Synthetic Applications of Fluorous Molecules

“It is ironic that organic synthesis and separation science are separate disciplines because synthesis and separation are inseparable.”

Dennis Curran

Stewart Hart

Michigan State University

October 20, 2004
Fluorous Seminar Outline

• Section I: General Fluorous Information
  – What is a fluorous compound (history, properties)?
  – Why fluorous molecules are immiscible with aqueous solution?
  – Why fluorous molecules are immiscible with organic solution?

• Section II: Fluorous Synthetic Techniques
  – Triphasic: tagging or vanishing
  – Biphasic: hydroformylation, dihydroxylation
  – Monophasic: fluorous reverse solid phase extraction (FRSPE), metathesis, [trans]esterification
History of Perfluorocarbons

• Before 1937 only CF_4, C_2F_6, and C_2F_4 were known
• Teflon (1938) is polytetrafluoroethylene
• In the 1940’s, fluorocarbons were used to separate ^{235}U isotope
• In the mid-1970’s the Green Cross Company in Japan developed emulsions for blood substitutes for oxygen transport
• Horvath (1994) introduces Fluorous Biphasic Synthesis

Banks, R. E. **Fluorocarbons 1970**, MacDonald & Co. LTD., 13-17
Properties of Perfluorocarbons

- Colorless, dense
- Practically non-toxic
  - Oral / rat: \( \text{LD}_{50} = 5 \text{g/kg} \) (perfluorohexane)
  - Thermal decomposition to toxic products at temperatures above 400 °C
  - Carbon skeleton inaccessible to nucleophilic attack
- Solidify as glasses or soft waxy crystals
- MP usually are higher than hydrocarbon analogs
- Surface tension and refractive indices are really low

Banks, R. E. *Fluorocarbons* 1970, MacDonald & Co. LTD., 13-17
Miscibility in Aqueous Solutions: Like Dissolves Like

- Water is a polar molecule
- Fluorocarbons are non-polar molecules
- For this reason fluorocarbons are not miscible in aqueous solution
- Why are perfluorocarbons insoluble in organics (non-polar)?
**Hildebrand’s Solubility Parameters**

- Start with the heats of vaporization ($\Delta H$) and molar volume ($V_m$)
- From this we can derive the cohesive energy density ($c$) = all the attractive forces acting on a liquid (polarization, dipole-dipole, and H-bonding)
- The square root of $c$ is the Hildebrand Parameter (number less than 3.4 MPa$^{1/2}$ apart are generally missible)

\[
\delta = c^{1/2} = \left[ \frac{\Delta H - RT}{V_m} \right]^{1/2}
\]

### Polarizability: Hildebrand Parameters

<table>
<thead>
<tr>
<th>Solvent</th>
<th>MPa$^{1/2}$ ($\delta$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>47.5</td>
</tr>
<tr>
<td>EtOH</td>
<td>26.0</td>
</tr>
<tr>
<td>ACN</td>
<td>20.3</td>
</tr>
<tr>
<td>Benzene</td>
<td>18.8</td>
</tr>
<tr>
<td>Toluene</td>
<td>18.4</td>
</tr>
<tr>
<td>Xenon</td>
<td>16.5</td>
</tr>
<tr>
<td>Krypton</td>
<td>15.7</td>
</tr>
<tr>
<td>F-Methane</td>
<td>15.7</td>
</tr>
<tr>
<td>n-Pentane</td>
<td>15.5</td>
</tr>
<tr>
<td>F-Heptane</td>
<td>15.5</td>
</tr>
<tr>
<td>n-Hexane</td>
<td>14.9</td>
</tr>
<tr>
<td>n-Butane</td>
<td>14.8</td>
</tr>
<tr>
<td>Methane</td>
<td>14.4</td>
</tr>
<tr>
<td>F-Butane</td>
<td>12.4</td>
</tr>
<tr>
<td>F-Hexane</td>
<td>12.2</td>
</tr>
<tr>
<td>F-Pentane</td>
<td>11.8</td>
</tr>
</tbody>
</table>

