Stereogenic-Only-at-Metal Asymmetric Catalysis

Bill Darrow

SED Group Meeting

April 17, 2018

Overview

- Chiral Metal Complexes
- A Historical Perspective on Stereogenic-Only-at-Metal
- Meggers' Catalyst Design
- Survey of Meggers' Publications Using These Complexes
- Conclusion and Critiques

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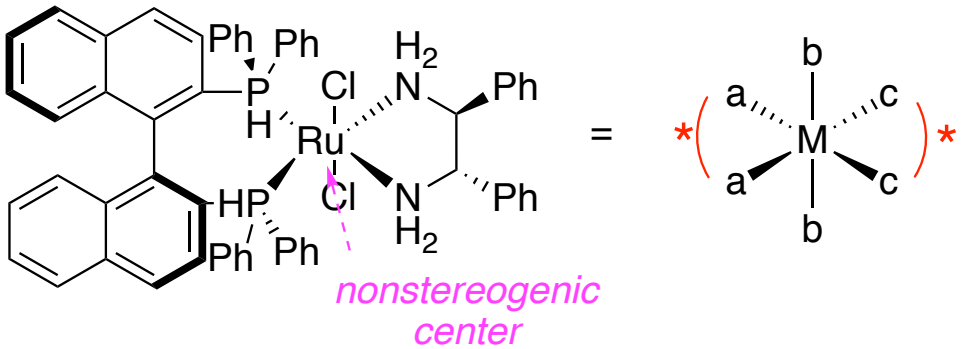
Chiral Metal Complexes

Source of Chirality



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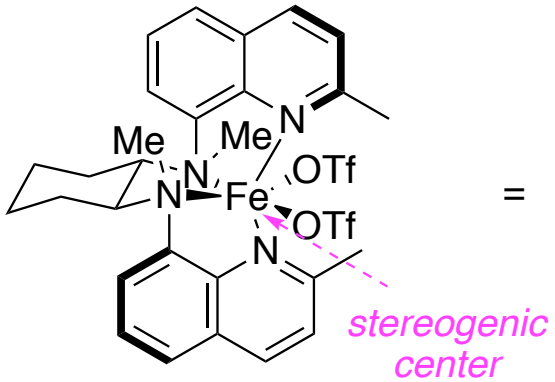
Stereogenic center within chiral ligand



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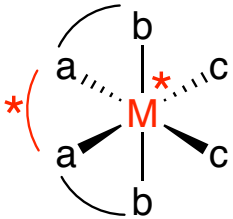
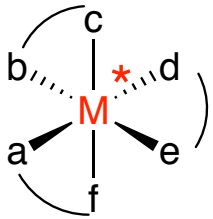
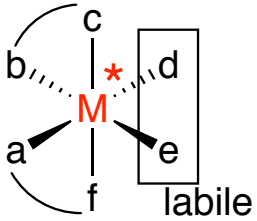


Stereogenic center within ligand and configuration of chiral ligand about stereogenic metal center



inert metal center
catalysis via ligand sphere



reactive metal center
catalysis via metal binding

Configuration of achiral ligands about stereogenic metal center

Ohkuma, T.; Ooka, H.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.*, **1995**, *117*, 2675.
Zang, C.; Liu, Y.; Xu, Z.; Tse, C.; Guan, X.; Wei, J.; Huang, J.; Che, M. *Angew. Chem. Int. Ed.*, **2016**, *55*, 10253.
Zhang, L.; Meggers, E. *Chem. Asian J.*, **2017**, *12*, *2335*.

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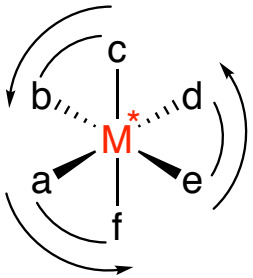
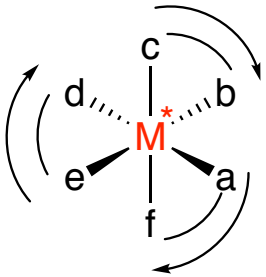
A Historical Perspective on Stereogenic-Only-at-Metal

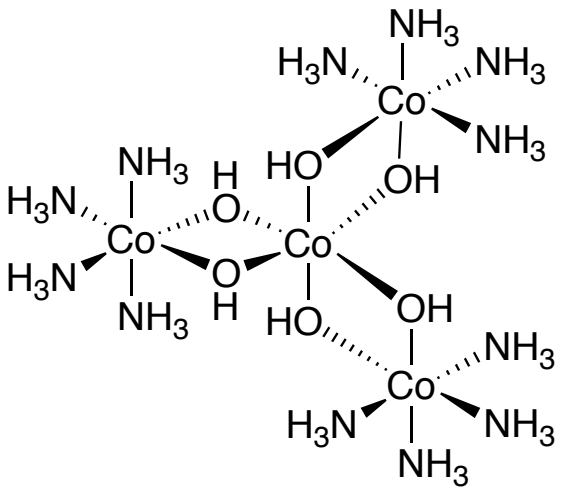
Octahedral Metal Complex Notation



Λ - configuration
(left handed propeller)



Δ - configuration
(right handed propeller)

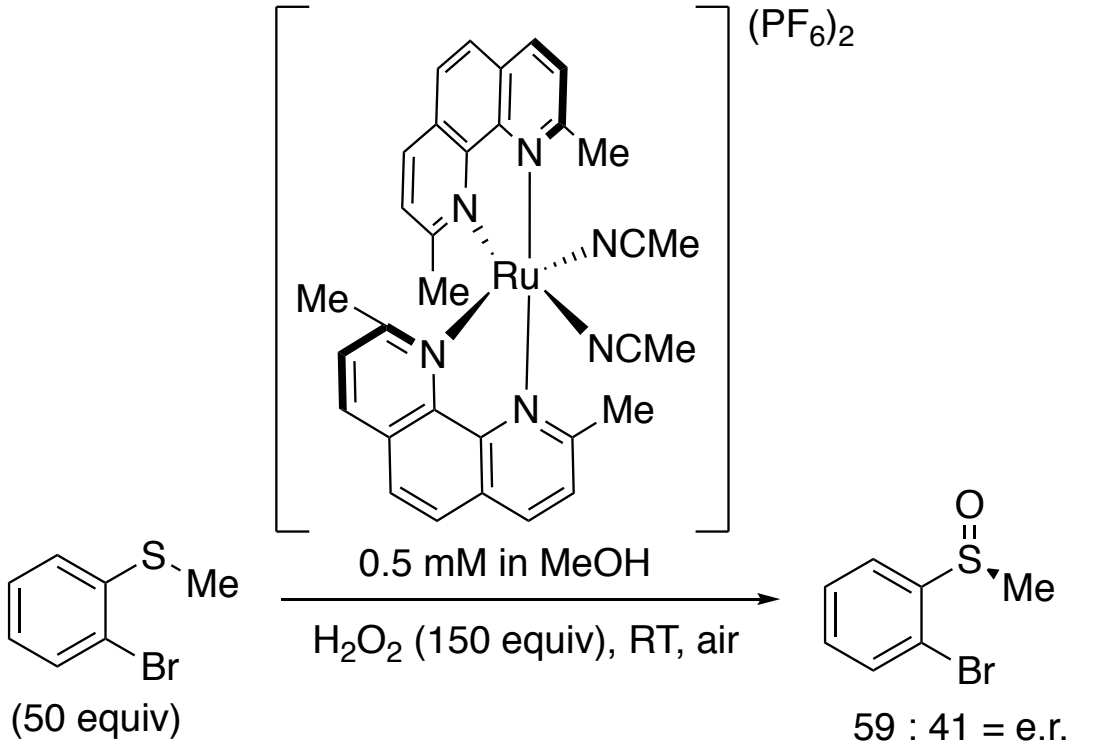


hexol

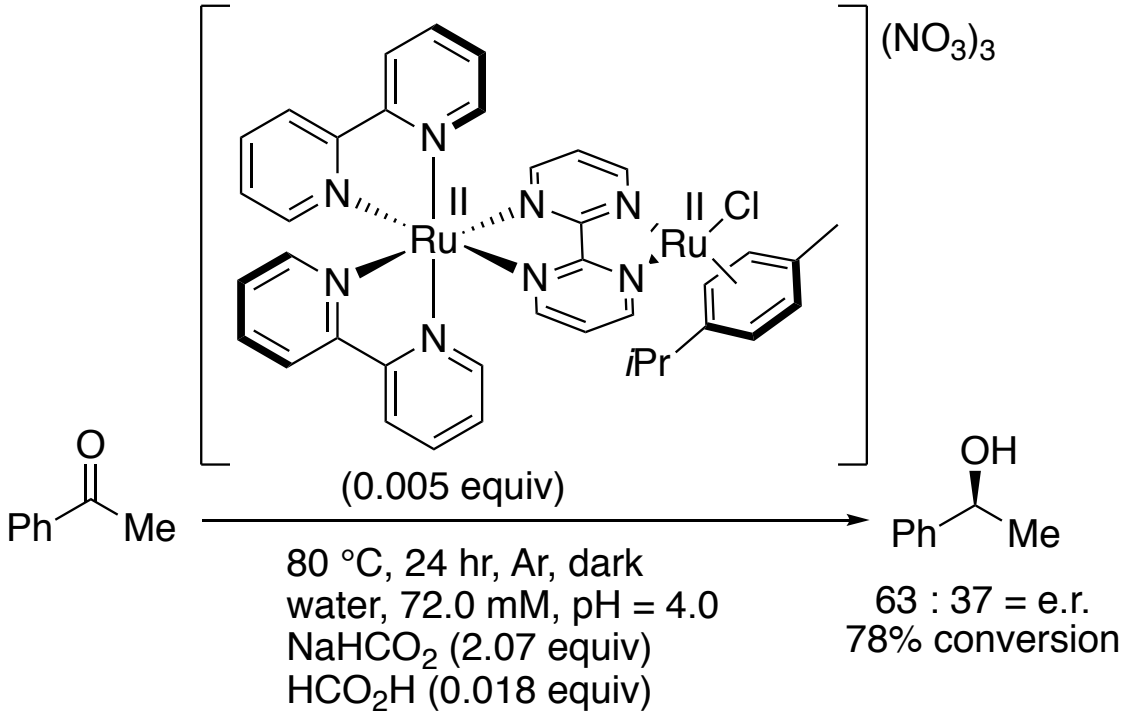
First isolated by Jörgensen in 1898
First resolved by Werner in 1914

Jörgensen, S. M. *Z. Anorg. Chem.*, **1898**, *16*, 184.
Werner, A.; Kuh, H.; Wust, P. *Ber.*, **1914**, *47*, 1961.

First Use of Stereogenic-Only-at-Metal Catalysts



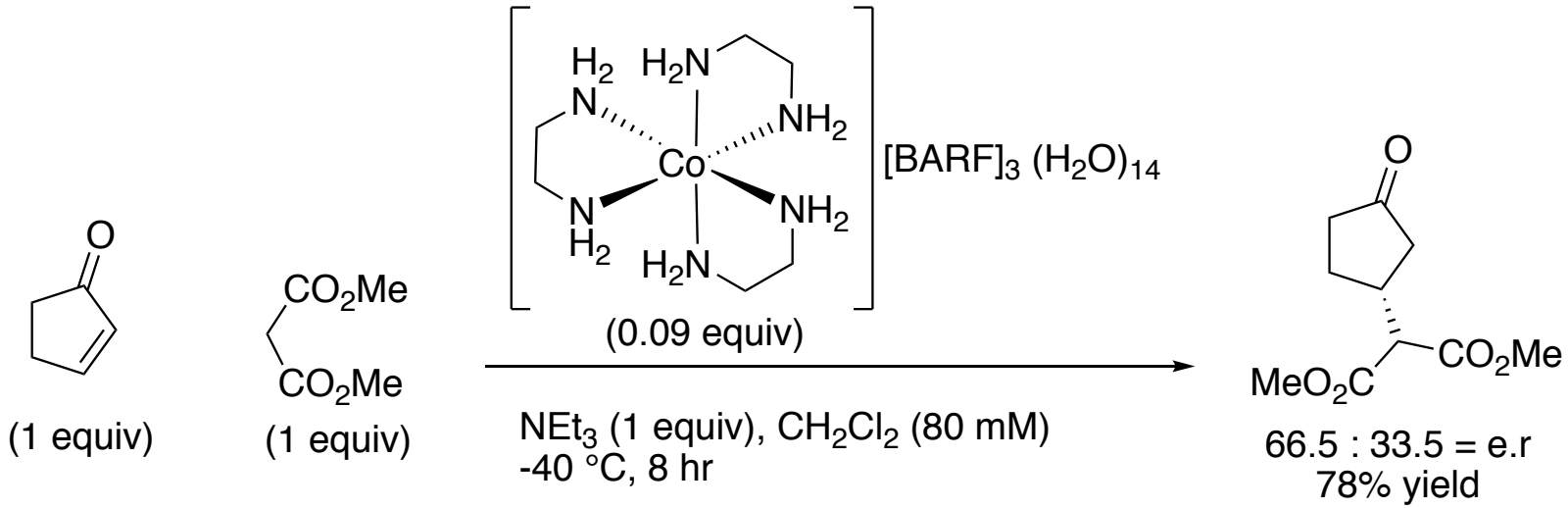
Fontecave, 2003



Fontecave, 2007

Chavarot, M.; Ménage, S.; Hamelin, O.; Charnay, F.; Pécaut, J.; Fontecave, M. *Inorg. Chem.*, **2003**, *42*, 4810.
Hamelin, O.; Rimboud, M.; Pécaut, J.; Fontecave, M. *Inorg. Chem.*, **2007**, *46*, 5354.

First Catalytic Stereogenic-Only-at-Metal Werner Complex



Gladysz, 2008

Kromm, K.; Osborn, P. L.; Gladysz, J. A.; *Organometallics*, **2008**, *21*, 4275.

Professor Eric Meggers

- Received a degree in chemistry from University of Bonn in 1995
- Ph.D., University of Basel (Prof. Bernd Giese) 1996-1999
- Postdoctoral researcher, The Scripps Research Institute, La Jolla, USA (Prof. Peter G. Schultz)
- Assistant Professor Philipps-Universität Marburg 2002-2007
- Full Professor since 2007
- First stereogenic-only-at-metal publication in 2013

Zhang, L.; Meggers, E. *Chem. Asian J.*, **2017**, *12*, *2335*.

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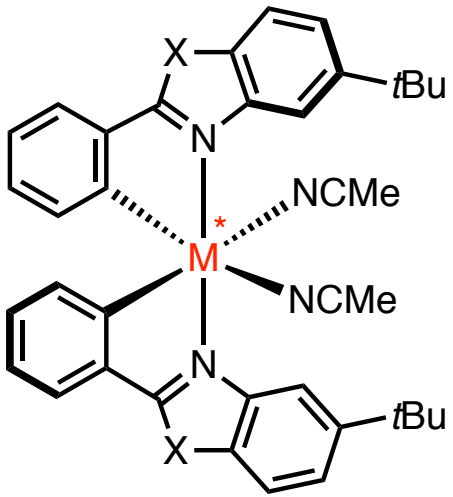
Meggers' Catalyst Design

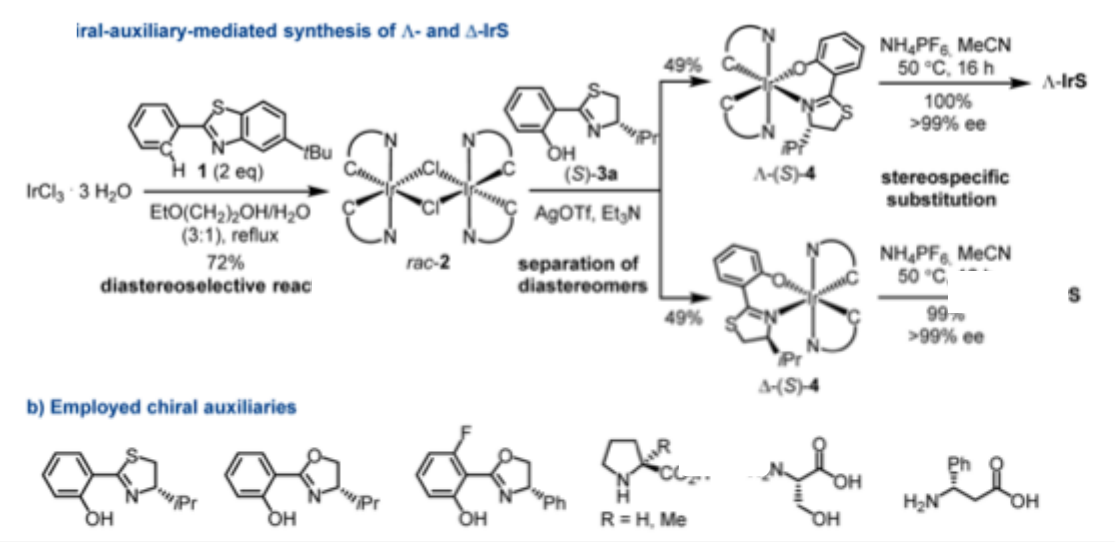
- Early ideas
  - Ease of tuning steric and electronic properties
  - *tert*-butyl groups will provide steric hindrance to give better asymmetric induction
- Key Features
  - Ligand nitrogen atoms bound to metal prefer to be *trans*, while carbon atoms bound to metal prefer to be *cis*—high diastereoselectivity during catalyst synthesis
  - Coordinating acetonitriles are made more labile by a kinetic *trans* effect from the σ-donating phenyl substituents
  - Direct interaction of substrate with stereogenic metal center gives rise to excellent asymmetric induction



Λ–**Ir**
X = S or O
M = Rh, Ru, or Ir

Zhang, L.; Meggers, E. *Chem. Asian J.*, **2017**, *12*, *2335*.
Zhang, L.; Meggers, E. *Acc. Chem. Res.*, **2017**, *50*, 320.

