Transition Metal-Catalyzed Non-Traditional Cycloadditions

Ian Mangion  
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- 5-membered ring formation:  
  - [3+2]  
  - [2+2+1]

- 6-membered ring formation:  
  - [4+2]
  - [2+2+2]

- 7-membered ring formation:  
  - [4+3]
  - [5+2]

- 8-membered ring formation:  
  - [5+2]
  - [5+2+1]
  - [4+4]

- Useful references:
  - General
    - Bogdanov, J. T. White Group Seminar, 2002
  - Pauser-Khand reaction
  - Wender’s [4+2] and [5+2]
    - Wender, P.; Smith, T. Tetrahedron. 1999, 54, 1205

Cycloadditions: Woodward-Hoffman Rules

- Frontier orbital theory dictates non-4m+2 cycloadditions to be thermally forbidden

- Some "allowed" cycloadditions do not proceed in practice

- Can transition metals be used to alter reactivity patterns?

\[ \text{Wender, P.; Jenkins, T. J. Am. Chem. Soc. 1999, 111, 6432} \]
### Transition Metal-Alkene Complexes

- Zeise creates the first known metal-alkene complex:
  \[
  \text{K}_2\text{PtCl}_4 + \text{EtCH} \rightarrow \text{KCl, PtCl}_2, \text{EtOH} \quad \text{Zeise, 1827}
  \]

- α-basic metals bind alkenes more strongly due to backbonding interactions:

  \[
  \begin{align*}
  \text{C-C bond distance:} & \quad 1.327 \text{ Å} \quad 1.375 \text{ Å} \quad 1.430 \text{ Å} \quad 1.490 \text{ Å} \\
  \text{Increasing metalacylcyclopropane character}
  \end{align*}
  \]

- Alkene binding equilibria are sensitive to electronic (and steric) effects:

  \[
  \text{Ni}(\text{P}(\sigma, \pi-\text{tol}))_2 + \text{olefin} \rightleftharpoons (\text{olefin})\text{Ni}(\text{P}(\sigma, \pi-\text{tol}))_2 + \text{P}(\sigma, \pi-\text{tol})
  \]

  \[
  K = 2.5 \times 10^2
  \]

  \[
  K = 4.0 \times 10^6
  \]

  \[
  \text{Increasing electronegativity}
  \]


### Forbidden Cycloadditions: First Leads

- Ziegler and Reed discover the cyclodimerization of butadiene:

  \[
  \begin{align*}
  \text{Ni catalyst} + \text{butadiene} & \rightarrow \text{oligomers} \\
  \text{Reed, W. J. Chem. Soc.} & \text{1954, 1951} \\
  \text{Ziegler, K., Holzmann, E.} & \text{Bret, H. Angew. Chem. 1955, 67, 420}
  \end{align*}
  \]

- Evidence suggests stepwise mechanism:

  \[
  \begin{align*}
  \text{Ni}_{\text{III}} & \rightarrow \text{Ni}_{\text{II}} \rightarrow \text{Ni}_{\text{III}} \\
  \text{isolated, resubjected} \\
  \text{Heinrich, F., Greuter, W. Angew. Chem. Int Ed} & \text{1967, 6, 830}
  \end{align*}
  \]

- New modes of reactivity seen for known reactions:

  \[
  \begin{align*}
  \text{Me} & \rightarrow \Delta \rightarrow \text{Me} \rightarrow \text{Me} \rightarrow \text{Me} \rightarrow \text{Me} \rightarrow P(\sigma, \pi-\text{tol}) \rightarrow \text{Me} \rightarrow \text{Me} \\
  \text{DiMeCO} & \rightarrow 40^\circ C \rightarrow \text{DiMeCO} \\
  \text{Barrett, P., Wyatt, M. J. Chem. Soc.} & \text{1974, 331}
  \end{align*}
  \]

- Could transition metals be used to catalytically perform forbidden cycloadditions in a practical fashion?
Forbidden Cycloadditions Made Practical: The Holy Grail

