π-Acid Catalyzed C-H Alkylation

*Part of the C-H Activation seminar series*

John Thompson
Dong Group - Literature Review
February 18th, 2015
Alkylation pathways for olefins with metals

- Activation of C-H bond (sp² and sp³)

- Activation of olefin for alkylation
Lewis acid activation

- The fundamental role of a Lewis-acid catalyst lies in the activation of the C=X bond; where (X = O, NR, CR₂), thereby decreasing the LUMO energy and promoting nucleophilic addition to the C=X bond.

- **Classic Lewis acids** (i.e. BCl₃, AlCl₃, etc.) make strong σ-complexes with carbonyl and imine groups
  - Used in Friedel-Crafts, Diels-Alder, and other electrophilic reactions

- **Transition metal Lewis acids** can be bifunctional
  - Activating olefins through π-binding or (and) make the σ-complexes with heteroatoms

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*J. Org. Chem. 2007, 72, 7817-7831*
Choosing your metal
Heats of formation for generated LA-olefin complexes

The halogenides of all four metals follow the same trend: the heats of formation increase with decreasing nucleophilicity of the anion (from Br to F). Simultaneously, the relative ability of corresponding Lewis acids to bind with phenylacetylene, which is reflected in decreasing values of $\Delta H_{1}/\Delta H_{3}$ and $\Delta H_{2}/\Delta H_{3}$, increases. For AuCl and CuCl, the same trend prevails when coming to the completely non-nucleophilic anions (BF$_4^-$, PF$_6^-$, SbF$_6^-$): the heats of formation increase together with relative affinity to the triple bond. This effect is almost absent for silver, whereas platinum demonstrates irregular behavior caused by

TABLE 1. Computed Heats of Formation (B3LYP/SDD, kcal mol$^{-1}$)$^a$ and Their Selected Ratios (Shown in Bold) of the Substrates 1–8 with Representative Lewis Acids

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>BCl$_3$</th>
<th>MgCl$_2$</th>
<th>AlCl$_3$</th>
<th>CuCl</th>
<th>CuCl$_2$</th>
<th>AgCl</th>
<th>AuCl</th>
<th>AuCl$_3$</th>
<th>PtCl$_2$</th>
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<tbody>
<tr>
<td>H$_2$</td>
<td>18.9</td>
<td>34.5</td>
<td>40.7</td>
<td>37.4</td>
<td>25.4</td>
<td>26.4</td>
<td>33.1</td>
<td>35.9</td>
<td>46.9</td>
</tr>
<tr>
<td>H$_3$</td>
<td>42.1</td>
<td>44.2</td>
<td>55.1</td>
<td>51.8</td>
<td>41.2</td>
<td>39.6</td>
<td>53.6</td>
<td>60.3</td>
<td>71.5</td>
</tr>
<tr>
<td>H$_4$</td>
<td>0.9</td>
<td>15.2</td>
<td>19.1</td>
<td>33.1</td>
<td>14.3</td>
<td>22.6</td>
<td>34.7</td>
<td>32.5</td>
<td>49.4</td>
</tr>
<tr>
<td>H$_5$</td>
<td>0.4</td>
<td>15.7</td>
<td>19.2</td>
<td>33.6</td>
<td>18.1</td>
<td>24.4</td>
<td>37.5</td>
<td>36.8</td>
<td>53.9</td>
</tr>
<tr>
<td>H$_6$</td>
<td>17.2</td>
<td>33.1</td>
<td>38.7</td>
<td>36.6</td>
<td>23.9</td>
<td>26.0</td>
<td>32.7</td>
<td>35.1</td>
<td>38.9</td>
</tr>
<tr>
<td>H$_7$</td>
<td>42.6</td>
<td>44.4</td>
<td>55.4</td>
<td>52.2</td>
<td>41.9</td>
<td>40.4</td>
<td>54.3</td>
<td>61.1</td>
<td>72.4</td>
</tr>
<tr>
<td>H$_8$</td>
<td>1.3</td>
<td>18.7</td>
<td>18.4</td>
<td>35.3</td>
<td>16.1</td>
<td>25.2</td>
<td>36.2</td>
<td>30.9</td>
<td>49.5</td>
</tr>
<tr>
<td>H$_9$</td>
<td>8.8</td>
<td>25.6</td>
<td>26.4</td>
<td>43.6</td>
<td>25.2</td>
<td>34.7</td>
<td>48.1</td>
<td>43.2</td>
<td>68.8</td>
</tr>
</tbody>
</table>

$^a$In the gas phase. The heats of formation were calculated by subtraction of the absolute energies of the starting compounds from the absolute energy of the optimized complex between the substrate and the Lewis acid.

