A manganese Catalyst for Highly Reactive yet Chemoselective Intramolecular C(sp^3)-H Amination

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Aaron L. Petronico, Shannon M. Miller and M. Christina White.
Nature Chemistry, **2015**, 7, 987-994

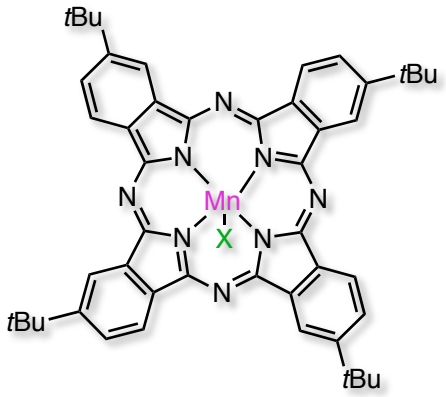
799688 ALDRICH

White-Paradine catalyst NEW

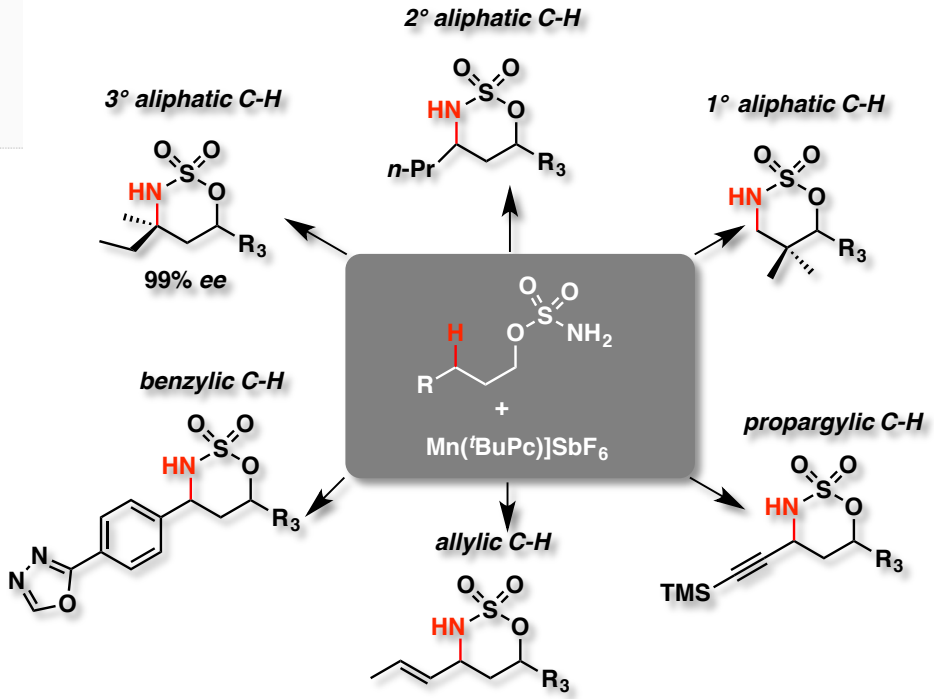
Synonym: Manganese 2,9,16,23-tetra-*tert*-butyl-29*H*,31*H*-phthalocyanine chloride, [2,9,16,23-Tetra-*tert*-butyl-29*H*,31*H*-phthalocyanine]manganese(III) chloride, [Mn(t-BuPc)]Cl

SDS

Empirical Formula (Hill Notation) $C_{48}H_{48}ClMnN_8$ | Molecular Weight 827.34



[Mn(*t*BuPc)]

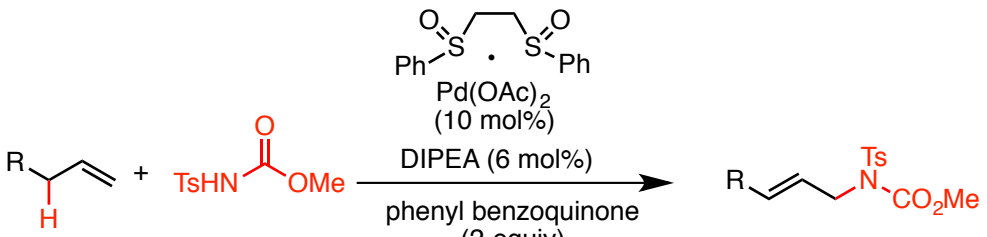


Steph McCabe
Wipf Group- Current Literature
19th December 2015

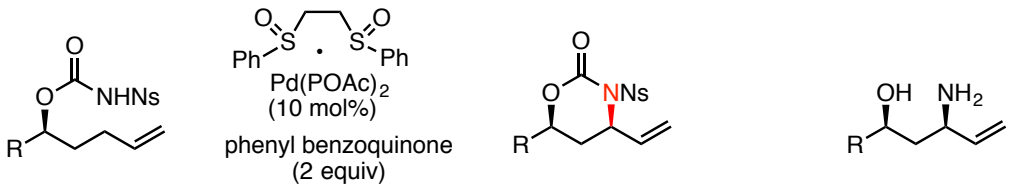
C-H Amination:
Previous Work by the White Group

