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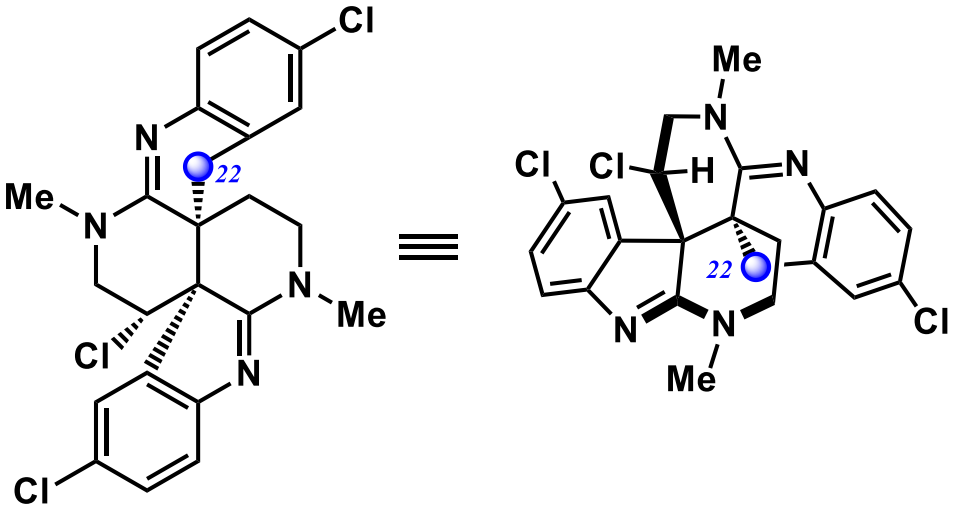
Communication

Enantioselective Total Synthesis of (−)-Caulamidine A

Zhouyang Zhu and Thomas J. Maimone*



caulamidine A (**1**)

