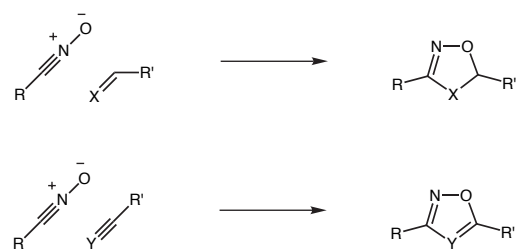


# Nitrile Oxide Cycloadditions in Organic Synthesis

A presentation by  
David Halstead

- I. Generation of Nitrile Oxides
- II. Regiochemistry
- III. Stereochemistry
- IV. Derivatizing Isoxazoles
- V. Synthetic Utility

## General Reaction



X = CR<sub>2</sub>, O, S, NR

Y = CR, N

C=N > C=C ≈ C≡C > C=S > C=N > C=O

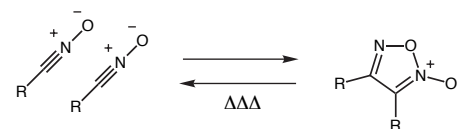
- Solvent polarity has little effect
- Electronic influences of the dipolarophile on reaction regiochemistry are minimal
- Conjugation of the dipolarophile enhances rates
- Steric effects generally dominate

C. Grundmann, *Synthesis* **1970**, 344 - 359

- Reaction *may* also follow a stepwise pathway

Morrocchi et al., *Tet. Lett.* **1969**, 3329 - 3332

## Nitrile Oxides

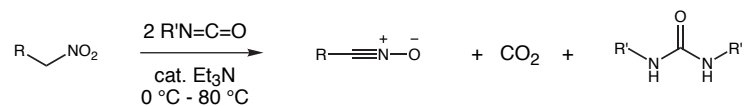


- Unhindered nitrile oxides readily dimerize to furoxans
- Under extreme conditions (FVP), furoxans can be cracked to regenerate nitrile oxides
- Hindered nitrile oxides (e.g. R = *t*-butyl, mesityl) are stable enough to be isolated and dimerize only slowly
- Instability tends to require that nitrile oxides be generated *in situ* from stable precursors

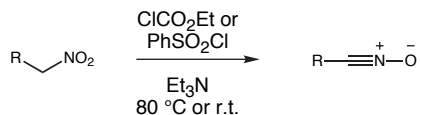
C. Grundmann and S. Datta, *J. Org. Chem.* **1969**, 2016 - 2018

C. Grundmann, *Synthesis* **1970**, 344 - 359

## Dehydration of Nitro Compounds



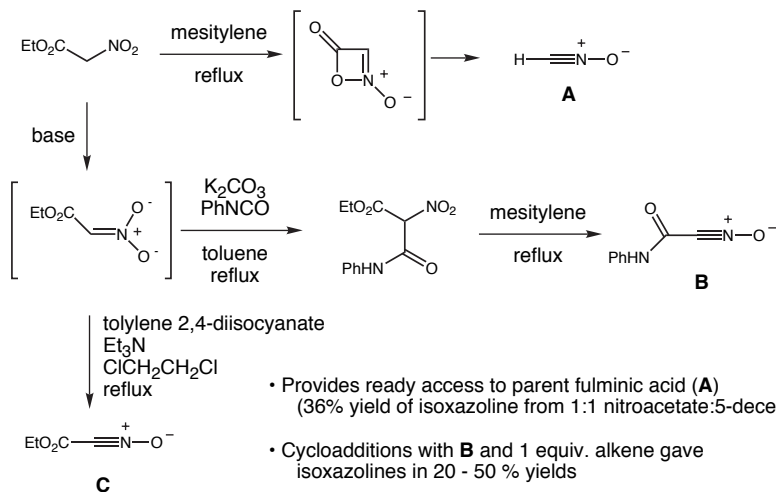
T. Mukaiyama and T. Hoshino, *J. Am. Chem. Soc.* **1960**, *82*, 5339 - 5342



- This procedure has the advantage of producing extractable byproducts
- Yields tend to be lower
- Catalytic TsOH also effects dehydration, but at higher temperatures (140 °C)
- Other reagents that effect this transformation include Ac<sub>2</sub>O/AcONa, AcCl/MeONa, POCl<sub>3</sub>, H<sub>2</sub>SO<sub>4</sub>, and diketene/Na

T. Shimizu et al., *Bull. Chem. Soc. Japan* **1986**, *59*, 2827 - 2831

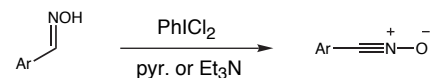
## Intramolecular Case



- Provides ready access to parent fulminic acid (A) (36% yield of isoxazoline from 1:1 nitroacetate:5-decene)
- Cycloadditions with B and 1 equiv. alkene gave isoxazolines in 20 - 50 % yields
- One cycloaddition with C and 1 equiv. 5-decene gave 48% of the isoxazoline

