Intermolecular Anti-Markovnikov Hydroamination of Unactivated Alkenes

Speaker： Ye Wenshao
Supervisor: Prof. Zhang Junliang
Dr. Yang Junfeng

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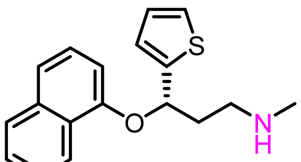
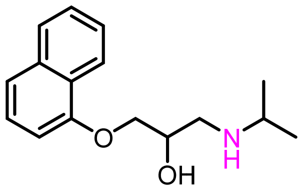
Background

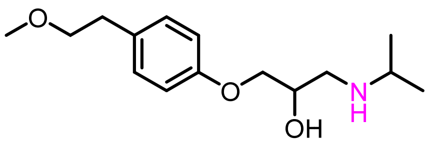


HCl

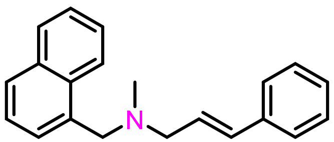
Duloxetine Hydrochloride



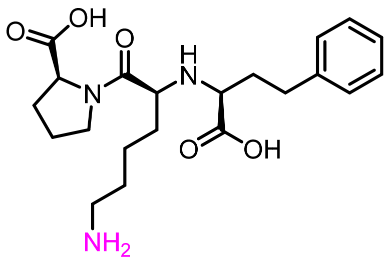
Propranolol



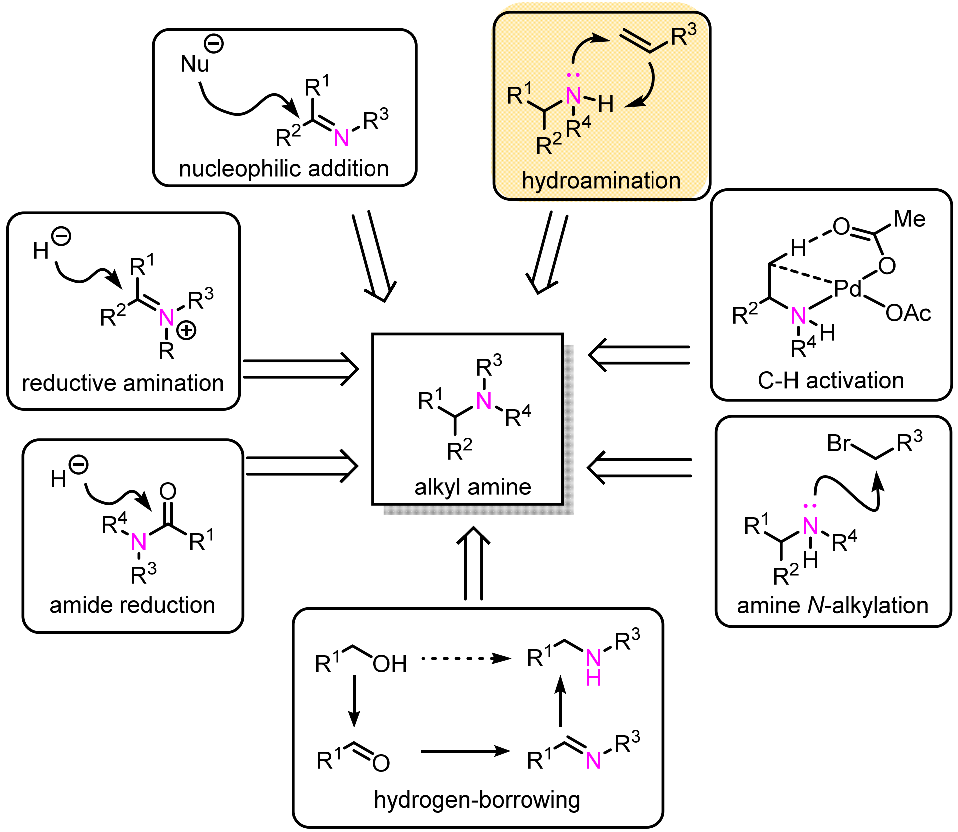
Metoprolol



Naftifine



Lisinopril

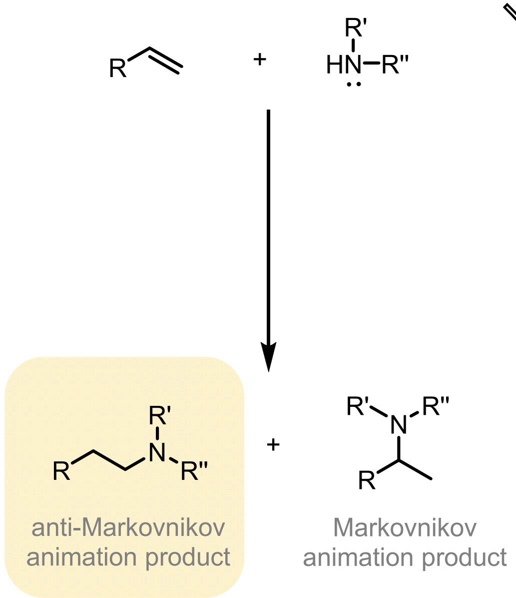


Gaunt, M. J. et. al. *Chem. Rev.* **2020**, *120*, 2613–2692

Background

Challenges:

- Controlling selectivity
- Negative entropy
- Electrostatic repulsion



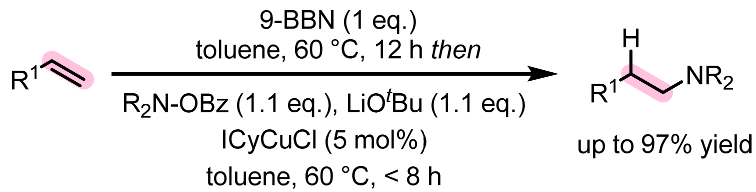
- Acid Catalysis
- Base Catalysis
- Hydroboration-amination
- Transition Metal Catalysis
- Radical Catalysis

Gaunt, M. J. et. al. *Chem. Rev.* **2020**, *120*, 2613–2692

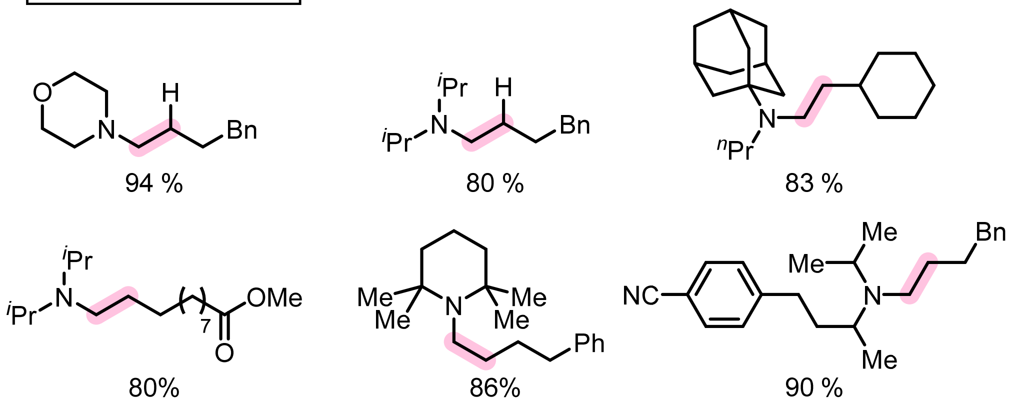
Contents

One-pot Hydroboration−amination

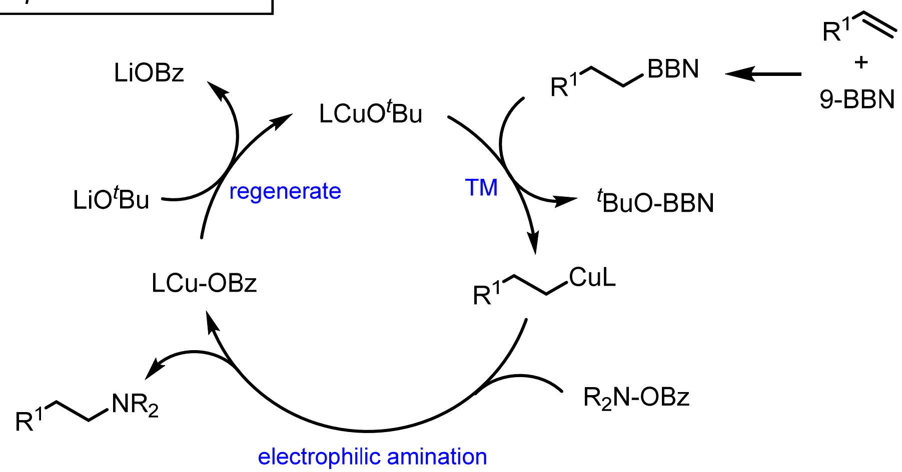
Lalic (2012)



Selected Substrate



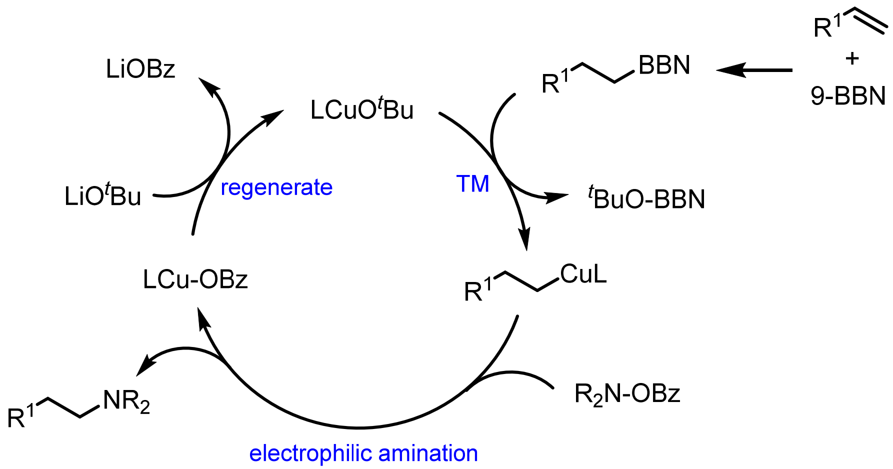
Proposed Mechanism

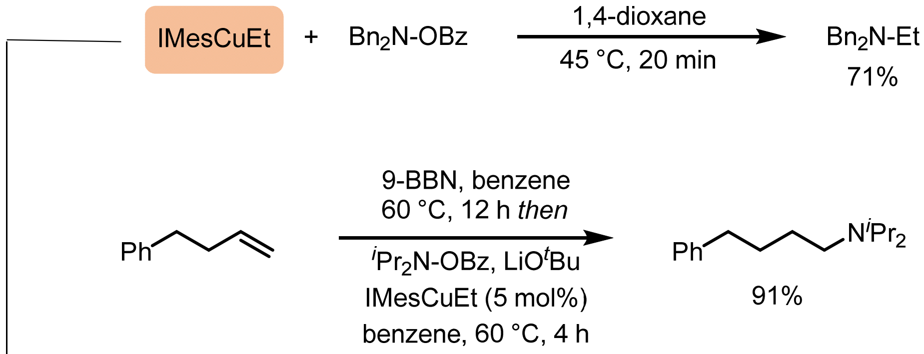


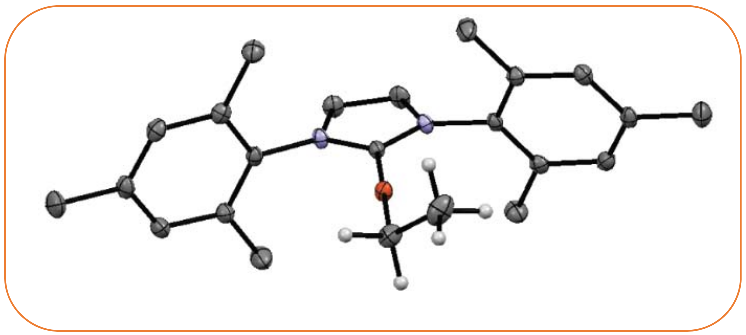
Lalic, G. et. al. *J. Am. Chem. Soc.* **2012**, *134*, 6571–6574.