antimalarial (IC_{50} 8.3-12.9 mM)
biosynthesis unknown

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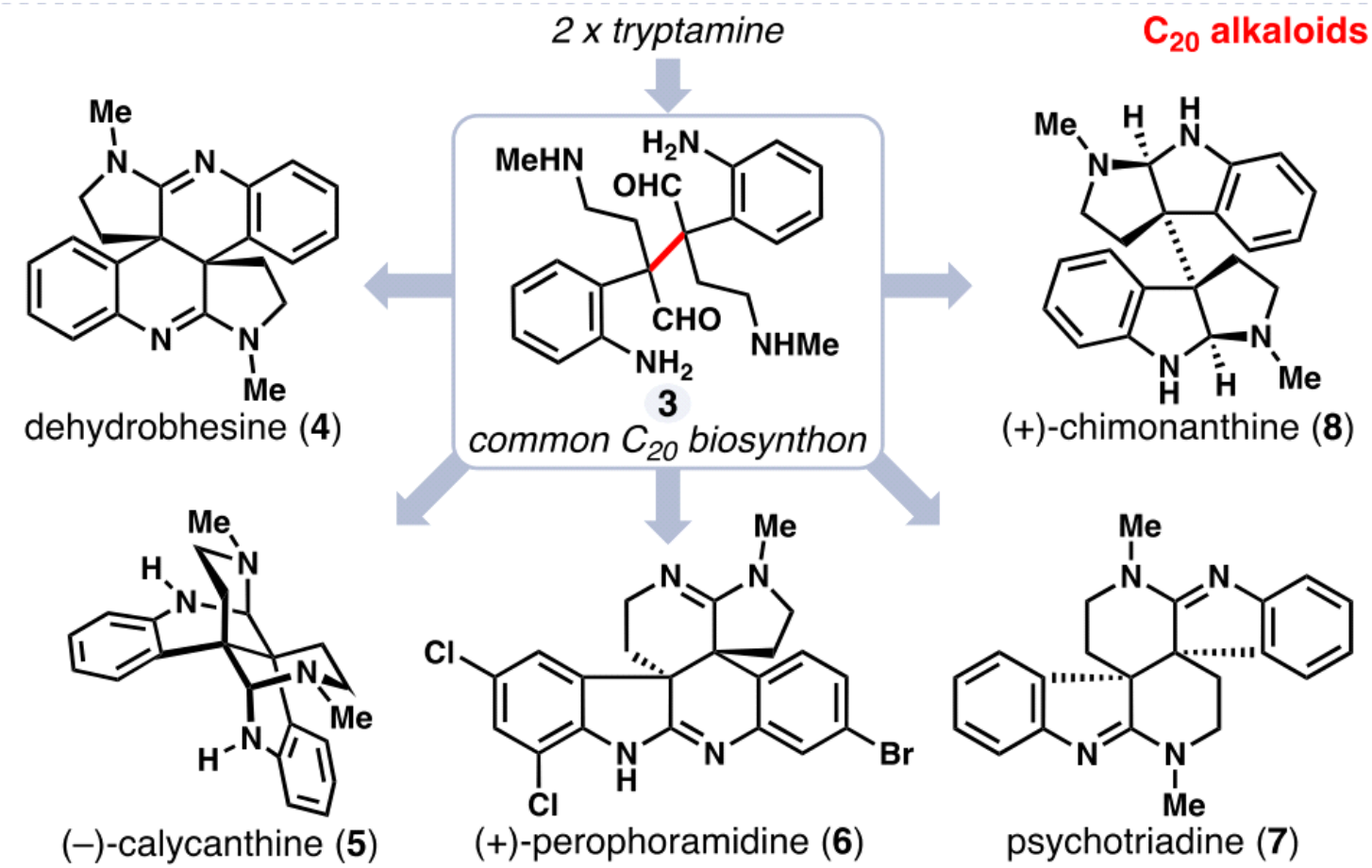
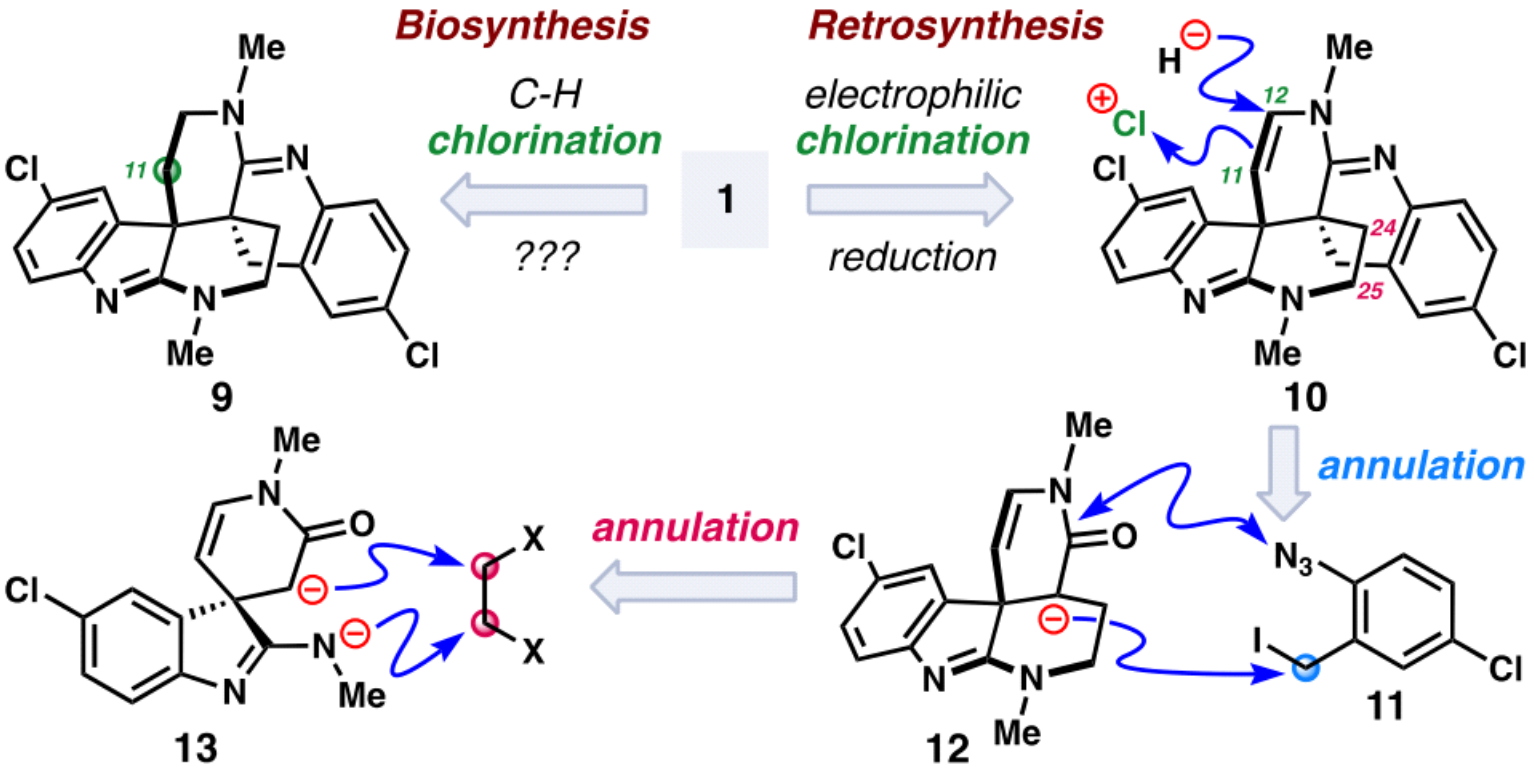
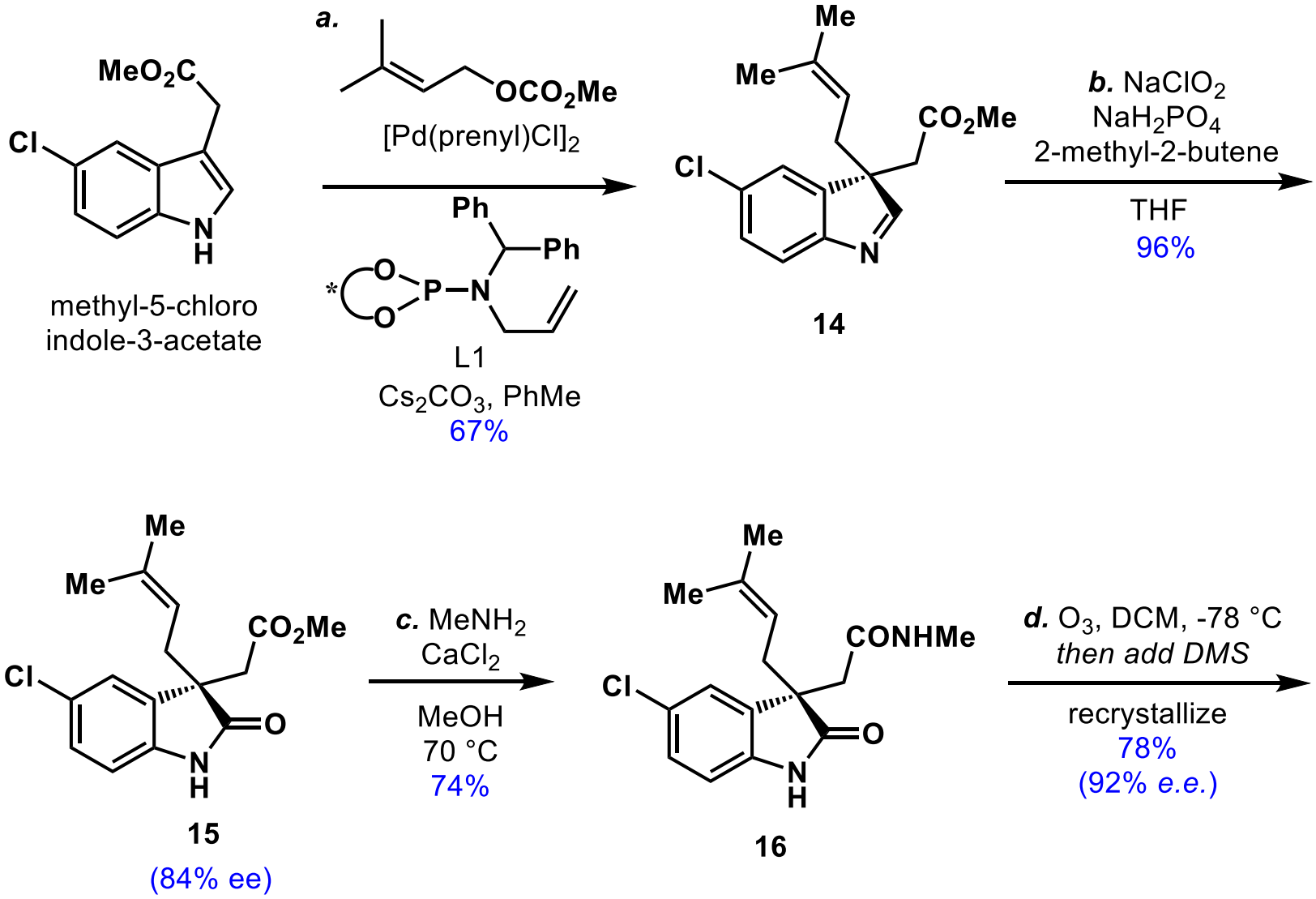
Representative bis(cyclotryptamine) alkaloids.



