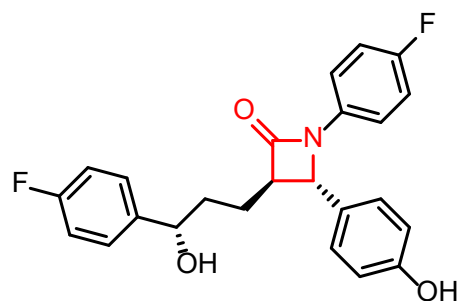
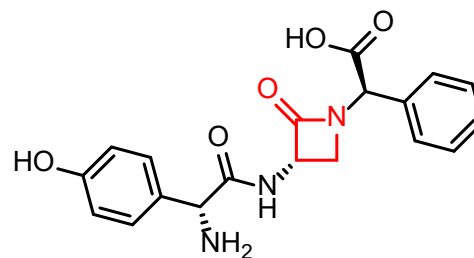


Developments and Mechanistic Insights of the Kinugasa Reaction

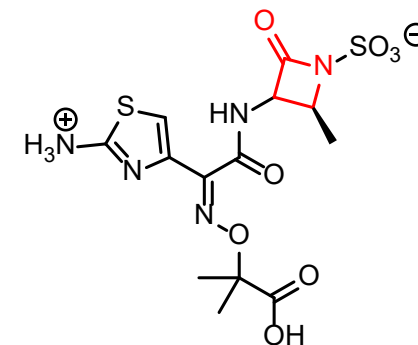
Felix Xi
Denmark Group Meeting
3/31/2026



Ezetimibe



Nocardicin G



Azactam

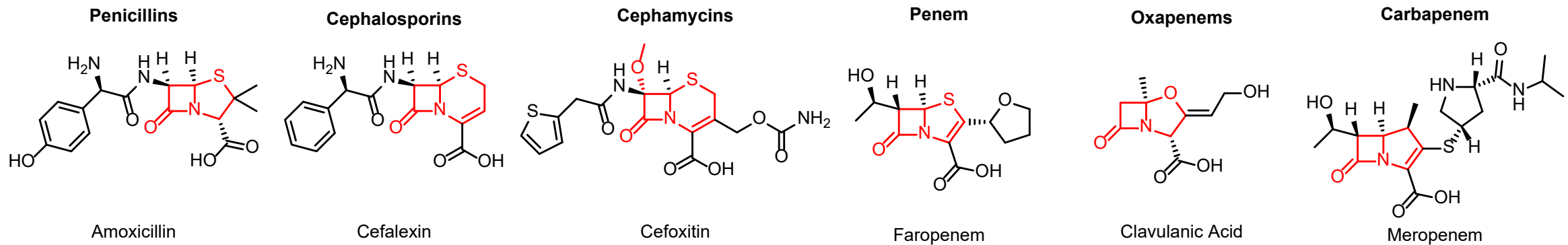
β-Lactams in Drugs

Number of Outpatient Prescriptions for Antibiotics in 2024:

Characteristics	Number of Antibiotic Prescriptions (Millions)	Antibiotic Prescriptions Per 1,000 Persons, Rate ^a
Antibiotic Class		
Penicillins	58.3	171
Cephalosporins	39.4	116
Macrolides	37.5	110
B-lactams, increased activity	34.5	101
Tetracyclines	31.0	91
Antibiotic Agent		
Amoxicillin	55.2	162
Azithromycin	36.3	107
Amoxicillin-clavulanic acid	34.5	101
Doxycycline	28.4	84
Cephalexin	22.9	67

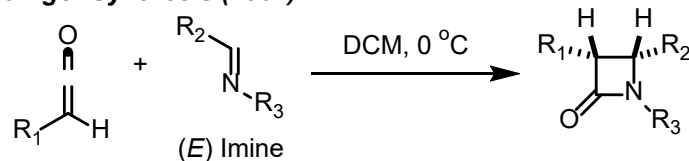
β-Lactams in drugs are typically bicyclic in nature, are heteroatom dense, and have specific stereochemistry at both C3 and C4.

Structural Class of Drugs and Specific Examples:

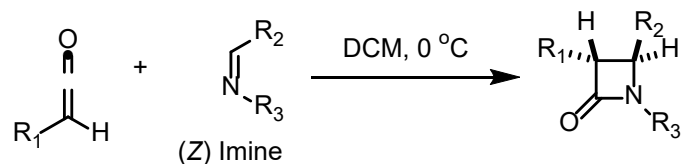


How are β -Lactams Synthesized?

Staudinger Synthesis (1907):

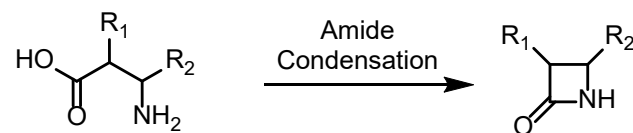


Imine geometry determines *cis* or *trans* selectivity



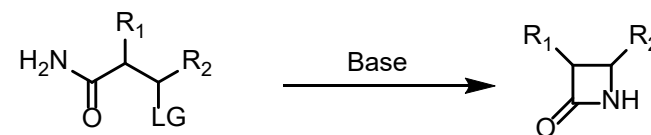
Ketenes are sensitive and can undergo side reactions

Intramolecular N-Acylation:



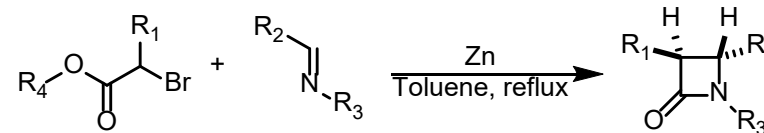
Does not generate new stereocenters

Intramolecular N-Alkylation:



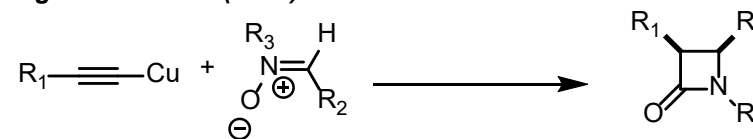
Similar pK_a of *N*-H and *C*-H leading to side reactions

Gilman-Speeter (1943):



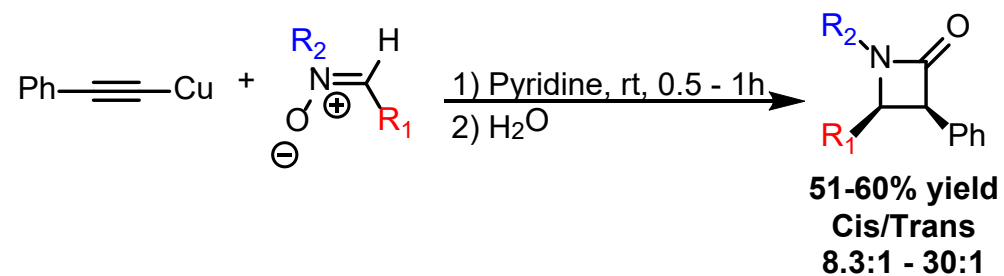
Zinc enolate preferentially makes the *trans* isomer

Kinugasa Reaction (1972):



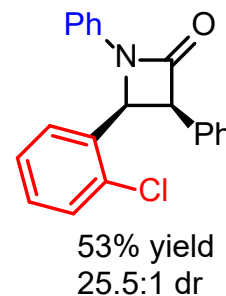
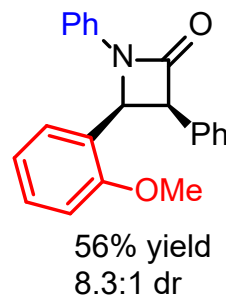
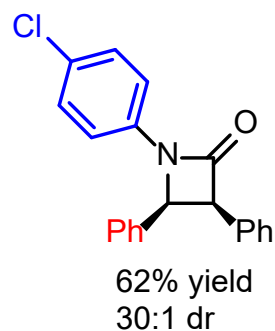
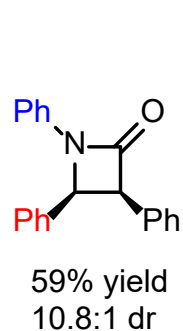
New disconnects and inherent *cis*-selectivity

First Report by Kinugasa (1972):



Only comprised of aryl substituents, required preformed copper acetylides, unclear role of pyridine, and small substrate scope.

Substrate Scope, Yields and dr:

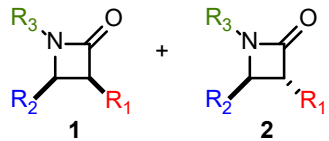
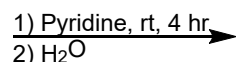
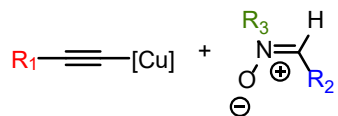


However, allowed for access of cis- β -lactams. What is the mechanism to selectively generate the cis isomer?

