

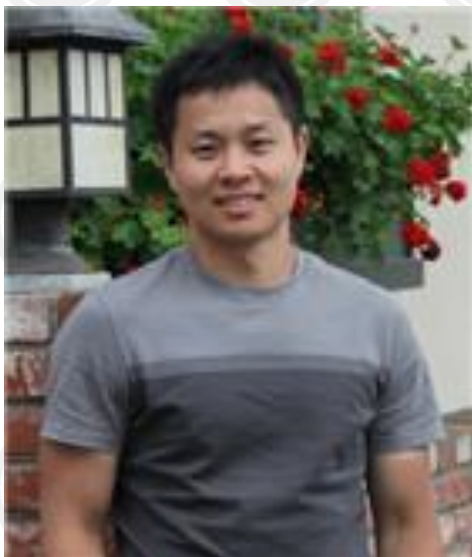
蔡泉课题组工作介绍

——2-吡喃酮的不对称DA反应及其在全合成中应用



1852946 · Shenghan Cai

AUTHOR



蔡泉

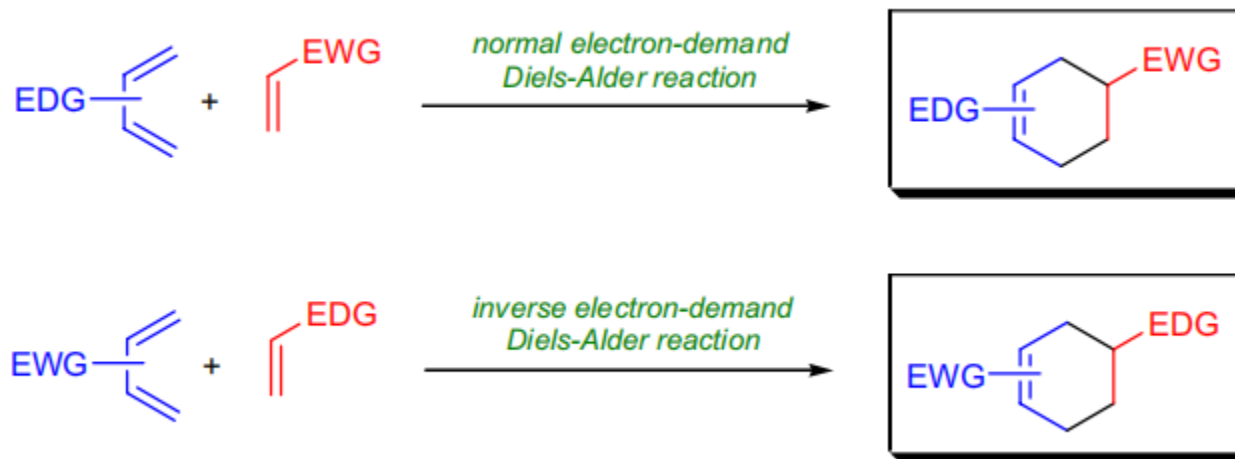
Education

- 2003.9-2007.7 本科 华东理工大学
- 2007.9-2012.7 博士 上海有机所 (Shu-Li You)
- 2012.9-2013.7 博士后 Scripps研究所(K. C. Nicolaou)
- 2013.8-2016.3 博士后 Rice大学(K. C. Nicolaou)
- 2016.4-2017.6 博士后 哈佛大学 Dana-Farber癌症研究所 (Prof. Nathanael Gray)
- From 2017.6 复旦大学 青年研究员 博士生导师

Research interests

- 不对称催化反应
- 活性天然产物和药物分子合成
- 药物化学及化学生物学研究

BACKGROUND



EDG (electron-donating group)
= alkyl, O-alkyl, N-alkyl, etc.

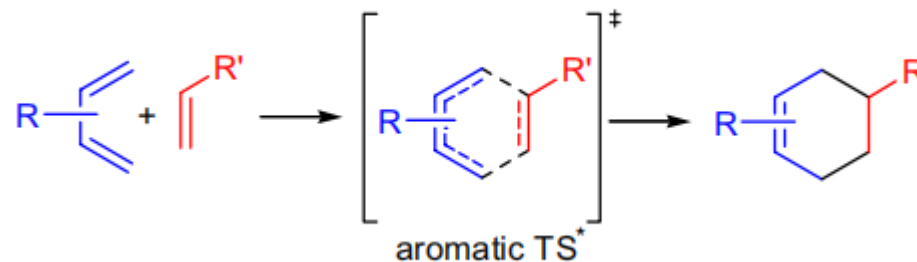
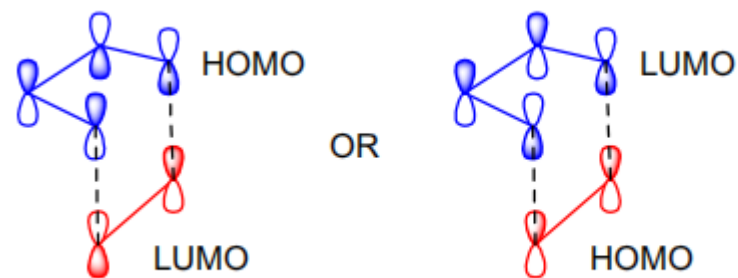
EWG (electron-withdrawing group) = CN, NO₂, CHO, COR, COAr, CO₂H, CO₂R, COCl etc.

NEDDA:

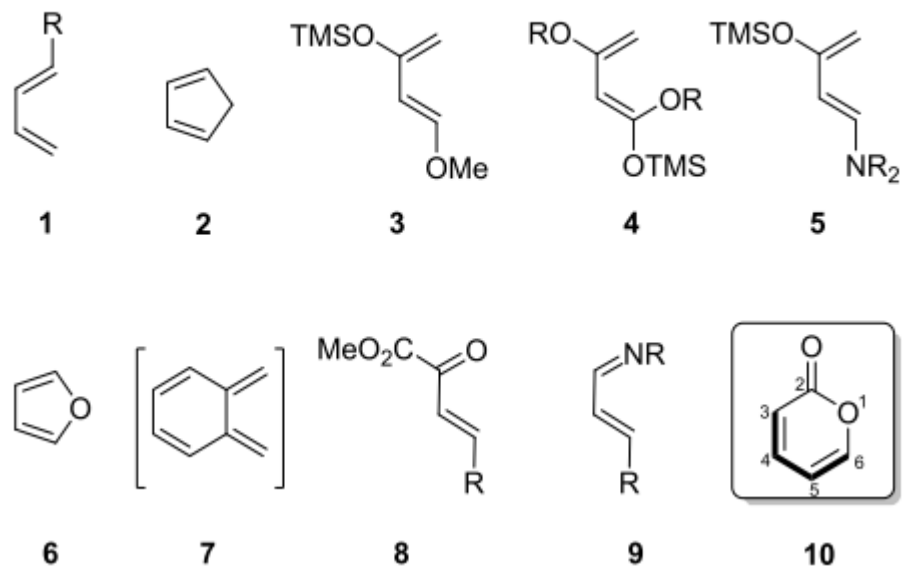
IEDDA:

富电子共轭双烯+缺电子烯炔

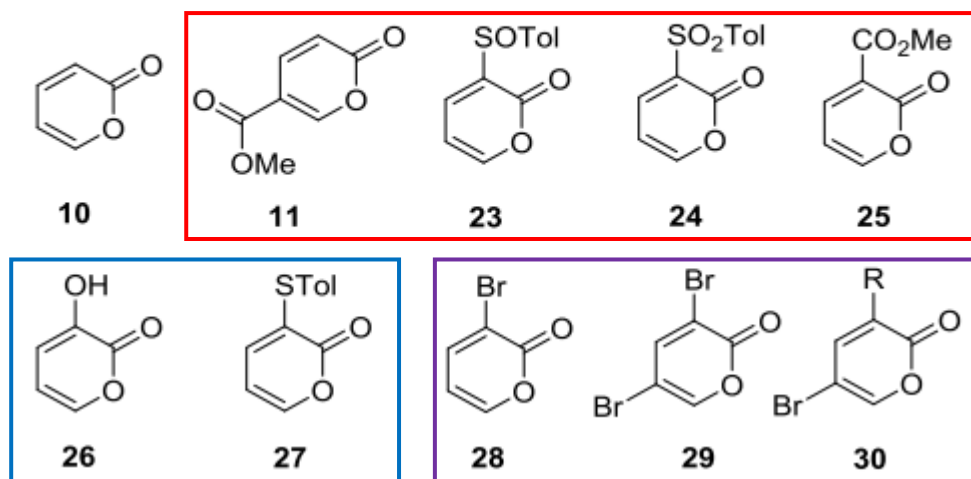
缺电子共轭双烯+富电子烯炔



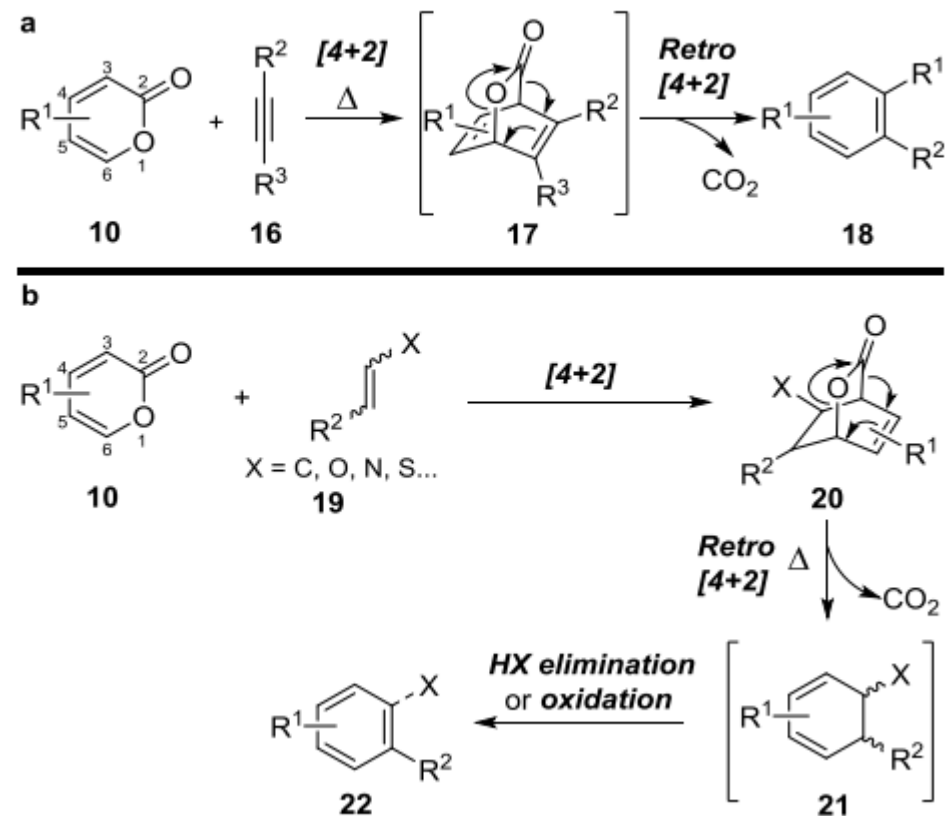
Scheme 1 Representative diene component of Diels-Alder reaction

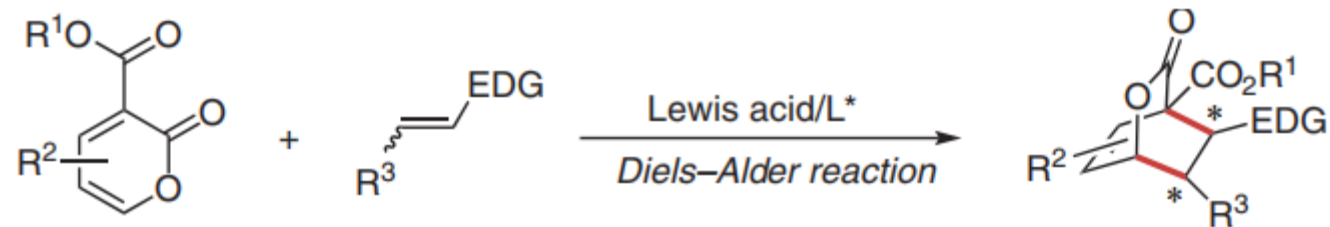


Scheme 4 Representative substituted 2-pyrones utilized in Diels-Alder reaction



Scheme 3 Diels-Alder reaction of 2-pyrone with alkyne or alkene

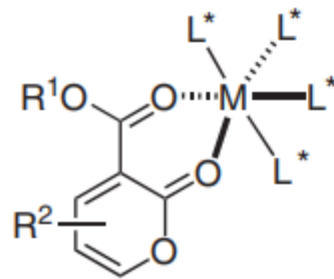




Advantages

- Readily available reaction partners
- Various types of electron-rich dienophiles
- Inverse-electron-demand fashion

via



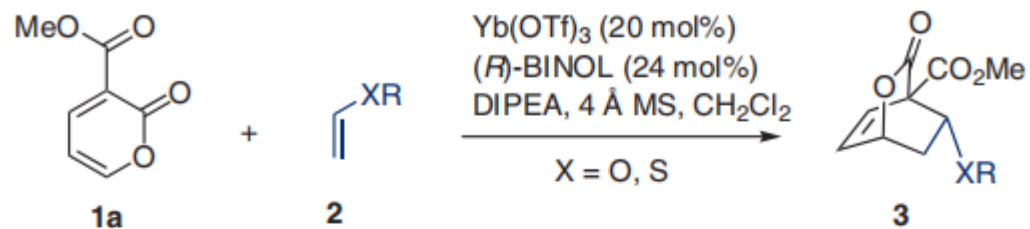
Advantages

- Bridged lactone
- Highly functionalized
- Multiple chiral centers
- Excellent control of stereochemistry

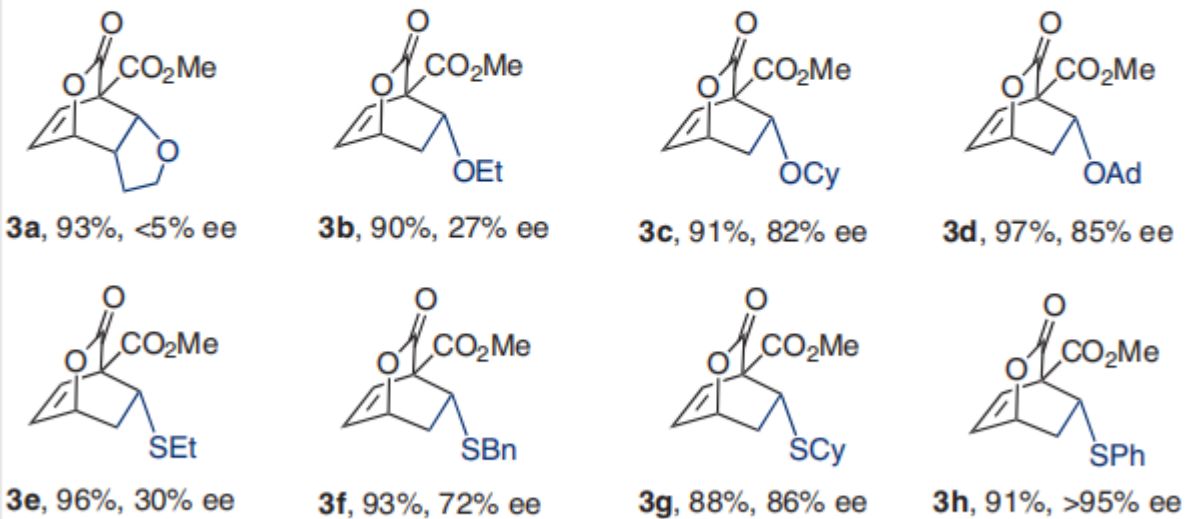
Scheme 3 Enantioselective inverse-electron-demand Diels-Alder (IED-DA) reaction of 2-pyrones with Lewis acid catalysis

1. 镍催化的不对称IEDDA反应

• Markó (1994)



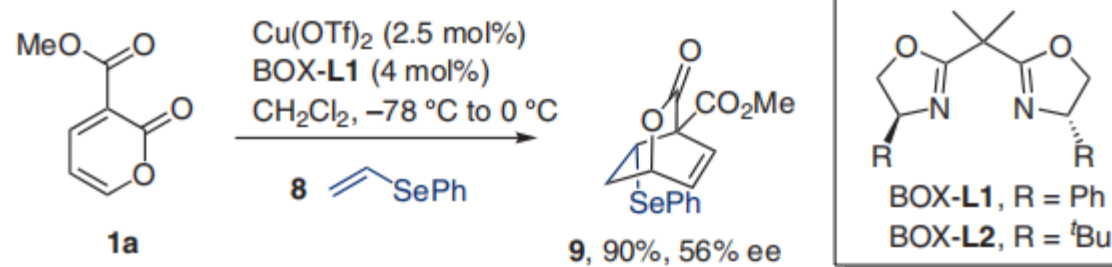
Selected examples:



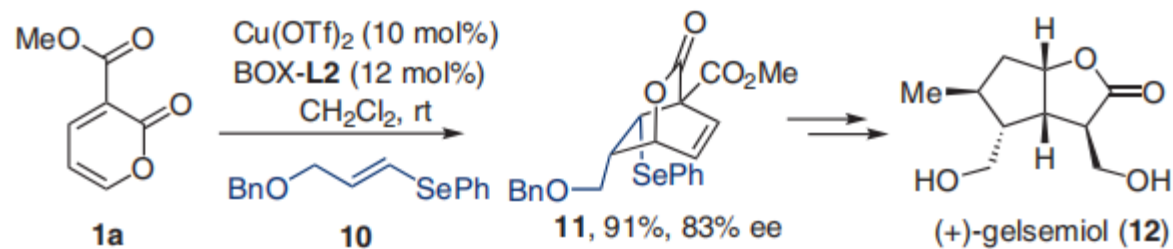
Scheme 4 Ytterbium-catalyzed enantioselective inverse-electron-demand Diels-Alder reactions of 2-pyrone

2. 铜催化的不对称IEDDA反应

• Markó (2000)



• Gademann (2013)



Scheme 6 Copper-catalyzed asymmetric inverse-electron-demand Diels-Alder reactions of 2-pyrone

Asymmetric Catalysis

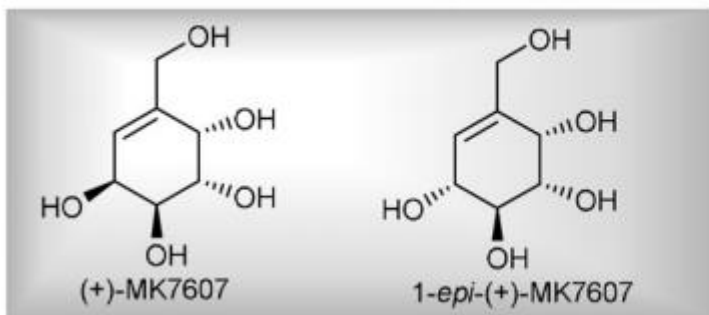
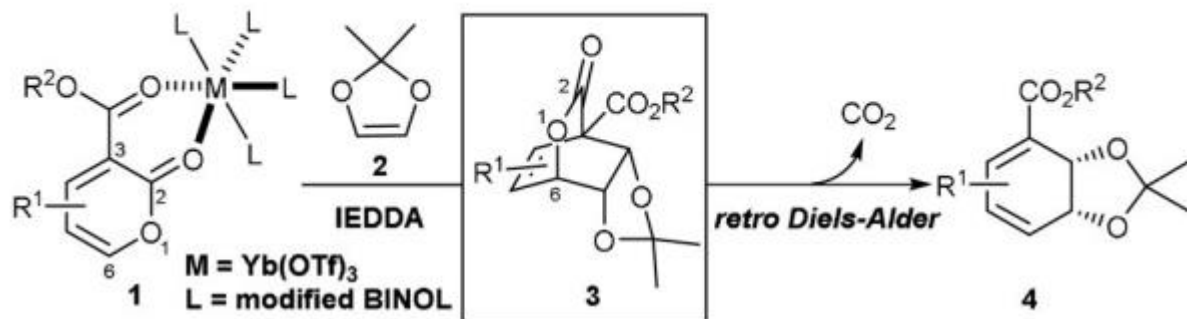
International Edition: DOI: 10.1002/anie.201908284

