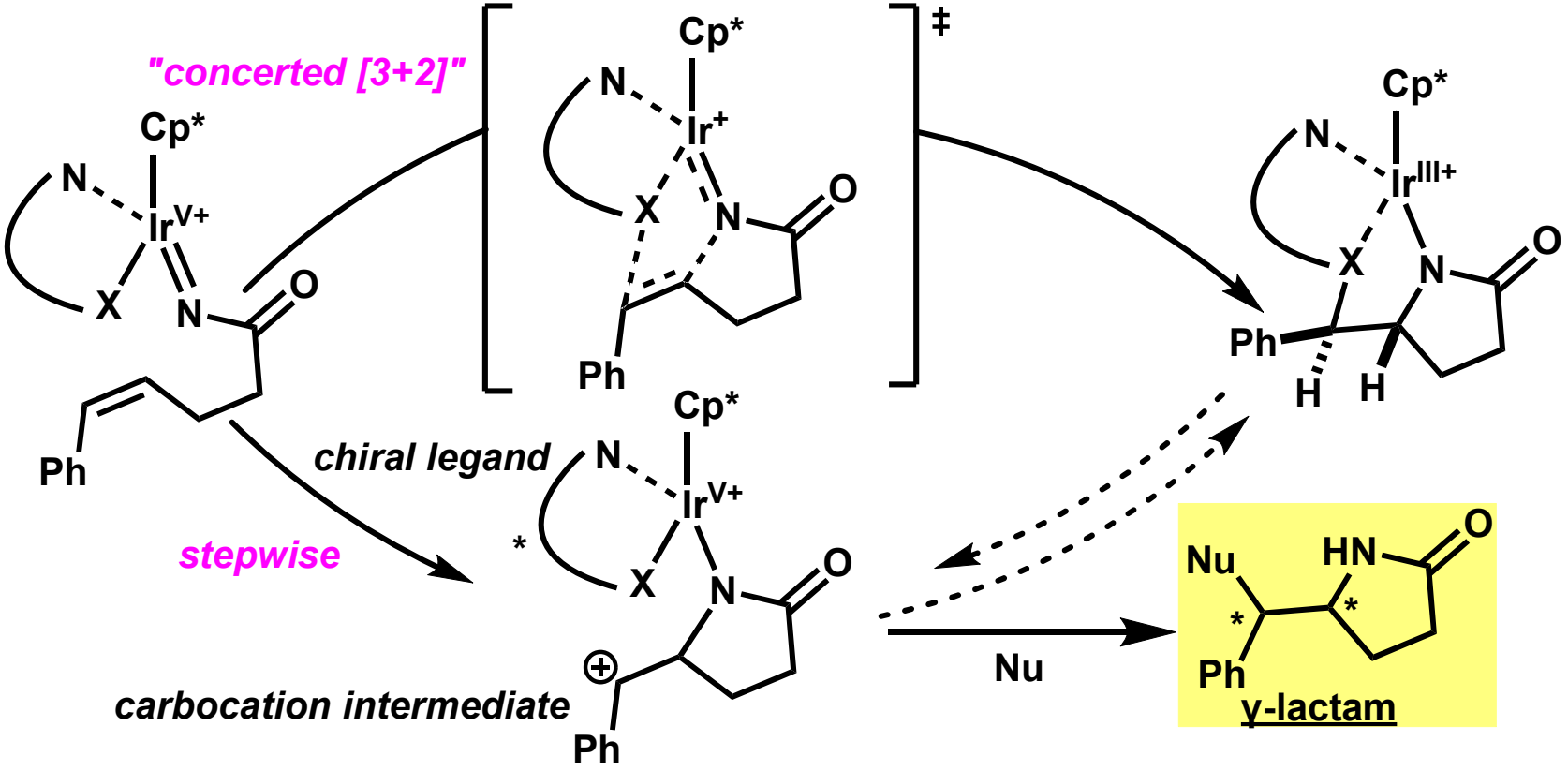
Access to β- and γ-Lactams via Olefin Difunctionalization

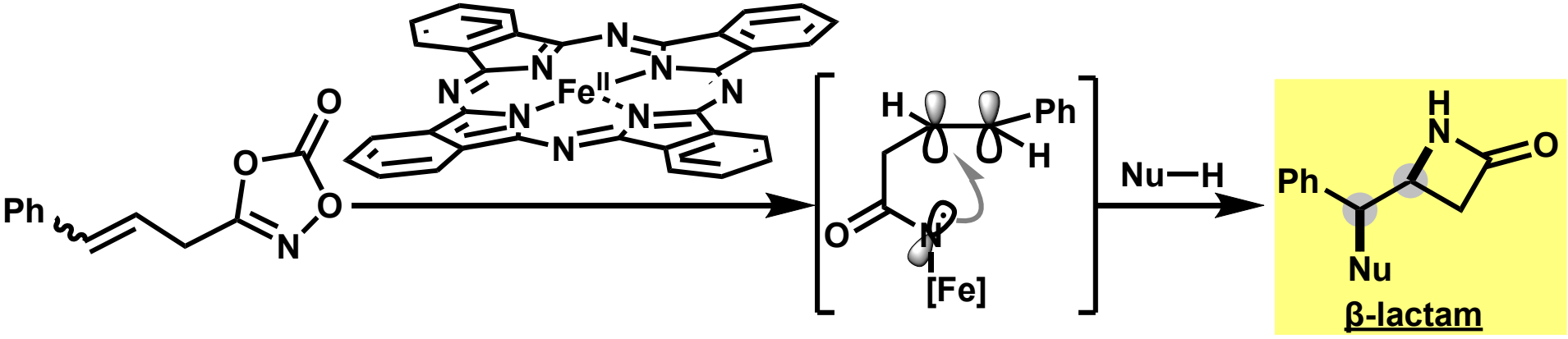
2022.5.7. LS Junichi Taguchi

Contents

1. Introduction (An Alternative to Acyl Azides)
2. Stereodefined Access to γ-Lactams via Olefin Difunctionalization



3. Access to β-Lactams via Iron-Catalyzed Olefin Oxyamidation Enabled by the π- Accepting Phthalocyanine Ligand (Main Paper) (*J. Am. Chem. Soc.* 2022, *144*, 1872)



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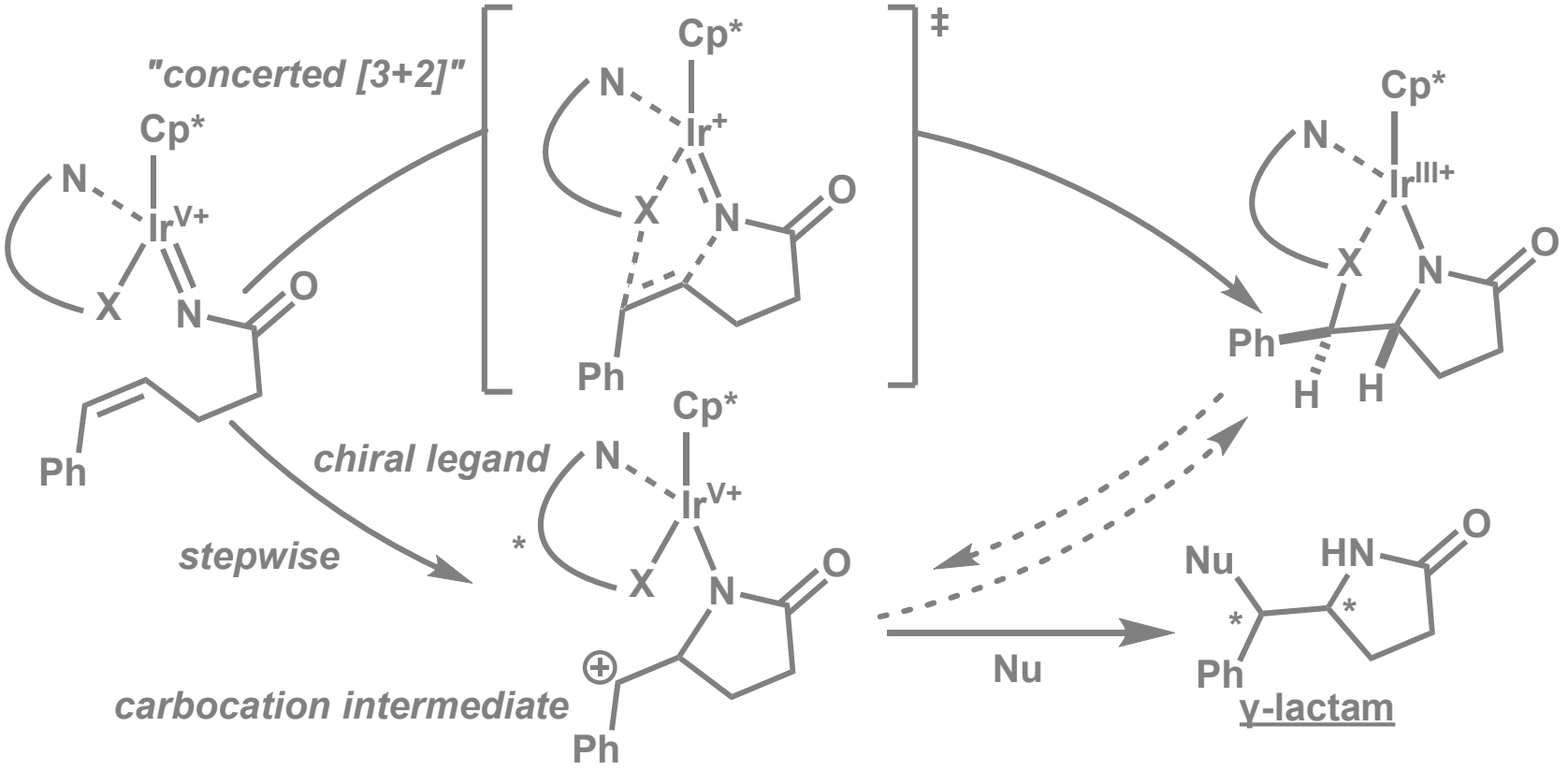

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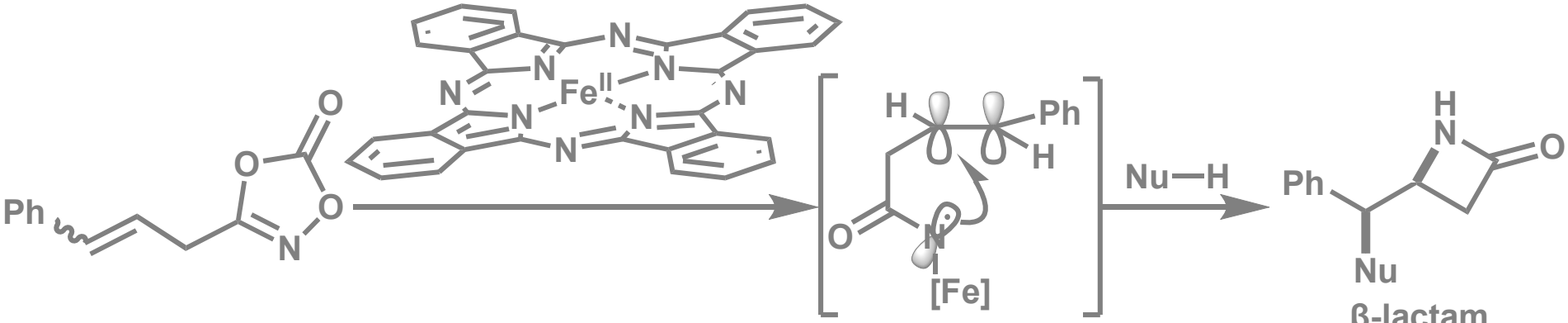


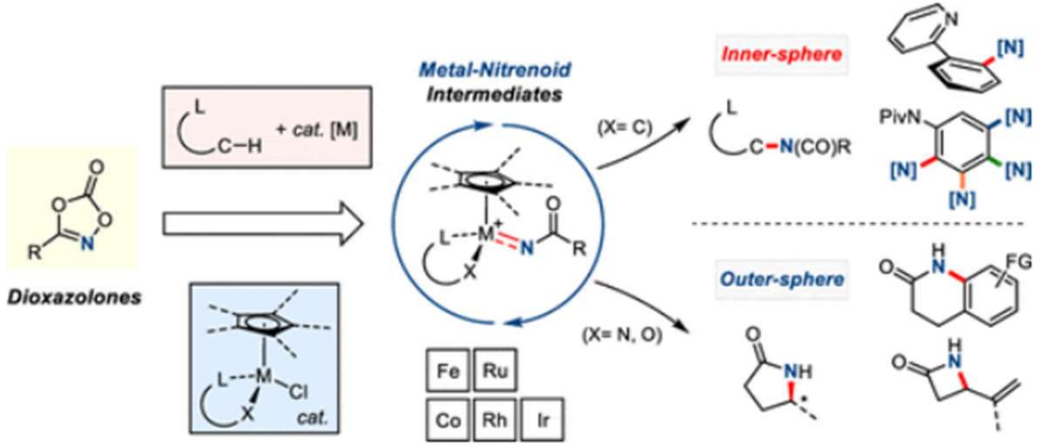
Prof. Sukbok Chang

Education and Professional Careers:

1985	B.S. @ Korea university
1987	M.S. @ KAIST (Advisor: Prof. Sunggak Kim)
1996	Ph.D. @ Harvard University (Advisor: Prof. Eric. N. Jacobsen)
1996-1998	Post Doctoral Fellow @ Caltech (Advisor: Prof. Robert H. Grubbs)
1998-2002	Assistant Professor @ Ewha Womans University
2002-	Professor @ KAIST
2018-	Distinguished Professor @ KAIST

Research Interests:

1. Site-selective C-H activation strategies especially for C-C, C-N and C-O bond formations (Today's topic)



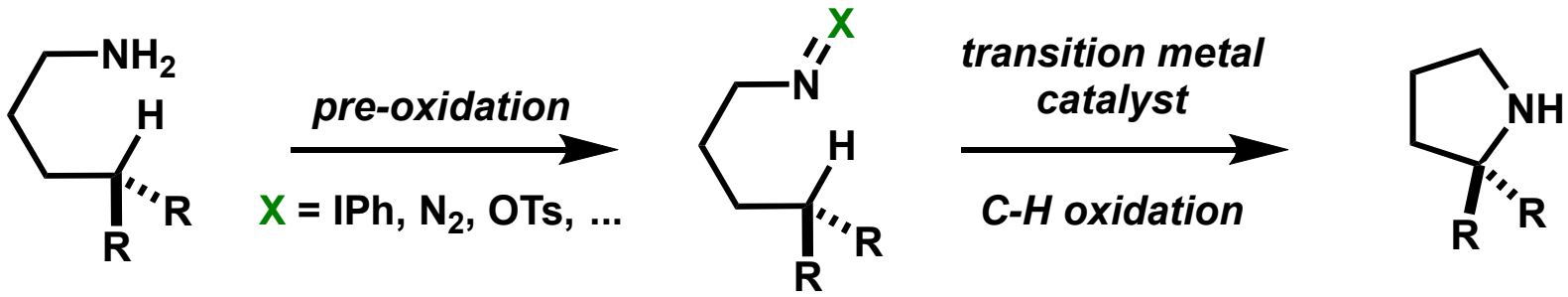
2. Methane functionalization

3. Catalytic selective defunctionalization

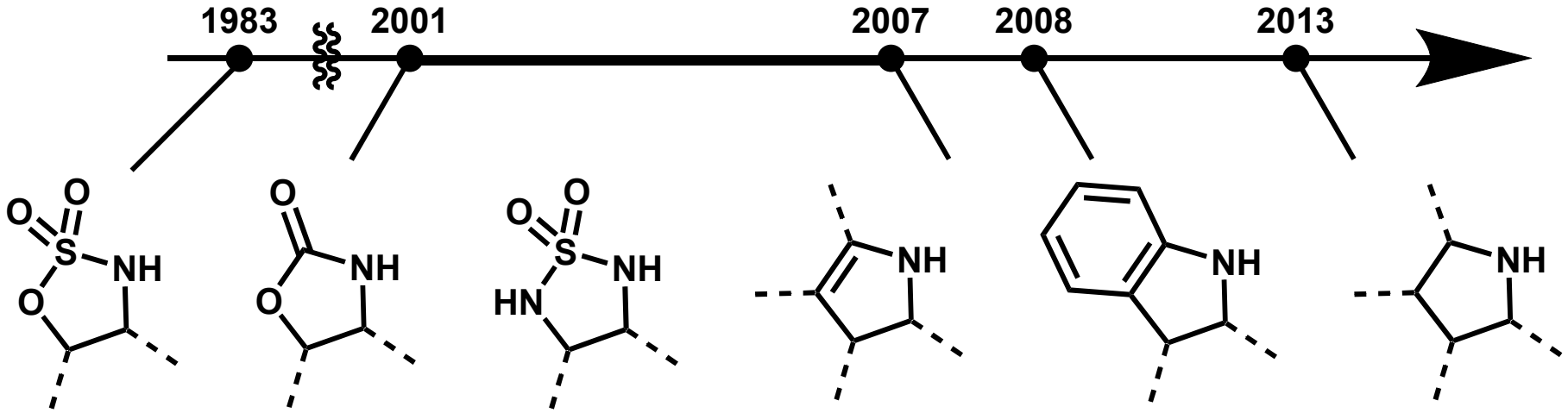
1. https://sbchang.kaist.ac.kr/ 2. Hong, S. Y.; Hwang, Y.; Lee, M.; Chang, S. *Acc. Chem. Res.* **2021**, *54*, 2683.

C-H Amination

Intramolecular insertion of nitrenes into carbon-hydrogen bonds

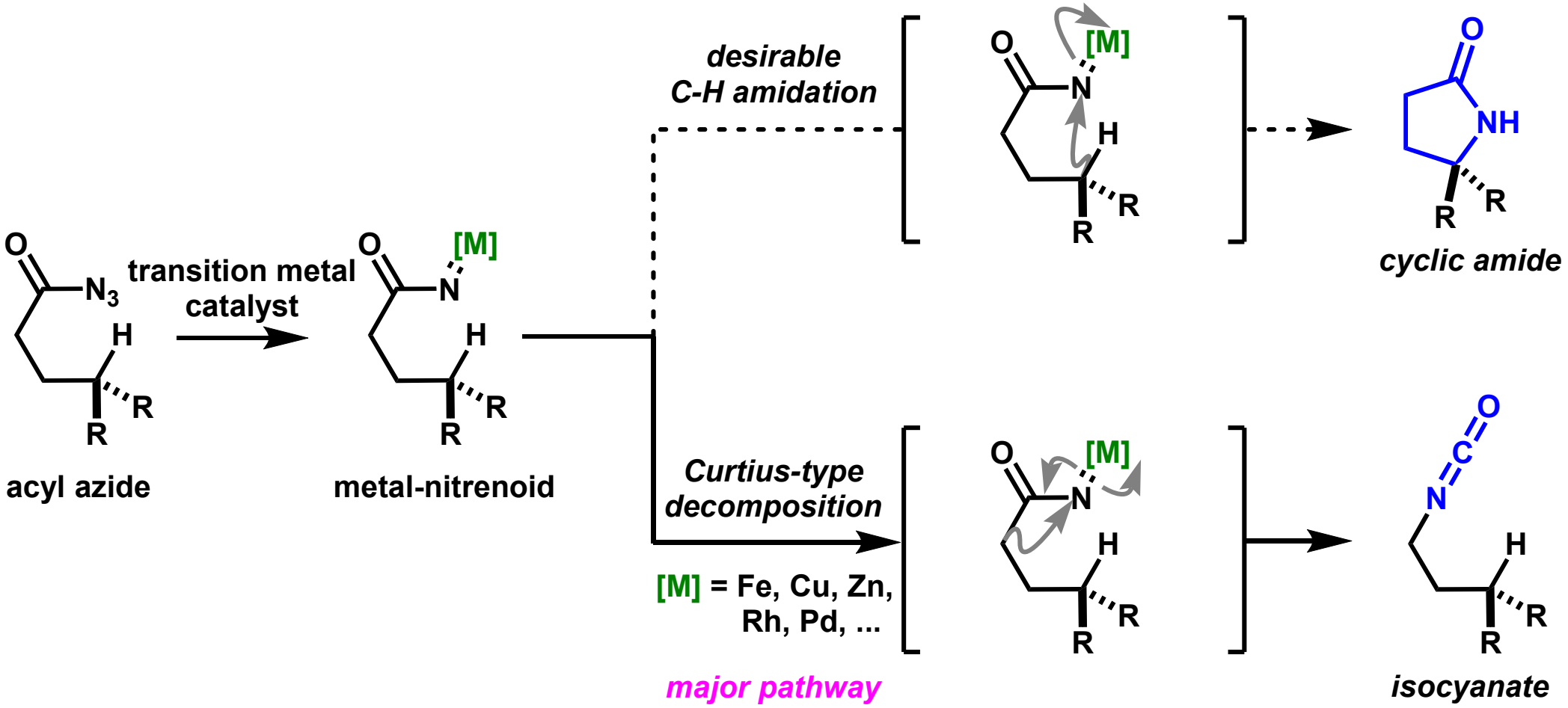


history of C-H amination



Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M. -H.; Chang, S. *Science.* **2018**, *359*, 1016.

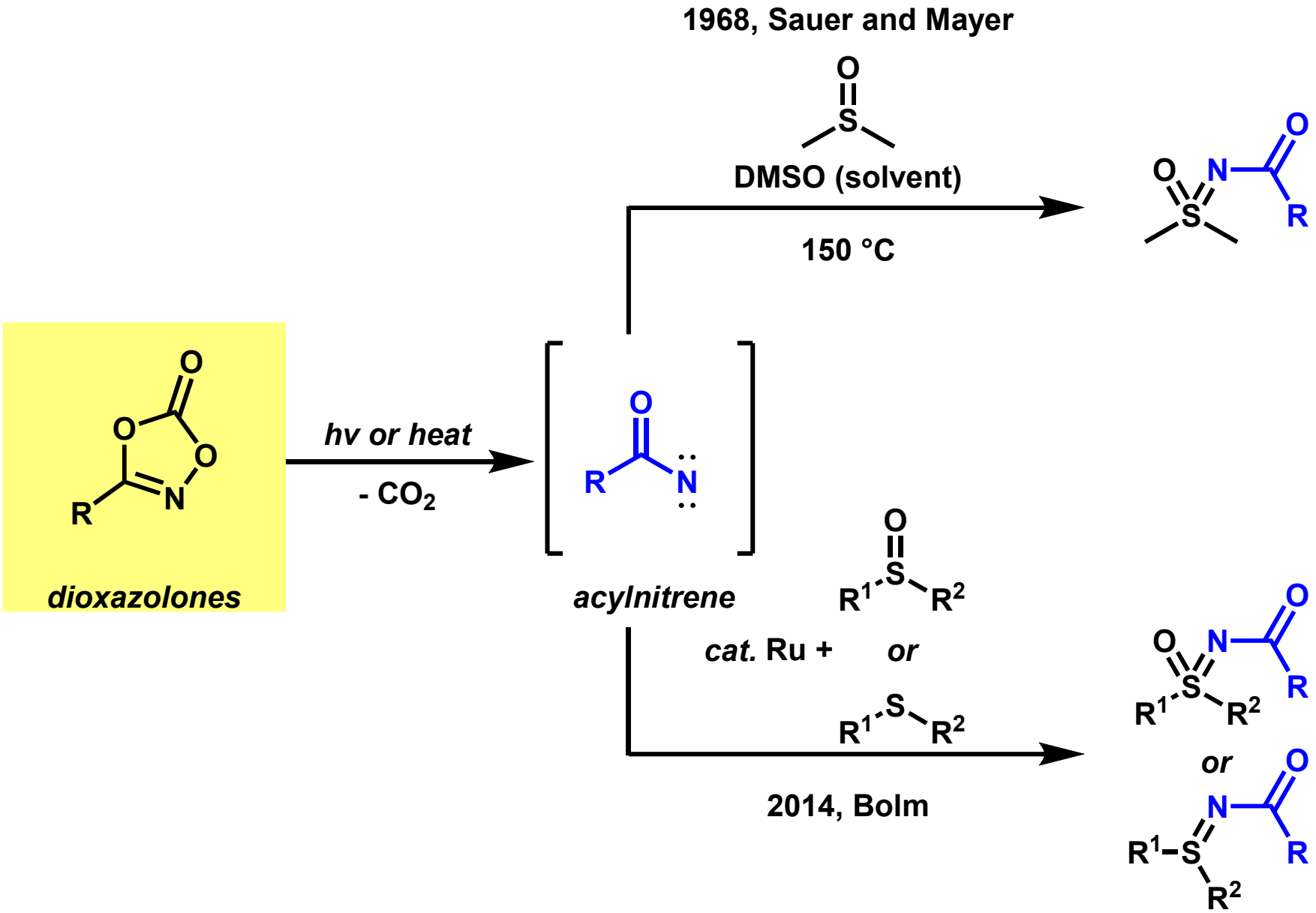
Why Is C-H Amidation Challenging?



The instablility of acyl azides makes it difficult to construct cyclic amides via C-H functionalizations

Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M. -H.; Chang, S. *Science.* **2018**, *359*, 1016.