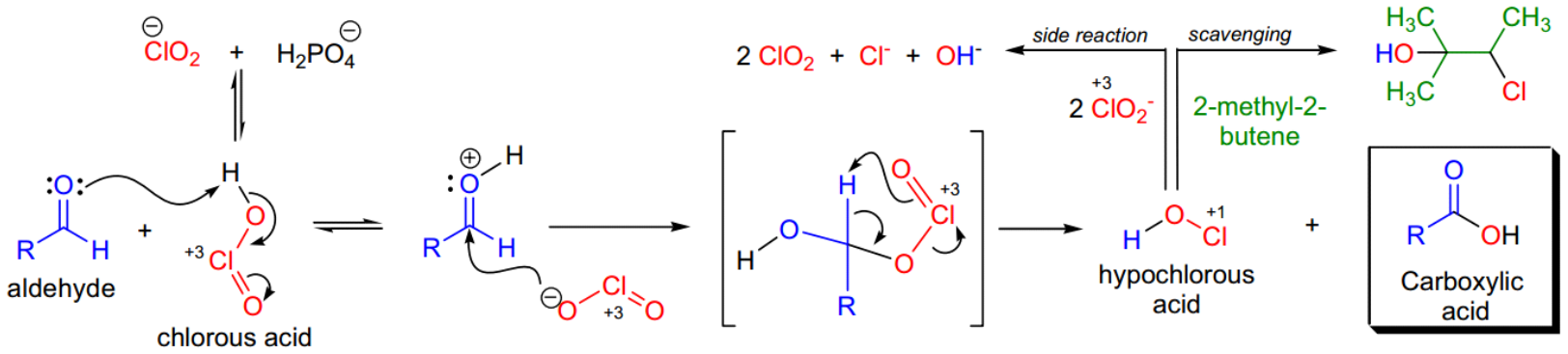
Initial synthetic plan toward **1**.

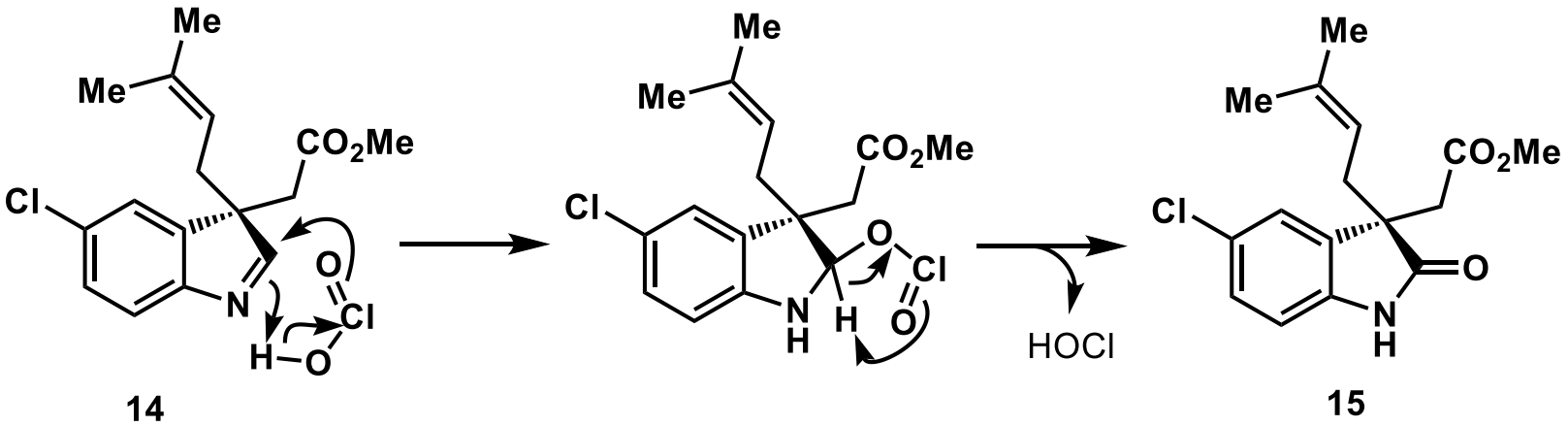



MeO2C
Cl
N
H
methyl-5-chloro
indole-3-acetate
a.
OCO2Me
[Pd(prenyl)Cl]2
Ph
Ph
O
P
N
O
*
L1
Cs2CO3, PhMe
67%
Me
Me
CO2Me
Cl
N
14
b. NaClO2
NaH2PO4
2-methyl-2-butene
THF
96%
Me
Me
CO2Me
Cl
O
N
H
15
(84% ee)
c. MeNH2
CaCl2
MeOH
70 °C
74%
Me
Me
CONHMe
Cl
O
N
H
16
d. O3, DCM, -78 °C
then add DMS
recrystallize
78%
(92% e.e.)