Meggers' Catalyst Synthesis



Zhang, L.; Meggers, E. *Chem. Asian J.*, **2017**, *12*, *2335*.
Zhang, L.; Meggers, E. *Acc. Chem. Res.*, **2017**, *50*, 320.

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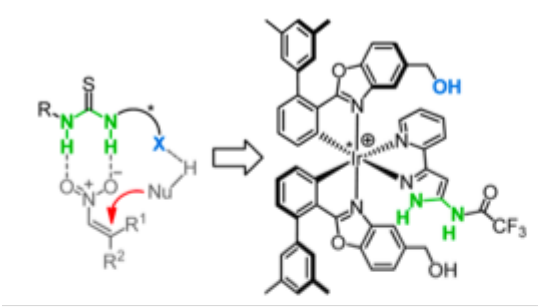
Asymmetric Transfer Hydrogenation: A Proof of Concept

- Limited synthetic utility
- Jacobsen-inspired
- No direct metal substrate coordination
- Low catalyst loadings (down to 0.1 mol %) with high enantiomeric ratios (up to 99.5 to 0.5)

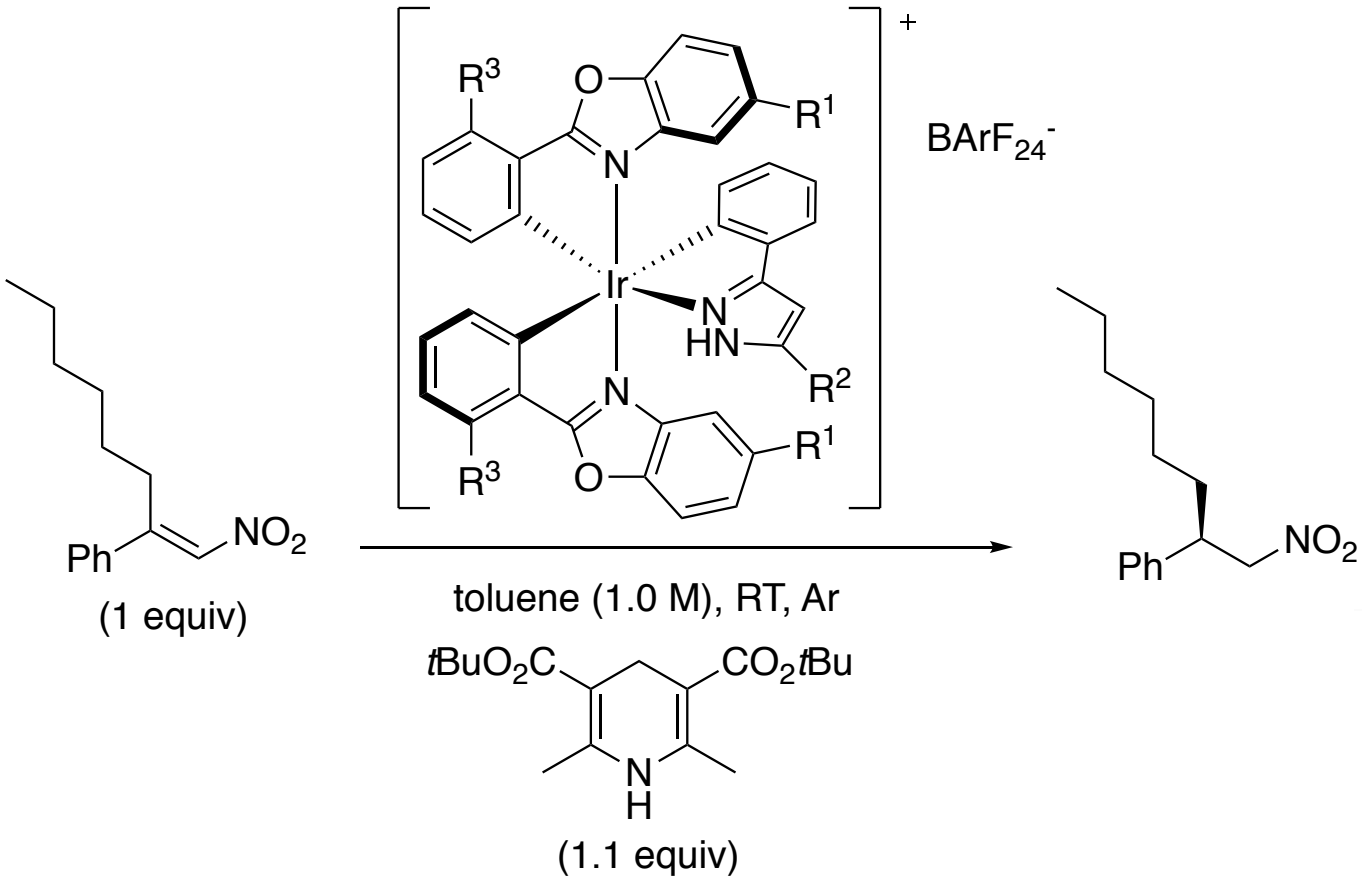


Organic H-Bonding Catalyst

Stereogenic-Only-at-Metal H-Bonding Catalyst

Chen, L.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.*, **2013**, *135*, 10598.

Asymmetric Transfer Hydrogenation: Catalyst Design

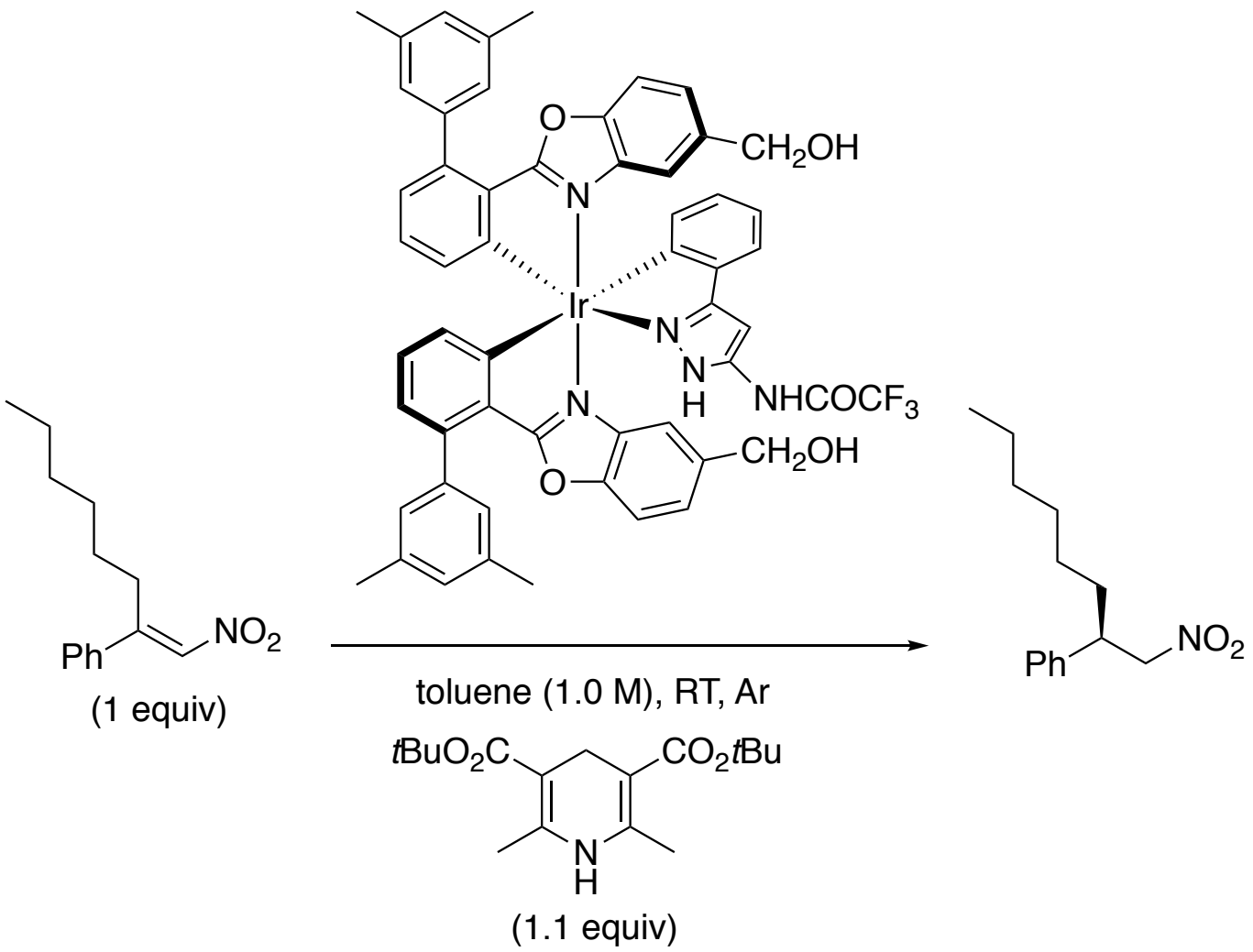


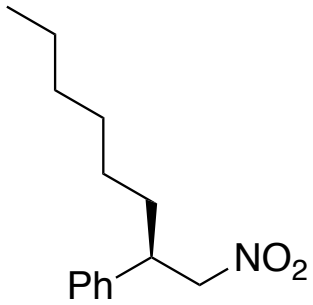
e2C6H3

entry	catalyst	loading (mol %)	t (h)	conv. (%)[b]	ee (%)[c]
1	Λ-Ir1	20	22	92	63
2	Λ-Ir2	20	24	82	70
3	Λ-Ir3	20	20	94	84
4	Λ-Ir4	20	7	96	90
5	Λ-Ir5	20	1	100	99
6	Λ-Ir5	1	20	96	98
7	Λ-Ir6	1	14	94	99
8	Λ-Ir7	20	20	<20	0

Chen, L.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.*, **2013**, *135*, 10598.

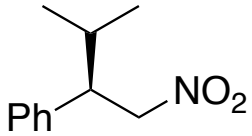
Asymmetric Transfer Hydrogenation: Scope



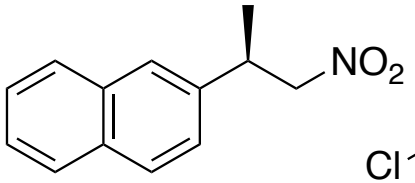


t = 18 hr
1 mol % cat.
94% yield
99.5 : 0.5 e.r.

t = 96 hr
0.1 mol % cat.
89% yield
97 : 3 e.r.



t = 24 hr
1 mol % cat.
92% yield
98 : 2 e.r.



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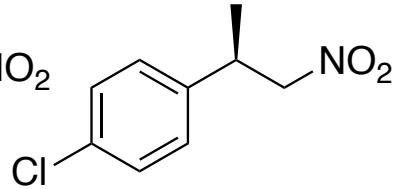

t = 24 hr
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92% yield
97 : 3 e.r.

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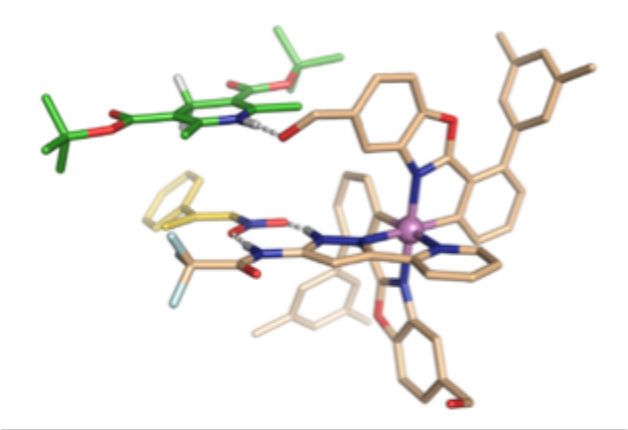
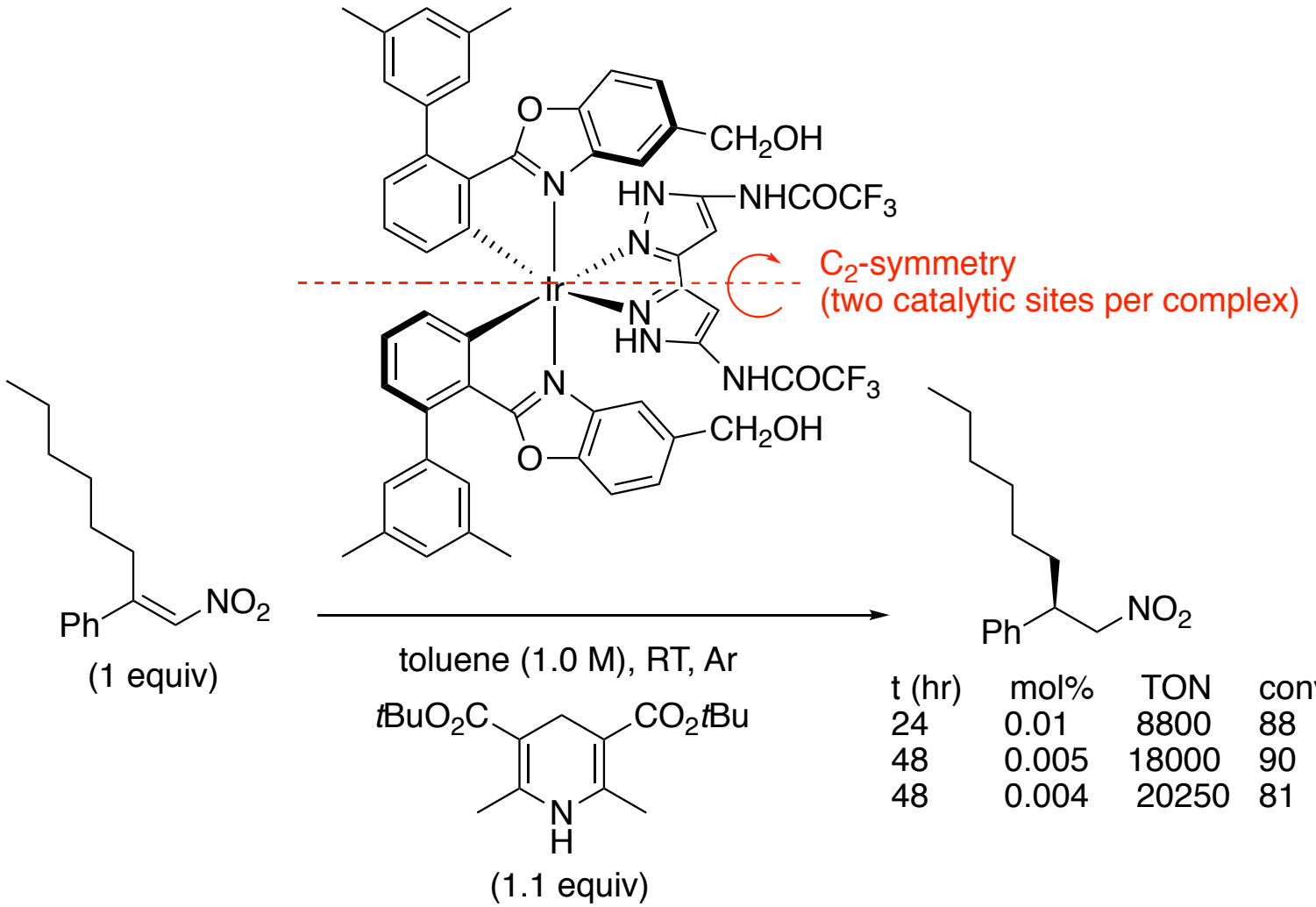
Asymmetric Transfer Hydrogenation: Explaination

- It is presumed that the aminopyrazole activates the nitroalkene by double hydrogen bonding and that one hydroxyl activates the hydride donor ability of the Hantzsch ester.
- Experimental data indicate that the hydroxyl is necessary for reaction to take place.
- This proves that a metal stereogenic center is capable of providing good asymmetric induction .

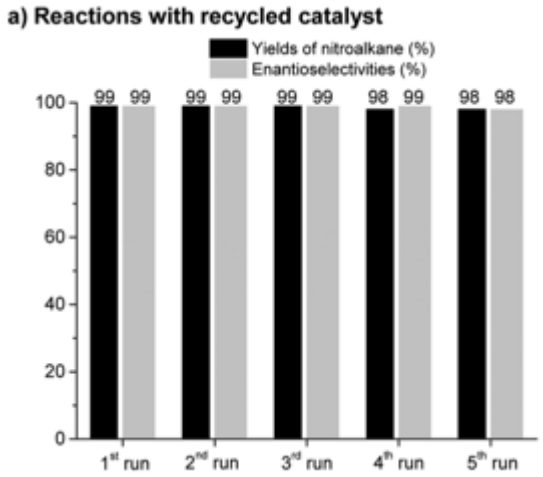


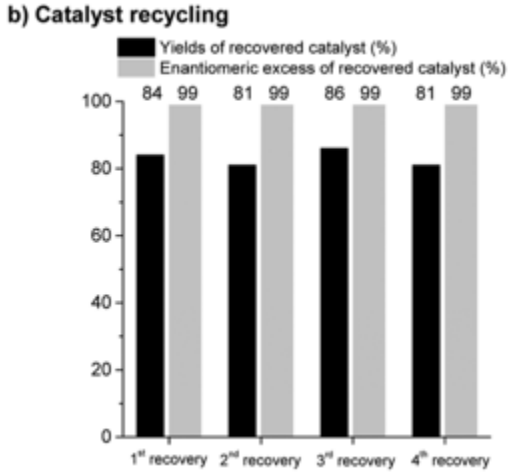
Chen, L.; Xu, W.; Huang, B.; Ma, J.; Wang, L.; Xi, J.; Harms, K.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.*, **2013**, *135*, 10598.
Xu, W.; Arieno, M.; Löw, H.; Huang, K.; Xie, X.; Cruchter, T.; Ma, Q.; Xi, J.; Huang, B.; Wiest, O.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.*, **2016**, *138*, 8774.

