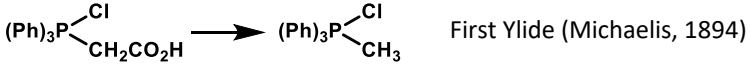
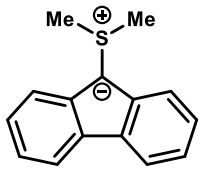
B. Derstine

Sulfur Ylides in Ring Formation

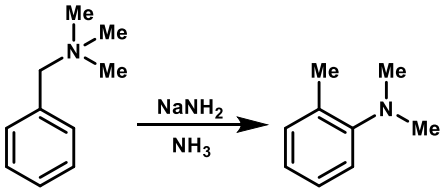
November 13, 2020



First Ylide (Michaelis, 1894)

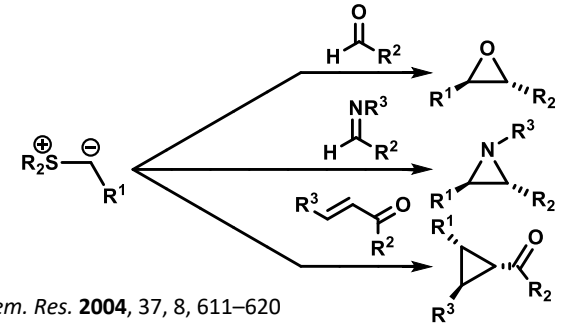


First Sulfur Ylide (Ingold, 1930)

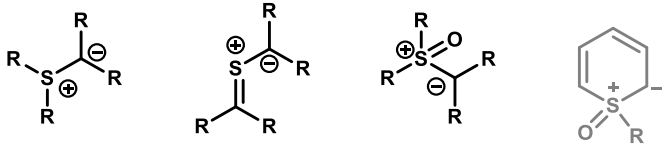


Somelet-Hauser rearrangement (1937)

Johnson-Corey-Chaykovsky reaction



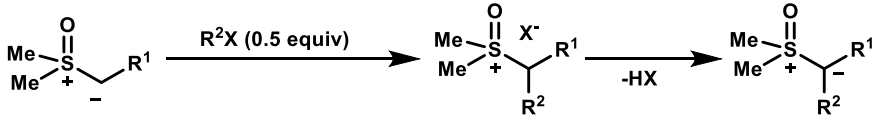
Acc. Chem. Res. **2004**, 37, 8, 611–620



Sulfonium **Thiocarbonyl** **Sulfoxonium** Thiopyranoxide

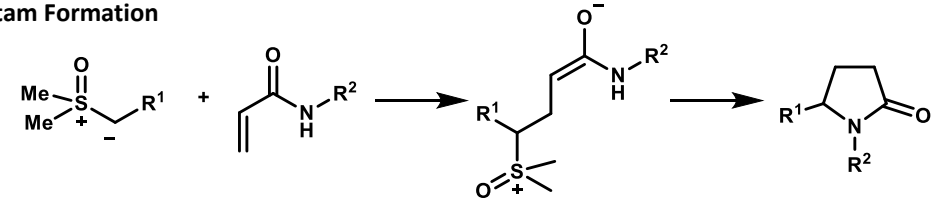
What is Covered: Generation and application of sulfur-containing ylides that are precedented to form >4 membered rings.
Bonus: Thiopyranoxides ylide generation