J. Org. Chem. 2007, 72, 7817-7831
What type of olefins are we looking for

- mono- to tetra- substituted olefins

- Simple alkyl or styrene type olefins
  - Styrene olefins are somewhat “activated” (Suffer from polymerizations)

- Avoid 1,4-type Michael acceptors
Overview

- **Hydroalkylation of pronucleophiles**
  - 1,3-Diene alkylation
  - Intramolecular olefin alkylation
  - Intermolecular olefin alkylation

- **Hydroalkylation of electron rich arenes**
  - Electron rich benzene rings
  - Electron rich heterocycles

Ross Widenhoefer
Duke University
~20 years

Chi-Ming Che
University of Hong Kong
~25 years

Chao-Jun Li
McGill University
~20 years
Pronucleophile alkylation of 1,3-dienes

- Palladium catalyzed telomerization of dienes – discovered in 1967 by Smutny
  - Dimerization of butadiene (or even trimerization)
  - Similar to allylic substitution pathways – alleviates use of bases and leaving groups

\[
\begin{align*}
2 \text{NuH} & \xrightarrow{\text{[Pd]}} \text{linear isomer (E/Z)} + \text{branched isomer} \\
& \text{byproducts:} \\
& 1,3,7-octatriene \\
& \text{vinylcyclohexene}
\end{align*}
\]

- C-C bond formed from activated methylene species with electron-withdrawing groups, or pronucleophiles

Most difficult
First alkylation with 1,3-butadiene

- Hata group in 1971 disclosed first activated methylene alkylation
  - PdCl₂ salts were effective catalysts, with Pd(0) species also showing reactivity without the basic additive – but lower yields

\[
\text{MeOC} + \text{CO}_2\text{Et} \xrightarrow{\text{PdCl}_2(\text{PPh}_3)_2} \xrightarrow{\text{PhONa or MeONa}} \text{MeOC} + \text{CO}_2\text{Et} \text{R}\]

```
R= \text{2,7-octadienyl species}
```

- Reactivity trend

```
\text{\begin{array}{c}
\text{pka} = 9 \\
\text{R}\text{CO}_2\text{Me} \\
93%
\end{array}} \quad \text{\begin{array}{c}
\text{pka} = 11 \\
\text{R}\text{CO}_2\text{Me} \\
87%
\end{array}} \quad \text{\begin{array}{c}
\text{pka} = 13 \\
\text{R}\text{CHO} \\
87%
\end{array}}
```

- Importantly, no O-alkylation observed
- Pt(II) salts also worked, but not efficiently
- Without PPh₃ → phenol would add into the telomer
- Authors believed a Pd(0)-PPh₃ species was active catalyst

Expansion of this chemistry

- Bidentate ligands inhibit dimerization of dienes
- Substituted dienes only afford 1:1 adduct formation

\[
\text{PdBr}_2(\text{dppe})_2 \quad \text{(0.3 mol\%)} \\
\text{PhONa} \quad \text{(3 mol\%)} \\
137\text{-}150 \, \text{°C}
\]

Internal substitution = linear product

Terminal substitution = branched


- Years later, expanded additions to more important dienes

\[
\text{PdCl}_2 \quad \text{(2 mol\%)} \\
\text{dppe} \quad \text{(2 mol\%)} \\
\text{NaOPh} \quad \text{(20 mol\%)} \\
\text{EtOH} \quad \text{(5 M)} \\
100 \, \text{°C}, 18 \text{h}
\]

57% 57%

Switching to Ni(II) lead to branched products selectively

Mechanistic Analysis

- Electron rich palladium(0) deprotonates acidic C-H bond of the pronucleophile

- Without bulky bidentate ligands, the telomerization reaction can occur

- *Not a carbometallation reaction!*


Improving diene alkylation

- Modifying the basicity and bidendicity of the palladium(0)-ligands eliminated the usage of alkoxides.

\[
\begin{align*}
\text{COMe} + \text{COMe} & \xrightarrow{\text{THF, r.t., 15-40 h}} \text{COMe} \quad \text{R} = \begin{cases} 
\text{Me} & 81\% (9.4:1 \text{ E/Z}) \quad + 17\% \text{ branched} \\
\text{Et} & 82\% (9.3:1 \text{ E/Z}) \quad + 18\% \text{ branched} \\
\text{H} & 31\% (4.7:1 \text{ E/Z}) [80^\circ \text{C}] \quad + 21\% \text{ branched}
\end{cases}
\end{align*}
\]

- Trost used simpler dppe to achieve alkylation with more detailed substrate scope

\[
\begin{align*}
\text{R} + \text{SO}_2\text{Ph} & \xrightarrow{\text{(allyl)}_2\text{PdCl}_2 \text{ (1 mol%), dppe (4 mol%), NaOMe (3%)}} \text{THF, 100 }^\circ \text{C}} \quad \text{R} = \begin{cases} 
\text{(CH}_2\text{)}_2\text{CH}=\text{C}(\text{CH}_3)_2 & 58\% \\
\text{(CH}_2\text{)}_2\text{CHOH} & 12\% \\
\text{(CH}_2\text{)}_2\text{CO}_2\text{CH}_3 & 57\% \\
\text{(CH}_2\text{)}_2\text{COPh} & 57\%
\end{cases}
\end{align*}
\]


