Tunable, Chemo- and Site-Selective Nitrene Transfer Reactions through Transition Metal Catalysts

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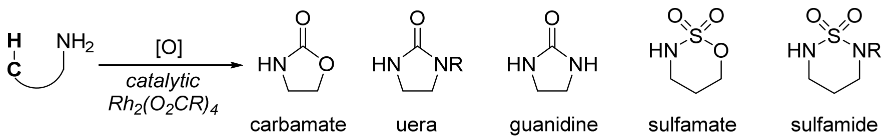
08/21/2017

Literature Talk

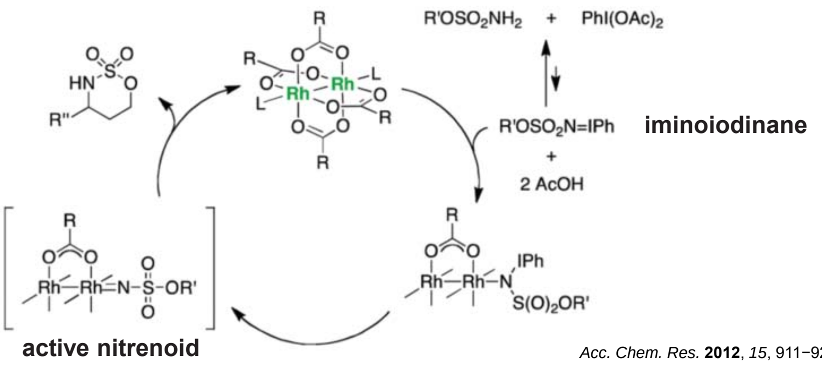
C–H Amination

- **Nitrene Precursor:**

Heterocycle synthesis through Rh-catalyzed C-H amination



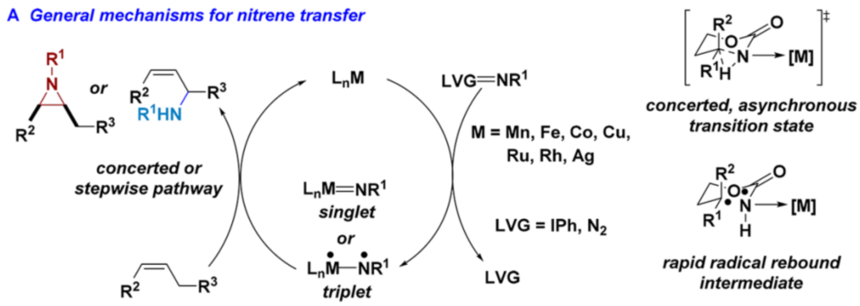
- **Dirhodium-Catalyzed C-H Amination**



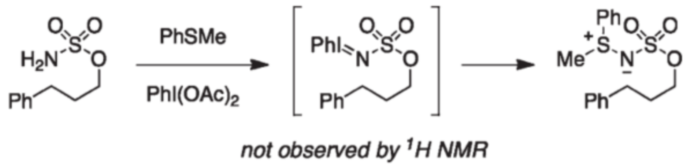
Acc. Chem. Res. **2012**, *15*, 911−922

C–H Amination

- **Putative Mechanisms for Rh-catalyzed C–H Insertion.**



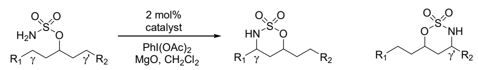
- **Sulfilimine Formation**

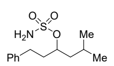
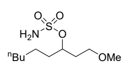
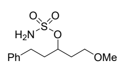
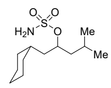
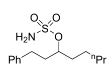
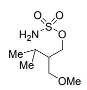
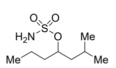
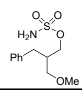


Tetrahedron **2009**, *65*, 3042–3051

Rh Catalyzed C–H Amination

- **Catalyst Influence on Reaction Chemoselectivity**



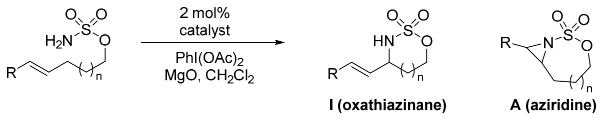
Entry	Substrate	Catalyst	γ/γ'	Entry	Substrate	Catalyst	γ/γ'
1		$Rh_2(OAc)_4$ $Rh_2(O_2CtBu)_4$ $Rh_2(esp)_2$ $Rh_2(O_2CCPh_3)_4$	1:1.5 1:1.5 1:7 1:14	5		$Rh_2(OAc)_4$ $Rh_2(O_2CtBu)_4$	1:11 1:14
2		$Rh_2(OAc)_4$ $Rh_2(O_2CtBu)_4$	1:1 1:15	6		Rh2(OAc)4 Rh2(O2CtBu)4 Rh2(esp)2	1:2 1:2 1:6
3		$Rh_2(OAc)_4$ $Rh_2(O_2CtBu)_4$	8:1 1:1.5	7		Rh2(OAc)4 Rh2(O2CtBu)4	1:1 1:3.5
4		$Rh_2(OAc)_4$ $Rh_2(O_2CtBu)_4$	1:20 1:4.5	8		Rh2(OAc)4 Rh2(O2CtBu)4	1:3 1:10

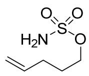
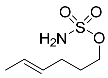
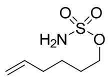
- 6-membered ring favored
- 3° > ethereal/benzylic > 2° >> 1°
- catalyst structure can influence product selectivity

