A General and Efficient Catalyst System for a Wacker-Type Oxidation Using TBHP as the Terminal Oxidant: Application to Classically Challenging Substrates


Total Synthesis of the Antibiotic Kendomycin by Macrocyclization using Photo-Fries Rearrangement and Ring-Closing Metathesis


Short Literature
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PhD – Washington State University, B. E. Eaton (Iron-mediated 4+1 Cycloadditions)
NIH Postdoc Fellow – Harvard, 1999, Jacobsen (Asymmetric Strecker Reactions)
Assistant Professor – University of Utah, 1999-2004
Associate Professor – University of Utah, 2004-2008
Professor – University of Utah, 2008-present

Main Research Interest: Aerobic Oxidation Reactions
The Wacker Oxidation Process

- 1894 - Discovery of the reaction with stoechiometric Pd(II)

- 1959 - Use of CuCl₂ to reoxidize Pd(0) (Smidt et al. at Wacker Chemie)

- First organopalladium reaction applied on an industrial scale
**Problems with Protected Allylic Alcohols**

**Homoallylic Alcohols**

\[
\begin{align*}
\text{PdCl}_2 \text{ (cat.)} & \quad \text{CuCl, O}_2 \\
\text{DMF/H}_2\text{O (7:1), rt} & \quad 90\% \text{ yield}
\end{align*}
\]

**Allylic Alcohols**

\[
\begin{align*}
R = \text{Bn} & : 75\% \\
R = \text{MOM} & : 65\% \\
1 : 1 \text{ ratio}
\end{align*}
\]

Known Method Employed in Total Syntheses to Access Acyloin Compounds

1. 1.2 eq. Hg(OAc)$_2$, THF/H$_2$O
2. 1 eq. PdCl$_2$, 2 eq. LiCl
3 eq. CuCl$_2$, 55 °C

89% yield


1. 1.2 eq. Hg(OAc)$_2$, THF/H$_2$O
2. 1 eq. PdCl$_2$, 2 eq. LiCl
3 eq. CuCl$_2$, 55 °C

65% yield

Origin of Regioselectivity

Homoallylic

\[
\text{OP} \quad \text{δ}^+ \quad \text{H}_2\text{O} \\
\text{Pd(II)}
\]

\[
\text{H}^+ \\
\text{OP} \quad \text{OH} \\
\text{Pd(II)}
\]

Markovnikov

Alllylic

\[
\text{PO-Pd(II) coordination: nonsymmetrical bonding of Pd to olefin}
\]

\[
\text{H}^+ \\
\text{OP} \quad \text{Pd(II)} \\
\text{OH}
\]

\[
\text{H}^+ \\
\text{OP} \quad \text{Pd(II)} \\
\text{OH}
\]

\[
\text{PO-Pd(II)} \\
\text{Pd(II)}
\]

\[\text{R} \quad \text{PO} \quad \text{OP} \quad \text{H}^+ \quad \text{H}^+ \quad \text{OP} \quad \text{H}_2\text{O} \quad \text{R} \quad \text{PO} \quad \text{OP} \quad \text{H}^+ \quad \text{H}^+ \quad \text{OP} \quad \text{H}_2\text{O} \]

Anti-Markovnikov

Proposed Solution by Sigman

Prevent Coordination of Protected Alcohol:

- Use of Bidentate Ligand
- TBHP-Mediated Wacker Process

![Chemical Structure]
Proposed Solution by Sigman

Prevent Coordination of Protected Alcohol:
- Use of Bidentate Ligand
- TBHP-Mediated Wacker Process

- Intramolecular 1,2-migration of oxygen
- No Cu(II) required
### Optimization of Reaction Parameters

![Chemical structure]

5 mol% Pd(CH$_3$CN)$_2$Cl$_2$
6 mol% Ligand
12 mol% AgBF$_4$
15 equiv. TBHP(aq)
CH$_2$Cl$_2$, rt, 0.1 M

<table>
<thead>
<tr>
<th>Ligand</th>
<th>GC Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMEDA</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>Pyridine</td>
<td>10</td>
</tr>
<tr>
<td>Bipyridine</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>(-)-Sparteine</td>
<td>5</td>
</tr>
<tr>
<td>Quinox-diMe</td>
<td>73</td>
</tr>
<tr>
<td>Quinox</td>
<td>95</td>
</tr>
</tbody>
</table>
Substrate Scope

\[
\begin{align*}
\text{R} & \xrightarrow{\text{x mol\% Pd(Quinox)Cl}_2, 2.5x \text{ mol\% AgSBF}_6, 12 \text{ eq TBHP(aq)}} \text{R} \\
& \text{CH}_2\text{Cl}_2, 0 \degree \mathrm{C} \rightarrow \text{rt, 0.1 M}}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>x</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PG = Ac</td>
<td>5</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>PG = TBS</td>
<td>2</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>PG = CH_2OCH_2CH_3</td>
<td>5</td>
<td>81</td>
</tr>
<tr>
<td>4</td>
<td>R = HOC_9H_{18}</td>
<td>1</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>R = 4-BOCNHPh</td>
<td>5</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>R = 3-NO_2Ph</td>
<td>5</td>
<td>60</td>
</tr>
</tbody>
</table>

- No aldehyde detected by GC
- **Drawback:** PMB and Bn protecting Groups give mixture of aldehyde and ketone
Substrate Scope

5 mol% Pd(Quinox)Cl₂
12 mol% AgSBF₆
12 eq TBHP\(_{(aq)}\)
CH₂Cl₂, 0 °C ⇒ rt, 0.1 M