M. Leslie-Smith et al., *Tet. Lett.* **1994**, *35*, 9251 - 9254

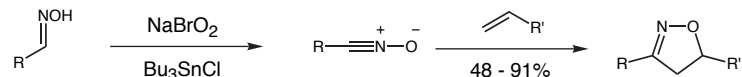
## Oxidation of Oximes



- Only aromatic oximes are reported

- 65 - 70% yields of furoxans

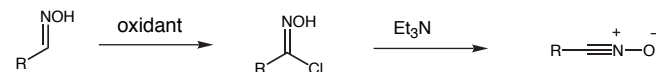
B. Singh et al., *Synth. Comm.*, **1991**, *21*, 1625 - 1629



- NaBrO<sub>2</sub> has a low reactivity towards alkenes
- NaBrO<sub>2</sub> is known to oxidize sulfides and alcohols
- Reasonable yields of cycloadducts were obtained with a variety of alkenes and alkynes
- Bu<sub>3</sub>SnCl can be replaced with Bu<sub>2</sub>SnCl<sub>2</sub> or TMSCl

O. Moriya et al., *Tet. Lett.* **1989**, *30*, 3987 - 3990

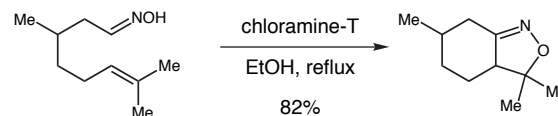
## From Hydroximoyl Chlorides



- Oxidants include NCS, *t*-BuOCl, and NaOCl

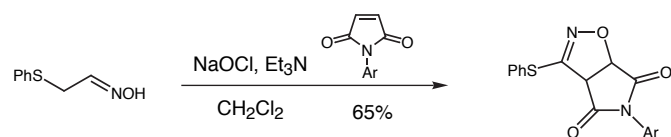
K.-C. Liu et al., *J. Org. Chem.* **1980**, *45*, 3916 - 3918  
G. Lee, *Synthesis* **1982**, 508 - 509

- Chloramine-T (EtOH, reflux) and 1-chlorobenzotriazole (CH<sub>2</sub>Cl<sub>2</sub>, rt) give the nitrile oxide directly



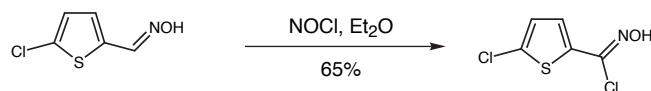
A. Hassner and K. Rai, *Synthesis* **1989**, 57 - 59  
J. Kim and E. Ryu, *Synth. Comm.* **1990**, *20*, 1373 - 1377

## Sulfur-Containing Oximes



- Although the nitro compound dehydrates well, it proved difficult to prepare
- Other dipolarophiles also performed acceptably

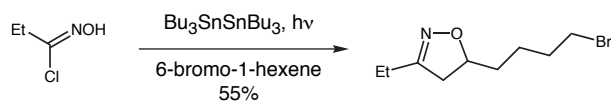
S. Kanemasa et al., *Bull. Chem. Soc. Japan* **1988**, 61, 3973 - 3982



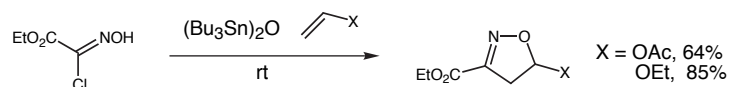
- Treatment of the hydroximoyl chloride with Et<sub>3</sub>N and dipolarophiles gave reasonable yields of cycloadducts

Y. Iwakura et al., *Bull. Chem. Soc. Japan* **1968**, 41, 2954 - 2959

## A Kinder, Gentler Method



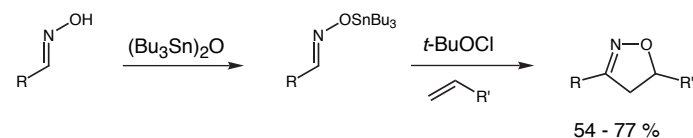
B. Kim, *Synth. Comm.* **1987**, 17, 1199-1206



- Tetraphenyltin also facilitates this reaction

O. Moriya et al., *Chem. Comm.* **1991**, 17 - 18

## From Stanny Oximes



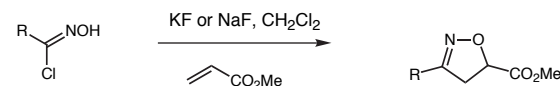
- Oxime stannylates within 5 min., faster than alcohols
- NBS and NCS were also effective oxidants
- (Bu<sub>2</sub>ClSn)<sub>2</sub>O failed as a dehydrating agent, and trimethylsilyloximes failed to give isoxazoles
- Both reactions can be run in one pot

O. Moriya et al., *Perkins I* **1994**, 413 - 417

- Bu<sub>3</sub>SnH and catalytic Et<sub>3</sub>N at 80 °C stannylates oximes

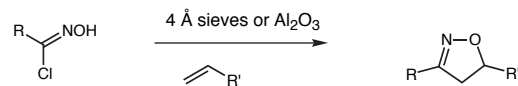
O. Moriya et al., *Chem. Comm.* **1991**, 1671 - 1672

## Please, Sir, May I Have Some More?



- Yields ≥90% for R = 2,6-Cl<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, CO<sub>2</sub>Et, Ac, and Br

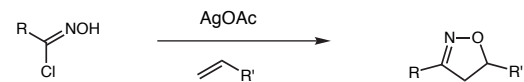
E. Ryu et al., *Heterocycles* **1991**, 32, 477 - 479.