Most recent 1,3-diene alkylations

Hartwig greatly expanded the field

Nucleophiles

- 77% (96:4)
- 70% (82:18)
- 97% (96:4)
- 91% (48:52)
- 52% (57:43)
- 97% (100:0)
- 53% (93:7)
- 88% (88:12)

DCyPP = Cy2P \longrightarrow PCy2

confirmed X-ray


Hartwig. JOC 2004, 69, 7552
Overview

- **Hydroalkylation of pronucleophiles**
  - 1,3-Diene alkylation
  - Intramolecular olefin alkylation
  - Intermolecular olefin alkylation

- **Hydroalkylation of electron rich arenes**
  - Electron rich benzene rings
  - Electron rich heterocycles
Intramolecular olefin alkylation

- Pioneered by Widenhoefer of Duke University
- Analogous transformation to the Michael reaction, except no preactivation required
- Major issue with this chemistry = *avoiding over oxidation*

\[
\text{R} \quad \overset{\text{PdCl}_2(\text{MeCN})_2 (10 \text{ mol\%})}{\text{NH}_2} \quad \text{Me} \quad \overset{\text{benzoquinone LiCl, THF}}{\rightarrow} \quad \text{Me} \quad 86\%
\]


- \(\text{PdCl}_2\) salts were found to catalyze diketone alkylation without oxidants at room temp!

\[
\text{R}_1 = \text{Me, Et, } \text{tBu, OEt, OBn} \\
\text{R}_2 = \text{Me, Bn} \\
\text{R}_3 = \text{Me, } n\text{-Bu, Ph} \\
\text{R}_4 = \text{H, Me}
\]

- *Endo* selective alkylation
- Trisubstituted olefins were poor substrates

Widenhoefer. *JACS* 2001, 123, 11290

- Less acidic substrates required stoichiometric TMSCl and CuCl\(_2\) oxidants

\[
\text{R}_1 = \text{alkyl, benzyl} \\
\text{R}_2 = \text{alkyl, alkylester}
\]

- TMSCl proposed to increase enol tautomer
- CuCl\(_2\) prevents catalyst decomposition

Mechanism study

- So why did Pd(II) not get reduced to Pd(0) under these conditions?

- Utilized deuterium studies

Widenhoefer. *JACS* 2003, 125, 2056
Mechanism study

- So why did Pd(II) not get reduced to Pd(0) under these conditions?

Utilized deuterium studies

\[
\begin{align*}
\text{cis-7} & \quad \text{trans-7} \\
4 & \quad 5' \quad 6' \quad 5 \quad 6
\end{align*}
\]

Widenhoefer. *JACS* 2003, 125, 2056
How does the protonolysis work? – Why no elimination?

- Reaction fails to form 5-membered rings
  - Highly endo selective
- Authors propose highly restricted enolic attack
  - 6-endo actually then is kinetically favored
Deeper investigations

- Original work with TMSCl additives increased yields presumably due to the silyl enol ether
  - NMR studies showed that TMSCl was hydrolyzed forming HCl in the reaction
- Substitute the internal olefin position?

\[
\begin{align*}
\text{PdCl}_2(\text{MeCN})_2 (10 \text{ mol}\%) & \quad \text{CuCl}_2 (30 \text{ mol}\%), \text{HCl} (10 \text{ mol}\%) \\
\text{Dioxane, 70 °C} & \quad \text{R} = \text{alkyl, aryl} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\text{61-79%}
\]

\[
\begin{align*}
\text{PdCl}_2(\text{MeCN})_2 (10 \text{ mol}\%) & \quad \text{CuCl}_2 (30 \text{ mol}\%), \text{HCl} (10 \text{ mol}\%) \\
\text{Dioxane, 70 °C} & \quad \text{R} = \text{alkyl, aryl} & \quad \text{CO}_2\text{Me}
\end{align*}
\]

\[
\text{59%}
\]

- Extend alkene position?

