



Communications

**Angewandte
Chemie**
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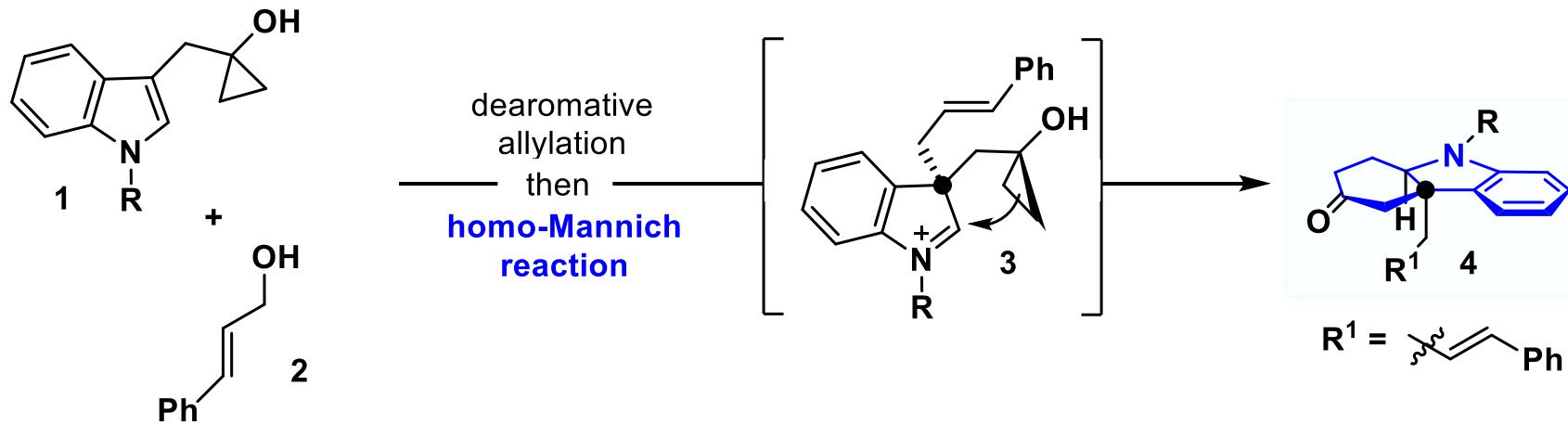
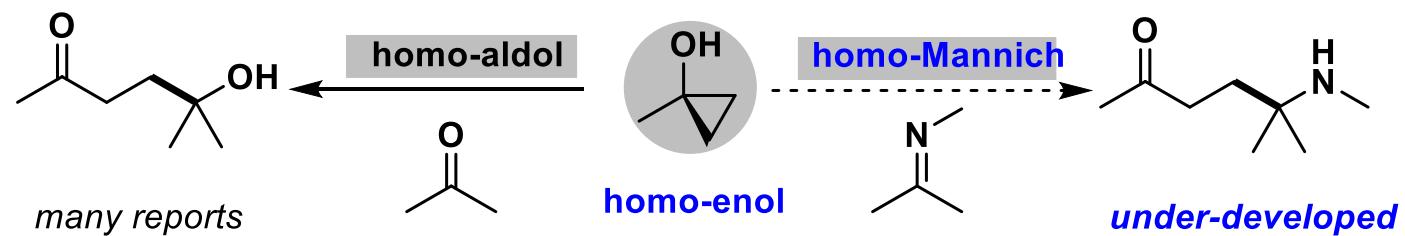
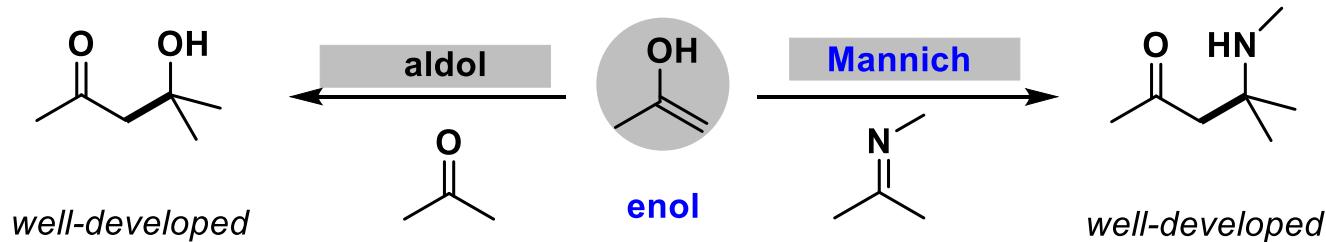


Total Synthesis **Hot Paper**

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doi.org/10.1002/anie.202307286

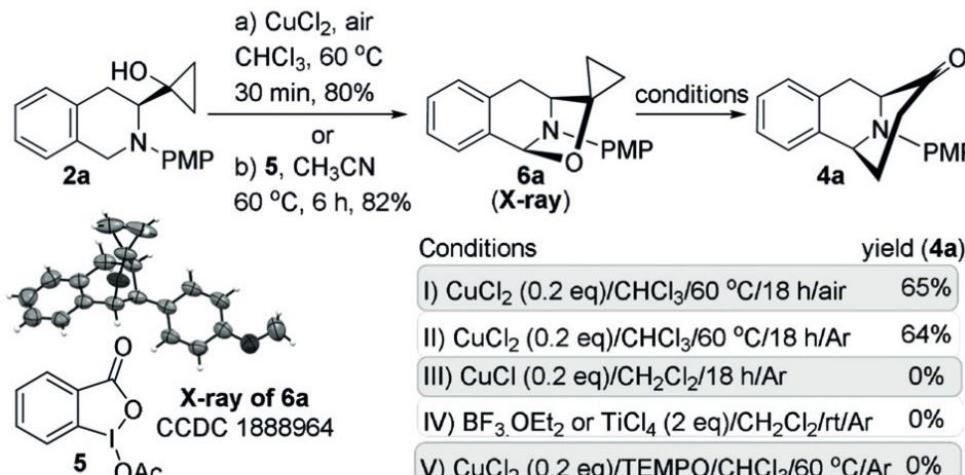
A Homo-Mannich Reaction Strategy Enables Collective Access to Ibophyllidine, *Aspidosperma*, *Kopsia*, and *Melodinus* Alkaloids

*Dan Jiang, Peng Tang, Hongbing Xiong, Shuai Lei, Yulian Zhang, Chongzhou Zhang,
Ling He, Hanyue Qiu, and Min Zhang**

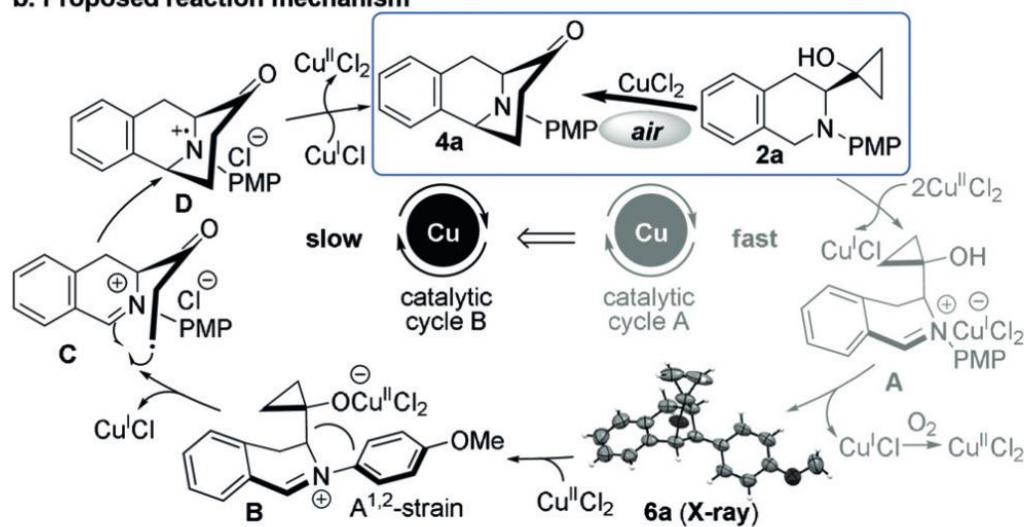


Copper-Catalyzed Aerobic Oxidative Cyclization Cascade to Construct Bridged Skeletons: Total Synthesis of (–)-Suaveoline

a. Preliminary mechanistic studies

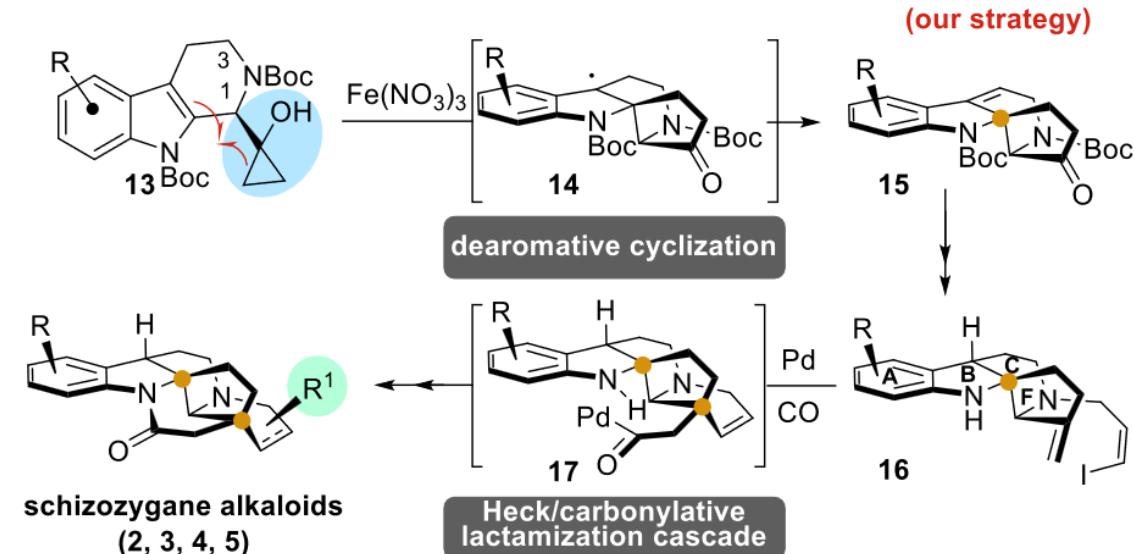


b. Proposed reaction mechanism

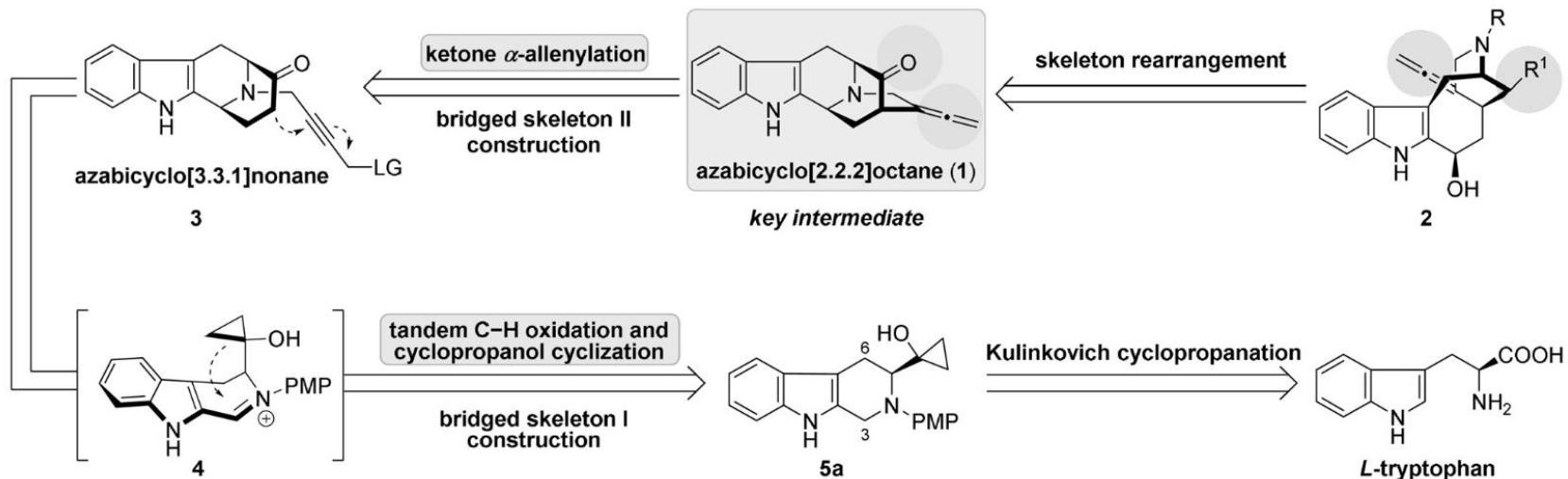


Asymmetric Total Syntheses of Schizozygane Alkaloids

C) Dearomative cyclization and Heck cascade for schizozygane alkaloids (our strategy)