Palladium Sulfoxide Catalyzed Allylic Amination

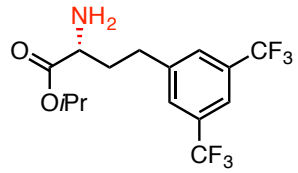
JACS, **2009**, *131*, 11701-11706



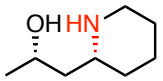
JACS, **2009**, *131*, 11707-11711



Applications

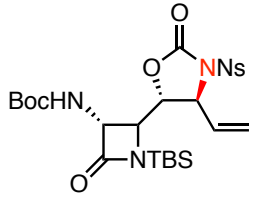


OL, **2012**, *14*, 1386



(+)-allosedrine
6 steps, 27% yield

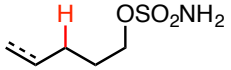
JACS, **2009**, *131*, 11707-11711



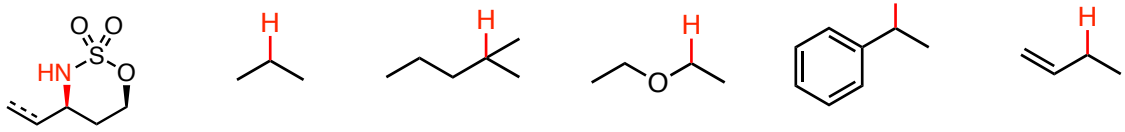
Tetrahedron, **2010**, *66*, 4816-4826

Metallonitrene C-H Amination:

JACS, **2012**,*134*, 2036-2039



[FePc]Cl (10 mol%)
$AgSbF_6$ (10 mol%)
$PhI(OPiv)_2$,
4:1 PhMe/ MeCN
rt, 6 h



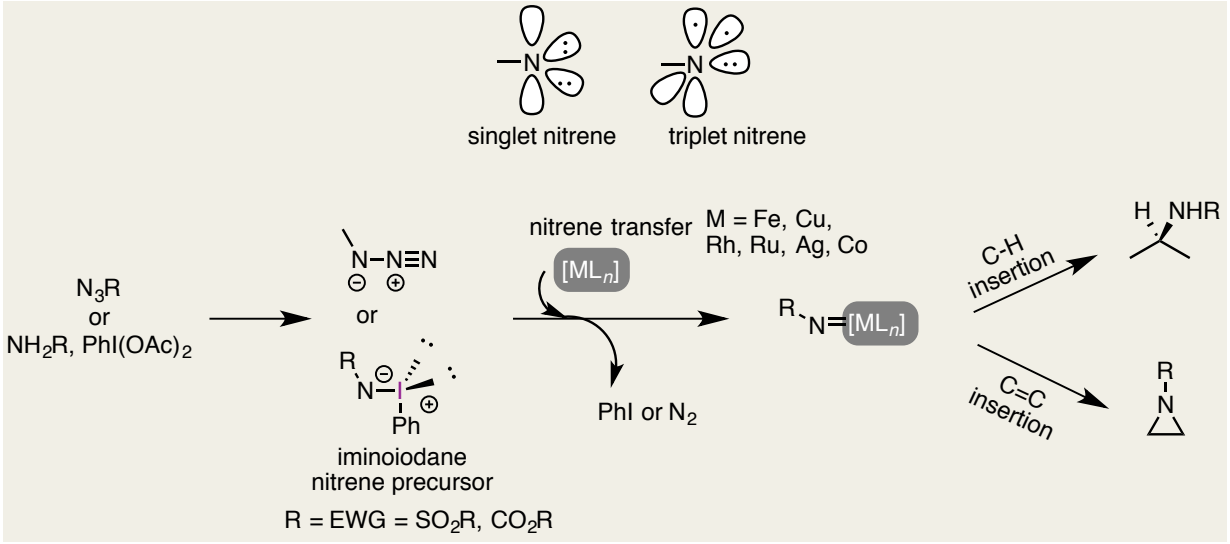
relative rate of C-H amination

C-H Bond strength

Nature Chemistry, **2015**,*7*, 987-994 **<-- TITLE PAPER**

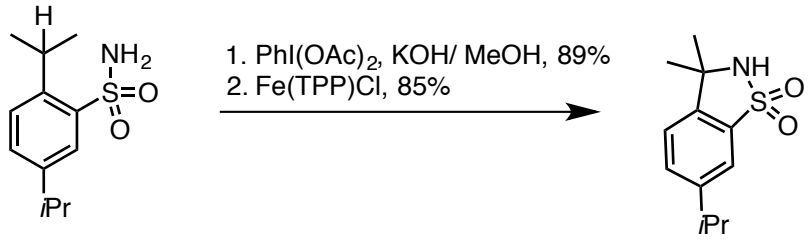
2

Metallonitrene C-H Amination:

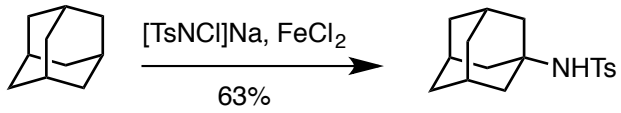


Seminal Papers:

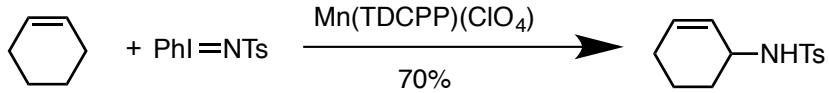
Breslow & Gellman: *JACS*, **1983**, *105*, 6728



Barton: *J. Chem. Soc. Perkin. Trans. 1,* **1983**, 445

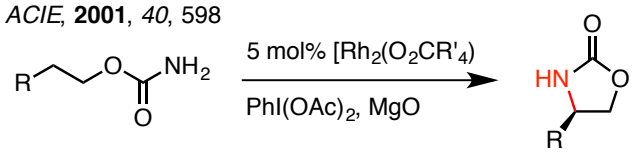


Mansuy: *Tet. Lett.,* **1988**, *29*, 1927

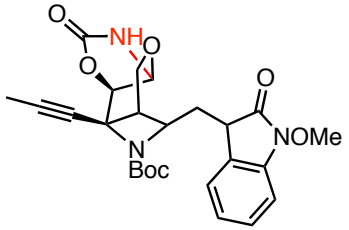


Metallonitrene C-H Amination: Current Methodologies & Applications

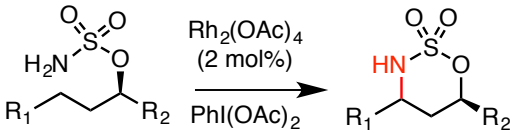
ACIE, **2001**, *40*, 598

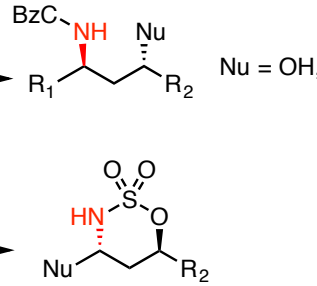


Application

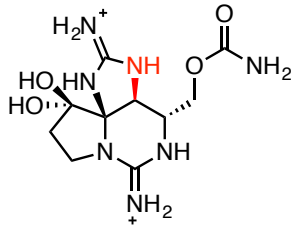


JACS, **2015**, *137*, 6084





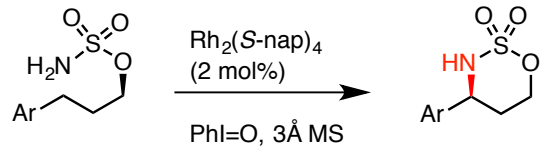
Application



(+)-Saxitoxin

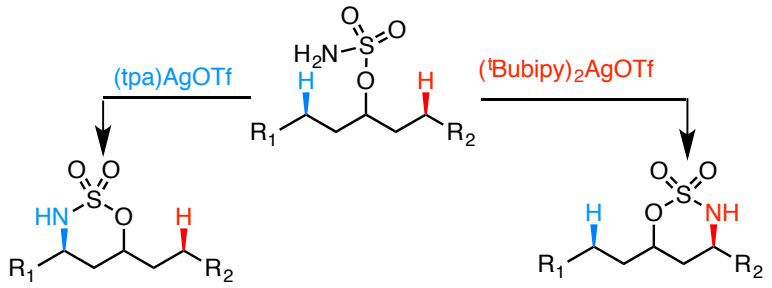
JACS, **2006**, *128*, 3926

JACS, **2008**, *130*, 9220-9221



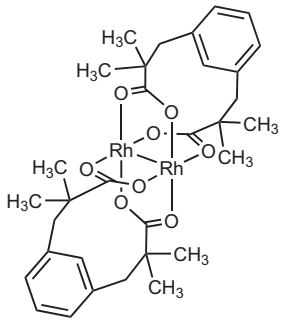
Benzylic, allylic substrates: 43-98% yield, 12-99% ee

JACS, **2014**, *136*, 16720

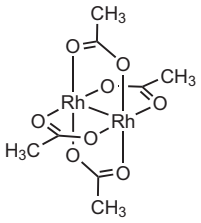


C-H Oxidation Reactivity/ Selectivity Paradigm

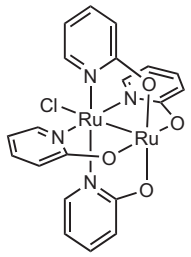
Previous Work:



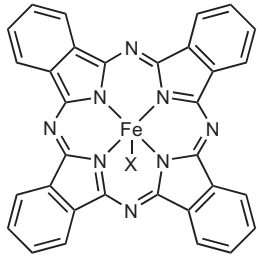
$Rh_2(esp)_2$



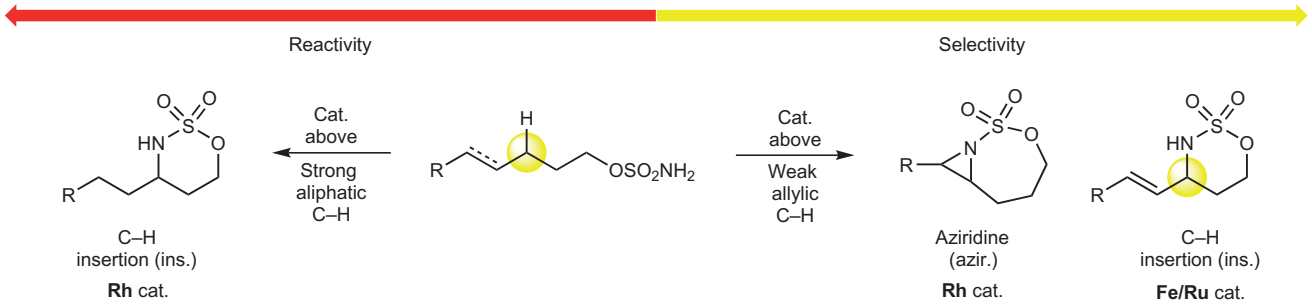
$Rh_2(OAc)_4$



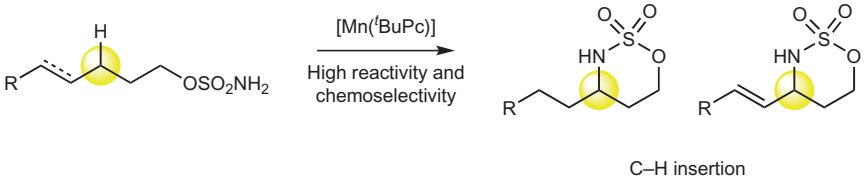
$[Ru_2(hp)_4]Cl$

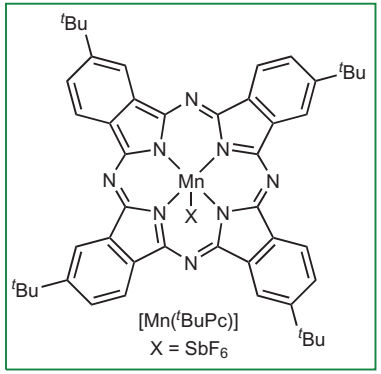


$[FePc]\cdot SbF_6$



This Paper:





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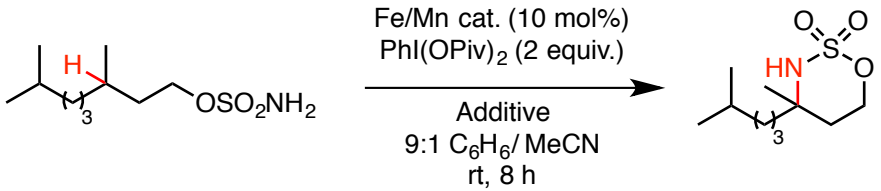
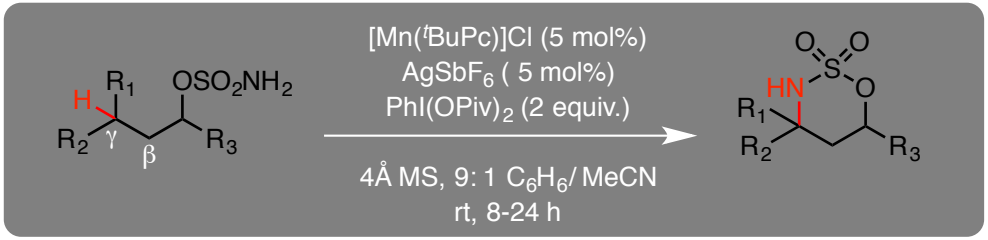
Reaction Development

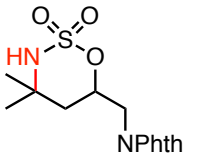


Entry	Catalyst	Additive	% yield (% rsm)
1	[FePc]·SbF6 (**1**)*	–	29 (32)
2	[MnPc]·SbF6 (**2**)*	–	43 (27)
3	Fe(TPP)·SbF6*	–	4 (85)
4	Mn(TPP)·SbF6*	–	18 (62)
5	Fe(*R,R*-salen)·SbF6*	–	<1 (85)
6	Mn(*R,R*-salen)·SbF6*	–	4 (78)
7	Fe(*R,R*-PDP)(SbF6)2	–	<1 (91)
8	Mn(*R,R*-PDP)(SbF6)2	–	7 (82)
9	[MnPc]·SbF6 (**2**)*	4 Å MS	60 (11)
10	[MnPc]·SbF6 (**2**)*	4 Å MS	58 (20)†
11	[Mn(^{t}BuPc)]·SbF_6 (**3**)*	4 Å MS	75 (<5)
12	[Fe(^{t}BuPc)·SbF_6]*	4 Å MS	29 (34)
13	[Mn(^{t}BuPc)]·SbF_6 (**3**)*	4 Å MS	72 (14)†
14	[Mn(^{t}BuPc)]·SbF_6 (**3**)*	4 Å MS	71 (13)‡
15	[Mn(^{t}BuPc)]·SbF_6 (**3**)*	4 Å MS	68 (16)†,§