- Cyclohexenes have conceptually trivial retrotrons

- Transition metals might provide Diels-Alder equivalents for other ring systems

- Transition metals may also allow for enantioselective ring synthesis via chiral ligands
5-Membered Rings: [3+2] Cycloaddition

- Noyori explores the use of transition metals to open strained cyclopropanes

\[
\begin{align*}
\text{Ni(CN)}_2 & \quad \text{CO}_2 \text{Et} \\
\text{EtO}_2 \text{C} & \quad \text{CO}_2 \text{Et} \\
\end{align*}
\]


- Binger discloses a more practical system using methylenecyclopropane

\[
\begin{align*}
\text{Pd} & \quad \text{(acac)}_2 & \quad \text{(Pr)}_2 \text{P} \\
\text{EtO}_2 \text{C} & \quad \text{CO}_2 \text{Et} \\
\end{align*}
\]


\[
\begin{align*}
\text{Pd}(0) & \quad \text{(Pr)}_2 \text{P} \\
\text{Me} \quad \text{CO}_2 \text{Et} \\
\end{align*}
\]


5-Membered Rings: [3+2] Cycloaddition

- Mechanistic studies reveal a deuterium scrambling

\[
\begin{align*}
\text{Ni(CN)}_2 & \quad \text{Cp}_0 \quad \text{H_2} \\
\text{EtO}_2 \text{C} & \quad \text{CO}_2 \text{Et} \\
\end{align*}
\]


- Binger proposes two mechanisms to account for the observed products

Proximal attack
Favored by "naked" Ni catalysts
(e.g. Ni(COD)X)

Distal attack
Favored by Ni-phosphine and Pd catalysts
(e.g. Pd(PPPH)_3)

Noyori, R., Hamada, T. Chem. Rev. 1993, 93, 113
5-Membered Rings: [3+2] Cycloaddition

- Trost discovers a Pd-catalyzed system effective for cyclopentane synthesis

  \[
  \text{TMS-CH} = \text{CHCH}_{2}\text{OAc} \xrightarrow{5 \text{ mol}\% \text{Pd}(\text{PPh}_3)_4} \text{PhMe, 85 \degree C} \rightarrow \text{CO}_2\text{Et}
  \]
  \[39\% \text{ yield} \quad 12.1 \text{ anti-syn} \]

  \[
  \text{TMS-CH} = \text{CHCH}_{2}\text{OAc} \xrightarrow{5 \text{ mol}\% \text{Pd}(\text{PPh}_3)_4} \text{PhMe, 110 \degree C} \rightarrow \text{H}
  \]
  \[52\% \text{ yield} \quad 1 \text{ diastereomer} \]

- The observed reactivity is explained by a proposed Pd-TMM active species

  \[
  \text{TMS-CH} = \text{CHCH}_{2}\text{OAc} \xrightarrow{\text{Pd}^0} \text{TMS} \xrightarrow{\text{AcO}^-} \xrightarrow{\text{PdL}_4^-} \xrightarrow{\text{EWG}} \text{EWG}
  \]

  \[\text{Trist, B., Chen, D. J. Am. Chem. Soc. 1999, 121, 6405} \]

5-Membered Rings: [3+2] Cycloaddition

- Mechanistic studies reveal an ambiphilic active species

  \[
  \text{TMS-CH} = \text{CHCH}_{2}\text{OAc} \xrightarrow{\text{Pd}^0} \text{MeO}_2\text{C} \xrightarrow{\text{SO}_2\text{Ph}} \xrightarrow{\text{PdL}_4^-} \xrightarrow{\text{D, D}} \xrightarrow{91\% \text{ deuterium incorporation}} \]

- Deuterium scrambling experiments suggest a slow equilibrium between \(\eta^2\)- and \(\eta^4\)-bound TMM complexes

- Efforts towards enantioselectivity imply a distal approach for cycloaddition

  \[
  \text{TMS-CH} = \text{CHCH}_{2}\text{OAc} \xrightarrow{\text{Pd}^0} \text{MeO}_2\text{C} \xrightarrow{\text{SO}_2\text{Ph}} \xrightarrow{\text{PdL}_4^-} \xrightarrow{\text{EWG}} \text{EWG}
  \]

  \[77\% \text{ ee} \]

  \[\text{Trist, B., Chen, D. J. Am. Chem. Soc. 1999, 121, 2326} \]
5-Membered Rings: [3+2] Cycloaddition