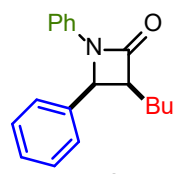
Expansion of Alkynyl Substrates and Mechanism Proposal

Expansion of Substrate Scope (Irwin 1976):

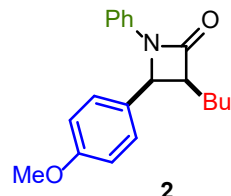
Selected Substrate Scope:



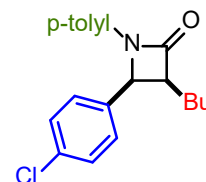
22 Examples
9-75% Yield
Cis:Trans
1:1 - 12:1



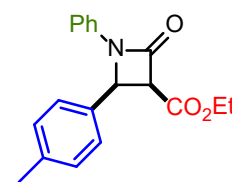
66% yield
Cis/Trans
12:1



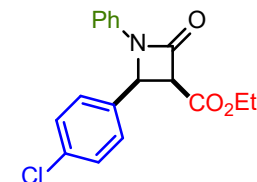
55% yield
Cis/Trans
N/A



9% yield
Cis/Trans
N/A

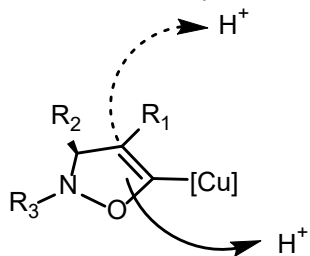


51% yield
Cis/Trans
3:1

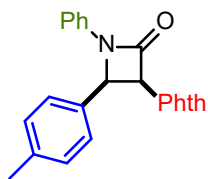


50% yield
Cis/Trans
N/A

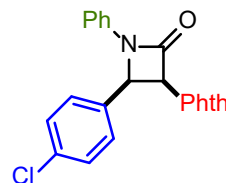
Rationale for Cis-β-lactam in Irwin's Proposed Mechanism:



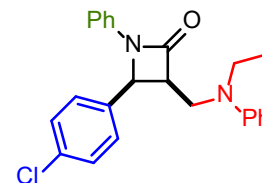
Steric hinderance from R_2 during protonation rationalizes cis-β-lactam



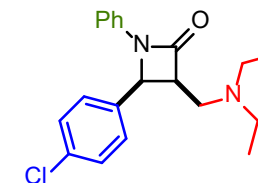
31% yield
Cis/Trans
9:1



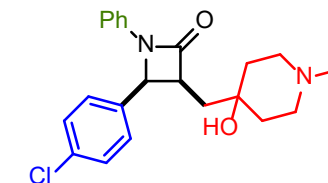
12% yield
Cis/Trans
N/A



52% yield
Cis/Trans
1:1

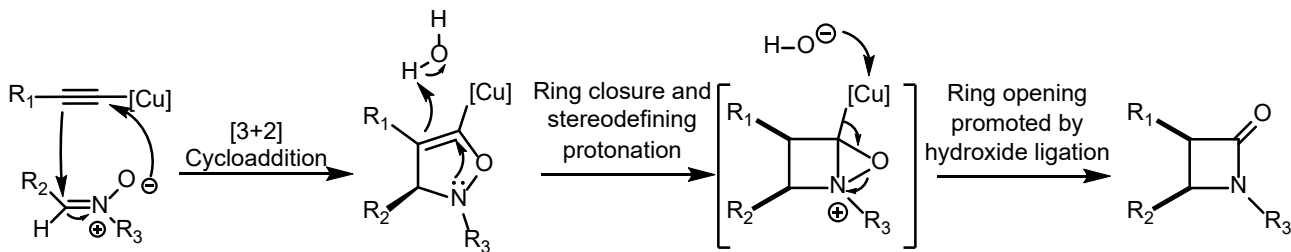


44% yield
Cis/Trans
N/A



50% yield
Cis/Trans
1:1

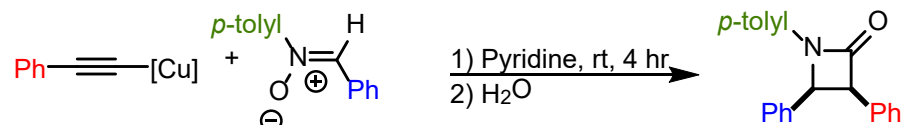
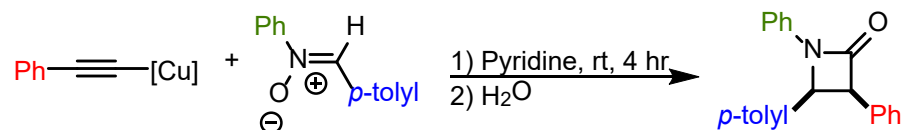
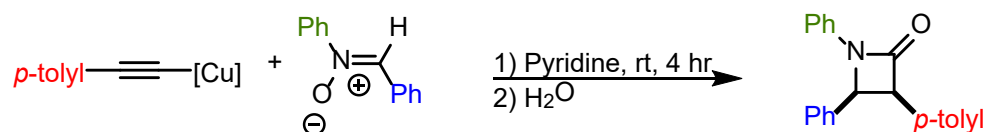
Irwin's Proposed Mechanism (1976):



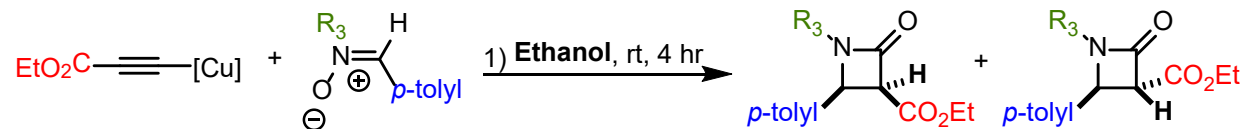
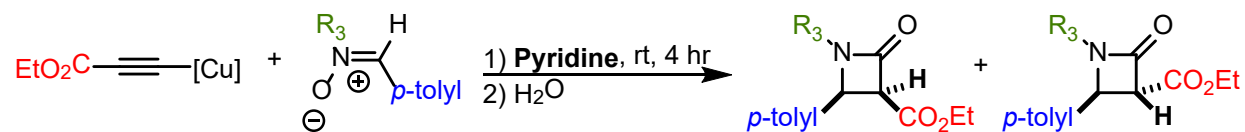
What experiments were performed in confirming this proposed mechanism?

Mechanistic Insight by Irwin

Confirmation of Substitution in β -lactam (Irwin 1976):

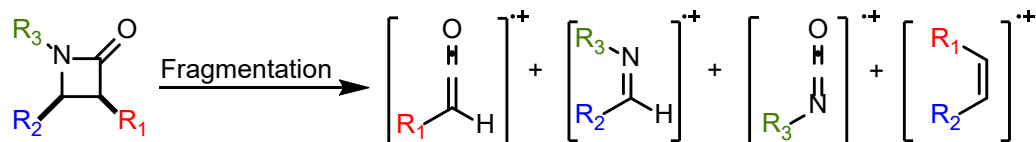


Solvent Replacement to Inhibit Isomerization:

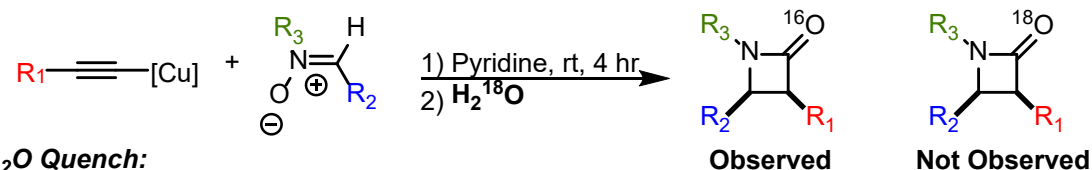


Cis/Trans
3:1

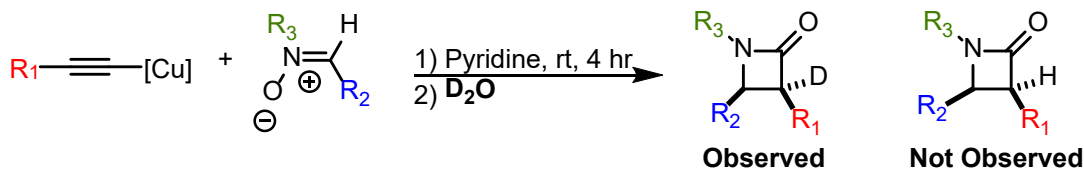
MS Fragmentation of β -lactam:



^{18}O Labeled Water Quench:



D_2O Quench:

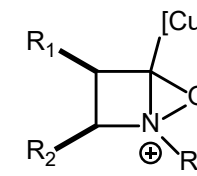


Determined the positions of each of the substituents in the Kinugasa

Oxygen comes from the nitron, but the proton must be exogenous and protonation determines stereochemistry

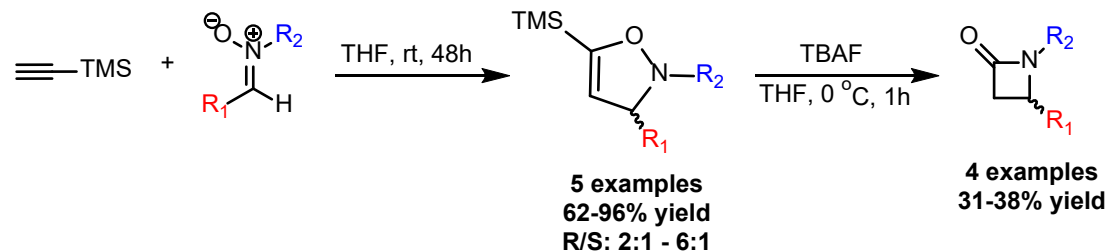
Bases causes isomerization depending on the substituent

Still no evidence to support this bicyclic intermediate

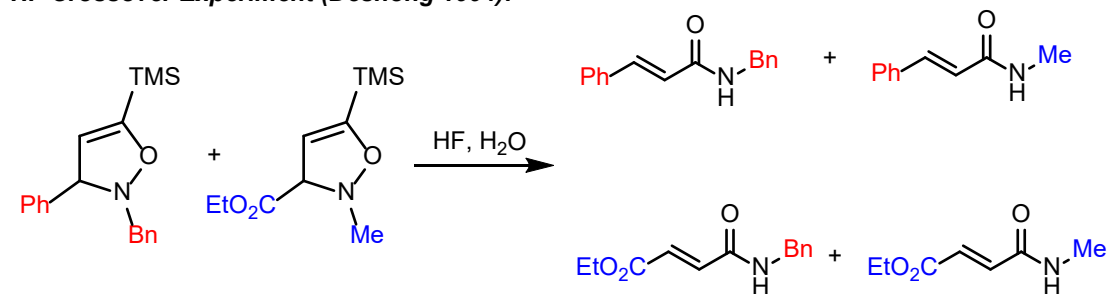


Deshong's Inspiration of a Different Intermediate

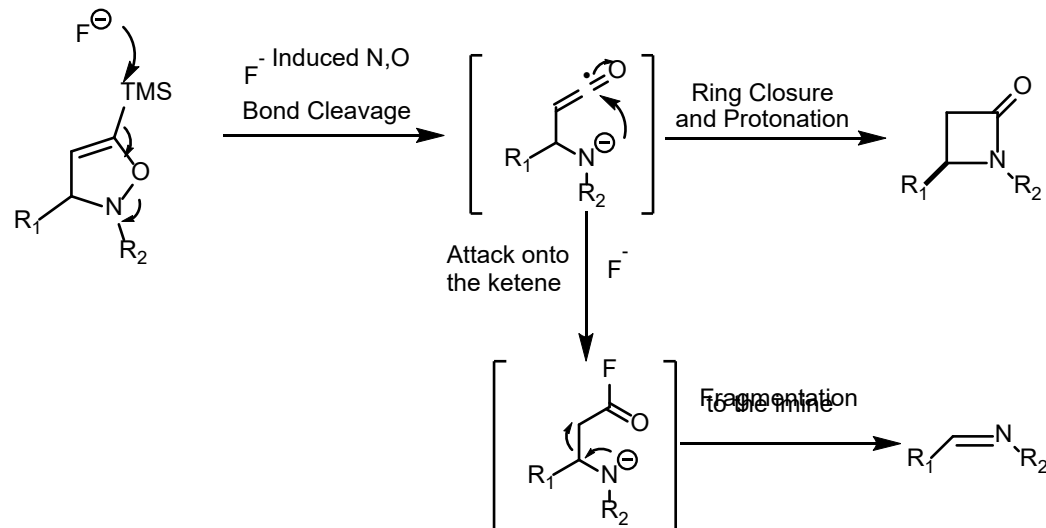
β -Lactams via TMS-acetylene (DeShong 1994):



HF Crossover Experiment (DeShong 1994):



Proposed Mechanism of TMS Acetylenes (DeShong 1994):

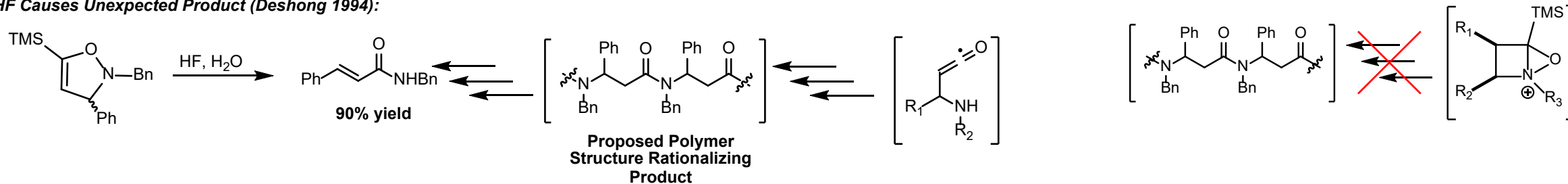


Although not mediated through copper, isolated isoxazoline heavily supports initial [3+2] cycloaddition.

In acidic conditions, byproduct from cleavage of a polymer supports ketene intermediate. Scrambling of substituents also supports this intermediate.

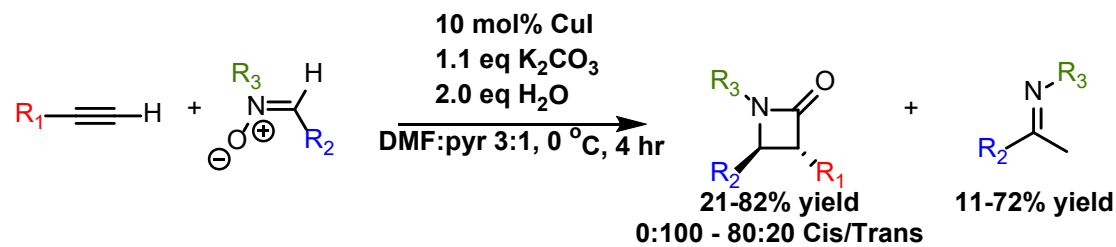
Proposed polymer structure is highly unlikely to originate from Irwin's bicyclic intermediate.

HF Causes Unexpected Product (DeShong 1994):



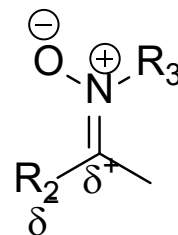
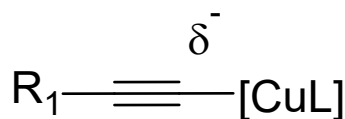
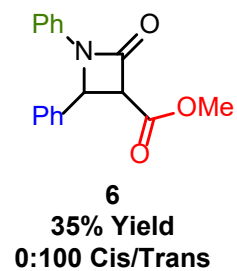
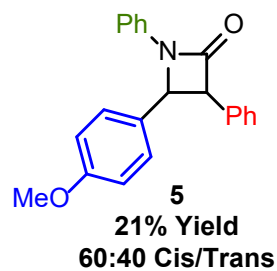
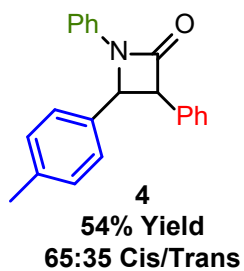
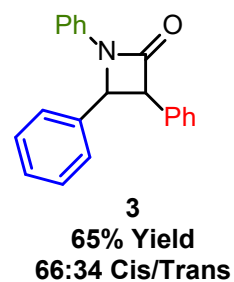
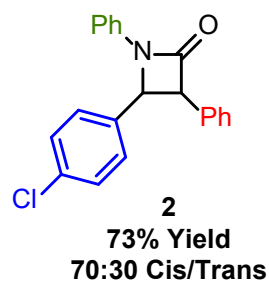
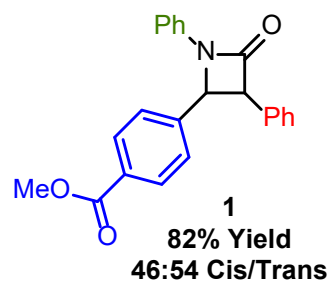
Miura's Catalytic System and Insight on the RDS