\[
\begin{align*}
\text{PdCl}_2(\text{MeCN})_2 (10 \text{ mol}\%) & \quad \text{CuCl}_2 (30 \text{ mol}\%), \text{HCl} (10 \text{ mol}\%) \\
\text{Dioxane, 70 °C} & \quad \text{Hindered tertiary Pd-complex} & \quad \text{Widenhoefer. Chem. Eur. J. 2004, 10, 6343}
\end{align*}
\]

\[
\begin{align*}
\text{PdCl}_2(\text{MeCN})_2 (5 \text{ mol}\%) & \quad \text{CuCl}_2 (2 \text{ equiv}), \text{TMSCl} (2 \text{ equiv}) \\
\text{Dioxane, r.t., 12 h} & \quad \text{Optimized for enone} & \quad \text{Widenhoefer. Chem. Eur. J. 2004, 10, 6333}
\end{align*}
\]

\[
\begin{align*}
\text{PdCl}_2(\text{MeCN})_2 (10 \text{ mol}\%) & \quad \text{CuCl}_2, \text{TMSCl}, \text{Dioxane, 70 °C} \\
\text{not observed} & \quad \text{Optimized for alkylation: Widenhoefer. Chem. Eur. J. 2004, 10, 6333}
\end{align*}
\]
Alkylation practicality

- PEG-400 [poly(ethylene glycol-400)] – used as a solvent (non volatile or mixing)
  - Acidic and improves stability of catalyst → recyclable

\[
\text{O} \quad \text{PdCl}_2(\text{MeCN})_2 (1 \text{ mol}) \quad \text{CuCl}_2 (1 \text{ equiv}), \text{PEG-400, 55°C}\quad 86\%
\]

\[
\text{O} \quad \text{PdCl}_2(\text{MeCN})_2 (10 \text{ mol}) \quad \text{CuCl}_2 (1 \text{ equiv}), \text{PEG-400, 55°C} \quad \text{run 1} = 90\% \quad \text{run 2} = 98\% \quad \text{run 3} = 100\% \quad \text{run 4} = 100\% \quad \text{run 5} = 100\%
\]

- Lewis acid additives could replace HCl to promote enol formation

\[
\text{O} \quad \text{PdCl}_2(\text{MeCN})_2 (5-20 \text{ mol}) \quad \text{Yb(OTf)}_2 (1 \text{ equiv}) \quad \text{Dioxane (0.03 M), 50°C}
\]

- Could reduce LA loadings to catalytic, but slower reactions
- First formation of larger rings!

\[\text{Yang. JOC 2005, 70, 5347}\]

Pt catalysis

- Alkyl Pt(II) complexes are less receptive towards β-hydride elimination pathways
  - Combined with LA additive, reaction was highly effective

Chi-Ming Che enters the game towards the synthesis of biologically relevant molecules

- First gold catalysis in this field with unactivated olefins
- \( \text{Au(PPh}_3\text{)Cl/AgOTf} \) results in 87% yield

All exo-trig cyclizations, no endo!

- 5g scale – 90% yield / or with water as solvent for 94% yield

\[
\begin{align*}
\text{Bn} & \quad \text{O} \\
& \quad \text{N} \\
& \quad \text{C} \quad \text{O} \\
& \quad \text{N} \quad \text{C} \quad \text{O} \\
\text{Bn} & \quad \text{O} \\
& \quad \text{N} \\
& \quad \text{C} \quad \text{O} \\
& \quad \text{N} \quad \text{C} \quad \text{O} \\
\text{Bn} & \quad \text{O} \\
& \quad \text{N} \\
& \quad \text{C} \quad \text{O} \\
& \quad \text{N} \quad \text{C} \quad \text{O} \\
\end{align*}
\]

99% (3:1 dr)

99%

97% (1.3:1 dr)

98%

99%

91% (1.5:1 dr)

99%

Che. JACS 2007, 129, 5828
Gold becomes the top choice

Che. Angew. Chem. Int. Ed. 2011, 50, 4937


Overview

- **Hydroalkylation of pronucleophiles**
  - 1,3-Diene alkylation
  - Intramolecular olefin alkylation
  - Intermolecular olefin alkylation

- **Hydroalkylation of electron rich arenes**
  - Electron rich benzene rings
  - Electron rich heterocycles
Intermolecular olefin alkylation

- More uncommon and difficult than **intra**molecular counterpart
- First discovery was with ethylene gas from Widenhoefer

![Chemical reaction diagram]

- Used previous conditions for intramolecular cyclizations
- Increasing ethylene leads to oxidized product
  - Ethylene association favored over protonolysis pathway

- **Pt(II) species utilized to slow down β-Hydride elimination**

Moving back to Gold

- First alkylation with [activated] olefins by gold catalysis was accomplished by Li

\[
\text{MeO} \quad \text{(5 mol\%)} \quad \text{AuCl}_3 \quad \text{MeO} \\
\text{MeO} \quad \text{AgOTf (15 mol\%)} \quad \text{MeO}
\]

- **Regioselective Markovnikov product**
- **Styrene used in excess due to dimerization issue**

\[
\text{R}_1 \quad \text{R}_2 \quad \text{AuCl}_3 \quad \text{AgOTf (15 mol\%)} \quad \text{MeNO}_2, \text{ reflux}
\]

- **Ligands stabilizing gold reduced yields**
- **Electron rich olefins reduce yields**

Li. *JACS* 2004, 126, 6884
First alkylation with olefins (activated) by silver catalysis was accomplished by Li