- Studies on stereochemical retention imply a highly ordered nonconcerted reaction

- Several efficient natural product syntheses have appeared exploiting the Pd-TMM technology


Paquette et al. J. Am. Chem. Soc. 1992, 114, 7375
5-Membered Rings: [2+2+1] Cycloaddition

- Pauson and Khand report a [2+2+1] synthesis of cyclopenentones using stoichiometric Co

- Rautenstrauch describes the first catalytic Pauson-Khand reaction using nonconstrained alkenes

- Livinghouse demonstrates the first catalytic intramolecular Pauson-Khand reaction under low CO pressure

5-Membered Rings: [2+2+1] Cycloaddition

- Mural develops intra- and intermolecular [2+2+1] carbonocyloadditions to make \( \gamma \)-butyrolactones

- Wender uses a Rh-catalyzed system to perform a Pauson-Khand variant
5-Membered Rings: [2+2+1] Cycloaddition

- Buchwald describes a new titanocene system for enantioselective, catalytic Pauson-Khand reactions.

- Shibata finds an Ir system that provides the first enantioselective, catalytic intermolecular Pauson-Khand reaction.

6-Membered Rings: New Methods and New Substrates

- How can transition metal-mediated cycloadditions be applied to 6-membered rings?

- Thermal cyclotrimerization of acetylene is a difficult but well-known process.

- Several metals (e.g., Ni, Co, Pd, Cr, Fe, Ru, Ta) are now known to catalyze acetylene cyclotrimerizations.
6-Membered Rings: [2+2+2] Cycloaddition

- Vollhardt shows that [2+2+2] cyclization can be used to generate Diels-Alder precursors.

- This strategy is applied towards the synthesis of estrone and steroid analogs.

6-Membered Rings: [4+2] Cycloaddition

- Low-valent Fe catalyst systems first demonstrate thermally impractical [4+2] cyclizations.

- Wender renders intramolecular [4+2] cyclizations general for yne-diene substrates.

- This strategy is first applied to the synthesis of Vitamin D analogs.
6-Membered Rings: [4+2] Cycloaddition

- Wender extends his [4+2] methodology to diene-allene cycloadditions

![Chemical structures and reaction schemes](image)

Wender, P.; Jencks, T. J. Am. Chem. Soc. 1985, 107, 1843

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An exceptionally rapid synthesis of guanacastepene was envisioned utilizing Wender [4+2] methodology

![Chemical structures and reaction schemes](image)

Wender, W.S.; MacMillan, D.W.C.; unpublished results

- Yohimbine alkaloid synthesis proves to be a more viable application

![Chemical structures and reaction schemes](image)

Wender, P.; Smith, T. J. Org. Chem. 1996, 61, 624

- Trost designs a hetero-[4+2] cycloaddition

![Chemical structures and reaction schemes](image)

7-Membered Rings: A Medium Ring Diels-Alder?

- Two conceptually different cycloaddition approaches have been applied towards 7-membered ring synthesis

- Binger and Trost extended their [3+2] systems to [4+3] cycloadditions, with varying degrees of success

- Trost designs a substrate class that avoids issues of regioselectivity

- Sarel discovers a [5+2] Diels-Alder homolog using vinylicyclopropanes
7-Membered Rings: [5+2] Cycloaddition

- Wender performs the first transition metal-catalyzed [5+2] cycloaddition

- A mechanism is proposed based on known metallacyclopentene structures

- The [5+2] concept is extended to ene-vinylcyclopropanes

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7-Membered Rings: [5+2] Cycloaddition

- Ene-vinylcyclopropanes prove to be amenable to steric bulk and chiral catalysis

- Relative stereochemistry is thought to arise from a kinetic preference for a cis-cyclopentene intermediate
7-Membered Rings: [5+2] Cycloaddition

- Studies on substituted yne-vinylcyclopropanes prove access to a variety of substituted 5,7-ring systems