Tetrahedron **2009**, *65*, 3042–3051

Rh Catalyzed C–H Amination

- **C–H Insertion versus Alkene Aziridination**

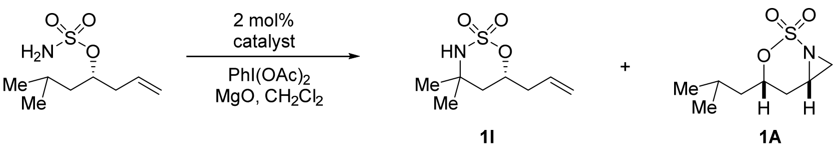


Entry	Substrate	Catalyst	I/A
1		$Rh_2(OAc)_4$ $Rh_2(esp)_2$ $Rh_2(O_2CCPh_3)_4$ $Rh_2(NHCOCF_3)_4$	1:1 1:1.5 1:20 1:4
2		$Rh_2(OAc)_4$ $Rh_2(esp)_2$ $Rh_2(O_2CCPh_3)_4$ $Rh_2(NHCOCF_3)_4$	2:1 1:1 1:5 1:2
3		$Rh_2(OAc)_4$ $Rh_2(esp)_2$ $Rh_2(O_2CCPh_3)_4$ $Rh_2(NHCOCF_3)_4$	1:1 1:2.5 1:20 1:4
4		$Rh_2(OAc)_4$ $Rh_2(esp)_2$ $Rh_2(O_2CCPh_3)_4$	1:1 1:1 1:7

Tetrahedron **2009**, *65*, 3042–3051

Rh Catalyzed C–H Amination

- **Alkene Aziridination versus 3º C–H Bond Insertion**



Catalyst	1I/1A
$Rh_2(OAc)_4$	1 : 6
$Rh_2(esp)_2$	1 : 6
$Rh_2(O_2CCPh_3)_4$	1 : 20
$Rh_2(NHCOCF_3)_4$	1: 4.5

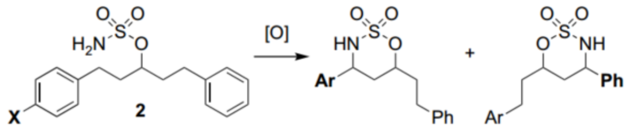
6-9:1 cis/trans selectivity

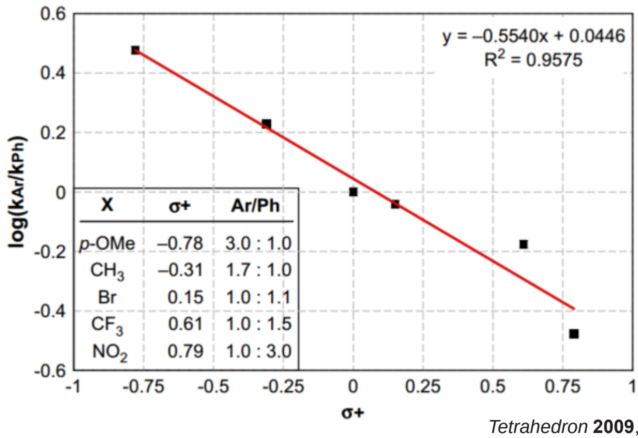
- Aziridine favored
- Electronic effects

Tetrahedron **2009**, *65*, 3042–3051

Rh Catalyzed C–H Amination

- Hammett Studies



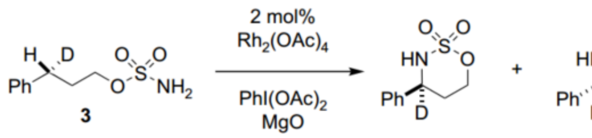


X	σ+	Ar/Ph
p-OMe	–0.78	3.0 : 1.0
CH_3	–0.31	1.7 : 1.0
Br	0.15	1.0 : 1.1
CF_3	0.61	1.0 : 1.5
NO_2	0.79	1.0 : 3.0

Tetrahedron **2009**, *65*, 3042–3051

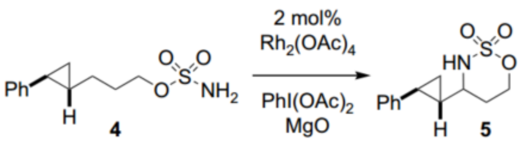
Rh Catalyzed C–H Amination

- KIE for Rh-based Intermolecular C–H Amination



k_H/k_D = 1.9(±0.2)

- C–H amination of a radical-clock containing substrate.



91% isolated yield

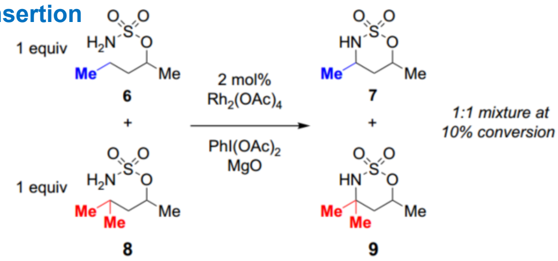
no ring-opened products observed

- concerted, asynchronous pathway for C–H insertion
- three-centered transition structure for the nitrenoid insertion

