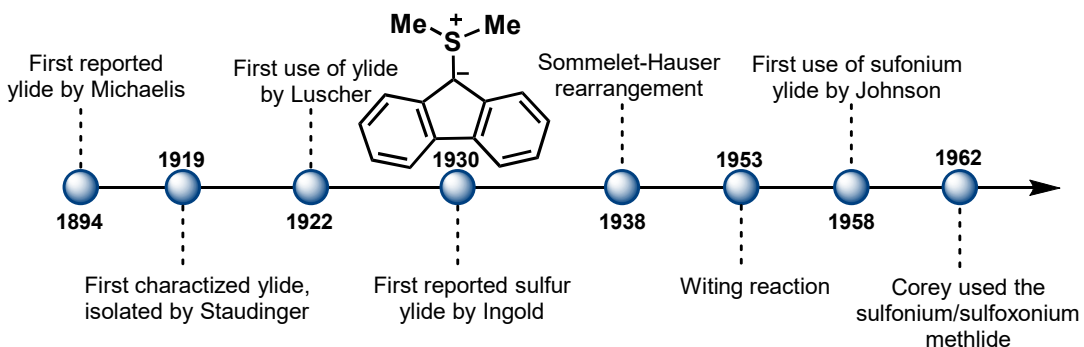


Previous Baran Lab Group Meeting Topics Centered on Sulfur:

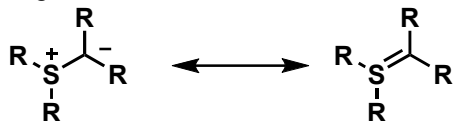
Sulfur Containing Natural Products (Knouse, 2019)

Sulfur in Organic Synthesis (Yan, 2016)



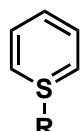
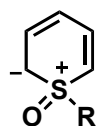
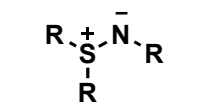
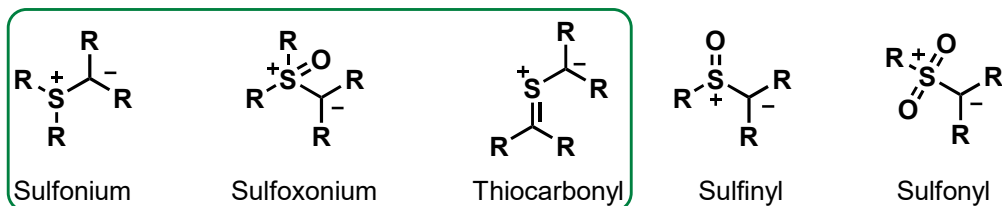
Introduction

Definition: Sulfur ylides are zwitterionic compounds defined by a carbanion and a neighboring positively charged sulfur atom. It is also called π -sulfuranes.

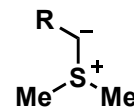
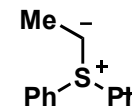
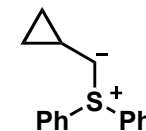
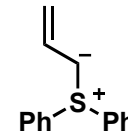


Main use: Ylides have long been used as one-carbon synthons in a number of classical transformations, most notably for the synthesis of small rings such as epoxides, aziridines and cyclopropanes through ylide addition to electron-poor π -systems. The popularity of the method is illustrated by the very large number of citations of Corey's work (~2000).

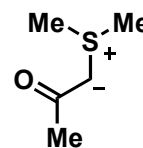
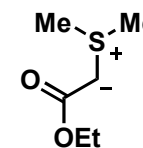
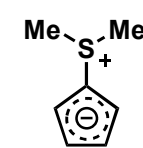
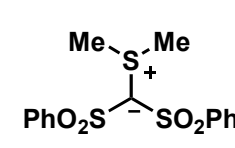
Types of Sulfur Ylides:



Ylide Stability

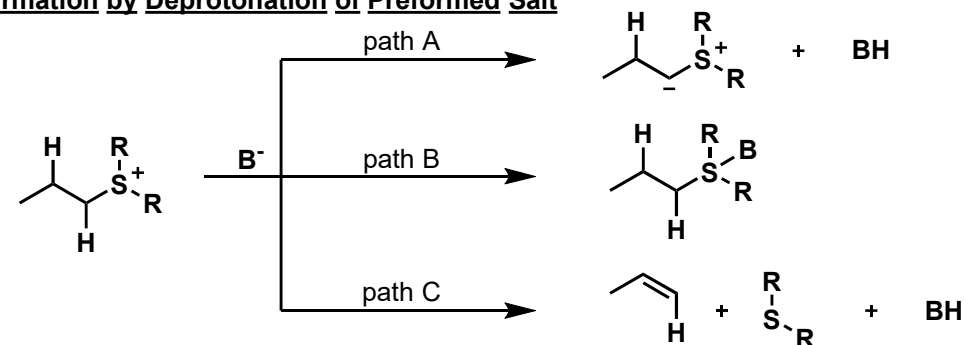
Generated at -70°C 5 min (20°C)2.5 min (25°C)30 min (-15°C)

Isolabile Ylides

b.p. $135^\circ\text{C}/0.8\text{mm}$ b.p. $40^\circ\text{C}/0.003\text{mm}$ m.p. 134°C m.p. 214°C

Note: Generally, the order of ylide stability has been shown to be $\text{S} > \text{P} > \text{N}$.

Formation by Deprotonation of Preformed Salt



Group Meeting includes:

- Introduction of classes of sulfur ylides
- Preparation and synthesis of sulfur ylides.
- Reaction of sulfur ylides

Group Meeting does not include:

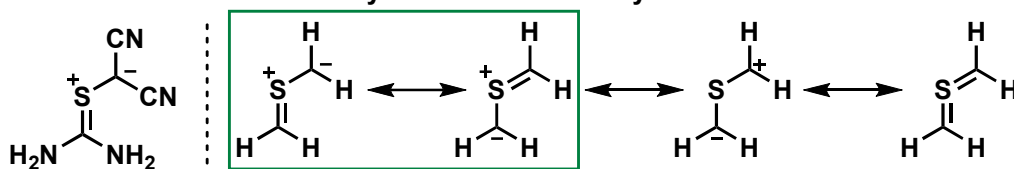
- Johnson-Corey-Chaekovsky reaction
- Metal Complexes of Sulfur Ylides.

Books and reviews:

- Russ. Chem. Rev.*, **2001**, 70, 655
- Chem. Soc. Rev.*, **2017**, 46, 4135
- Eur. J. Org. Chem.* **2013**, 5005
- Acc. Chem. Res.* **2004**, 37, 611-620
- Top Curr Chem, **2018**, 15, 376
- Science of Synthesis, **2004**, 27, 21
- Chem. Rev.* **2019**, 119, 8701

Thiocarbonyl Ylides

The Resonance Forms of Methylene-sulfonium Methylide

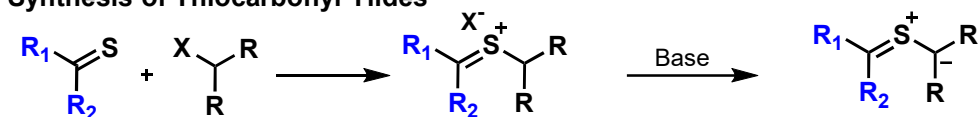


The electronic structure of thiocarbonyl ylides has been extensively studied and the proportions of the five possible resonance forms of the parent ylide have been calculated using natural resonance theory.

J. Org. Chem. **1997**, *62*, 1766

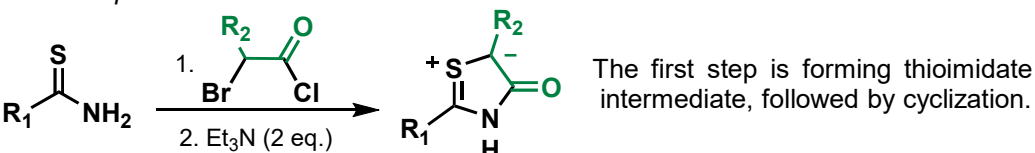
J. Org. Chem., **1966**, *31*, 3731

Synthesis of Thiocarbonyl Ylides



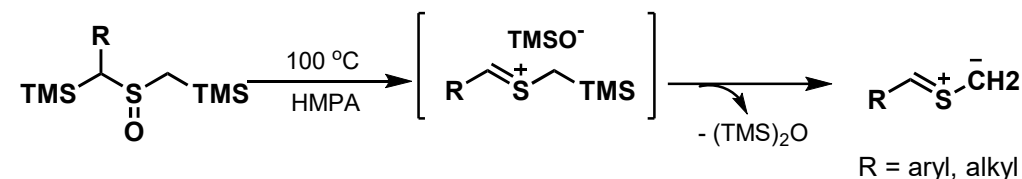
The range of substrates prepared using this method is limited to R_1 or R_2 being a nitrogen based functional group, presumably to facilitate alkylation of the thiocarbonyl compound. Also R_1 and R_2 must not possess alpha-hydrogens.

