The synthesis of cyclopropenes and their applications in cycloadditions from 2006 to nowadays

- Bond lengths
- Angles
- Strain energy
- Reactivity

(2+1) Cycloaddition
1,2-Elimination
From other cyclopropenes

(2+2+1) Pauson-Khand
(3+2+1)
(2+2)
(4+2)
(3+3)
Vinylic nature of C₃ protons

Reacts sometimes like an alkyne

Short bond

1.088 Å

1.296 Å

h₃C₃h₃ = 115°

c₃C₂c₁ = 51°

Vinylic nature of C₃ protons

Reacts sometimes like an alkyne

Ethylene: C-C 1.34 Å
Acetylene: C-C 1.20 Å

\[ \text{c}_3\text{C}_2\text{c}_1 = 51° \]

\[ h_3\text{C}_3h_3 = 115° \]

1.088 Å
1.296 Å

Short bond

Vinylic nature of C₃ protons

Strain Energy (kcal/mol):
- Cyclohexane: 0.1
- Cyclobutane: 26.3
- Cyclopropane: 27.5
- Cyclopropene: 54.1

Reacts sometimes like an alkyne

Cyclopropane: 27.5

Short bond

Because the ring is **highly strained**, cyclopropenes are both **difficult to prepare** and **interesting to study**

General scheme of all the ways to synthesize cyclopropenes

From carbenes and carbenoids

(2+1) cycloaddition

1,1-elimination/
1,2-Si shift

1.3/1.2-elimination

1.2-elimination

1.3-elimination

From other
3-membered rings

Rearrangement
and isomerization

Retro-DA and other
retrocyclizations

Cycloisomerization

Isomerization

Photochemical
rearrangement

MG

From other
cyclopropenes

5-membered ring contraction,
extrusion of CO2

5-membered ring contraction,
extrusion of N2

4-membered ring contraction

Ring contraction

Cycloisomerization
of vinyl carbenes

1,3-elimination
(2+1) Cycloaddition between alkynes and carbenes or carbenoids
IUPAC Nomemclature of cycloaddition

Website: http://goldbook.iupac.org/C01496.html
IUPAC Nomemclature of cycloaddition

Use \([x+y]\) (square brackets) for the number of \textit{electrons} involved in the transformation
Use \((x+y)\) (parenthesis) for the number of \textit{atoms} involved in the transformation
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Example of a 1,3-dipolar cycloaddition:
IUPAC Nomemclature of cycloaddition

Use \([x+y]\) **(square brackets)** for the number of electrons involved in the transformation
Use \((x+y)\) **(parenthesis)** for the number of atoms involved in the transformation

Example of a **1,3-dipolar cycloaddition**:

1,3-dipolar cycloadditions can be called:

\((3+2)\) **cycloaddition** (number of atoms)

or **[4+2] cycloaddition** (number of electrons)

Website: http://goldbook.iupac.org/C01496.html
(2+1) Cycloaddition between alkynes and carbenes or carbenoids
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General scheme
(2+1) Cycloaddition between alkynes and carbenes or carbenoids

General scheme

Two types of cycloadditions
(2+1) Cycloaddition between alkynes and carbenes or carbenoids

General scheme

Two types of cycloadditions

Transition-Metal-Catalysed (carbenoids):

- Rh
- Ag
- Ir
- Co
- Cu
- Zn
(2+1) Cycloaddition between alkynes and carbenes or carbenoids

General scheme

Two types of cycloadditions

Transition-Metal-Catalysed (carbenoids):
- Rh
- Ag
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- Co
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- Zn

Transition-Metal-Free:
In situ generated carbenes
Transition-Metal-Catalysed cycloadditions

First general method for cyclopropenation that tolerates ß-hydrogens
Highly substituted cyclopropenes bearing an ester and different aromatics
Transition-Metal-Catalysed cycloadditions

First general method for cyclopropenation that tolerates β-hydrogens
Highly substituted cyclopropenes bearing an ester and different aromatics

Creation of distinct types of complex molecules from identical starting materials based solely on catalyst selection

Transition-Metal-Catalysed cycloadditions

\[
\text{Ar} = \text{EWG} \quad + \quad \text{R}^1 = \text{R}^2 \quad \xrightarrow{10 \text{ mol} \% \ \text{AgOTf}} \quad \text{DCM, rt} \\
\text{Ar} = \text{Ar} \quad \text{R}^2 = \text{Ar or Alk} \\
\text{EWG} = \text{CO}_2\text{Me, CN P(O)(OiPr)}_2, \text{CF}_3 \\
\text{R}^1, \text{R}^2 = \text{Ar or Alk} \\
\text{30 examples 64 to 98\% yield}
\]
Transition-Metal-Catalysed cycloadditions

Silver triflate: efficient for the **cyclopropenation of internal alkynes** using donor-/acceptor-substituted diazo compounds as carbenoid precursors.
Transition-Metal-Catalysed cycloadditions

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Highly substituted cyclopropenes
Transition-Metal-Catalysed cycloadditions

Silver triflate: efficient for the **cyclopropenation of internal alkynes** using donor-/acceptor-substituted diazo compounds as carbenoid precursors.

