1,3-Dipolar Cycloadditions
(3+2)-Cycloadditions: the problem

allyl anion, resonance stabilized

propargyl/allenyl anion, resonance stabilized

unstabilized, thermodynamically unfavorable
How to make acetaldehyde enolate

\[
\text{pentane} \xrightarrow{n-\text{BuLi}} \text{pentane}^- \xrightarrow{\text{r.t.}} \text{enolate}
\]
*(3+2)-Cycloadditions: the solution*

Put a hypervalent heteroatom ("Q") with a formal positive charge in the middle:

thermodynamically downhill, charges “dissolve”

1,3-dipolar cycloadditions are suprafacial with respect to both components. Six electrons are involved and 0 antarafacial components. As such, they abide to the Woodward-Hoffmann rules.
1,3-Dipolar cycloadditions

conceptualized by Rolf Huisgen

Four generations: Huisgen, Mulzer, Trauner, Magauer. Inset: Edda Goessinger
1,3-dipoles: allyl anion type

Octet structures

Sextet structures

Azomethine ylide

Azomethine imine

Nitronate

Nitro compound

Carbonyl ylide

Carbonyl imine

Carbonyl oxide

Ozone

Thiocarbonyl ylide
1,3-dipoles: propargyl/allenyl anion type

octet structures

sextet structures

nitrile ylide

Note: oxygen in the middle is not possible here.
1,3-dipolar cycloadditions are suprafacial with respect to both components. Six electrons are involved and 0 antarafacial components. As such, they abide to the Woodward-Hoffmann rules.
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Cycloadditions

- Nitrile ylide
- Nitrile imine
- Nitrile oxide
- Diazo compound
- Azide

- Pyrrolidine
- Pyrazole
- Isoxazole
- Pyrazoline
- Triazole
The Criegee mechanism of ozonolysis

1,3-dipolar cycloaddition

Primary ozonide

Retro-1,3-dipolar cycloaddition

Carbonyl oxide

Reorient

Carbonyl oxide

1,3-dipolar cycloaddition

Secondary ozonide

DMS

DMSO
The coolest 1,3-dipolar cycloaddition

phenyldiazonium chloride + sodium azide → phenyl pentazole
Nitrones can often be isolated and even occur as natural products.

Nitrones

lycoposerramine X

cibrochalamine oxide B

stephacidin B
The strategic value of nitrone cycloadditions

The reaction proceeds through the formation of an isoxazolidine intermediate, which is then reduced to a 1,3-N,O product.

Cocaine, histrionicotoxin, and adalin are shown as examples of compounds that can be synthesized through this reaction pathway.
**Generation of nitrones**

through electrocyclic ring opening of oxaziridines:

\[
\begin{align*}
\text{Ph} & \quad \text{N} & \quad \text{t-Bu} & \quad \xrightarrow{\Delta} & \quad \text{Ph} & \quad \text{N} & \quad \text{O} & \quad \text{t-Bu} \\
\end{align*}
\]

through oxidation of amines or imines (via oxaziridines):

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{N} & \quad \text{OH} & \quad \xrightarrow{\text{m-CPBA}} & \quad \text{N} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

through N-alkylation of oximes with deprotonation:

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{H} & \quad \text{N} & \quad \text{OH} & \quad \xrightarrow{\text{BnBr}} & \quad \text{N} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]

through condensation of hydroxylamines with carbonyl compounds:

\[
\begin{align*}
\text{O} & \quad \xrightarrow{\text{Bn} \cdot \text{N} \cdot \text{OH}} & \quad \text{N} & \quad \text{O} & \quad \text{O} \\
\end{align*}
\]
The Tufariello synthesis of cocaine

A methodology-oriented synthesis. A nitrone 1,3-dipolar cycloaddition is employed twice, establishing the 1,3-N,O-motif. The nitrone in itself is transiently protected as a cycloadduct. The reversibility of nitrone cycloadditions was previously established by Edda Gössinger (University of Vienna). 

[Reference]
The nitrone was made through HgO oxidation of pyrrolidine.

**key step**: 1,3-dipolar cycloaddition

oxidation and elimination to regioselectively generate a second nitrone, possibly via:

1,3-dipolar cycloaddition
N-methylation

key step: nitrene is deprotected via a retro-1,3-dipolar cycloaddition, which triggers an intramolecular 1,3-dipolar cycloaddition via:

mesylation, dehydration (elimination)

7) Mel

6) 144 °C

4) MsCl
5) DBN

DBN =

\[
\text{MeOOC} \quad \text{MeOOC} \quad \text{MeOOC}
\]

\[
\text{COOMe} \quad \text{COOMe} \quad \text{COOMe}
\]
8) Zn, AcOH

9) BzCl, NaOH

reductive $N$-$O$ bond cleavage

benzoyl ester formation

(±)-cocaine
Poison dart frogs

Dendrobates histrionicus

Histrionicotoxin

Batrachotoxin

Pumiliotoxin 251D
Retrosynthetic analysis of histrionicotoxin

- identify the 1,3-N,O motif and implement nitrone cycloadditions
- take advantage of the pairwise occurrence of FGs
- consider C=O and C=C as easily interchangeable (olefination !)
- count methylenes and watch out for symmetries
The Stockman-Fuchs synthesis of histrionicotoxin

The best synthesis to date, taking advantage of hidden symmetry elements in histrionicotoxin.
Initially, the undesired regioisomer is formed.

