Green Chemistry Innovation in the Synthesis of Medicines

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http://www.drreddys.com/products/green-chemistry.html (Green Chemistry Website)

Nature Medicine 2013, 19, 1200-1203 (Finding Right Chemistry)
Significance of Chemistry

• Whatever you hear, see, smell, taste, and touch involves chemistry and chemicals (matter).
• And all these processes involve intricate series of chemical reactions and interactions in the biological system.
• With such an enormous range of biological actions which are governed by chemistry therefore it is essential to know about this subject at some level in order to understand the world around us.

Green Tea  Coffee  Cigarette

>200  >1000  >7000

200  >1000  >7000

Evolving Path of Chemistry

Value added products from nature

Utility Science

Core and Integrative Science

Sustainability Science

Resource stressed planet

Understanding of life processes and chemical matter at molecular level

Life  Research  Hope
-To quote Linus Pauling, Nobel Laureate in chemistry, from a 1983 UC Berkeley lecture:

*Chemistry is wonderful! I feel sorry for people who don't know anything about chemistry. They are missing an important source of happiness -- that of satisfying one's intellectual curiosity. The world is wonderful. Chemistry is an important part of it.*

Chemistry Signifies Love and Hate Relationship
- *can’t live without it but can’t accept everything that it has*
Evolving discipline it does mean that the definition of green may change tomorrow e.g. Grignard reaction was considered to be one of the best reactions but today it is being replaced with greener metal catalyzed transformations.

It is a subject that deals with prevention of waste in any activity around us by design.
Industry Sectors

Energy alternatives

Textile, printing, agro and construction

Electronics and semiconductors

**Pharmaceutical**, medical and biotech

Cosmetics

Retail and everyday commodity
Higher E Factor $\alpha$ Degree of Complexity?

Material Demand in Tonnage

E-Factor in Kg

1. Pharma; 2. Fine; 3. Bulk; 4. Oil
Understanding the Pivotal Role of Organic Chemistry in Addressing the Challenges

Organic Chemistry

- Eco-friendly
- Consistent Quality
- Low Cost
- Scalable Synthesis of Genric API
- Safe Process
- Speed of Development
- Engineering Challenges
- Consistent in Polymorphic forms
- Control of Impurites
- Scalable Solvents & Reagents
- Application of recent trends i.e. OC, OM, BC etc
- IP Challenges (IP-free)

Life Research Hope
Approaches

1. Consideration of GC (TP and GM) in design phase
2. Minimize the number of steps while maintaining the desired cost component intact
3. Minimize or replace (Switch) non-green solvents
4. Work through multi-disciplinary scientific interface (Collaboration)
5. Renewable material based synthesis
6. Net output based energy efficient waste (unavoidable) management
7. Non-toxic and hazard free practices
8. Continuous mode of Chemistry/Engineering (flow technology)
9. In-expensive catalyst based transformations
10. Opt for asymmetric transformations
11. Use of immobilized recombinant enzymes for transformations with very low dilutions
12. Educate and prepare young generation considering intuitive knowledge potential to take a lead in this field
Approaches: Flow Technology

BATCH (space-resolved process)

• Conventional method
• Several Disadvantages
  - Time and labor intensive
  - A number of unit processes
  - Needs extensive optimization

FLOW MICROREACTION TECHNOLOGY (time-resolved process)

• Emerging Technology
• Advantages over batch process
  - High surface area, precisely controlled conditions
  - Rapid screening of reaction conditions
  - “Scale-out” instead of “Scale-up”
  - Safety
Approaches: Biocatalysis

- **Screening**
  - Microbe, enzyme collection
  - Shake Flask

- **Optimization**
  - Lab Fermenter
  - Seed Fermenter

- **CPP**

- **Production**
  - Production Fermenter

Life Research Hope
Innovative Research Since 2007

Citalopram


Esclicarzepine


Ritonavir

Tetrahedron Lett. 2011, 52, 6968-6970

Lopinavir

Ramipril

Synthetic Commun. 2011, 41, 1186-1191

Dexlansoprazole


Levetiracetam


Amtolmetin


Rizatriptan

Monatsh. Chem., 2008, 139, 1091-1094

Pioglitazone


Rimonabant

Aprepitant

Life

Research

Hope
Types of Innovation

1. Incremental
2. Medium Size
3. Process
4. Technology based
   a. Biocatalysis
   b. Continuous
5. Major
Incremental: Reductive Amination

Direct

\[ \text{catalyst} \rightarrow \text{catalyst} \]

\[ \text{reagent} \rightarrow \text{reagent} \]