One-pot Hydroboration−amination

Proposed Mechanism







Lalic, G. et. al. *J. Am. Chem. Soc.* **2012**, *134*, 6571–6574.

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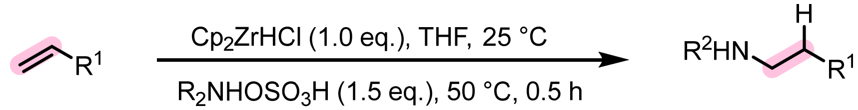
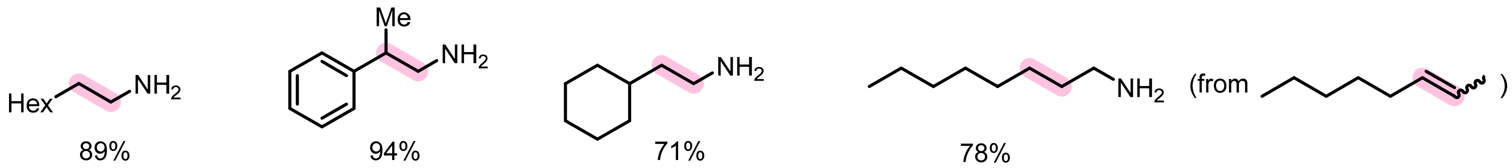
Metal-Involved Hydroamination

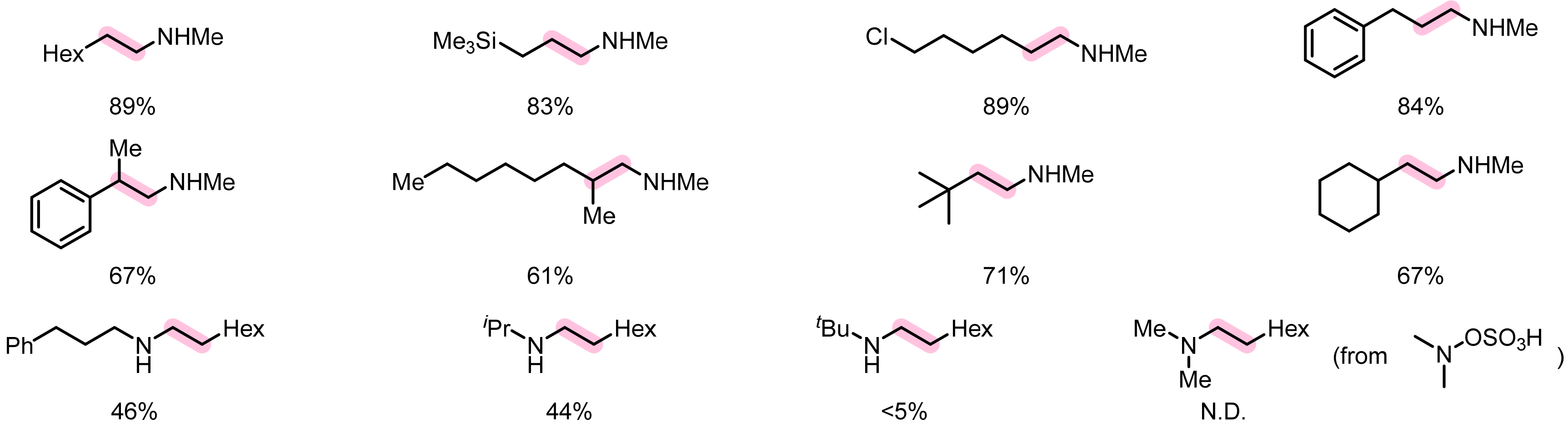
Hartwig (2013)



Primary Amines Scope



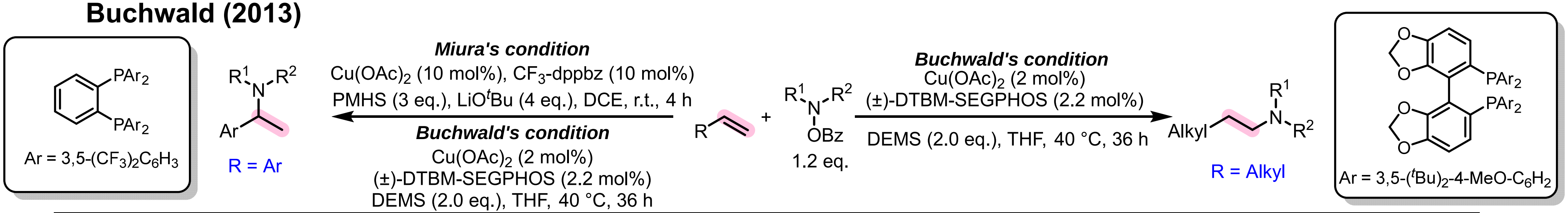
Secondary Amines Scope



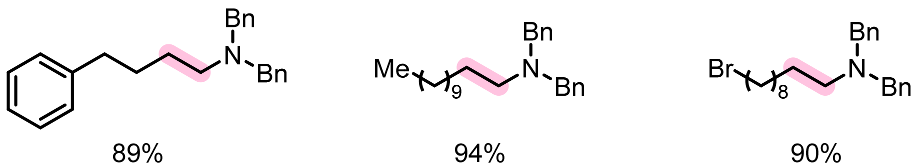
Hartwig, J. F. et. al. *J. Org. Chem.* **2013**, *78*, 8909−8914.

Metal-Involved Hydroamination

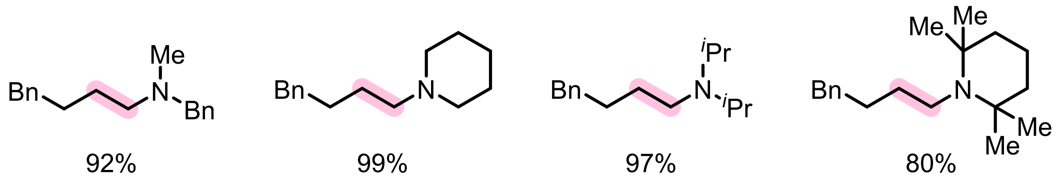
Buchwald (2013)



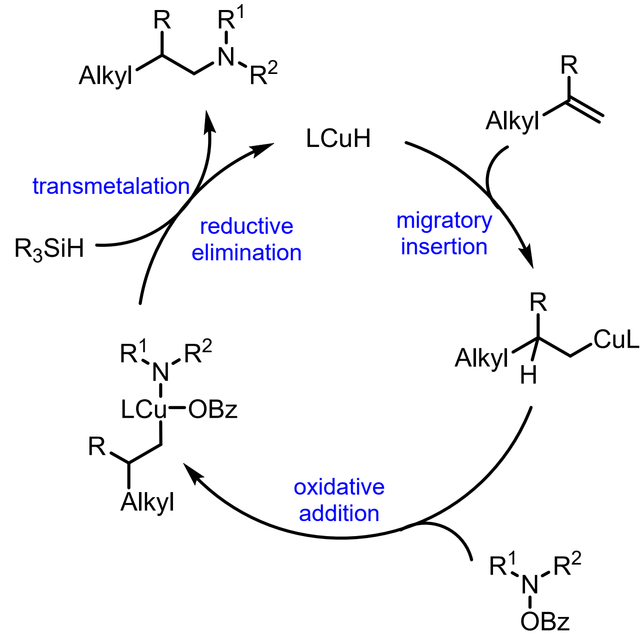
Olefin Scope



Amine Scope



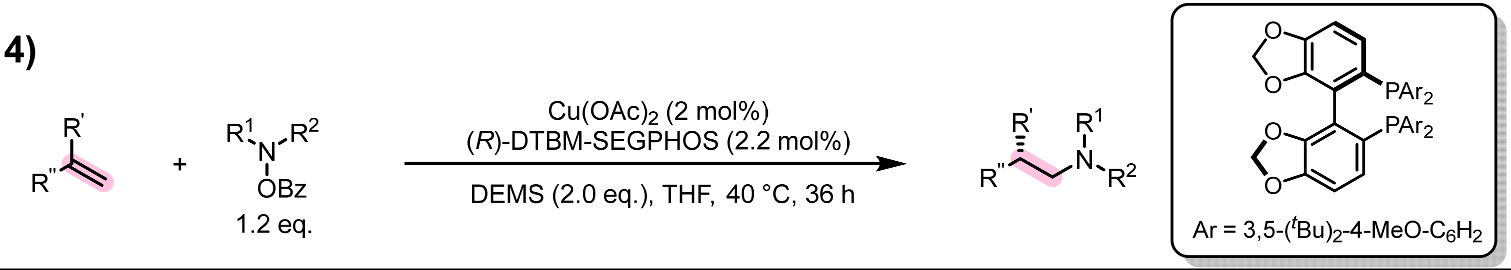
Proposed Mechanism



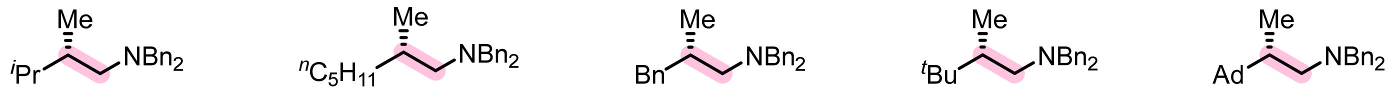
Buchwald, S. L. et. al. *J. Am. Chem. Soc.* **2013**, *135*, 15746−15749.
Miura, M.; Hirano, K. et. al. *Angew. Chem. Int. Ed.* **2013**, *52*, 10830−10834.

Metal-Involved Hydroamination

Buchwald (2014)

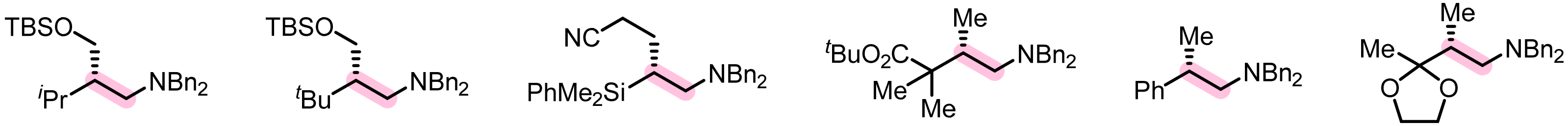


Steric Differentiation Scope



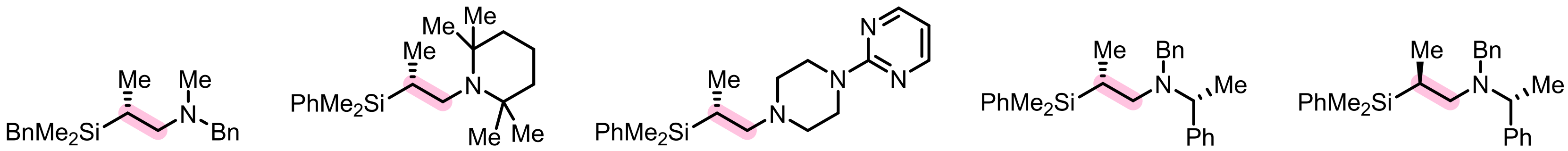
90% yield 83% ee	90% yield 59% ee	88% yield 60% ee	86% yield 92% ee	90% yield 98% ee

Functional Group Scope



92% yield 91% ee	91% yield 99% ee	58% yield 92% ee	52% yield 90% ee	56% yield 52% ee	96% yield 90% ee

Amine Scope

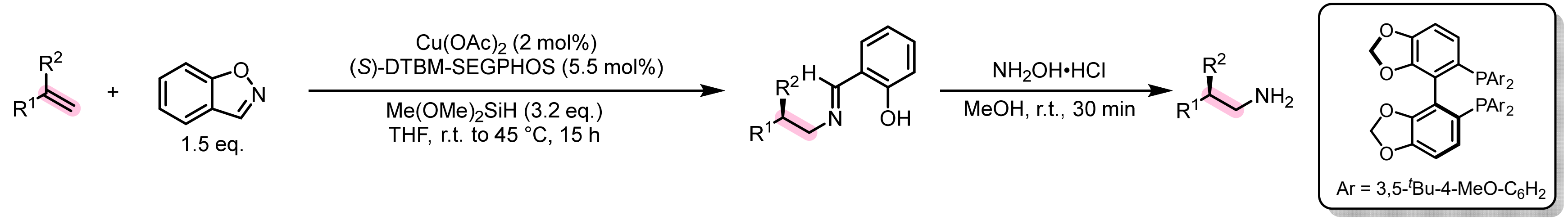


94% yield 95% ee	90% yield 96% ee	92% yield 96% ee	90% yield > 50:1 dr	with *ent*-Ligand 91% yield < 1:50 dr

Buchwald, S. L. et. al. *J. Am. Chem. Soc.* **2014**, *136*, 15913−15916.