For example

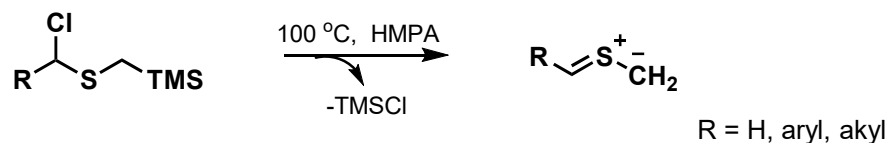


1,3-Elimination Reaction

Thermal Decompositions

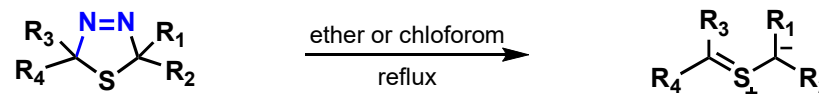


Halosilanes



1,3-Elimination reactions are useful method for the generation of relatively unsubstituted thiocarbonyl ylides from simple starting materials, and are commonly employed for the synthesis of thiocarbonyl ylide analogues such as oxonium and azomethine ylides

Nitrogen extrusion

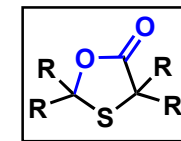


Starting material can be prepared by chlorination of azines followed by cyclization with hydrogen sulfide or by the cyclization of azines with hydrogen sulfide followed by dehydrogenation using diethyl azodicarboxylate.

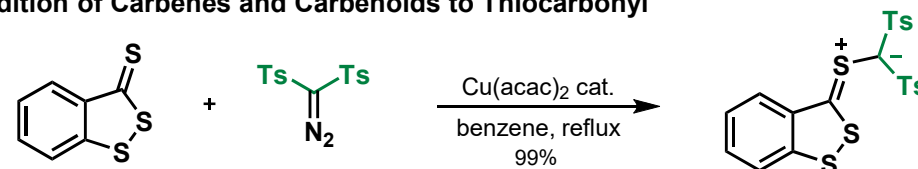
In an analogous manner, the extrusion of carbon dioxide from 1,3-oxathiolan-5-ones is also known.

J. Org. Chem. **1972**, *37*, 4045

J. Am. Chem. Soc. **1980**, *102*, 744

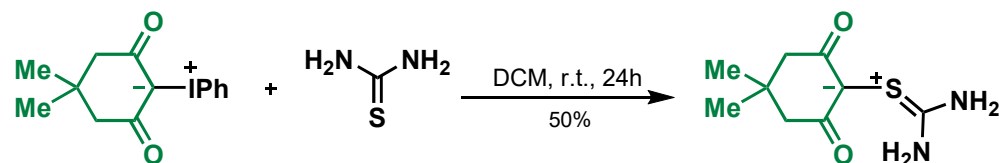


Addition of Carbenes and Carbenoids to Thiocarbonyl



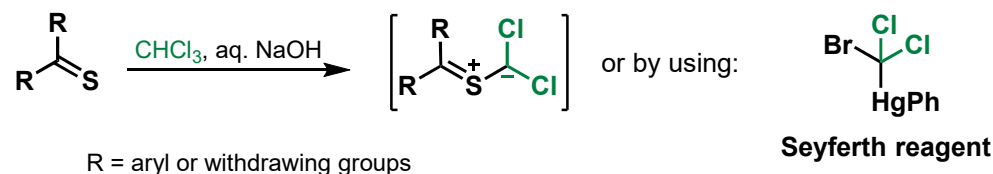
The generation of carbenes by transition-metal-catalyzed decomposition of diazo compounds is frequently more efficient than their photolysis and thermolysis reactions and allows the carbene to be generated under milder and safer conditions. Rh and Cu and the most used metal complex for the generation of the ylide.

J. Am. Chem. Soc. **1990**, *112*, 2003



Note: When the thiocarbonyl compound bears no such alpha-heteroatoms, a transition-metal catalyst is required for the reaction to occur.

J. Am. Chem. Soc. **1985**, *107*, 7178



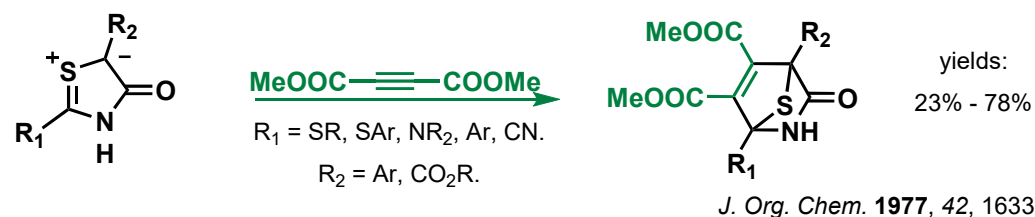
One of the principle restrictions of this method is the need for non-enolizable substrates, as the generation of the carbene is performed under quite basic conditions.

J. Org. Chem. **1972**, *37*, 1537 *Pol. J. Chem.* **1996**, *70*, 1093

Reactions of Thiocarbonyl Ylides

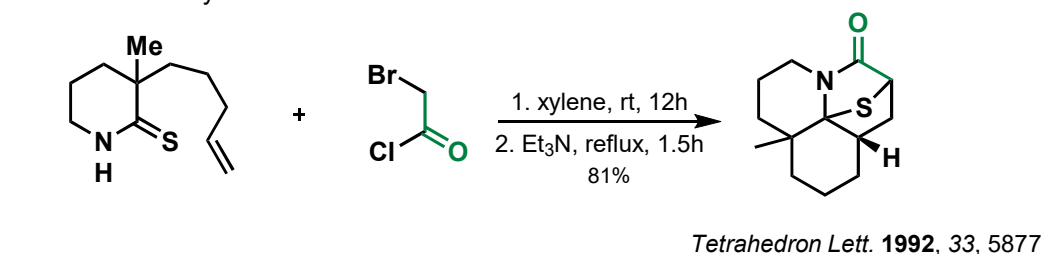
The chemistry of thiocarbonyl ylides is very dependent on their structure. The most common applications of thiocarbonyl ylides are in the synthesis of thiiranes and in 1,3-dipolar cycloaddition reactions.

1,3-Dipolar Cycloaddition - Synthesis of sulfur containing heterocycle

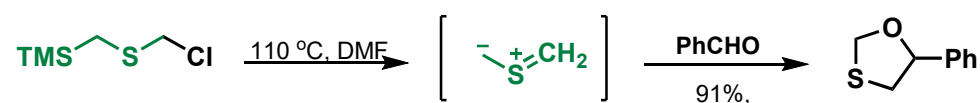


Note: Thiocarbonyl ylides generated from reaction between thiocarbonyl compound and a carbene cannot be used in such reactions.