- 72 - 99% for sieves

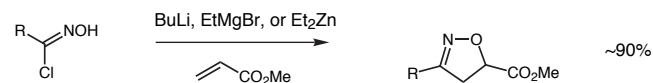
E. Ryu and J. Kim, *Heterocycles* **1990**, 31, 1693 - 1697

K. Torssell et al., *Tetrahedron* **1985**, 41, 5569 - 5575



- 76 - 99% yields

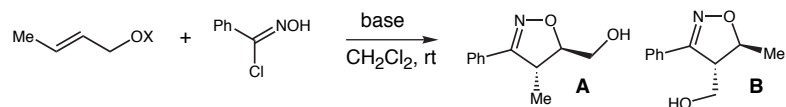
K. Fukumoto et al., *Heterocycles* **1996**, 43, 1771 - 1775



- Alkylaluminum chlorides failed to mediate reaction
- The metal-complexed nitrile oxide is a less reactive species

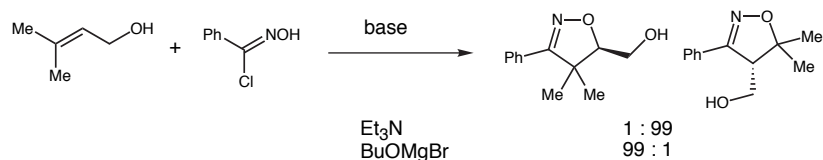
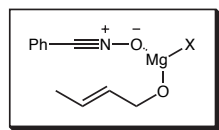
S. Kanemasa et al., *Tet. Lett.* **1991**, 32, 6367 - 6370

## Regiocontrol with Allyl Alcohols



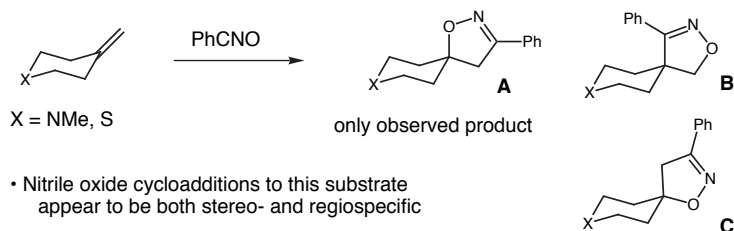
X	Base	Time	A : B	Yield
H	Et <sub>3</sub> N	1.5 h	46:54	46%
Li	BuLi	30 min.	60:40	13%
MgBr	Et <sub>3</sub> N	30 min.	96:4	62%
MgCl	<i>t</i> -BuMgCl	30 min.	96:4	47%
MgBr	<i>n</i> -BuLi	30 min.	95:5	55%
MgBr	<i>i</i> -PrOLi	30 min.	96:4	62%
Li	EtMgBr	2.5 h	>99:1	66%
MgBr	BuOMgBr	1 h	>99:1	83%

- Control presumably achieved by chelation
- Excellent results obtained for both *cis* and *trans* olefins



S. Kanemasa et al., *Tet. Lett.* **1992**, 33, 1357 - 1360

**Duh!**

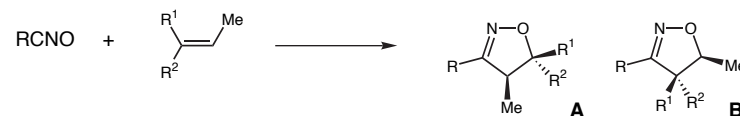


- Nitrile oxide cycloadditions to this substrate appear to be both stereo- and regiospecific
- X-ray crystallography was used to determine that isomer **A** (derived from 'syn' attack) and not **C** (derived from 'anti' attack) was formed
- The researchers acknowledge in the second paper that in fact **A** and **C** can interconvert

F. Sauter et al., *Monat. Für Chemie* **1994**, 125, 553 - 563

F. Sauter et al., *Monat. Für Chemie* **1995**, 126, 75 - 84

## Disubstituted Olefins

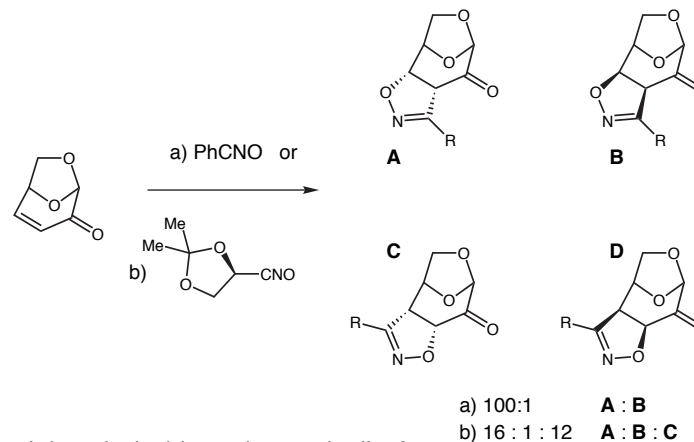


R	R <sup>1</sup> —R <sup>2</sup>	A : B	Yield
<i>t</i> -Bu	<i>i</i> -Pr H	100 : 0	26%
	H <i>i</i> -Pr	70 : 30	50%
Ph	<i>i</i> -Pr H	100 : 0	28%
	H <i>i</i> -Pr	68 : 32	58%
mesityl	<i>i</i> -Pr H	100 : 0	92%
	H <i>i</i> -Pr	62 : 38	94%