Hydrogen Bonding

Dipole-Dipole Interactions

Polarizability

If d values are close (3.4 MPa$^{1/2}$) numerically then they are miscible

---

Adams D., Dyson; P., Tavener, S.  *Chemistry in Alternative Reaction Media* 2004, John Wiley & Sons
Miscibility in Organic Solvents: Boiling Point And Density Data

Polarizability Data

- The boiling points of a hydrocarbon and the analog fluorocarbon are very similar despite the vast difference in molecular weight.
- The densities (g/L) of fluorocarbons are roughly twice those of the hydrocarbon analogs.
- Fluorocarbons have large intermolecular repulsive forces and very small intermolecular attractive forces.

![Solution Phase](image1)

![Gas Phase](image2)
## Commercially Available Solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Formula</th>
<th>Price ($/g)</th>
<th>Common Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfluorohexane</td>
<td>C₆F₁₄</td>
<td>123/500</td>
<td>FC-72</td>
</tr>
<tr>
<td>Perfluoroheptane</td>
<td>C₇F₁₆</td>
<td>157/500</td>
<td>FC-84</td>
</tr>
<tr>
<td>Perfluorooctane(s)</td>
<td>C₈F₁₈</td>
<td>168/500</td>
<td>FC-77</td>
</tr>
<tr>
<td>α,α,α-Trifluorotoluene</td>
<td>CF₃C₆H₅</td>
<td>-</td>
<td>Oxsol-2000</td>
</tr>
<tr>
<td>Perfluorotributylamine</td>
<td>C₁₂F₂₇N</td>
<td>167/500</td>
<td>FC-43</td>
</tr>
<tr>
<td>Perfluorotripentylamine</td>
<td>C₁₅F₃₃N</td>
<td>-</td>
<td>FC-71</td>
</tr>
<tr>
<td>Perfluoromethylcyclohexane</td>
<td>CF₃C₆F₁₁</td>
<td>125/100</td>
<td>PFMC</td>
</tr>
</tbody>
</table>

Prices from Oakwood Prod.

Fluorous Triphasic Synthesis
Vanishing Phase Reactions


60% Fluorine by weight generally needed to separate a compound by liquid extraction
Vanishing Phase Reaction: Bromination

\[ \text{Cyclohexene} \xrightarrow{\text{Br}_2, \text{hexane FC-77, rt. Dark 4 h, gentle stirring}} \text{Brominated Product} \]

90% yield

Hexane (d = 0.66)

C\textsubscript{6}F\textsubscript{14} (d = 1.67)

Br\textsubscript{2} (d = 3.12)

product

C\textsubscript{6}F\textsubscript{14} (d = 1.67)

A = triphasic system
B = completed reaction

Fluorous Triphasic Synthesis: Detagging Reaction

Kinetic Resolution with Fluorous Tagging

1. *Candida antarctica* B lipase
2. Filter and add to source phase

Detagging Reaction

from source phase
45% yield, 89% ee

from receiving phase
48% yield, 95% ee

Source Phase
MeOH
MeOH MeO-
FC-77

Receiving Phase
MeOH

stir 2-3 days
(R)-2
(S)-2

(RfCH₂CH₂CO₂Me)

MeOH


(S) - 1, 99% ee

(R) - 2, 91% ee

C₈F₁₇CH₂CH₂CO₂Bu, 3
Fluorous Biphasic Synthesis

Biphasic

Warm

Monophasic

Cool

Biphasic

Fluorous Phase Recycle

Fluorous in Green
Organic in Blue

Hydroformylation: Birth of FBS

- Produces terminal aldehydes from olefins with H_2 and CO in the presence of catalyst
- Industrial process with use of PPh_3-modified Rh catalyst
- Separation of higher C_n (n > 8) from catalyst is a problem

