Diazo Species and Their Use in Palladium Catalyzed Carbenylation Reactions
Synthesis \[ \overset{\rightarrow}{\text{Uses}} \]

\[ R^1 \overset{\text{N}_2}{\sim} R^2 \]

Reactions Post-Carbenylation

Carbenylation

\[ L\text{-Pd} \overset{\text{R}^1}{\sim} \overset{\text{X}}{\sim} \overset{\text{R}^2}{\sim} \rightarrow L\text{XPd} \overset{\text{R}^1}{\sim} \overset{\text{R}^2}{\sim} \]
Synthesis of Diazo-Compounds

Synthesis of Diazo-Compounds

**Diazo-Group Transfer**

- Choice of base, azide, and solvent strongly influences the Diazo-Transfer yields
- Activated methylenes are required

**Tosyl Azide**
- Easily made
- Dangerous compared to other reagents

**p-Acetamidobenzenesulfonyl Azide**
- Moderately Priced, Safe
- Commonly used, and reliable

**Imidazole-1-sulfonyl Azide**
- Easily Made and Safe

**2-Napthalensulfonyl Azide**
- Expensive
- Byproduct is highly crystalline

**p-Dodecylbenzenesulfonyl Azide**
- Expensive
- Byproduct is not crystalline

**p-Carboxybenzenesulfonyl Azide**
- Expensive
- Byproduct easily separated by basic wash

**Functional Group Modification**

- Nucleophile Acceptor
- Michael Acceptor
- Alcohol Acceptor
- Mukaiyama Reagent

More Synthesis of Diazo-Compounds

**Nucleophilic Substitution**

\[
R^1 \text{H} + H_{\text{N}_2} \xrightarrow{\text{Base}} R^1 \text{H} + N_{\text{O}} \text{OR}^2
\]

- Yields are typically good to excellent
- Up to >97% ee using chiral catalysis
- Up to 95:5 dr using auxiliary chemistry


**Electrophilic Substitution**

\[
H_{\text{N}_2} \text{OR} \xrightarrow{\text{Nu}} \text{Nu}
\]

then Nu yields 53-95%

Nu:
- SMe₂
- AsPh₃
- NEt₃
- SbPh₃


**Dehydration of Hydrazones**

\[
\text{NH}_2 \xrightarrow{1)} \text{oxalyl chloride, DMSO, Et}_3\text{N, THF, -78 °C}
\]

2) filter salts yields 42-99%

\[R^1 \text{H, or ary} \quad R^2 \text{= alkyl, aryl, or H}\]


**Alkaline Cleavage of alkyl-N-nitroso Compounds**

\[
\text{NaOH} \quad \xrightarrow{76-86\% \text{ yield}} H_2C=\text{N=N=}
\]

(2 equiv)


**Diazotization of Azides**

\[
\text{THF/H}_2\text{O} \quad \xrightarrow{\text{then sat. aq. NaHCO}_3} \text{N}_3 \quad \xrightarrow{49-97\% \text{ yields}} \text{Nu}
\]

• This reaction proceeds through the intermediate to the right, and it avoids both the Staudinger Ligation and the Staudinger Reaction


**Diazotization of Aliphatic Amines**

\[
\text{NC\_NH}_2 \quad \xrightarrow{\text{NaNO}_2} \quad \text{NC\_N}_2
\]

Uses of Diazocompounds

Uses of Diazo Compounds

Uses of Diazoo Compounds

Uses of Diazo Compounds

Synthesis \[ \rightarrow \] \[ R^1 \sigma R^2 \] \[ \rightarrow \] Uses

\[ \text{Carbenylation} \]

\[ L-Pd \rightarrow R^1 \sigma R^2 \rightarrow LXPd \rightarrow R^1 \sigma R^2 \]

Reactions Post-Carbenylation
Carbenylation

**Mechanism of Carbenylation**

\[
\text{RPdXL} \xleftrightarrow{\text{X}} \text{LPd}=\text{C}=\text{O} \xrightarrow{\text{LXp}} \text{RPd} \quad \text{RPdXL} \xleftrightarrow{\text{X}} \text{LPd}=\text{R}^1 \text{C}=\text{R}^2 \xrightarrow{\text{LXp}} \text{RPd} \quad \text{R} \text{C}=\text{R}^1
\]

**Migratory Insertion of CO**

**Migratory Insertion of Carbenes**

**Stoichiometric Reaction of Palladium with Diazoacetate**

\[
\text{N}_2\text{CHCO}_2\text{Et} (3.3 \text{ equiv}) \xrightarrow{\text{PhMe, rt 51% yield}} \text{N}_2\text{CHCO}_2\text{Et} \xrightarrow{\text{Carbenylation}} \text{Pd=CHCO}_2\text{Et}
\]