German Edition: DOI: 10.1002/ange.201908284

Enantioselective Synthesis of Arene *cis*-Dihydrodiols from 2-Pyrones

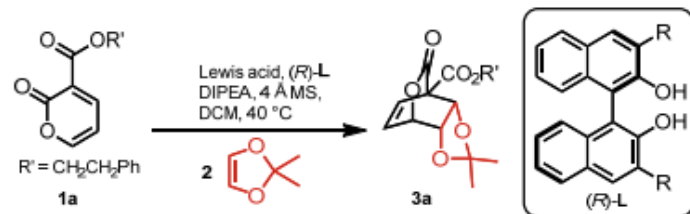
Xiao-Wei Liang⁺, Yunlong Zhao⁺, Xu-Ge Si, Meng-Meng Xu, Jia-Hao Tan, Zhi-Mao Zhang, Cheng-Gong Zheng, Chao Zheng, and Quan Cai*

c This work: catalytic asymmetric synthesis of arene *cis*-dihydrodiols from 2-pyrones



- high yields, high ee
- wide substrate scope
- cascade reaction for 6-substituted pyrones
- highly valuable in natural product syntheses

Table 1. Optimization of reaction conditions for the initial Diels-Alder reaction

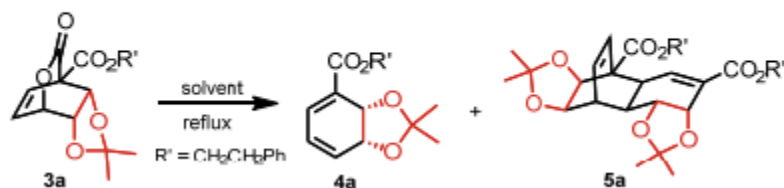


Entry ^a	Lewis acid	(R)-L, R	<i>t</i> [h]	Yield [%] ^b	<i>ee</i> [%] ^c
1	Yb(OTf) ₃	L1 , R = H	24	58	40
2	Yb(OTf) ₃	L2 , R = 2,4,6-(^{<i>i</i>} Pr) ₃ -C ₆ H ₂	48	10	0
3	Yb(OTf) ₃	L3 , R = 9-anthryl	48	11	1
4	Yb(OTf) ₃	L4 , R = Ph ₃ Si	48	15	0
5	Yb(OTf) ₃	L5 , R = Cl	20	74	79
6	Yb(OTf) ₃	L8 , R = I	10	85	94
7	Yb(OTf) ₃	L6 , R = Br	6	87	94
8	Sc(OTf) ₃	L6 , R = Br	22	67	12
9	Y(OTf) ₃	L6 , R = Br	23	76	58
10	Sm(OTf) ₃	L6 , R = Br	7	81	72
11	Eu(OTf) ₃	L6 , R = Br	8	61	73
12	Ho(OTf) ₃	L6 , R = Br	4	67	80
13	Er(OTf) ₃	L6 , R = Br	5	47	74
14	Tm(OTf) ₃	L6 , R = Br	4	69	84
15	Yb(OTf) ₃	L9 , R = 4-F-C ₆ H ₄	11	85	94
16	Yb(OTf) ₃	L10 , R = 3,5-F ₂ -C ₆ H ₃	15	83	97
17	Yb(OTf) ₃	L11 , R = 3,5-(CF ₃) ₂ -C ₆ H ₃	3	74	95
18	Yb(OTf) ₃	L7 , R = C ₆ F ₅	3	85	98
19 ^d	Yb(OTf) ₃	L7 , R = C ₆ F ₅	3	87	98

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), 20 mol% Lewis acid, 24 mol% (R)-L, 48 mol% DIPEA, 4 Å molecular sieves (50 mg) in DCM (1.0 mL) at 40°C. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC on a chiral stationary phase. [d] 10 mol% Yb(OTf)₃, 12 mol% (R)-L7, 24 mol% DIPEA, Conc. = 0.4 M.

增加催化剂的刘易斯酸度，可能有利于立体控制

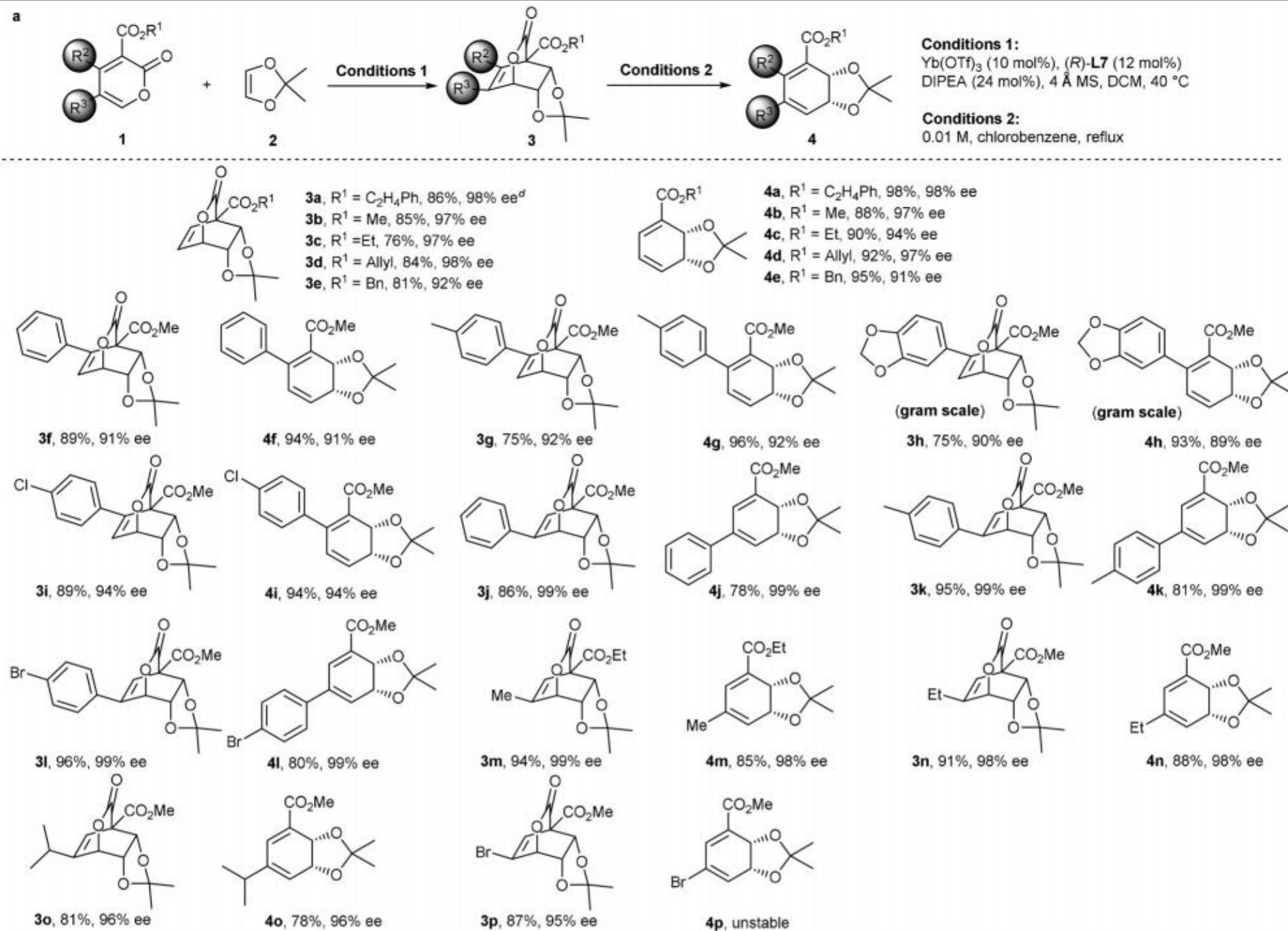
Table 2. Optimization of reaction conditions for the retro Diels-Alder extrusion of CO₂

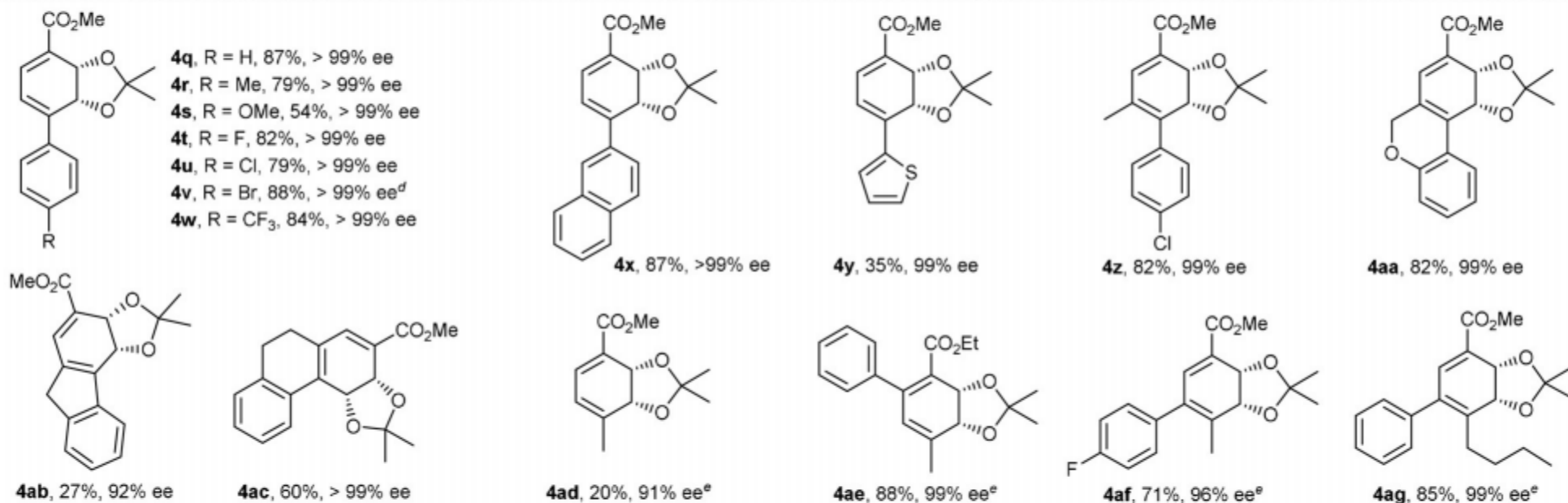
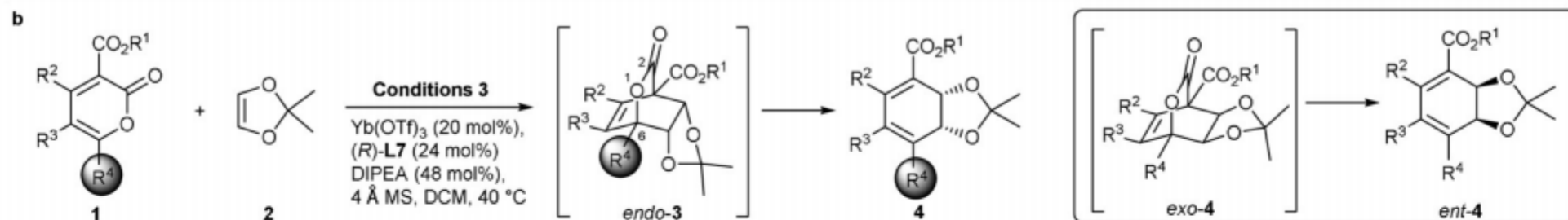


Entry	solvent	Conc. [M]	T [h]	Yield [%] ^a		<i>ee</i> [%] ^b	
				4a/5a		4a/5a	
1	toluene	0.5	24	--/91		--/>99	
2	toluene	0.1	24	26/70		93/>99	
3	toluene	0.05	24	56/28		97/>99	
4	toluene	0.01	24	79/20		98/>99	
5	1,4-dioxane	0.01	24	trace		--	
6	<i>o</i> -xylene	0.01	3	91		98	
7	<i>m</i> -xylene	0.01	5	92		98	
8	<i>p</i> -xylene	0.01	5	93		98	
9	ClC ₆ H ₅	0.01	4	98		98	

[a] Yield of isolated product. [b] Enantiomeric excess was determined by HPLC on a chiral stationary phase.

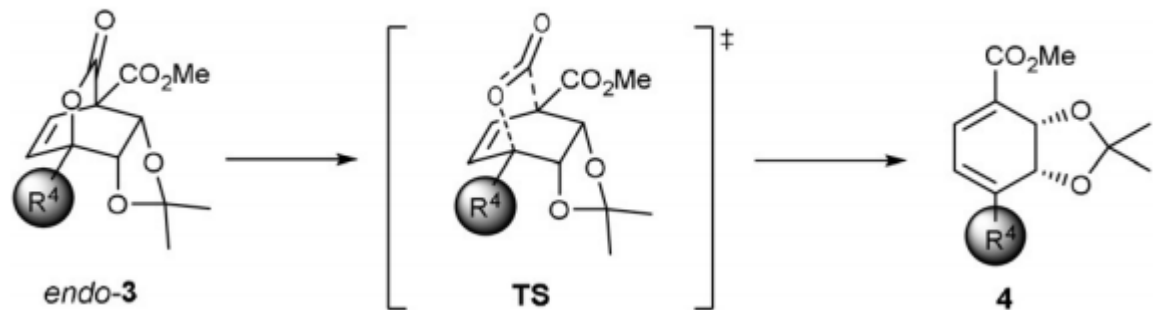
Table 2: Substrate scope with respect to substituted 2-pyrones.^[a,b,c]





[a] Reaction conditions 1: **1** (0.2 mmol), **2** (0.6 mmol), 10 mol % Yb(OTf)₃, 12 mol % (*R*)-**L7**, 24 mol % DIPEA, 4 Å molecular sieves (50 mg) in DCM (1.0 mL) at 40 °C; Reaction conditions 2: **3** (0.1 mmol) in chlorobenzene (0.01 M) at reflux; Reaction conditions 3: **1** (0.2 mmol), **2** (0.6 mmol), Yb(OTf)₃ (20 mol%), (*R*)-**L7** (24 mol%), DIPEA (48 mol%), 4 Å molecular sieves (50 mg) in DCM (1.0 mL) at 40 °C. [b] Yield of isolated product. [c] Enantiomeric excess was determined by HPLC on a chiral stationary phase. [d] The structure and absolute configurations of **3a** and **4v** were assigned by an X-ray crystallographic analysis of enantiopure samples (see the Supporting Information for details). [e] The reaction was conducted at 40 °C, and then heated at 80 °C.

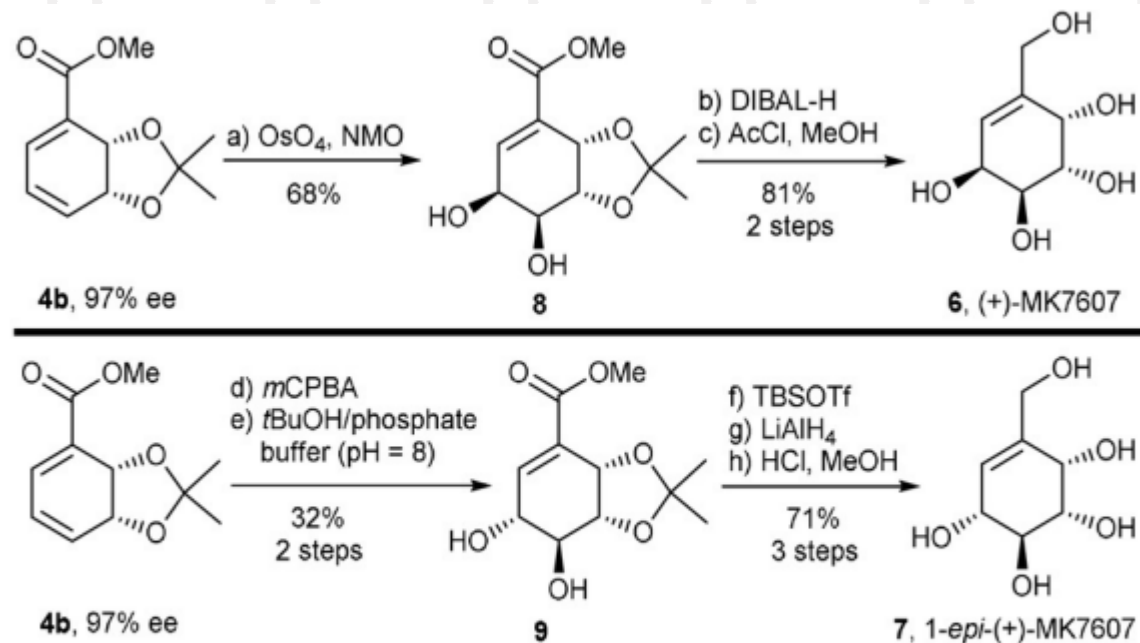
Table 3: Calculated energy profiles of the CO₂ extrusion process.^[a]



Entry, R ⁴	<i>endo</i> -3	TS	4
1, R = H	0.0	24.2	-25.5
2, R = Me	0.0	20.0	-25.9
3, R = Ph	0.0	15.4	-29.5

[a] Relative Gibbs free energies in dichloromethane (in kcal mol⁻¹) are reported. Calculated at the B3LYP/6-31G** level of theory.

R4基团有利于CO₂离去
动力学：结构拥挤(endo-3)
热力学：稳定相邻C+



Scheme 2. Enantioselective total synthesis of (+)-MK7607 and 1-*epi*-(+)-MK7607.

Cycloaddition

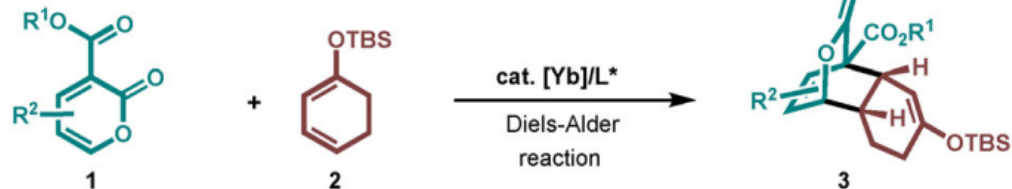
How to cite: *Angew. Chem. Int. Ed.* **2020**, 59, 18412–18417

International Edition: doi.org/10.1002/anie.202006841

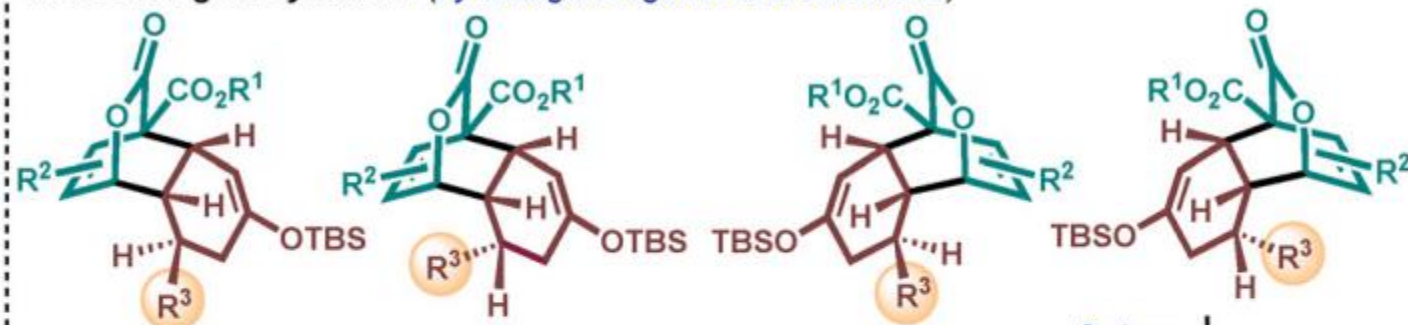
German Edition: doi.org/10.1002/ange.202006841

Enantioselective Synthesis of *cis*-Decalin Derivatives by the Inverse-Electron-Demand Diels–Alder Reaction of 2-Pyrones*Xu-Ge Si⁺, Zhi-Mao Zhang⁺, Cheng-Gong Zheng, Zhan-Ting Li, and Quan Cai**

c) This work

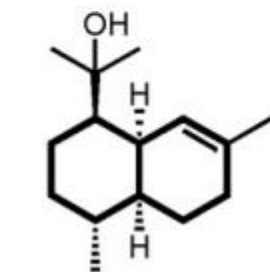


stereodivergent synthesis (by tuning the ligands and substrates)



- Chemoselective
- High ee, high dr
- Highly functionalized decalins
- With up to five continuous chiral centers
- Valuable in natural product synthesis

