Direct, Catalytic Hydroaminoalkylation of Unactivated Olefins with N-Alkyl Arylamines

DOI: [10.1021/ja0718366](http://dx.doi.org/10.1021/ja0718366)
Biological Activation of CH Bonds

- Cytochrome P450, a family of over 60 enzymes, participates in a variety of cellular redox processes

\[
\begin{align*}
\text{R}_1\text{R}_2\text{N} & \xrightarrow{\text{P450}} \text{R}_1\text{R}_2\text{N}^+ \\
& \xrightarrow{\text{H}^+, 2\text{e}^{-}} \text{R}_1\text{R}_2\text{NH}^+ + \text{R}_1\text{R}_2\text{O}
\end{align*}
\]

- Ability of P450 to transform endogenous and foreign compounds has a tremendous impact on the metabolism of drugs

For recent studies on the metabolism of cyclopropylamines, see:

- Many efforts have been focused on developing a catalytic system mimicking activity of P450. Metals such as Pd(0), Ru(II), Cu(I) are successful candidates for the catalytic activation of CH bonds.
Activation of sp³ CH Bonds Adjacent to Nitrogen

- Catalytic carbonylation via pyridine-directed activation of pyrrolidine has been achieved using Rh(I) catalysts

\[
\text{RhCl(cod)₂ (4 mol\%)} \quad \text{CO, H₂C=CH₂, i-PrOH} \quad 160 \, ^\circ\text{C}, 60 \, \text{h}, \, 70\%
\]

- Similarly, imines are viable substrates in Ir(I) promoted 3 component coupling with alkynes

\[
\text{[IrCl(cod)₂ (10 mol\%)} \quad \text{CO, H₂C=CH₂, i-PrOH} \quad 160 \, ^\circ\text{C}, 60 \, \text{h}, \, 73\%
\]


- Similarly, imines are viable substrates in Ir(I) promoted 3 component coupling with alkynes

\[
\text{[IrCl(cod)₂ (10 mol\%)} \quad \text{THF, 60 \, ^\circ\text{C}} \quad \text{45-74%}
\]

Activation of sp³ CH Bonds Adjacent to Nitrogen

Aerobic oxidation of alkyl amines using RuCl₃ has been successfully applied to dimethyl aryl amines

\[
\text{Ar-N} + \text{CuBr (5 mol %)} \xrightarrow{\text{TBHP, 100 °C, 3 h}} \text{Ar-N} + \text{R} \xrightarrow{\text{CuBr (5 mol %)}} \text{Ar-N} \xrightarrow{\text{TBHP, rt, 6 h}} \text{Ar-N} \xrightarrow{\text{TBHP, 100 °C, 3 h}} \text{R-NO}_2
\]

81-88% 12-82% 30-75%

Murahashi et al. J. Am. Chem. Soc. 2003, 125, 15312

Similarly, Li showed that CuBr can catalyze oxidative coupling of amines in the presence of TBHP

Li, Li J. Am. Chem. Soc. 2004, 126, 11810
Li, Li J. Am. Chem. Soc. 2004, 126, 3672
Activation of \( \text{sp}^3 \) CH Bonds Adjacent to Nitrogen

Nitrogen protecting groups are commonly applied as directing moieties in Pd-promoted CH activations

Imine-directed coupling of boronic esters was carried out in the presence of reducing agent (ketone) in good yields and modest selectivities

Pastine, Gibkov, Sames

A conceptually different approach was applied by Davis - catalytic CH insertion into CH bonds afforded pyrrolidines and piperidines in high chemoslectivities, de’s, and ee’s.

Activation of sp³ CH Bonds Adjacent to Nitrogen

CH activation in the Hartwig Group


Zirconaaziridines

- Many metal $\eta^2$-imine complexes of early TM and lanthanides are known

\[
\begin{align*}
R'\text{}\text{N-Li}\text{ } & \text{Cp}_2\text{ZrMeX} \quad X = \text{Cl, OTf} \\
\text{H-R''} & \quad \text{Cp}_2\text{ZrN-R''} \quad -\text{CH}_4 \\
\text{Cp}_2\text{ZrN-Me} & \quad +\text{L} \\
\text{Cp}_2\text{ZrN-R'} & \\
\text{L = THF, PPh}_3
\end{align*}
\]


- Rate of methane elimination is dependent on nitrogen substitution ("availability of nitrogen lone pair")

\[
\begin{align*}
\text{Cp}_2\text{ZrN-Me} & \quad 10^3 \text{ times faster than} \\
\text{Cp}_2\text{ZrN-Pr}
\end{align*}
\]

- Unlike $\eta^1$-complexes, metallaaziridines undergo typical d$^0$ Ti/Zr (IV) reactions - insertion of multiple bonds and coupling reactions

Maciej Walczak @ Wipf Group

5/12/2007
Group 5 Metals

- Stoichiometric reactions of $\eta^2$-complexes with aldehydes and ketones have been described (umpolung)

\[
\text{NbCl}_3(\text{DME}) + \text{Ph}-\text{N} \rightarrow (\text{THF})_2\text{Cl}_2\text{Nb}-\text{N} \rightarrow \text{O} \rightarrow \text{R} \rightarrow \text{R}' \rightarrow \text{R}'' \rightarrow \text{Ar} \rightarrow \text{R} \rightarrow \text{R}' \rightarrow \text{R}''
\]