- In all cases where R<sup>1</sup> or R<sup>2</sup> was *t*-Bu, isomer **A** was the exclusive product
- Other nitrile oxides (R = PhCO, 4-MeOPh, Ph<sub>3</sub>C) follow the same trends

S. Martin and B. Dupre, *Tet. Lett.* **1983**, 24, 1337 - 1340

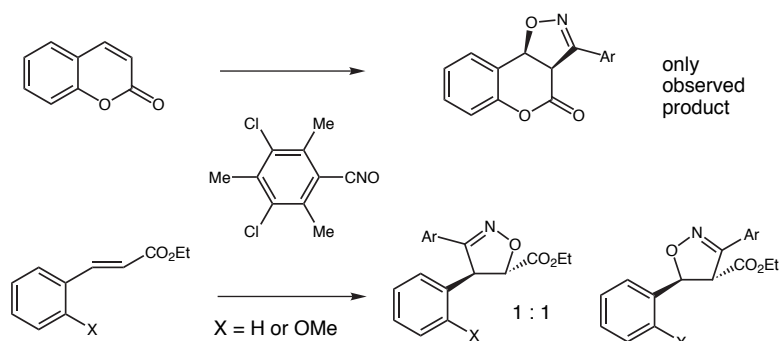
## Effects of Nitrile Oxide Structure



- Is loss of selectivity an electrostatic effect?

R.M. Paton et al., *Tetrahedron* **1992**, 48, 8053 - 8064

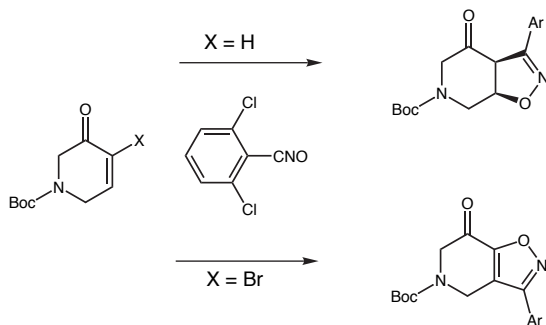
## Effects of Dipolarophile Structure



- "It can be argued that both coulombic and overlap terms of the interaction energy" serve to provide the regioselectivity of the lactone case

G. Zecchi, *J. Heterocyc. Chem.* **1994**, 31, 251 - 253

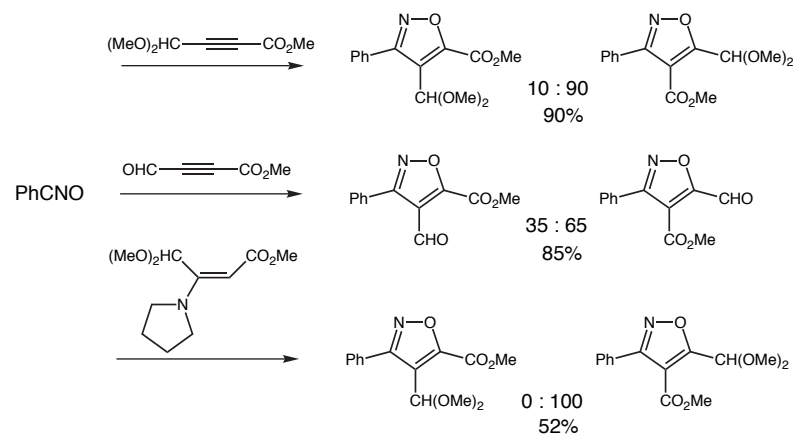
## Effects of Dipolarophile Structure



- This is presumed to be a steric effect

G. Simpson et al., *Tet. Lett.* **1994**, 35, 3589 - 3592

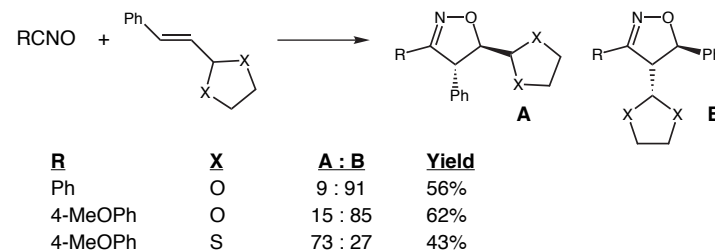
## Effects of Dipolarophile Structure



- MeCNO and BrCNO follow the same trend, though BrCNO favors the opposite isomer 85 : 15 when reacted with the aldehyde

M. Fraile et al., *Heterocycles* **1995**, 40, 285 - 292

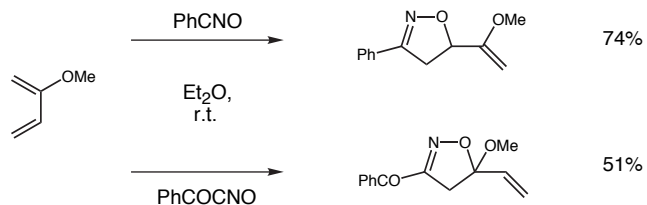
## Subtler Yet...