Indirect

Mechanistic Considerations

**Class 1 (toxic)**
Pt, Pd, Ir, Rh, Ru, Os

**Class 2 (less toxic)**
Cu, Mn, Ti, Sc

**Class 3 (non-toxic)**
Zn, Fe
Generality of the Method

1. \( \text{R} + \text{H}_2\text{NR}_1 + 1 \text{ mol% Fe(OTf)}_3 \xrightarrow{1 \text{ eq. NaBH}_4} \text{R}^1 \text{NR}_1 \)  
   \( \text{R, R}_1 = \text{alkyl, aryl or heterocyclic} \)

2. \( \text{3a 90\%} \)  
   \( \text{3b 90\%} \)  
   \( \text{3c 92\%} \)  
   \( \text{3d 90\%} \)  
   \( \text{3e 80\%} \)  
   \( \text{3f 88\%} \)  
   \( \text{3g 90\%} \)  
   \( \text{3h 90\%} \)  
   \( \text{3i 82\%} \)  
   \( \text{3j 87\%} \)  
   \( \text{3k 88\%} \)  
   \( \text{3l 89\%} \)  
   \( \text{3m 92\%} \)  
   \( \text{3n 89\%} \)  
   \( \text{3o 90\%} \)  
   \( \text{3p 90\%} \)  
   \( \text{3q 90\%} \)  
   \( \text{3r 89\%} \)  
   \( \text{3s Cinacalcet 80\%} \)  
   \( \text{3t Aliskiren intermediate 88\%} \)
Superfast Acylation

Incremental: Acylation

Kumar, U. Tetrahedron Lett. 2013, in print

Conventional
Ac$_2$O, DMAP

Pyridine 0-5 °C

Zn(OTf)$_2$, 25 °C

Ac$_2$O, DMAP

Catalytical

ROH  Acetylation

High yield

Less Toxic

Rapid reaction time

low cost, stable

Life

Research

Hope

Less than a minute
Incremental: Acylation

Generality of the Method

\[ R-XH + Ac_2O \xrightarrow{0.1\text{ mol}\%\ Zn(OTf)_2, \text{Neat or CH}_2\text{Cl}_2, 25^\circ\text{C}} R-XAc \]

\( R = \text{alkyl, benzyl, phenyl; } X=\text{O, S} \)

1. \( R=\text{phenyl, } X=\text{O} \)
   - \( 3a \): 98%
   - \( 3b \): 95%
   - \( 3c \): 98%
   - \( 3d \): 93%
   - \( 3e \): 94%

2. \( R=\text{phenyl, } X=\text{S} \)
   - \( 3f \): 97%
   - \( 3g \): 98%
   - \( 3h \): 95%
   - \( 3i \): 98%
   - \( 3j \): 92%

3. \( R=\text{aromatic, } X=\text{O} \)
   - \( 3k \): 98%
   - \( 3l \): 90%
   - \( 3m \): 85%
<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reagent/catalyst</th>
<th>Conditions</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2l</strong></td>
<td>cat. DMAP, Py/AC\textsubscript{2}O</td>
<td>CH\textsubscript{2}Cl\textsubscript{2}, Reflux</td>
<td>2 h</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Zn(OTf\textsubscript{2}) (0.1 mol%) /AC\textsubscript{2}O</td>
<td>25-25 °C</td>
<td>60s</td>
<td>90</td>
</tr>
<tr>
<td><strong>2j</strong></td>
<td>Py/AC\textsubscript{2}O</td>
<td>25-25 °C</td>
<td>3 h</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>Zn(OTf\textsubscript{2}) (0.1 mol%) /AC\textsubscript{2}O</td>
<td>25-25 °C</td>
<td>30s</td>
<td>92</td>
</tr>
</tbody>
</table>
**Incremental: Amide Reduction**

\[
\begin{align*}
\text{R}_1^\text{N} & \quad \text{O} & \quad \text{R}_2^\text{R}_3^\text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{TMSCl} & \quad \text{LAH} & \quad \text{DCM} \\
0-10 \, ^\circ\text{C}, \, 30 \, \text{min} & \quad \text{R}_1^\text{R}_2^\text{R}_3^\text{H}
\end{align*}
\]

Mechanistic Considerations

\[
\begin{align*}
\text{R}^2\text{N} & \text{R}^3 \\
\text{TMSCl (LA)} & \rightarrow \\
\text{Cl}^- & \text{R}^2\text{N} \text{R}^3 \\
\text{LAH} & \rightarrow \\
\text{R}^2\text{N} \text{R}^3 \\
\text{TMSOAlH}_3 & \rightarrow \\
\text{R}^2\text{N} & \text{R}^3
\end{align*}
\]
Generality of the Method