First Catalytic System by Miura (1993, 1995):



Ligand	time (h)	Cis/Trans	Yield [%]
None	10	N/A	18
P(n-Bu) ₃	5	N/A	36
dppe	4	N/A	3
1,10-phen	3	44:56	55
pyr	8	69:31	71

Selected Substrate Scope:



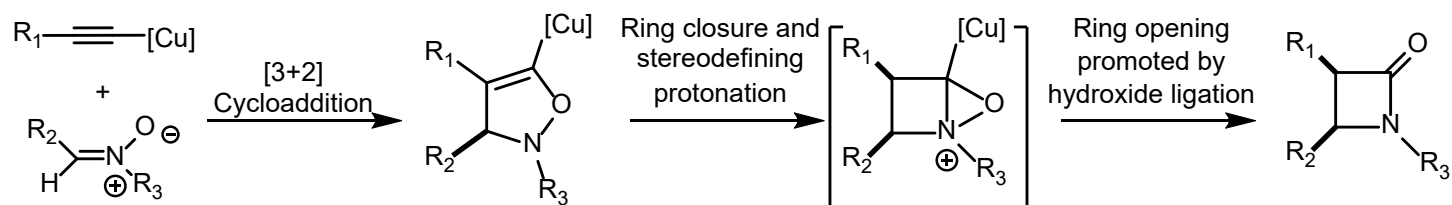
Hypothesized that phosphine ligands suppressed [3+2]

Electron withdrawing groups on R₂ increased desired product

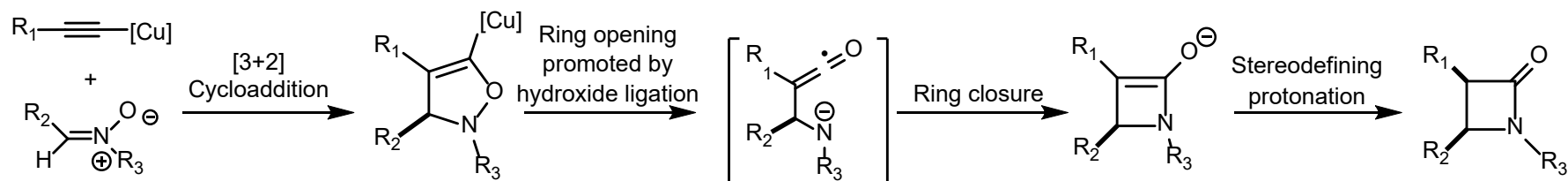
Without any ligand, precipitates formed due to Cu (I) acetylide aggregates

Third Proposed Mechanism

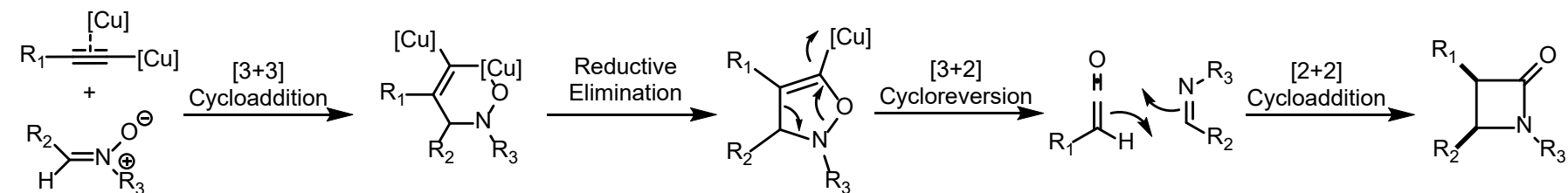
Irwin's Proposed Mechanism (1976):



Mechanism Adapted From Deshong (1994):



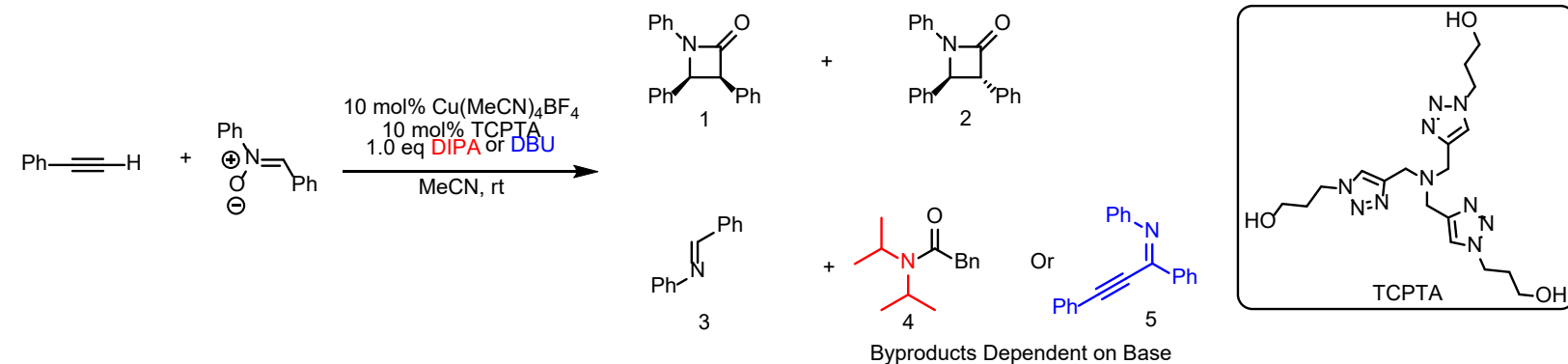
Mechanism Involving a [3+2] Cycloreversion (Hein 2018):



Why are two Cu species proposed? and why the cycloreversion?

Recent Investigations by Hein

Selection of the model system, Hein (2018):



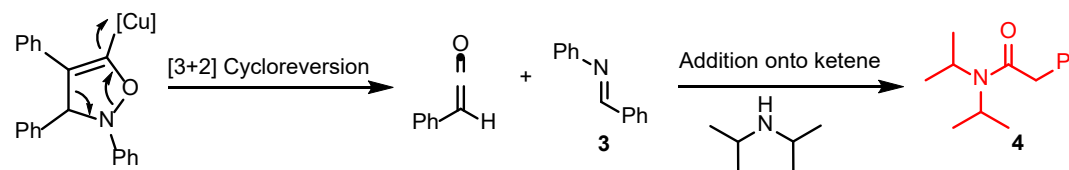
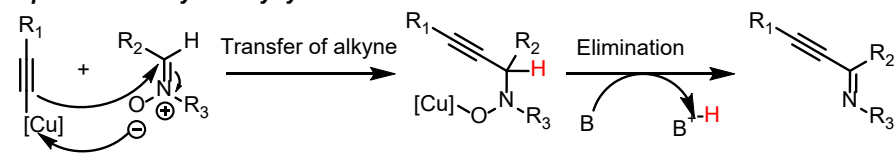
With DIPA as a base, only observed 17% of both product 1 and 2, and observed product 3 and 4 in equimolar amounts, yet how are they formed?

Proposed Pathways for Formation of Byproducts:
Miura (1995):

Hein (2018):

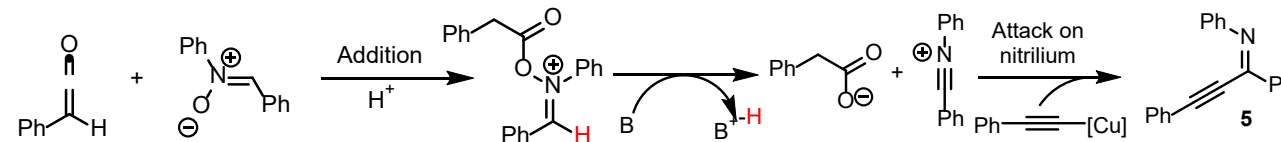
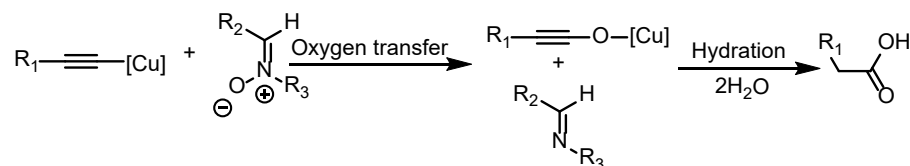
Proposed Pathway to Alkynyl Imine:

Proposed Pathway to Imine and Amide:



Proposed Pathway to Imine and Phenylacetic Acid:

Proposed Pathway to Alkynyl Imine and Phenylacetic Acid:

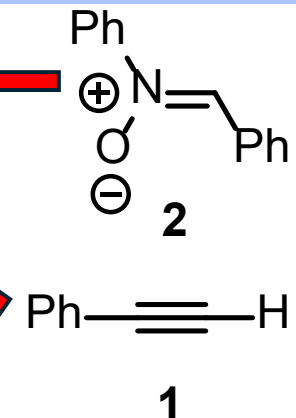
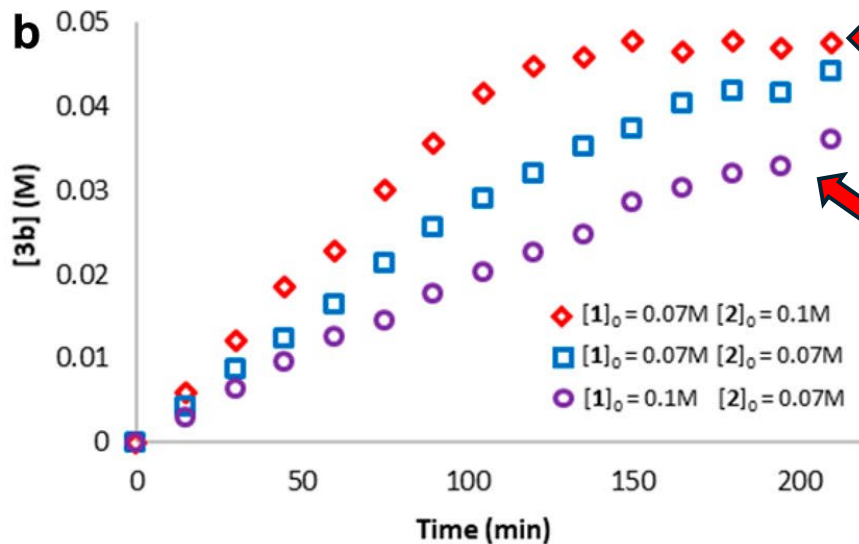
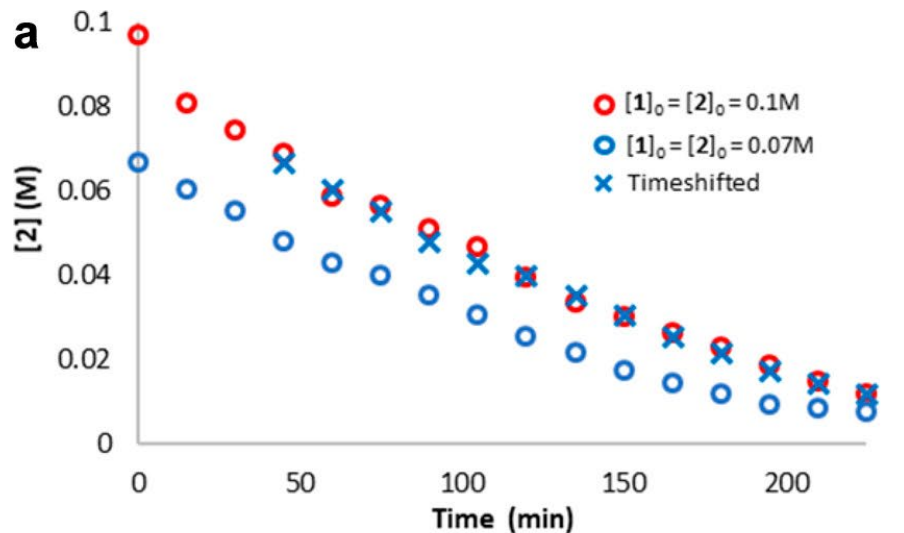


Hein and coworkers argue that byproduct 4 in DIPA implies a free ketene and subsequently a [3+2] cycloreversion

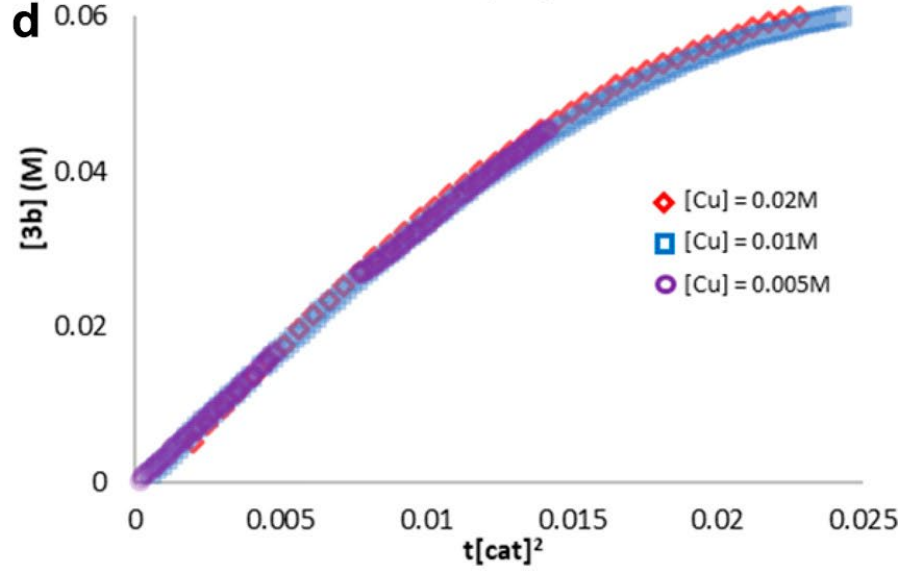
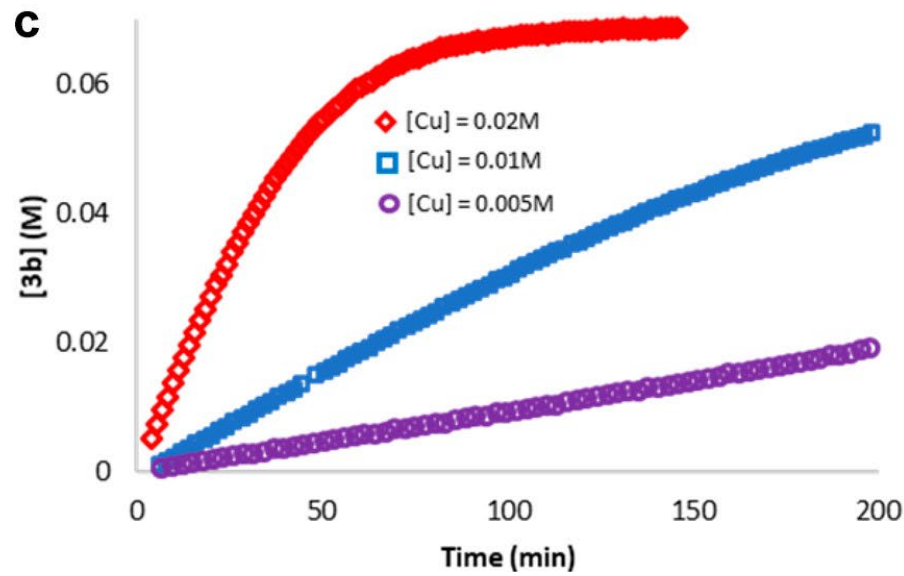
Hein also argues that Miura's proposed byproduct 5 would also slow down the reaction rate by removing the active Cu species.

So what is the rate of reaction? it's RDS? and why were two copper species and a new intermediate proposed?

