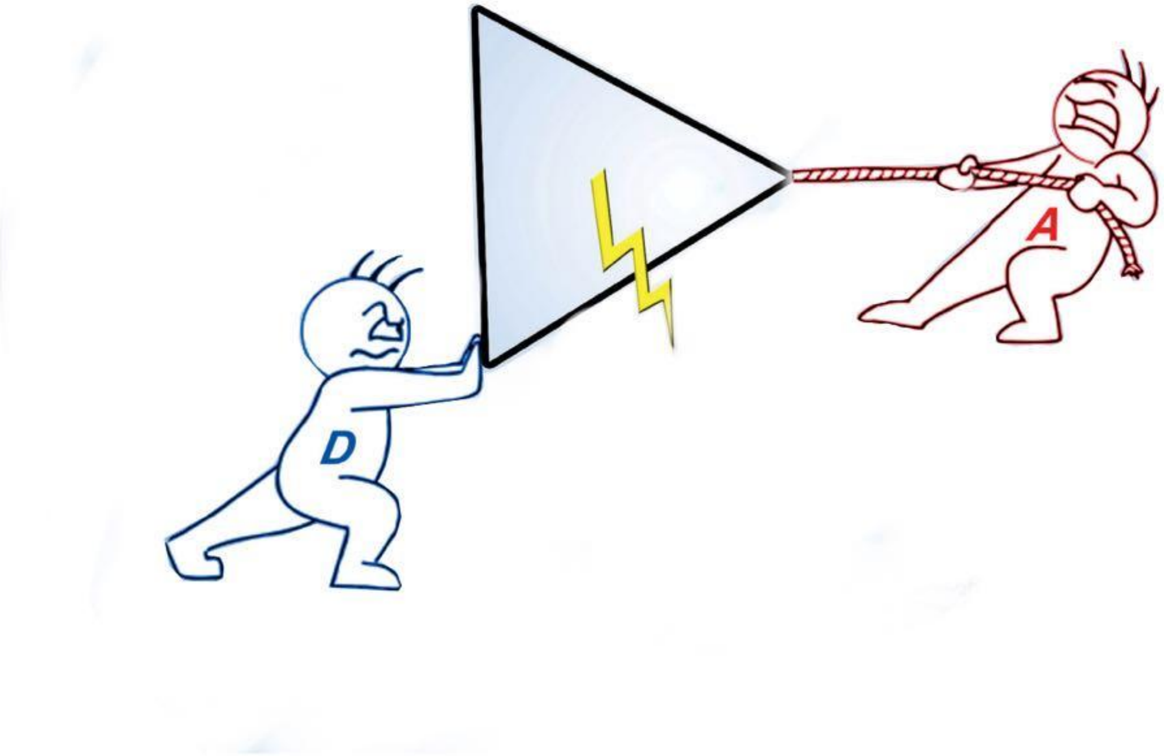
Construction of carbocycles with donor-acceptor cyclopropane



2024.11.14 Literature Seminar
D3 Yuyan Liang

Contents

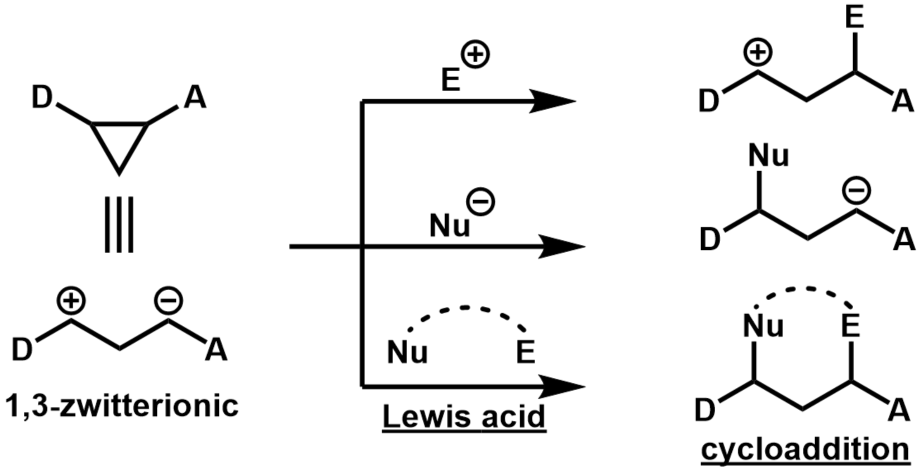
0. Introduction

1. Lewis acid catalyzed intramolecular [3+2] cross-cycloaddition of cyclopropane 1,1-diester with alkene.
(*Angew. Chem. Int. Ed.* **2013**, *52*, 2032.**)**

2. Lewis acid catalyzed dearomative [3+2] parallel-cycloaddition of cyclopropane with benzene.
(*Nat. Commun.* **2024**, *15*, 9206.**)**

Donor-Acceptor Cyclopropanes

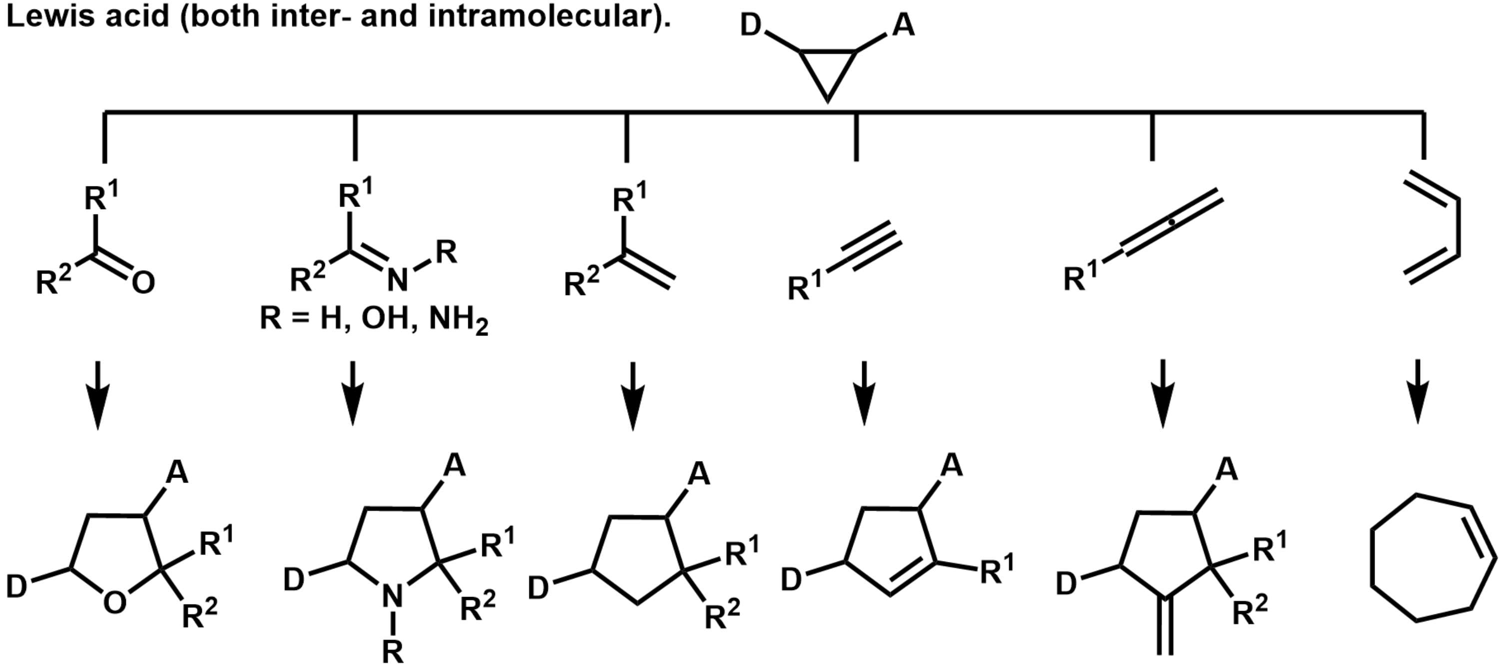
1. Activated cycloprppane with donor and acceptor substituents
→ electronic density distribution (significant polarization)



D = Donor = EDG =
R_2N-, RO-, RS-, Ar-, $SiCH_2$-...

A = Acceptor = EWG =
ketone, ester, amide, cyano...

2. Cycloaddtions of activated Donor-Acceptor cyclopropanes with diverse dipolarophiles catalyzed by Lewis acid (both inter- and intramolecular).



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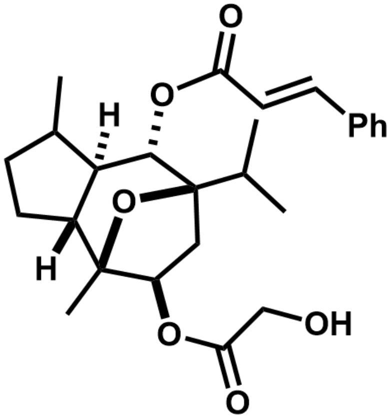
1) Ivanova, O. A.; Trushkov, I. V. *Chem. Rec.* **2019**, *19*, 2189-2208.

Prof. Zhongwen Wang

career:
-1990: B.S. @ Nankai University
1990-1996: Ph.D. @ Nankai University
1999-2001: Postdoctoral : @ Nagoya University, Japan (Prof. H. Shinohara)
2001-2004: Postdoctoral : @ University of Kentucky, USA
(Prof. Mark S. Meier, Prof. H.Peter Spielmann)
2004- : Professor, Nankai University

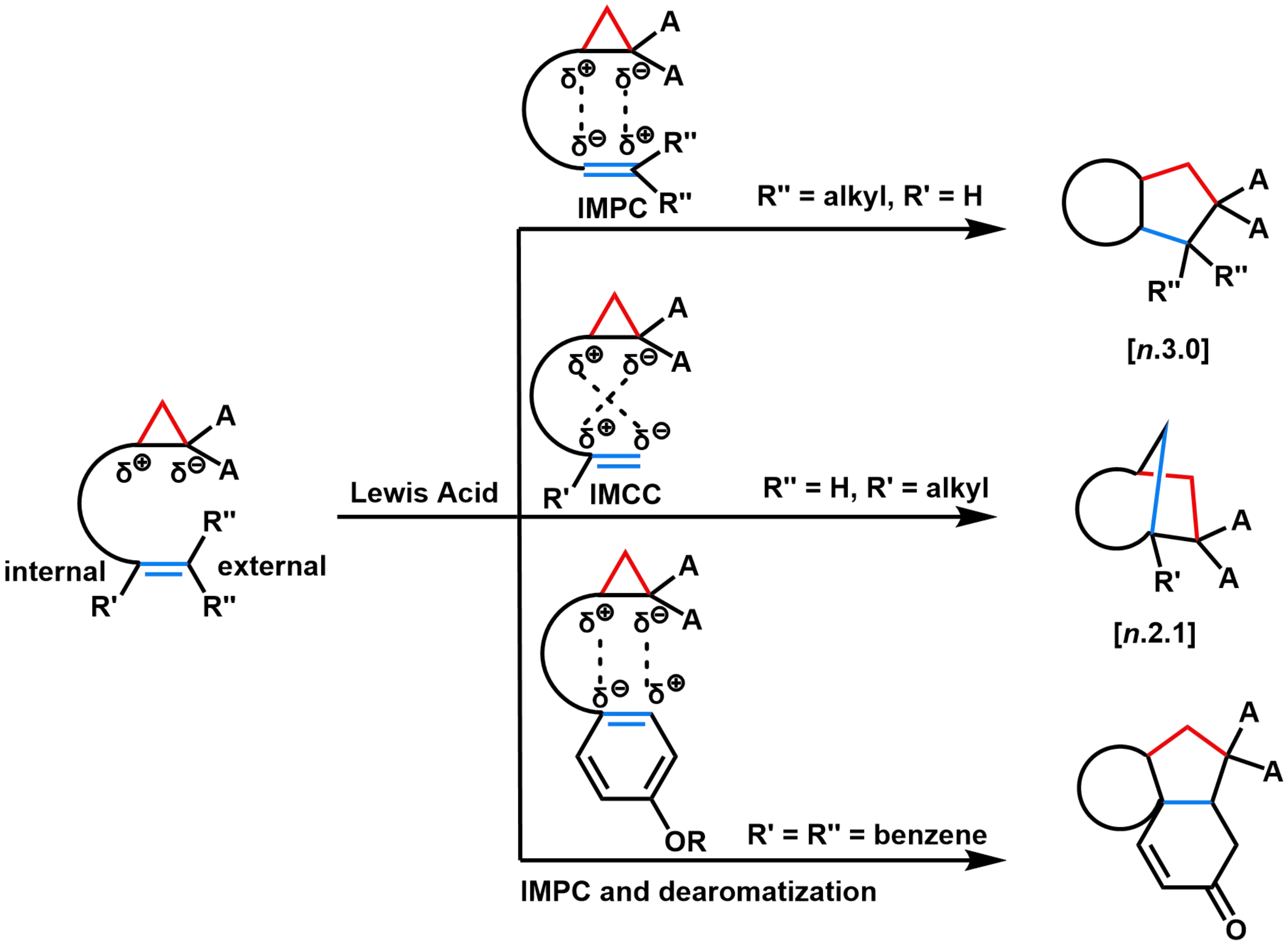
Research interests:
1. Synthetic methodology (Highly efficient and general strategy for construction of polycyclic skeletons); Novel cycloaddition and tandem reactions of strained rings
2. Natural products total synthesis;
3. New pharmaceutical and agrochemical leads discovery