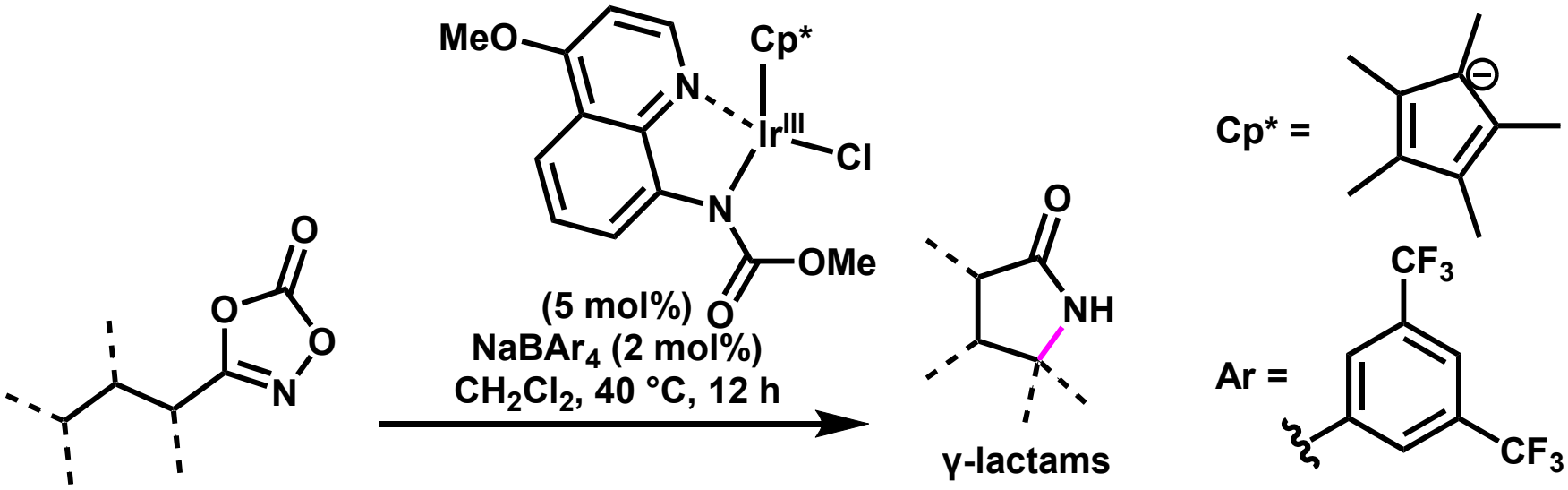
Alternatives of Acyl Azides ~Dioxazolones~



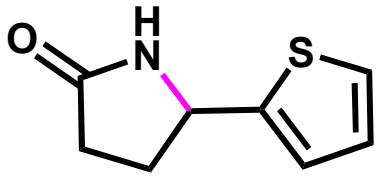
Inspired by these works, Prof. Sukbok Chang used dioxazolones as versatile amidating reagents.

1. Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534. 2. Sauer, J.; Mayer, K. K. *Tetrahedron Lett.* **1968**, *9*, 319. 3. Bizet, V.; Burglioni, L.; Bolm, C. *Angew. Chem. Int. Ed.* **2014**, *53*, 5639.

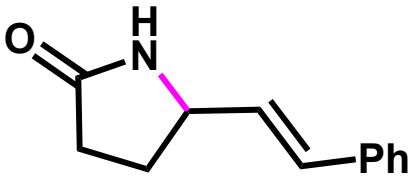
Substrate Scope



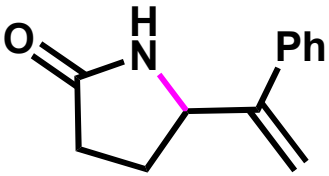
(yields with acyl azides are given in parentheses)



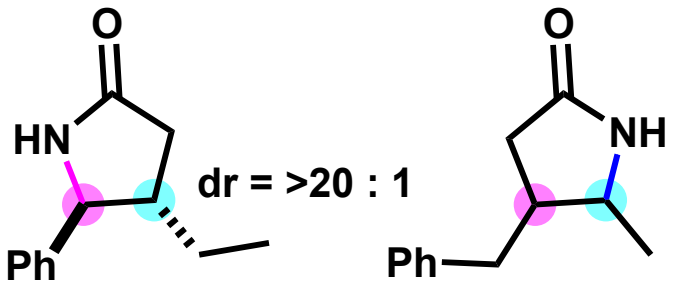
84%[a,b]



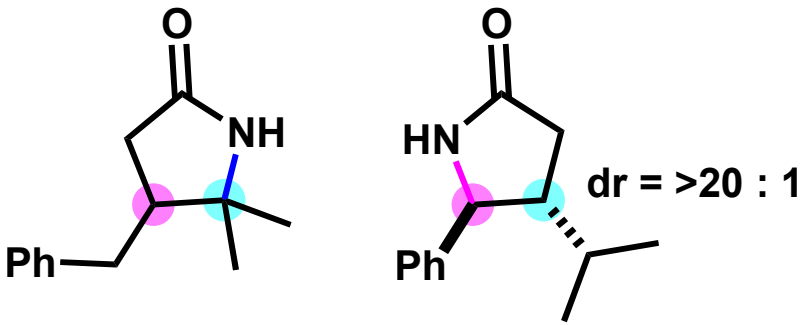
88%[a]



48%[a]



90% (12.6 : 1)



96% (1.3 : 1)

See also LS_191026_Tsukasa_Shimakawa

a) 10 mol% of the catalyst was used. b) 80 °C for 48 hours

Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M. -H.; Chang, S. *Science.* **2018**, *359*, 1016.

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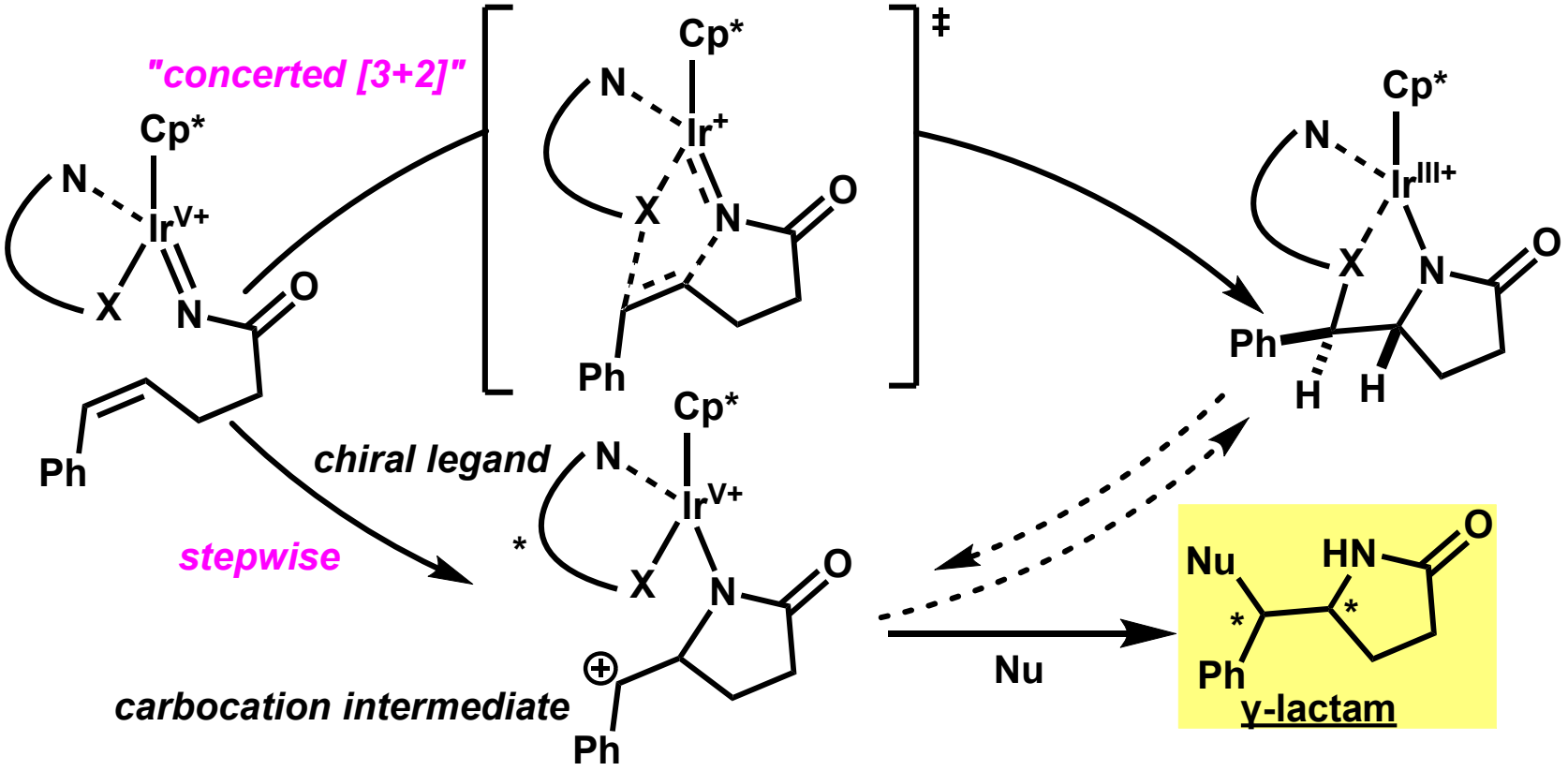

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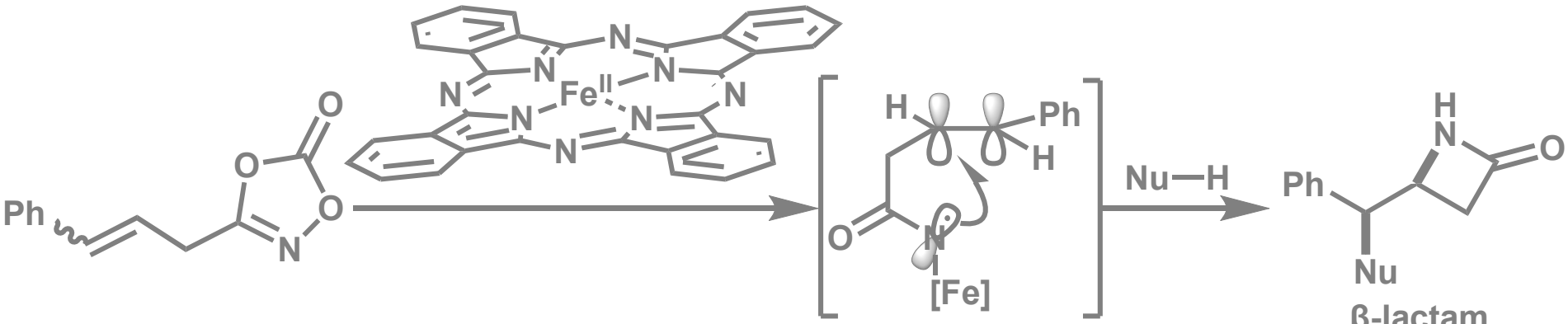
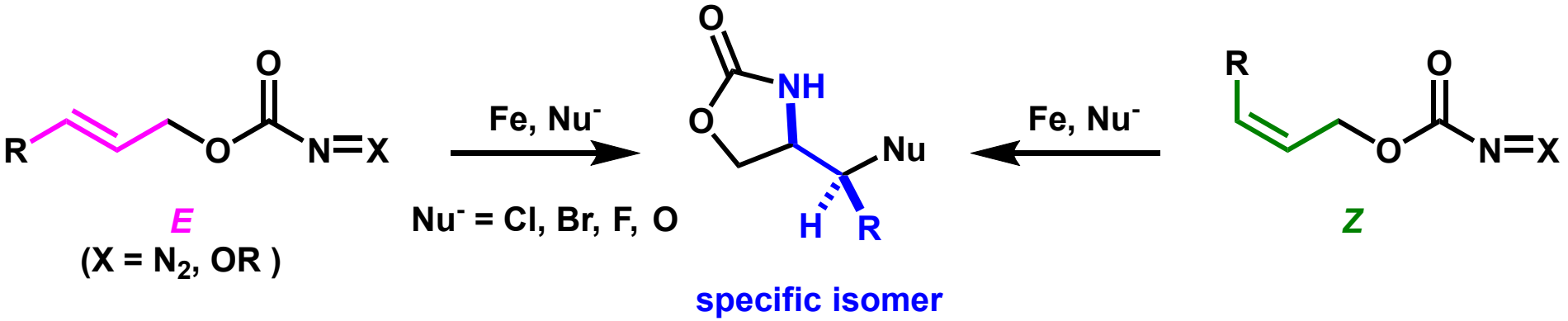
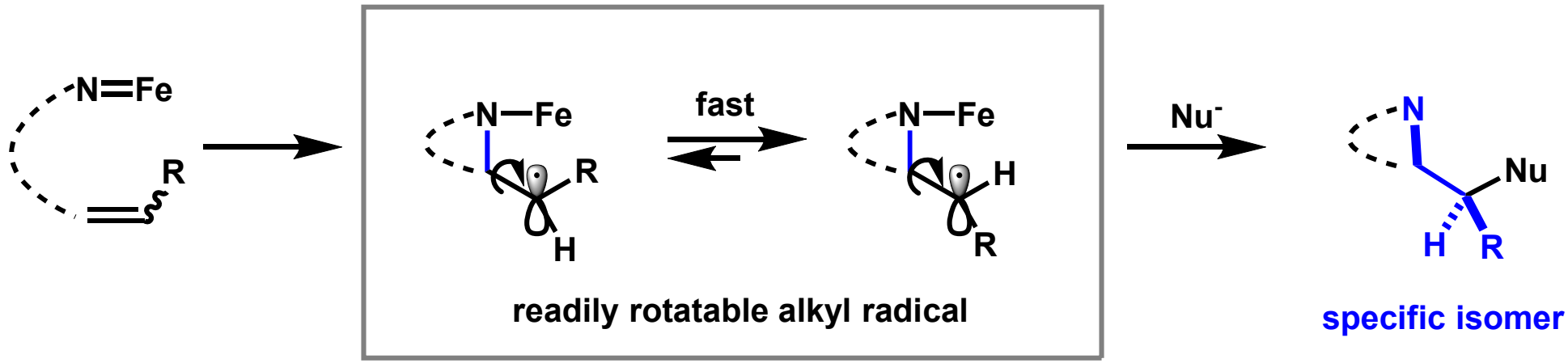


Olefin Difunctionalization via a Nitrenoid Transfer

- a powerful tool for forging versatilre aminated molecules with the installation of an additional functional group at the C=C bonds in a single operation.

Previous studies: *stereoconvergent* nitrene transfer to olefins (Bach, Xu)

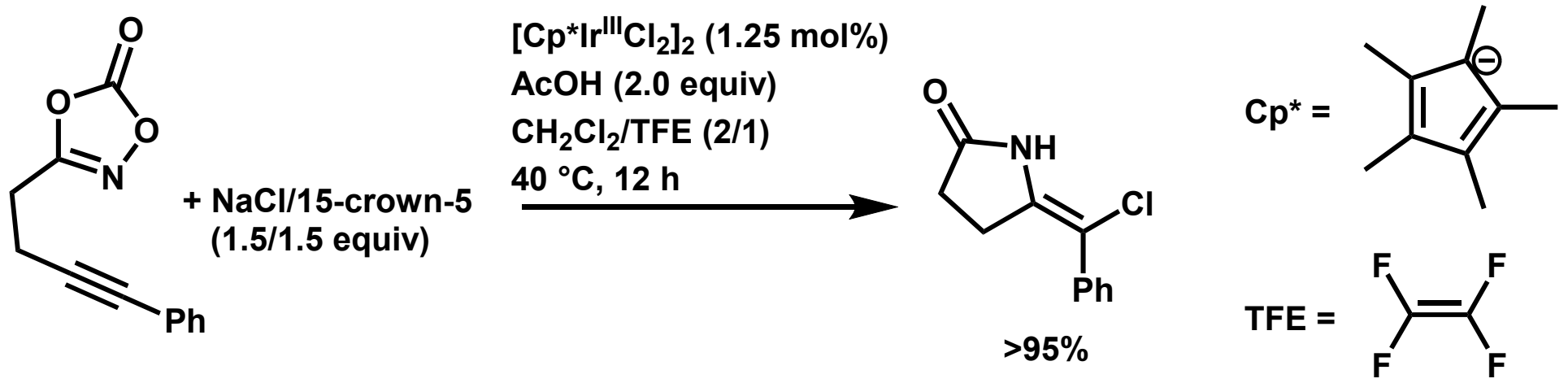




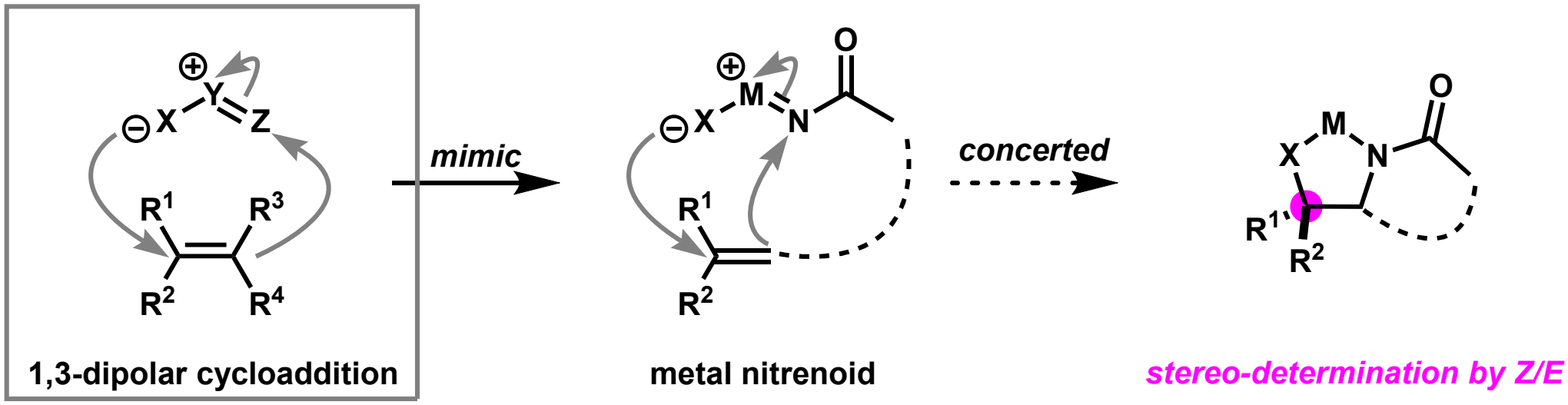
1. Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2019**, *141*, 10399. 2. (a) Kluegge, J.; Herdtweck, E.; Bach, T. *Synlett* **2004**, *2004*, 1199. (b) Liu, G. -S.; Zhang, Y. -Q.; Yuan, Y. -A.; Xu, H *J. Am. Chem. Soc.* **2013**, *135*, 3343.

Working Hypothesis

previous work: Ir(III)-Catalyzed Haloamidation of Alkynes Enabled by Ligand Partcipation

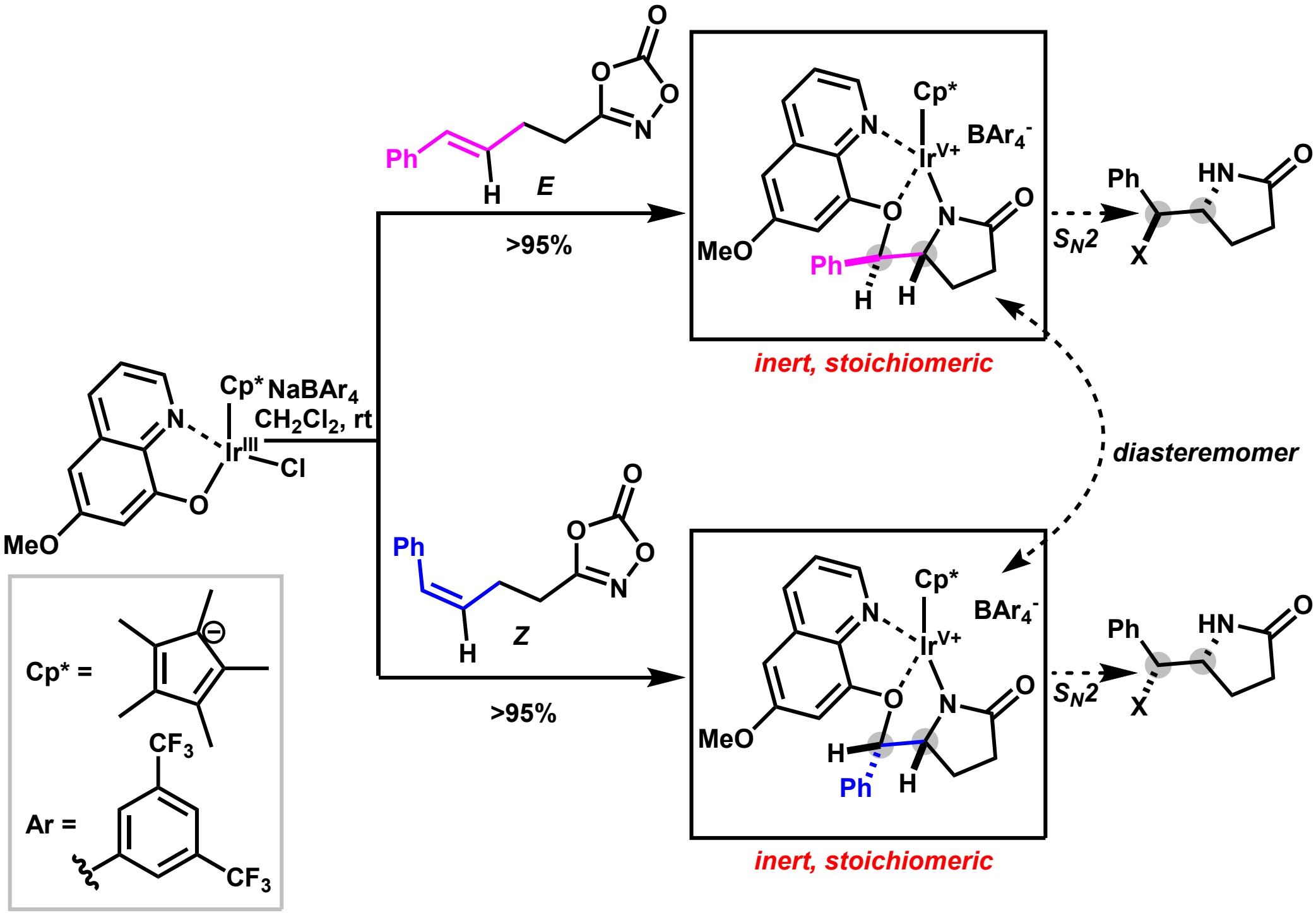


metal nitrenoids as a motif of 1,3-dipoles



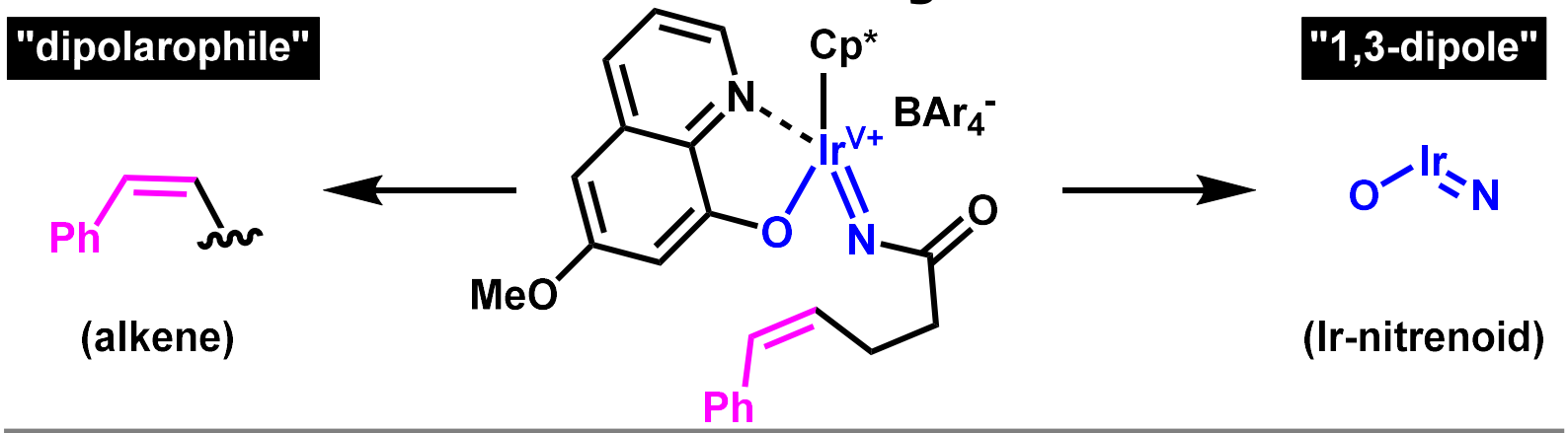
1. Hong, S. Y.; Son, J.; Kim, D.; Chang, S. *J. Am. Chem. Soc.* **2018**, *140*, 12359. 2. Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2019**, *141*, 10399.

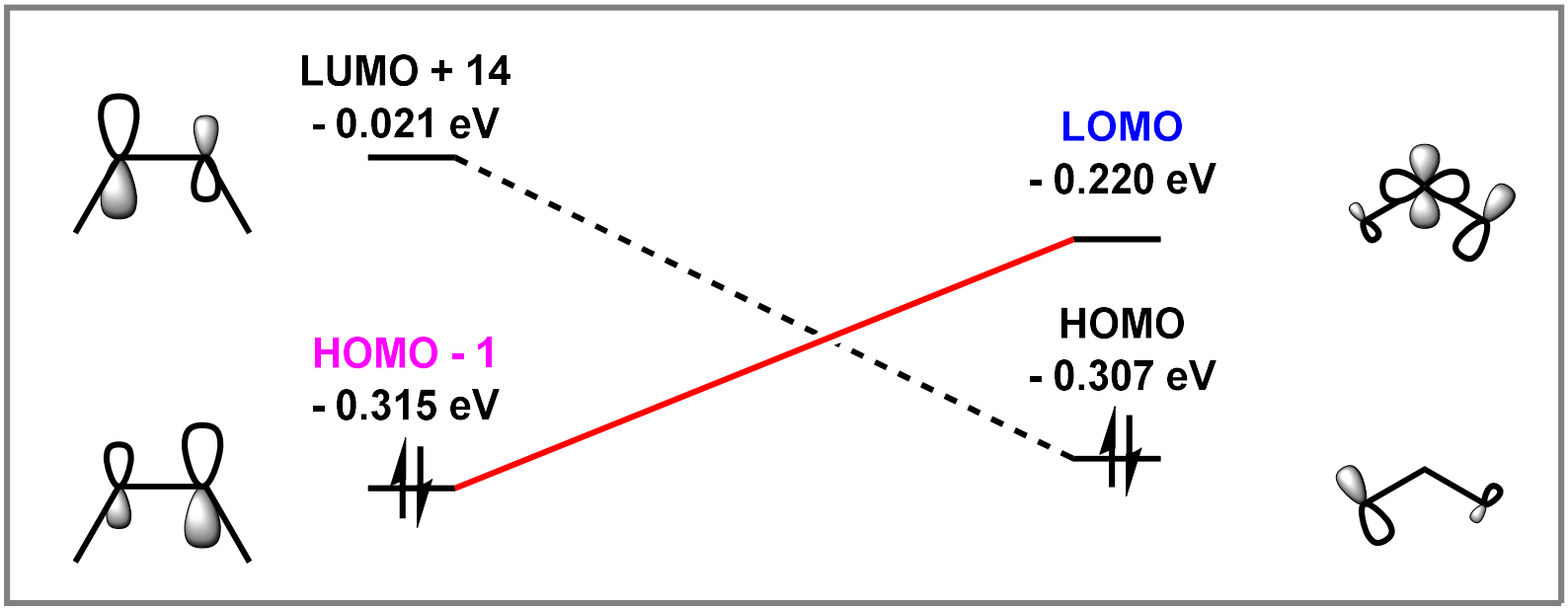
Stoichiometric Model Reactions

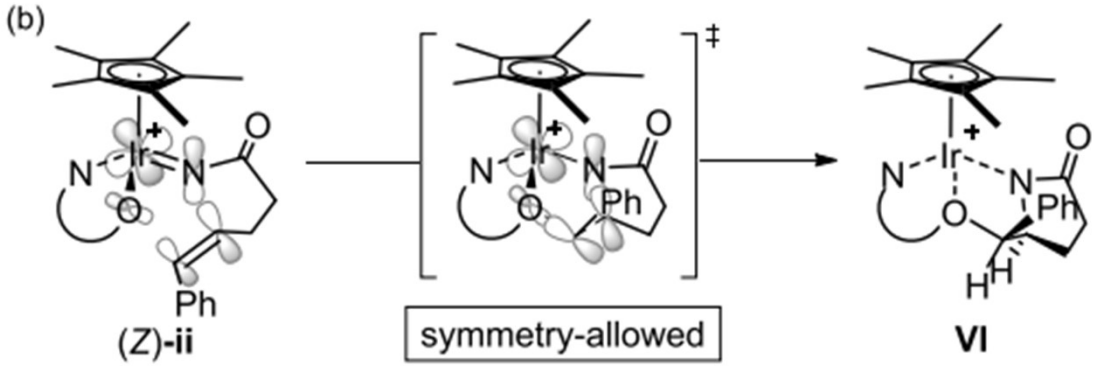


1. Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2019**, *141*, 10399.