Highly substituted cyclopropenes

Cannot be synthesized via Rh(II)-catalysed carbenoid chemistry *(steric hindrance)*
Transition-Metal-Catalysed cycloadditions

Simmons-Smith does not work with alkynes

Transition-Metal-Catalysed cycloadditions

Simmons-Smith does not work with alkynes

First zinc-catalyzed cyclopropenation
Inexpensive and less toxic catalyst
Mild conditions (25 °C, DCM, 0.5-7 h)
Transition-Metal-Catalysed cycloadditions

Highly useful subunits (CF₃ groups and functionalisable cyclopropenes)
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First cyclopropenation of alkynes with trifluoromethylidiazomethane

Transition-Metal-Catalysed cycloadditions

Highly useful subunits (CF$_3$ groups and functionalisable cyclopropenes)

First cyclopropenation of alkynes with trifluoromethyldiazomethane

Key: identification of a robust catalyst to support harsh conditions

B. Morandi, E. Carreira, Angew. Chem., 2010, 49, 4294
Enantioselective Transition-Metal-Catalysed cycloadditions

[\text{Rh}_2(\text{S-DOSP})_4] \text{ effective catalyst for highly enantioselective cyclopropenation}

Enantioselective Transition-Metal-Catalysed Cycloadditions

$[\text{Rh}_2(\text{S-DOSP})_4]$ effective catalyst for highly enantioselective cyclopropenation

High enantioselectivity governed by: Specific orientation of the approach of the alkyne due to hydrogen bonding

Enantioselective Transition-Metal-Catalysed cycloadditions

First catalytic asymmetric route to diacceptor cyclopropenylphosphonates

**Enantioselective Transition-Metal-Catalysed cycloadditions**

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Takes advantages of the *particular reactivity* of the cyanocarbenes

Enantioselective Transition-Metal-Catalysed cycloadditions

First catalytic asymmetric route to diacceptor cyclopropenylphosphonates

Takes advantages of the particular reactivity of the cyanocarbenes

Scope extented to ester cyclopropenes and substituted allenes

V. Lindsay, D. Fiset, P. Gritsch, S. Azzi, A. Charrette,
Transition-Metal-Free cycloadditions

PhHgCF₃, MeSnCF₃, TMSCF₃, BrCF₂CO₂Na, FSO₂CF₂CO₂Me, CF₂Br₂/Zn or PPh₃, C₃F₆O

base free
alkenes or alkynes

Increasing demand for gem-difluorocyclopropa(e)nes and hetereoatom difluoromethyl compounds

L. Li, F. Wang, C. Ni, J. Hu, Angew. Chem., 2013, 52, 12390
Transition-Metal-Free cycloadditions

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alkenes or alkynes

FSO₂CF₂CO₂H, HCF₂Cl, CICF₂CO₂Na, TMSCF₂Cl, TMSCF₂Br (this work)

BrCF₂P(O)(OEt)₂, CICF₂SO₂Ph, CICF₂COPh, n-Bu₃N⁺(CF₂H)Cl⁻
HCF₂S(O)(NTs)Ph, HCF₂SO₂CF₃

Nu-H → Nu—CF₂H
(Nu = O, S, N, P)

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Increasing demand for *gem*-difluorocyclopropa(e)nes and hetereoatom difluoromethyl compounds

Highly efficient method for the difluoromethylation

**Transition-Metal-Free cycloadditions**

**Increasing demand** for *gem*-difluorocyclopropa(e)nes and heteroatom difluoromethyl compounds

**Highly efficient method** for the difluoromethylation

**Much safer** and **more convenient** for large-scale application than other methods

---

Transition-Metal-Free cycloadditions

First Hypervalent iodine-mediated cyclopropenation under mild conditions
Transition-Metal-Free cycloadditions

