Overview

1. The role of DMAP

2. Amide formations
   i. Carbodimides
   ii. Mixed anhydrides of carbon
   iii. Acyl azides & cyanides
   iv. Mixed anhydrides of phosphorus
   v. Pentafluorophenyl esters
   vi. Phosphonium & aminium reagents
   vii. Acid fluorides
   viii. Obscurities

3. The coupling of hindered amino acids

4. Complex peptide synthesis:
   i. Didemnin
   ii. Microcystin LA

Lead References:
K. Devries, Evans group Friday seminar, 4/9/91
Pentafluorophenyl Esters

Preactivation method:

\[
\begin{align*}
\text{Pentafluorophenyl Acetate} & \xrightarrow{\text{DCC/PFPOH or PFP- Trifluoroacetate pyr.}} \text{Stable, Isolable Active Ester} \\
& \xrightarrow{H_2NR} \text{Product}
\end{align*}
\]

Green Tet. Lett. 1990, 31, 5851

Joullie Tet. Lett. 1998, 39, 7211

Schmidt Chem. Commun. 1994, 1003
Pentafluorophenyl Esters

\[
\begin{array}{c}
\text{FDPP, DIEA, } H_2NR' \\
\text{DMF, room temp.} \\
\rightarrow \\
\text{R - NHR'}
\end{array}
\]

Xu *Tet. Lett.* **1991**, *32*, 6711


Pentafluorophenyl Esters

Shioiri Tet. Lett. 1996, 37, 2261

Ulrich Schmidt Chem. Commun. 1994, 2381

<table>
<thead>
<tr>
<th>Coupling agent</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDC/HOBt</td>
<td>16</td>
</tr>
<tr>
<td>DPPA</td>
<td>8</td>
</tr>
<tr>
<td>DEPC</td>
<td>12</td>
</tr>
<tr>
<td>PFP ester</td>
<td>8</td>
</tr>
<tr>
<td>FDPP (^{*})</td>
<td>57</td>
</tr>
</tbody>
</table>

\(^{*}\) FDPP, i-Pr₂NEt, DMF, r.t. 14h

<table>
<thead>
<tr>
<th>Coupling agent</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPPA</td>
<td>low</td>
</tr>
<tr>
<td>FDPP</td>
<td>60</td>
</tr>
<tr>
<td>HATU</td>
<td>50</td>
</tr>
<tr>
<td>PFP ester</td>
<td>85</td>
</tr>
</tbody>
</table>

\(^{*}\) CHCl₃-NaHCO₃, room temp. 5h

Coupling agent
Phosphonium Reagents

Highly active coupling reagents with "built-in" additive:

- HOAt derivatives invariably preform better than the corresponding HOBt derivatives
- Pyrollidine derivatives generally preform better than the corresponding dimethylamino derivatives

Pentafluorophenyl Esters

The "first" in situ activation method:

Synthesized in 13 steps on solid phase (tentagel) in an overall yield of 76% (98%/step):
(Hunig's base, collidine, PyPyU, NMP)


Phosphonium Reagents

Carpino Chem. Commun. 1994, 201
Aminium Reagents

\[
\begin{array}{c}
\text{RO} \\
\text{O}_{\text{H}} \\
\text{O}_{\text{R}} \\
\end{array}
\]

Aminium reagent
amine base

\[
\begin{array}{c}
\text{RO} \\
\text{O}_{\text{H}} \\
\text{O}_{\text{R}} \\
\end{array}
\]

• Higher reactivity than carbodiimide reagents
• Added base is necessary
• HOAt derivatives invariably perform better than the corresponding HOBt derivatives
• Pyrrolidine derivatives generally perform better than the corresponding dimethylamino derivatives

Knorr Tet. Lett. 1989, 1927

Aminium Salt Couplings — Effects of the Amine Base

<table>
<thead>
<tr>
<th>Aminium Salt</th>
<th>DIEA</th>
<th>NMM</th>
<th>Pyridine</th>
<th>collidine</th>
<th>lutidine</th>
<th>DMAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBPyU</td>
<td>10.7</td>
<td>5.7</td>
<td>7.7</td>
<td>0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HATU</td>
<td>2.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAPyU</td>
<td>2.3</td>
<td>1.7</td>
<td>6.2</td>
<td>0.1</td>
<td>0.6</td>
<td>10.4</td>
</tr>
<tr>
<td>HBPyU</td>
<td>26.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HATU</td>
<td>6.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HAPyU</td>
<td>6.3</td>
<td>5.9</td>
<td>0.1</td>
<td>2.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

