Microwave-Accelerated Palladium-Catalyzed Organic and Medicinal Chemistry

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Microwave UGM
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An Improved in situ Amino-Carbonylation Protocol with Mo(CO)₆ as a solid CO Source

M(CO)₆ Yield
- Cr(CO)₆ 80%
- Mo(CO)₆ 84%
- W(CO)₆ 77%
- Fe₂(CO)₆ 0%
- Co₂(CO)₆ 28%

- DBU mediated CO release
- Improved method with sluggish amines and amino acids
- ArCl work with (iBu)₂PhtBF₃ and Harmann’s pallada-cycle

Aminocarbonylation or Heck Reaction with Allylamine?

Scale-Up of Aminocarbonylation

\[
\text{MeO} + \text{H}_2\text{NCH} = \text{CH}_2 + \text{Mo(CO)}_6 \quad \text{DBU, Dioxane}\quad \text{MW, 125 °C, 10 min}
\]

- 0.4 mmol in 3 mL dioxane (91%)
- 2.0 mmol in 10 mL dioxane (78%)
- 25.0 mmol scale in 125 mL dioxane (80%)
- Direct scalability
- No problem with Mo(CO)₆ 4 bars pressure

Aminocarbonylations of Aryl Triflates in Neat Water

- Under development
- Mo(CO)₆ as a solid CO-source
- X-Phos needed
- Only small amounts of benzoic acid generated

2007 - the Carl von Linnaeus Tercentenary
**Hepatitis C Virus (HCV)**

- 170 million infected
- 3-4 million newly infected/year
- Primary indication for liver transplantations
- Urgent need for better therapies

**Development of Novel Peptidomimetic HCV Protease Inhibitors**

- Ongoing
- Sandström et al.

**Synthesis of Acyl Sulfonamides with Mo(CO)₆**


**Synthesis of a Hepatitis C Virus NS3 Protease Inhibitor**


**Novel HCV Protease Inhibitors by Amidocarbonylation**

- Wu et al. Chem. Rev. 2005, 105, 7

**Preparative Advances and Lessons Learned**

- Mo(CO)₆ serves as a reliable solid CO liberator both with classic heating and microwave heating
- Inter- and intramolecular Pd(0)-catalyzed amino-, amido-, hydrazido- and alkoxycarbonylations proceed smoothly in organic solvents, fluorous solvents or water
- Aryl iodides, bromides, chlorides and -triflates are all good substrates
- The methodology is useful for lead optimization
- Limitation: The reaction mixture must be directly sealed after addition of Mo(CO)₆ and efficiently stirred

**Microwaves**

- Variation of the acyl sulfonamides, 52%

**HCV Full-length NS3 Protease Inhibitor**


**Heterocyclic backbone**

- Sandström et al.

**Aromatic backbone**

- Sandström et al.

**HCV Full-length NS3 Protease Inhibitor**


**HCV Full-length NS3 Protease Inhibitor**

The Oxidative Heck Reaction

The Heck Reaction:

\[ R + Ar \rightarrow X \xrightarrow{[Pd(0)\text{]}} Ar \]

The Oxidative Heck Reaction:

\[ R + Ar\text{--B(OH)}_2 \xrightarrow{[Pd(I)]} Ar + \text{Pd(0)} \]

Reoxidation

Oxidative Heck Reactions

Relation between the classic Heck reaction, the oxidative Heck reaction and the Suzuki coupling

- Boronics readily undergo trans-metallation
- Which reoxidant to use?
- Very few mechanistic studies
- Microwave scale-up?

Base-Free Oxidative Heck

- Homocoupling intermediate detected by ESI-MS
- Produced from the p-Tolyl-Pd intermediate and p-Tolyl boronic acid
- Small amount biaryl side-product observed in all Oxidative Heck reactions
- Base needed for Suzuki-type biaryl formation
- Base screen showed no need for base in Oxidative Heck
- Jung reported the base-free Oxidative Heck during our studies (Jung et al., J. Am. Chem. Soc. 2006, 12884) with \( \text{O}_2 \) as oxidant
- Can we perform this chemistry with air instead of \( \text{O}_2 \)?
- Improved chemoselectivity? Microwaves?

Reaction Investigated with ESI-MS

Electron-rich olefin
NaOAc as base
Samples for ESI-MS removed during reaction

The Plausible Catalytic Cycle of the Oxidative Heck Reaction

The palladium acetate catalyzed dmphen-modulated oxidative Heck reaction in acetonitrile with an electron-rich olefin. Cationic intermediates in the catalytic cycle are assigned letters from \( A \)-\( C \).

