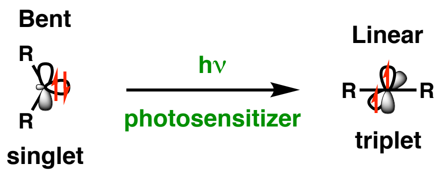
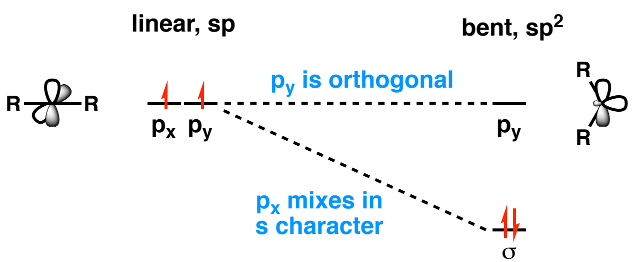
Carbene Generation

Sajan Patel

Carbene Geometry:

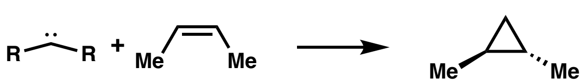


Simplified MO Diagram:

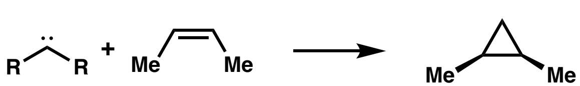


Triplet vs. Singlet Reactivity:

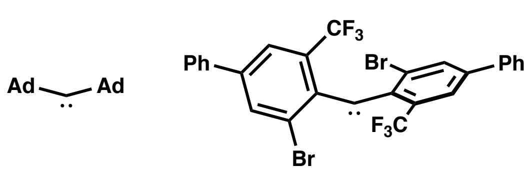
Triplet - stepwise mechanism



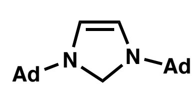
Singlet - concerted mechanism



Persistent Linear Carbenes:

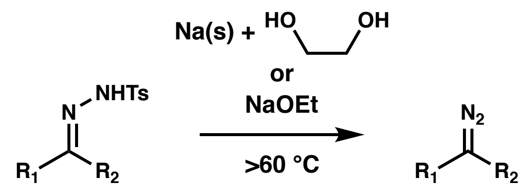


Persistent Bent Carbenes:



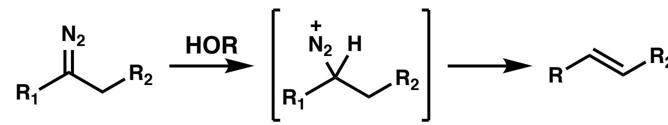
Sulfonyl Hydrazones:

Bamford-Stevens



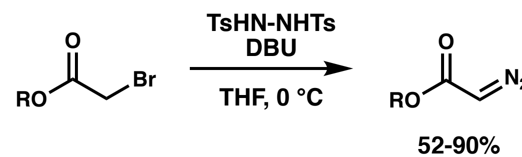
occurs faster with *o*-nitrophenylsulfonyl instead of Ts, but gives a comparable yield

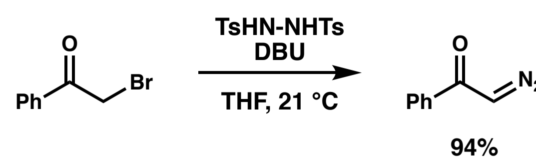
Shapiro



in protic solvents, diazos can decompose to olefins

Fukuyama



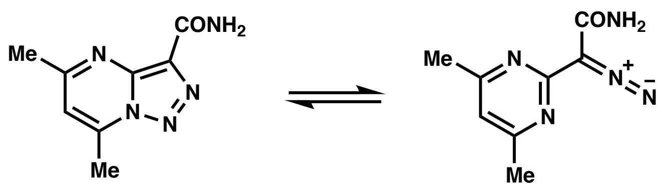


J. Am. Chem. Soc., **1967**, 89 (22), 5736-5737
J. Chem. Soc., **1952**, 0, 4735-4740
J. Am. Chem. Soc., **1959**, 81 (20), 5512-5513
J. Org. Chem., **1963**, 28 (3), 870-872
Org. Lett., **2007**, 9 (16), 3195-3197
Alkenes from Tosylhydrazones, John Wiley and Sons, 2011