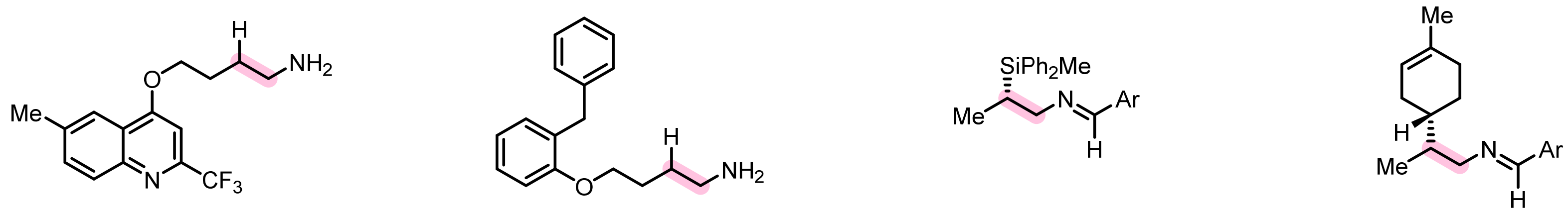
Metal-Involved Hydroamination

Buchwald (2018)



Selected Substrate

86% | 65% | 81% | 85%

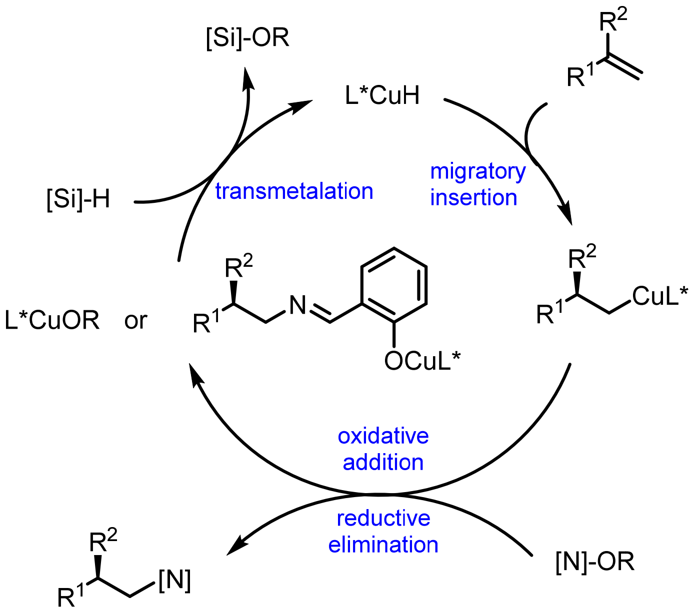


79% | 76% | 70% yield, 99% ee | 65% yield, 97:3 dr

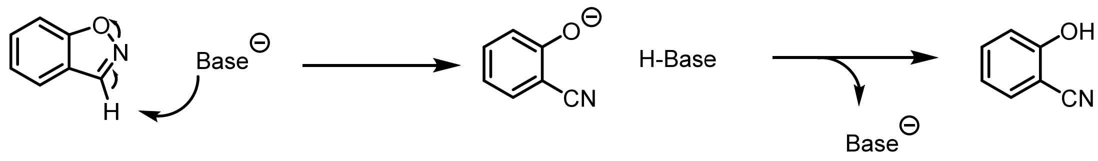
Buchwald, S. L. et. al. *J. Am. Chem. Soc.* **2018**, *140*, 15976–15984.

Metal-Involved Hydroamination

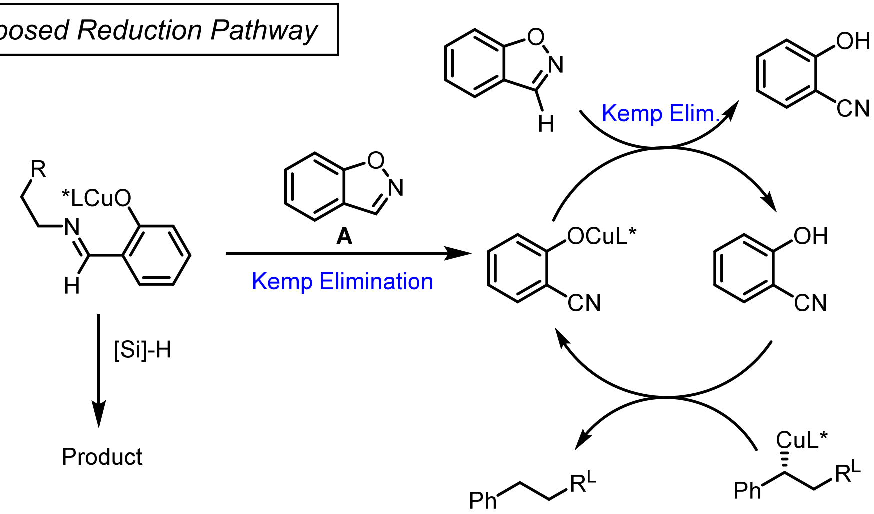
Proposed Mechanism



Kemp Elimination



Proposed Reduction Pathway

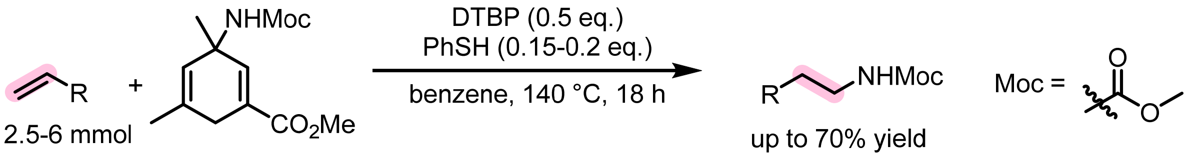


Buchwald, S. L. et. al. *J. Am. Chem. Soc.* **2018**, *140*, 15976–15984.

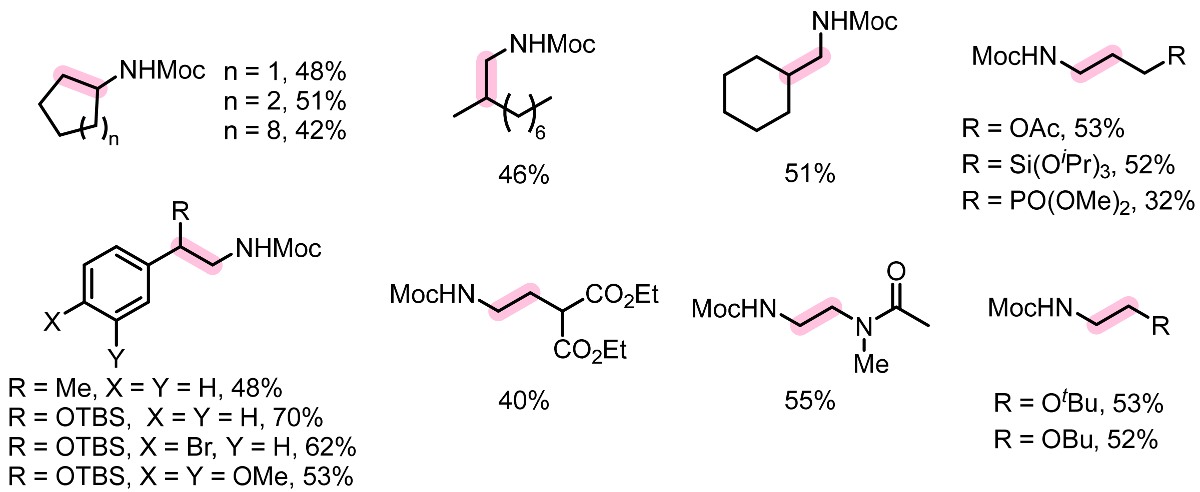
Contents

Radical Transfer Hydroamination

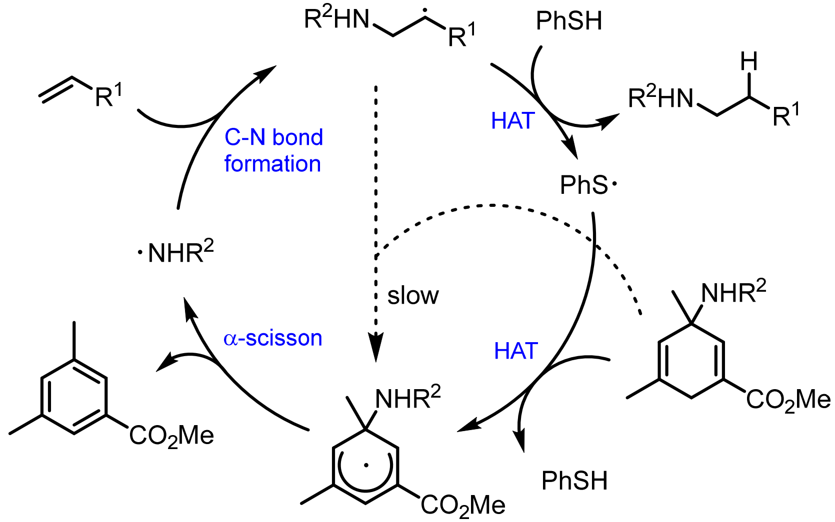
Studer (2007)



Selected Substrate



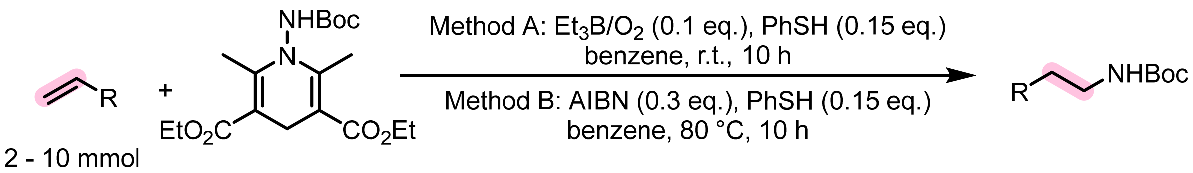
Proposed Mechanism



Studer, A. et. al. *J. Am. Chem. Soc.* **2007**, *129*, 4498–4503.

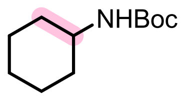
Radical Transfer Hydroamination

Studer (2008)

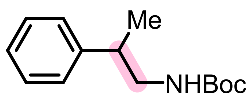


Selected Substrate

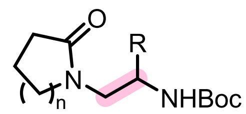
Method A, 44%



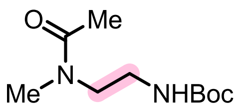
Method B, 52%



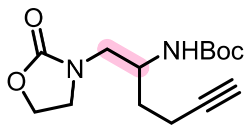
Method A, 50%



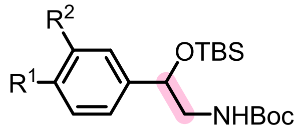
n = 1, R = H, Method A, 58%
n = 3, R = H, Method A, 55%
n = 1, R = Et, Method A, 52%



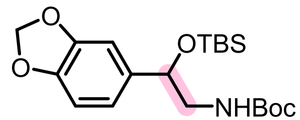
Method A, 55%



Method A, 33%



$R^1 = R^2$ = H, Method B, 59%
R^1 =Br, R^2 = H, Method B, 42%
$R^1 = R^2$ = OMe, Method B, 62%

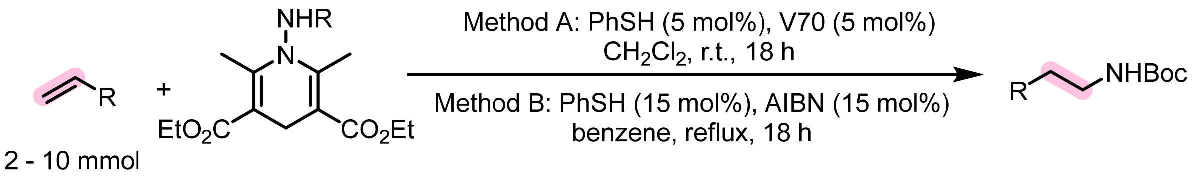


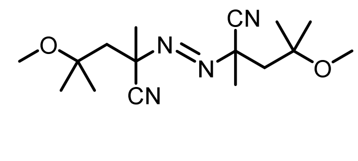
Method B, 59%

Studer, A. et. al. *Angew. Chem. Int. Ed.* **2008**, *47*, 779–782.