- Only works with higher temps and OTf counter-anion

Substrate scope was equivalent to previous report, with slightly diminished yields

Highlight of this paper:

- C-C bond formation is reversible with silver-catalyzed C-C bond cleavage

Li. JOC 2005, 70, 5752
More abundant earth metals


➢ Gets rid of hazardous DCM solvent
More abundant earth metals


**Unsolved Problems for Intermolecular Alkylation:**

*Monoketo compounds still unattainable*

*Simple linear unactivated olefins have not yet been used*


➤ *Gets rid of hazardous DCM solvent*
Overview

- Hydroalkylation of pronucleophiles
  - 1,3-Diene alkylation
  - Intramolecular olefin alkylation
  - Intermolecular olefin alkylation

- Hydroalkylation of electron rich arenes
  - Electron rich benzene rings
  - Electron rich heterocycles
Alkylation of electron rich benzenes

- Mild/selective alternative towards Friedel-Crafts reactions

- Need really electron deficient metal species to activate olefins for weaker nucleophiles

- Major limitation ➔ product formed is highly susceptible towards β-hydride elimination
Alkylation of electron rich benzenes

- Utilized very electrophilic Pd(II) or Pt(II) cationic species (Pt was less reactive)
  - Main scope of this transformation is for alkynes

\[
\text{Ar}_1 - \text{H} + \text{R} = \text{Ar}_2 \xrightarrow{\text{Pd(OAc)}_2 (1 \text{ mol})} \xrightarrow{\text{TFA, DCM, } 25^\circ\text{C, } 10 \text{ h}} \text{Ar}_1 - \text{R} + \text{Ar}_2
\]

- Phenols allowed for bicycle formation – with esterification occurring before or after alkylation

Phenolic alkylation through telomerization

- Earlier report in the late 1960s only saw O-alkylation with phenols with Pd(II) catalysis
- Beller tried conditions from telomerization reaction with methanol

**Equation:**

\[
\text{PhOH} + \text{RCH} = \text{CH}_2 \rightarrow \text{PhOH} \quad 25\% \quad \text{PhO} - \text{CH} = \text{CH}_2 \quad 30\% \quad \text{PhO} - \text{R} \quad 7\%
\]

**Conditions:**

1. **First Reaction:**
   - \(\text{Pd(OAc)}_2 (0.1 \text{ mol\%})\)
   - \(\text{PPh}_3 (1 \text{ equiv.})\)
   - THF, 90 °C
   - 84%

2. **Second Reaction:**
   - \(\text{Pd(OAc)}_2 (0.5 \text{ mol\%})\)
   - \(\text{PPh}_3 (1.5 \text{ mol\%})\)
   - NEt₃, THF, 90 °C
   - 84%

**Mechanism:**

Intramolecular hydroarylation

- Sames group is the first to utilize ruthenium in this field
  - Other metals screened promoted olefin isomerization

- Highly versatile methodology
- Easy reaction conditions
- Favors 6-exo attack
- Unactivated arenes
- Can form quat center!

\[
\text{RuCl}_3 \cdot x\text{H}_2\text{O} \quad (10 \text{ mol}\%)
\]
\[\text{AgOTf} \quad (10 \text{ mol}\%)
\]
\[
\text{DCE}, \quad 60^{\circ}\text{C}
\]

![Chemical structures and reactions](image)

- Promotes polyene cyclizations
- Substrate chirality can promote stereoselectivity

More general arene alkylation procedure

- Don Tilley’s group did in-depth Pt catalyst examinations
  - Original goal was to make a Pt(IV) species

- They did discover that Pt(II) salts with Ag additives could promote this transformation
  - AgOTf and AgBF₄ were necessary

- HOTf could catalyze this reaction separately, but they ruled out its involvement in this process

![Chemical diagram and reaction scheme showing the alkylation process with various product yields.](image-url)

Tilley. *Organometallics* 2004, 23, 4169
Annulation reaction of phenols

- Used catalytic system discovered for 1,3-diketone alkylations

![Reaction scheme]

- EWGs or increasing tether size lowers reaction yield
- Analines did not participate in this reaction

Allylation of phenol could occur before hydroarylation

Li. Org. Lett. 2006, 8, 2397
Bismuth catalysis

- Bi(III) salts are bench stable, inexpensive, and nontoxic
- Was very effective for neat reaction conditions

\[
\text{OR}_1 + \text{R}_2 \xrightarrow{\text{BiCl}_3 (10 \text{ mol\%})} \text{R}_1\text{O} \xrightarrow{100 ^\circ \text{C}} \text{R}_2
\]

\[
\begin{align*}
R_1 &= \text{Et}, \ R_2 = \text{H} & 94\% (80 : 20) \\
R_1 &= \text{Et}, \ R_2 = \text{Me} & 95\% (98 : 2) \\
R_1 &= \text{Me}, \ R_2 = \text{Ph} & 61\% (>99 : 1)
\end{align*}
\]

