

# Rolf Huisgen

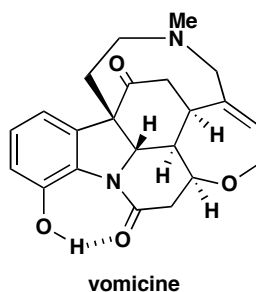
## The Chemical Adventurer

Born: 1920

"Luckily, the uninspiring high school chemistry instruction was limited to 1 year, not enough to squelch my enthusiasm."

PhD: Student of Heinrich Wieland

-Work focused around vomicine, a strychnine alkaloid from *Strychnos nux vomica* parts of which were conducted in air raid bunkers during World War II

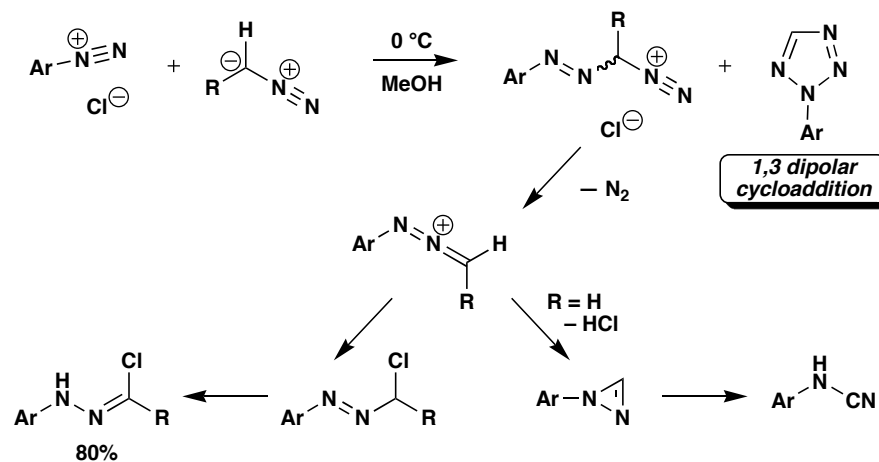


Faculty Positions:

- University of Tübingen (1949 – 1952)
- University of Munich (1952 – present)

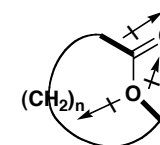
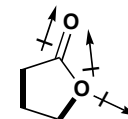


The Beginning Adventures: Diazo Compounds



Investigations into the Reactivity of Lactones: *cis* vs *trans*

- Dipole moments indicative of conformation in lactones



n	Dipole Moment (Debye)
5	4.09
6	4.22
7	4.45
8	3.7
9	2.25
10	2.01
11	1.88
12	1.86
13	1.86
14	1.86
16	1.86
Butyl caproate	1.79

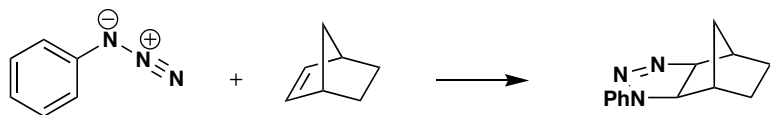
- Open chain aliphatic esters have a dipole moment ~ 1.79 D
- Rates of hydrolysis decrease by  $10^4$ – $10^5$  in the transition from *cis* to *trans*
- Analysis extended to cyclic carbonates, lactams, *N*-nitrosolactams

## The 1,3 Dipolar Cycloaddition Story

- 94 full papers, 109 communications, 28 review articles with ~80 full papers yet to be written as of 1994 involving 1,3 dipolar cycloadditions, 513 references by SciFinder®  
 - General concept solidified under Huisgen's guidance in 1958 but had been recognized by L. I. Smith in 1938 but never exploited

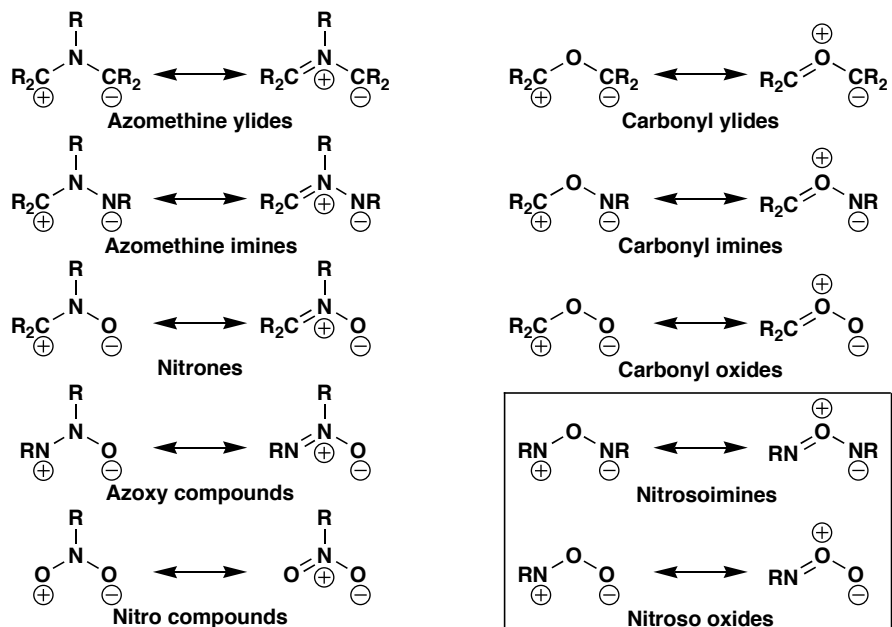
L. I. Smith *Chem. Rev.* 1938, 23, 193–285

- Project began modestly, growing in three years to 17 co-workers



Rates unaffected by solvent polarity, evidence for non-zwitterionic intermediates

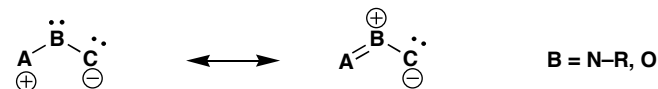
$R_2C$ ,  $RN$ ,  $O$  are isoelectronic as well as  $RC$  and  $N$  leading to the postulation of new 1,3 dipoles in 1960, nitrosoimines and nitrosoxides have yet to be used in 1,3 dipolar cycloaddition to date



## The Principles

### - Sextet vs Octet

- Atom A of sextet structure has incomplete valence with a positive charge (six electrons), C has a negative charge and nonbonding electron pair  
 - Atom A of octet structure has a complete valence (8 electrons) and atom B is cationic, C retains the negative charge and nonbonding electron pair

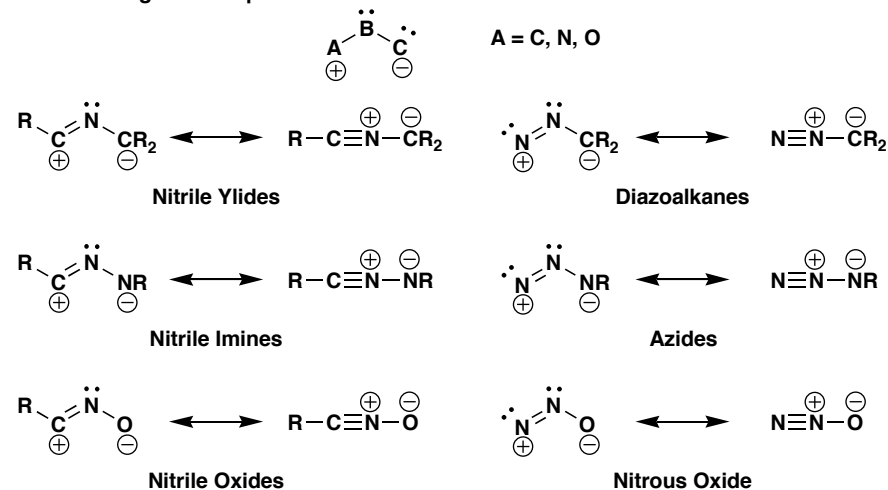


sextet

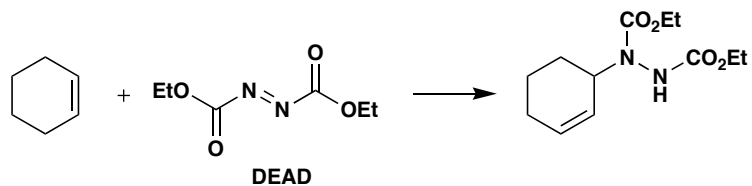
octet

### Internal Octet Stabilization

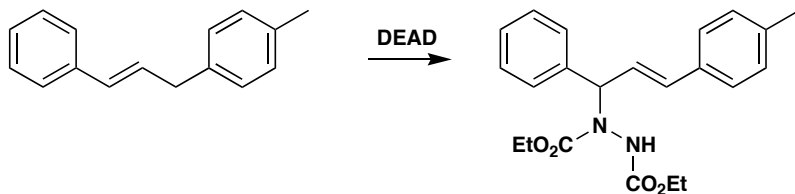
- Cations of C, O, N in the A position are stabilized by resonance donation from a nonbonding electron pair on B



- Investigations into *ene* reactions:

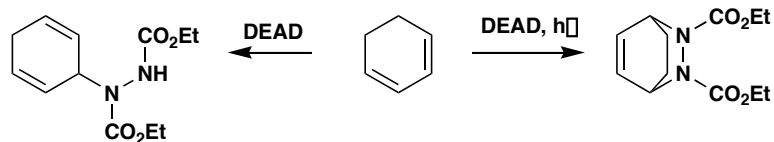


- Rate increased by radical initiators and decreased by inhibitors



- No effect on rate due to radical initiators or inhibitors  
- Postulated synchronous process

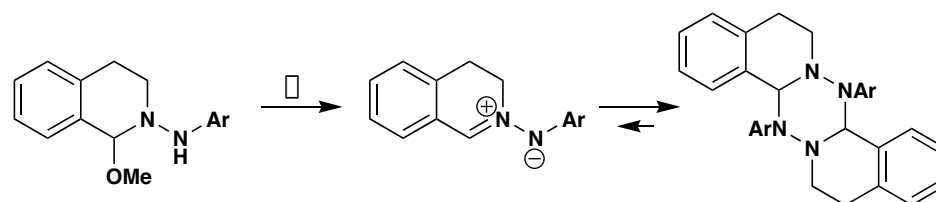
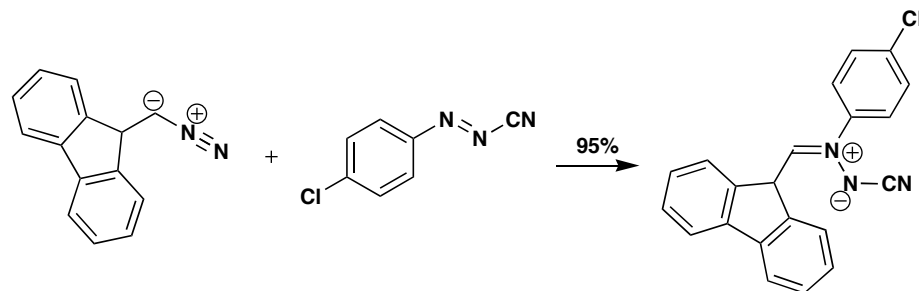
R. Huisgen, F. Jakob *Justus Liebigs Ann. Chem.* 1954, 590, 37–47  
R. Huisgen, H. Bohl *Chem. Ber.* 1960, 93, 527–540



- light needed for isomerization of NN double bond

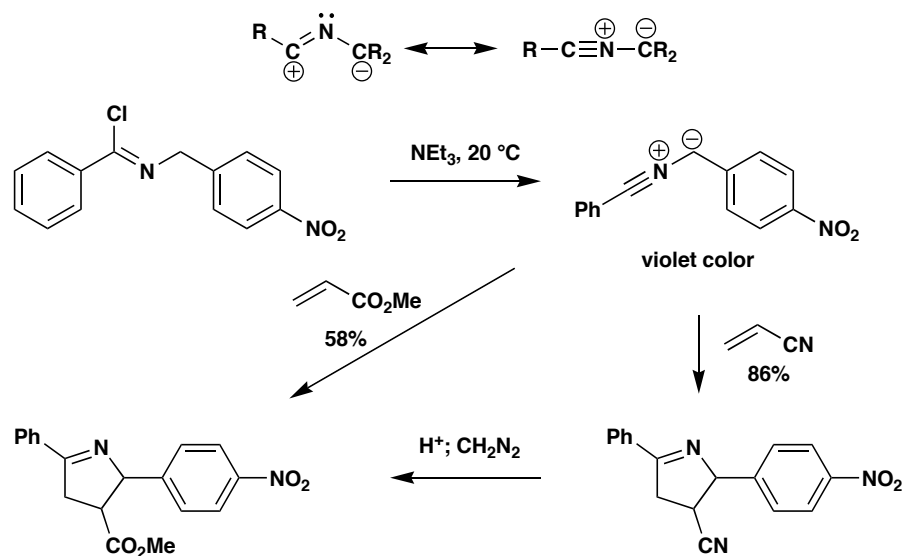
R. Askani *Chem. Ber.* 1965, 98, 2551–2555  
G. O. Schenk, H. R. Kopp, B. Kim, E. Z. Koerner von Gustorf *Naturforsch.* 1965, 20b, 637–639

Venturing towards Azomethine Imines: Beginnings of 1,3 dipolar cycloadditions

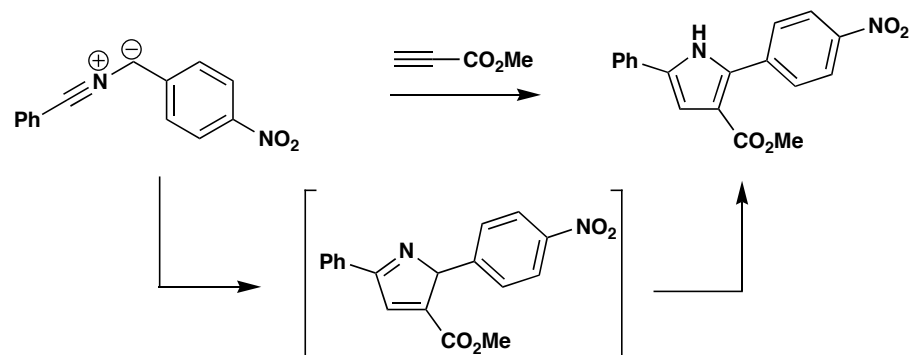


R. Huisgen, R. Fleischmann, A. Eckell *Tetrahedron Lett.*, 1960, 12, 1–4

## Nitrile Ylides

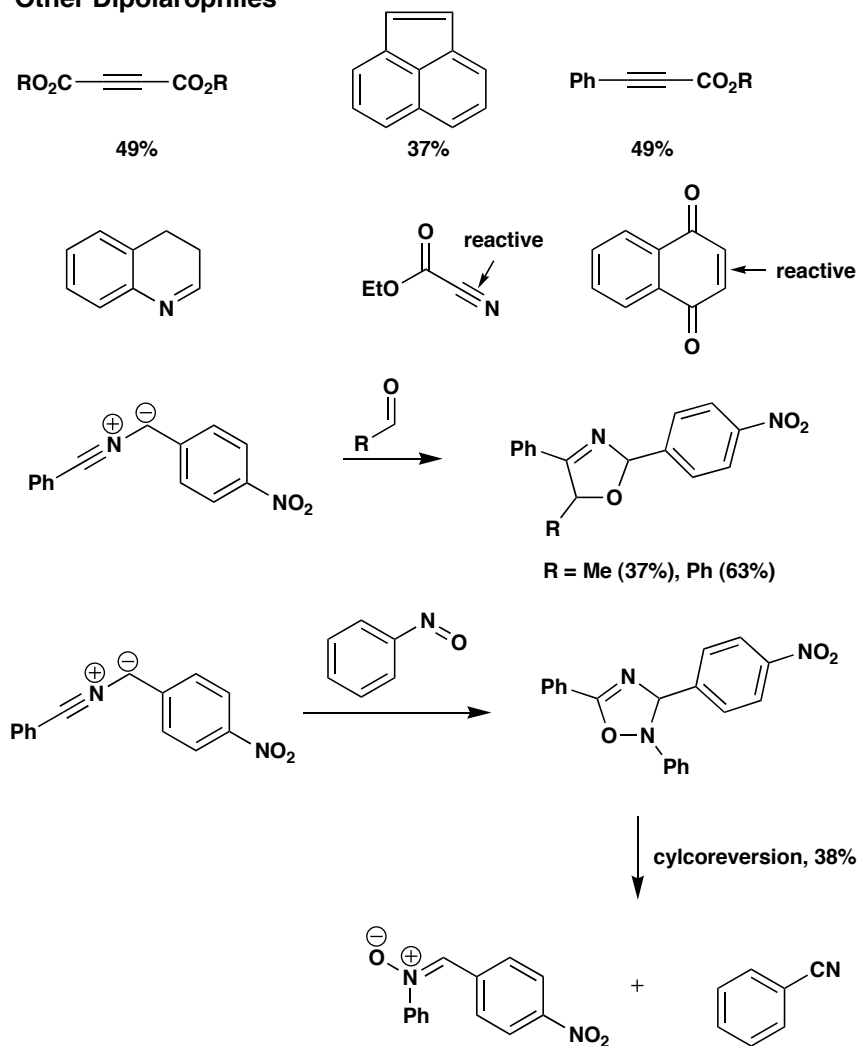


## Pyrrole Synthesis

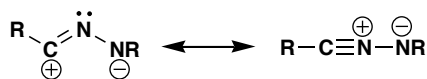


R. Huisgen, H. Stangl, H. J. Sturm, H. Wagenhofer *Angew. Chem. Int. Ed. Eng.* 1962, 1, 50

## Other Dipolarophiles

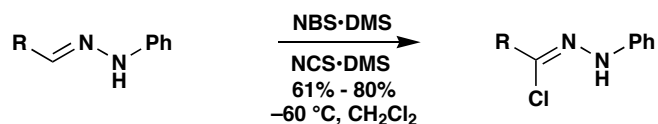
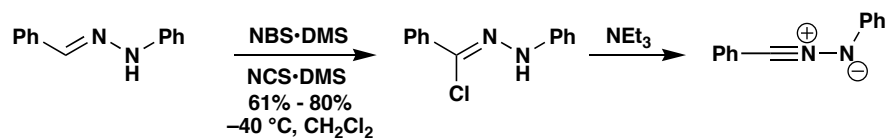
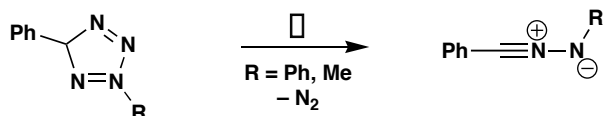