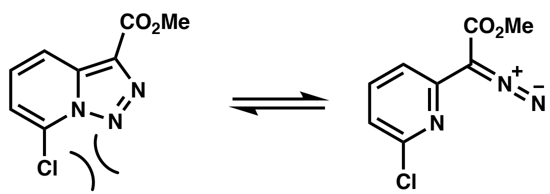
Carbene Generation

Sajan Patel

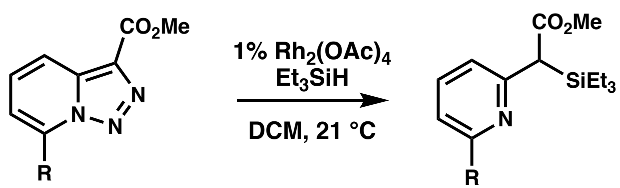
Triazoles:



- Me ^{1}H NMR signals coalesce at 88 °C

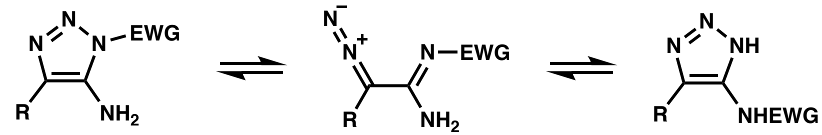


- lone pair repulsion promotes diazo formation



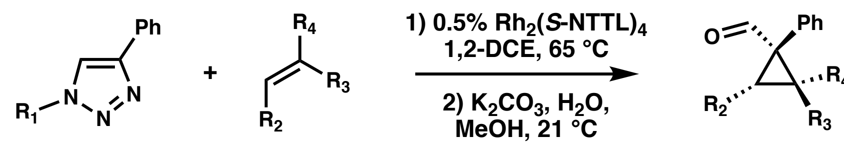
R = H, no reaction
R = Cl, 88%

Dimroth Rearrangement



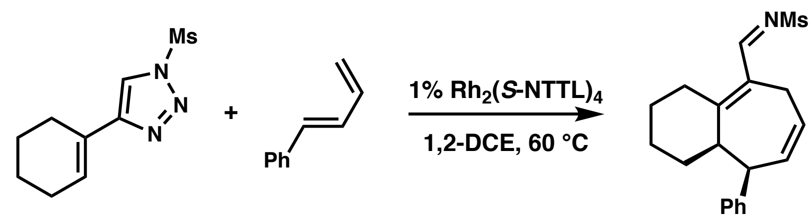
EWG = -CN, $-NO_2$, $-SO_2R$

- equilibirum favors side with EWG on excocyclic nitrogen
- conversion proceeds more rapidly with an EWG at N1 (160 °C)



$R_1 = SO_2Me$ or $SO_2C_8H_{17}$

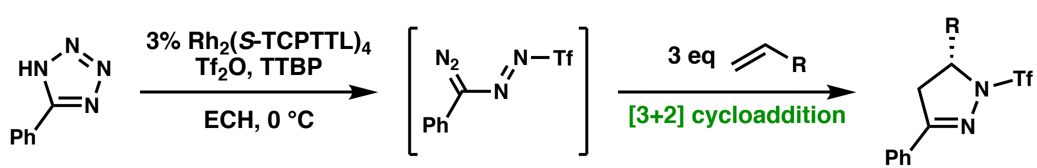
59-92%
>20:1 dr
8-98% ee



82%
>30:1 dr
97% ee

J. En. In. Med. Chem., **2002**, 17 (6), 359-367
Angew. Chem., **2013**, 125, 10228-10231
J. Am. Chem. Soc., **2009**, 131, 18034-18035
Angew. Chem. Int. Ed., **2007**, 46, 4757-4759
Adv. Het. Chem., **1974**, 16, 33-85
Bull. Soc. Chim. Belg., **1990**, 99 (4)
Bull Soc. Chim. Belg., **1981**, 90 (6)
J. Chem. Soc. Perkin Trans., **1972**, 0, 2623-2630
Angew. Chem. Int. Ed., **2018**, 57, 5497-5500