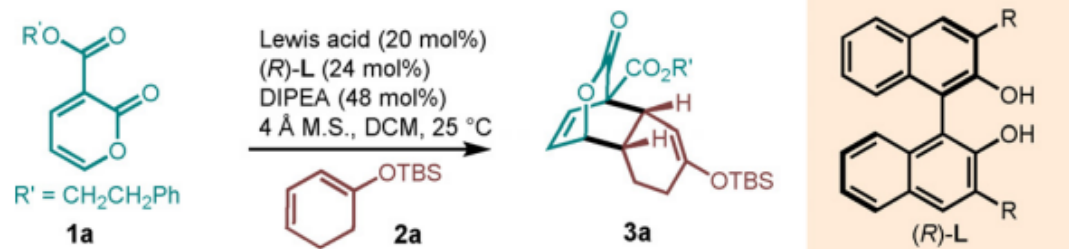
synthetic applications



4-amorphen-11-ol

6 steps

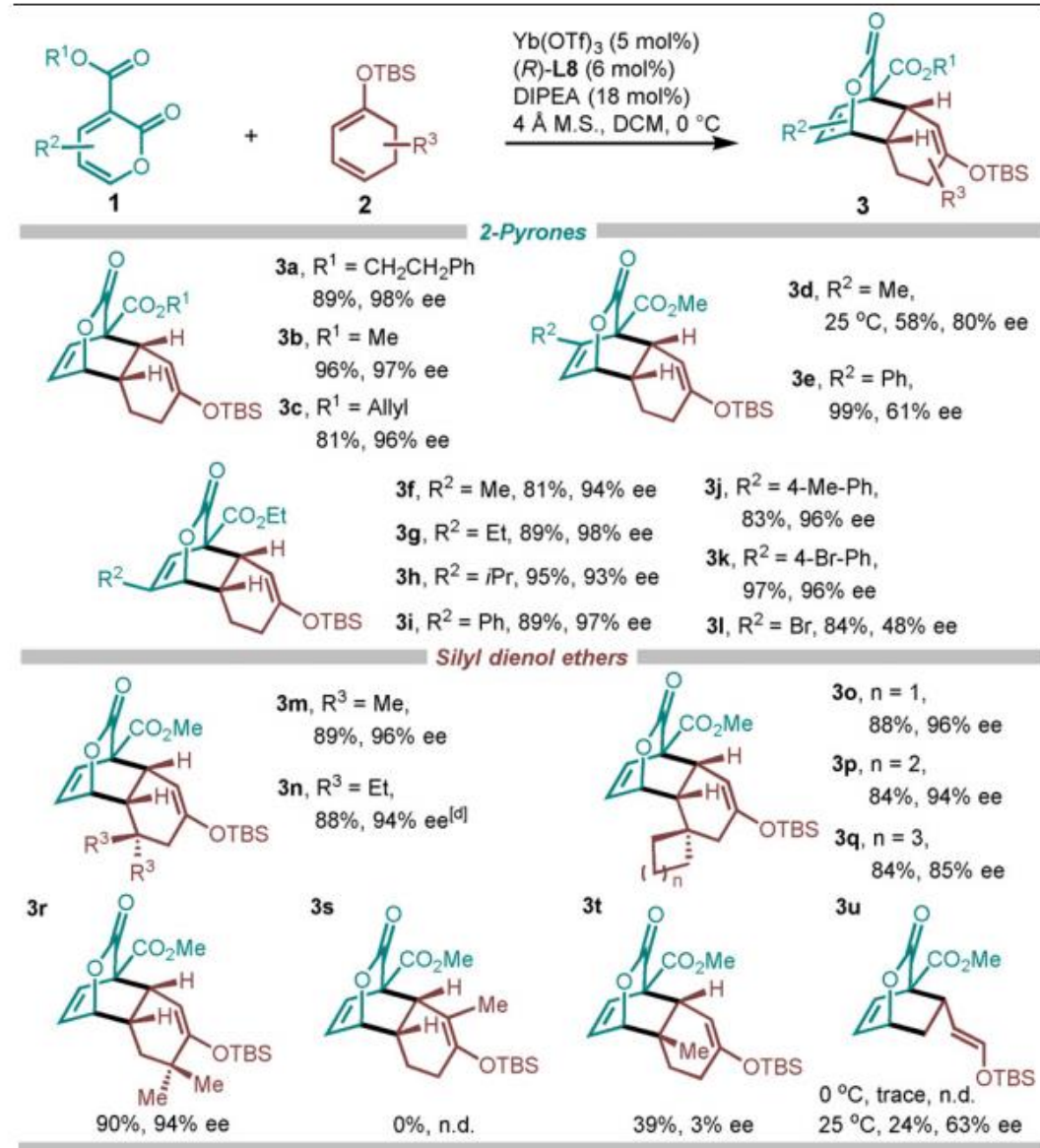
*cis*-crotonin

Table 1: Optimization of the reaction conditions.

Entry ^[a]	Lewis acid	(<i>R</i>)-L, R	<i>T</i> [min]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	Yb(OTf) ₃	L1 , R = H	120	80	34
2	Yb(OTf) ₃	L2 , R = Br	30	79	65
3	Yb(OTf) ₃	L3 , R = 4-F-C ₆ H ₄	120	79	47
4	Yb(OTf) ₃	L4 , R = 4-CF ₃ -C ₆ H ₄	120	50	-11
5	Yb(OTf) ₃	L5 , R = 4-NO ₂ -C ₆ H ₄	30	76	52
6	Yb(OTf) ₃	L6 , R = 3,5-(CF ₃) ₂ -C ₆ H ₃	30	63	8
7	Yb(OTf) ₃	L7 , R = 3,5-F ₂ -C ₆ H ₃	120	88	84
8	Yb(OTf) ₃	L8 , R = C ₆ F ₅	10	82	91
9	Y(OTf) ₃	L8 , R = C ₆ F ₅	10	71	87
10	Lu(OTf) ₃	L8 , R = C ₆ F ₅	10	73	89
11	Gd(OTf) ₃	L8 , R = C ₆ F ₅	30	78	78
12	Eu(OTf) ₃	L8 , R = C ₆ F ₅	30	trace	n.d.
13 ^[d]	Yb(OTf) ₃	L8 , R = C ₆ F ₅	10	89	97
14 ^[d,e]	Yb(OTf) ₃	L8 , R = C ₆ F ₅	10	89	98

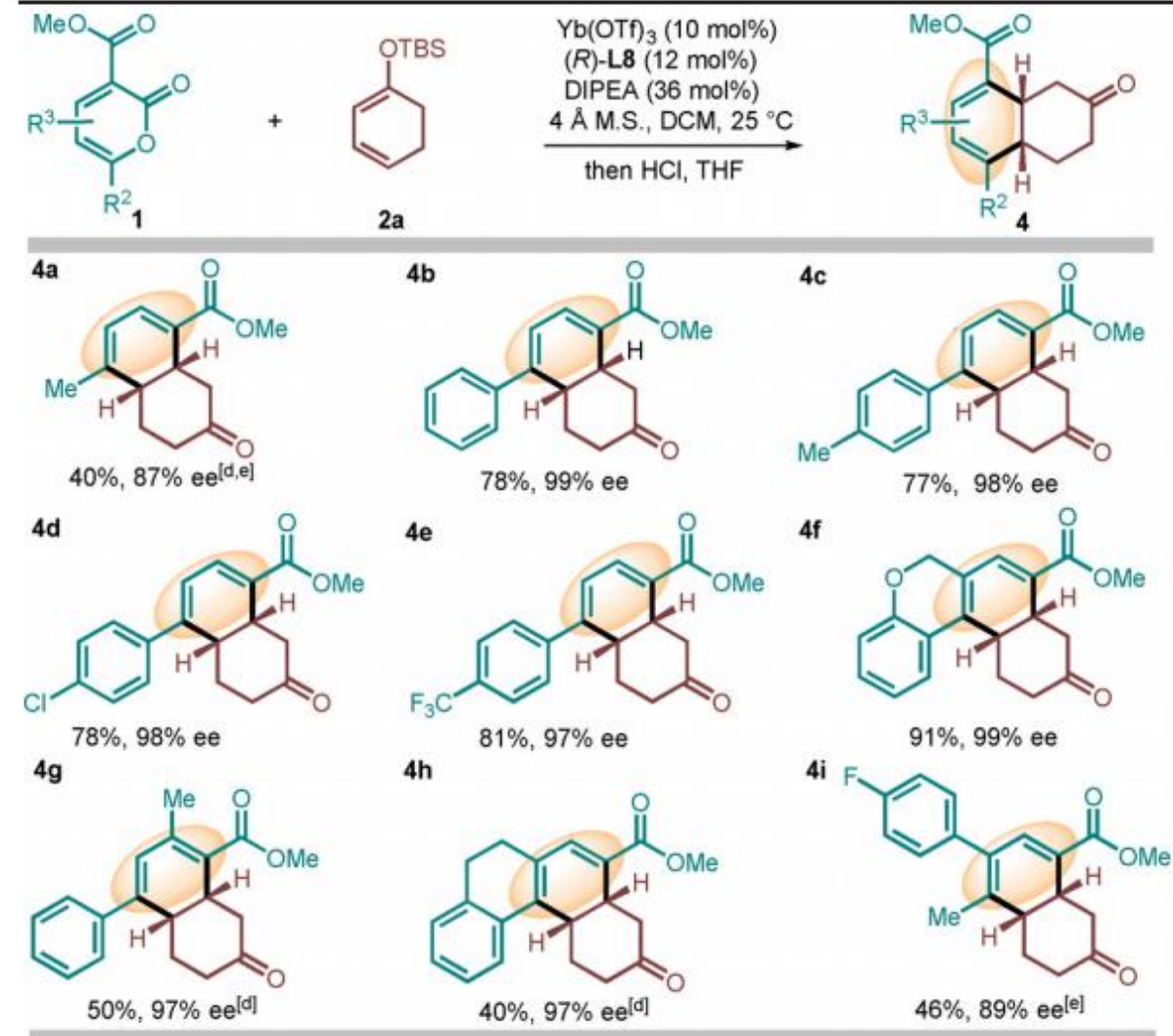
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), Yb(OTf)₃ (20 mol%), (*R*)-L (24 mol%), DIPEA (48 mol%), 4 Å M.S. (25 mg) in DCM (0.5 mL) at 25 °C. [b] Yield of isolated **3a**. [c] Determined by HPLC analysis. [d] The reaction was conducted at 0 °C. [e] **1a** (0.2 mmol), **2a** (0.3 mmol), Yb(OTf)₃ (5 mol%), (*R*)-L (6 mol%), DIPEA (18 mol%), 4 Å M.S. (50 mg) in DCM (0.5 mL). DIPEA = *N,N*-diisopropylethylamine, M.S. = molecular sieves, n.d. = not determined.

Table 2: Substrate scope with respect to substituted 2-pyrone and silyl dienol ethers.^[a,b,c]

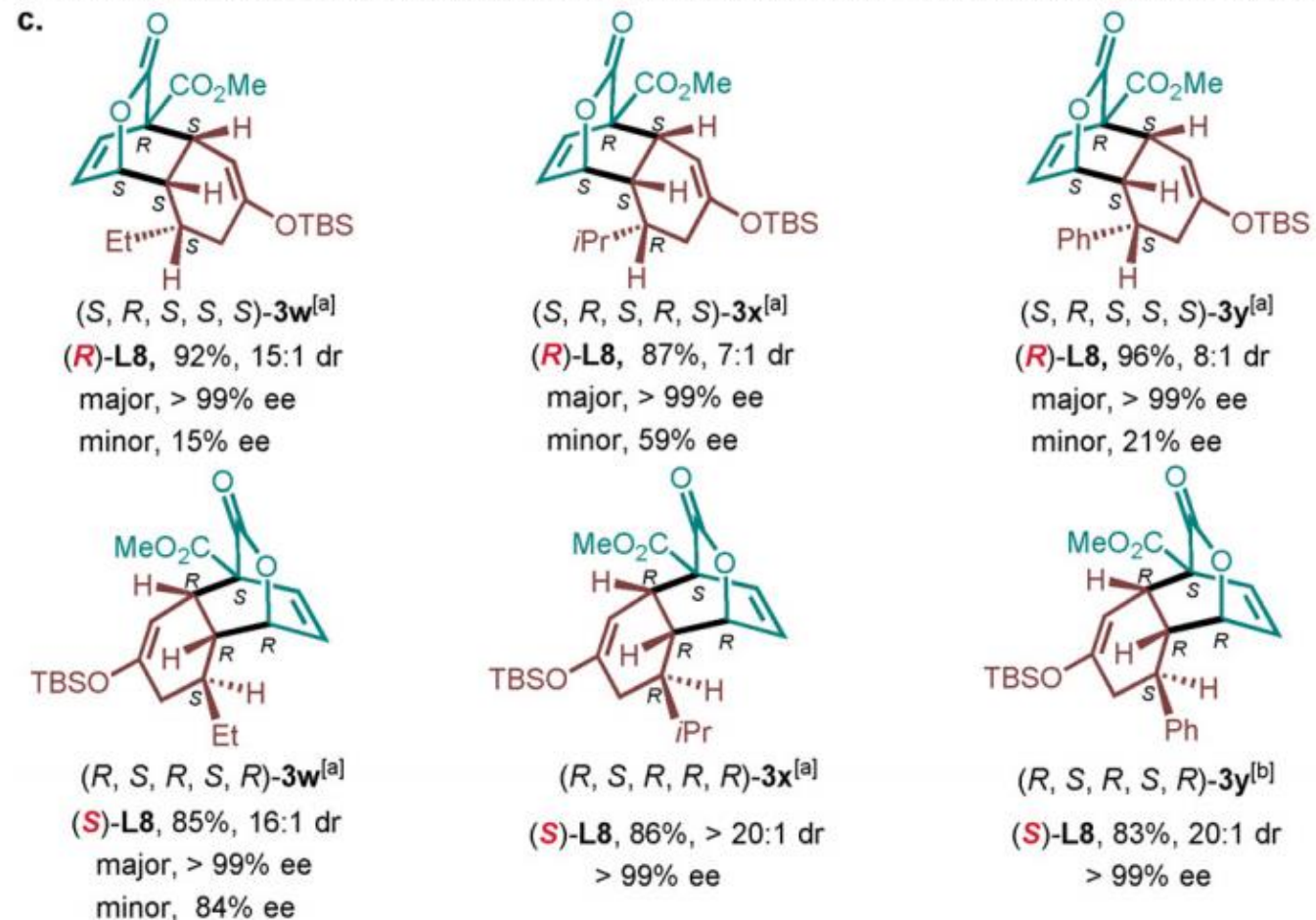
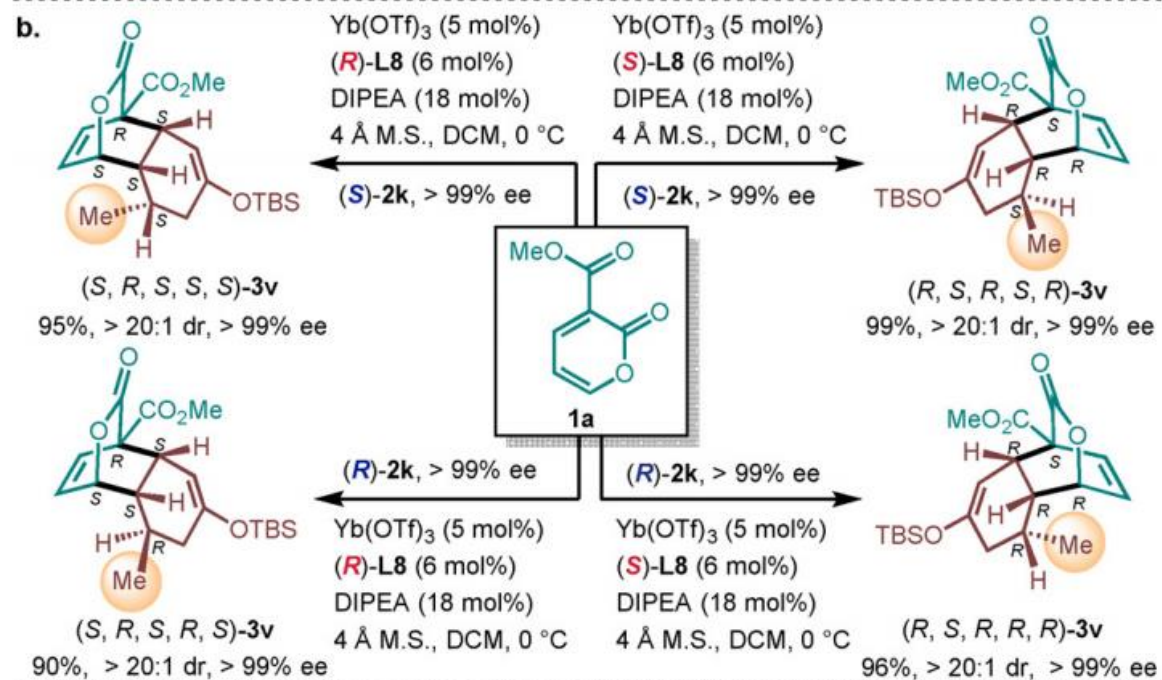
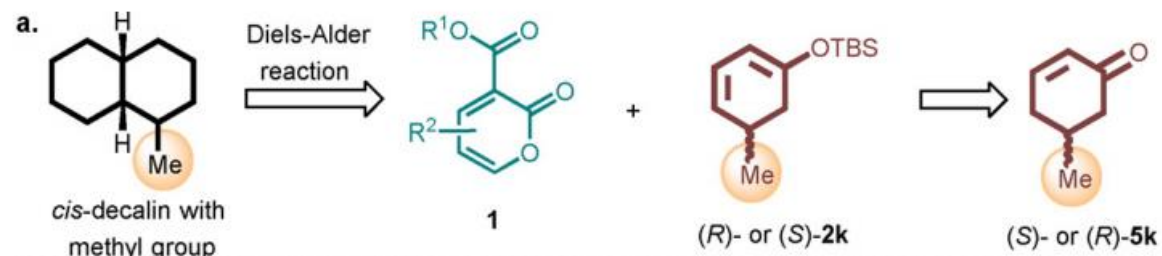


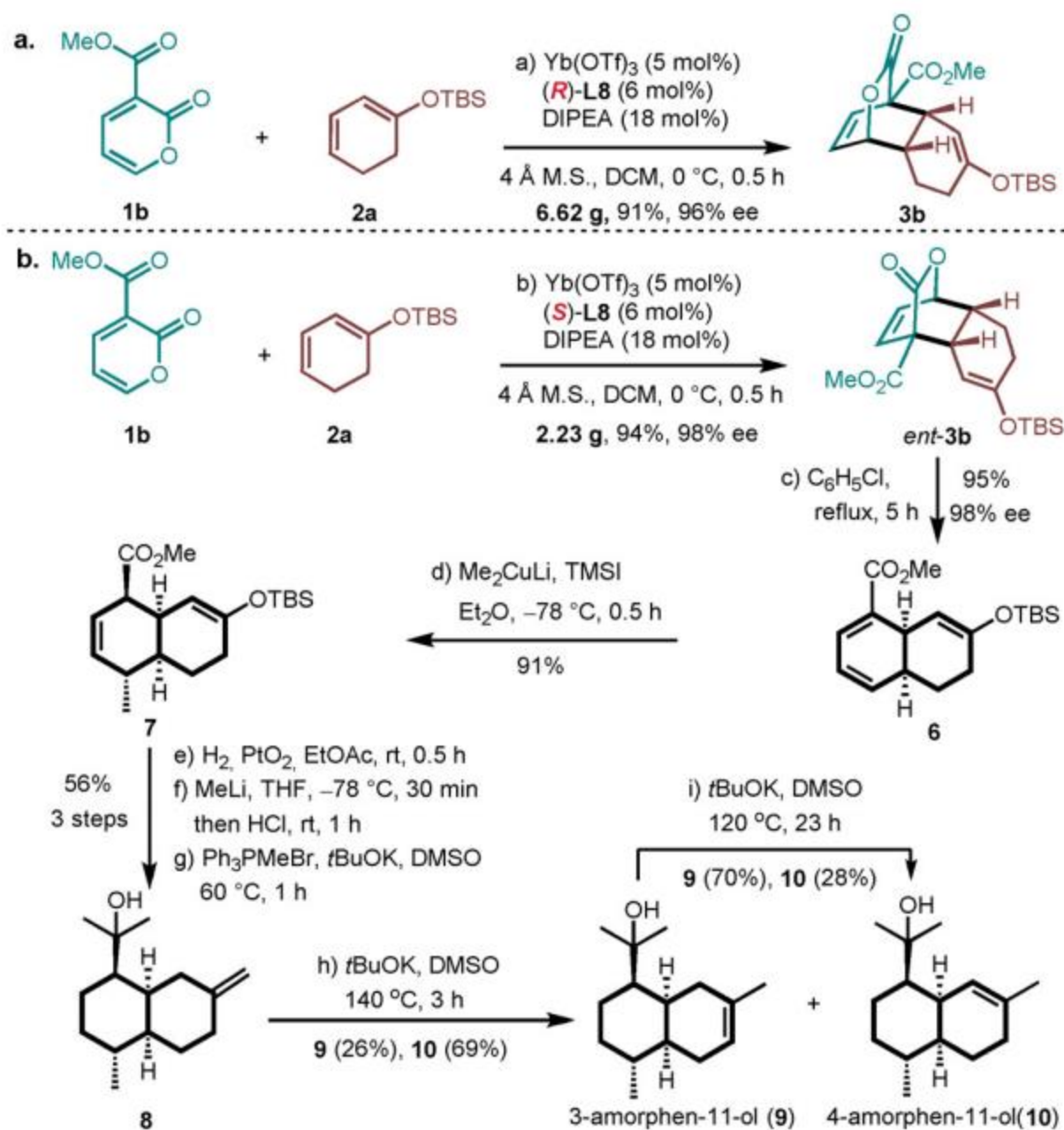
[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol) were used. [b] Yield of isolated **3**. [c] The *ee* of **3** was determined by HPLC analysis. [d] The absolute configuration of **3 n** was assigned by the X-ray crystallographic