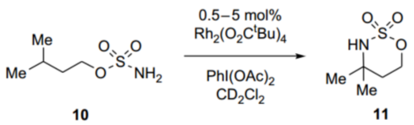
Tetrahedron **2009**, *65*, 3042–3051

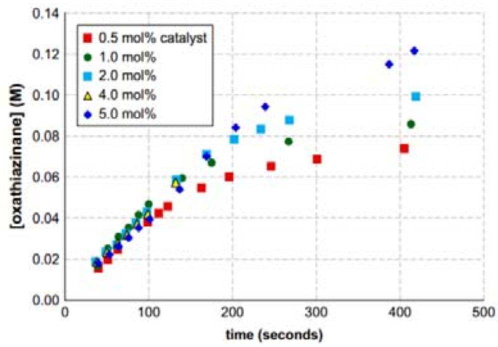
Rh Catalyzed C–H Amination

- **Competition Results of C–H Insertion**



- **Oxathiazinane Formation versus Time at Different Catalyst Loadings**

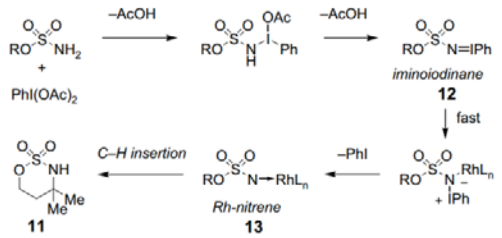




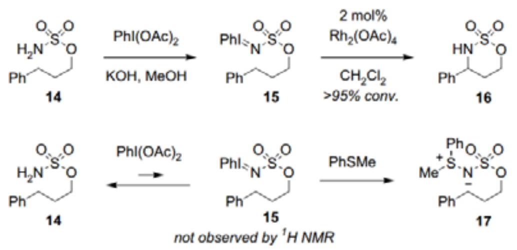
Tetrahedron **2009**, *65*, 3042–3051

Rh Catalyzed C–H Amination

- **Kinetics Analysis**
  - Rate = k[substrate]^1[oxidant]^1[catalyst]^0
- **Proposed Mechanism for Rh-nitrene Formation**



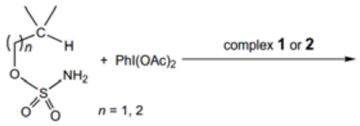
- **Control experiments with iminoiodinane starting material**

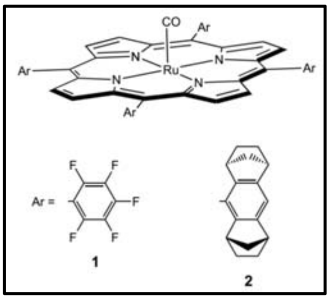


Tetrahedron **2009**, *65*, 3042–3051

Ru Catalyzed C–H Amination

➢ **Intramolecular Amidation of C-H Bonds Catalyzed by Ruthenium Porphyrins**



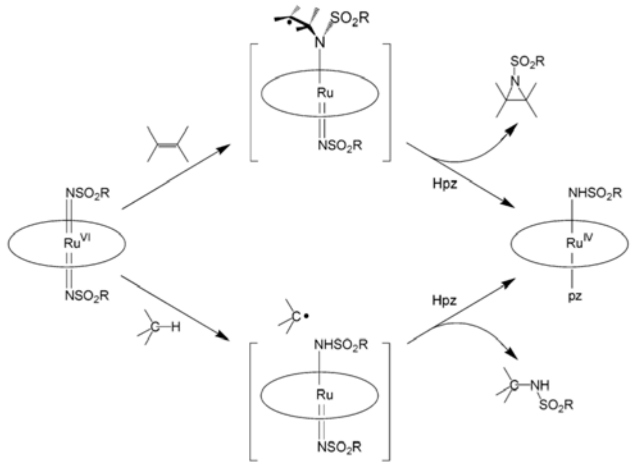


Entry	Substrate	Product	Yield [%][b]
1[c]	3	4	52
2	3	4	61
3	5	10	56
4	6	11	77
5	7	12	76
6	8	13	88
7	9	14	88

Angew. Chem. Int. Ed. **2002**, *41*, 3465–3468

Ru Catalyzed C–H Amination

➢ **Imido Transfer Reactions Proceed by a Mechanism**

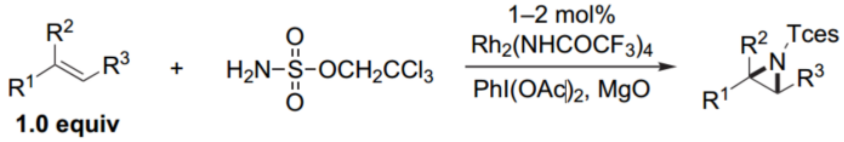


- radical-rebound mechanism
- KIEs of 6–12

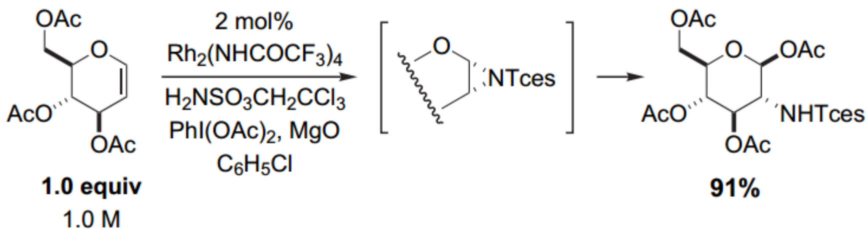
J. Am. Chem. Soc. **2005**, 127, 16629–16640

Rh-catalyzed alkene oxidation

- A Method for Intermolecular Olefin Aziridination



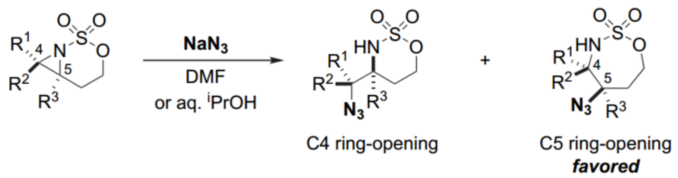
- Glycal oxidation



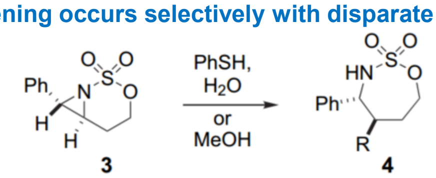
Tetrahedron **2006**, *63*, 11331–11342

Rh-catalyzed alkene oxidation

- Regioselective nucleophilic opening favors seven-membered ring product

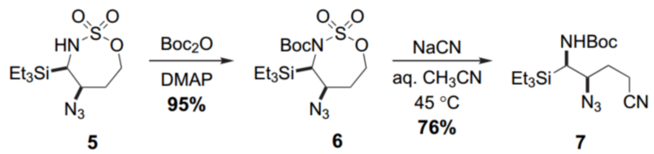


- Ring opening occurs selectively with disparate nucleophiles



R = SPh	**66%**
= OH	**85%**
= OMe	**88%**

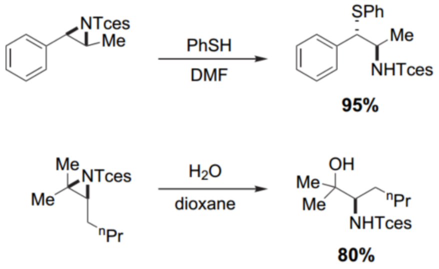
- Ring opening of seven-membered oxathiazepane