(-)-englerin A

https://chemen.nankai.edu.cn/2021/0629/c24618a379084/page.htm

Intramolecular Cycloaddition of cyclopropane



IMPC: intramolecular parallel cycloaddition
IMCC: intramolecular cross cycloaddition

Regioselectivity could be finely tuned by changing substituents of alkene.

---

1) Zhu W. J.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 2032.

Contents

0. Introduction

1. Lewis acid catalyzed intramolecular [3+2] cross-cycloaddition of cyclopropane 1,1-diester with alkene.
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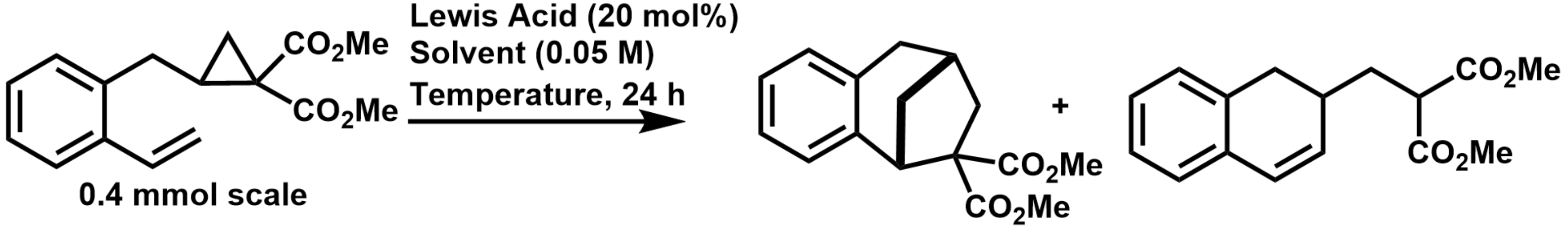
2. Lewis acid catalyzed dearomative [3+2] parallel-cycloaddition of cyclopropane with benzene.
(*Nat. Commun.* **2024**, *15*, 9206.**)**

Optimization



Entry	Lewis Acid	Solvent	Temperature	Yield [%]
1	$Sc(OTf)_3$	1,2-dichloroethane	40-45	67
2	$Sc(OTf)_3$ (10 mol%)	1,2-dichloroethane	60-65	80
3	$Sc(OTf)_3$	1,2-dichloroethane	60-65	78*
4	$Sc(OTf)_3$	toluene	60-65	67
5	$Sc(OTf)_3$	THF	60-65	29
6	$Sc(OTf)_3$	DMF	60-65	NR
7	$Sc(OTf)_3$	CH_3NO_2	60-65	79
8	$Yb(OTf)_3$	1,2-dichloroethane	60-65	NR
9	$Cu(OTf)_3$	1,2-dichloroethane	60-65	43
10	$Zn(OTf)_3$	1,2-dichloroethane	60-65	NR
11	$In(OTf)_3$	toluene	60-65	72
12	ZnCl	THF	60-65	NR
13	$BF_3 \cdot Et_2O$ (100 mol%)	CH_2Cl_2	-78 °C	NR
14	$SnCl_4 \cdot Et_3N$	1,2-dichloroethane	60-65	NR
15	trifluoroacetic acid	1,2-dichloroethane	60-65	0
16	triflic acid	1,2-dichloroethane	60-65	complex

* Byproduct was ontained in 15%, other entries did not mention.

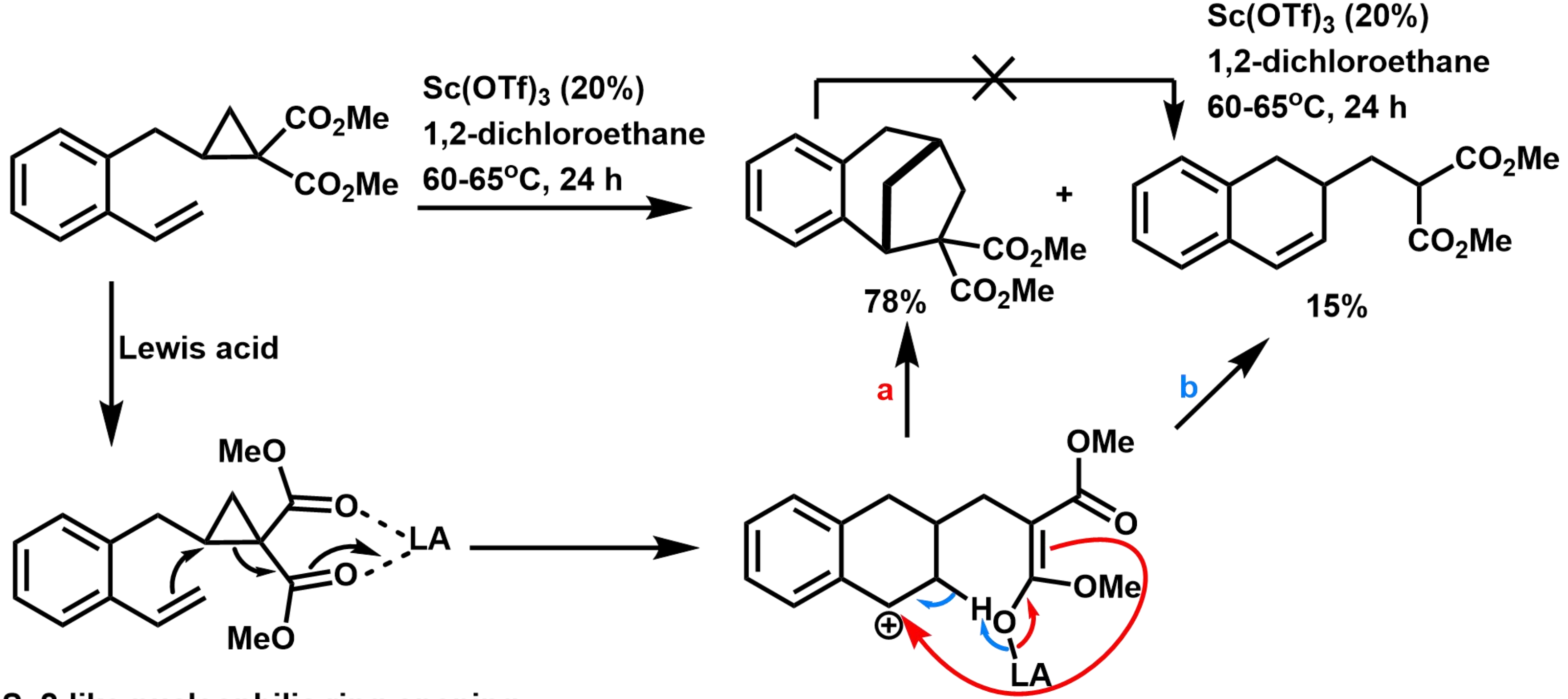
---

1) Zhu W. J.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 2032.

Mechanism

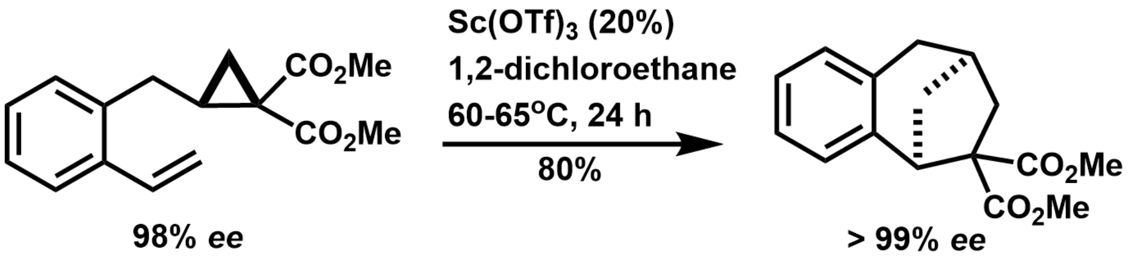
The S_N2-like stepwise mechanism is proposed based on 2 evidences.

1. Irreverseble transformation



S_N2-like nucleophilic ring opening

2. Asymmetric experiment: no erusion of enantiomeric excess



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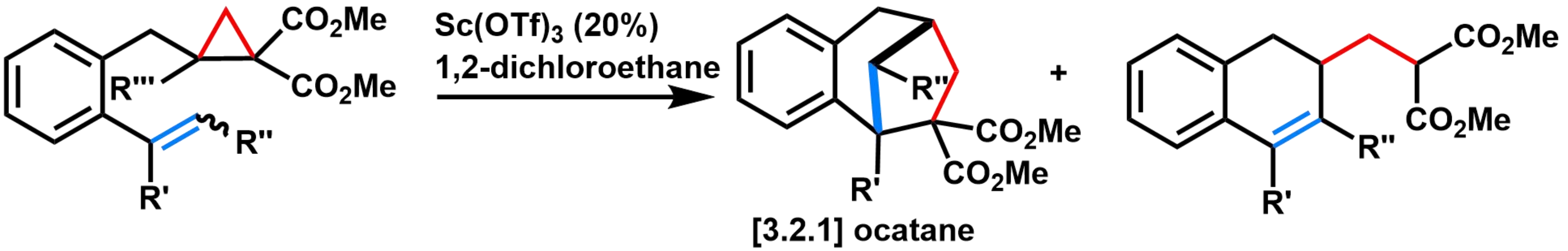
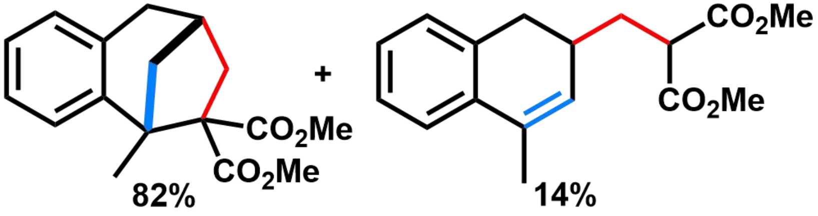
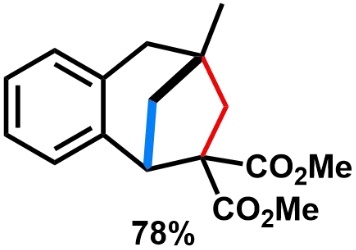
1) Zhu W. J.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 2032.