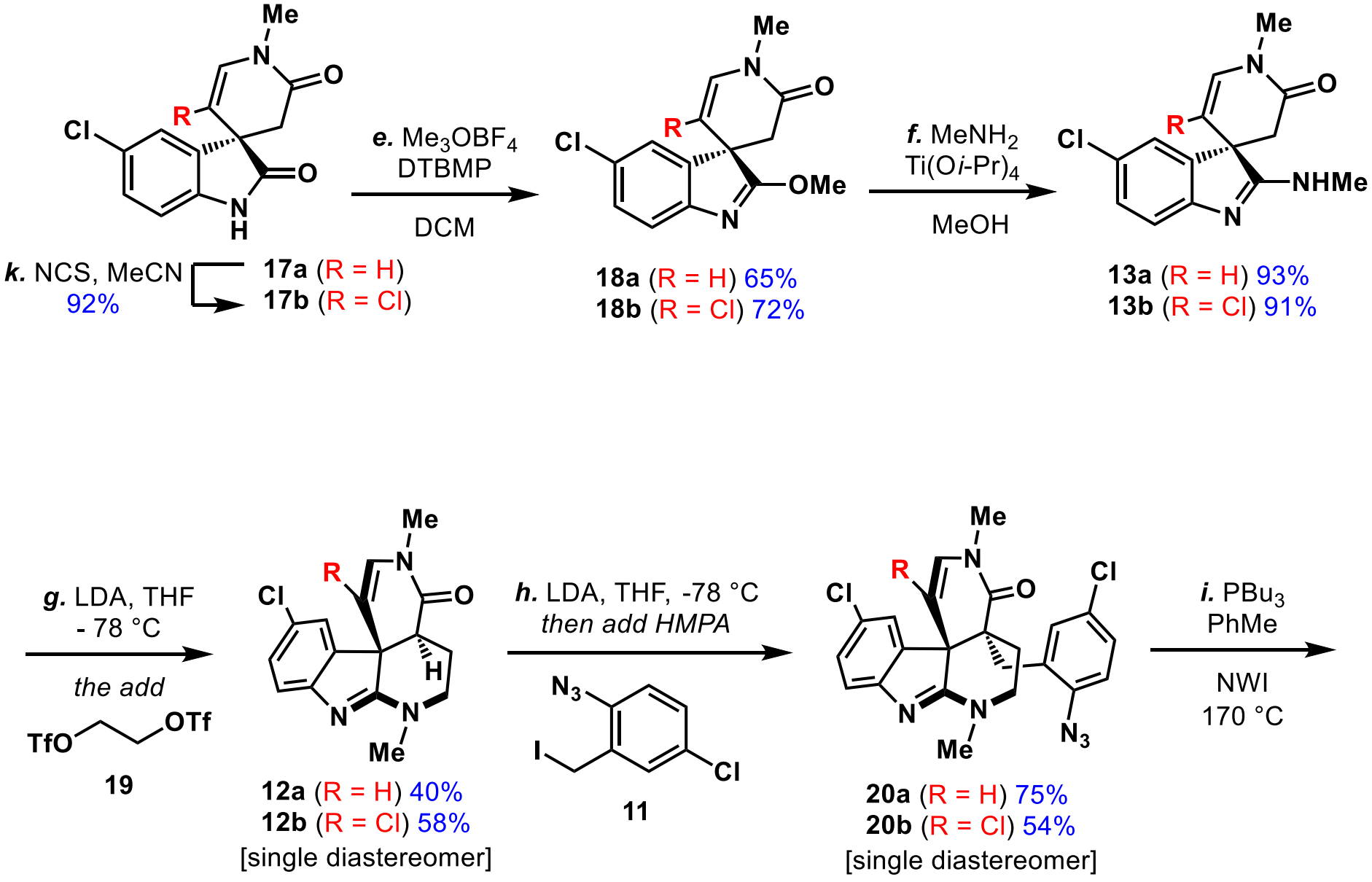
PINNICK OXIDATION

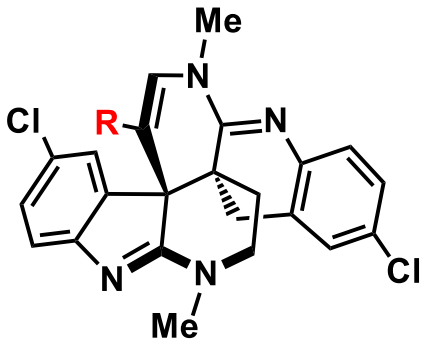
Mechanism: [10,6]





14 15


Me
N
O
R
Cl
O
N
H
17a (R = H)
17b (R = Cl)
k. NCS, MeCN
92%
e. Me3OBF4
DTBMP
DCM
OMe
18a (R = H) 65%
18b (R = Cl) 72%
f. MeNH2
Ti(Oi-Pr)4
MeOH
NHMe
13a (R = H) 93%
13b (R = Cl) 91%
g. LDA, THF
- 78 °C
the add
TfO
OTf
19
H
Me
12a (R = H) 40%
12b (R = Cl) 58%
[single diastereomer]
h. LDA, THF, -78 °C
then add HMPA
N3
I
11
20a (R = H) 75%
20b (R = Cl) 54%
[single diastereomer]
i. PBu3
PhMe
NWI
170 °C



10a (R = H) 74%
10b (R = Cl) 95%

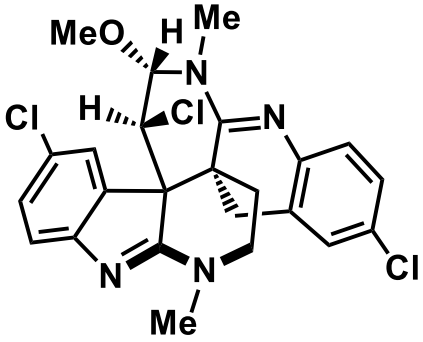
(R = H)

(R = Cl)

j. NCS, MeOH

80%

[single diastereomer]



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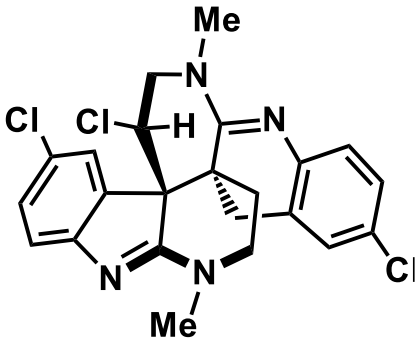
I. $Mn(dpm)_3$
$Ph(i\text{-}PrO)SiH_2$
PhSH, $B(Oi\text{-}Pr)_3$

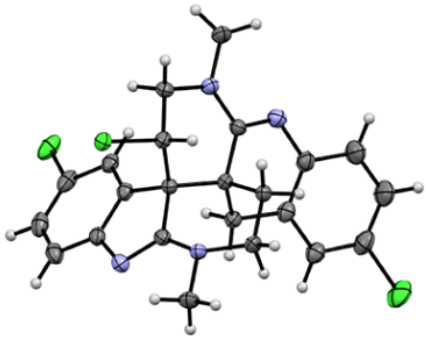
i-PrOH

49%

[single diastereomer]