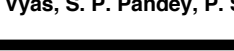
## Nitrile Imines



Nitrile Imines

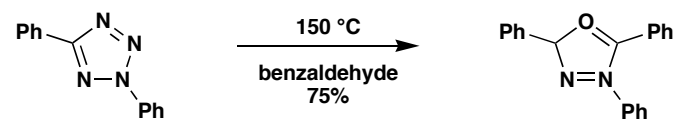
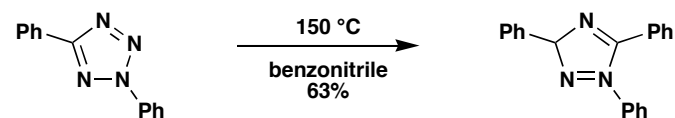
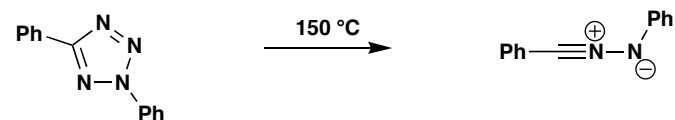
## Synthesis



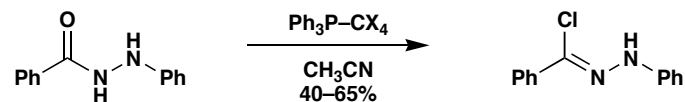
R	Yield
	69%
	41%
	71%
	29%
	69%

H. V. Patel, K. A. Vyas, S. P. Pandey, P. S. Fernandes *Tetrahedron*, 1996, 52, 661-668

- nitrile imines must be generated in situ, can dimerize



R. Huisgen, M. Seidel, J. Sauer, J. W. McFarland, G. Wallbillich *J. Org. Chem.* 1959, 24, 892-893

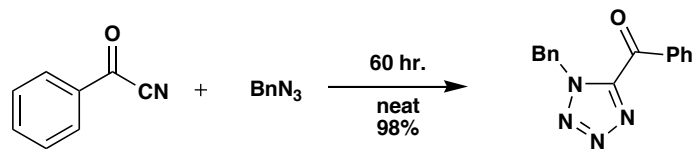


P. Wolkoff *Can. J. Chem.* 1975, 53, 1333-1335



J. Sauer, R. Huisgen, H. J. Sturm *Tetrahedron*, 1960, 11, 241-251

R. Huisgen, J. Sauer, M. Seidel *Chem. Ber.* 1961, 94, 2503-2509



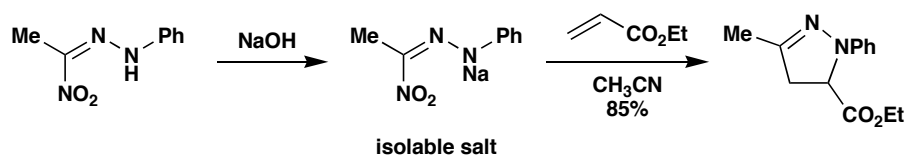
Z. Demko, K. B. Sharpless *Angew. Chem. Int. Ed.* 2002, 41, 2113-2116

F. Himo, Z. Demko, L. Noodleman, K. B. Sharpless *J. Am. Chem. Soc.* 2003, 125, 9983-9987

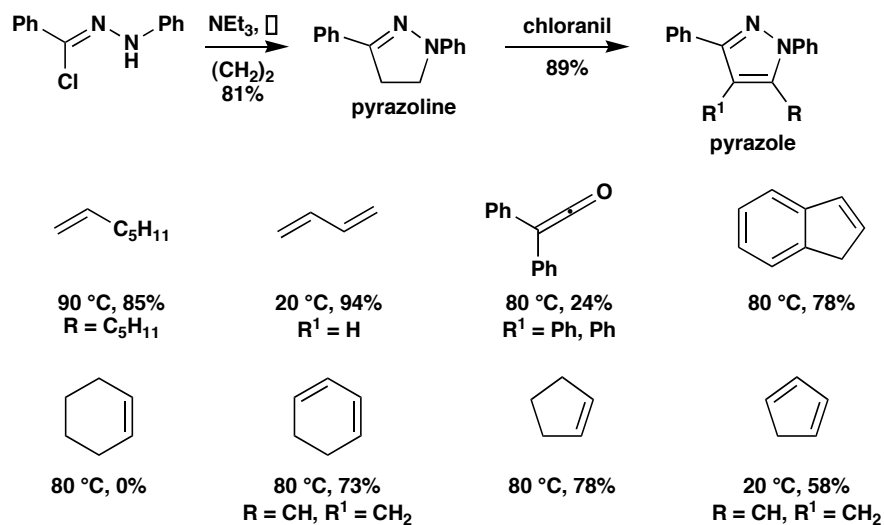
## Nitrile Imines



## Synthesis

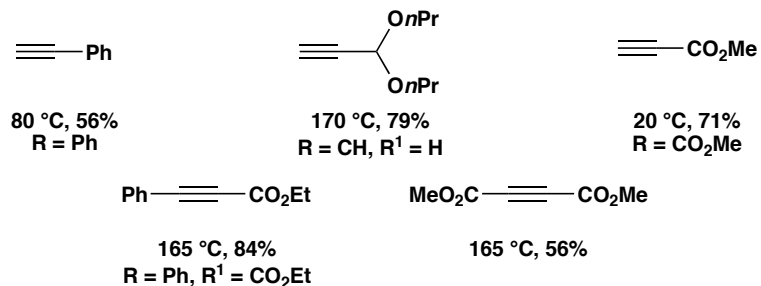


## Dipolarophile: Alkene, Alkyne



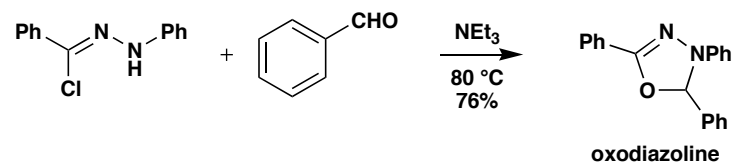
- increased conjugation increases reactivity, tri and tetrasubstituted unreactive

R. Huisgen, M. Seidel, G. Wallbillich, H. Knupfer *Tetrahedron*, 1962, 17, 3-29



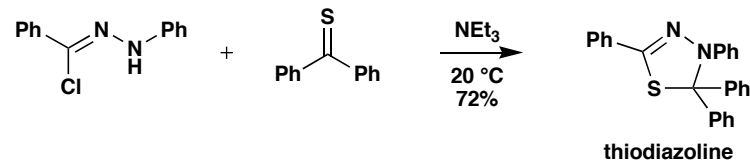
- monosubstituted acetylenes give 5-substituted pyrazoles directly

## Dipolarophile: C=O, C=S

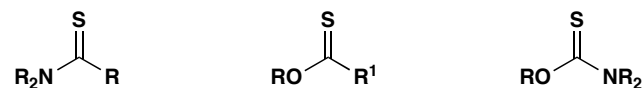


R. Huisgen, R. Grashey, M. Seidel, H. Knupfer, R. Schmidt *Liebigs Ann. Chem.* 1962, 658, 169

- C=S is a great dipolarophile, not a good dienophile



- other good thiocarbonyl dipolarophiles



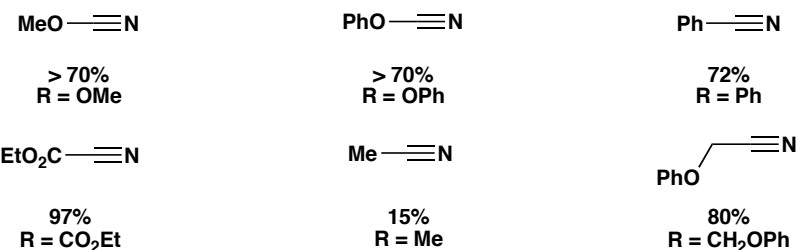
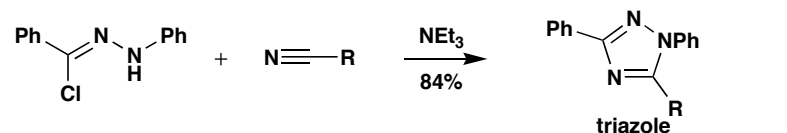
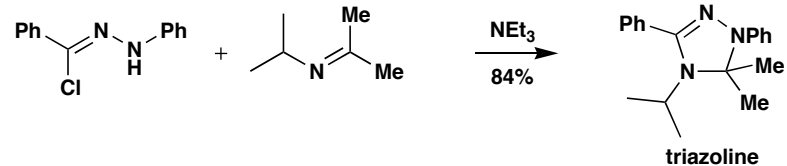
- isothiocyanates undergo cycloaddition but with low regioselectivity