- Chiral 7-membered rings can be fashioned through allene-vinylcyclopropane cyclization

7-Membered Rings: [5+2] Cycloaddition

- First attempts at intermolecular reactions prove fruitless

- Activated vinylcyclopropanes facilitate the first transition metal-catalyzed [5+2] intermolecular cycloaddition

- Stoichiometric reaction studies provide mechanistic evidence

Wender, P., Dzymak, A. Org. Lett. 1999, 1, 2069


Observed by $^1$H NMR
7-Membered Rings: [5+2] Cycloaddition

- Wender finds that unactivated, substituted vinylcyclopropanes function well in cycloaddition reactions

\[
\begin{align*}
\text{MeO}_2\text{C} & \equiv \equiv \text{H} \\
\text{R}^1 & = \text{Me, } \text{4-Pr, TMS} \\
\text{R}^2 & = \text{H, D}_{4} \text{O, D}
\end{align*}
\]

\[
\text{5 mol\% RhCl(CO)}_2 \quad \text{DCE, 80°C} \quad 65-93\% \text{ yield} \quad >10:1 \text{ regioselectivity}
\]

- The higher activity of substituted cyclopropanes is rationalized by a higher population of an active conformation

\[
\begin{align*}
e\text{cis} & \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \\
\text{e-trans} & \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv
\end{align*}
\]

- The only effective unsubstituted cyclopropane substrates reported contain trisubstituted olefins

\[
\begin{align*}
\text{MeO}_2\text{C} & \equiv \equiv \text{H} \\
\text{TBSC} & = \text{Me, } \text{4-Pr, TMS} \\
\text{R}^1 & = \text{Me, } \text{4-Pr, TMS} \\
\text{R}^2 & = \text{H, D}_{4} \text{O, D}
\end{align*}
\]

\[
\text{5 mol\% RhCl(CO)}_2 \quad \text{DCE, 80°C} \quad \text{MeO}_2\text{C} \\
\text{TBSC} \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv
\]


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7-Membered Rings: [5+2] Cycloaddition

- Trost uses his cationic Ru system towards [5+2] cycloadditions - room temperature and low cost

\[
\begin{align*}
\text{CpRu} & \equiv \equiv \text{Me} \\
\text{TBSC} & = \text{Me, } \text{4-Pr, TMS} \\
\text{R}^1 & = \text{Me, } \text{4-Pr, TMS} \\
\text{R}^2 & = \text{H, D}_{4} \text{O, D}
\end{align*}
\]

\[
\text{10 mol\% CpRu(CH}_2\text{CN})_3\text{PF}_6 \quad \text{Acetone, RT} \quad 73\% \text{ yield} \quad 10:1 \text{ anti/syn}
\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \equiv \equiv \text{Me} \\
\text{TBSC} & = \text{Me, } \text{4-Pr, TMS} \\
\text{R}^1 & = \text{Me, } \text{4-Pr, TMS} \\
\text{R}^2 & = \text{H, D}_{4} \text{O, D}
\end{align*}
\]

\[
\text{10 mol\% CpRu(CH}_2\text{CN})_3\text{PF}_6 \quad \text{Acetone, RT} \quad \text{MeO}_2\text{C} \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv
\]

\[
\text{R} = \text{CHO} \quad 80\% \text{ yield}
\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \equiv \equiv \text{Me} \\
\text{TBSC} & = \text{Me, } \text{4-Pr, TMS} \\
\text{R}^1 & = \text{Me, } \text{4-Pr, TMS} \\
\text{R}^2 & = \text{H, D}_{4} \text{O, D}
\end{align*}
\]

\[
\text{10 mol\% CpRu(CH}_2\text{CN})_3\text{PF}_6 \quad \text{Acetone, RT} \quad \text{MeO}_2\text{C} \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv
\]

\[
\text{R} = \text{CH}_2\text{OTIPS} \quad 85\% \text{ yield}
\]