1b, 85%
2b, 78%
3b, 79%
4b, 77%
5b, 81%
6b, 75%
7b, 77%
8b, 81%
9b, 74%
10b, 84%
11b, 79%
Generality of the Method

1b', 85%, 99% de

1b'', 79%, 99% de

12b, 77%, 98.5% ee

13b, 72%, 98.5% ee

14b, 81%, 99% ee

15b, 79%, 99% ee

16b, 82%, 98.5% ee

17b, 79%, 98.5% ee
Medium Size: Enantioselective Grignard addition to Nitroolefin

\[
\begin{align*}
R^1\text{-}\text{NO}_2 & \quad \xrightarrow{6 \text{ mol}\% \ L_3, \ 5 \text{ mol}\% \ Cu(I), \ 1.2 \text{ eq of } R^2\text{MgX}} \quad \text{MTBE, } 3 \text{ h} \\
& \quad \Rightarrow \quad R^2 \text{-}R^1\text{-}\text{NO}_2 \\
\end{align*}
\]

upto 97\% ee

Potential Application

\[
\text{CHO} \quad \xrightarrow{\text{Nitromethane}} \quad \text{NO}_2
\]

\[
\text{NH}_4\text{OAc, AcOH} \quad \xrightarrow{97\%} \quad \text{NH}_4\text{Cl, H}_2\text{O}
\]

\[
\text{MeMgCl, Toluene} \quad \xrightarrow{80\%} \quad \text{Naproxen}
\]

\[
\text{NO}_2 \quad \xrightarrow{\text{Mg, THF, 5 °C, 1h}} \quad \text{Br}
\]

Life  Research  Hope
**Medium Size: Enantioselective Grignard Addition to Nitroolefin**

**Screening**

\[
\text{R}^1\text{=\text{-NO}_2} \xrightarrow{20 \text{ mol}\% \text{ catalyst}} \text{R}^2\text{=\text{-NO}_2}
\]

1.2 eq of \(\text{R}^2\text{MgX}\)

THF, 8 h

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Catalyst</th>
<th>(\text{R}^1/\text{R}^2/X)</th>
<th>°C</th>
<th>er (R/S) (HPLC)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuTC/L1</td>
<td>6Mn/Me/Br</td>
<td>-60</td>
<td>49.5/50.5</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>CuTC/L1</td>
<td>6Mn/Me/Br</td>
<td>-20</td>
<td>49/51</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>CuI/L1</td>
<td>6Mn/Me/Br</td>
<td>-60</td>
<td>45/55</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>CuI/L1</td>
<td>6Mn/Me/Br</td>
<td>-20</td>
<td>48.6/51.4</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>Zn(OTf)(_2)/L1</td>
<td>6Mn/Me/Br</td>
<td>-60</td>
<td>49.5/50.5</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>Zn(OTf)(_2)/L1</td>
<td>6Mn/Me/Br</td>
<td>-20</td>
<td>49.5/50.5</td>
<td>70</td>
</tr>
<tr>
<td>7</td>
<td>CuTC/L2</td>
<td>6Mn/Me/Br</td>
<td>-60</td>
<td>49.5/50.5</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>CuTC/L2</td>
<td>6Mn/Me/Br</td>
<td>-20</td>
<td>49.5/50.5</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>CuI/L2</td>
<td>6Mn/Me/Br</td>
<td>-60</td>
<td>49/51</td>
<td>70</td>
</tr>
<tr>
<td>10</td>
<td>CuI/L2</td>
<td>6Mn/Me/Br</td>
<td>-20</td>
<td>49.7/50.3</td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td>Zn(OTf)(_2)/L2</td>
<td>6Mn/Me/Br</td>
<td>-60</td>
<td>49.2/50.8</td>
<td>70</td>
</tr>
<tr>
<td>12</td>
<td>Zn(OTf)(_2)/L2</td>
<td>6Mn/Me/Br</td>
<td>-20</td>
<td>49.6/50.4</td>
<td>70</td>
</tr>
<tr>
<td>13</td>
<td>CuTC/L1</td>
<td>6Mn/Me/Cl</td>
<td>-70</td>
<td>49.2/50.8</td>
<td>70</td>
</tr>
<tr>
<td>14</td>
<td>CuTC/L1</td>
<td>6Mn/Me/Cl</td>
<td>-20</td>
<td>49.3/50.7</td>
<td>70</td>
</tr>
<tr>
<td>15</td>
<td>CuTC/L1</td>
<td>6Mn/Me/Cl</td>
<td>-35</td>
<td>48/52</td>
<td>72</td>
</tr>
</tbody>
</table>

**Catalyst Structures**

- \(L_1\): (SS)-isopropyl bis oxazoline
- \(L_2\): (R)-BINAP
- \(L_3\): [(S)-1-[(Rp)-2-(Dicyclohexylphosphino)ferrocenylethyl]diphenylphosphine]
### Medium Size: Enantioselective Grignard Addition to Nitroolefin

**Screening**

The reaction is carried out with 20 mol% catalyst and 1.2 eq of $R^2$MgX in MTBE for 8 hours.