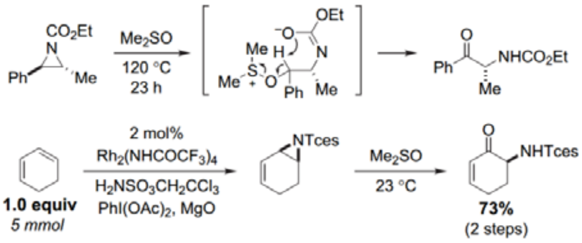
Tetrahedron **2006**, *63*, 11331–11342

Rh-catalyzed alkene oxidation

- Intermolecular olefin amination and ring opining



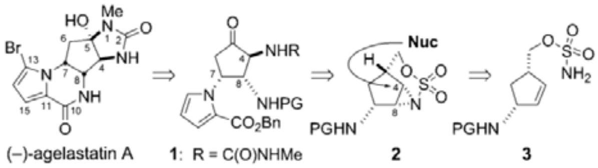
- DMSO-promoted oxidative ring opening affords an α-aminoketone



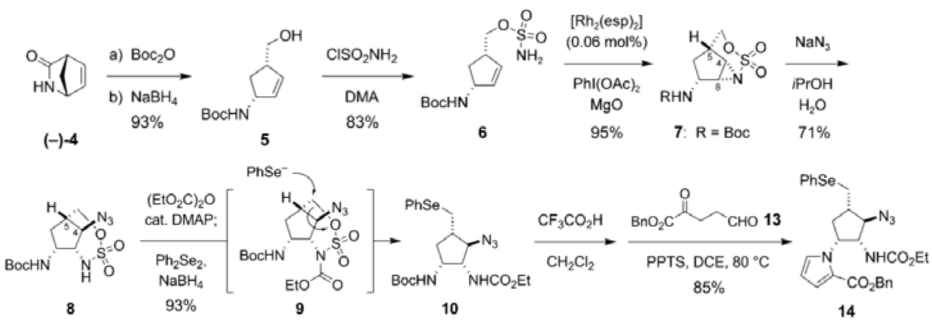
Tetrahedron **2006**, *63*, 11331–11342

Total Synthesis via C-H Amination

- Retrosynthetic analysis of (–)-agelastatin A



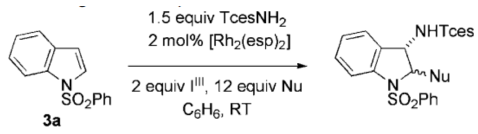
- Synthesis of Highly Substituted Cyclopentane Intermediate

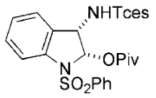
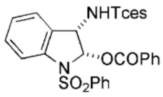
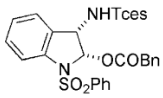
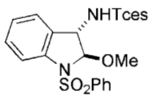


Angew. Chem. Int. Ed. **2009**, *48*, 3802–3805

Nitrene Additions to Indoles

- **Screening of Nucleophiles with Indole**

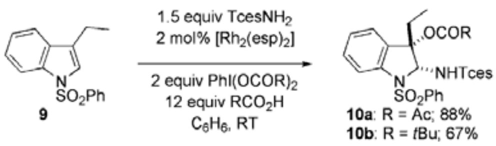


Entry	I^{III} oxidant	Nucl.	Product		Yield [%][a]	
1	$PhI(OCOtBu)_2$	$tBuCO_2H$		5	51	cis-oxyaminated
2	$PhI(OAc)_2$	$PhCO_2H$		6	23[b]	cis-oxyaminated
3	$PhI(OCOtBu)_2$	$PhCO_2H$		6	37[c]	cis-oxyaminated
4	$PhI(OCOtBu)_2$	$BnCO_2H$		7	40[d]	cis-oxyaminated
5	PhIO	$BnCO_2H$		7	52	cis-oxyaminated
6	$PhI(OCOtBu)_2$	MeOH		8	97[e]	trans-oxyaminated
7	$PhI(OCOtBu)_2$	MeOH		8	81[f]	trans-oxyaminated

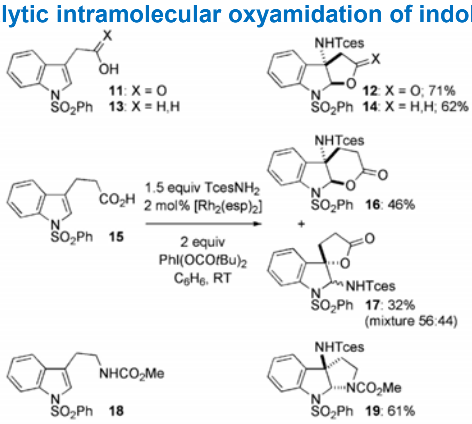
Angew. Chem. Int. Ed. **2010**, *49*, 1634 –1637