- Trost then demonstrates convenient polycycle synthesis

\[
\begin{align*}
\text{MeO}_2\text{C} & \equiv \equiv \text{Me} \\
\text{TBSC} & = \text{Me, } \text{4-Pr, TMS} \\
\text{R}^1 & = \text{Me, } \text{4-Pr, TMS} \\
\text{R}^2 & = \text{H, D}_{4} \text{O, D}
\end{align*}
\]

\[
\text{20 mol\% CpRu(CH}_2\text{CN})_3\text{PF}_6 \quad \text{Acetone, 50°C} \quad \text{MeO}_2\text{C} \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv \quad \equiv \equiv
\]

\[
\text{n = 1} \quad 85\% \text{ yield} \\
\text{n = 2} \quad 81\% \text{ yield}
\]

7-Membered Rings: [5+2] Cycloaddition

- Trost uses his cationic Ru system towards [5+2] cycloadditions - room temperature and low cost

- Trost then demonstrates convenient polycycle synthesis

7-Membered Rings: [5+2] Cycloaddition

- Wender applies his [5+2] technology in a few short syntheses


8-Membered Rings: [6+2] Cycloaddition

- Wender extends [5+2] concepts to 8-membered rings

\[ \text{M} \quad \text{M} \]

- Cyclobutanones provide activated cyclobutane equivalents

\[ \text{MeO} \quad \text{O} \]

Wender, P.; Comes, A.; Gute, Y. J. Am. Chem. Soc. 2000, 122, 7615

8-Membered Rings: [5+2+1] Cycloaddition

- Interception of a 7-membered metallacycle furnishes 8-membered rings

\[ \text{M} \quad \text{M} \]

- Activated vinyl cyclopropanes under CO pressure facilitate a three-component cycloaddition

\[ \text{Me} \quad \text{Me} \]

8-Membered Rings: [4+4] Cycloaddition

- Ni-catalyzed oligomerization of 1,3-dienes offers a conceptually novel way to synthesize 8-membered rings

Ni catalyst + 1,3-dienes + oligomers


- Wender explores Ni-catalyzed intramolecular [4+4] reactions

\[
\text{MeO}_2\text{C} \quad \xrightarrow{11 \text{ mol}\% \text{Ni(CO)}_2} \quad 33 \text{ mol}\% \text{PPh}_3 \quad \text{PhMe, 60 }^\circ\text{C} \\
\text{MeO}_2\text{C} \quad \xrightarrow{11 \text{ mol}\% \text{Ni(CO)}_2} \quad 33 \text{ mol}\% \text{PPh}_3 \quad \text{PhMe, 60 }^\circ\text{C} \\
\text{MeO}_2\text{C} \quad \xrightarrow{11 \text{ mol}\% \text{Ni(CO)}_2} \quad 33 \text{ mol}\% \text{PPh}_3 \quad \text{PhMe, 60 }^\circ\text{C} \\
\]


8-Membered Rings: [4+4] Cycloaddition

- Studies demonstrate the possibility of a [4+4] approach to taxane skeletons

Studies demonstrate the possibility of a [4+4] approach to taxane skeletons

Tascol

**[4+4] Approach to (+)-Asteriscanolide**

- The synthesis of (+)-asteriscanolide compellingly displays the value of transition metal-catalyzed cycloadditions.

Cycloaddition chemistry has been conceptually altered by transition metal catalysis:

- Many "forbidden" cycloadditions (e.g. [4+4]) are now practical.
- Electronically disfavored Diels-Alder reactions can be performed under mild conditions.
- Precedents unprecedented cycloadditions have been successfully explored.
- Diels-Alder equivalents are gaining generally in the synthesis of 5-, 7-, and 8-membered rings.
- Rapid approaches to medium rings have been proven in natural product synthesis.

Transition metal-mediated cycloadditions would benefit from several improvements:

- More general substrate scope for intermolecular cycloadditions.
- More highly active catalyst systems (i.e. can vicinal quaternary centers be set in medium rings?).
- Enantioselective catalysis.
- Demonstration of principle on highly complex natural products (taxol, resinarubin, phorbol, etc.)

The field of transition metal-mediated cycloadditions is gaining momentum - more than half of the methodology described here is derived from developments after the 1995 Chem. Rev. article.