% Racemization for 2+1 segment coupling of Z-Phe-Val-Ala-OMe in DMF

<table>
<thead>
<tr>
<th>Aminium Salt</th>
<th>Additive</th>
<th>NMM (2 equiv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAPyU</td>
<td>none</td>
<td>12.2</td>
</tr>
<tr>
<td>HAPyU</td>
<td>HOAt</td>
<td>3.3</td>
</tr>
</tbody>
</table>

% Racemization for 2+1 segment coupling of Z-Phe-Val-Pro-\(t\)-Bu in DMF

% Racemization for 2+1 segment coupling of Z-Phe-Val-Pro-NH\(_2\) in DMF

• Added HOAt/HOBt is shown to have a deliterious effect for solid phase coupling reactions

Amino Acid Fluorides

Acid Fluoride Formation:

- Bench stable compounds for most Fmoc-protected amino acids
- Do not form oxazolone intermediates in the presence of tertiary amines
- Relatively unreactive to neutral oxygen nucleophiles
- React readily with anionic oxygen nucleophiles and neutral amines
- Silicon protecting groups are problematic


For segment condensations, HOAt is needed to suppress racemization:

Carpino Chem. Lett. 1998, 671
Amino Acid Fluorides

\[
\begin{align*}
\text{PhN} & \quad \text{H$_2$N-CO$_2$Me} \\
\text{R} & \quad \textrm{DIEA} \\
\text{H} & \quad \text{PhN} \\
\text{X} & \quad \text{CO$_2$Me}
\end{align*}
\]

\[
\begin{array}{|c|c|c|}
\hline
X & \text{equiv of DIEA} & \% \text{Conversion} \\
\hline
F & 0 & 100^* \\
F & 1 & 100 \\
Cl & 0 & 50 \\
Cl & 1 & 100 \\
\hline
\end{array}
\]

* Reaction rate is only slightly retarded

- No-base approach has been shown to be general for both solid- and solution-phase couplings
- No epimerization is observed

Carpino, Chem. Commun. 1995, 669

Acid Fluorides — Racemization

\[
\begin{align*}
\text{PhN} & \quad \text{HN-CO$_2$R} \\
\text{R} & \quad \text{Solvent, base} \\
\text{H} & \quad \text{PhN} \\
\text{O} & \quad \text{CO$_2$R}
\end{align*}
\]

\[
\begin{array}{|c|c|c|}
\hline
\text{Solvent} & \text{base} & \% \text{epimer} \\
\hline
\text{DMF} & \text{DIEA} & 19.0 \\
\text{DMF} & \text{collidine} & 11.6 \\
\text{CH$_2$Cl$_2$} & \text{collidine} & <0.1 \\
\hline
\end{array}
\]

- Highly racemization-prone amino acids still require carefully controlled conditions