Nitrene Additions to Indoles

- **Catalytic oxyamidation of 3-ethylindole**

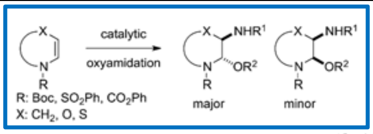


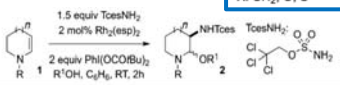
- **Catalytic intramolecular oxyamidation of indole derivatives**



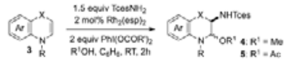
Angew. Chem. Int. Ed. **2010**, *49*, 1634 –1637

Nitrene Additions to Enamides





Entry	Substrate		R^1OH	Product		Yield [%][a]	cis/trans[b]
1	N-CO2Ph	1a	MeOH	NHTces, OMe, N-CO2Ph	2a	66	42:58
2	N-Boc	1b	MeOH	NHTces, OMe, N-Boc	2b	71	37:63
3	N-SO2Ph	1c	MeOH	NHTces, OMe, N-SO2Ph	2c	94	30:70
4	N-Boc	1d	MeOH	NHTces, OMe, N-Boc	2d	87	0:100
5	N-SO2Ph	1e	MeOH	NHTces, OMe, N-SO2Ph	2e	88	0:100
6	N-SO2Ph	1f	AcOH	NHTces, OAc, N-SO2Ph	2f	74[c]	0:100

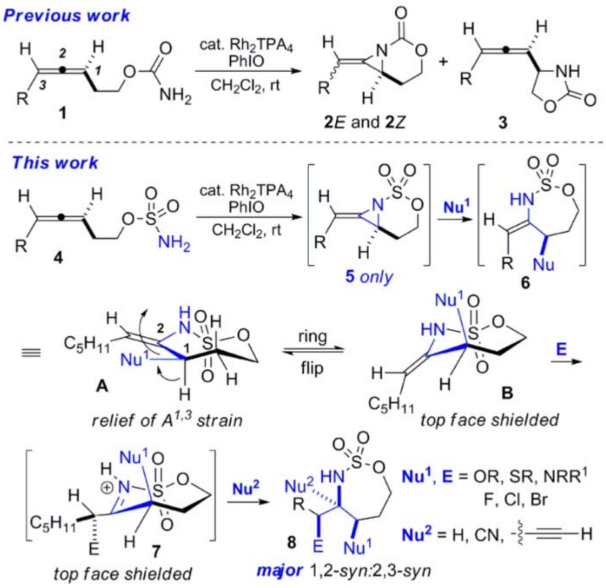


Entry	Substrate		R^1OH	Product		Yield [%][a]	cis/trans[b]
1	O, N-Boc	3a	MeOH	NHTces, OMe, N-Boc	4a	94[c,d]	34:66
2	O, N-Boc	3a	AcOH	NHTces, OAc, N-Boc	5a	82[c,d]	23:77
3	O, N-SO2Ph	3b	MeOH	NHTces, OMe, N-SO2Ph	4b	98[c]	10:90
4	O, N-SO2Ph	3b	AcOH	NHTces, OAc, N-SO2Ph	5b	83[c,d]	30:70
5	O, N, N-Boc	3c	MeOH	NHTces, OMe, N-Boc	4c	61[c]	28:72
6	O, N, N-Boc	3c	AcOH	NHTces, OAc, N-Boc	5c	54[c]	12:88
7	O, N-Boc	3d	MeOH	NHTces, OMe, N-Boc	4d	68[c]	36:64
8	S, N-Boc	3e	MeOH	S=NTces, N-Boc	6	55	–

Chem. Eur. J. **2012**, *18*, 90 – 94

Functionalization of Allenes

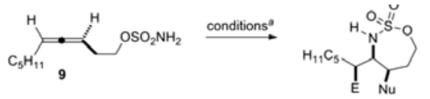
- **Preparation of Nitrogen-Containing Stereotriads**



J. Am. Chem. Soc. **2012**, *134*, 10807-10810

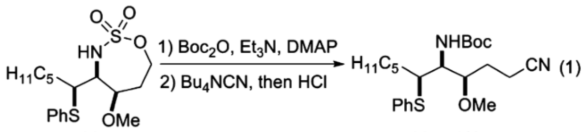
Functionalization of Allenes

➢ **One-Pot Stereotriad Synthesis**



entry	NuH	electrophile	rxn time/temp[b]	yield		*dr*
1	AcOH	NBS	2 h, rt	60%	**18**	5:1
2	AcOH	NBS	15 min, 0 °C	61%	**18**	20:1
3	MeOH	NBS	45 min, 0 °C	60%	**26**	1.7:1
4	MeOH	NBS	10 min, −10 °C	58%	**26**	2.6:1
5[c]	PhSH	NBS	10 min, 0 °C	61%	**29**	15:1
6	MeOH	DIAD[d]	2 h, 70 °C	64%	**31**	4.6:1
7	MeOH	PhSCl	30 min, rt	74%	**32**	2.6:1

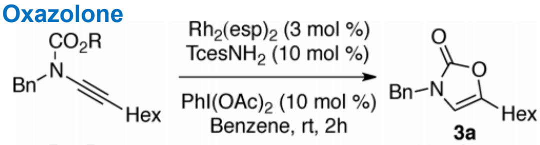
➢ **Stereotriad Deprotection**



J. Am. Chem. Soc. **2012**, *134*, 10807-10810

Reaction of Ynamides with Nitrenes:

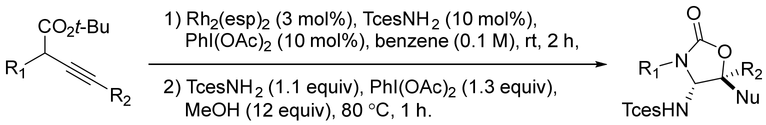
➢ **Formation of Oxazolone**

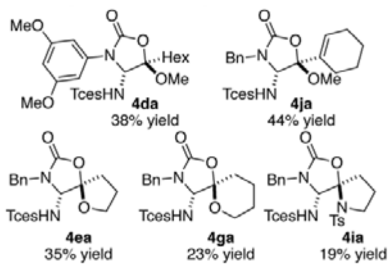


1: R = Bn
2a: R = *t*-Bu

60% from **1**
99% from **2a**

➢ **Tandem Cyclization-Oxyamination Reaction**

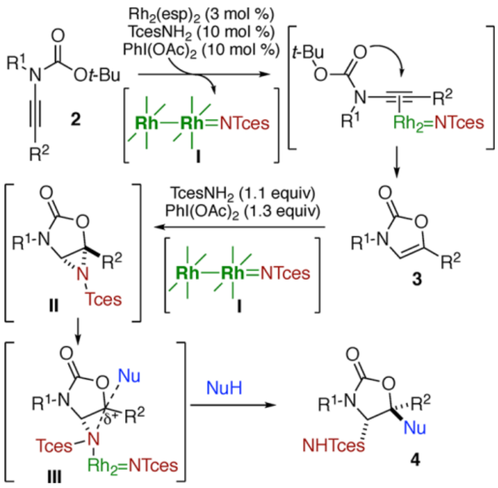




J. Org. Chem. **2017**, *82*, 11897-11902

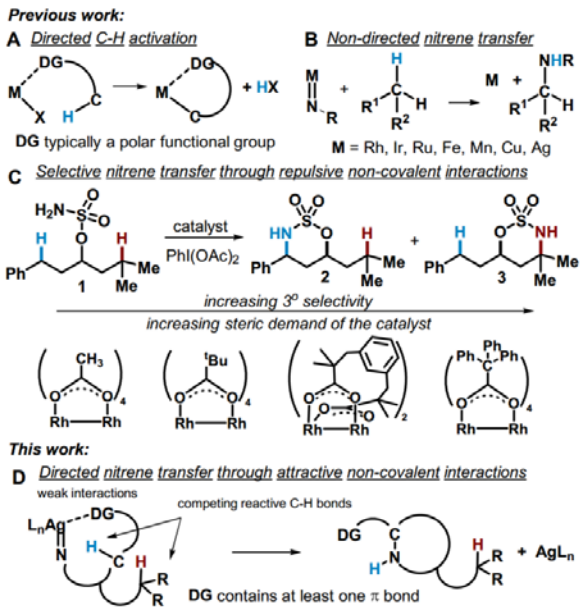
Reaction of Ynamides with Nitrenes:

Scheme 3. Proposed Mechanism for the Formation of Oxazolidinones



J. Org. Chem. **2017**, *82*, 11897-11902

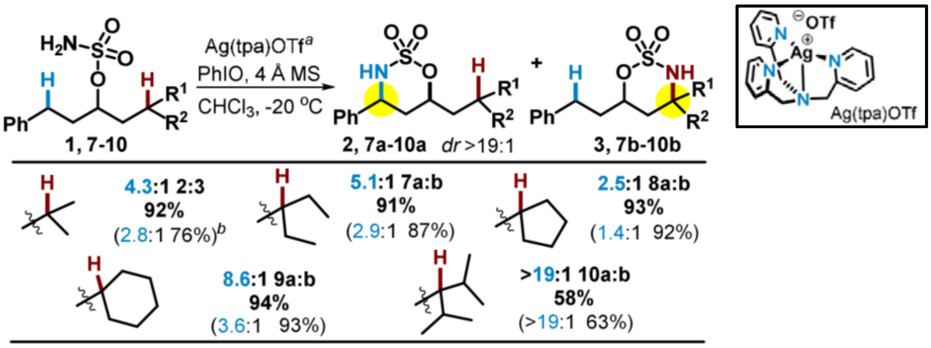
General Strategies for C-H Functionalization



J. Am. Chem. Soc. **2017**, *139*, 17376-17386

Silver-Catalyzed Nitrene Transfer

➢ **2° benzylic vs. 3° alkyl C(sp3)–H bond aminations with Ag(tpa)OTf.**



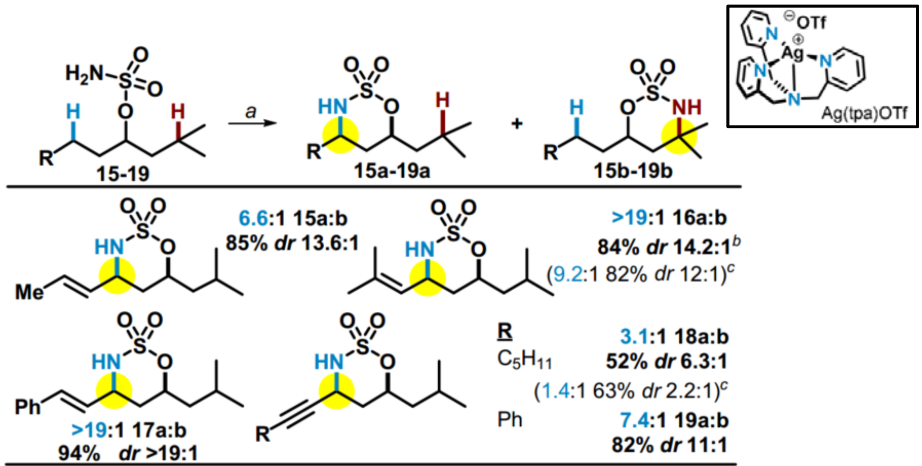
[a] 10 mol% Ag(tpa)OTf formed by combining 10 mol % AgOTf and 12.5 mol % tpa. [b] Previous results in CH_2Cl_2 at rt are shown in parenthesis.

