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Article

Enantioselective Total Synthesis of (−)-Himalensine A via a Palladium and 4-Hydroxyproline Co-catalyzed Desymmetrization of Vinyl-bromide-tethered Cyclohexanones

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Cite This: J. Am. Chem. Soc. 2023, 145, 5422–5430

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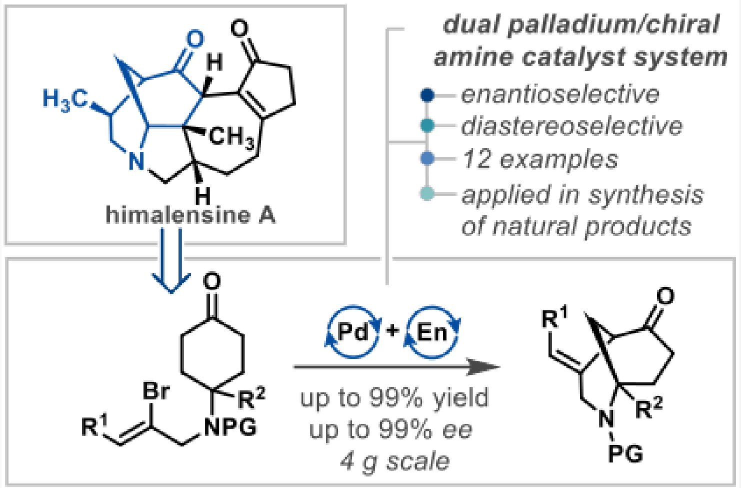
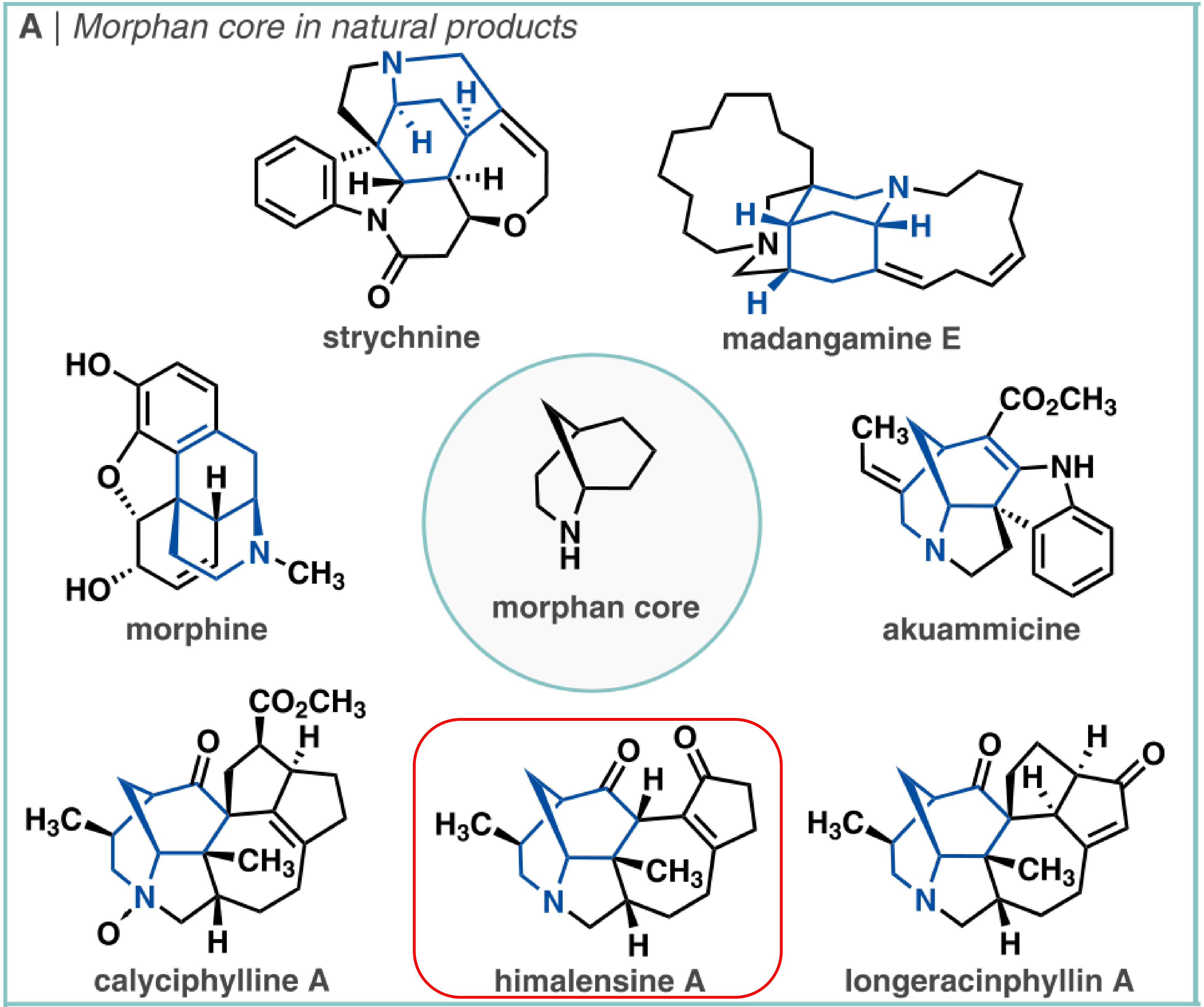
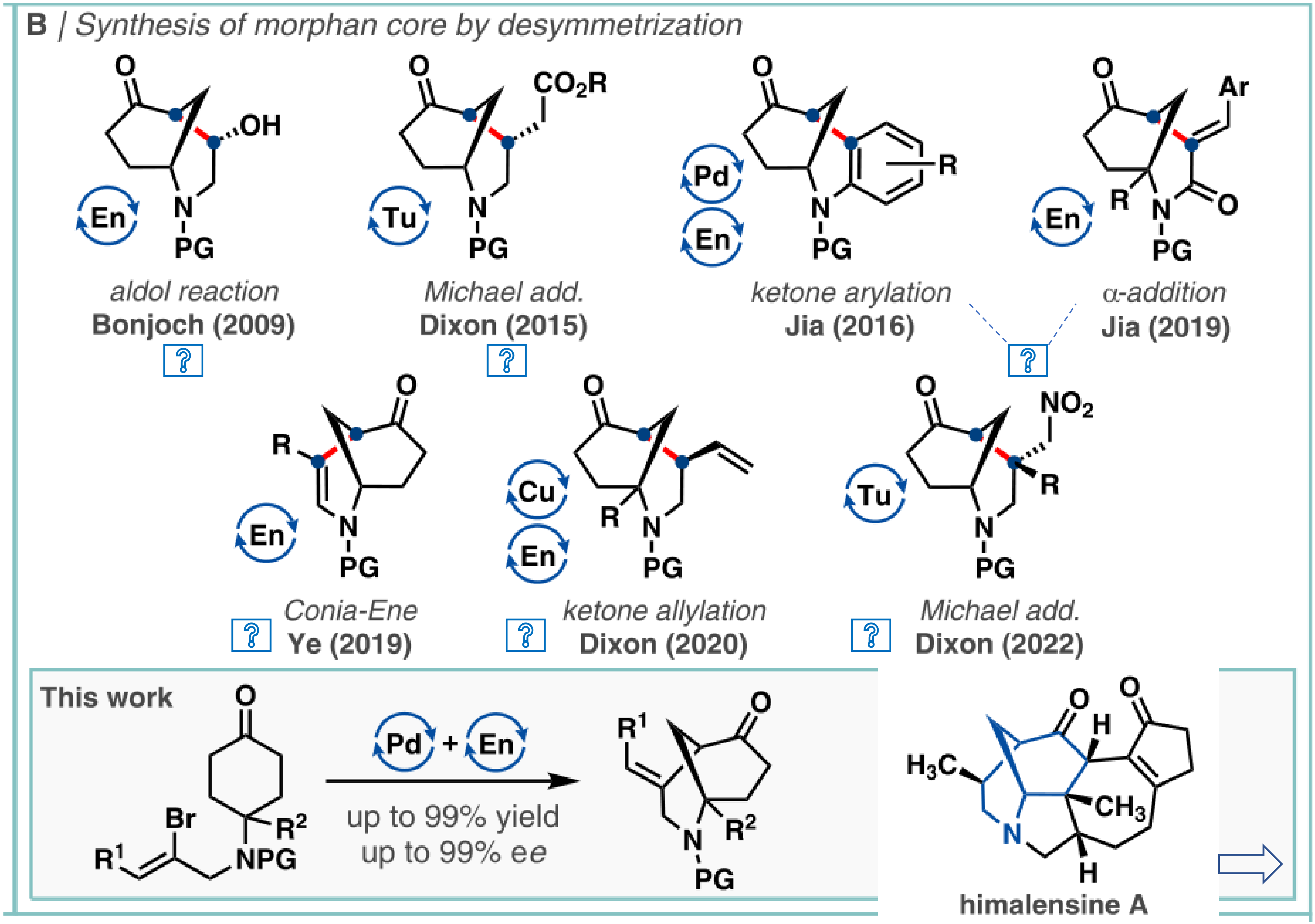
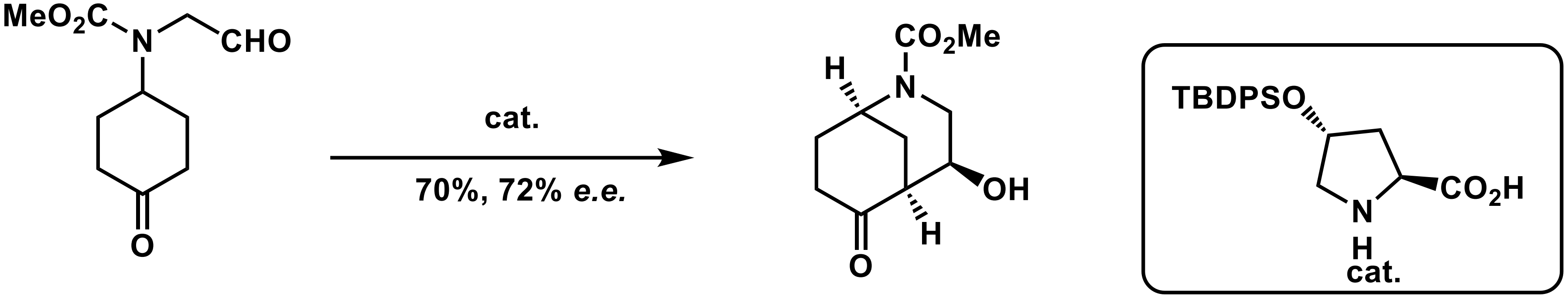
ABSTRACT: Herein, we describe the convergent enantioselective total synthesis of himalensine A in 18 steps, enabled by a highly enantio- and diastereoselective construction of the morphan core via a palladium/hydroxy proline co-catalyzed desymmetrization of vinyl-bromide-tethered cyclohexanones. The reaction pathway was illuminated by density functional theory calculations, which support an intramolecular Heck reaction of an *in situ*-generated enamine intermediate, where exquisite enantioselectivity arises from intramolecular carboxylate coordination to the vinyl palladium species in the rate- and enantio-determining carbopalladation steps. The reaction tolerates diverse *N*-derivatives, all-carbon quaternary centers, and trisubstituted olefins, providing access to molecular scaffolds found in a range of complex natural products. Following large-scale preparation of a key substrate and installation of a β-substituted enone moiety, the rapid