- Was very successful cyclic dimer formation of unactivated styrenes
  - Trisubstituted olefins were not compatible

\[
\text{R} \xrightarrow{\text{BiCl}_3 (10 \text{ mol\%})} \text{R} \xrightarrow{100 ^\circ \text{C}} \text{R}
\]

\[
\begin{align*}
R &= 4\text{-Me} & 65\%
\end{align*}
\]

\[
\begin{align*}
R &= 4\text{-Cl} & 92\%
\end{align*}
\]

Other lewis acid systems

\[
\begin{align*}
\text{In(OTf)}_3 (10 \text{ mol\%}) & \quad \text{DCE, 90°C} \\
\text{R} = \text{H, Me} \\
\end{align*}
\]


\[
\begin{align*}
\text{AuCl}_3 (5 \text{ mol\%}) & \quad \text{AgSbF}_6 (15 \text{ mol\%}) \\
\text{DCE, 50°C} \\
\end{align*}
\]


\[
\begin{align*}
\text{AuCl}_3 (5 \text{ mol\%}) & \quad \text{AgSbF}_6 (15 \text{ mol\%}) \\
\text{DCE, 50°C} \\
\end{align*}
\]

Weghe. *Tet. Lett.* **2011, 52, 3509
Some mechanistic analysis

- Protonolysis was presumed the limiting step

![Chemical reaction diagram]

- Question that remains for these systems, is it Bronstead acid catalysis?

![Chemical reaction diagram]

Could the combination of AuCl₃ and AgOTf simply generate TfOH?

Getting unique in this catalysis

- Goal: overcome the inability of Friedel-Crafts incapability with anilines

- Anti-Bredt electrophilic carbenes
  - Found use in hydroaminations of alkynes and allenes

\[
\begin{align*}
R &= \text{mesityl, tolyl, phenyl, nitrobenzyl, toluenesulfonyl} \\
\text{Electron Rich} &\quad \rightarrow \quad \text{Electron Poor}
\end{align*}
\]

- Synthesis of ligand is built in coordination sphere of metal

\[
\begin{align*}
a: R &= 2,4,6-\text{Me}_3(\text{C}_6\text{H}_2); \\
b: R &= \text{Ph}; \\
c: R &= 4-\text{Me}(\text{C}_6\text{H}_4); \\
d: R &= 4-\text{NO}_2(\text{C}_6\text{H}_4); \\
e: R &= 4-\text{Me}(\text{C}_6\text{H}_4)\text{SO}_2\text{CH}_2
\end{align*}
\]

Hu and Bertrand. *JACS* 2014, 136, 13594
Getting unique in this catalysis

- Goal: overcome the inability of Friedel-Crafts incapability with analines

Table 1. Hydroarylation of α-Methylstyrene with N,N-Diethylaniline

<table>
<thead>
<tr>
<th>entry</th>
<th>catalytic system</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[3a + KB(C\textsubscript{6}F\textsubscript{5})\textsubscript{4}] (5 mol %)</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>[3b + KB(C\textsubscript{6}F\textsubscript{5})\textsubscript{4}] (5 mol %)</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>[3c + KB(C\textsubscript{6}F\textsubscript{5})\textsubscript{4}] (5 mol %)</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>[3d + KB(C\textsubscript{6}F\textsubscript{5})\textsubscript{4}] (5 mol %)</td>
<td>69</td>
</tr>
<tr>
<td>5</td>
<td>[3e + KB(C\textsubscript{6}F\textsubscript{5})\textsubscript{4}] (5 mol %)</td>
<td>38</td>
</tr>
<tr>
<td>6</td>
<td>3a (5 mol %)</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>[3a + AgOSO\textsubscript{2}CF\textsubscript{3}] (5 mol %)</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>[AuCl\textsubscript{3} + 3 AgSbF\textsubscript{6}] (5 mol %)</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>FeCl\textsubscript{3} (10 mol %)</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>BiCl\textsubscript{3} (10 mol %)</td>
<td>4</td>
</tr>
</tbody>
</table>

\textsuperscript{a}After 24 h; determined by GC.
Getting unique in this catalysis

alkyl + alkyl

\[
N\begin{array}{c}
\text{Me} \\
\text{alkyl} \end{array} + R \begin{array}{c}
\text{H/OMe} \\
\text{alkyl} \end{array} \xrightarrow{\text{AuCl (1 mol%)}} \text{Alkyl} \begin{array}{c}
\text{Me} \\
\text{N} \end{array} \begin{array}{c}
\text{R} \\
\text{alkyl/Me} \end{array} + \text{MeO} \begin{array}{c}
\text{H/OMe} \\
\text{alkyl} \end{array} \xrightarrow{\text{KB(C\text{6}F\text{5})\text{4} (1 mol%)}} \text{Alkyl} \begin{array}{c}
\text{Me} \\
\text{N} \end{array} \begin{array}{c}
\text{R} \\
\text{alkyl} \end{array} \begin{array}{c}
\text{H/OMe} \\
\text{alkyl} \end{array} \begin{array}{c}
49-99\% \\
80-155 \^\circ C \end{array}
\]