First Hypervalent iodine-mediated cyclopropenation under mild conditions

Hypervalent iodine-mediated cyclopropenation mechanism postulated by the authors

S. Lin, M. Li, Z. Dong, F. Liang, J. Zhang, 
1,2-Elimination - General scheme
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Limitations of the (2+1) cycloaddition:
- Poorly applicable to some substrates (i.a. aryl diazoacetates with EWG substituents)
- Poor chemoselectivity in some cases: dimerization or further transformation into furans
1,2-Elimination - General scheme

Limitations of the (2+1) cycloaddition:
- Poorly applicable to some substrates (i.a. aryl diazoacetates with EWG substituents)
- Poor chemoselectivity in some cases: dimerization or further transformation into furans

Good alternative: 1,2-Elimination

W. Sherrill, R. Kim, M. Rubin, *Tetrahedron*, 2008, 64, 8610
1,2-Elimination - Examples

\[
\begin{align*}
\text{R}^1\text{R}^2\overset{\text{HClBr}_3}{\rightarrow} \text{H} \text{ClBr} \text{Br} \\
\text{Nucleophilic addition} \\
\end{align*}
\]

1,2-Elimination - Examples

Rh-Catalyzed Stereoselective C(sp³)H insertion

A. Archambeau, F. Miege, C. Meyer, J. Cossy
*Angew. Chem.*, **2012**, *51*, 11540

1,2 Elimination followed by Nucleophilic addition

1,2-Elimination - Examples

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1,2 Elimination followed by Nucleophilic addition


**Au-Catalysed cycloisomerisation**

From other cyclopropenes
From other cyclopropenes

\[
\text{MeO}_2\text{C} \begin{array}{c}
\text{CO}_2\text{Me} \\
\text{SiMe}_3
\end{array} + \text{PhH} \xrightarrow{\text{PR}_3 \text{ dioxane, rt}} \text{MeO}_2\text{C} \begin{array}{c}
\text{CO}_2\text{Me} \\
\text{Ph} \\
\text{OSiMe}_3
\end{array}
\]

11 examples, 58-80% yield

Sila Morita-Baylis-Hillman Reaction of Cyclopropenes

From other cyclopropenes

Sila Morita-Baylis-Hillman Reaction of Cyclopropenes

Mechanism

From other cyclopropenes

Stille Coupling Reactions with Base-Sensitive Cyclopropenes

Ring-opening of Cyclopenyl Lithium Species
From other cyclopropenes

**Stille Coupling Reactions with Base-Sensitive Cyclopropenes**

**Ring-opening** of Cyclopenyl Lithium Species

**Stannylation** of various cyclopropenes

From other cyclopropenes

**Stille Coupling Reactions with Base-Sensitive Cyclopropenes**

Ring-opening of Cyclopenyl Lithium Species

Stannylation of various cyclopropenes

Stille Coupling

Reactivity of cyclopropenes – General scheme
Reactivity of cyclopropanes – General scheme

- Cycloaddition reactions
  - with ring-opening
  - with preservation of the ring

- Ene reactions
- Ring-opening metathesis
- Double-bond migration
- Ring expansions
  - with ring-opening
  - with preservation of the ring

- Formal substitution

M. Rubin, M. Rubina, V. Gevorgyan, *Synthesis, 2006, 8, 1221*
(2+2+1) Pauson-Khand Cycloaddition
(2+2+1) Pauson-Khand Cycloaddition

**General mechanism**

- **Alkyne insertion**:
  - \( R = R \) \( \rightarrow \) \( \text{alkyne complexation} \) \( \xrightarrow{-2 \text{ CO}} \) \( \text{alkyne insertion} \) 

- **Alkene complexation**:
  - \( \text{alkene} \) \( \xrightarrow{\text{complexation}} \) \( \text{alkene insertion} \) 

- **CO insertion**:
  - \( \text{CO} \) \( \xrightarrow{\text{insertion}} \) \( \text{reductive elimination} \)  

- **Reductive elimination**:
  - \( \text{reductive elimination} \) \( \xrightarrow{\text{CO}} \) \( \text{decobaltation} \) 

- **Decobaltation**:
  - \( \text{decobaltation} \)
(2+2+1) Pauson-Khand Cycloaddition

**General mechanism**

- **Alkyne insertion**
- **Alkene complexation**
- **CO insertion**
- **Reductive elimination**
- **Decobaltation**

**Applicable to cyclopropanes**
(2+2+1) Pauson-Khand Cycloaddition - Application to cyclopropenes

Enantioselective Synthesis of (−)-Pentalenene
(2+2+1) Pauson-Khand Cycloaddition - Application to cyclopropenes