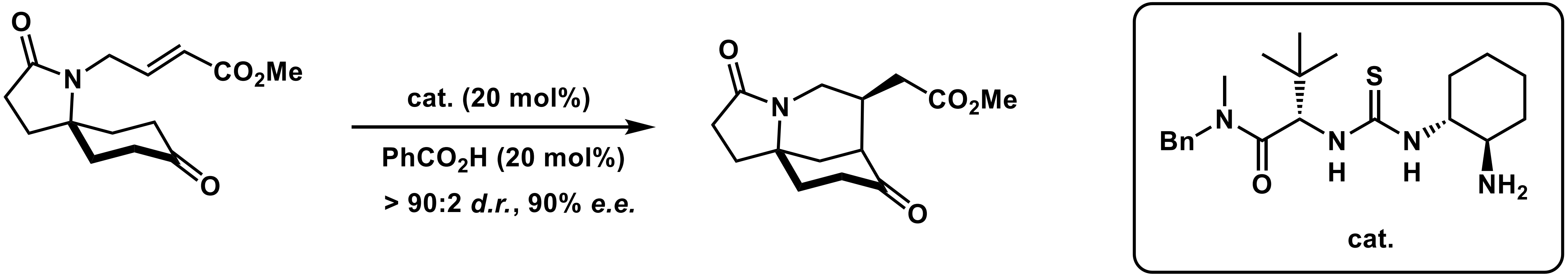



A | Morphan core in natural products
strychnine
madangamine E
morphine
morphan core
akuammicine
calyciphylline A
himalensine A
longeracinphyllin A

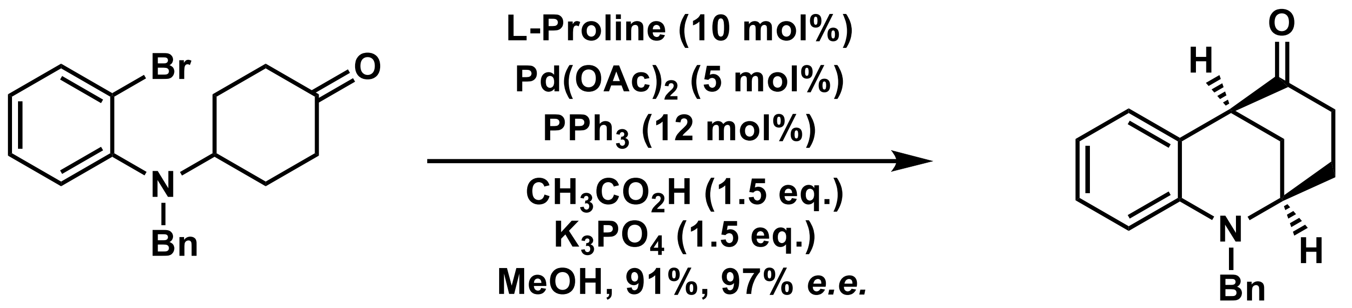

B | Synthesis of morphan core by desymmetrization
OH
En
N
PG
aldol reaction
Bonjoch (2009)
CO2R
Tu
Michael add.
Dixon (2015)
Pd
En
R
ketone arylation
Jia (2016)
Ar
α-addition
Jia (2019)
Conia-Ene
Ye (2019)
Cu
ketone allylation
Dixon (2020)
NO2
Michael add.
Dixon (2022)
This work
Br
R1
R2
NPG
Pd + En
up to 99% yield
up to 99% ee
H3C
H
CH3
himalensine A



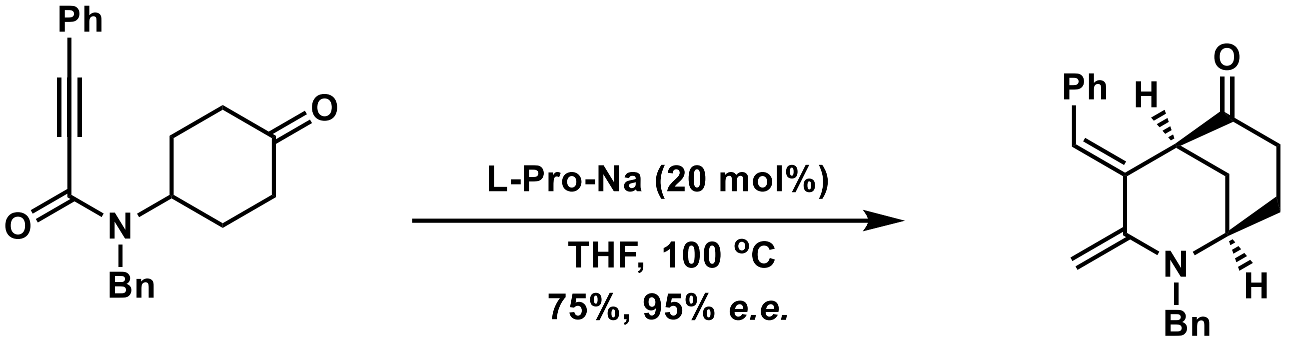
Org. Biomol. Chem., **2009**, *7*, 2517.