- π···π interactions between one of the pyridine ligand arms and the aryl group
- Ag···π interactions
- lower C–H BDEs of benzylic C–H vs. 3° alkyl C(sp3)–H bonds

J. Am. Chem. Soc. **2017**, *139*, 17376-17386

Silver-Catalyzed Nitrene Transfer

➢ **2° allylic and propargylic C–H vs. 3° alkyl C(sp3)–H bond aminations**

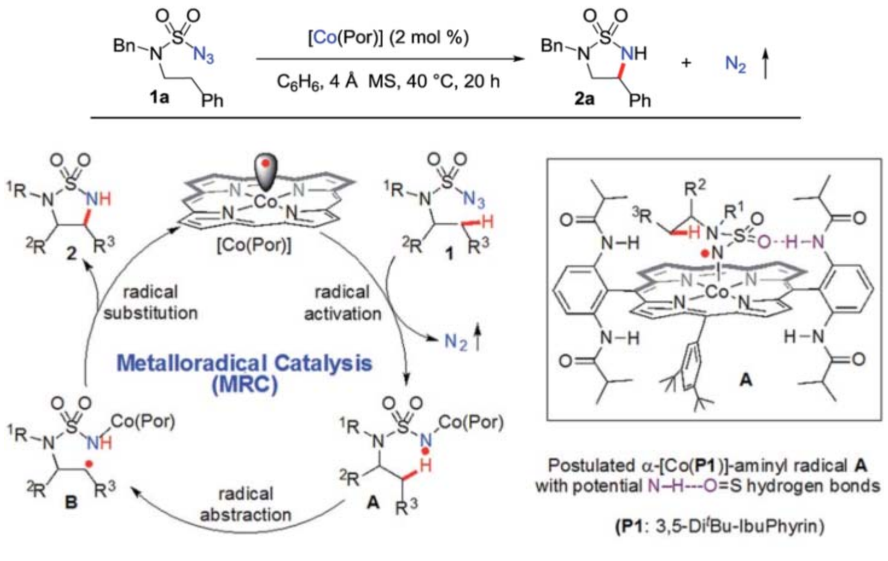


[a] 10 mol % AgOTf, 12.5 mol % tpa, 3.5 equiv PhIO, 0.05 M $CHCl_3$, 4 Å MS, -20 °C. [b] 5% rearranged aziridine. [c] Previous conditions using CH_2Cl_2 at rt.

J. Am. Chem. Soc. **2017**, *139*, 17376-17386

Co(II)-based metalloradical catalysis

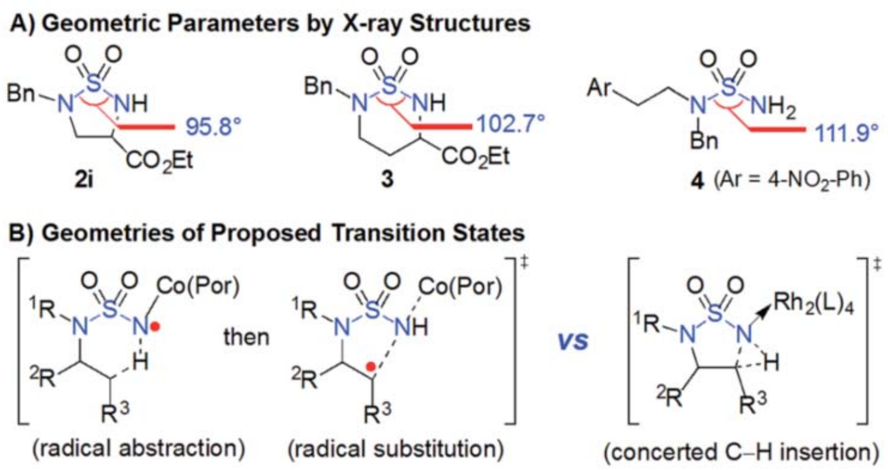
- **C-H Amination for 5-membered cyclic sulfamides**



Chem. Sci., **2016**, *7*, 6934–6939

Co(II)-based metalloradical catalysis

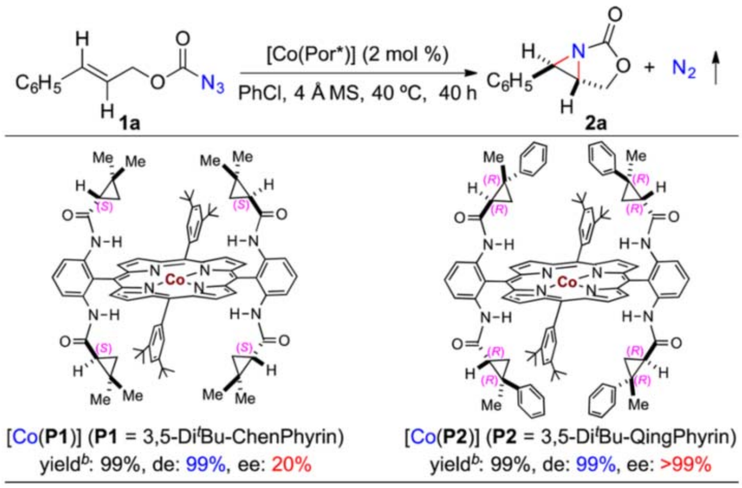
- **Geometries of Intramolecular 1,5-C(sp3)–H Amination**