Segment Couplings

Z-Phe-Val-Pro-NH$_2$ via 2+1 segment coupling in DMF

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Base (equiv)</th>
<th>% Yield</th>
<th>% epimer</th>
<th>Reagent</th>
<th>Base (equiv)</th>
<th>% Yield</th>
<th>% epimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDC/HOAt</td>
<td>85</td>
<td>4.7</td>
<td></td>
<td>HATU/HOAt</td>
<td>DIEA (2)</td>
<td>76</td>
<td>10.9</td>
</tr>
<tr>
<td>EDC/HOBt</td>
<td>87</td>
<td>18.9</td>
<td></td>
<td>HATU/HOAt</td>
<td>DIEA (3)</td>
<td>88</td>
<td>15.8</td>
</tr>
<tr>
<td>EDC/EDCI_ht</td>
<td>89</td>
<td>7.3</td>
<td></td>
<td>HATU/HOAt</td>
<td>TMP (2)</td>
<td>72</td>
<td>2.4</td>
</tr>
<tr>
<td>EDC/EDCI/HT</td>
<td>TMP (1)</td>
<td>89</td>
<td>5.3</td>
<td>HATU/HOAt</td>
<td>TMP (3)</td>
<td>87</td>
<td>4.5</td>
</tr>
<tr>
<td>EDC/EDCI/HT</td>
<td>TMP (1)</td>
<td>87</td>
<td>19.9</td>
<td>HAPyU</td>
<td>TMP (2)</td>
<td>87</td>
<td>3.5</td>
</tr>
<tr>
<td>HATU</td>
<td>TMP (2)</td>
<td>83</td>
<td>5.3</td>
<td>HAPyU/HTOAt</td>
<td>TMP (2)</td>
<td>76</td>
<td>1.6</td>
</tr>
<tr>
<td>HATU</td>
<td>DIEA (2)</td>
<td>86</td>
<td>13.9</td>
<td>HAPyU/HTOAt</td>
<td>TMP (3)</td>
<td>89</td>
<td>2.3</td>
</tr>
<tr>
<td>HBTU</td>
<td>TMP (2)</td>
<td>81</td>
<td>14.2</td>
<td>HAPyU/HTOAt</td>
<td>DIEA (2)</td>
<td>77</td>
<td>3.2</td>
</tr>
<tr>
<td>BOP</td>
<td>TMP (2)</td>
<td>81</td>
<td>13.9</td>
<td>HAPyU/HTOAt</td>
<td>DIEA (3)</td>
<td>90</td>
<td>12.1</td>
</tr>
</tbody>
</table>

Carpino J. Org. Chem 1995, 60, 3561

Obscurities — Couplings with kinetic resolution

<table>
<thead>
<tr>
<th>Coupling partners (substrate ratio)</th>
<th>% Yield</th>
<th>ee or de</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-Gly-OH + D.L-Ala-OEt (1:2)</td>
<td>87</td>
<td>93 (L)</td>
</tr>
<tr>
<td>Z-D.L-Ala-OH + Gly-OEt (2:1)</td>
<td>86</td>
<td>100 (L)</td>
</tr>
<tr>
<td>Z-D.L-Ala-OH + L-Leu-OMe (2:1)</td>
<td>72</td>
<td>100 (L,L)</td>
</tr>
<tr>
<td>Z-D.L-Ala-OH + L-Phe-OEt (2:1)</td>
<td>75</td>
<td>100 (L,L)</td>
</tr>
</tbody>
</table>

*Kaminski Synthetic Communications 1998, 28, 2689*
Secondary Amine Coupling

More Powerful activation is needed for Secondary Amines:

\[
\begin{align*}
\text{R}^1\text{H} & \quad \text{+ MeCO\textsubscript{2}Me} \\
\text{Coupling agent} & \\
\text{R}^2\text{Me} & \quad \text{R}^1\text{H} \quad \text{MeCO\textsubscript{2}Me}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Sequence</th>
<th>% Yield (hours) PPyBOP</th>
<th>% Yield (hours) PPyBroP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-MeVal-Val-OMe</td>
<td>90 (1)</td>
<td>85 (1)</td>
</tr>
<tr>
<td>Z-Val MeVal-OMe</td>
<td>11 (1)</td>
<td>70 (1)</td>
</tr>
<tr>
<td>Fmoc-Val MeVal-OMe</td>
<td>30 (24)</td>
<td>84 (3)</td>
</tr>
<tr>
<td>Boc-Val MeVal-OMe</td>
<td>45 (24)</td>
<td>44 (3)</td>
</tr>
</tbody>
</table>

CH\textsubscript{2}Cl\textsubscript{2}, DIEA, room temp.

Obscurities — Polymer-bound coupling reagents

\[
P\text{-Xxx-OH} \quad \text{+ H-Yyy-OR} \quad \text{Resin} \quad \text{PF\textsubscript{6}}^- \quad \text{Br}^- \\
\text{imidazole, CH\textsubscript{2}Cl\textsubscript{2}} \quad \text{25 \degree C, 2 hr, 90-99\%} \\
P\text{-Xxx-Yyy-OR}
\]