Radical Transfer Hydroamination

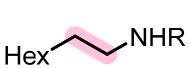
Studer (2011)





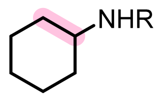
V70

Selected Substrate



R = Boc, Method A, 48%
R = COPh, Method A, <2%

R = Boc, Method B, 74%
R = Alloc, Method A, 53%
R = COPh, Method B, 74%
R = COPh, Method A, 42%
R = CO(2,6-$F_2C_6H_3$), Method B, 88%
R = CO(3,5-$F_2C_6H_3$), Method B, 92%
R = CO(4-FC_6H_4), Method B, 85%

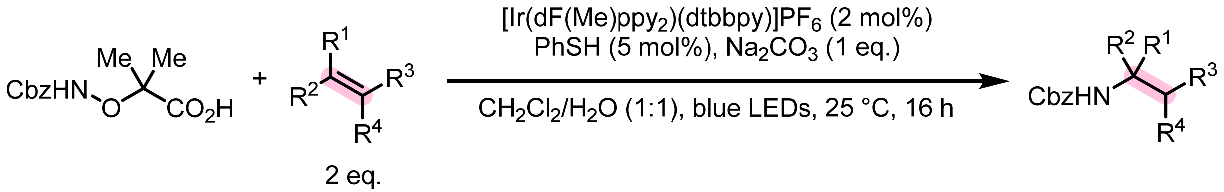


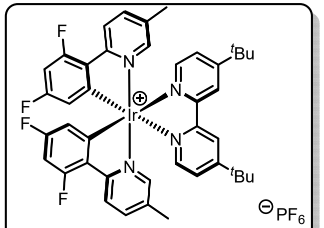
R = Boc, Method A, 75%
R = COPh, Method B, 36%
R = CO(3,5-$F_2C_6H_3$), Method B, 50%

Studer, A. et. al. *Chem. - Asian J.* **2011**, *6*, 1197–1209.

Radical Transfer Hydroamination

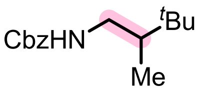
Studer (2019)



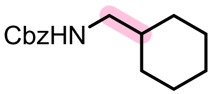


$[Ir(dF(Me)ppy_2)(dtbbpy)]PF_6$

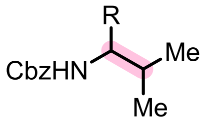
Selected Substrate



77%

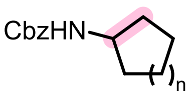


79%

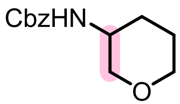


R = Me, 68%
R = ^{n}Pr, 51%

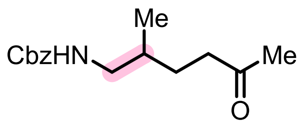
R = Hex, 65%
R = ^{t}Bu, 67%



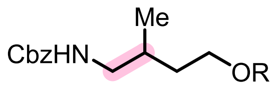
n = 1, 63%
n = 2, 70%
n = 3, 85%
n = 4, 79%
n = 12, 71%



62%



78%

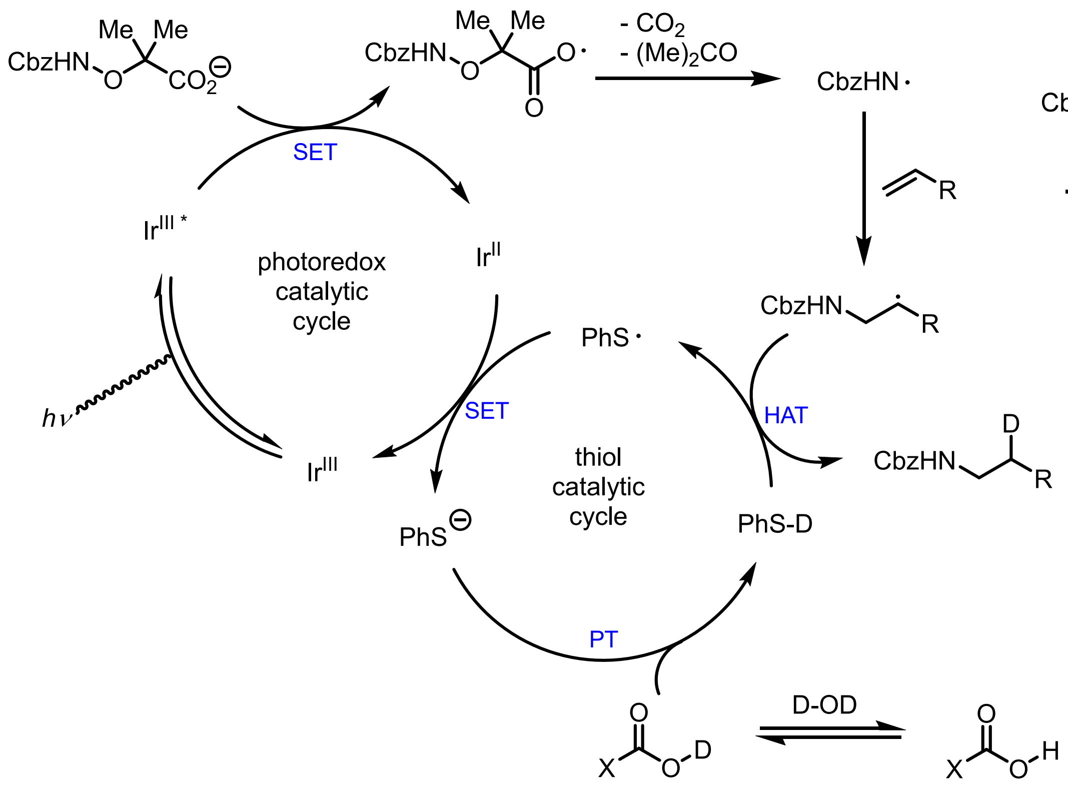


R = H, 68%
R = Bz, 85%
R = Ac, 77%
R = TBS, 83%

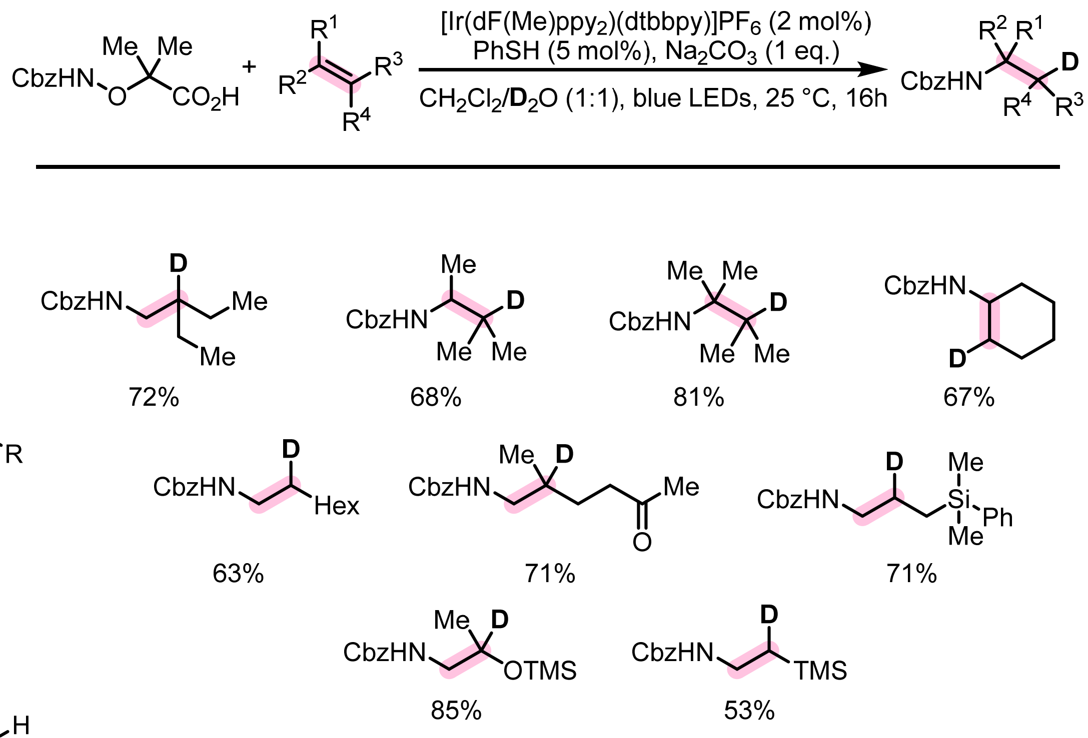
Studer, A. et. al. *Chem. - Eur. J.* **2019**, *25*, 7105–7109.

Radical Transfer Hydroamination

Proposed Mechanism



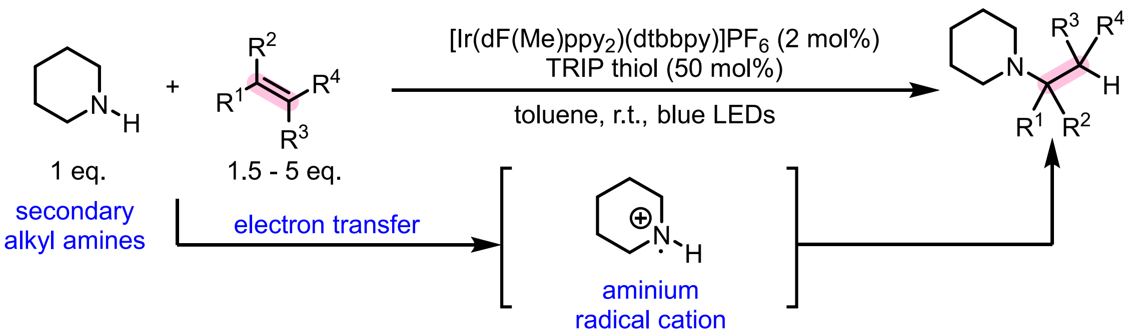
Deuteroamidation Scope

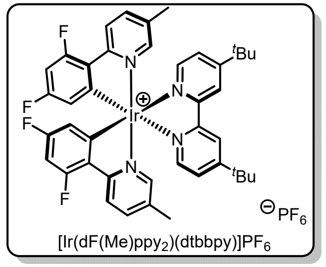


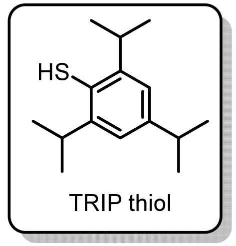
Studer, A. et. al. *Chem. - Eur. J.* **2019**, *25*, 7105–7109.

