Metal Mediated Intramolecular Cross-Couplings To Access Benzannulated Rings

What Are The Common Ways In Literature To Form Benzannulated Rings?

Covered in this GM:
- Focus on Reductive Cross-Coupling
- Major focus on usage of Ni\(^{II}\) and Ni\(^{0}\) catalysts
- Use of Fe, Cu, Pd, Ru Catalysts
- Applications in Total Synthesis
- Hydroalken-, Acyl- & Arylations
- Exploitation of Minisci reactivity

Retrosynthetic Case Studies:

Not Covered – Honorable Mentions in Annulation Strategies:
- Macrocyclizations - 2020 - Reisberg
- Saturated Heterocycles - 2017 - Chu
- Hetero and All-Carbon Spirocycles - See 2017 & Cherney 2012
- Cycloisomerization in Synthesis - Dam 2008
- "Anti-Baldwin" Cyclizations - 2013 - Wengryniuk

Advances in [2+2+2] Cycloaddition:
Chem. Soc. Rev. 2011, 40, 3430

Intramolecular Reductive Coupling Reactions Promoted by SmI\(_2\)

Synthesis of Cycloalkenes by Intramolecular Titanium-Induced Dicarbonyl Coupling

Nickel-catalyzed Reductive Coupling of Alkynes and Epoxides
J. Am. Chem. Soc 2003, 125, 8076

A Journey of Kobayashi Aryne Precursors
Chem. Rev. 2021, 121, 3892

SnAP reagents for one-step synthesis of medium rings
ACIE 2013, 52, 1705
Nat. Chem. 2014, 6, 310
Org. Lett. 2014, 16, 1236
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Nickel mediated Intramolecular reductive C–C coupling

Stereoactive synthesis of a *Podophyllum* lignan core
Chem. Commun. 2018, 54, 2040

Proposed Mechanism:
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Intramolecular Nickel-Catalyzed Reductive Coupling enables enantiodivergent synthesis of Linoxepin Chem. Commun. 2024, 60, 694
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**Intramolecular Nickel-Catalyzed Reductive Cross-Coupling of Benzylic Esters**
*Angew. Chem. 2016, 128, 6842*

**Nickel mediated Intramolecular C–S coupling of Thiols and Thioacetates**
*Org. Lett. 2013, 15, 550*

**Nickel-Catalyzed Reductive Cyclization of Alkyl Dihalides**
*Org. Lett. 2014, 16, 4984*

**Nickel-Catalyzed Intramolecular Amination**
*Org. Lett. 2003, 13, 2311*
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Nickel catalyzed intramolecular Hydroalkenylation
Org. Lett. 2021, 23, 7900

Nickel catalyzed intramolecular C–H/C–H oxidative coupling
ACS Catal. 2021, 11, 12384

Nickel-NHC Catalyzed Intramolecular Hydroacylation
JACS 2004, 126, 11802, ACIE 2012, 51, 10812

for Palladium Variant see: Organometallics 2008, 27 4841
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**Copper-Catalyzed Inter- and Intramolecular reductive Cross-Coupling**

\[
\text{CuI (10 mol%) LiOMe (1 eq), THF, 0 °C, 24 h}
\]

[A] TMEDA (20 mol%) [B] DPPM (20 mol%)  

X = Br; 54%  

X = OTs; 94%

**Iron-Catalyzed Inter- and Intramolecular reductive Cross-Coupling**

\[
\text{FeCl}_3 (1-5 mol%) iPrOH, DCE (R = H or Aryl)
\]

\[
\text{FG}\_\text{OH}
\]

\[
\text{FG}\_\text{OH}
\]

**Iron-Catalyzed Intramolecular Reductive Coupling of Arylalkenes**

**Proposed Prins-MPV-type mechanism**

**Proposed Prins hydride transfer**

**Hydropyridation of Olefins by Intramolecular Minisci Reaction**
*Org. Lett.* **2017**, *19*, 2290

11 examples 24-89%

**Co-Catalyzed Hydroarylation of Unactivated Olefins**
*Org. Lett.* **2016**, *18*, 3622

\[
\text{[Co(Salen)] (3 mol%) Me}_3\text{NFPY-OTf (2 eq)}
\]

Me$_3$NFPY-OTf
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Rapid Access to Tetracyclic Core of Wortmannin via an Intramolecular Olefin Coupling *Org. Lett.* 2020, 22, 6308