Table 3: Substrate scope with respect to 6-substituted 2-pyrone.^[a,b,c]

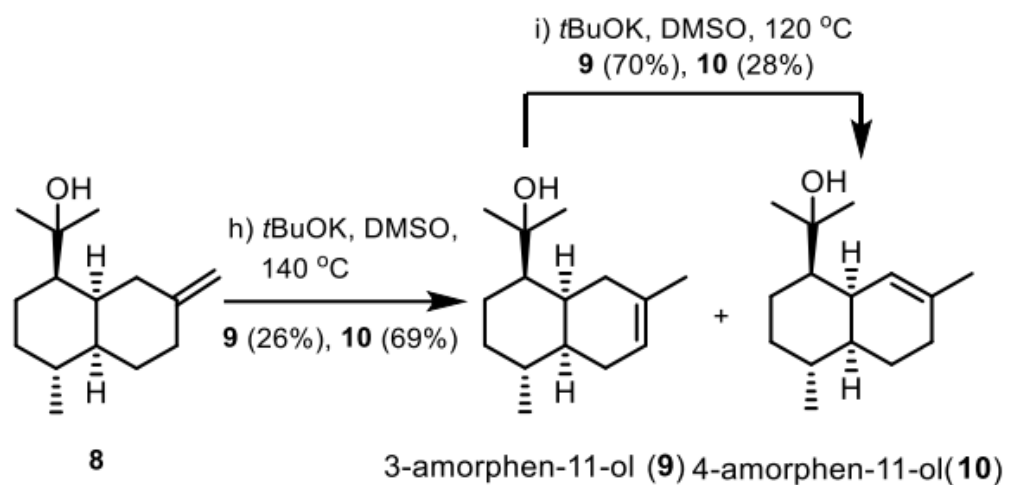
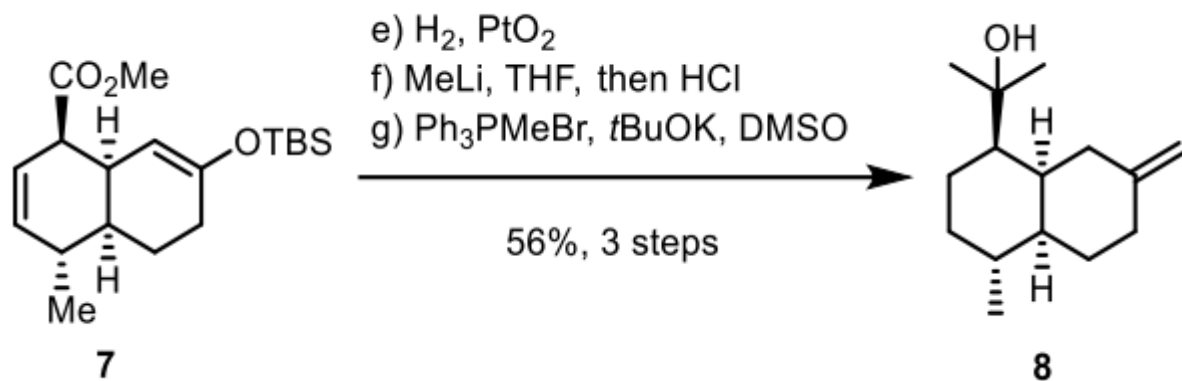
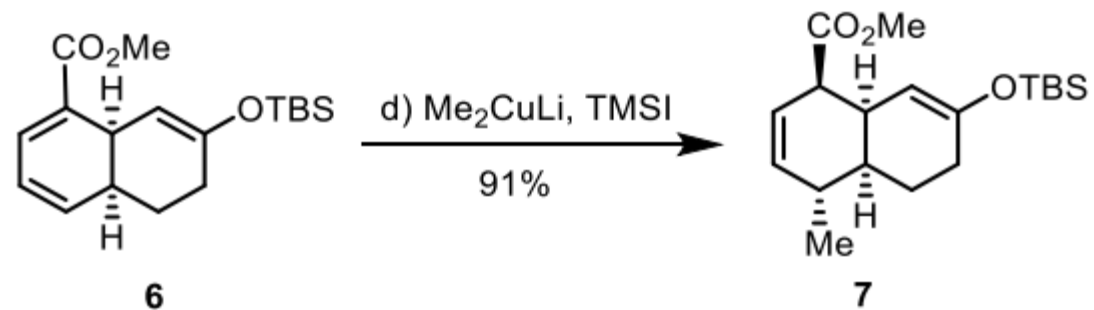


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol) were used. [b] Isolated yield of **4**. [c] The *ee* of **4** was determined by HPLC analysis. [d] The reaction was conducted at 40 °C. [e] The reaction was heated at 80 °C for the complete extrusion of CO₂ after the Diels–Alder reaction was finished. For details, see the Supporting Information.





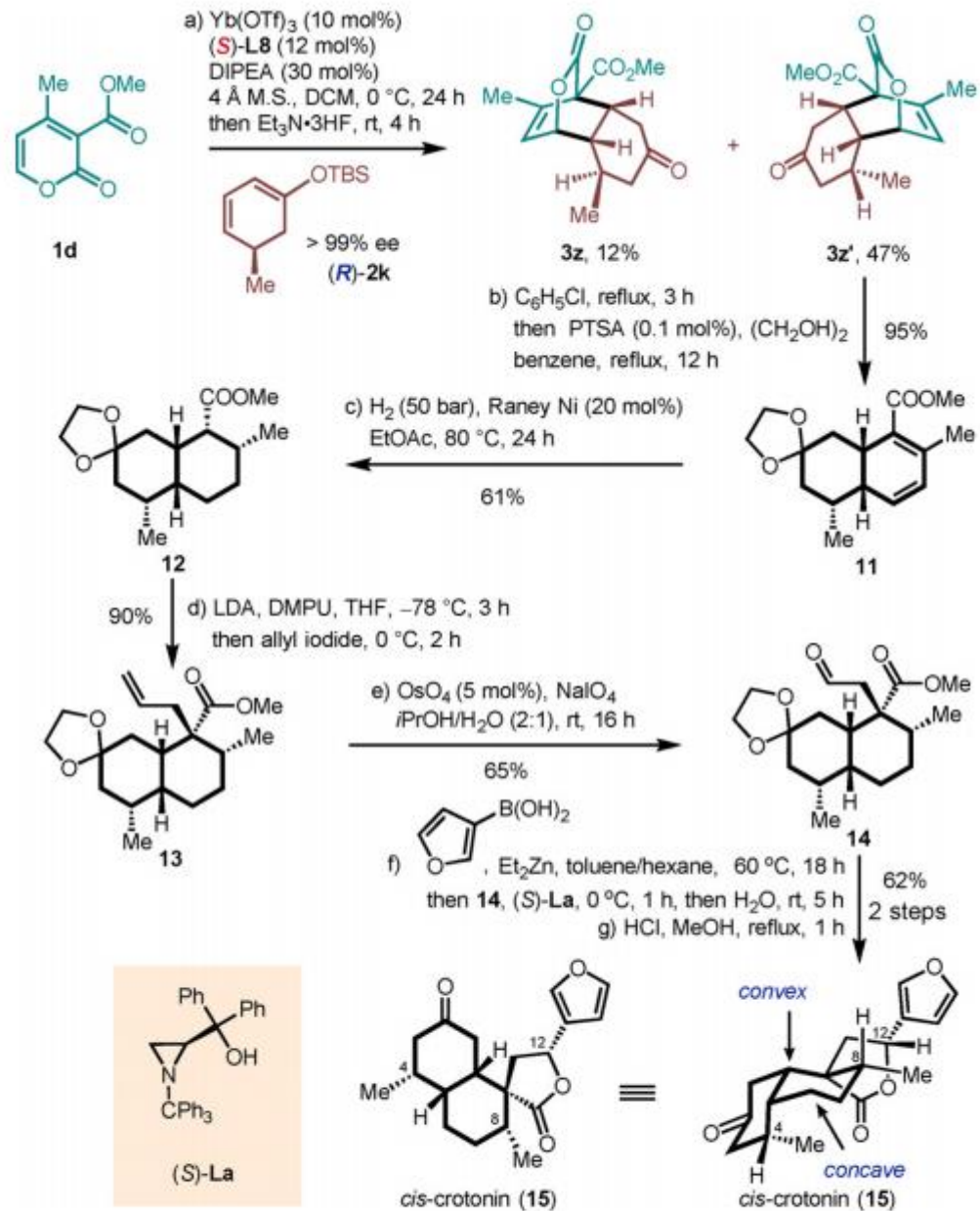
Scheme 3. Gram-scale experiment and enantioselective total synthesis of 4-amorphen-11-ol.



1,6-Michael addition

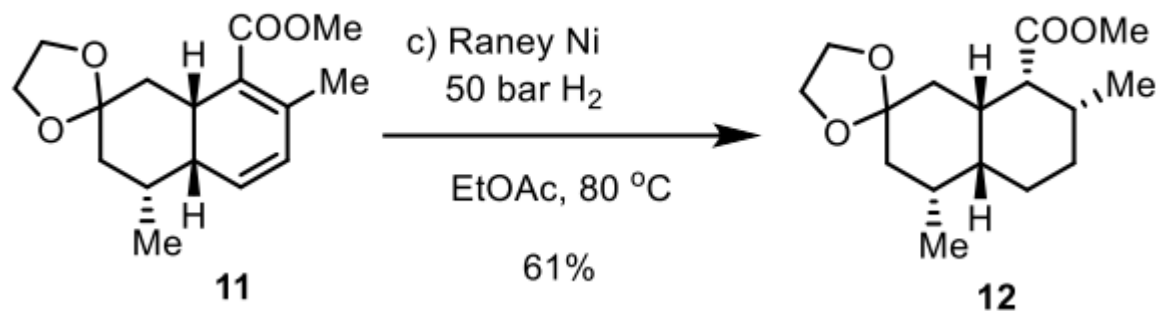
1. 烯烃氢化还原
2. 酯的甲基化，烯醇硅醚水解
3. Wittig reaction

碱诱导的[1,3] σ 键迁移

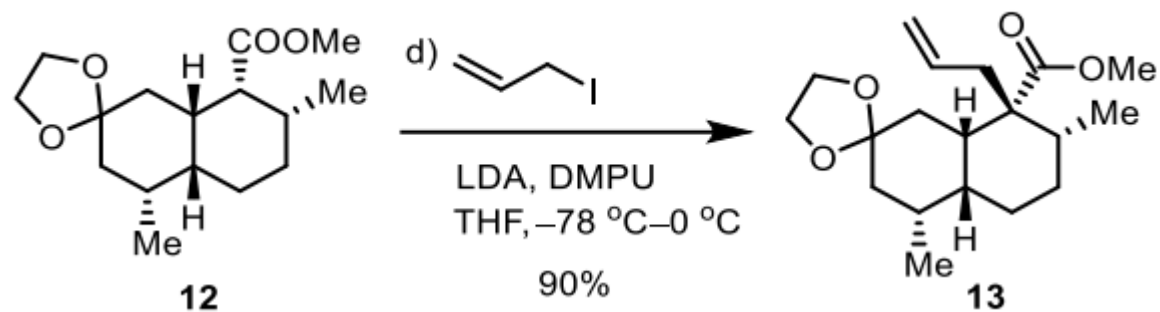


Scheme 4. Enantioselective total synthesis of *cis*-crotonin. PTSA = *p*-toluenesulfonic acid, LDA = lithium diisopropylamide, DMPU = 1,3-dimethyl-tetrahydropyrimidin-2(1*H*)-one.

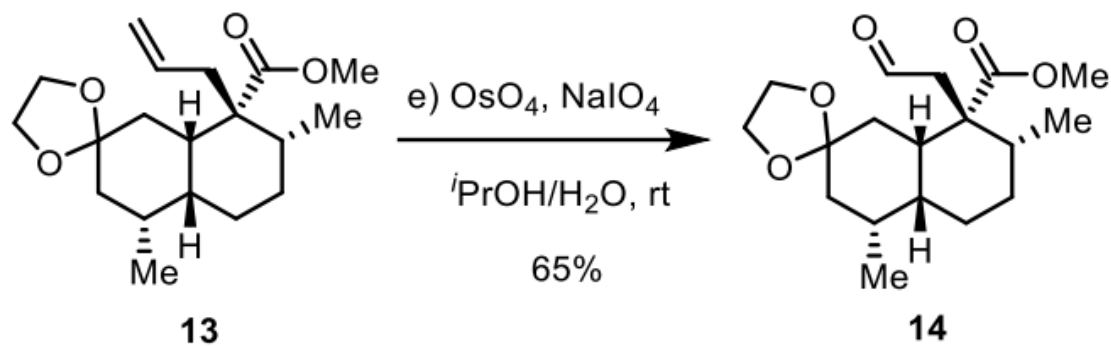
Raney Ni加氢还原

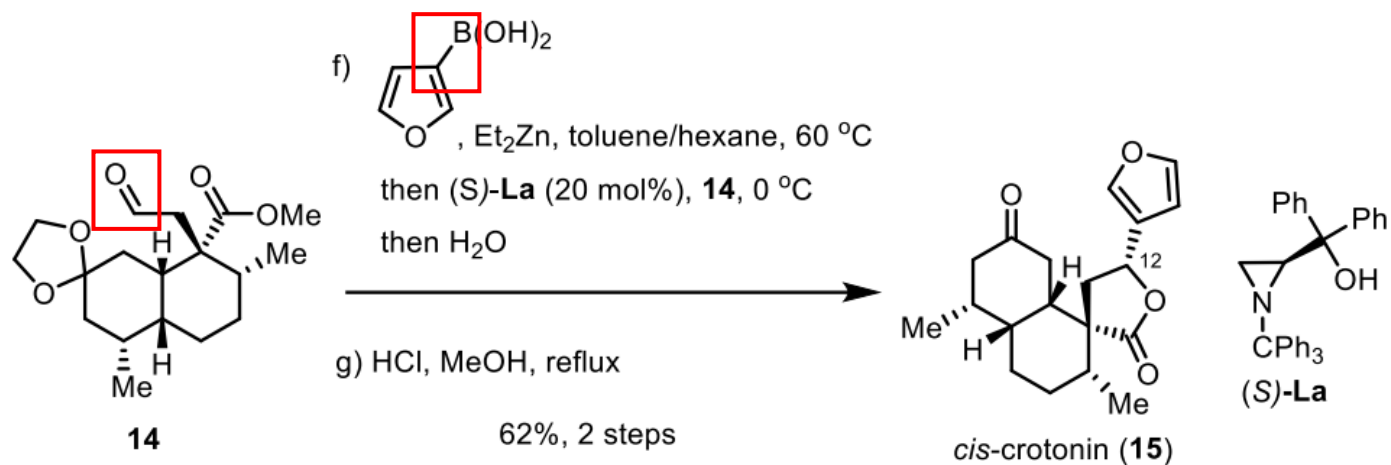


烯丙基化

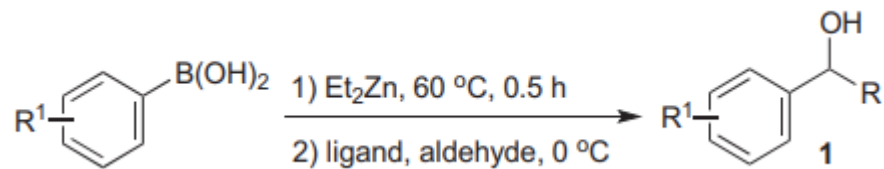


四氧化锇+高碘酸钠 双键氧化为醛





1. B/Zn exchange reaction (有机锌试剂对羰基的亲核加成)

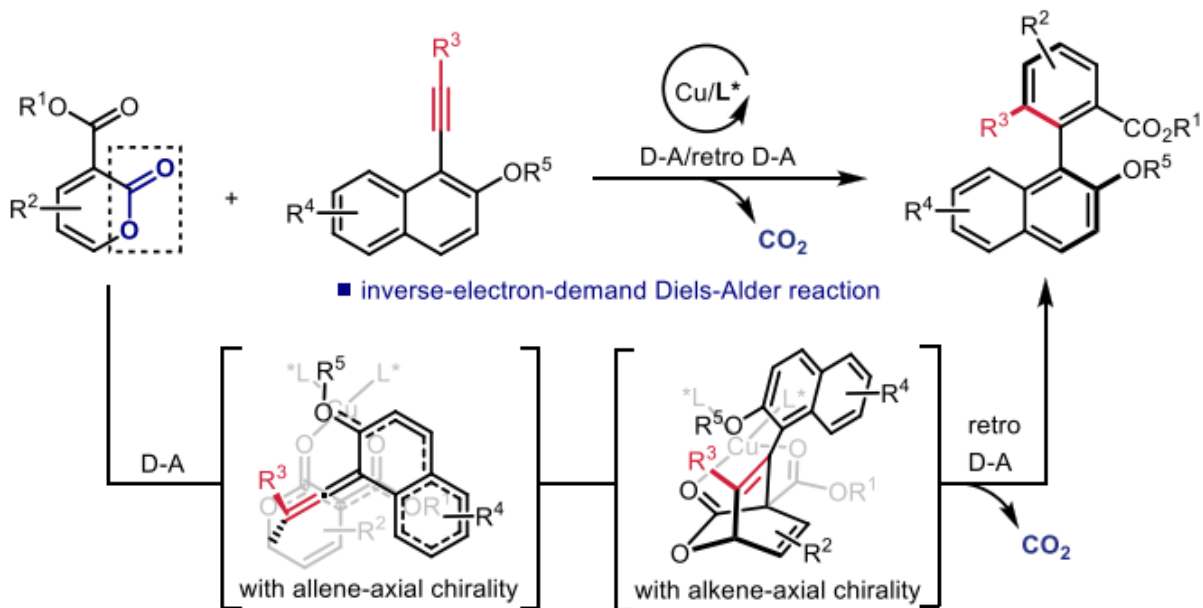


2. 酯的醇解

3. 脱保护 (双缩酮变回酮)

Enantioselective Synthesis of Axially Chiral Biaryls by Diels–Alder/Retro-Diels–Alder Reaction of 2-Pyrones with Alkynes

Meng-Meng Xu, Xin-Yu You, Yu-Zhen Zhang, Yang Lu, Kui Tan, Limin Yang,* and Quan Cai*