## Nitrile Imines



## Dipolarophile: C–N multiple bonds

- imine both aromatic and aliphatic good dipolarophiles (better than carbonyls)



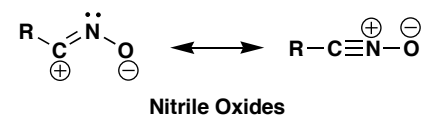
- isocyanates reactive, carbodiimides give bis-adducts

- C≡N less reactive than C≡C

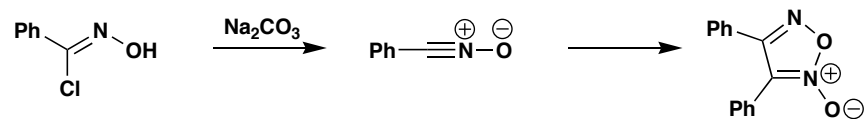
- strongest C–N bond formation in products allows prediction of regiochemistry

R. Huisgen, R. Grashey, M. Seidel, G. Wallbillich, H. Knupfer, R. Schmidt *Leibigs Ann. Chem.* 1962, 653, 105

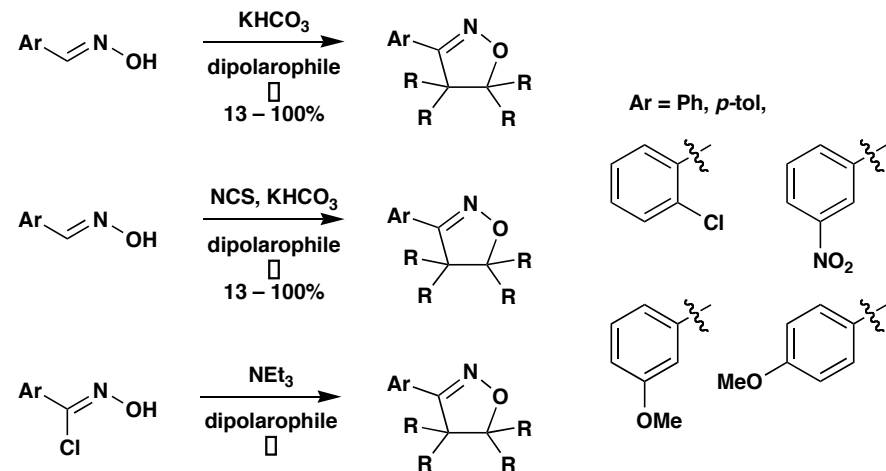
## Nitrile Oxides



## Synthesis

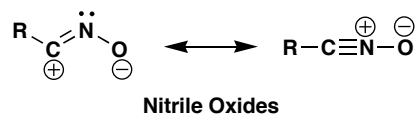


A. Warner, H. Buss *Ber. Dtsch. Chem. Ges.* 1894, 27, 2193  
H. Weiland *Ber. Dtsch. Chem. Ges.* 1907, 40, 1667

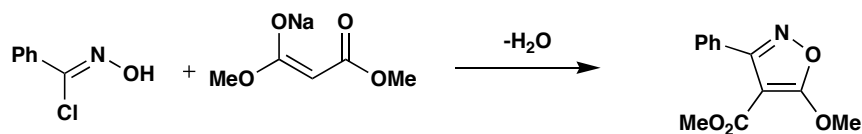


A. R. Katritzky, M. A. C. Button, S. N. Denisenko *J. Heterocyclic Chem.* 2000, 37, 1505–1510

## Nitrile Oxides

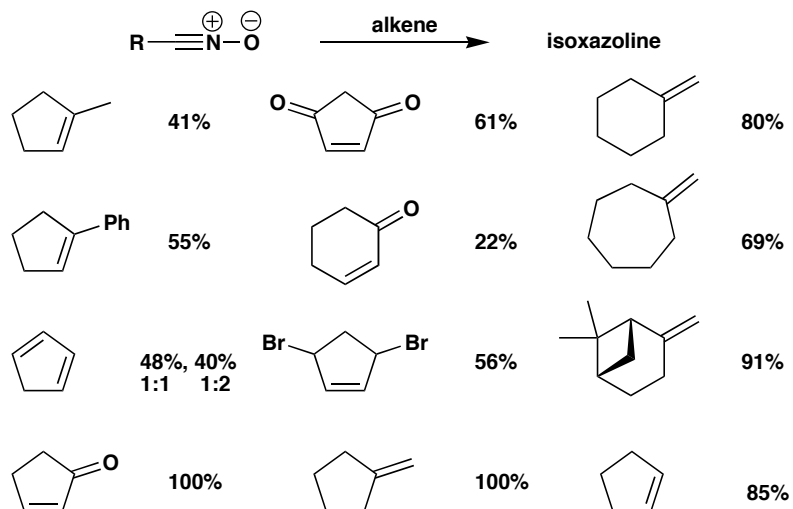


## Synthesis

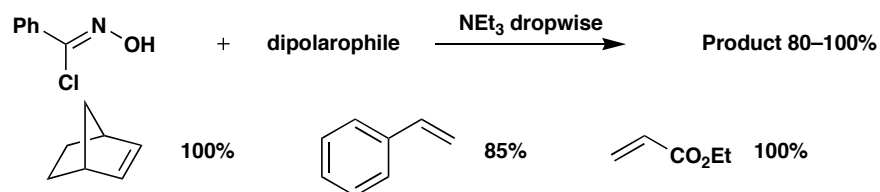


T. Mukaiyama, T. Hoshino, *J. Am. Chem. Soc.* 1960, **82**, 5339  
 A. Quilico, G. Stagno d'Alcontres, P. Grünanger *Gazz. Chim. Ital.* 1950, **80**, 479  
 N. Barbulescu, P. Grünanger, M. R. Langella, A. Quilico *Tetrahedron Lett.* 1961, **2**, 89–91

## Dipolarophile: Alkene



- dimerization of nitrile oxides extremely facile



- to avoid dimerization, dipolarophile and dipole precursor are mixed,  $\text{NEt}_3$  is added dropwise to reaction solution

- mono substituted and 1,1 disubstituted olefins give 5-substituted isoxazolines

- tri- and tetrasubstituted olefins are unreactive

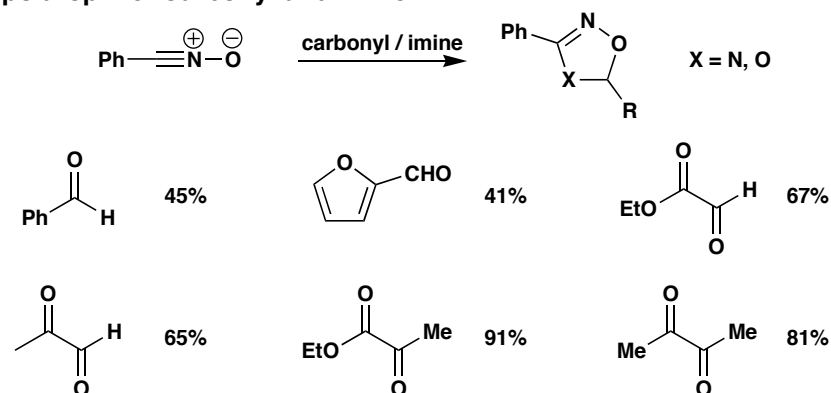
- allenes react slowly to give bis adducts

## Dipolarophile: Alkyne

- high yields and isoxazoles formed directly

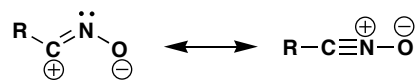
A. Quilico, G. Speroni *Gazz. Chim. Ital.* 1946, **76**, 148  
 A. Quilico, G. Gaudinau, A. Ricca *Tetrahedron* 1959, **7**, 24

## Dipolarophile: Carbonyl and Imine



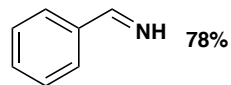
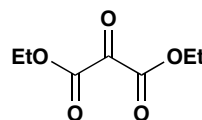
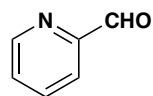
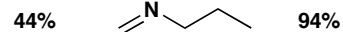
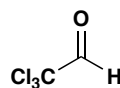
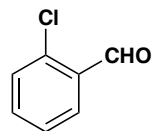
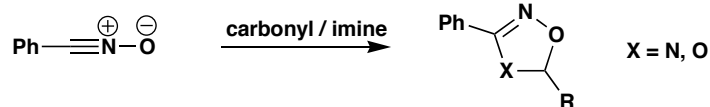


## Nitrile Oxides



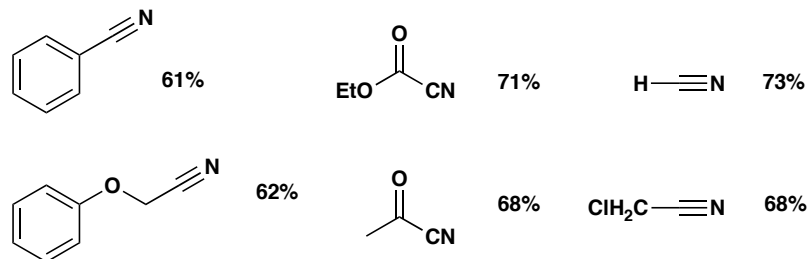
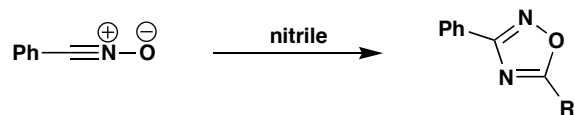
Nitrile Oxides