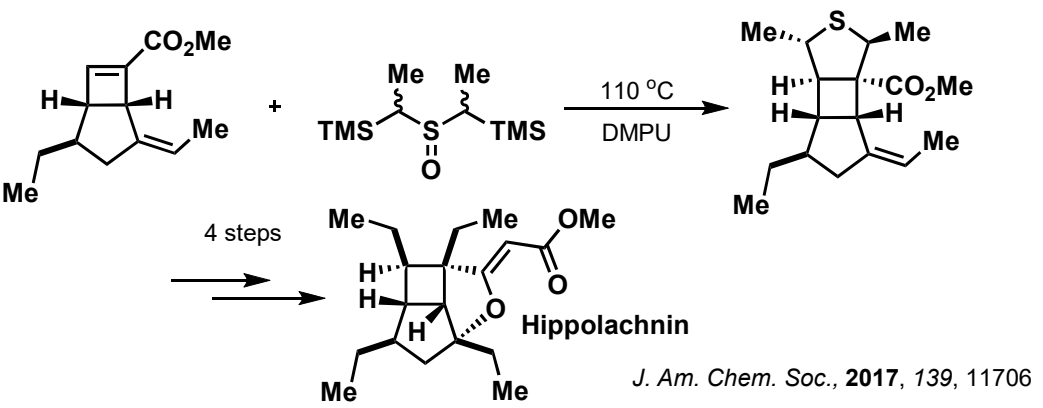
Intramolecular Cycloaddition



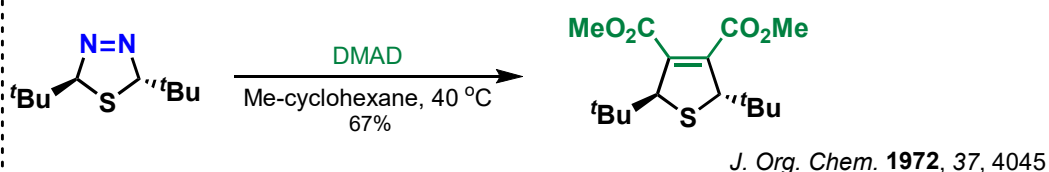
from 1,3-Elimination Reactions



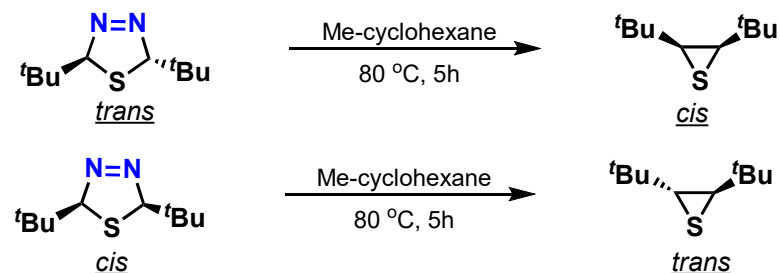
Note: The cycloaddition reactions of thiocarbonyl ylides and cyclic symmetrical dipolarophiles tend to be highly diastereoselective



from Nitrogen Extrusion



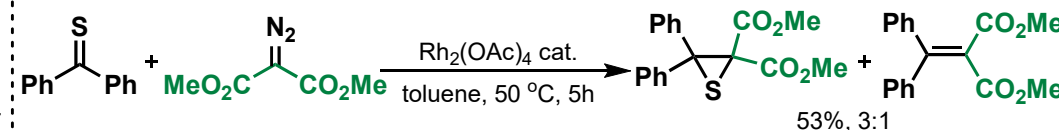
1,3-Electrocyclization Reactions



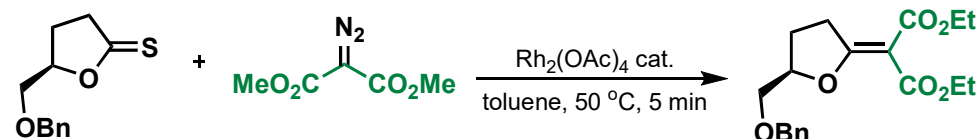
Note: According to the Woodward–Hoffman rules for conservation of orbital symmetry, this cyclization occurs in a conrotatory fashion

Tetrahedron Lett., **1970**, 37, 4689

Alkene Formation from Thiocarbonyl Compounds

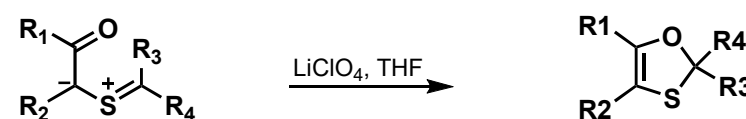


Not all thiiranes are stable and some undergo spontaneous extrusion of sulfur to give the corresponding alkenes. For those that are stable, the alkene can be generated by the addition of a phosphine. This type of extrusion reaction represents a convenient method for the preparation of sterically hindered alkenes.



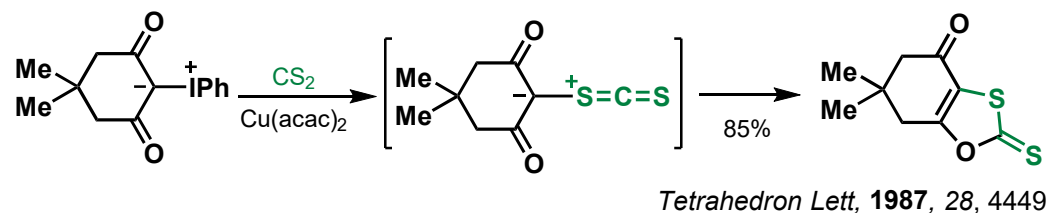
Synthesis, **1987**, 1116 *Helv. Chim. Acta*, **1996**, 79, 1785

1,5-Electrocyclization Reactions

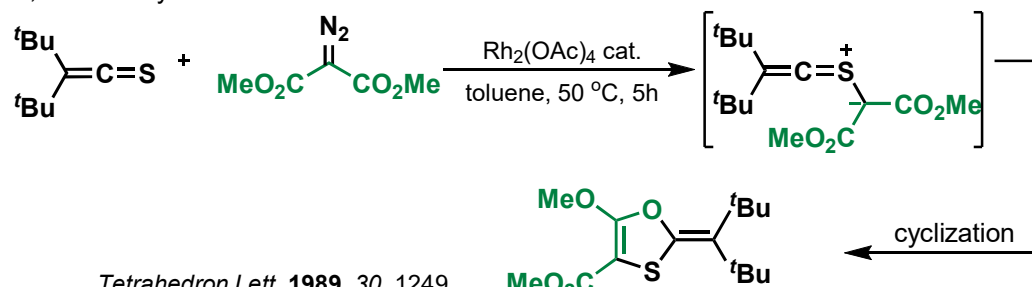


Stabilized thiocarbonyl ylide ($\text{R}_1 = \text{tBu}, \text{Ph}$) preferentially undergoes 1,5-electrocyclization, whilst ($\text{R}_1 = \text{OEt}$) favors 1,3-electrocyclization and ($\text{R}_1 = \text{NMePh}$) gives both possible electrocyclization products

Helv. Chim. Acta, **1998**, 81, 285

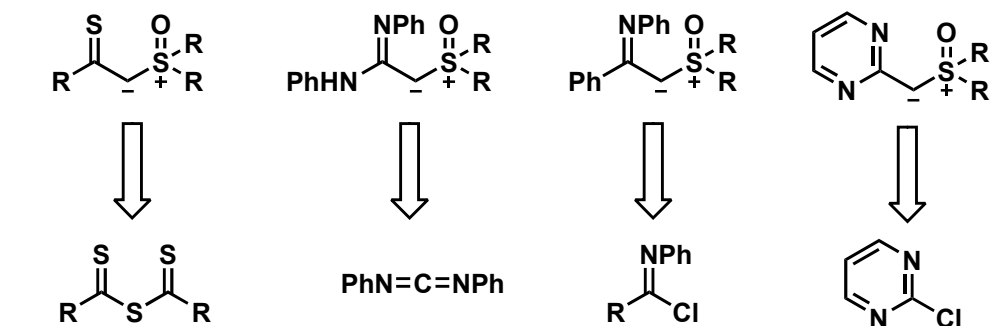
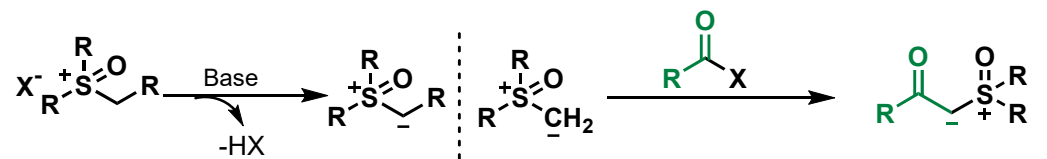


1,5-Electrocyclization with thioketene

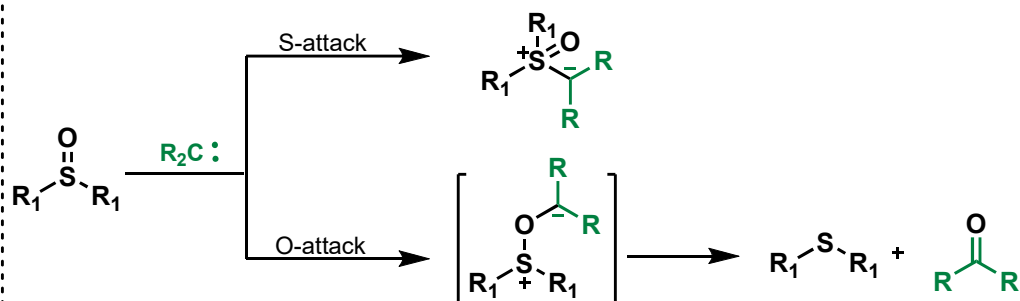
**Synthesis of Sulfoxonium Ylides**

The chemistry of sulfoxonium ylides is dominated by their ability to react firstly as nucleophiles and secondly as electrophiles. Sulfoxonium ylides are quite stable species and can be stored for months under nitrogen at 0 °C.