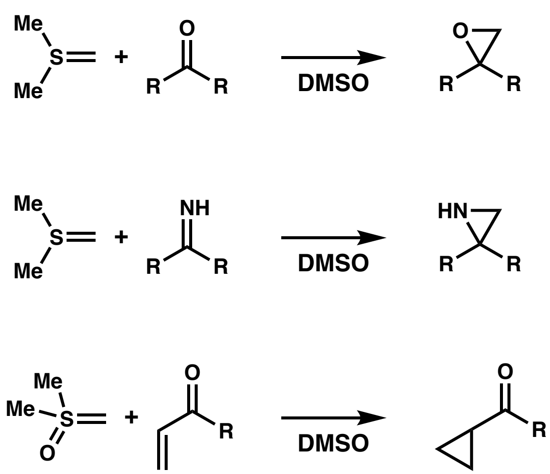
Tetrazoles:



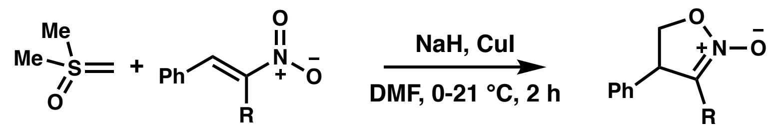
46-88%
22-99% ee

Sulfonium and Sulfoxonium Ylides:

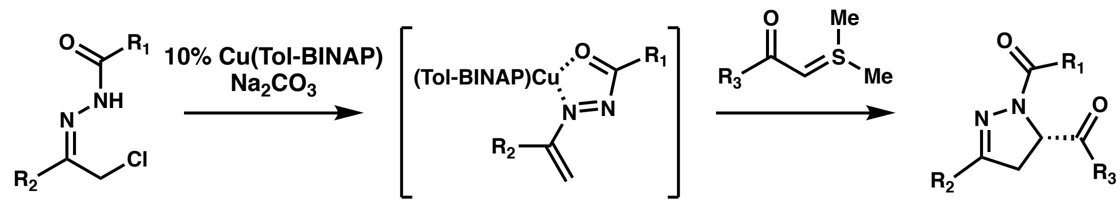
Corey-Chaykovsky Reaction

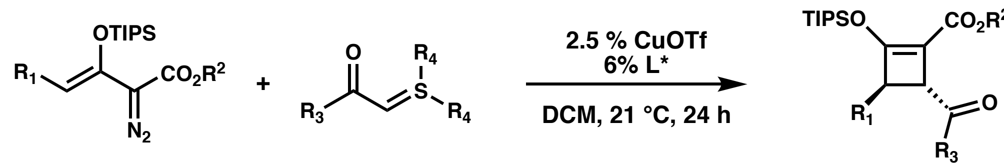


n + 1 Cycloaddition

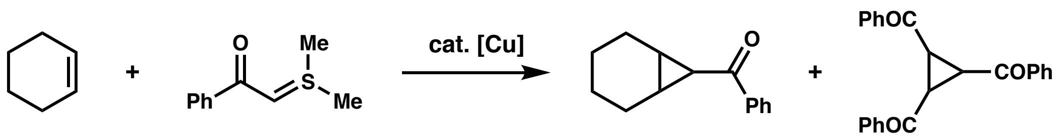


R = H, 71%
R = Me, 64%

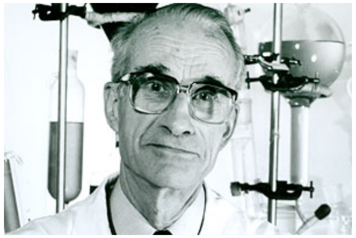


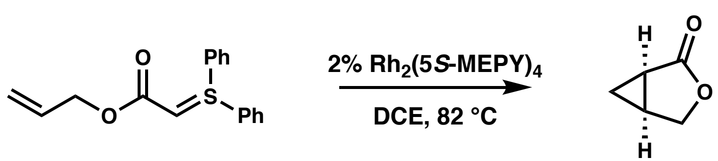


Cyclopropanation (Sulfonium Ylides)