Hydrogen Atom Substitution

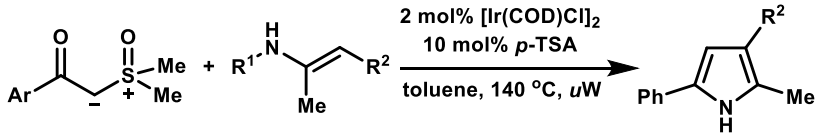


numerous substitutions have been reported

γ-Lactam Formation

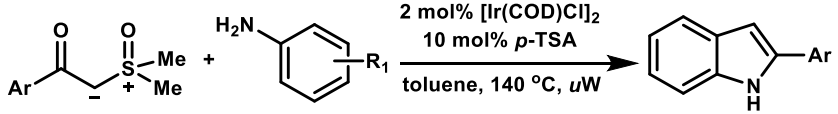


Pyrrole Formation



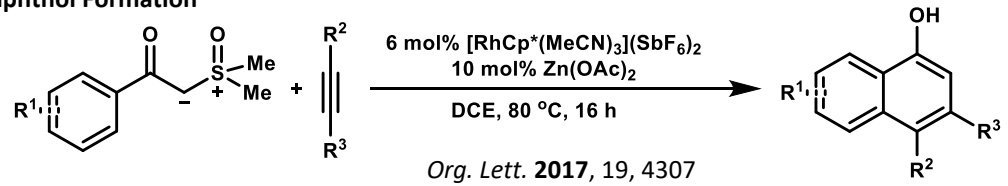
Angew. Chem. Int. Ed. **2017**, 56, 4277

Indole Formation



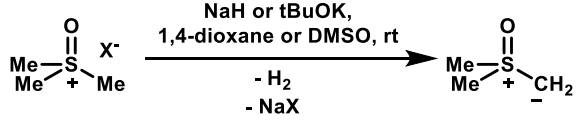
Angew. Chem. Int. Ed. **2017**, 56, 4277

Naphthol Formation



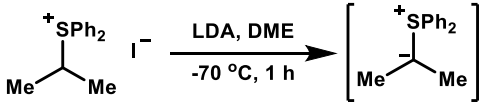
Org. Lett. **2017**, 19, 4307

Sulfoxonium Ylides: Generation by Deprotonation

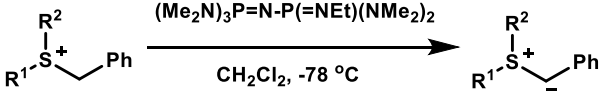


Tip: Do not add to $CHCl_3$

Sulfonium Ylides: Deprotonation of Sulfonium Salts



J. Am. Chem. Soc. ***1965***, 87, 1353



Angew. Chem. Int. Ed. ***1998***, 37, 1689

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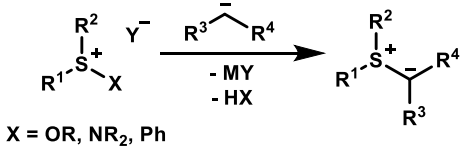
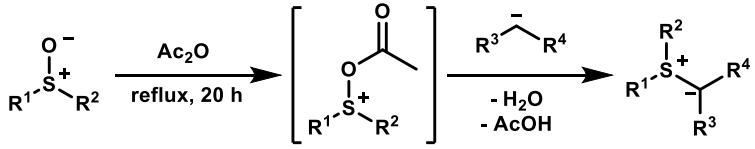
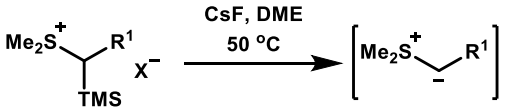
Generation: Sulfonium Salt Substitution



X = OR, NR_2, Ph

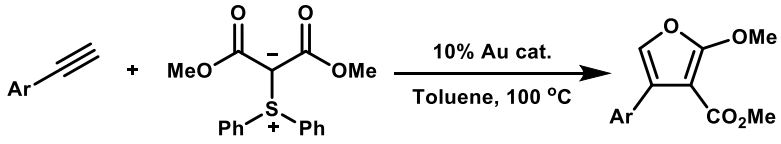


Generation: Desilylation



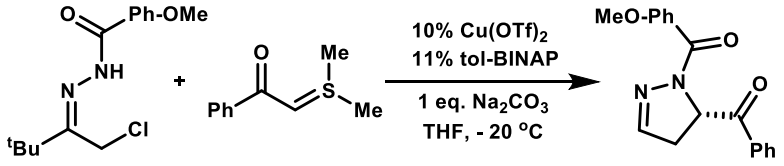
Other methods: reaction of sulfides with carbenes and carbenoids