Asymmetric Transfer Hydrogenation: Improved Catalyst



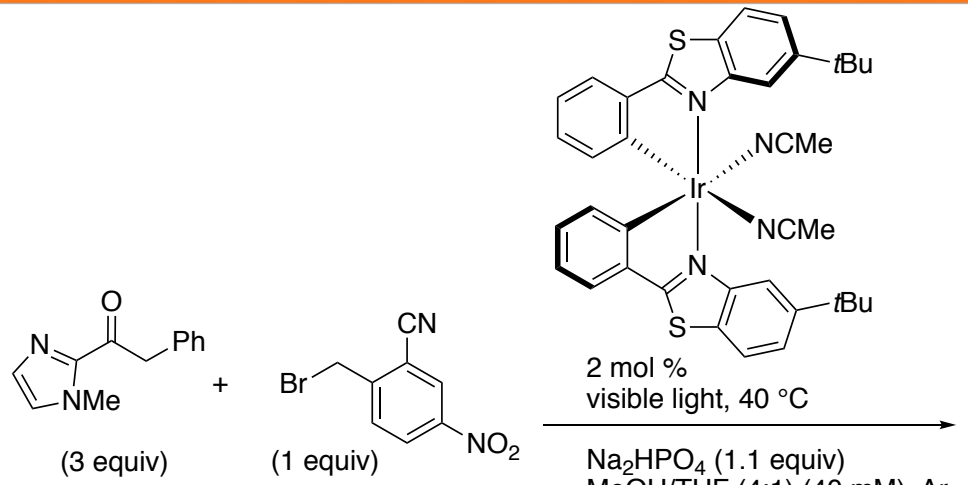
t (hr)	mol%	TON	conv (%)	e.r
24	0.01	8800	88	98 : 2
48	0.005	18000	90	97 : 3
48	0.004	20250	81	95.5 : 4.5

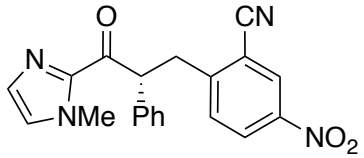




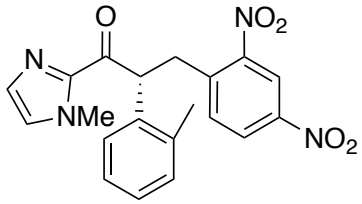
Xu, W.; Arieno, M.; Löw, H.; Huang, K.; Xie, X.; Cruchter, T.; Ma, Q.; Xi, J.; Huang, B.; Wiest, O.; Gong, L.; Meggers, E. *J. Am. Chem. Soc.*, **2016**, *138*, 8774.

Asymmetric Photoredox Metal Enolate Addition: Scope

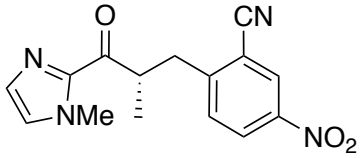




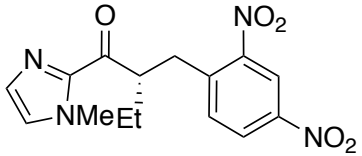
1.5 hr, 100% yield, 99.5 : 0.5 e.r.



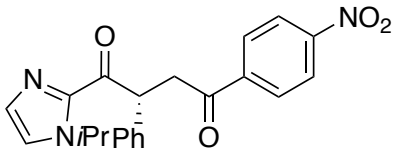
2 hr, 93% yield, 99.5 : 0.5 e.r.



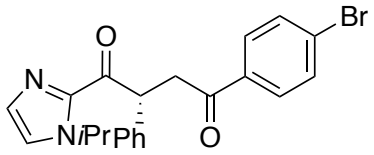
24 hr, 87% yield, 98.5 : 1.5 e.r.



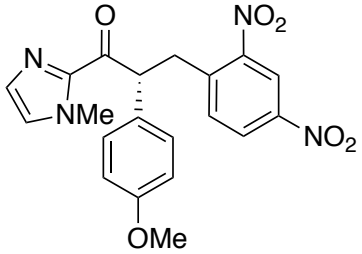
36 hr, 84% yield, 95.5 : 4.5 e.r.



6 hr, 91% yield, 95 : 5 e.r.



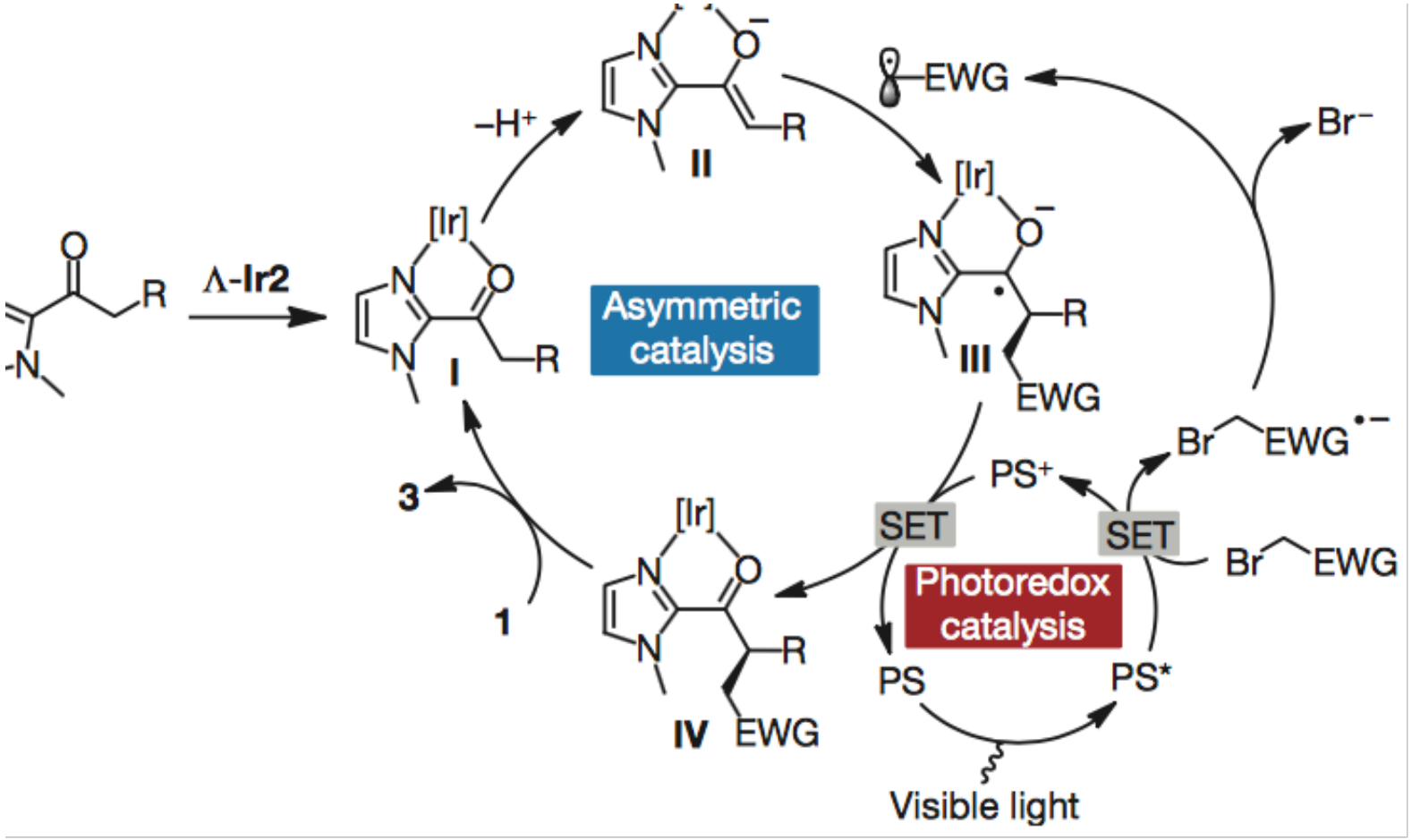
2 hr, 86% yield, 95.5 : 4.5 e.r.



24 hr, 91% yield, 95.5 : 4.5 e.r.

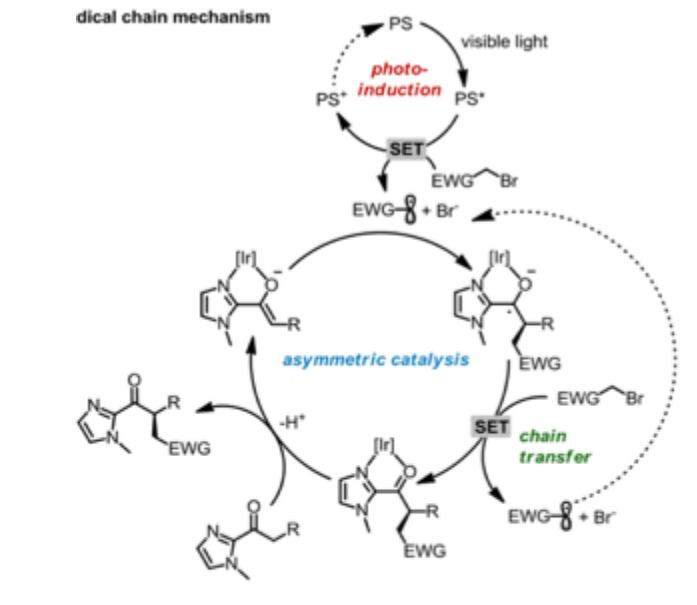
Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature*., **2014,** *515*, 100.

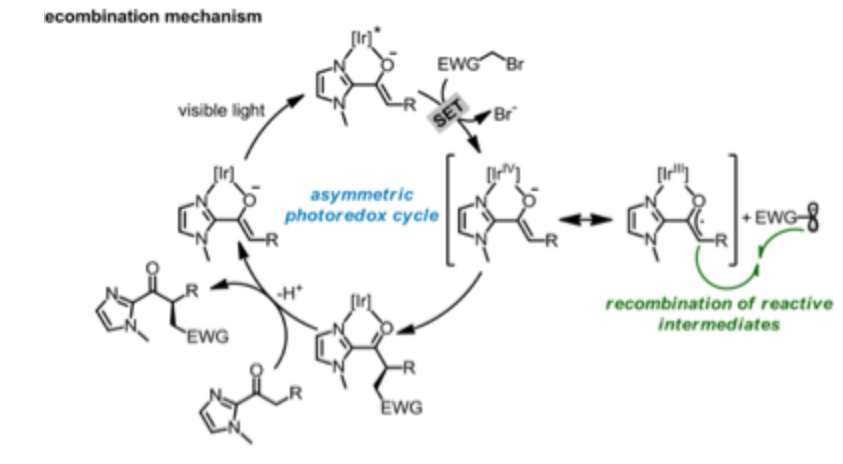
Proposed Mechanism



Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature*., **2014,** *515*, 100.

Alternate Mechanisms

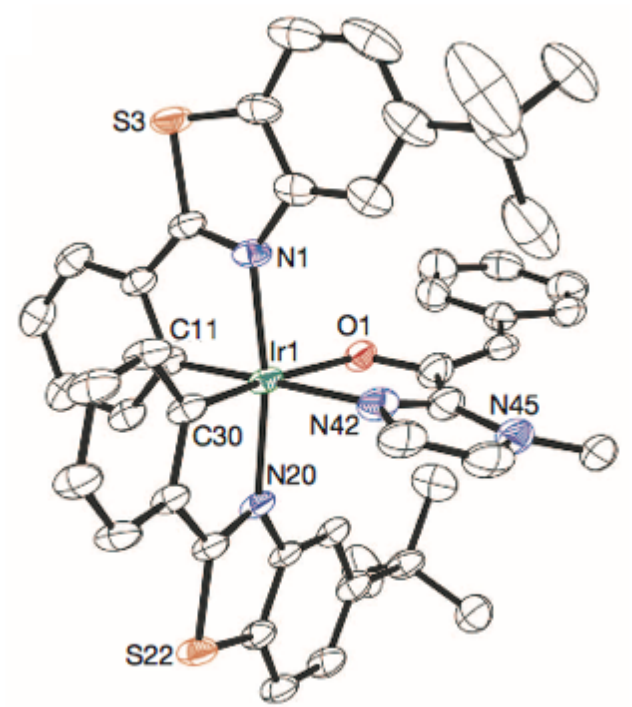




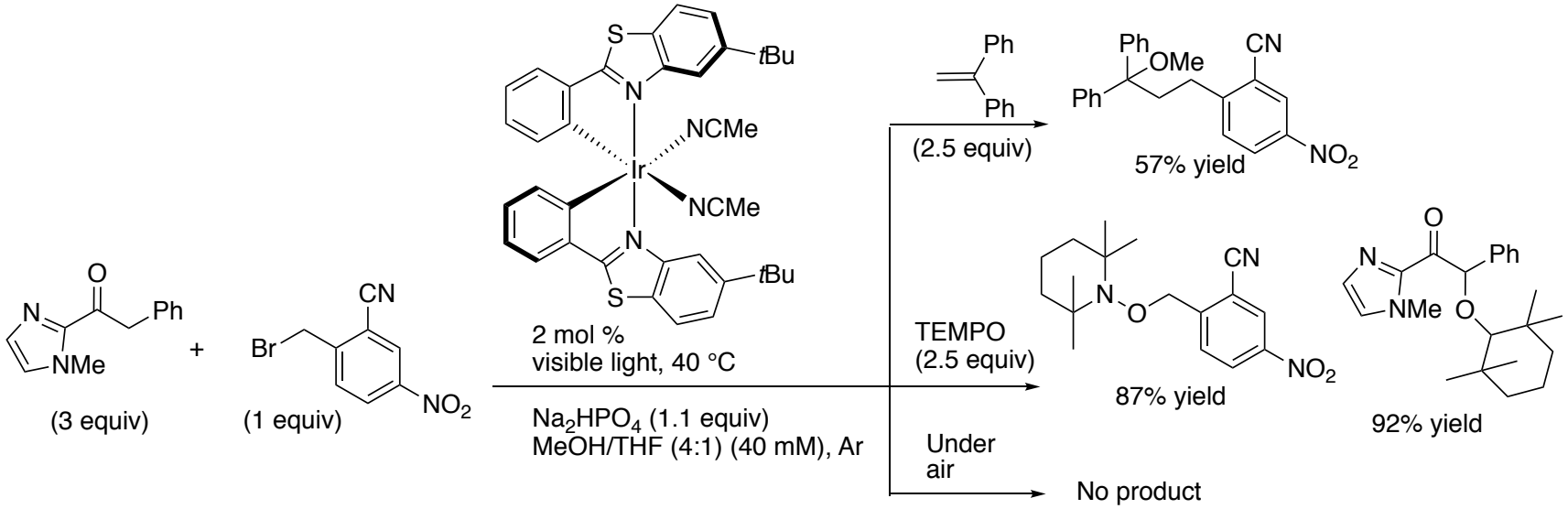
Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature*., **2014,** *515*, 100.