Trost, $CuSO_4$	5%	major product
Julia, $Cu(pentacac)_2$	86%	not observed

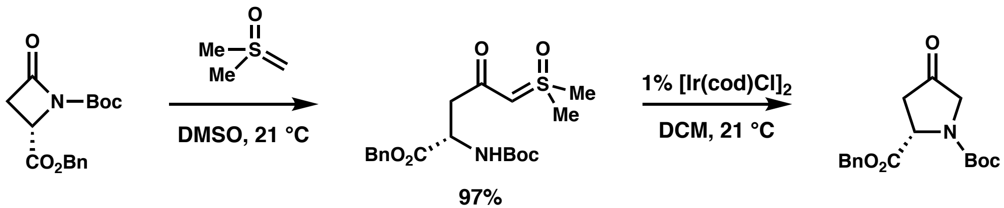




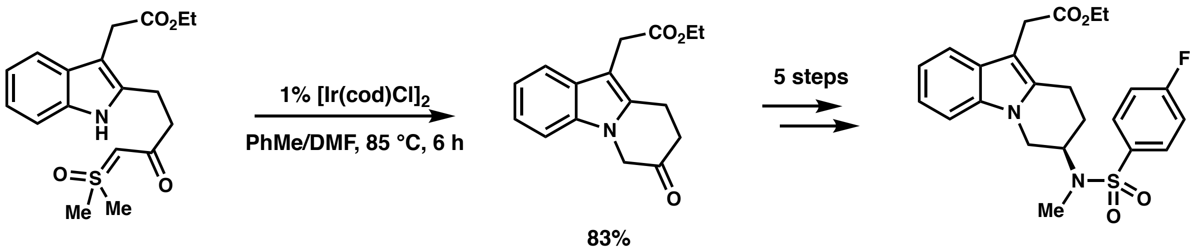
40%, 69% ee

in all cases, diazo compounds show higher yields but comparable diastereo- and enantioselectivity

N-H Insertion (Sulfoxonium Ylides)

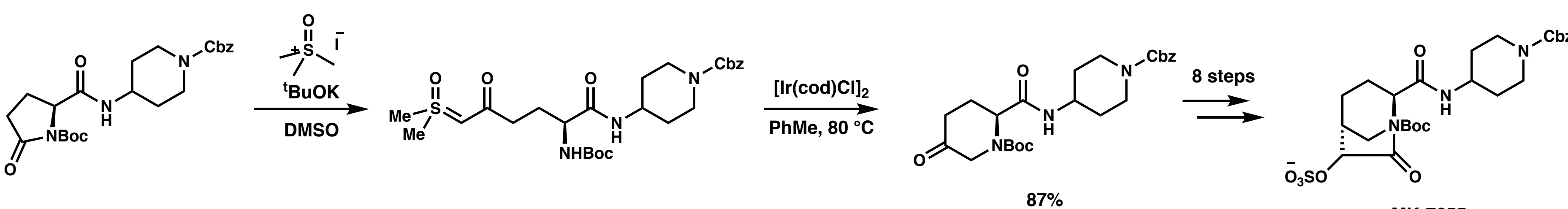


ring expansion of lactams



MK-7246
49% overall yield

- selective CRTH2 antagonist
- potential treatment of respiratory disease

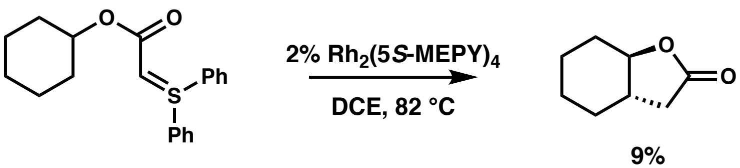


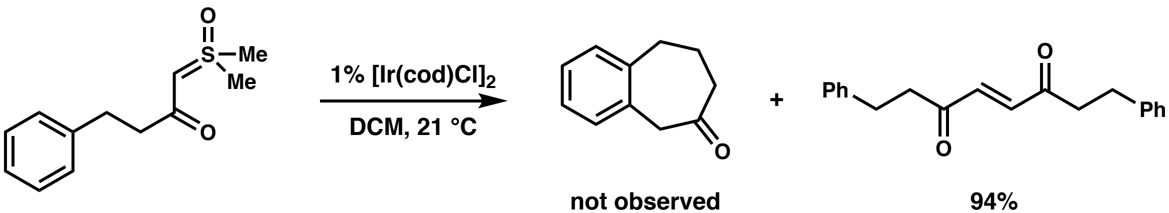
MK-7655
10% overall yield
ß-lactamase inhibitor

Sulfur Ylides in Organic Synthesis and Transition Metal Catalysis, Springer, 2017
J. Chem. Soc., Chem. Commun., **1993**, 0, 1434-1435
Org. Lett., **2018**, 20, 2464-2467
Org. Lett., **2017**, 19, 5256-5259