Enantioselective Synthesis of (−)-Pentalenene

Using [2+2+1] Pauson-Khand cycloaddition of cyclopropenes as key step

M. Pallerla, J. Fox, Org. Let., 2007, 9, 5625
Serendipity in the (2+2+1) Pauson-Khand Cycloaddition

An unexpected discovery...

\[
\begin{align*}
\text{Me} & \quad \text{TMS} \\
\text{CO}_2\text{Et} & \\
\text{TMS} & \quad \text{Et}_2\text{OC} \\
\text{NMO} & \quad \text{NMO} \\
\text{Me} & \quad \text{TMS} \\
(\text{OC})_3\text{Co-CO(CO)}_3 & \quad \text{Et}_2\text{OC} \\
\end{align*}
\]
Serendipity in the (2+2+1) Pauson-Khand Cycloaddition

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Why is the isolation of this cobalt complex interesting?

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Alkene insertion is the rate-determining step in Pauson-Khand reactions

Hard to have information about intermediates formed after the alkene insertion

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An unexpected discovery...

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Hard to have information about intermediates formed after the alkene insertion.

First insight of what happens after the alkene insertion.

Serendipity in the (2+2+1) Pauson-Khand Cycloaddition

Purification of the complex

By silica gel chromatography
Only 13% yield due to partial decomposition during the purification
Serendipity in the (2+2+1) Pauson-Khand Cycloaddition

**Purification** of the complex

By silica gel chromatography
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**Description** of the complex

Serendipity in the (2+2+1) Pauson-Khand Cycloaddition

Purification of the complex

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Description of the complex

From the Fragmentation of cyclopropane

Serendipity in the (2+2+1) Pauson-Khand Cycloaddition

IR Analysis

υ = 4 external carbonyls: 2067, 2038, 2008 (I= 2)
υ(free CO) = 2170 cm⁻¹  (retro donation of Co)

υ = 1 bridging carbonyl: 1853 cm⁻¹
υ(classic carbonyl) = 1760-1665 cm⁻¹  (smaller angle, greater s-character)
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X-Ray analysis

Selected bond lengths:
Co¹-Co² 2.469 Å
Co²-C⁵ 2.183 Å (longest Co-C bond)
Co²-C⁸ 1.884 Å (smallest Co-C bond)

Serendipity in the (2+2+1) Pauson-Khand Cycloaddition

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- \( \text{Co}^2-\text{C}^8 \ 1.884 \ \text{Å} \) (smallest Co-C bond)

**Selected angles:**
- \( \text{Co}^1-\text{C}^3-\text{Co}^2 \ 76.22 ^\circ \)
- \( \text{Co}^1-\text{C}^8-\text{Co}^2 \ 79.31 ^\circ \) (very small C(sp\(^2\)) angle)

Serendipity in the (2+2+1) Pauson-Khand Cycloaddition

$^{13}$C NMR Analysis

Serendipity in the (2+2+1) Pauson-Khand Cycloaddition

\(^{13}\text{C} \text{ NMR Analysis}

At 25°C: Three picks at 197, 202 and 212 ppm (I= 3)
for the 5 carbonyls
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At $25^\circ$C: Three picks at 197, 202 and 212 ppm ($I=3$) for the 5 carbonyls
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Slow exchange between bridging and terminal carbonyls at -60 °C

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Coalescence observed at -25 °C (signals too broad to be seen)
Regioselectivity of the Pauson-Khand cycloaddition

High regioselectivity
Opposite regioselectivity between cyclopentenone 9 and complex 10
Regioselectivity of the Pauson-Khand cycloaddition

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Opposite regioselectivity between cyclopentenone 9 and complex 10

Selectivity in alkene insertion

Kinetic discrimination after alkene insertion
Regioselectivity of the Pauson-Khand cycloaddition

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Selectivity in alkene insertion
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Facts: After alkene insertion:
- Product 13 leads to **ring-opening** of the cyclopropane to Co complex 10
- Diastereomers 12 and 12' leads to **Pauson-Khand** cyclopentenone product 9
Regioselectivity of the Pauson-Khand cycloaddition

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Possible explanations:
- Stabilisation of the α-carbon-metal bond by Si
- Steric interactions
(3+2+1) Cycloaddition

Much less developed than other carbonylative cycloadditions

(3+2+1) Cycloaddition

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Difficulty to introduce the required three-carbon component ...
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Stereochemistry confirmed by NOESY experiment