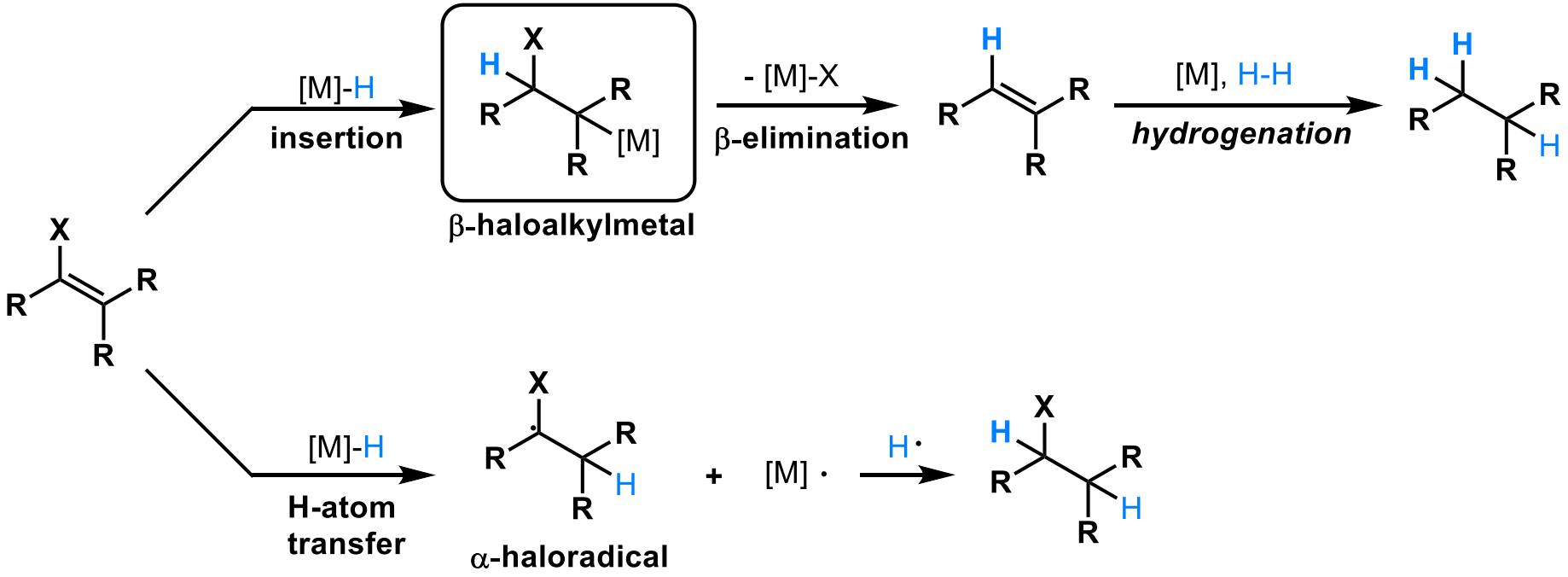


(-)-caulamidine A (**1**)



1 [Xray]

Hydrogenation of Alkenyl Halides to Alkyl Halides



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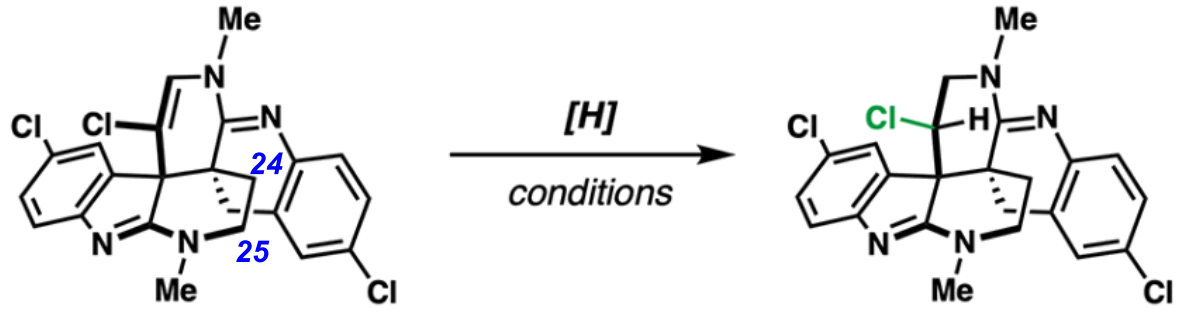
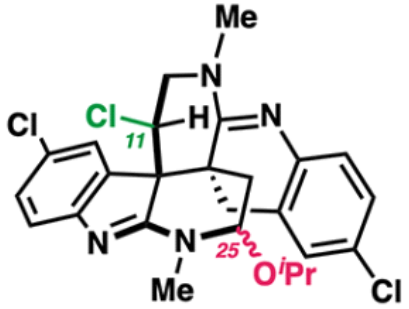
A



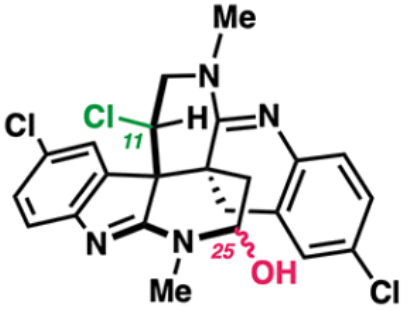
10b caulamidine A (**1**)

Entry	*Conditions*	*Reaction Products* [a]
1	TFA, Et_3SiH, DCM	**10b**
2	H_2, PtO_2, AcOH/EtOAc	**10b**, **9** (14%), **1** (6%)
3	$Fe_2(ox)_3$, $NaBH_4$, EtOH/H_2O	**10b**
4	$Co(acac)_2$, Et_3SiH, 1,4-CHD, TBHP, *n*-PrOH, air	**10b**
5	$Fe(acac)_3$, $PhSiH_3$, PhSH, EtOH	**10b**
6	$Mn(dpm)_3$, $PhSiH_3$, TBHP, *i*-PrOH	**10b**
7[b]	$Mn(dpm)_3$, $Ph(i\text{-PrO})SiH_2$, TBHP, *i*-PrOH	**10b**, **1** (trace)
8[c]	$Mn(dpm)_3$, $Ph(i\text{-PrO})SiH_2$, TBHP, *i*-PrOH	**10b** (21%), **1** (15%), **22** (16%), **23** (9%), **24** (7%)
9[d]	$Mn(dpm)_3$, $Ph(i\text{-PrO})SiH_2$, PhSH, *i*-PrOH	**10b** (62%), **1** (12%)
10[e]	$Mn(dpm)_3$, $Ph(i\text{-PrO})SiH_2$, PhSH, $B(Oi\text{-Pr})_3$, *i*-PrOH	**10b** (24%), **1** (49%)[f]