C-H Insertion (Sulfonium and Sulfoxonium Ylides)

- poor relation of N-H Insertion
- dimerization is the key challenge
- sulfur ylides are more nucleophilic than diazos and will attack metal carbenoids more readily

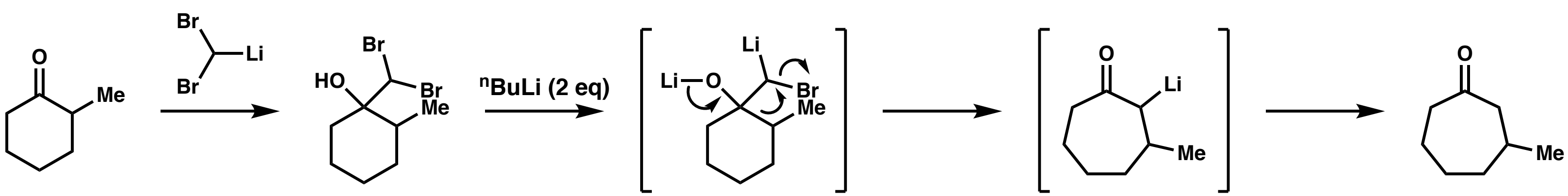


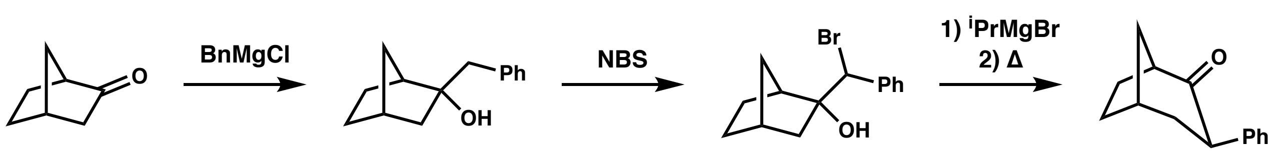


ß-oxido Carbenoids:

- superior selectivity for single-homologation than the Büchner-Curtius-Schlotterbeck reaction

Tetrahedron, **1987**, 43 (1), 3-38
Bull. Chem. Soc. Jpn., **1977**, 50 (6), 1592-1595
J. Org. Chem., **1970**, 35 (8)



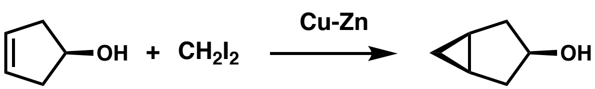


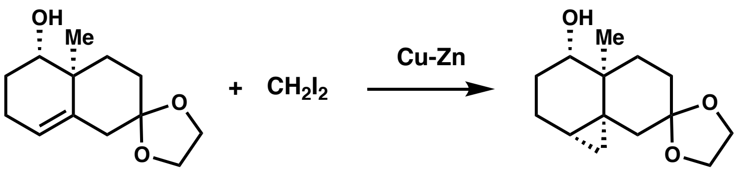
Dihalogenated Alkanes and Alkenes:

Simmons-Smith

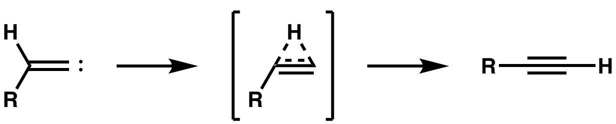
$$2\ CH_2I_2 + 2\ Zn \longrightarrow 2\ (ICH_2)ZnI \rightleftharpoons (ICH_2)_2Zn + ZnI_2$$

- usually requires alcohol directing group

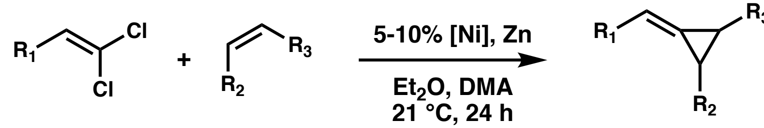




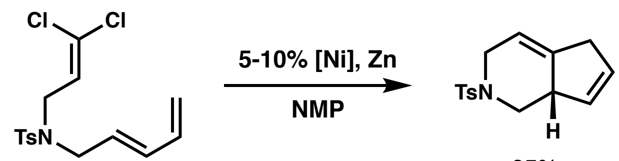
Fritsch-Buttenberg-Wiechell Rearrangement