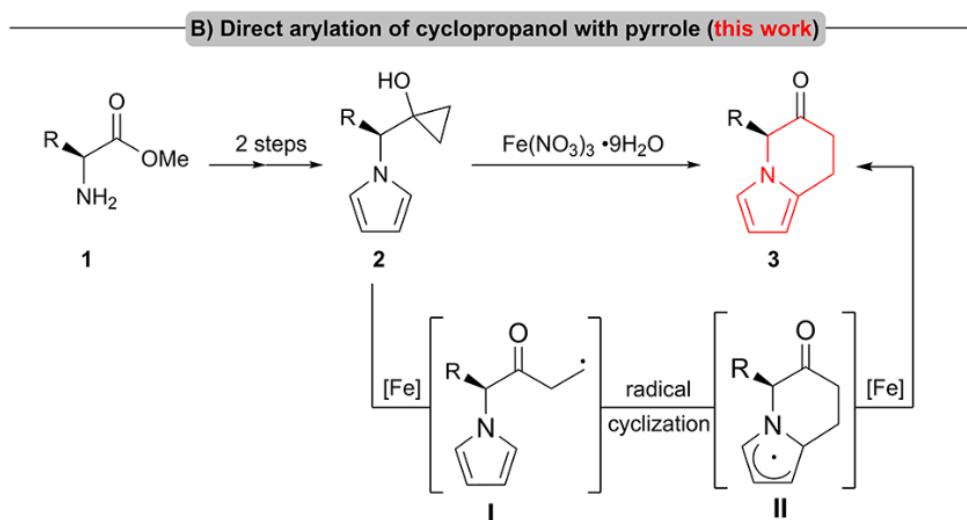
Asymmetric Total Synthesis of Sarpagine and Koumine Alkaloids



Scheme 1. Retrosynthetic analysis of sarpagine and koumine alkaloids.

Angew.Chem.Int.Ed., **2021**, *60*, 13105.

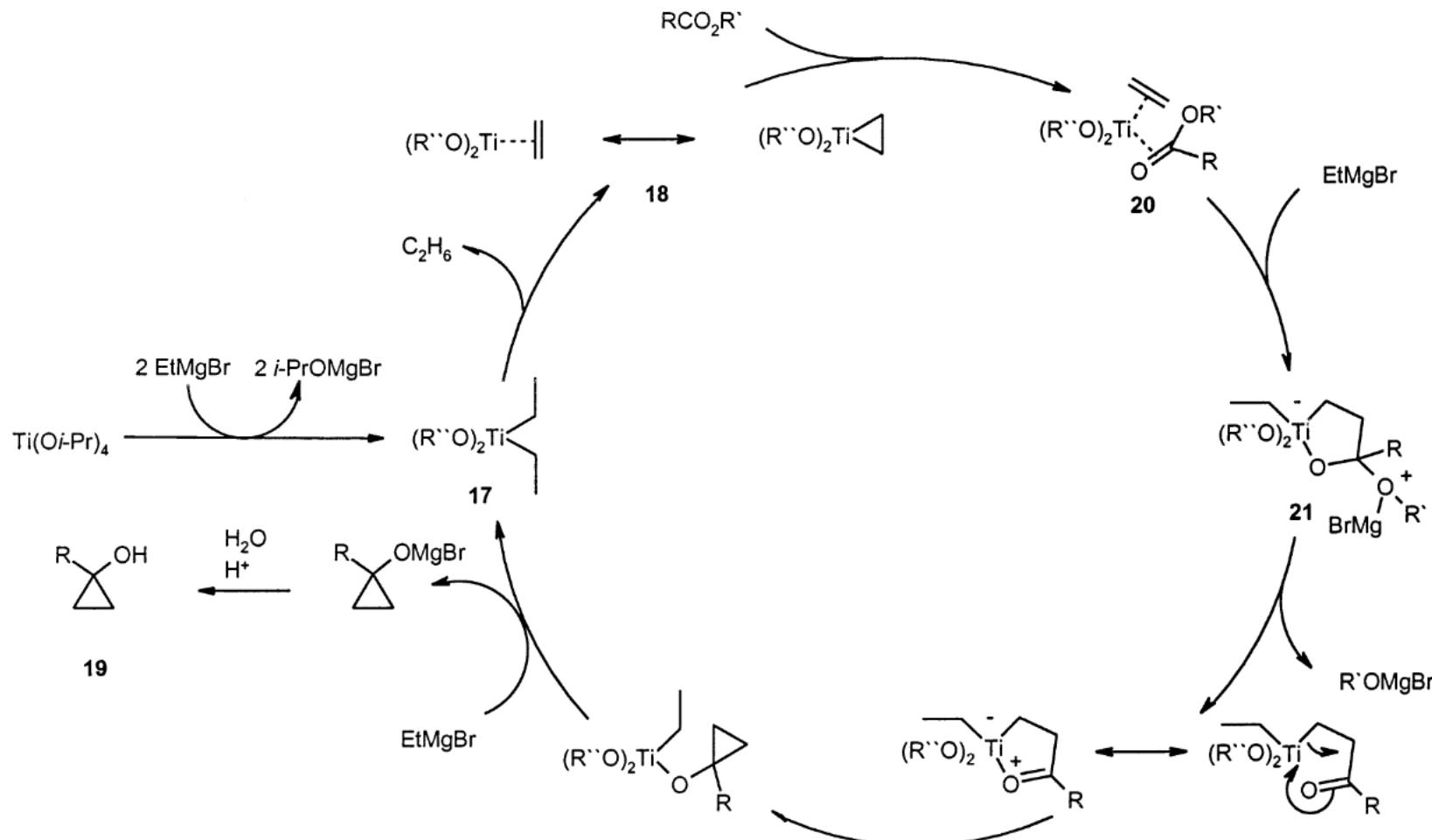
Arylation of Cyclopropanol with Pyrrole: Asymmetric Synthesis of Indolizidine 167B, Indolizidine 209D, and Monomorine I



Org. Lett., **2023**, *25*, 2058.

环丙醇的制备 Kulinkovich Reaction

Scheme 9^a

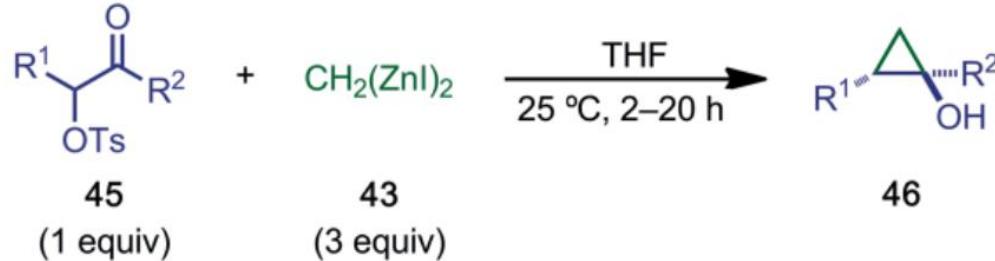


^a $\text{R}'' = i\text{-Pr}$ or R' .