- Chemical structures of ligands L1, L2, and L3 are shown.

<table>
<thead>
<tr>
<th>S.No.</th>
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<th>$R^1$/R$^2$/X</th>
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<th>$er$ (R/S) (HPLC)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuTC/L$_1$</td>
<td>6Mn/Me/Cl</td>
<td>-40</td>
<td>48.7/51.3</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>CuTC/L$_1$</td>
<td>6Mn/Et/Cl</td>
<td>-40</td>
<td>49/51</td>
<td>69</td>
</tr>
<tr>
<td>3</td>
<td>CuTC/L$_1$</td>
<td>6Mn/iPr/Cl</td>
<td>-40</td>
<td>51/49</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>CuTC/L$_1$</td>
<td>6Mn/tBu/Cl</td>
<td>-40</td>
<td>72/28</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>CuTC/L$_1$</td>
<td>6Mn/tBu/Cl</td>
<td>-70</td>
<td>77/23</td>
<td>69</td>
</tr>
</tbody>
</table>
**Medium Size: Enantioselective Grignard Addition to Nitroolefin**

**Screening**

\[
\begin{align*}
R^1\text{\(\rightarrow\)}_{\text{NO}_2} & \overset{20 \text{ mol\% catalyst}}{\text{\(\rightarrow\)}} \\
& \overset{1.2 \text{ eq of } R^2\text{MgX}}{\text{\(\rightarrow\)}} \\
& \overset{\text{MTBE, 8 h}}{\text{\(\rightarrow\)}} \\
R^1\text{\(\rightarrow\)}_{\text{NO}_2}
\end{align*}
\]

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Catalyst</th>
<th>(\text{R}^1/\text{R}^2/\text{X})</th>
<th>°C</th>
<th>(er (R/S) \text{ (HPLC)})</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuI/L(_3)</td>
<td>6Mn/Me/Cl</td>
<td>-70</td>
<td>49.2/50.8</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>CuI/L(_3)</td>
<td>6Mn/Et/Cl</td>
<td>-70</td>
<td>49.5/50.5</td>
<td>64</td>
</tr>
<tr>
<td>3</td>
<td>CuI/L(_3)</td>
<td>6Mn/iPr/Cl</td>
<td>-70</td>
<td>51.97/48.03</td>
<td>64</td>
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<tr>
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<td>6Mn/iBu/Cl</td>
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<td>61/39</td>
<td>62</td>
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<tr>
<td>5</td>
<td>CuI/L(_3)</td>
<td>6Mn/iBu/Cl</td>
<td>-70</td>
<td>98.5/1.5</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>CuI/L(_3)</td>
<td>6Mn/iBu/Cl</td>
<td>-70</td>
<td>97.9/2.1</td>
<td>64</td>
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<tr>
<td>7</td>
<td>CuI/L(_3)</td>
<td>6Mn/iBu/Cl</td>
<td>-70</td>
<td>97.9/2.1</td>
<td>65</td>
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<tr>
<td>8</td>
<td>CuI/L(_3)</td>
<td>6Mn/iBu/Cl</td>
<td>-70</td>
<td>97.8/2.2</td>
<td>63</td>
</tr>
<tr>
<td>9</td>
<td>CuI/L(_3)</td>
<td>iBu/6Mn/Br</td>
<td>-70</td>
<td>25/75</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>CuTC/L(_3)</td>
<td>6Mn/Ph/Br</td>
<td>-70</td>
<td>50.56/49.44</td>
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<td>CuTC/L(_3)</td>
<td>6Mn/Benzyl/Cl</td>
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<td>49.49/50.51</td>
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<td>CuI/L(_3)</td>
<td>Ph/iBu/Cl</td>
<td>-70</td>
<td>39.5/60.5</td>
<td>60</td>
</tr>
<tr>
<td>13</td>
<td>CuI/L(_3)</td>
<td>p-EtO-Ph/iBu/Cl</td>
<td>-70</td>
<td>23/77</td>
<td>65</td>
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<td>p-F-Ph/iBu/Cl</td>
<td>-70</td>
<td>4/96</td>
<td>60</td>
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</tbody>
</table>
Medium Size: Enantioselective Grignard Addition to Nitroolefin

Article Usage Dashboard

Enantioselective Grignard addition to nitroolefin

Reddy, P.; Bandichhor, R.

