Disulfonimide-Catalyzed Asymmetric Vinylogous and Bisvinylogous Mukaiyama Aldol Reactions

Convergent Total Synthesis of (+)-TMC-151C by a Vinylogous Mukaiyama Reaction and Ring-Closing Metathesis

Short Literature Presentation
1/11/2011
Erika A. Crane
Prof. Dr. Benjamin List

1968: born in Frankfurt, Germany
1993: undergraduate degree from Free University Berlin
1997: PhD at University Frankfurt with J. Mulzer
1997-98: Postdoc at Scripps with R. A. Lerner
1999-03: Assistant Professor at Scripps
2003-05: Group leader at Max-Planck-Institut Fur Kohlenforschung
July 2005: director of at Max-Planck-Institut Fur Kohlenforschung
Asymmetric Induction for \( \beta \)-Hydroxy-Dioxinone

**Carreira methodology (JACS 1995)**

- **Pros**
  - First example
  - Good selectivity
  - Inexpensive catalyst system

- **Cons**
  - Limited substrates (sp\(^2\) v. sp\(^3\))
  - Sensitive conditions (reproducibility)

![Chemical structure of Carreira methodology]

**Scettri methodology (Tet. Asymm. 2003)**

- **Pros**
  - Inexpensive catalyst system
  - Alkyl aldehydes

- **Cons**
  - Sensitive conditions (reproducibility)

![Chemical structure of Scettri methodology]
Asymmetric Induction for β-Hydroxy-Dioxinone

**Denmark methodology (JACS 2003)**

![Chemical structure of Denmark methodology]

- **Pros**
  - Novel approach (activation of nucleophile)
  - Compatible with alkyl aldehydes

- **Cons**
  - Stoichiometric catalyst
  - Catalyst availability

**Rawal methodology (Org. Lett. 2005)**

![Chemical structure of Rawal methodology]

- **Pros**
  - Non-metallic catalyst
  - Hydrogen-bonding catalysis

- **Cons**
  - Aryl or sp² hybridized aldehydes only
  - General selectivity
Fuson (1935): Electron density and reactivity is amplified along conjugated bonds of a π system

DFT calculations for attack by an electrophile gave the condensed Fukui functions (CFF) & electrostatic potentials (ESP)
Catalyst Development

pseudo $C_2$-symmetry

exposed acid

buried acid

phosphoric acid

disulfonimide

resembles the relative reactivity of TfOH and Tf$_2$NH!

Catalyst Development


\[
RCHO + \text{RCH(O)OR} \rightarrow \text{RCH(O)OR}
\]

<table>
<thead>
<tr>
<th>Product</th>
<th>% Yield</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{OTMS}\text{CO}_2\text{Me})</td>
<td>98</td>
<td>97:3</td>
</tr>
<tr>
<td>(\text{OTBS}\text{CO}_2\text{iPr})</td>
<td>92</td>
<td>96:4</td>
</tr>
<tr>
<td>(\text{OTBS}\text{CO}_2\text{iPr})</td>
<td>95</td>
<td>93:7</td>
</tr>
<tr>
<td>0.05 mol %</td>
<td>90</td>
<td>93:7</td>
</tr>
<tr>
<td>(\text{OTBS}\text{CO}_2\text{iPr})</td>
<td>5 mol %</td>
<td>59</td>
</tr>
</tbody>
</table>

Et\(_2\)O (0.2 M), –78 °C, 12-24 h
Substrate Scope of Vinylogous MAR

$$R\text{CHO} + R\text{OSiR}_3\text{OR} \rightarrow \text{Et}_2\text{O (0.2 M), } -78 \, ^\circ\text{C} \rightarrow 12-24 \, \text{h}$$

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<th>product</th>
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<tbody>
<tr>
<td>OTMS OMe</td>
<td>67</td>
<td>96:4</td>
</tr>
<tr>
<td>OTIPS OMe</td>
<td>73</td>
<td>95:5</td>
</tr>
<tr>
<td>OTBS OMe</td>
<td>96</td>
<td>97:3</td>
</tr>
</tbody>
</table>

silyl group didn’t affect yield or selectivity
**Substrate Scope of Vinylogous MAR**

The reaction involves the use of a catalyst at 5 mol% and proceeds in Et$_2$O (0.2 M) at $-78^\circ$C for 12-24 h. The product is characterized by the following structures with their respective yields and e.r. values:

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<th>e.r.</th>
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<tbody>
<tr>
<td>OTBS</td>
<td>96</td>
<td>93:7</td>
</tr>
<tr>
<td>OMe</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPr</td>
<td>61</td>
<td>95:5</td>
</tr>
<tr>
<td>OtBu</td>
<td>30</td>
<td>94:6</td>
</tr>
<tr>
<td>Me</td>
<td>80</td>
<td>92:8</td>
</tr>
</tbody>
</table>

Increasing ester bulkiness significantly reduced yields.
Substrate Scope of Vinylogous MAR

\[ \text{RCHO} + \text{R} \text{OSiR}_3 \text{R} \rightarrow \text{R} \text{OSiR}_3 \text{R} \text{OR} \]