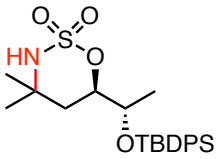
Reaction Scope



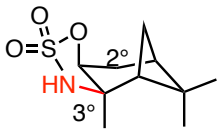
aliphatic



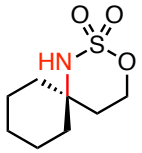
79%



71%



63%



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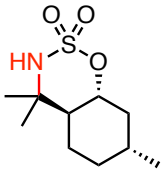
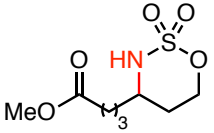
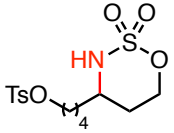


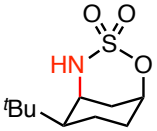
86%



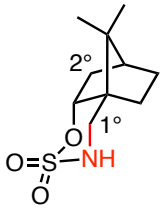
57%



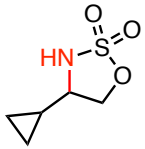
54%



90%
>20: 1 *dr*

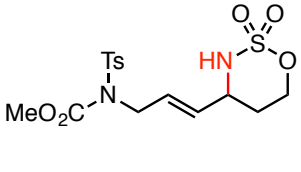


53%
(+27% 2°)
2:1 1°/ 2°



51%

allylic



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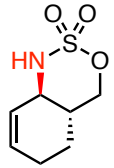

69%
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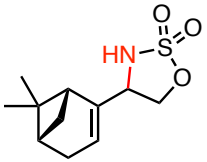
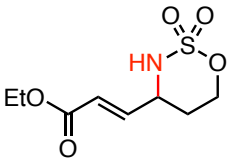
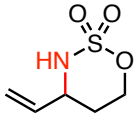


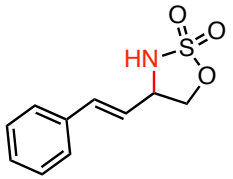
60%
2: 1 *dr*



77%
[FePc]: 12%
[Ru2(hp)4: 25%

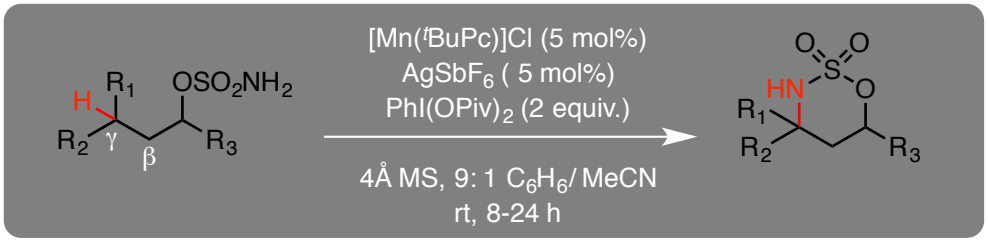


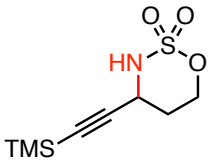
50% 7: 1 (ins./azr.)
[FePc]: 22% 7: 1
[Ru2(Hp)4: 2: 1
Rh2(esp)2: 1: 1.5

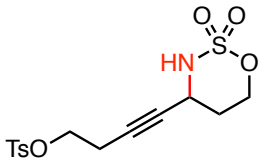


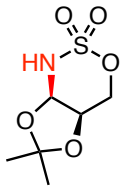
62% 7:1 (ins./azr.)
[Rh2(*S*-nap)4]: 2:1
Rh2(OAc)4: 1: 20

Reaction Scope




64%


48%
1:1 *dr*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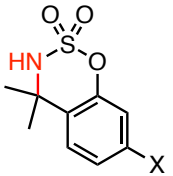
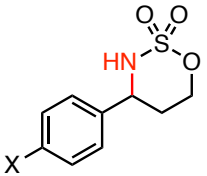
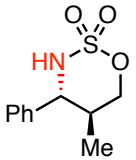
>20:1 *dr*


X = H, 69%
X = OBoc, 69%


X = Br, 68%
X =CF_3, 58%


64%
>20:1 *dr*


68%
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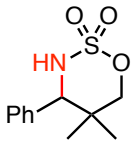
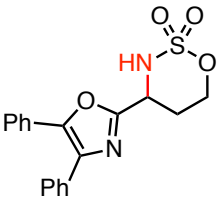

63%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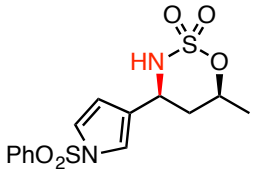
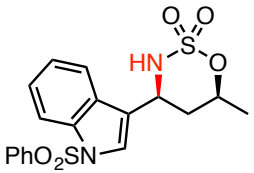
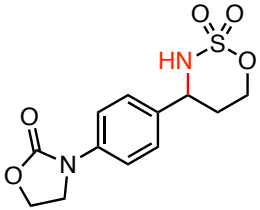