MeO \begin{array}{c}
\text{alkyl} \\
\text{alkyl} \end{array} \xrightarrow{\text{AuCl (1 mol%)}} \text{MeO} \begin{array}{c}
\text{alkyl} \\
\text{alkyl} \end{array} \begin{array}{c}
\text{H/OMe} \\
\text{alkyl} \end{array} \begin{array}{c}
\text{alkyl} \\
\text{alkyl} \end{array} \begin{array}{c}
25\% \\
r.t. \end{array}

Alkyl + Alkyl

\[
N\begin{array}{c}
\text{alkyl} \\
\text{alkyl} \end{array} + \begin{array}{c}
\text{O} \\
\text{alkyl} \end{array} \xrightarrow{\text{AuCl (1 mol%)}} \text{Alkyl} \begin{array}{c}
\text{N} \\
\text{alkyl} \end{array} \begin{array}{c}
\text{alkyl} \\
\text{alkyl} \end{array} \begin{array}{c}
\text{O} \\
\text{alkyl} \end{array} \begin{array}{c}
44-68\% \\
80-155 \^\circ C \end{array}
\]

Hu and Bertrand. JACS 2014, 136, 13594
Overview

- **Hydroalkylation of pronucleophiles**
  - 1,3-Diene alkylation
  - Intramolecular olefin alkylation
  - Intermolecular olefin alkylation

- **Hydroalkylation of electron rich arenes**
  - Electron rich benzene rings
  - Electron rich heterocycles
Electron rich heterocycles

- Focus lies mainly on indole systems
- First report by Sames in 2004 in previously discussed paper (only 2 examples)

Actually a very unique example, where alkylation takes place at the less nucleophilic C(2) position

Sames. Org. Lett. 2004, 6, 581
Alklyation at the C3 position of indoles

- C3 alkylation of indoles is most widely seen in the literature

\[
\begin{align*}
N &\quad Me \\
N &\quad Bn \\
N &\quad MeO \\
N &\quad Me
\end{align*}
\]

92% 85% 94% 91% 82% (>50:1) 90%

\[\text{[PtCl}_2(\text{H}_2\text{C=CH}_2)_2 (2 \text{ mol\%}) \text{ HCl (5 mol\%)} \] Dioxane, 90 °C

Widenhoefer. *JACS* 2004, 126, 3700
More abundant earth metals

\[
\text{PhCOO} + \text{Ph} \rightarrow \text{PhCOO}
\]

FeCl₃ (30 mol%) DCE, 80 °C, 5 h

33 R₁ = H, R₂ = Cl
34 R₁ = H, R₂ = OMe
35 R₁ = Me, R₂ = H

72%
23%
96%

Duan and Wu. *Tet. Lett.* 2007, 48, 5157

Unsolved Problems for Intermolecular Alkylation:

Monoketo compounds still unattainable

Simple linear unactivated olefins have not yet been used


- Gets rid of hazardous DCM solvent
Widenhoefer’s contribution

Tandem cyclization/carboalkoxylation

Widenhoefer. *JACS* 2004, 126, 10250

Assymetric alkylation

Widenhoefer. *Org. Lett.* 2006, 8, 3801

First intramolecular addition


\[
\text{FG} \quad \text{H/Me} \\
\begin{array}{c}
\text{PdCl}_2(\text{MeCN})_2 \text{ (5 mol%)}
\end{array}
\begin{array}{c}
\text{CuCl}_2 \text{ (3 equiv.)}
\end{array}
\begin{array}{c}
\text{R'OH} \text{ (10 equiv.)}
\end{array}
\rightarrow
\begin{array}{c}
\text{FG} \quad \text{H/Me}
\end{array}
\begin{array}{c}
\text{R'}
\end{array}
\begin{array}{c}
\text{CO}_2\text{R''}
\end{array}
\]

THF, CO (1 atm), 25 °C

\[\text{FG} = \text{H, OMe, F} \quad \text{R'} = \text{alkyl, ester, ketone, cyclohexenyl} \quad n = 0, 1, 2\]

\[\text{R''} = \text{alkyl} \quad n = 1, 2 \quad 45-92\%
\]

\[\text{L2-PtCl}_2 \text{ (10 mol%)} \quad \text{AgOTf} \text{ (10 mol%)}
\]

