<thead>
<tr>
<th>Diastereomer</th>
<th>Structure</th>
<th>ΔΔH (kcal/mol)</th>
<th>Diastereomer</th>
<th>Structure</th>
<th>ΔΔH (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15ba’</td>
<td>SASA</td>
<td>1.77</td>
<td>15ba’</td>
<td>SAS’A</td>
<td>3.73</td>
</tr>
<tr>
<td>15ba”</td>
<td>AASA</td>
<td>0.07</td>
<td>15ba”</td>
<td>AAS’A</td>
<td>0.43</td>
</tr>
<tr>
<td>15ba’</td>
<td>SSSA</td>
<td>2.30</td>
<td>15ba’</td>
<td>ASAS</td>
<td>2.16</td>
</tr>
<tr>
<td>15ba”</td>
<td>ASSA</td>
<td>1.81</td>
<td>15ba”</td>
<td>SSAS</td>
<td>2.11</td>
</tr>
<tr>
<td>15ba’</td>
<td>SASA2</td>
<td>4.87</td>
<td>15ba’</td>
<td>S’AAA’</td>
<td>2.69</td>
</tr>
<tr>
<td>15ba”</td>
<td>AASA2</td>
<td>4.27</td>
<td>15ba”</td>
<td>A’AAS’</td>
<td>1.88</td>
</tr>
<tr>
<td>15ba’</td>
<td>SSAA</td>
<td>1.63</td>
<td>15ba’</td>
<td>ASSS</td>
<td>1.10</td>
</tr>
<tr>
<td>15ba”</td>
<td>ASAA</td>
<td>1.90</td>
<td>15ba”</td>
<td>SSSS</td>
<td>2.25</td>
</tr>
<tr>
<td>15ba’</td>
<td>SAAA</td>
<td>1.38</td>
<td>15ba’</td>
<td>AASS</td>
<td>1.04</td>
</tr>
<tr>
<td>15ba”</td>
<td>AAAA</td>
<td>0.00</td>
<td>15ba”</td>
<td>SASS</td>
<td>2.07</td>
</tr>
<tr>
<td>15ba’</td>
<td>SA’AA</td>
<td>1.67</td>
<td>15ba’</td>
<td>AAAS</td>
<td>0.94</td>
</tr>
<tr>
<td>15ba”</td>
<td>AA’AA</td>
<td>0.51</td>
<td>15ba”</td>
<td>SAAS</td>
<td>1.63</td>
</tr>
</tbody>
</table>

Figure 2. Lowest Energy Structures of 15ba
The next transition state in which geometry optimizations were done was 15bb, in which \( n \)-propyl chloride was used as the electrophile. For both diastereomers, some of the lowest energy structures are very close in energy. Four of the 16 structures noted in Table 3 were chosen to analyze the selectivity of the reaction (Figure 3). The structures 15bb” AASA and 15bb” AAAA have a very insignificant difference in \( \Delta \Delta H \), which is even smaller than the 0.07 kcal/mol difference for the analogous structures of 15ba. The only difference is the orientation of the ethyl group relative to the 1-methoxyvinyl group. The lowest energy structure found for 15bb’ was SA’AA. The energy is affected by the torsional strain resulting from the \textit{gauche} orientation of the two alkyl groups (dihedral angle of 41.4°). 15bb’ AASS is similar in energy, being only 0.03 kcal/mol higher than 15bb’ SA’AA. The defining factor here is the repulsion of the methoxy O and the n-
propyl cation, which is larger than that with the smaller methyl cation in structures of 15ba.

