



手性晶体在绝对不对称 合成中的应用

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时 间 : 2025.11.21



1

背景介绍

2

手性晶体作反应试剂

3

手性晶体作手性催化剂或手性引发剂

4

总结与展望

01 PART TWO

背景介绍





1. 自然界手性起源
2. 绝对不对称合成
3. 晶体手性
4. 晶体手性保留



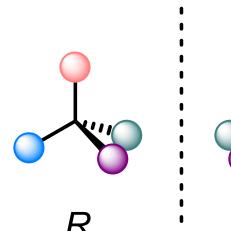
背景介绍 — 自然界手性起源

- ## 手性起源假说
- 自然界的[手性](#)
 - 偏振光 — 不对称光解为例
 - 结晶诱导自发拆分 — 巴斯德实验
 - 绝对不对称合成 — 从化学反应的角度解释自然界手性的产生
- 自然界的[手性](#)**

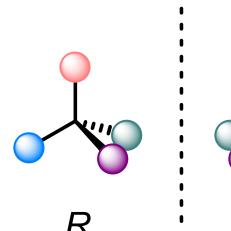
NC(C(=O)O)C([R])C
L-Amino Acid

O[C@H]1OC(O)[C@H](O)[C@H](O)[C@H]1O
D-Sugars

CCNCC[C@H](O)C1=CC(O)=CC(O)=C1
L-Epinephrine

OC1=C(O)C(O[C@H]2[C@H](O)[C@H](O)[C@H]2O)[C@H](O)[C@H]1O
Ascorbic Acid
- 自然界广泛存在手性分子
手性现象对生命有重要作用
- 

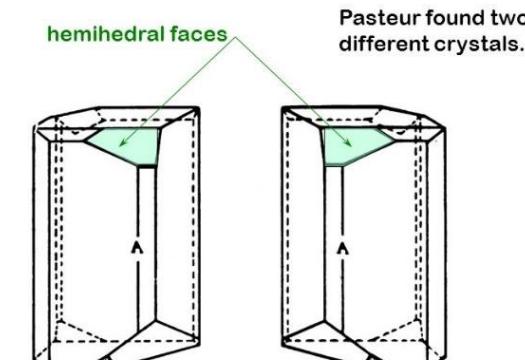
偏振光 — 不对称光解为例



(I)-CPL

(r)-CPL

$R \rightarrow S^* + R$ → R excess, S degradation

$S \rightarrow S + R^*$ → S excess, R degradation
- 结晶诱导自发拆分 — 巴斯德实验
- Crystals of Sodium Ammonium Tartrate**
- 

hemihedral faces

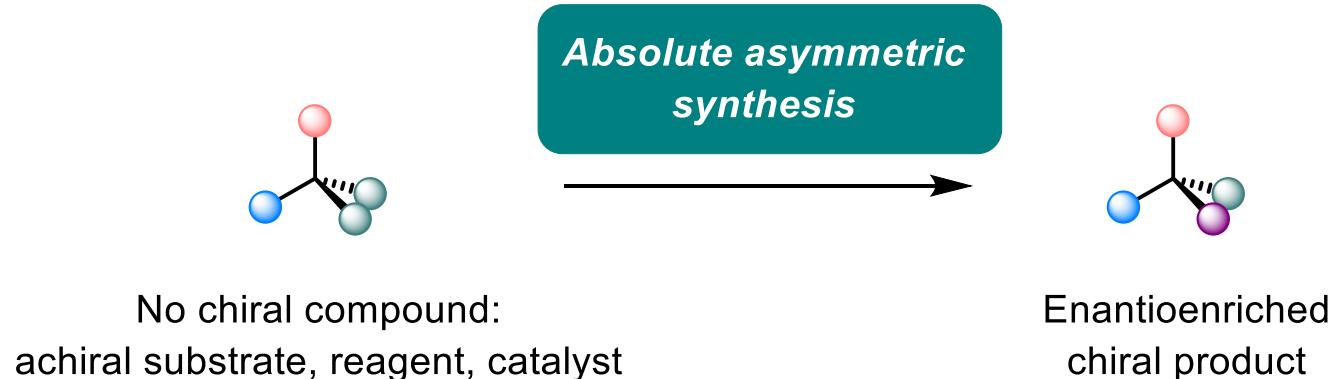
mirror images

Pasteur found two different crystals.
- M. Raynal et al. *Chem. Soc. Rev.* 2022, 51, 3436–3476.
- 5