Tetrahedron Letters, Volume(s) 54, 10-May-2013, Pages 3911-3915

Views by geography

<table>
<thead>
<tr>
<th>Top countries</th>
<th>Rank</th>
<th>Views</th>
<th>Pct</th>
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<tbody>
<tr>
<td>India</td>
<td>1</td>
<td>148</td>
<td>21%</td>
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<tr>
<td>China</td>
<td>2</td>
<td>126</td>
<td>18%</td>
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<tr>
<td>United States</td>
<td>3</td>
<td>109</td>
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<tr>
<td>Japan</td>
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<td>59</td>
<td>8%</td>
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<tr>
<td>Spain</td>
<td>5</td>
<td>20</td>
<td>3%</td>
</tr>
</tbody>
</table>

Trend and cumulative views

695 total views

Corporate versus Public Sector

Public 86%

Corpo 14%
Medium Size: Regioselective Methylation

Medium Size: Regioselective Methylation

Different Methods

Basic condition: No selectivity
Acidic condition: N-1 (thermodynamic); N-2 (kinetic)
Trimethyloxonium tetrafluoroborate (Meerwein’s reagent) is considered to be the best reagent for regioselective methylation.
Medium Size: Regioselective Methylation

**Generality of the Methods**

\[ \text{R} = \text{NO}_2, \text{CO}_2\text{Me}, \text{Cl}, \text{I}, \text{H}, \text{OMe} \]

\[ \text{R}^1 = \text{H,Me} \]

\[ \text{5a}  \quad 87\% \]

\[ \text{5b}  \quad 96\% \]

\[ \text{5c}  \quad 97\% \]

\[ \text{5d}  \quad 95\% \]

\[ \text{5e}  \quad 94\% \]

\[ \text{5f}  \quad 87\% \]

\[ \text{5g}  \quad 85\% \]

\[ \text{5h}  \quad 83\% \]

\[ \text{5i}  \quad 79\% \]

\[ \text{5j}  \quad 90\% \]

\[ \text{5k}  \quad 78\% \]

\[ \text{4} \]

\[ \text{HCl} \]

\[ \text{5a} \]

\[ \text{5a} \]

\[ \text{5a} \]

\[ \text{5a} \]

\[ \text{5a} \]

\[ \text{5a} \]

\[ \text{5a} \]

This reagent is suitable to both EWG and EDG containing substrates.
First reported synthesis of Citalopram 1

1. Reaction of 3 and MgBr in Ether, THF at 10°C to 25°C.
2. Deprotonation of 4 with LiAlH₄ or NaBH₄.
3. Reaction of 5 with Br₂ in H₃PO₄, TsOH or H₂SO₄ at 100°C.
4. Reaction of 6 with Cu₂(CN)₂ in DMF at 140°C.

Life Research Hope
1. Can we freshly prepare GR and use it *in situ*?
2. Can we avoid the use of LAH or Sodium borohydride reagent?
3. Can we avoid Copper cyanide?
4. Can we avoid NaH during alkylation?
5. Can we do most of the transformations at room temperature or at least can we avoid higher temperature (>100 °C)?
6. Is it possible to telescope this process to all possible extent?
7. .......................etc
Outline Towards Realizing the Strategies: One Pot Synthesis of Diol HBr

1. **Step 1.1**
   - Reactant (10) + Reactant (4) + Reactant (11)

2. **Step 1.2**
   - Product transition

3. **Step 1.3**
   - Product transition

4. **Step 1.4**
   - Product transition

5. **Step 2**
   - Product transition

6. **Step 3**
   - Product transition

Diol HBr 1

Crude Citalopram HBr

Life
Research
Hope
## Role of Solvents and Inherent KF

<table>
<thead>
<tr>
<th>Solvent Combination</th>
<th>% Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCM/THF 0.1%/0.1% WC</td>
<td>71</td>
</tr>
<tr>
<td>DCM/THF 0.2%/0.1% WC</td>
<td>52</td>
</tr>
<tr>
<td>DCM/THF 0.3%/0.1% WC</td>
<td>30</td>
</tr>
<tr>
<td>DCM/THF 0.1%/0.1% WC</td>
<td>72</td>
</tr>
<tr>
<td>DCM/THF 0.1%/0.2% WC</td>
<td>71</td>
</tr>
<tr>
<td>DCM/THF 0.1%/0.3% WC</td>
<td>28</td>
</tr>
</tbody>
</table>
Temperature Profile