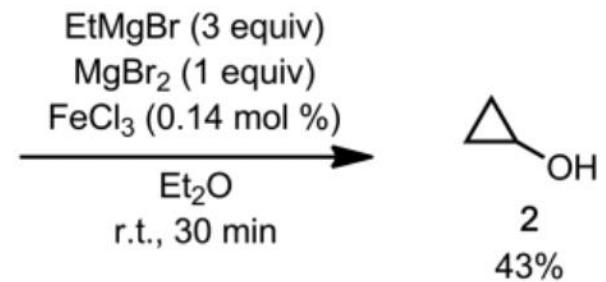
环丙醇的制备

Cyclopropanation Using *gem*-Dizincioalkanes

a) Matsubara, 2007

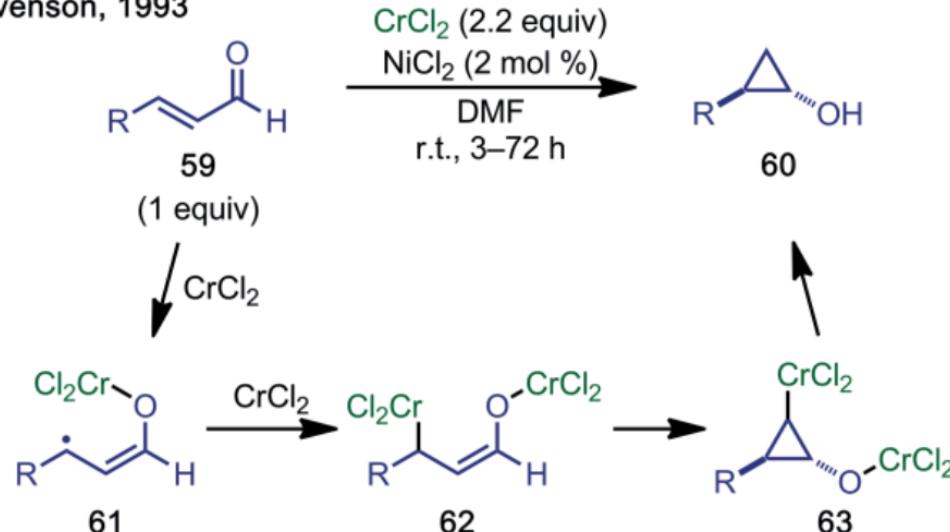


Cottle, 1943



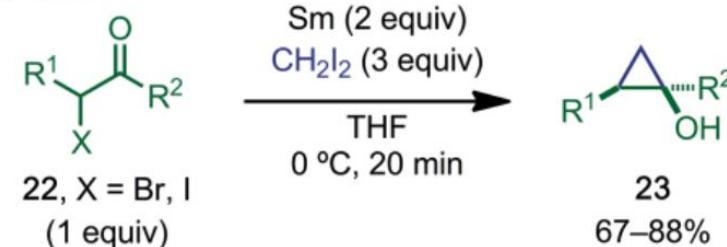
Reduction of Enone Derivatives

Stevenson, 1993

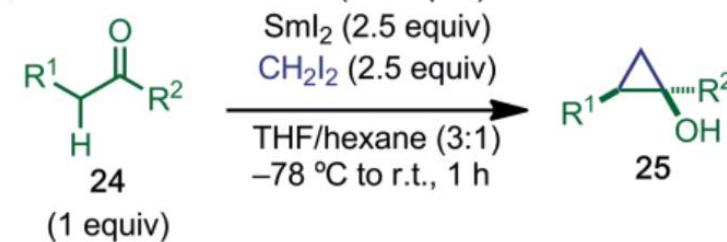


Carbene Equivalents

a) Imamoto, 1986

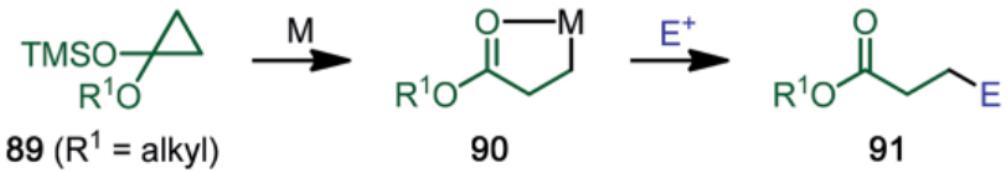


b) Imamoto, 1987



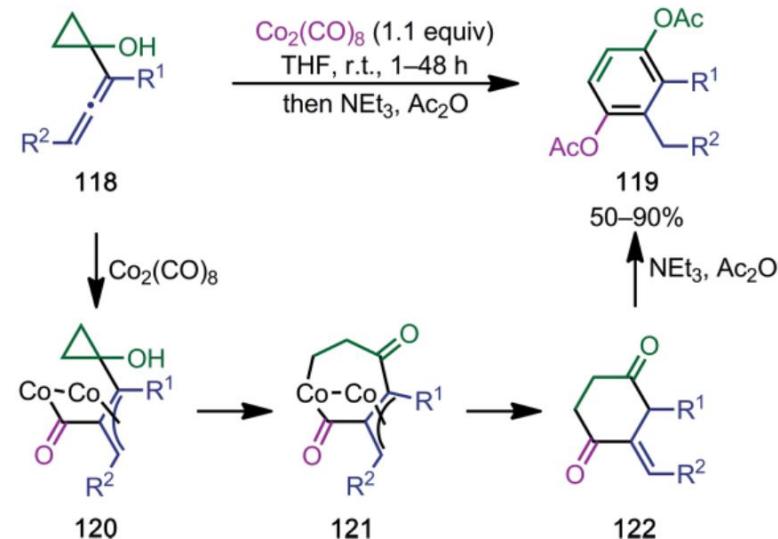
环丙醇的应用

Reactions of Cyclopropanols with “Classical” Electrophiles

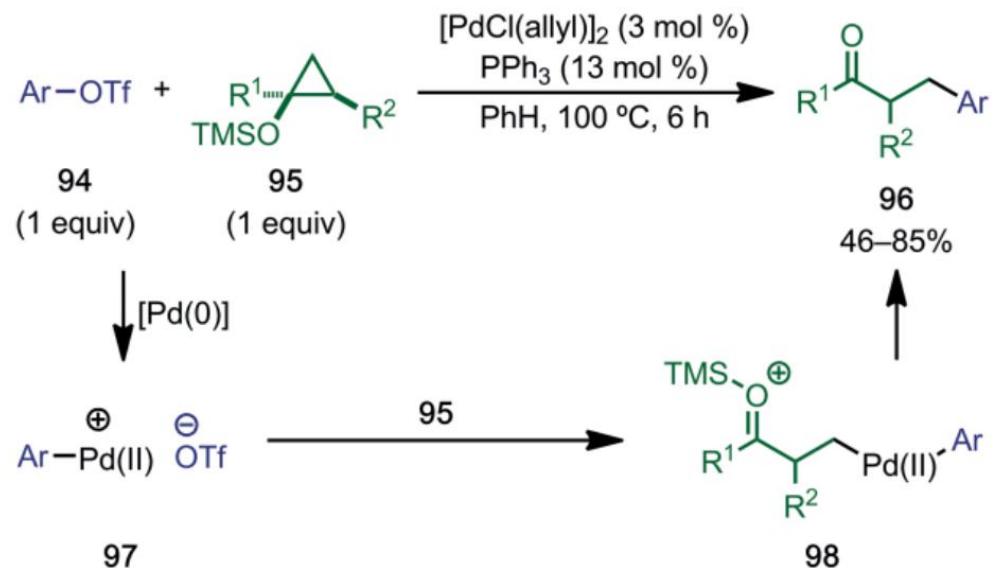


Ring-Expansion Reactions of Cyclopropanols

b) Iwasawa, 1995

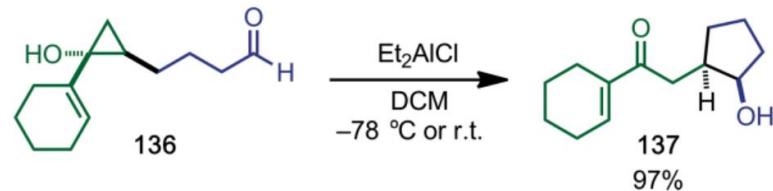


Transition Metal-Catalyzed Cross-Couplings of Cyclopropanols

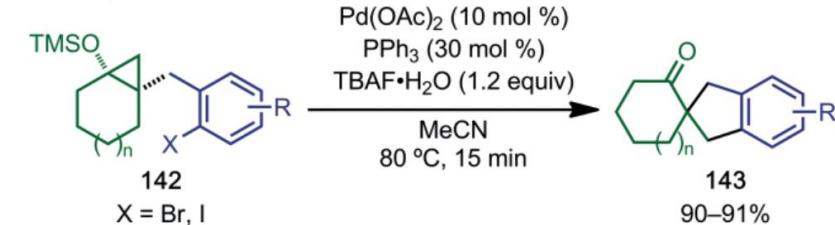


Ring-Forming Reactions of Homoenolates

Cha, 2001



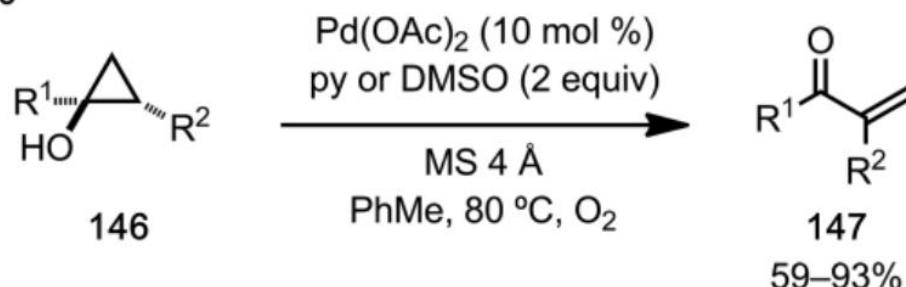
Orellana, 2011



环丙醇的应用

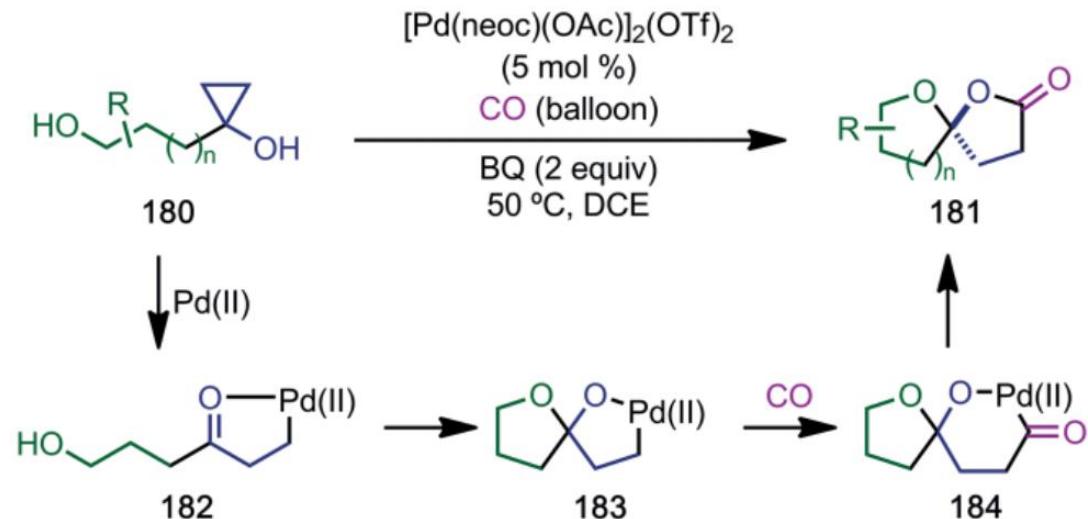
Cyclopropanol Ring-Opening

Cha, 2000



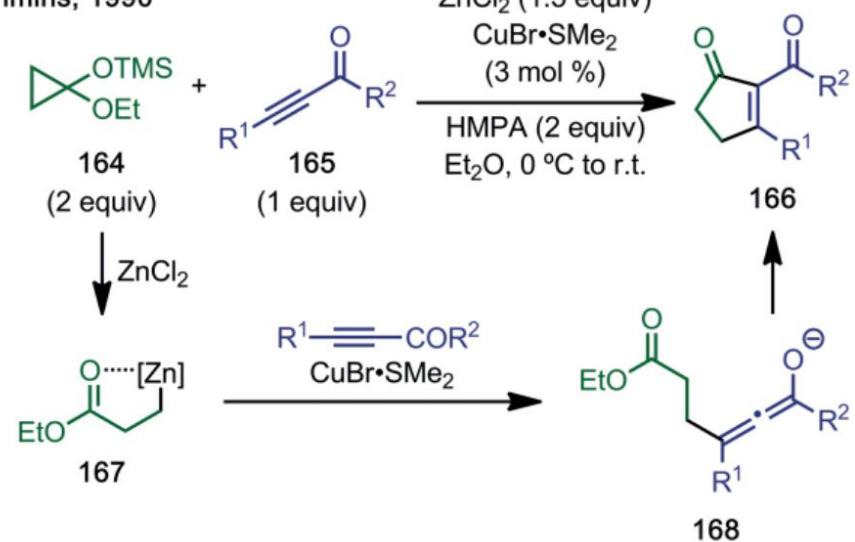
Direct Trapping of Homoenolates as Electrophiles

