Hydroacylation and Related Topics
Dong Group Seminar
Brandon Reinus
Wed, Sept. 5th 2012
Why?

- Looking at the reaction, it is a highly atom-economical approach to synthesizing ketones.
- Umpolung (ex: deprotonating dithioacetals).
- Using acrylate derivatives generates a 1,4 diketone relationship, a hard relationship to establish using classical organic synthesis.
Presentation Overview

1. Hydroformylation (extremely brief)

2. Rh-Catalyzed Hydroacylation
   - Intramolecular
   - Intermolecular
   - Other

3. NHC Catalyzed Hydroacylation
   - Benzoin reaction
   - Stetter reaction
   - other
Part 1: Background

Reppe

Roelen

Science of Synthesis, Stereoselective Synthesis 1, 2011, pg.409
Hydroformylation
Part 2: Rh-Catalyzed Hydroacylation

Decarbonylation can be suppressed by using high pressures of ethylene or CO or by generating a *metallacycle*.

More on Decarbonylation:
- Organometallics 1999, 18, 5311
- JACS 2008, 130, 5206
- Chem. Commun. 2008, 6215
Historical Reactions

- Sakai (1972)

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{R}_1 & \quad \text{R}_2
\end{align*}
\]

\[
\frac{\text{RhCl(PPPh}_3)_3 (1 \text{ equiv.})}{\text{CHCl}_3, \text{MeCN or C}_6\text{H}_6, \text{rt}}
\]

\[
\begin{align*}
\text{3} & \quad 17\% - 34\% \\
\text{4} & \quad 20\% - 35\%
\end{align*}
\]

- Milstein (1982)

\[
\begin{align*}
\text{R}_2 & \quad \text{H} \\
\text{R}_3 & \quad \text{R}_4
\end{align*}
\]

\[
\frac{\text{RhCl(PMe}_3)_3}{\text{PhMe, rt.}}
\]

\[
\begin{align*}
\text{5} & \quad \text{50}^\circ\text{C} \\
\text{6} & \quad 72\%
\end{align*}
\]

- Miller and Coworkers (1976)

\[
\begin{align*}
\text{R}_2 & \quad \text{H} \\
\text{R}_3 & \quad \text{R}_4
\end{align*}
\]

\[
\frac{\text{RhCl(PPPh}_3)_3 (10 \text{ mol %})}{\text{CHCl}_3, \text{C}_2\text{H}_4, \text{rt, 88 h}}
\]

\[
\begin{align*}
\text{72%}
\end{align*}
\]

- Larock (1980)

\[
\begin{align*}
\text{Me} & \quad \text{CHO} \\
\text{Me} & \quad \text{CHO}
\end{align*}
\]

\[
\frac{[\text{RhCl(COD)}_2 (50 \text{ mol %})]}{\text{C}_2\text{H}_4 \text{ saturated CH}_2\text{Cl}_2, \text{rt}}
\]

\[
\begin{align*}
\text{8} & \quad \text{51%}
\end{align*}
\]