Substrate scope (1)

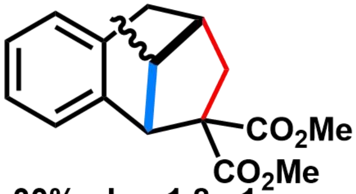




R' = Me, R'' = R''' = H

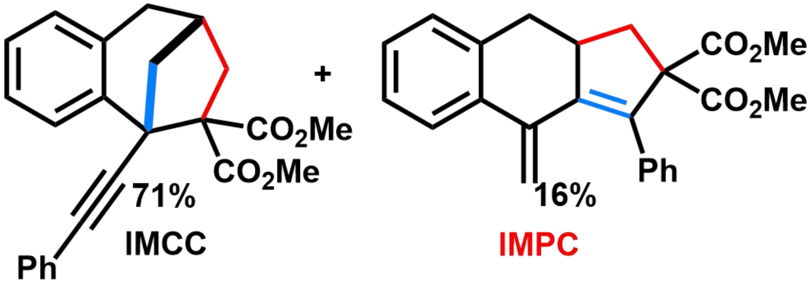


R' = R'' = H, R''' = Me

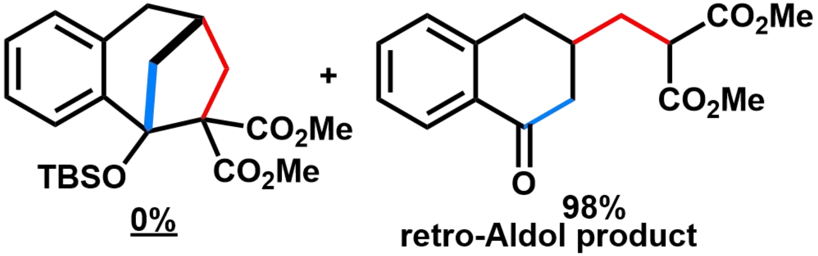


30%, dr = 1.8 : 1

R' = R''' = H, R'' = Me



R' = phenylpropynyl, R'' = R''' = H



R' = OTBS, R'' = R''' = H

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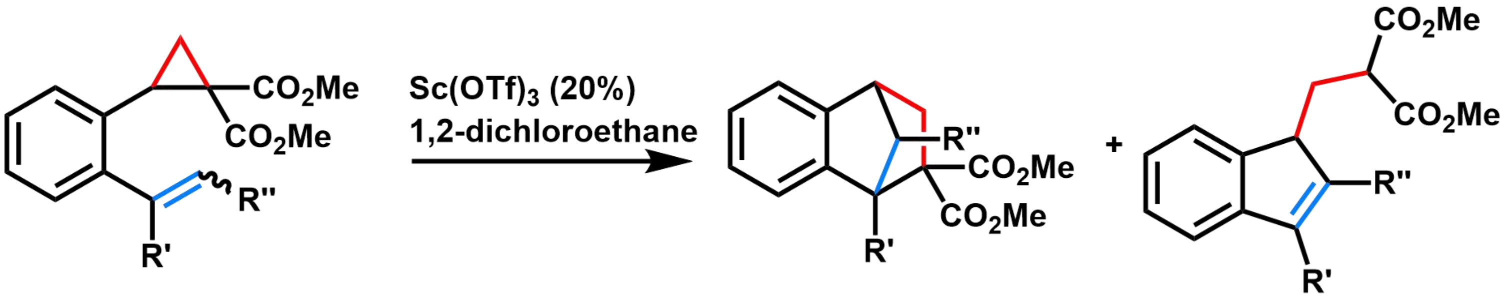
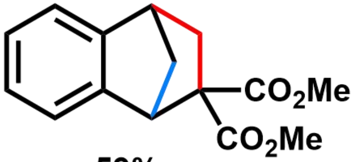
1) Zhu W. J.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 2032.

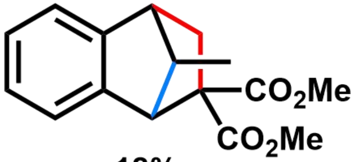
Substrate scope (1)





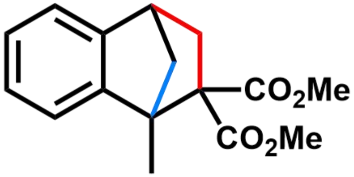
59%

R' = R'' = H



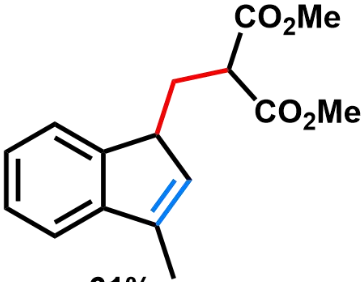
18%

R' = H, R'' = Me



NOT obtain

+



61%

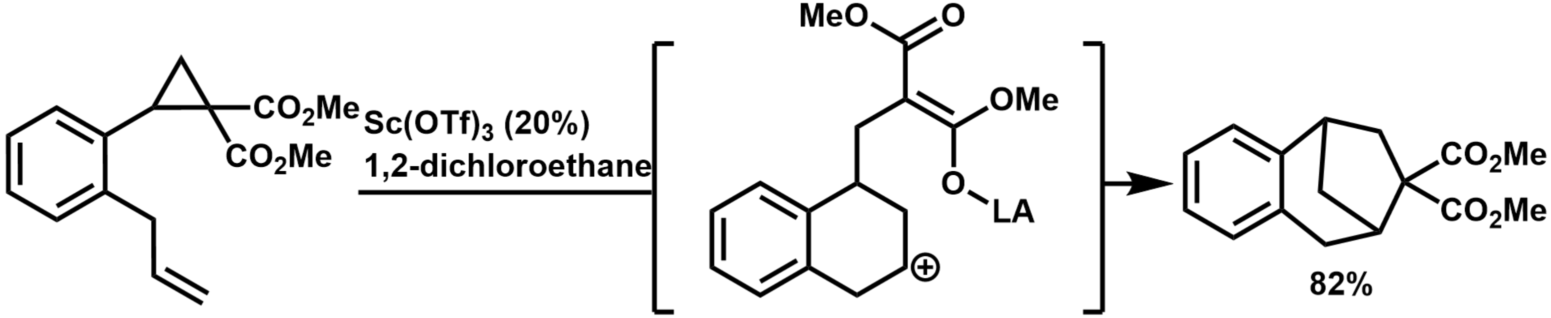
R' = Me, R'' = H

---

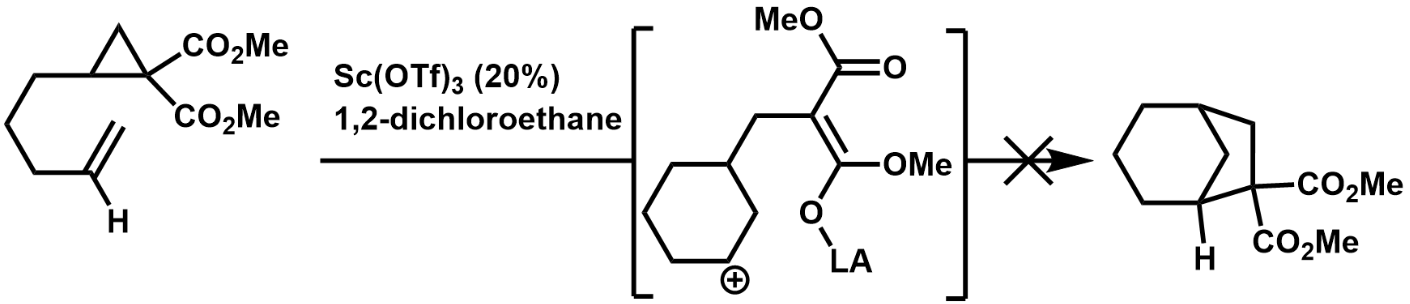
1) Zhu W. J.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 2032.

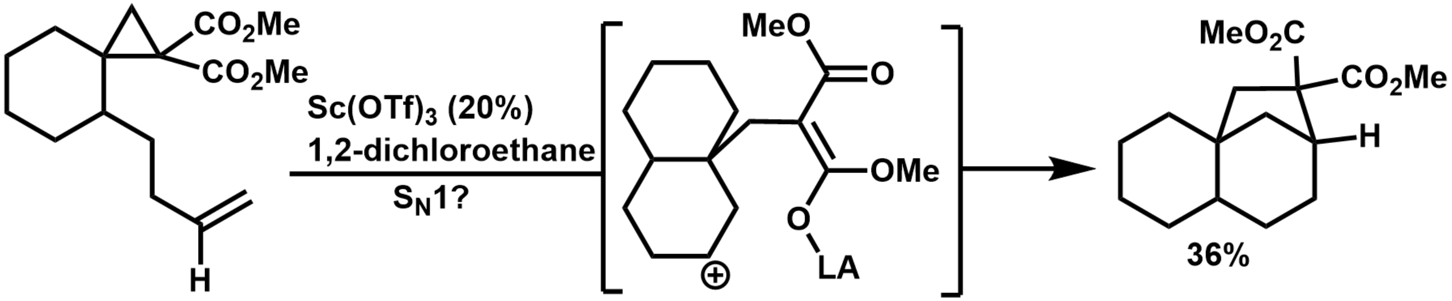
Substrate scope (2)

non-activated substrates



The first example of cycloaddition with non-activated alkene.





cleavage of highly stained cyclopropane may be a driving forse too.

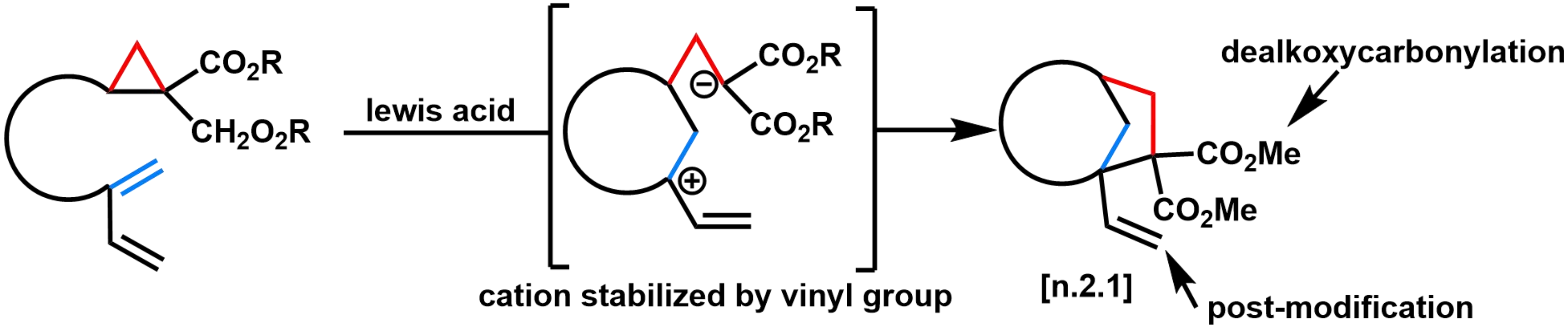
Stablization of carbenium is necessary for high reaction yield.