Dichloroalkenes

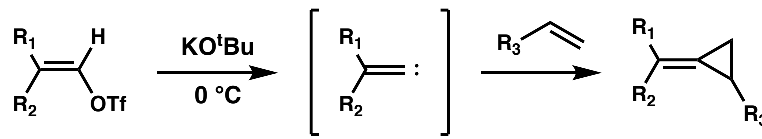


50-99%



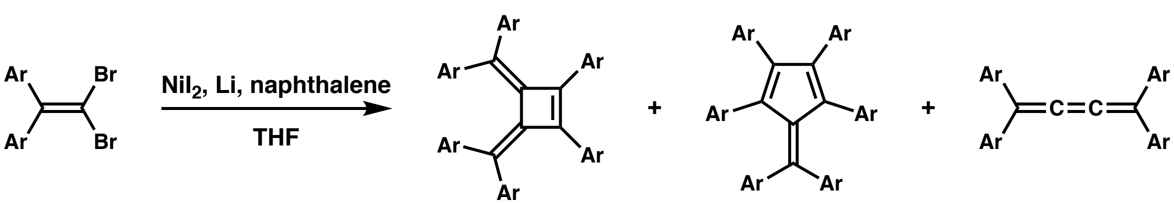
65%
90% ee

Alternative Strategy, Primary Vinyl Triflates



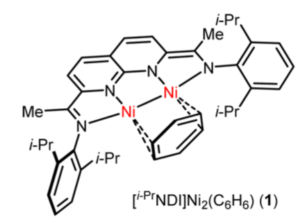
temperature must be kept low to prevent FBW decomposition

Dibromoalkenes



Ar = Ph	23%	0%	23%
Ar = p-Me-C_6H_4	10%	11%	trace

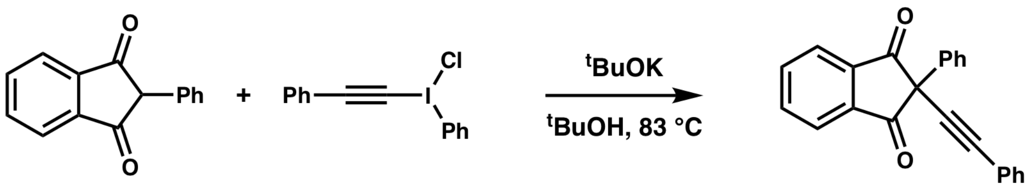
[Ni] =

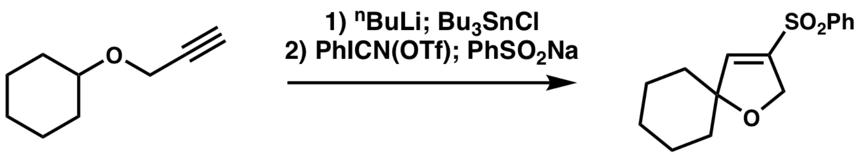


Chem. Rev., **2004**, 104, 3795-3849
Chem. Lett., **1988**, 149-152
J. Am. Chem. Soc., **2017**, 139, 11686-11689
Science, **2019**, 363, 857-862

Alkynyl and Alkenyl Iodonium Salts:

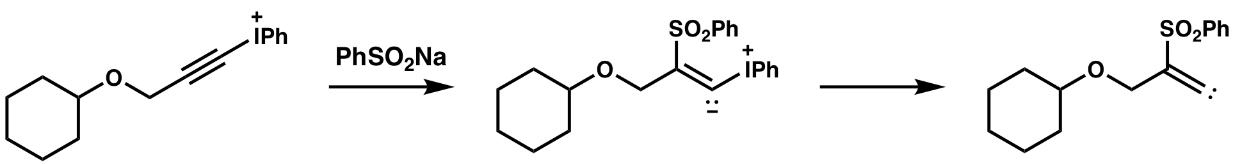
Angew. Chem. Int. Ed. Engl., **1992**, 31, 274-285
J. Am. Chem. Soc., **1994**, 116, 93-98
J. Am. Chem. Soc., **1988**, 110, 6566-6568
Org. Lett., **2006**, 8 (17), 3659-3662

