Exercise session: Solutions – 11.04.2019 – Alexandre Leclair


**Possible mechanism:**

1. $\text{Fe (10 equiv), AcOH (cat.)}$
   $\text{Mg_{2}SiCl (cat.), THF, }\theta, 89\%$
2. $\text{KHMDS (1.1 equiv)}$
   $\text{Comins reagent (1.2 equiv)}$
   $\text{THF, }-78\degree\text{C}$
3. $\text{Pd(OAc)}_{2} (10 \text{ mol%),}$
   $\text{PPh}_{3} (20 \text{ mol%),}$
   $\text{Et}_{3}N (2 \text{ equiv, CO (1 atm)}}$
   $\text{MeOH-DMF, 40\degree \text{C}}$
   $49\% \text{ over 2 steps}$

**Mechanism?**

**C-H activation using Sanford’s methodology**


Bad yield due to the C-H activation of the diastereotopic CH$_3$
Epimeric at C$_4$ + small amount of the double C-H activated product

Exercise 2  Zhang et al., Org.Lett. 2015, 17, 5480-548

**Mechanism:** See paper for detailed mechanism

1) Deprotonation of the TMSCH$_2$ with BuLi
2) Cleavage of the aldehyde + alcohol with LiCl
3) Addition to the aldehyde
4) 1,2-Brook rearrangement
5) Proton transfer
6) Addition of the alkoxide to the carbene followed by protonation OR O-H insertion after protonation

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\begin{align*}
\text{O} & \quad \text{O} \\
\text{Br} & \quad \text{Br} \\
\text{PPh}_2\text{AuNTf}_2 \text{(4 mol\%)} & \quad \text{Au}^{\text{I}} \text{cat. hydration} \\
\text{H}_2\text{O}, 1,2-\text{DCE} & \quad 25 \degree \text{C}, 29 \text{ h} \\
\text{A} & \quad \text{A} \\
\text{PhSiH}_2 \text{butylen oxide} \text{(10 mol\%)} & \quad \text{Dioctoephones A and B} \\
\text{1,4-dioxane}, 150 \degree \text{C}, 20 \text{ h} & \quad \text{sealed tube} \\
& \quad 60\%, 96\% \text{ ee} \\
\end{align*}
\]

- [(S,S)-Me-DuPhos]: gave the best ee
- PhSiH$_2$ used to regenerate the phosphines
- Butylene oxide: used as a masked base: after substitution of the bromide by the phosphine, opening of the epoxide by the bromide, generate an alkoxide which acts as a base to deprotonate the phosphonium


\[
\begin{align*}
\text{MeO} & \quad \text{NH}_2 \\
\text{R} & \quad \text{O} \\
\text{O} & \quad \text{CO}_2\text{Me} \\
\text{Toluene/EtJN (1:2)} & \quad \text{reflux, 16 h} \\
\text{R} & \quad \text{H} \text{ or c}_2\text{H}_9 \\
\end{align*}
\]

Mechanism: For detail mechanism see the publication

1) Condensation of the amine with the ketone
2) Tautomerization: imine/enamine and cyclization on the methyl ester to form the pyrrolidino
3) Claisen rearrangement with transfer of chirality from the R group

Basic conditions important to avoid Pictet-Spengler pathway
Mixture of Z/E enamine (in favor of E) but to explain the good ee authors proposed:
\[
\begin{align*}
\rightarrow \text{Chair transition state for Z enamine / Boat transition state for E enamine favored} \\
\end{align*}
\]

\[
\begin{align*}
\text{Seyferth-Gilbert homologation} & \quad \text{using Bestman-Ohira reagent} \\
\text{79\%, 89:11 er} & \quad \text{56\%, >99:1 er (after crystallization)} \\
\end{align*}
\]
Mechanism:

Initiation with Et3B, O2
Polarity-reversal conditions
(using thiol as intermediate H-donor)
→ Speed up the HAT