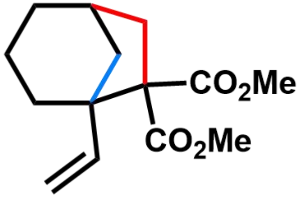
---

1) Zhu W. J.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 2032.

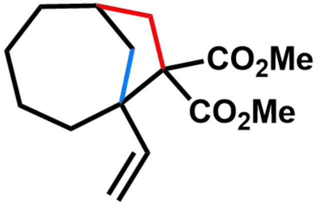
Substrate scope (2)

non-benzofused substrates activated with vinyl group

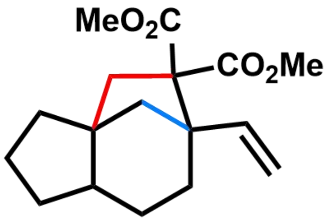




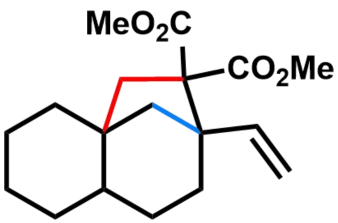
77%



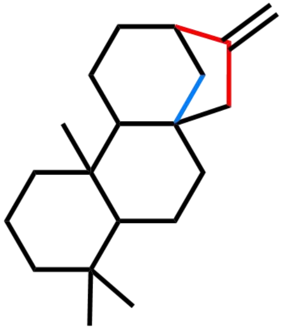
30%



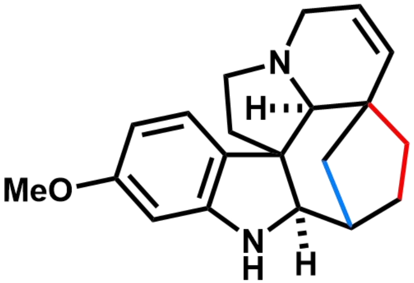
82%



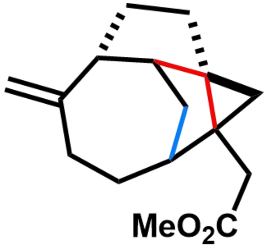
74%



phyllocladene



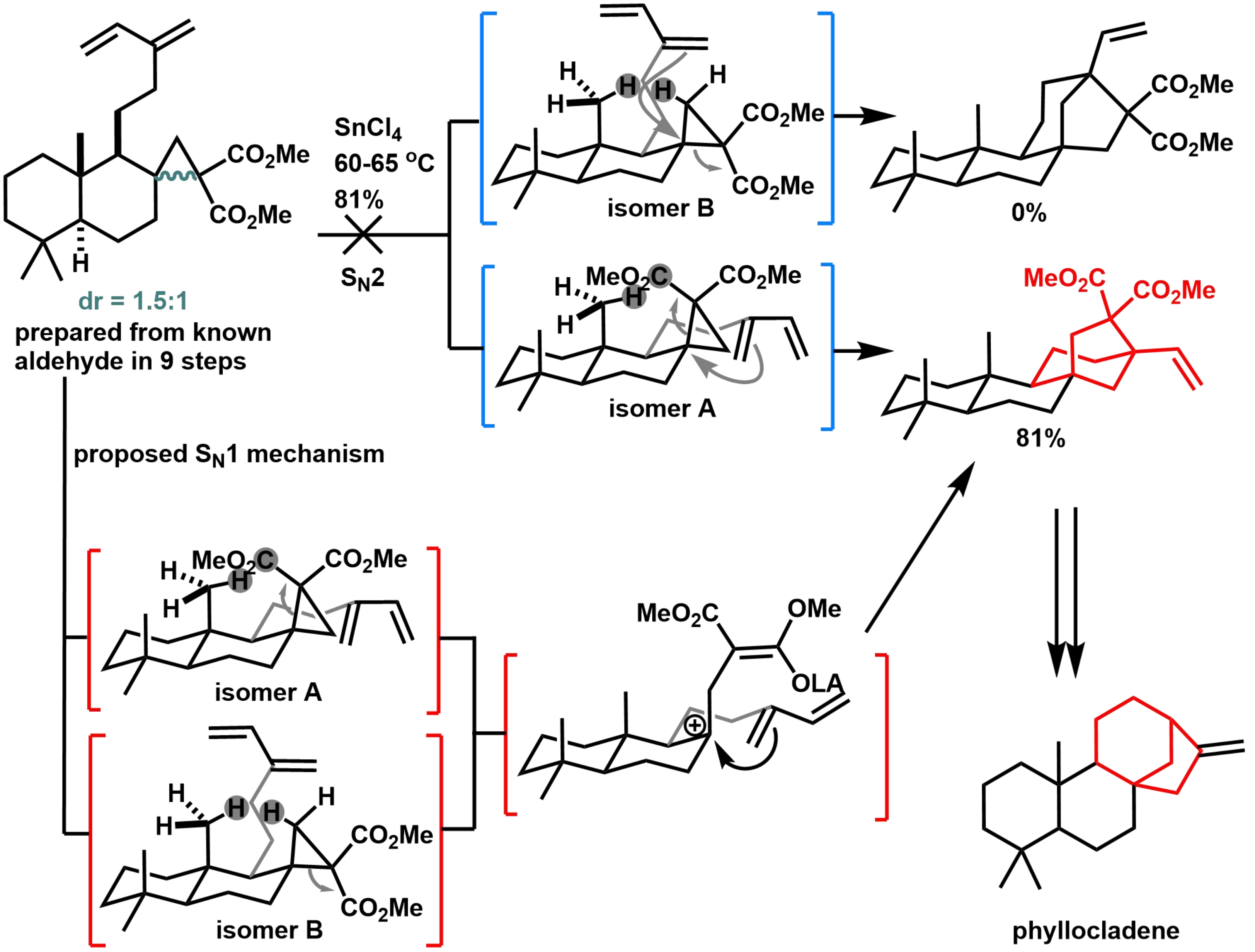
kopsifoline F



echinopine B

1) Zhu W. J.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 2032.

Synthesis of phyllocladene



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1) Zhu W. J.; Fang, J.; Liu, Y.; Ren, J.; Wang, Z. W. *Angew. Chem. Int. Ed.* **2013**, *52*, 2032.

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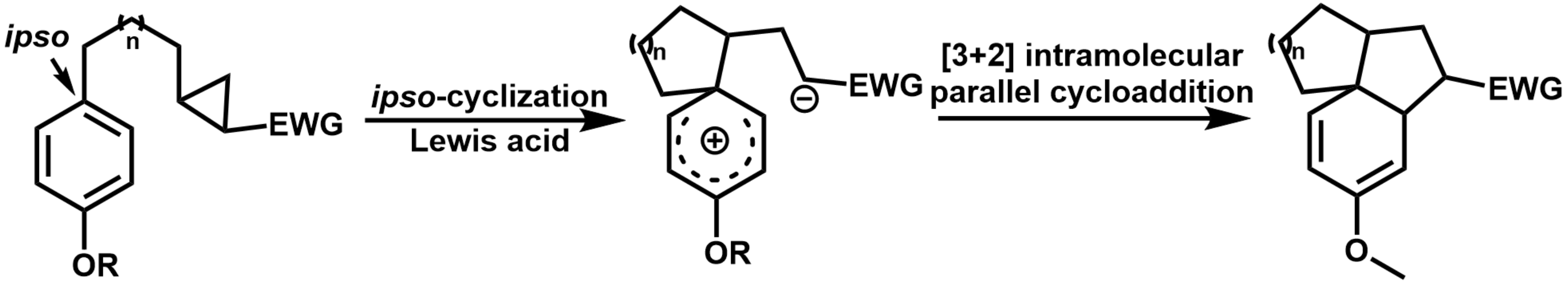
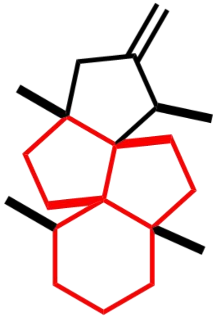
   (*Nat. Commun.* **2024**, *15*, 9206.**)**

dearomative (3+2) intramolecular parallel cycloaddition of donor-acceptor cyclopropane

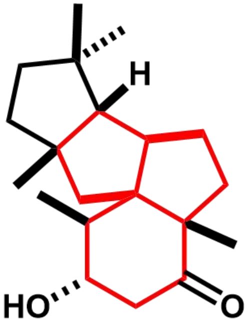
Design concept



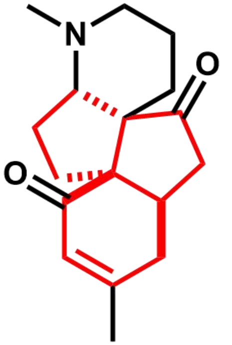
Overcome the inherent rearomatization of aryl compounds;
The angular tricycle skeletons are widely embedded in complex natural products



waihoensene
200919_PS_Yuma_Komori



conidiogenone
221029_LS_Manaka_Matsumoto



lycojaponicumin C
170715_PS_Keshu_Zhang

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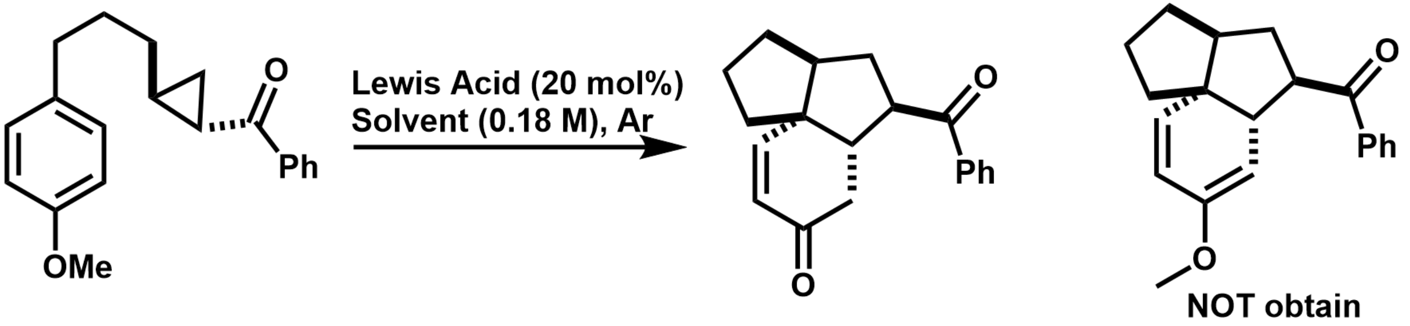
1) Sun, Y.; Huang, X. B.; Ren, J.; Wang, Z. W.; *Nat. Commun.* **2024**, *15*, 9206.

