Asymmetric Alkylation Reactions of Chiral Imide Enotes. A Practical Approach to the Enantioselective Synthesis of α-Substituted Carboxylic Acid Derivatives

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The development of chiral enolate synths and their practical utility in bond construction have been the subject of intensive investigation, and several enolate systems have been reported to exhibit high levels of diastereoselection in alkylation reactions. The purpose of this communication is to report our investigation of the general trends are evident from the data in the table. First, the lithium and sodium enolates derived from N-acyl oxazolidones 1 and 2 in complex diastereoselective alkylation processes (Scheme I). In a recent communication we disclosed the general procedures for the synthesis of imides 1 and 2, which are readily derived from 1-(1S,2R)-norephedrine and S-valinol, respectively.

The optical purities of the oxazolidone chiral auxiliaries employed in this study were determined to be >99%. During the course of this study we have developed a number of useful transformations that nondestructively remove the chiral auxiliaries from the desired chiral synthon. For example, the alkylation imides may be transformed into benzyl esters with <0.2% racemization (eq 2). The reaction of 6a (4.3% = 99.9:0.1)%

![Diastereofacial bias in the alkylation process. For the alkylation reactions summarized in Table I, lithium enolates were employed except for entries K and M–P. General reaction conditions involved treatment of a 0.2–0.5 M solution of the lithium enolate in THF with 3 equiv of alkylation at 0 °C (2–4 h). In several instances we have scaled these alkylation up to the 0.3 M level without loss in yield. Diastereomer analysis (3.4) was carried out by capillary gas chromatography. A number of general trends are evident from the data in the table. First, diastereomeric alkylation can be anticipated from the enolates derived from 1 and 2, with the latter system exhibiting somewhat greater selectivity. For example, in the reactions of the lithium enolates derived from 1 and 2 with benzyl bromide (entries A, B), the kinetic diastereoselection (3.4) was found to be 49:1 for 1 (R = Me) and 1:120 for 2 (R = Me), respectively. These data provide an important calibration for the stereoselectivities encountered in both the enolation and alkylation processes. Second, we have found that, as anticipated, electrophile structure plays a significant role in dictating reaction stereoselectivity. Qualitatively, "small" alkyl halides are less stereoselective than their more sterically demanding counterparts (cf. PhCH2Br vs. MeI). In general, enolate methylations (entries M–P) with methyl iodide have been the least stereoselective processes encountered to date. In surveying conditions for optimizing this particular process, we have found that alkylation of the sodium enolates (−78 °C) is superior to the analogous reactions of the corresponding lithium enolates (0 °C). One unanticipated benefit encountered in the development of these imide enolate systems has been the ease with which the diastereomeric alkylation products 3 and 4 may be resolved by column chromatography. Overall, the major limitation encountered with the lithium and sodium enolates derived from 1 and 2 is highlighted in entries K and L in the table. One must employ alkylation agents that will react at a convenient rate at temperatures ≤0 °C. The counterpoint to this limitation is the superb diastereofacial selection noted for these systems in both alkylations and aldol condensations and the ease with which these chiral oxazolidinones may be synthesized and recycled. In all of the alkylation reactions carried out during the course of this study, the sense of asymmetric induction is readily interpreted by assuming a metal-chelated (Z)-enolate (see 5) where diastereofacial selectivity is dictated by the C4-substituent on the oxazolidine ring. During the course of this study we have developed a number of useful transformations that nondestructively remove the chiral auxiliaries from the desired chiral synthon. For example, the alkylation imides may be transformed into benzyl esters with <0.2% racemization (eq 2). The reaction of 6a (4.3% = 99.9:0.1)%