Radical Transfer Hydroamination

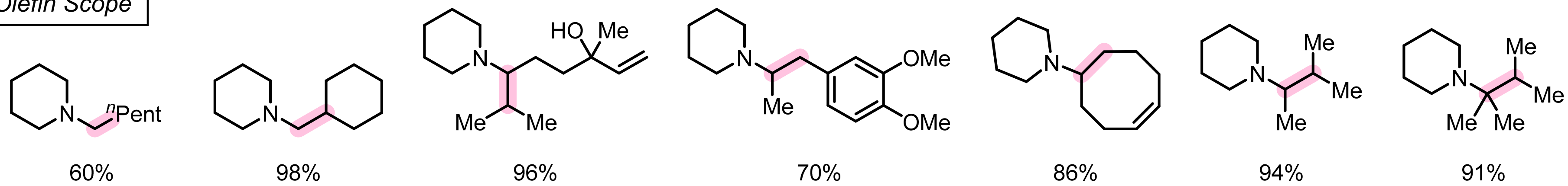
Knowles (2017)



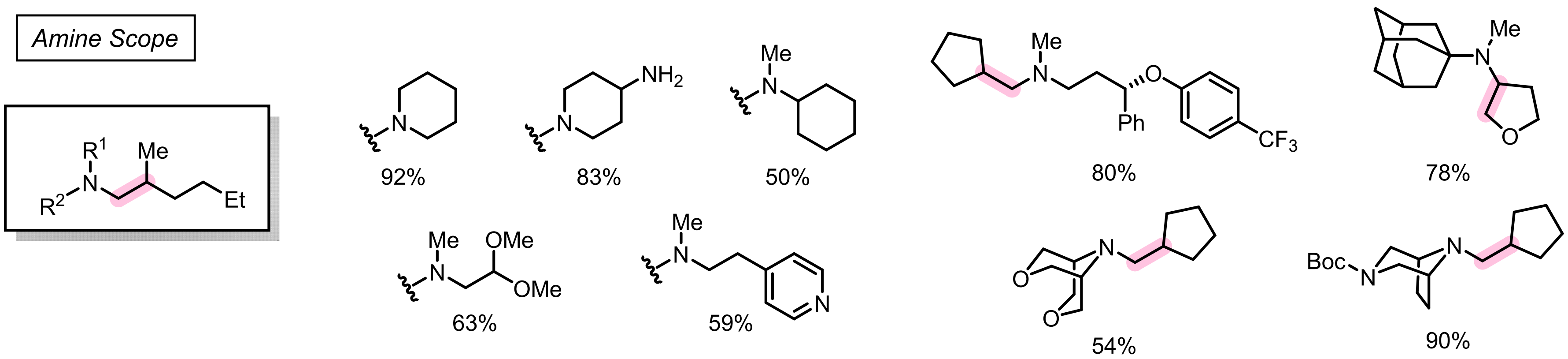




Olefin Scope



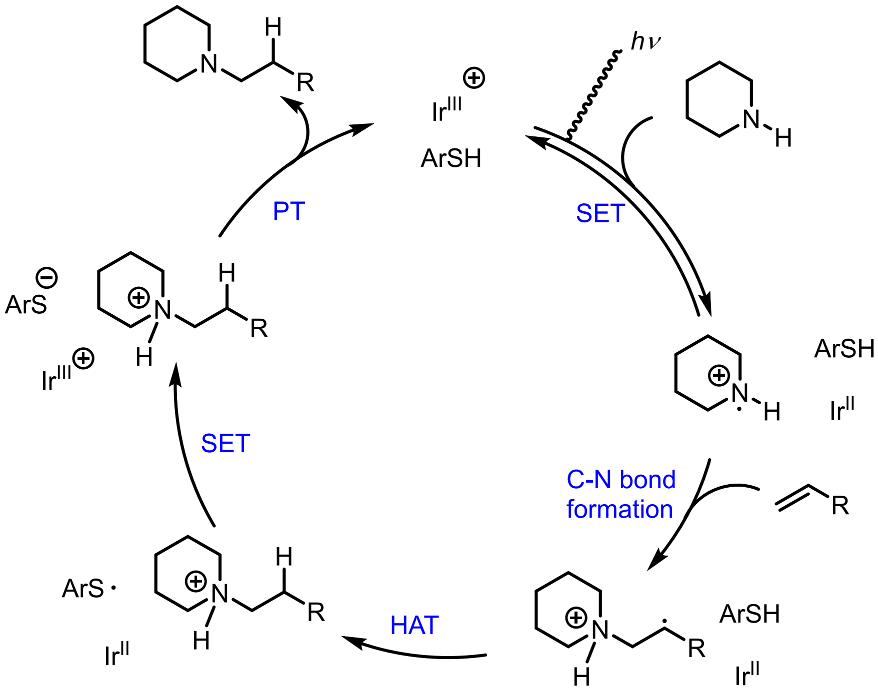
Amine Scope



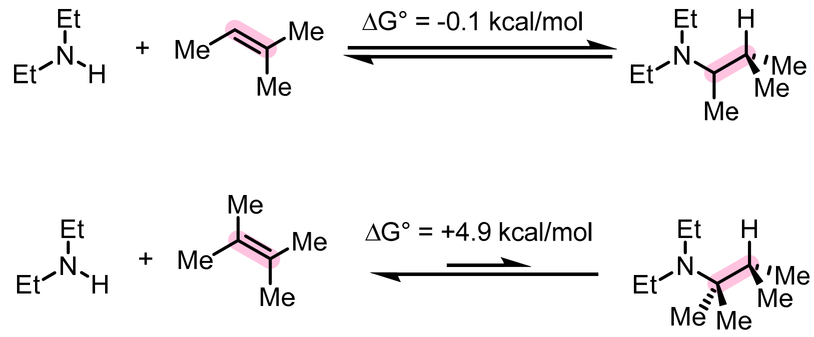
Knowles, R. R. et. al. *Science* **2017**, *355*, 727–730.

Radical Transfer Hydroamination

Proposed Mechanism

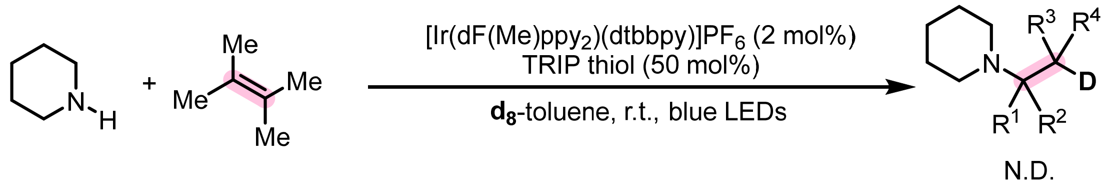


Thermodynamic Challenges



*using the composite method CBS-QB3

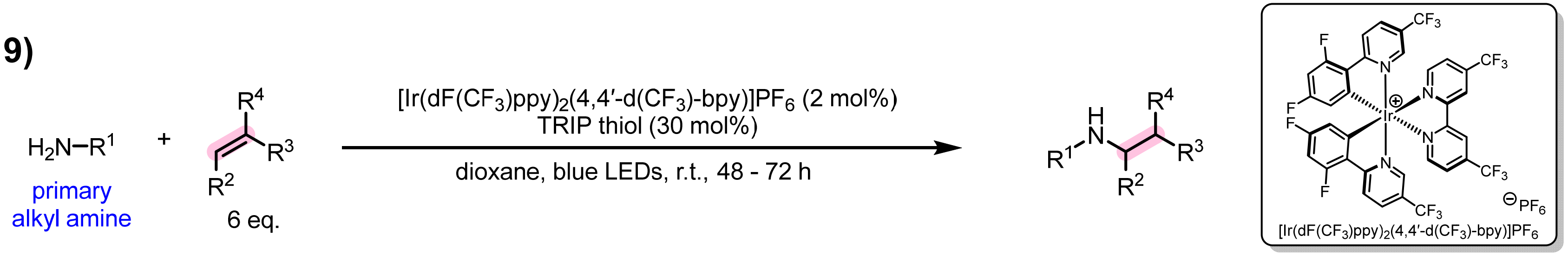
Deuterium Labeling Studies



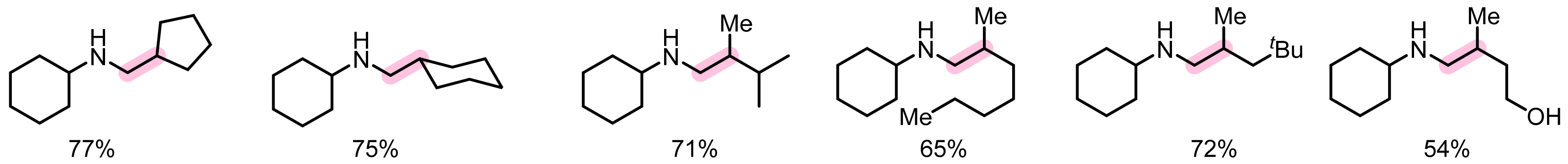
Knowles, R. R. et. al. *Science* **2017**, *355*, 727–730.

Radical Transfer Hydroamination

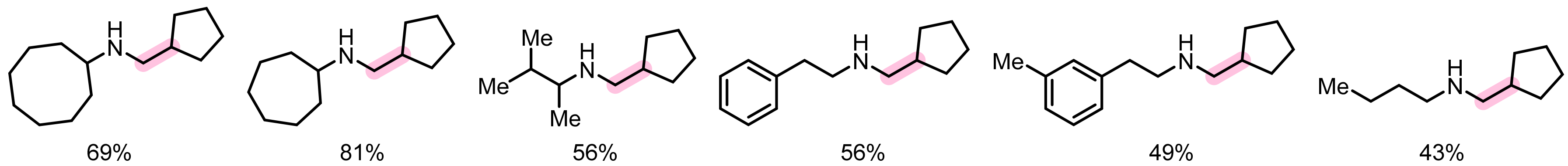
Knowles (2019)



Olefin Scope



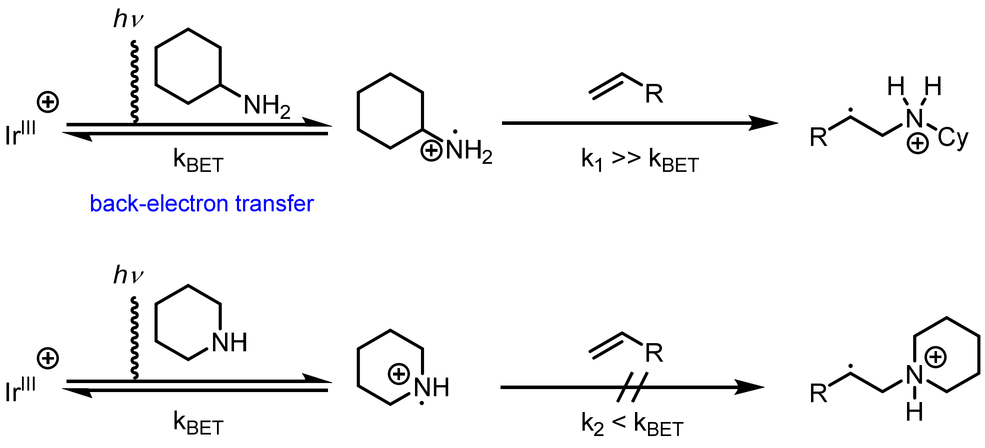
Amine Scope



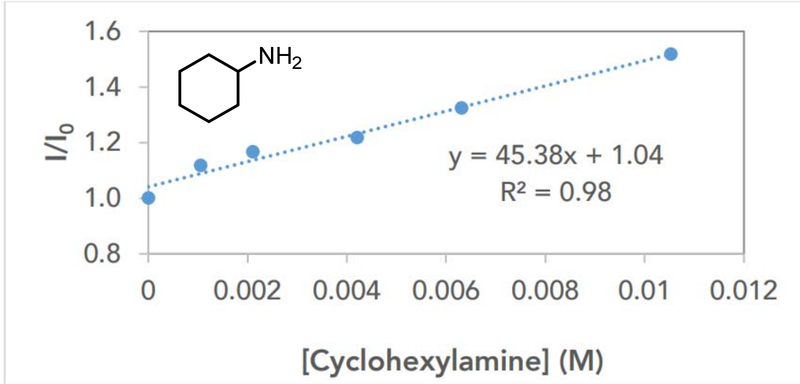
Knowles, R. R. et. al. *J. Am. Chem. Soc.* **2019**, *141*, 16590–16594.