*Trimethyl phosphine is slow to dissociate

*Also isolated ethylene insertion products

Chemical Reviews, 2010, p. 725
Intramolecular Reactions

Table 1. Scope of Bosnich's Cationic Rh(I) Cyclizations

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde</th>
<th>catalyst mol%</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-ethyl-4-pentenal</td>
<td>1</td>
<td>[Rh(dppe)]ClO4</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>2-methyl-3-pentenal</td>
<td>1</td>
<td>[Rh(dppe)]ClO4</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>2-methyl-3-pentenal</td>
<td>1</td>
<td>[Rh(dppe)]ClO4</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>2-phenyl-2-pentenal</td>
<td>1</td>
<td>[Rh(dppe)]ClO4</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>2-phenyl-2-pentenal</td>
<td>2</td>
<td>[Rh(dppe)]ClO4</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>2-methyl-4-pentenal</td>
<td>4</td>
<td>[Rh(dppe)]ClO4</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>3-methyl-2-pentenal</td>
<td>1</td>
<td>[Rh(dppe)]ClO4</td>
<td>70</td>
</tr>
<tr>
<td>8</td>
<td>2,4-pentadienal</td>
<td>1</td>
<td>[Rh(dppe)]ClO4</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>3-methyl-2-pentenal</td>
<td>1</td>
<td>[Rh(dppe)]ClO4</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>3,4-pentadienal</td>
<td>2</td>
<td>[Rh(dppe)]ClO4</td>
<td>94</td>
</tr>
<tr>
<td>11</td>
<td>2,3-pentadienal</td>
<td>2</td>
<td>[Rh(dppe)]ClO4</td>
<td>30</td>
</tr>
</tbody>
</table>

* [Rh(dppe)]ClO4; CD3NO2, 20 °C. + Determined by GC and 1H NMR methods. + 65 °C.

Tandem Reaction:

Organometallics 1988, 7, 936-945
Angew Chem, Int. Ed. 2003, 42, 2385
Larger Rings

The formation of ring systems larger than cyclopentanones is disfavored due to the ring strain that would be present in five-ring formation and decarbonylation can become problematic. For example, reaction with the use of a suitable catalyst, it is possible to couple the reactions of both the 5-alkenyl and the 5-alkenone to a limited range of substrates.

Scheme 8 gives two examples; the use of RhCl(PPh3)3 (50 mol %) in CH2Cl2, rt was found to be optimal. A polystyrene-supported rhodium catalyst has also been used in related transformations. A variety of synthetically useful substituents on the alkenyl group is allowed. Rh(I) catalysts in cyclizations analogous to those shown in Scheme 12 were obtained as the exclusive product if suitable additional functionality is incorporated throughout. For an application of this methodology to natural product synthesis, see Scheme 31.

The cationic rhodium systems favored by Bosnich were used in related transformations. Cyclopentanones was efficient for a number of substrates.

The use of a relatively high loading of Wilkinson's complex allowed a variety of synthetically useful substituents on the alkenyl group is allowed. Rh(I) catalysts in cyclizations analogous to those shown in Scheme 12 were obtained as the exclusive product if suitable additional functionality is incorporated throughout. For an application of this methodology to natural product synthesis, see Scheme 31.

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Diastereo- and Enantioselective Hydroacylation

Scheme 17

Scheme 18

Scheme 19

Scheme 20

Table 3 allowed double diastereoselection to be explored, Table 4. Stereoselective Synthesis of 3,4-Disubstituted

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>catalyst</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>cis/trans</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3R</td>
<td>Rh[(S)-BINA]</td>
<td>1.5</td>
<td>85</td>
<td>&lt;1:99</td>
</tr>
<tr>
<td>2</td>
<td>3R</td>
<td>Rh[(R)-BINA]</td>
<td>4</td>
<td>74</td>
<td>97:3</td>
</tr>
<tr>
<td>3</td>
<td>3S</td>
<td>Rh[(R)-BINA]</td>
<td>2</td>
<td>86</td>
<td>&lt;1:99</td>
</tr>
<tr>
<td>4</td>
<td>3S</td>
<td>Rh[(S)-BINA]</td>
<td>5</td>
<td>82</td>
<td>96:4</td>
</tr>
</tbody>
</table>

Enantioselective cyclizations of the same substrate with the (S)-configured product with 36 % of the catalyst employing (S)-configured substrate. A similar pattern was observed for the (3S,4S)-substrate with 5 mol % catalyst loadings compared with the 5 mol % catalyst loadings. The neutral complexes were no longer active catalysts. The cationic complexes allowed the selective synthesis of all four possible enantiomers.