Determining the RDS



Rate of reaction over time does not significantly slow, implying no deactivation of Cu species

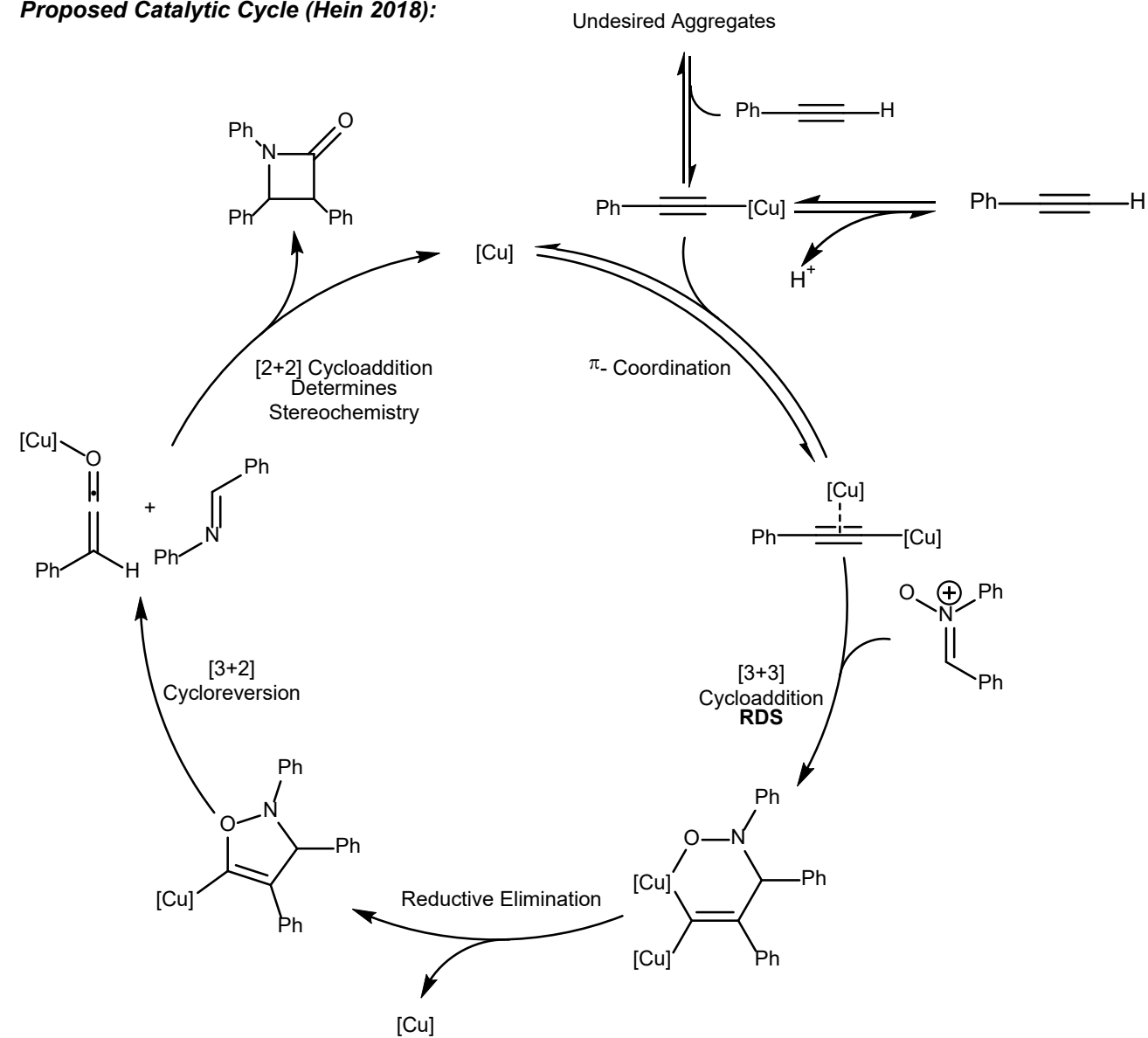


Alkyne is inverse first order and nitron is first order implying the [3+2] is the RDS

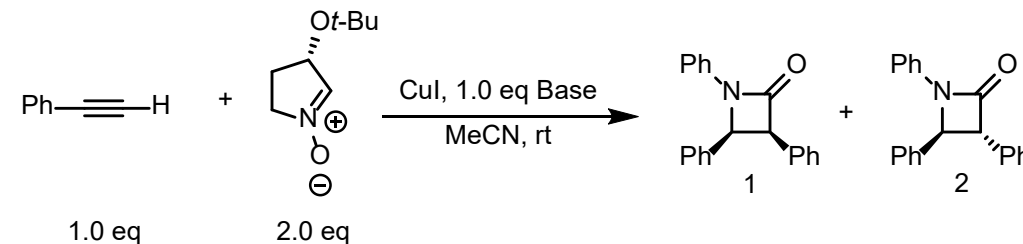
Plots C and D show that the RDS is dependent on two Cu species.

Hein's Proposed Catalytic Cycle and Inconsistencies

Proposed Catalytic Cycle (Hein 2018):



Base Optimization Screen (Chmielewski 2008):

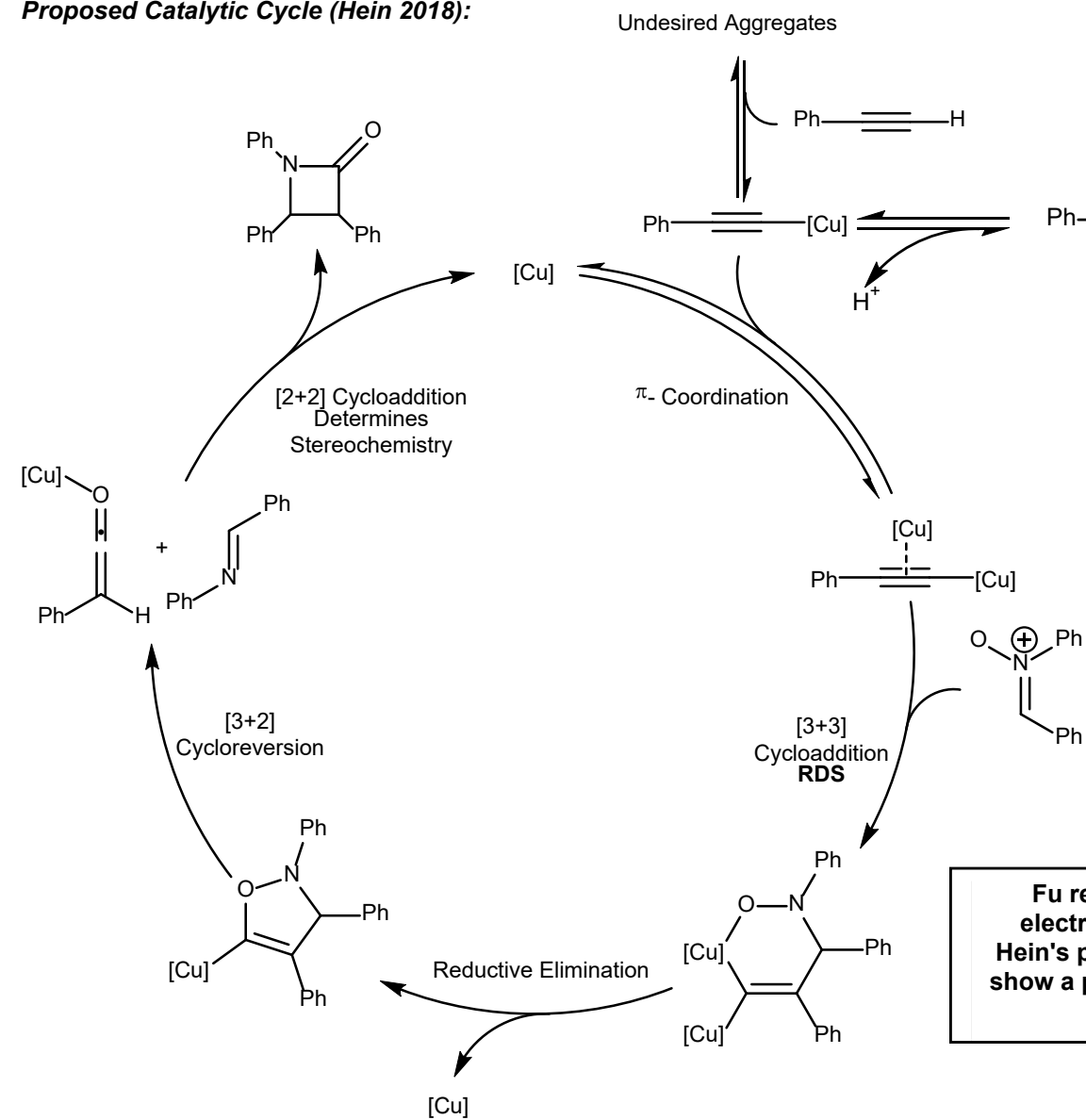


entry	amine a	time [h]	yield [%]	<i>cis:trans</i> b
1	Et ₃ N	20	56	85:15
2	Et ₃ N	48	58	52:48
3	<i>i</i> -Pr ₂ NEt	20	38	98:2
4	(<i>c</i> -C ₆ H ₁₁) ₂ NMe	21	50	95:5
5	pyridine	22	10	54:46
6	TMEDA	20	26	55:45
7	Et ₃ N	24	80 c	74:26
8	Et ₃ N	48	70 c	60:40
9	NH ₂ NH ₂ ·H ₂ O	21	58	70:30

