Every Rose Has Its Thorn: Development and Application of Selective Palladium Hydrogenation Catalysts

Pd/C(en)-Catalyzed Chemoselective Hydrogenation in the Presence of Aryl Nitriles


Formal Synthesis of (−)-Lepadiformine


Brooks Maki, January 15, 2008
Lepadiformine - Retrosynthesis

(-)-lepadiformine

previous work

[3,3] Claisen Rearrangement

imine formation / cyanide addition

RCM

- Isolated in 1994 (assigned incorrect structure)
- Shows cytotoxic / cardiovascular effects
- Kibayashi published first racemic synthesis and structure correction (2000)
- Weinreb published first enantioselective synthesis (2002)
- Other syntheses have been published by Funk and Hsung
- Tetrasubstituted carbon has been set by cycloaddition (Kibayashi and Funk)
  or addition to imine/iminium (Weinreb/Hsung)
Claisen Rearrangement and Manipulation

1) (COCl)_2, DMSO
   Et_3N, CH_2Cl_2
2) Ph_3PCH_3I
   n-BuLi, THF
84% yield

1) (COCl)_2, DMSO
   Et_3N, CH_2Cl_2
2) Ph_3PCH_3I
   n-BuLi, THF
62% over 3 steps

LHMDS, TBSCI
THF, -78 °C
[3,3] Claisen

79% yield
8:1 ds

1) Mel, K_2CO_3, Acetone
2a) 9-BBN, TIOEt, THF
2b) Pd(dpff)_2Cl_2, AsPh_3
   THF/DMF
3) LiAlH_4, THF
The Necessity of a Chemoselective Hydrogenation

If only there were a way to hydrogenate without hydrogenolyzing the benzyl ether...
**Poisoned Palladium Catalysts**

1:1 complex of Pd/C and ethylenediamine [Pd/C(en)] has shown remarkable chemoselectivity.


\[
\text{Cyclic enamine} \xrightarrow{\text{Pd/C(en), } H_2} \text{Aromatic amine}
\]

92% yield


\[
\text{Cyclic hydrocarbon} \xrightarrow{\text{Pd/C, } H_2} \text{Cyclic epoxide}
\]

93% yield


\[
\text{Aromatic substrate} \xrightarrow{\text{Pd/C, } H_2} \text{Aromatic product}
\]

72% yield

\[
\text{Aromatic substrate} \xrightarrow{\text{Pd/C(en), } H_2} \text{Aromatic product}
\]

97% yield
Suppression of Nitrile Hydrogenation

\[
\text{Suppression of Nitrile Hydrogenation}
\]

- **Complete conversion observed after 24 hours**
  \[
  \begin{align*}
  \text{CN} + \text{H}_2 & \xrightarrow{5\% \text{ Pd/C}, \text{MeOH, 20°C}} \text{NH}_2 + \text{N}
  \\
  \text{complete conversion observed after 24 hours}
  \end{align*}
  \]
- **80% recovery of unhydrogenated nitrile**
  \[
  \begin{align*}
  \text{CN} & \xrightarrow{5\% \text{ Pd/C(en), H}_2, \text{MeOH}} \text{CN}
  \\
  \text{80% recovery of unhydrogenated nitrile}
  \end{align*}
  \]

Polar aprotic solvents were found to be the most effective in suppression of hydrogenation (92-94% recovery with THF or 1,4-dioxane)
Hydrogenation of Benzonitrile Derivatives

5% Pd/C(en)

>90% recovery of starting nitrile in all reported cases

52% recovery of nitrile

100% recovery of nitrile

~90% hydrogenation of nitrile observed

5% Pd/C
Chemoselective Hydrogenation

- 96% yield
- 84% yield
- 91% yield
- Quantitative
- 83% yield
Formal Synthesis of (−)-Lepadiformine

\[ \text{Formal Synthesis of } (-)-\text{Lepadiformine} \]

\[ \text{Grubbs II} \quad \text{CH}_2\text{Cl}_2, 40 \degree \text{C} \quad 98\% \text{ yield} \]

\[ \text{H}_2, \text{Pd/C, NEt}_3 \quad \text{MeOH} \quad 95\% \text{ yield} \]

\[ \text{1) TBAF, THF} \quad \text{2) DMP, CH}_2\text{Cl}_2 \quad 95\% \text{ yield, 2 steps} \]

\[ \text{13 steps from amino-aldehyde} \quad 22\% \text{ overall yield} \]
Other Applications to Target-Oriented Synthesis