Entry | R | ligand | ee (%) |
|------|---|--------|--------|
| 1
| Me | (S,S)-McDuphos | 94 |
| 2
| iPr | (S,S)-McDuphos | 96 |
| 3
| cyclopentyl | (S,S)-McDuphos | 96 |
| 4
| tBu | (S)-BINA | >99 |
| 5
| SiMe3 | (S)-BINA | >99 |
| 6
| Ph | (S,S)-chiraphos | 78 |
| 7
| 4-MeO-Ph | (S,S)-chiraphos | 75 |
| 8
| C(OMe) | (S)-BINA | 87 |
| 9
| C(O)Ph | (S)-BINA | 94 |
| 10
| CO2Et | (S)-BINA | >99 |
| 11
| CO2tPr | (S)-BINA | >99 |

a PF6− salt (5 mol %) used. b Acetone. c CH2Cl2.
Application

(-)-limonene-10-ol → 43 → 44

Me

OAc

OAc

[\text{RhCl(PPh}_3\text{)}_3 (30 \text{ mol} \%)] \quad \text{CH}_2\text{Cl}_2, \text{rt, 2.5 h}

88\%

Scheme 22

Scheme 21

Scheme 20

Table 6

Chemical Reviews, 2010, Vol. 110, No. 2
Intermolecular Hydroacylation

\[
\text{[\(\eta^5\text{-C}_3\text{H}_7\text{Rh(C}_2\text{H}_4\text{)}_2\text{]} (3.6 \text{ mol } \%)} \quad \text{C}_2\text{H}_4 (1000 \text{ psi}) \quad \text{C}_6\text{D}_6, 100 ^\circ \text{C}
\]

\[
\text{H} \quad \overset{\text{RhCl(PPh}_3)_3}{\text{CH}_2\text{Cl}_2} \quad \text{Ph}_3\text{P} \quad \text{Rh} \quad \text{Cl} \quad \text{PPh}_3
\]

\[
\text{H}_4\text{C} \quad \overset{\text{RhCl(PPh}_3)_3}{\text{CH}_2\text{Cl}_2} \quad \text{H} \quad \text{PPh}_3
\]

\[
\text{H}_4\text{C} \quad \overset{\text{RhCl(PPh}_3)_3}{\text{CH}_2\text{Cl}_2} \quad \text{H} \quad \text{PPh}_3
\]

\[
\text{H}_4\text{C} \quad \overset{\text{RhCl(PPh}_3)_3}{\text{CH}_2\text{Cl}_2} \quad \text{H} \quad \text{PPh}_3
\]

1. AgBF\(_4\)  
2. Me  
55%
Chelation Assisted

![Chemical structures and reactions](image)

Chem reviews 2010, p.725
Aldimines

![Chemical reaction diagram](image)

Chem reviews 2010, p.725
Stereoselective Intermolecular reactions

Very limited in scope, still needs a lot of work
Fu group has more recently reported the cyclization of an alkyne hydroacylation product. An attempted aldehyde decarbonylation, employing stoichiometric conditions, was performed to support this hypothesis. A single example of a similar reaction was conducted using the equivalent BINAP-derived catalyst. An impressive range of 4-alkynals was converted to cyclopentenones (Scheme 61). An impressive range of reactions has received significantly less attention compared to the intermolecular hydroacylation of alkynes.

4. Intramolecular Alkyne Hydroacylation

4.1. Catalytic Achiral Systems

The group found that it was necessary to employ aromatic substituents (4-position) to obtain high enantioselectivity. The authors also showed that the process was not a simple kinetic resolution of a racemic mixture. A quaternary center was employed in desymmetrization reactions. Racemic 4-alkynals bearing substituents in the 3-position could tolerate a variety of aryl, hetero aryl, and alkyl groups.

During these studies, the Tanaka group observed that when a quaternary center was employed in desymmetrization reactions, the process was established as the formation of the corresponding cyclopentenones and cyclohexenones. The 5- and 6-alkynal cyclizations were conducted at elevated temperature, and substitution at the 3-, 4-, and 7-alkynal positions was unsuccessful and resulted in the return of starting material.