FMO Analysis

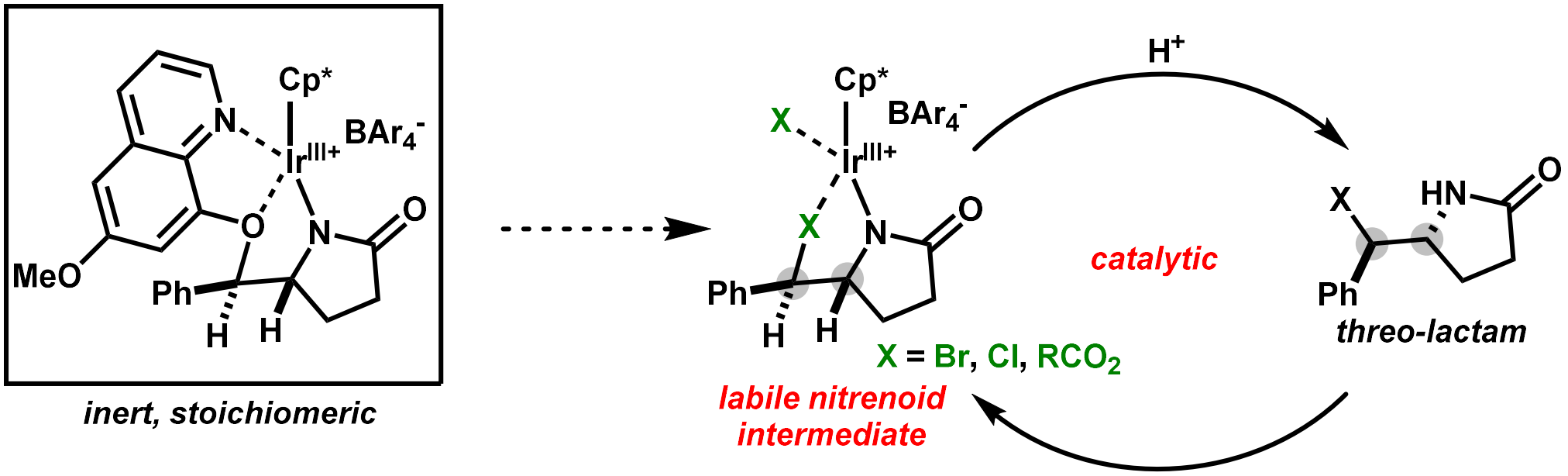






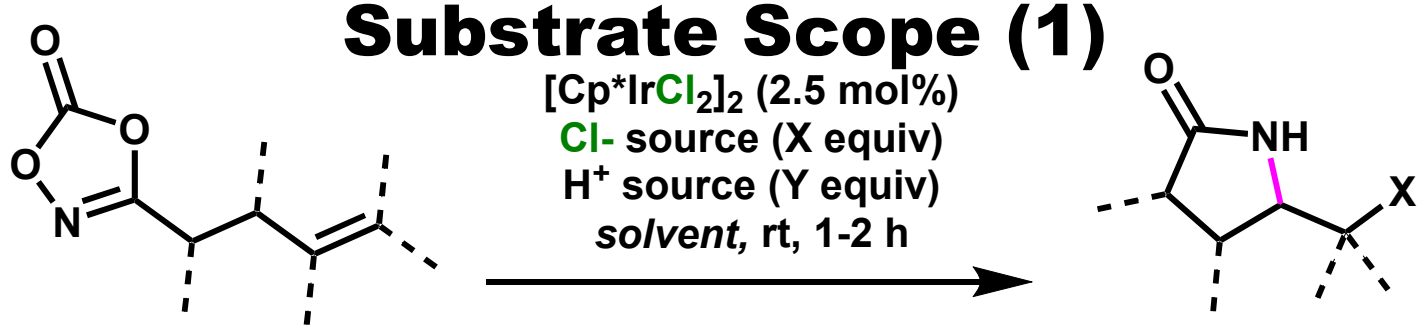
1. Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2019**, *141*, 10399.

Catalyst Design (1)

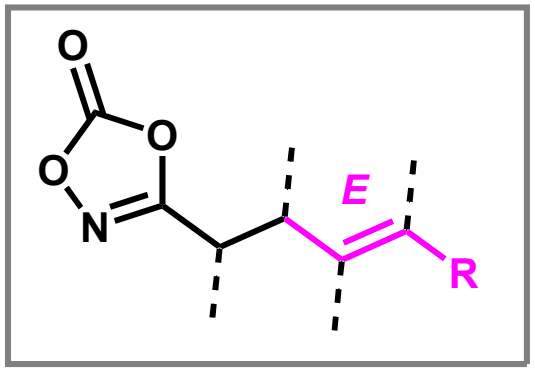


1. Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2019**, *141*, 10399.

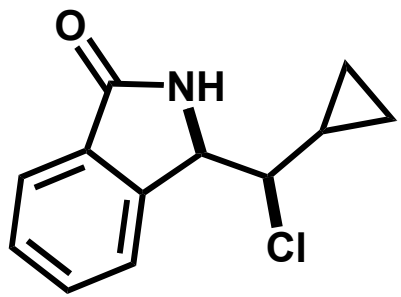
Substrate Scope (1)



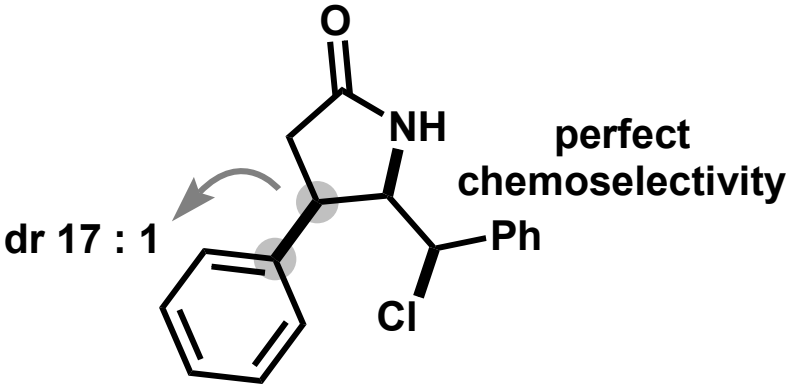
A slight erosion in deastereoselectivity was accompanied in these cases mainly due to the olefin isomerization induced by the acid.



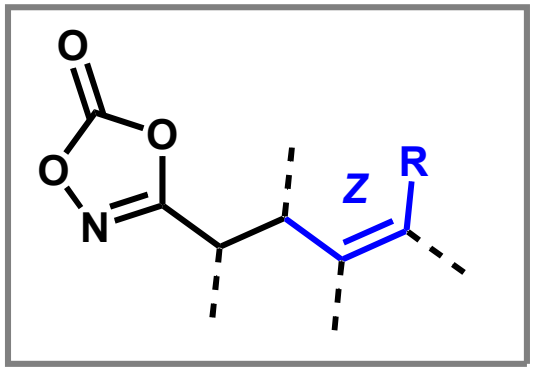
HCl (X =Y = 1.0)
CH_2Cl_2/TFE (1/1)



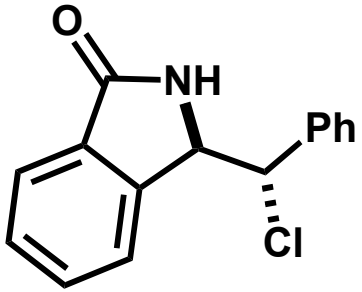
72%[b] (dr 9.1 : 1)



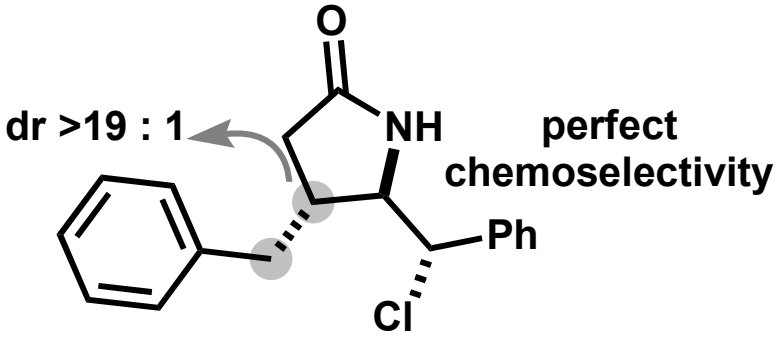
93% (dr >19 : 1)



NaCl/15-crown-5 (X = 1.5)
HOAc (Y = 2.0), HFIP



80% (dr 15 : 1)

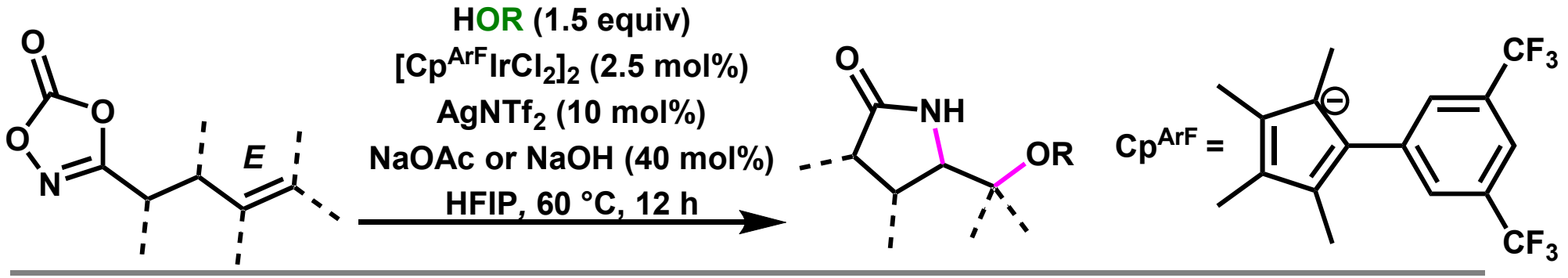


75% (dr >19 : 1)

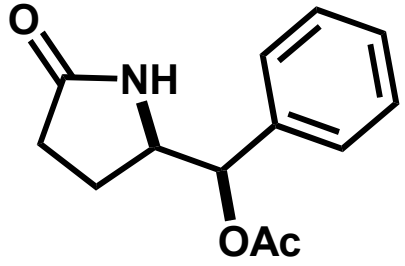
a) Ratio of diastereomers, determined by 1H NMR analysis of the crude reaction mixture.
b) 5 mol% of $[Cp^*Ir^{III}Cl_2]_2$ was used.

1. Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2019**, *141*, 10399.

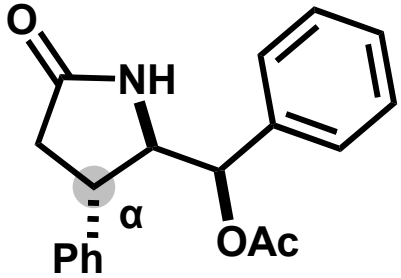
Substrate Scope (2)

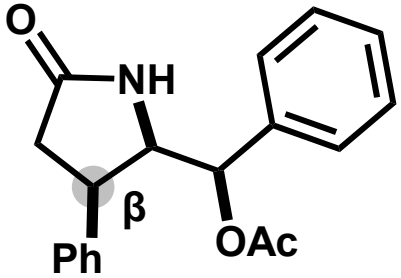


variation of dioxazolones



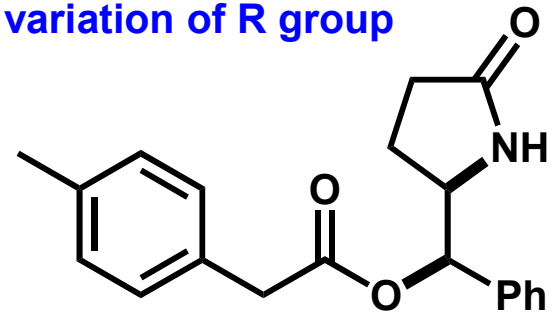
90% (dr >19 : 1)



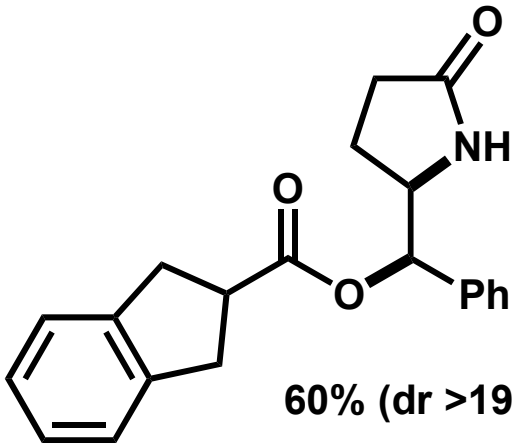


80% (α : β = 3 : 1, dr = >19 : 1)

variation of R group



55% (dr >19 : 1)



60% (dr >19 : 1)

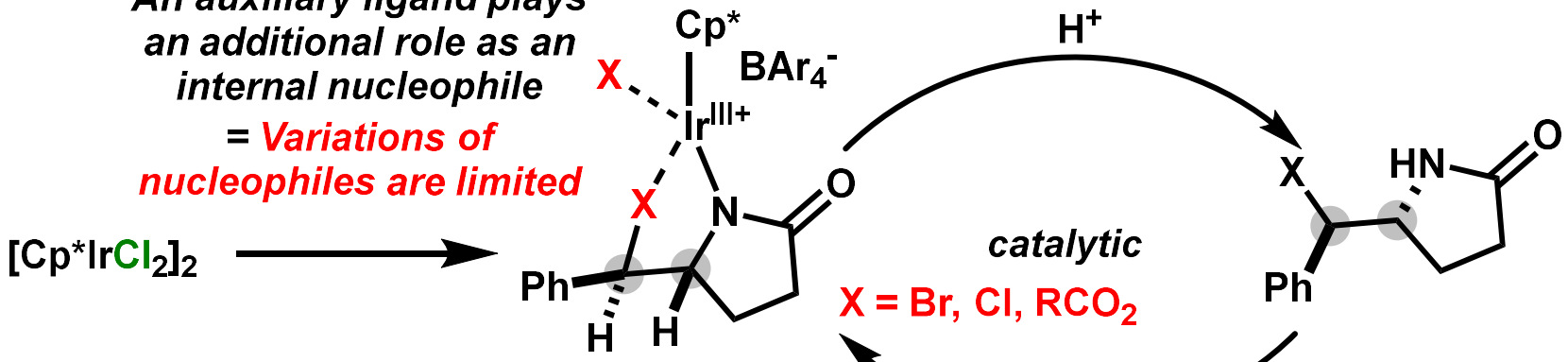
1. Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2019**, *141*, 10399.

Limitations and Solutions

limitations:

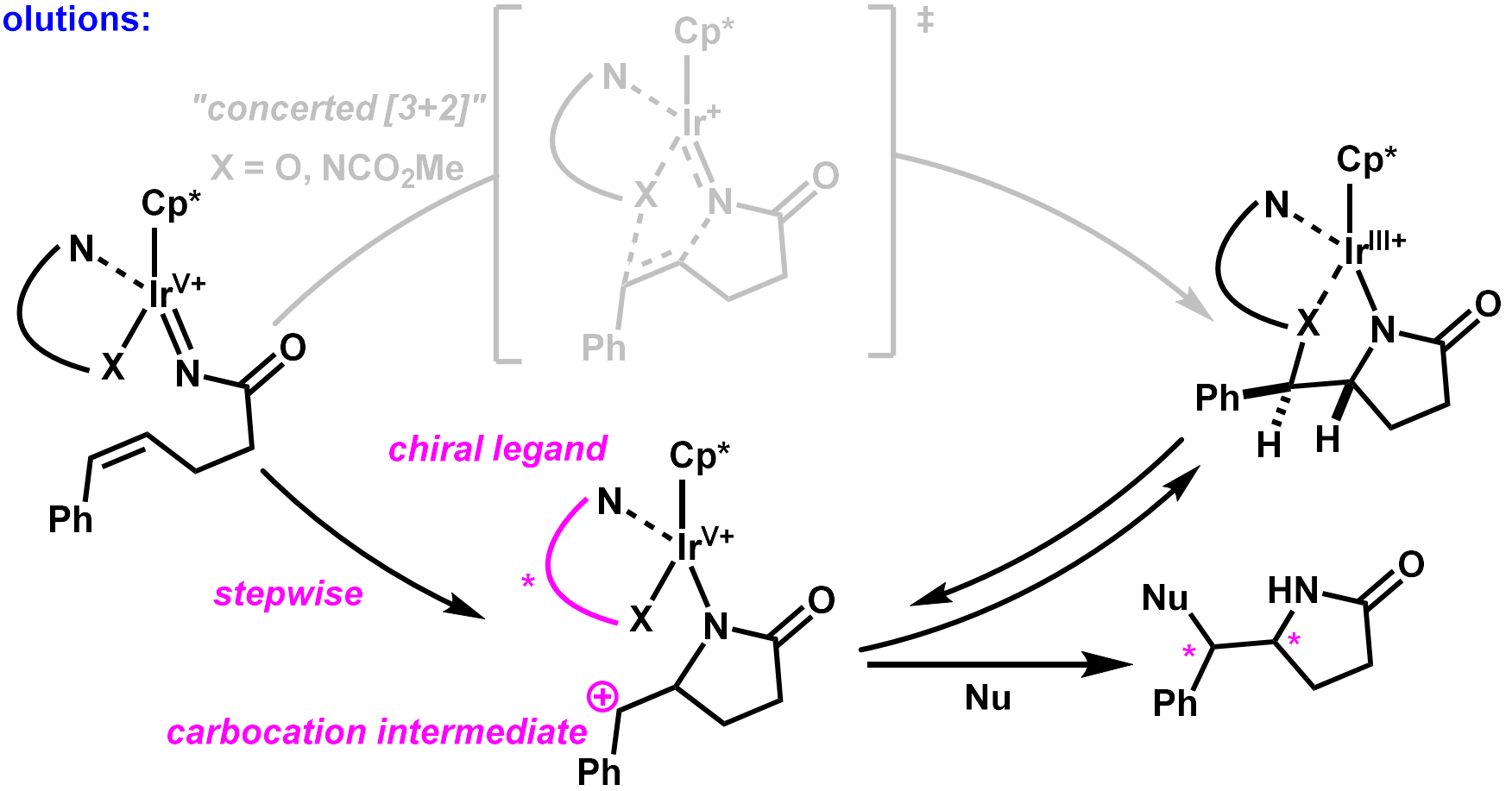
An auxiliary ligand plays an additional role as an internal nucleophile

= Variations of nucleophiles are limited



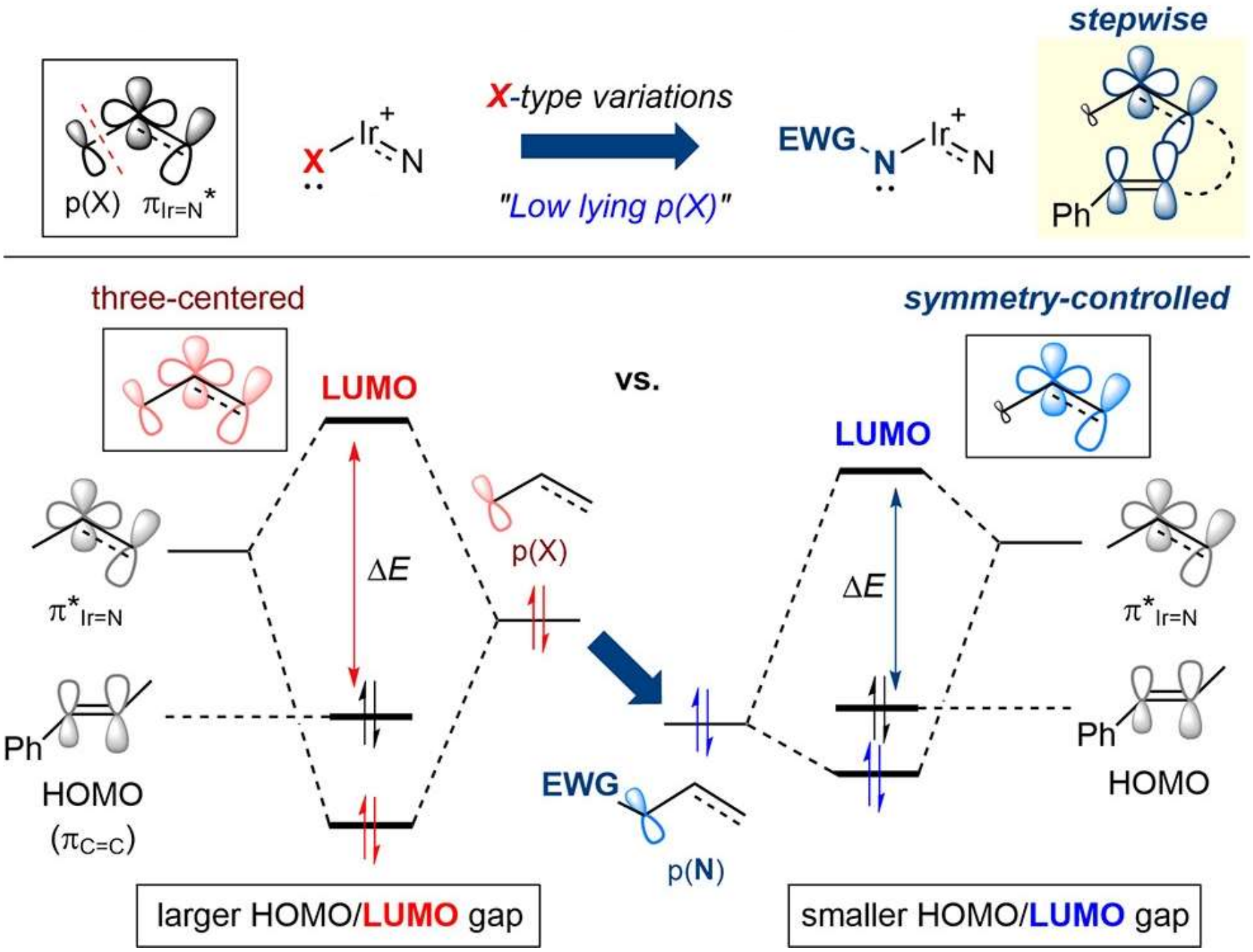
no enantioselectivities

solutions:



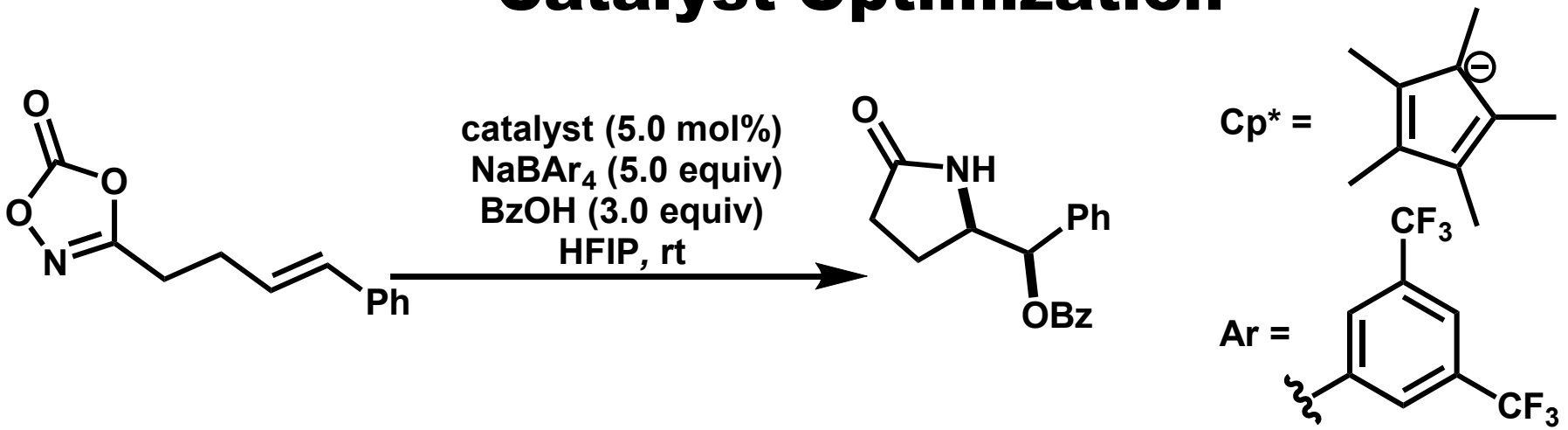
1. Kim, S.; Kim, D.; Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2021**, *143*, 3993.