## Dipolarophile: Carbonyl and Imine

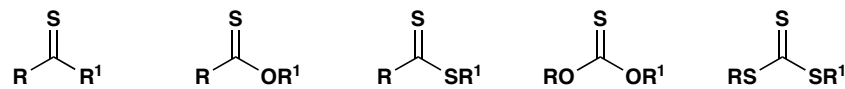
R. Huisgen, W. Mack *Tetrahedron Lett.* 1961, 2, 583

## Dipolarophile: Nitriles

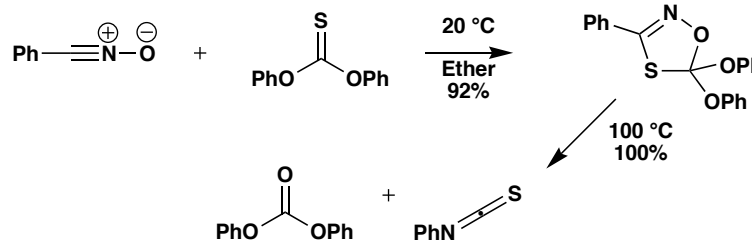
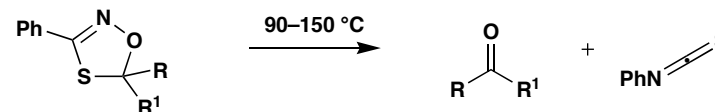
- aromatic nitriles reactive
- aliphatic nitriles containing electron withdrawing group are reactive

G. Leandri, M. Pallotti *Ann. Chim.* 1957, 47, 376R. Huisgen, W. Mack, E. Anneser *Tetrahedron Lett.* 1961, 2, 587

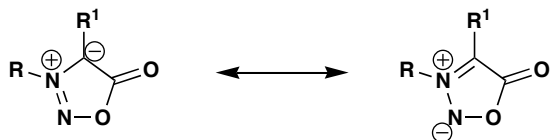
## Dipolarophile: Thiocarbonyl



- cycloreversions are possible to give the isothiocyanates

R. Huisgen, W. Mack, E. Anneser *Angew. Chem.* 1961, 73, 656

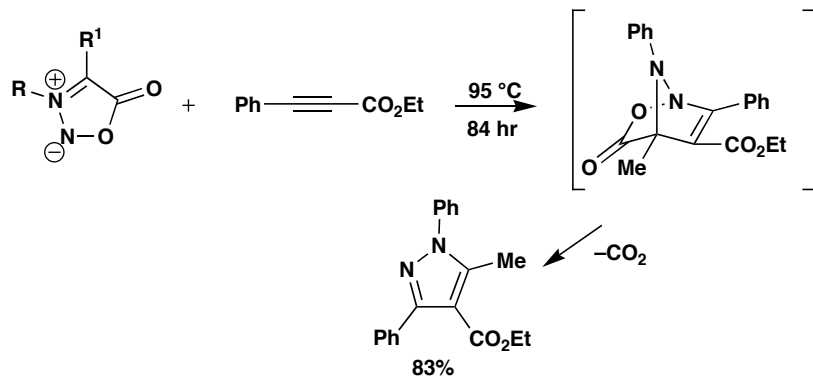
## Sydnone



- 1,2,3 oxadiazolium-5-olates were discovered by Sydney in 1935
- much work done by D. Ollis in addition to Huisgen's efforts

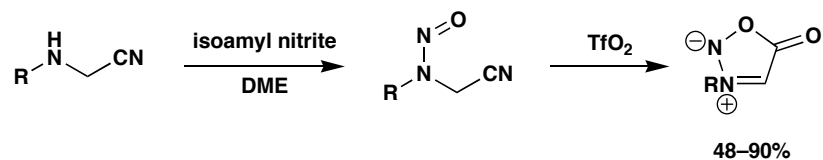
D. Ollis, C. A. Ramsden *Adv. Het. Chem.* 1976, 19, 1–122

- first experiments by the Huisgen group were immediately successful

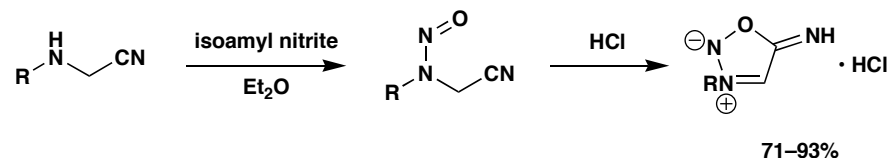


- regioselectivity follows that of nitrile imines
- methyl propiolate is a bidentate dipolarophile giving regioisomers
- CO<sub>2</sub> is released only at higher temperatures

## Synthesis



J. Applegate, K. Turnbull *Synthesis* 1988, 12, 1011–1012



71–93%

E. N. Beal, K. Turnbull *Syn. Comm.* 1992, 22, 673–676

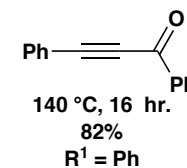
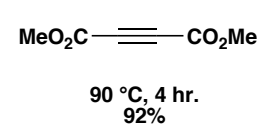
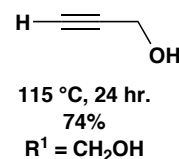
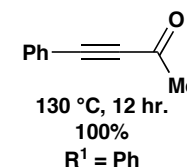
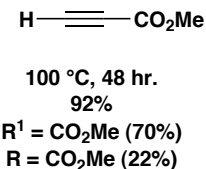
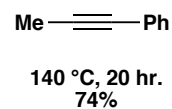
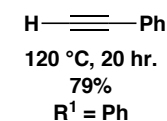
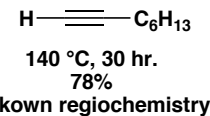
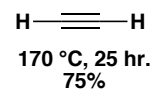
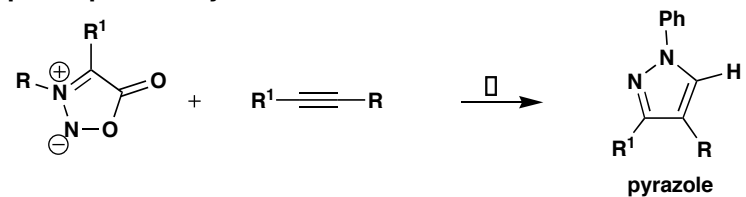
M. Sindler-Kulyk, K. Jakopcic, A. D. Mance *J. Het. Chem.* 1992, 29, 1013–1015

C. W. Lo, W. L. Chen, Y. S. Szeto, C. W. Yip *Heterocycles*, 1999, 51, 1433–1436

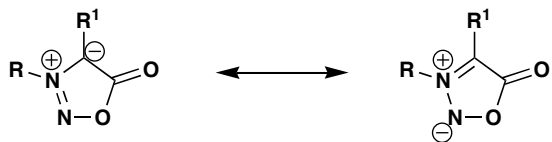
K. Turnbull, R. N. Beladakere, N. D. McCall *J. Het. Chem.* 2000, 37, 383–388

W. H. Nyberg, C. C. Cheng *J. Med. Chem.* 1965, 8, 531–533

## Dipolarophile: Alkynes

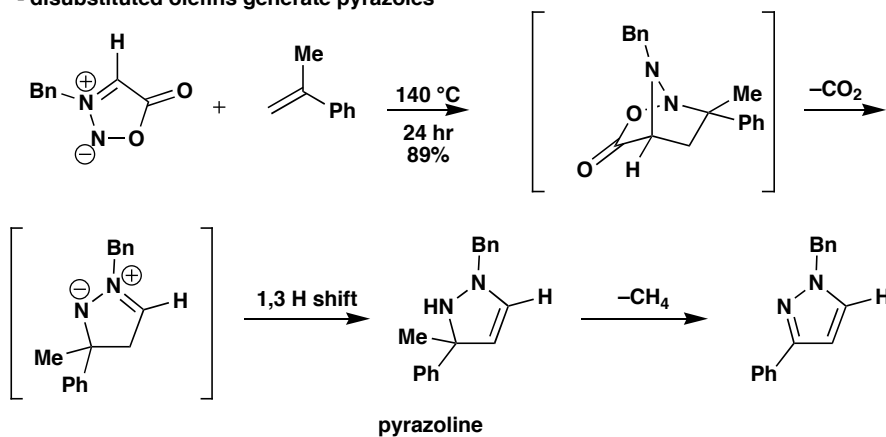


## Sydnone



## Dipolarophile: Alkenes

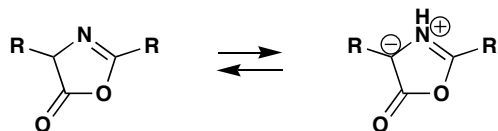
- olefins generate pyrazolines
- disubstituted olefins generate pyrazoles