Intermolecular hydroacylation of alkynes has been shown to generate a range of 4-alkynals such as 2-amino-3-alkylidenecyclohexanones in good regio- and enantioselectivity. This approach could tolerate a variety of aryl, hetero aryl, and alkyl groups. Interestingly, the major products in this transformation were the desired 5-exo and 6-endo alkenes.

5. Intermolecular Alkyne Hydroacylation

5.1. Catalytic Achiral Processes

During their study of S-chelation-assisted intramolecular alkyne hydroacylations, the authors established that alkynes could generate lactones and ketones. The process was significantly less efficient than the intermolecular hydroacylation of alkynes. The reactions were conducted at room temperature, and substitution at the 3-, 4-, and 7-alkynal positions was unsuccessful and resulted in the return of starting material.

The optimized procedure involved performing the whole process at room temperature, and substitution at the 3-, 4-, and 7-alkynal positions was unsuccessful and resulted in the return of starting material.

Some examples of intramolecular alkyne hydroacylations are shown in Scheme 66. A single example transformation is shown in Scheme 67. A quaternary center was employed in desymmetrization reactions. Racemic 4-alkynals bearing substituents in the 3-position could tolerate a variety of aryl, hetero aryl, and alkyl groups.

Jun has applied his rhodium-based methodology to the intermolecular hydroacylation of alkynes. The catalytic system generated from Wilkinson's complex, 2-amino-3-alkylidenecyclohexanones, was shown to be significantly less efficient than the intermolecular hydroacylation of alkynes. The reactions were conducted at room temperature, and substitution at the 3-, 4-, and 7-alkynal positions was unsuccessful and resulted in the return of starting material.

An impressive range of reactions has received significantly less attention compared to the intermolecular hydroacylation of alkynes. The process was not a simple kinetic resolution of a racemic mixture. A quaternary center was employed in desymmetrization reactions. Racemic 4-alkynals bearing substituents in the 3-position could tolerate a variety of aryl, hetero aryl, and alkyl groups.
Alkynes Intermolecular

Application:

Chem reviews 2010, p.725
Angew. Chem. Int. Ed. 2011, 50, 10657
Other substrates

\[
\begin{align*}
\text{acylation} & \quad \text{are much less studied.}
\end{align*}
\]

Species across a ketone or an aldehyde—carbonyl hydro-promoted variant—the Tishchenko reaction—is a relatedhydres has traditionally been achieved under basic conditions reaction conditions, to be replaced by a selective, atom formation can often allow a traditional reaction, perhaps one
economy.

\[\text{acylation reactions offer advantages in terms of step and atom} \]

Michael C. Willis*

[Image -383x-589 to -260x-562]

Department of Chemistry, University of Oxford

Transition-metal-catalyzed hydroacylation reactions usu-

\[\text{[1, 5]}\]

\[\text{/C0} \]

\[\text{/C0} \]

\[\text{Cooling the reactions to room temperature allows the}

\[\text{temperatures needed for reaction disrupt a H-bonding}

\[\text{examples.} \]

\[\text{employed, with 2-amino-4-picoline taking the place of}

\[\text{modification of the system allowed primary}

\[\text{triphenylphosphine and a stoichiometric amount of 2-amino-}

\[\text{as described previously. The most efficient catalyst was found}

\[\text{with minimal loss of activity.} \]

\[\text{The disproportionation of alde-

\[\text{The Kim group has utilized the Jun methodology in the}

\[\text{Efforts to aid catalyst recovery have also been reported.}

\[\text{As an alternative to these}

\[\text{As can be seen from the examples presented in Scheme 42,}

\[\text{in hydroacylation and related reactions are available.} \]

\[\text{The catalyst could be}

\[\text{A similar concept has been}

\[\text{chemo selective ketone hydroacylation.} \]

\[\text{Scheme 1.} \]

\[\text{Few examples, C-O bond formation} \]

Chem reviews 2010, p.725
Angew. Chem. Int. Ed. 2010,49,6026-6027
My take:

- **Intramolecular** - start with cationic or other coordinatively unsaturated Rh(I)

- **Intermolecular**
  - **Chelation** - toss-up both are used in the literature, see if anyone has used similar substrates, if not lean towards starting with cationic Rh(I)
  - **Aldimines** – start with Wilkinson’s catalyst or other neutral Rh(I)
Extending NHC-Catalysis to Uncommon Electrophiles

Biju et al.