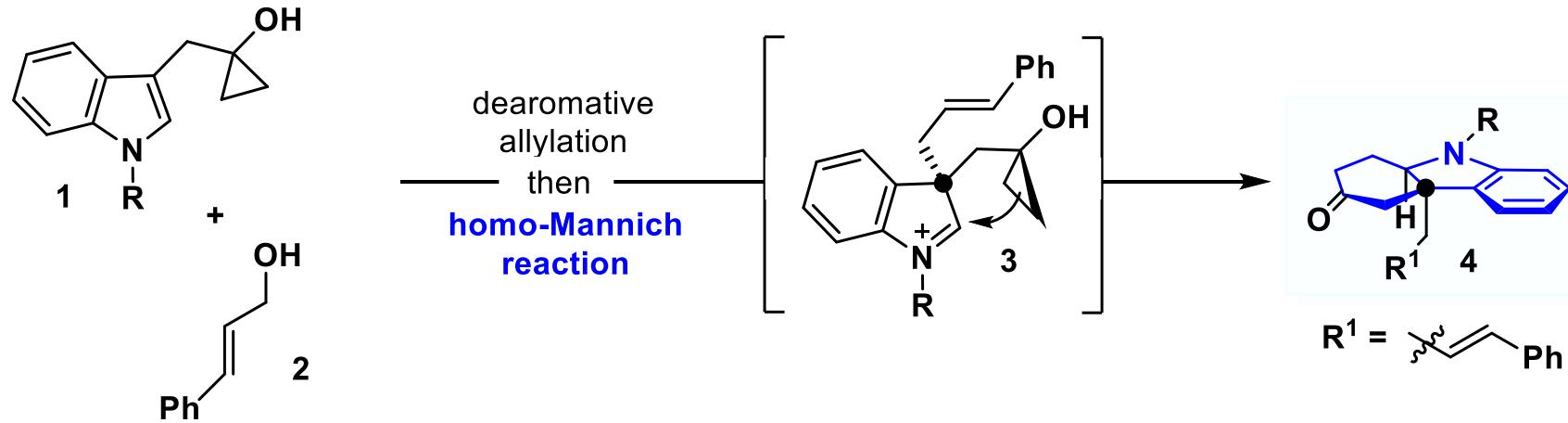
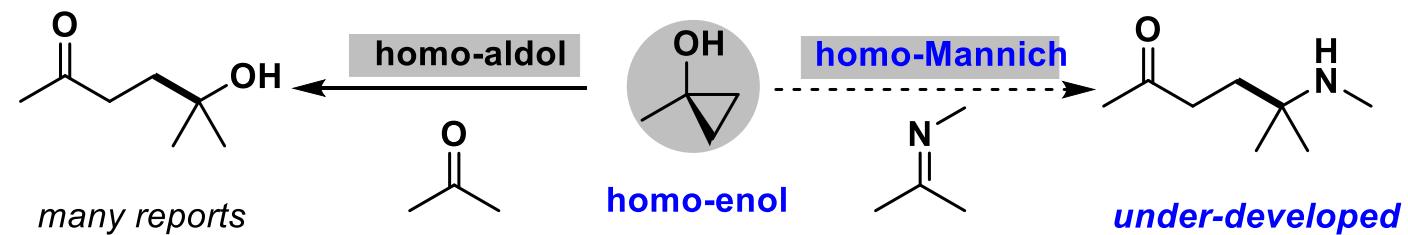
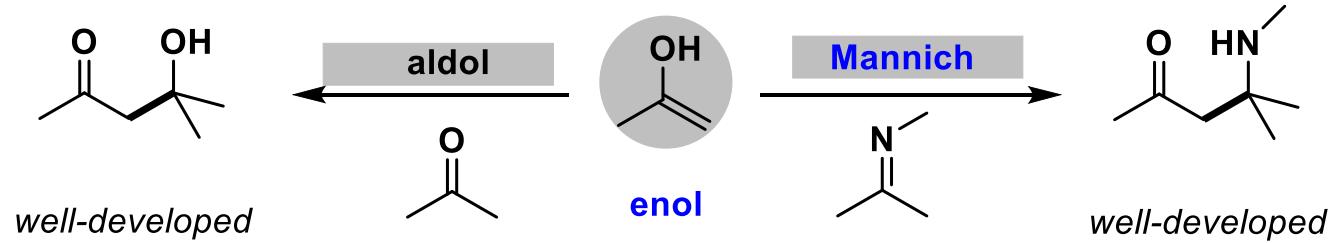
Waymouth and Dai, 2016



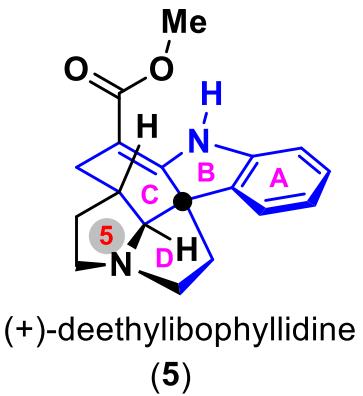
Domino Sequences That Functionalize the Homoenolate Carbonyl After Nucleophilic Trapping

Crimmins, 1990

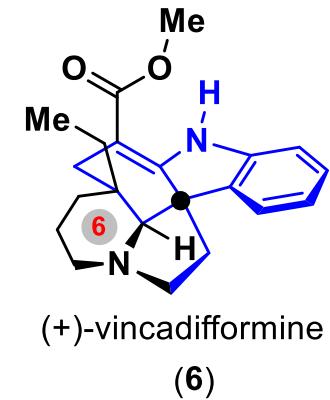




[Ibophyllidine]

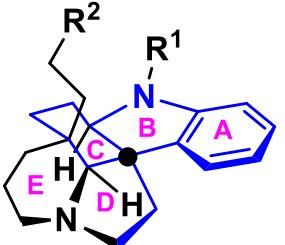


[Aspidosperma]



hydrocarbazole
core

[Aspidosperma]



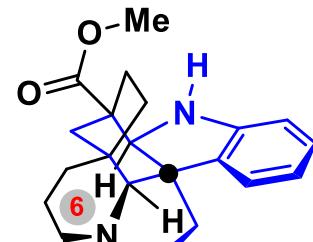
(+)-N-methylaspidospermidine (7):

R¹ = Me, R² = H

(+)-aspidospermidine (8): R¹ = H, R² = H

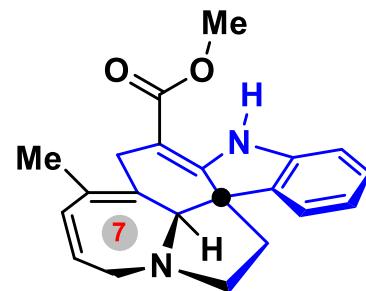
(+)-limaspermidine (9): R¹ = H, R² = OH

[Kopsia]

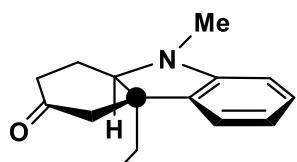
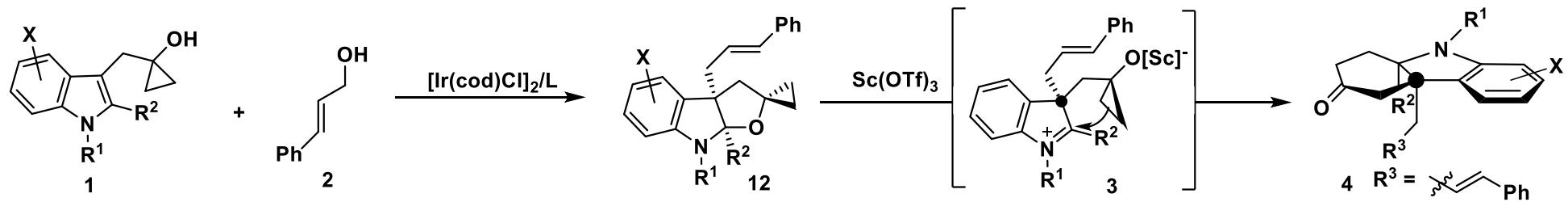


(+)-tetrahydrokopsifoline D
(10)

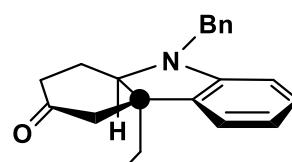
[Melodinus]



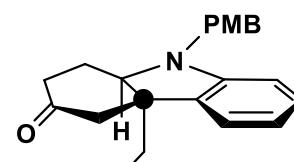
(+)-melotenine A
(11)