Optimization



Entry	Lewis Acid	Solvent	Temperature	time (h)	Yield [%]
1	$Sc(OTf)_3$	DCE	50	18	-
2	$Yb(OTf)_3$	DCE	50	18	-
3	$Cu(OTf)_3$	DCE	50	18	6
4	$Al(OTf)_3$	DCE	50	18	28
5	$AgSbF_6$	DCE	50	18	29
6	$FeCl_3$	DCE	50	18	28
7	$Bi(OTf)_3$	DCE	50	18	27
8	$Al(OTf)_3$	HFIP	50	18	67
9	$AgSbF_6$	HFIP	60	18	47
10	$FeCl_3$	HFIP	60	18	48
11	$Bi(OTf)_3$	HFIP	60	18	74
12*	$Bi(OTf)_3$	HFIP	60	2	79

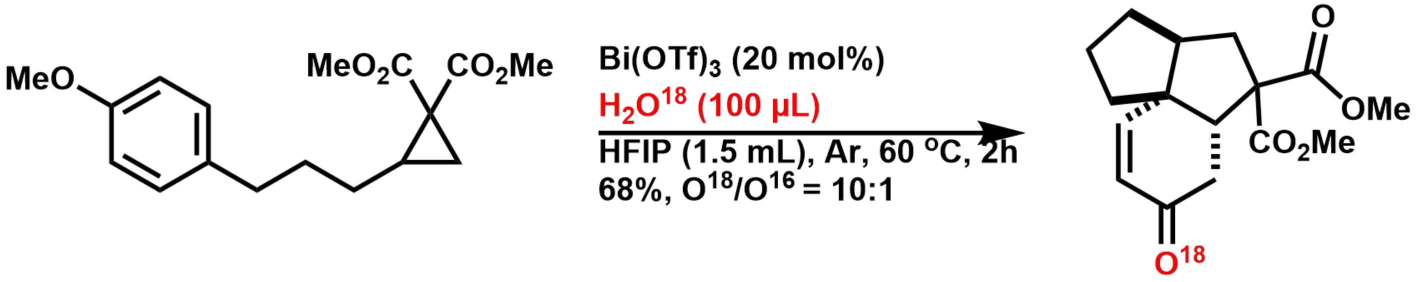
* Gram scale preparation: with addition of H_2O (1.5 eq),
2 grams of cyclopropane afforded 1.33 grams product.

---

1) Sun, Y.; Huang, X. B.; Ren, J.; Wang, Z. W.; *Nat. Commun.* **2024**, *15*, 9206.

Mechanism

1. O^{18}-labeled experiment



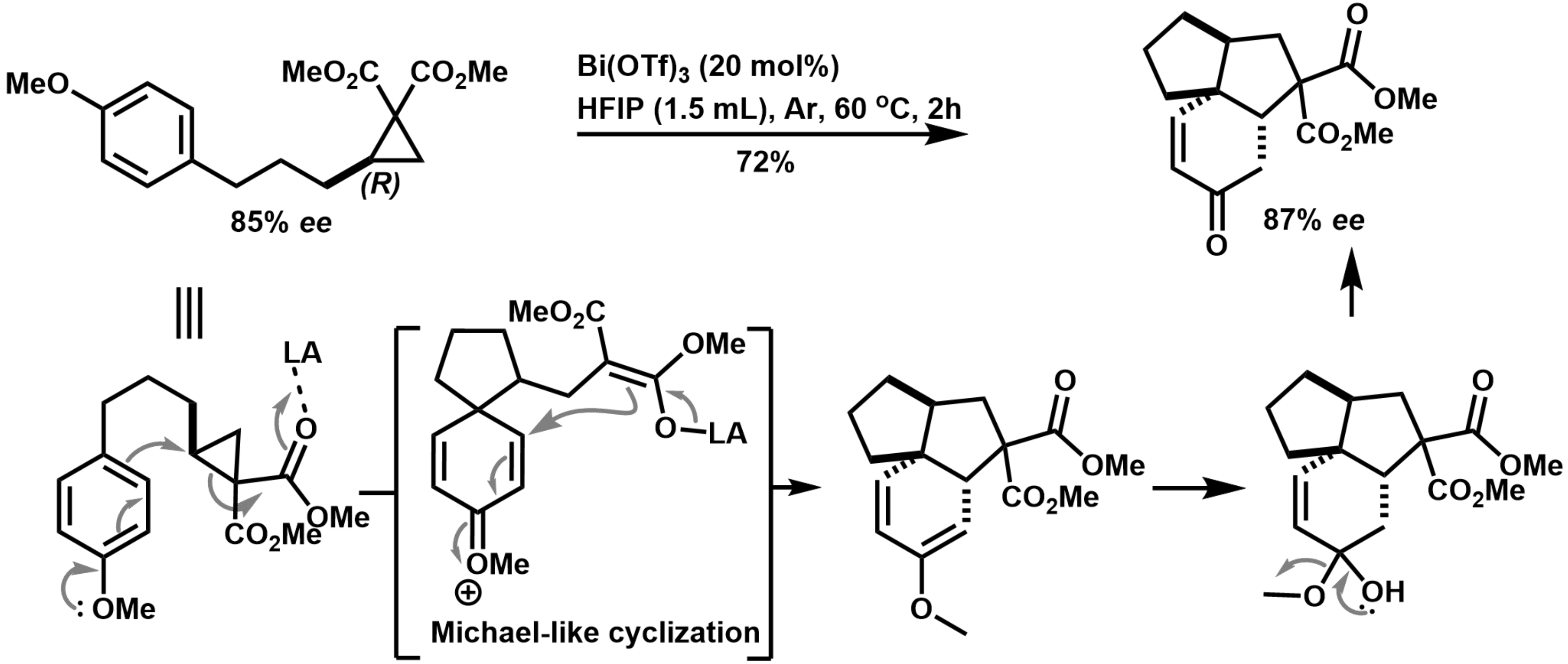
$Bi(OTf)_3$ (20 mol%)

H_2O^{18} (100 μL)

HFIP (1.5 mL), Ar, 60 °C, 2h

68%, O^{18}/O^{16} = 10:1

2. Asymmetric experiment



$Bi(OTf)_3$ (20 mol%)

HFIP (1.5 mL), Ar, 60 °C, 2h

72%

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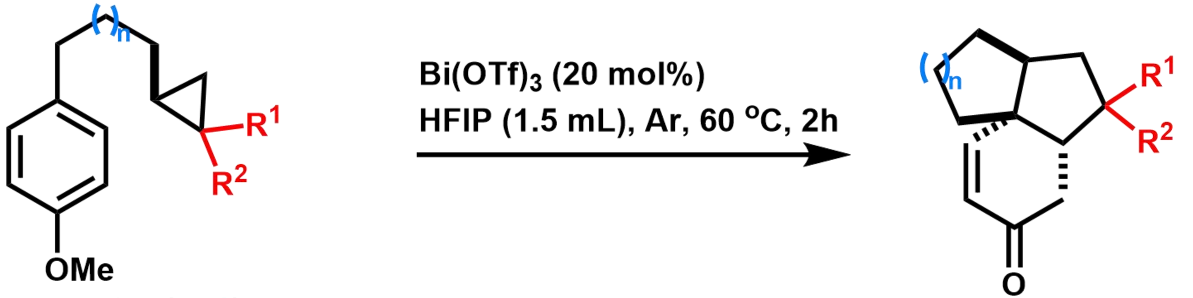
1) Sun, Y.; Huang, X. B.; Ren, J.; Wang, Z. W.; *Nat. Commun.* **2024**, *15*, 9206.

Substrate scope (1)

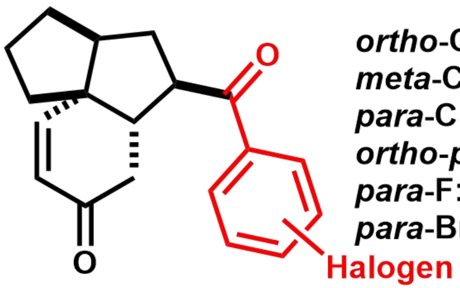


$Bi(OTf)_3$ (20 mol%)

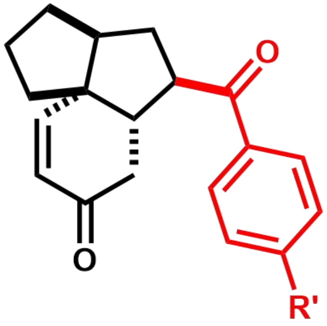
HFIP (1.5 mL), Ar, 60 °C, 2h

1. variation on acceptor (*n*=1)

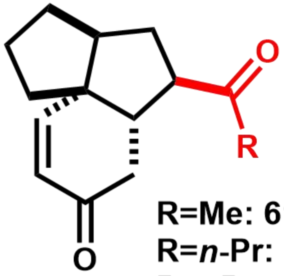
1.1 *mono*-acceptor on cyclopropane (R^2=H)



***ortho*-Cl: 71%**
***meta*-Cl: 79%**
***para*-Cl: 80%**
***ortho-para*-2Cl: 80%**
***para*-F: 66%**
***para*-Br: 73%**

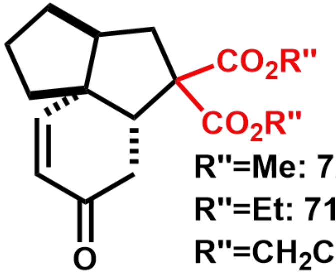


R'=Me: 75%
R'=CF_3: 74%
R'=OCF_3: 78%
R'=OMe: 78%
R'=Ph: 63%
R'=NO_2: 92%
R'=-SO_2Me: 86%

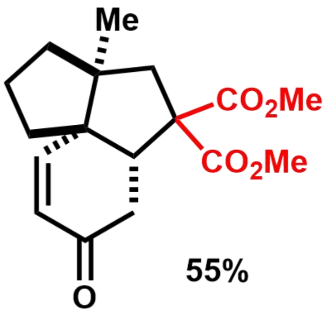


R=Me: 61%
R=*n*-Pr: 52%
R=*t*-Bu: 61%

1.2 *double*-acceptor on cyclopropane (R^1=R^2=CO_2R)

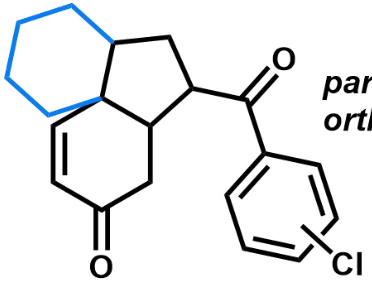


R''=Me: 72%
R''=Et: 71%
R''=CH_2CF_3: 62%



55%

2. variation on tether (*n*=2)



***para*-Cl: 49%**
***ortho-para*-Cl: 55%**

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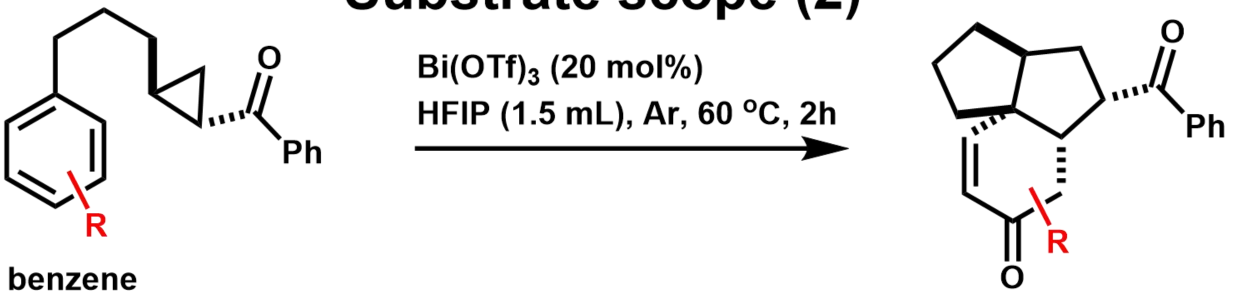
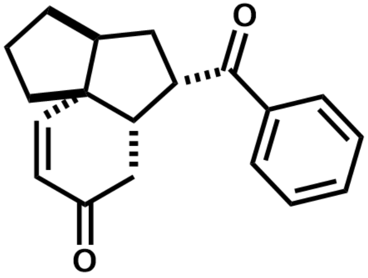
1) Sun, Y.; Huang, X. B.; Ren, J.; Wang, Z. W.; *Nat. Commun.* **2024**, *15*, 9206.