- The same turnover is observed with the crotyl series, though selectivities are diminished
- Authors claim that electronic effects dominate in the acetal cases, while sterics govern reactions with thioacetals

A. Kamimura and K. Hori, *Tetrahedron* **1994**, 50, 7969 - 7980

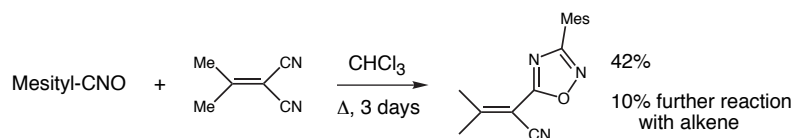
### Given the Choice...



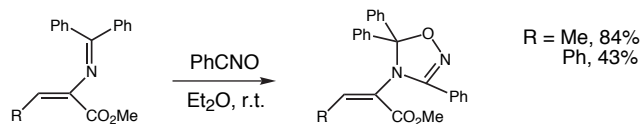
- Authors claim complete selectivity

Y. Kheruze et al., *Zh. Org. Chim.* **1988**, 24, 944 - 949

### When C=C Just Won't Do



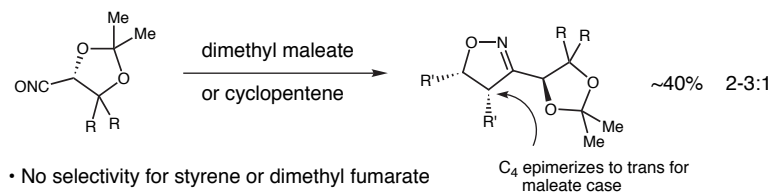
P. Lianis et al., *J. Heterocyc. Chem.* **1989**, 26, 1683 - 1686



- Where R = H, only addition to C=C is observed, in good yield
- Cis analogs show same reactivity pattern, but much lower yields

C. Balsamini et al., *J. Heterocyc. Chem.* **1992**, 29, 1593 - 1598

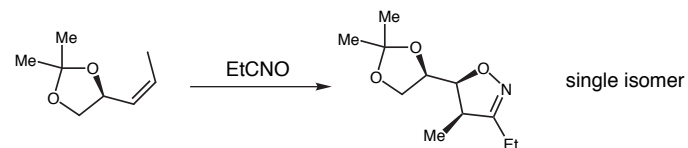
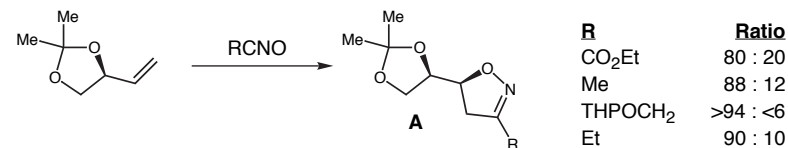
### Chiral Nitrile Oxides



- No selectivity for styrene or dimethyl fumarate
- Selectivities only slightly enhanced for R = Me
- Stereochemistry determined by X-ray for R = Me adduct with maleate

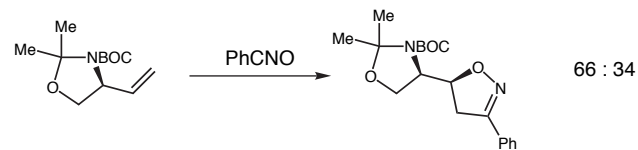
E. Thomas et al., *Tetrahedron* **1984**, 40, 177 - 184

### Chiral Alkenes



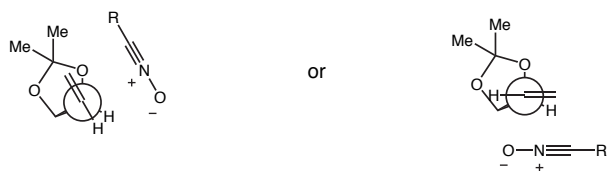
- Application to the *trans*-alkene gave a 1:1 mixture of regioisomers
- Treatment of **A** with LDA and MeI cleanly gives the *trans*-disubstituted isoxazoline

A. Kozikowski and A. Ghosh, *J. Org. Chem.* **1984**, 49, 2762 - 2772



R. M. Paton et al., *Perkins I* **1994**, 2841 - 2850

## Inside Alkoxy Effect

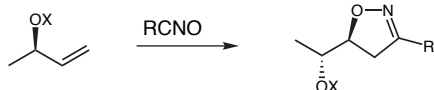


K. Houk et al., *J. Am. Chem. Soc.* **1986**, 108, 2754 - 2755

A. Kozikowski and A. Ghosh, *J. Org. Chem.* **1984**, 49, 2762 - 2772

M. Cinquini et al., *Chem. Comm.* **1987**, 529 - 530

More examples:



X	R	Selectivity
Bn	CO <sub>2</sub> Et	68 : 32
TBS	CO <sub>2</sub> Et	71 : 29
Ac	Me	52 : 48
H	Ph	50 : 50