**Crystal Structure of Palladium Carbene**


Palladium Catalyzed Polymerization of Diazooacetates

Initiation

Propagation

Termination

Reactions of Palladium Carbenes

Possibility to Make Tetra-Substituted Olefins

Possibility to Make Quaternary Centers

Possibility to Make Quaternary Centers and Tri-Substituted Olefins
Seminal Discovery of Palladium Carbene Mediated Carbenylation

Tetrasubstituted Olefins Synthesized by Palladium Carbenylation

\[
\text{PdCl}_2(\text{MeCN})_2 \text{ (5 mol\%)} + \text{dppp (10 mol\%)} \rightarrow \text{CsCO}_3 \text{ (3 equiv)}
\]

\[
\text{dioxane, 90 °C} \quad X = \text{I, Br, OTf, SO}_2\text{Im}
\]

\[
\text{27 examples} \quad 62-95\% \text{ yield}
\]

\[
\text{Shapiro Synthon for Cross-Couplings}
\]

Tetrasubstituted Olefins Synthesized by Palladium Carbenylation

\[
\begin{align*}
\text{PdCl}_2(\text{MeCN})_2 (5 \text{ mol\%}) & \quad \text{dppp (10 \text{ mol\%})} \\
\text{CsCO}_3 (3 \text{ equiv}) & \quad \text{dioxane, 90 °C}
\end{align*}
\]

\[X = \text{I, Br, Otf, SO}_2\text{Im}\]

Brion = \text{N}

Carbenylation

\[
\begin{align*}
\text{Bamford-Stevens} & \quad \text{Diaz Formation}
\end{align*}
\]

Expeditious Synthesis to CYP17 Inhibitor

Palladium Catalyzed Arylation of $\alpha$-Chiral Ketones

**Problems with $\alpha$-Chiral Ketones**

- **Loss of Chiral Information**
- **Epimerization**
- **Kinetic Control Required**

Palladium Catalyzed Arylation of α-Chiral Ketones

Combining Organocatalysis with Palladium-Carbene Catalysis

\[
\text{\begin{align*}
\text{K} + \text{H}_2\text{H} & \xrightarrow{\text{L-proline (10 mol\%)} \atop \text{DMSO, MW}} \text{K-NHAr} \\
& \xrightarrow{\text{TsNNH}_2 \atop \text{ether, rt, 12 h}} \text{92-99\% ee}
\end{align*}}
\]

\[
\text{\begin{align*}
\text{R} & \xrightarrow{\text{TsHNN-NHAr} \atop \text{Pd}_{2}(\text{dba})_{3} (4 \text{ mol\%}) \atop \text{XPhos (16 mol\%)} \atop \text{LiOrBu (4.1 equiv)} \atop \text{dioxane/H}_2\text{O} \atop 150 \degree\text{C, 120 min, MW}} \text{17 examples} \\
& \begin{align*}
\text{40-62\%} & \text{30-90\% yield} \\
\text{99\% ee} & \end{align*}
\end{align*}}
\]

Conjugated Enynes Synthesis by Carbenylation

Reactions of Palladium Carbenes

Possibility to Make Tetra-Substituted Olefins

Possibility to Make Quaternary Centers

Possibility to Make Quaternary Centers and Tri-Substituted Olefins
Three Component Couplings N-TosylHydrazones, Alkynes, and Aryl Halides

Formation of Quaternary Carbon Centers via Palladium Carbene Catalysis

\[
\begin{align*}
\text{Donating} & \quad \text{Withdrawing} \\
\text{Ortho-Substituted} & \quad \text{Neutral} \\
\text{Withdrawing} & \\
\end{align*}
\]

15 examples
33-68\% yield

Formation of Quaternary Carbon Centers via Palladium Carbene Catalysis

Reactions of Palladium Carbenes

Possibility to Make Tetra-Substituted Olefins

Possibility to Make Quaternary Centers

Possibility to Make Quaternary Centers and Tri-Substituted Olefins
Three Component Carbene Trapping with Nucleophiles

\[
\text{Nu} + R^1 + \text{N}_2 \xrightarrow{\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 (2.5 \text{ mol\%}) \text{ PPh}_3 (15 \text{ mol\%), THF, 66 ^\circ \text{C}}} \text{Nu} \xrightarrow{\text{R}^1 \text{R}^2 = \text{alkyl}} \text{R}^1 \text{R}^2 + \text{SiMe}_3
\]