Applications, NHCs are mainly used for the umpolung of aldehydes. In these reactions, addition of the NHC to the aldehyde finally results in the generation of an acyl anion equivalent, the Breslow intermediate. The benzoin condensation and Stetter reaction are the two most well-known transformations, which employ the Breslow intermediate as key intermediate (eq 1). Generally, imidazolium, thiazolium, or triazolium salt-derived NHCs have been used successfully for umpolung reactions, and during recent years there has been an increased interest in NHC-catalyzed transformations and many new reactions have been developed. The purpose of the present Account is to provide an update about the recent developments in NHC organocatalysis. Mainly, the Account is focused on NHC-catalyzed reactions of unconventional electrophiles developed in our laboratory, but adequate description of related work carried out by others is also given.

From a historical perspective, a report by Ukai et al. in 1943 demonstrating that thiazolium salts could be used as catalysts in the benzoin reaction constitutes an early example for the involvement of azolium salts in organocatalysis. Breslow proposed a mechanistic explanation for the thiazolium salt-catalyzed benzoin condensation in 1958. In this mechanism, the catalytically active species was represented as a thiazolium zwitterion, the resonance structure of an NHC, and the reaction was postulated to proceed via the enaminol intermediate, the “Breslow intermediate” (Scheme 1). However, the existence of carbenes as catalytically active species in these processes was only realized almost three decades later when the synthesis of stable phosphinocarbene was reported by Bertrand and co-workers in 1988 and the isolation and characterization of stable NHC was unequivocally established by Arduengo and co-workers in 1991. Although NHCs were used long before these findings, these seminal discoveries marked a true breakthrough and initiated extensive research in the application of NHCs in catalysis.

Following the proposal of Breslow, a key step in benzoin condensation is the nucleophilic attack of the in situ generated carbene to the aldehyde, leading to the tetrahedral intermediate, which undergoes proton transfer to the nucleophilic enaminol intermediate. This acyl anion equivalent reacts as a nucleophile with another molecule of aldehyde to furnish the final product, the R-hydroxy ketone, and the original NHC catalyst is regenerated (Scheme 1).

The phenomenal success of NHCs in organocatalysis can be attributed primarily to their electronic properties leading to different modes of action in catalysis (Figure 1). The pronounced nucleophilicity of NHCs allows the addition to electrophiles such as aldehydes leading to the formation of the tetrahedral intermediate (A). The azolium moiety is strongly electron-withdrawing, acidifying the R-position (E). Alternatively, the same tetrahedral intermediate can undergo hydride transfer in the presence of easily reducible substrates such as activated carbonyl compounds resulting in an acyl azolium species and a reduced reaction partner (H). The enaminol moiety (Breslow intermediate) prepared in mode (E) is highly nucleophilic and acts as an acylating agent in a variety of NHC-catalyzed transformations (B, then F).

Furthermore, the addition of an NHC to R,β-unsaturated aldehydes can lead to a dienaminol intermediate, rendering the β-carbon atom nucleophilic (C). Additionally, the enaminol can trigger an elimination, if there is a leaving group at the R-position of the aldehyde (D). In this process, a nucleophilic enol(ate) can form, in which the attached azolium species acts as a bystander (I). Moreover, the catalyst can increase the electrophilicity in acyl azolium species and act as a good leaving group, re-entering the catalytic cycle (G). A variety of NHC-catalyzed redox processes lead to the formation of acyl azolium species using an oxidant. Finally, the Breslow intermediate can also act in a dual push/C pull process.
Extending NHC-Catalysis to Uncommon Electrophiles

Biju et al.