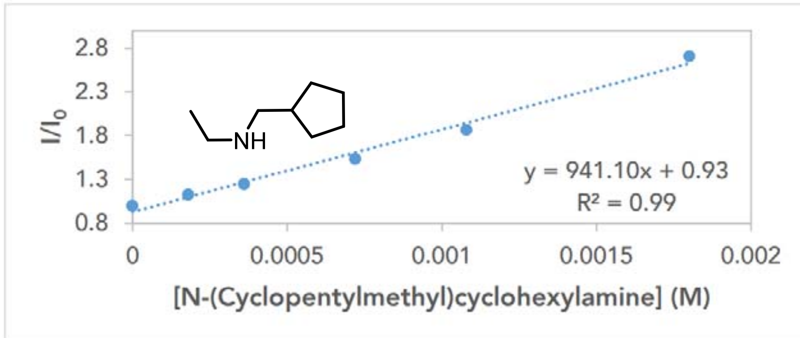
Radical Transfer Hydroamination

Kinetic Competition Study



Stern–Volmer Quenching Studies

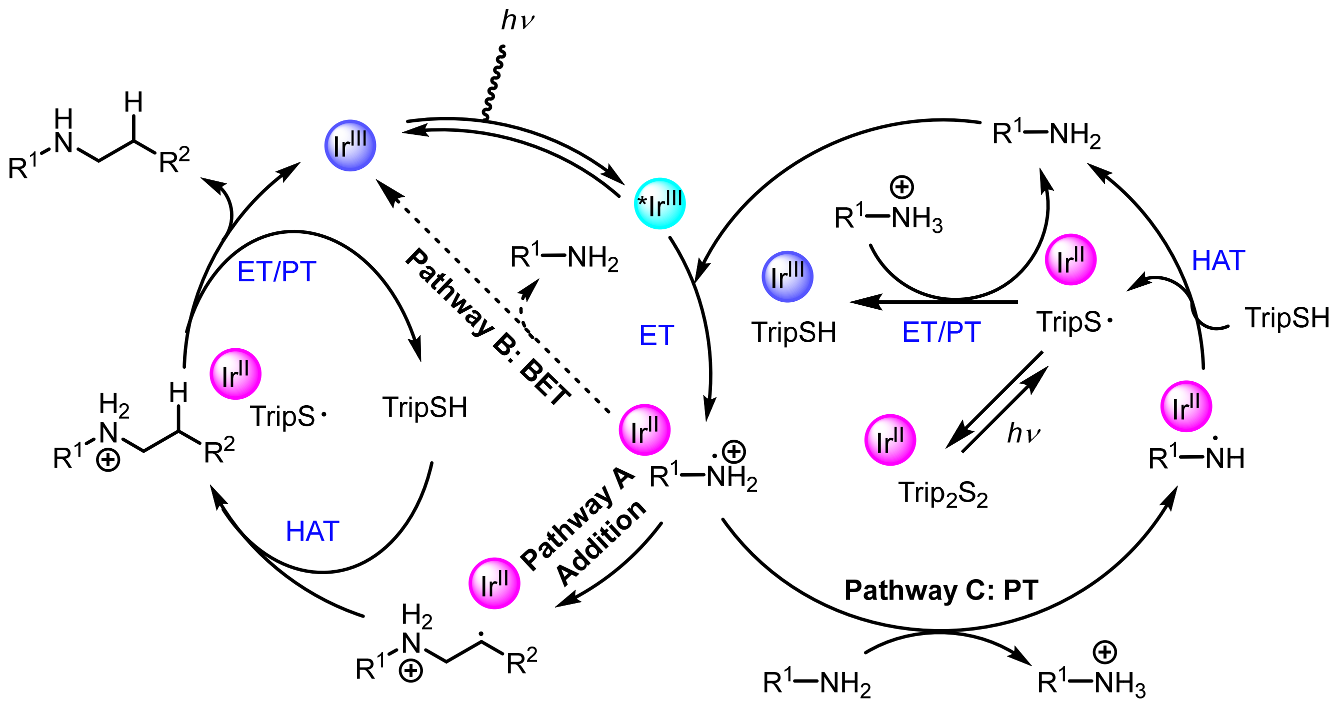




Knowles, R. R. et. al. *J. Am. Chem. Soc.* **2019**, *141*, 16590–16594.

Radical Transfer Hydroamination

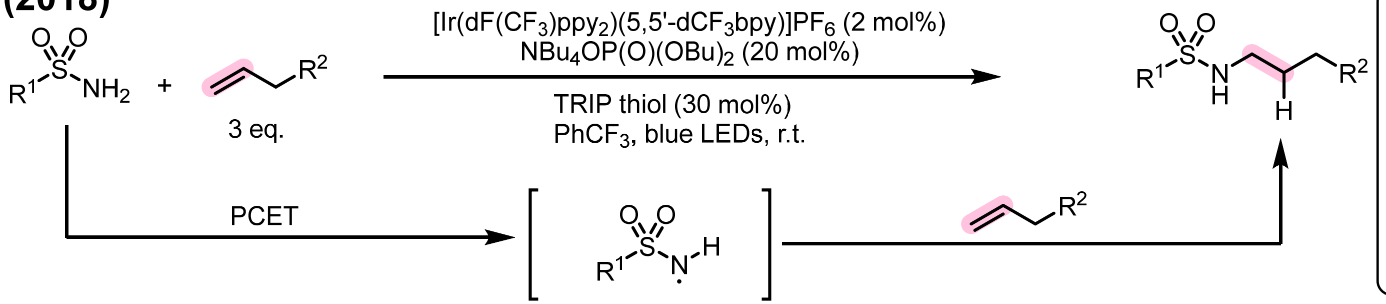
Complete reaction cycle

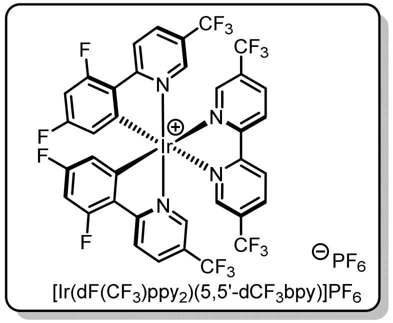


Knowles, R. R.; Nocera, D. G. et. al. *J. Am. Chem. Soc.* **2021**, *143*, 10232-10242.

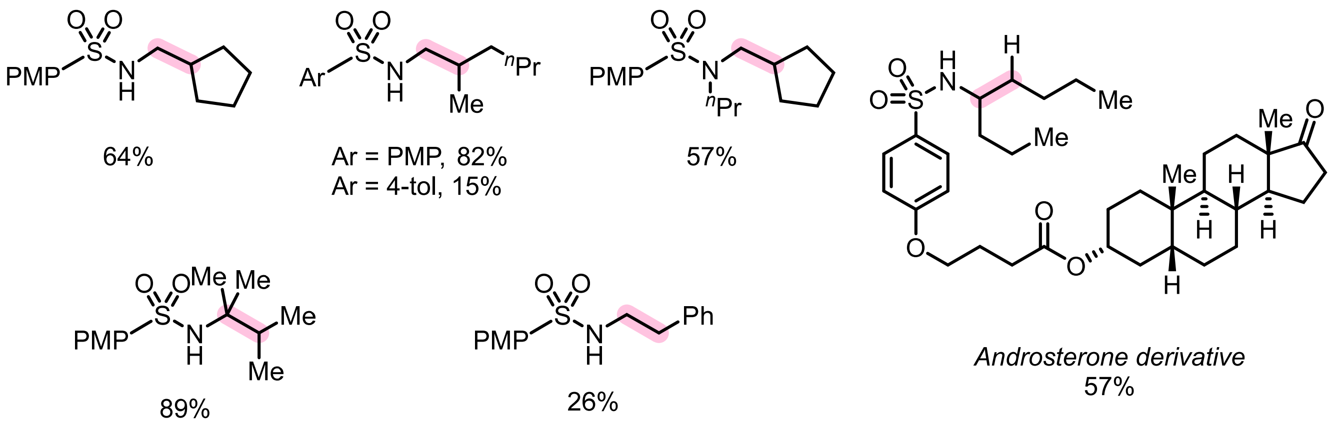
Radical Transfer Hydroamination

Knowles (2018)





Selected Substrate

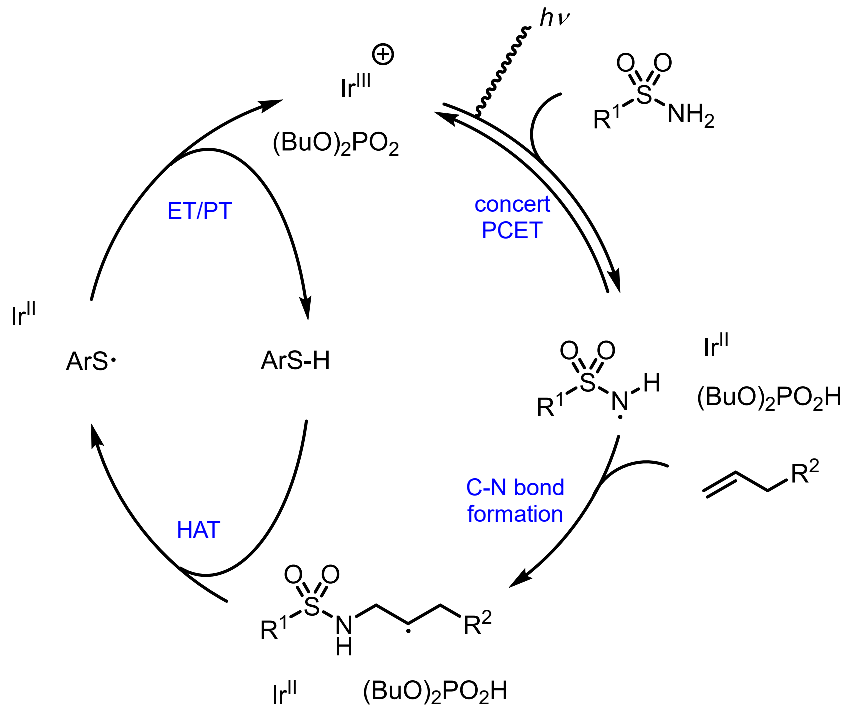


Changes from standard condition	yield(%)
no light	<1
no photocatalyst	<1
no $NBu_4OP(O)(OBu)_2$	1
no 2,4,6-TRIP thiophenol	1

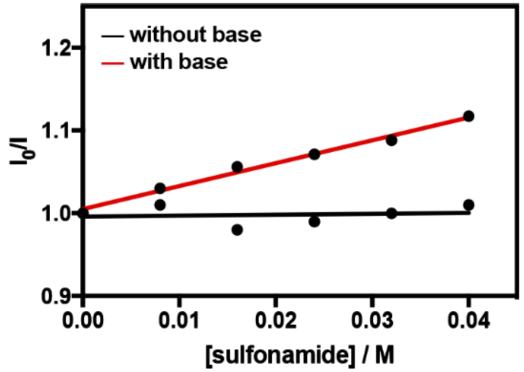
Knowles, R. R. et. al. *J. Am. Chem. Soc.* **2018**, *140*, 741–747.