**key step:** diastereoselective bidirectional cross-metathesis

*The (E)-configuration determines the stereochemical outcome of the next step.*

**key step:** domino reaction, consisting of a condensation to form an oxime, conjugate addition, and 1,3-dipolar cycloaddition:

Initially, the undesired regioisomer is formed.
key step: retro-[3+2] cycloaddition, followed by 1,3-dipolar cycloaddition to yield the thermodynamically more stable isoxazolidine regioisomer with the desired stereochemistry via:

twofold reduction
double cis-selective Wittig reaction
8) DBU = twofold elimination of HCl

9) NaHMDS = twofold elimination of HCl

10) CrCl₂, PrSH = chromium(II)-mediated reductive cleavage of the C–Cl and N–O bonds

histrionicotoxin
Formation of 1,3-dipoles via electrocyclic ring opening

3-membered heterocycle (aziridine) → 1,3-dipole (azomethine ylide) (racemate) → (achiral)
The Prato reaction

Reaction with an azomethine ylide is one of the best ways to functionalize buckyball.

The azomethine ylides can be generated in various ways:

1. HN\text{COOH} \xrightarrow{\text{H}_2\text{CO}} \xrightarrow{-\text{H}_2\text{O}} \xrightarrow{-\text{CO}_2} \text{N}^\oplus\text{N}^\ominus

2. \text{CPh}_3\xrightarrow{\Delta} \text{Tr}^\oplus\text{N}^\ominus \xrightarrow{-\text{CO}_2} \text{O}^\ominus\text{O}
Copper catalyzed azide alkyne cycloadditions

thermal:

\[
\begin{align*}
\text{Ph} - & \equiv & \equiv \\
\rightarrow & 190 \, ^{\circ} \text{C} & \rightarrow \\
\text{Ph} - & \equiv & \equiv \\
\end{align*}
\]

Cu(I) catalysis:

\[
\begin{align*}
\text{Ph} - & \equiv & \equiv \\
& \rightarrow & \\
\text{Ph} - & \equiv & \equiv \\
\end{align*}
\]

“click reaction”

use for peptidomimetics [reference]:

\[
\begin{align*}
\text{H}_2\text{N} - & \equiv & \equiv \\
+ & \rightarrow & \\
\text{N}_3 - & \equiv & \equiv \\
\end{align*}
\]
Strain promoted click chemistry

Ac₄ManAz

feeding to cells

azido sialic acid displayed on surface

strain promoted click chemistry

sialic acid (N-acetyl neuraminic acid)

[Reference]
Nitrile oxides

Nitrile oxides are unstable and highly reactive and are typically made through dehydration of alkyl nitro compounds.

Their cycloaddition yields oxazolines, which can be further functionalized through nucleophilic addition to the oxime ether moiety:
The Hoffman la Roche synthesis of racemic biotin

An industrial effort to make biotin (vitamin H) through total synthesis based on a nitrile oxide cycloaddition.
1) Allylic radical bromination

1) NBS, AIBN, CCl₄

2) Formation of thioester through nucleophilic substitution

2) AcSH, NEt₃

3) Thioester cleavage

3) NaOEt, EtOH

4) Michael addition

4) NO₂CH₂CH₂OAc

NaS

[O₂N] + [HS -]
5) PhNCO, NEt₃

Key step. Intramolecular nitrile oxide cycloaddition

6) LiAlH₄

6) Diastereoselective hydride reduction of the oxime ether with cleavage of the N,O-bond

7) CH₃OCOCl

7) Formation of a methyl urethane
8) Oxidation
9) Formation of an oxime

Key step. Beckmann rearrangement via:

11) Lactam hydrolysis and cyclic urea formation
The Hoffman la Roche synthesis of (+)-biotin

An asymmetric version that starts from cystine and involved a transannular nitrone cycloaddition.
Cystine is the simplest S-protected cysteine

1) Acylation

2) Reductive cleavage of the disulfide bond and cyclization (Z:E = 9:1)
   A 10-membered ring is formed.

3) Reduction of the ester to an aldehyde
   4) Nitrone formation
Key step. Opening of the amide and subsequent closure of the urea moiety:

5) Cyclization via

6) Reductive cleavage of the N,O-bond (opening of the isoxazolidine ring)
7) Carbamate formation

6, 7) Zn, AcOH
7) ClCOOMe, Na₂CO₃

5) Δ

8) Ba(OH)₂
9) Ester formation and hydroxy-chlorine exchange under retention of the configuration due to neighbouring effect of the thio ether:

10) Reductive dechlorination
11) Debenzylation and ester cleavage
Thiocarbonyl ylides typically react stepwise, i.e. non-concerted, and require a polarized alkene (Michael alkenes):

Their cycloaddition, followed by reductive desulfurization) amounts to the net addition of an alkane to an alkene:
The Trauner synthesis of hippolachnin

[Reference]

A demonstration of the strategic value of thiocarbonyl ylides.
1) MeI, dicyclohexyl-18-crown-6, K$_2$CO$_3$

2) h$_\nu$

3) EtMgBr, Cul

disrotatory 4π-electrocyclization, followed by rearrangement; the mechanism is discussed [here]

1,4 cuprate addition
4) Ph₃PCH₂CH₃Br, KOTBu
5) pTSA

Wittig olefination, enol ether cleavage

6) KHMDS, Comins’ reagent

enol triflation

7) Pd(OAc)₂, PPh₃, CO, MeOH

Pd-mediated carboxmethoxylation
1,3-dipolar cycloaddition of thiocarbonyl ylide

\[ \text{TMS}-\text{S}^+\text{TMS} \]

DMPU, 100 °C

Reduction

Oxidation to aldehyde

Aldol addition

Oxidation to β-ketoester
Lewis-acid mediated $O$-alkylation

13) SnCl$_4$

carbonyl attacks from bottom side of carbocation

reductive desulfurization

14) Raney Nickel

(±)-hippolachnin A