Mechanistic Evidence

- A crystal structure of Ir enolate II was obtained
- Radical traps confirmed the presence of radical species



Ir enolate II



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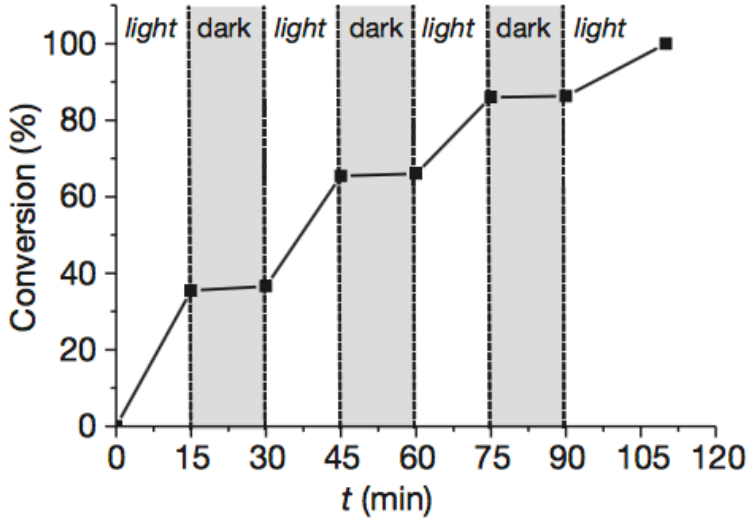
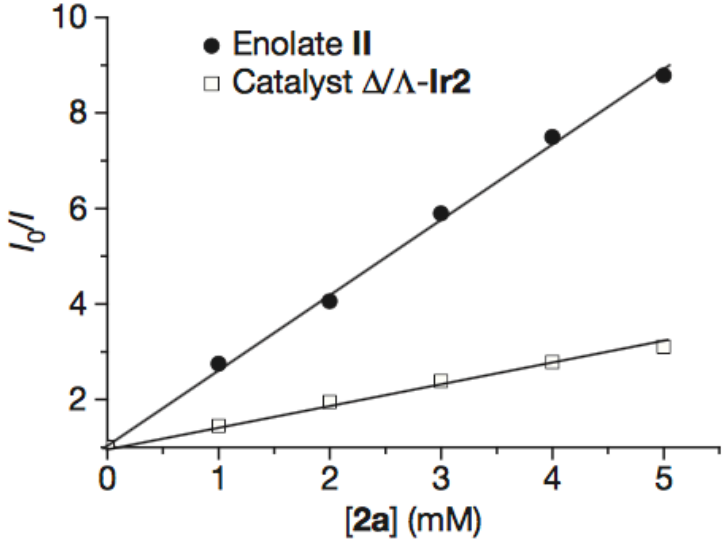
Additional Mechanistic Evidence

- Reaction stops when removed from light
- As BnBr is added, the luminescence emission of enolate II is quenched more effectively than unbound Ir cat.
- Enolate II has a longer lambda max and wider range of high absorption wavelengths than unbound Ir cat, allowing for easier excitation
- Enolate II has a lower ox. potential than Ir cat, so it is a stronger reducing agent capable of engaging in SET





Complex	Absorbance λ_{max}	Emission λ_{max} (E^{00})	$E_{1/2}$(PS$^+$/PS)	$E_{1/2}$(PS$^+$/PS*)
Δ/Λ-**Ir2**	425 nm	560 nm (2.21 eV)	> +1.5 V	> –0.71 V
Enolate **II**	440 nm	550 nm (2.25 eV)	+0.51 V	–1.74 V

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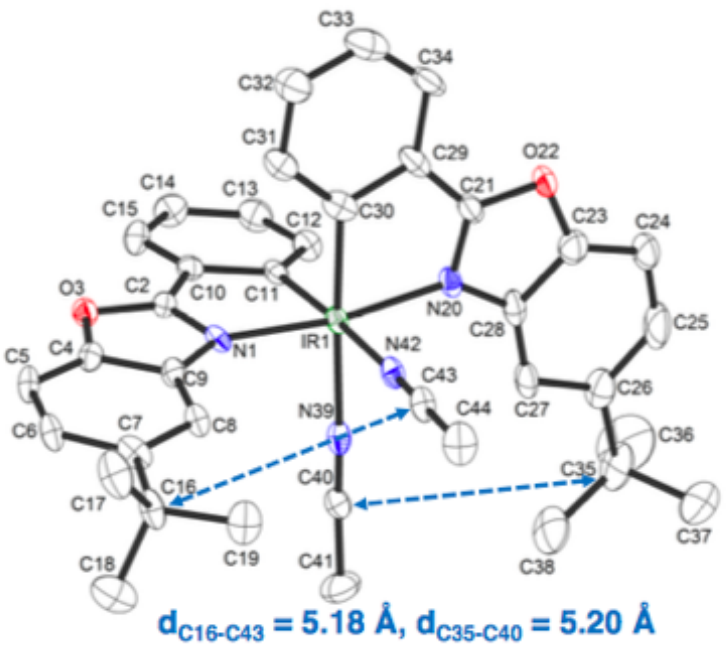
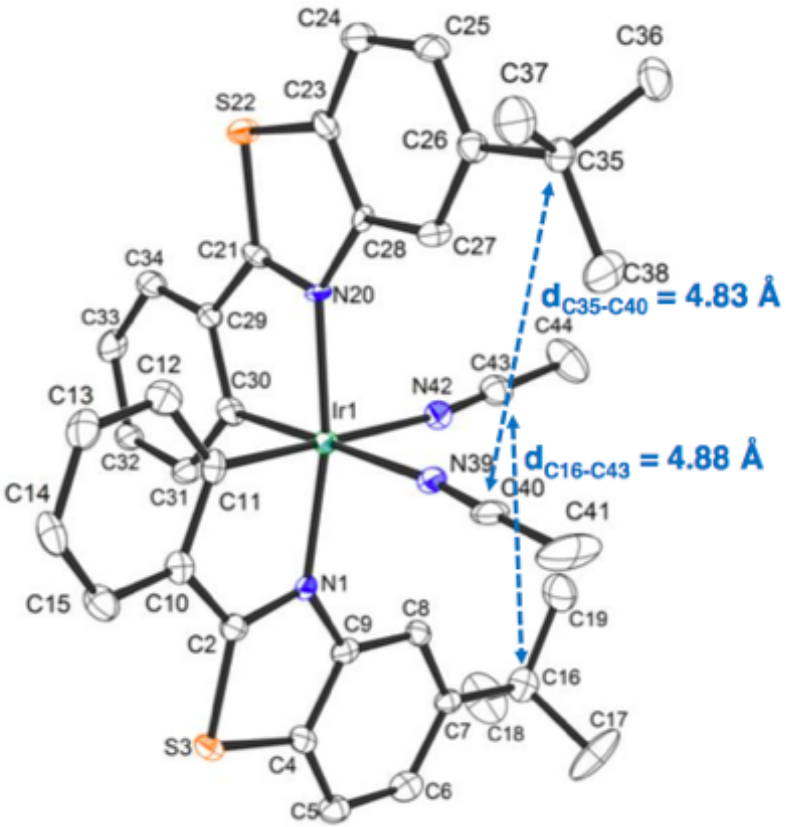
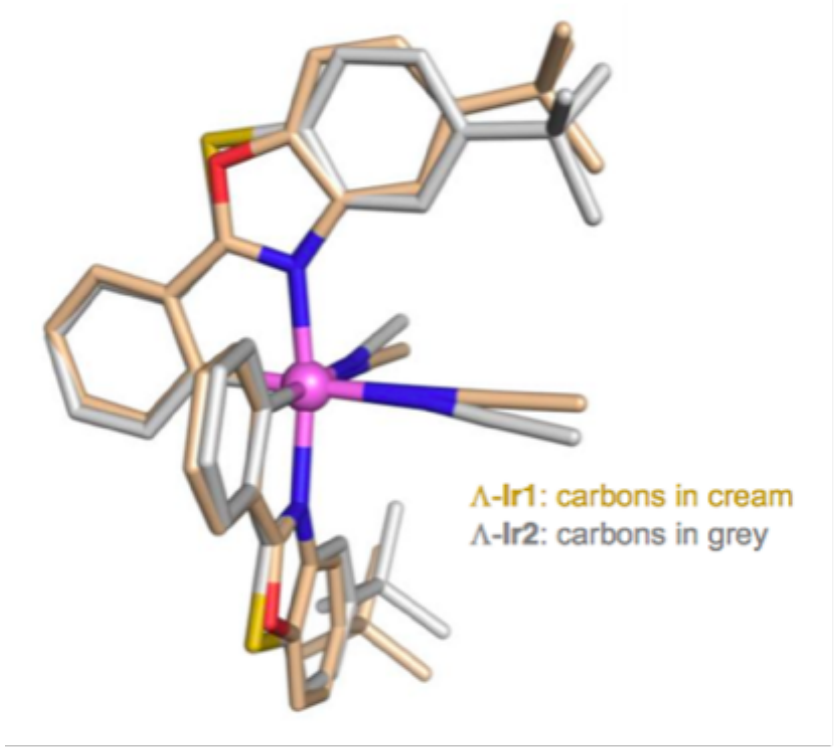
Benzoxazole/Benzothiazole Steric Effects



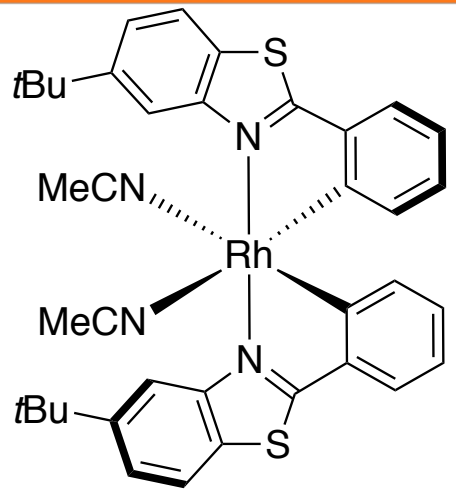


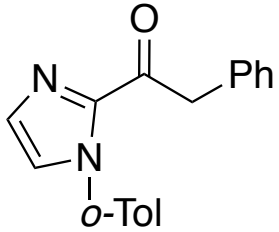


Longer benzothiazole C-S bonds relative to benzoxazole C-O bonds position bulky *t*Bu groups closer to substrate binding site, providing better asymmetric induction

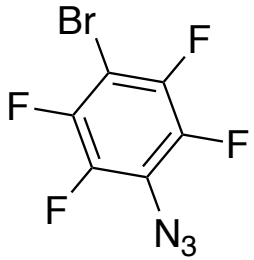
Huo, H.; Shen, X.; Wang, C.; Zhang, L.; Röse, P.; Chen, L.; Harms, K.; Marsch, M.; Hilt, G.; Meggers, E. *Nature*., **2014,** *515*, 100.

α-Amination of Acylimidazoles: Aryl Azide Scope





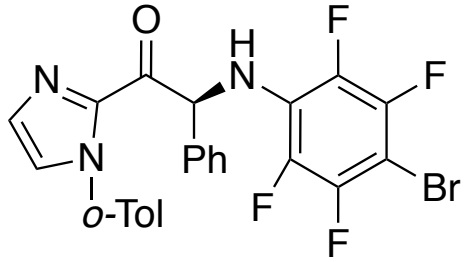
(1 equiv)



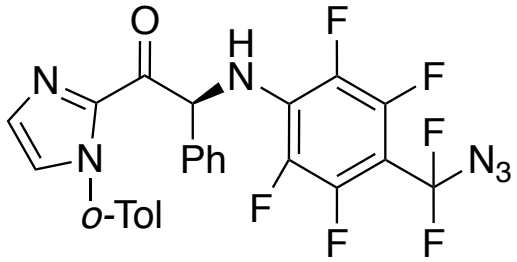
(3.0 equiv)

4 mol %
visible light, RT

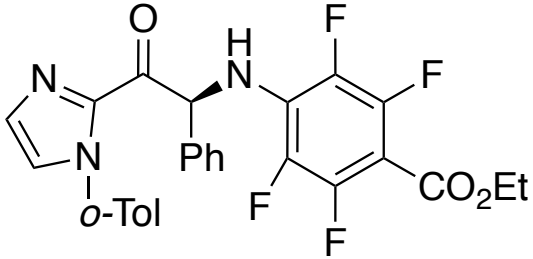
$[Ru(bpy)_3](PF_6)_2$ (2.5 mol%)
Na_2HPO_4 (20 mol %)
water (20 equiv)
acetone/DMSO (9:1) (0.2 M), N_2



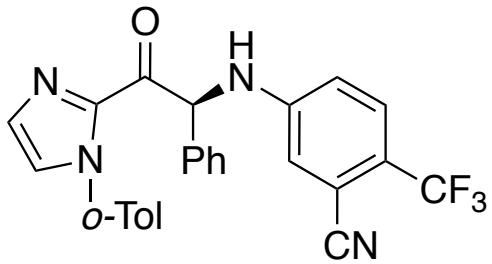
5 hr, 90% yield, 99.5 : 0.5 e.r.



11 hr, 48% yield, 99 : 1 e.r.



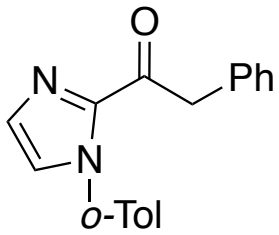
6 hr, 81% yield, 99.5 : 0.5 e.r.



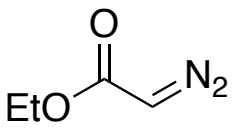
6 hr, 74% yield, 98 : 2 e.r.

Huo, H.; Webster, R. D.; Harms, K.; Meggers, E. *J. Am. Chem*. Soc., **2017,** *138*, 12636.

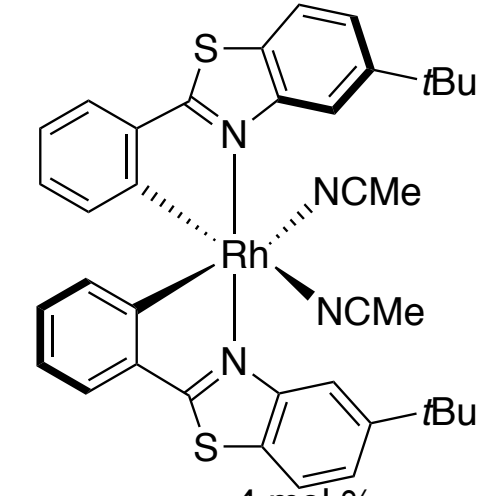
α-Alkylation of Acylimidazoles: Diazo Carboxylic Ester Scope



(1 equiv)

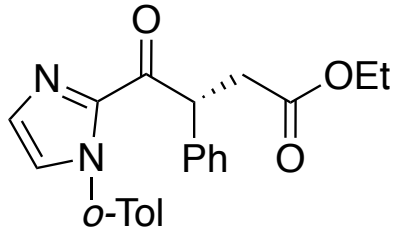


(3.0 equiv)

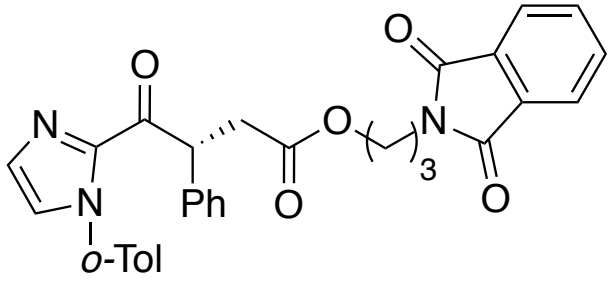


4 mol %
visible light, RT

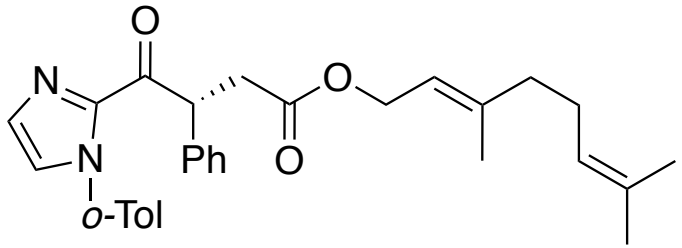
$[Ru(bpy)_3](PF_6)_2$ (1.5 mol%)
Na_2HPO_4 (20 mol %)
water (20 equiv)
acetone/DMSO (9:1) (0.2 M), N_2



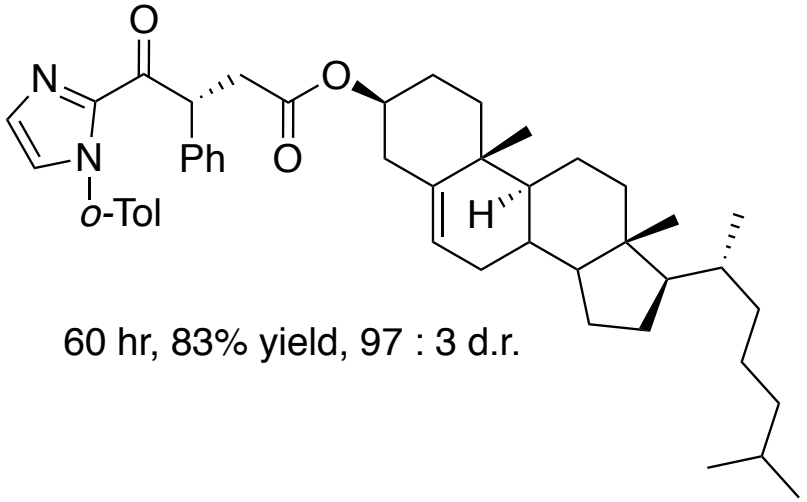
15 hr, 99% yield, 98.5 : 1.5 e.r.



16 hr, 98% yield, 98 : 2 e.r.



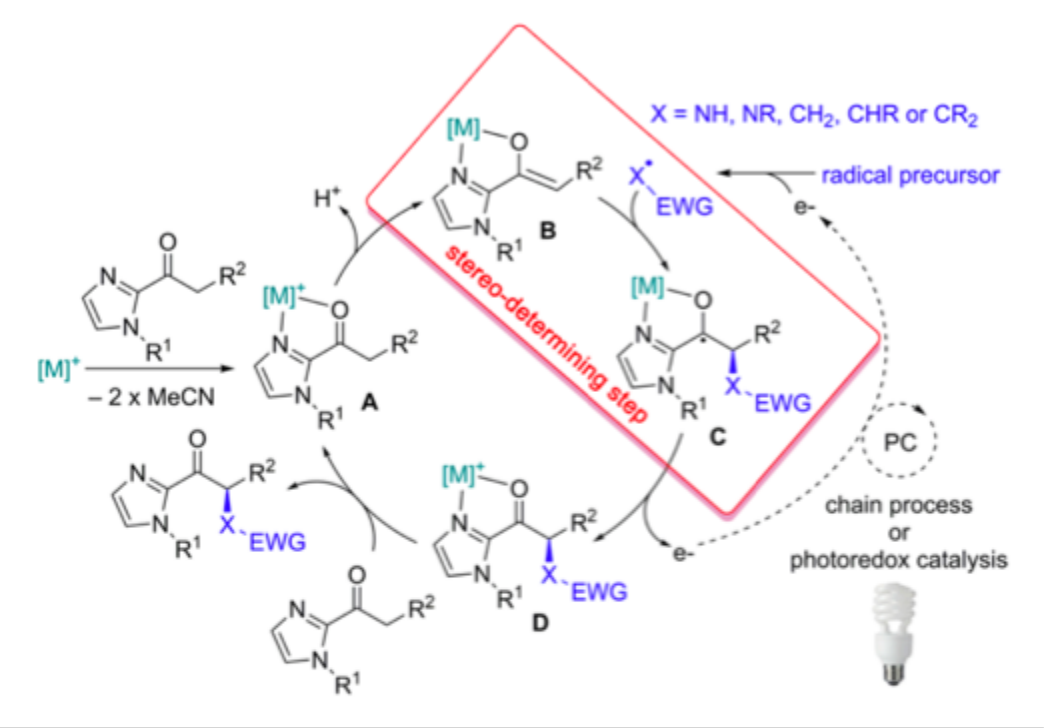
24 hr, 82% yield, 98 : 2 e.r.