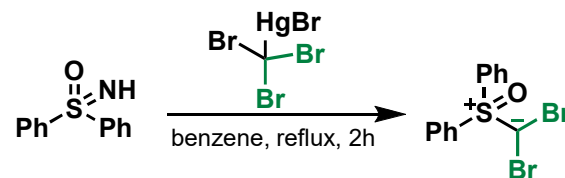
The reaction of sulfoxonium ylides with electrophiles often creates new stereogenic centers. For this reason, aminosulfoxonium ylides, which are chiral, have been prepared in optically active form for application in asymmetric synthesis.



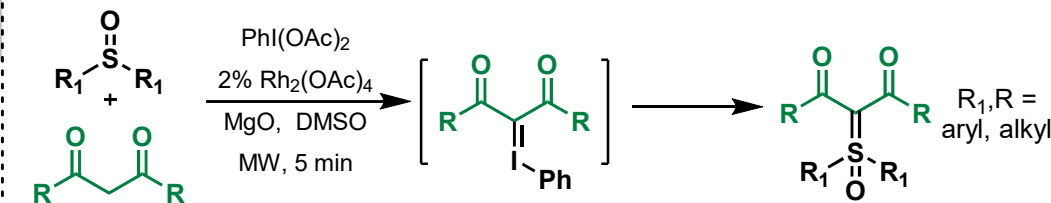
Other electrophiles that can be used to form stabilized sulfoxonium ylides: halo-cyanogen, beta-halo-michael acceptors, electron-deficient alkyne, isocyanates

Direct Generation of Sulfoxonium Ylides from Sulfoxides

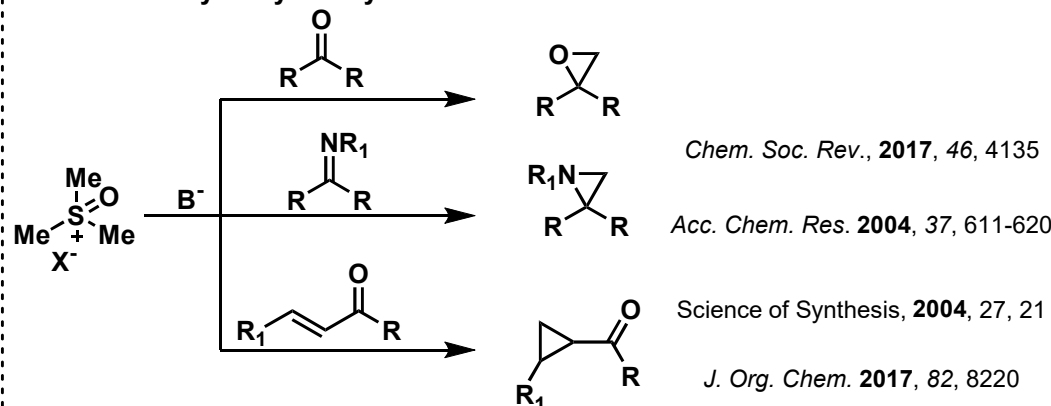
Aryl and dihalocarbenes generally lead to deoxygenation of the sulfoxide giving the corresponding sulfide and carbonyl. Acylcarbenes, which are readily prepared by photolysis, thermolysis, or transition-metal-catalyzed decomposition of the corresponding diazo compounds, show a strong preference for reaction at the sulfur atom of sulfoxides to give the corresponding sulfoxonium ylides



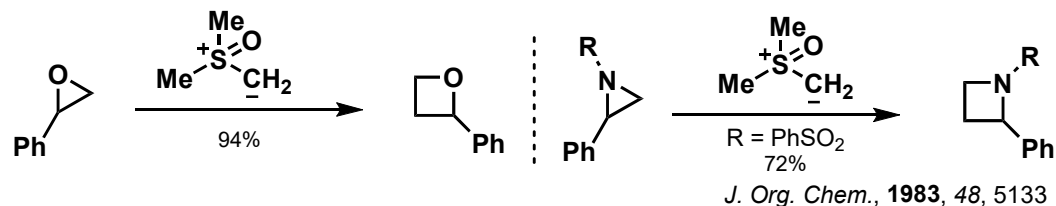
Seyferth reagent compounds can be used to generate sulfoxonium ylides bearing two halogens from the corresponding sulfoximides.

Direct Sulfoxonium Ylide formation - Vaitla - 2017

Org. Lett. 2017, 19, 6688

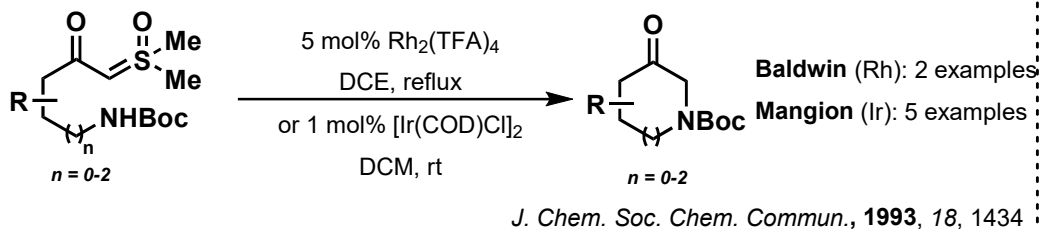
Reactions of Sulfoxonium Ylides**Johnson-Corey-Chaykovsky**

Ring Expansion of Epoxides and Aziridines



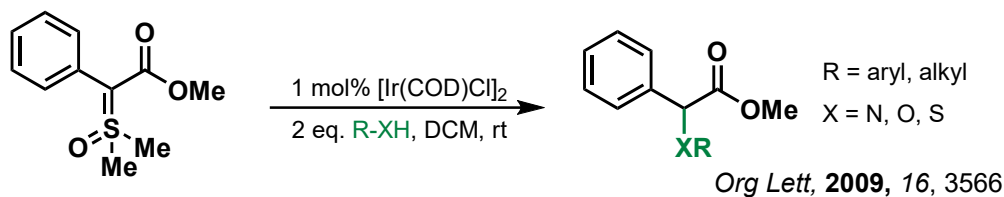
Insertion Reactions into X-H Bonds

Baldwin - 1993



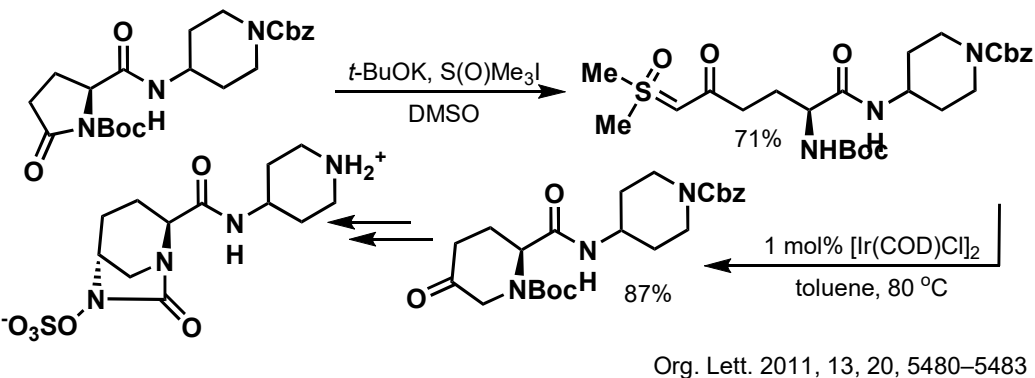
The efficiency of these reactions drew interest to the extent that Merck began their own research programme, and in 2009 Mangion and co-workers published a more general methodology, based on Baldwin and co-workers' original conditions.