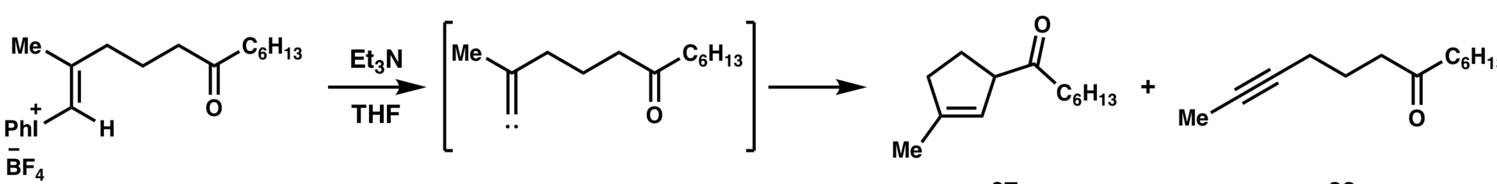




54%

via



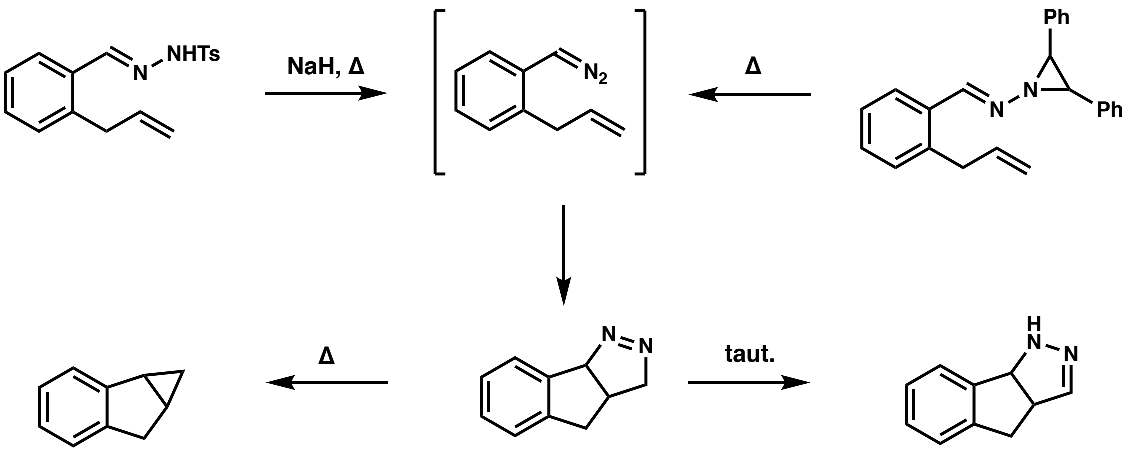


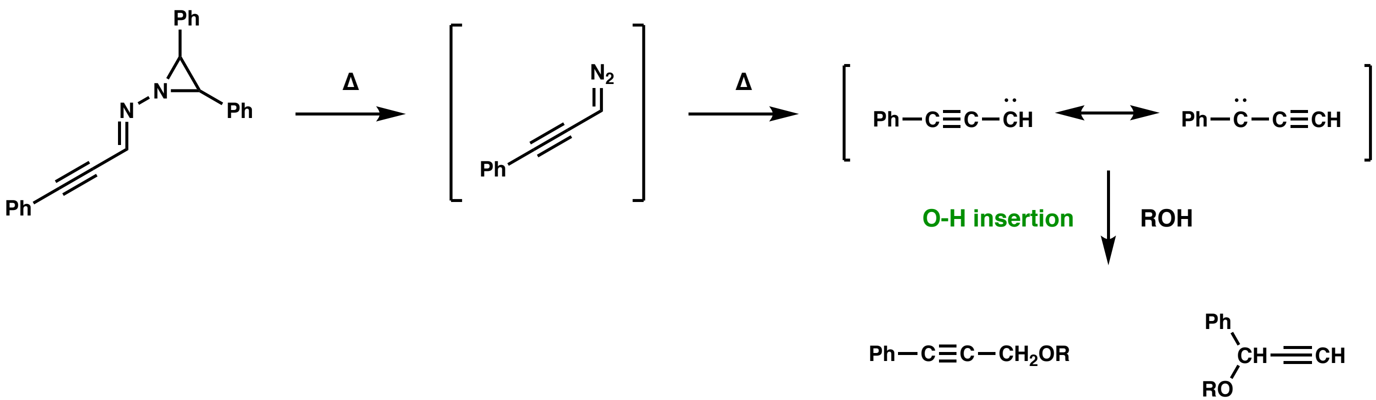
67 : 33

67%

Aziridinylimines:

- alternative to tosyl hydrazones
- cleaved thermally, good for base-sensitive substrates





R = OMe, 60%	2	:	3
R = O^{i}Pr, 52%	5	:	1

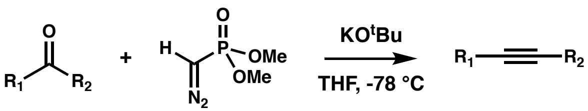
Albert Eschenmoser, ETH Zürich

Albert Padwa, Emory University

Helv. Chim. Acta., **1972**, 55, 1276
Tet. Lett., **1979**, 46, 4425-4428
Tet. Lett., **1991**, 32 (8), 983-986

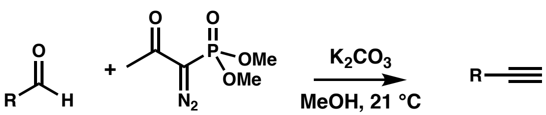
Diazo Transfer:

Seyferth-Gilbert Homologation

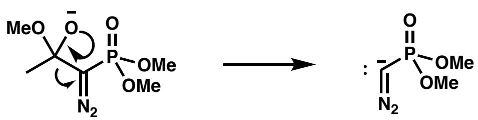


Bestman-Ohira Modification

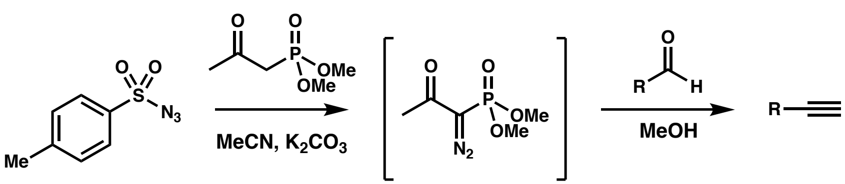
good for base-sensitive substrates, such as enolizable aldehydes



via

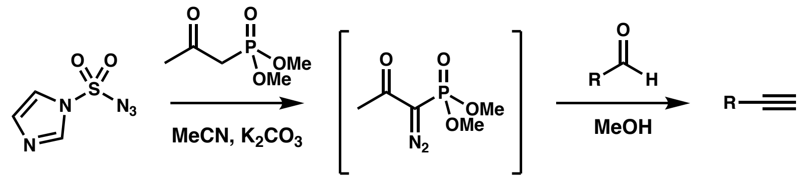


in situ generation of Bestman-Ohira Reagent

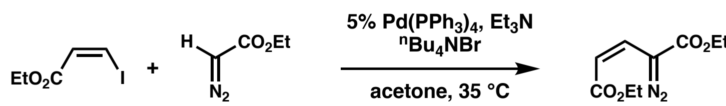


Kristensen Modification

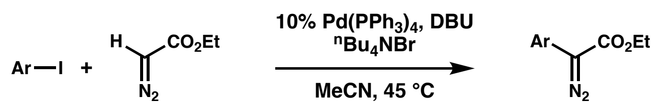
- uses bench-stable diazo transfer agent
- convenient, scalable



Pd-Catalyzed Cross-Coupling of Diazoacetates

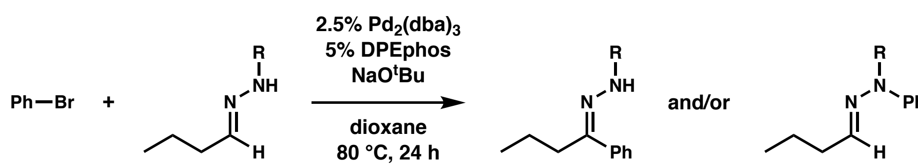


48-86%



0-80%

Hydrazones as Acyl Anions



C-arylation N-arylation

R = ^{t}Bu, 98% (C-arylation)
R = Boc, no reaction
R = Bz, no reaction
R = Ph, 91% (N-arylation)

Synthesis, **2004**, 1, 59-62
J. Am. Chem. Soc., **2006**, 128, 14800-14801
J. Org. Chem., **2014**, 79, 9423-9426
J. Am. Chem. Soc., **2007**, 129, 8708-8709