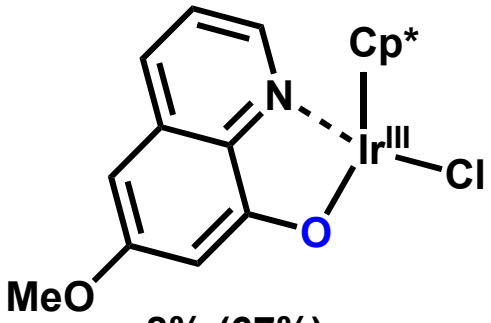
Catalyst Design (2): Electron-withdrawing Group



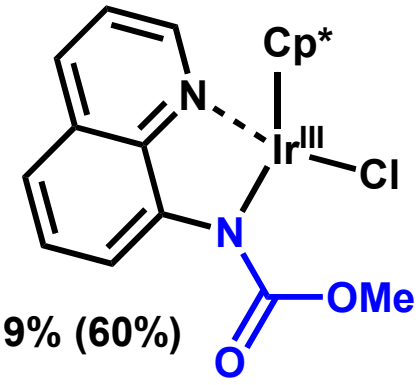
1. Kim, S.; Kim, D.; Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2021**, *143*, 3993.

Catalyst Optimization

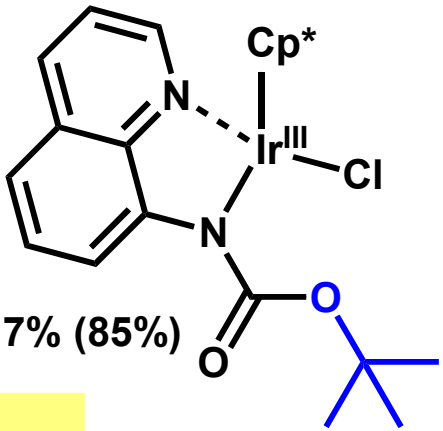




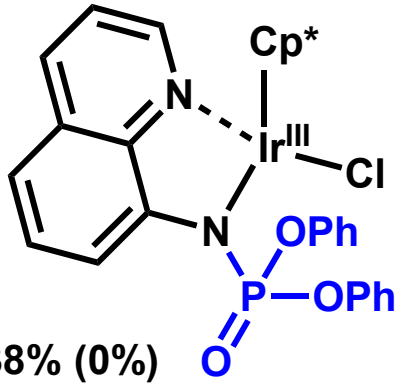
8% (67%)



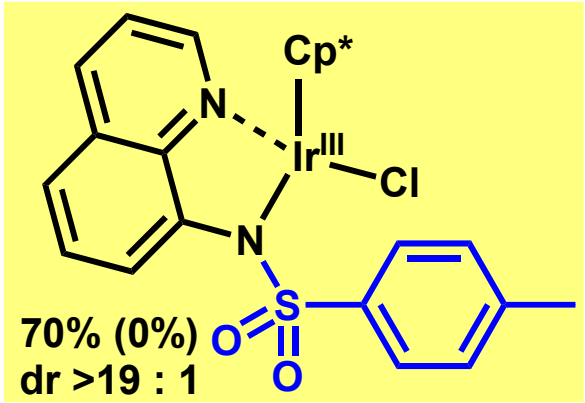
9% (60%)



7% (85%)



38% (0%)

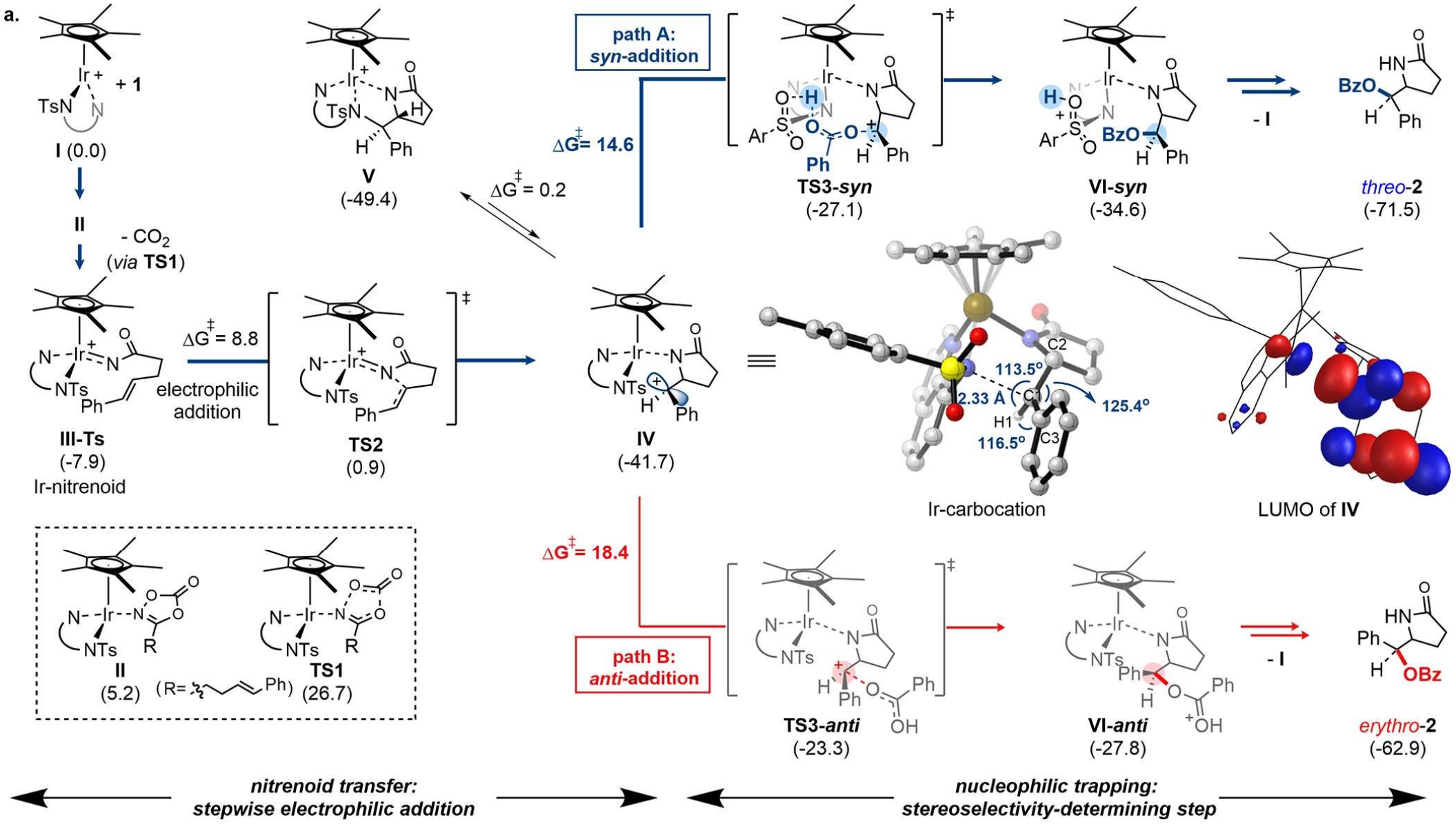


70% (0%)
dr >19 : 1

Yields were based on a ^{1}H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard.

1. Kim, S.; Kim, D.; Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2021**, *143*, 3993.

Computational Modeling

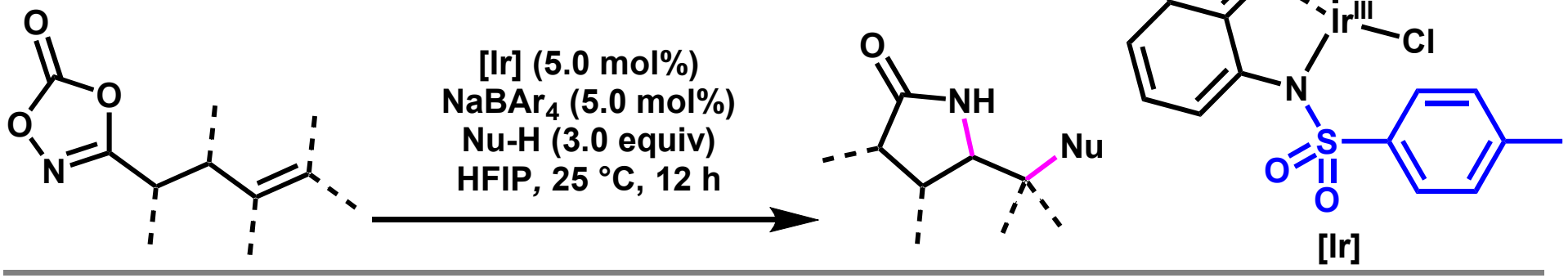


PCM(HFIP)-M06/SDD+6+6-311++G//M06/Lanl2dz+6-31G****

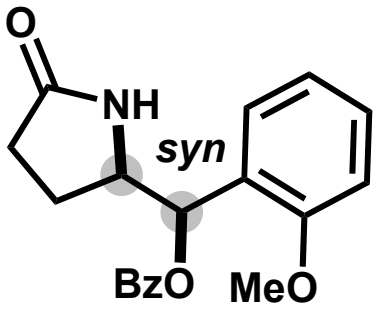
A hydrogen bond between a sulfonyl oxygen atom of the catalyst and an O-H hydrogen of benzoic acid plays an important role for determing a diastereoselectivity.

1. Kim, S.; Kim, D.; Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2021**, *143*, 3993.

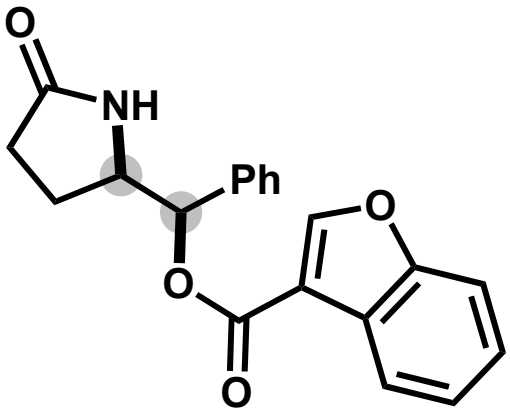
Substrate Scope (3)



from (*E*)-olefins

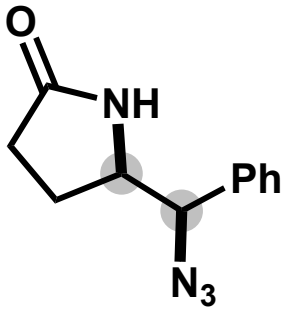


83% (dr 16 : 1)



68% (dr 16 : 1)

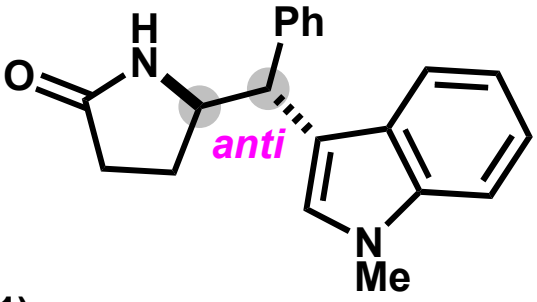
other nucleophiles



75%[a,b] (dr >19 : 1)

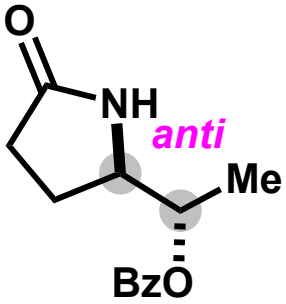
$TMSN_3$ (1.0 equiv)

no hydrogen bond



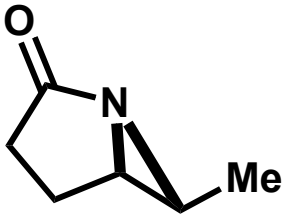
57%[b] (dr 16 : 1)

carbocation without resonance stabilization

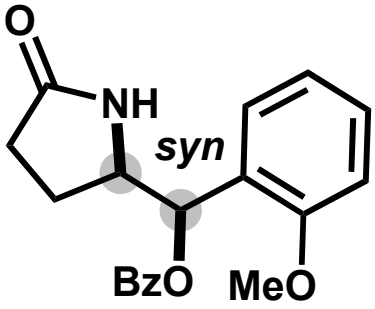


60%[c] (dr >19 : 1)

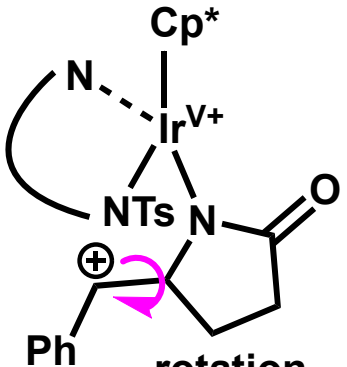
via aziridine



from (*Z*)-olefins



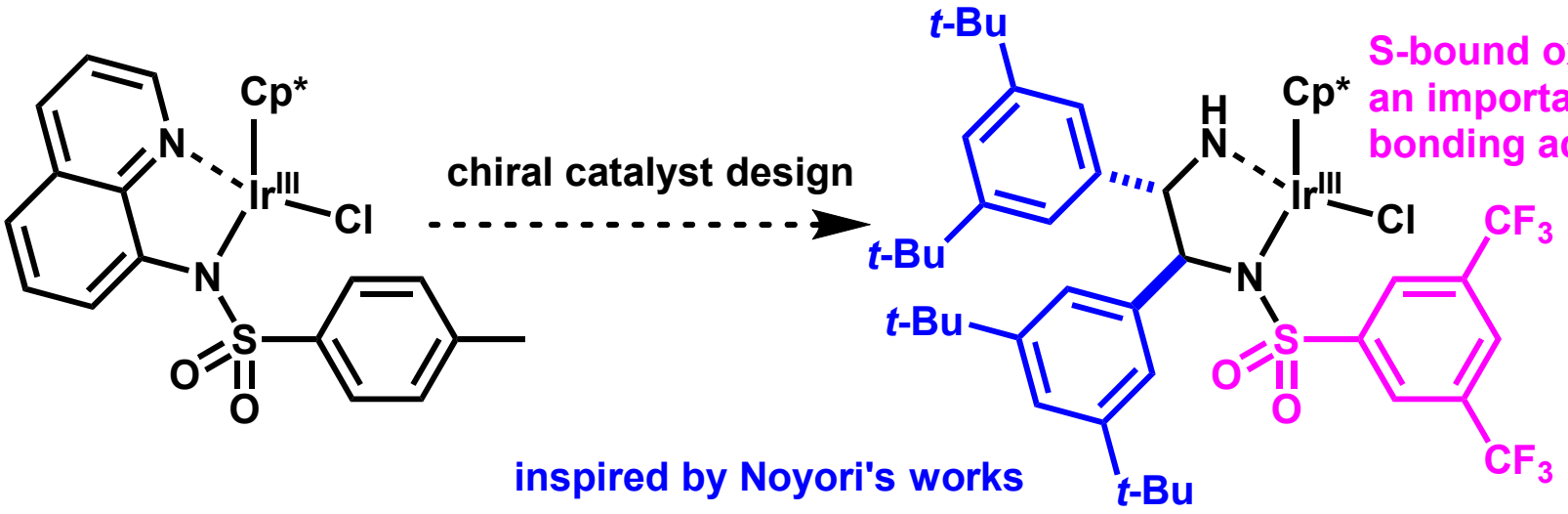
40%[a,b,c] (dr 2.3 : 1)



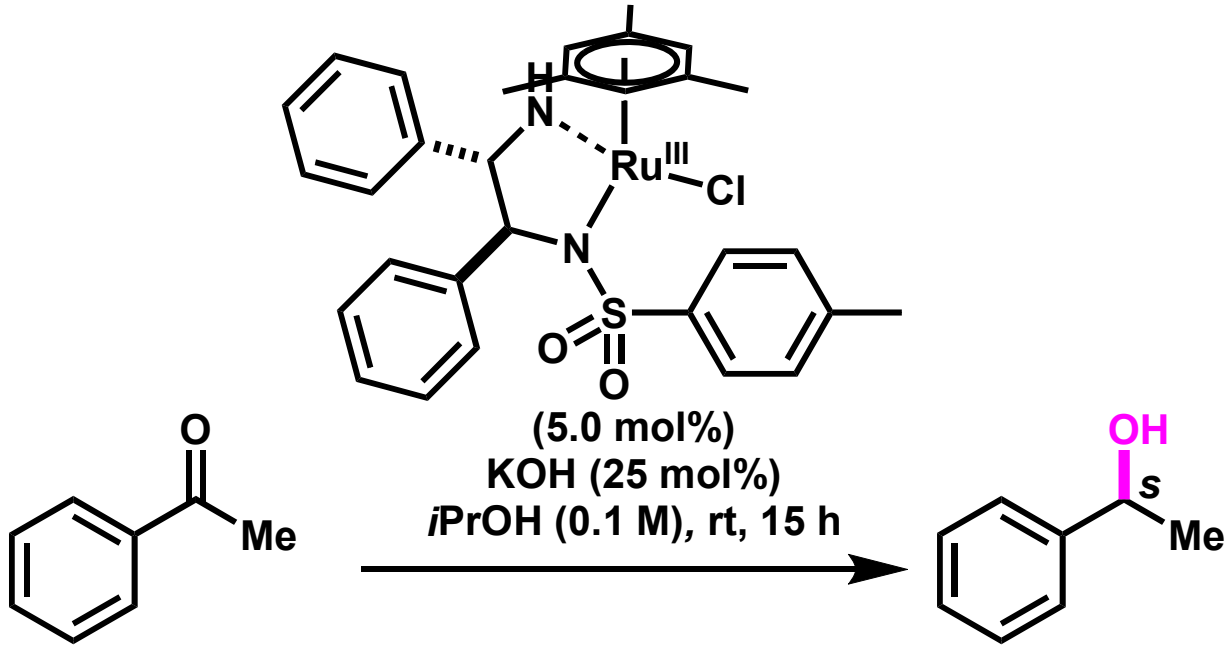
a) [Ir] (10 mol%) and $NaBAr_4$ (10 mol%) were used. b) NFTB solvent was used. c) Run at 60 °C.

1. Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2019**, *141*, 10399.

Development of Asymmetric Oxyamidation

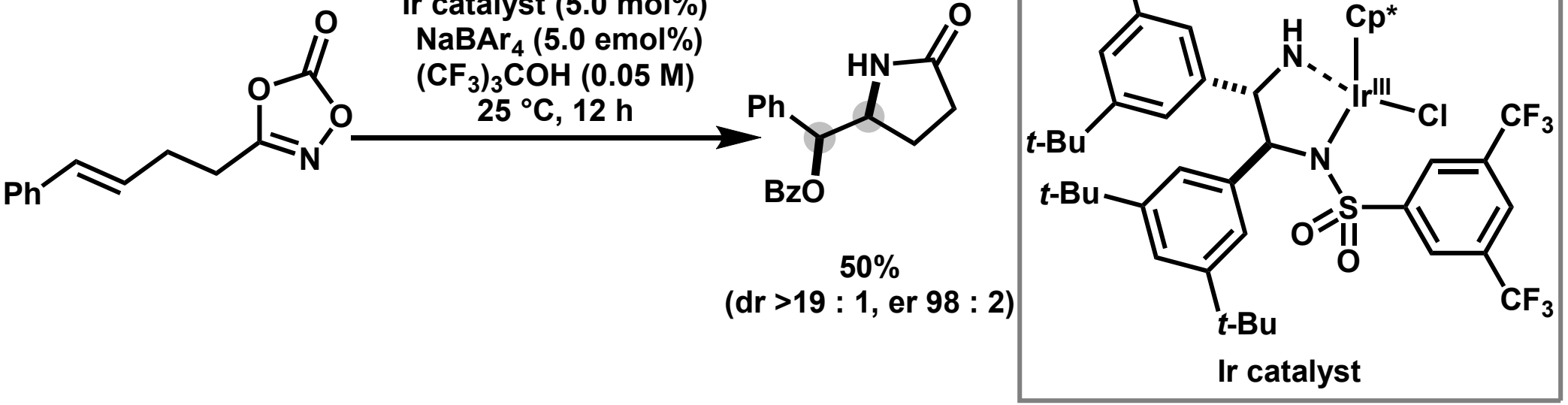


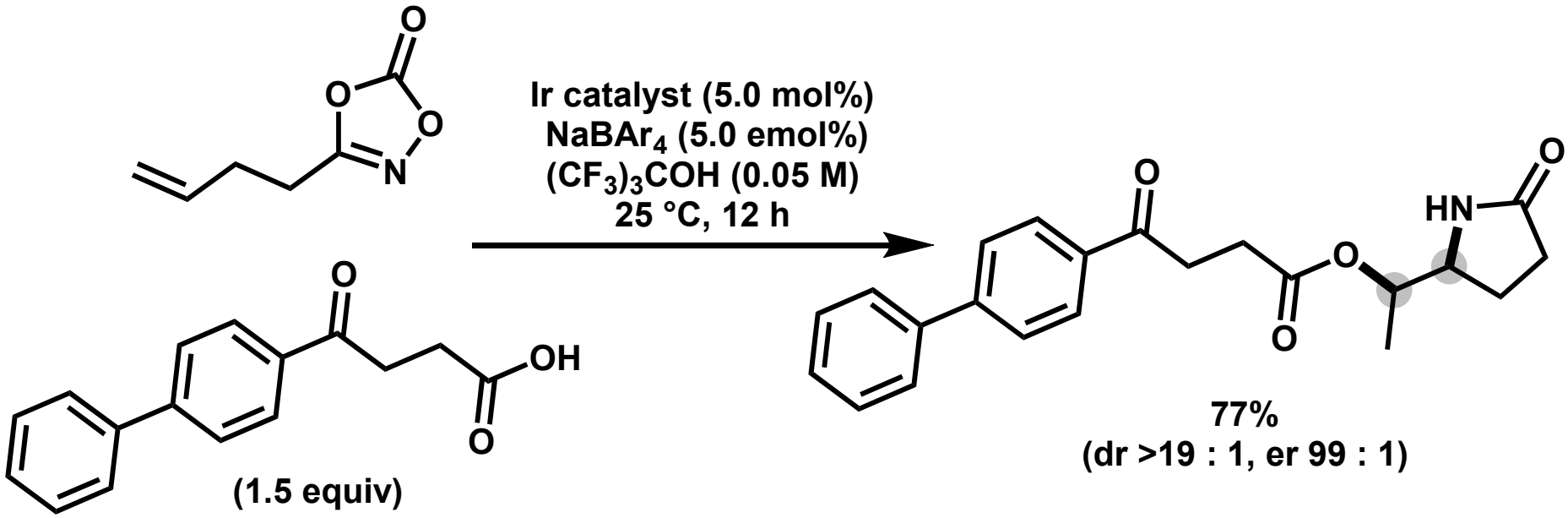
Asymmetric hydrogenation reaction by the Noyori group[2]



1. Kim, S.; Kim, D.; Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2021**, *143*, 3993.
2. Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562.

Substrate Scope (4)

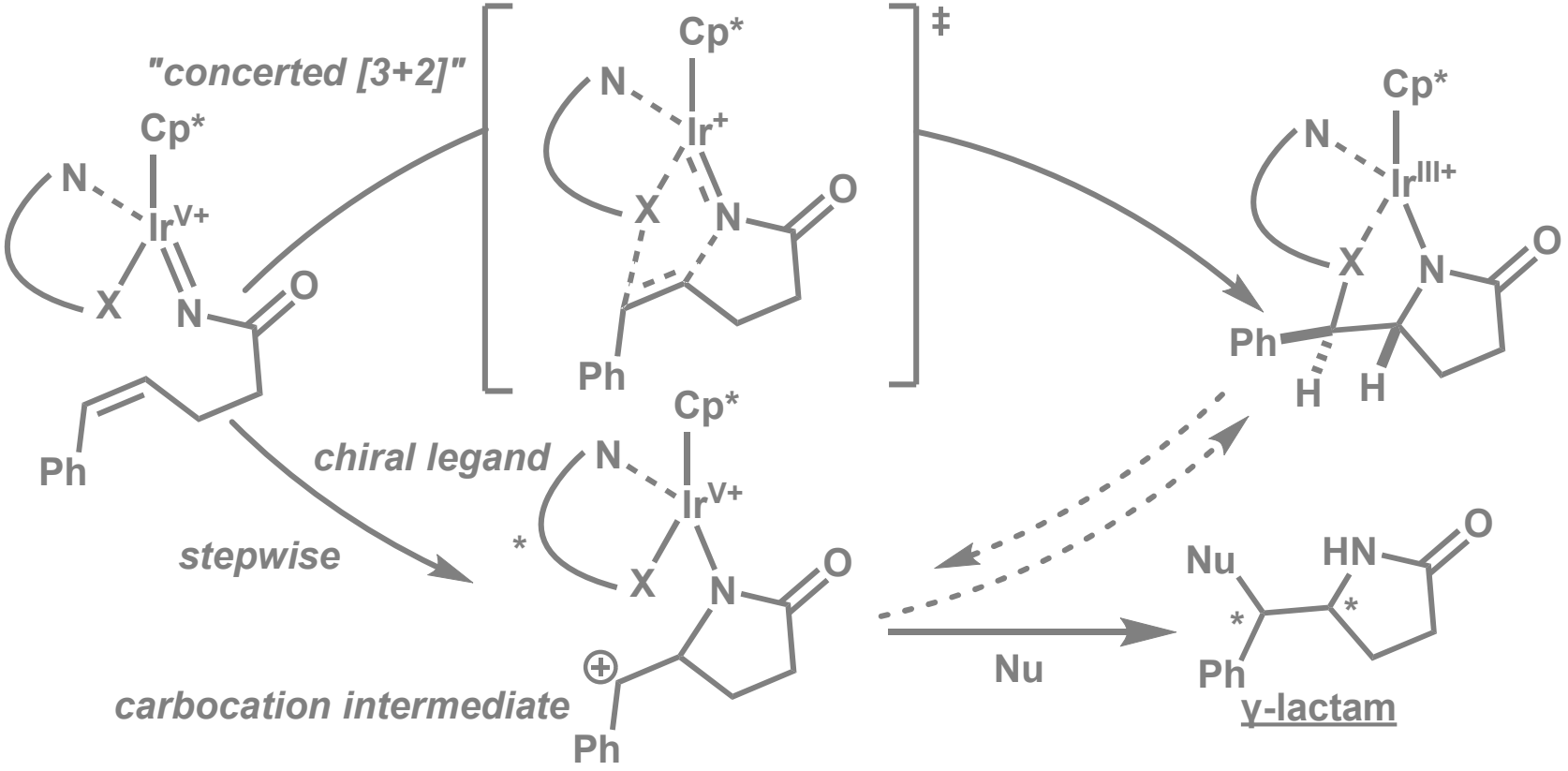




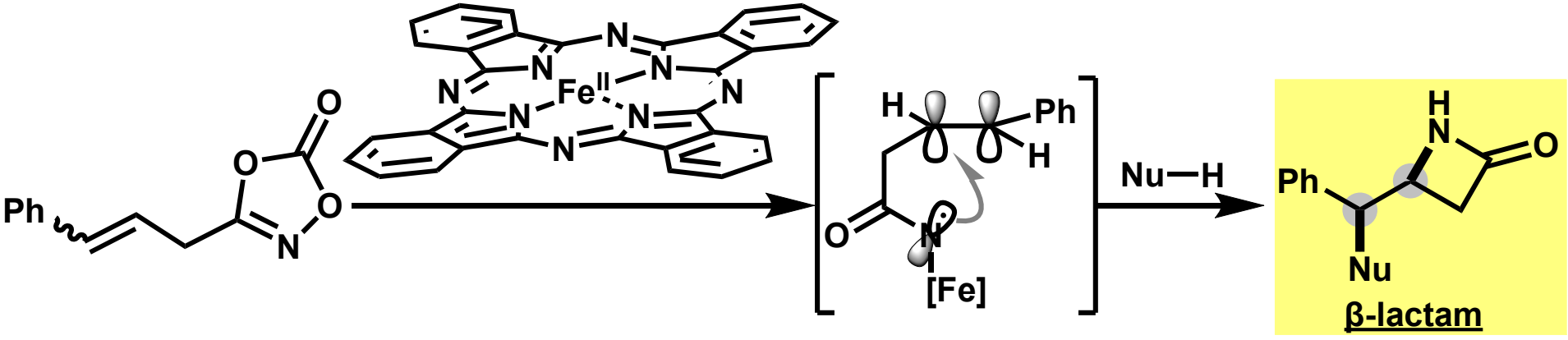
1. Kim, S.; Kim, D.; Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2021**, *143*, 3993.