60 hr, 83% yield, 97 : 3 d.r.

Huo, H.; Webster, R. D.; Harms, K.; Meggers, E. *J. Am. Chem*. Soc., **2017,** *138*, 12636.

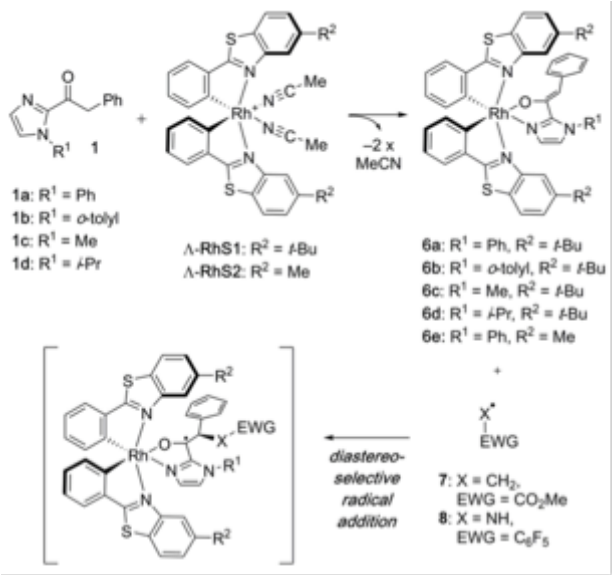
Proposed Mechanism

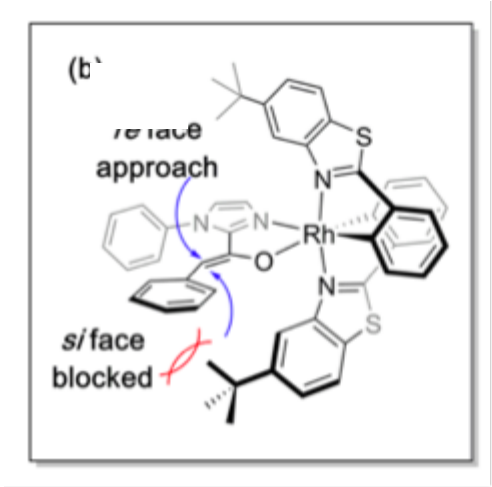


- Based on similar mechanistic evidence to the earlier Ir enolate chemistry
- Independently synthesized Rh enolate is a competant catalyst
- Air prevents product formation, aryl olefin gave radical addition product, and TEMPO gives the adduct
- No cyclopropanation of olefin implies mechanism does not involve a carbene

Chen, S.; Huang, X.; Houk, K. N.; Meggers, E. *J. Am. Chem. Soc.*, **2017,** *139*, 17902.

Substrates Used in Computational Study



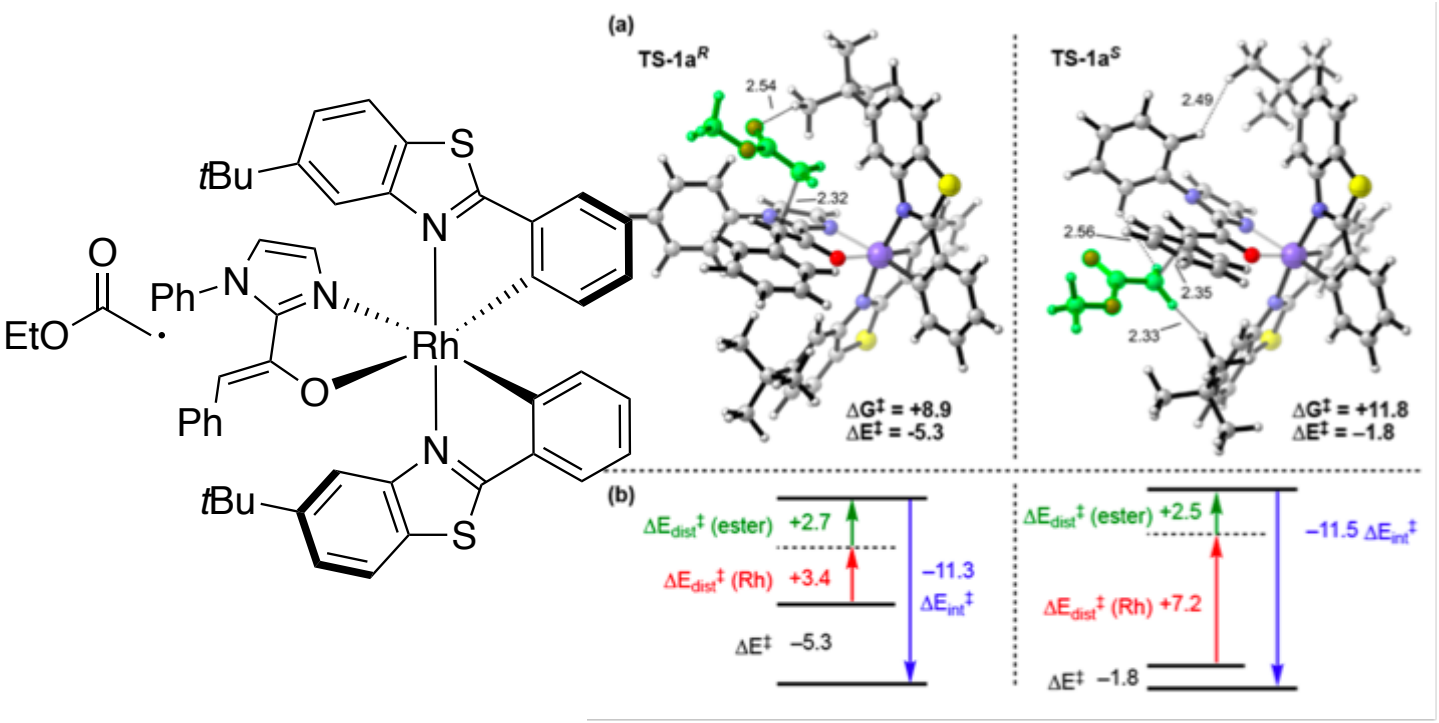


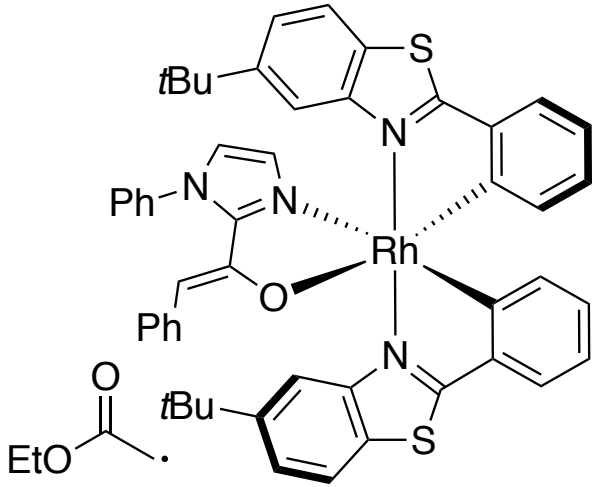
Gas phase transition state (TS) geometries:
LANL2DZ basis set was used for Rh;
6-31G(d) for all other atoms

Distortion-interaction energies: M06/6-311G++(d,p)-SDD level
Using previous TS geometries

Chen, S.; Huang, X.; Houk, K. N.; Meggers, E. *J. Am. Chem. Soc.*, **2017,** *139*, 17902.

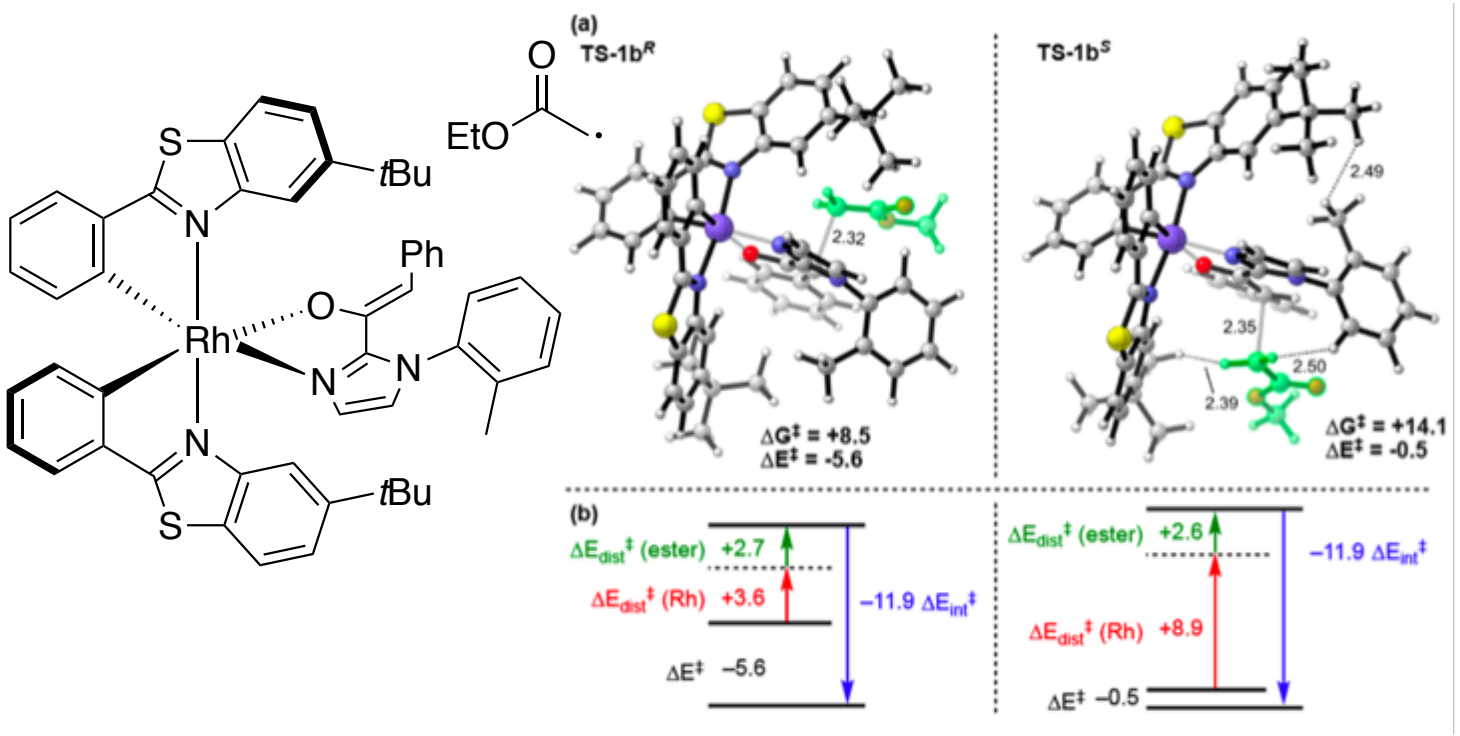
Rationalizing Favorability of Re Face Approach Preference

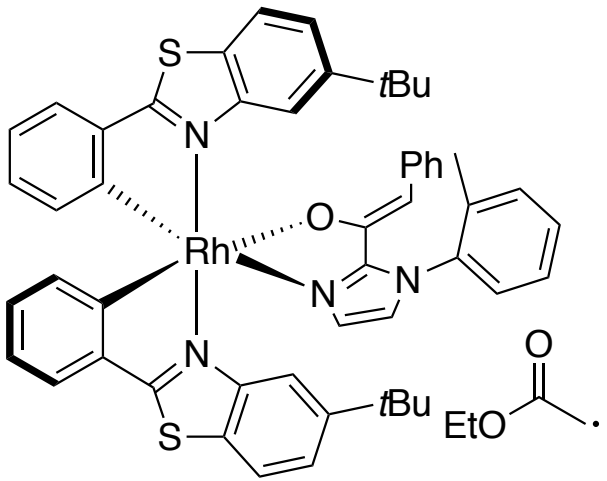




Chen, S.; Huang, X.; Houk, K. N.; Meggers, E. *J. Am. Chem. Soc.*, **2017,** *139*, 17902.

A More Sterically Hindered System

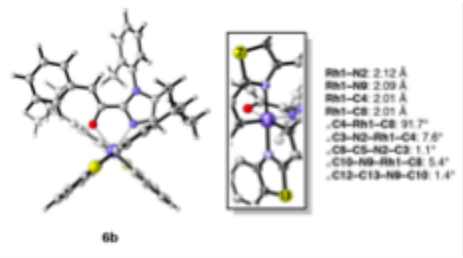




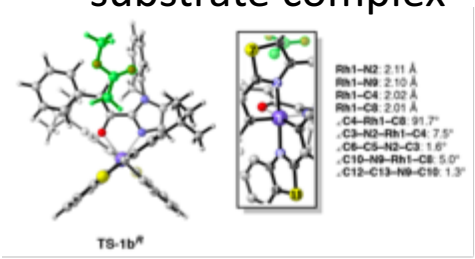
Chen, S.; Huang, X.; Houk, K. N.; Meggers, E. *J. Am. Chem. Soc.*, **2017,** *139*, 17902.

Source of Distortion in Octahedral Framework

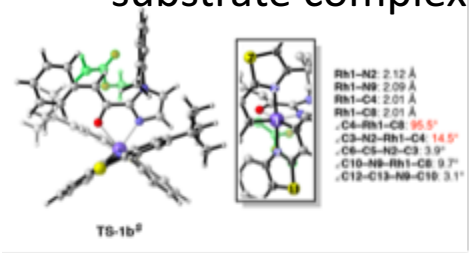
Catalyst-substrate complex



Re approach to Catalyst-substrate complex

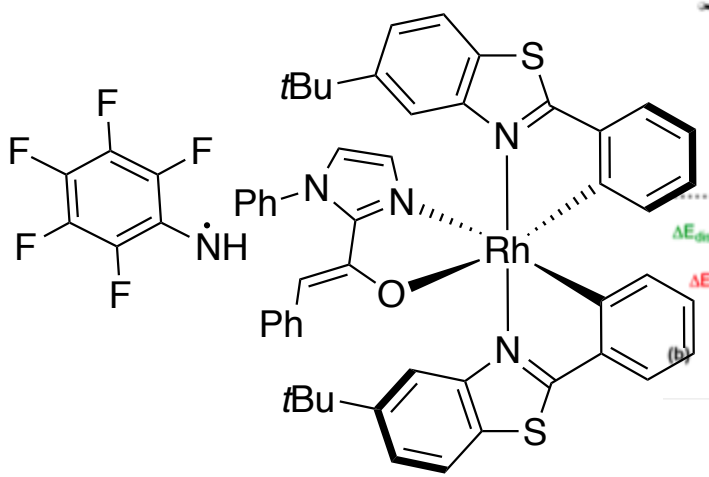


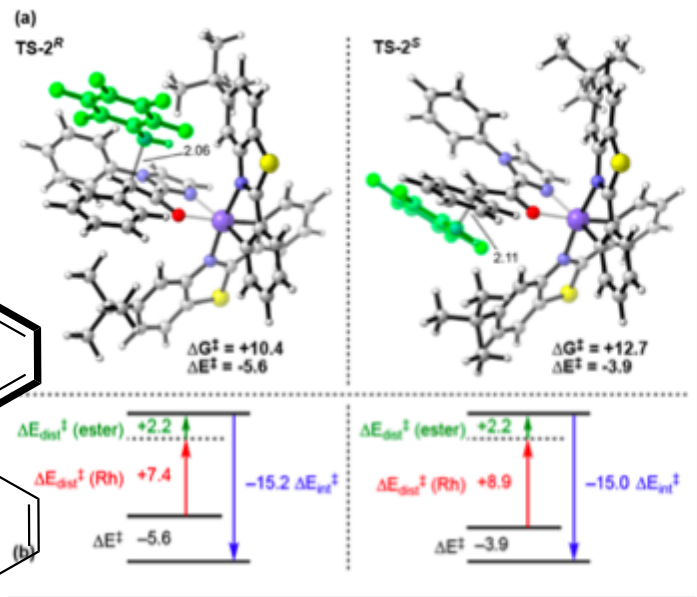
Si approach to Catalyst-substrate complex

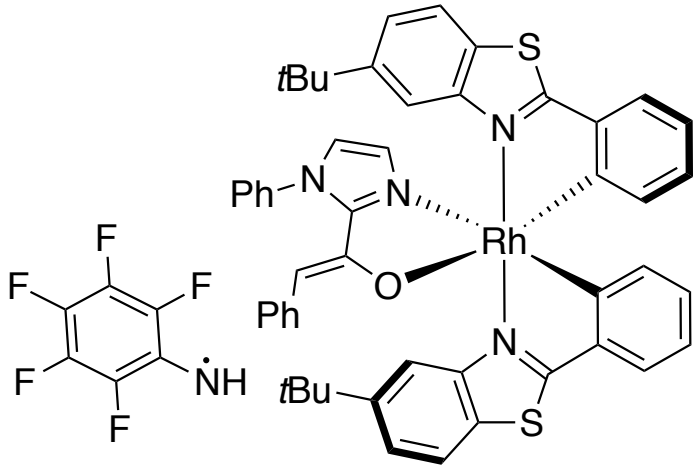


Chen, S.; Huang, X.; Houk, K. N.; Meggers, E. *J. Am. Chem. Soc.*, **2017,** *139*, 17902.

