Reductive Coupling of Alkynes

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6/1/04
**Introduction to Three-Component Coupling**

How do we effect activation of the alkyne

\[
\begin{align*}
\text{R}^1 & \equiv \text{R}^2, \\
\text{Nu} & \rightarrow \text{Ni}(0)/\text{phosphine catalyst} \\
& \rightarrow \text{Nu} \text{El}
\end{align*}
\]

How do we control the regioselectivity

\[
\begin{align*}
\text{R}^1 & \equiv \text{R}^2, \\
\text{M} & \rightarrow \text{R}^1 \equiv \text{R}^2 \\
& \rightarrow \text{R}^1 \equiv \text{R}^2
\end{align*}
\]

How do we catalytically couple two different functional groups

\[
\begin{align*}
\text{C} & \equiv \text{C}, \\
\text{Me} & \equiv \text{Me}
\end{align*}
\]


Intramolecular Coupling of an Enone, Alkyne, and Organozinc

These methods generate alklidene cyclopentanes

Coupling of Enone, Alkyne, and Organozinc Mechanism

Proposed mechanism involves formation of metallacycle

Coupling of Two Enones and an Alkyne

[2+2+2] cycloaddition proceeds in the absence of organozinc

Montgomery, J. et. al. J.A.C.S. 1999, 121, 476
Mechanism of Two Enones and Alkyne

Montgomery, J. et. al. J.A.C.S. 1999, 121, 476
Coupling of an Aldehyde, Alkyne, and Organozinc or Silane

\[
\text{PhCHO} + \text{R}^1\text{CN} + \text{R}^2\text{Li} / \text{ZnCl}_2 \xrightarrow{\text{Ni(COD)}_2} \text{PhCN} \text{R}^1
\]

R\(^1\) = hex, R\(^2\) = Bu (74%)
R\(^1\) = Ph, R\(^2\) = Me (60%)

Triethylsilane proved to be an effective reducing agent

Qi, X., Montgomery, J. J. Org. Chem. 1999, 64, 9310
Intramolecular cyclization of allenes generate substituted homoallylic alcohols

Scope of Allene Aldehyde Coupling

Cis isomer preferred in all cases

Mechanism of Allene Aldehyde Coupling


There are two potential mechanistic pathways
Total Synthesis of (+)-Testudinariol A

Ni-cat cyclization of allenyl aldehydes assembled the cyclopentanol framework

Montgomery, J., Amarsinghe, K.K.D. J.A.C.S. 2002, 124, 9366
**Proposed Mechanism of Cyclization**

The mechanism proceeds through a Ni(0)-complex π-complex 8

Montgomery, J., Amarsinghe, K.K.D. J.A.C.S. **2002**, 124, 9366
Catalytic Intermolecular Coupling

Heterocyclic carbene provide three-component addition of terminal and internal alkynes to aldehydes

Montgomery, J. et. al. J.A.C.S. 2004, 126, 3698
The combination of crossover experiments demonstrates that mechanism of the two procedures differ.

Proposed Mechanism from Crossover

Experiments with PBu₃ involve either a nickel hydride or nickel silyl species.

Experiments with NHC involve formation of the metallacycle followed by σ-bond metathesis.

Selective Intermolecular Coupling of Alkynes and Aldehydes

Allylic alcohols were achieved with good yield and conditions are highly (E)-selective.

Effect of Phosphine and Scope

Smaller trialkylphosphines exhibited the highest regioselectivity.

No trace of (Z)-isomer observed.
Catalytic Asymmetric Reductive Coupling

\[
R_1\equiv R_2 + H\text{C}R_3 \xrightarrow{\text{Ni(COD)\textsubscript{2} (10 mol\%)} \atop (+)-NMDPP (20 mol\%)} \xrightarrow{\text{Et\textsubscript{3}B (200 mol\%)} \atop \text{EtOAc:DMI (1:1)}} R_1\equiv R_2 R_3
\]

Enantioselectivity was achieved using a chiral phosphine ligand

\[\text{DMI} = 1,3\text{-dimethylimidazolidinone}\]

Jamison, T.F., et. al. J.A.C.S. 2003, 125, 3442
## Scope of Asymmetric Reductive Coupling

$$R_1 = Ar \quad R^3 = Ar$$
$$R^2 = Alkyl \quad Alkyl$$

**Conditions:**
- Ni(COD)$_2$ (10 mol%)
- (+)-NMDPP (20 mol%)
- Et$_3$B (200 mol%)
- EtOAc:DMI (1:1)

**Examples:**
- R1 = Ar, R2 = Alkyl, CH$_2$OTBS, CH$_2$NHBOc, SiMe$_3$
- R1 = Ar, R2 = Alkyl, 100% cis addition, 90:10 to >95:5 regioselectivity up to 96%ee