Contents

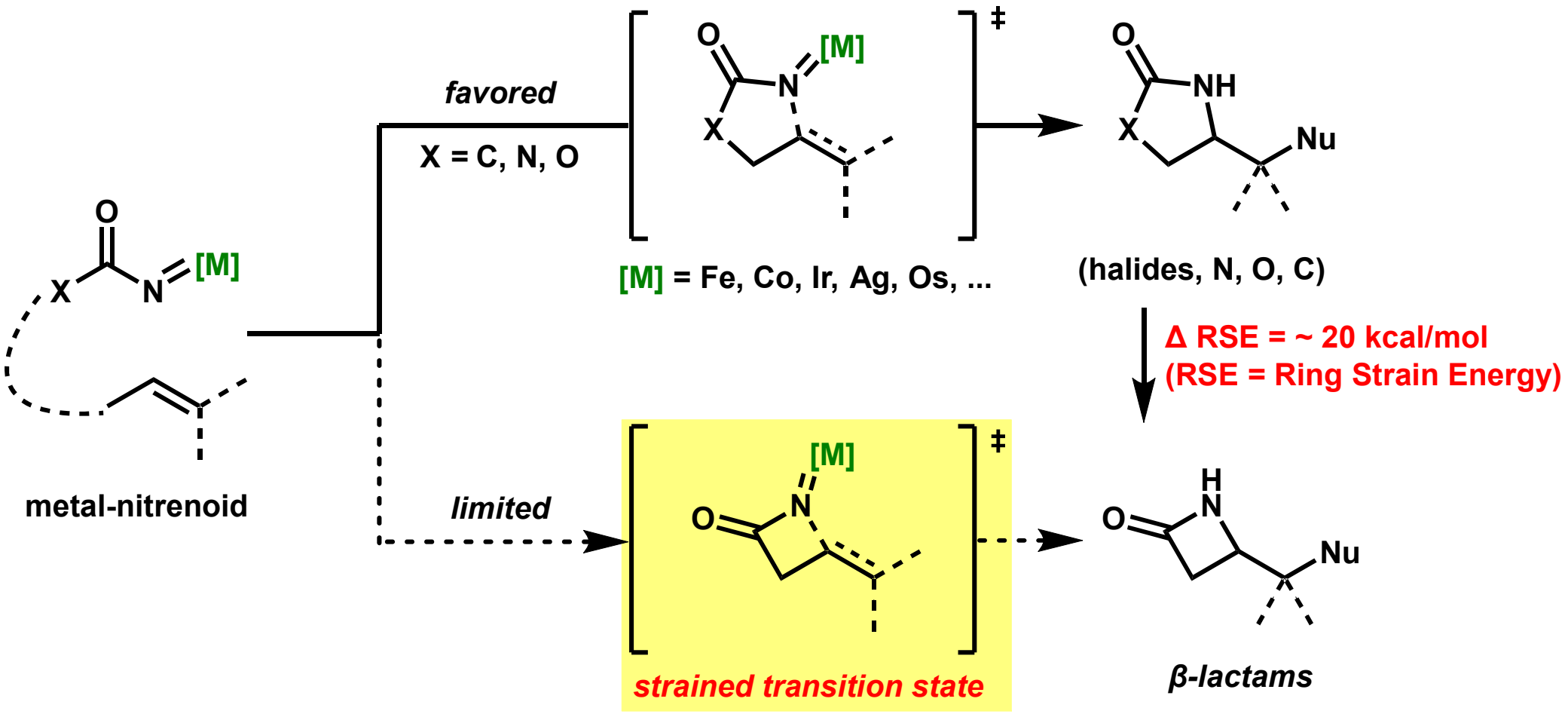
1. Introduction (An Alternative to Acyl Azides)
2. Stereodefined Access to γ-Lactams via Olefin Difunctionalization



3. Access to β-Lactams via Iron-Catalyzed Olefin Oxyamidation Enabled by the π- Accepting Phthalocyanine Ligand (Main Paper) (*J. Am. Chem. Soc.* 2022, *144*, 1872)



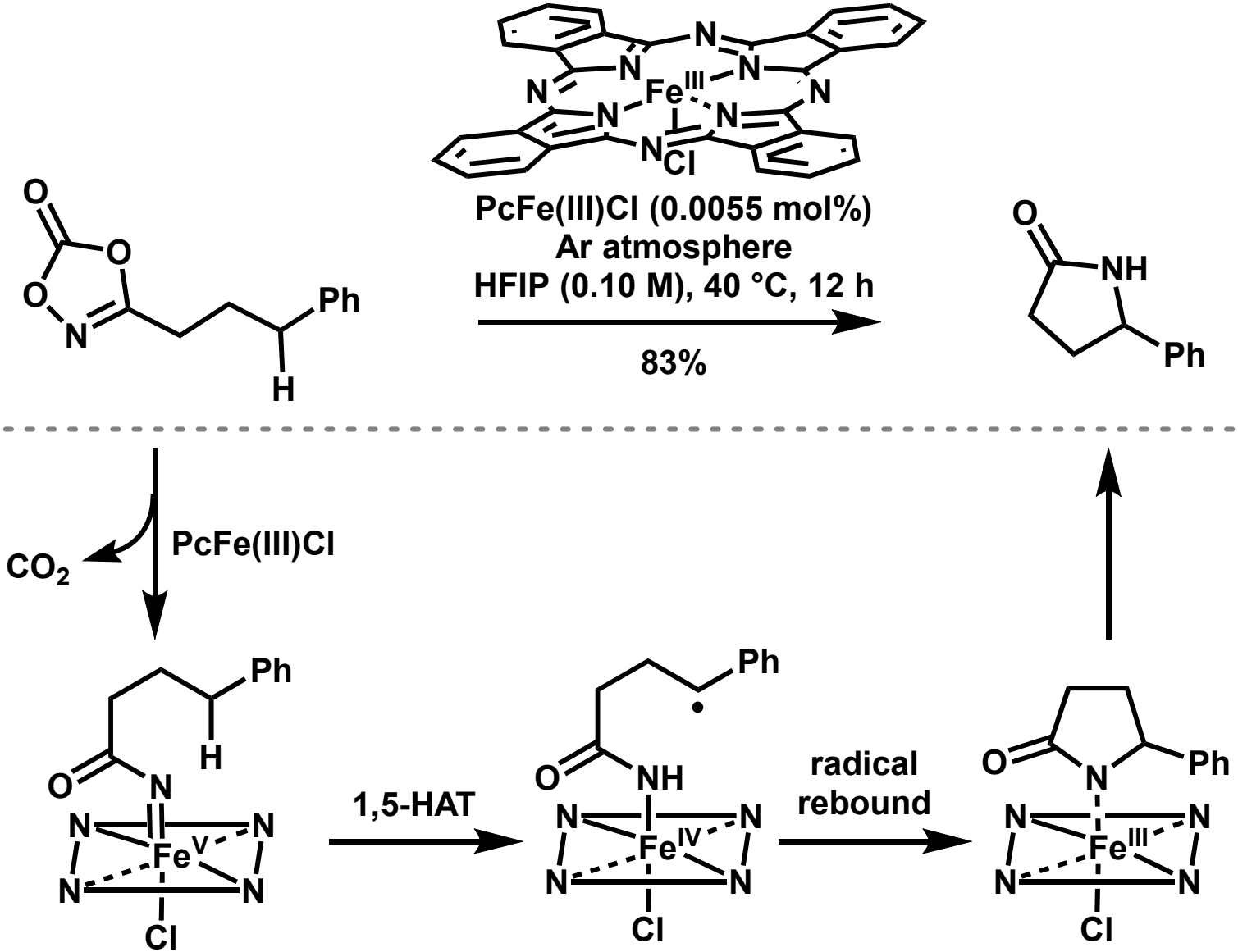
Access to β-Lactams via Metal-Catalyzed Olefin Difunctionalization Approaches



→How to realize this challenging conversion?

Kweon, J.; Kim, D.; Kang, S.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 1872.

Iron Catalyst System for Intramolecular C-H Amidation

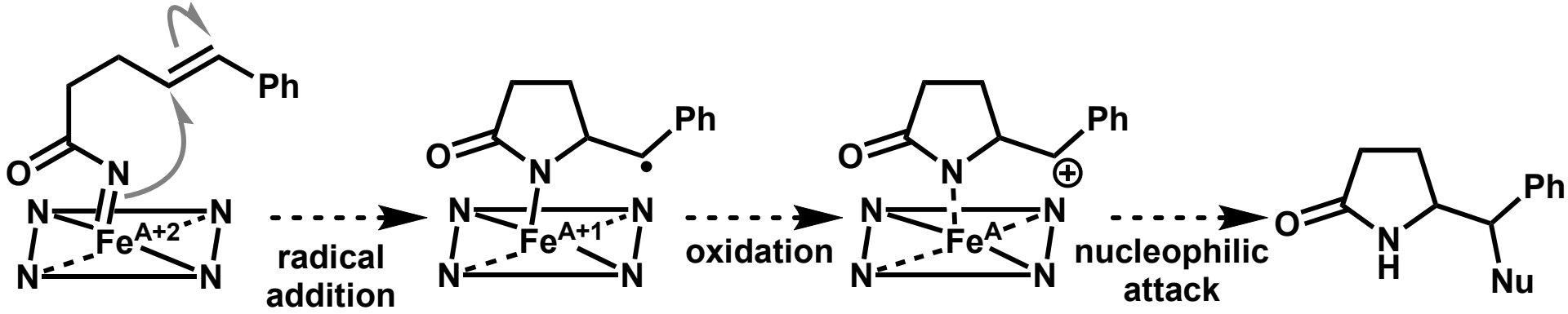


→**Radical reaction is a powerful tool to construct C-C bonds.**

Kweon, J.; Chang, S. *Angew. Chem. Int. Ed.* **2021**, *60*, 2909.

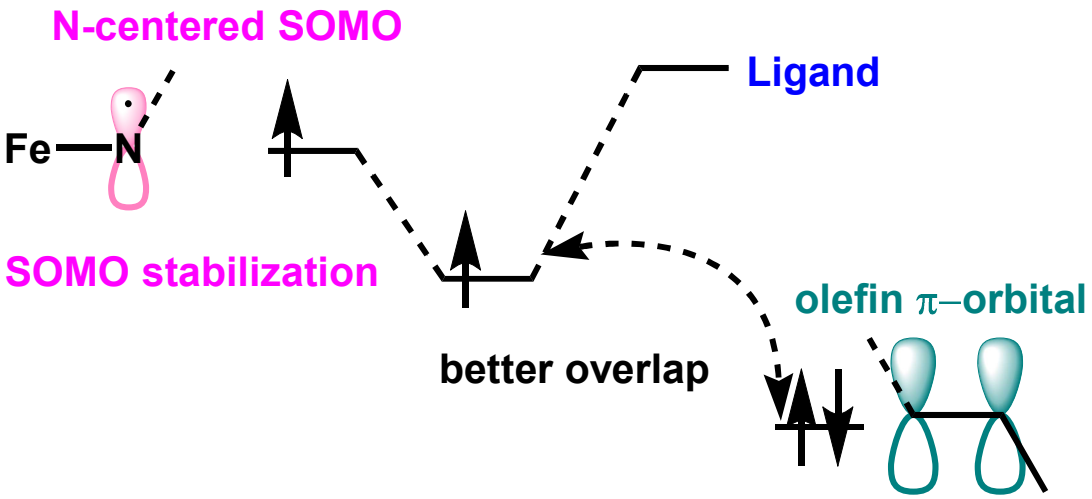
The Strategy for Olefin Oxiamidation

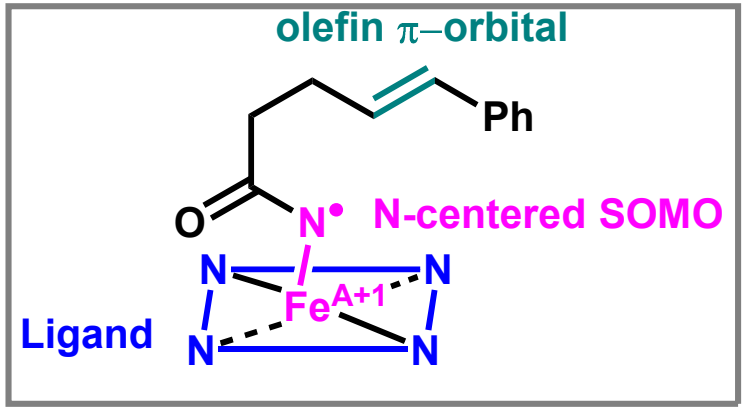
1. Powerful radical reaction → Fe catalyst
2. The formation of a carbocation intermidiate → The oxidation by Fe catalyst



A = III or II

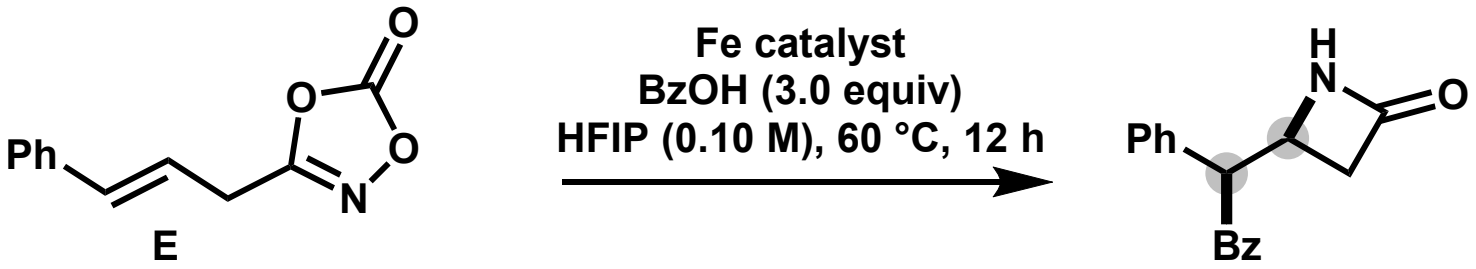
3. Potent π–accepting abilities of ligands enhance orbital interactions between the N-centered SOMO and the olefin π–orbital.



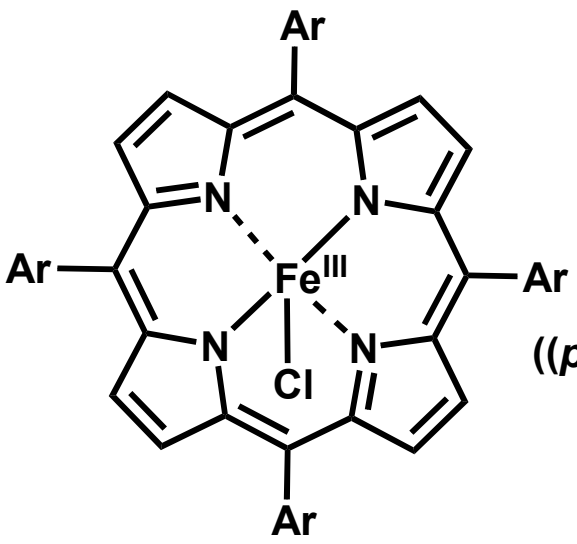


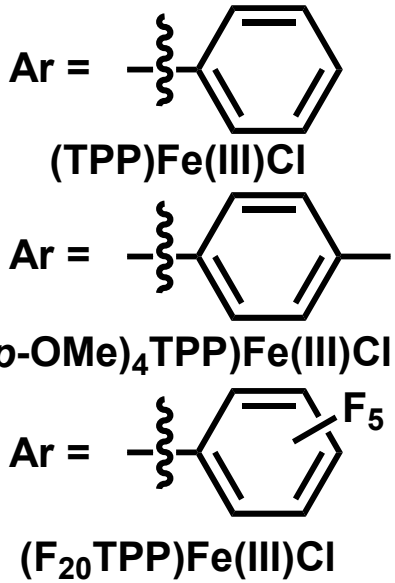
Kweon, J.; Kim, D.; Kang, S.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 1872.

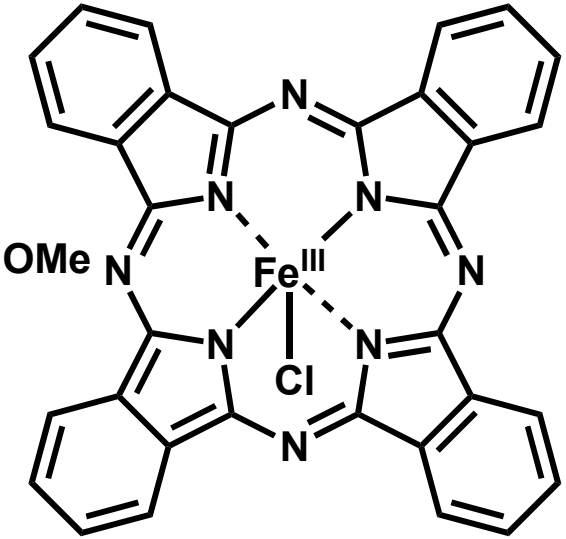
Reaction Optimization



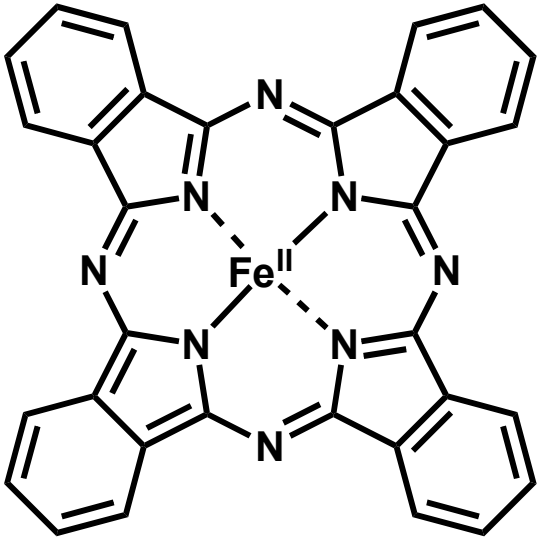
entry	*Fe catalyst* (mol%)	conv. (%)	yield (%)	d.r.
1	$FeCl_2$ (10)	72	N.D.	
2	(TPP)Fe(III)Cl (5.0)	37	11	4:1
3	((*p*-OMe)$_4$TPP)Fe(III)Cl (5.0)	37	9	5:1
4	(F_{20}TPP)Fe(III)Cl (5.0)	40	13	5:1
5	PcFe(III)Cl (1.0)	>95	70	10:1
6	PcFe(II) (1.0)	>95	77	10:1







PcFe(III)Cl

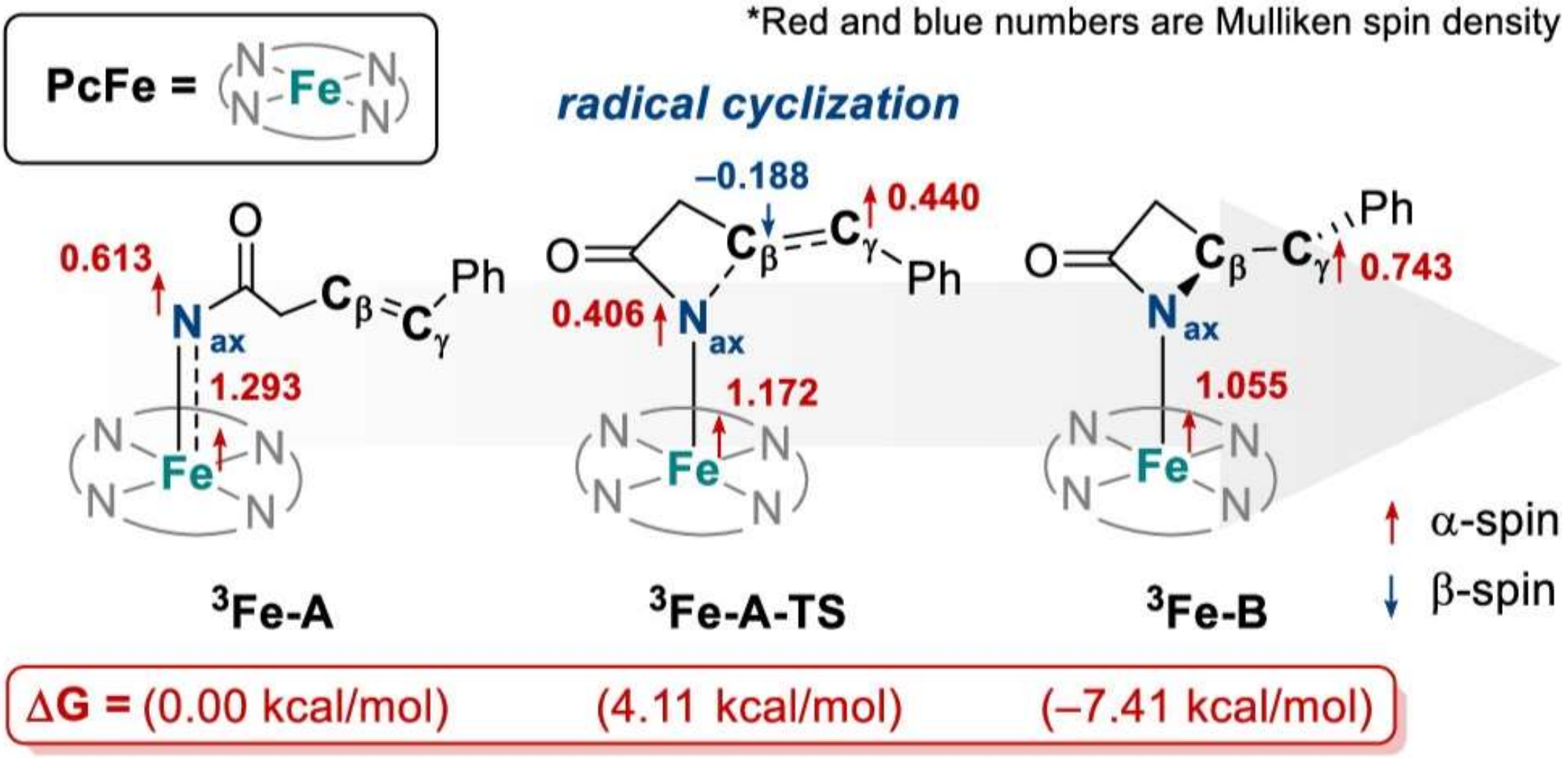


PcFe(II)Cl

Kweon, J.; Kim, D.; Kang, S.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 1872.