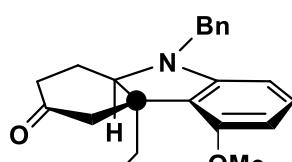
4a: 81% yield, 95% ee



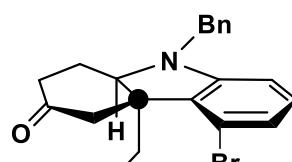
4b: 82% yield, 97% ee



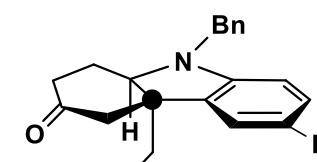
4c: 75% yield, 94% ee



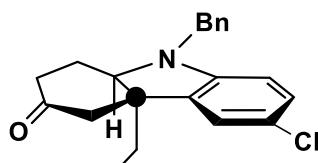
4d: 61% yield, 99% ee



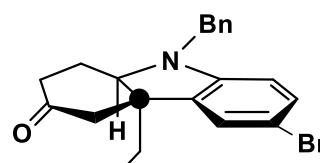
4e: 56% yield, 95% ee



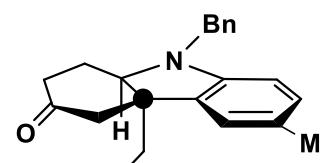
4f: 55% yield, 97% ee



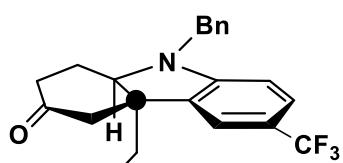
4g: 65% yield, 98% ee



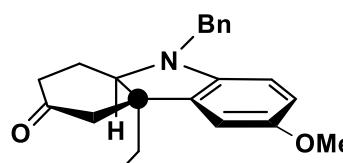
4h: 51% yield, 97% ee



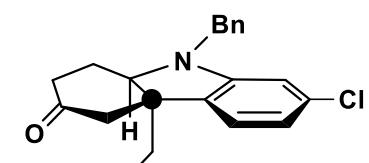
4i: 71% yield, 97% ee



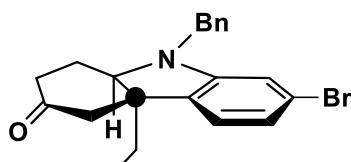
4j: 42% yield, 99% ee



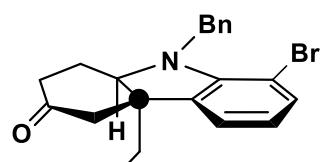
4k: 62% yield, 96% ee



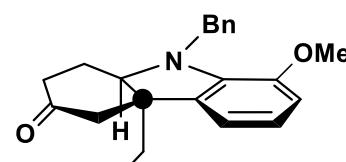
4l: 46% yield, 89% ee



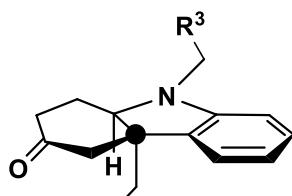
4m: 60% yield, 97% ee



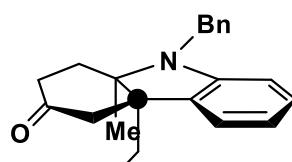
4n: 40% yield, 97% ee



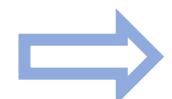
4o: 64% yield, 93% ee



4p: 51% yield, 96% ee

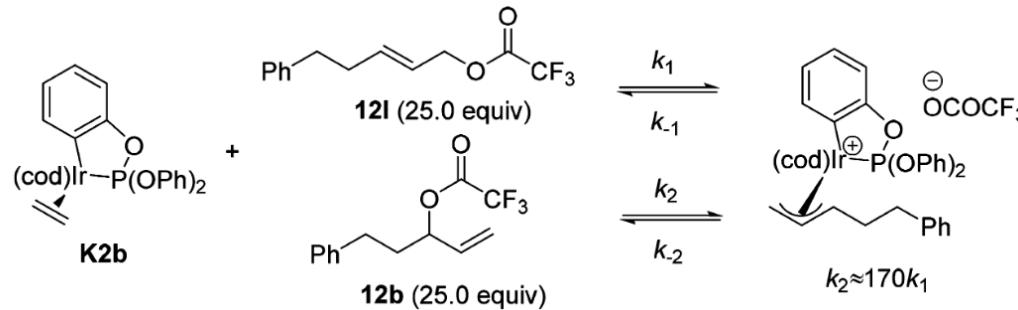


4q: 39% yield, 65% ee

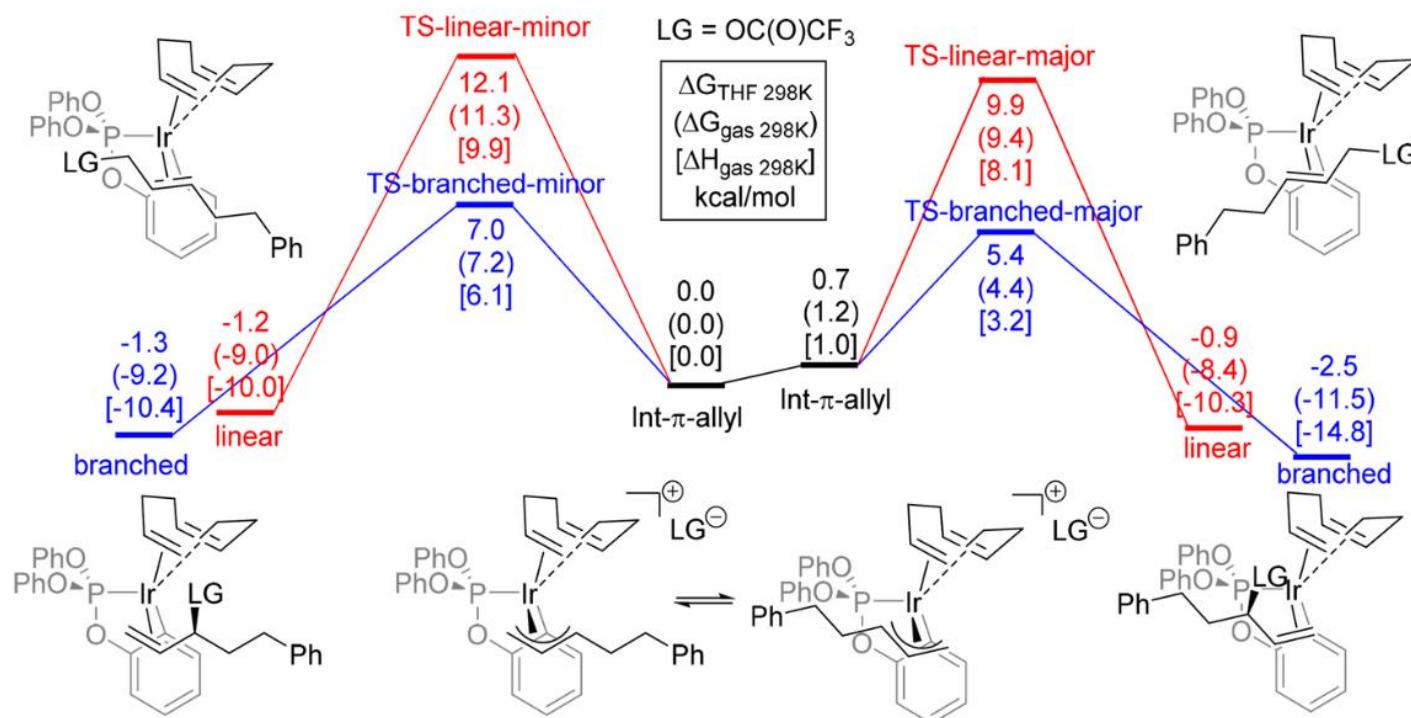


Ir催化的吲哚C3位烯丙基化反应

一般情况

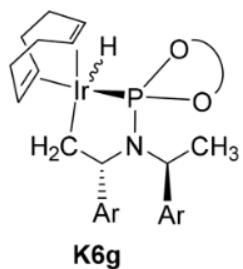
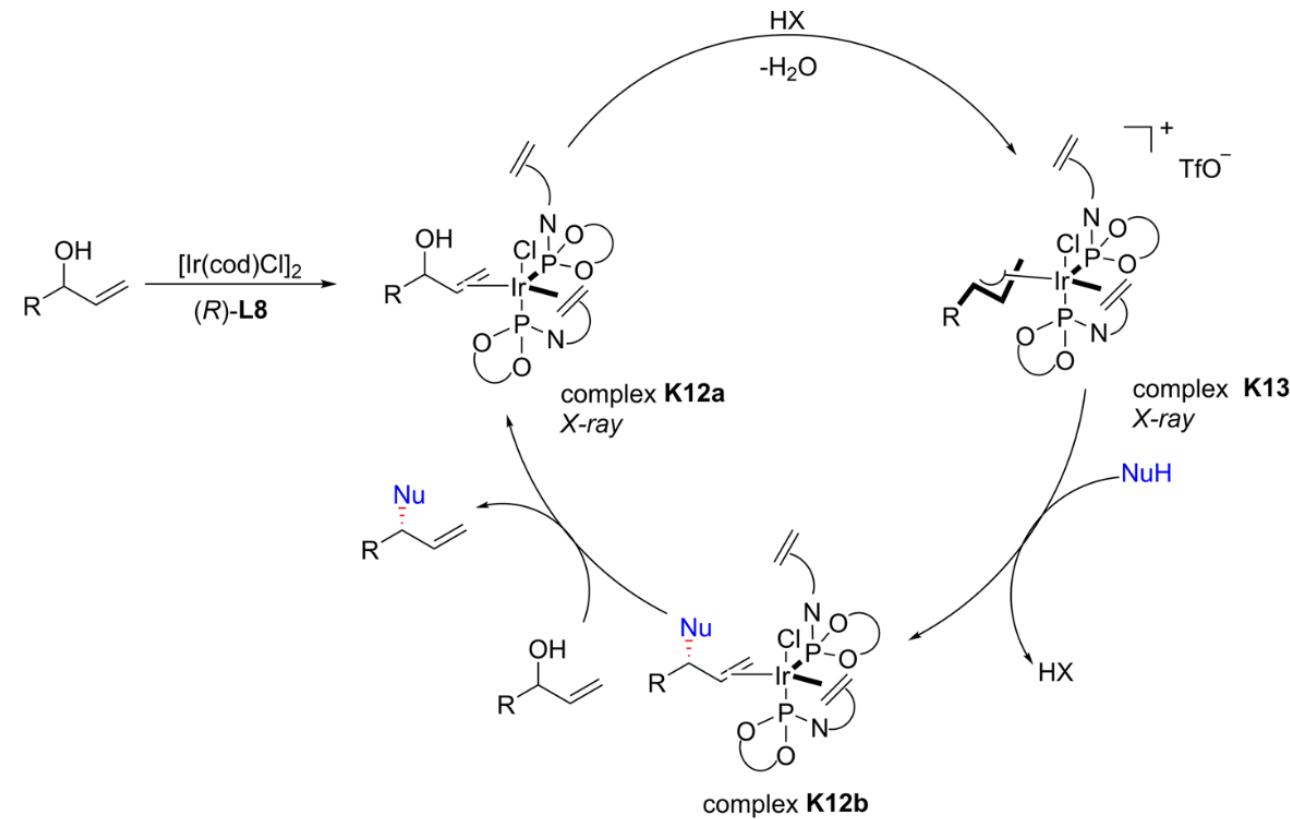
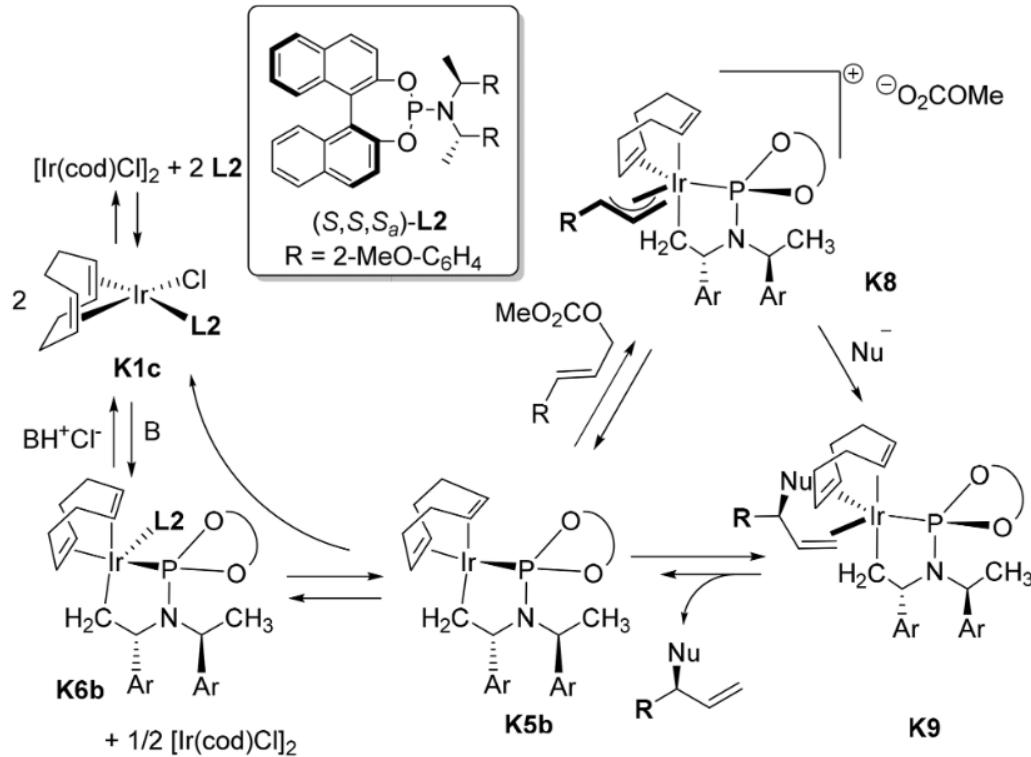


regioselectivity. By a kinetic study of the oxidative addition reaction of metallacyclic iridium complex **K2b** with branched or linear allylic trifluoacetate **12I** or **12b**, respectively, the branched substrate was found to react approximately 170 times faster than the linear one (Scheme 21). According to the principle of microscopic reversibility, it could be deduced that the nucleophilic attack to form the branched product should also be faster than that of the linear one, which was supported by DFT calculations (Scheme 22). Since, in the crystal