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Scheme 1. Proposed Mechanism of Benzoin Condensation

The Old

The New

Justus Von Liebig
Nikolay Zinin
Cross-Benzoin

\[
R^1 \text{SiEt}_3 + H - R^2 \overset{\text{NHC}}{\rightarrow} \overset{\text{6 (5 mol\%)} \text{ n-BuLi (5-20 mol\%)}}{\text{THF, 0-25 °C, 0.5 h}} \rightarrow \overset{\text{6 (5 mol\%)} \text{ n-BuLi (5-20 mol\%)}}{\text{THF, 0-25 °C, 0.5 h}} \rightarrow \overset{\text{THF, 0-25 °C, 0.5 h}}{\text{13 examples, 65-88\% yield 41-90\% ee}} \text{Johnson et al.}^{13}
\]

\[
\text{OTES} + H - R^2 \overset{\text{CsF (1.5 equiv)}}{\overset{i-\text{PrOH (0.2 M)}}{\rightarrow} \overset{\text{Scheidt et al.}^{14}}{\text{12 examples, 41-80\% yield}}}
\]

\[
R^1 = \text{alkyl, aryl} \quad R^2 = \text{alkyl, aryl, heteroaryl}
\]

\[
R^1 = \text{alkyl} \quad R^2 = \text{alkyl}
\]

\[
\overset{\text{7 (10 mol\%)} \text{ DBU (20 mol\%)}}{\text{THF, rt, 15 h}} \rightarrow \overset{\text{12 examples, 64-99\% yield}}{\text{Enders et al.}^{16a}}
\]

Chem. Rev. 2007, 107, 5606-5655
Accounts of Chem. Res. 1182-1195, 2011

Suzuki and Coworkers
Extending NHC-Catalysis to Uncommon Electrophiles

Biju et al.

We envisioned the synthesis of enantioenriched R-amino acid derivatives by an intermolecular enantioselective Stetter reaction using N-acylamido acrylate as the Michael acceptor. In this process, the two important steps, the C/C0C bond formation between the Breslow intermediate and the Michael acceptor as well as an asymmetric protonation are efficiently merged. A variety of aldehydes reacted with the dehydroamino ester in the presence of NHC generated from L-phenyl alaninol derived triazolium salt yielding R-amino acid derivatives in excellent yield and stereoinduction (Table 2).

32 The mechanism and mode of asymmetric induction are still unclear, but can be rationalized as follows. First, the reaction between the free carbene derived from 17 and the aldehyde leads to the formation of a nucleophilic Breslow intermediate (Scheme 2). The Michael acceptor approaches from the bottom face in an anti fashion, most likely supported by a hydrogen bond between the enol hydrogen and the carbonyl oxygen of the Michael acceptor (19, Scheme 2). In this process, ester enolate bearing a new but transient stereocenter is formed highly stereoselectively. The stereochemistry is relayed to the R-position by a stereoselective protonation of the transiently formed enolate. Finally, the NHC is released, destroying the initially formed stereocenter and forming the final product 18.

Alternatively, a concerted transition state could directly generate intermediate 22. This reaction is remarkable because of the rather low electronic activation of substrate and because it represents the first asymmetric intermolecular Stetter reaction that generates only an R-stereocenter.

4. NHC-Catalyzed Reaction of Aldehydes with Unconventional Electrophiles

Although the NHC-catalyzed umpolung of aldehydes and the subsequent interception of the nucleophilic acyl anion intermediates with various electrophiles, such as aldehydes, ketones, imines, and activated, C\textsubscript{d}C\textsubscript{d}C double bonds, is well-known, the analogous transformations with unconventional electrophiles such as unactivated C/C0C multiple bonds...
H-Acylation of Unactivated Compounds

\[
\begin{align*}
\text{CHO} & \quad \text{DBU (70 mol\%)} \\
\text{OH} & \quad \text{xylene, reflux} \\
\text{24} & \quad \text{25 mol\%} \\
\end{align*}
\]