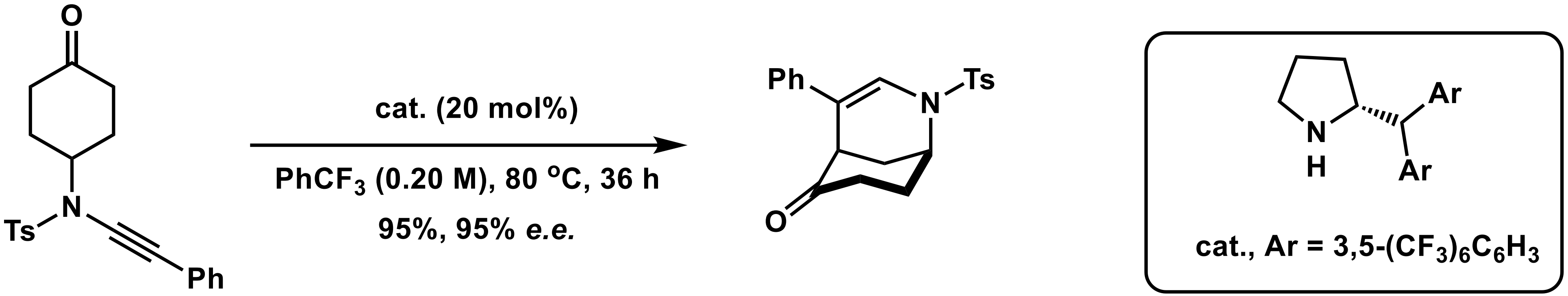
Angew. Chem. Int. Ed., **2015**, *54*, 4899.



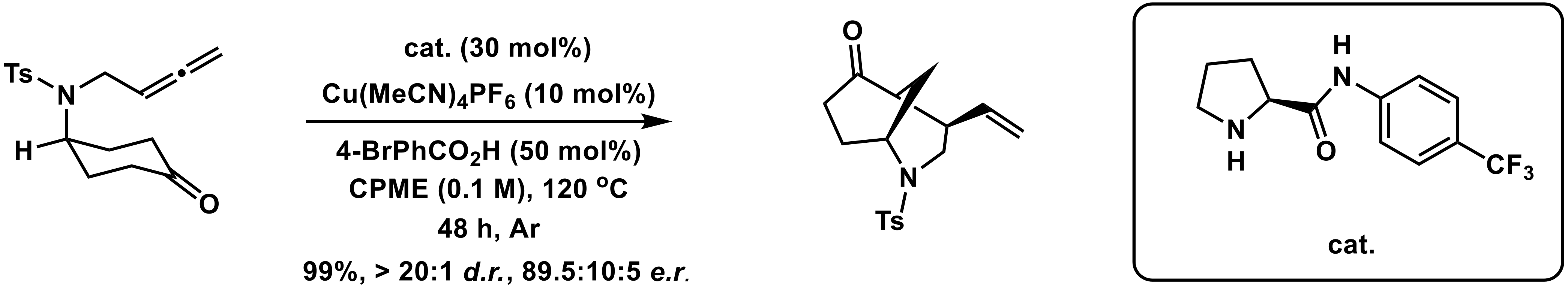
J. Am. Chem. Soc., **2016**, *138*, 5198.



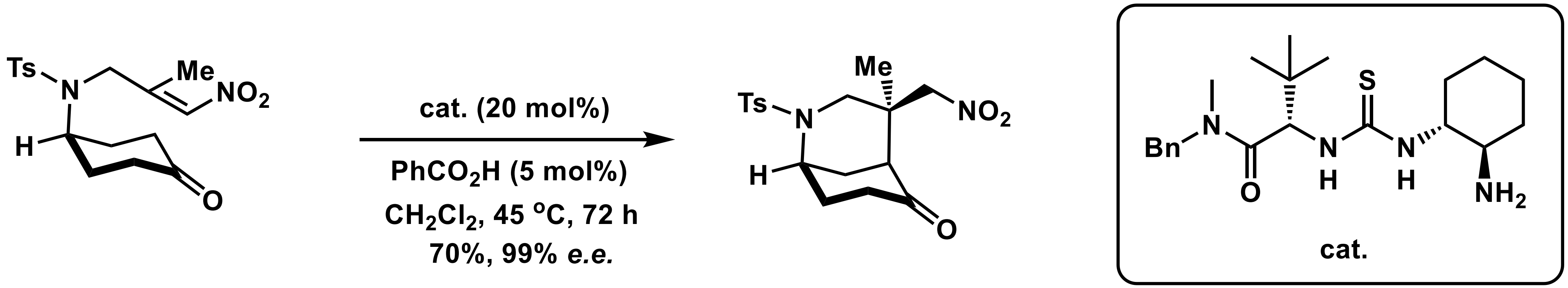
Chin. J. Chem., **2019**, *37*, 63.



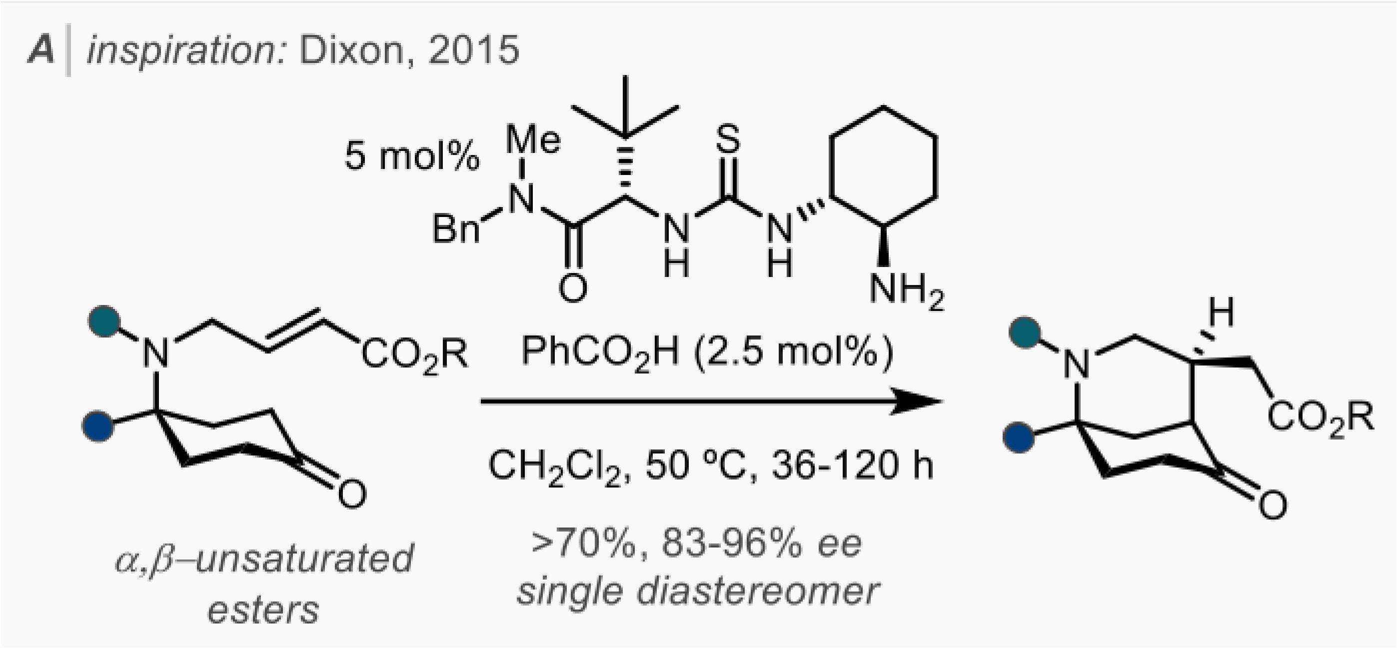
Angew. Chem. Int. Ed., **2019**, *58*, 16252.



Chem. Sci., **2020**, *11*, 7444.