69%
7: 1 *dr*


71%
12: 1 *dr*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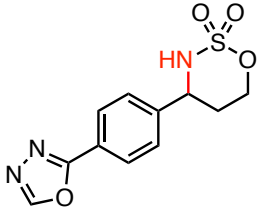
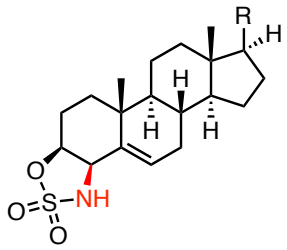
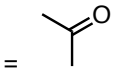

63%

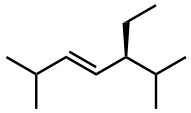
Late-Stage Diversification of Complex Molecules



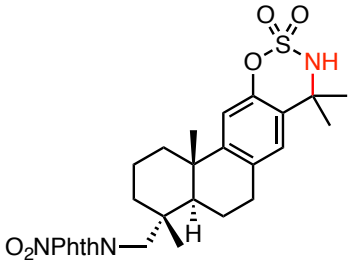
R =



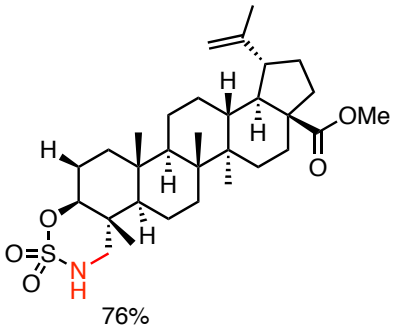
51%



66%

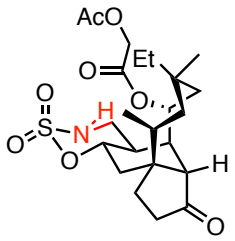


70%



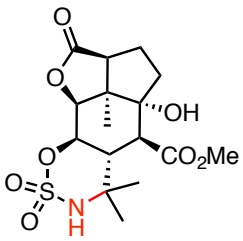
76%

1 regioisomer,
1 stereoisomer

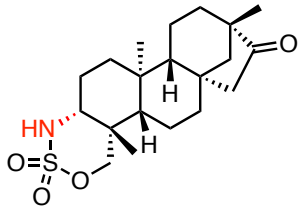


84%

1 regioisomer



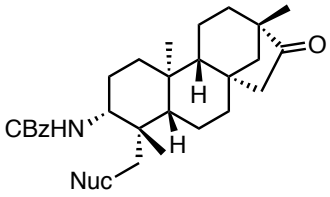
57%



92% (5 mol%)
75% (2.5 mol%, 1.5 equiv [O], gram scale)

(i) CBzCl, Et_3N, DMAP, THF, 2 h, 83%

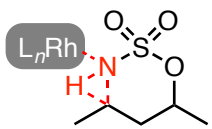
(ii) NaN_3, DMF, 40 °C
or KOAc, DMF, 80 °C