<table>
<thead>
<tr>
<th>Diastereomer</th>
<th>Structure</th>
<th>ΔΔH (kcal/mol)</th>
<th>Diastereomer</th>
<th>Structure</th>
<th>ΔΔH (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15bb'</td>
<td>SASA</td>
<td>3.34</td>
<td>15bb''</td>
<td>AAA</td>
<td>1.76</td>
</tr>
<tr>
<td>15bb''</td>
<td>AASA</td>
<td>0.00</td>
<td>15bb'</td>
<td>ASAS</td>
<td>2.79</td>
</tr>
<tr>
<td>15bb'</td>
<td>SSSA</td>
<td>2.88</td>
<td>15bb''</td>
<td>SSAS</td>
<td>2.90</td>
</tr>
<tr>
<td>15bb''</td>
<td>ASSA</td>
<td>1.91</td>
<td>15bb'</td>
<td>ASSS</td>
<td>3.03</td>
</tr>
<tr>
<td>15bb'</td>
<td>SSAA</td>
<td>3.02</td>
<td>15bb''</td>
<td>SSSS</td>
<td>2.88</td>
</tr>
<tr>
<td>15bb''</td>
<td>ASAA</td>
<td>0.69</td>
<td>15bb'</td>
<td>AASS</td>
<td>1.68</td>
</tr>
<tr>
<td>15bb'</td>
<td>SAAA</td>
<td>1.92</td>
<td>15bb''</td>
<td>SASS</td>
<td>3.20</td>
</tr>
<tr>
<td>15bb''</td>
<td>AAAA</td>
<td>0.00</td>
<td>15bb'</td>
<td>AAAS</td>
<td>1.76</td>
</tr>
<tr>
<td>15bb'</td>
<td>SAAA</td>
<td>1.65</td>
<td>15bb''</td>
<td>SAAS</td>
<td>5.99</td>
</tr>
</tbody>
</table>

Figure 3. Lowest Energy Structures of 15bb
Lastly, the structures of the 15bc transition state, which include the isopropyl chloride electrophile, were optimized. Nine different structures were found for this transition state (Table 4). It should be noted that the letters a and b represent different orientations of the isopropyl cation relative to the nucleophile. The two lowest energy structures of 15bc' and 15bc'' as well as the second lowest energy structure of 15bc' are shown in Figure 4. Once more, the difference in $\Delta \Delta H$ between 12b' SAAA and 12b'' AAAA is attributed to the torsional strain resulting from the gauche conformation of the alkyl groups (dihedral angle of 53.4°). Also, 15bc' AAAS has the electrophile approaching from the same side as the 1-methoxyvinyl group, and the energy difference is attributed to the repulsion between the isopropyl cation and the oxygen atom, though the difference is lower than the analogous ones in 15ba and 15bb.
Table 4. Structures and Energies of 15bc

<table>
<thead>
<tr>
<th>Diastereomer</th>
<th>Structure</th>
<th>ΔΔH (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15bc'</td>
<td>SASA</td>
<td>1.34</td>
</tr>
<tr>
<td>15bc''</td>
<td>AASAb</td>
<td>0.56</td>
</tr>
<tr>
<td>15bc''</td>
<td>AASAb</td>
<td>0.69</td>
</tr>
<tr>
<td>15bc'</td>
<td>SSSA</td>
<td>1.68</td>
</tr>
<tr>
<td>15bc''</td>
<td>ASSAa</td>
<td>2.03</td>
</tr>
<tr>
<td>15bc''</td>
<td>ASSAb</td>
<td>2.51</td>
</tr>
<tr>
<td>15bc'</td>
<td>SAAA</td>
<td>0.46</td>
</tr>
<tr>
<td>15bc''</td>
<td>AAAA</td>
<td>0.00</td>
</tr>
<tr>
<td>15bc'</td>
<td>AAAS</td>
<td>0.62</td>
</tr>
</tbody>
</table>

Figure 4. Lowest Energy Structures of 15bc
A number of observations can be made from these results. It is shown that torsional strain from the gauche orientation of the alkyl groups is an important factor in determining stereoselectivity. Also, in some structures of the minor transition state, if the electrophile were to approach from the same side as the 1-methoxyvinyl group, steric repulsion between the alkyl cation and the methoxy oxygen atom would occur. It is also shown that comparing the lowest energy transition structure is an effective way to analyze the reasons for the diastereoselectivity of reactions.

The $\Delta\Delta H$ values from the lowest energy transition states of each diastereomer in all three systems are compared with the experimental diastereomeric ratios in Table 5. It is observed that the value for the PrX system is higher than that of the MeX system, and that the value for the iPrX system is lower than the other systems. Approximate diastereometric ratios have been calculated
from the ΔΔH values. These ratios have a strong correlation with the experimental diastereomeric ratios (Table 5), showing that computational chemistry is effective for predicting trends in diastereoselectivity.