Applications in Synthesis: Gold-catalyzed Furan Formation



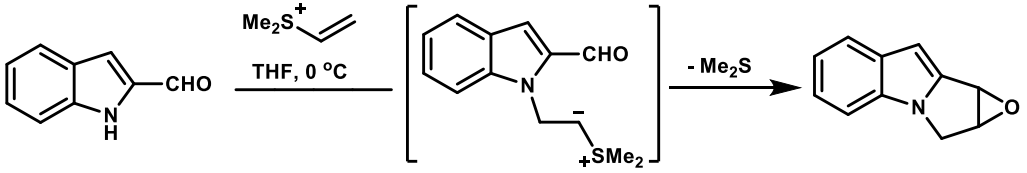
Angew. Chem. Int. Ed. **2010**, 49, 8979
Angew. Chem. Int. Ed. **2012**, *51*, 8886

(4+1) Cycloadditions

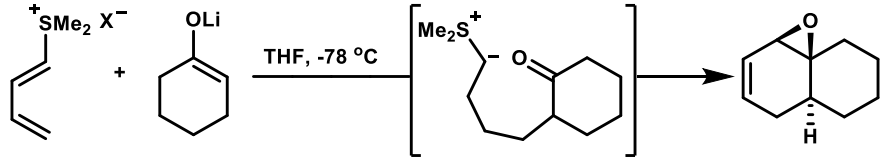


Conditions also exist for substituted oxazalidinones

Intramolecular Cyclization through Epoxidation

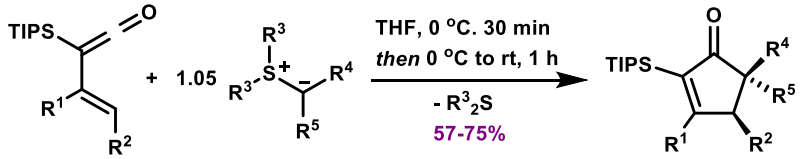


J. Am. Chem. Soc. **1994** 116, 4977



J. Org. Chem. **1974** 39, 3607

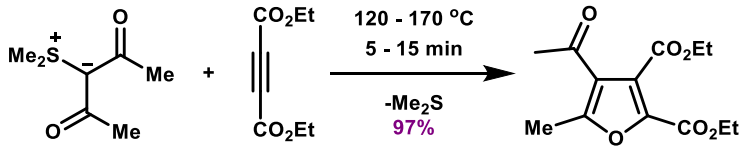
Butenolide Formation from Ketenes



$R^1 = R^4 = R^5$ = H, Me; $R^2 = R^3$ = Me, Ph

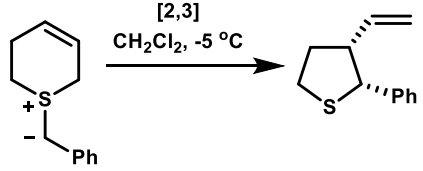
J. Am. Chem. Soc. **1998** 120, 9690

Furan Formation from Alkynes



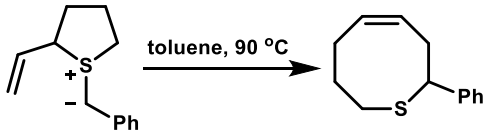
Tetrahedron **1970**, 26, 4353

Ring Contraction



J. Chem. Soc. Perkin Trans. **2001,** 1, 2269

Ring Expansion



J. Am. Chem. Soc. **1975**, 97, 6878

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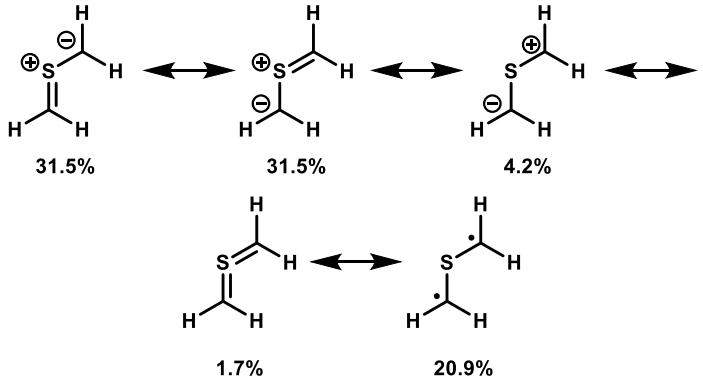
Formation of 4*H*-Pyrans from Allenes