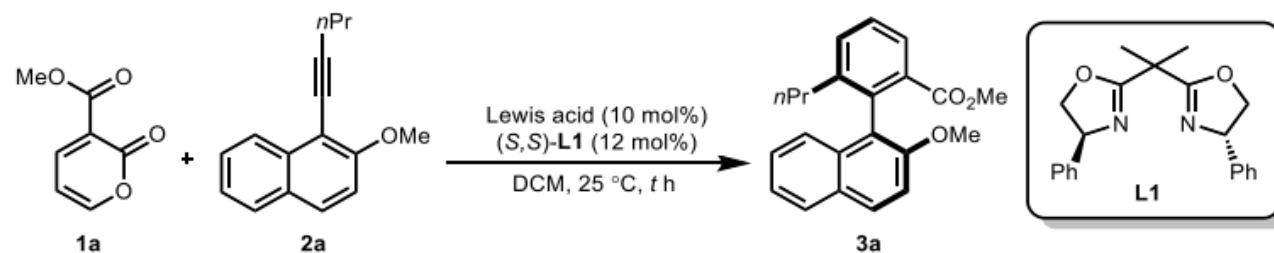


■ ambient reaction conditions

■ densely substituted axially chiral biaryls

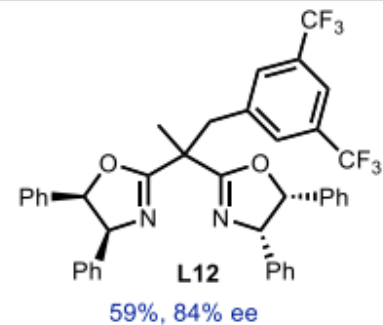
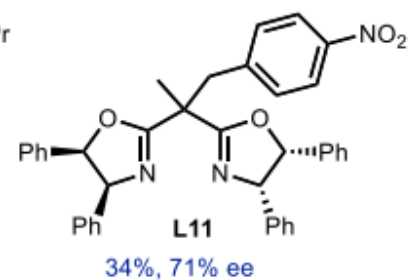
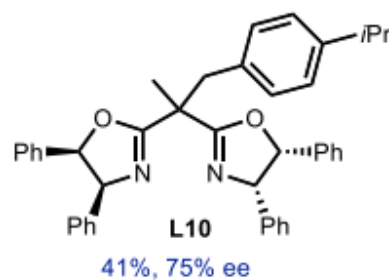
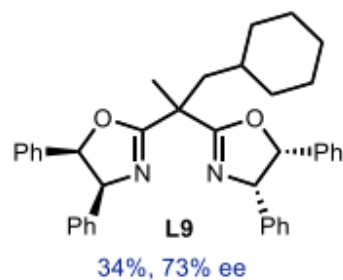
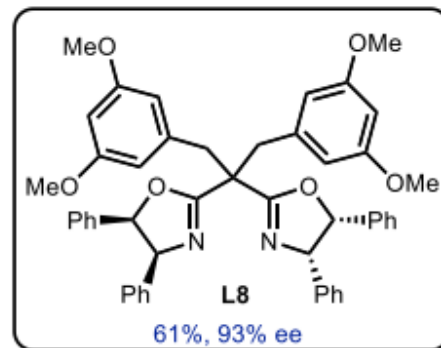
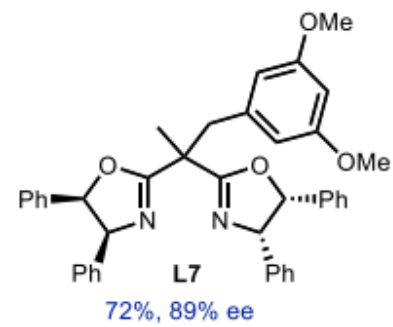
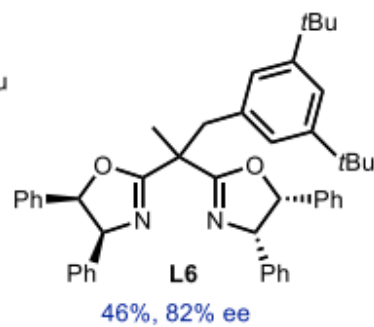
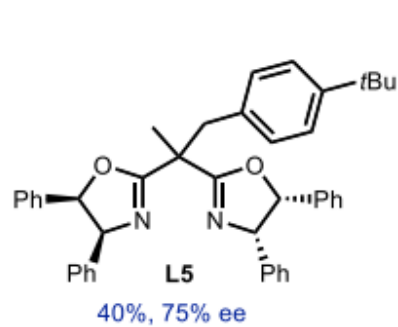
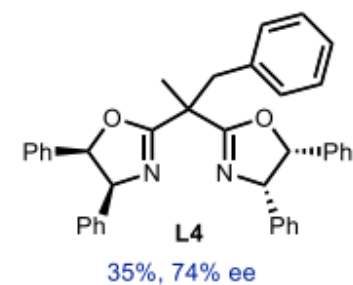
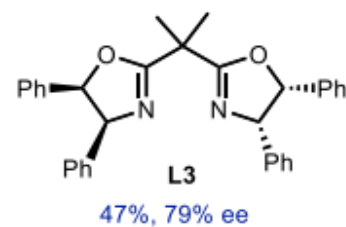
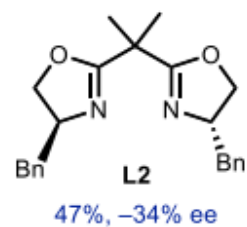
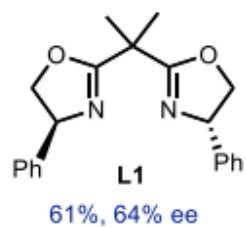
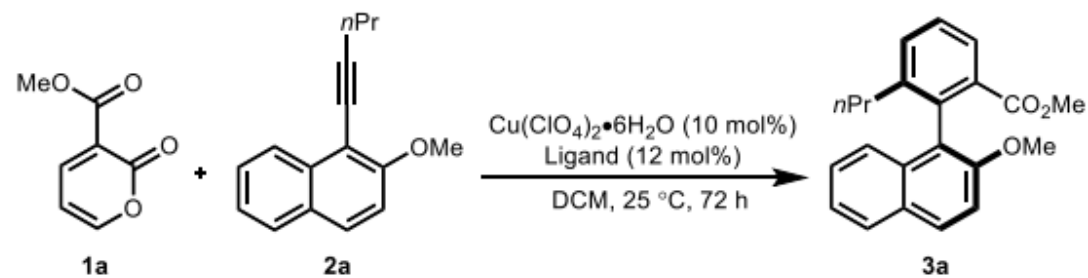
■ up to 97% yield, >99% ee

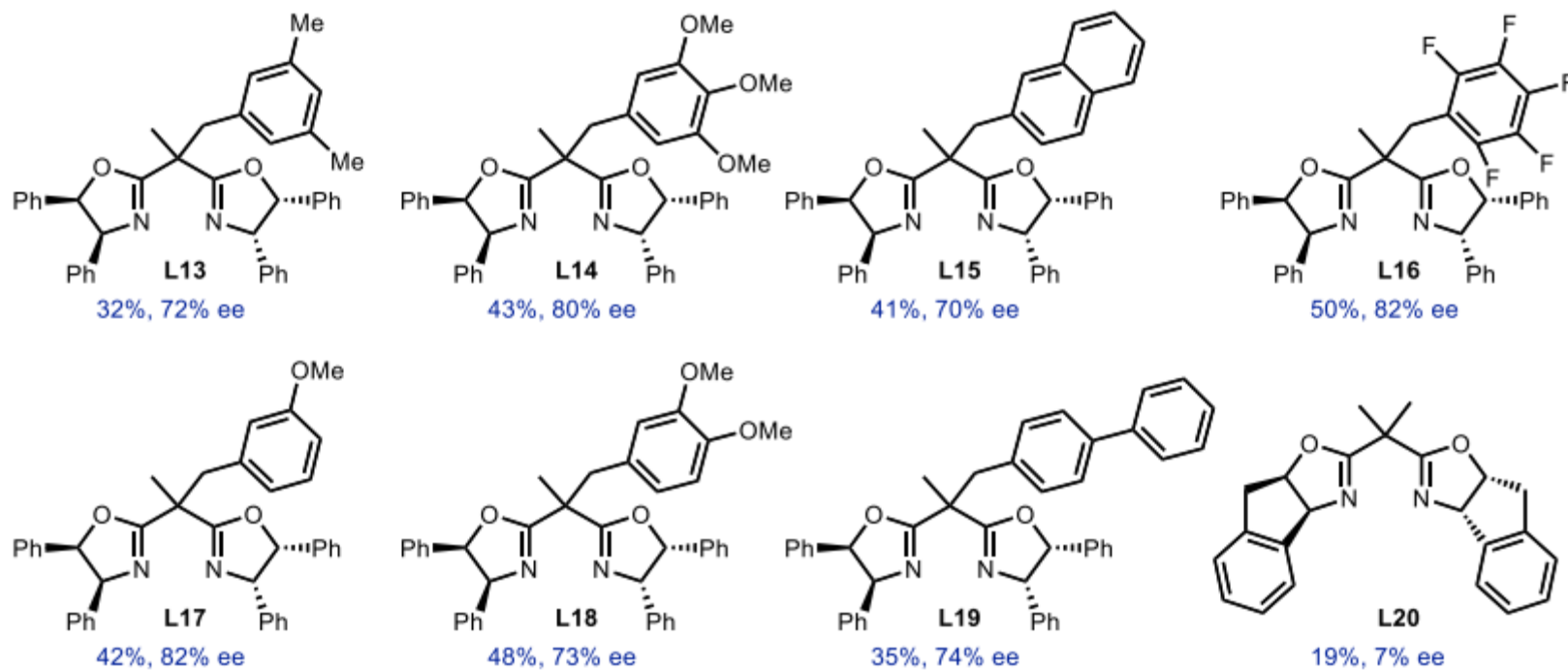
■ readily convertible functionalities

Table S1. Investigation of the Lewis acids.^a

entry	Lewis acid	<i>t</i> (h)	yield (%) ^b	ee (%) ^c
1	Cu(ClO ₄) ₂ •6H ₂ O	72	61	64
2	Cu(BF ₄) ₂ •XH ₂ O	72	9	60
3	Cu(NTf) ₂	72	0	--
4	Cu(OTf) ₂	72	37	66
5	Cu(SbF ₆) ₂	72	0	--
6	Cu(PF ₆) ₂	72	0	--
7	In(OTf) ₃	72	0	--
8	Ni(ClO ₄) ₂ •6H ₂ O	72	0	--
9	Co(ClO ₄) ₂ •6H ₂ O	72	0	--

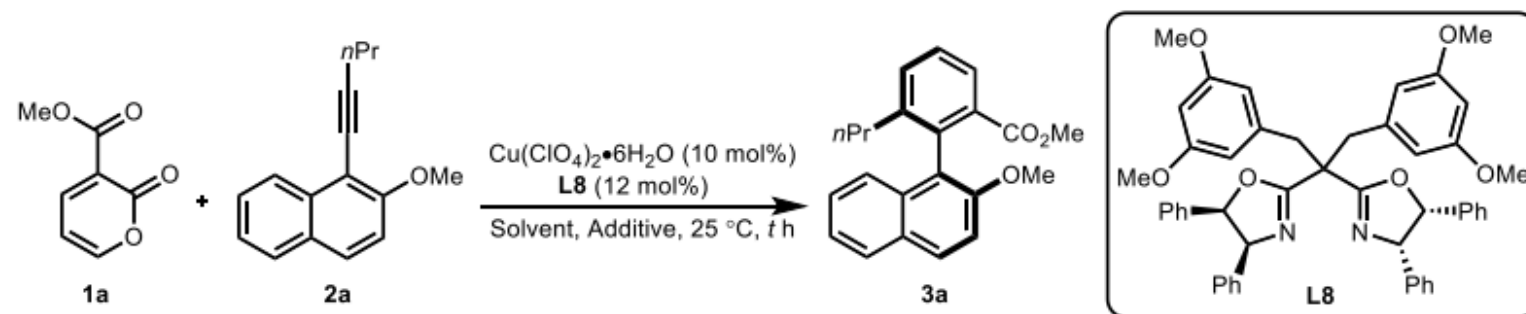
^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Lewis acid (10 mol%) and (*S,S*)-**L1** (12 mol%) in DCM (1.0 mL) at 25 °C. ^b Isolated yield. ^c Determined by HPLC analysis.

Table S2. Investigation of the ligands. ^{a, b, c}



^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), Cu(ClO₄)₂•6H₂O (10 mol%) and ligand (12 mmol%) in DCM (1.0 mL) at 25 °C. ^b Isolated yield. ^c Determined by HPLC analysis.

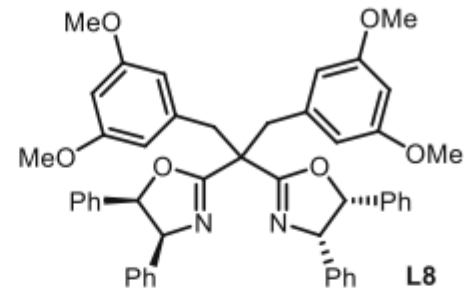
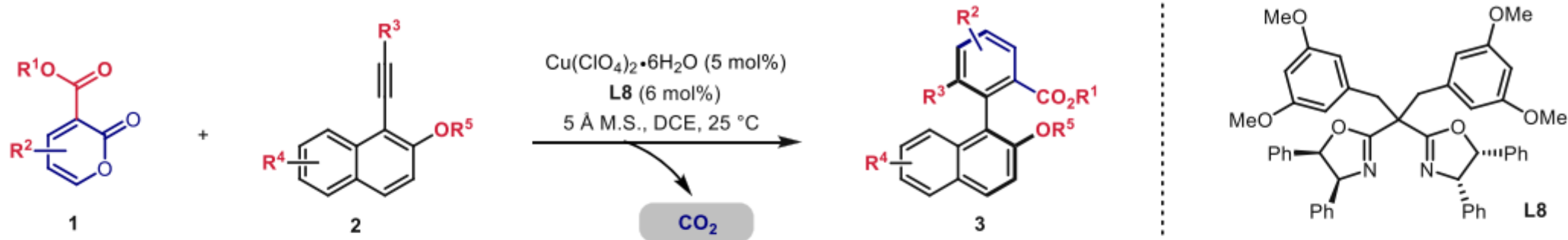
BOX配体的侧臂在调节反应性和立体控制方面起着关键作用

Table S3. Investigation of the solvents and additives.^a

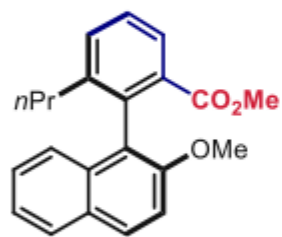
entry	solvent	additive	t (h)	yield (%) ^b	ee (%) ^c
1	DCM	-	72	61	93
2	DCE	-	36	88	95
3	DCE	3 Å M.S.	36	90	96
4	DCE	4 Å M.S.	36	89	96
5	DCE	5 Å M.S.	36	91	96
6 ^d	DCE	5 Å M.S.	72	97	96

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.3 mmol), $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (10 mol%) and **L8** (12 mol%) in DCM (1.0 mL) at 25 °C. ^b Isolated yield. ^c Determined by HPLC analysis. ^d **1a** (0.2 mmol), **2a** (0.3 mmol), $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (5 mol%), **L8** (6 mol%) and 5 Å M.S. (50 mg) in DCE (1.0 mL) at 25 °C.

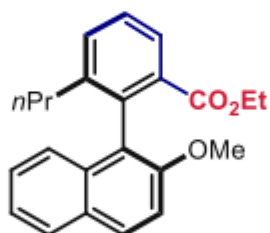
Table 2. Substrate Scope^{a,b,c}



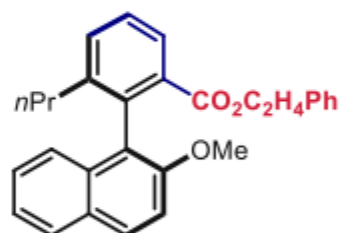
Scope of 2-pyrone



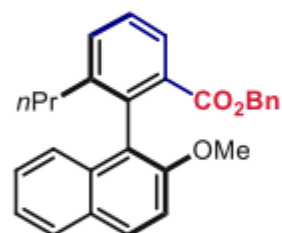
3a, 97%, 96% ee



3b, 84%, 95% ee



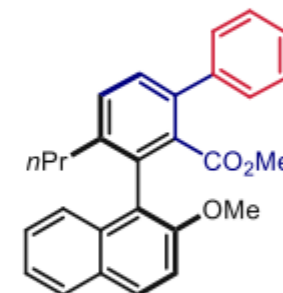
3c, 73%, 95% ee



3d, 73%, 94% ee



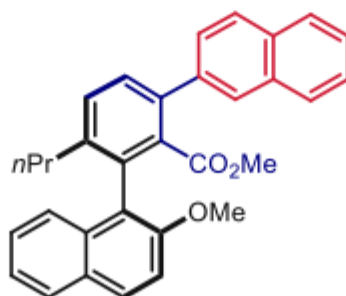
3e, 72%, 95% ee^d



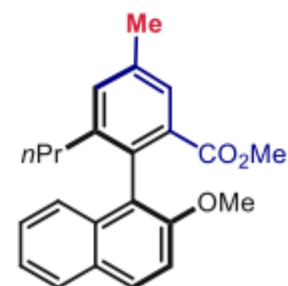
3f, 96%, 92% ee^d



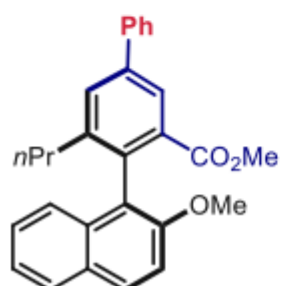
3g, 83%, 93% ee^d



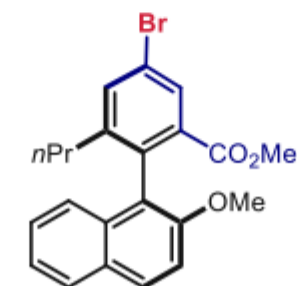
3h, 93%, 93% ee^d



3i, 70%, 81% ee^d



3j, 82%, 82% ee^d



3k, 66%, 72% ee^d



3l, trace, n.d.^d

可能由于空间效应，产率与ee下降

Scope of 1-naphthyl acetylenes



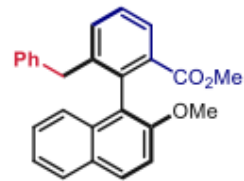
3m, 84%, 95% ee



3n, 75%, 96% ee



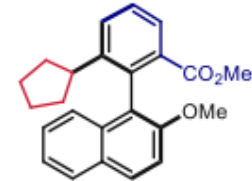
3o, 92%, 96% ee



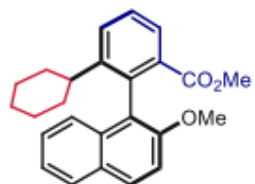
3p, 88%, 95% ee



3q, 87%, 96% ee^d



3r, 81%, 96% ee



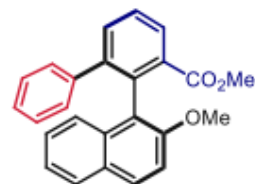
3s, 95%, 95% ee^d



3t, 95%, 96% ee^d



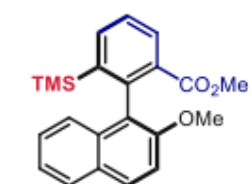
3u, 37%, 94% ee^d



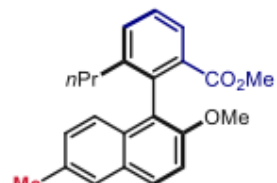
3v, 16%, 96% ee^d



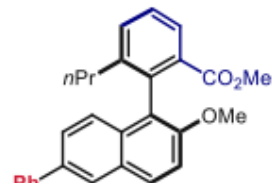
3w, 89%, 94% ee^e



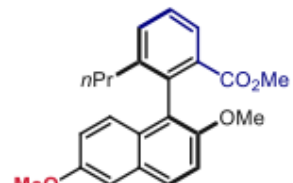
3x, 84%, 94% ee



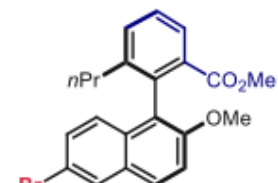
3y, 88%, 99% ee



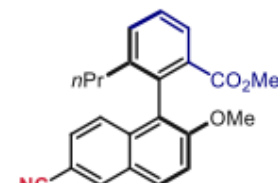
3z, 93%, 98% ee



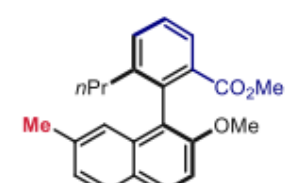
3aa, 97%, 98% ee^d



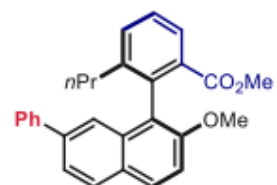
3ab, 96%, 98% ee^d



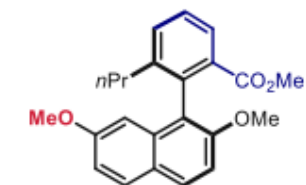
3ac, 10%, 91% ee^d



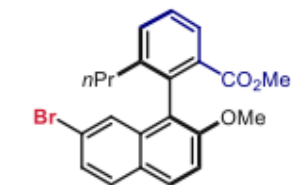
3ad, 93%, 93% ee



3ae, 89%, 94% ee



3af, 86%, 85% ee



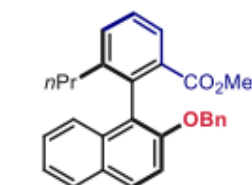
3ag, 92%, 86% ee^d



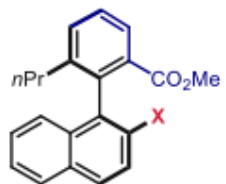
3ah, 93%, 97% ee



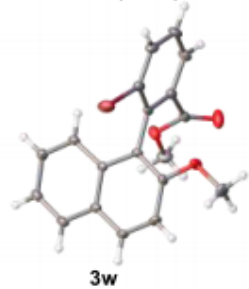
3ai, 65%, 91% ee^d



3aj, 96%, 94% ee

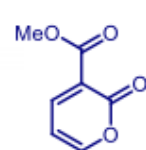


3ak, X = H, 0%, n.d.
3al, X = OH, 52%, 32% ee

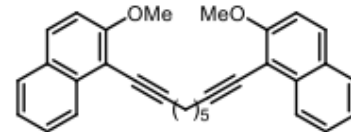


3w

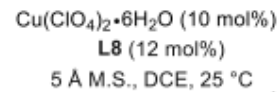
Double atroposelective Diels-Alder/retro-Diels-Alder reactions of **1a** and **2ab**



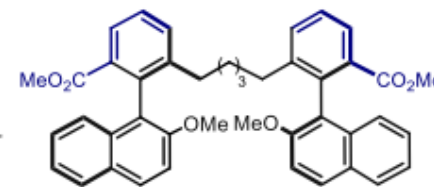
1a (1.0 equiv.)