A. Kozikowski and A. Ghosh, *J. Org. Chem.* **1984**, 49, 2762 - 2772

## Intramolecular Cases



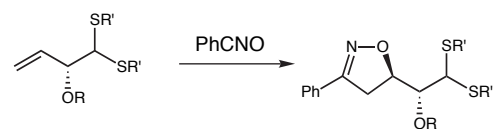
n	R	Yield	Selectivity
1	Me	57%	75 : 25
2	Me	62%	80 : 20
2	BnOCH <sub>2</sub>	72%	83 : 17

• Selectivities somewhat lower for *E*-alkenes

F. Cozzi et al., *Chem. Comm.* **1987**, 529 - 530

F. Cozzi et al., *J. Org. Chem.* **1987**, 52, 4674 - 4681

## With Thioacetals

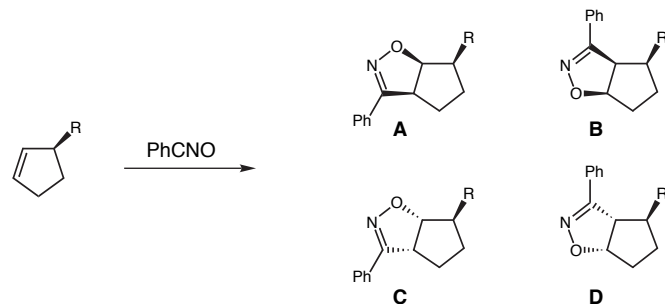


R	R'	Yield	Ratio
Bn	Ph	92%	90 : 10
TBS	Ph	87%	91 : 9
TBS	(CH <sub>2</sub> ) <sub>3</sub>	78%	91 : 9
TBS	<i>t</i> -Bu	98%	92 : 8

• Selectivities hold for a wide range of nitrile oxides

F. Cozzi et al., *Tetrahedron* **1988**, 44, 4645 - 4652

## Substrate-Directed Addition



R	Solvent	A	B	C	D
Me	Et <sub>2</sub> O	3	1	63	33
NMe <sub>2</sub>	Et <sub>2</sub> O	7	0	23	70
OMe	Et <sub>2</sub> O	3	4	22	71
OAc	Et <sub>2</sub> O	5	3	15	77
OH	Et <sub>2</sub> O	30	5	12	53
OH	PhH	50	0	17	33
NHCOPh	PhH	90	0	0	10
NHCOPh	DMF	26	0	15	59
N(Me)COPh	PhH	5	0	19	76

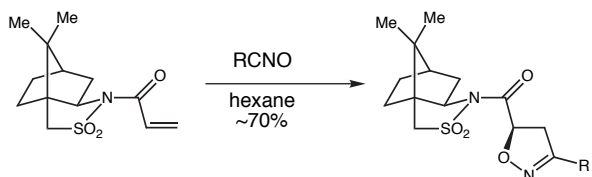
• Selectivities are high for a variety of secondary amides, thioamides, and sulfonamides

• *t*-BuCNO is also selective

• Yields for amides are generally 80 - 90%

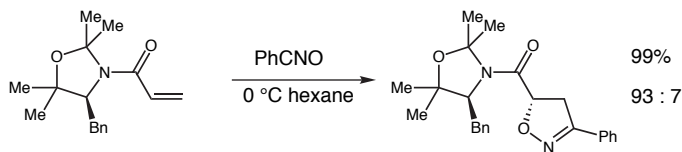
D. Curran et al., *J. Org. Chem.* **1990**, 55, 3710 - 3712

## Auxiliary Control



- For R = *t*-Bu, Ph, and Me, selectivities are >90 : 10

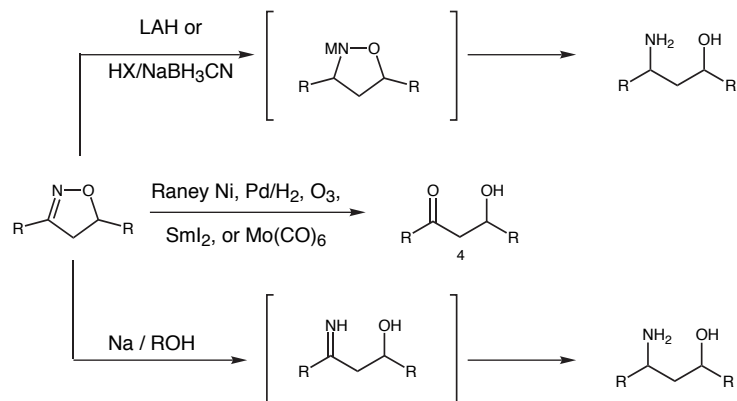
D. Curran et al., *Tet. Lett.* **1988**, 29, 3555 - 3558



- A wide range of related auxiliaries were tested with varying degrees of success

S. Kanemasa and K. Onimura, *Tetrahedron* **1992**, 48, 8645 - 8658

## Isoxazole: What Is It Good For?

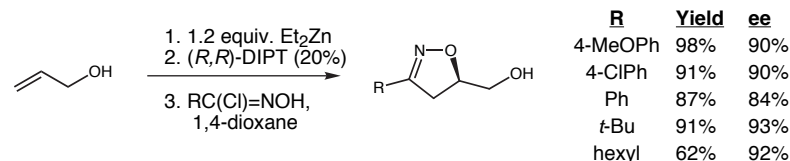


- DIBAL also reduces to the aminoalcohol
- LAH tends to give the best yields and selectivities (~ 3:1 favoring syn)
- C<sub>4</sub> epimerization (via the enamine) during reduction to the ketoalcohol can be suppressed by using Raney Ni with strong acids (HCl) or by using O<sub>3</sub>