Re Approach Preference in the Aniline System



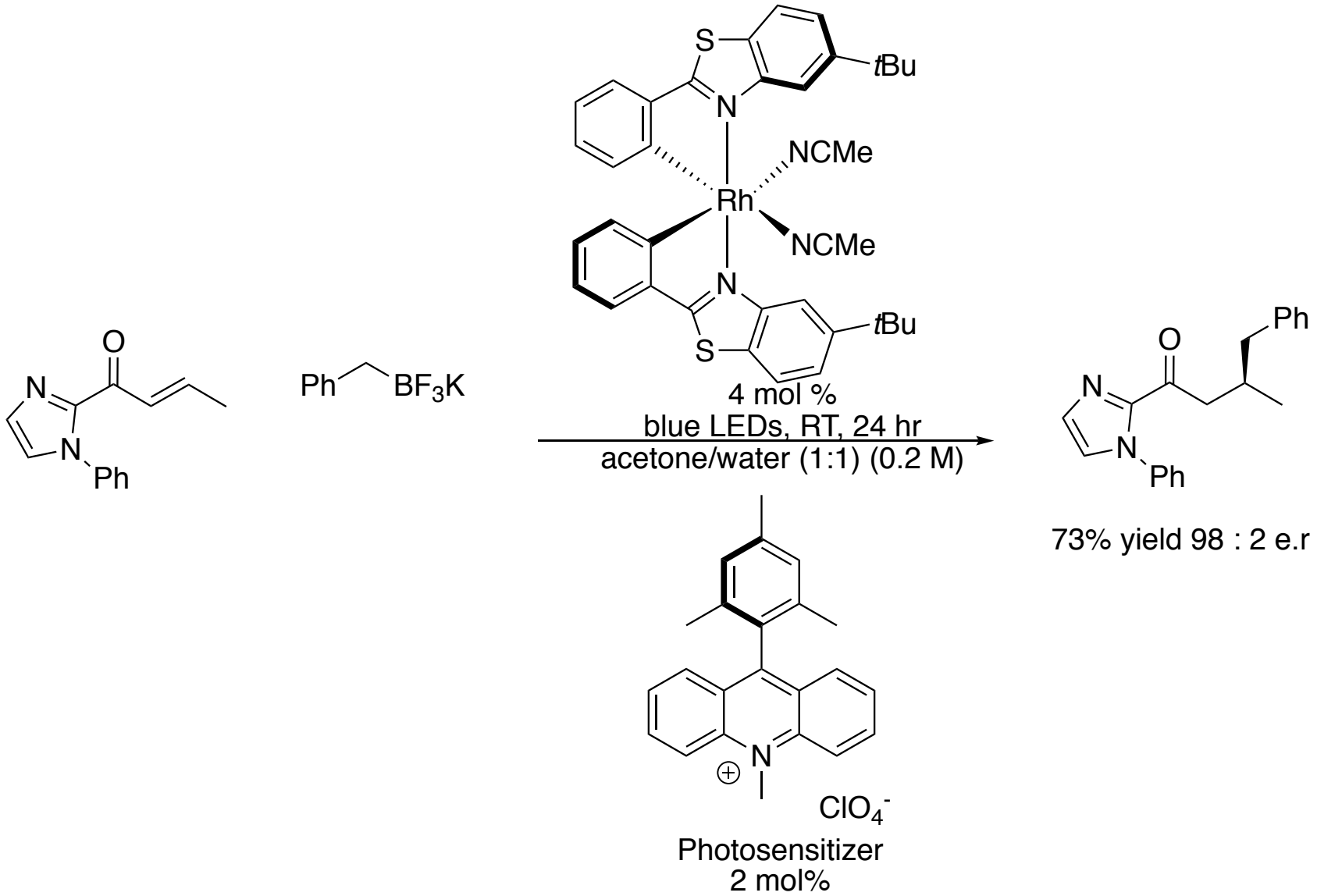




Chen, S.; Huang, X.; Houk, K. N.; Meggers, E. *J. Am. Chem. Soc.*, **2017,** *139*, 17902.

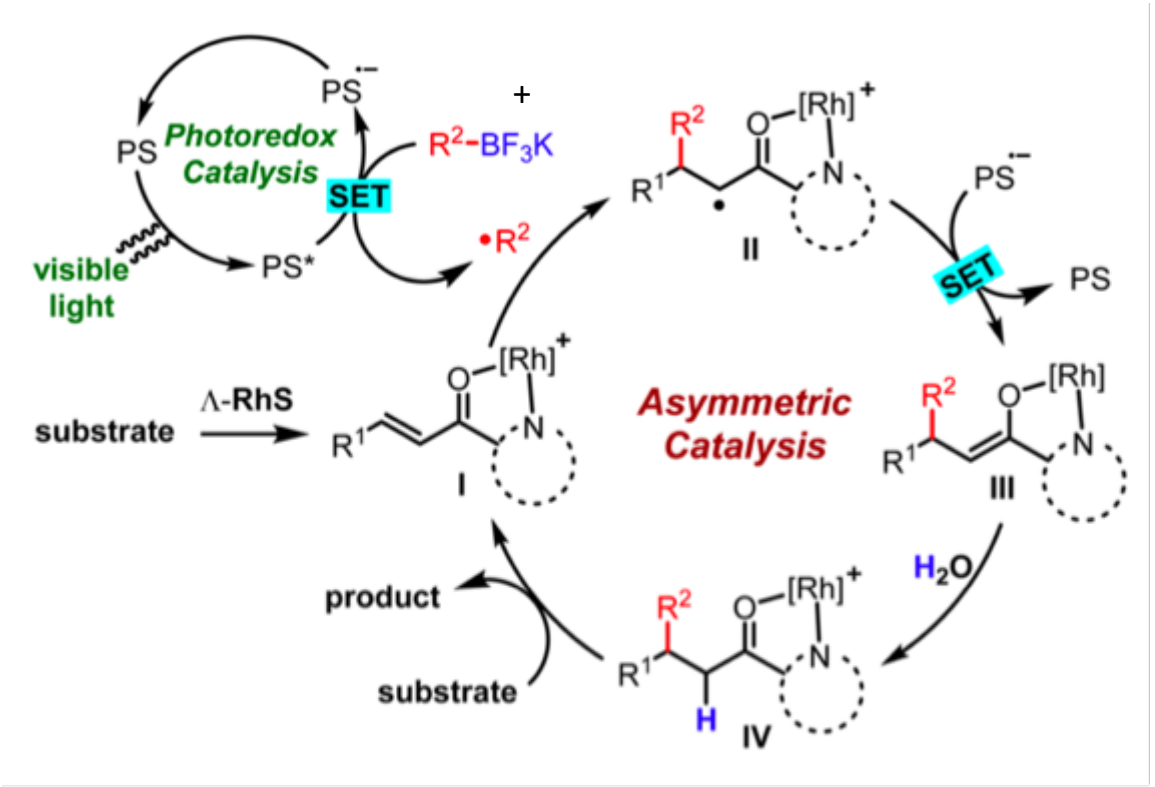
Group Problem

Draw a catalytic cycle for the following transformation:



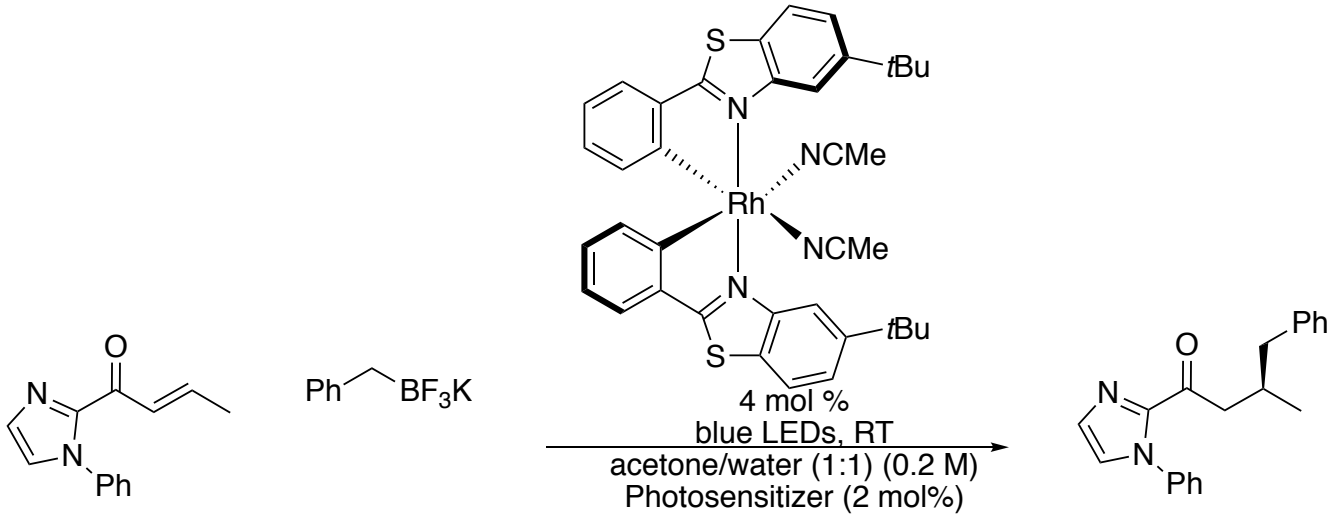
73% yield 98 : 2 e.r

Solution

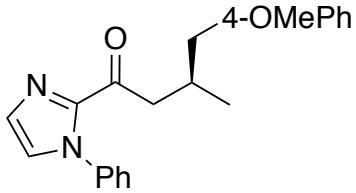


Huo, H.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.*, **2016,** *138*, 6936.

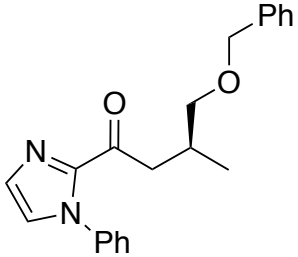
Scope



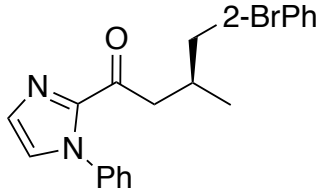
24 hr, 73% yield 98 : 2 e.r.



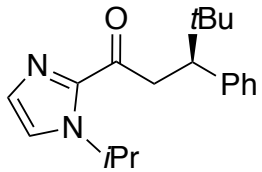
4 hr, 89% yield 96.5 : 3.5 e.r.



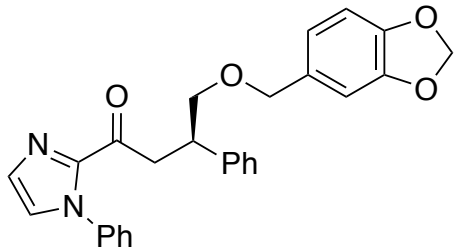
12 hr, 57% yield 96 : 4 e.r.



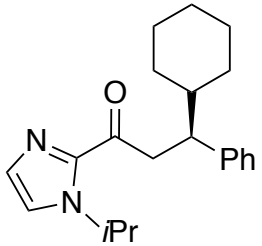
9 hr, 72% yield 97 : 3 e.r.



14 hr, 93% yield 99 : 1 e.r.



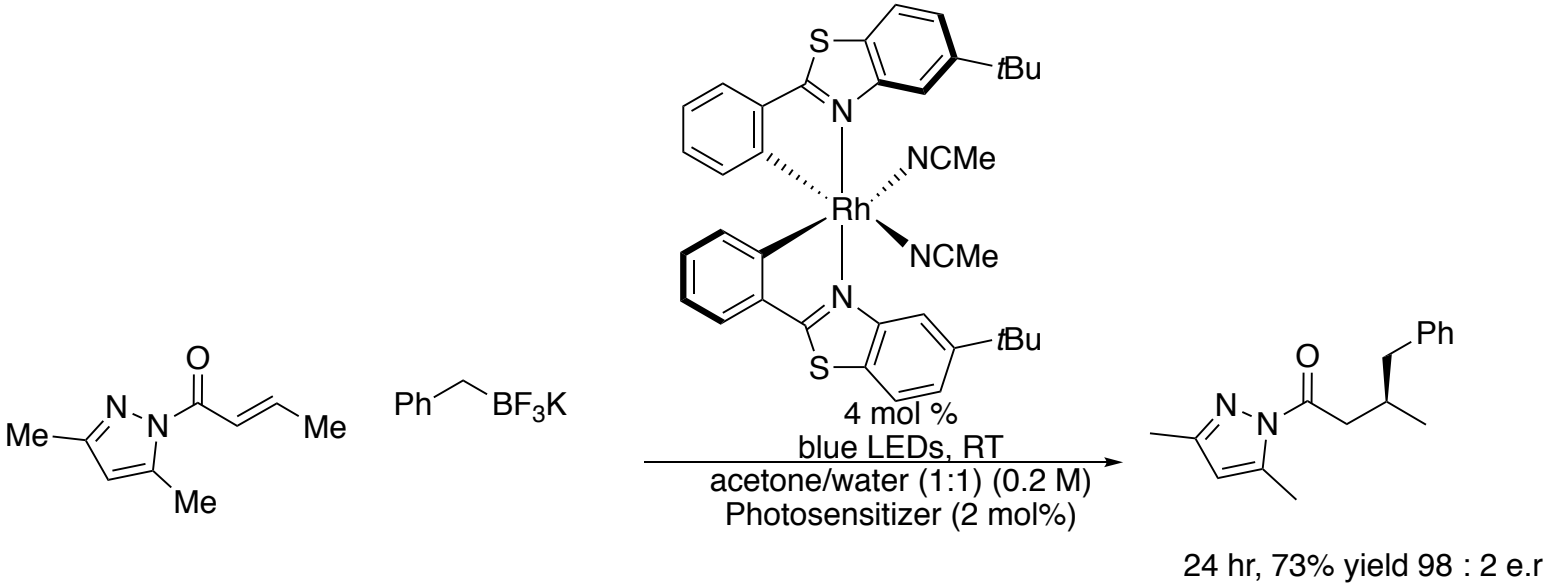
14 hr, 80% yield 97.5 : 2.5 e.r.



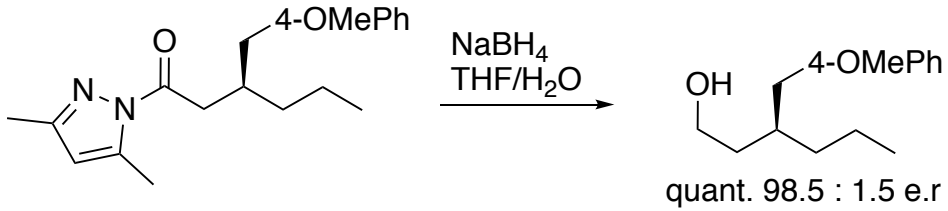
14 hr, 85% yield 98.5 : 1.5 e.r.

Huo, H.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.*, **2016,** *138*, 6936.

Manipulation of Heterocycles

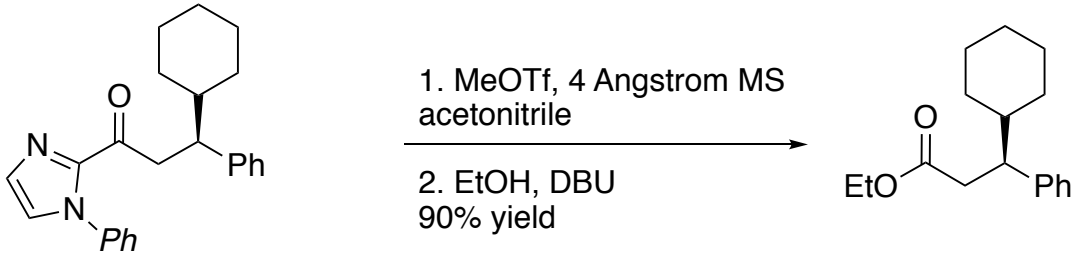


24 hr, 73% yield 98 : 2 e.r



14 hr, 75% yield, 98.5 : 1.5 e.r.

quant. 98.5 : 1.5 e.r

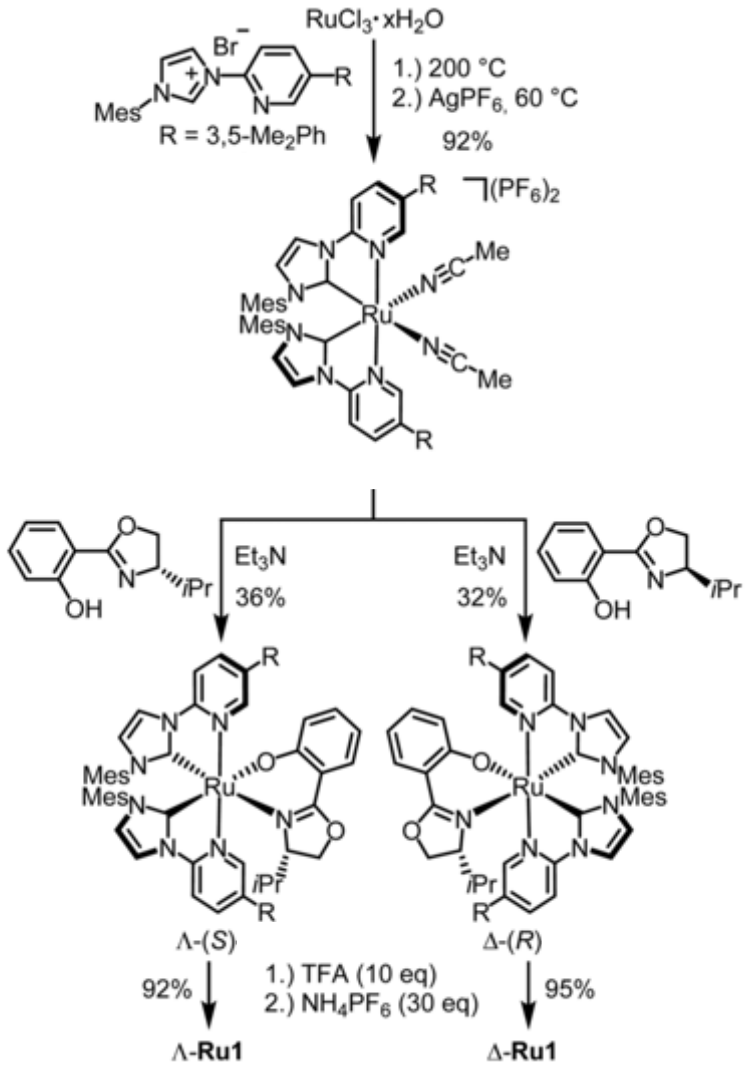


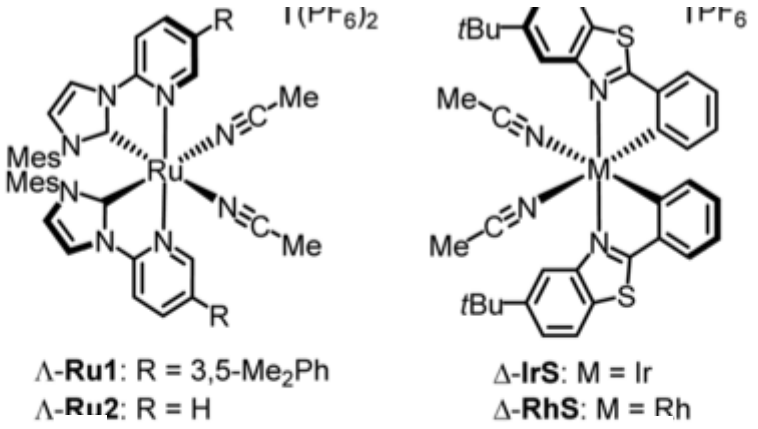
14 hr, 85% yield 98.5 : 1.5 e.r.

