The Diels–Alder Reaction

Historical Background

“... I consider the teaching and study of the historical development of science as indispensable... Our textbooks fail in this respect...”

Richard Willstätter

“... Science is not an abstract thing, but rather, as a product of human labor, is tightly bound in its development to the particularity and fate of the individuals who dedicate themselves to it.”

Emil Fischer
**Discovery and Invention**

Alternate Paths for the Development of New Synthetic Methods

**Discovery:**
- to find something not previously known

**Invention:**
- deriving from a deliberate attempt to solve a problem

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**The Diels–Alder Reaction**

The single most powerful ring-forming reaction in the arsenal of organic chemistry!
Invention of New Annulation Strategies for the Synthesis of Five–Membered Rings

[4 + 1] Annulation Strategy

[3 + 2] Annulation Strategy
Annulation Strategies for the Synthesis of Carbocyclic and Heterocyclic Compounds

Annulation strategies previously developed in our laboratory

[4+1] Annulation Strategy
Stereocontrolled synthesis of five-membered carbocycles based on anion-accelerated vinylcyclopropane rearrangements

[3+2] Annulation Strategy
Stereocontrolled synthesis of five-membered carbocycles and heterocyclic compounds based on allenyilsilanes and allylsilanes

Reaction of Carbenes with 1,3-Dienes

Potential Basis for a [4 + 1] Annulation Strategy
Reaction of Carbenes with 1,3–Dienes

Potential Basis for a [4 + 1] Annulation Strategy

\[
\text{Re} + \text{C} \xrightarrow{not\ observed} \text{O} \\
\text{tio of Carbenes with 1,3–Dienes}
\]

The Vinylcyclopropane Rearrangement

Potential Basis for a [4 + 1] Annulation Strategy

\[
\text{notobserved}
\]

\[
\text{notobserved}
\]
Stereocontrolled [4 + 1] Annulation Strategy
Anion–accelerated Vinylcyclopropane Rearrangement

Invention of New Annulation Strategies for the Synthesis of Five–Membered Rings
Invention of New Annulation Strategies for the Synthesis of Five–Membered Rings

\[ \text{Allyl Anions} + \text{Oxyallyl Anions} \rightarrow \text{Homoenolate Anions} + \text{Vinylcarbenes} \]

\[ \text{Allylmetal Compounds} + \text{Electrophilic Cyclopropanes} \rightarrow \text{Trimethylenemethane Diradicals} + \text{Trimethylenemethane Zwitterions} \]

\[ \left[ 3 + 2 \right] \text{Annulation Strategy Based on Allylmetal Compounds} \]
Invention of New Annulation Strategies for the Synthesis of Five-Membered Rings

Electrophilic addition of alkene to nucleophilic allylmetal compound

Carbocation stabilized by the β effect

Reversible 1,2-shift of metal group
Invention of New Annulation Strategies for the Synthesis of Five–Membered Rings

Ring closure furnishes five-membered ring

Stereocontrolled [3 + 2] Annulation Strategy

1 equiv
1.2 equiv TiCl₄, CH₂Cl₂

89%

74%
11.5 : 1 stereoisomers
Stereocontrolled [3 + 2] Annulation Strategy

Application to the Synthesis of Five–Membered Heterocycles

\[ X^+ \quad + \quad H_2C=CHC\equiv SiMe_3 \quad \rightarrow \quad X^+ \quad + \quad H_2C=CHC\equiv SiMe_3 \quad \rightarrow \quad X^+ \quad + \quad H_2C=CHC\equiv SiMe_3 \]

\[ R^1C=CR^2 \quad + \quad SiMe_3 \quad \rightarrow \quad R^1C=CR^2 \quad + \quad SiMe_3 \quad \rightarrow \quad R^1C=CR^2 \quad + \quad SiMe_3 \]

\[ X = O, S, NR \]
\[ Y = N, CR \]

1 eq NOBF_4, CH_3CN, -30 °C; then add Br_2, CCl_4

72%

Ph\[O\]

Hept\[C=\equiv Si-BuMe_2\]

[1 eq NOBF_4, CH_3CN, -30 °C; then add Br_2, CCl_4] 72%

Ph\[O\]

Hept\[C=\equiv Si-BuMe_2\]

Ph\[O\]

Hept\[C=\equiv Si-BuMe_2\]

80%