**Halenaquinone**

**Viridin**

**Wortmannin**

**Li, NH₃, t-BuOH, Et₂O, 30 min**

**-78 to -50 °C**

**isoprene, then NCCO₂Et 69%**

**LiOH**

**THF/MeOH/H₂O (4:1:1), 50 °C**

**then citric acid 91%**

**LiOH**

**THF/MeOH/H₂O (4:1:1), 50 °C**

**then citric acid 91%**

**OTBS**

**H₂ (balloon)**

**Pd/BaSO₄ (3 mol%)**

**MeOH, r.t.**

**i. Pd(OAc)₂ (10 mol%)**

**dpff (11 mol%)**

**Et₃SiH, THF/DMF (1:8:1), rt, 87%**

**MeOH, r.t.**

**OTBS**

**TMSCHN₂**

**PhH/MeOH, rt**

**81% for 2 steps**

**NaH, Commins' reagent**

**DME, rt 92%**
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Philipp Neigenfind

Intramolecular Palladium-Catalyzed:

**Stille-Coupling:** J. Chem. Soc. 1999, 1235
**C–H Arylation:** J. Am. Chem. Soc. 2010, 132, 10706
**C–O Bond Formation:** J. Am. Chem. Soc. 2001, 123, 12202
**C–N Bond Formation:** Tetrahedron 1996, 52, 7525

More to read in: Chem. Rev. 2006, 106, 4644


\[
\text{9-BBN, THF, } 0 \, ^\circ \text{C, 4 h then PdCl}_2(dppf) (1.5 mol\%) \text{ NaOH (3 eq.)}
\]

86%

**Intramolecular Palladium-Catalyzed Homocoupling of Aryl Halides** Org. Lett. 1999, 1, 1205

\[
Pd(OAc)_2 (2-5 mol\%) \text{ P(o-tol)}_3 (2-5 mol\%) \text{ Hydroquinone (50 mol\%) Cs}_2\text{CO}_3 (1 eq.), DMA 75\, ^\circ \text{C, 48 h}
\]

82%

**Palladium-Catalyzed Intramolecular Reductive Cross-Coupling** Chem. Eur. J. 2014, 20, 8308

\[
\begin{align*}
&[\text{PdCl}_2(dppf)/\text{TFP LiBrCs}_2\text{CO}_3] \\
&\text{DMA, 150 } ^\circ \text{C, } \Delta
\end{align*}
\]

Helical Alkenes via Palladium Catalyzed Domino Reaction

**Org. Lett. 2012, 14, 3648**

More to read in: Chem. Rev. 2006, 106, 4644

**Intramolecular Palladium-Catalyzed:**

**Stille-Coupling:** J. Chem. Soc. 1999, 1235
**C–H Arylation:** J. Am. Chem. Soc. 2010, 132, 10706
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**Intramolecular Minisci Acylation under Silver-Free Neutral Conditions**
*Org. Biomol. Chem. 2017, 15, 2199*

![Chemical Structure](image)

**Sequential Isomerization and Ring-Closing Metathesis**
*Tet. Lett. 2003, 44, 6483*

![Chemical Structure](image)

**Decarboxylative Intramolecular Arene Alkylation using an Organic Photocatalyst**
*– J. Org. Chem. 2019, 84, 8360*

![Chemical Structure](image)

**N-Acylamide Methylenation-Enamide Ring-Closing Metathesis**
*J. Org. Chem. 2006, 71, 7028*

![Chemical Structure](image)

**Deoxygenative Intramolecular Minisci Reaction to Access Fused Heterocyclic Scaffolds**
*– Eur. J. Org. Chem. 2023, 26, e202201176*

![Chemical Structure](image)

**Couple-close construction of polycyclic rings from diradicals**
*– Nature 2024*

![Chemical Structure](image)

**Conclusions - Lessons Learned - Open Questions:**

- Wide array of Strategies to form Benzannulated Rings involving various metals
- Most Processes Mediated by Nickel are proposed to involve Ni<sup>0</sup>
- Many Methods only mediocremly Strategic due to laborious Starting Material Synthesis
- How to Overcome Simple Radical Reactivity (e.g. Minisci) through directed Cross-Coupling Strategy?
- Utilization of Decarboxylation possible?