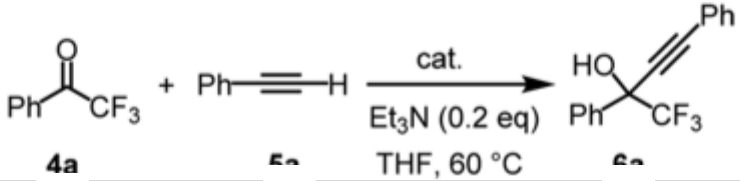
98.5 : 1.5 e.r.

Huo, H.; Harms, K.; Meggers, E. *J. Am. Chem. Soc.*, **2016,** *138*, 6936.

Asymmetric Alkynylation of Trifluoromethyl Ketones

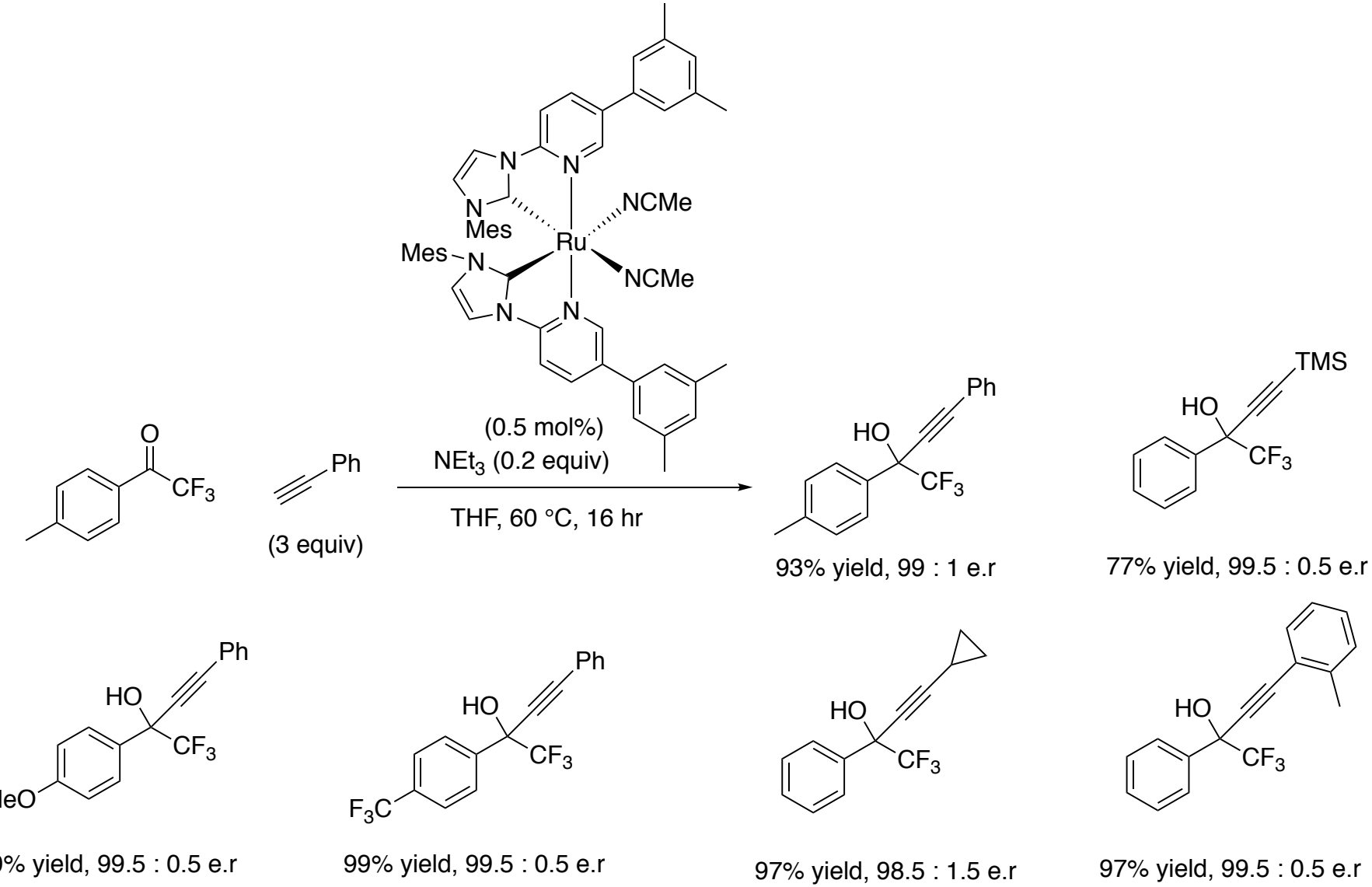






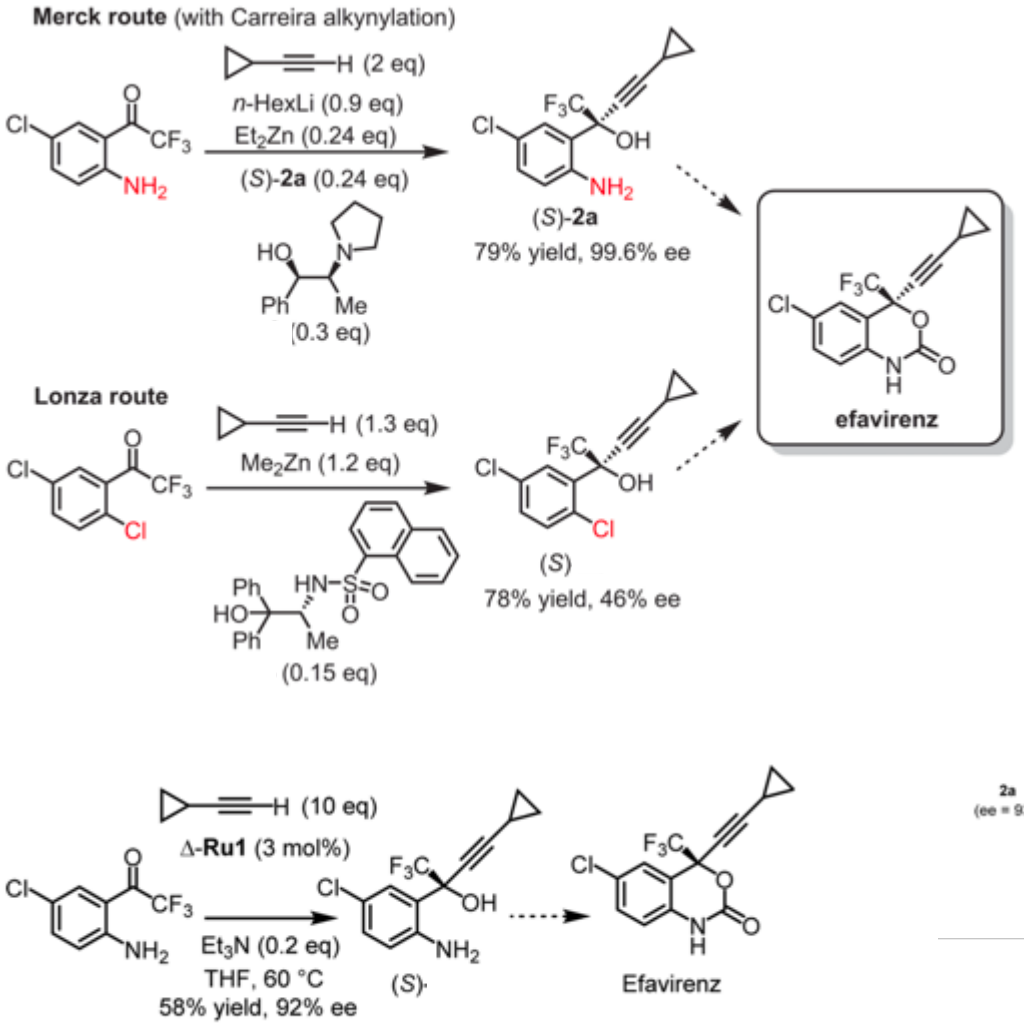
Zheng, Y.; Tan, Y.; Harms, K.; Marsh, M.; Riedel, R.; Zhang, L.; Meggers, E. *J. Am. Chem. Soc.*, **2017,** *139*, 4322.

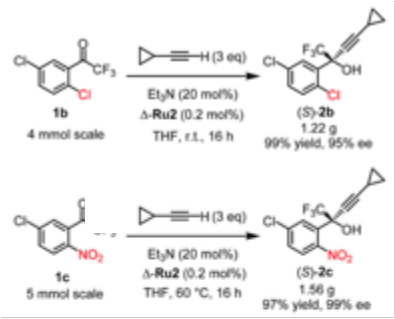
Scope



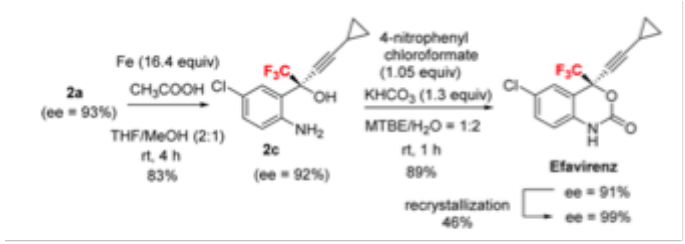
Zheng, Y.; Tan, Y.; Harms, K.; Marsh, M.; Riedel, R.; Zhang, L.; Meggers, E. *J. Am. Chem. Soc.*, **2017,** *139*, 4322.

Application to a Commercial HIV Inhibitor





2a



Zheng, Y.; Zhang, L.; Meggers, E. *Org. Process Res. Dev.*, **2018**, *22*, 103.

Determination of Source of Enantioselectivity

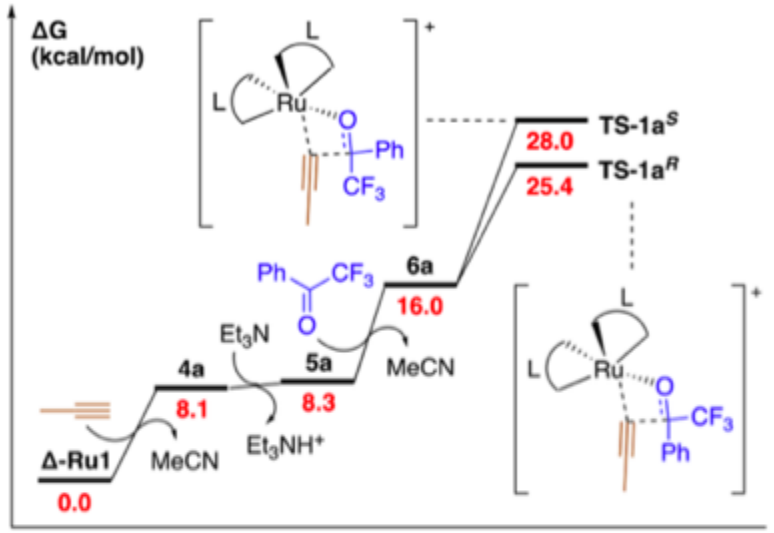
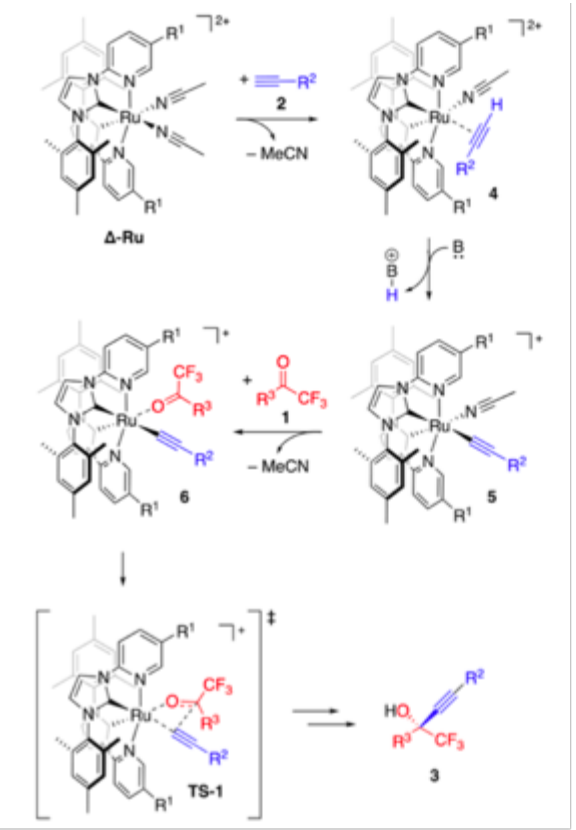


Figure 2. Free energy diagram of the formation of ruthenium acetylide complex **6a** from **Δ-Ru1**, and alkynylation transition states **TS-1a**^{R} and **TS-1a**^{S}.

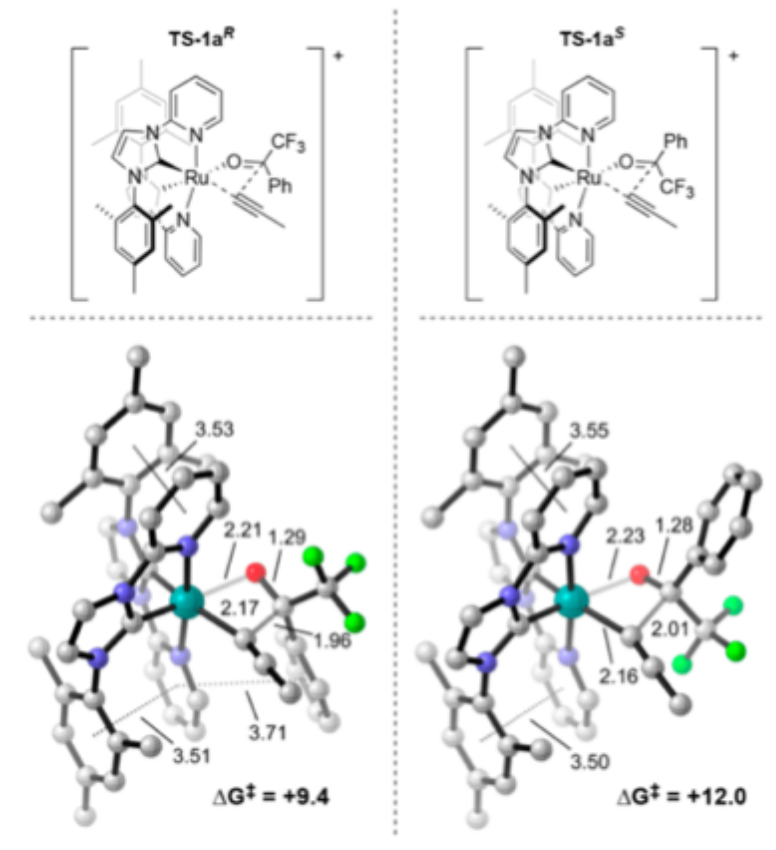


Transition state (TS) gas phase geometries:
LANL2DZ basis set was used for Rh;
6-31G(d) for all other atoms

Distortion-interaction energies: M06/6-311G++(d,p)-SDD level
Using previous TS geometries

Chen, S.; Zheng, Y.; Cui, T.; Meggers, E. Houk, K. N. *J. Am. Chem. Soc.*, **2018**, ASAP.