R. Huisgen, H. Gotthardt, R. Grashey *Angew. Chem. Int. Ed. Eng.* 1962, 1, 49

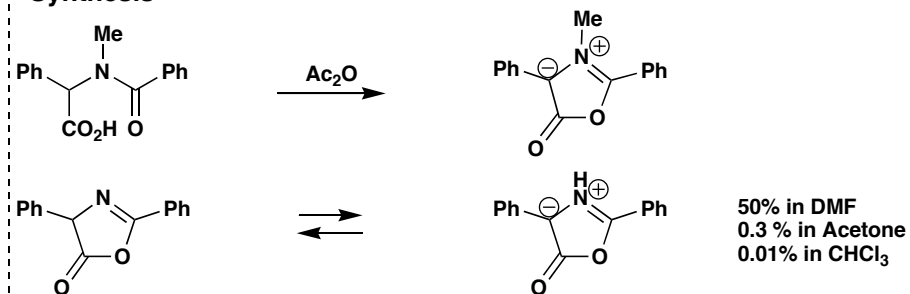
R. Huisgen, R. Grashey, H. Gotthardt, R. Schmidt *Angew. Chem. Int. Ed. Eng.* 1962, 1, 48–49

## Münchnones



- term coined by the Huisgen group stems from the nomenclature established for sydnone

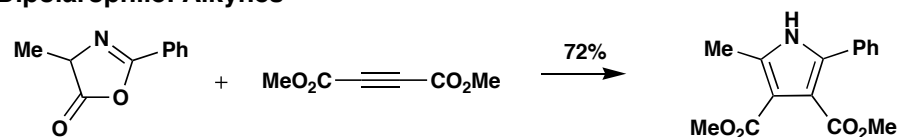
## Synthesis



R. Huisgen, H. Gotthardt, H. O. Bayer, F. C. Schaefer *Angew. Chem. Int. Ed. Eng.* 1964, 3, 136–137

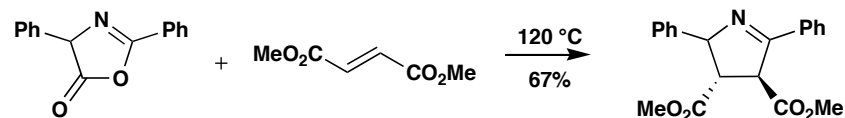
H. O. Bayer, R. Huisgen, R. Knorr, F. C. Schaefer *Chem. Ber.* 1970, 103, 2581–2597

## Dipolarophile: Alkynes



- Huisgen Pyrrole synthesis
- yields range from 55–98% with activated alkynes

## Dipolarophile: Alkenes



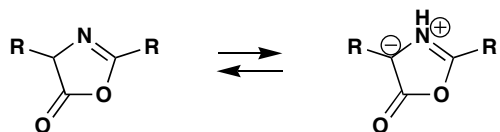
R. Huisgen, H. Gotthardt, H. O. Bayer *Tetrahedron Lett.* 1964, 481–485

R. Huisgen, H. Gotthardt, H. O. Bayer *Chem. Ber.* 1970, 103, 2368–2387

R. Knorr, R. Huisgen *Chem. Ber.* 1970, 103, 2598–2610

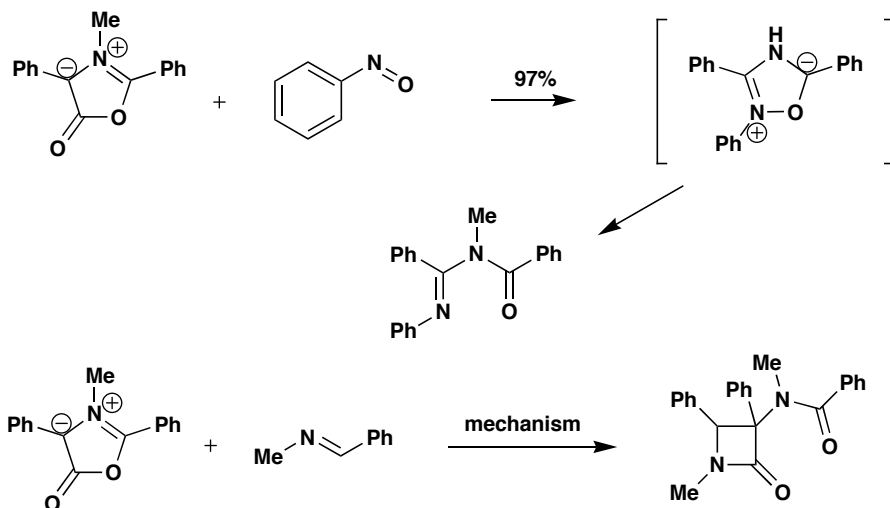
R. Knorr, R. Huisgen *Chem. Ber.* 1970, 103, 2611–2624

## Münchnones



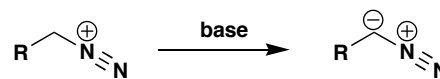
## Dipolarophile: imines, thioketones, aldehydes, nitroso compounds

- addition occurs followed by cycloreversion for aldehydes, nitroso compounds, and thioketones

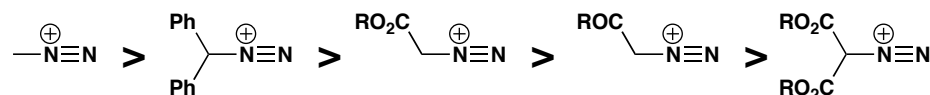


E. Funke, R. Huisgen, F. C. Schaefer *Chem. Ber.* 1970, 103, 2611–2624  
 Review: K. T. Potts in *1,3 Dipolarcycloaddition Chemistry*; A. Padwa, Ed.; Wiley: NY, 1984, 12, 1–84  
 W. D. Ollis, S. P. Stanforth, C. A. Ramsden *Tetrahedron* 1985, 41, 2239–2329

## Diazoalkanes

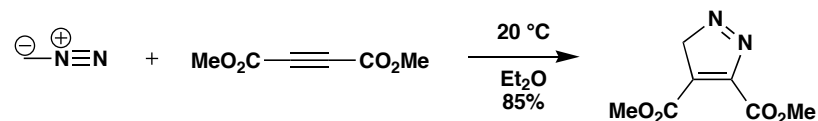


## Reactivity

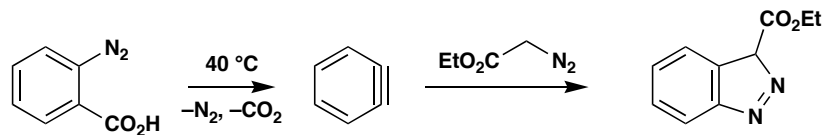
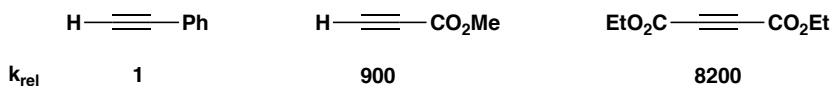
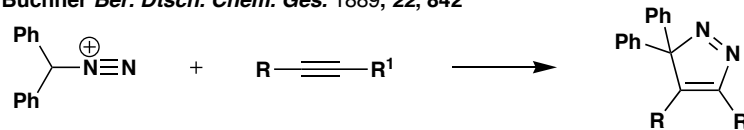


- reactions with alkenes yield pyrazolines
- pyrazolines when heated evolve  $N_2$  and cyclopropanes are formed
- C-terminus is nucleophilic

## Dipolarophile: Alkynes

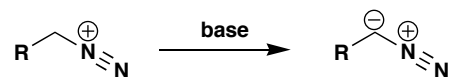


E. Buchner *Ber. Dtsch. Chem. Ges.* 1889, 22, 842



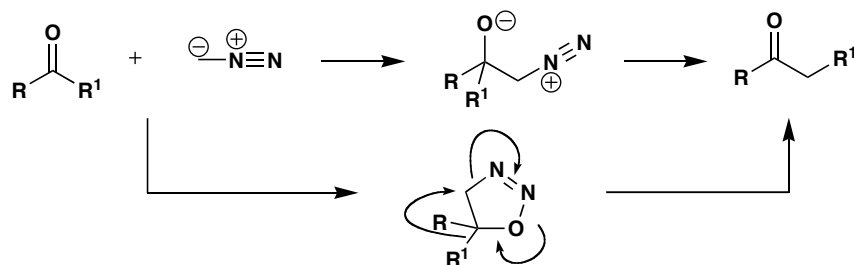
R. Huisgen, H. Stengl, H. J. Sturm, H. Wagenhofer *Angew. Chem.* 1961, 73, 170  
 R. Huisgen, R. Knorr *Naturwissenschaften* 1961, 48, 716