2ab (0.5 equiv.)



CO₂



3am, 51%, >99% ee, 19:1 dr

1.0 kcal/mol 导致产生手性 (计算68%ee, 实验64%)

TS1-A 甲氧基上的C-H距离
BOX配体的苯基取代基中心距离
为2.58Å

TS1-B 甲氧基远离Ph
C-H... π 相互作用和有利过渡
结构TS1-A的能量降低

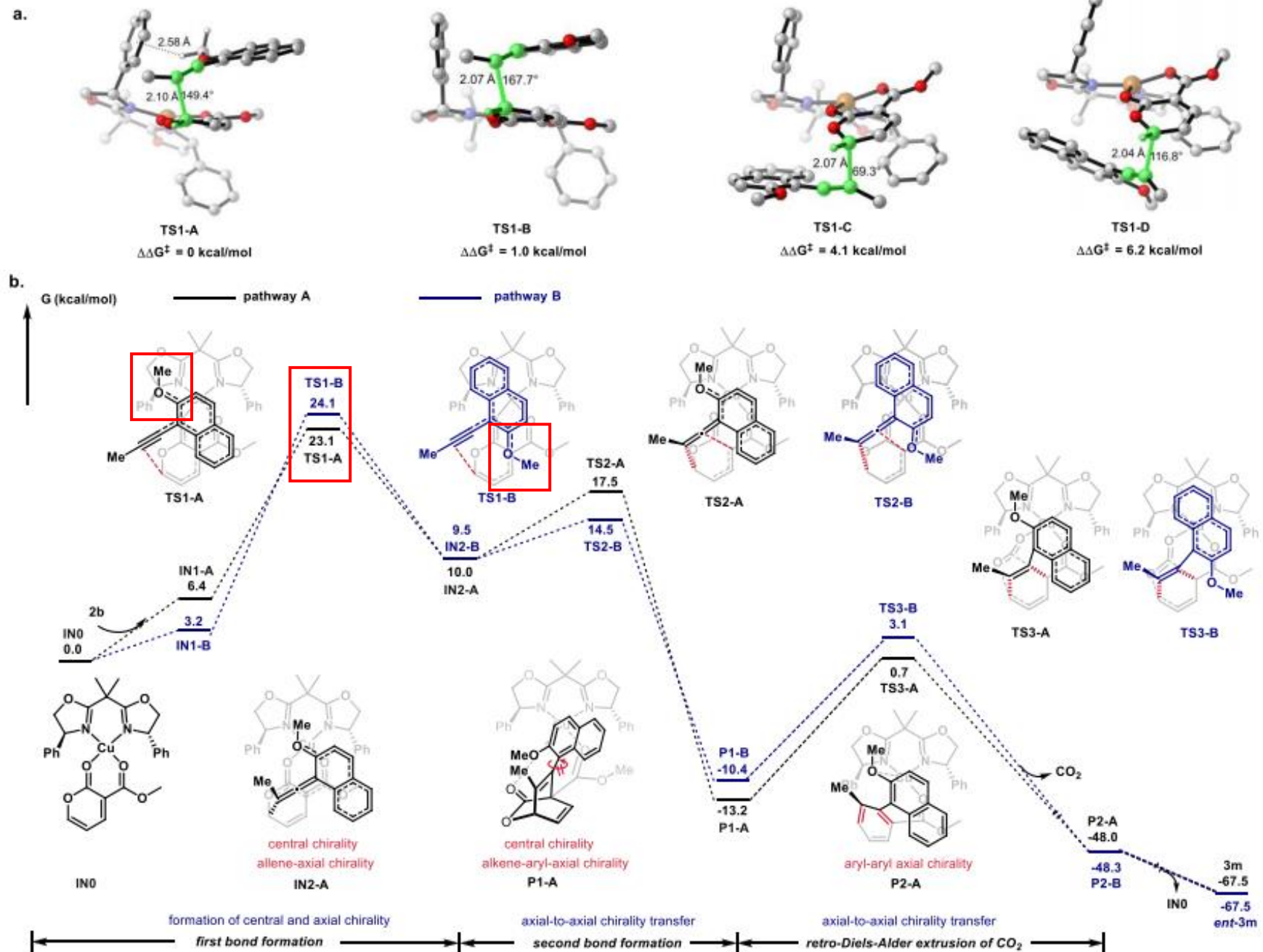
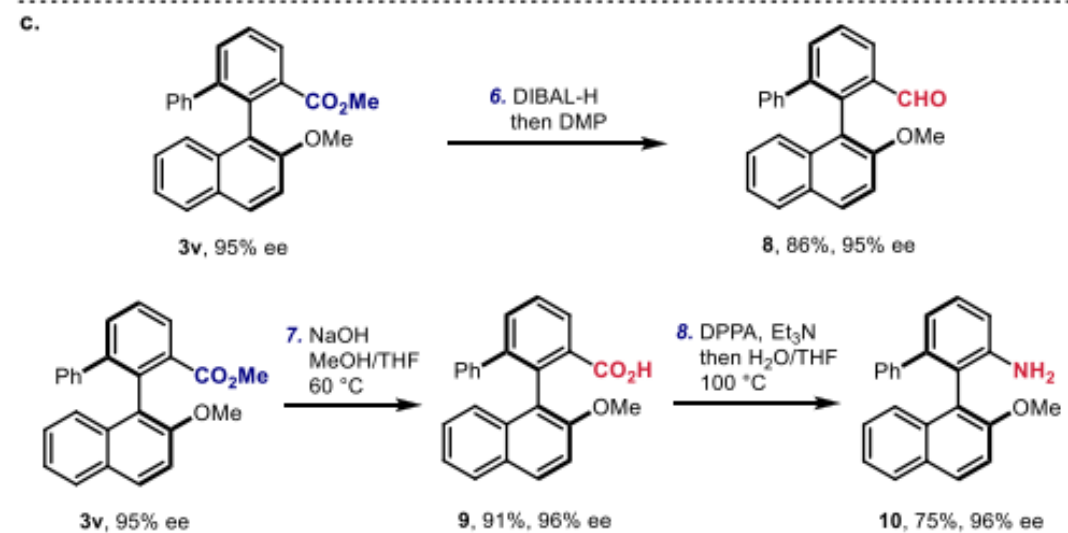
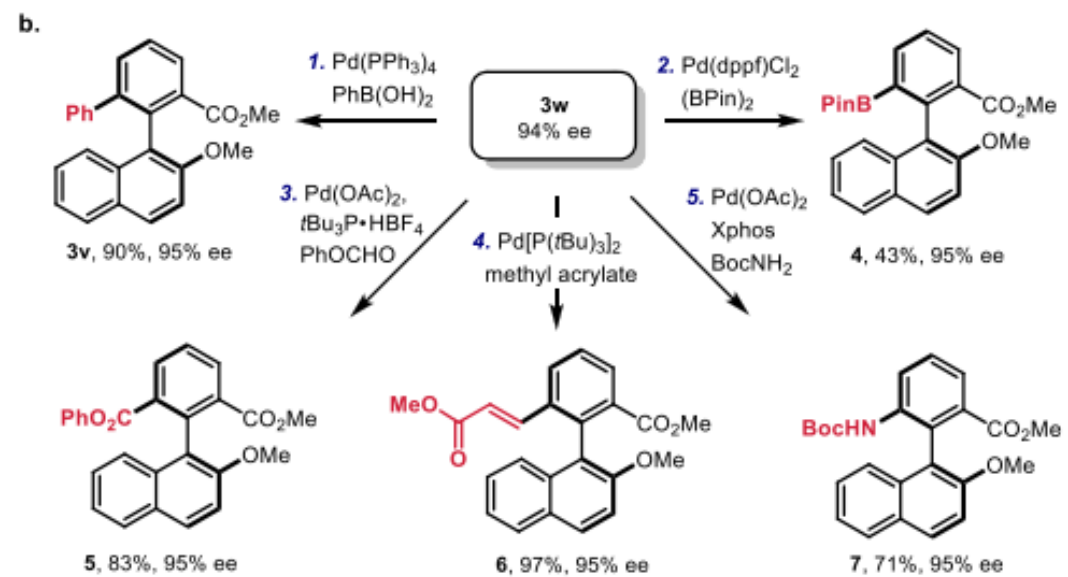
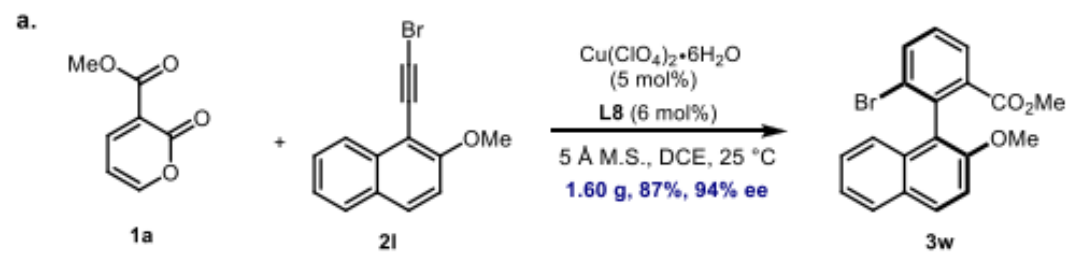


Figure 1. DFT calculations. (a) DFT-optimized transition structures and relative free energies. (b) Calculated free energy profile for pathways A and B.



Asymmetric Catalysis

 How to cite: *Angew. Chem. Int. Ed.* **2021**, *60*, 26610–26615

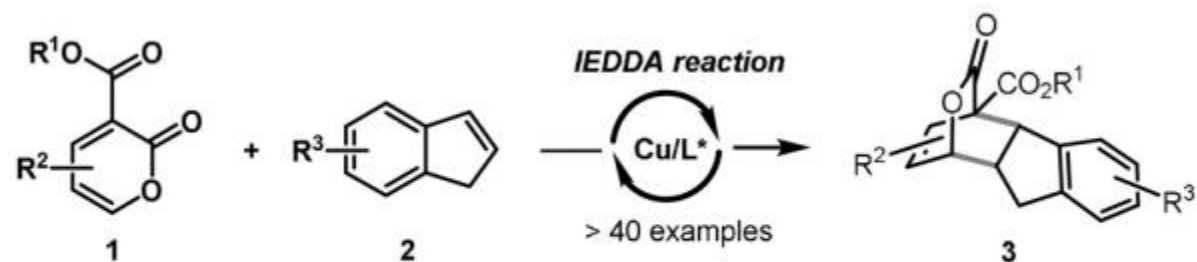
 International Edition: doi.org/10.1002/anie.202112223

 German Edition: doi.org/10.1002/ange.202112223

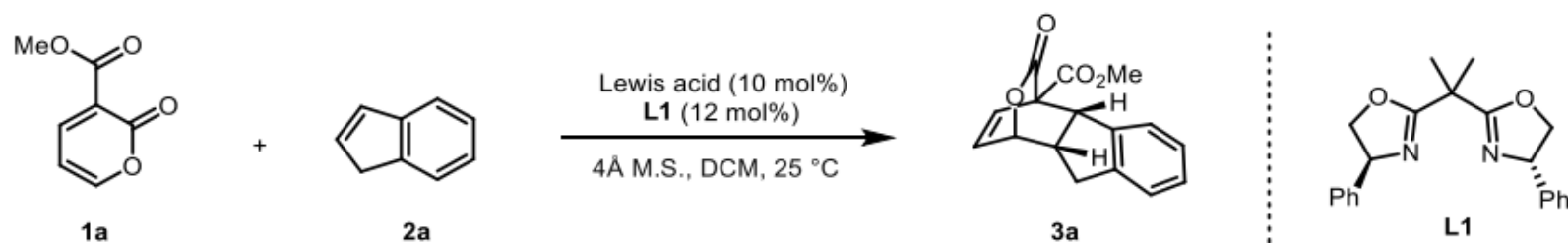
Catalytic Asymmetric Inverse-Electron-Demand Diels–Alder Reactions of 2-Pyrones with Indenes: Total Syntheses of Cephanolides A and B

Yang Lu, Meng-Meng Xu, Zhi-Mao Zhang, Junliang Zhang, and Quan Cai*

c. Enantioselective IEDDA reactions of 2-pyrones with indenenes (this work)



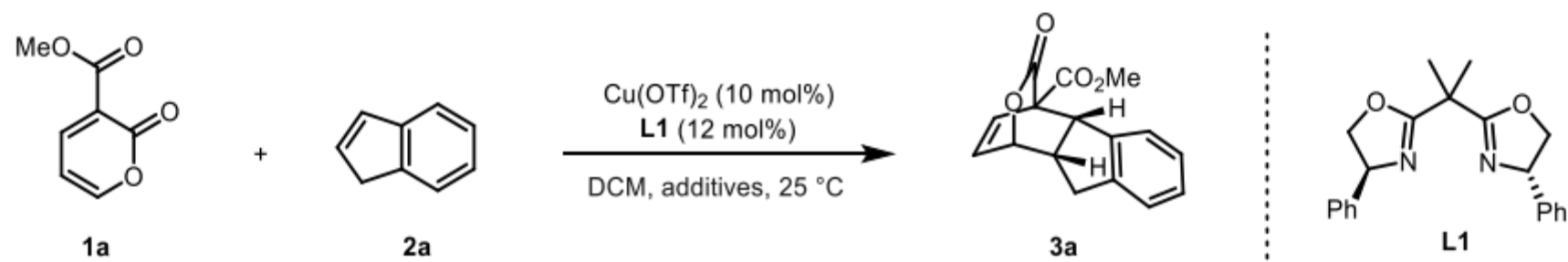
- electron-deficient 2-pyrones
- electronically unbiased indenenes
- highly functionalized hexahydrofluorenyl lactones
- high yield, high dr, high ee
- asymmetric total syntheses of cephanolides A and B

Table S1. Investigation of Lewis acids^a

entry	Lewis acid	t/h	yield (%) ^b	ee (%) ^c
1	Cu(OTf) ₂	12	99	62
2	Cu(ClO ₄) ₂ •6H ₂ O	12	98	59
3	Cu(OAc) ₂	24	3	0
4	Cu(OCOCF ₃) ₂	24	3	0
5	Cu(NTf ₂) ₂	12	99	49
6	CuBr ₂	12	trace	--
7	Cu(CH ₃ CN)PF ₆	24	6	0
8	Cu(BF ₄) ₂ •xH ₂ O	12	97	63
9	Cu(CH ₃ CN) ₄ BF ₄	24	6	0

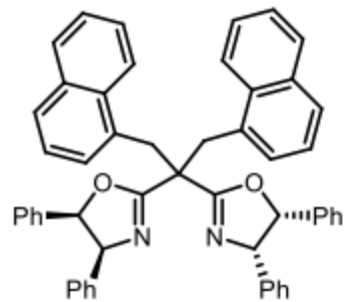
^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), Lewis acid (10 mol%), **L1** (12 mol%), 4 Å M.S. (50.0 mg) in DCM (1.0 mL) at 25 °C. ^b Isolated yield. ^c Determined by HPLC analysis. M.S., molecular sieves. DCM = dichloromethane.

Table S2. Investigation of Additives^a



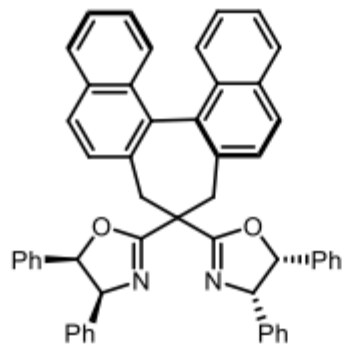
entry	additives	<i>t</i> /h	yield (%) ^b	ee (%) ^c
1	-	12	77	62
2	3 Å M.S.	12	76	62
3	4 Å M.S.	12	99	62
4	5 Å M.S.	12	97	62

^aReaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $\text{Cu}(\text{OTf})_2$ (10 mol%), **L1** (12 mol%), additives (50.0 mg) in DCM (1.0 mL) at 25 °C. ^bIsolated yield. ^cDetermined by HPLC analysis.