Chem. Sci., **2016**, *7*, 6934–6939

Radical Bicyclization of Allyl Azidoformates

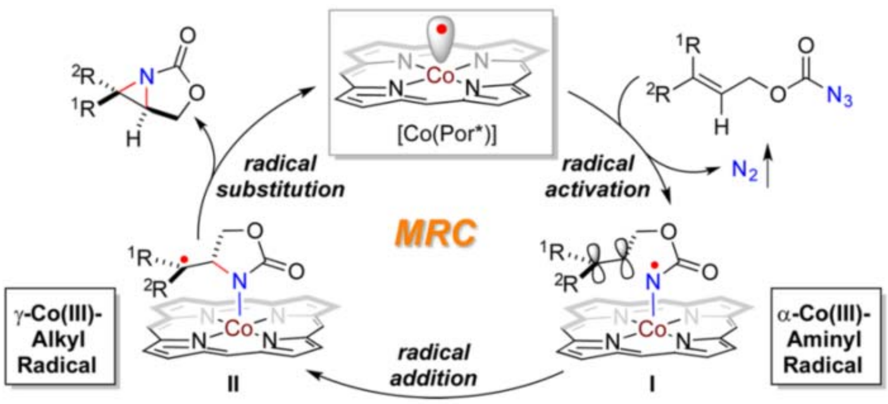
- **Asymmetric Radical Bicyclization of Cinnamyl Azidoformate**



J. Am. Chem. Soc. **2017**, *139*, 9164-9167

Radical Bicyclization of Allyl Azidoformates

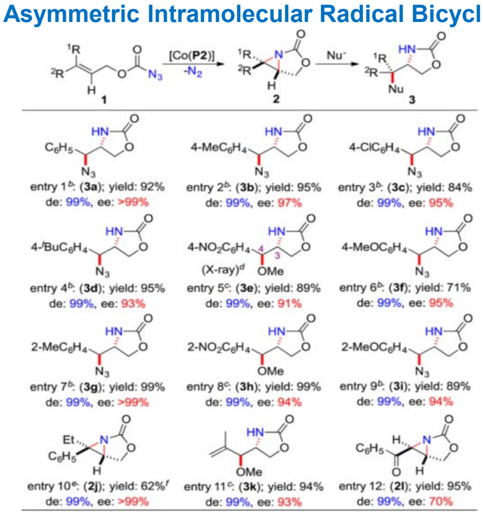
- **Proposed Catalytic Pathway**



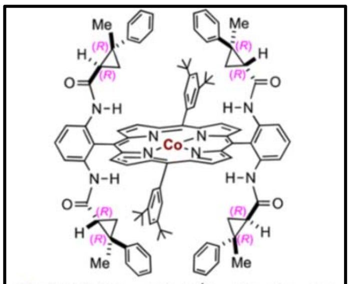
J. Am. Chem. Soc. **2017**, *139*, 9164-9167

Radical Bicyclization of Allyl Azidoformates

➢ **Asymmetric Intramolecular Radical Bicyclization**



[a]Performed in PhCl at 40 °C for 40 h using 2 mol % [Co(**P2**)] under N_2 in the presence of 4 Å MS; [azide **1**] = 0.1 M; isolated yields. [b]In situ addition of $TMSN_3$ (1.1 equiv) and TBAF (1.1 equiv). [c]In situ addition of MeOH (2.0 mL) and H_2SO_4 (30 mol %). [d]Absolute configuration was determined by X-ray as (3*R*, 4*S*). [e]At 80 °C for 20 h. [f]100% conversion; >90% NMR yield.

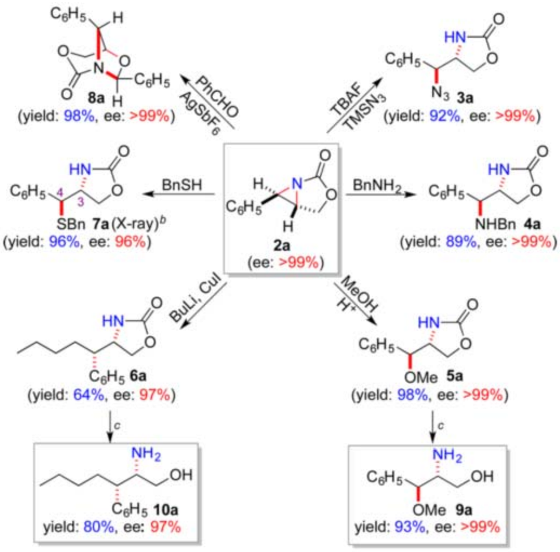


[Co(**P2**)] (**P2** = 3,5-Di^{t}Bu-QingPhyrin)

J. Am. Chem. Soc. **2017**, *139*, 9164-9167

Radical Bicyclization of Allyl Azidoformates

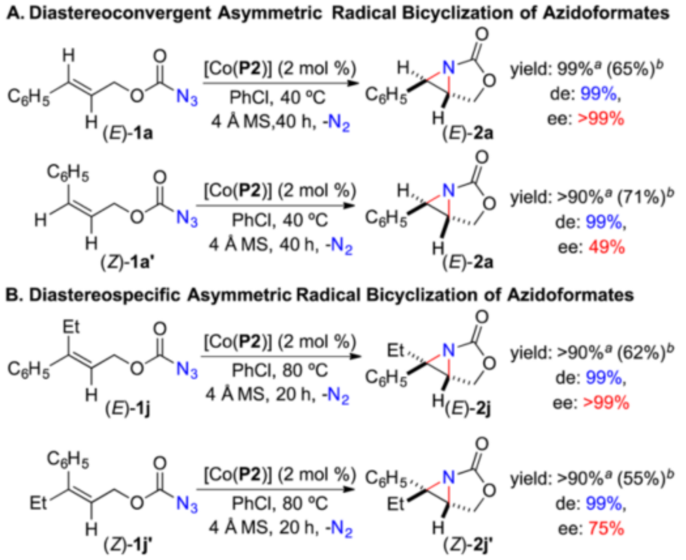
➢ **Regioselective Ring-Opening**



J. Am. Chem. Soc. **2017**, *139*, 9164-9167

Radical Bicyclization of Allyl Azidoformates

➤ Radical Bicylization Mechanism



J. Am. Chem. Soc. **2017**, *139*, 9164-9167

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