**Stepwise temperature profile during diol synthesis**

- Reaction progress of CPA Grignard (Step 1.3)
- Initiation of CPA Grignard (Step 1.3)
- Reaction progress of BFB Grignard (Step 1.1)
- Initiation of BFB Grignard (Step 1.1)
- Addition of Grignard reagents to 5CP (Step 1.2 & 1.4)
DoE: Full Factorial

1. Pre DoE experiments
2. Based on domain knowledge, deciding on the variable and response factors
3. Use of software e.g. Design Expert
4. Augmentation of initial results with the help of Response Surface Model to arrive on the optimal conditions
5. Analysis of results by considering ANOVA variance method to derive significant model
Operable ranges for DoE based on pre-DoE experiments

<table>
<thead>
<tr>
<th>process variables</th>
<th>low</th>
<th>high</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFB (mol equiv.)</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Mg (mol equiv.)</td>
<td>1.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Iodine (% w/w)</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>process variables</th>
<th>low</th>
<th>high</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPA (mol equiv.)</td>
<td>1.8</td>
<td>3.0</td>
</tr>
<tr>
<td>Mg (mol equiv.)</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Iodine (% w/w)</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

Response Factors
>75% yield and >98% purity
Design space obtained for BFB and CPA Grignard reactions.

Overlay Plot

- **B: Mg-1**
  - Yield: 79.575
  - Purity: 90.1
  - X1: 1.30
  - X2: 1.33

- **A: BFB**

Overlay Plot

- **B: Mg-1**
  - Yield: 77.9552
  - Purity: 90.159
  - X1: 2.23
  - X2: 3.22

- **A: CPA**
Optimized Conditions

1. Process:
   - **Step 1.1:**
     - 1.3 mol Mg
     - 0.04 mol iodine
     - THF, 65 °C, 2h
   - **Step 1.2:**
     - 1.0 mol
     - 4, DCM
     - -5 °C, 40 min
   - **Step 1.3:**
     - 3.0 mol Mg
     - 0.06 mol iodine
     - toluene, THF
     - 90 °C, 3h

2. Reaction Media:
   - 47% aq. HBr
   - IPA
   - 95% HBr
   - 98% H₂SO₄

3. Overall Yields:
   - 44%

4. Overall E-factor:
   - 53
Process Innovation: Grignard Reaction

Work up Simplification

Reaction

- Quenching
- Unwanted solids filtration
- Acid-base treatment
- Product extraction
- Distillation
- Saltification

Quenching
- Unwanted solids filtration
- Saltification

Life
Research
Hope
1. Understanding the heat of reaction and adiabatic temperature rise
2. Comparison of the batch temperature profile inside the reactor (Tr) with the reactor jacket temperature profile (Tj) in isothermal mode reveals whether the reaction is instantaneous or not. (Exo or Endothermic)
3. Enthalpy can be calculated which indicates temperature rise in a given batch size
4. This helps to avoid accidents at a scale by keeping control system in place without compromising on process variables and responses
For 100g input of 10; Temperature rise for BFB Grignard is from 0 °C to 3 °C, E=170.2 KJ and Tad=146.69 °C; Temperature rise for CPA Grignard is from 0 °C to 1.5 °C, E=148.15 KJ and Tad=91.2 °C. Recommendation: Rate of heat exchange must be controlled by keeping efficient cooling in Jacket.
Michael E Kopach <kopach_michael@lilly.com>
05/10/2013 04:45 AM
To
"rakeshwarb@drreddys.com" <rakeshwarb@drreddys.com>
Cc
Subject
Citalopram Paper
Dear Rakesh,
From on Grignard practioner to another – this is an outstanding paper:
http://pubs.acs.org/doi/abs/10.1021/op3002596

Best Regards,

Mike

Asymmetric Reduction of a Key Intermediate of Esclicarbazepine Acetate Using Whole Cell

Glucose $\xrightarrow{\text{Gluconic acid}}$ NADPH

\[ \text{NADP}^+ \]

30°C, 150 rpm

10-oxo-10,11-dihydro-5H-dibenzo[\(b,f\)]azepine-5-carboxamide

\[ \text{1} \]

(S)-10-hydroxy-10,11-dihydro-5H-dibenzo[\(b,f\)]azepine-5-carboxamide

\[ \text{2} \]

Catalysis Science & Technology 2012, 2, 1602-1605. (One of the Hot Articles).
Bioreduction of Ketone 1 by *P. methanolica* whole-cells in biphasic system at 30°C
Effect of Substrate Concentration