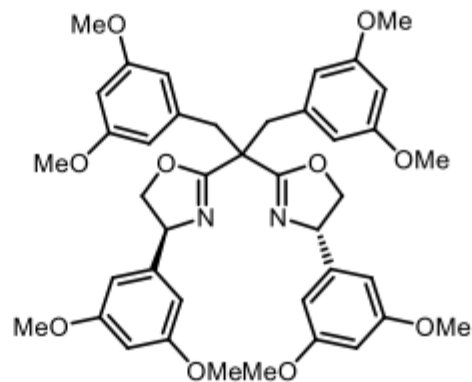
L21

99%, 63% ee



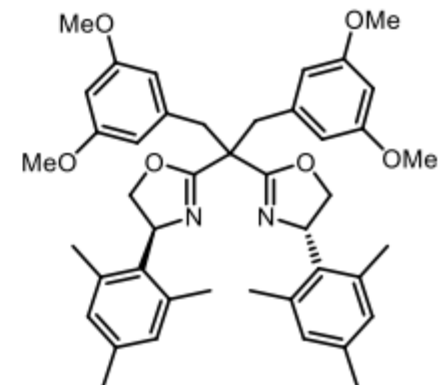
L22

85%, 66% ee



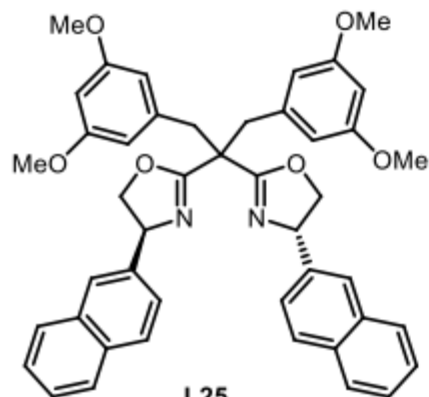
L23

98%, 79% ee



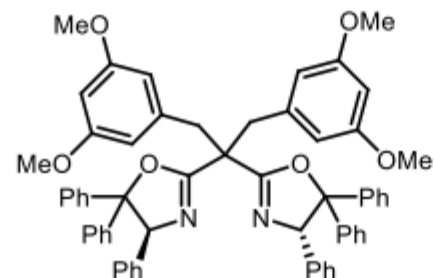
L24

93%, 78% ee



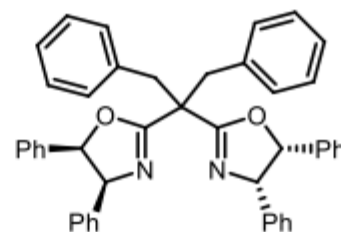
L25

88%, 70% ee



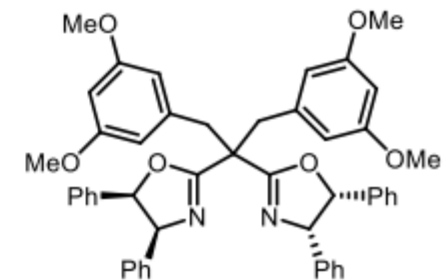
L26

99%, 53% ee



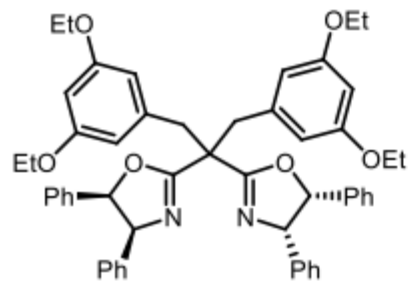
L27

98%, 69% ee



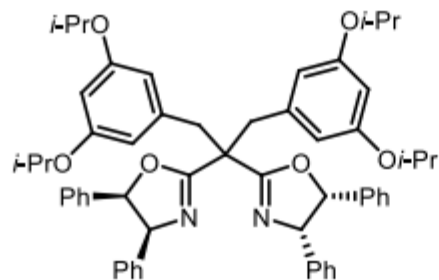
L28

94%, 78% ee



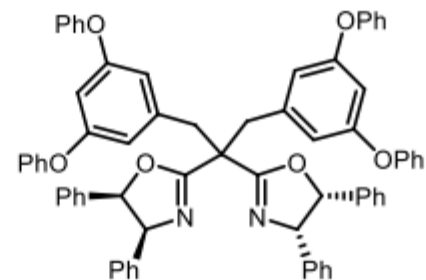
L29

99%, 81% ee



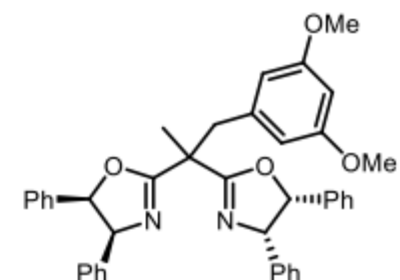
L30

99%, 85% ee



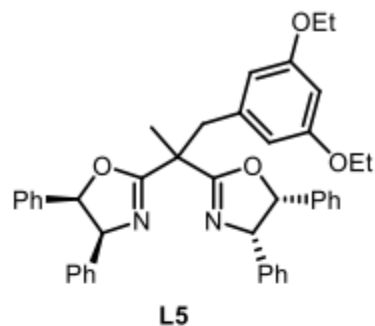
L31

93%, 90% ee



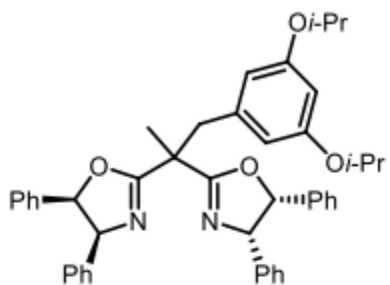
L4

97%, 81% ee



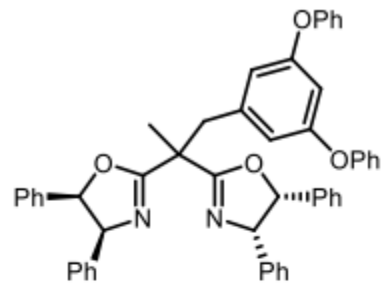
L5

98%, 85% ee



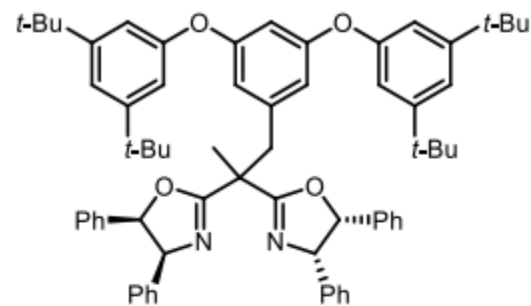
L6

99%, 87% ee



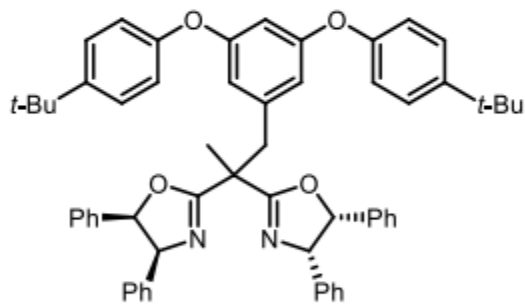
L7

99%, 92% ee



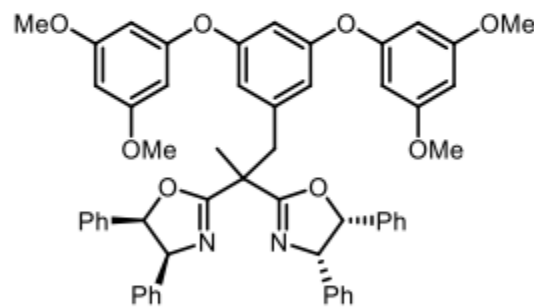
L32

99%, 88% ee



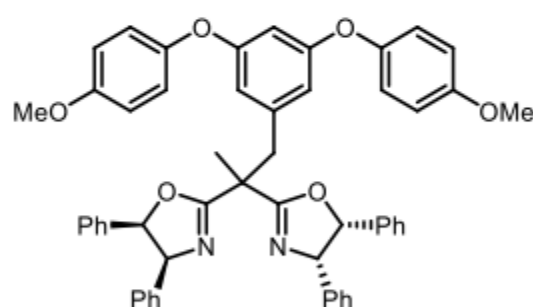
L33

99%, 91% ee



L34

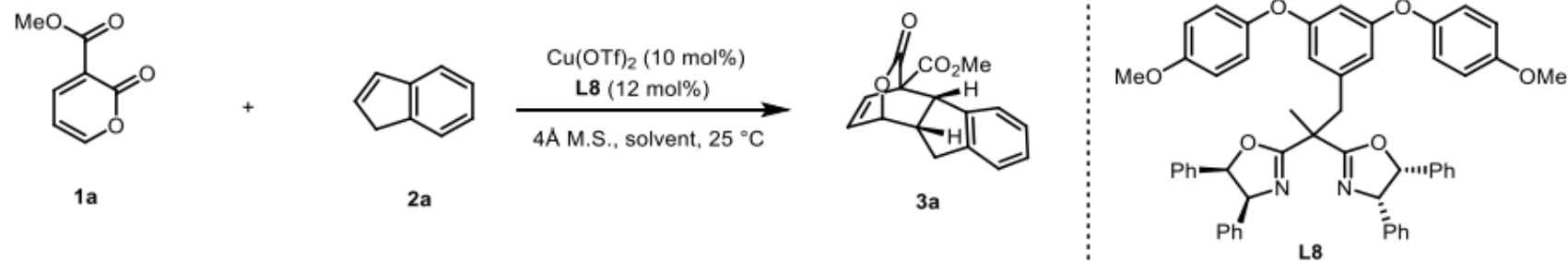
98%, 92% ee



L8

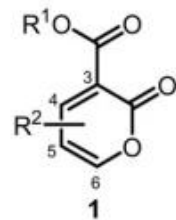
93%, 94% ee

^aReaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), Cu(OTf)₂ (10 mol%), Ligand (12 mol%), 4 Å M.S. (50.0 mg) in DCM (1.0 mL) at 25 °C. ^bIsolated yield. ^cDetermined by HPLC analysis.

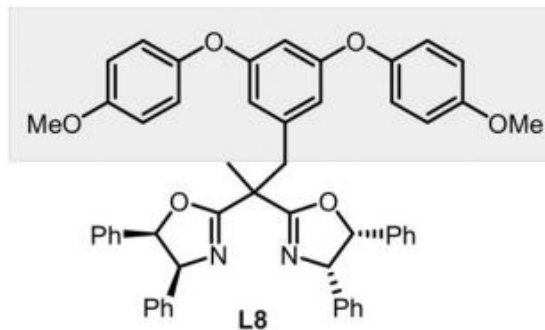
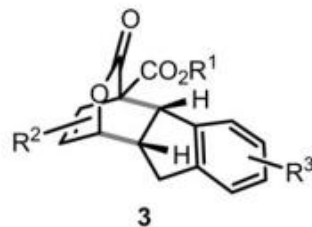
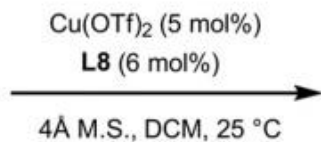
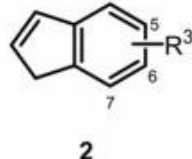
Table S4. Investigation of Solvents^a

entry	solvent	<i>t</i> /h	yield (%) ^b	ee (%) ^c
1	DCM	12	93	94
2	DCE	12	86	94
3	CHCl_3	12	99	94
4	PhCl	12	99	84
5	Toluene	22	94	79
6	THF	22	99	70
7 ^d	DCM	12	99	94

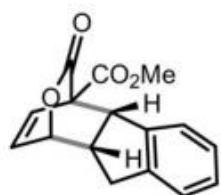
^aReaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $\text{Cu}(\text{OTf})_2$ (10 mol%), **L8** (12 mol%), 4 Å M.S. (25 mg) in DCM (0.5 mL) at 25 °C. ^bIsolated yield. ^cDetermined by HPLC analysis. ^d**1a** (0.2 mmol), **2a** (0.3 mmol), $\text{Cu}(\text{OTf})_2$ (5 mol%), **L8** (6 mol%), 4 Å M.S. (50 mg) in DCM (1.0 mL) at 25 °C. DCE = dichloroethane; THF = tetrahydrofuran.