Merck - 2009

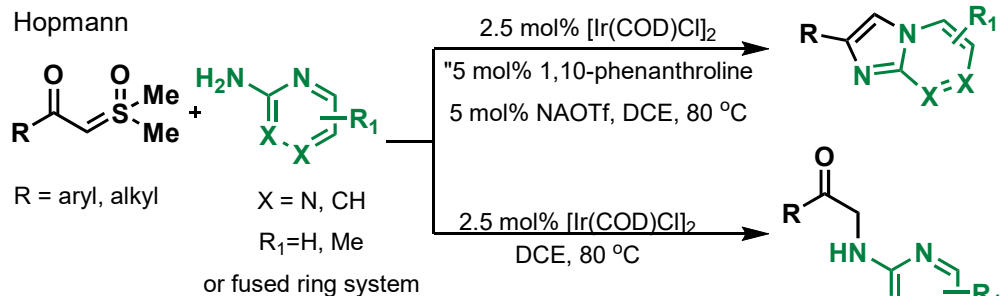


When $\text{Rh}_2(\text{TFA})_4$ was used as the catalyst for the reaction with aniline, only 22% of the desired product was obtained. As a rationale for this observation the authors proposed that the DMSO released after formation of the metal-carbenoid poisoned the catalyst

Further studies proved that Au and Pt salts were also competent catalysts for these transformations.

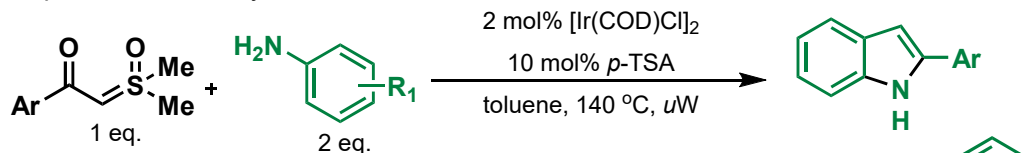


Hopmann

*J. Org. Chem.*, **2016**, *81*, 4158

When 1,10-phenanthroline and NaOTf were added as ligand and additive, respectively, the key iridium carbenoid preferred to react with the pyridine lone pair.

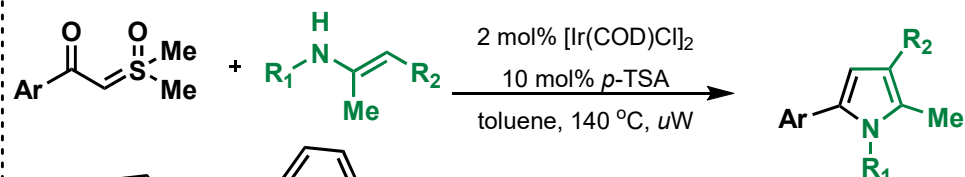
Hopmann's Indole Synthesis



A cascade of carbenoid formation and N-H insertion followed by acid-catalysed imine formation, substitution and aromatisation was active, explaining why the aniline involved in the N-H insertion step was not incorporated into the final product.

Angew. Chem. Int. Ed., **2017**, *56*, 4277

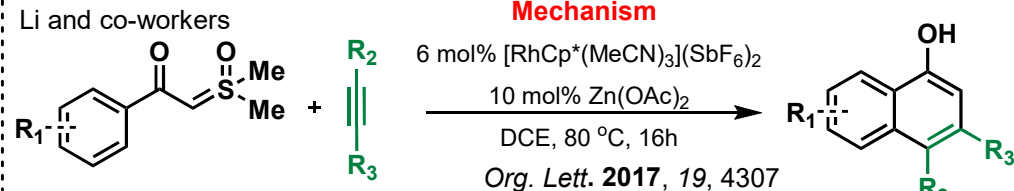
C-H insertion reactions



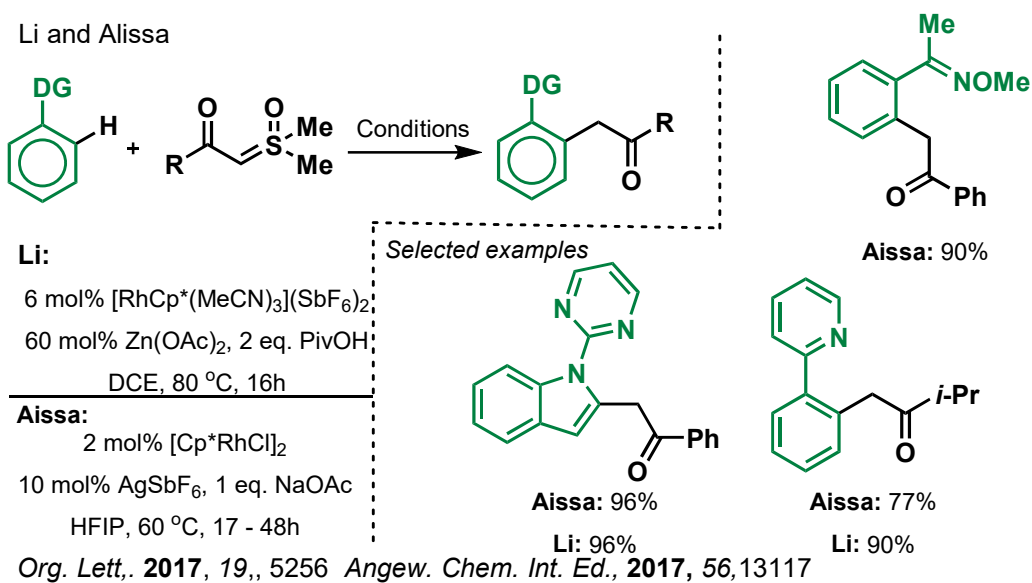
By combining enamines with sulfoxonium ylides, it was possible, through the action of an iridium catalyst, to afford the products of C-H insertion, which in the presence of an acid additive readily cyclised to form highly substituted pyrroles

Angew. Chem. Int. Ed., **2017**, *56*, 4277

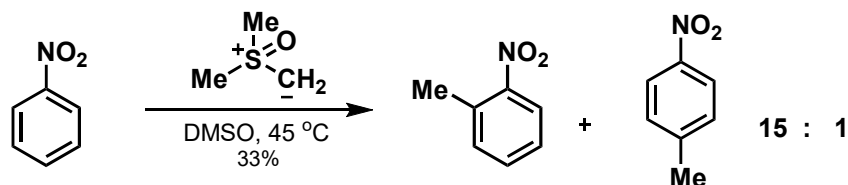
C-H Functionalization



Li and Alissa

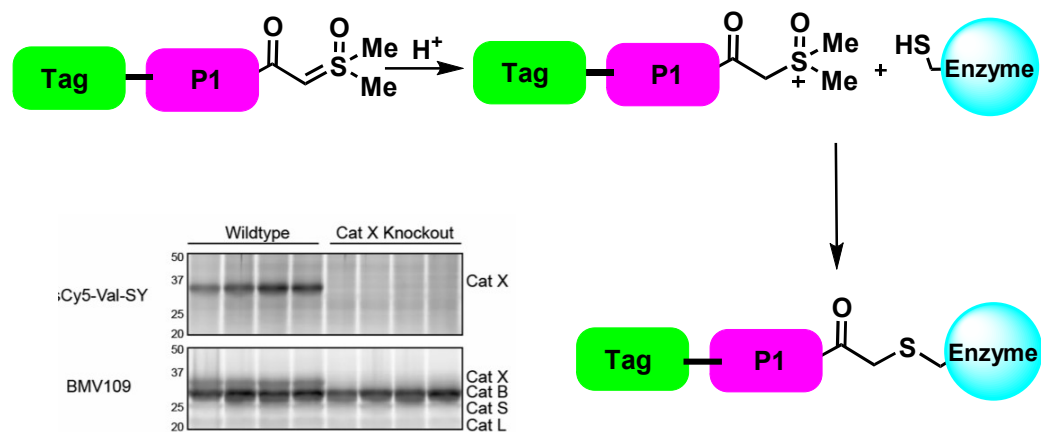


Reaction with Aromatic Compounds



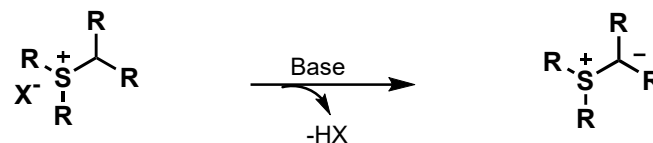
Methylation is directed to the ortho position in preference to the para-, and with meta-substituted nitrobenzenes the methylation proceeds primarily at the more hindered ortho position.
J. Org. Chem., **1966**, *31*, 243