Mechanistic Investigations (1)

DFT calculation for PcFe-catalyzed *4-exo-trig*-cyclization

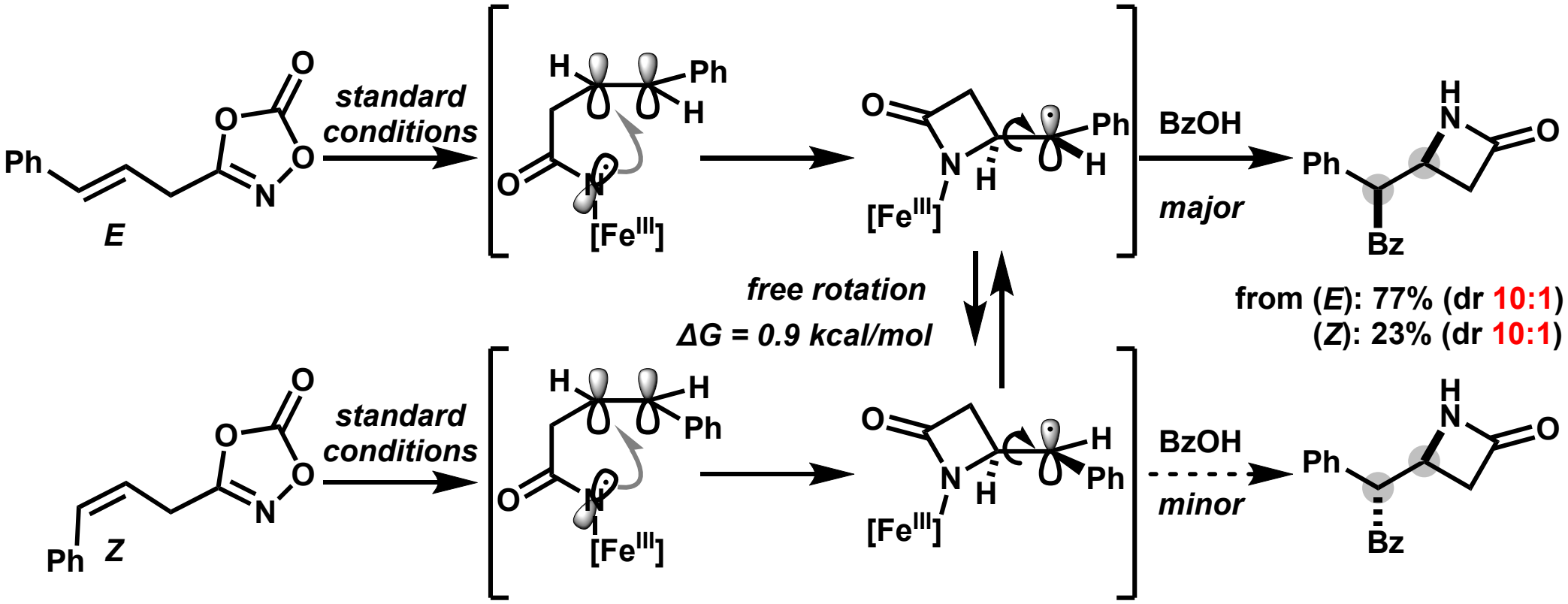


***Mulliken spin density provides a means of estimating partial atomic charges from calculations carried out by the methods of computational chemistry.**

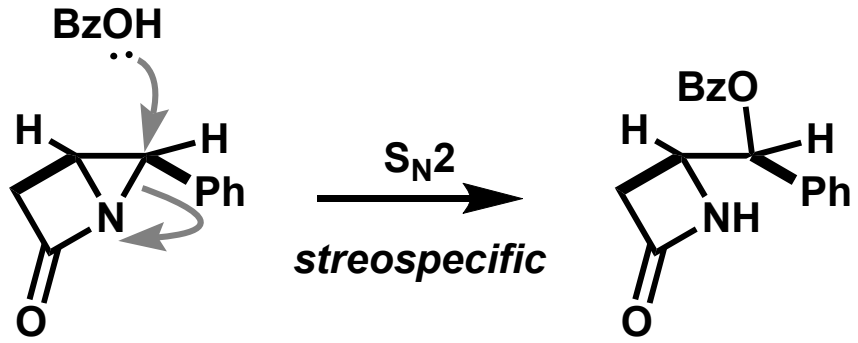
Kweon, J.; Kim, D.; Kang, S.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 1872.

Mechanistic Investigations (2)

Stereoconvergent lactamization

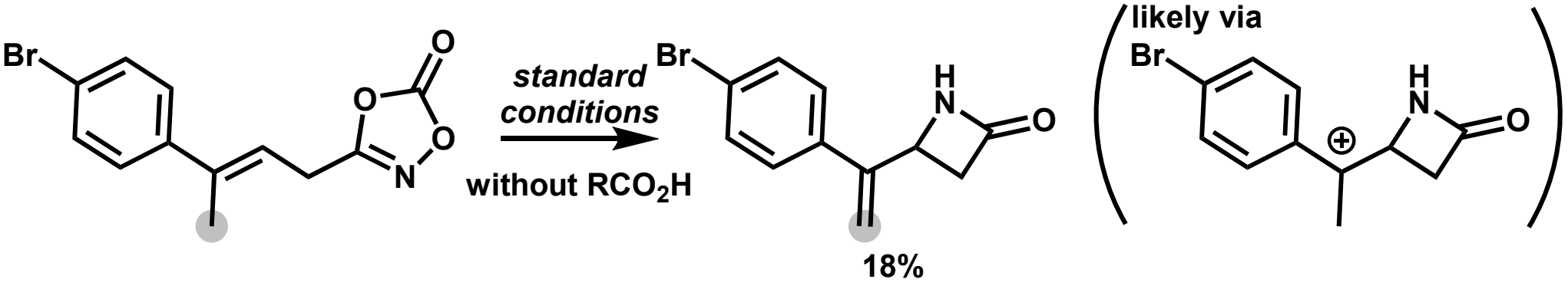


Two-step aziridination/ring-opening mechanism could be ruled out in the present oxyamidation, where the reaction would instead be stereospecific to the olefin geometry.



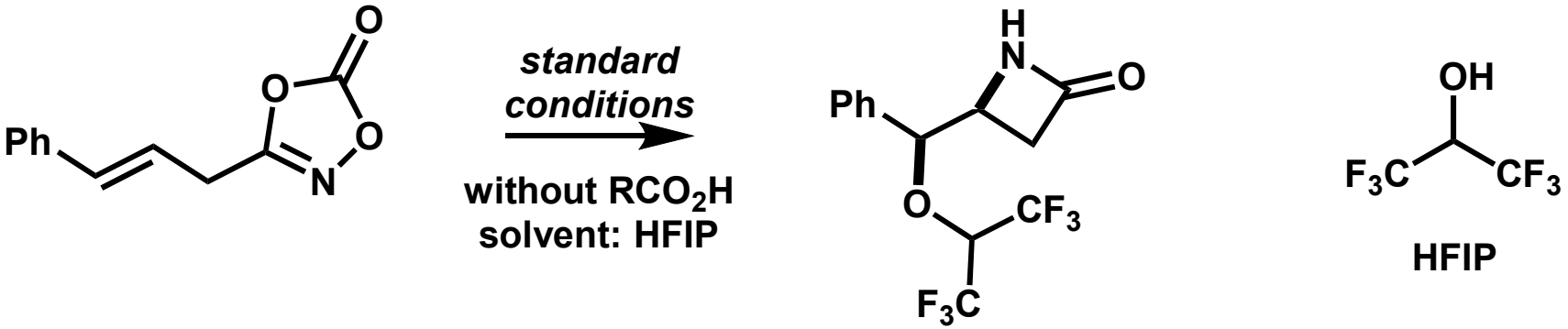
Mechanistic Investigations (3)

Allylic β-lactam formation



18%

Solvolysis

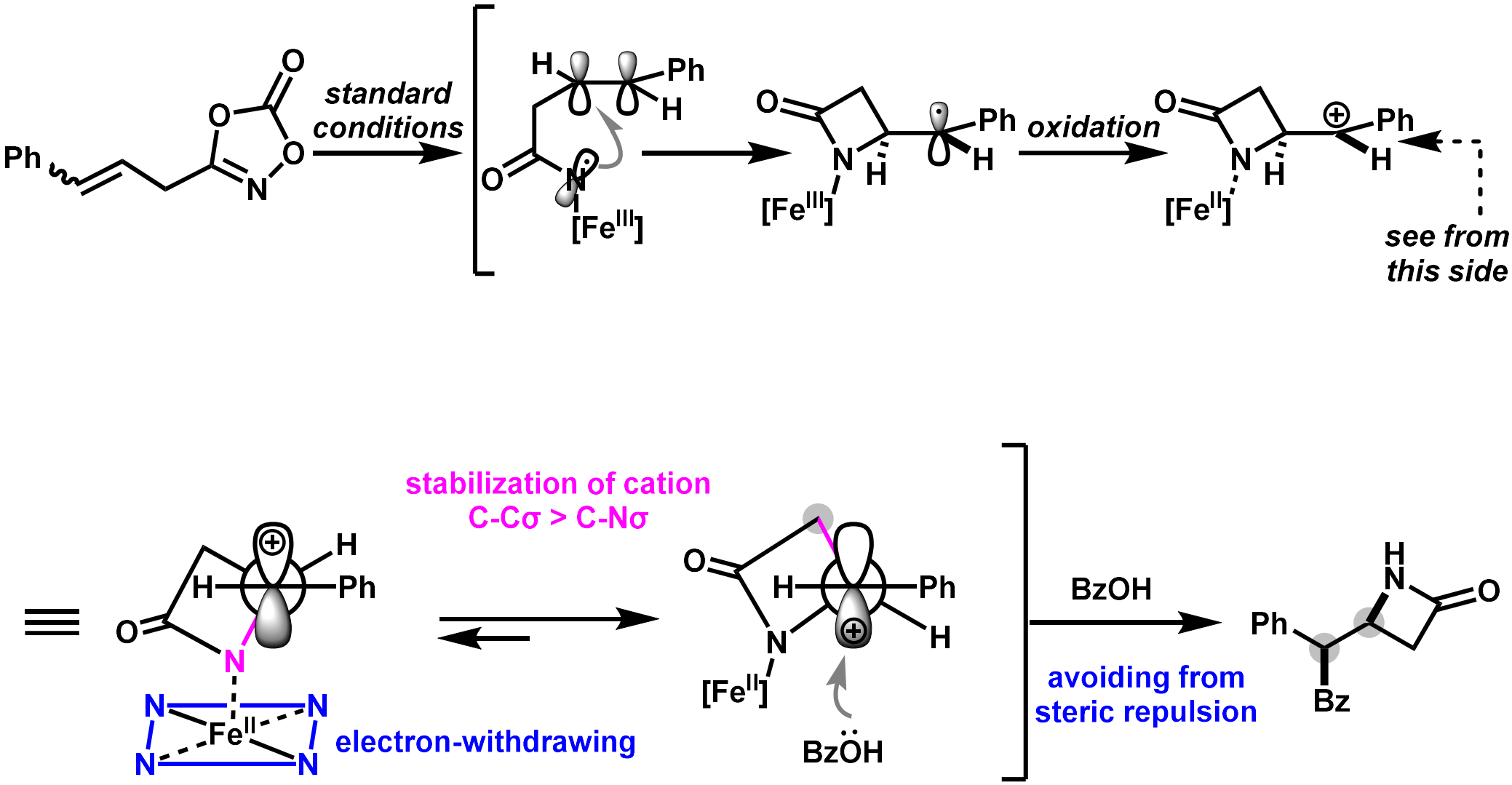


42% (dr 7:1)

HFIP

These results are suggestive of the carbocationic intermediacy.

Rationale for Stereoselectivity (My Opinion)

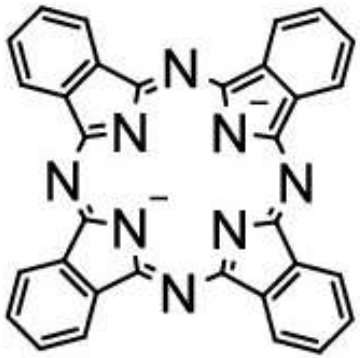


Kweon, J.; Kim, D.; Kang, S.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 1872.

Ligand effects (1)

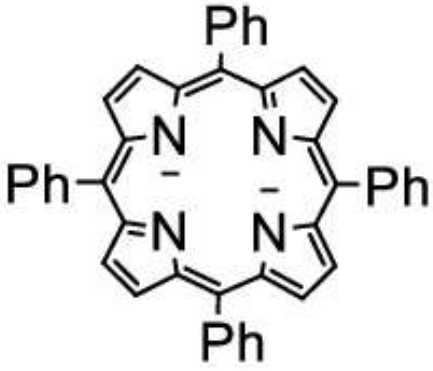
Catalyst: [Ligand]Fe(III)Cl

Ligand =

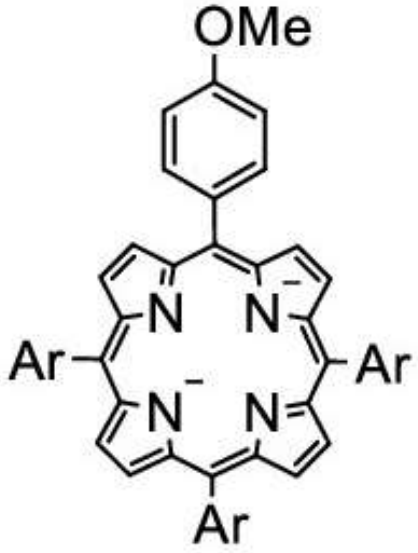


Pc^{2-}

$F_{20}TPP^{2-}$



TPP^{2-}



$(p\text{-}OMe)_4TPP^{2-}$

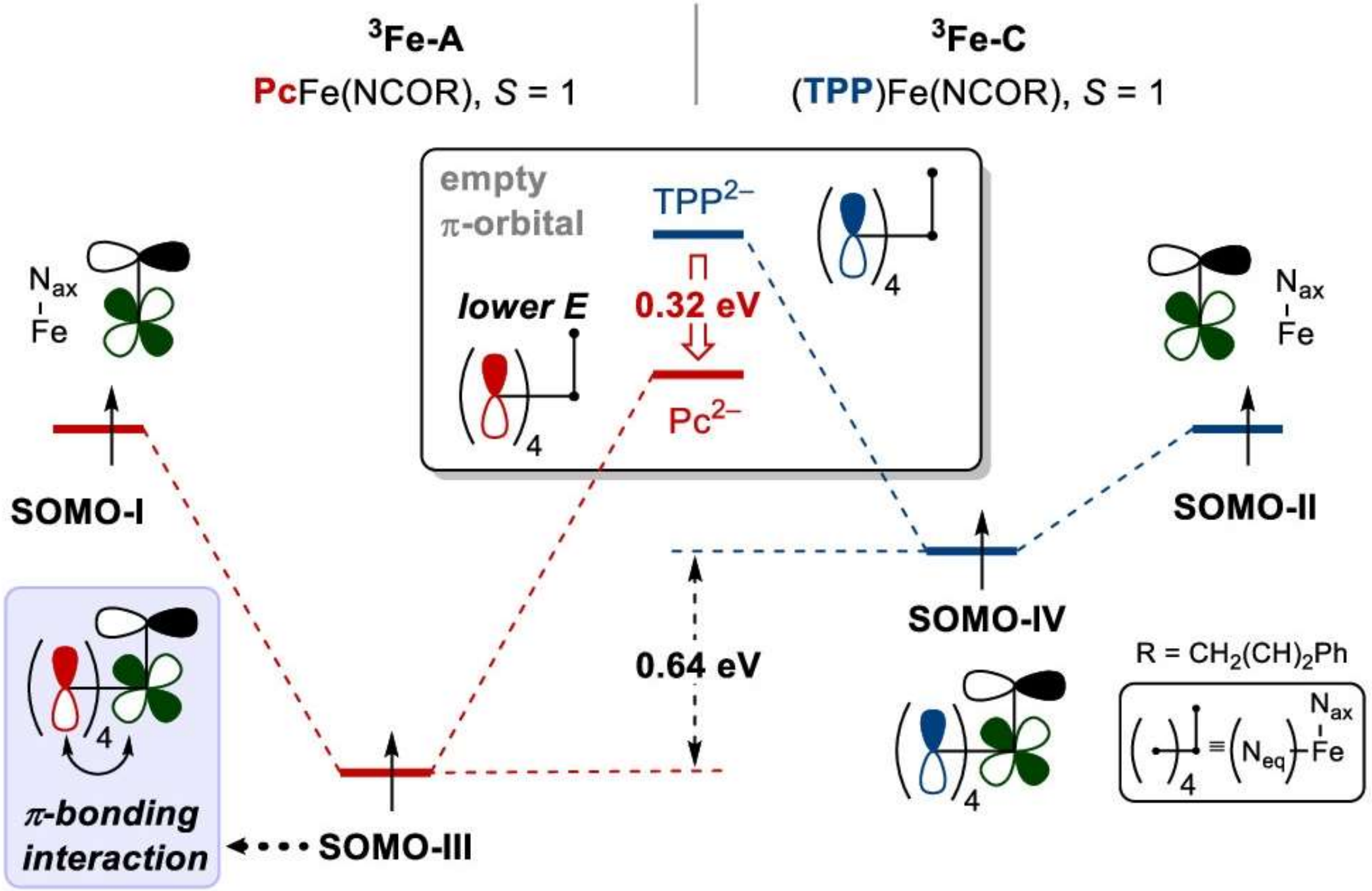
positive redox potential (vs Fc/Fc^+)

$E_{1/2,\ II/III}$ =	**–0.050 V**	**–0.382 V**	**–0.546 V**	**–1.169 V**
Yield/Conv.=	0.71	0.33	0.30	0.24

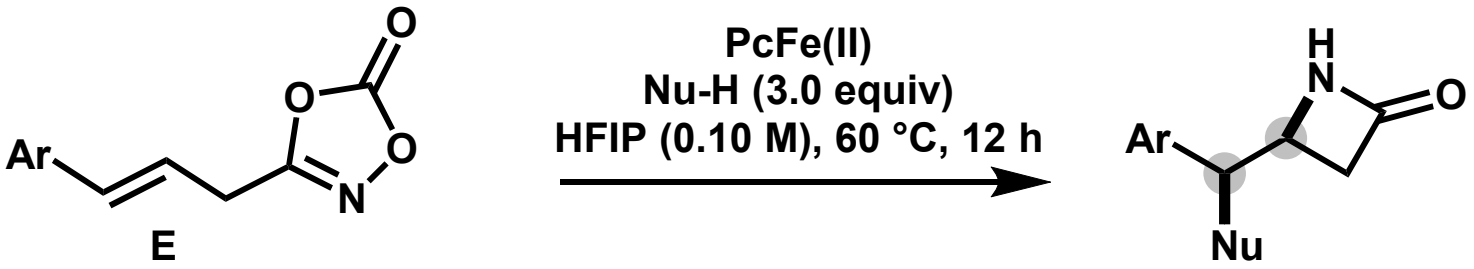
Among these ferric complexes employed, PcFe(III)Cl exhibited the most positive reduction potential, which can be assigned to Fe(III)/Fe(II) reduction.

Kweon, J.; Kim, D.; Kang, S.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 1872.

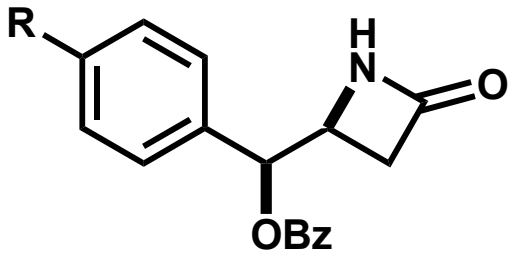
Ligand effects (2)



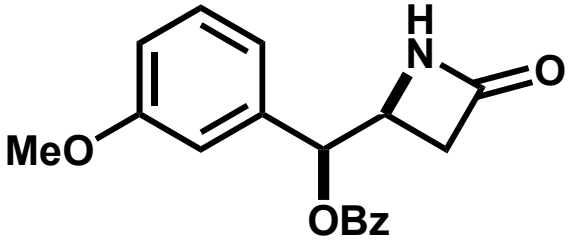
Substrate Scope



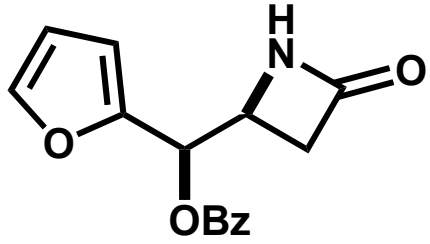
variation of dioxazolones



R = Br: 80% (dr 11:1)
R = Me: 70% (dr 2.4:1)

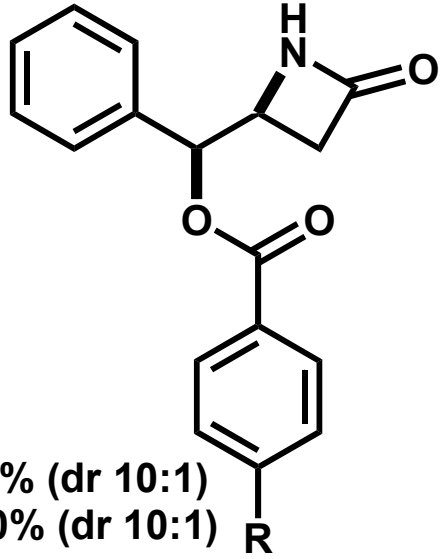


73% (dr 11:1)

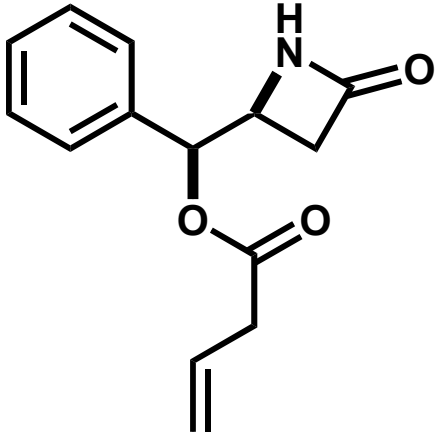


49% (dr 1.4:1)

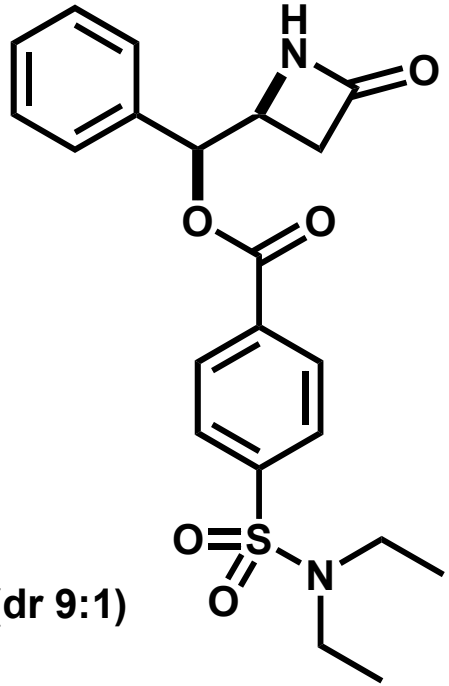
variation of carboxylic acid



R = NO_2: 75% (dr 10:1)
R = OMe: 70% (dr 10:1)



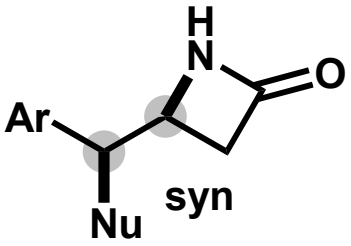
65% (dr >20:1)



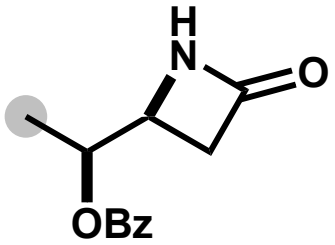
78% (dr 9:1)

Kweon, J.; Kim, D.; Kang, S.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 1872.

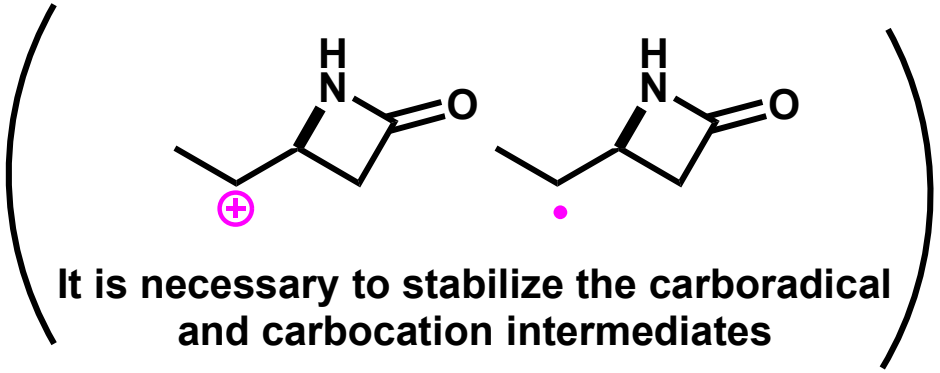
Limitation (My Opinion)



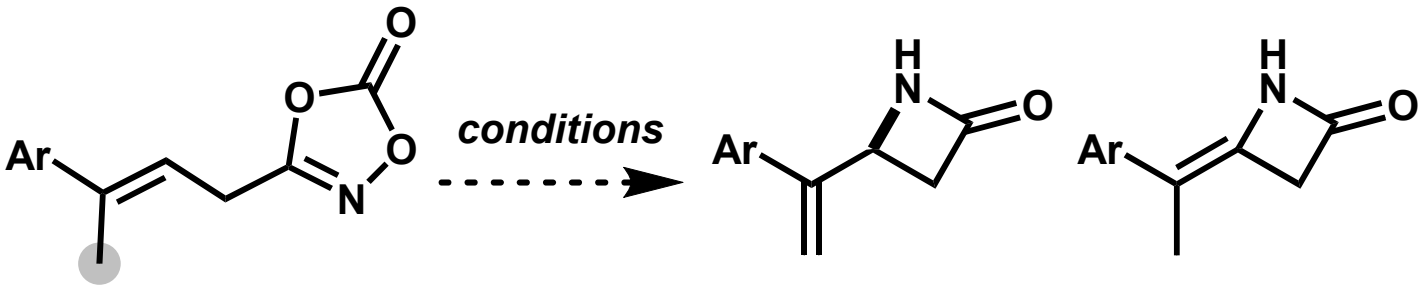
In most cases, only syn products are obtained.



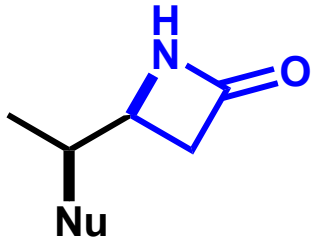
<5%



It is necessary to stabilize the carboradical and carbocation intermediates



E-1-like elimination should be kept in mind.