Hydroformylation Mechanism

\[
\text{R}=\text{H} \xrightarrow{\text{Addition}} \text{R}_2\text{HL}_3(\text{CO}) \xrightarrow{\text{Alkyl Migration}} \text{R}_2\text{H}_{\text{L}_2}\text{O}^+ \xrightarrow{\text{H}_2} \text{RCH}_2\text{CHO}
\]
# Synthesis of the Fluorous Rh Hydroformylation Catalyst

\[
\begin{align*}
\text{PH}_3 & \xrightarrow{\text{AIBN}} \text{P[R}^f\text{]}_3 & \xrightarrow{\text{Rh(CO)}_2(\text{acac})} \text{HRh(CO)}\{\text{P[R}^f\text{]}_3\}_3 \\
\text{CH}_2=\text{CH( CF}_2\text{)}_5\text{CF}_3 & \xrightarrow{80-85^\circ \text{C, 24h}} 53\% & \text{C}_6\text{F}_{11}\text{CF}_3 \\
\end{align*}
\]

\[R^f = \text{CH}_2\text{CH}_2(\text{CF}_2)_5\text{CF}_3\]

<table>
<thead>
<tr>
<th>Species</th>
<th># of Spacers</th>
<th>P Lone-Pair level eV</th>
<th>Protonation energy, eV</th>
<th>P-H, Å</th>
<th>Angle HPL, Deg</th>
</tr>
</thead>
<tbody>
<tr>
<td>P[(CF_2)_3CF_3]_3</td>
<td>0</td>
<td>-11.7</td>
<td>-6.4</td>
<td>1.192</td>
<td>85.9</td>
</tr>
<tr>
<td>P[CH_2CF_2CF_3]_3</td>
<td>1</td>
<td>-10.6</td>
<td>-7.7</td>
<td>1.205</td>
<td>86.3</td>
</tr>
<tr>
<td>P[(CH_2)_2CF_2CF_3]_3</td>
<td>2</td>
<td>-9.9</td>
<td>-8.3</td>
<td>1.218</td>
<td>92.3</td>
</tr>
<tr>
<td>P[(CH_2)_3CF_2CF_3]_3</td>
<td>3</td>
<td>-9.5</td>
<td>-8.6</td>
<td>1.225</td>
<td>91.8</td>
</tr>
<tr>
<td>P[(CH_2)_3CH_3]_3</td>
<td>0</td>
<td>-8.7</td>
<td>-9.3</td>
<td>1.230</td>
<td>91.7</td>
</tr>
</tbody>
</table>

Hydroformylation Catalyst Leaching

Dihydroxylation using a Fluorous Catalyst Recovery System

- The high cost of Osmium Tetroxide ($111.70/gram)
- The toxicity of Osmium Tetroxide
- Oral / mouse: LD$_{50} = 153$mg/kg
- Volatile
What is the OsO$_4$ catalyst?

Huang, Y; Meng, W. D.; Qing, F. L. *Tetrahedron Letters*, 2004, 45, 1965
Fluorous OsO$_4$ Dihydroxylation

\[
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\end{array}
\xrightarrow{\text{F-OsO}_4 \text{ (2 mol%), NMO (1.2 eq.)}}
\begin{array}{c}
\text{Ph} \\
\text{C} \\
\text{OH} \\
\end{array}
\]

<table>
<thead>
<tr>
<th>Organic Phase</th>
<th>Run 1</th>
<th>Run 2</th>
<th>Run 3</th>
<th>Run 4</th>
<th>Run 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t$-BuOH/H$_2$O (2:1)</td>
<td>100</td>
<td>94</td>
<td>79</td>
<td>55</td>
<td>45</td>
</tr>
<tr>
<td>$t$-BuOH/CH$_2$Cl$_2$/H$_2$O (10:5:1)</td>
<td>100</td>
<td>98</td>
<td>62</td>
<td>74</td>
<td>52</td>
</tr>
<tr>
<td>Acetone/H$_2$O (10:1)</td>
<td>98</td>
<td>92</td>
<td>87</td>
<td>53</td>
<td>53</td>
</tr>
<tr>
<td>$t$-BuOH/acetone/H$_2$O (10:5:1)</td>
<td>97</td>
<td>100</td>
<td>95</td>
<td>97</td>
<td>80</td>
</tr>
</tbody>
</table>