Bio-organic Application of Sulfoxonium Ylides

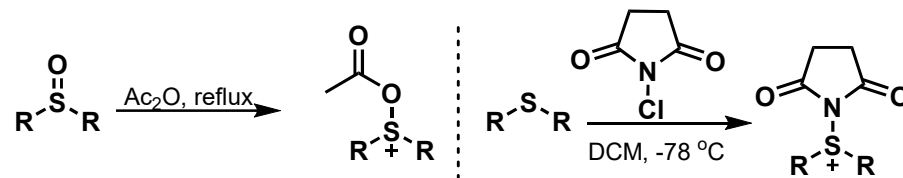
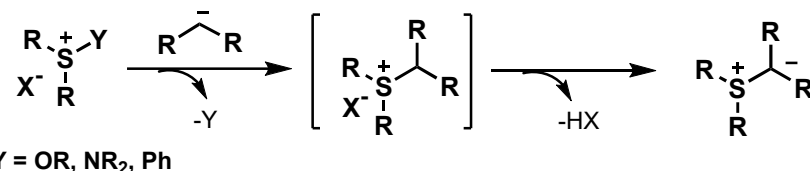


Synthesis of Sulfonium Ylides

Deprotonation of Sulfonium Salts

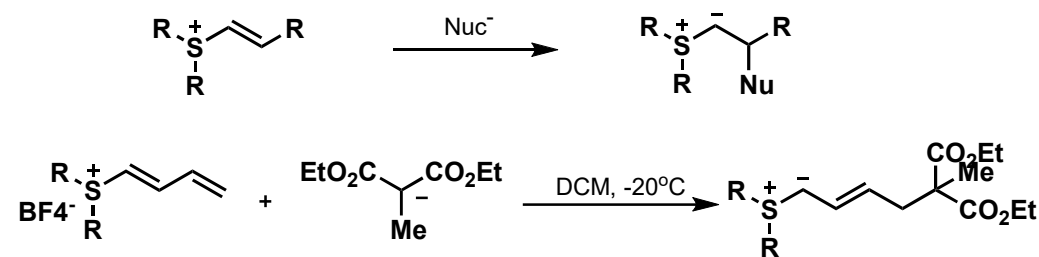


Substitution of Groups on Sulfonium Salts

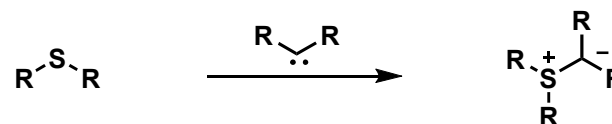


other reagent: trifluoroacetic anhydride, dicyclohexylcarbodiimide, phosphorus pentoxide/Et₃N

Nucleophilic Attack on Vinyl Sulfonium Salts

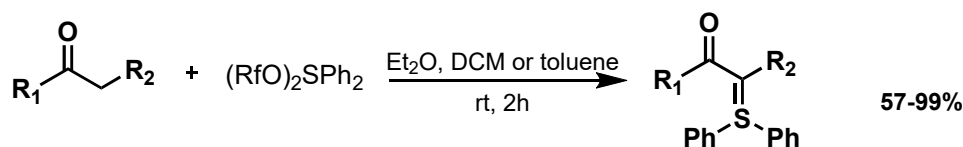


Reaction of Sulfides with Carbenes



Like certain thiocarbonyl compounds and sulfoxides, a variety of sulfides can trap carbenes to give sulfonium ylides. Diazo compounds are the most commonly employed carbene precursors.

Maulide - 2010



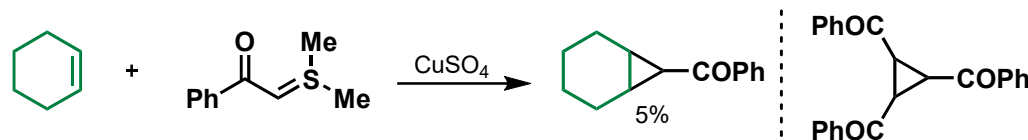
Maulide and co-workers employed Martin's sulfurane for direct ylide transfer to ketones, diketones, and keto esters in very good yields and under mild conditions.

Angew. Chem. Int. Ed., 2010, 49, 8979

Reactions of Sulfonium Ylides

Cyclopropanation of Alkenes

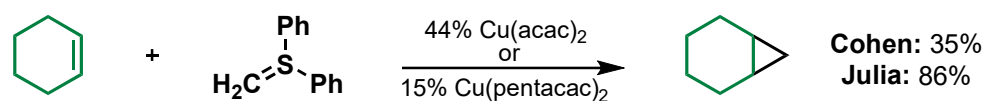
Trost - 1966



The expected cyclopropane was only isolated in trace quantities, instead, cyclopropane tri-mer side product was the major product

J. Am. Chem. Soc. 1966, 88, 1587

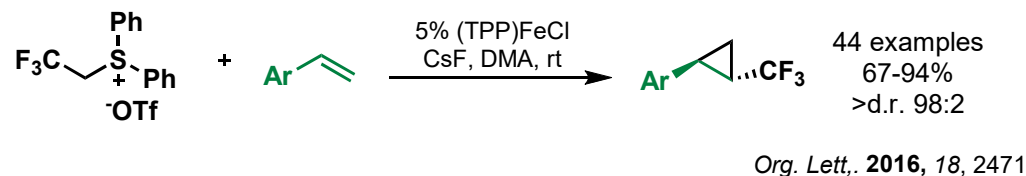
Cohen and Julia



It was not until 1999 that the first enantioselective process was developed by Müller and co-workers. By using either a Cu(I) or Rh(II) chiral catalyst could be used to generate cyclopropanes in moderate e.e%.

J. Am. Chem. Soc., 1974, 96, 5627

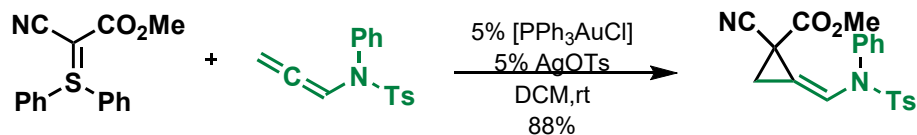
Gu - 2016



Org. Lett., 2016, 18, 2471

Cyclopropanation of Allenamides

Maulide - 2014

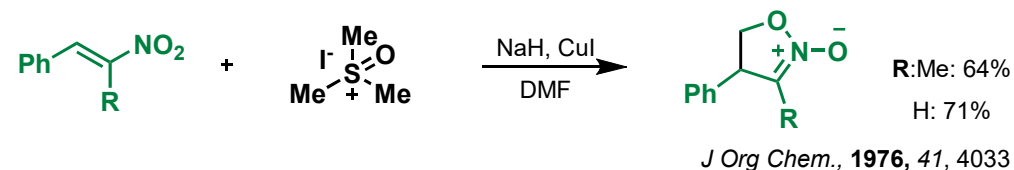


The reaction works with ketones, esters, nitriles and halogens

Chem. Eur. J., 2014, 20, 10636

Formal (4+1) Cycloaddition

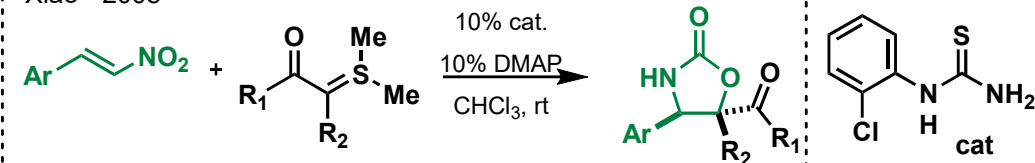
Holy - 1976



J. Org. Chem., 1976, 41, 4033

(4 + 1)-Cycloaddition/Rearrangement of Nitrostyrenes

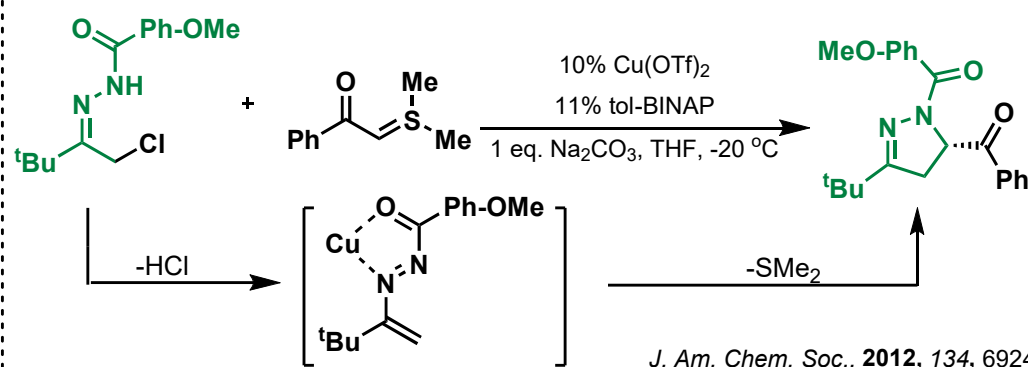
Xiao - 2008



This transformation affords a range of oxazolidinones in moderate to good yields with good to excellent diastereoselectivities.