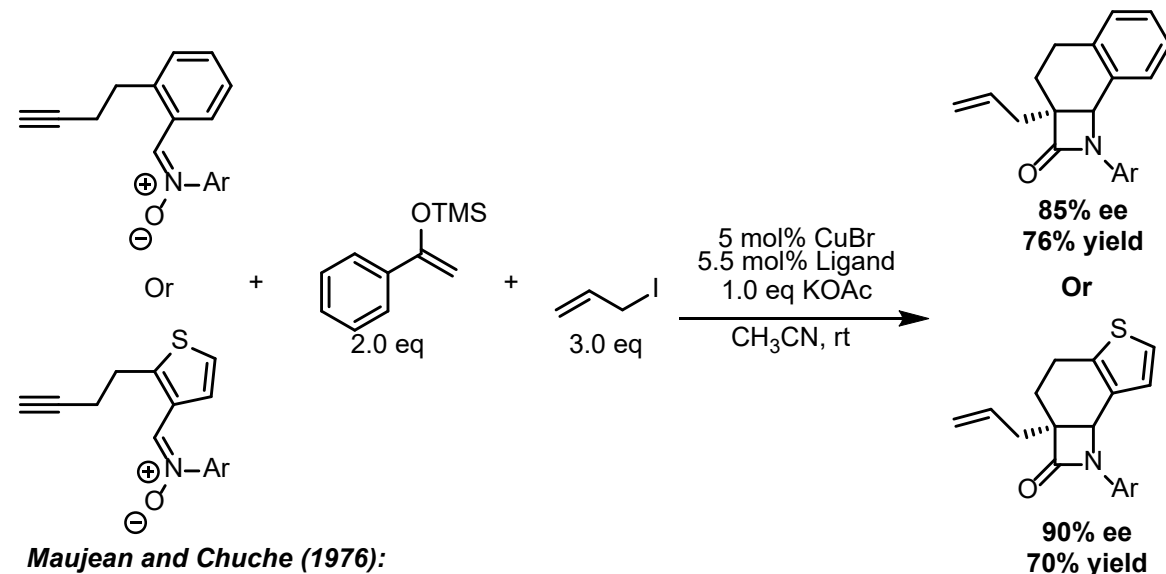
If the [2+2] determines the stereochemistry, then the bulkiness of the base shouldn't affect cis/trans ratio

Hein's Proposed Catalytic Cycle and Inconsistencies

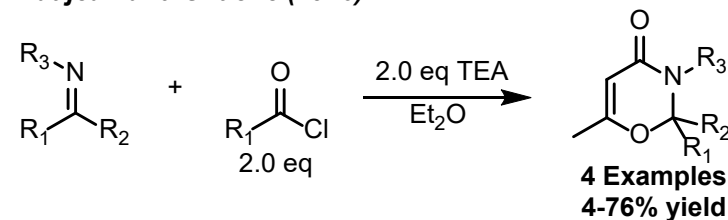
Proposed Catalytic Cycle (Hein 2018):



Trapping Allyl Iodide (Fu 2003):



Maujean and Chuche (1976):

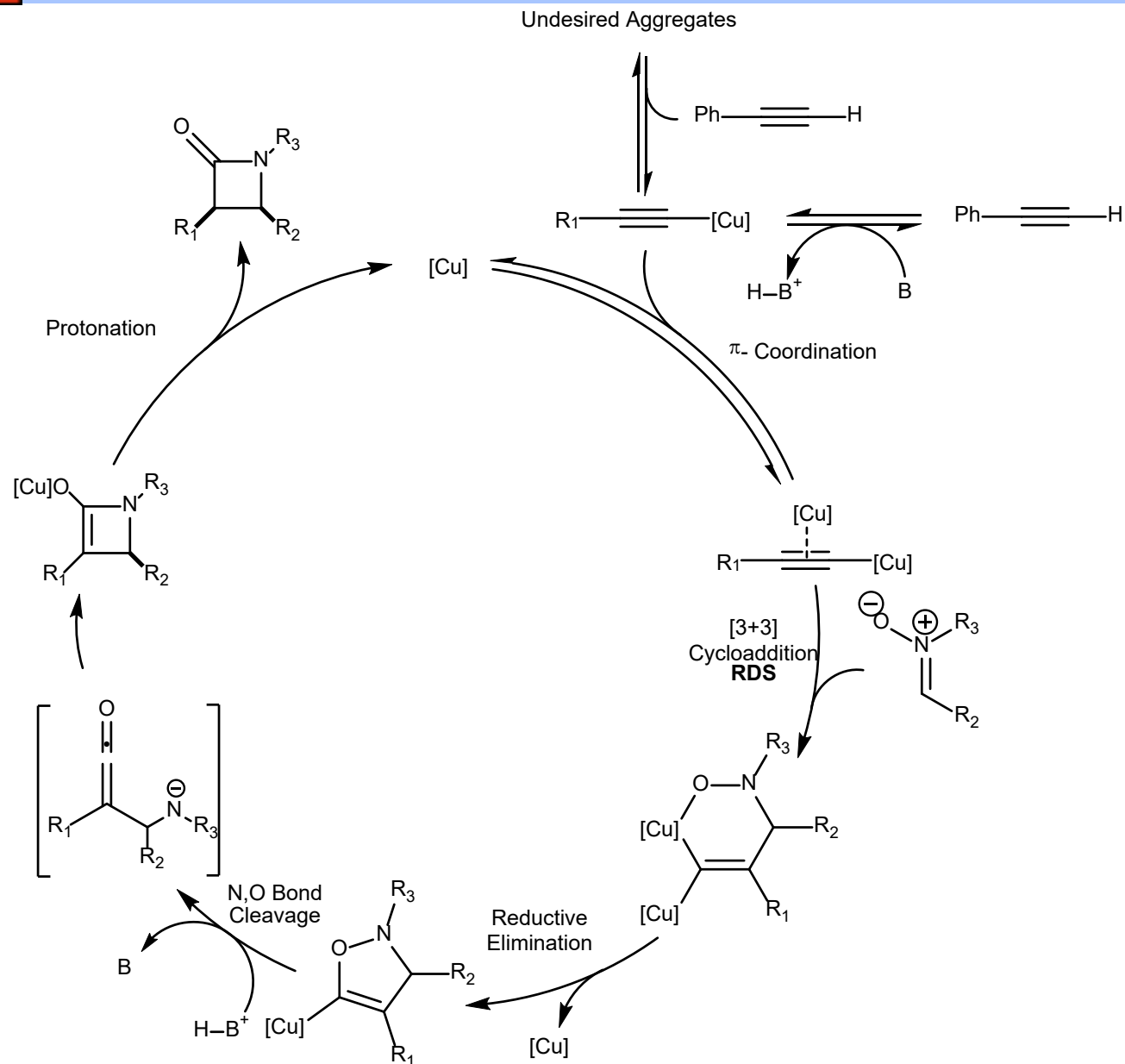


Fu reported the ability for electrophiles to be trapped, Hein's proposed cycle does not show a potent nucleophile at the alpha carbon.

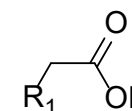
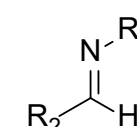
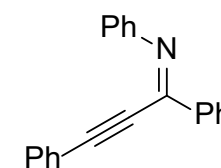
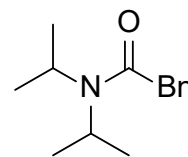
Maujean and Chuche have reported that free ketenes and imines generate oxazinones, yet none were reported.

The proposed [3+2] cycloreversion cannot be the true intermediate, there are too many inconsistencies with experimental data

Plausible Mechanism



Compounds Observed, Yet Unknown How They're Formed:

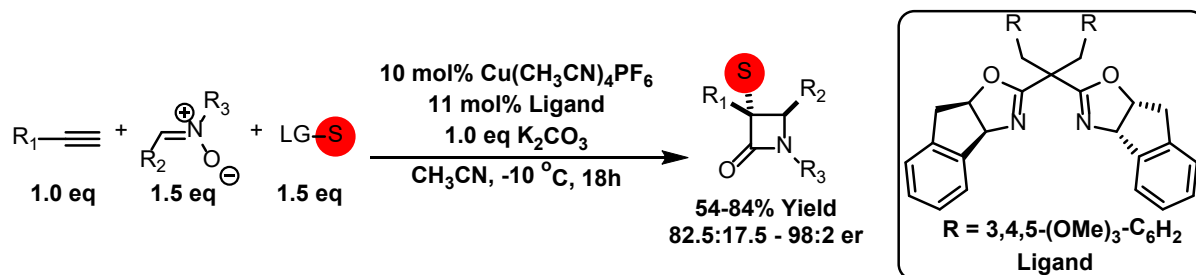


Further mechanistic studies need to be done to identify how off cycle byproducts are formed. ie: does the aminoketene fragment in the presence of exogenous nucleophile?