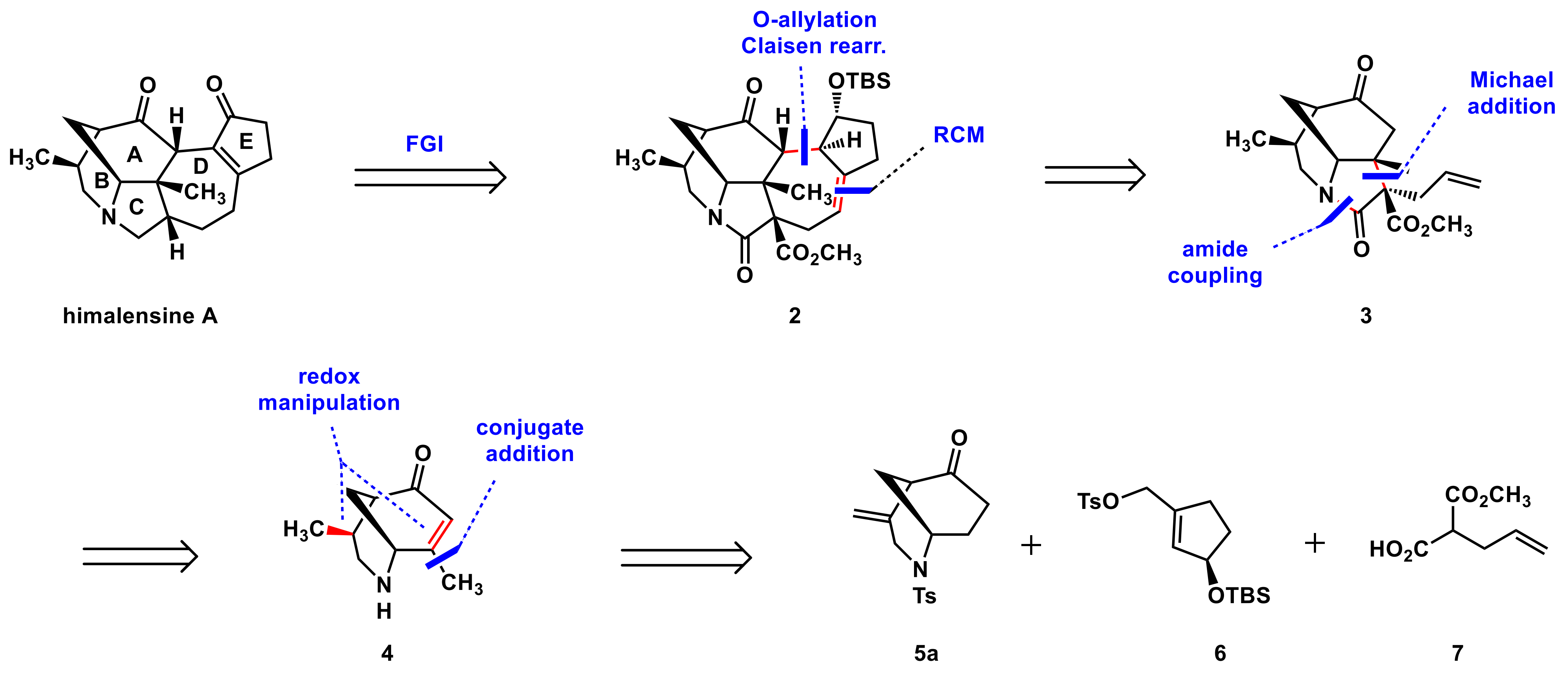


J. Am. Chem. Soc., **2022**, *144*, 1407.



Angew. Chem. Int. Ed., **2015**, *54*, 4899.

Retrosynthesis of himalensine A



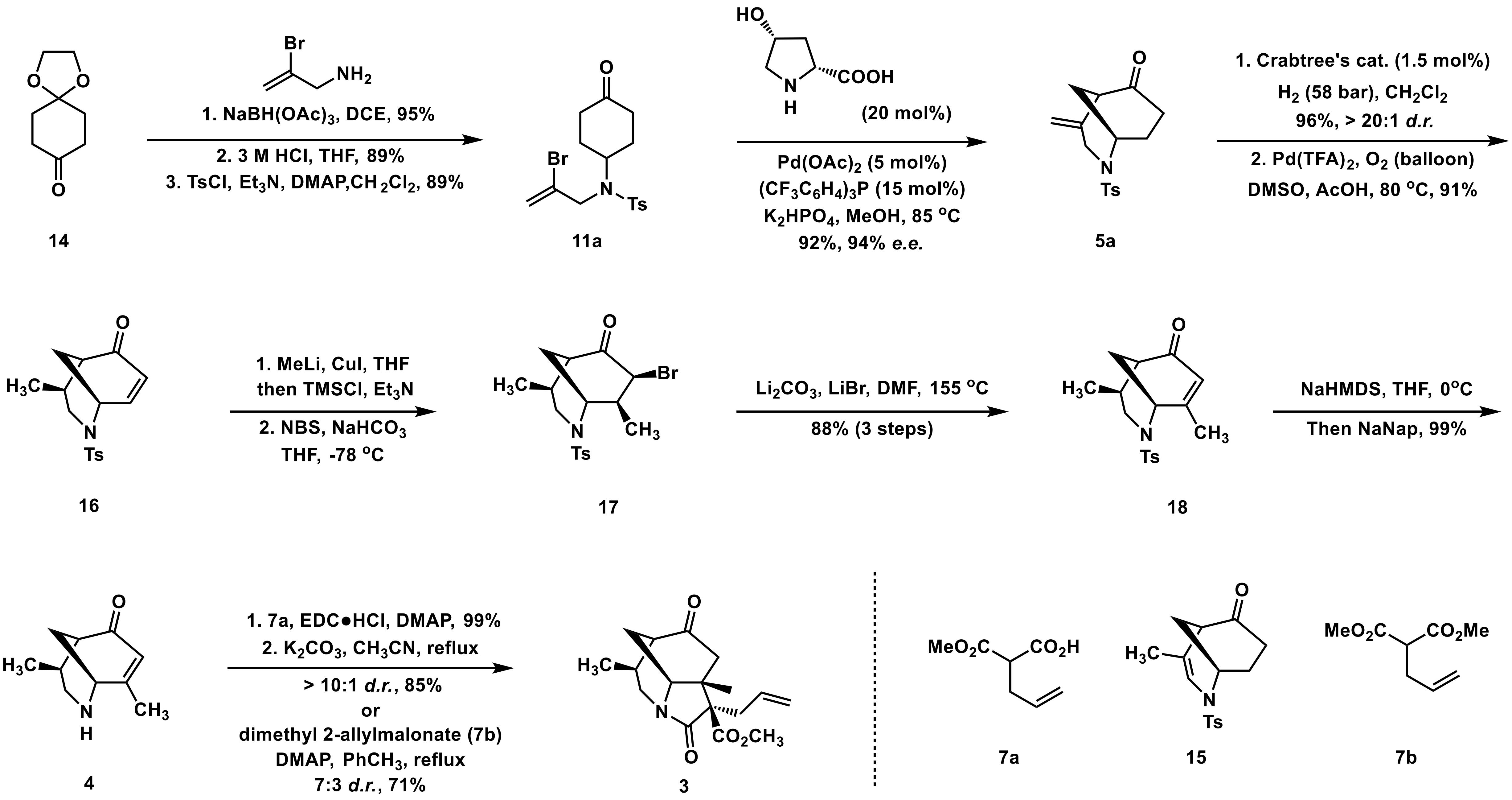
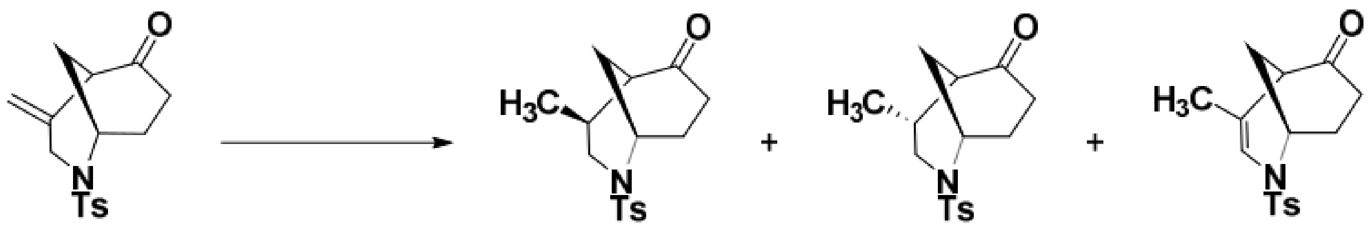

14
Br
NH2
1. NaBH(OAc)3, DCE, 95%
2. 3 M HCl, THF, 89%
3. TsCl, Et3N, DMAP,CH2Cl2, 89%
11a
Br
N
Ts
HO
N
H
COOH
(20 mol%)
Pd(OAc)2 (5 mol%)
(CF3C6H4)3P (15 mol%)
K2HPO4, MeOH, 85 °C
92%, 94% e.e.
5a
1. Crabtree's cat. (1.5 mol%)
H2 (58 bar), CH2Cl2
96%, > 20:1 d.r.
2. Pd(TFA)2, O2 (balloon)
DMSO, AcOH, 80 °C, 91%
16
H3C
1. MeLi, CuI, THF
then TMSCl, Et3N
2. NBS, NaHCO3
THF, -78 °C
17
Br
CH3
Li2CO3, LiBr, DMF, 155 °C
88% (3 steps)
18
NaHMDS, THF, 0°C
Then NaNap, 99%
4
1. 7a, EDC●HCl, DMAP, 99%
2. K2CO3, CH3CN, reflux
> 10:1 d.r., 85%
or
dimethyl 2-allylmalonate (7b)
DMAP, PhCH3, reflux
7:3 d.r., 71%
3
CO2CH3
MeO2C
CO2H
7a
15
MeO2C
CO2Me
7b

Table S2. Catalyst screening.