Radical Transfer Hydroamination

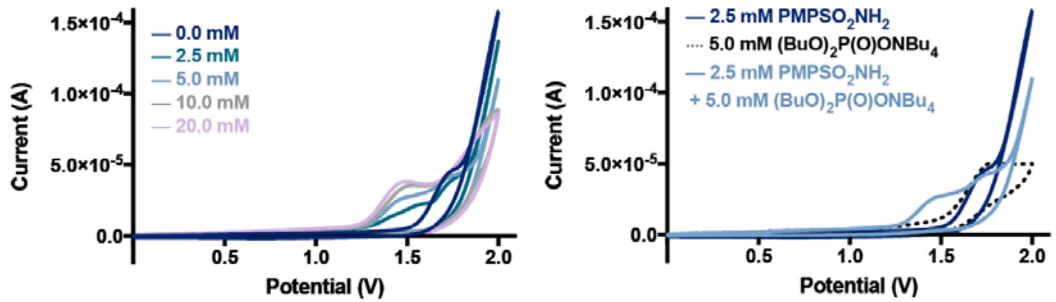
Proposed Mechanism



Stern−Volmer Quenching Studies



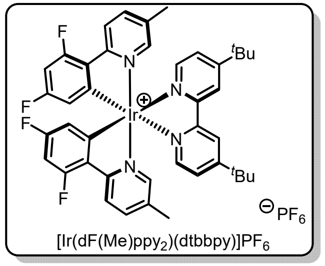
Cyclic Voltammograms Studies



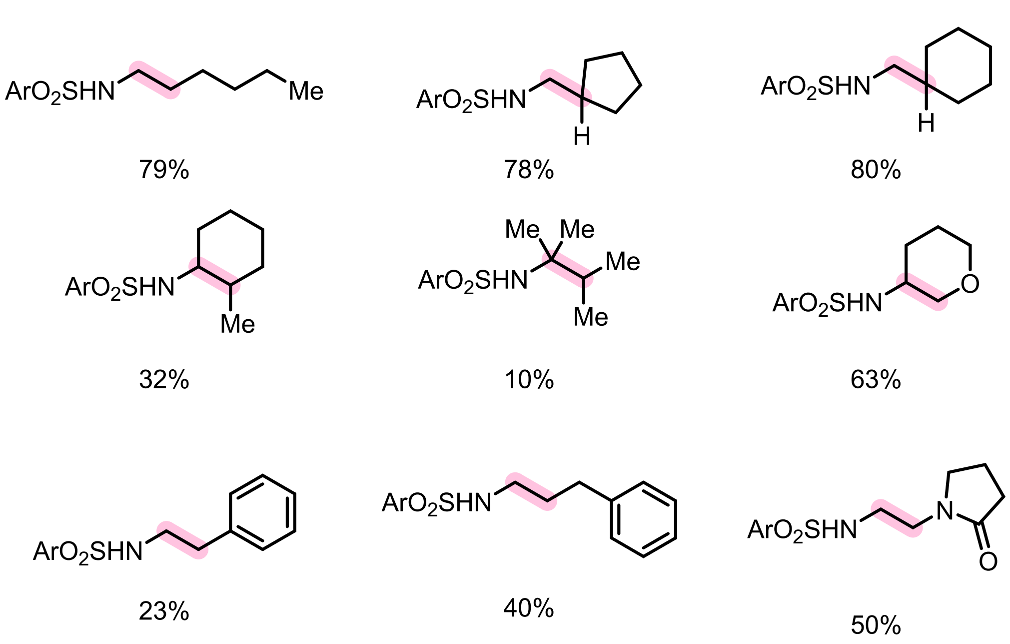
Knowles, R. R. et. al. *J. Am. Chem. Soc.* **2018**, *140*, 741–747.

Radical Transfer Hydroamination

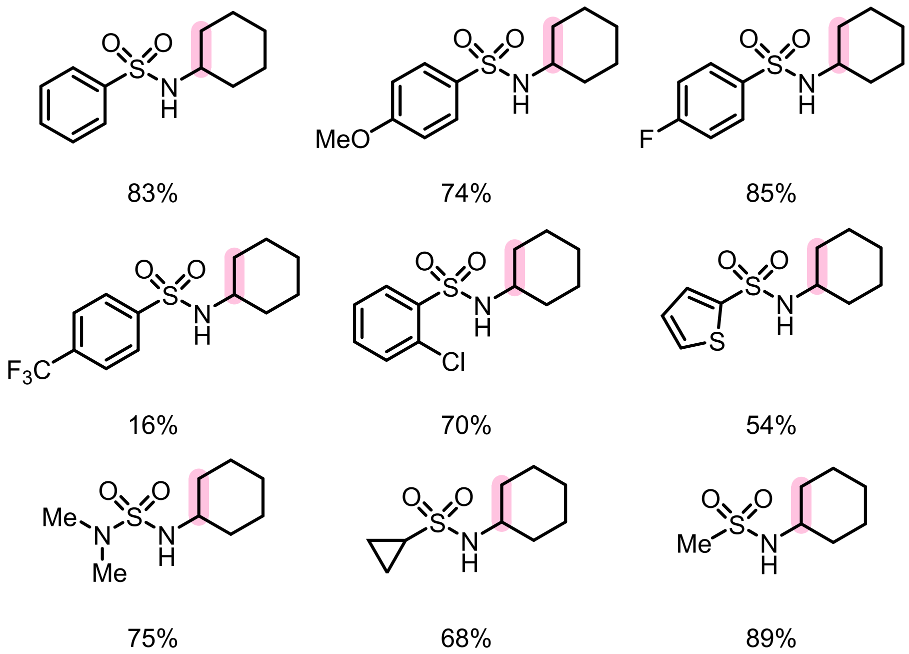
Doyle (2021)



Olefin Scope



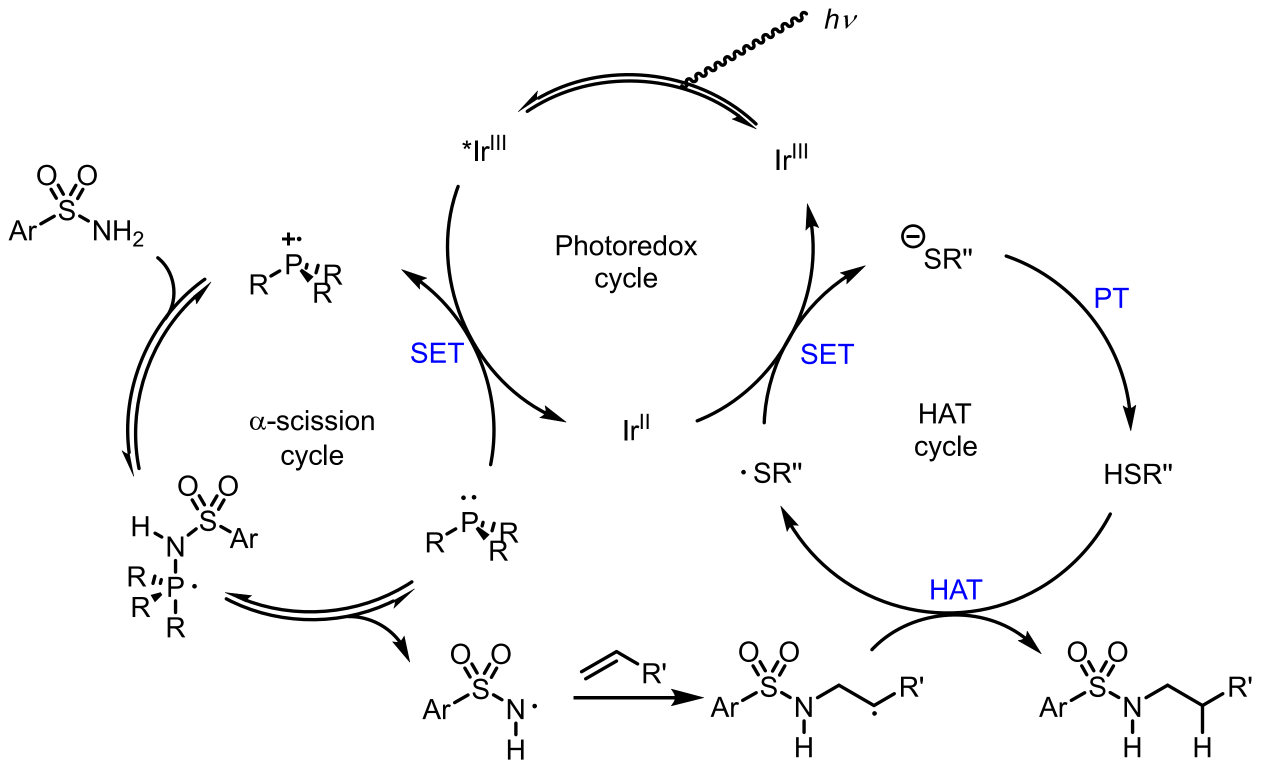
Sulfonamide Scope



Doyle, A. G. et. al. *J. Am. Chem. Soc.* **2021**, *143*, 18331–18338.

Radical Transfer Hydroamination

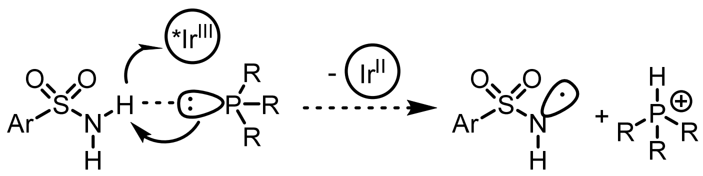
Proposed Mechanism



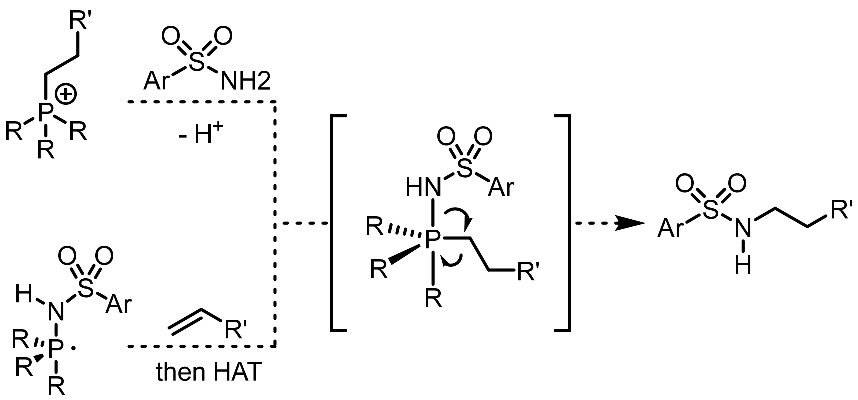
Doyle, A. G. et. al. *J. Am. Chem. Soc.* **2021**, *143*, 18331–18338.

Radical Transfer Hydroamination

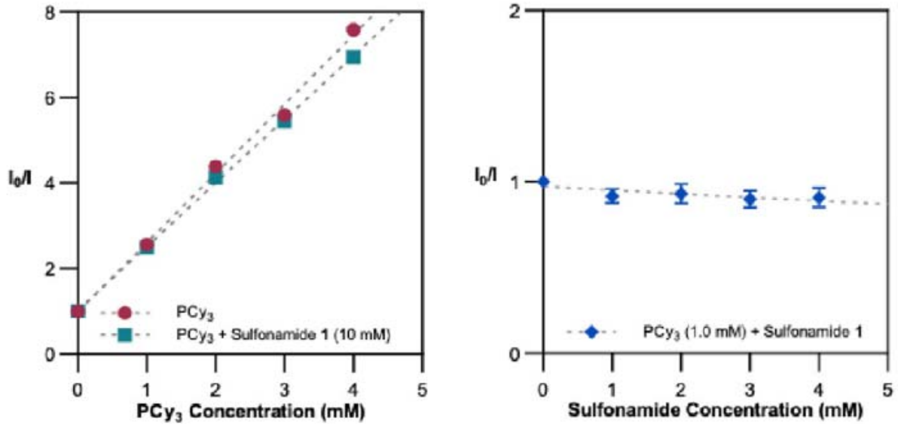
Alternative mechanism: PCET



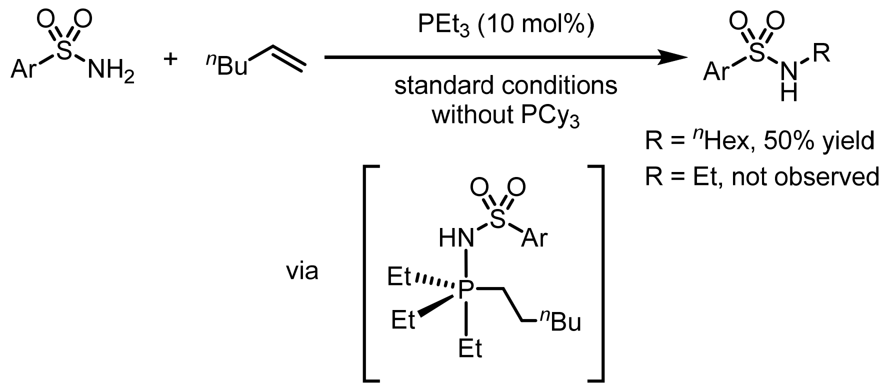
Alternative mechanism: P(V) intermediate