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<tr>
<th>Product</th>
<th>% Yield</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTBS Me</td>
<td>60</td>
<td>94:6</td>
</tr>
<tr>
<td>OTBS</td>
<td>78</td>
<td>81:19</td>
</tr>
</tbody>
</table>

\( \beta \) substituents are well-tolerated, while \( \alpha \) substituents result in product with decreased enantioselectivity

\( \rightarrow \text{compliments Denmark’s chemistry!} \)
Substrate Scope of Vinylogous MAR

electron rich or neutral aromatic aldehydes work the best

RCHO + R\(\text{OSiR}_3\) \(\rightarrow\) R\(\text{OSiR}_3\)R

Et\(_2\)O (0.2 M), –78 °C
12-24 h

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<tr>
<th>product</th>
<th>% yield</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTBS Me OMe</td>
<td>65</td>
<td>82:18</td>
</tr>
<tr>
<td>Me(\text{OTBS})\text{OEt}</td>
<td>62</td>
<td>61:39</td>
</tr>
<tr>
<td>OTBS Me(\text{OEt}</td>
<td>45</td>
<td>72:28</td>
</tr>
<tr>
<td>OTBS Me(\text{OEt}</td>
<td>33</td>
<td>72:28</td>
</tr>
</tbody>
</table>
Substrate Scope of Bisvinylogous MAR

The first catalytic, asymmetric bisvinylogous aldol reaction!

\[ \text{RCHO} + \text{O} \rightarrow \text{RCHO} \]

<table>
<thead>
<tr>
<th>product</th>
<th>% yield</th>
<th>e.r.</th>
<th>( \varepsilon/\alpha )</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Product" /></td>
<td>75</td>
<td>95:5</td>
<td>5:1</td>
</tr>
<tr>
<td><img src="image2.png" alt="Product" /></td>
<td>46</td>
<td>87:13</td>
<td>8.4:1</td>
</tr>
<tr>
<td><img src="image3.png" alt="Product" /></td>
<td>47</td>
<td>54:46</td>
<td>3.2:1</td>
</tr>
</tbody>
</table>
1966-70: undergraduate degree from Tokyo Institute of Technology
1970-75: PhD at Tokyo Institute of Technology with Prof. Mukaiyama
1975: Assistant Professor at Tokyo University
1981-82: Research at Yale with Prof. Danishefsky
1982: Associate Professor at Tokyo University
1993-96: Research Fellow at Sagami Research Center
1996: Professor at Tokyo University of Science

Prof. Dr. Susumu Kobayashi
(+)\text{-TMC-151C}

isolated in 1999 from *Gliocladium catenulatum* (fungus)

Has significant cytotoxicity against HCT-116, B16 and HeLa cancer cell lines

3 contiguous anti homoallylic alcohols \(\beta\)-D-manoside & D-mannitol moieties
remote asymmetric induction

\[ \text{anti-} \delta\text{-hydroxy-} \]
\[ \alpha, \gamma\text{-dimethyl} \]
\[ \alpha, \beta\text{-unsaturated carbonyl product} \]

\[ \text{d.r. > 20:1} \]

\[ (\pm)\text{-TMS-151C} \]

3 iterative VMARs & 2 late-stage glycosylations

Shirokawa, S., Kamiyama, M., Nakamura, T., Okada, M., Nakazaki, A., Hosokawa, S., Kobayashi, S.

1st Generation Route

Excess TiCl₄ and N,O-acetal necessary to get reaction to completion

Aldehyde made with Negishi’s Zr-catalyzed asymmetric carboalumination methodology

VMAR
2nd Generation Route

E-selective silicon-tethered ring-closing metathesis

HG-II benzoquinone

93%
> 20:1 E:Z

(+)-TMS-151C

crownlike conformation
β-mannoside formation is often regarded as one of the most difficult glycosylation reactions.

2nd Generation Route: Left-Hand Fragment

developed by Crich & Karatholuvhu, 2008

β-mannosylation

\[ \text{β-mannosylation \~82\%} \]

1.) LiBH$_4$
2.) Li, NH$_3$ (l)
\~86\% over 2 steps

Birch reduction

1.) TESOTf
2.) AcOH, H$_2$O

\~94\% over 4 steps
2nd Generation Route: Right-Hand Fragment

a problematic substrate

\[
\begin{align*}
\text{VMAR} & \quad 65 \% \\
& > 20:1 \text{ d.r.}
\end{align*}
\]

1.) PMB imidate
2.) LiOH $\cdot$ H$_2$O
$\sim 76 \%$
over 2 steps

anhydride formation & esterification

\[
\begin{align*}
& \text{1.) Piv}_2\text{O} \\
& 2.) \text{HO} \\
& 3.) \text{DDQ}
\end{align*}
\]
2nd Generation Route: Fragment Coupling

(+)-TMS-151C

HF:pyr; HF 54%

> 20:1 d.r.

RCM 87%

Et₂NPh₂SiCl 81% b.r.s.m.