## Scope of the Fluorous Dihydroxylation

<table>
<thead>
<tr>
<th></th>
<th>Run 1</th>
<th>Run 2</th>
<th>Run 3</th>
<th>Run 4</th>
<th>Run 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>97</td>
<td>100</td>
<td>95</td>
<td>97</td>
<td>80</td>
</tr>
<tr>
<td>Ph Ph</td>
<td>100</td>
<td>99</td>
<td>94</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Ph Ph</td>
<td>98</td>
<td>96</td>
<td>95</td>
<td>99</td>
<td>94</td>
</tr>
<tr>
<td>Ph Ph</td>
<td>99</td>
<td>100</td>
<td>83</td>
<td>77</td>
<td>73</td>
</tr>
<tr>
<td>Ph Ph</td>
<td>97</td>
<td>95</td>
<td>94</td>
<td>93</td>
<td>81</td>
</tr>
<tr>
<td>Ph Ph</td>
<td>97</td>
<td>92</td>
<td>71</td>
<td>58</td>
<td>72</td>
</tr>
</tbody>
</table>

Fluorous Monophasic Synthesis
Fluorous Solvent-Free & Single Solvent

Organic Phase contains light fluoruous molecules

Monophasic

Fluorous or Organic Solvent

F-Solid Phase Extraction/ F-Flash Chromatograph

F-HPLC

Compound Library

Fluorous Reverse Solid Phase Extraction (FRSPE)

- Use of FluoroFlash silica gel (Si-(CH₃)₂CH₂CH₂C₈F₁₇)
- $39.50 for 2 grams and 8 cc tubes (25g/$139.00)
- HPLC columns: $407.50 (4.6mm i.d., 50mm, 5µm)

Curran D. *Synlett* **2001**, 9, 1488
Fluorous Swern and Corey-Kim Oxidations

Normal Swern [O]

\[
\text{R}^1\text{OH} \xrightarrow{\text{(COCl)}_2, \text{DMSO}} \text{R}^1\text{R}^2 \xrightarrow{\text{CH}_2\text{Cl}_2, -30^\circ \text{C, EtN(i-Pr)}_2} \text{R}^1\text{R}^2\text{O}
\]

Normal Corey-Kim

\[
\text{R}^1\text{OH} \xrightarrow{\text{NCS, DMS, then NEt}_3, \text{CH}_2\text{Cl}_2} \text{R}^1\text{R}^2
\]

Synthesis of fluorous DMSO

\[
\text{R}_f\text{I} \xrightarrow{\text{NaBH}_4, \text{Me}_2\text{S}_2 \text{ or NH}_2(\text{NH}=)\text{C}-\text{SO}_2\text{Me}_2\text{S}_2} \text{R}_f\text{S} \xrightarrow{\text{H}_2\text{O}_2, \text{MeOH, or mCPBA}} \text{R}_f\text{SO}_2\text{S}
\]

1: \( R_f = \text{C}_6\text{F}_{13} \)
2: \( R_f = \text{C}_4\text{F}_9 \)
3: \( R_f = \text{C}_6\text{F}_{13} \)
4: \( R_f = \text{C}_4\text{F}_9 \)
Usefulness of Fluorous Swern and Corey-Kim Oxidations

• Decent recovery of fluorous DMS or DMSO (70-90%)
• Reaction proceeds with the same mechanism (D-study)
• Odorless
A Fluorous Metathesis

Yao, Q.; Zhang, Y. J. Am. Chem. Soc. 2004, 126, 74
Hoveyda Recyclable Catalyst

- Separated by column chromatography
- Complete separation of product and catalyst is sometimes difficult due to coelution
- Good yields for monosubstituted olefins but problems with disubstituted

Synthesis of the Fluorous Metathesis Catalyst

\[
\text{2} + \text{3} \quad \text{(1 eq.)} \\
\text{2. DMAP, Et}_3\text{N, PhCF}_3
\]

5 (m/n ~ 10:1; loading: 0.19 mmol/g)

Yao, Q.; Zhang, Y. J. Am. Chem. Soc. 2004, 126, 74
Is the catalyst reusable?