98% ee

> 99% GC yield

98% ee
(-)-Kendomycin Timeline

- Endothelin receptor antagonist
- Antibacterial activity \( \sim 5 \mu M \) vs MRSA strains (Multi Resistant Staphilococcus Aureus)
- Cytotoxic vs many cancer cell lines: IC\(_{50} < 100\)nM

1996 – Isolation by Funahashi from *Streptomyces violaceoruber*
2000 – Elucidation of structure by X-ray analysis
2004 – First total synthesis by Lee and coworkers
2005 – Total synthesis by Amos B. Smith, III and coworkers
2008 – Formal Synthesis by S. D. Rychnovsky and coworkers
2008 – Total Synthesis by S. J. Panek and coworkers

Covered by E. Crane Sept. 23, 2008
Unsuccessful Macrocyclization Attempts


Smith, A. B., III et al., JACS 2006, 128, 5292.
Conformational Analysis by Mulzer: Atropisomerism Around C4-C5 Bond

NMR experiments: Unreactive atropisomer dominates

Successful Macrocyclizations by Lee and Rychnovský

Lee’s Solution: Macroglycosidation

\[
\begin{align*}
\text{SnCl}_4 & \quad 4 \text{ Å MS} \\
\text{CHCl}_3 & \\
\end{align*}
\]

\[
\text{40-70% yield}
\]

JACS 2004, 126, 14720.

Rychnovský’s Solution: Prins-Cyclization

\[
\begin{align*}
\text{AcOH, BF}_3\cdot\text{OEt}_2 & \quad 0 \degree \text{C, CH}_2\text{Cl}_2 \\
\end{align*}
\]

\[
X=\text{OAc, 33%} \\
X=\text{F, 48%}
\]

JACS 2008, 130, 13177.
Alternative Solution by Mulzer:
Macrolactonization / Photo-Fries Rearrangement
Retroynthetic Plan

(-)-Kendomycin

[O] → THP Ring Formation

Photo-Fries

Ireland-Claisen

Aldol

Macrolactonization
**Synthesis**

![Chemical reaction diagram]

1. **Reaction 1**
   - Starting material: Acetone
   - Reagents: TMSCHN$_2$, nBuLi
   - Conditions: THF, -78 °C to rt
   - Products:
     - First product: 83% yield
     - Second product: 76% yield

2. **Reaction 2**
   - Starting material: TBDPS
   - Reagents: Cp$_2$ZrHCl, benzene, 50 °C
   - Additional reagent: I$_2$, 0 °C
   - Product: 76% yield

3. **Reaction 3**
   - Starting material: TBDPS
   - Reagents: [Pd(PPh$_3$)$_4$], tBuLi, ZnCl$_2$
   - Conditions: Et$_2$O/THF, 0 °C
   - Product: 67% yield

4. **Reaction 4**
   - Starting material: TBDPS
   - Reagents: DMDO
   - Conditions: Acetone, rt
   - Product: 99% yield

5. **Final Product**
   - Product: 1.1:1.0 dr
   - (-)-Kendomycin

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*Note: The diagram includes chemical structures and reactions, along with yields and reaction conditions.*
Synthesis

**Synthesis**

1. TfOH (cat) toluene/EtOH (4/1) 4Å mol sieves, 80 °C
2. MOMCl, NaH DMF, 0 °C

**90% yield over 2 steps**

1. TBAF THF, rt
2. IBX DMSO, rt
3. Pinnick Ox.

**85% yield over 3 steps**

1. TBDPSO + Br\_2 + CrCl\_2, NiCl\_2 (cat) DMF, 0 °C to rt

**86% yield 1.4:1 dr**
**Synthesis**

1. LiHMDS, HMPA
   TBSCI
   THF, -78 °C to reflux

2. LiAlH₄
   Et₂O, 0 °C

3. TBAF, THF, rt
4. IBX, DMSO, rt

84% yield
over 2 steps

4:1 dr

81% yield
over 4 steps

87% yield
6:1 dr

**Stereogenic center is stable to SiO₂ and mild acidic or basic conditions!**

Synthesis

1. Me$_4$NBH(OAc)$_3$
   MeCN/AcOH (2:1)
   -30 °C to 0 °C
2. LiOH, H$_2$O$_2$
   THF/H$_2$O (3:1)

69% yield
over 2 steps

20:1 dr

1. 3M HCl
dioxane, 50 °C
2. (CH$_3$)$_2$C(OMe)$_2$
   CSA, rt
3. LiOH,
   MeOH:THF:H$_2$O (2:1:1)
   rt

71% yield
over 3 steps

55% yield

(-)-Kendomycin
The Fries Rearrangement

Lewis-acid catalysis
The Fries Rearrangement

Lewis-acid catalysis

\[
\begin{align*}
\text{O} & \text{O} \\
\text{O} & \text{O}
\end{align*}
\]

\[
\text{O} \text{LA} \quad \Theta
\]

\[
\text{R} \text{=} \text{O} \quad \Theta
\]

\[
\text{O} \text{O} \\
\text{O} \text{O}
\]

Photo-Fries

\[
\text{O} \text{O} \\
\text{O} \text{O}
\]

\[
\text{Me} \text{Me} \quad \text{Me} \text{Me}
\]

\[
\text{Me} \text{Me} \quad \text{Me} \text{Me}
\]

For Mechanistic Studies, see:
End Game

1. NaBH₄, MeOH, rt then HCl 0.5M
2. TsOH, toluene, 60 °C

71% yield over 2 steps

1. TESOTf, Et₃N, CH₂Cl₂, 0 °C
2. IBX, DMF

60% yield over 2 steps

Kendomycin

75% yield