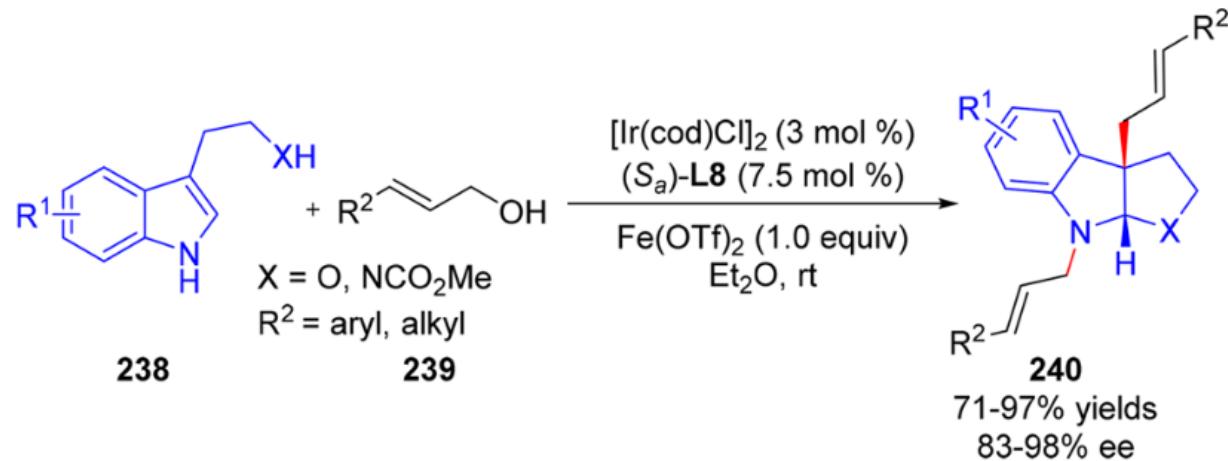
Ir催化的吲哚C3位烯丙基化反应

一般情况



Ir催化的吲哚C3位烯丙基化反应

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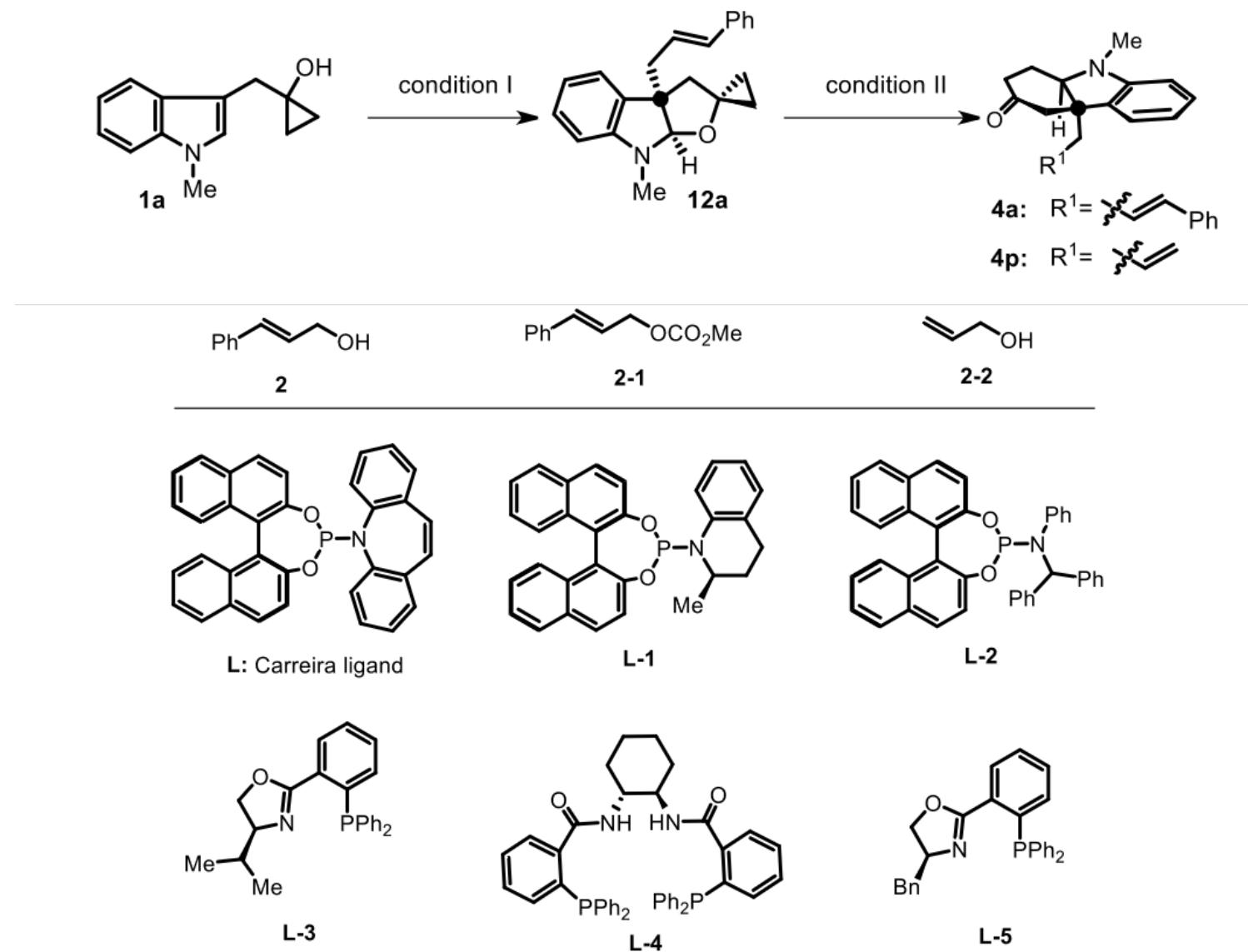
It was surprising that, for the first time, the reaction with linear allylic alcohols gave linear allylic substitution products exclusively rather than the branched products. The formation of the linear allylic alkylation products is likely due to a high steric hindrance of the nucleophiles. Preliminary mechanistic

allylic alcohol hydroxyl group. This process is among the only limited number of examples where Ir-catalyzed asymmetric allylic substitution reactions proceed via discrimination of the enantiotopic faces of prochiral nucleophiles.³⁰ Remarkably different from the regular pattern seen in Ir-catalyzed asymmetric allylic substitution reactions, nucleophile attack takes place at the terminal allylic position probably as a result of steric congestion at the C3 position of 32. In addition, the

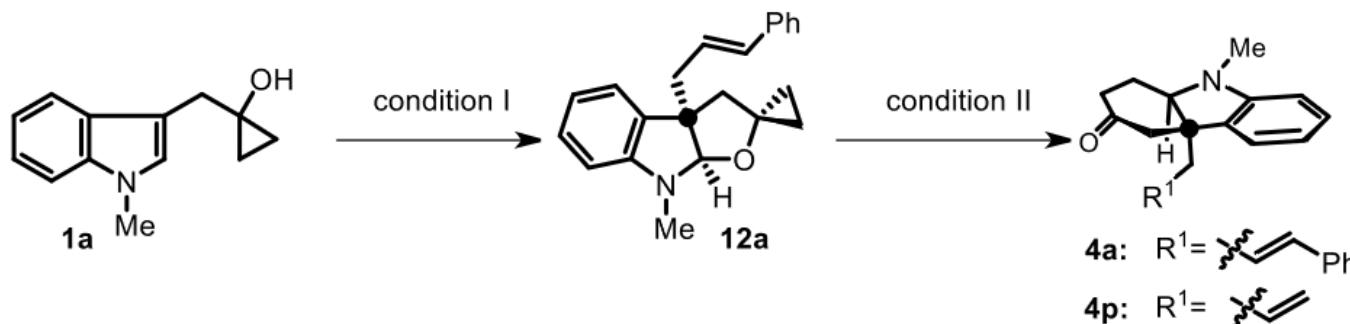
Acc. Chem. Res., 2014, 47, 2558.

Chem. Rev., 2019, 119, 1855.

2.1 Table S1: Optimization of the sequential asymmetric allylic dearomatization/homo-Mannich reaction^[a]



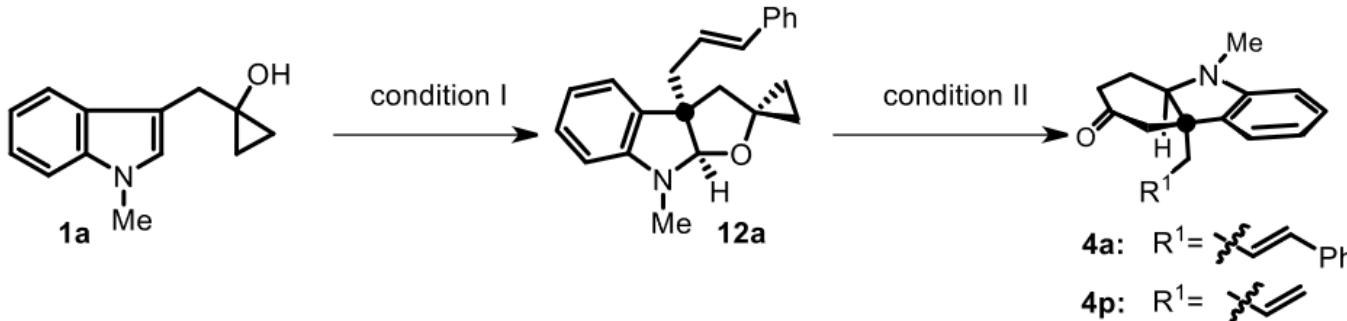
2.1 Table S1: Optimization of the sequential asymmetric allylic dearomatization/homo-Mannich reaction^[a]



Entry	Condition I	Condition II	Yield (%) ^[b]	ee (%) ^[c]
1	L-2/[Ir(cod)Cl]₂/Fe(OTf)₂/Et₂O	—	37	95
2	L-1-2/[Ir(cod)Cl]₂/Fe(OTf)₂/Et₂O	—	0	—
3	L-2-2/[Ir(cod)Cl]₂/Fe(OTf)₂/Et₂O	—	0	—
4	L-3-2/[Ni(cod)₂]/Ti(O<i>i</i>Pr)₄/CH₃CN	—	0	—
5	L-4-2-1/Pd₂(dba)₃/Ti(O<i>i</i>Pr)₄/CH₂Cl₂	—	0	—
6	L-5-2-1/Pd₂(dba)₃/Cs₂CO₃/THF	—	0	—
7	L-1-2-1/[Ir(cod)Cl]₂/Et₃N/THF	—	0	—

[a] Condition I: **1a** (0.10 mmol, 1 eq), **AP** (3 eq), metal (0.05 eq), ligand (0.11 eq), Lewis acid (1 eq) or base (2 eq), solvent (3 mL), rt, 10–72 h. Condition II: metal (0.2 eq), solvent (3 mL), 1–10 h. [b] Isolated yield of **4a** or **4p** from **1a**. [c] ee value of **4a** or **4p**, determined by HPLC analysis. [d] Sc(OTf)₃ (1 eq) was used. AP: allyl precursor. DMF: *N,N*-dimethylformamide. DCE: 1,2-dichloroethane.

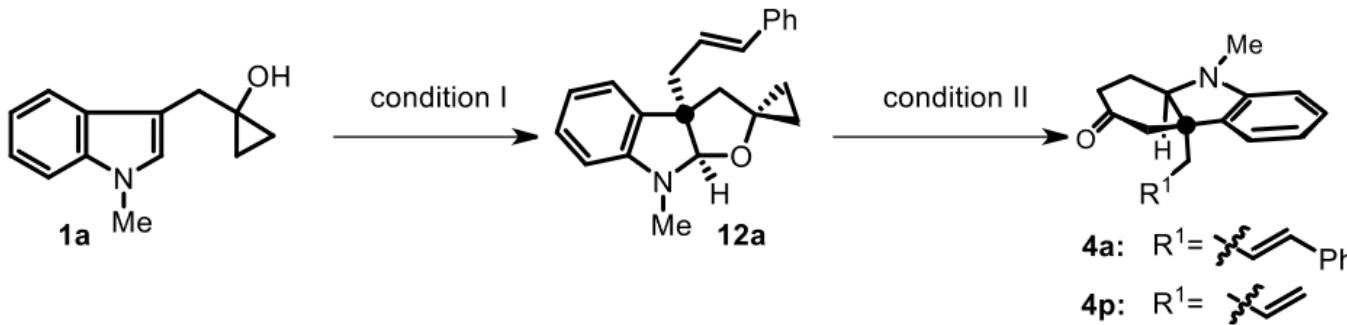
2.1 Table S1: Optimization of the sequential asymmetric allylic dearomatization/homo-Mannich reaction^[a]



Entry	Condition I	Condition II	Yield (%) ^[b]	ee (%) ^[c]
8	L/2-2/[Ir(cod)Cl]₂/Fe(OTf)₂/Et₂O	—	25	58
9	L/2/[Ir(cod)Cl]₂/Zn(OTf)₂/Et₂O	—	10	69
10	L/2/[Ir(cod)Cl]₂/Ni(OTf)₂/Et₂O	—	22	92
11	L/2/[Ir(cod)Cl]₂/Sc(OTf)₃/Et₂O	—	19	31
12	L/2/[Ir(cod)Cl]₂/Fe(OTf)₂/Et₂O	CuCl ₂ /CHCl ₃ /60 °C	26	94
13	L/2/[Ir(cod)Cl]₂/Fe(OTf)₂/Et₂O	CuCl ₂ /DMF/60 °C	29	94
14	L/2/[Ir(cod)Cl]₂/Fe(OTf)₂/Et₂O	CuCl/EtOAc/60 °C	37	95

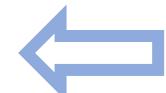
[a] Condition I: **1a** (0.10 mmol, 1 eq), **AP** (3 eq), metal (0.05 eq), ligand (0.11 eq), Lewis acid (1 eq) or base (2 eq), solvent (3 mL), rt, 10–72 h. Condition II: metal (0.2 eq), solvent (3 mL), 1–10 h. [b] Isolated yield of **4a** or **4p** from **1a**. [c] ee value of **4a** or **4p**, determined by HPLC analysis. [d] Sc(OTf)₃ (1 eq) was used. **AP**: allyl precursor. DMF: *N,N*-dimethylformamide. DCE: 1,2-dichloroethane.