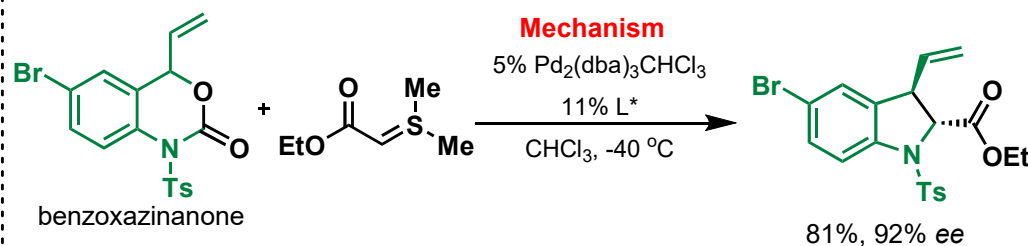
J. Am. Chem. Soc., 2008, 130, 6946

Bolm - 2012



J. Am. Chem. Soc., 2012, 134, 6924

Xiao - 2014



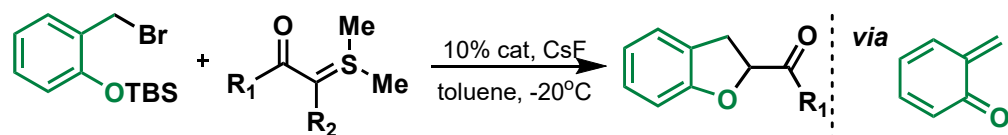
81%, 92% ee

Nat. Commun., 2014, 5, 5500

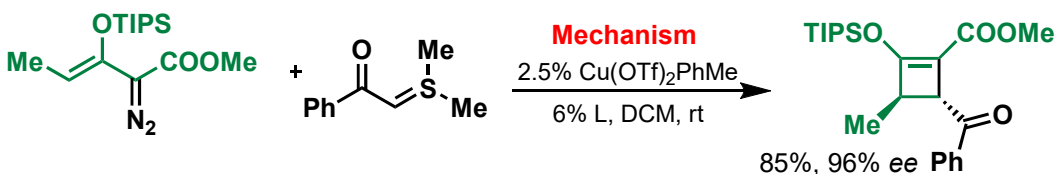
- In 2016, the same reaction was revisited in the context of Fe-catalysis.
- Thereafter, the same group explored the ability of copper-allenyldiene intermediates to act as reactive 1,4-dipoles.
- In 2019 the groups of Gouverneur and Shibata showed that this could be extended to CF₃-substituted benzoxazinones.

J. Am. Chem. Soc., 2016, 138, 8360
Angew. Chem., Int. Ed., 2016, 55, 2840

Xiao - 2017

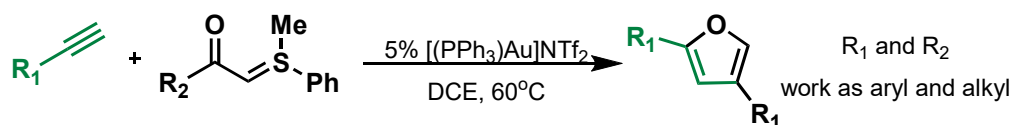
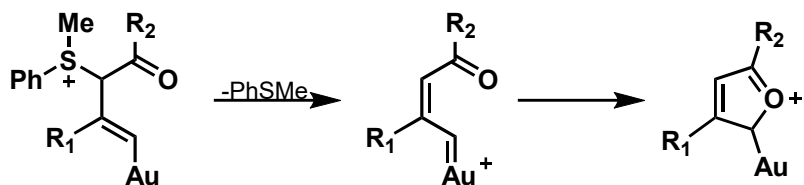
*Eur. J. Org. Chem.*, **2017**, 2017, 233**Formal (3 + 1) Cycloaddition**

Doyle - 2017

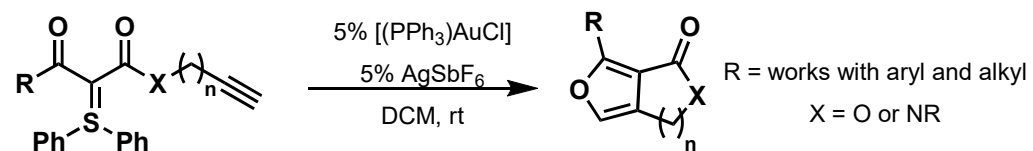
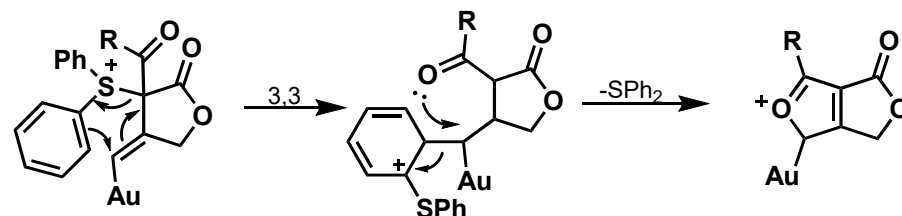
*Angew. Chem., Int. Ed.*, **2017**, 56, 7479**Formal (3+2) cycloaddition - Furan synthesis**

In 2012, the groups of Skrydstrup and Maulide independently reported synthesis of furans based on a cationic π -acidic gold complex promoted a formal (3+2) cycloaddition.

Skrydstrup

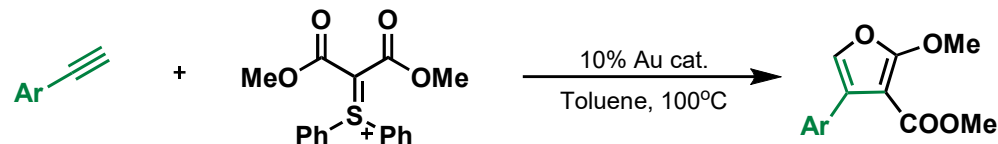
*Angew. Chem., Int. Ed.*, **2012**, 51, 4681**Mechanism**

Maulide

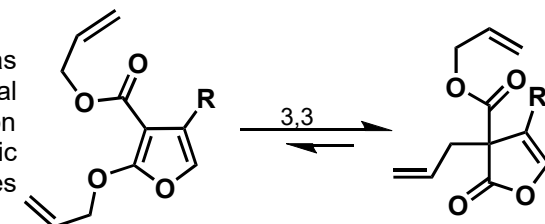
*Angew. Chem., Int. Ed.*, **2012**, 49, 8979**Mechanism - Supported by DFT**

In the same study, Maulide and co-workers investigated the behaviour of doubly stabilised ylides in an intermolecular context, analogous to the Skrydstrup procedure. While such reactions resulted in the efficient formation of 2,3,4-trisubstituted furans, higher temperatures were required on account of the lower reactivity of the starting materials

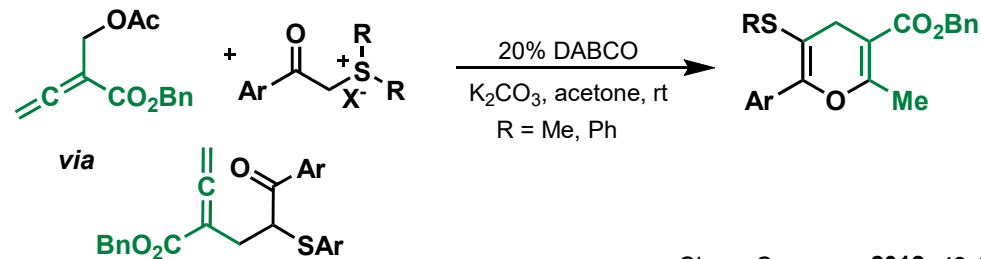
Maulide



When allyl esters were used as stabilising substituents, the final product of the intermolecular cyclisation can rearrange through a [3,3] sigmatropic shift, affording dearomatised furanones bearing a quaternary stereocentre.