![Thermal stability at >0 °C the lithium enolates will decompose via a ketene pathway. The corresponding sodium enolates exhibit reasonable stability at <−20 °C. Gas chromatographic analyses employed a Hewlett-Packard instrument (Model 5880A) and 30 m × 0.32 mm id, cross-linked columns of the latter system is significant role in dictating reaction stereoselectivity. Qualitatively, "small" alkyl halides are less stereoselective than their more sterically demanding counterparts (cf. PhCH2Br vs. MeI). In general, enolate methylations (entries M–P) with methyl iodide have been the least stereoselective processes encountered to date. In surveying conditions for optimizing this particular process, we have found that alkylation of the sodium enolates (−78 °C) is superior to the analogous reactions of the corresponding lithium enolates (0 °C). One unanticipated benefit encountered in the development of these imide enolate systems has been the ease with which the diastereomeric alkylation products 3 and 4 may be resolved by column chromatography. Overall, the major limitation encountered with the lithium and sodium enolates derived from 1 and 2 is highlighted in entries K and L in the table. One must employ alkylation agents that will react at a convenient rate at temperatures ≤0 °C. The counterpoint to this limitation is the superb diastereofacial selection noted for these systems in both alkylations and aldol condensations and the ease with which these chiral oxazolidinones may be synthesized and recycled. In all of the alkylation reactions carried out during the course of this study, the sense of asymmetric induction is readily interpreted by assuming a metal-chelated (Z)-enolate (see 5) where diastereofacial selectivity is dictated by the C4-substituent on the oxazolidine ring. During the course of this study we have developed a number of useful transformations that nondestructively remove the chiral auxiliaries from the desired chiral synthon. For example, the alkylation imides may be transformed into benzyl esters with <0.2% racemization (eq 2). The reaction of 6a (4.3% = 99.9:0.1)%

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Stereoselective Alkylation of the Enolates Derived from Imides

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imide</th>
<th>Electrophilic (EI')</th>
<th>Kinetic ratio (3:4)</th>
<th>Purified ratio (3:4)</th>
<th>Isolated yield, %</th>
<th>[α]_D (c, CHCl₃)</th>
<th>mp (bp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1 (R = Me)</td>
<td>PhCH₂Br</td>
<td>98:2</td>
<td>&gt;99:1</td>
<td>78</td>
<td>+78.5 (1.68)</td>
<td>(150)°</td>
</tr>
<tr>
<td>B</td>
<td>2 (R = Me)</td>
<td>PhCH₂Br</td>
<td>&lt;1:99</td>
<td>&lt;1:99</td>
<td>92</td>
<td>+9.42 (2.06)</td>
<td>liquid</td>
</tr>
<tr>
<td>C</td>
<td>1 (R = Me)</td>
<td>CH₂=CM(Me)CH₂I</td>
<td>97:3</td>
<td>&gt;99:1</td>
<td>73</td>
<td>+33.7 (5.9)</td>
<td>42-44</td>
</tr>
<tr>
<td>D</td>
<td>2 (R = Me)</td>
<td>CH₂=CM(Me)CH₂Br</td>
<td>2:98</td>
<td>&lt;1:99</td>
<td>62</td>
<td>+71.4 (1.79)</td>
<td>liquid</td>
</tr>
<tr>
<td>E</td>
<td>1 (R = Me)</td>
<td>CH₃=CHCH₂Br</td>
<td>98:2</td>
<td>&gt;99:1</td>
<td>75</td>
<td>+47.0 (2.36)</td>
<td>69-70</td>
</tr>
<tr>
<td>F</td>
<td>2 (R = Me)</td>
<td>CH₃=CHCH₂Br</td>
<td>2:98</td>
<td>&lt;1:99</td>
<td>71</td>
<td>+62.9 (3.48)</td>
<td>liquid</td>
</tr>
<tr>
<td>G</td>
<td>1 (R = Me)</td>
<td>PhCH₂OCH₂CH₂Br</td>
<td>98:2</td>
<td>&gt;99:1</td>
<td>72</td>
<td>+37.0 (2.07)</td>
<td>(180)°</td>
</tr>
<tr>
<td>H</td>
<td>2 (R = Me)</td>
<td>PhCH₂OCH₂CH₂Br</td>
<td>2:98</td>
<td>1:99</td>
<td>77</td>
<td>+35.4 (2.88)</td>
<td>(180)°</td>
</tr>
<tr>
<td>I</td>
<td>1 (R = Me)</td>
<td>EtO₂CH₂Br</td>
<td>93:7</td>
<td>99:1</td>
<td>51</td>
<td>+35.7 (1.78)</td>
<td>(160)°</td>
</tr>
<tr>
<td>J</td>
<td>2 (R = Me)</td>
<td>EtO₂CH₂I</td>
<td>5:95</td>
<td>&lt;1:99</td>
<td>51</td>
<td>+48.7 (1.64)</td>
<td>(150)°</td>
</tr>
<tr>
<td>K</td>
<td>1 (R = Me)</td>
<td>EtI</td>
<td>88:12</td>
<td>&gt;99:1</td>
<td>53</td>
<td>+54.7 (1.38)</td>
<td>71-72</td>
</tr>
<tr>
<td>L</td>
<td>2 (R = Me)</td>
<td>EtI</td>
<td>6:94</td>
<td>&lt;1:99</td>
<td>36</td>
<td>+61.6 (0.85)</td>
<td>liquid</td>
</tr>
<tr>
<td>M</td>
<td>1 (R = Et)</td>
<td>MeI</td>
<td>87:13</td>
<td>&gt;99:1</td>
<td>82</td>
<td>+6.1 (1.72)</td>
<td>65-66</td>
</tr>
<tr>
<td>N</td>
<td>2 (R = Et)</td>
<td>MeI</td>
<td>11:89</td>
<td>1:99</td>
<td>79</td>
<td>+112.6 (4.1)</td>
<td>(180)°</td>
</tr>
<tr>
<td>O</td>
<td>1 (R = n-C₅H₁₁)</td>
<td>MeI</td>
<td>89:11</td>
<td>&gt;99:1</td>
<td>70</td>
<td>-1.41 (1.56)</td>
<td>42-43</td>
</tr>
<tr>
<td>P</td>
<td>2 (R = n-C₅H₁₁)</td>
<td>MeI</td>
<td>9:91</td>
<td>&gt;99:1</td>
<td>77</td>
<td>+33.3 (2.03)</td>
<td>(160)°</td>
</tr>
</tbody>
</table>