Base-Free Oxidative Heck

- Reactions at room temperature:
  - Open vessel charged with boronic acid, n-butyl acrylate, Pd(OAc)\(_2\) (0.02 equiv), dmphen (0.024 equiv) and acetonitrile under vigorous stirring
  - Reactions at elevated temperatures: Microwave-transparent vessel charged with boronic acid, n-butyl acrylate, \( \text{Pd(OAc)}_2 \) (0.02 equiv), dmphen (0.024 equiv), acetonitrile, sealed under air and exposed to microwave irradiation
- Scale-up at room temp from 1 mmol to 50 mmol scale
Batch Scale-Up of Oxidative Heck

- From 0.5 mmol to 50 mmol
- β-Benzquinone as palladium reoxidant
- Advanced instrument
- Air as reoxidant instead of O₂ or β-benzquinone?

Modern Palladium Catalysts at High Temperature (Microwave Conditions)

- A multitude of available new palladium catalysts (or precatalysts)
- Palladacycles, pincer complexes, encapsulated polyurea polymers .......
- Not much known regarding the structure of catalytically active species at high temperature (microwave conditions)
- Pd(0)/(IV) mechanism or sophisticated Pd(0) sources? Compare with old-fashioned Pd(OAc)₂, Pd₂dba₂, Pd/C

EnCat 30, EnCat Pd(0)

Modern Palladium Catalysts at High Temperature (Microwave Conditions)

- Design of experiments:
- Bidentate ligand-controlled regioselective cationic Heck arylation reaction
- Oxidative addition intermediates detected by ESI-MS analysis of ongoing microwave heated reaction mixture - in accordance with Pd(0) catalysis by Pd(0) release from Pd source
- Internal α-product selectivity support Pd(0)-catalysis (α/β-ratio)

Catalysts as Pd(0) Sources at 150 °C

<table>
<thead>
<tr>
<th>Catalysts</th>
<th>α-product (%)</th>
<th>β-product (%)</th>
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</thead>
<tbody>
<tr>
<td>Pd(0) OTf</td>
<td>87</td>
<td>71</td>
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<tr>
<td>Pd(0) Ac-ac</td>
<td>71</td>
<td>0</td>
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<tr>
<td>Pd(0) PPh₃</td>
<td>82</td>
<td>0</td>
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<tr>
<td>EnCat 30, EnCat Pd(0)</td>
<td>82</td>
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<tr>
<td>EnCat 30, EnCat Pd(0)</td>
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</table>

Mießen andSpiess et al. Submitted

Examples of ESI-MS Detected Cationic Catalytic Intermediates

Modern Palladium Catalysts at High Temperature (Microwave Conditions)

Asymmetric Chelation-Assisted Heck Arylation with Aryl Chlorides

Diastereofacial Selection

Requirements for High Selectivity
**Spiro[cyclohexane-1,1'-isobenzofuran] compounds**

- 4.3 million newly infected
- New constrained products by 5-exo cyclization

**HIV/AIDS Statistics 2006**

- 40 million people infected
- 4.3 million newly infected
- 2.9 million deaths in AIDS
- 1930-15 years transmission of SIV to humans
- Early 1980s AIDS
- 1993 isolation of HIV
- 1997 first antiretroviral therapy
- 1995 first protease inhibitor

**Microwave-Assisted Heck Spiro-Cyclizations of o-Halobenzyl Cyclohexenyl Ethers**

- 8 starting materials in good yields

**Transition-state mimics inhibit the enzyme**

- HIV-1 protease is an aspartic protease
- Dihydroxyethylamin
- Hydroxyethylamin
- tert-Hydroxyethylamin

**Target: HIV-1 Protease**

**Cyclization Precursors**


**HIV-1 Protease**

-关切s:
  1. Active mutants
  2. Metabolic stability
  3. Improved cell permeability

**Heck Spiro-Cyclizations**

<table>
<thead>
<tr>
<th>Starting material</th>
<th>Reaction (% yield)</th>
<th>Solvent</th>
<th>Temp</th>
<th>Heating time</th>
<th>Yield</th>
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<td>Toluene/10:1</td>
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<td>Toluene/10:1</td>
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<td>120 °C</td>
<td>18 h</td>
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<td>DMF</td>
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<tr>
<td>o-Br</td>
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<td>18 h</td>
<td>20%</td>
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**Microwave-Assisted Heck Spiro-Cyclizations of o-Halobenzyl Cyclohexenyl Ethers**