<table>
<thead>
<tr>
<th>Ring Formation</th>
<th>Conversion (%)</th>
<th>% Conv</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-membered ring formation</td>
<td>1 to 16</td>
<td>&gt;98</td>
</tr>
<tr>
<td>7-membered ring formation</td>
<td>1 to 9</td>
<td>&gt;98</td>
</tr>
<tr>
<td>6-membered ring formation</td>
<td>1 to 5</td>
<td>&gt;98</td>
</tr>
</tbody>
</table>

Cat 1 (0.5-1 mol%) 
(1.19 v/v, 0.05 M) 
50°C, 1-2h

Yao, Q.; Zhang, Y. J. Am. Chem. Soc. 2004, 126, 74
## Activity of the Fluorous Ru-Catalyst

<table>
<thead>
<tr>
<th>Substrate / Product</th>
<th>Cat. Batch</th>
<th>Mol % of Cat.</th>
<th>Time</th>
<th>% Conv. (%Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E=CO₂Et</td>
<td>Batch A</td>
<td>2</td>
<td>1 h</td>
<td>&gt;98 [2], 98 [2], 95, 93, 92</td>
</tr>
<tr>
<td>Ts</td>
<td>Batch B</td>
<td>2</td>
<td>3 h</td>
<td>&gt;98 (94)</td>
</tr>
<tr>
<td>O-SO₂</td>
<td>Batch B</td>
<td>2</td>
<td>1.5 h</td>
<td>&gt;98 (90)</td>
</tr>
<tr>
<td>OBz</td>
<td>Batch B</td>
<td>2</td>
<td>1.5 h</td>
<td>&gt;98 (94)</td>
</tr>
<tr>
<td>Ts</td>
<td>Batch B</td>
<td>2</td>
<td>1.5 h</td>
<td>&gt;98 (96)</td>
</tr>
<tr>
<td>O-SO₂</td>
<td>Batch B</td>
<td>5</td>
<td>3 h</td>
<td>&gt;98 (91)</td>
</tr>
</tbody>
</table>

## Further Activity of Fluorous Ru-Catalyst

<table>
<thead>
<tr>
<th>Substrate / Product</th>
<th>Cat. Batch</th>
<th>Mol % of Cat.</th>
<th>Time</th>
<th>% Conv. (%Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph₂O₂C₂H₃</td>
<td>Batch C</td>
<td>2</td>
<td>2 h</td>
<td>&gt;98 (95)</td>
</tr>
<tr>
<td>Ph₂O₂C₂H₃</td>
<td>Batch D</td>
<td>5</td>
<td>6 h</td>
<td>43 (39)</td>
</tr>
<tr>
<td>Ph₂O₂C₂H₃</td>
<td>Batch E</td>
<td>2</td>
<td>2.5 h</td>
<td>96 (96)</td>
</tr>
</tbody>
</table>

Fluorous Metathesis Advantages

- Easily separated by liquid extraction
- Extremely reusable
- Using one batch of catalyst for different substrates is effective
- Tetrasubstituted products are accessible with small condition modifications
Mizoroki-Heck Reaction

\[
R-X + \overset{\text{Pd(0)}}{\text{Z}} \rightarrow R\text{-}Z \text{-}X
\]

\[\text{X} = \text{I, Br, OTf, etc.} \]
\[\text{Z} = \text{H, R, Ar, CN, CO}_2\text{R, OR, OAc, NHAc, etc.} \]

Li, J. J. *Name Reactions* 2nd Ed.; Springer: Ann Arbor, MI, 2003; p 179
A Fluorous Mizoroki-Heck