a Ratios determined by capillary GLC (ref 8); values obtained from the lithium enolates (THF, 0 °C); values in parentheses are for alkylations carried out on the sodium enolates (THF, -78 °C). b See ref 9. c In all cases, the yields are reported on chromatographed material whose diastereomer composition is noted in preceding column. d All rotations were determined in methylene chloride (c = g/100 mL). e Reaction carried out at -40 °C with 3 equiv of alkyl bromide. f Preparative experiment carried out on the sodium enolate (-78 °C) with 5 equiv of methyl iodide. g In these instances analytically pure samples were prepared by high-vacuum solvent removal. h 5 x 10⁻⁵ mm. i 8 x 10⁻⁴ mm.

**Scheme 1**

![Scheme 1](image)

**6** Conditions: (a) MNR₂; (b) EI'.

8c ([α]D = -10.0° (c 4.2, CH₂Cl₂) [lit. -9.8° (neat)](15) in ≥85% yield. It is noteworthy that the chiral synthon (S)-8 and its enantiomer (S)-8 can be prepared from 2 (R = Me) and 1 (R = Me), respectively, in two steps in overall yields of 55-60%.

Additional chemical operations that both establish the sense of asymmetric induction in the alkylation process and provide information as to the tolerance of these imides to oxidants are illustrated below in eq 4 and 5. Hydroboration of 9 (1.1 equiv of (Sia)₂BH, THF, 0 °C, 2 h) followed by oxidation and lactonization afforded lactone (S)-10 ([α]D = +67.3° (6.59, MeOH)) in good agreement with calculated rotations ([α]D = -58.1°, -64.4°) for the (R)-enantiomer. h Alternatively, 11 was ozonized (-78 °C, MeOH) and the resultant aldehyde reduced with sodium borohydride to the carbinol, which spontaneously lactonized to (R)-12 upon distillation ([α]D = +21.2° (8.6, EtOH)). This value is again in good agreement with the highest literature value [+23.1° (9.7, EtOH)] reported for this lactone.

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**Registry No.**

1 (R = Me), 7787-20-4; 1 (R = Et), 80697-91-2; 1 (R = n-C₅H₁₁), 80697-92-3; 2 (R = Me), 77877-19-1; 2 (R = Et), 80697-93-4; 2 (R = n-C₅H₁₁), 80719-69-3; 3 (R = Me; E = CH₂=Ph), 8229-18-26; 4 (R = Me; E = CH₂=Ph), 8229-18-26.