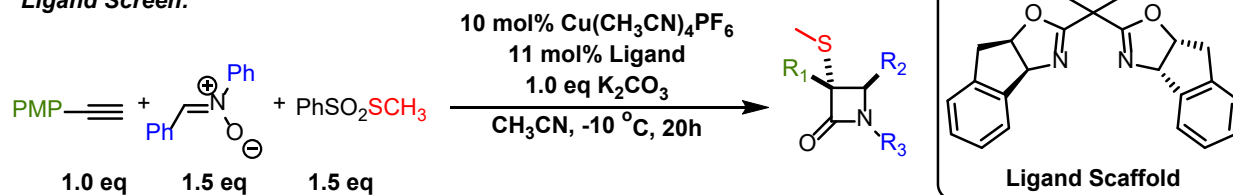
Understanding the formation of off cycle byproducts can lead to rationale design of improvements of the catalytic Kinugasa

Asymmetric Thio-Functionalization at C3

Chiral α -Thiofunctional β -Lactams (Xu 2021):

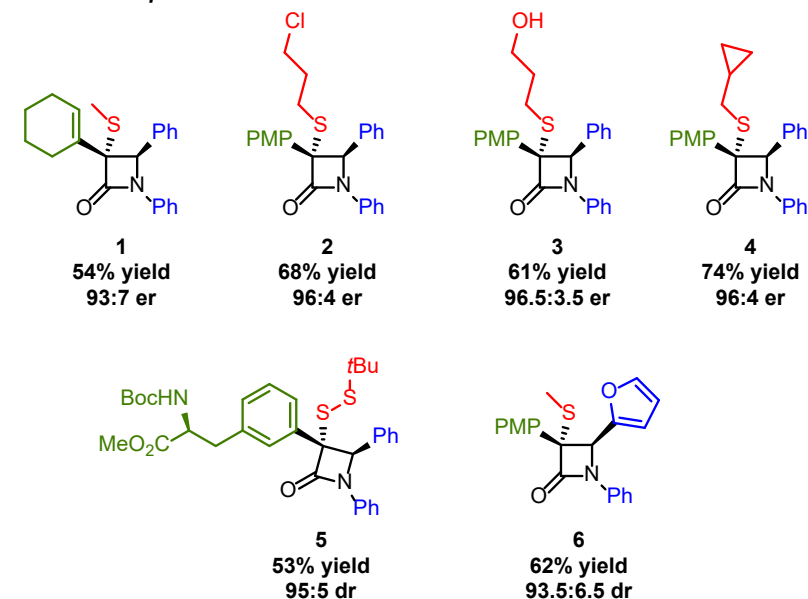


Ligand Screen:

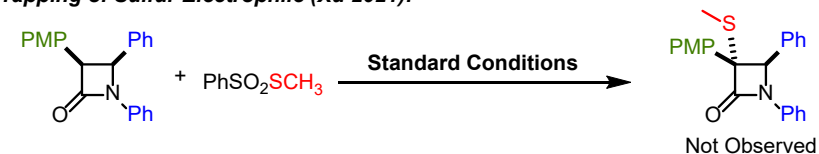


R	T [°C]	Yield [%]	er
R = Ph	25	80	84:16
R = 1-Naphthyl	25	82	88:12
R = 4-BrC ₆ H ₅	25	67	90:10
R = 4-tBuC ₆ H ₅	25	71	93:7
R = 4-OMeC ₆ H ₅	25	83	91:9
R = 3,4,5-(OMe) ₃ C ₆ H ₂	25	90	95:5
R = 3,4,5-(OMe) ₃ C ₆ H ₂	-10	80	96.5:3.5
R = 3,4,5-(OMe) ₃ C ₆ H ₂	-20	59	96.5:3.5

Substrate Scope:



Trapping of Sulfur Electrophile (Xu 2021):



Resubjection did not result in any of the desired product, so electrophile trapping must occur immediately, or protons must be removed

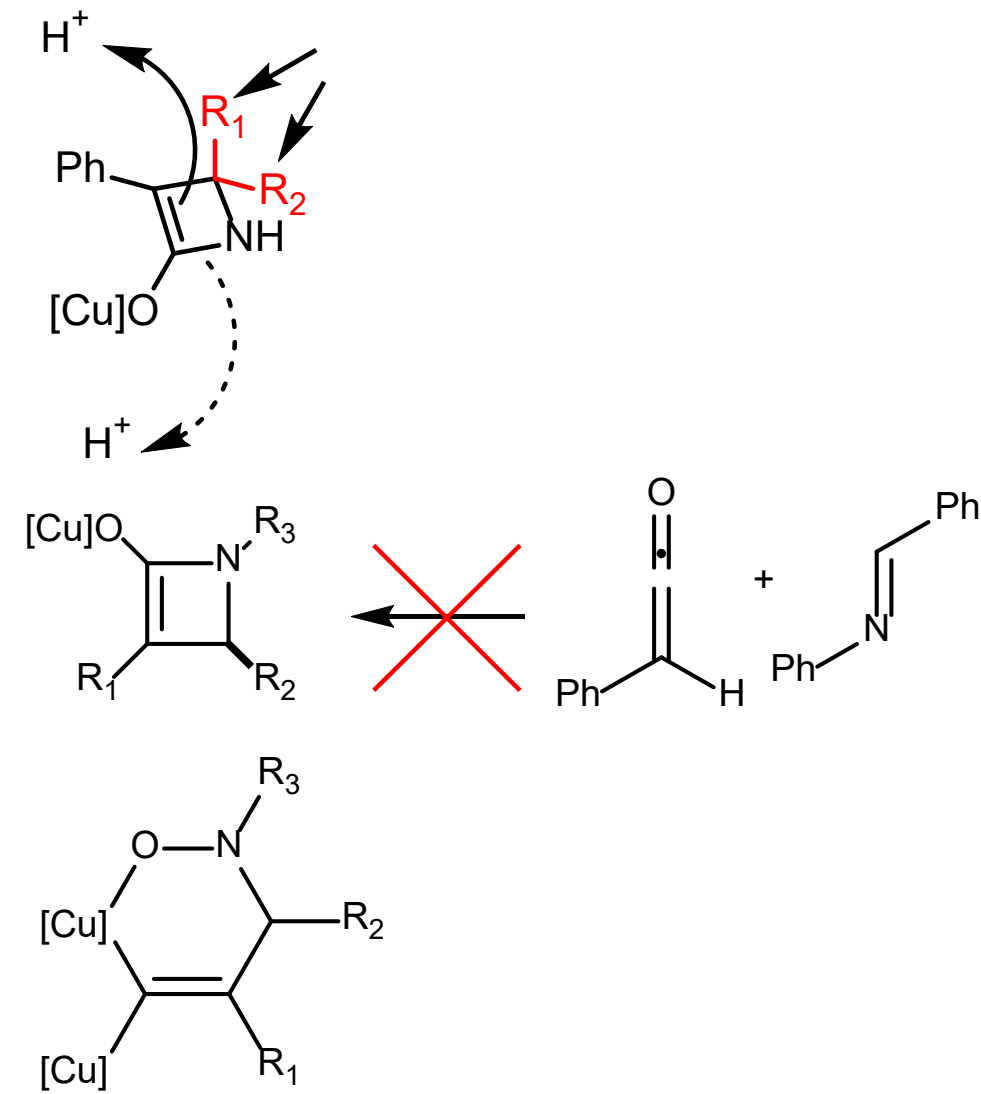
Trapping the enolate is challenging due to protonation being favorable, and copper acetylide acts as a competitive nucleophile

Summary

1) Nitroene substitution influences stereoselectivity during either protonation or attack, tri-substituted nitrones are less commonly employed due to competitive sterics.

2) Studies by Fu (2003) and Xu (2021) demonstrate electrophile trapping prior to protonation, providing evidence against a post-protonation [3+2] cycloreversion pathway.

3) A six-membered, bimetallic intermediate may account for the observed second-order dependence on copper.



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Yunlin Ao, Haowen Ma, Binghan Gan, Wenjing Wang, Jiehao Zhang, Wei Zhou, Xiaoqi Zhang*, and Qian Cai*

DOI: [10.1039/D4QO01388C](https://doi.org/10.1039/D4QO01388C) (Research Article) *Org. Chem. Front.*, 2025, **12**, 167-172

A two-step Kinugasa/Conia-ene-type sequential reaction for the asymmetric synthesis of 8-methylene-2,6-diazaspiro[3.4]octane-1,5-diones[†]

Shanyue Li ^a, Qicai Ma ^a, Bohua Wu ^a, Haowen Ma ^b, Wei Zhou  ^{*a} and Qian Cai  ^{*b}

Questions?