- 0.5g/l
- 1.0g/l
- 1.5g/l
- 2.0g/l
- 2.5g/l
- 3.0g/l

Conversion (%) vs Time (h)
Effect of Cell Concentration

Conversion (%)

Cell concentration (gL⁻¹)
Output at a Scale with Optimized Conditions

1. Resting cells of *P. methanolica* (150.0 gl⁻¹), H₂O: hexane (2 L), glucose (0.5%)
2. Reaction at 30 °C for 48 h
3. 85% isolated with >98% ee
Application of Flow Technology in the Process Development of Prazoles

![Chemical Structure]

<table>
<thead>
<tr>
<th>Drug name</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>R4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lansoprazole</td>
<td>-H</td>
<td>F₃CCH₂O⁻</td>
<td>Me</td>
<td>-H</td>
</tr>
<tr>
<td>Pantaprazole</td>
<td>-H</td>
<td>MeO</td>
<td>MeO</td>
<td>F₂CHO⁻</td>
</tr>
<tr>
<td>Raberprazole</td>
<td>Me</td>
<td>MeO (CH₂)₃O</td>
<td>Me</td>
<td>-H</td>
</tr>
</tbody>
</table>
Technology Based Innovation: Flow Chemistry

Synthesis of Prazoles

4a-4c + \[ \text{NaOH} \rightarrow \text{H}_2\text{O} \]

5a-5c \[ \text{Aq. NaOCl} \rightarrow \text{NaOH} \rightarrow \text{CH}_3\text{CN} \]

6a-6c

7a-7c
Continuous Flow Micromixing Reactor Set up
Effect of Flow Rate on Conversion

<table>
<thead>
<tr>
<th>entry</th>
<th>flow rate (mL/min)</th>
<th>6a</th>
<th>1a</th>
<th>7a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>0.95</td>
<td>95.72</td>
<td>0.30</td>
</tr>
<tr>
<td>2</td>
<td>150</td>
<td>0.75</td>
<td>96.92</td>
<td>0.04</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>0.30</td>
<td>97.94</td>
<td>0.02</td>
</tr>
<tr>
<td>4</td>
<td>250</td>
<td>0.70</td>
<td>97.70</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Flow rate vs conversion

Graph showing the relationship between flow rate and conversion for different compounds.
## Batch vs Flow

<table>
<thead>
<tr>
<th>entry</th>
<th>oxid’n of 6</th>
<th>synthesis method</th>
<th>residence time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a</td>
<td>batch process</td>
<td>2.5 h</td>
</tr>
<tr>
<td>2</td>
<td>6b</td>
<td></td>
<td>2.5 h</td>
</tr>
<tr>
<td>3</td>
<td>6c</td>
<td></td>
<td>2.5 h</td>
</tr>
<tr>
<td>4</td>
<td>6a</td>
<td>CFMMR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>~1 s</td>
</tr>
<tr>
<td>5</td>
<td>6b</td>
<td></td>
<td>~1 s</td>
</tr>
<tr>
<td>6</td>
<td>6c</td>
<td></td>
<td>~1 s</td>
</tr>
</tbody>
</table>
## Batch vs Flow

<table>
<thead>
<tr>
<th>Yield (%)</th>
<th>Purity (%) Before Purification</th>
<th>Purity (%) After Purification</th>
<th>Yield (%)</th>
<th>Overall Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1a–1c</td>
<td>7a–7c</td>
<td>1a–1c</td>
<td>7a–7c</td>
</tr>
<tr>
<td>85.0</td>
<td>97.5</td>
<td>0.13</td>
<td>99.6</td>
<td>0.18</td>
</tr>
<tr>
<td>92.9</td>
<td>97.2</td>
<td>0.05</td>
<td>99.7</td>
<td>0.08</td>
</tr>
<tr>
<td>85.0</td>
<td>98.2</td>
<td>0.08</td>
<td>99.5</td>
<td>0.05</td>
</tr>
<tr>
<td>89.0</td>
<td>96.5</td>
<td>–</td>
<td>99.9</td>
<td>0.06</td>
</tr>
<tr>
<td>94.8</td>
<td>97.9</td>
<td>–</td>
<td>99.5</td>
<td>0.07</td>
</tr>
<tr>
<td>88.2</td>
<td>98.7</td>
<td>0.10</td>
<td>99.5</td>
<td>0.03</td>
</tr>
</tbody>
</table>