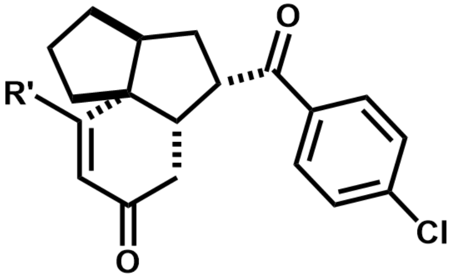
Substrate scope (2)



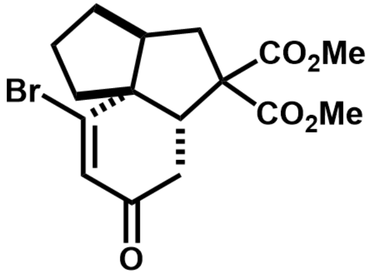
3. variation on benzene



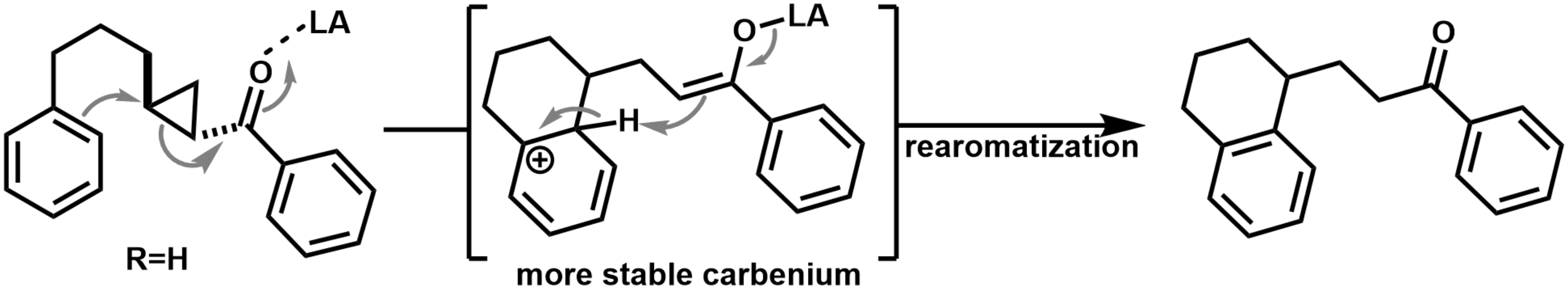
R=*para*-OCH$_2$CH$_2$Br: 74%
R=*para*-OH:61%



R'=Me: 69%
R'=OMe: 26%



84%



In absence of directing group on benzene, only the *ortho*-Friedel-Crafts product was obtained.

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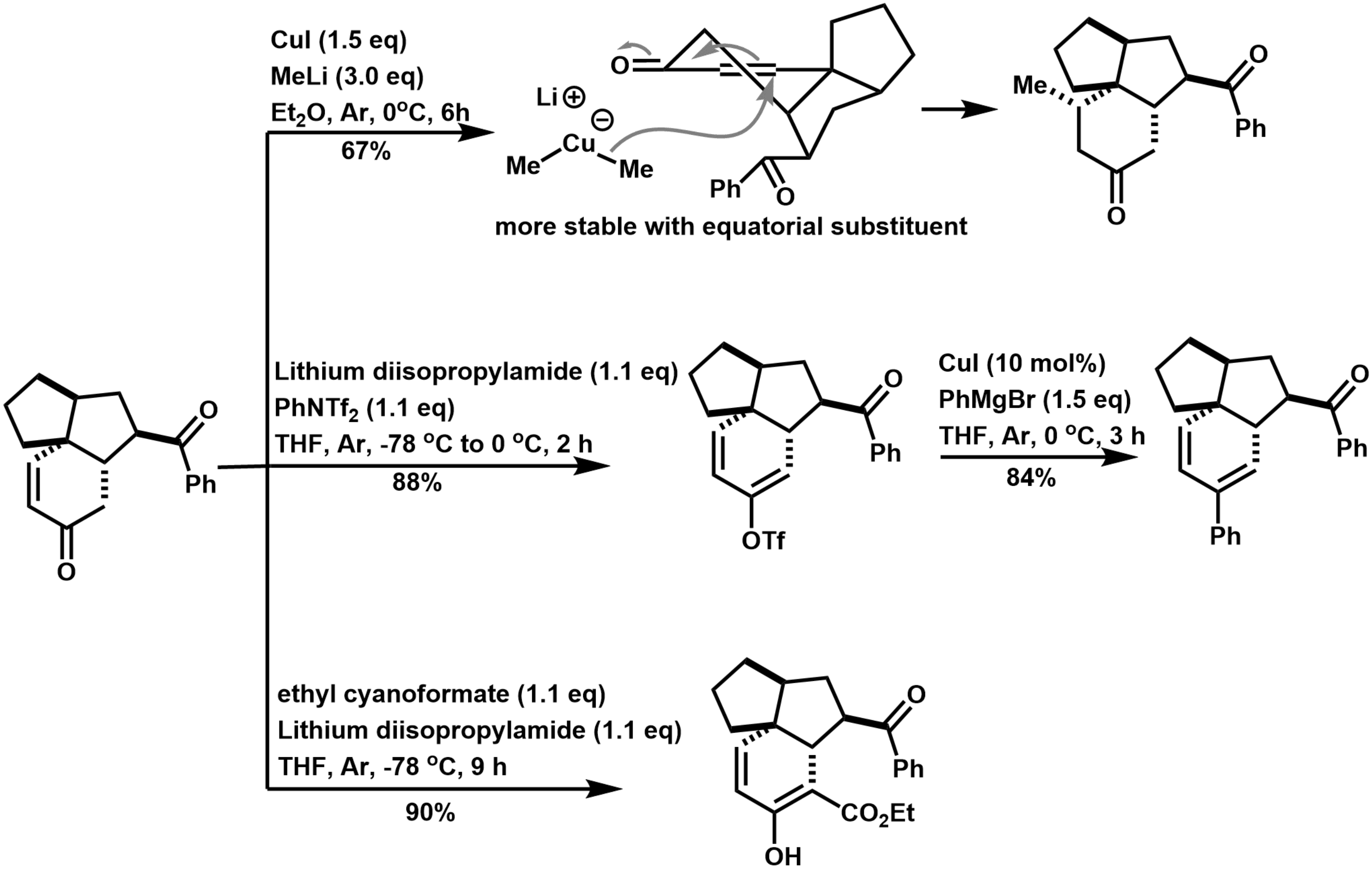
1) Sun, Y.; Huang, X. B.; Ren, J.; Wang, Z. W.; *Nat. Commun.* **2024**, *15*, 9206.

Post-functionalization (1)

ring decoration



CuI (1.5 eq)
MeLi (3.0 eq)
Et_2O, Ar, 0^{o}C, 6h
67%

more stable with equatorial substituent

Lithium diisopropylamide (1.1 eq)
$PhNTf_2$ (1.1 eq)
THF, Ar, -78 ^{o}C to 0 ^{o}C, 2 h
88%

CuI (10 mol%)
PhMgBr (1.5 eq)
THF, Ar, 0 ^{o}C, 3 h
84%

ethyl cyanoformate (1.1 eq)
Lithium diisopropylamide (1.1 eq)
THF, Ar, -78 ^{o}C, 9 h
90%

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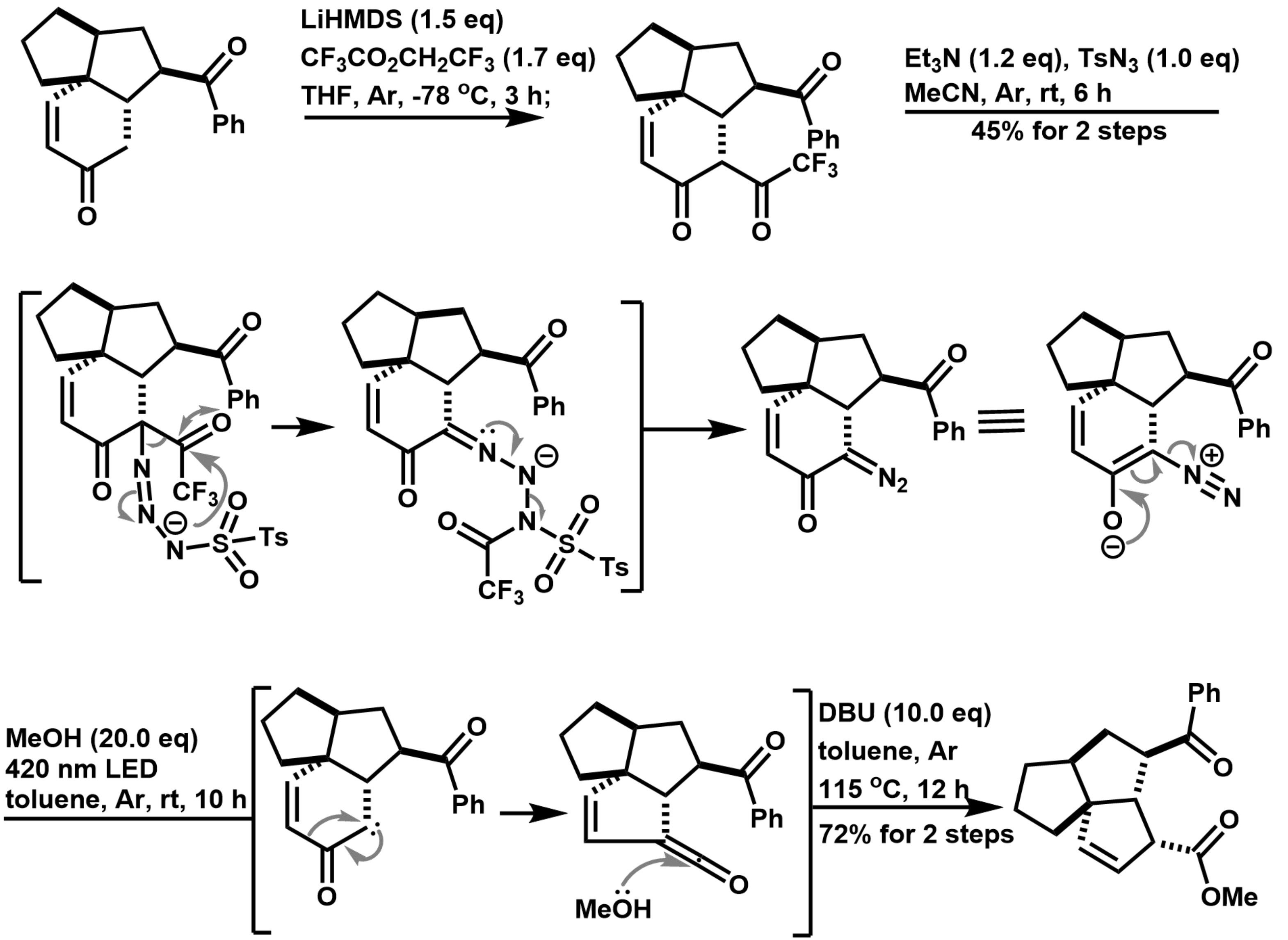
1) Sun, Y.; Huang, X. B.; Ren, J.; Wang, Z. W.; *Nat. Commun.* **2024**, *15*, 9206.