**Carbon Nucleophiles: 7 examples 47-89% Yield**

- EtO₂C
  - CO₂Et
  - TMS
  - 89% yield

- Ph
  - Me
  - CO₂Et
  - TMS
  - 66% yield

- NC
  - CN
  - TMS
  - 61% yield

**Amine Nucleophiles: 7 examples 19-93% Yield**

- Ph
  - Ph
  - 93% yield

- Ph
  - Ph
  - 91% yield

- Ph
  - NH
  - Bn
  - TMS
  - 19% yield

- Me
  - Ph
  - 55% yield

**Heck Dimerization Outcompetes Carbene Formation for Bromostyrenes**

\[
\text{MeO} \xrightarrow{\text{TMSCHN}_2, \text{PhSnBu}_3, \text{Pd}_2(\text{dba})_3, \text{AsPh}_3 \text{ NMP, 60 ^\circ \text{C}}} \text{MeO} \xrightarrow{60 \text{% yield}} \text{Ar} \xrightarrow{\text{Br} \cdot \text{PdBr}_L} \text{Ar}
\]

Three Component Carbene Trapping with Nucleophiles

Three Component Synthesis of α,β-Unsaturated γ-Amino Acids

\( \text{R}^1 \text{NH} + \text{R} \text{C}=\text{C} \text{I} + \text{R}^2 \text{CO}_2\text{Et} \xrightarrow{\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3 (2.5 \text{ mol\%}), \text{PPh}_3 (15 \text{ mol\%}), \text{THF}, 66 \degree \text{C}} \text{R}^1 \text{R}^2 \text{N} = \text{C} = \text{C} \text{CO}_2\text{Et} \)

12 examples 40-94% yields

Three Component Carbenylative Amination

\[
\begin{array}{c}
\text{NH}_{\text{Bn}} \quad \text{HN} \quad \text{NH}_{\text{Bn}} \\
\text{BnHN} \quad \text{HN} \quad \text{NH}_{\text{Bn}} \\
\text{NHC} \text{HPh} \quad \text{HN} \quad \text{NH}_{\text{Bn}} \\
\text{NH} \quad \text{HN} \quad \text{NH}_{\text{Bn}} \\
\text{NHMe} + \text{NNHTs} + \text{C}_6\text{H}_4\text{OMe} \quad \text{2) NaSCH}_3, \text{DMF, 130 °C} \\
\end{array}
\]

1) Pd$_2$(dba)$_3$, PPh$_3$, t-BuOLi, 80 °C, 10 min, 70% yield
2) NaSCH$_3$, DMF, 130 °C, 2 h, 68% yield

Caulophyllumine B

Attempts at Enantioselective Carbene Trapping with Nucleophiles

![Chemical Reaction Diagram]


- Slow enatio-insertion may be due to cationic palladium
- Chiral LX ligands may accelerate insertion
Novel Generation of Diazo Compounds by C-C Cross-Coupling

R + HCO2Et
(2.5 equiv)

Et3N or DBU (1.5 equiv)

n-Bu4NBr (1 equiv)

Pd(PPh3)4 (5-10 mol%) acetone or acetonitrile 35 - 45 °C

R - vinyl or aryl
Addition of a CO balloon produces carboxylative products

Aryl iodides: 9 examples, 39-96% yield
Vinyl iodides: 6 examples 55-88% yield
Carbonylation: 6 examples 43-66% yield

- Ortho substitution is not tolerated on the arene
- Electron-donating substituents on the arene produce poor yields
- Aryl bromides do not perform well, producing trace to poor yields
- Electron-withdrawing group is necessary for reactivity with vinyl iodides
- Olefin geometry of the vinyl iodide is retained in the product
- Carbonylation can occur on both vinyl and aryl iodides

Conclusion

Uncovered Topics
- Carbenylative Cascades
- Coupling Carbenylation with Nucleophilic Cross-Coupling Species

\[
\begin{align*}
    \text{R} & \quad \equiv \quad \text{R}' \\
    \text{R} & \quad \equiv \quad \text{R}
\end{align*}
\]

Future Directions
- Enantio-Induction

\[
\begin{align*}
    \text{Me} \quad \equiv \quad \text{Ph}
\end{align*}
\]

- Use in Total synthesis

- C-H Functionalization / Carbenylation

\[
\begin{align*}
    \text{X} & \quad \equiv \quad \text{R}
\end{align*}
\]