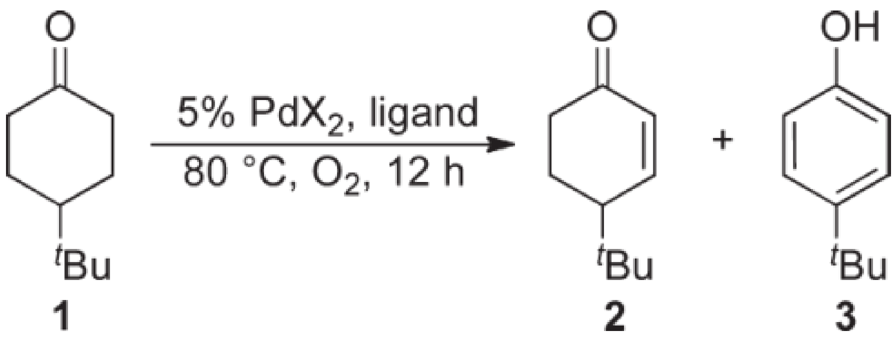


5a → S28 + S33 + 15

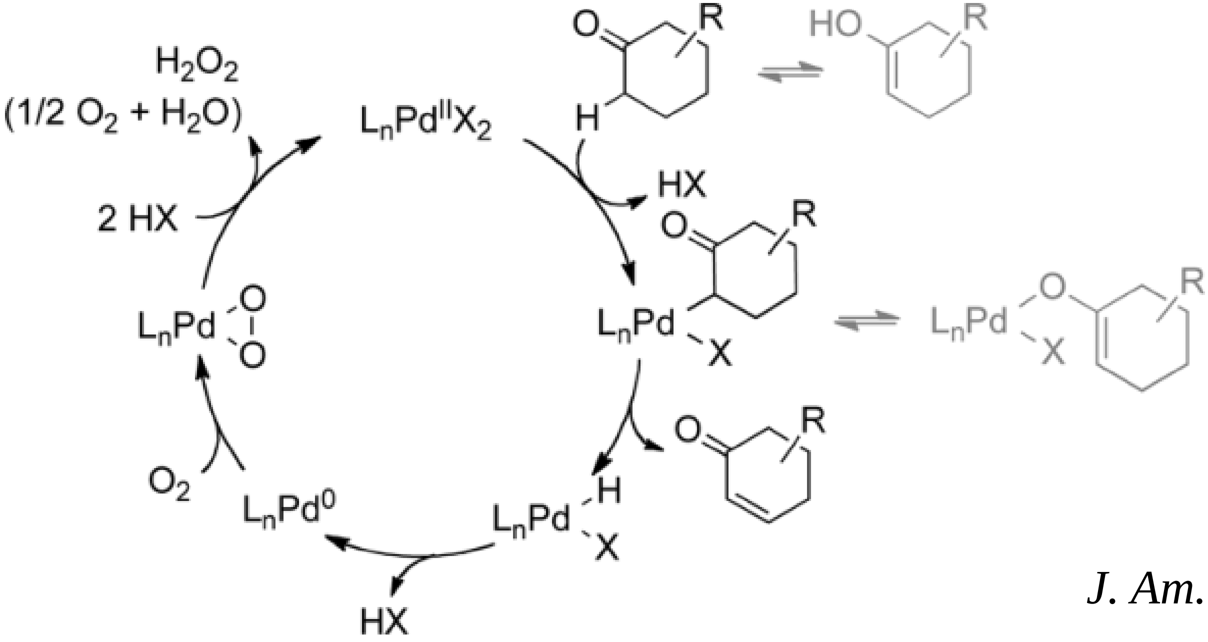
Entry	Catalyst	Pressure (bar)	Hydrog. (%)	d.r. (S28:S33)	15 (%)
1[a]	Pd/C (10 mol %)	1	15	1:3.0	40
2	$Rh(PPh_3)_3Cl$ (5.0 mol %)	1	38	1:2.3	14
3	$[Rh(dppb)(nbd)]ClO_4$ (5.0 mol%)	1	20	1:2.5	2
4	$[Rh(dppb)(nbd)]ClO_4$ (10 mol%)	1	14	1:5.2	<1
5	$[Ir(cod)(PPh_3)py]PF_6$ (20 mol%)	1	18	>20:1	82
6	**$[Ir(cod)(PPh_3)py]PF_6$ (5.0 mol%)**	**9**	**86**	**>20:1**	**14**
7	$Mn(dpm)_3$ (10 mol%), $PhSiH_3$ (1.0 equiv), TBHP (1.5 equiv), *i*-PrOH[22]	-	68	<1:20	<1
8	$Rh(cod)Cl_2$ (5.0 mol %), PPh_3(10 mol%), $AgBF_4$ (15 mol %)	1	74	>20:1	24
9	$Rh(cod)Cl_2$ (2.5 mol %), PPh_3(5.0 mol%), $AgBF_4$ (7.5 mol %)	1	69	>20:1	20
10	$Rh(cod)Cl_2$ (5.0 mol %), PPh_3(10 mol%), $AgBF_4$ (15 mol%)	9	53	5:1	2

Reagents and conditions: Catalyst, H_2 (1 bar), CH_2Cl_2, r.t., 5–16 h. [a]EtOAc used as a solvent. Yields were determined by analysis of ^1H NMR spectra of crude reaction mixtures.

Stahl's condition

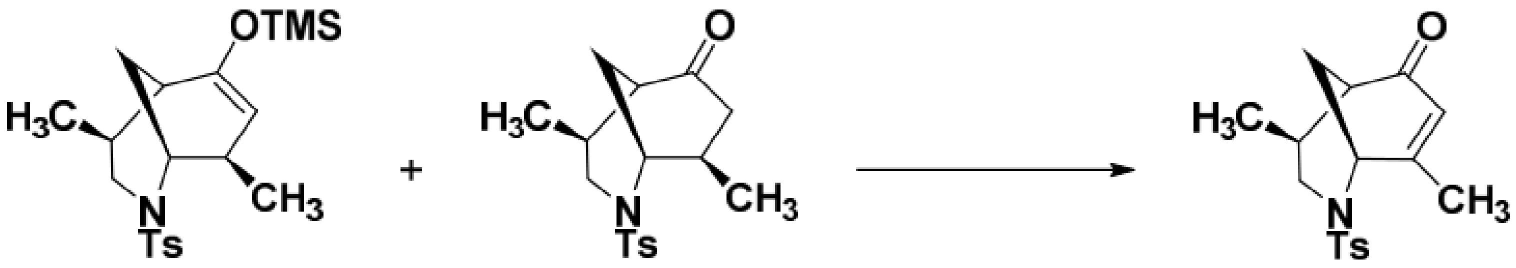


entry	PdX_2	ligand (mol %)	solvent	2 (%)[b]	3 (%)[b]
7	**$Pd(TFA)_2$**	**DMSO (10)**	**HOAc**	**91**	**8**



J. Am. Chem. Soc., **2011**, *133*, 14566.

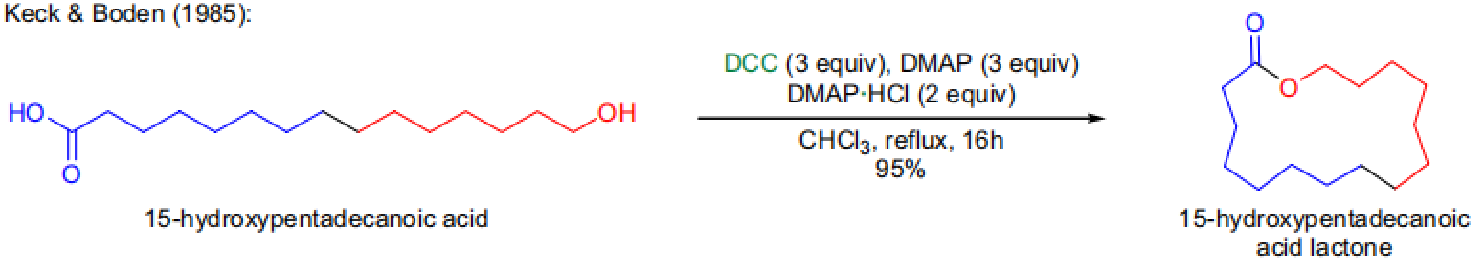
Table S4. Conditions screening for oxidation to enone.