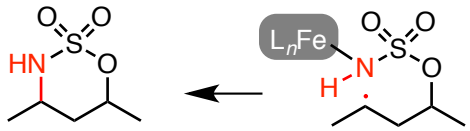
Nuc = N_3, 56%
Nuc = OAc, 76%

Mechanistic Studies

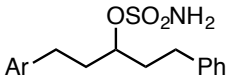
Reactivity ← → Chemoselectivity



concerted asynchronous

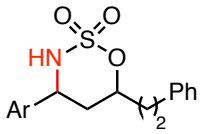


stepwise radical abstraction/ rebound

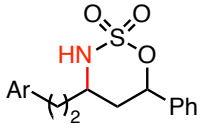


Hammett Analysis

Standard conditions

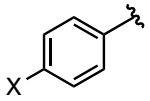


H



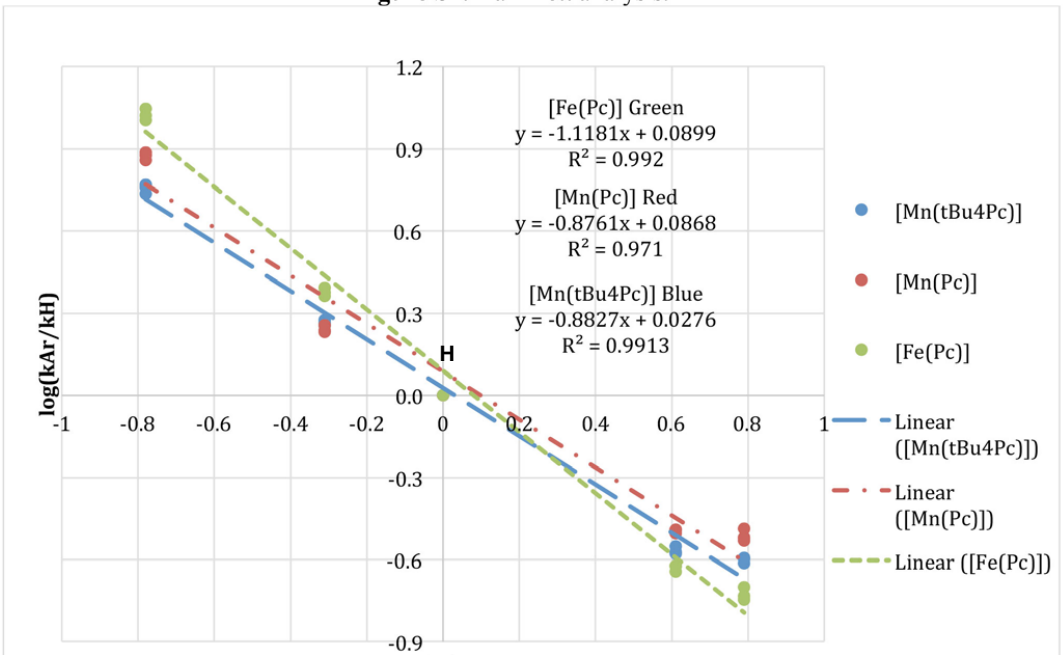
Ar

Ar =



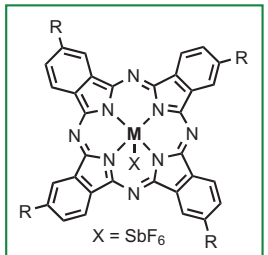
X = OMe, Me, CF_3, NO_2

Figure S1. Hammett analysis.



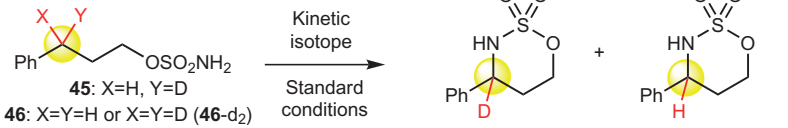
Fe $\rho_{\sigma+}$ = -1.12
Mn $\rho_{\sigma+}$ = -0.88
Rh $\rho_{\sigma+}$ = -0.55 (lit. value)

Mechanistic Studies



1 R = H; M = Fe
2 R = H; M = Mn
3 R = ^{t}Bu; M = Mn

a



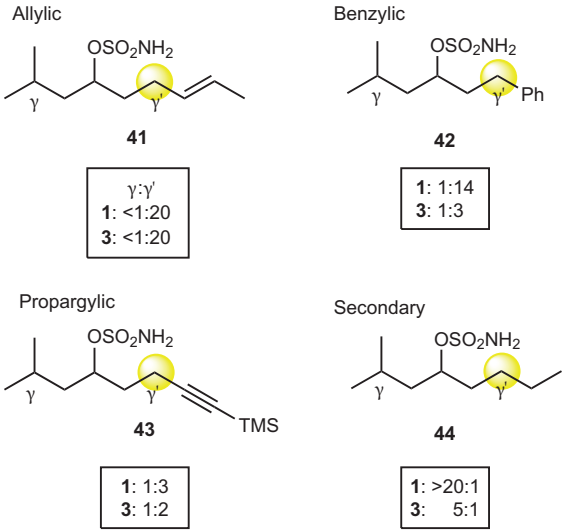
45: X=H, Y=D
46: X=Y=H or X=Y=D (**46**-d_2)

Intramolecular competition (**45**)
1: k_H/k_D = 4.8±0.1
2: k_H/k_D = 4.5±0.1
3: k_H/k_D = 4.2±0.1
$Rh_2(OAc)_4$: k_H/k_D = 3.8±0.1

Parallel reactions (**46** or **46**-d_2)
2: k_H/k_D = 1.9±0.2
3: k_H/k_D = 1.7±0.1

Intermolecular competition (**46** and **46**-d_2)
2: k_H/k_D = 1.9±0.1
3: k_H/k_D = 1.6±0.1

b

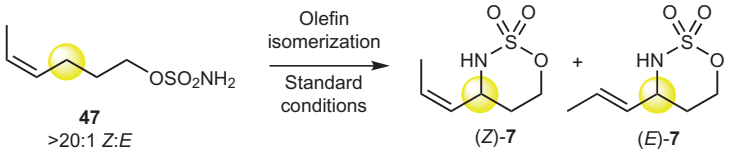


BDE's (kcal/mol)

R-R ⟶ R· + R·

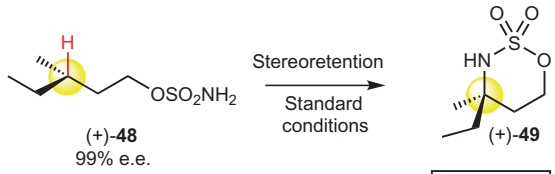
allylic (85l) < benzylic (88) < propargylic (132) < 3° (93.2l) < 2° (98.2)