We have found that tungsten alkylidene complexes are especially stable when a strong σ-donor such as an oxo2 or imido1 ligand is present and that a neopentylidene ligand in two such species is less distorted than any we have encountered in tantalum or niobium chemistry.3 We also know that oxo and imido alkylidene complexes are olefin metathesis catalysts.34,6 An important question is what the structure and reactivity of tungsten alkylidene complexes will be when no strong σ-donor ligand is present. We report three examples of such species here. These results along with recent results concerning the structure of analogous methylene complexes and the formation of W(VI) neopentylidene complexes4 reinforce the notion that the tungsten alkylidenes are likely to be highly distorted in the absence of a strong σ-donor ligand and, when the electron count is less than 18, may form an alkylidene ligand by loss of an α proton.

Preparation and Structure of Tungsten Neopentylidene Hydride, Neopentylidene Carbonyl, and Neopentylidene Ethylene Complexes

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We have found that tungsten alkylidene complexes are especially stable when a strong σ-donor such as an oxo2 or imido1 ligand is present and that a neopentylidene ligand in two such species is less distorted than any we have encountered in tantalum or niobium chemistry.3 We also know that oxo and imido alkylidene complexes are olefin metathesis catalysts.34,6 An important question is what the structure and reactivity of tungsten alkylidene complexes will be when no strong σ-donor ligand is present. We report three examples of such species here. These results along with recent results concerning the structure of analogous methylene complexes and the formation of W(VI) neopentylidene complexes4 reinforce the notion that the tungsten alkylidenes are likely to be highly distorted in the absence of a strong σ-donor ligand and, when the electron count is less than 18, may form an alkylidene ligand by loss of an α proton.

Figure 2. W(CHCMe3)COCl2(PMe3)2 molecule, showing the orientation of the α-hydrogen atom (H2) relative to the P1–Cl2–C2 octahedral face.

Yellow W(CCMes)2ClL2 (L = PMe3) reacts with molecular hydrogen (30 psi, 12 h, CH2Cl2) to give pale yellow W(CCMes)(H)ClL2 (1, eq 1). The pentagonal bipyramidal structure is suggested by the fact that only a single type of phosphorus (78 Hz), and by comparison with the structure of Ta(CCMes)2(dmpe)2ClAlMe3 (dmpe = bis(dimethylphosphino)ethane).5 The neopentylidene ligand is highly distorted, as judged by a low value for NCH, = 1.35 ppm, and the relatively high-field chemical shift of Hα = 1.35 ppm.

Although the spectra of 1 do not change down to -60 °C, the neopentylidene ligand in 1 is likely to be rotating rapidly on the NMR time scale (i.e., Hα is not localized) as found in other complexes such as Ta(CHCMe3)(PMe3)ClL2, which contain grossly distorted neopentylidene ligands. W(CCMes)2(H)ClL2 is the first example of an alkylidene hydride complex of tungsten(VI),12

(9) Prepared by treating W(CCMes)2Cl(PMe3)4 with C2Cl4 in CH2Cl2. [Et3PCI]Cl was filtered off and the residue that remained after removing all volatiles was recrystallized from ether/pentane; yield 85%. δ Cα (CDCl3) = 357 (1/2Jα = 26 Hz).

(10) Anal. Calcd for WC11H26P2: C, 25.73; H, 5.69. Found: C, 25.63; H, 5.69. Found: C, 26.13; H, 5.95. δ Cα (CDCl3) = 236 (1/2Jα = 84 Hz, 1/2Jβ = 82 Hz), δ Hα = 1.35 (2 JHH = 1 Hz), 1/2JHH = 2 Hz), δ Hβ = 9.88 (1/2JHH = 1 Hz, 1/2JZZ = 16 Hz). αW = 0.90 (1/2Jα = 82 Hz, 1/2Jβ = 82 Hz, 1/2JZZ = 142 Hz). NCH = 2395 cm⁻¹, NCH = 1999 cm⁻¹.


(12) Related tantalum complexes such as Ta(CHCMe3)(H)Cl2(PMe3)4 have been reported recently.11

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1 Massachusetts Institute of Technology.
2 State University of New York.
3 Multiple Metal–Carbon Bonds. 25. For part 24 see ref 5a.
5 Pedersen, S., unpublished results.