Post-functionalization (2)

Construction of the 5-5-5-tricyclic carbocycles via ring contraction



LiHMDS (1.5 eq)
$CF_3CO_2CH_2CF_3$ (1.7 eq)
THF, Ar, -78 ^oC, 3 h;

Et_3N (1.2 eq), TsN_3 (1.0 eq)
MeCN, Ar, rt, 6 h
45% for 2 steps

MeOH (20.0 eq)
420 nm LED
toluene, Ar, rt, 10 h

DBU (10.0 eq)
toluene, Ar
115 ^oC, 12 h
72% for 2 steps

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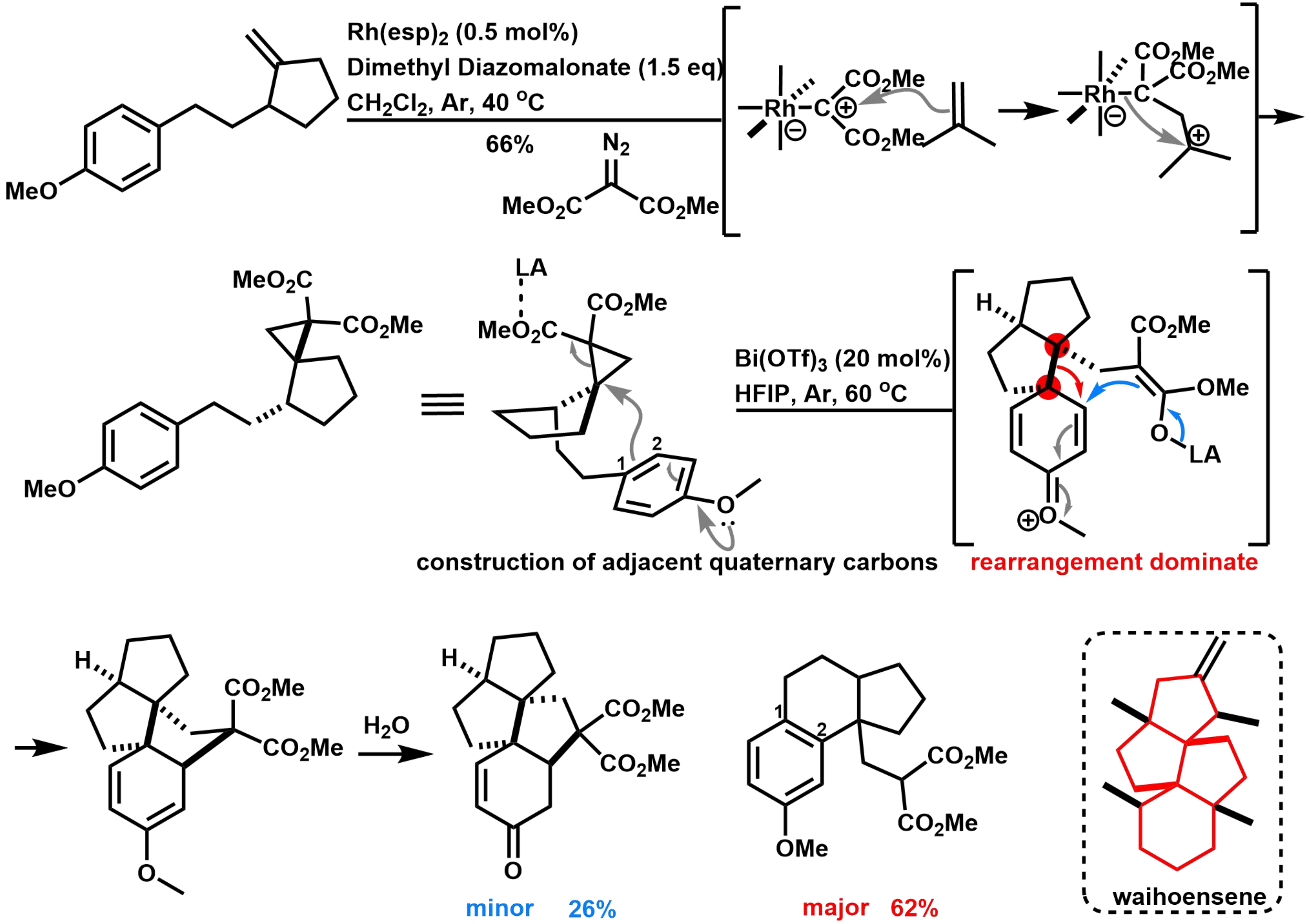
1) Sun, Y.; Huang, X. B.; Ren, J.; Wang, Z. W.; *Nat. Commun.* **2024**, *15*, 9206.

Post-functionalization (3)

Construction of the 5-5-5-6-tetracyclic carbocycles via tetra-substituted cyclopropane



construction of adjacent quaternary carbons

rearrangement dominate

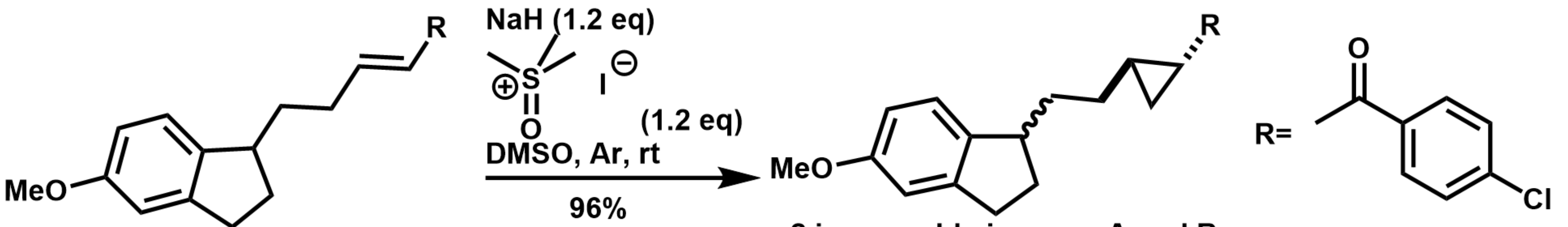
minor 26%

major 62%

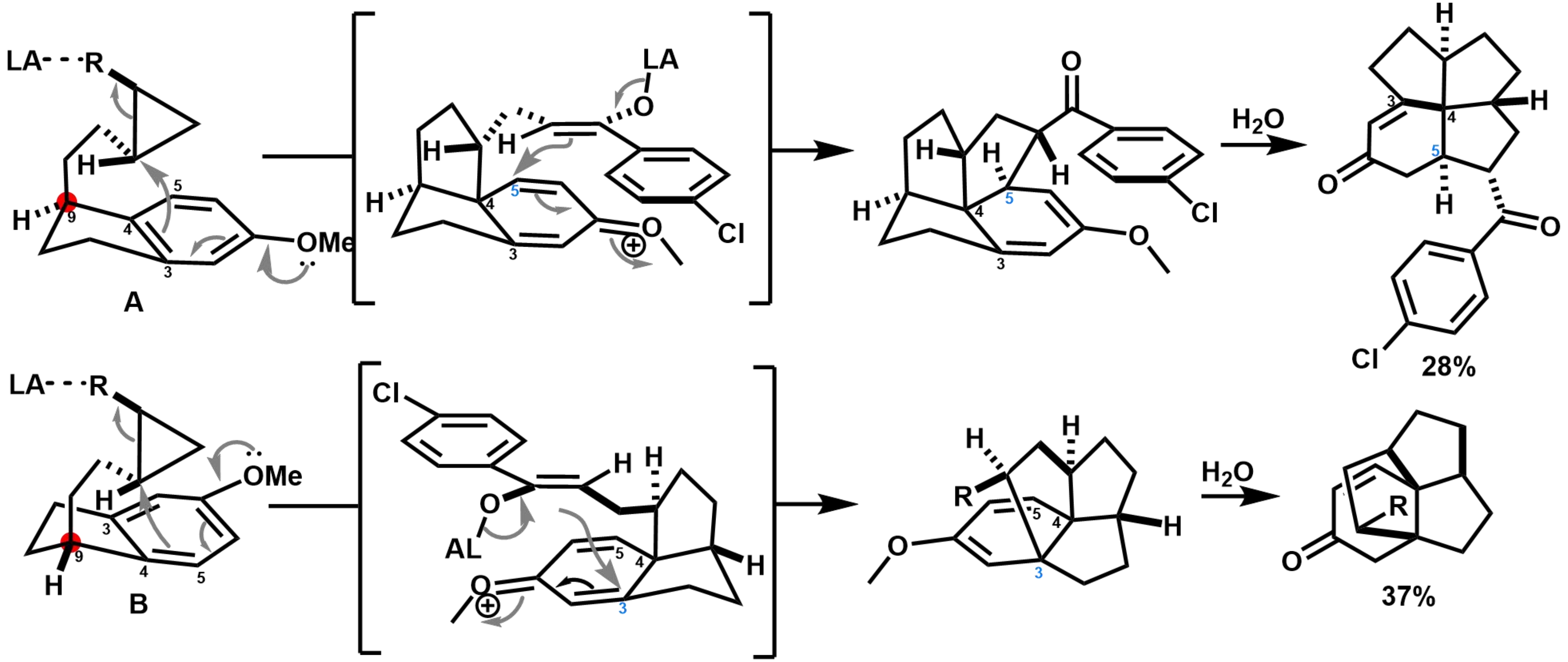
1) Sun, Y.; Huang, X. B.; Ren, J.; Wang, Z. W.; *Nat. Commun.* **2024**, *15*, 9206.

Post-functionalization (4)

Construction of the 5-5-5-6-tetracyclic carbocycles



2 inseperable isomers A and B
ratio not mentioned



Condition: Bi(OTf)$_3$ (20 mol%), HFIP, Ar, 60 ^{o}C, 2 h
Skeleton types are subsrate dependent, chiral center at C9 direct different regio-selectivity in the second cyclization.