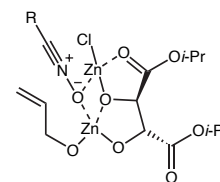
A. Kozikowski, *Acc. Chem. Res.* **1984**, 410 - 416 and references therein

R. Jones et al., *Perkins I* **1993**, 1715 - 1716 and references therein

## Catalytic Asymmetric Cycloaddition



- There is a positive non-linear effect observed
- A stoichiometric variant gives slightly higher ee's (93 - 98%)
- Crotyl alcohol fails, but the stoichiometric version works, giving 64% ee with low yields and regioselectivity; *cis*-crotyl alcohol was not tested

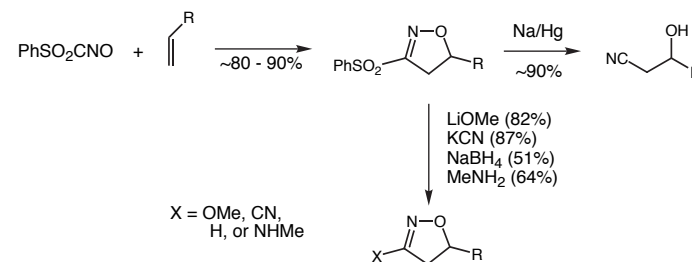


Proposed transition state

Y. Ukaji et al., *Chem. Lett.* **1993**, 1847 - 1850

Y. Ukaji et al., *Chem. Lett.* **1996**, 455 - 456

## Special Nitrile Oxides



- Reduction allows access to a wide range of cyanoalcohols
- Substitution reactions provide an entry to compounds formally derived from unknown or troublesome nitrile oxides

P. Wade and H. Hinney, *J. Am. Chem. Soc.* **1979**, 101, 1319 - 1320

P. Wade and J. Berezna, *J. Org. Chem.* **1987**, 52, 2973 - 2976

W. Anderson and N. Raju, *Synth. Comm.* **1989**, 19, 2237 - 2242

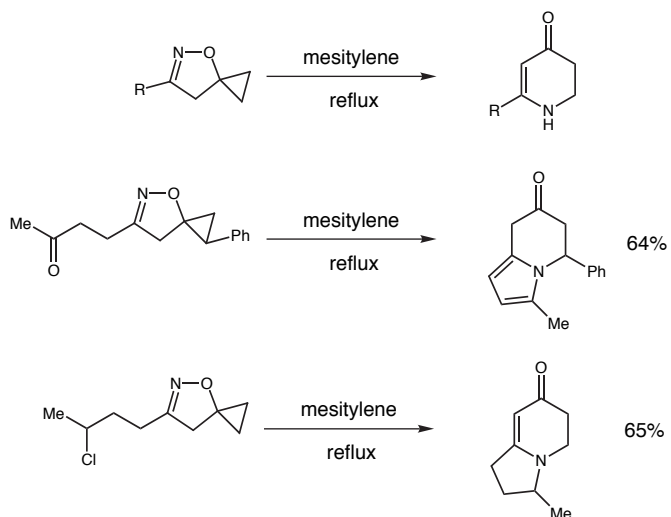
- 3-Carboxyisoxazolines undergo decarboxylative opening to cyanoalcohols

A. Kozikowski and M. Adamczyk, *J. Org. Chem.* **1983**, 48, 366 - 372

- TMSCNO, which does not dimerize, reacts with acetylenes to give cyanoketones directly
- 3-TMS-isoxazolines can be isolated, but decompose on heating to give cyanoalcohols

F. de Sarlo et al., *Heterocycles* **1983**, 20, 511 - 518

## Radical Rearrangements

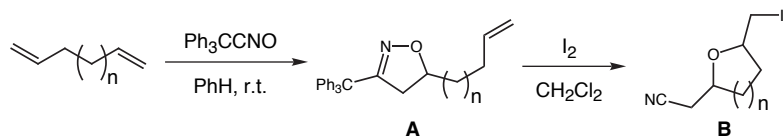


A. Guarna et al., *J. Org. Chem.* **1992**, 57, 4206 - 4211

A. Guarna et al., *Tetrahedron* **1993**, 49, 10629 - 10642

F. de Sarlo et al., *J. Org. Chem.* **1988**, 53, 2426 - 2429

## Unusual Cleavage



n	Yield A	Yield B	Cis : Trans
1	100%	85%	1 : 4
2	98%	82%	1 : 9
3	96%	80%	1 : 3

• Cyclization fails for n = 4

• Replacement of Ph<sub>3</sub>C with TMS for n = 2 gives 40% yield of **B**, 6.6 : 1 cis : trans