Trans configuration of the fused rings
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**ene-cyclopropene**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Reaction Conditions</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="ene-cyclopropene" /></td>
<td>[Rh(CO)₂Cl]₂ (5 mol%) CO (1 atm) DCE, 80 °C 1 to 12 h</td>
<td>8 examples 36-73% yield</td>
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(3+2+1) Cycloaddition

Steps of the mechanism:

C. Li, H. Zhang, J. Feng, Y. Zhang, J. Wang, Org. Let., 2010, 12, 3082
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Path a: C: CO insertion; D: alkene insertion
Path b: F: alkene insertion; D: CO insertion

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Path b: F: alkene insertion; D: CO insertion

E’ cis-fused not observed
only cis-fused cycloadduct G

C. Li, H. Zhang, J. Feng, Y. Zhang, J. Wang, Org. Let., 2010, 12, 3082
(3+2+1) Cycloaddition

Steps of the mechanism:

A: complexation of Rh(I)
B: oxidative addition of the Rh(I) to σ-bond of the cyclopropene generating rhodacyclobutene

Path a: C: CO insertion; D: alkene insertion
Path b: F: alkene insertion; D: CO insertion

E' cis-fused not observed
only cis-fused cycloadduct G

Conclusion: likely Path a

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(2+2) Cycloaddition - Original formation of substituted benzene


(2+2) Cycloaddition - Original formation of substituted benzene


(4+2) Cycloaddition - Cyclopropenes as Reactive and Selective Dienophiles

(3+2) Cycloaddition

Formation of **isoxazolidines**, **aziridines** and **pyrroles** thermically controlled

Before I thank you for your kind attention ...
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Let’s go back to the Hypervalent iodine mechanism described before ...
Reaction

\[ \text{R}^1\equiv\text{R}^2 + \text{PhI(OAc)}_2 (1.2 \text{ eq}) \xrightarrow{\text{DCE, 50 } ^\circ\text{C, 2h}} \text{NC} \equiv \text{CN} \xrightarrow{\text{10 examples, 26-96% yield}} \text{NC} \equiv \text{CN} \]

Postulated mechanism

**Postulated mechanism**

**Exercise:** Find 2 possibles flaws of the mechanism
Which electrophile is the strongest in the medium?
How this electrophile could react with hypervalent iodine? Write a mechanism.

What is the strongest electrophile in the medium? \( \text{R}^1 \equiv \text{R}^2 \) or \( \text{N} \equiv \text{CN} \)?
What is the strongest electrophile in the medium? $R^1 = R^2$ or $\text{NC} \equiv \text{CN}$
What is the strongest electrophile in the medium?

Possible flaws of mechanism:
What is the strongest electrophile in the medium?

Possible flaws of mechanism: \( R^1\equiv R^2 \xrightarrow{\text{Phl(OAc)}_2} \)

Why would the weakest electrophile react first?
What is the strongest electrophile in the medium?

Possible flaws of mechanism:

- Why would the weakest electrophile react first?
- Reductive elimination to create an even more strained cycle
What is the strongest electrophile in the medium?

Possible flaws of mechanism: \[ R^1 \equiv R^2 \overset{\text{Ph}(\text{OAc})_2}{\longrightarrow} \]

Why would the weakest electrophile react first?

Reductive elimination to create an even more strained cycle

Sir XB’s approved postulated Concerted Deprotonation-Electrophilic Iodination Mechanism:
What is the strongest electrophile in the medium?

Possible flaws of mechanism: $R^1\equiv R^2$ or $\text{NC-CN}$

Why would the weakest electrophile react first?

Reductive elimination to create an even more strained cycle

Sir XB’s approved postulated Concerted Deprotonation-Electrophilic Iodination Mechanism:
What is the strongest electrophile in the medium?

Possible flaws of mechanism: $R^1\equiv R^2 \xrightarrow{\text{PhI(OAc)}_2} R^1\equiv R^2$ or $\text{NC} \equiv \text{CN}$

Why would the weakest electrophile react first?

Reductive elimination to create an even more strained cycle

Sir XB’s approved postulated Concerted Deprotonation-Electrophilic Iodination Mechanism:
What is the strongest electrophile in the medium?

Possible flaws of mechanism: $R^1\equiv R^2 \xrightarrow{\text{Phl(OAc)}_2} \text{Reductive elimination to create an even more strained cycle}$

Sir XB’s approved postulated Concerted Deprotonation-Electrophilic Iodination Mechanism:
Now I can thank you for your kind attention.