First three entries are from Batch and last three belong to Flow

*Org. Process Res. Dev., 2010, 14, 229–233 (DRL, India)*

Precedent Approaches

Recently Developed Asymmetric Reduction Involving Biocatalysis is More Prefered

Major Innovation: Diastereoselective Reduction

Innovative Approaches

**Strategy I**

\[
\text{F} \quad \text{HN} \quad \text{O} \quad \text{N} \quad \text{CF}_3
\]

\[
\text{Yield ??; dr ??}
\]

**Strategy II**

\[
\text{F} \quad \text{HN} \quad \text{O} \quad \text{N} \quad \text{CF}_3
\]

\[
\text{Yield ??; dr ??}
\]

Life Research Hope
**Major Innovation: Diastereoselective Reduction**

**Evolution of Concept**

\[
\begin{align*}
\text{dr} & : 83:17 \\ 
\text{undesired isomer}
\end{align*}
\]

\[
\begin{align*}
\text{dr} & : 85:15 \\ 
\text{desired isomer}
\end{align*}
\]
Major Innovation: Diastereoselective Reduction

**NaBH₄, MsOH**

DME:IPA (20:7)

-40 °C, 12h

Yield 85%;

$dr = 85:15$

Required diastereomer crystallized with

$dr > 99%$

-90 °C: $dr = 93:07$, Yield = >90%

**7000 vs 700 USD**

Bandichhor, R.; et al. WO 2011025932 A2 20110303
**Major Innovation: Amino Acid**

*Discovery of Redox System Enabling C-N-C Bonds Formation: Indicator of Prebiotic Synthesis of Amino Acid*

**Miller-Urey**

- **H$_2$O**
- **N$_2$**
- **NH$_3$**
- **CO**
- **CH$_4$**

\[ \text{H$_2$O} \xrightarrow{\text{N$_2$}} \text{NH$_3$} \xrightarrow{\text{CO}} \text{NH$_3$} \xrightarrow{\text{CH$_4$}} \text{Amino acids} \]

**Calvin**

\[ \text{CO}_2 \xrightarrow{\text{HCO}_2\text{H}} \text{Amino acids} \]

**Karat**

\[ \text{HCN} \xrightarrow{\text{NH$_3$}} \text{Amino acids} \]

**Our work**

*prebiotic high energy induced*

\[ \text{CO}_2 \xrightarrow{\text{Citric and Glyoxylate cycles}} \text{NH$_3$} \xrightarrow{\text{starting point}} \text{Amino acids} \]

Different conceived approaches towards the synthesis of amino acids
Redox chemistry on ethyl glyoxylate and Cannizzaro reaction
Major Innovation: Amino Acid

Synthesis of glycine

1. EtO\_2C\_2H\_2O\_2 \xrightarrow{\text{NH}_4\text{OAc}} \text{EtO}_2C\_2H\_2\text{NH}

2. \text{EtO}_2C\_2H\_2\text{NH} \xrightarrow{\text{no metal-H}_2\text{ source}} \text{EtO}_2C\_2H\_2\text{NH}_2 + \text{HO}_2C\_\text{CO}_2\_\text{H}

3. \text{no hydride source}

Life Research Hope

Life  Research  Hope
Two different reaction pathways (a and b)
Major Innovation: Amino Acid

Life Research Hope

Energy, kJ/mol

0 257 TS1 267 TS2 136 InS1 -50 InS2 228 TS3 -142 FS

Reaction coordinate

IS TS1 TS2 TS3 InS1 InS2 InS3 TS1 TS2 TS3 FS
Major Innovation: Amino Acid

Energy, kJ/mol

IS

TS1

220

TS2

-39

InS

-142

FS

Reaction coordinate

Bandichhor et al. *Chem. Com.* 2014 under revision

Life

Research

Hope
HALAVEN is a clear, colorless, sterile solution for intravenous administration. Each vial contains 1 mg of eribulin mesylate as a 0.5 mg/mL solution in ethanol: water (5:95).

**Eribulin**

19 stereocenters

**Late Stage Breast Cancer (Two Chemotherapies and Treated With Anthramycin and Taxane Class of Medicine)**
Major Innovation: Synthesis of Eribulin

Sulfone addition

Nozaki-Hiyama-Kishi (NHK) reaction

Olefination

Ketal formation

NHK reaction / Cross metathesis

Life

Research

Hope
“A chain is as strong as its weakest link”

Reading Materials:
1. Scalable Green Chemistry: Case Studies from the Pharmaceutical Industry
2. Green Chemistry in the Pharmaceutical Industry

Apart from Leading Journals
1. OPRD
2. Journal of Chemical Education
Recognition

Green Innovation Award-2013 in the Large MNC Category
The management of the Dr. Reddy’s Laboratories Ltd. is highly acknowledged for supporting the innovative research.
Thank You