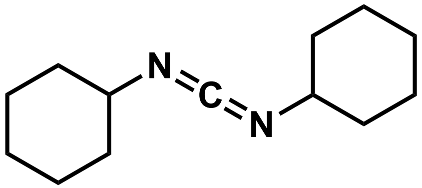


S29 S34 18

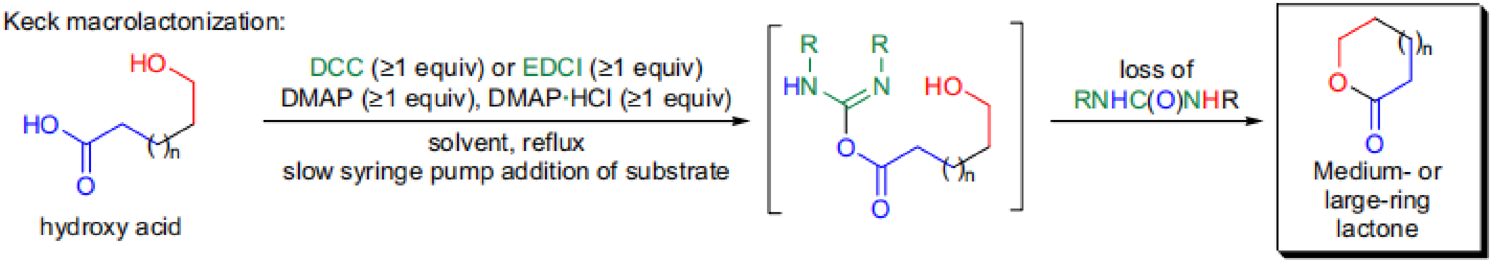
Entry	Starting material	Reagents and conditions	Observation
1	S34	$Pd(TFA)_2(DMSO)_2$, O_2, AcOH, 80 °C	No reaction
2	S29	$Pd(TFA)_2(DMSO)_2$, O_2, AcOH, 80 °C	Hydrolysis of enol ether
3	S34	IBX, EtOAc, 100 °C	Traces of product
4	S29	IBX, EtOAc, 100 °C	Traces of product
5	S29	IBX, MPO, EtOAc, 100 °C	Traces of product
6	S29	$Pd(OAc)_2$ (20 mol%), *p*-benzoquinone	Traces of product
7	S29	$Pd(OAc)_2$ (20 mol%), O_2 DMSO, Na_2HPO_4, 90 °C	Traces of product
8	S29	$Pd(OAc)_2$ (20 mol%), Oxone, DMSO, Na_2HPO_4, 90 °C	25%
9	S29	$Pd(OAc)_2$ (50 mol%), O_2, DMSO, Na_2HPO_4, 90 °C	56%

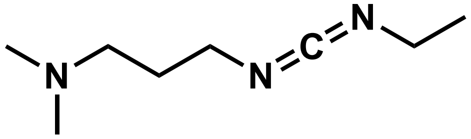
Keck & Boden (1985):





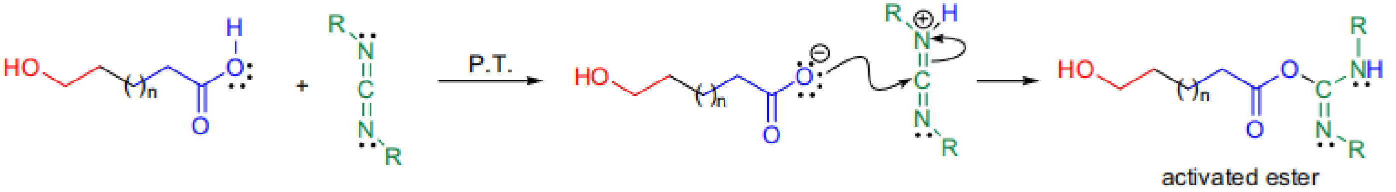
Keck macrolactonization:



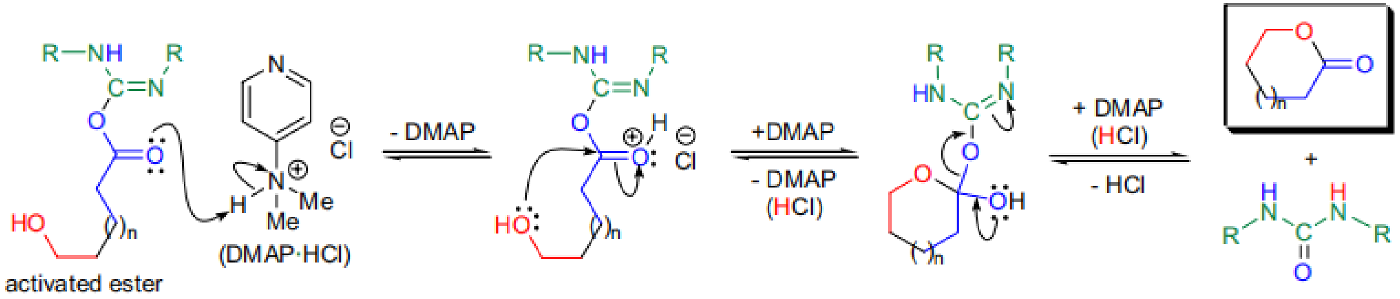


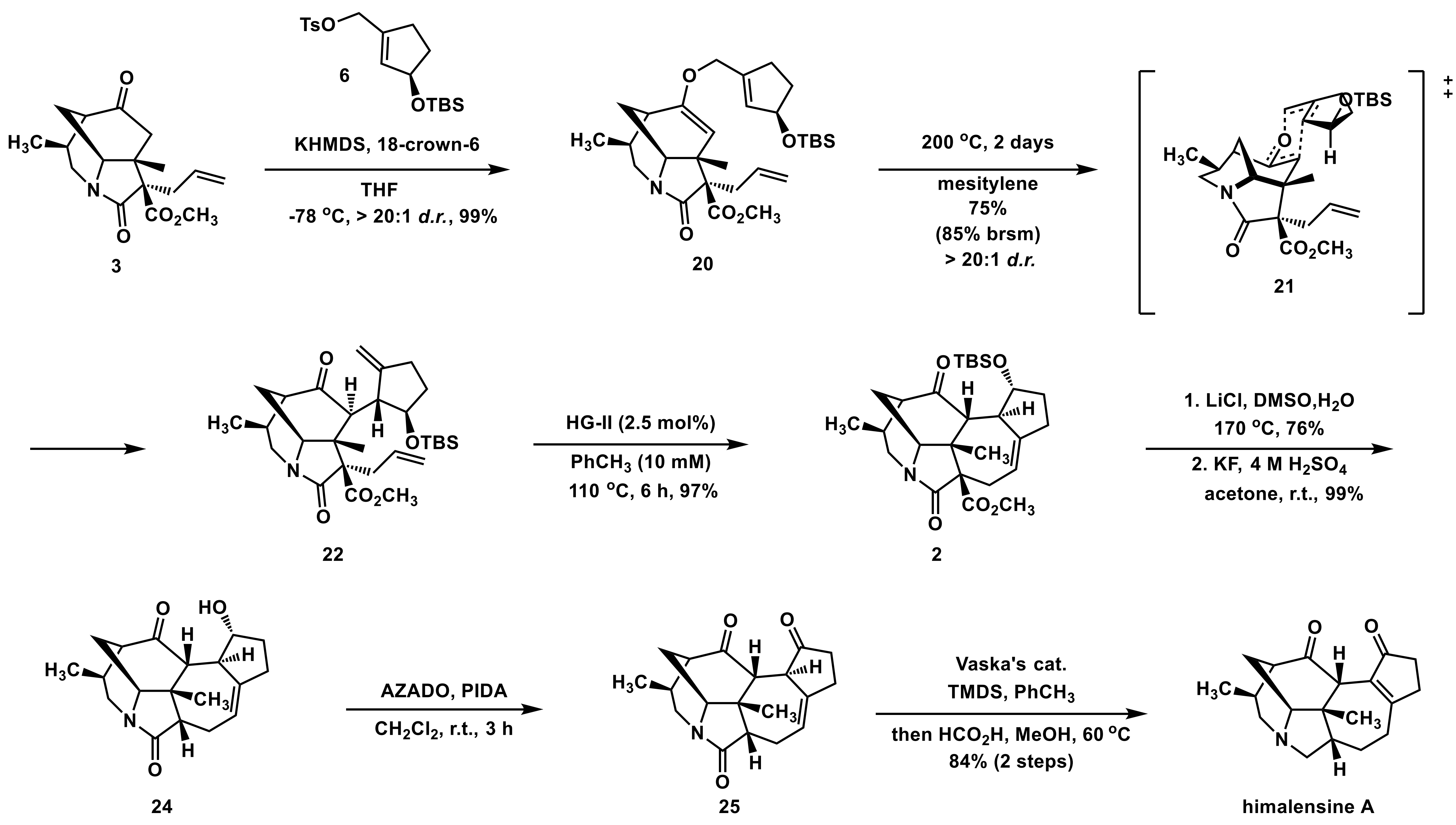
Mechanism:

Formation of the activated ester intermediate:



Formation of the macrolactone and the N,N'-dialkylurea by-product:

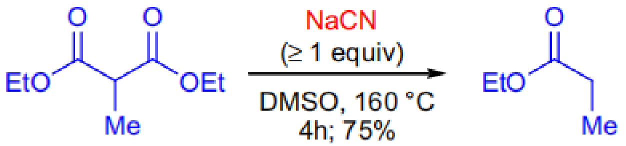



TsO
6
OTBS
H3C
O
N
O
CO2CH3
3
KHMDS, 18-crown-6
THF
-78 °C, > 20:1 d.r., 99%
20
200 °C, 2 days
mesitylene
75%
(85% brsm)
> 20:1 d.r.
21
22
HG-II (2.5 mol%)
PhCH3 (10 mM)
110 °C, 6 h, 97%
2
1. LiCl, DMSO,H2O
170 °C, 76%
2. KF, 4 M H2SO4
acetone, r.t., 99%
24
AZADO, PIDA
CH2Cl2, r.t., 3 h
25
Vaska's cat.
TMDS, PhCH3
then HCO2H, MeOH, 60 °C
84% (2 steps)
himalensine A

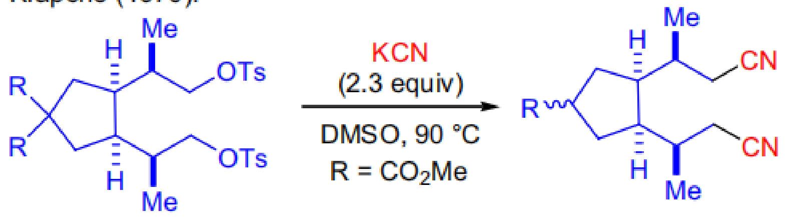
KRAPCHO DEALKOXYCARBONYLATION (KRAPCHO REACTION)

(References are on page 617)

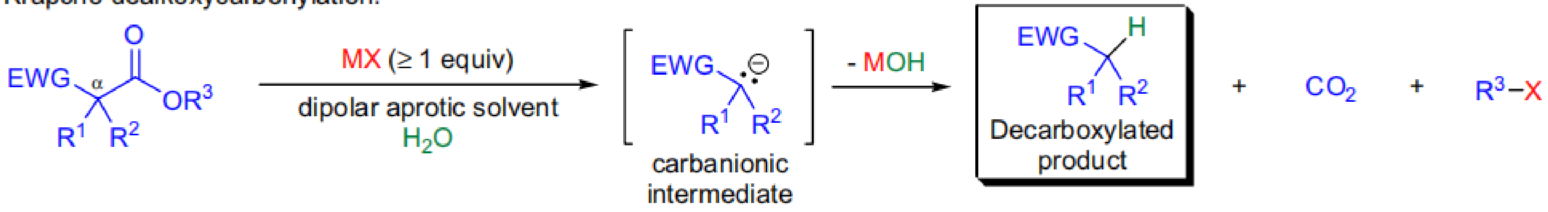
Krapcho (1967):



Krapcho (1970):

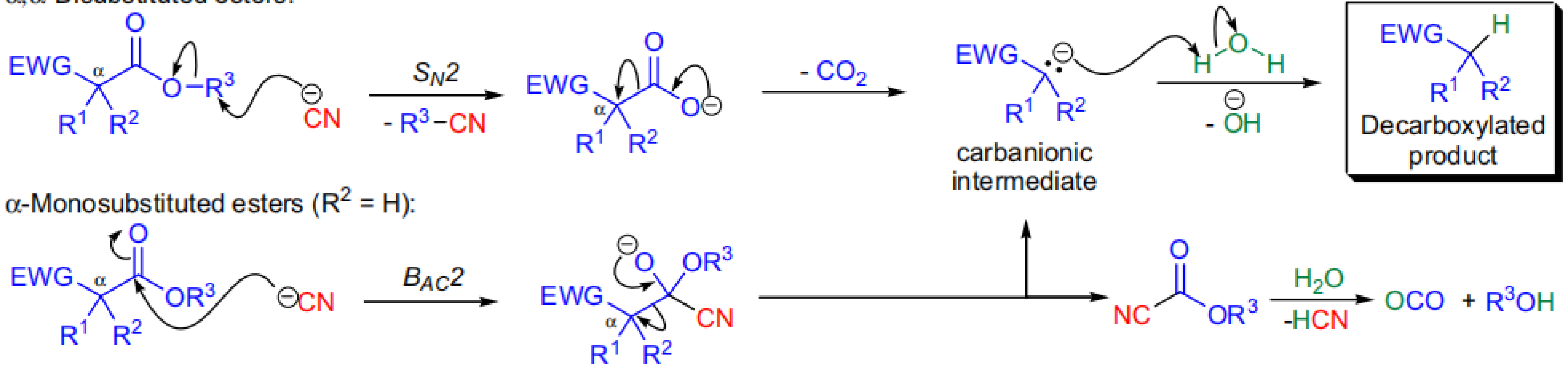


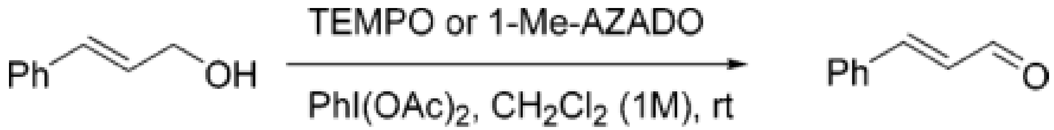
Krapcho dealkoxycarbonylation:



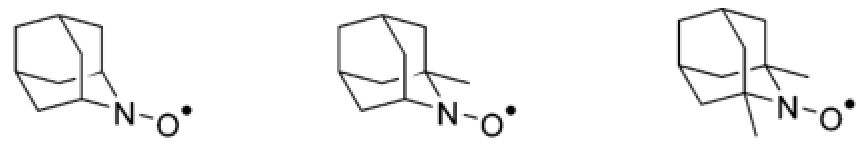
EWG = CO_2-alkyl, CO_2-aryl, CN, CO-alkyl, SO_2-alkyl, SO_2-aryl; $R^{1\text{-}2}$ = H, alkyl, aryl; R^3 = Me, Et; MX = NaCN, KCN, LiCl, NaCl, NaBr, NaI, $LiI{\cdot}H_2O$, $Na_2CO_3{\cdot}H_2O$, $Na_3PO_4{\cdot}12H_2O$, Me_4NOAc ; solvent: DMSO, DMF, DMA, HMPT

α,α-Disubstituted esters:

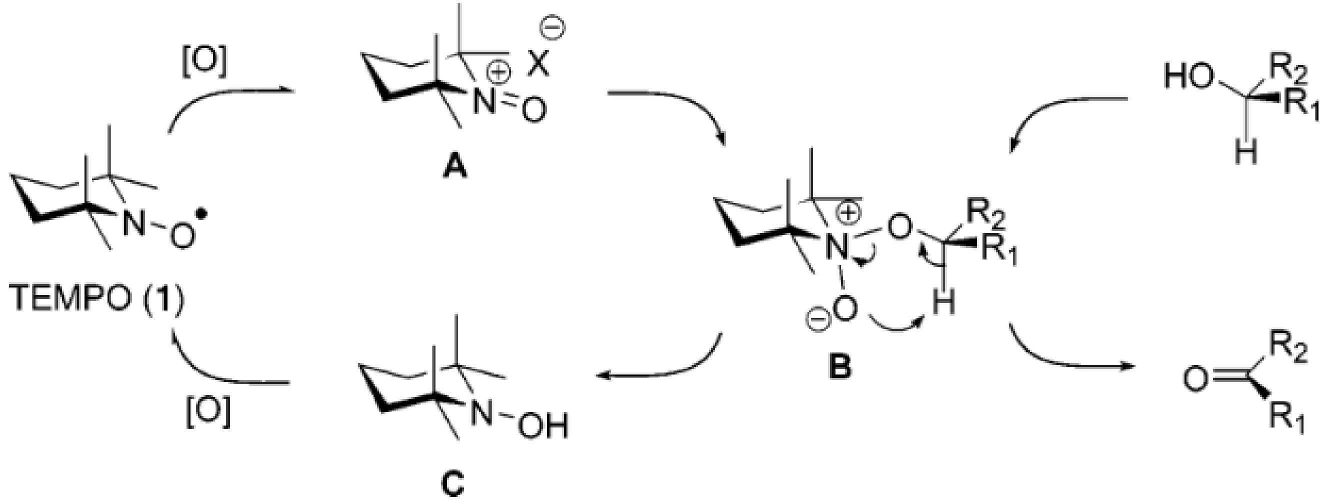




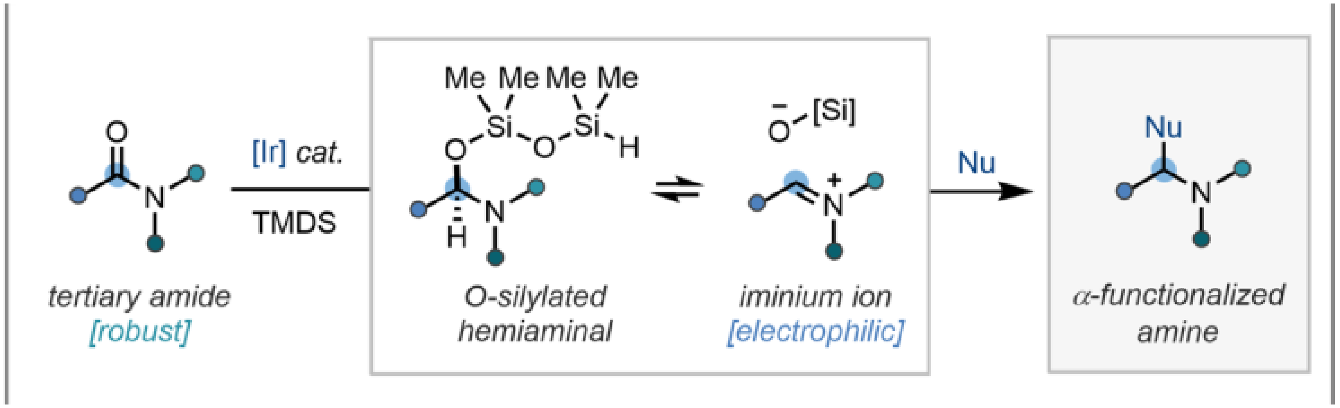
loading amount (mol%)	yield (%) / time (h)	
	TEMPO	1-Me-AZADO
10	95 / 1.5	96 / 0.1
1	42 / 6	93 / 0.7
0.1	n.d.	39 / 3

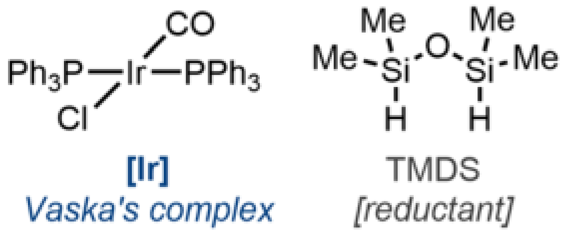


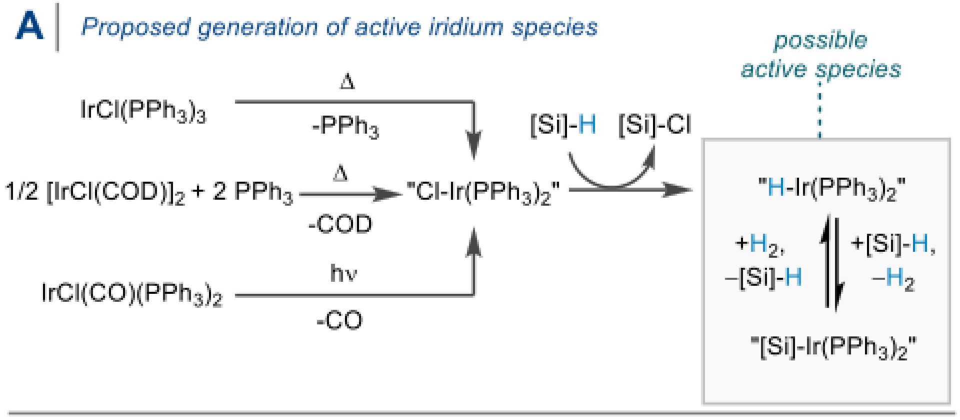
AZADO (**2**) 1-Me-AZADO (**3**) 1,3-dimethylAZADO (**4**)

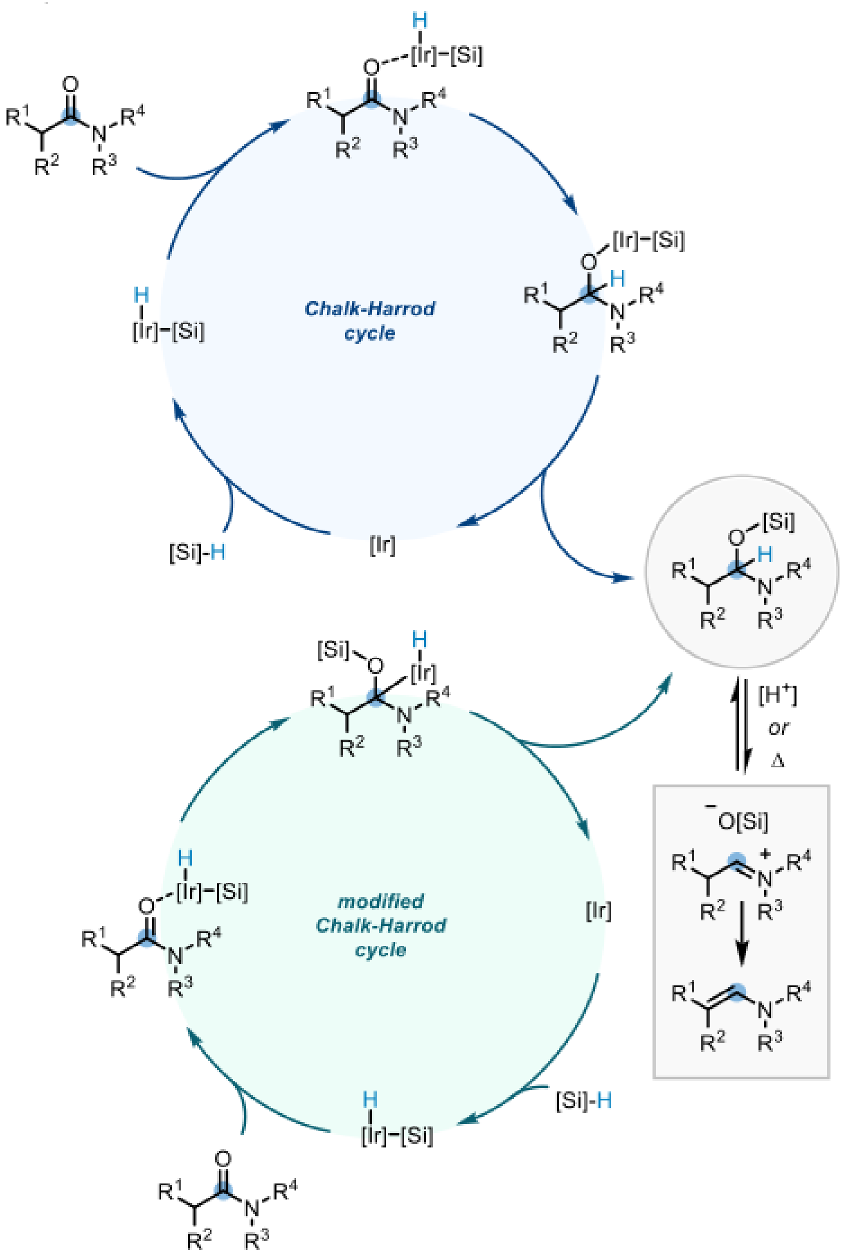


J. Am. Chem. Soc., **2006**, *128*, 8412.









ACS Catal., **2020**, *10*, 8880.