Table 5. Comparison of Theoretical and Experimental Results

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>Product</th>
<th>Experimental ratio</th>
<th>Computed ΔΔH (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeX</td>
<td>R(^1) = Bn</td>
<td>6.5:1 (R(^1) = Bn)</td>
<td>0.94 (4.9:1)</td>
</tr>
<tr>
<td></td>
<td>R(^1) = Me</td>
<td>8.5:1 (R(^1) = Me)</td>
<td></td>
</tr>
<tr>
<td>Pr(^+)</td>
<td>R(^1) = Bn</td>
<td>1:0 (R(^1) = Bn)</td>
<td>1.65 (16.2:1)</td>
</tr>
<tr>
<td>iPr(^+)</td>
<td>R(^1) = Bn</td>
<td>2.3:1 (R(^1) = Bn)</td>
<td>0.46 (2.2:1)</td>
</tr>
</tbody>
</table>

The reasons for the diastereoselectivity of these reactions are rather unclear. However, it is possible to compare the structures of the different transition states to observe whether there are any steric factors contributing to these differences. This can be accomplished by comparing the properties of the three electrophiles. The Me\(^+\) cation has a low steric demand and relatively high symmetry (C\(_{3v}\)). Due to this, it can be assumed that the stereoselectivity of the MeX system is primarily dependent on the nucleophile. Conversely, the Pr\(^+\) and iPr\(^+\) cations have a higher steric demand and lower symmetry. It is possible that these electrophiles are partially controlling the stereoselectivity of their respective systems.
It is important to note the shapes of the structures of 15bb (Figure 3). In the structures 15bb’ AASA and 15bb’’ AAAAA, the atoms 1C, 2C, 3C, and 6C are nearly coplanar with 3C-1C-2C-6C dihedral angle values of 175.6° and 173.8°, respectively. This gives the Pr+ cation a relatively easy approach to the nucleophile. These carbon atoms are in a gauche orientation in 15b’ SA’AA, resulting in them being non-coplanar with a dihedral angle of 41.4°, which makes it more difficult for the Pr+ cation to approach. It should also be noted that in the structure 15b’ AASS, the repulsion between the lone pairs on the methoxy oxygen atom and the electrophile is larger than that in the MeCl system due to the larger size of the Pr+ cation.

Looking at the 15bc structures in an alternate view (Figure 5) shows the factors that contribute to the low stereoselectivity of the iPrX system. These structures are shown in a perspective that has the axis of SN2 displacement perpendicular to the plane of the page. This way, it is easier to view possible steric interactions between the electrophile and the carbon backbone of the nucleophile. In the structure 15bc’’ AAAAA, the anti conformation of the alkyl groups increases the difficulty for the bulky iPr+ cation to approach it. However, in the 15bc’ SAAA structure, the gauche conformation of the alkyl groups allows the iPr+ cation to approach more easily since its steric bulk does not clash with that of the nucleophile. As for 15bc’ AAAS, the energy is relatively low because the nearest two hydrogen atoms to the methoxy oxygen atom are bound to two different carbon atoms. This can be compared to similar structures in the other two systems that are higher in energy. The nearest two hydrogen atoms to the methoxy oxygen in 15ba’ AAAS are bound to the same carbon atom. 15bb’ AASS has three hydrogen atoms
near the methoxy oxygen atom: one bound to the electrophilic carbon and two bound to the adjacent carbon.

**Figure 5. Lowest Energy Structures of 15bc in an Alternate View**

15bc’ SAAA  
15bc’’ AAAAA

**CONCLUSION**

Using density functional theory (DFT), geometry optimizations were run on structures of transition states 15bx in order to determine why the reactions of 13 to 16 are stereoselective. Transition structures 15bx’’ were found to be favored over 15bx’ due to steric interactions including torsional strain resulting from a gauche orientation of the alkyl groups and repulsion of the lone pairs of the methoxy oxygen atom and the electrophile alkyl cation. Also it was found that larger electrophiles such as PrX and iPrX have the ability to control stereoselectivity, since steric repulsion between the alkyl cation and nucleophile carbon backbone is
possible. These steric interactions influence diastereoselectivity by raising the
energy values of these structures, making the higher energy structures unfavored
and the lower energy structures more favored. This research allows for an improved
synthetic methodology for the alkylations of acyclic nitriles.
REFERENCES


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