<table>
<thead>
<tr>
<th>P</th>
<th>Xxx</th>
<th>Yyy</th>
<th>R</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fmoc</td>
<td>Ala</td>
<td>Leu</td>
<td>Ally</td>
<td>99</td>
</tr>
<tr>
<td>Cbz</td>
<td>Met</td>
<td>Ala</td>
<td>Me</td>
<td>98</td>
</tr>
<tr>
<td>Boc</td>
<td>Leu</td>
<td>Phe</td>
<td>tBu</td>
<td>95</td>
</tr>
<tr>
<td>Fmoc</td>
<td>Val</td>
<td>Val</td>
<td>Ally</td>
<td>99</td>
</tr>
<tr>
<td>Fmoc</td>
<td>Cys(Tri)</td>
<td>Cys(Tri)</td>
<td>Me</td>
<td>95</td>
</tr>
<tr>
<td>Boc</td>
<td>Trp</td>
<td>Leu</td>
<td>Me</td>
<td>94</td>
</tr>
</tbody>
</table>

* Authors propose an acyl iodide as the active species

Caputo et. al. Synthesis 1995, 141
Phosphonium Reagents — Active Coupling Species

For PyBroP, the "active ester" is a mixture of species:

Secondary Amine Coupling: Side-product Pathways

Coste Tet. Lett. 1992, 33, 2815
Secondary Amine Couplings

An electron-poor HOBt additive can increase reactivity:

<table>
<thead>
<tr>
<th>Sequence</th>
<th>% Yield PyBroP</th>
<th>CF$_3$-NO$_2$-PyBOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-Val-Val-OMe</td>
<td>89</td>
<td>98</td>
</tr>
<tr>
<td>Z-Val-MeVal-OMe</td>
<td>49</td>
<td>76</td>
</tr>
<tr>
<td>Fmoc-Val MeVal-OMe</td>
<td>57</td>
<td>85</td>
</tr>
<tr>
<td>Boc-Val MeVal-OMe</td>
<td>25</td>
<td>62</td>
</tr>
<tr>
<td>Boc-MeLeu MeLeu-OMe</td>
<td>47</td>
<td>87</td>
</tr>
<tr>
<td>Z-MeVal MeVal-OMe</td>
<td>22</td>
<td>71</td>
</tr>
</tbody>
</table>

CH$_2$Cl$_2$, DIEA, room temp., 1 hr

Bloemhoff Tet. Lett., 1995, 36, 4643

α,α-Dialkylamino Acids

<table>
<thead>
<tr>
<th>Sequence</th>
<th>% Yield PyBOP</th>
<th>BOP</th>
<th>BroP</th>
<th>PyBroP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-Ab-Gly-OMe</td>
<td>92</td>
<td>87</td>
<td>89</td>
<td>87</td>
</tr>
<tr>
<td>Z-Ab-Val-OMe</td>
<td>88</td>
<td>87</td>
<td>84</td>
<td></td>
</tr>
<tr>
<td>Z-Ab-Pro-OtBu</td>
<td>82</td>
<td>84</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Z-Ab-Alb-OMe</td>
<td>89</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boc-Ab-Alb-OMe</td>
<td>80</td>
<td>76</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

*With added DMAP

• Ab-Alb coupling is still sluggish — reaction times are 16 to 24 hours
• While good yields can be obtained, sluggish and varied reaction conditions make this unsuitable for solid phase

Coste Tetrahedron 1991, 47, 259
DMAP Acylation Catalysis

\[
\text{Me} = O \quad \text{Ac}_2O, \text{base} \quad \text{CDCl}_3, 27^\circ C \quad \text{Me} = O \quad \text{Ac}_2O
\]

General Base Acceleration:

Steglich ACIE 1978, 17, 569

DMAP — Equilibrium Concentrations

\[
\text{Me} = O \quad \text{Pyridine} \quad \text{Me} = O \quad \text{X}\quad \text{Pyridinium in solution}
\]

\[
\begin{array}{|c|c|c|}
\hline
\text{Base} & \text{Acylation Reagent} & t\frac{1}{2} (\text{min}) \\
\hline
\text{DMAP} & \text{Ac}_2O & 7 \\
\text{DMAP} & \text{AcCl} & 20 \\
\text{pyridine} & \text{Ac}_2O & 1000 \\
1:1 \text{pyridine:NEt}_3 & \text{Ac}_2O & 1000 \\
\hline
\end{array}
\]

\[
\text{X} \quad \text{Cl} \quad >95 \\
\text{X} \quad \text{OAc} \quad 5-10
\]

\text{CDCl}_3, \text{room temperature}
α,α-Dialkylamino Acids

Aminium salts and acid fluorides for solid-phase α,α-dialkyl and N-methylamino acid synthesis:

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Sequence purity</th>
</tr>
</thead>
<tbody>
<tr>
<td>HATU</td>
<td>94%</td>
</tr>
<tr>
<td>TFFH</td>
<td>92%</td>
</tr>
<tr>
<td>HBTU</td>
<td>43%</td>
</tr>
</tbody>
</table>

7 min. activation, 30 min. coupling in DMF

\[ \text{H-Tyr-Aib-Aib-Phe-Leu-NH}_2 \]

\[ \text{H-D- Ala-MeLeu-MeLeu-MeVal-Phe-Val-OH} \]

Carpino, Chem. Commun. 1994, 201

---

Peptaibols

- Bioactive linear peptide sequences
- Sequences are approx. 20 residues and contain unusually high amounts of α,α-dialkylamino acids
- Aib-Pro linkages are acid sensitive (cleaved by TFA)

\[ \text{Ac-Alb-Pro-Aib-Ala-Alb-Ala-Gln-Alb-Val-Alb-Gly-Leu-Alb-Pro-Val-Alb-Alb-Glu-Gln-Pheol} \]

alamethicin F-30

Synthesized on solid phase via Fmoc-amino acid fluorides in 78% purity

\[ \text{Ac-Alb-Ala-Alb-Leu-Alb-Gln-Alb-Alb-Alb-Alb-Pro-Leu-Alb-Iva-Gln-Valol} \]

trichotoxin A-50

Synthesized on solid phase via Fmoc-amino acid fluorides in 60% purity

Didemnin

\[
\begin{align*}
1. & \text{ PFPOH, DCC, DMAP} \\
2. & \text{ Pd/C, 4-PPY, 95 °C} \\
& \text{72%}
\end{align*}
\]

- FDPP, BOP and HBTU were unsuccessful

\[
\begin{align*}
\text{DPPA, 0 °C, 72h, 42%} \\
\text{or} \\
\text{FDPP, room temp. 4h, 68%}
\end{align*}
\]

\[
\begin{align*}
\text{FDPP, 30%} \\
\text{or} \\
\text{HBTU, 50%}
\end{align*}
\]

cyclized product

Didemnin

HBTU/HOBt - Stepwise coupling

DIC/DMAP - Segment coupling

DIC/DMAP/CF₃COOH - Stepwise coupling

HATU/HOAt - Macrolactamization

R = TBS, R' = Boc-(R)-N(Me)-Leu-OH: 28% yield

R = H, R' = H: 76% yield

Cyclized product, 1 isomer

Overview

Stepwise couplings:
Standard amino acids — EDC/HOBt. DEPC, or BOP are also good choices
Racemization-prone amino acids — If EDC/HOBt is insufficient, try EDC/HOAi or HATU/collidine

Segment couplings:
Phosphonium or aminium salts are good choices, HOAi/pyrrolidine derivatives for the difficult cases

Macrolactamizations:
FDPP/PFP esters, DPPA and HAPyU/collidine are good bets

Hindered couplings:
Acid fluorides and HAPyU/collidine are good choices. PyBroP and BOP-Cl work for solution phase.
**DMAP Acylation Catalysis**

B1 and B2 are observable by $^1$H NMR in CDCl$_3$ or CD$_2$Cl$_2$ at low temperature

- Rate of pyridinium-acylations is tied to:
  - Concentration/solubility
  - Identity of counterion
  - Tightness of ion pair
DMAP Acylation Catalysis

A Reactivity Reversal:

\[
\text{DMAP Acylation Catalysis}
\]

Rate of pyridinium-acylations is tied to:

- Tightness of ion pair
- Concentration/solubility
- Identity of counterion

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   i. Carbodiimides
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   v. Pentafluorophenyl esters
   vi. Phosphonium & aminium reagents
   vii. Acid fluorides
   viii. Obscurities
3. The coupling of hindered amino acids
4. Complex peptide synthesis:
   i. Didemnin
   ii. Microcystin LA
Carbodiimide Activation

Sheehan J. Am. Chem. Soc. 1955, 77, 1067
Rebek J. Am. Chem. Soc. 1973, 95, 4052

Carbodiimides — Reaction Pathways

O-acyl urea

symmetrical anhydride

stabilized active ester

oxazolone

increased racemization

N-acyl urea

HOBt
Modern Advances in Coupling Additives

Racemization Pathways

- Direct deprotonation of active esters does occur, but oxazolone formation is the major racemization pathway.
- Carbamate-protected amines help suppress oxazolone formation and deprotonation.
- Amide "amino-protection" is the main reason for increased racemization in segment couplings.