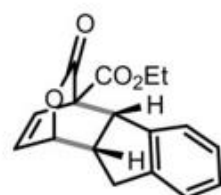
+



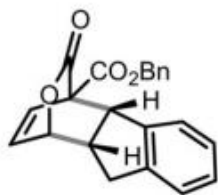
Scope of 2-pyrones



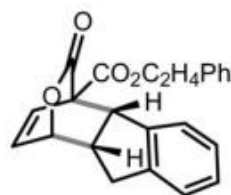
3a, 99%, 94% ee



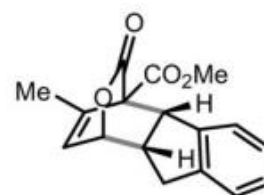
3b, 90%, 93% ee



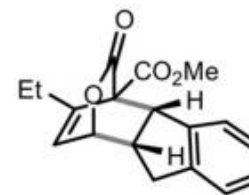
3c, 99%, 92% ee



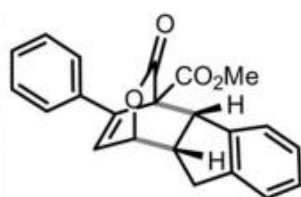
3d, 96%, 94% ee



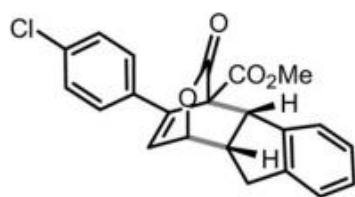
3e, 93%, 85% ee



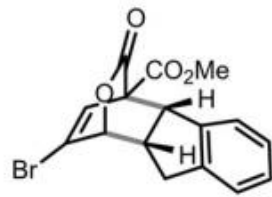
3f, 94%, 82% ee



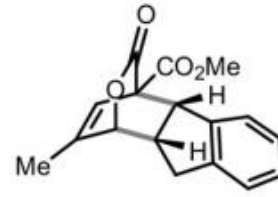
3g, 99%, 73% ee



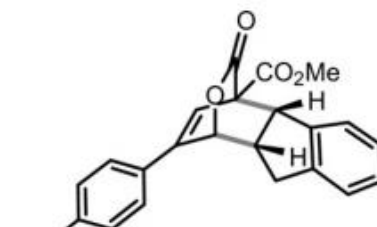
3h, 95%, 71% ee



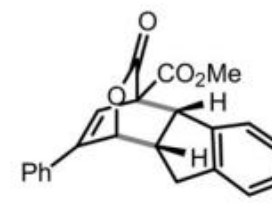
3i, 97%, 88% ee



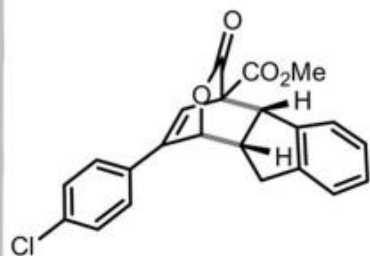
3j, 46%, 90% ee



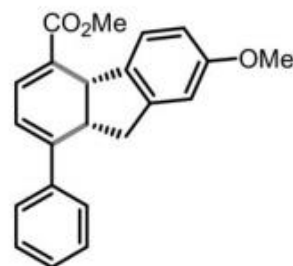
3k, 99%, 89% ee



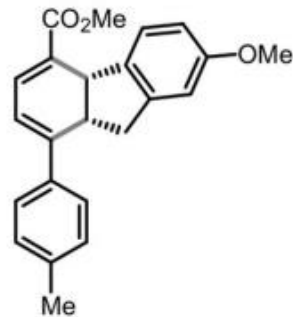
3l, 97%, 90% ee



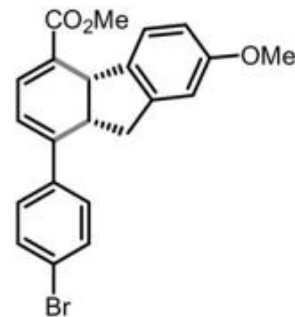
3m, 99%, 89% ee



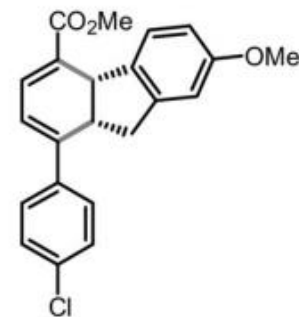
4a, 97%, 95% ee^d



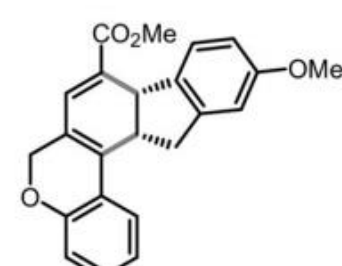
4b, 70%, 94% ee^d



4c, 91%, 93% ee^d

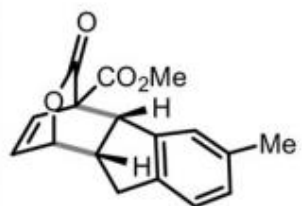


4d, 86%, 93% ee^d

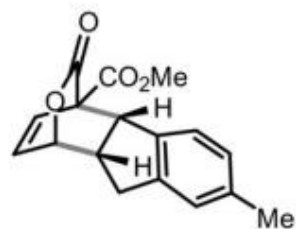


4e, 95%, 95% ee^d

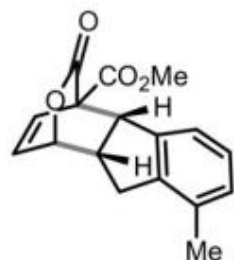
Scope of indenenes



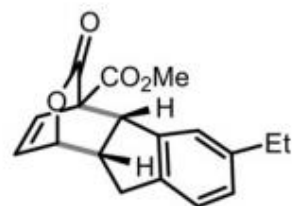
3n, 95%, 92% ee



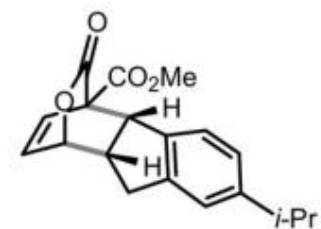
3o, 99%, 94% ee



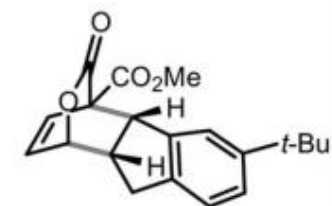
3p, 98%, 94% ee



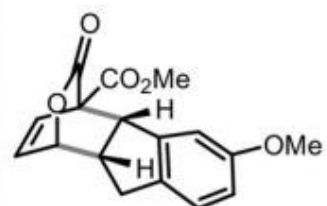
3q, 98%, 94% ee



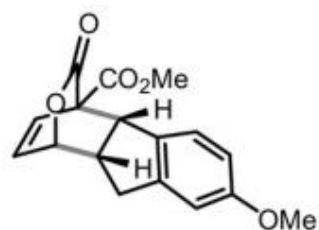
3r, 98%, 94% ee



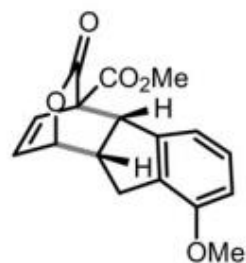
3s, 97%, 96% ee



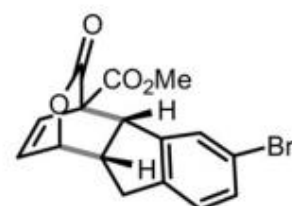
3t, 96%, 97% ee



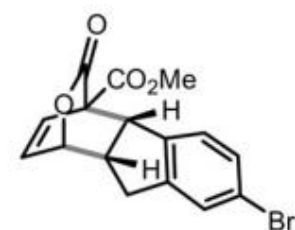
3u, 98%, 95% ee



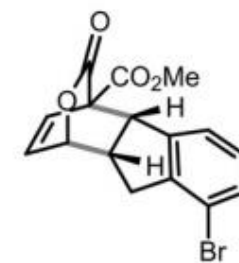
3v, 98%, 92% ee



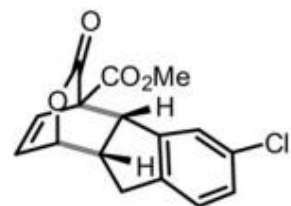
3w, 92%, 93% ee



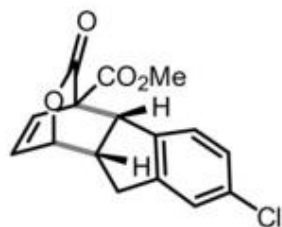
3x, 98%, 95% ee



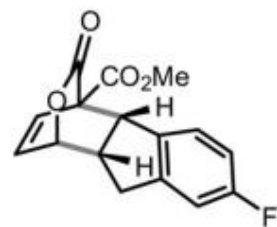
3y, 97%, 93% ee



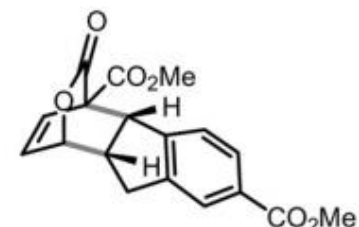
3z, 90%, 93% ee



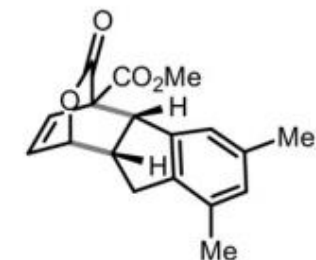
3aa, 98%, 95% ee



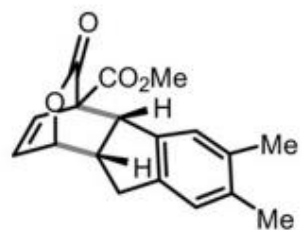
3ab, 99%, 95% ee



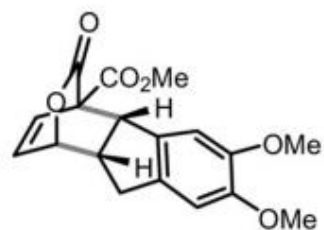
3ac, 93%, 92% ee



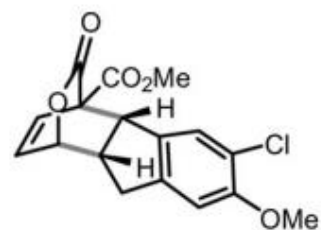
3ad, 95%, 92% ee



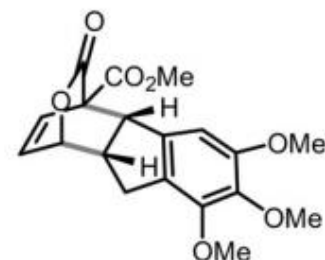
3ae, 89%, 92% ee



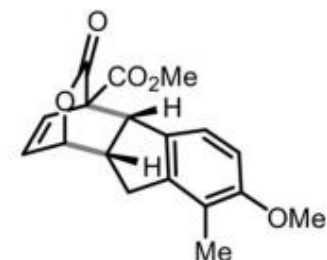
3af, 99%, 98% ee



3ag, 99%, 95% ee

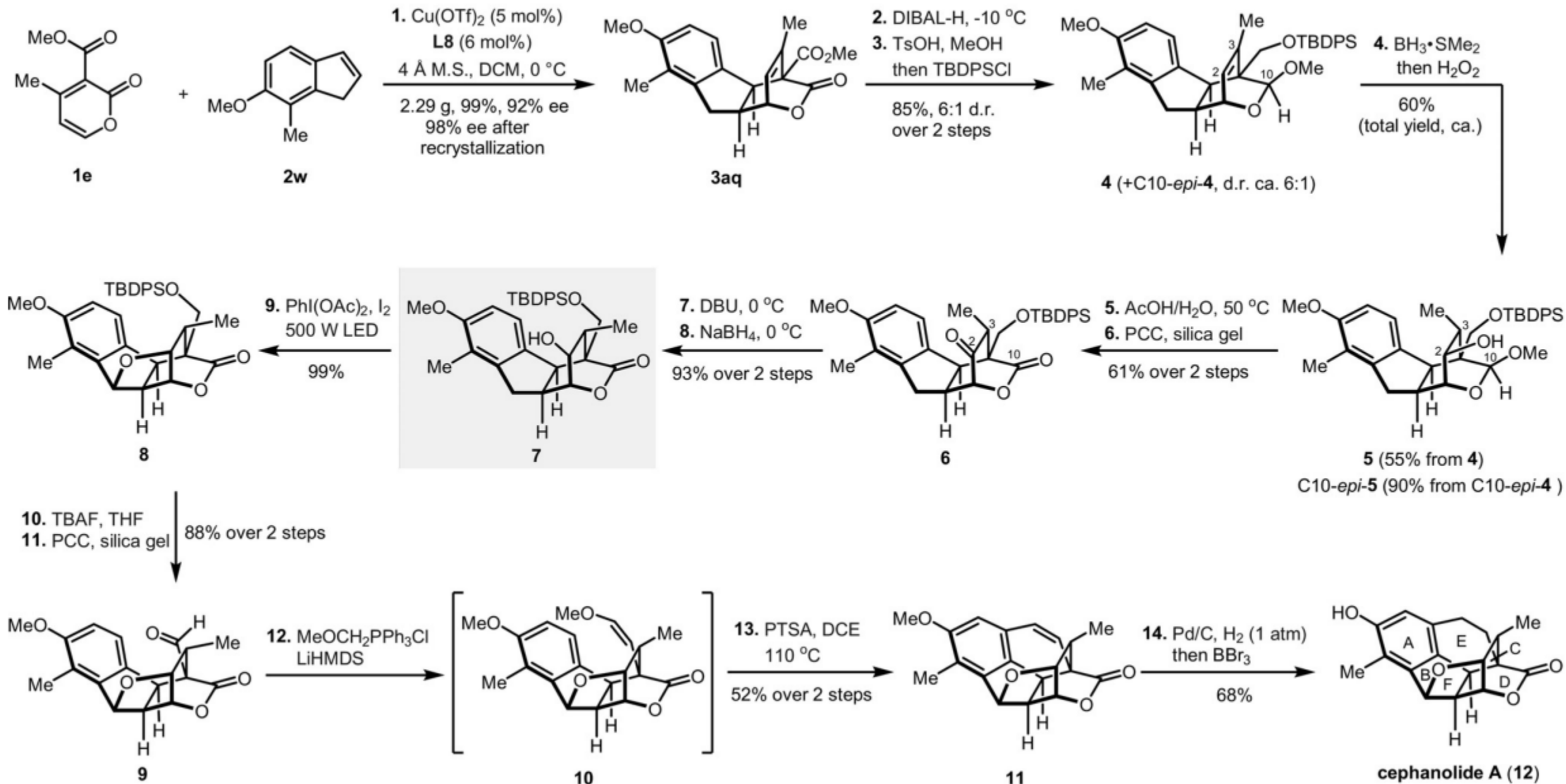


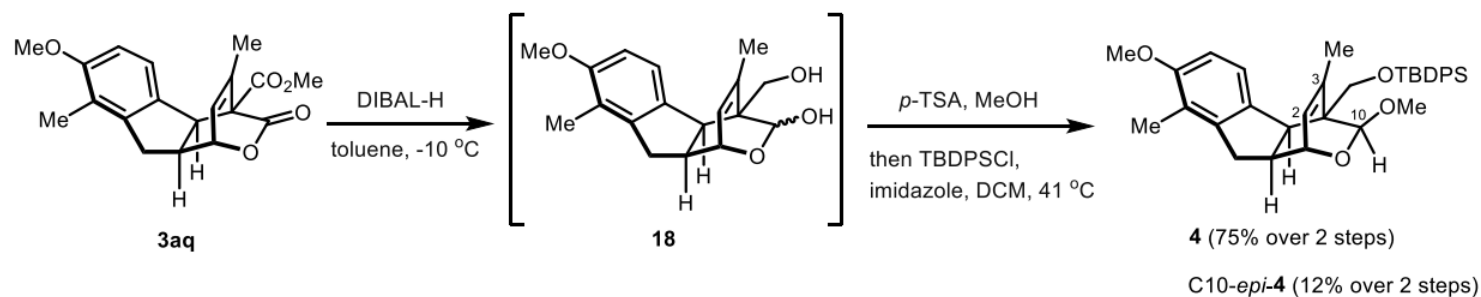
3ah, 99%, 97% ee



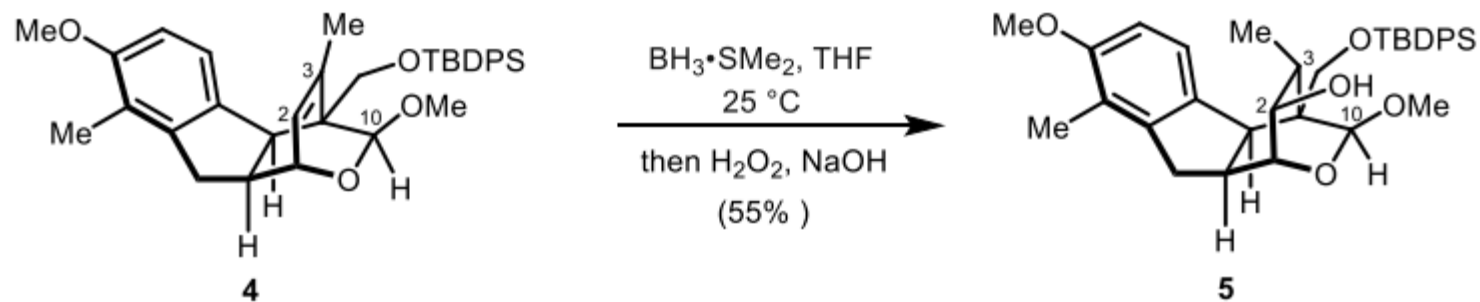
3ai, 96%, 94% ee

a. Asymmetric total synthesis of cephanolide A

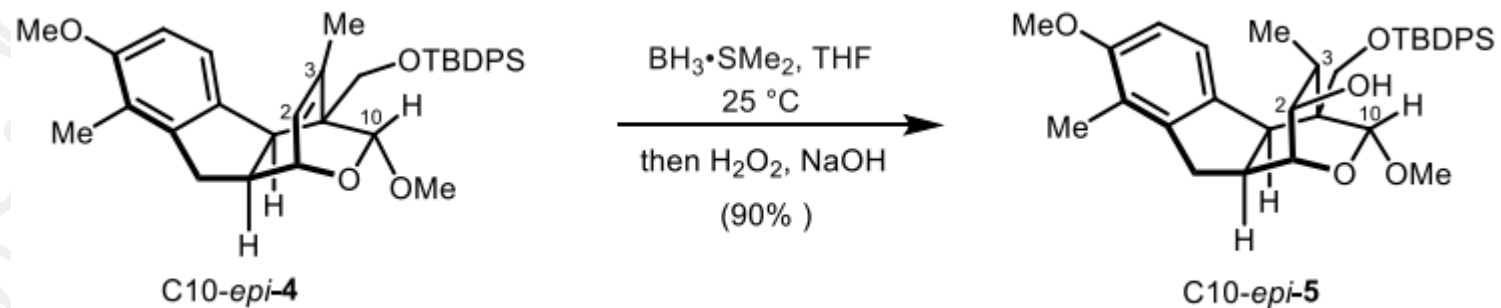


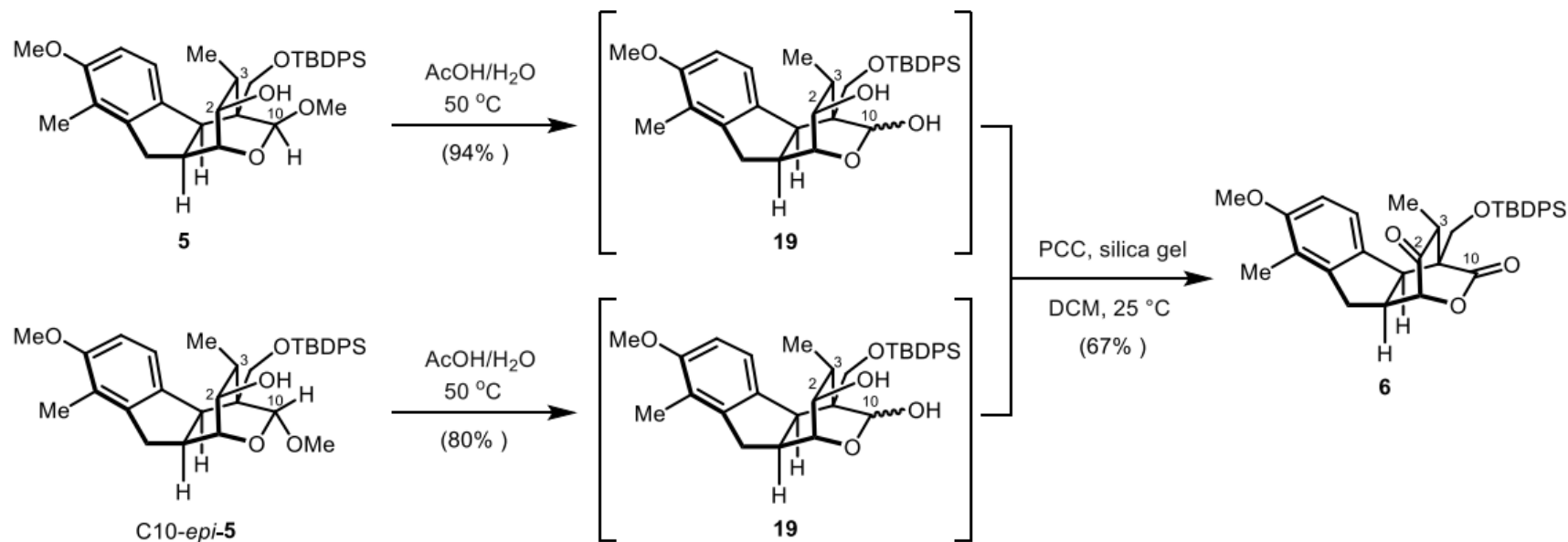


1. 酯基还原
2. 羟基的保护 (MeOH/TBDPSCI)



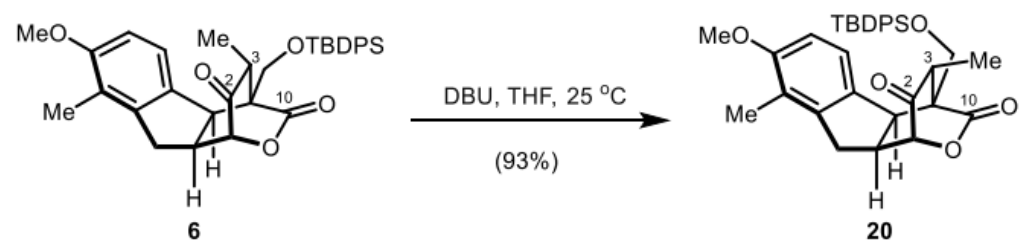
1. 硼氢化氧化 (顺式加成)



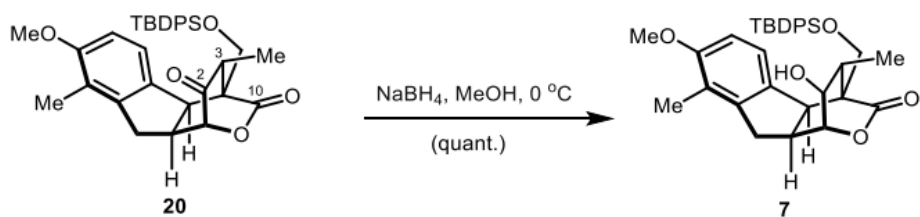


1. 水解

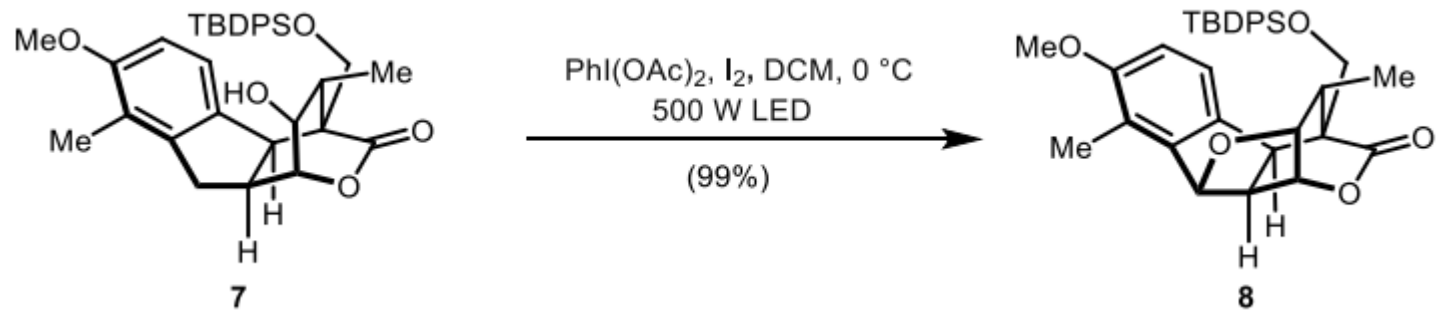
2. 羟基氧化(PCC氯铬酸吡啶盐)



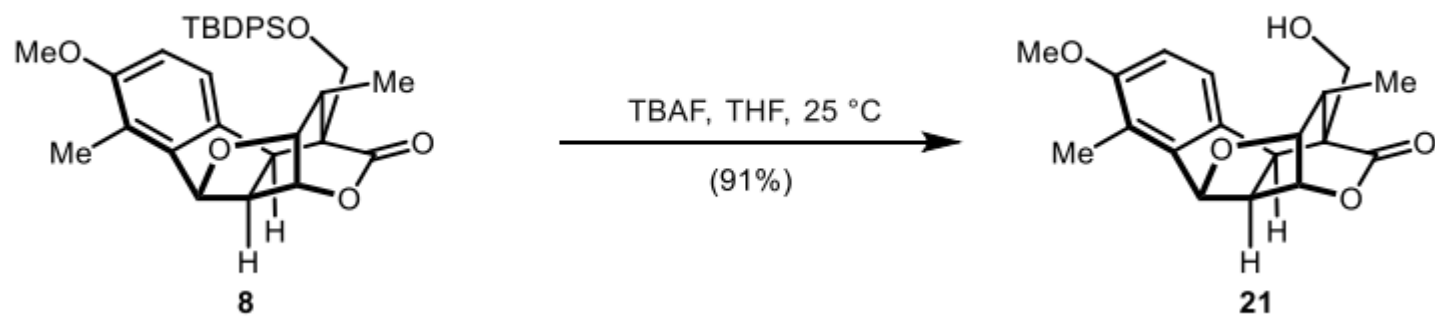
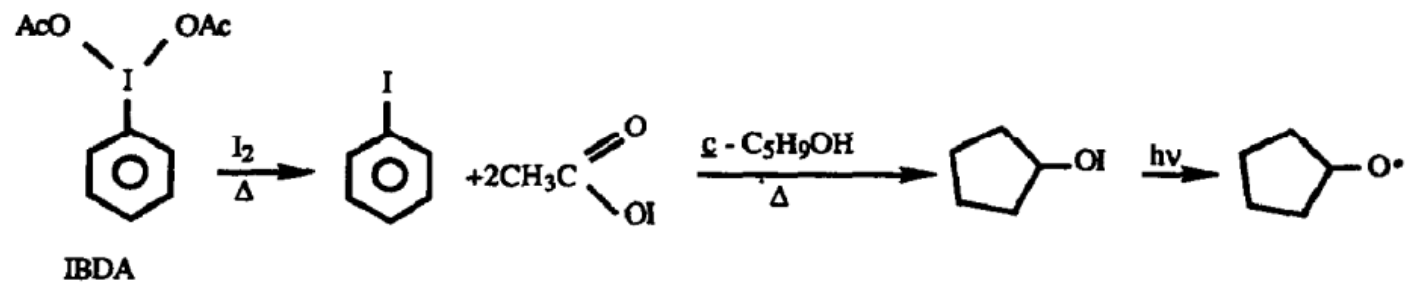
DBU 差向异构



酮的还原

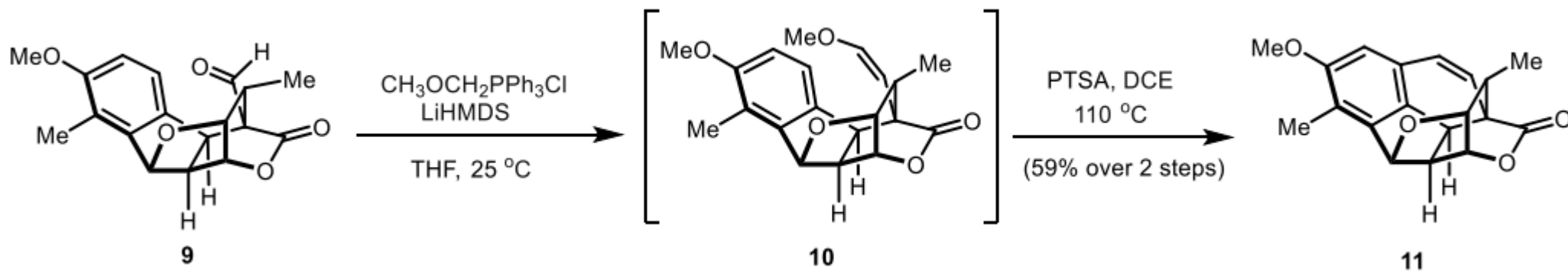
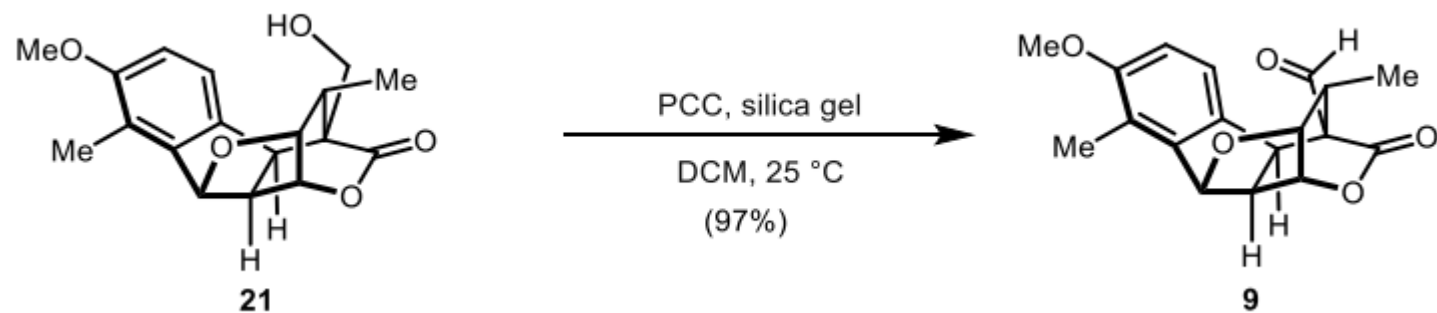


Suarez reaction

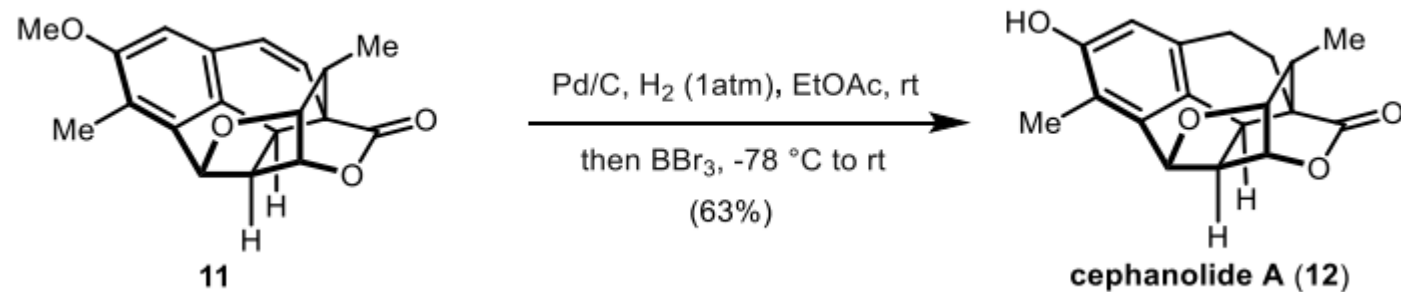


脱保护

羟基氧化



1. Wittig Reaction 2. intramolecular Friedel–Crafts reaction



1. 加氢还原
2. 脱保护

谢谢



1852946 · Shenghan Cai