<table>
<thead>
<tr>
<th>entry</th>
<th>R$^1$</th>
<th>R$^2$</th>
<th>R$^3$</th>
<th>yield (%)</th>
<th>regioselectivity</th>
<th>ee %</th>
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<tr>
<td>1</td>
<td>Ph</td>
<td>Me</td>
<td>i-Pr</td>
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<td>(&gt;95:5)</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
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<td>Me</td>
<td>c-C$<em>6$H$</em>{11}$</td>
<td>97</td>
<td>(&gt;95:5)</td>
<td>90</td>
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<tr>
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<td>Ph</td>
<td>Me</td>
<td>Ph</td>
<td>79</td>
<td>(&gt;95:5)</td>
<td>73</td>
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<td>4</td>
<td>(pMeo)Ph</td>
<td>Me</td>
<td>i-Pr</td>
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<td>(&gt;95:5)</td>
<td>88</td>
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<tr>
<td>5</td>
<td>(p-Cl)Ph</td>
<td>Me</td>
<td>i-Pr</td>
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<td>(&gt;95:5)</td>
<td>83</td>
</tr>
<tr>
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<tr>
<td>8</td>
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<td>n-Pr</td>
<td>i-Pr</td>
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<td>(-)</td>
<td>42</td>
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</tbody>
</table>

**High ee is achieved with NMDPP**

Jamison, T.F., et. al. J.A.C.S. 2003, 125, 3442
Proposed Steric and Electronic Control

The major enantiomer proceeds via oxametallocyclopentene complex D

Jamison, T.F., et. al. J.A.C.S. 2003, 125, 3442
Reductive Coupling of Alkynes and Epoxides

Opening of epoxides lead to homoallylic alcohols

Jamison, T.F., et al. J.A.C.S. 2003, 125, 8076
Intermolecular and Intramolecular Reductive Coupling

\[
R^1 \equiv R^2 + \begin{array}{c}
\text{Ni(cod)\textsubscript{2} (10 mol\%)}
\
\text{Bu\textsubscript{3}P (20 mol\%)}
\
\text{Et\textsubscript{3}B (200 mol\%)}
\end{array}
\rightarrow
\begin{array}{c}
R^1 \equiv R^2 \rightarrow R^3
\
\text{1a-d}
\end{array}
\]  

High endo epoxide opening regioselectivity

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<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
<th>additive</th>
<th>product</th>
<th>yield (%)</th>
<th>regioselectivity</th>
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<td>Me</td>
<td>Me</td>
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<td>1a</td>
<td>0</td>
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<td>2\textsuperscript{b}</td>
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<td>Me</td>
<td>Me</td>
<td>Bu\textsubscript{3}P</td>
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<td>Me</td>
<td>(n-Oct\textsubscript{3})P</td>
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<td>35</td>
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<td>Me</td>
<td>Me</td>
<td>Bu\textsubscript{3}P</td>
<td>1a</td>
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<td>&gt;95:5</td>
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<td>Me</td>
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<td>7</td>
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<td>Me</td>
<td>n-Hex</td>
<td>Bu\textsubscript{3}P</td>
<td>1b</td>
<td>68</td>
<td>&gt;95:5</td>
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<tr>
<td>8</td>
<td>Ph</td>
<td>Me</td>
<td>Ph</td>
<td>Bu\textsubscript{3}P</td>
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<td>50\textsuperscript{e}</td>
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<td>n-Pr</td>
<td>Et</td>
<td>Bu\textsubscript{3}P</td>
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<th>entry</th>
<th>X</th>
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<td>O</td>
<td>1</td>
<td>3b</td>
<td>50</td>
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<td>3</td>
<td>NBn</td>
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<td>3c</td>
<td>65</td>
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<td>4</td>
<td>C(CO\textsubscript{2}Me\textsubscript{2})</td>
<td>1</td>
<td>3d</td>
<td>88\textsuperscript{c}</td>
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<td>5</td>
<td>CH\textsubscript{2}</td>
<td>0</td>
<td>3e</td>
<td>54</td>
<td>&gt;95:5</td>
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</table>

Jamison, T.F., et. al. J.A.C.S. 2003, 125, 8076
Cyclization via a Nickella(II)oxetane

The Ni-C and Ni-O may accommodate the bridge olefin.