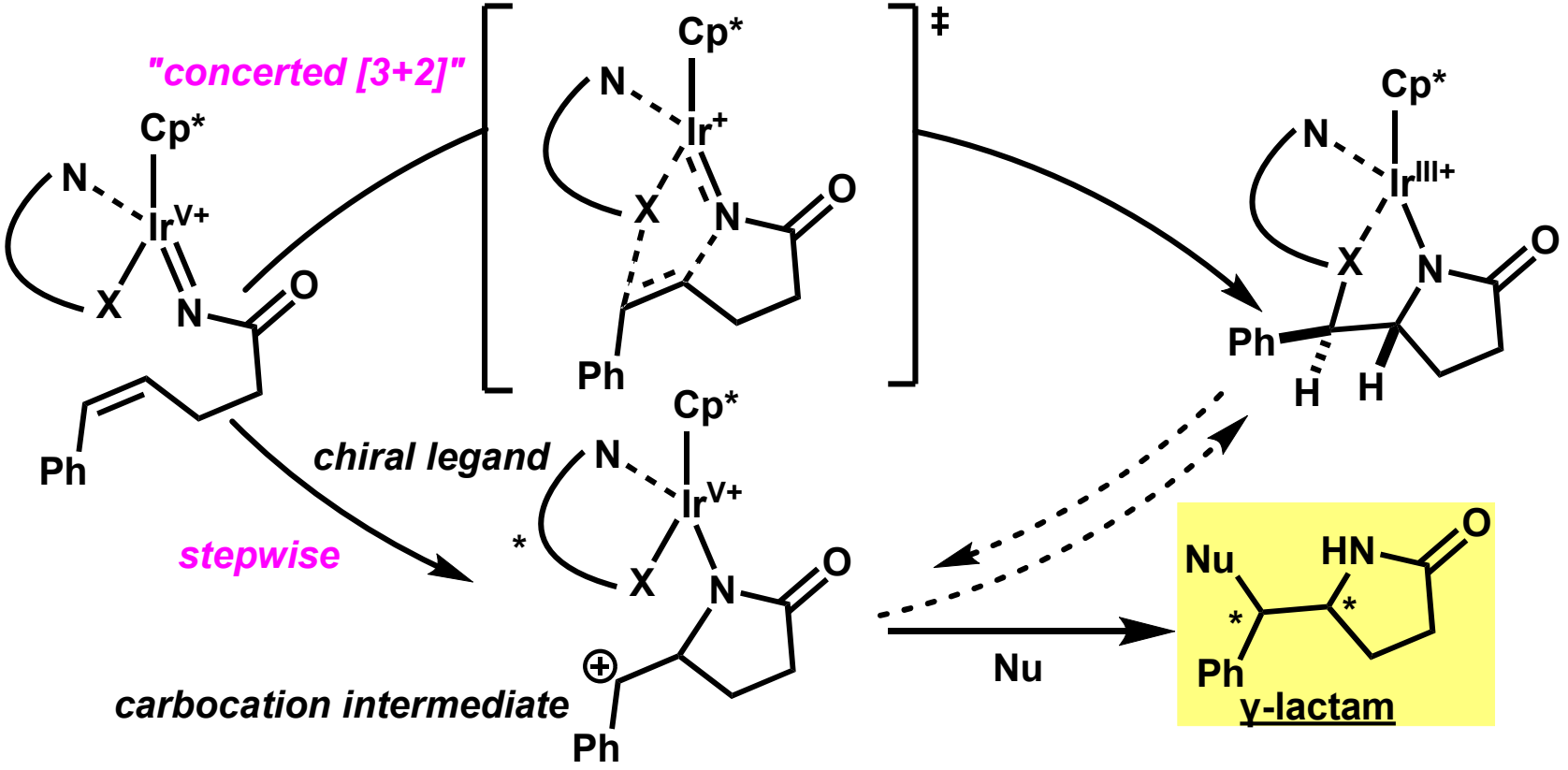


β-lactams are susceptible to nucleophilic attack.
→Only weak nucleophiles (such as carboxylic acids) are able to be used in this reaction?

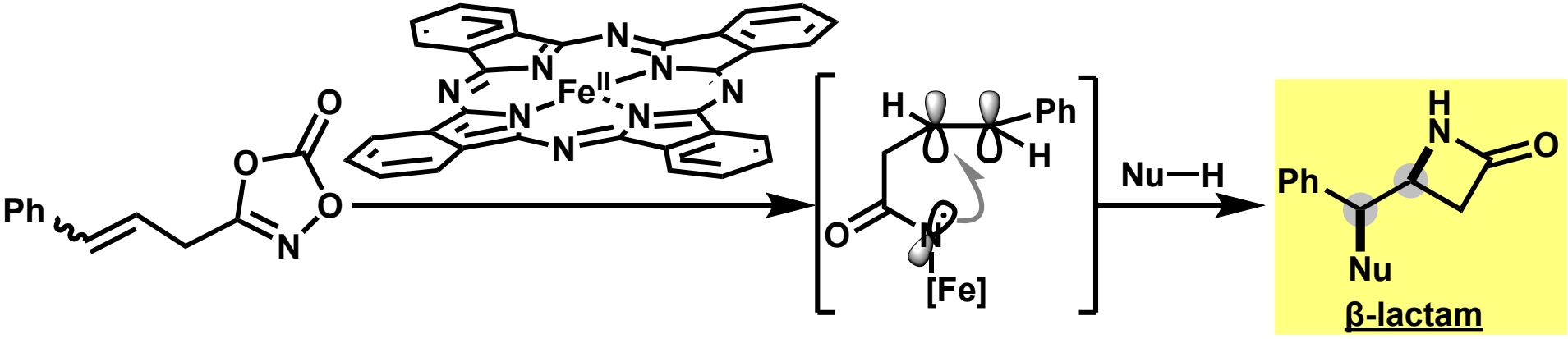
Kweon, J.; Kim, D.; Kang, S.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 1872.

Summary

Stereodefined Access to γ-Lactams via Olefin Difunctionalization

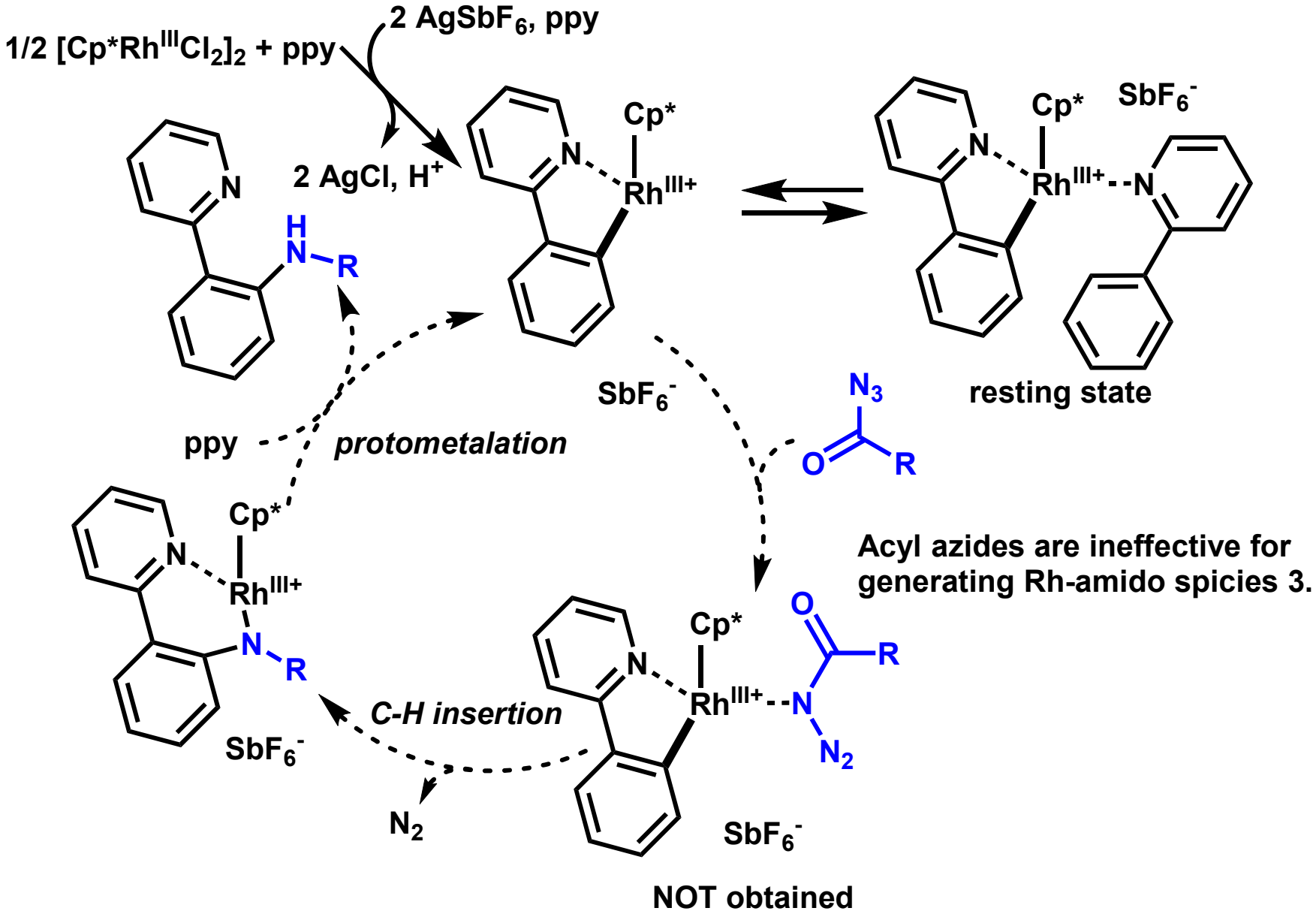


Access to β-Lactams via Iron-Catalyzed Olefin Oxyamidation Enabled by the π- Accepting Phthalocyanine Ligand



Appendix

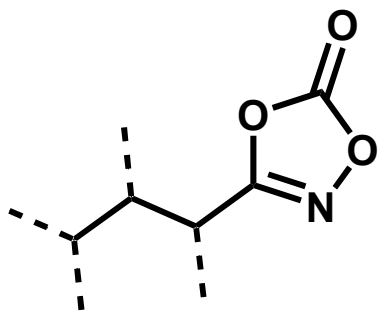
Identification of a Rate-limiting Factor



Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534.

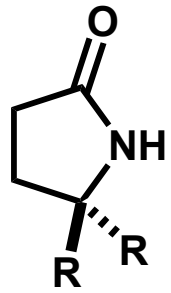
Viability of C-H Insertion

Aim:

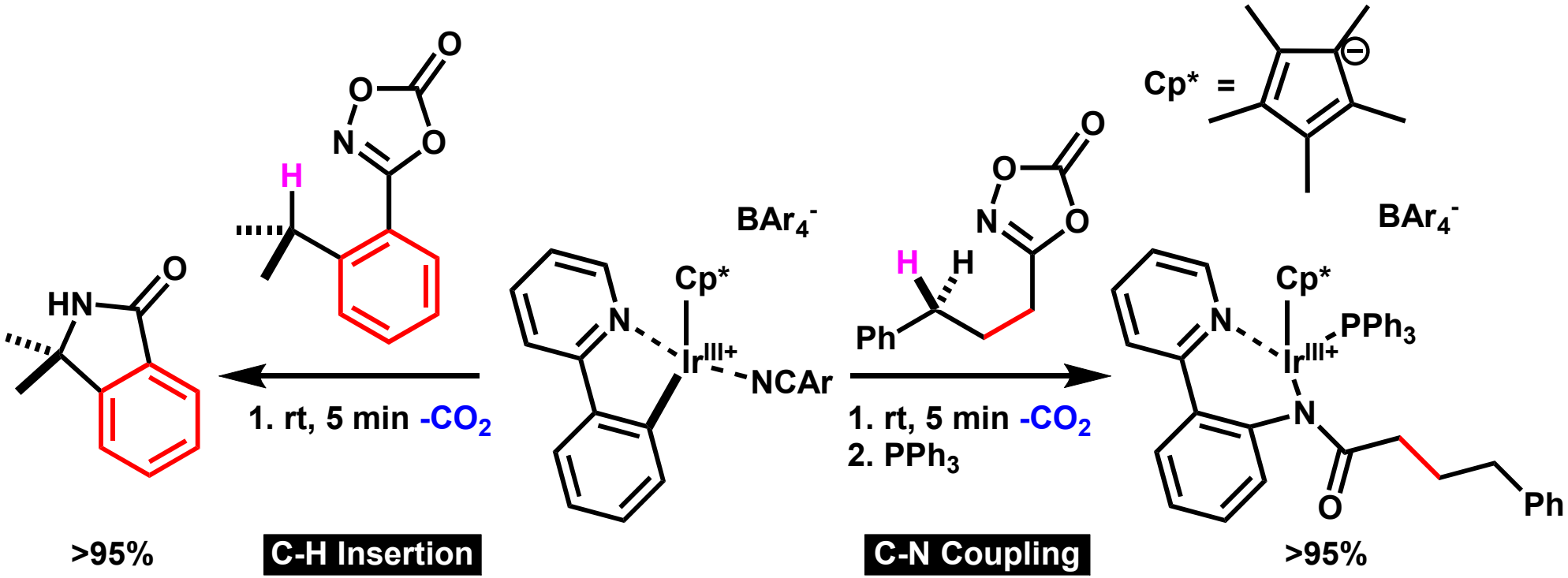


stable *N*-precursor

Ir catalyst

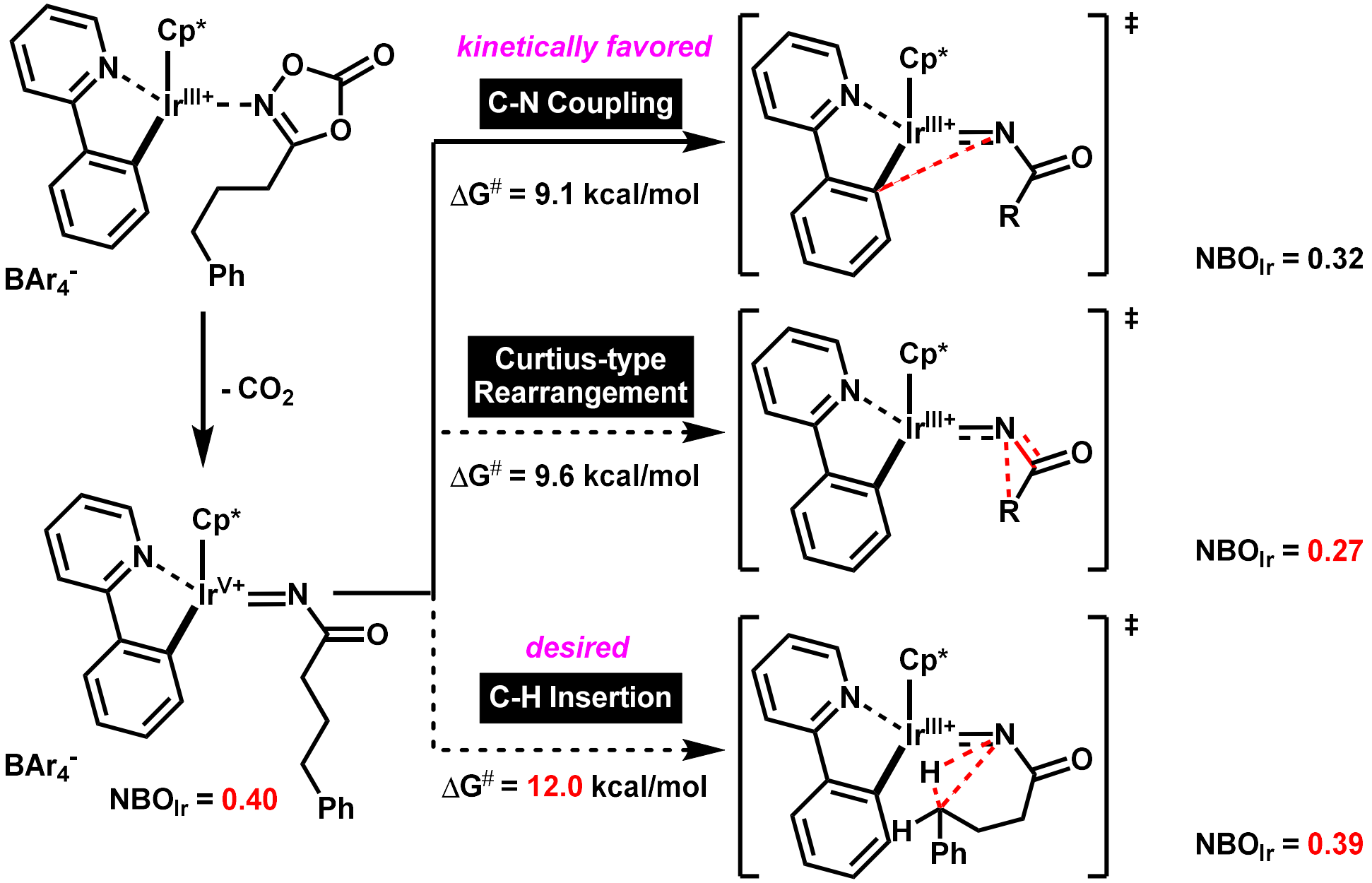


lactams



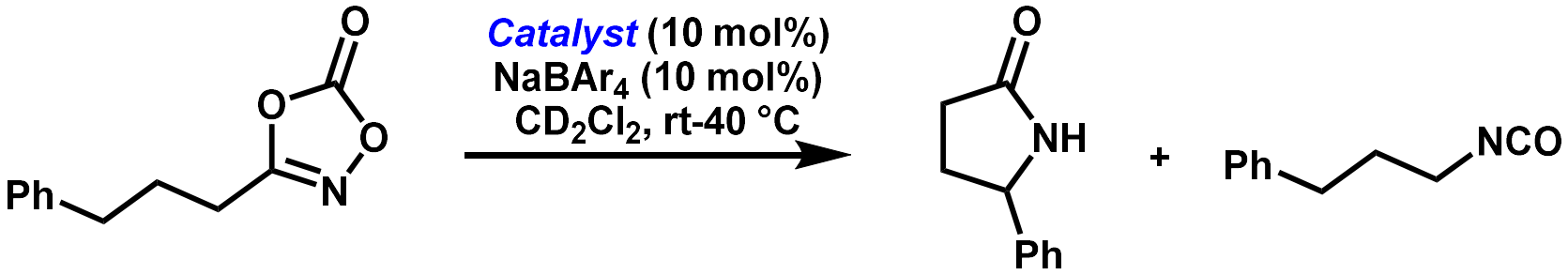
Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M. -H.; Chang, S. *Science.* **2018**, *359*, 1016.

DFT-Calculated Competitive Working Models



Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M. -H.; Chang, S. *Science.* **2018**, *359*, 1016.

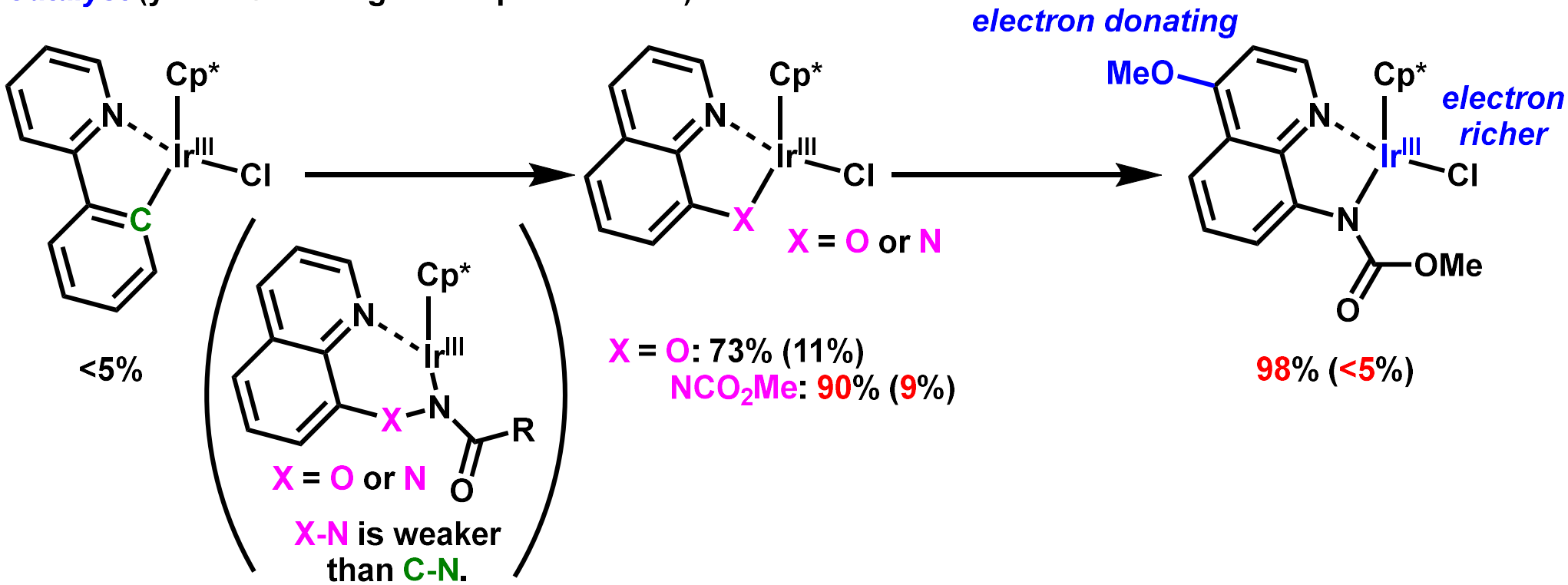
DFT-Calculated Competitive Working Models



5 (desired) — C-H Insertion

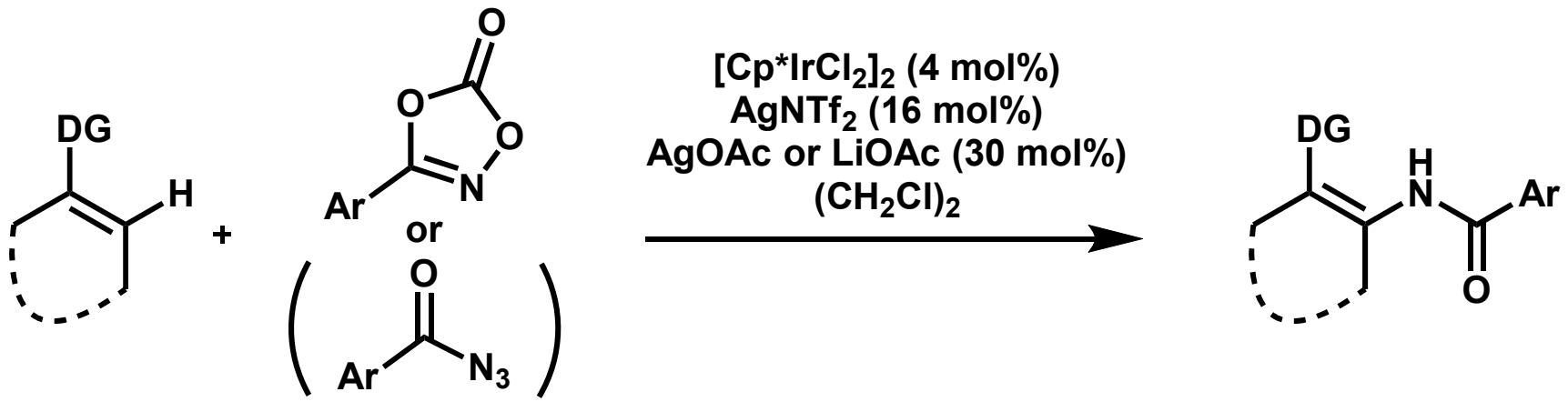
6 — Curtius-type Rearrangement

Catalyst (yields of 6 are given in parantheses)

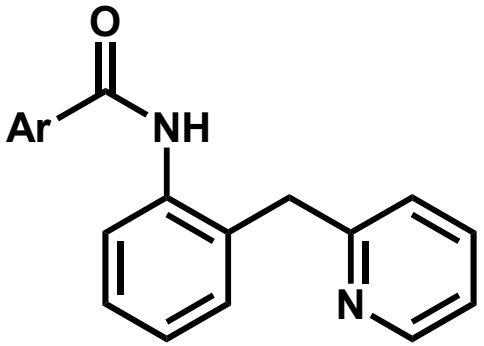


Hong, S. Y.; Park, Y.; Hwang, Y.; Kim, Y. B.; Baik, M. -H.; Chang, S. *Science.* **2018**, *359*, 1016.