c



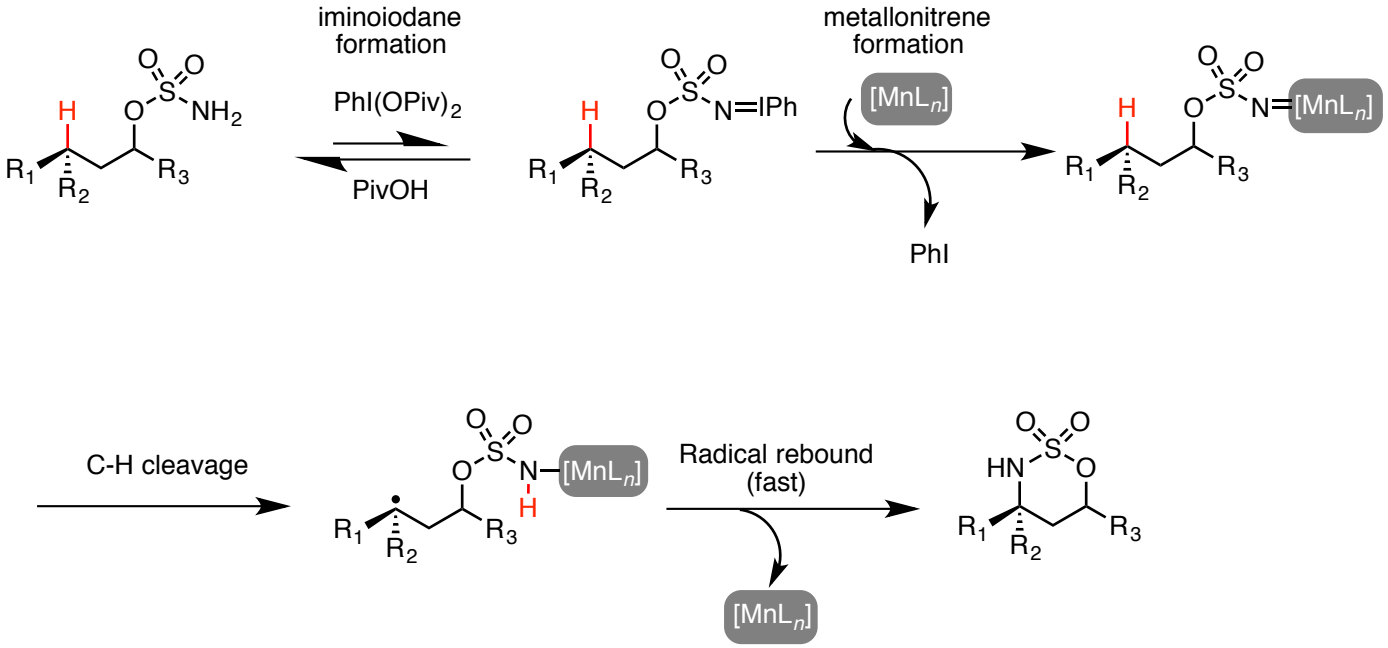
1: 10:1 *Z*:*E*
3: 10:1 *Z*:*E*

d

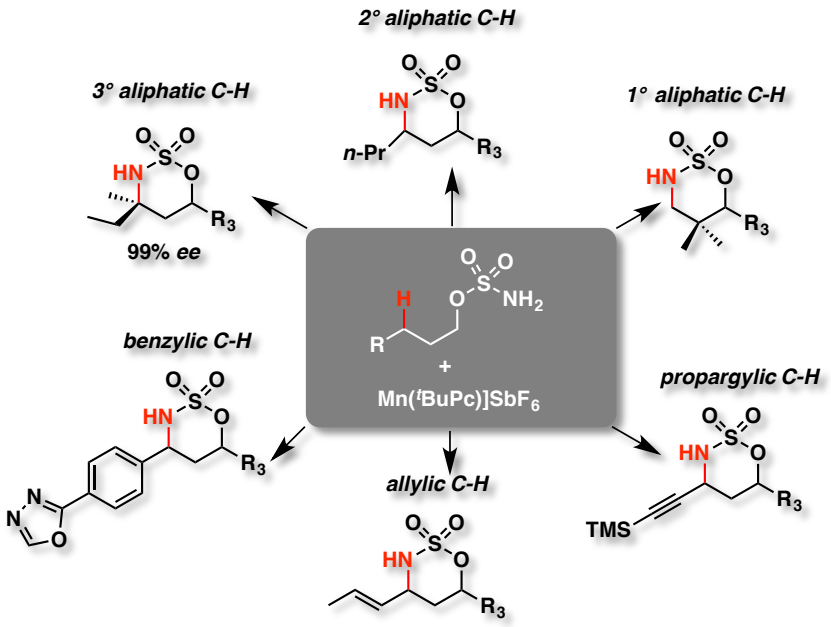


1: 99% e.e.
3: 99% e.e.

Proposed Mechanism



Conclusions/ Future Directions



Conclusions:

- Report a new C-H amination catalyst - Manganese tert-butylphthalocyanine [Mn(tBuPc)]
- 10 million x more abundant than noble metal predecessor
- Functionalizes all C(sp^3)-H bonds (including 1° aliphatic) (=highly reactive)
- Stereospecific
- Broad functional group tolerance (=highly selective)
  - increases it's potential for natural product synthesis & late-stage diversification of pharmaceuticals

Future Directions:

- Intermolecular variant
- Asymmetric variant