## Diazoalkanes



## Dipolarophile: Carbonyls, Thiocarbonyls, Imines

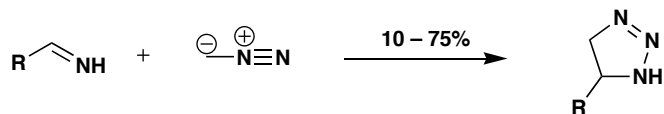
## - Arndt-Eistert homologation

R. Eistert *Angew. Chem.* 1941, 54, 99

## - reaction with ketenes

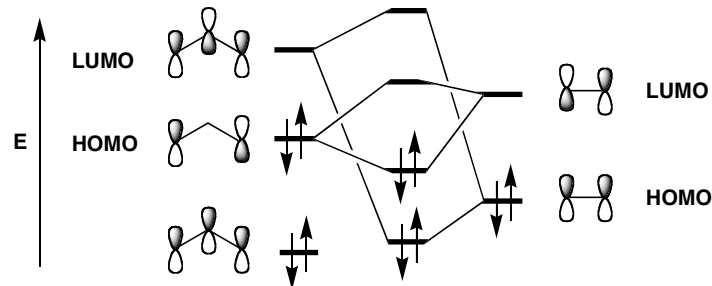


## - reaction with imines

P. K. Kabada, J. O. Edwards *J. Org. Chem.* 1961, 26, 2331

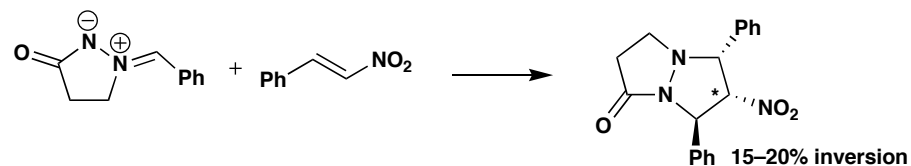
## Mechanistic Inquiries

- diazoalkanes, azides, nitrile ylides react with each end of the 1,3 dipole acting as electrophile and nucleophile
- regioselectivity changes as the interaction of molecular orbitals change
- with an electron deficient dipolarophile, LUMO of dipolarophile interacts with HOMO of 1,3 dipole
- with increasing electron density, LUMO of dipolarophile is elevated and less favorable overlap occurs



## Stereospecificity

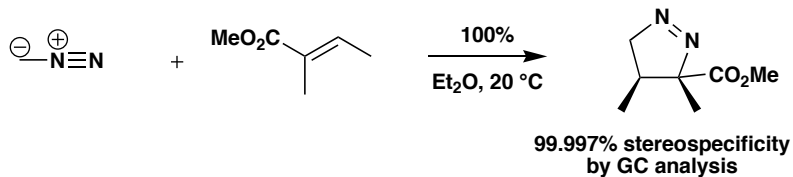
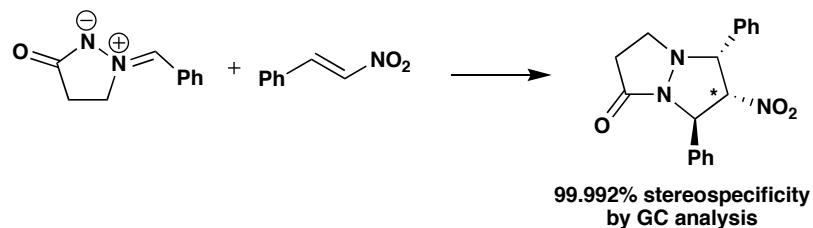
- H. Dorn proposed an acyclic zwitterionic intermediate due to 15–20% inversion

H. Dorn, R. Ozegowski, E. Gründemann *J. Prakt. Chem.* 1979, 321, 555–564

- inversion range is questionable because  $k_{\text{rot}}/k_{\text{cyc}}$  should be consistent if consistent reaction conditions are used
- *sec*-nitro alkanes are stronger acids than phenol

## Stereospecificity

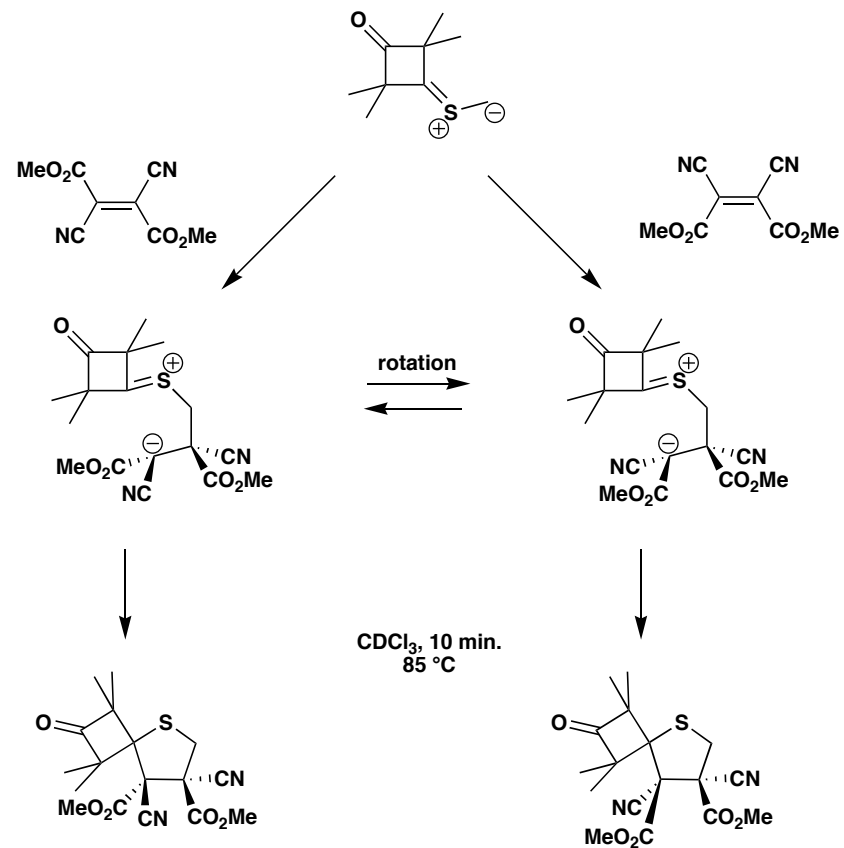
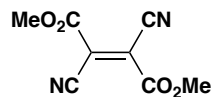
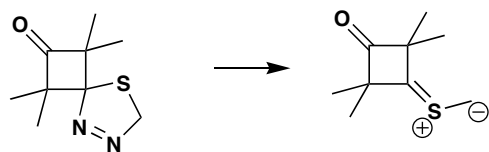
- under "highly sterile" conditions, full retention of alkene geometry maintained



R. Huisgen, J. Rapp *J. Am. Chem. Soc.* 1987, *109*, 902–903

## Forcing a Two Step Mechanism

- high energy ylides combined with low MO dipolarophiles would encourage a two step mechanism



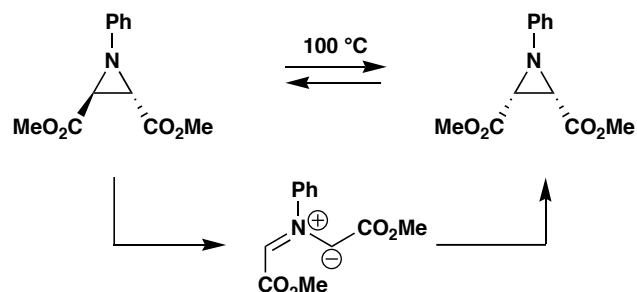
dimethyldicyanofumarate 61:39

dimethyldicyanomaleate 25:75

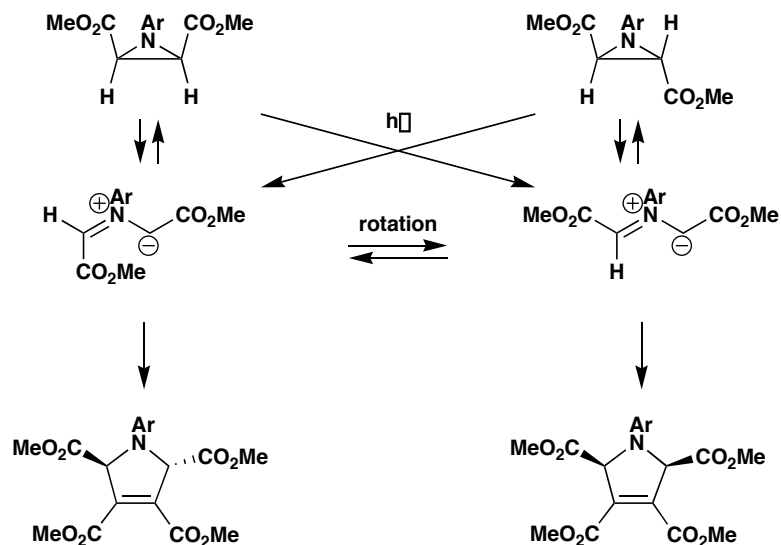
G. Molston, E. Langhals, R. Huisgen *Tetrahedron Lett.* 1989, *30*, 5373–5376

## Aziridines and Oxiranes

- aziridines and oxiranes can undergo ring opening to give azomethine ylides and carbonyl ylides