Jamison, T.F., et. al. J.A.C.S. 2003, 125, 8076
Three Component Coupling of Alkynes, Imines and Organoboranes

Ph—C≡C—Me + MeN=CHPh

Ni(COD)₂ (5 mol%) + Bu₃P (5 mol%)
Et₃B (300 mol%)
MeOAc / MeOH
50°C

Ph—C≡C—Me + MeN=CHPh

96:4 regioselectivity 96:4 80%

5% [Ni(cod)₂],
5% (c-C₅H₉)₃P
MeOH/MeOAc
50 °C

Ph—C≡C—Me + MeN=CHPh

72% (92:8 regioselectivity)

68% (92:8 regioselectivity)

More stable starting material provides milder reaction coditions

Enantioselectivity Observed with (S)-NMDPP Ligand

\[
\text{Ph} = \text{Me} + \begin{array}{c} \text{Me} \\ \text{N} \\ \text{H} \end{array} \text{Ar} \xrightarrow{10\% [\text{Ni(cod)}_2]} 20\% (S)-\text{NMDPP} \xrightarrow{300\% \text{Et}_3\text{B}} \text{MeOAc/MeOH} \xrightarrow{0 \, ^\circ \text{C}, 20 \, \text{h}} \text{Et} \xrightarrow{\text{NHMe}} \text{Ph} + \begin{array}{c} \text{Ph} \\ \text{Me} \end{array} \text{Ar} + \begin{array}{c} \text{Ph} \\ \text{H} \end{array} \text{NHMe}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>ee 1 [%][a]</th>
<th>ee 2 [%][a]</th>
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</tr>
<tr>
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<td>33</td>
</tr>
<tr>
<td>3</td>
<td>(p-CF_3)C_6H_4</td>
<td>40</td>
<td>39</td>
</tr>
</tbody>
</table>

ee for reductive coupling are the same for alkylative coupling

Proposed Pathway for Observed Selectivity

Regioselectivity is determined before intermediate A.

Alkene Directed Alkyne Coupling

C-C bond formation is proximal to the aryl subsistent

Jamison, T.F., J.A.C.S. 2004, 126, 4130
Scope of Alkene-Directed Coupling

Directing ability does not depend on nature, size or substitution of the alkyne

Jamison, T.F., J.A.C.S. 2004, 126, 4130
Hydrogen Mediated C-C Bond Formation

The hydrogenation intermediate is trapped by an electrophile

Synthesis of Amphidinolide T1

C13-C21 Fragment Using Intermolecular Nickel-Catalyzed Alkyne – Epoxide Reductive Coupling

Synthesis of C1-C12 Fragment

Synthesis of Amphidinolide T1 Cont.

Nickel Catalyzed Intramolecular Macrocyclization

1. 7, DCC, 4-PPY
2. TBAF
3. Dess-Martin

59% (3 steps)

Ni(cod)₂ (20 mol%), Bu₃P (40 mol%)
Et₃B, toluene, 60 °C ([8] = 0.05 M)
44%, >10:1 dr

1. TBSOTf, 2,6-lut
2. O₃; Me₂S
3. CH₂I₂, Zn
   ZrCl₄, PbCl₂
4. HF•py

25% (4 steps)

Overall 16 steps from aldehyde 4

Montgomery
- Intramolecular cyclization generates stereodefined olefins
- Phosphine ligands promote β-hydride elimination
- Coupling of two enones and an alkyne generate a single diasteromer
- Triethylsilane proved to be a good reducing agent in intramolecular alkyne aldehyde coupling
- Cyclization of allenyl aldehydes provided the core of (+)-Testudinariol A.
- NHC ligands enabled addition of terminal and internal alkynes to aldehydes

Jamison
- Demonstrated intermolecular coupling of alkynes and aldehydes with Ni and triethylborane
- Enantioselective intermolecular coupling was achieved with chiral phosphines
- Intermolecular coupling of alkynes and epoxides leads to homoallylic alcohols
- Allylic amines from alkynes, imines and organoboranes
- C=C directs C-C bond formation to the least hindered side of the alkyne
- Implication of intra and intermolecular coupling lead to the total synthesis of Amphidinolide T1

Kriche
- Developed hydrogen mediated coupling that is proximal to the aryl substitute by trapping with an electrophile
Catalytic Cycle
Oxocarbenium Ion/Vinyl Silane Condensation
Type II Allylation
Lead Reduction of Zinc Carbenoid

\[
\begin{align*}
\text{Zn} + \text{PbX}_2 & \rightarrow \text{ZnX}_2 + \text{Pb} \\
\text{ZnX}_2 + \text{PbX}_2 & \rightarrow \text{PbX}_2 \\
\text{Zn} + \text{ZnX} & \rightarrow \text{ZnX}_2
\end{align*}
\]

\[(X = \text{I} \text{ or } \text{Cl})\]