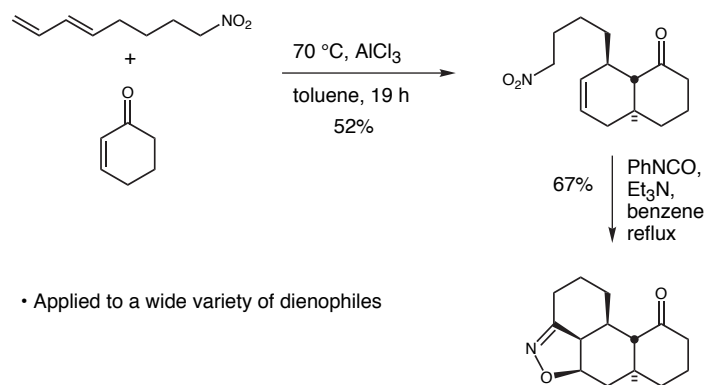
• Isoxazoline lacking alkenyl substituent is not cleaved by I<sub>2</sub>

M. Kurth et al., *J. Org. Chem.* **1990**, 55, 283 - 288

• Ph<sub>3</sub>C can be replaced with link to polymer support

M. Kurth et al., *J. Org. Chem.* **1995**, 60, 4196 - 4203

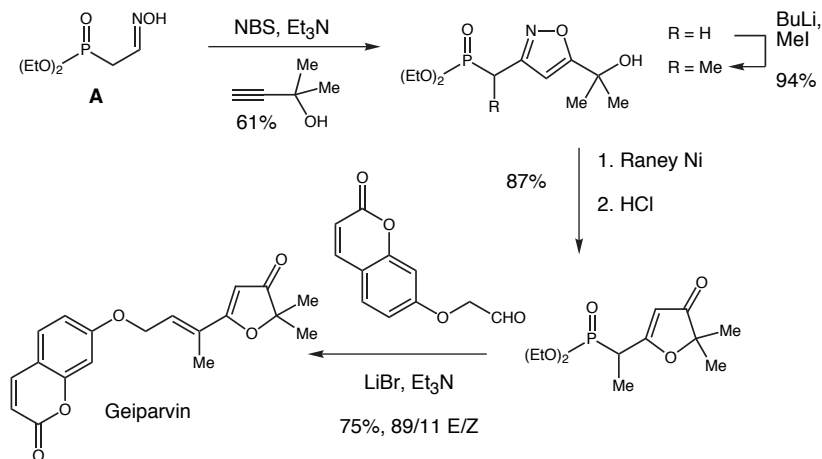
## Sequential Annulations



• Applied to a wide variety of dienophiles

A. Kozikowski et al., *J. Am. Chem. Soc.* **1984**, 106, 1845 - 1847

## Synthesis of Phosphonates



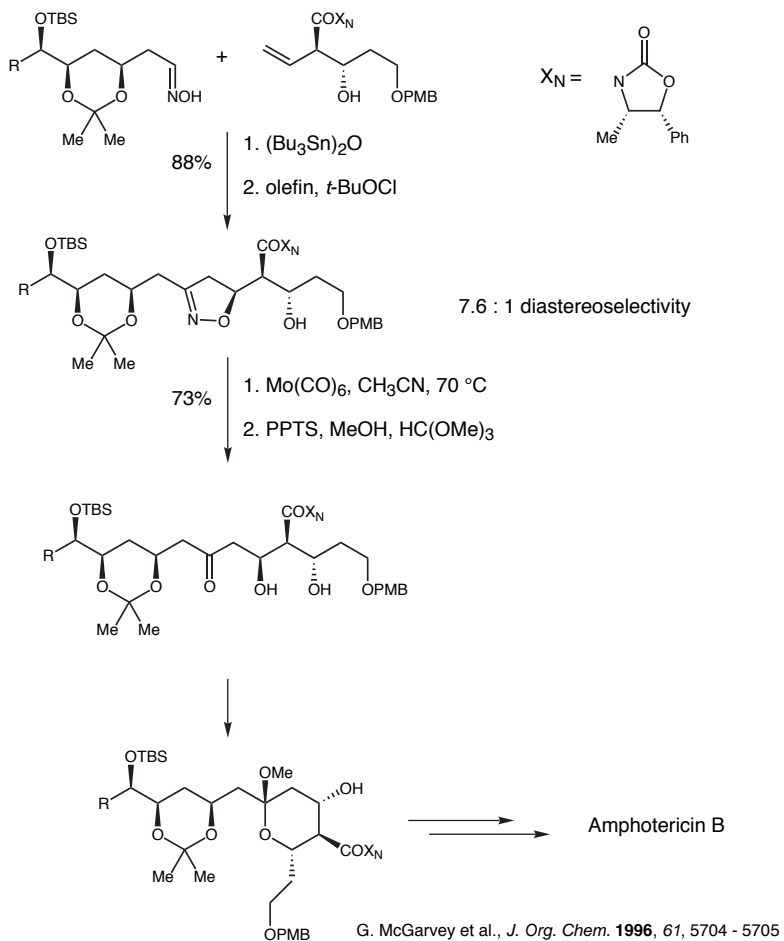
• Cycloadditions of **A** generally give 70 - 80% yield

• Olefinations and alkylations have been surveyed extensively

O. Tsuge et al., *Bull. Chem. Soc. Japan* **1987**, 60, 2463 - 2473

O. Tsuge et al., *Chem. Lett.* **1987**, 323 - 326

## Fragment Coupling



## Calicheamicinone Synthesis