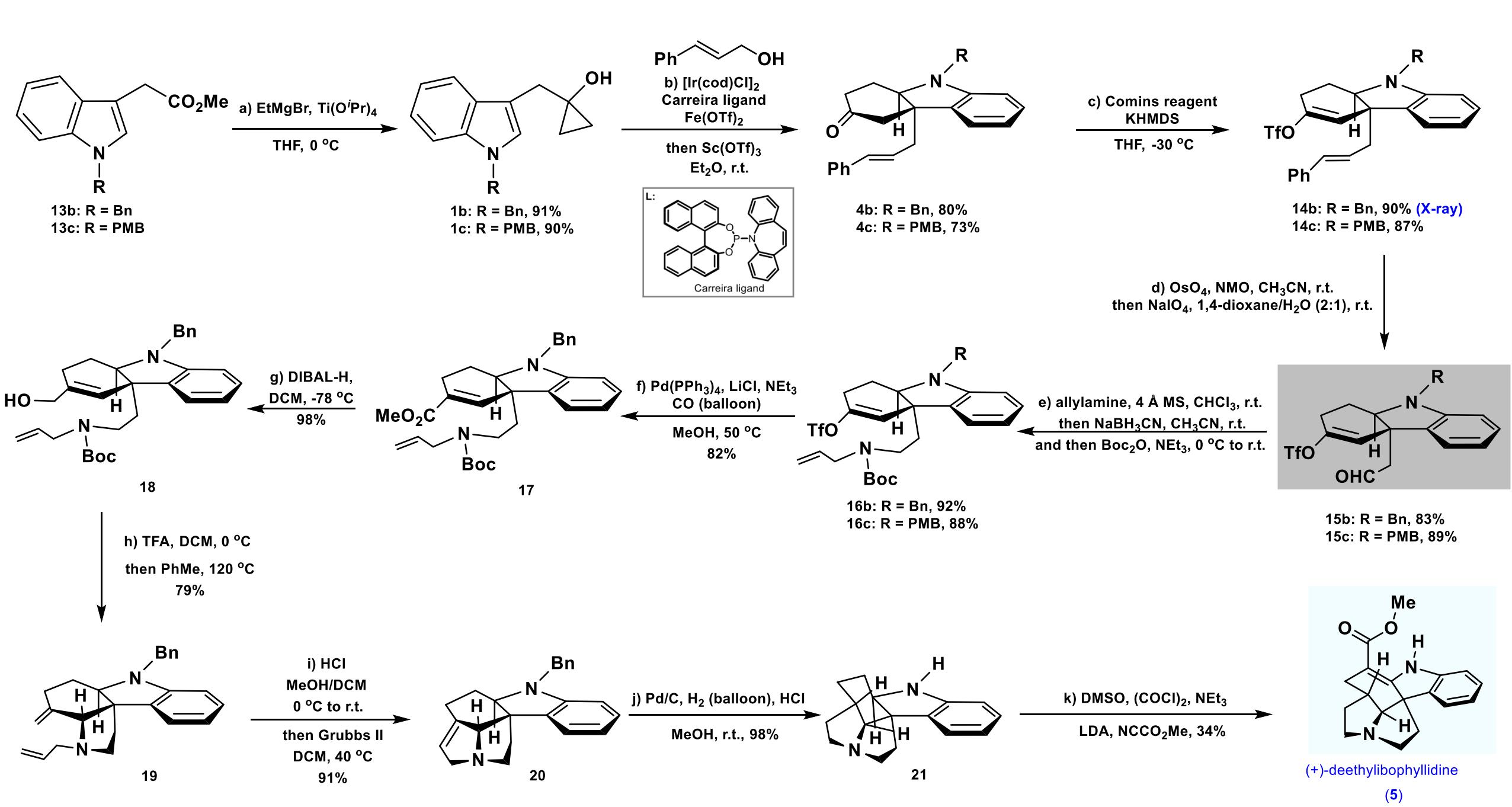
2.1 Table S1: Optimization of the sequential asymmetric allylic dearomatization/homo-Mannich reaction^[a]



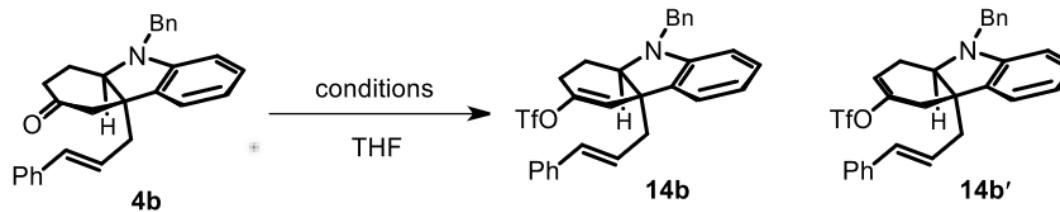
Entry	Condition I	Condition II	Yield (%) ^[b]	ee (%) ^[c]
15	L/2/[Ir(cod)Cl]₂/Fe(OTf)₂/Et₂O	ZnI ₂ /toluene/90 °C	0	—
16	L/2/[Ir(cod)Cl]₂/Fe(OTf)₂/Et₂O	Fe(OTf) ₃ /1,4-dioxane/60 °C	<5	—
17	L/2/[Ir(cod)Cl]₂/Fe(OTf)₂/Et₂O	Cu(OTf) ₂ /DCE/60 °C	61	95
18	L/2/[Ir(cod)Cl]₂/Fe(OTf)₂/Et₂O	Sc(OTf) ₃ /DCE/rt	26	95
19	L/2/[Ir(cod)Cl]₂/Fe(OTf)₂/Et₂O	Sc(OTf) ₃ /Et ₂ O/rt	30	95
20 ^[d]	L/2/[Ir(cod)Cl]₂/Fe(OTf)₂/Et₂O	Sc(OTf) ₃ /Et ₂ O/rt	81	95

[a] Condition I: **1a** (0.10 mmol, 1 eq), **AP** (3 eq), metal (0.05 eq), ligand (0.11 eq), Lewis acid (1 eq) or base (2 eq), solvent (3 mL), rt, 10–72 h. Condition II: metal (0.2 eq), solvent (3 mL), 1–10 h. [b] Isolated yield of **4a** or **4p** from **1a**. [c] ee value of **4a** or **4p**, determined by HPLC analysis. [d] Sc(OTf)₃ (1 eq) was used. **AP**: allyl precursor. DMF: *N,N*-dimethylformamide. DCE: 1,2-dichloroethane.





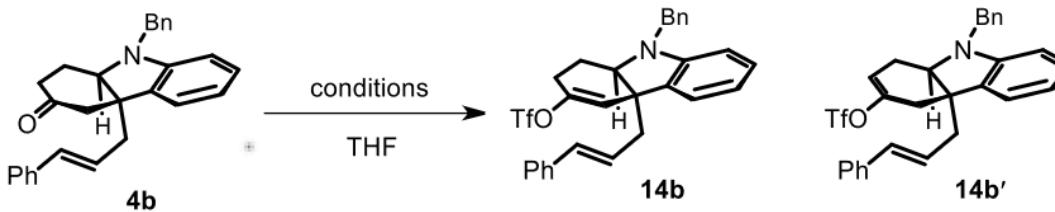
2.3.3 Table S2. Optimization of preparation of enol triflate^{[a][1]}



entry	conditions	T (°C)	yield of 14b (%) ^[b]	yield of 14b' (%) ^[b]	time for pre-stirring 4b and base (min)
1	Comins reagent, KHMDS	-78	50	42	25
2	Comins reagent, KHMDS	-60	50	36	25
3	Comins reagent, KHMDS	-45	60	28	25
4	Comins reagent, KHMDS	-30	88	0	25
5	Comins reagent, KHMDS	-15	46	0	25
6	Comins reagent, KHMDS	0	39	0	25
7 ^[c]	Comins reagent, KHMDS	-30	19	62	0
8	Comins reagent, KHMDS	-30	43	21	1
9	Comins reagent, KHMDS	-30	66	0	5
10	Comins reagent, KHMDS	-30	71	0	10

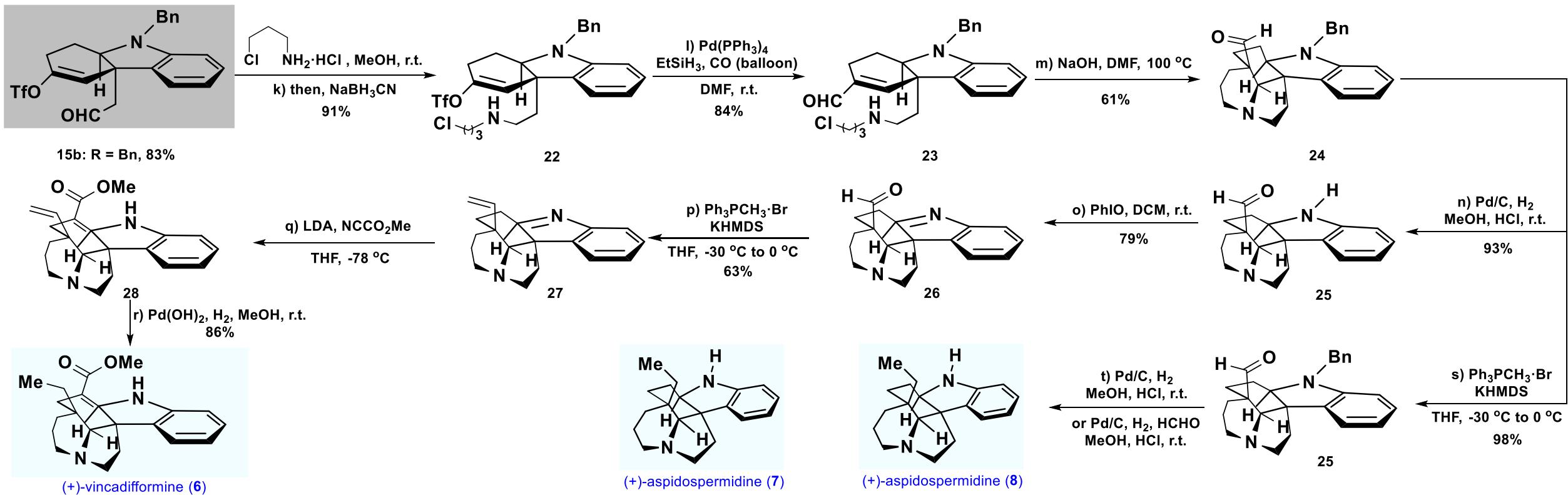
[a] Reaction conditions: **4b** (15 mg), base (3 eq), THF (1.4 mL); then Comins reagent or PhNTf₂ (2 eq) in THF (0.1 mL), 30 min. [b] Determined by ¹H NMR using dibromomethane as an internal standard. [c] Premixing **4b** and Comins reagent, and then added with KHMDS.