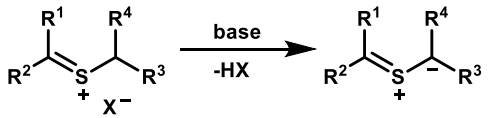
Chem. Commun. **2012**, 48, 2900

Thiocarbonyl Ylides: Resonance Forms



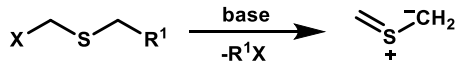
J. Am. Chem. Soc. **1976,** 98, 5020

Generation: Deprotonation of Sulfonium Salts

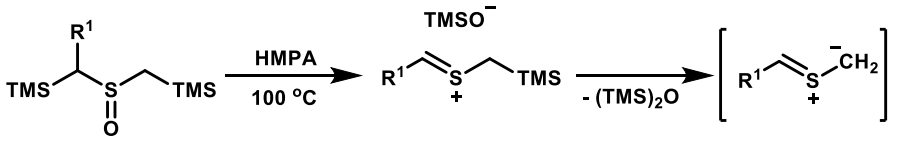


Limited substrate scope:
- R^1 or R^2 = nitrogen-based FG
- R^1/R^2 must not have alpha protons
- R^3/R^4 normally stabilize anion

Generation: 1,3-Elimination Reactions



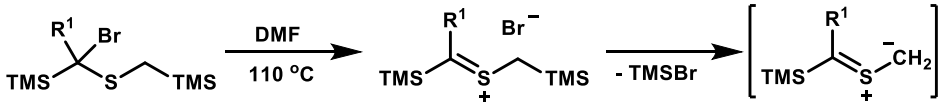
Variation 1: Thermal Decomposition



R^1 = aryl or alkyl

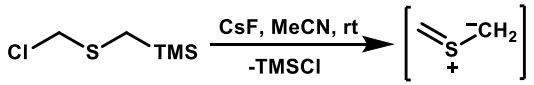
Heterocycles **1995**, 40, 249

Variation 2: Elimination of Halotrimethylsilanes



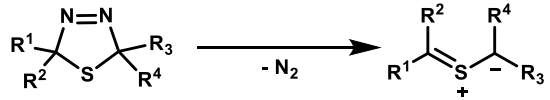
R^1 = H, Ph, TMS

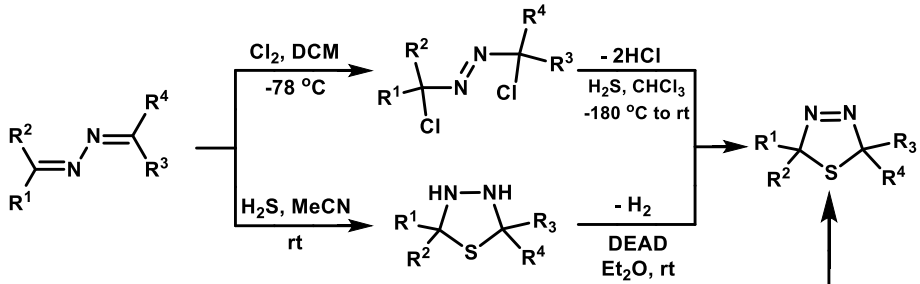
Tetrahedron Lett. **1985**, 26, 3011

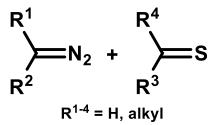


J. Chem. Soc., Chem Commun. **1986**, 1073

Variation 3: Extrusion of Nitrogen



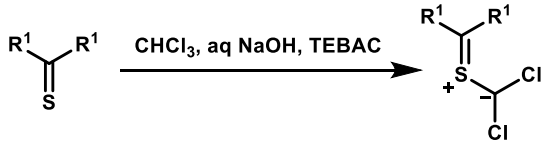




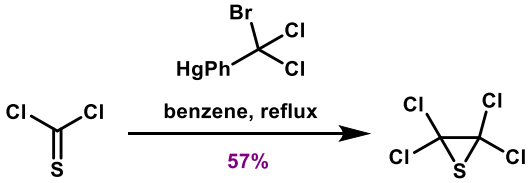
J. Org. Chem. **1972**, 37, 4045
Tetrahedron Lett. **1970**, 1987
Tetrahedron Lett. **1970**, 4689
J. Prakt. Chem. **1959**, 8, 285