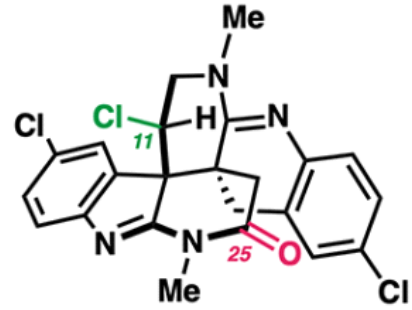
[a]Yields determined by ^1H NMR analysis. [b]Mn^{III} (5 mol%), silane (2 equiv.), TBHP (2 equiv.). [c]Mn^{III} (2 equiv.), silane (4 equiv.), TBHP (2 equiv.). [d]Mn^{III} (2 equiv.), silane (2 equiv.), PhSH (2 equiv.). [e]Mn^{III} (10 equiv.), silane (10 equiv.), PhSH (10 equiv.), $B(Oi\text{-Pr})_3$ (2 equiv.), with *aq.* NH_4OH workup. [f]Isolated yield. TFA = trifluoroacetic acid, TBHP = tert-butyl hydroperoxide.



22 (d.r. = 5.7:1)



23 (d.r. = 1.3:1)



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Entry 4

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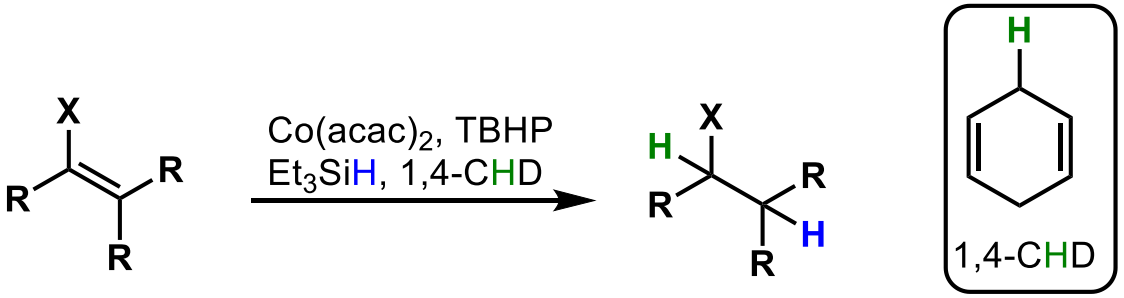
A Method for the Selective Hydrogenation of Alkenyl Halides to Alkyl Halides



J. Am. Chem. Soc., **2014**, *136*, 6884.

Entry 5

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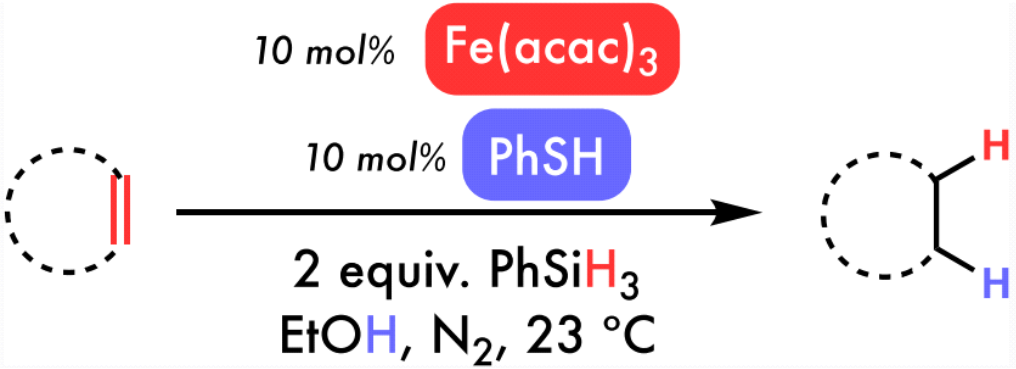
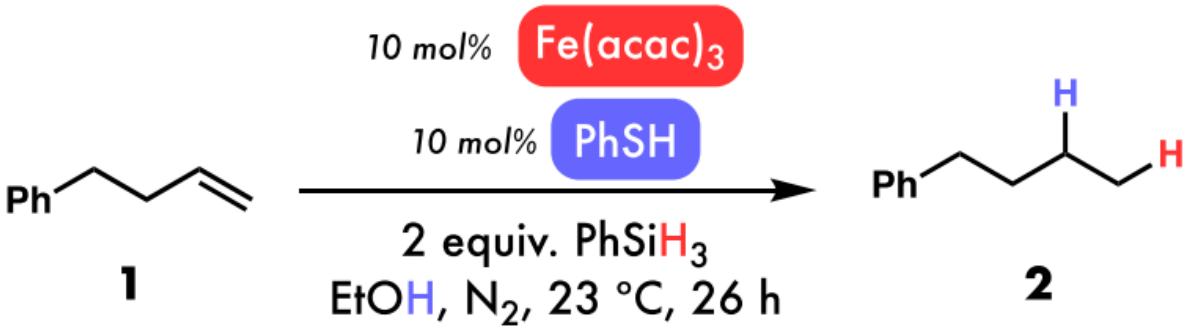
Article