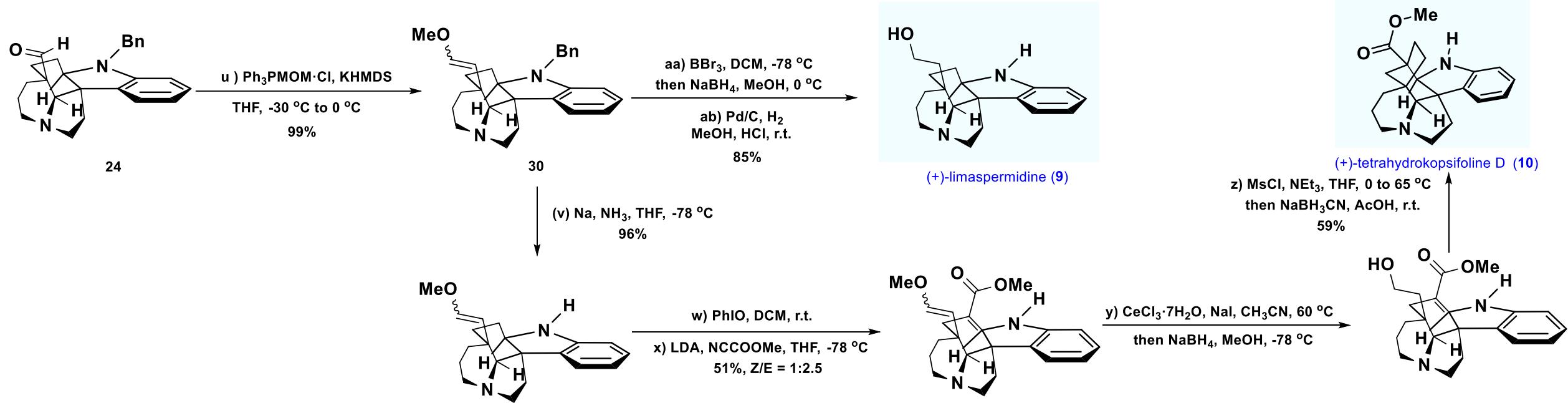
2.3.3 Table S2. Optimization of preparation of enol triflate^{[a][1]}



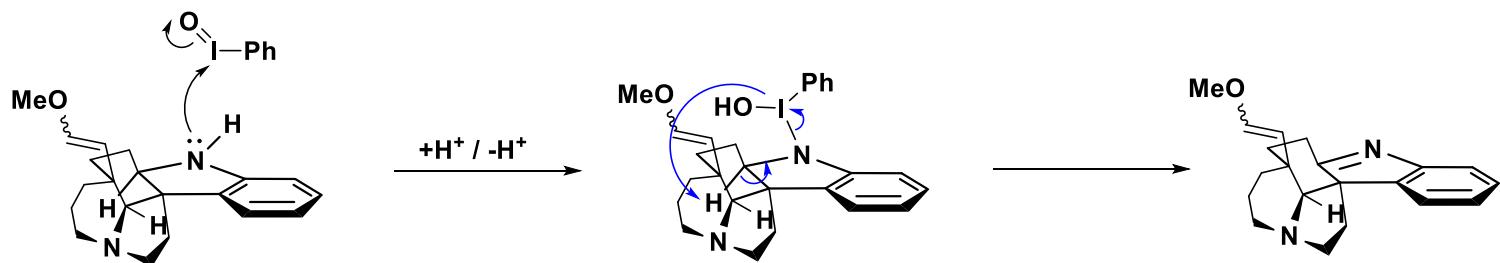
entry	conditions	T (°C)	yield of 14b (%) ^[b]	yield of 14b' (%) ^[b]	time for pre-stirring 4b and base (min)
11	Comins reagent, KHMDS	-30	77	0	15
12	Comins reagent, KHMDS *	-30	86	0	20
13	Comins reagent, LiHMDS	-30	27	52	25
14	Comins reagent, NaHMDS	-30	43	38	25
15	Comins reagent, LiHMDS	-30	26	54	60
16	Comins reagent, NaHMDS	-30	37	42	60
17	Comins reagent, KHMDS	-30	71	0	60
18	PhNTf ₂ , LiHMDS	-30	19	39	25
19	PhNTf ₂ , NaHMDS	-30	26	38	25
20	PhNTf ₂ , KHMDS	-30	72	0	25

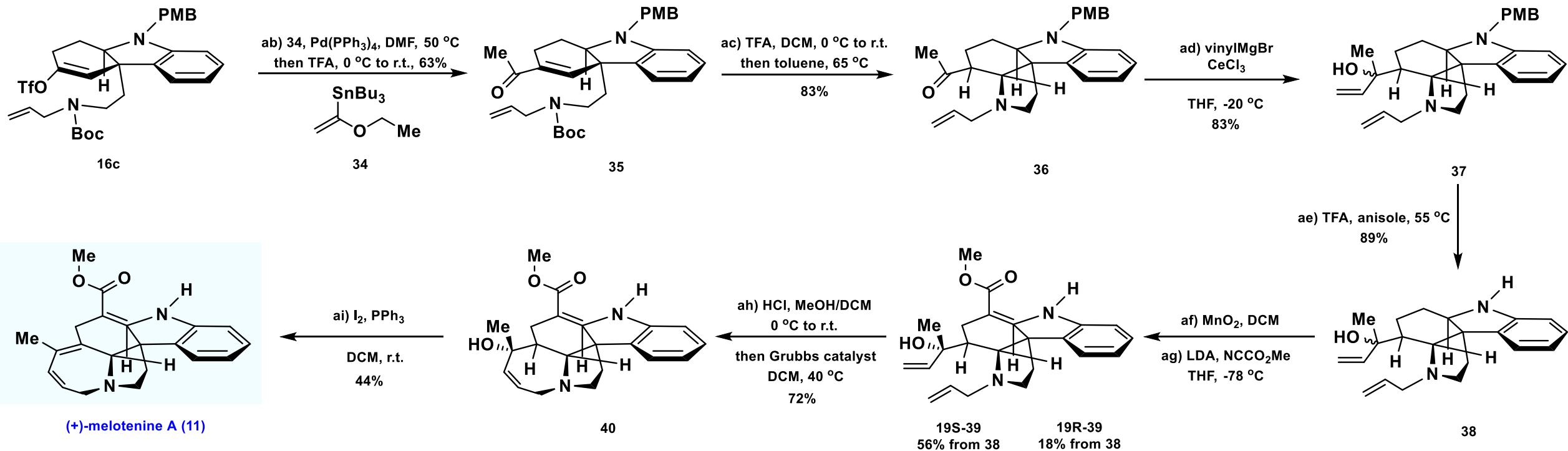
[a] Reaction conditions: **4b** (15 mg), base (3 eq), THF (1.4 mL); then Comins reagent or PhNTf₂ (2 eq) in THF (0.1 mL), 30 min. [b] Determined by ¹H NMR using dibromomethane as an internal standard. [c] Premixing **4b** and Comins reagent, and then added with KHMDS.





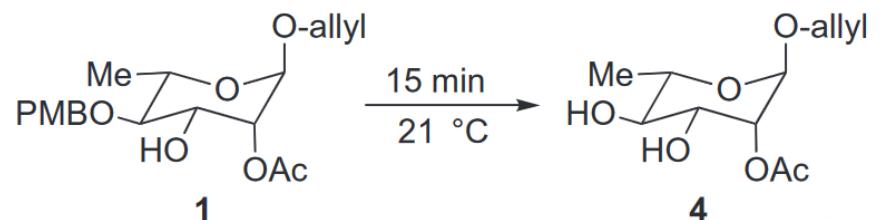
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TFA脱PMB

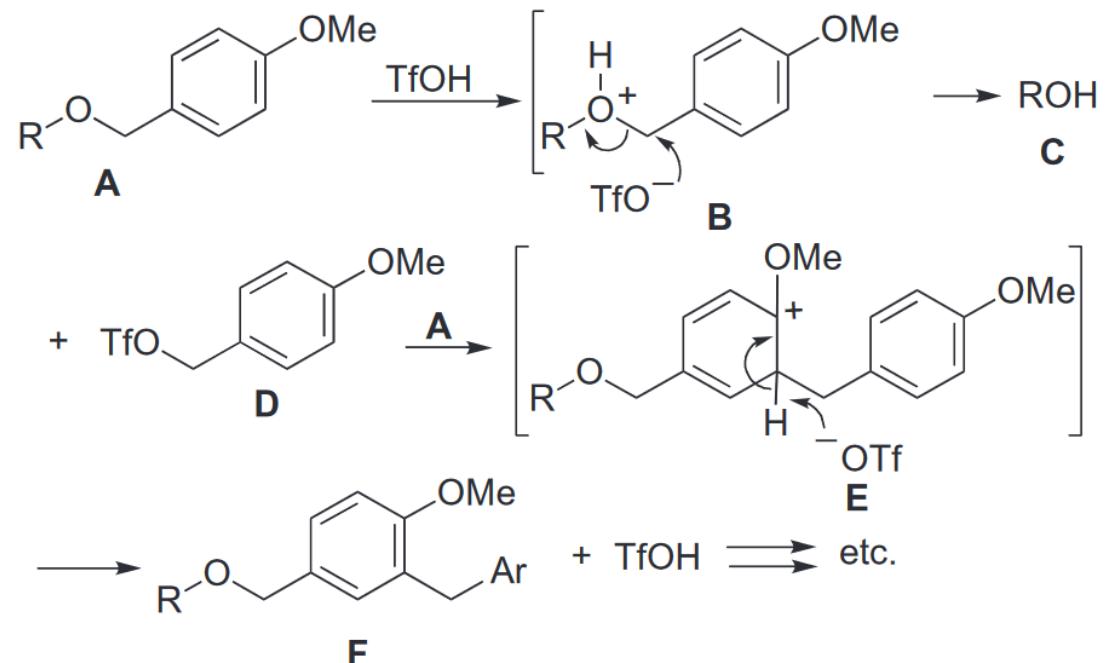
Cleavage of the PMB ether of **1**



Entry	Reagent	Amount (equiv)	Solvent	Yield (%)
a	TMSOTf	0.05	CH ₂ Cl ₂	50
b	TMSOTf	0.1	CH ₂ Cl ₂	54
c	TMSOTf	0.2	CH ₂ Cl ₂	51
d	TMSOTf	0.4	CH ₂ Cl ₂	27
e	TMSOTf	2 × 0.05	CH ₂ Cl ₂	63
f	TMSOTf	0.1	CH ₂ Cl ₂ ^a	36
g	TfOH	0.1	CH ₂ Cl ₂	50
h	TfOH	2 × 0.05	CH ₂ Cl ₂	59

^a Not dried.

Since yields of >50% can be achieved with only 10% of triflic acid in an aprotic solvent, there must be a way for additional protons to be generated during the reaction. We hypothesized that this production of protons occurred via an intermolecular Friedel-Crafts alkylation process (Scheme 2). Thus protonation of the PMB ether



If this mechanism (or a similar one) were active, we argue that we could improve the process by adding a more electron-rich aromatic ring to react with the triflate **D** and generate additional triflic acid more rapidly. This turned out to be the case. Addition of