Sulfur Ylides in Ring Formation

Method 4: Carbene/Carbenoid Addition to Thiocarbonyls

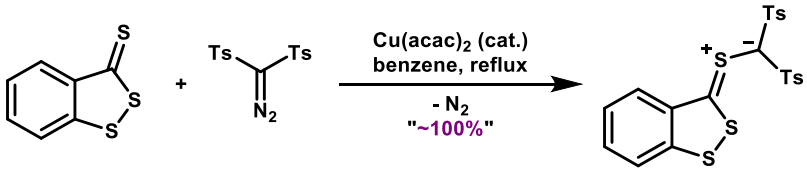


Helv. Chim. Acta. **1999**, 82, 946



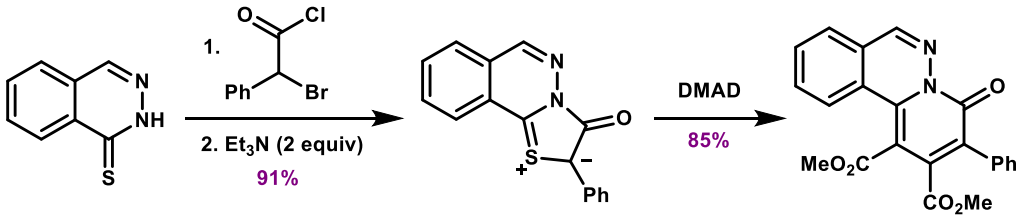
J. Am. Chem. Soc. **1969**, 91, 2138

Variation 2: Decomposition of Diazo Compounds

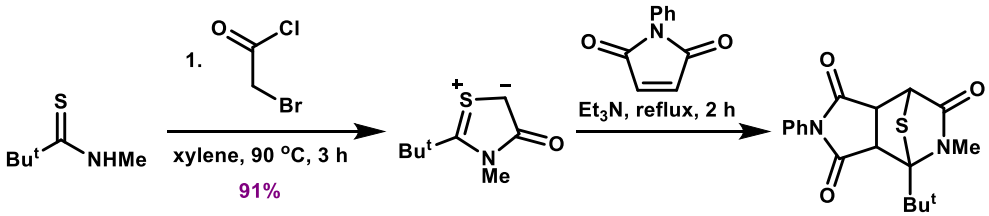


Tetrahedron Lett. **1972**, 1159

Applications in Synthesis

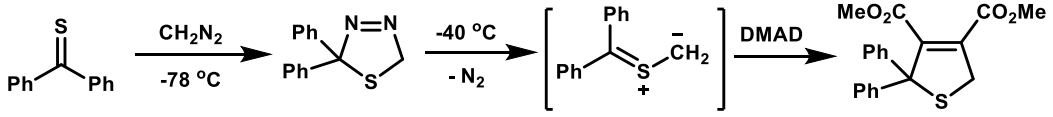


Synthesis **1994**, 993



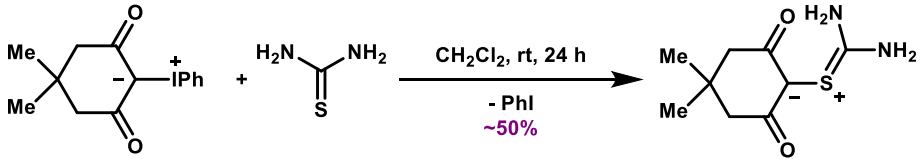
J. Org. Chem. **1985** 50, 1677

1,3-Dipolar Cycloaddition

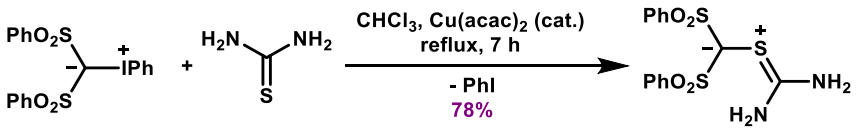