Hydrogenation of Alkenes via Cooperative Hydrogen Atom Transfer



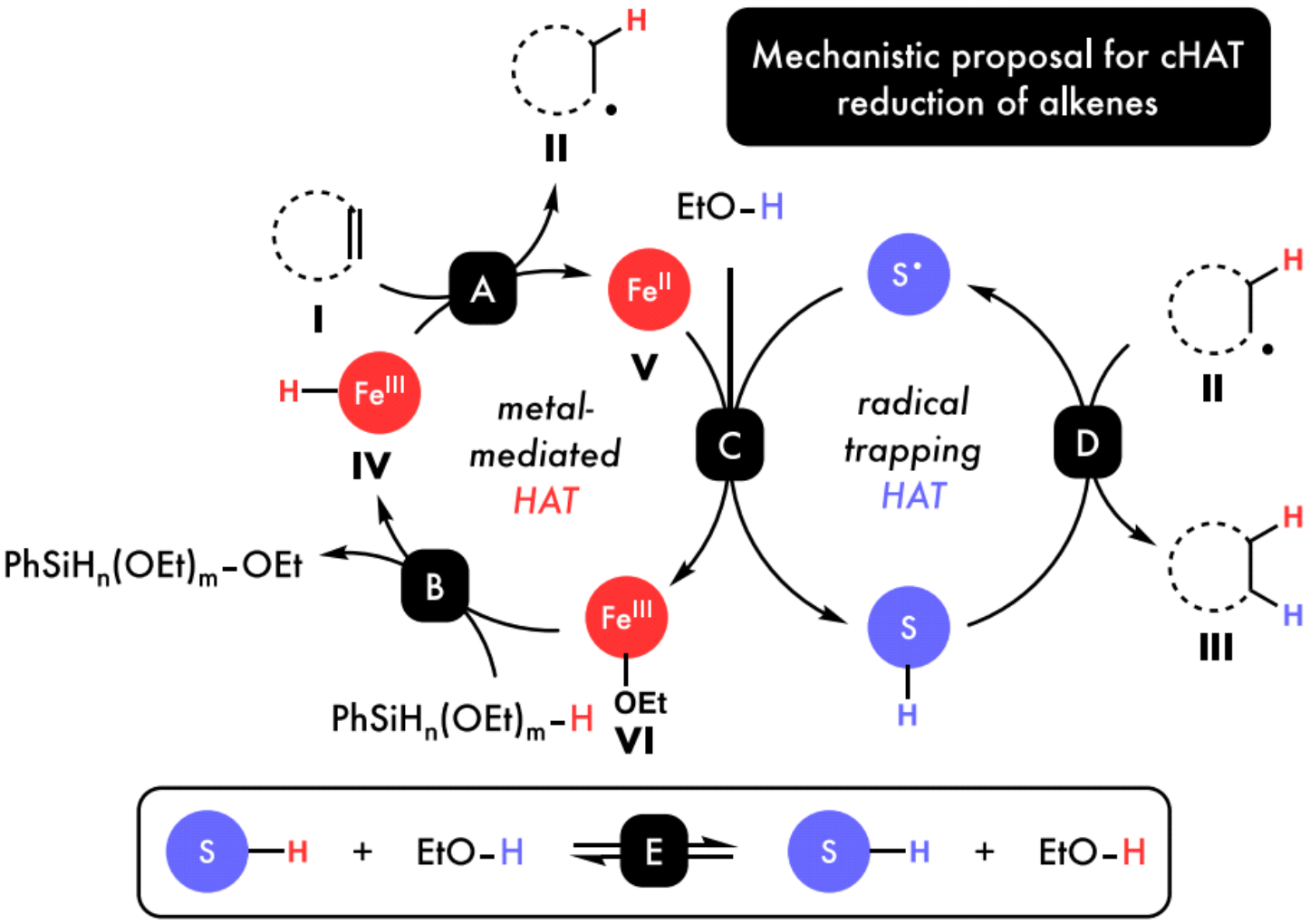
J. Am. Chem. Soc., **2020**, *142*, 19316.