- 1987 first antiretroviral therapy
- 1995 first protease inhibitor

**HIV-1 protease**

- C2 symmetric dimer

**Concerns:**

- Active mutants
- Metabolic stability
- Improved cell permeability

**Microwave-assisted synthesis of protease inhibitors:**


**Microwave-Assisted Heck Spiro-Cyclizations of o-Halobenzyl Cyclohexenyl Ethers**

- Microwave-assisted synthesis of protein inhibitors

**Target: HIV-1 Protease**

- C2 symmetric dimer

**Concerns:**

- Active mutants
- Metabolic stability
- Improved cell permeability
**Aim** – how to improve?

* New synthetic route needed
* Water coordination optimized

**Shielded tertiary alcohol by epoxide opening**

**Evaluation of the New Tertiary Alcohol C1 Transition-State Mimic**

- Biological results
- Binding mode
  - $K_i = 2.4 \text{nM}$
  - $EC_{50} = 1.1 \mu\text{M}$ – how to improve?
  - $P_{app} = 42 \times 10^4 \text{cm/s}$
  - $Cl_{int} = 286 \text{mL/min/mg}$

**P1’ Decorations by Microwave Pd(0)-Catalyzed Cross-Coupling Reactions**

- Enzyme inhibition and in vitro anti-HIV activity
- Improved Caco-2 and intrinsic clearance data

**A New HIV-1 Protease Inhibitor C1 Core Structure**

- A tertiary alcohol in the transition-state mimicking scaffold

**A New HIV-1 Protease Inhibitor C3 Core Structure**

- Water coordination optimized
- New synthetic route needed

**A New Elongated Tertiary Alcohol HIV Protease Inhibitor?**

- Water coordination optimized
- New synthetic route needed

**A New Elongated HIV-1 Protease Inhibitor C1 Core Structure**

- A tertiary alcohol in the transition-state mimicking scaffold

**A New Elongated HIV-1 Protease Inhibitor C3 Core Structure**

- $P_{app} = 33 \times 10^4 \text{cm/s}$

**P1’ optimization by Suzuki and Stille couplings**

**Catalyzed Cross-Coupling Reactions**

- Asp25 binds to backbone N instead of OH
- Only 2 of 9 compounds:
  - Meta
  - 48% average yield
  - 46-59%
  - [Pd], MW, EtOAc, rt
  - 1. [Pd], TBAF
  - 2. TBSO

**Intrinsic clearance data**

- Only 2 of 9 compounds:
  - Meta
  - 67/68% average yield
  - 46-59%
Antiviral Activity and X-Ray Binding Mode

- Improved water binding but tert-OH binds only to one aspartate residue

<table>
<thead>
<tr>
<th>R-group</th>
<th>Ki (nM)</th>
<th>EC50 (µM)</th>
<th>CC50 (µM)</th>
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<td>&gt;10</td>
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<td>0.17</td>
<td>&gt;10</td>
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<td>&gt;10</td>
</tr>
<tr>
<td>N3</td>
<td>3.6</td>
<td>0.48</td>
<td>&gt;10</td>
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<td>N3</td>
<td>7.3</td>
<td>0.60</td>
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<td>0.19</td>
<td>&gt;10</td>
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Mechanistic Investigation of the Oxidative Heck Reaction

Electrospray Ionization Mass Spectrometry ESI-MS

- A mass spectrometer needs the sample to be gaseous. The ESI technique solves this problem without heat.
MS Spectrum \((m/z = 100-800)\)

MS spectrum for the standard reaction

Single Charged Cationic Palladium(II) Complexes Detected in the Standard Oxidative Heck Reaction with Using ESI-MS(+) Analysis

MS Spectrum \((m/z = 440-454)\)

MS spectrum of Pd complex B2 \((C_23H_{22}N_3\text{Pd}, m/z 446)\) solid line, and theoretical isotopic pattern dotted line

MS-MS (Tandem Mass)

• MS-MS spectrum of Pd complex B2 \((m/z 446)\)

Chemical Verification and Conclusion

• Exchange of reaction components to chemically equivalent components with different mass provides the expected \(m/z\) ratios
• In conclusion
  – Three different types of observed palladium intermediates: (A) Starting intermediates, (B) Transmetallation intermediates, (C) Insertion intermediate
• The suggested catalytic cycle seems to be correct