Before Heating

While Heating

After Reaction

Reusability of Fluorous Pd Catalyst

\[
\text{C}_6\text{F}_{13} + \text{C}_7\text{H}_7\text{COOH} \xrightarrow{\text{Fluorous Pd Catalyst}} \text{C}_7\text{H}_7\text{C}(\text{COOH})\text{C}_7\text{H}_7 + \text{NPr}_3, \text{F-626} \\
\xrightarrow{120 \degree C, 2 h} \text{F-626 solution containing fluorous Pd catalyst} \\
\xrightarrow{\text{Filtration}} \text{Product}
\]

<table>
<thead>
<tr>
<th></th>
<th>Run 1</th>
<th>Run 2</th>
<th>Run 3</th>
<th>Run 4</th>
<th>Run 5</th>
<th>Run 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product</td>
<td>88%</td>
<td>85%</td>
<td>83%</td>
<td>84%</td>
<td>78%</td>
<td>83%</td>
</tr>
<tr>
<td>F-626</td>
<td>98%</td>
<td>97%</td>
<td>93%</td>
<td>96%</td>
<td>95%</td>
<td>94%</td>
</tr>
</tbody>
</table>

### Scope of Fluorous Mizoroki-Heck

<table>
<thead>
<tr>
<th>Halide</th>
<th>Olefin</th>
<th>Product</th>
<th>Yield (%)</th>
<th>F-626 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Halide 1" /></td>
<td><img src="image2" alt="Olefin 1" /></td>
<td><img src="image3" alt="Product 1" /></td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td><img src="image4" alt="Halide 2" /></td>
<td><img src="image5" alt="Olefin 2" /></td>
<td><img src="image6" alt="Product 2" /></td>
<td>56, $E/Z = 93:7$</td>
<td>97</td>
</tr>
<tr>
<td><img src="image7" alt="Halide 3" /></td>
<td><img src="image8" alt="Olefin 3" /></td>
<td><img src="image9" alt="Product 3" /></td>
<td>47, $E/Z = 94:6$</td>
<td>98</td>
</tr>
<tr>
<td><img src="image10" alt="Halide 4" /></td>
<td><img src="image11" alt="Olefin 4" /></td>
<td><img src="image12" alt="Product 4" /></td>
<td>74</td>
<td>95</td>
</tr>
</tbody>
</table>

The Ideal Transesterification

\[ \text{RCOOR'} + \text{R''OH} \rightleftharpoons \text{RCOOR''} + \text{R'OHH} \]

- Quantitative yields
- Atom economical (1:1 ester to alcohol ratio)
- Mild, recyclable catalyst
- Easy removal of co-product alcohol
- Large variety of substrates
- Non-equilibrium process
Distannoxane Catalyst in Transesterification
Solubility of the Distannoxane Catalyst

Nonpolar Soluble Distannoxane

A "reverse micelle"
How Ideal is the Distannoxane Transesterification

- Requires 2 equivalents of alcohol
- Sensitive to steric bulk at the $\alpha$-carbon of the ester
- Near quantitative yields for non-sterically hindered substrates
- Co-product alcohol removed by biphasic system (benzene and small alcohols are partially miscible)
- Mild conditions, but not recyclable
Reasons for the Steric Problems of the Distannoxane Catalyst
Distannoxane Fluorous Transesterification Catalyst

![Chemical structure of Distannoxane Fluorous Transesterification Catalyst](image)

<table>
<thead>
<tr>
<th>Organic Solvent</th>
<th>Partition (FC-72/organic Solvent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>toluene</td>
<td>~100:0</td>
</tr>
<tr>
<td>benzene</td>
<td>~100:0</td>
</tr>
<tr>
<td>hexanes</td>
<td>~100:0</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>99:1</td>
</tr>
<tr>
<td>MeOH</td>
<td>98:2</td>
</tr>
<tr>
<td>acetone</td>
<td>97:3</td>
</tr>
<tr>
<td>THF</td>
<td>96:4</td>
</tr>
</tbody>
</table>