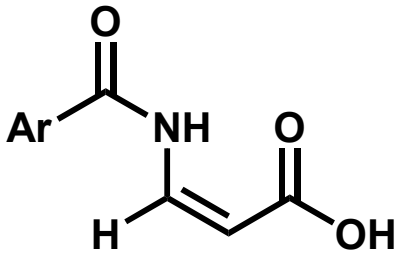
Ir(III)-catalyzed C-H Amidation



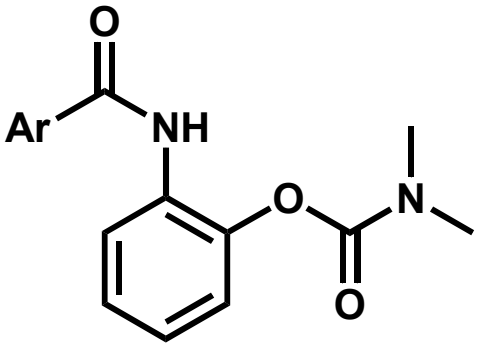
(yields with acyl azides are given in parentheses)



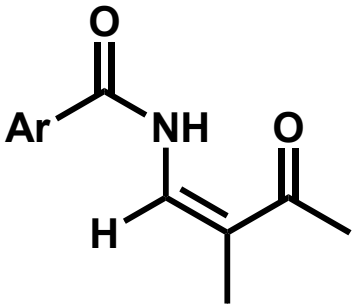
>95% (<5%)



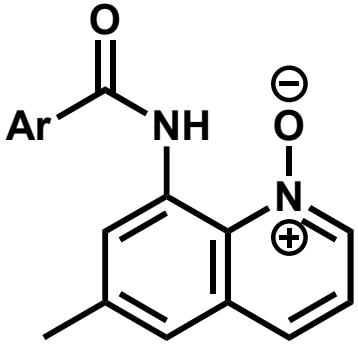
70% (<5%)



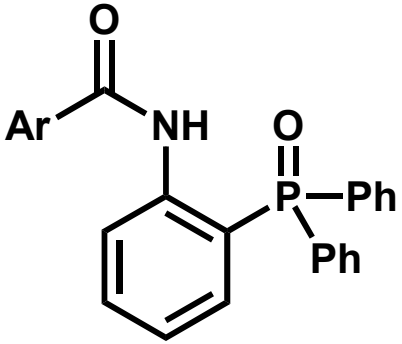
60% (<5%)



77% (25%)



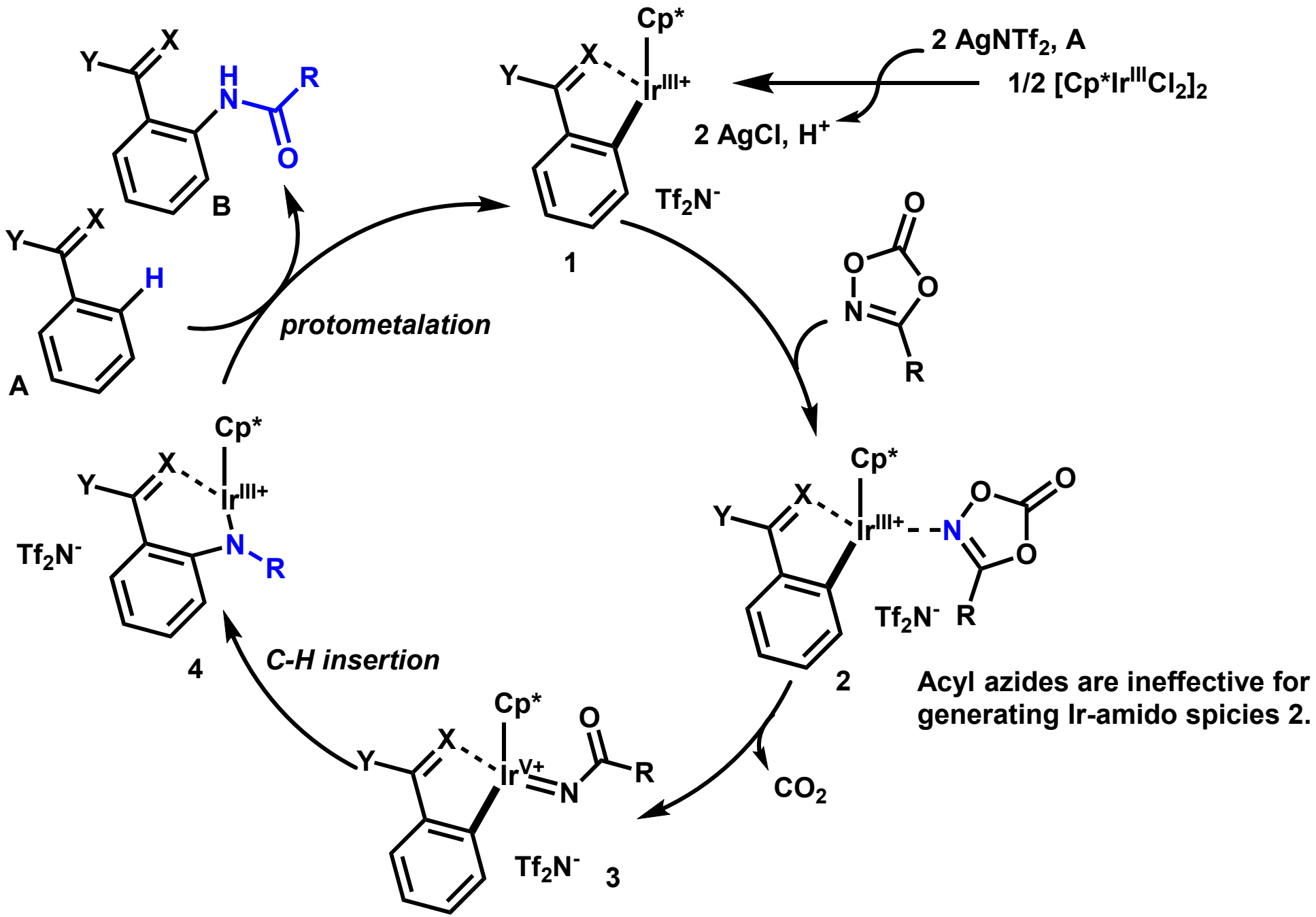
63% (<5%)



52% (9%)

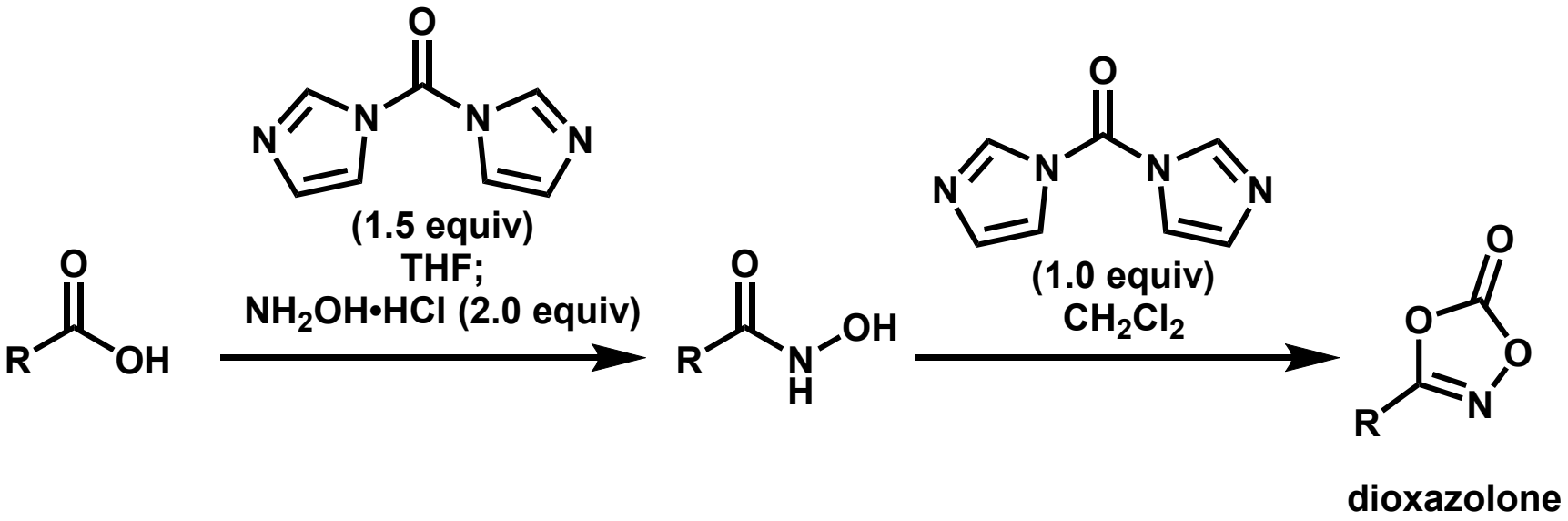
Hong, S. Y.; Hwang, Y.; Lee, M.; Chang, S. *Acc. Chem. Res.* **2021**, *54*, 2683.

Proposed Reaction Mechanism



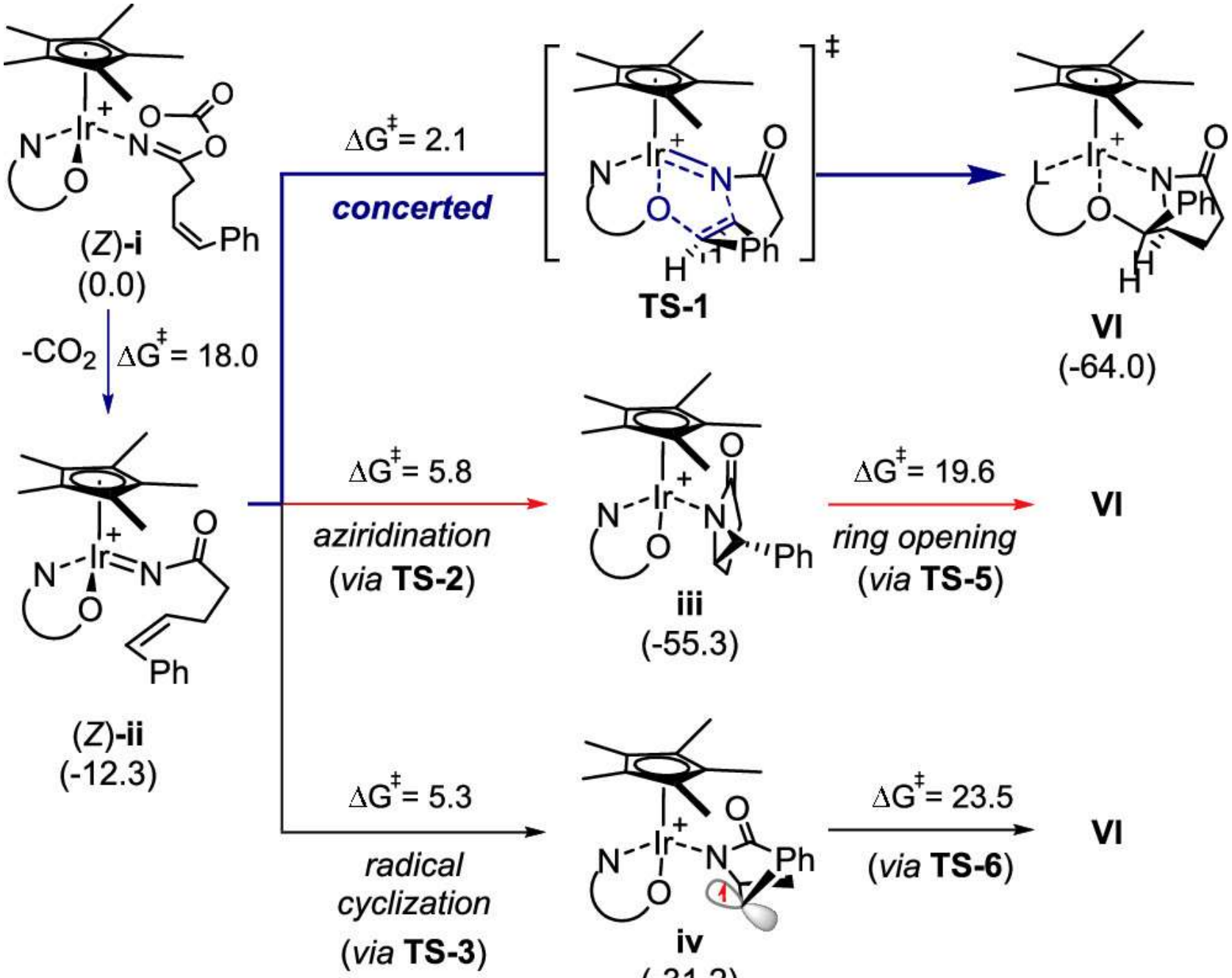
Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534.

Synthesis of Dioxazolones



1. Kim, S.; Kim, D.; Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2021**, *143*, 3993.

Plausible Working Modes of a Putative Ir-nitrenoid

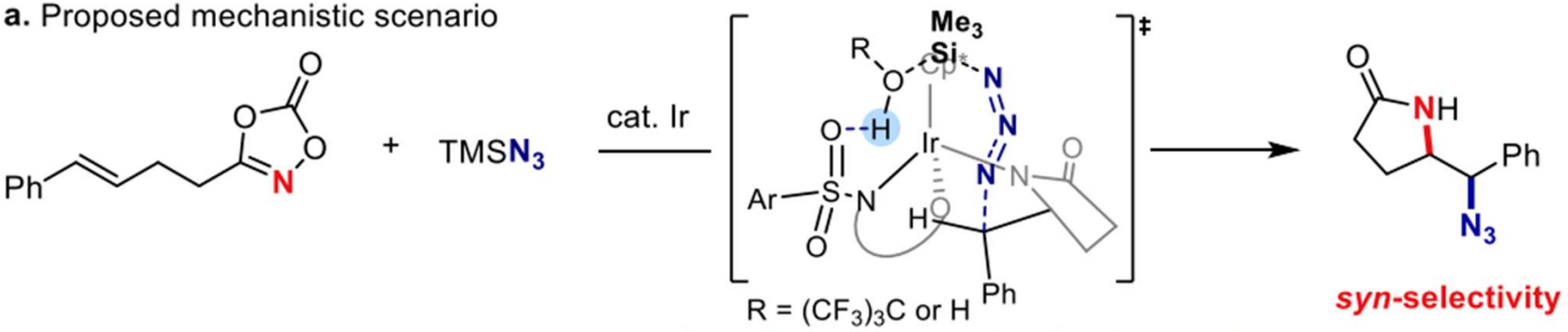


PCM(dichloromethane)-M06/SDD+6-311++G**//M06/Lanl2dz +6-31G**

1. Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2019**, *141*, 10399.

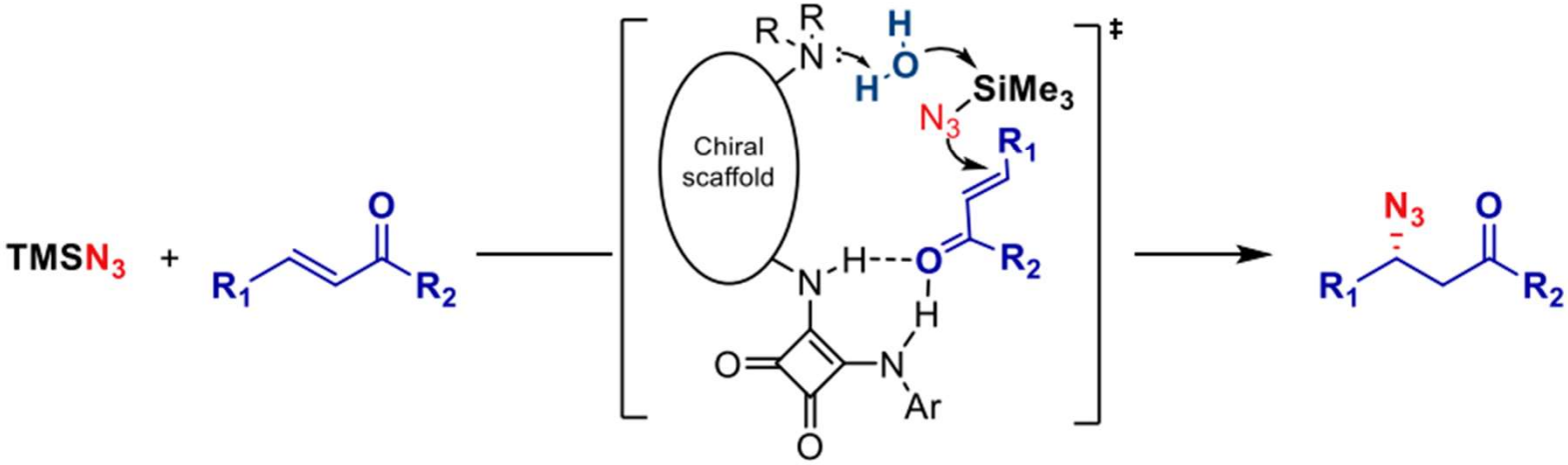
Proposed Mechanistic Mode for Syn-selective Pathway

a. Proposed mechanistic scenario



solvent/water-assisted activation mode

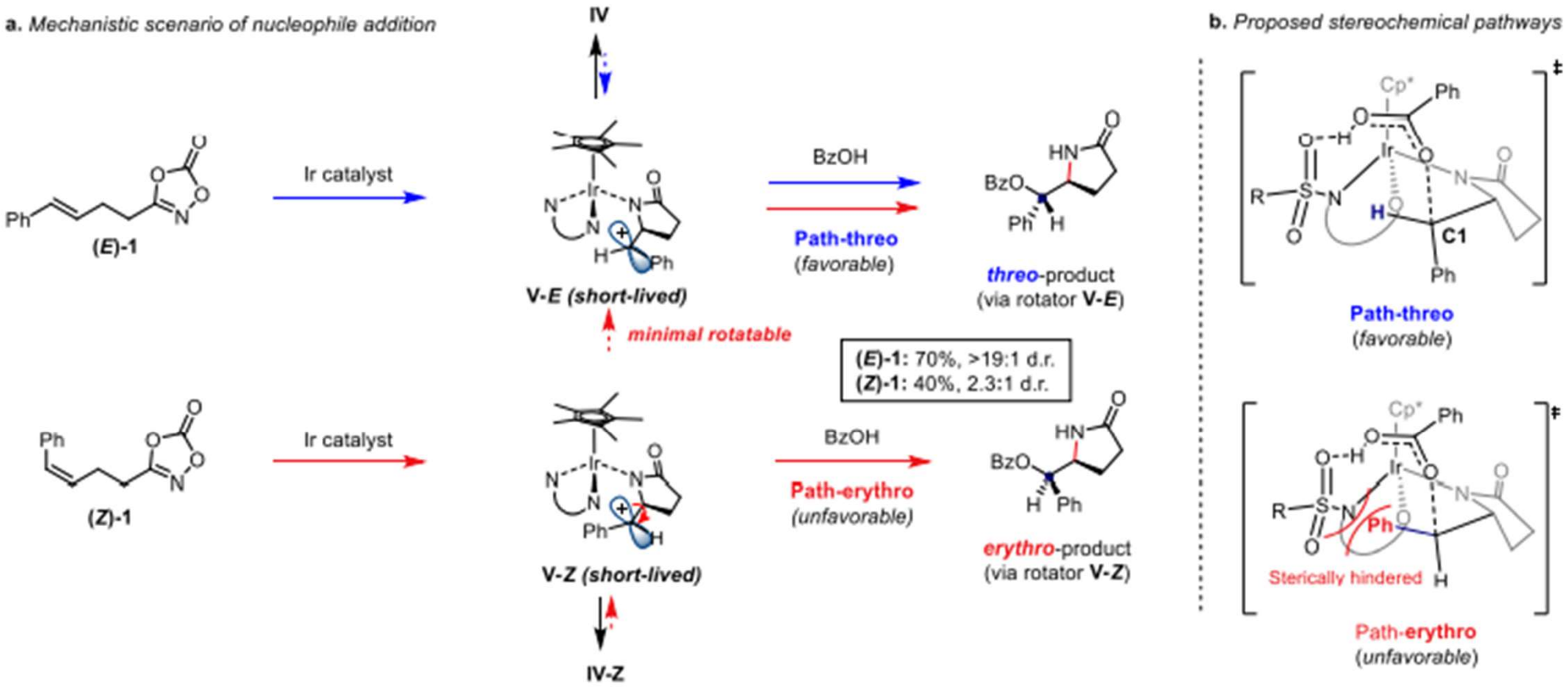
b. Water-assisted activation mode in catalysis (*Adv. Synth. Catal.* **2019**, 361, 4790)



1. Kim, S.; Kim, D.; Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2021**, *143*, 3993.

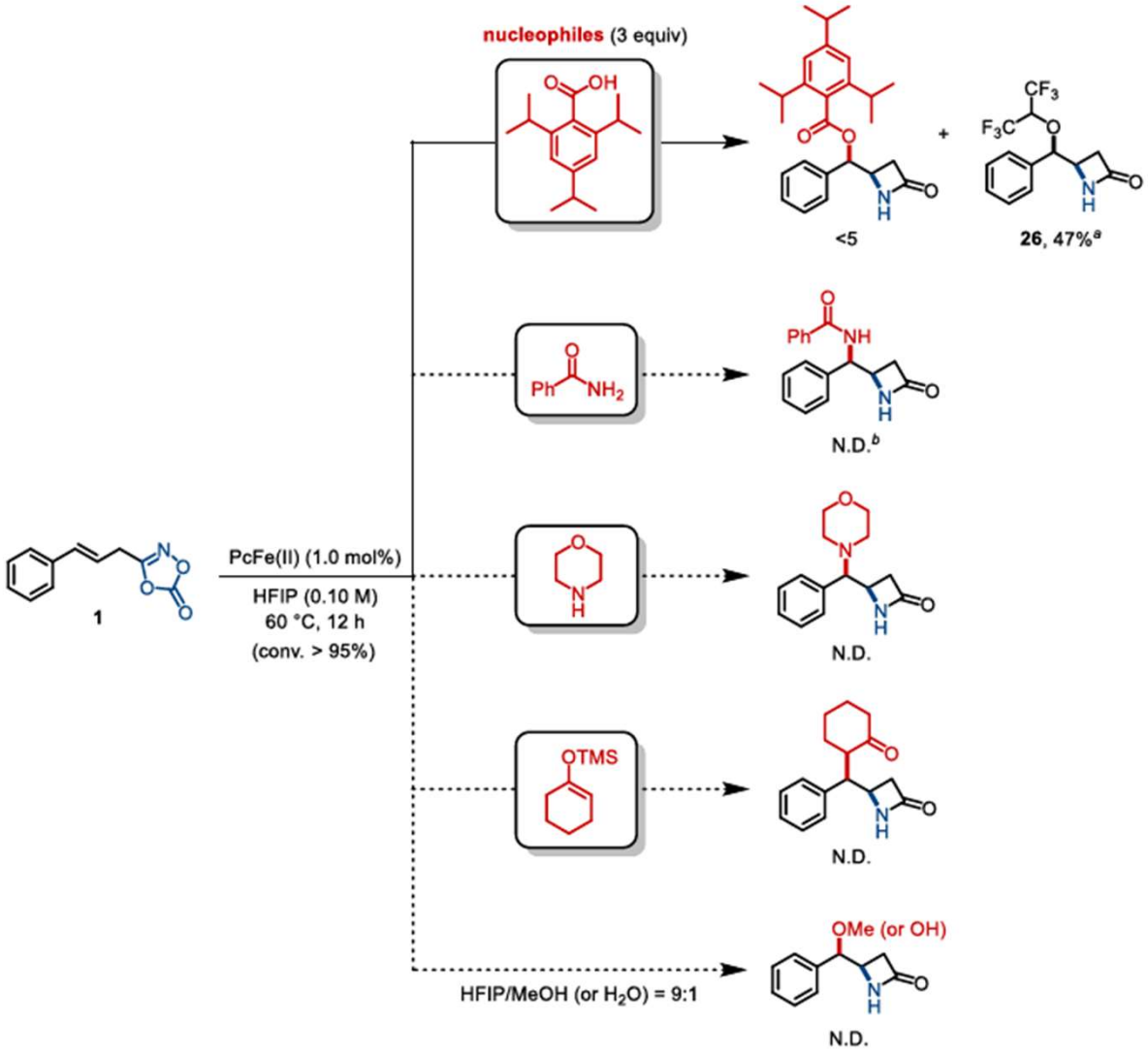
The Origin of the Partial Convergence

Scheme S2. The origin of the partial convergence.



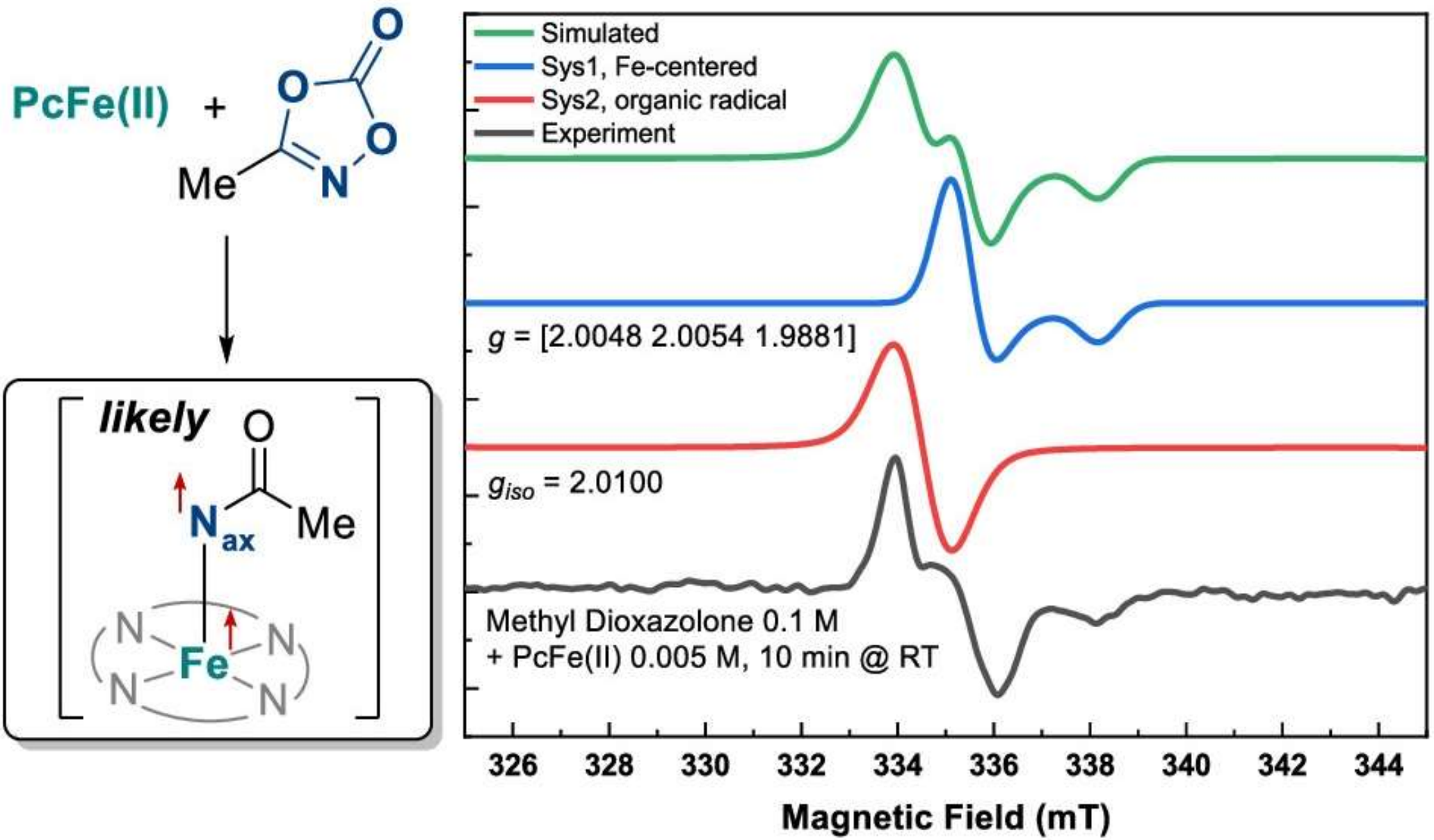
1. Kim, S.; Kim, D.; Hong, S. Y.; Chang, S. *J. Am. Chem. Soc.* **2021**, *143*, 3993.

Unsuccessful Results of PcFe(II)-catalyzed Olefin Difunctionalization



Kweon, J.; Kim, D.; Kang, S.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 1872.

Detection of Triplet PcFe-imidyl Radical by Low Temperature X-band EPR



Kweon, J.; Kim, D.; Kang, S.; Chang, S. *J. Am. Chem. Soc.* **2022**, *144*, 1872.