$R = \text{Bn}$, allyl
$R'$, $R'' = \text{H}$, alkyl

Yields: 34-90%


- $M(\text{NMe}_2)_5$, $M = \text{Nb}$, Ta have been shown to catalyze alkylation of alkene in low yields

\[
\text{R} + \text{R'} \rightarrow \text{cat., PhMe, 160 or 200 °C} \rightarrow \text{R} \rightarrow \text{R'} \rightarrow \text{Me}
\]

$R = \text{H, Me}$
$R' = \text{H, Me, -Bu}$

13-38%

Cleric, Maspero *Synthesis* 1980, 305
Nugent, Ovenall, Holmes *Organometallics* 1983, 2, 161
Title Paper - Experiment Design and Initial Studies

\[
\text{(Me}_2\text{N})_3\text{M}^\text{NMe}_2\text{NMe}_2 - \text{HNMe}_2 \rightarrow \text{(Me}_2\text{N})_3\text{M}^\text{N}\text{Me}_2\text{N}\text{Me}_2
\]

\[
\text{Ph}^\text{N}^\text{Me} + \text{CH}_2=\text{CH}_2\text{n-hexyl} \xrightarrow{\text{catalyst (4 mol%)}} \text{Ph}^\text{N}^\text{Me}_\text{n-hexyl}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst precursor</th>
<th>% yield</th>
<th>1.3 h</th>
<th>5.1 h</th>
<th>24 h</th>
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<tbody>
<tr>
<td>1</td>
<td>Ta[Me2N]3</td>
<td>32</td>
<td>60</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ta[Et2N]3</td>
<td>23</td>
<td>41</td>
<td>66</td>
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<tr>
<td>3</td>
<td>Nb[Me2N]3</td>
<td>20</td>
<td>29</td>
<td>35</td>
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<tr>
<td>4</td>
<td>Cp2Zr[Me2N]2</td>
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<td>1.2</td>
<td>3</td>
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<tr>
<td>5</td>
<td>Zr[Me2N]4</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
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<tr>
<td>6</td>
<td>none</td>
<td>0</td>
<td>0</td>
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</table>
Typically, high selectivity was observed although some olefins give a mixture of linear and branched isomers.

Only aromatic rings with \( m \)- and \( p \)-substituents were shown to undergo hydroaminoalkylation.
Title Paper - Mechanistic Proposal

- Exchange of aromatic protons occurs most likely faster than the insertion reaction

\[
\text{Ph}_2N\text{CD}_3^+ \xrightarrow{\text{Ta[NMe}_2]_5 (4 \text{ mol} \%) } \text{n-hexyl} \xrightarrow{\text{PhMe, 160-165} \text{ °C}} \text{N} \text{Me}\text{N} \text{Me} \text{n-hexyl} \quad 46\% \quad 45\% \quad 27\% \quad 12\%
\]

at 25% conversion:
15% D in *ortho* position

- Ligand exchange

\[
\text{Ta[NMe}_2]_5 + \text{Me}_2\text{NMe}_2 \xrightarrow{\text{PhMe-}d8 \quad \text{dodecane, 80} \text{ °C, 24 h}} \left[\text{Me}_2\text{N}_4\text{Ta}\right]_3 \text{Me} + \left[\text{Me}_2\text{N}_3\text{Ta}\right]_2 \quad 37% \quad 39%
\]

with 25 eq of toluidine, 1:1 ratio
Reactivity of Tantalum Complexes

- Primary amines form imido complexes with tantalum

\[
\text{Ta(NMe}_2\text{)}_5 + t\text{-BuNH}_2 \rightarrow (\text{NMe}_2)_3\text{Ta}=\text{Nt-Bu} + 2 \text{NHMe}_2
\]


- Neutral Ta complexes have been shown to catalyze hydroamination reactions of anilines and alkynes

\[
\text{Ph} = \overset{\text{Ph}}{\text{Ph}} \quad + \quad H_2\text{NPh} \quad \overset{\text{5 mol\% [Ta]}}{\text{C}_6\text{D}_5\text{Cl}, 135^\circ\text{C}} \quad \text{Ph} \quad \overset{\text{N}^\prime\text{Ph}}{\text{Ph}} \quad + \quad \overset{\text{HN}^\prime\text{Ph}}{\text{Ph}} \quad 3:1
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
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<td>1</td>
<td>Bn\text{Ta}=\text{NCMe}_3</td>
<td>30</td>
<td>&gt;95</td>
</tr>
<tr>
<td>2</td>
<td>[BnTa=\text{NCMe}_3]^+</td>
<td>8</td>
<td>&gt;95</td>
</tr>
<tr>
<td>3</td>
<td>Np\text{Ta}=\text{CMMe}_3</td>
<td>12</td>
<td>&gt;95</td>
</tr>
<tr>
<td>4</td>
<td>(Et\text{N})\text{Ta}=\text{NCMe}_3</td>
<td>30</td>
<td>&gt;95</td>
</tr>
<tr>
<td>5</td>
<td>Ta(NMe}_2\text{)}_5</td>
<td>30</td>
<td>&gt;95</td>
</tr>
<tr>
<td>6</td>
<td>Cl\text{Ta}=\text{NCMe}_3</td>
<td>30</td>
<td>NR</td>
</tr>
</tbody>
</table>

Anderson, Arnold, Bergman Org. Lett. 2004, 6, 2519
Summary and Future Prospective

• Catalytic hydroaminoalkylation of alkenes using Ta proceeded in high yields and appreciable selectivities
• Although electronic properties of amine control the selectivity, typical directing groups (e.g. pyridyl, iminoyl, carbamoyl) are not necessary

What needs to be done
   – Improve reaction conditions and scope
   – More mechanistic data is needed to explain the selectivity as well as reactivity of Ta complexes