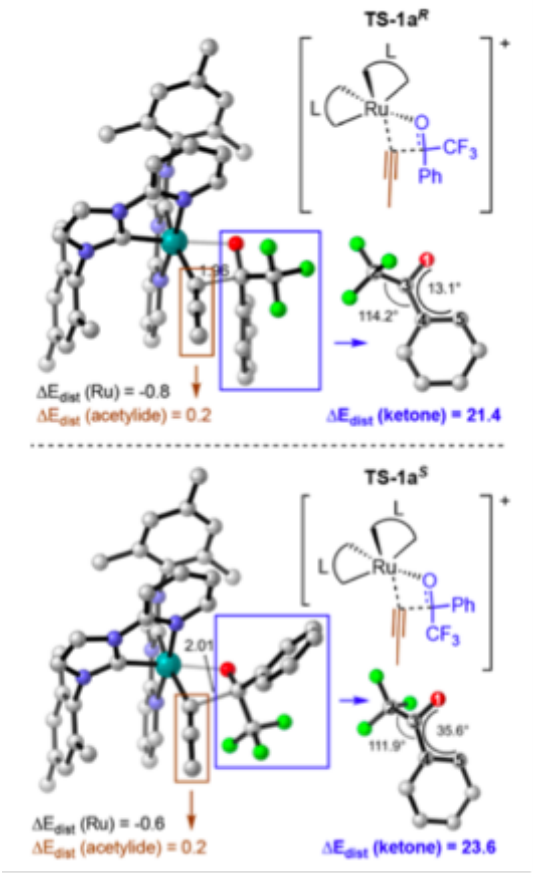
Distortion Energy Studies



Formation of C-C bond

Favorable π-π stacking

Formation of C-C bond

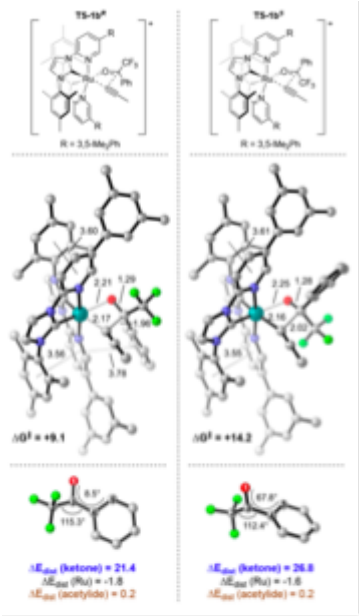


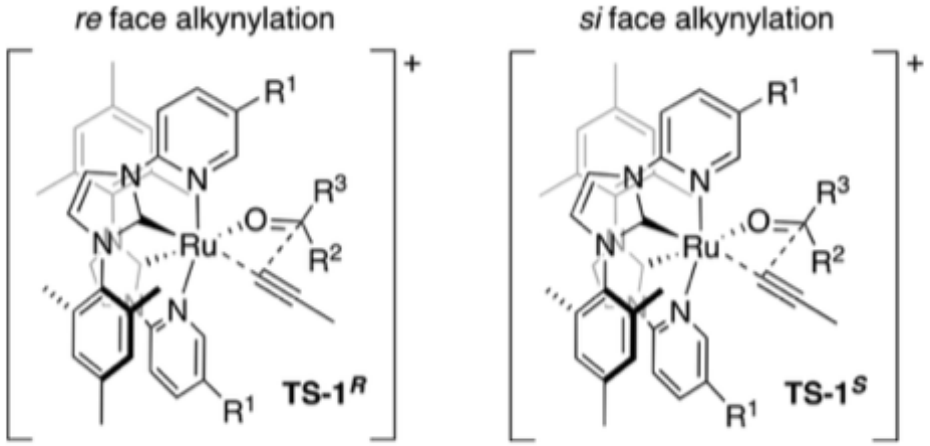
Dihedral angle is unchanged

Dihedral angle is distorted

Chen, S.; Zheng, Y.; Cui, T.; Meggers, E. Houk, K. N. *J. Am. Chem. Soc.*, **2018**, ASAP.

Distortion Energy Studies In a Bulkier System



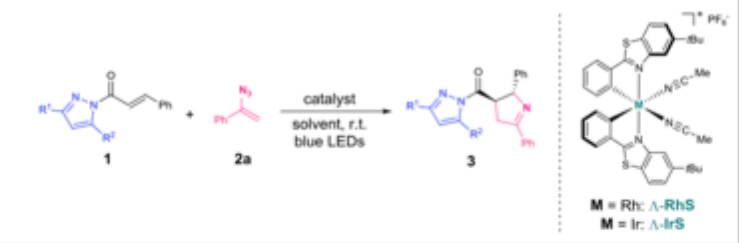


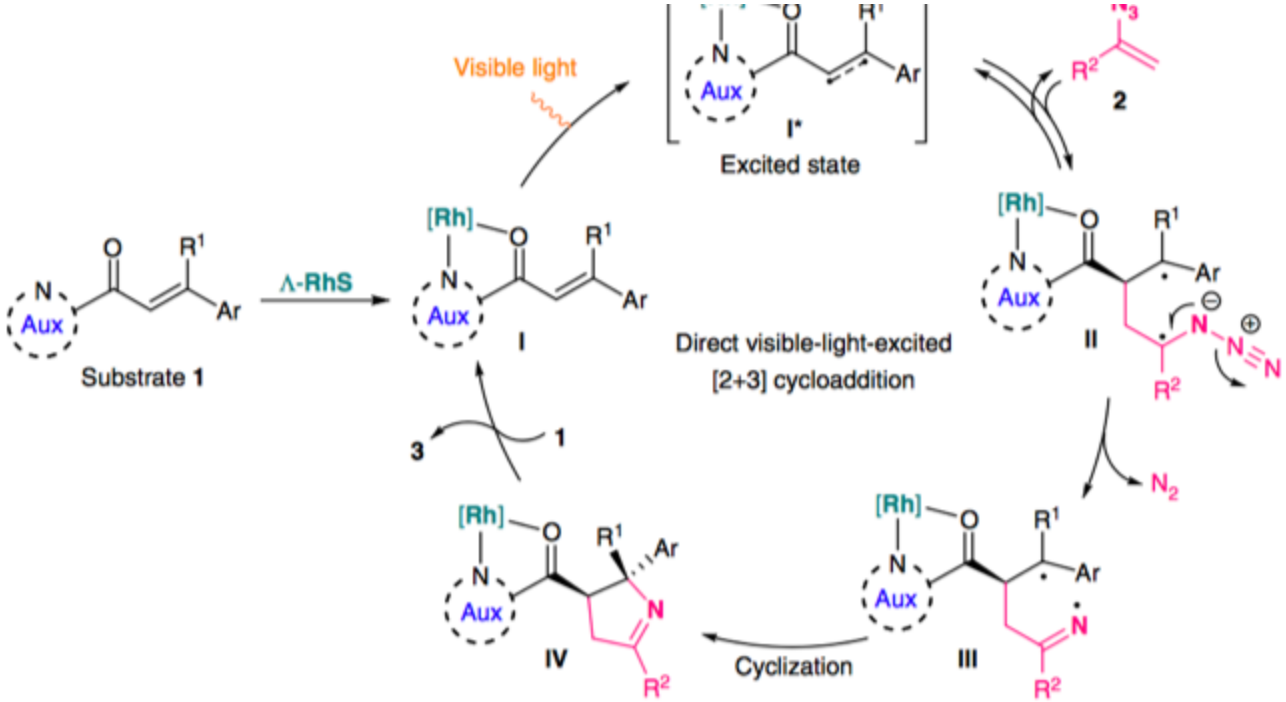
TS	R^1	R^2	R^3	calcd $\Delta G^{\ddagger}$	calcd $\Delta\Delta G^{\ddagger}$	exptl ee (%)	exptl $\Delta\Delta G^{\ddagger}$
TS-1a^R	H	Ph	CF_3	9.4	2.6	97	2.4
TS-1a^S	H	Ph	CF_3	12.0			

Dihedral angle is severely distorted

Chen, S.; Zheng, Y.; Cui, T.; Meggers, E. Houk, K. N. *J. Am. Chem. Soc.*, **2018**, ASAP.

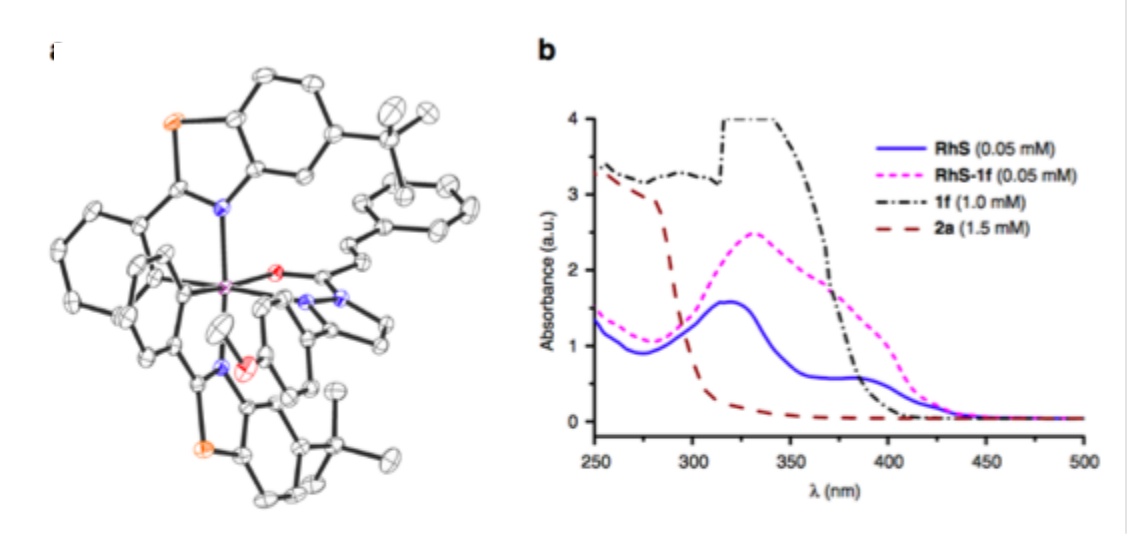
Catalytic Asymmetric Generation of a Nitrogen Heterocycle





Huang, X.; Li, X.; Xie, X.; Harms, K.; Riedel, R.; Meggers, E. *Nat. Commun.*, **2017**, *8*, 2245.

Mechanistic Evidence



Favorable pi-pi stacking

Catalyst-substrate complex

Crystal structure

(I) in previous slide

Blue = catalyst

Pink = catalyst-substrate complex

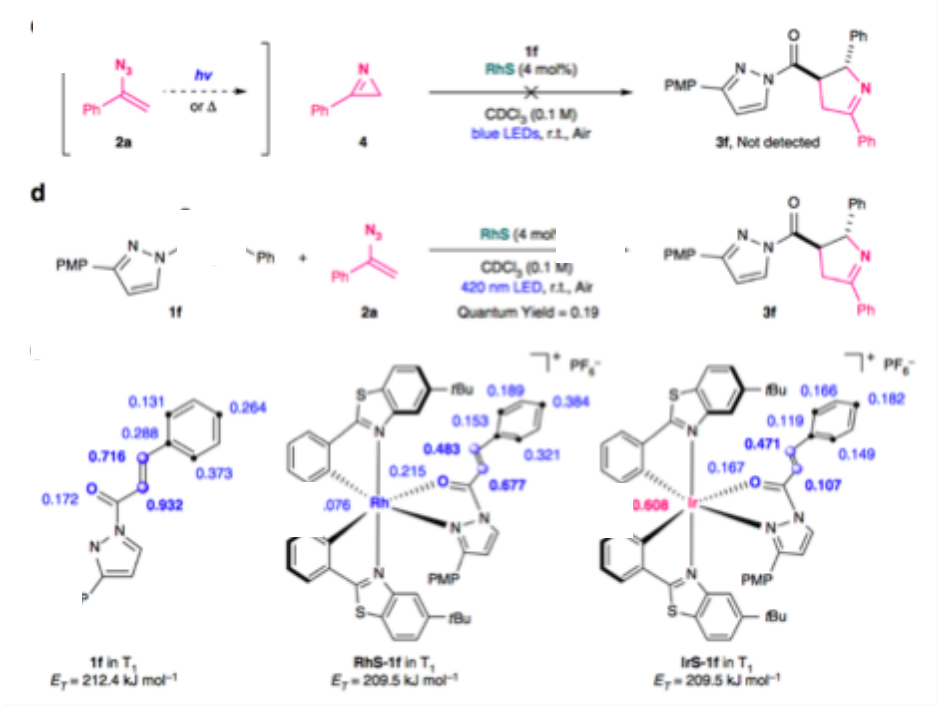
Black = olefin

Brown = azide

Visible light absorption is enhanced in catalyst-substrate complex relative to substrate

Huang, X.; Li, X.; Xie, X.; Harms, K.; Riedel, R.; Meggers, E. *Nat. Commun.*, **2017**, *8*, 2245.

Mechanistic Evidence



Use of azirine failed to give product, eliminating possibility of azirine intermediate

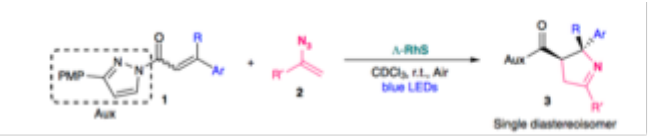
Suggests that a single photon is needed for each formed product molecule; not likely to be chain process

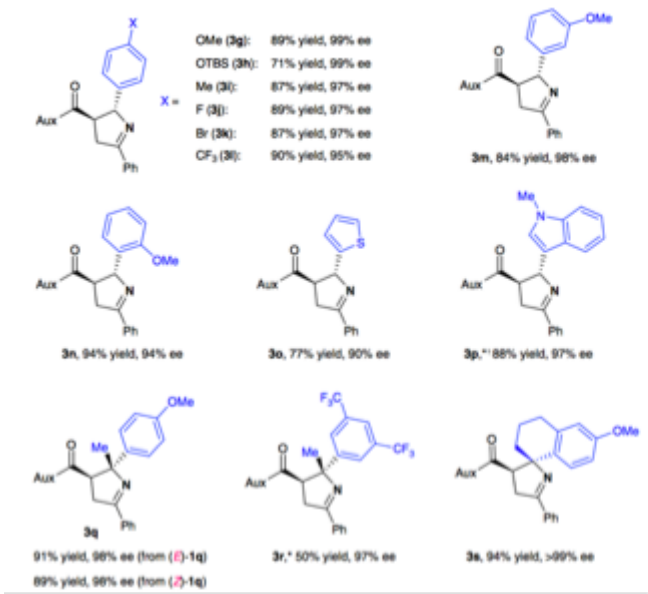
Calculated spin distribution and energy of triplet excited states reveals spin lies in olefin for RhS but in Ir for IrS. IrS bound substrate cannot react with azides and transfers energy to unbound olefins, promoting racemate formation

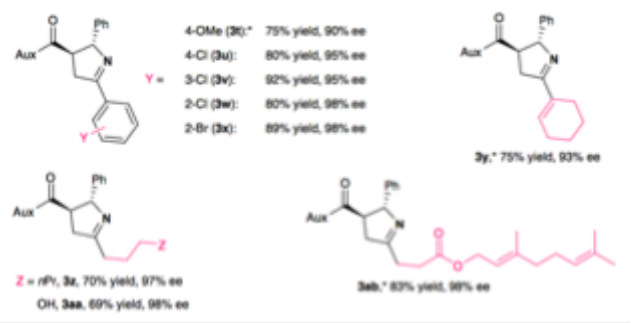
LANL2DZ basis set was used for Rh; 6-31G(d) for all other atoms

Huang, X.; Li, X.; Xie, X.; Harms, K.; Riedel, R.; Meggers, E. *Nat. Commun.*, **2017**, *8*, 2245.

Scope



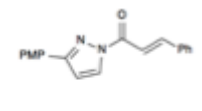


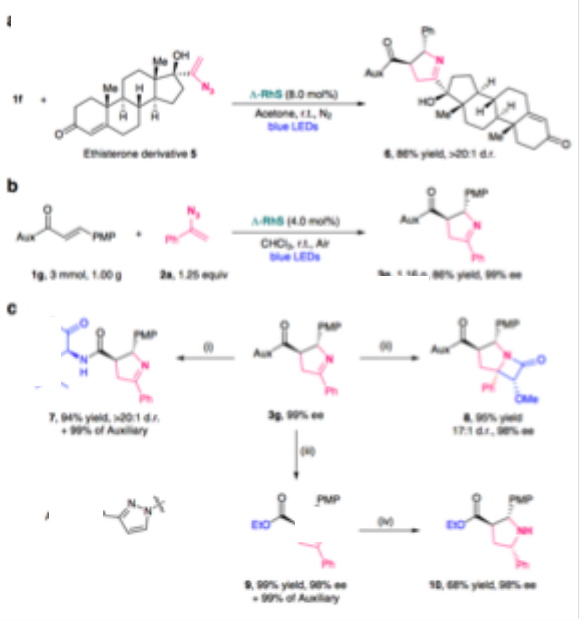


Huang, X.; Li, X.; Xie, X.; Harms, K.; Riedel, R.; Meggers, E. *Nat. Commun.*, **2017**, *8*, 2245.

Application to Useful Molecules

Estrone





Gram scale

Functional group conversions

L-Leucine-tBu ester HCl
NEt_3, HOBt
Toluene, 50 °C

2-Methoxyacetyl chloride
NEt_3, CH_2Cl_2
50 °C

LiCl, NEt_3
EtOH/THF, RT

Pd/C, H_2
EtOAc, RT

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Overview

- Chiral Metal Complexes
- A Historical Perspective on Stereogenic-Only-at-Metal
- Meggers' Catalyst Design
- Survey of Meggers' Publications Using These Complexes
- **Conclusion and Critiques**

Conclusion and Critiques

- Novel chiral metal complexes capable of acting as Lewis acids and photosensitizers
- Allows for low catalyst loadings
- Shows promise as a technique, especially based on the last example