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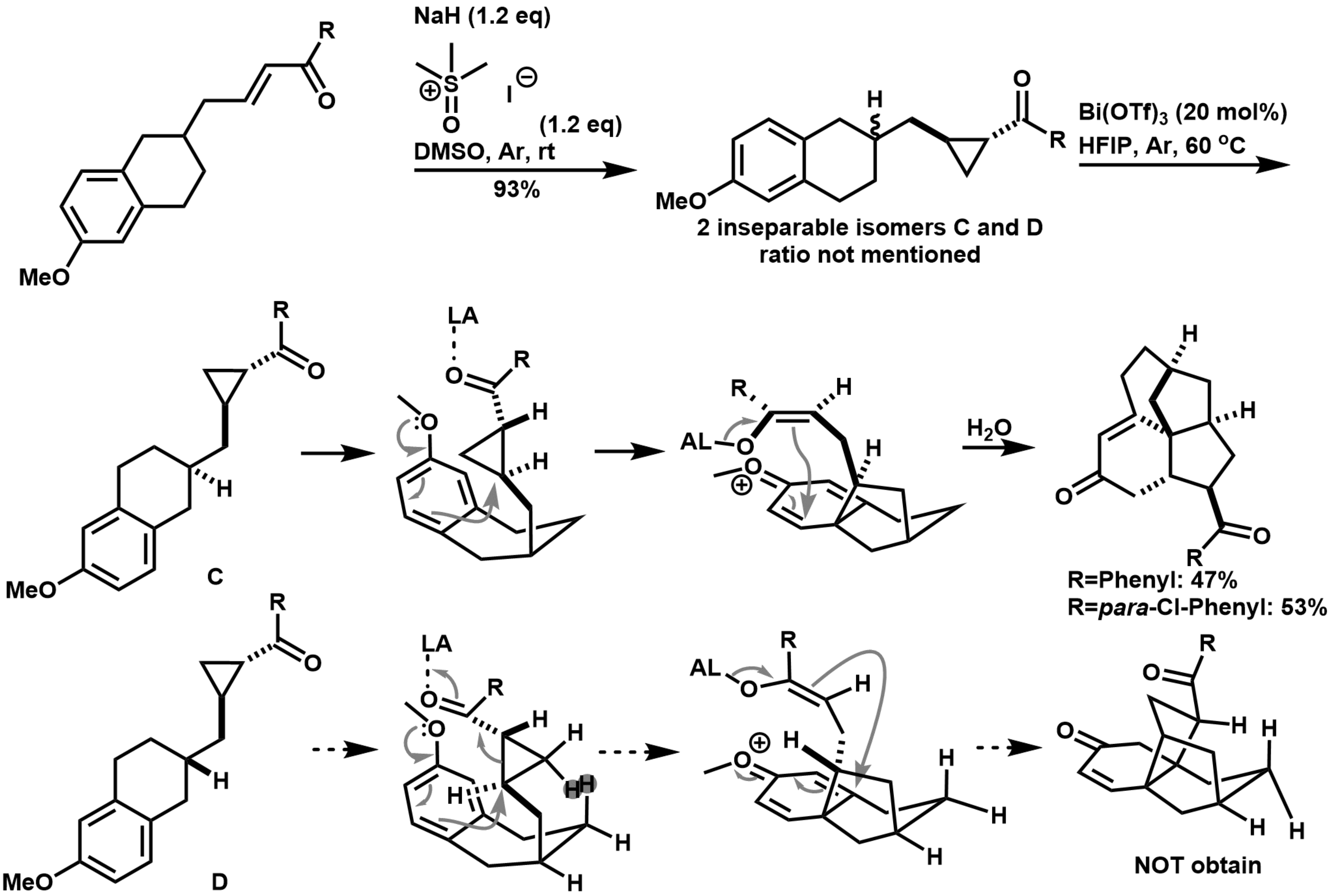
1) Sun, Y.; Huang, X. B.; Ren, J.; Wang, Z. W.; *Nat. Commun.* **2024**, *15*, 9206.

Post-functionalization (5)

Construction of the 5-5-6-6-tetracyclic carbocycles.



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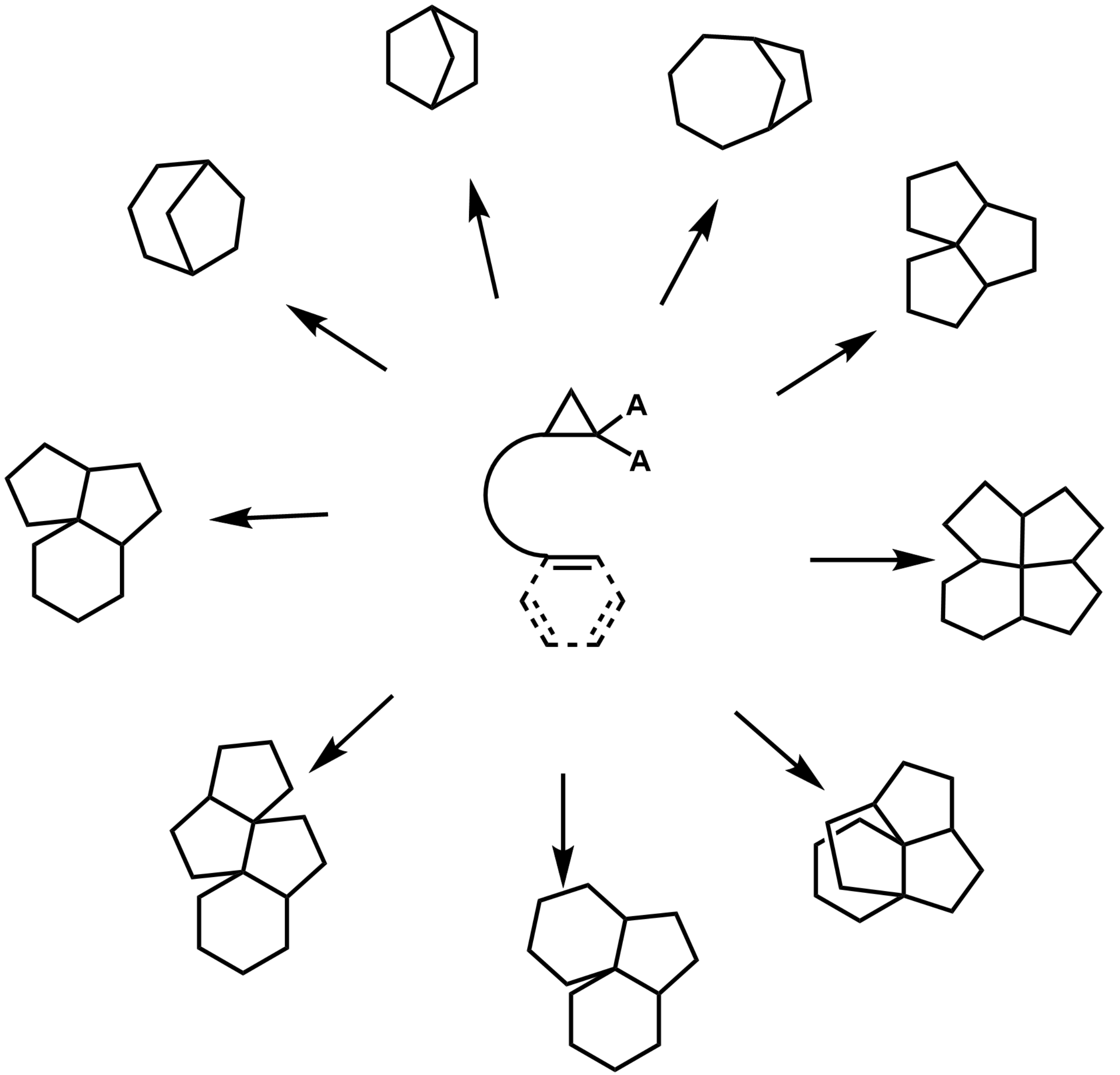
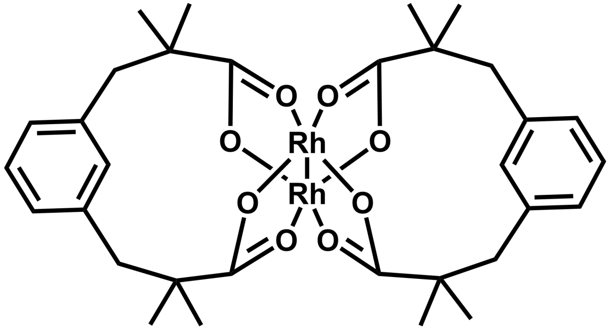
1) Sun, Y.; Huang, X. B.; Ren, J.; Wang, Z. W.; *Nat. Commun.* **2024**, *15*, 9206.

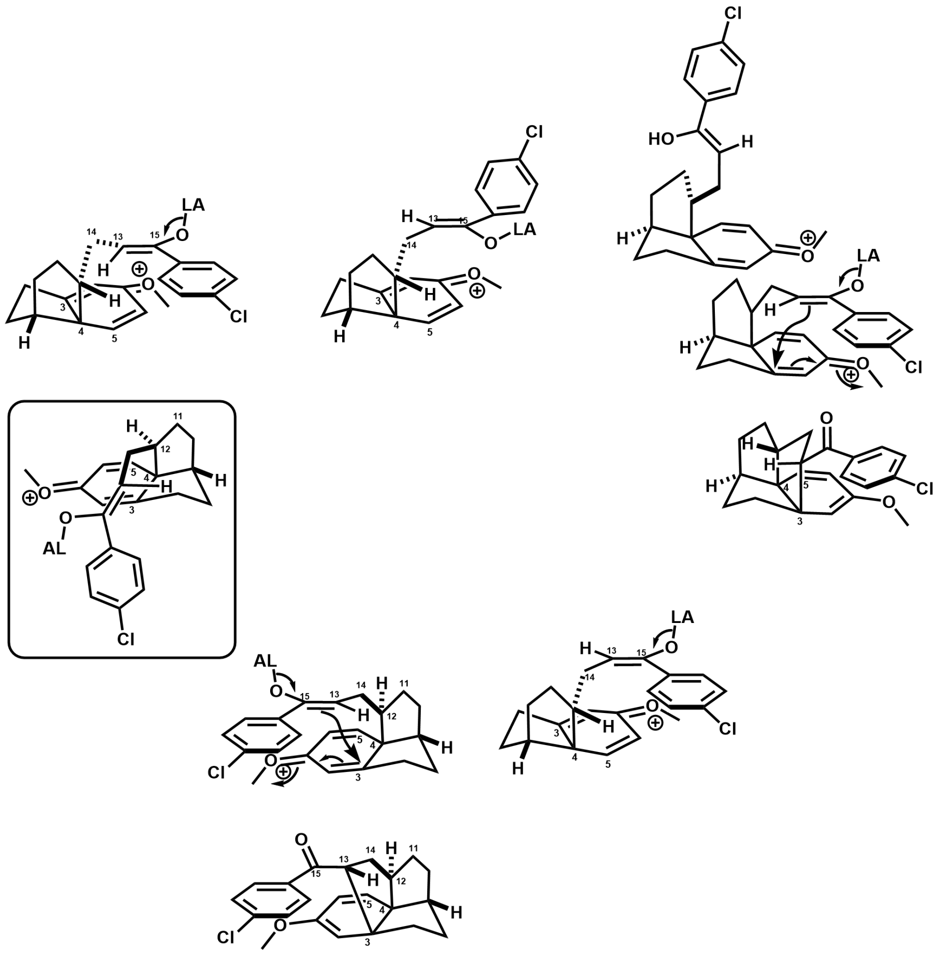
Summary



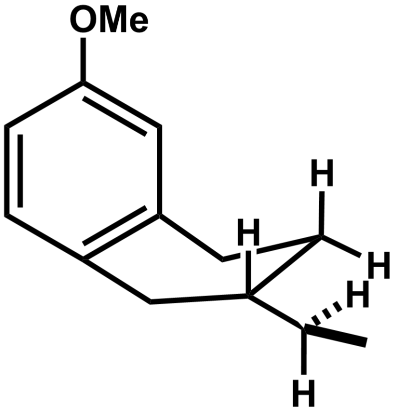
Thank you!

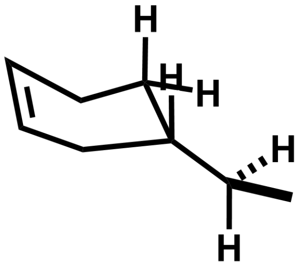


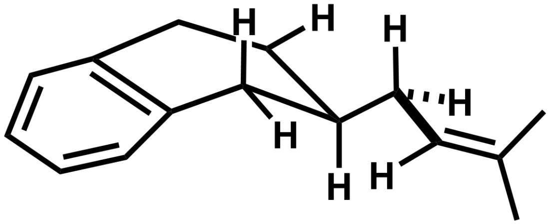
Rh(esp)$_2$



LA
O
14
13
15
H
Cl
3
4
5
H
H
O
LA
HO
H
O
LA
Cl
H
H
O
Cl
11
12
AL
O
Cl


OMe
H
H
H
H
H


H
H
H
H
H


H
H
H
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H