MeOH, 60 °C, 64 h

94% (9:1 cis/trans)

\[\text{L2} = \begin{array}{c}
\text{MeO} \\
\text{MeO}
\end{array} \begin{array}{c}
\text{PAr}_2 \\
\text{PAr}_2
\end{array}
\]

\[\text{Ar} = \begin{array}{c}
tBu \\
\text{OMe}
\end{array}
\]

\[\text{Me}
\]

\[\text{Me}
\]

\[\text{E}
\]

\[\text{E}
\]

\[\text{Me}
\]

\[\text{Me}
\]

\[\text{R}
\]

\[\text{R}
\]

\[\text{R} = \text{Me, Et, Pr, phenyl}
\]

\[\text{39-99\%}
\]
Gold discovery for indole alkylation

- An interesting side story, group working on reaction discovery from high-throughput screening of large collection of substrates – only looking for new bond formations

- Main focus in this group was with DNA hybridization reactions, but also wanted to test this on small molecule bond-forming reactions

- System works for evaluating > 50,000 potential new reactions

- Screened various metals (i.e. Cu, Pd, Au, etc)

\[
\begin{align*}
\text{Bs} & = \text{phenylsulfonyl} \\
\text{AuCl}_3 (10 \text{ mol}%) & + \text{AgOTf} (30 \text{ mol}%) \\
& \text{DCM, 25 °C} \\
& 93\%
\end{align*}
\]
Other Au catalysis for this alkylation

Che in the same year followed up with more analysis of this reaction and scope

\[
\begin{align*}
\text{NMe} & \text{[PPh}_3\text{AuCl]} (2 \text{ mol\%}) \\
& \text{AgOTf (2 mol\%)} \\
toluene, \ 85 \ ^\circ \text{C}, \ 1.25 \text{ h} \\
& 85\% \\
\text{TfOH (5 mol\%),} & \ \text{85 \ ^\circ \text{C},} & \ \text{12 \text{ h}} \\
& 72\% \\
\end{align*}
\]

\[
\begin{align*}
\text{NMe} & \text{[PPh}_3\text{AuCl]} (5 \text{ mol\%}) \\
& \text{AgOTf (5 mol\%)} \\
toluene, MW 130-140 \ ^\circ \text{C} \\
& 62-81\% \\
\end{align*}
\]

\[
\begin{align*}
\text{O}_2\text{N} & \text{NMe} \\
& \text{[PPh}_3\text{AuCl]} (5 \text{ mol\%}) \\
& \text{AgOTf (5 mol\%)} \\
\text{DCE, MW 140 \ ^\circ \text{C,}} & \ \text{5 min} \\
& 85\% \\
\text{TfOH (5 mol\%),} & \ \text{50 \ ^\circ \text{C,}} & \ \text{16 \text{ h}} \\
& 32\% \\
\end{align*}
\]

Future of this field

Alkylations of pronucleophiles

- Simple olefin alkylation of pronucleophiles is very rare and could be exploited
- Alkylation of simple ketones or weakly acidic C-H bonds is still open for exploration

Alkylations of arenes

- Trend is moving away from very expensive metals
- Functionalization of electron deficient arenes through this methodology is difficult
- With rise of Bronstead acid catalysts, this field must work to differentiate themselves with asymmetric transformations or with more diverse substrates
Questions
1. Propose a mechanism for the following transformation.

\[ \text{Ac} \quad \text{NaOMe, Br} \quad \text{Br} \quad \text{SO}_2 \quad \text{MeO}_2 \text{C} \quad \text{H} \quad \text{SO}_2 \text{Ph} \]

2. Predict the products (ignore stereochem & other isomers).

\[ \text{O} \quad \text{OH} \quad \text{acetone 40 °C, 24h} \quad 55\% \quad (3 \text{ diastereomers}) \]

\[ \text{Bn} \quad \text{O} \quad \text{N} \quad \text{Me} \quad \text{Au}[\text{P(t-Bu)}_2(\text{o-biphenyl})\text{Cl} (5 \text{ mol%}) \quad \text{AgOTf} (5 \text{ mol%}) \quad \text{toluene, 50 °C} \quad 95\% \]

\[ \text{OH} \quad \text{OH} \quad \text{AuCl}_3 (5 \text{ mol%}) \quad \text{AgOTf} (15 \text{ mol%}) \quad \text{DCM, 40 °C, 16 h} \quad 55\% \text{ yield (major)} \]

3. Propose a mechanism for the following transformation.

\[ \text{N} \quad \text{PdCl}_2(\text{MeCN})_2 (5 \text{ mol%}) \quad \text{CuCl}_2 (3 \text{ equiv.}) \quad \text{MeCl}_2 (10 \text{ equiv.}) \quad \text{THF, CO (1 atm), 25 °C} \quad \text{CO}_2 \text{Me} \]
Question 1

Question 2


**Che. JACS 2007, 129, 5828**

**Li. Org. Lett. 2006, 8, 2397**
Question 3