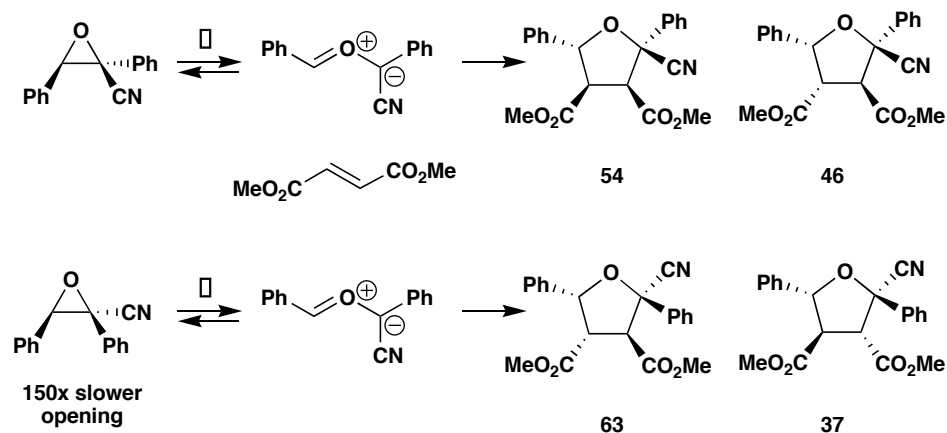


R. Huisgen, W. Scheer, H. J. Huber *J. Am. Chem. Soc.* 1967, *89*, 1753–1755  
R. Huisgen, H. Mäder *Angew. Chem. Int. Ed. Eng.* 1969, *8*, 604–606



"...our results...offer the first verification of [the Woodward–Hoffman] principle

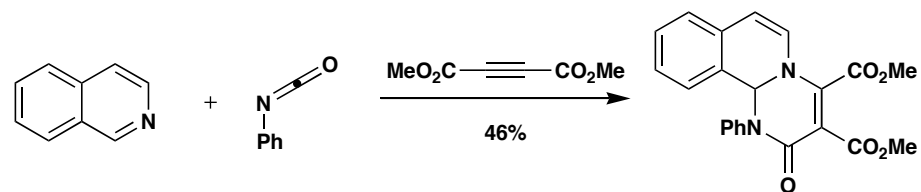
- ylides are ~8 kcal/mol higher in energy than the rings but have ~21 kcal/mol barrier to reconstitution



A. Dahmen, H. Hamberger, R. Huisgen, J. J. Markowski *J. Chem. Soc. Chem. Comm.* 1971, 1192–1194

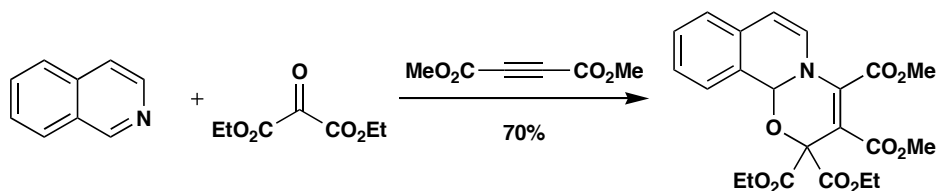
## 1,4 Dipolar Cycloaddition

- nucleophilic and electrophilic termini without conjugation between termini
- reactions proceed in two step fashion
- dipoles can easily dimerize or form 4–membered rings

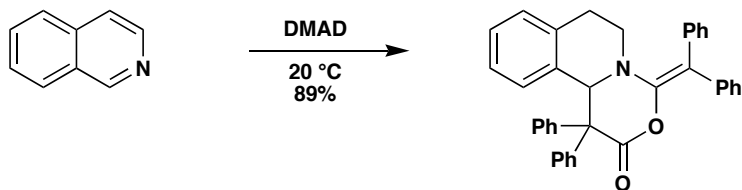
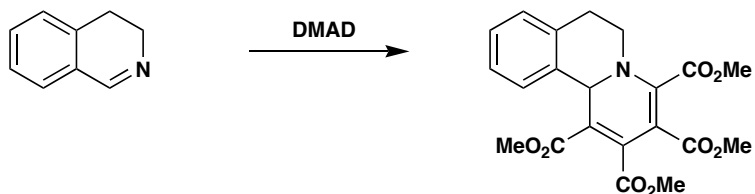


R. Huisgen, M. Morikawa, K. Herbig, E. Brunn *Chem. Ber.* 1967, *100*, 1094–1106

## 1,4 Dipolar Cycloaddition



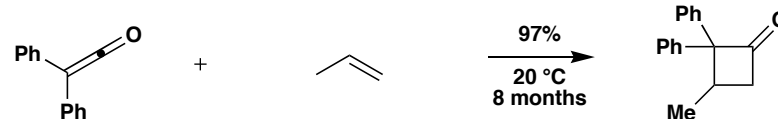
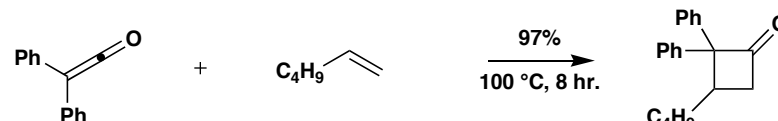
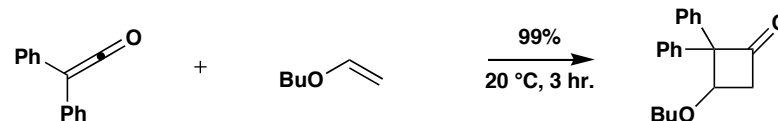
R. Huisgen, M. Morikawa, K. Herbig, E. Brunn *Chem. Ber.* 1967, *100*, 1094–1106



- heteroaromatic bases forfeit their aromaticity to engage in these reactions

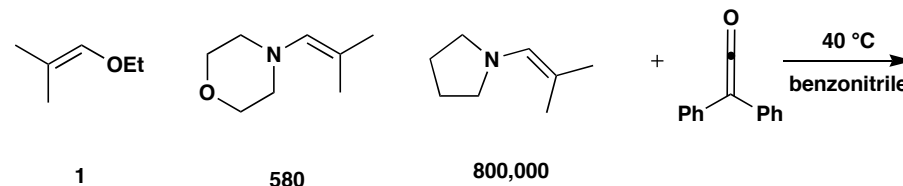
R. Huisgen, K. Herbig, M. Morikawa *Chem. Ber.* 1967, *100*, 1107–1115  
Review: W. D. Ollis, S. P. Sanforth, C. A. Ramsden *Tetrahedron*, 1985, *41*, 2239–2329

## 2+2 of Ketenes



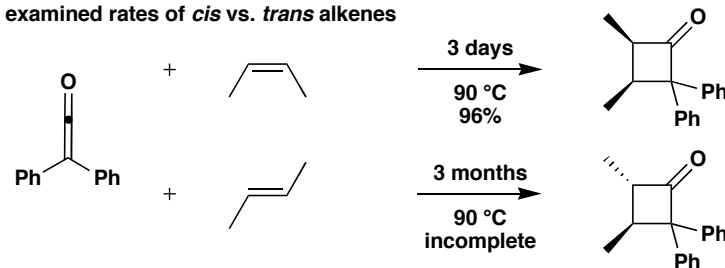
R. Huisgen, L. A. Feiler, P. Otto *Chem. Ber.* 1969, *102*, 3045–3427

- increased electron density of olefin increases rate significantly of 2+2



R. Huisgen, L. A. Feiler, P. Otto *Chem. Ber.* 1969, *102*, 3444–3459

- examined rates of *cis* vs. *trans* alkenes



R. Huisgen, H. Mayr *Tetrahedron Lett.* 1975, 2965–2968



## Quotes

"Wolfgang Scheer had magic hands in experimenting. I did not then object to the beer bottles on his bench."

"Playfulness is an incentive for the scientist and a driving force of progress"

"Stubborn pursuit of a goal is often praised as a virtue, and sometimes leads to success. However, accidental observations can disclose new horizons, far off the original target and sometimes more valuable. The luck chance might lurk just outside the experimenter's door, but the door is not always open. Opening it brings serendipity – acceptance of Fortuna's gift."

"The solution of one problem usually generates a bevy of new ones. The inexperienced young scientist often lacks the willpower to resist the temptation of dealing with a new problem while working on the first one."

"I am far from holding adverse conditions – maybe a crowded air raid shelter does not provide optimal conditions for creative thinking – responsible for my lackluster findings on the strychnine problem. At the age of 22 I was not experienced and mature enough to crack one of the hardest nuts of alkaloid chemistry. Children sometimes retain an aversion to books that are beyond their intellectual capacity when they first tackle them. I wonder whether similar reasons prevented my return to natural products after forays into other fields"

"What makes us praise novel achievements as imaginative or highly original?...Scientific imagination is not so much wild fantasy that is completely detached from the existing body of experience as it is absence of prejudice about what can be done and what cannot."

"I have profited immensely from these assets of Munich, all the more because I regard theater, music, and art as a world complimentary to that of science, with exposure to one acting as a stimulus for the other."

"Both art and science moreover are founded on creativity and the power of imagination."

"The effective techniques for motivating young associates are limited, I believe. The professor's own level of enthusiasm is, of course, essential. In the end, however, most of the motivation and enthusiasm must come from the student."

"Thorough thinking is valued over quickness."

"Fashions come and go in both ladies' apparel and scientific research."

"When I asked Bob Woodward in 1961 why he had wanted to synthesize chlorophyll, the roguish answer was 'because nobody else could do it'."

"The elegant and innovative synthesis will remain a domain of the masters. In my opinion, the mere stringing of known reaction steps for building complex natural products is not the most rational use of time and funds, and I hope the fashion will soon swing to more rewarding areas of research."

"The Adventure Playground of Mechanisms and Novel Reactions" by Rolf Huisgen, Profiles, Pathways, and Dreams; J. I. Seeman Ed.; American Chemical Society, Washington D.C., 1994