Tetrahedron Lett. **1983**, 24, 4181

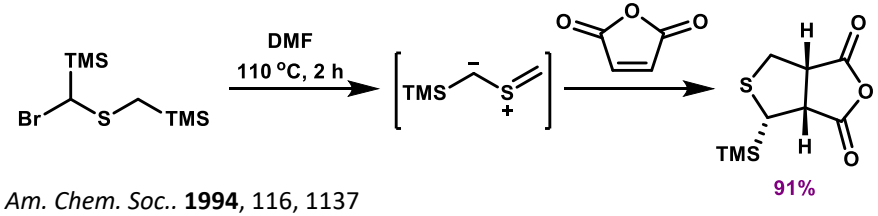
Variation 3: Phenyliodonium Ylides



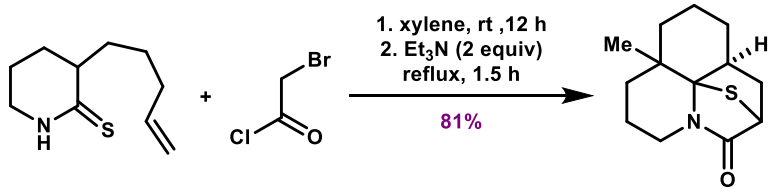
Heterocyl. Chem. **1996**, 33, 575



Synthesis **1988**, 913



J. Am. Chem. Soc.. **1994**, 116, 1137



Tetrahedron Lett. **1992**, 33, 5877

B. Derstine

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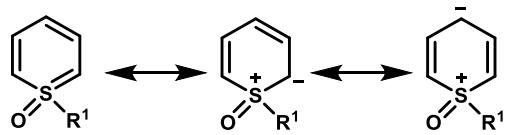
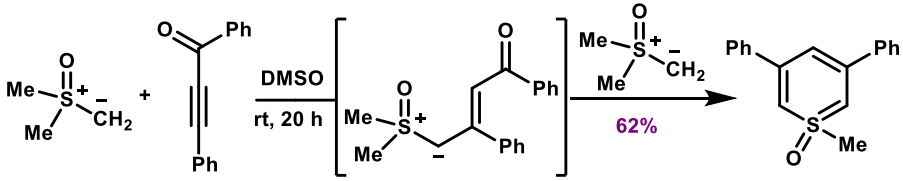
Cyclic Conjugated Sulfoxonium Ylides

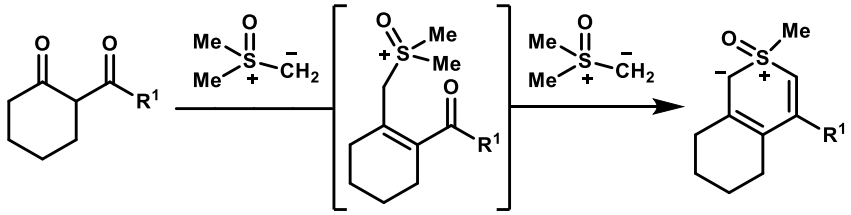


doesn't perform cyclization reactions – but is cool

Synthesis of Ylide:

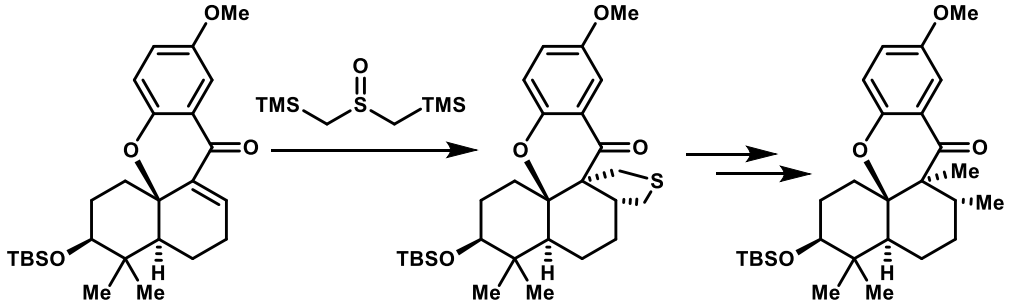


Generation: 1,3-Diketones



Isolable species that generally reacts as a weaker sulfoxonium ylides

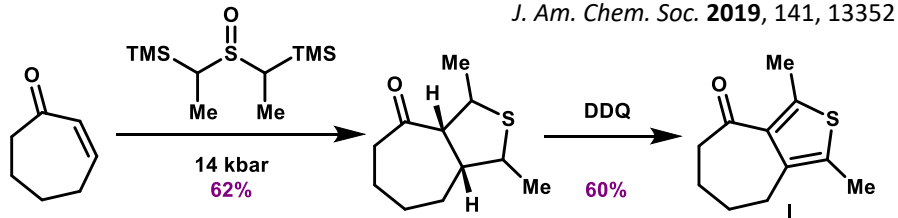
Synthesis of Cyclosmenospongine



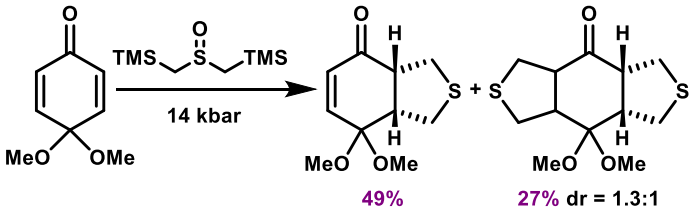
J. Am. Chem. Soc. **2019**, 141, 13352

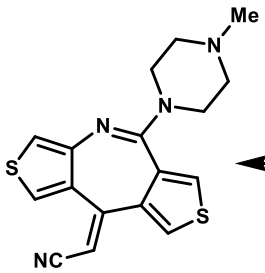
Applications of Sulfur Ylides in Total Synthesis *(extremely limited)*

J. Am. Chem. Soc. **2019**, 141, 13352



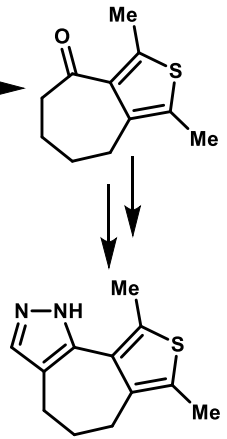
Formal Synthesis of Tenilapine





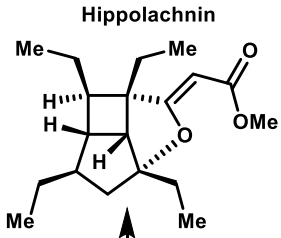
Tenilapine
[psychoactive]

J. Am. Chem. Soc. **2019**, 141, 13352



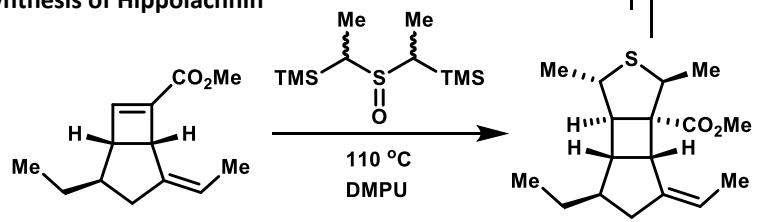
NGB 4420
[dopamine D_4 receptor]

Hippolachnin



4 Steps

Synthesis of Hippolachnin



J. Am. Chem. Soc. **2017**, 139, 11706

Best Resource: *Science of Synthesis* **2004**, 27, 21
Also: See Baran Lab GM on Sulfur Ylide Chemistry