Stern−Volmer Quenching Studies

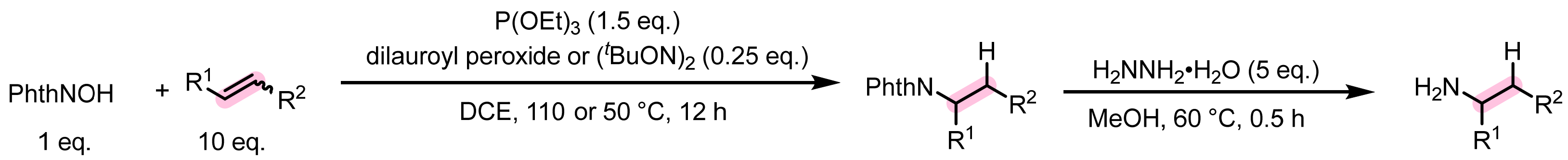


Evaluation of P(V) Reductive Elimination

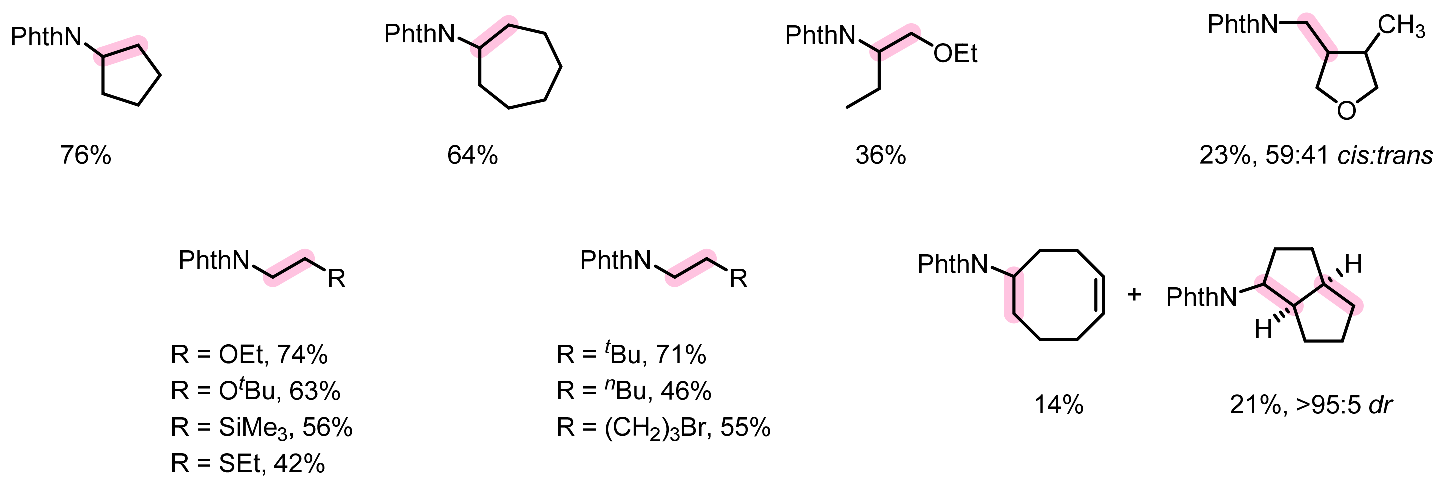


Radical Transfer Hydroamination

Schmidt (2018)



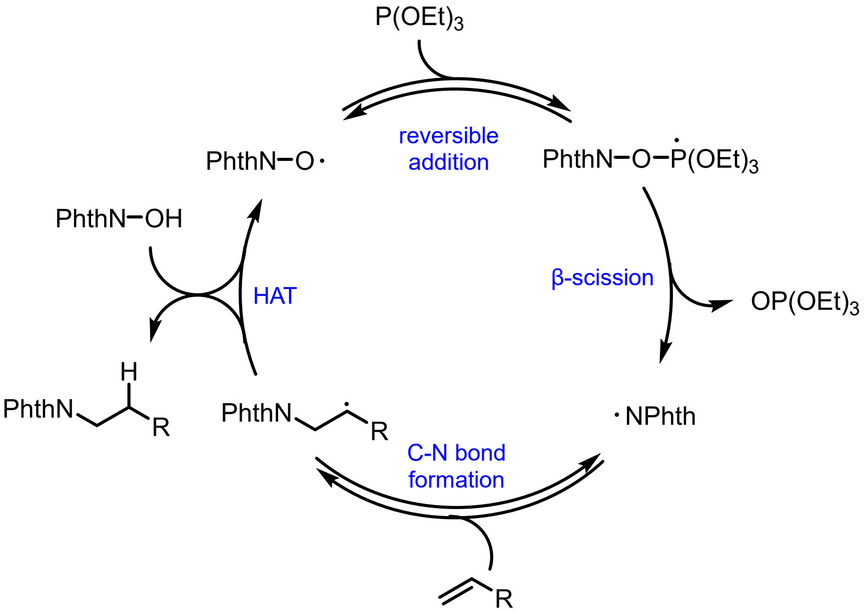
Selected Substrate



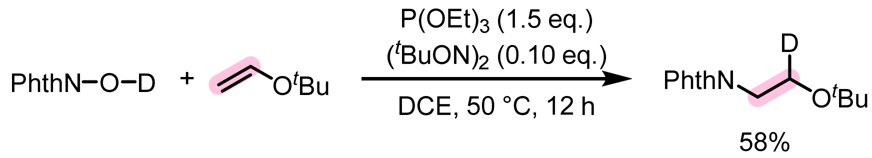
Schmidt, V. A. et. al. *J. Am. Chem. Soc.* **2018**, *140*, 12318–12322.

Radical Transfer Hydroamination

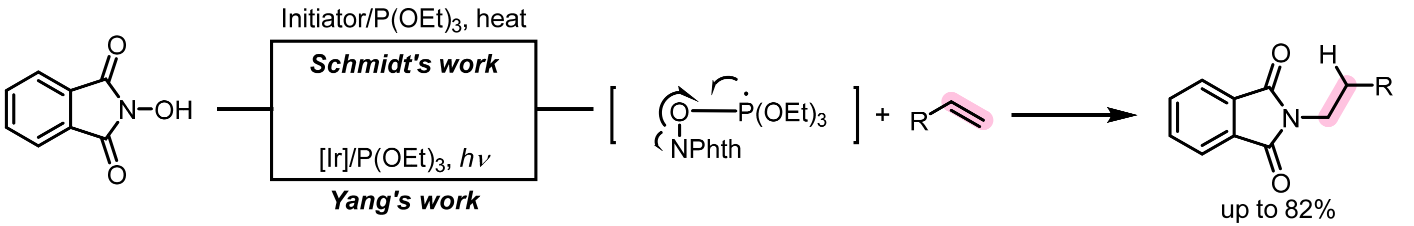
Proposed Mechanism



Deuterium Labeling Studies



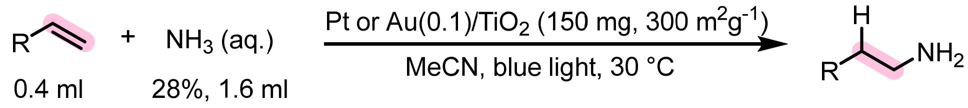
Yang (2021)



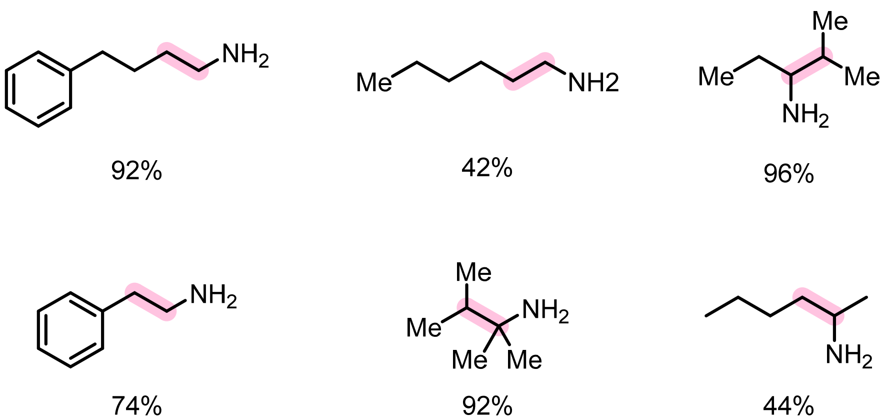
Schmidt, V. A. et. al. *J. Am. Chem. Soc.* **2018**, *140*, 12318–12322.
Yang, H. et. al. *Org. Chem. Front.* **2021**, *8*, 273–277.

Radical Transfer Hydroamination

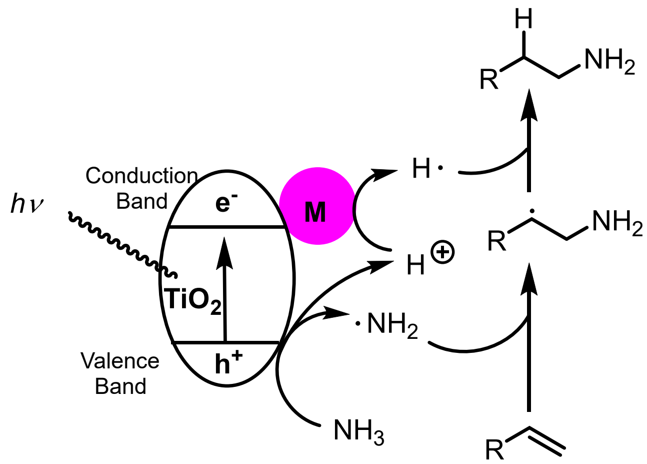
Yoshida (2020)



Selected Substrate



Proposed Mechanism



Yoshida, H. et. al. *J. Am. Chem. Soc.* **2020**, *142*, 12708–12714.

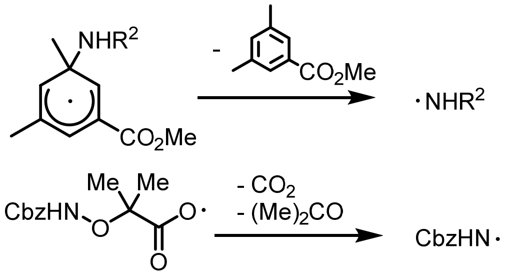
Contents

Summary

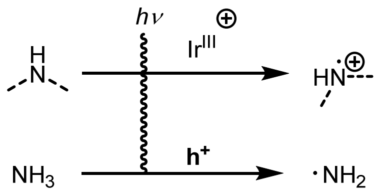
	Hydroboration–amination	Metal-catalyzed Hydroamination	Radical Transfer Hydroamination
Substrate scope of alkene	Terminal alkenes	Tri-substituted alkenes Terminal alkenes	Tetra-substituted alkenes Terminal alkenes Aromatic alkenes
Enantioselectivity	No	Yes	No
Equiv. of substrate	Low equiv., but extra hydroboration reagents	Low equiv., but extra [Si]-H reagents	1-10 equiv.
Product	Tertiary amines	Primary and tertiary amines	Primary to tertiary amines

Summary

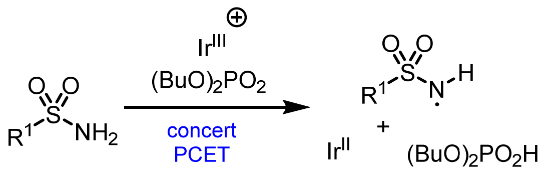
N-radical sources



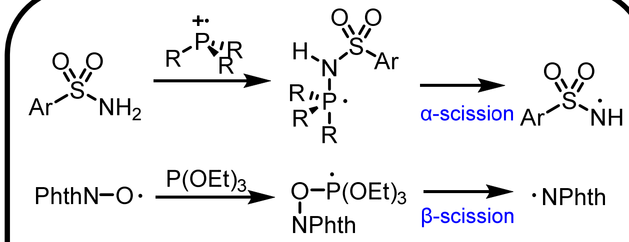
Thermodynamic Driving Force



Direct Oxidation



PCET



α or β Scission

Outlooks

- Cheaper photocatalyst instead of Iridium
- Enantioselectivity of radical transfer process by adding metals or ligands
- The anti-Markovnikov hydroamination of aromatic amines

Thanks for your attention!