7 examples, 86-99\% yield

She et al.\textsuperscript{34}

\[
\begin{align*}
\text{CHO} & \quad \text{DBU (40 mol\%)} \\
\text{H} & \quad \text{1,4-dioxane, 2 h, 120 °C} \\
\text{26} & \quad \text{8 (20 mol\%)} \\
\end{align*}
\]

28 examples, 39-96\% yield

\[
\begin{align*}
\text{CHO} & \quad \text{DBU (40 mol\%)} \\
\text{H} & \quad \text{1,4-dioxane, 2 h, 120 °C} \\
\text{26} & \quad \text{8 (20 mol\%)} \\
\end{align*}
\]

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Accounts of Chemical Research, 2011, 1182
Alkynes and Arynes

NHC-Catalyzed Hydroacylation of Unactivated Internal Alkynes

Extending NHC-Catalysis to Uncommon Electrophiles

4.3. Hydroacylation of Arynes.

Mechanistic studies indicate that the electronic nature of the aldehydes plays a prominent role in the rate-determining step, with electron-poor aldehydes reacting faster than electron-rich ones. Also, competition experiments carried out using electronically dissimilar arynes revealed no preference in product formation, indicating that the presence of carbene generated from KF in the reaction mixture does not affect product formation.

This process is appealing by virtue of the high levels of chemoselectivity observed. In addition, a variety of arynes have been examined, and in all cases the reaction resulted in the smooth formation of the expected chromanones in good to excellent yield (Table 7).

TABLE 7.

Encouraged by these results, we then turned our attention to a class of highly reactive intermediates in organic synthesis, namely, arynes.

Although arynes have been extensively utilized in transition-metal-catalyzed reactions, their application in organo-catalytic processes is scarce presumably due to the inherent complexity of their reactivity toward nucleophiles.

The reaction of a wide variety of aldehydes, the intermolecular hydroacylation of arynes, was achieved using 2.0 equiv each of KF and 18-crown-6 in the presence of carbene generated from KF. The aldehydes are reactive intermediates in organic synthesis, namely, arynes.

Accounts of Chemical Research, 2011, 1182
Metal Vs Organic

Metals:
- Have to worry about decarbonylation
- Rh is expensive, other metals are not as well documented
- Enantioselective reactions are pretty straightforward
- Screening catalysts is pretty straightforward

NHC:
- Can react with a wider range of substrates (benzoin reaction, stetter, and other substrates)
- Made from very accessible materials.
- Catalyze many transformations, so you have to be aware of possible side reactivity, or use that to your advantage..
- Have to find an NHC that works for you
Thank You

Questions for Me?
Questions for You..

Assume Aq.
Workup
Questions for You..
Answers for You..
C-C meets C-H
formaldehyde and acetaldehyde

$$\text{C}_2\text{H}_5\text{CHO} + \text{C}_2\text{H}_5\text{C} = \text{C} - \text{H} \rightarrow \text{C}_2\text{H}_5\text{CH}_2\text{C} = \text{C} - \text{H}$$

1 (10 mol %)
2 (20 mol %)
toluene
$$150^\circ\text{C}, 48\text{ h}$$

$$\text{C}_2\text{H}_5\text{CH}_2\text{C} = \text{C} - \text{H} \rightarrow \text{C}_2\text{H}_5\text{CH}_2\text{C} - \text{C}_2\text{H}_5$$

(1) 35 (3 mol %)
(2) $\text{H}_3\text{O}^+$
toluene, $170^\circ\text{C}, 1\text{ h}$

$$\text{C}_2\text{H}_5\text{CH}_2\text{C} - \text{C}_2\text{H}_5$$

$$\text{Ph} = \text{Ph}$$

97 % ($41/42=95:5$)

$$\text{C}_2\text{H}_5\text{CHO} \equiv \text{Pyridine}$$

40

Rh(I) catalyst
(n = 0, 1, 2)

$$\gamma$$