Development of a Cooperative Hydrogen Atom Transfer Catalyst System

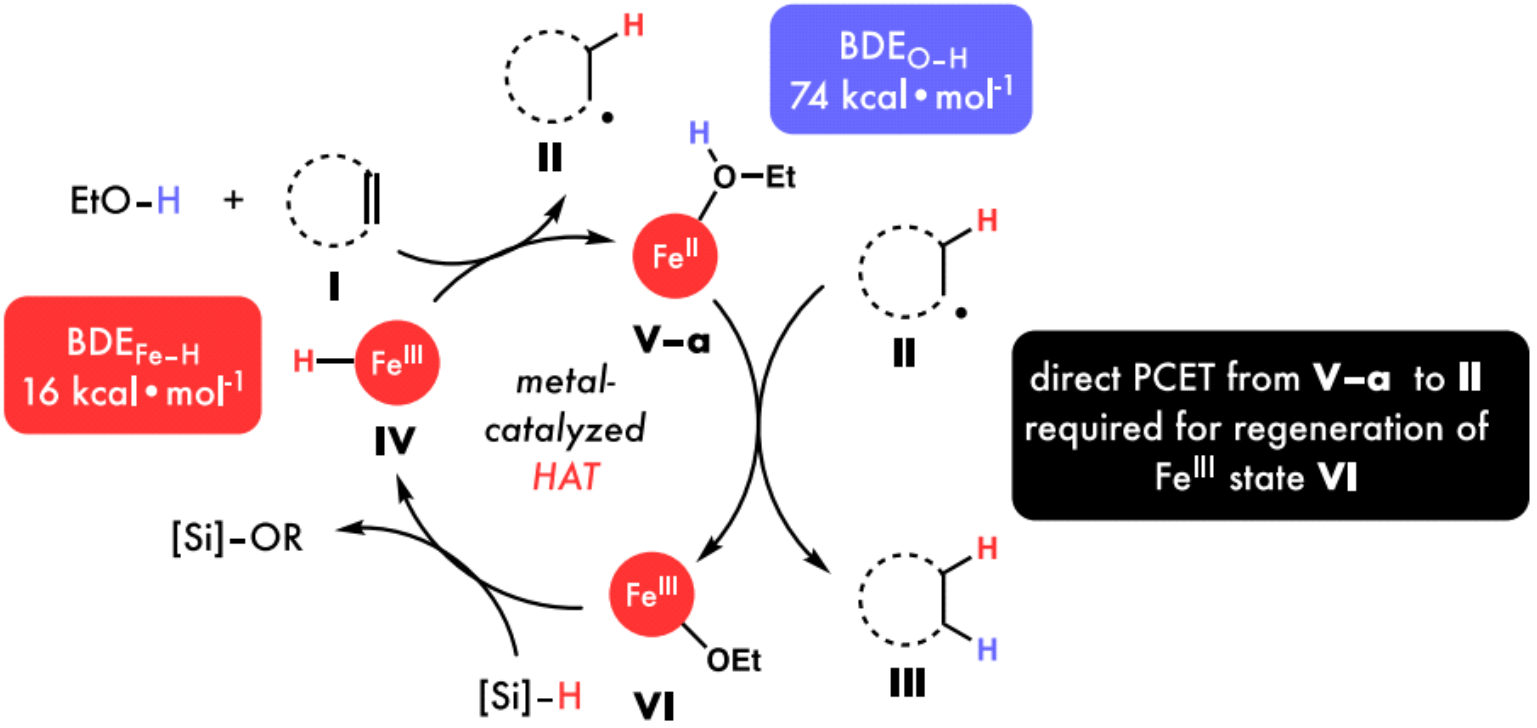


entry	deviation from conditions	yield (%)[b]
1	none	93[c]
2	no $Fe(acac)_3$	n.d.
3	no PhSH	27
4	under air	48[d]
5	dodecanethiol instead of PhSH, 72 h	43
6	$Mn(dpm)_3$ instead of $Fe(acac)_3$	30

Proposed catalytic mechanism for hydrogenation via cooperative hydrogen atom transfer (cHAT)

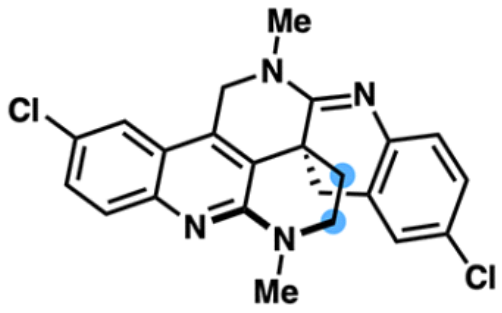


Potential catalytic cycle leading to inefficient hydrogenation under sole catalysis by iron.

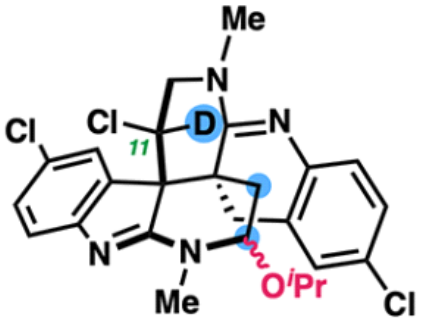


[entry 8]

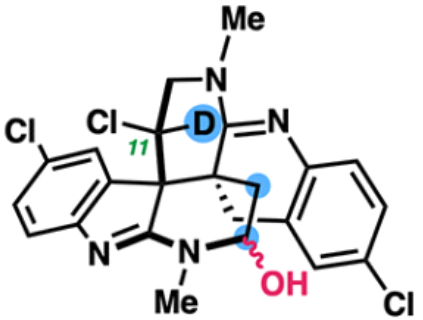
● = deuterium substitution



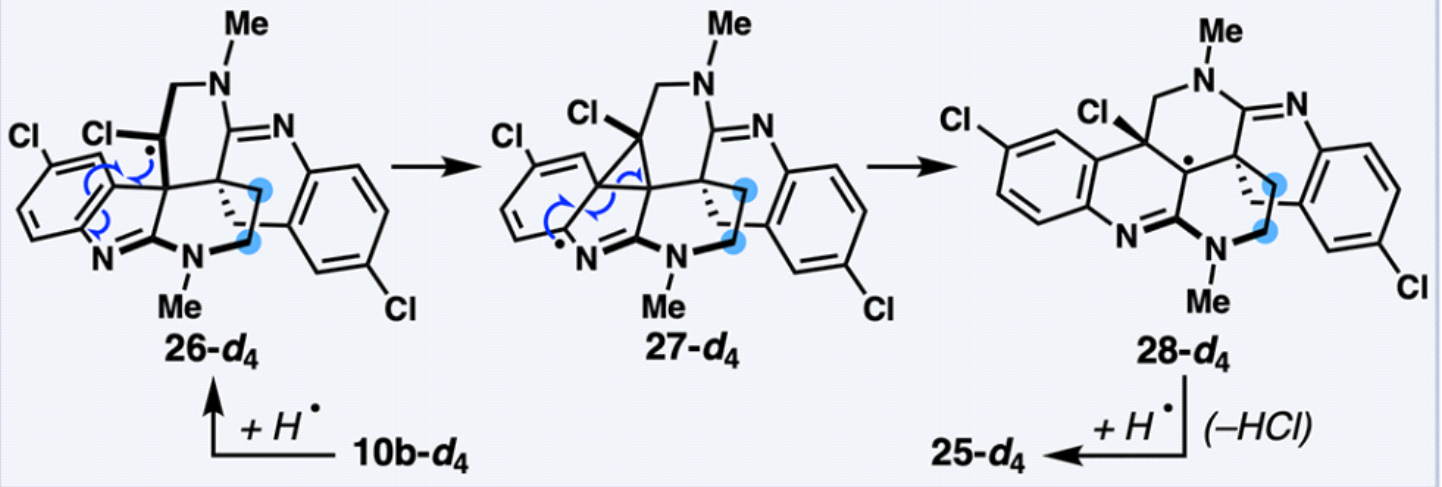
25-d_4 (13%)



22-d_4 (trace)



23-d_4 (trace)

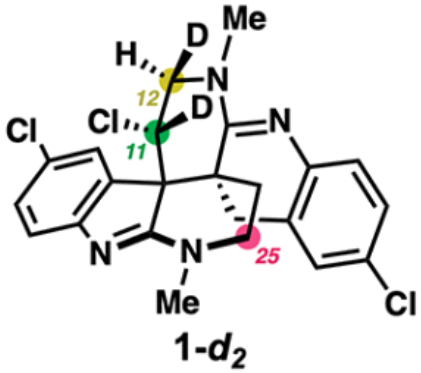


C

10b

$Mn(dpm)_3$
$B(O\textit{i}\text{-}Pr)_3$

silane, thiol solvent



1-d_2

Conditions	*Results*
Ph(*i*-PrO)SiH_2 PhS**D**, CD_3O**D**	*C12* 0% D *C11* 0% D *C25* 0% D
Ph(*i*-PrO)SiD_2 PhSH, *i*-PrOH	*C12* 97% D *C11* 94% D *C25* 0% D