Most common coupling additives:

<table>
<thead>
<tr>
<th>Additive</th>
<th>Formula</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HOAt</td>
<td><img src="HOAt.png" alt="Formula" /></td>
<td>Decreased racemization vs. HOBt but more side-reactions</td>
</tr>
<tr>
<td>HODhbt</td>
<td><img src="HODhbt.png" alt="Formula" /></td>
<td>Decreased racemization vs. HOBt but more side-reactions</td>
</tr>
<tr>
<td>HOBt</td>
<td><img src="HOBt.png" alt="Formula" /></td>
<td>Decreased racemization vs. HOBt but more side-reactions</td>
</tr>
</tbody>
</table>

Z-Phg-Pro-NH₂ formation in DMF:

<table>
<thead>
<tr>
<th>Reagent</th>
<th>% Yield</th>
<th>% epimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDC/HOAt</td>
<td>81</td>
<td>7</td>
</tr>
<tr>
<td>EDC/HOBt</td>
<td>80</td>
<td>25</td>
</tr>
<tr>
<td>EDC/HODhbt</td>
<td>82</td>
<td>10</td>
</tr>
</tbody>
</table>

- HOAt has the advantage of internal base acceleration.

Carpino, J. Org. Chem. 1995, 60, 3561
Mixed Anhydrides of Carbon

In situ generation (no preactivation) of mixed anhydrides:

- No additional base is necessary

Yajima Chem. Commun. 1972, 942
Belleau J. Am. Chem. Soc. 1968, 90, 1651
DPPA and DEPC

- Tends to be used for macrocyclizations
- Tends to be used for stepwise couplings

\[
\begin{align*}
\text{R-O} & \xrightarrow{\text{DPPA}} \text{R-O(DPh)_{2}} \\
& \xrightarrow{\text{N}_3^-} \text{R-N}_3
\end{align*}
\]

- Curtius rearrangement is slow relative to coupling
- Acyl azide relatively unreactive to non-amine nucleophiles

\[
\begin{align*}
\text{R-CH} & \xrightarrow{\text{DEPC}} \text{R-CH(OEt)_{2}} \\
& \xrightarrow{\text{CN}^-} \text{R-CN}
\end{align*}
\]

active species

Yamada J. Am. Chem. Soc. 1972, 94, 6203
Yamada Tet. Lett. 1973, 1595

DPPA

\[
\begin{align*}
\text{Conditions} & \xrightarrow{\text{Method}} \text{Product}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Method</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPPA</td>
<td>71</td>
</tr>
<tr>
<td>BOP</td>
<td>49</td>
</tr>
<tr>
<td>DCC, HOBt</td>
<td>31</td>
</tr>
</tbody>
</table>

Pritchard Tetrahedron 1992, 48, 8471
**BOP-Cl Activation**

- Mixed anhydride intermediate is very reactive and will form both esters and amides
- Less prone to side-reactions than chloroformate-based anhydrides
- Active enough to couple N-alkyl amino acids, but requires long reaction times

\[
\text{R} \overset{\text{BOP-Cl, DIEA, } \text{CH}_2\text{Cl}_2}{\longrightarrow} \text{R} \overset{\text{H}_2\text{NR}^+ \text{ (or HOR)}\text{, } \text{BOP-Cl}}{\longrightarrow} \text{R} \overset{\text{NH}_{\text{R}^+}}{\longrightarrow}
\]

*Active acylating species*

---

**BOP-Cl Macrolactamization**

- A. Palomo-Coll *Synthesis* 1980, 547

\[
\text{BOP-Cl Activation:}
\text{BOP-Cl, DIEA, } \text{CH}_2\text{Cl}_2 \\
\text{BOP-Cl, DIEA, } \text{BOP-Cl} \\
\text{Active acylating species}
\]

\[
\text{BOP-Cl Macrolactamization:}
\text{BOP-Cl, DIEA, } \text{BOP-Cl} \\
\text{DCC, DEPC, DPPA fail}
\]

---