Evaluation of the Fluorous Distannoxane in Transesterification

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>mol (%) cat.</th>
<th>GLC Yield (%)</th>
<th>Catalyst recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>&gt;99</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>&gt;99</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>none</td>
<td>65</td>
<td>-</td>
</tr>
</tbody>
</table>
**Use of F-Alkyltin Catalyst (1:1 Ester to Alcohol)**

\[
\begin{align*}
\text{RCOOR'} + \text{R''OH} & \quad \xrightarrow{\text{F-Distannoxane, FC-77}} \quad \text{RCOOR''} + \text{R'O}H \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>RCOOR'</th>
<th>R''OH</th>
<th>GLC (%)</th>
<th>Isolated (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph(CH(_2))(_2)COOMe</td>
<td>PhCH=CHCH(_2)OH</td>
<td>&gt;99</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Ph(CH(_2))(_2)COOEt</td>
<td>PhC≡CCH(_2)OH</td>
<td>&gt;99</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>&quot; &quot;</td>
<td>C(<em>8)H(</em>{17})OH</td>
<td>&gt;99</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>&quot; &quot;</td>
<td>geraniol</td>
<td>&gt;99</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>&quot; &quot;</td>
<td>THPO(CH(_2))(_8)OH</td>
<td>&gt;99</td>
<td>99</td>
</tr>
<tr>
<td>6</td>
<td>&quot; &quot;</td>
<td>&quot; &quot;</td>
<td>&gt;99</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>&quot; &quot;</td>
<td>2-octanol</td>
<td>&gt;99</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>&quot; &quot;</td>
<td>cyclohexanol</td>
<td>&gt;99</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>&quot; &quot;</td>
<td>menthol</td>
<td>&gt;99</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>&quot; &quot;</td>
<td>borneol</td>
<td>&gt;99</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>PhCH=CHCOOEt</td>
<td>PhCH=CHCH(_2)OH</td>
<td>&gt;99</td>
<td>99</td>
</tr>
<tr>
<td>12</td>
<td>PhCOOEt</td>
<td>&quot; &quot;</td>
<td>&gt;99</td>
<td>100</td>
</tr>
<tr>
<td>13</td>
<td>PhCOOMe</td>
<td>&quot; &quot;</td>
<td>&gt;99</td>
<td>100</td>
</tr>
</tbody>
</table>
How Ideal is the Fluorous Distannoxane Catalyst

- Still, suffers from steric issues at the $\alpha$-carbon (catalyst problem)
- No loss of chirality at the $\alpha$ carbon (catalyst benefit)
- Mild conditions and quantitatively recyclable
- Better liberation of coproduct alcohol in the fluororous solvent
- Very atom economical, alcohol to ester ratio is 1:1
Distannoxane Catalyst and Esterification

- Alcohol to Acid Ratio was 30:1
- Same steric problems as transesterification
- Non-sterically hindered substrates showed $\leq 90\%$ yield
- Not an equilibrium process so removal of water is not necessary
Fluorous Distannoxane Catalyst in Esterification

- Repeat of catalyst steric issues
- 1:1 alcohol/acid ratio
- For non-sterically hindered substrates, >99% conversion and >98% yield
- Recoverable catalyst

<table>
<thead>
<tr>
<th>run</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>99.8</td>
</tr>
<tr>
<td>2</td>
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<td>6</td>
<td>99.8</td>
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<td>7</td>
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<tr>
<td>8</td>
<td>99.7</td>
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<tr>
<td>9</td>
<td>99.5</td>
</tr>
<tr>
<td>10</td>
<td>99.6</td>
</tr>
</tbody>
</table>
Conclusion

• Perfluorocarbon immiscibility

• Triphasic Reactions
  – Vanishing: slow addition
  – Detagging: separation and deprotection in one step

• Biphasic Reactions
  – Hydroformylation: recyclable catalyst and easy separation of products
  – Dihydroxylation: recovery of toxic, expensive catalyst

• Monophasic Reactions
  – Metathesis: improved immobiliation and separation of Hoveyda’s catalyst
  – (Trans)esterification: 1:1 alcohol to (ester)acid ratio
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- Dr. Ned Jackson
- Dr. Mitch Smith
- Fluorous Technologies, Inc