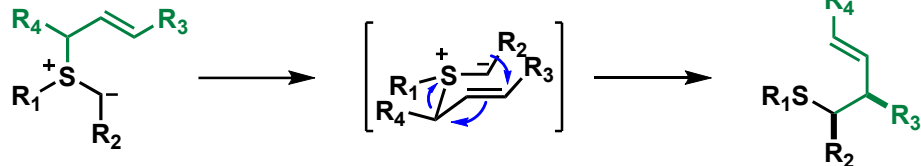
**3 + 3 Annulation**

Tang - 2012

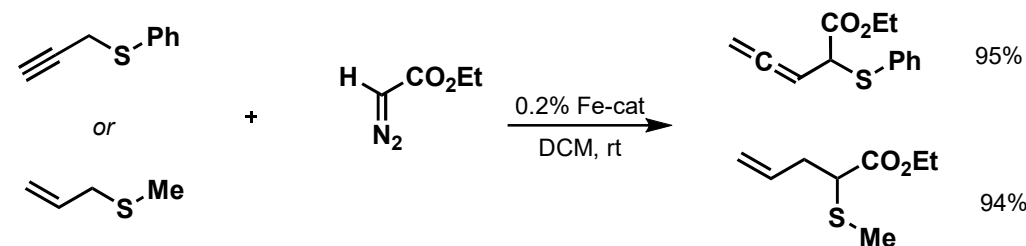
*Chem. Commun.*, **2012**, 48, 2900

Rearrangement Reactions

2,3-Sigmatropic Rearrangement



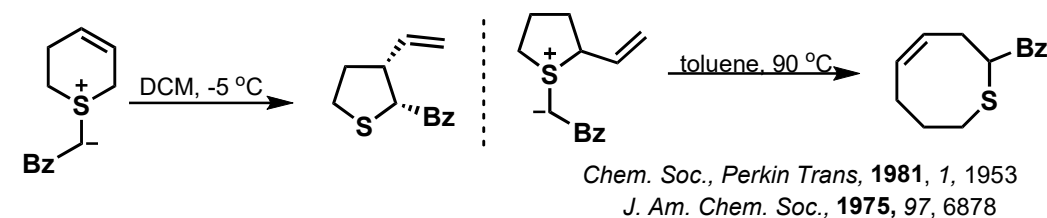
Rearrangement of Allyl and Propargylsulfides



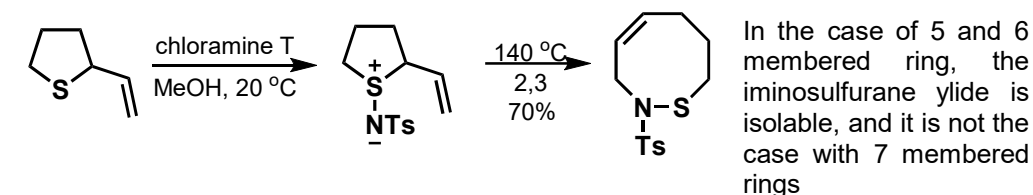
When using TBAFe as a catalyst, the reaction was performed chemoselectively in the presence of boronates, allyl ethers, secondary anilines, disulfides and free alcohols.

Nat. Chem. **2017**, *9*, 970

Ring Expansion and Contraction

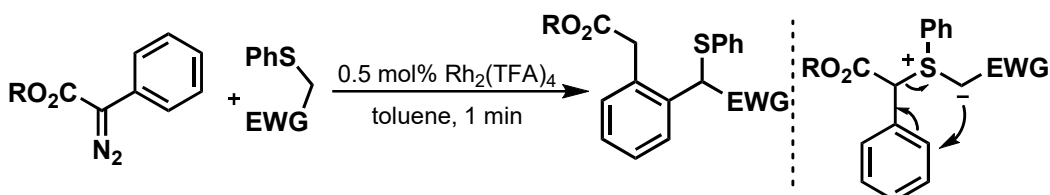


Chem. Soc., Perkin Trans. **1981**, *1*, 1953
J. Am. Chem. Soc., **1975**, *97*, 6878

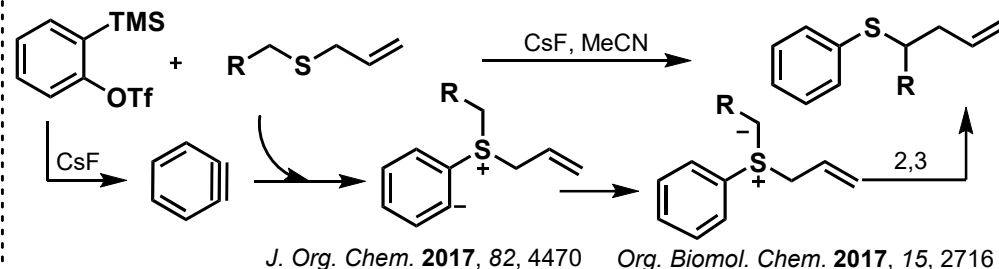


In the case of 5 and 6 membered ring, the iminosulfurane ylide is isolable, and it is not the case with 7 membered rings

thia-Sommelet-Hauser Rearrangement

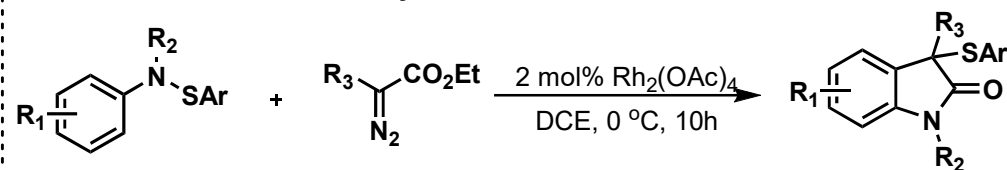


The first rhodium-catalysed thia-Sommelet-Hauser reaction between diazo(aryl)acetates and arylsulfides was reported by Wang's group in 2008.



J. Org. Chem. **2017**, *82*, 4470 *Org. Biomol. Chem.* **2017**, *15*, 2716

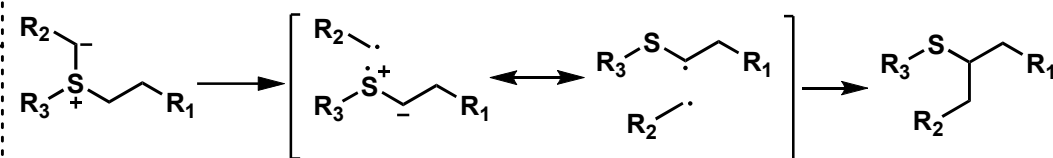
Modified Gassman Oxindole Synthesis



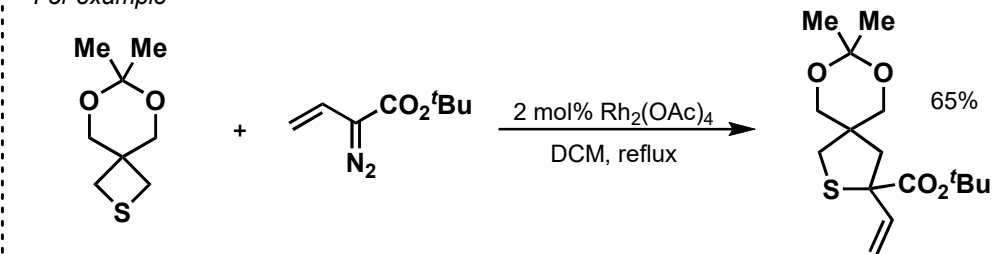
Org. Lett., **2011**, *13*, 1210

Thia-Stevens 1,2-Rearrangement

General Mechanism

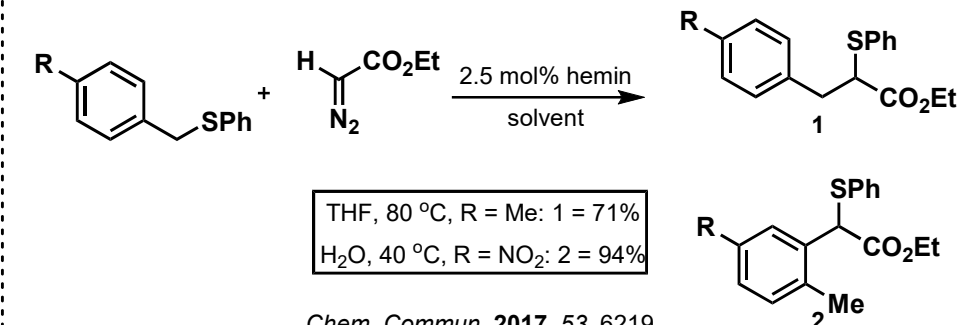


For example



J. Org. Chem. **2015**, *80*, 7581

Stevens vs Sommelet-Hauser



THF, 80 °C, R = Me: 1 = 71%
H₂O, 40 °C, R = NO₂: 2 = 94%

Chem. Commun. **2017**, *53*, 6219