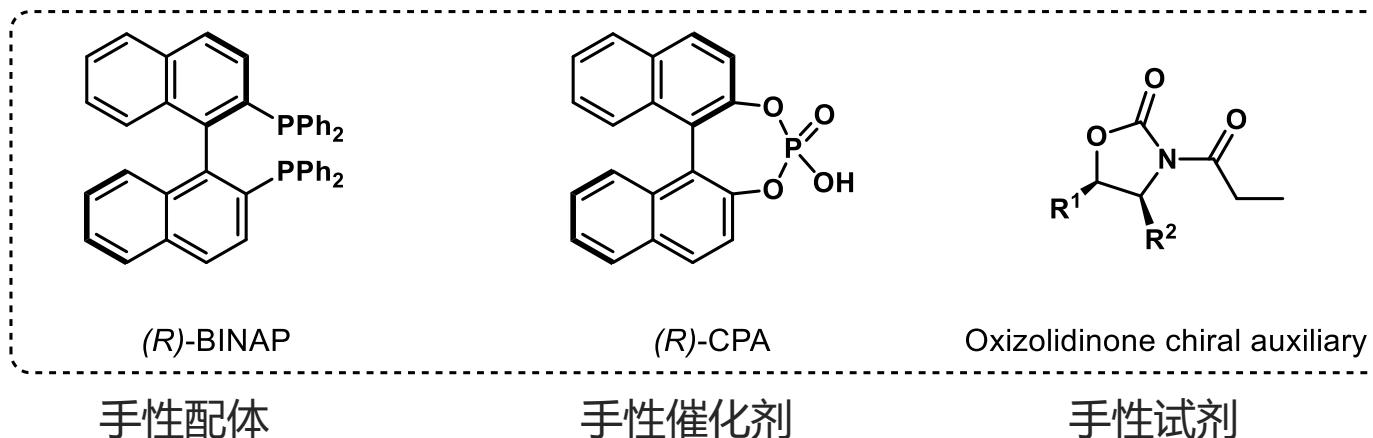
背景介绍 — 绝对不对称合成

绝对不对称合成



- ✓ 无手性催化剂
- ✓ 无手性底物
- ✓ 手性产物
- ✓ 手性的“从无到有”

不对称合成



- ✓ 外源手性分子诱导
- ✓ 手性配体
- ✓ 手性催化剂
- ✓ 手性试剂
- ✓ 手性在“分子间的传递”



背景介绍 — 绝对不对称合成

对映选择性放大

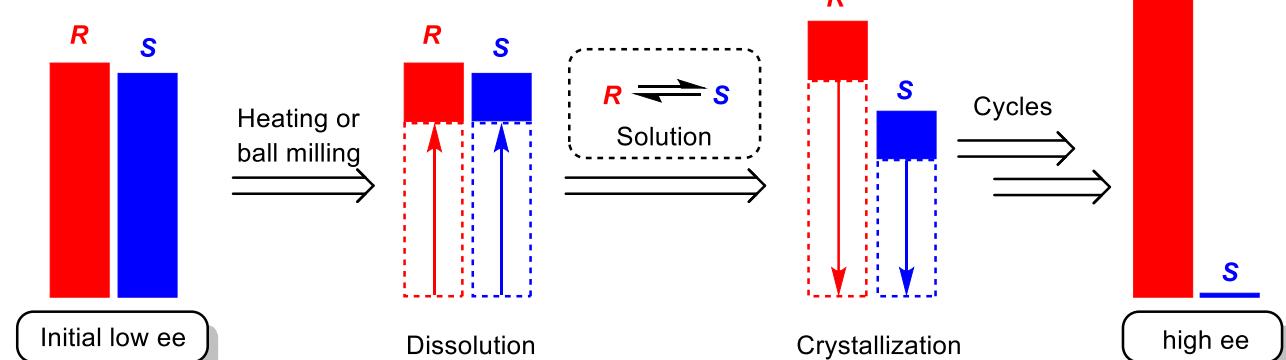
手性引发因素

- ✓ 统计学波动
- ✓ 偏振光
- ✓ **晶体手性**

起始诱导
ee值较低
手性放大策略

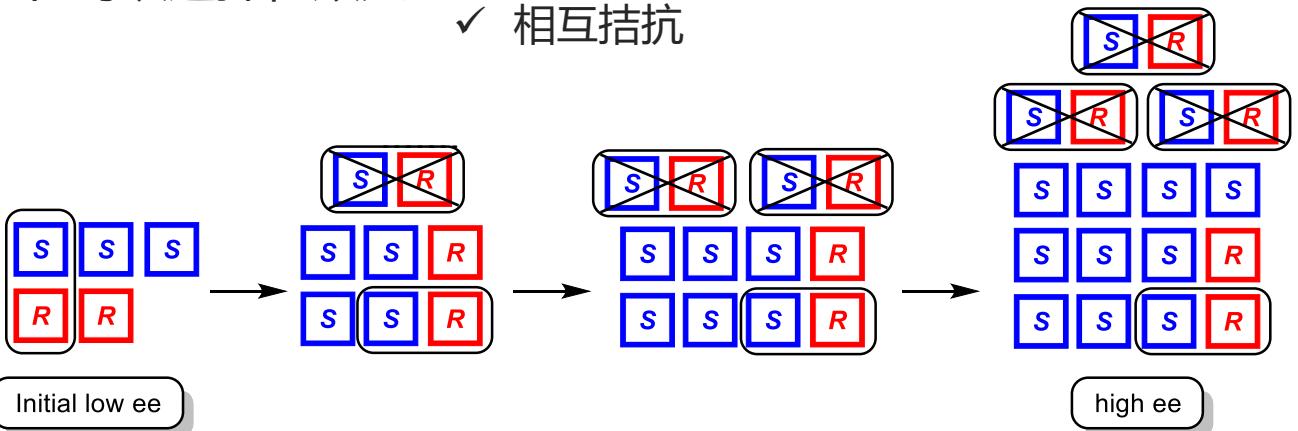
□ 结晶诱导的对映选择性放大

- ✓ 磨损增强
- ✓ 温度循环



□ 自催化对映选择性放大

- ✓ 对映体自我复制
- ✓ 相互拮抗



D. G. Blackmond, *Chem. Rev.* **2020**, *120*, 4831–4847.

E. Vlieg and F. P. J. T. Rutjes et al., *Chem. Soc. Rev.* **2015**, *44*, 6723–6732.



背景介绍 — 晶体手性

手性无机晶体

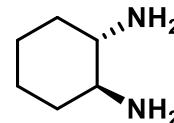


HgS 晶体

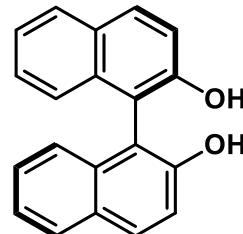


石英晶体

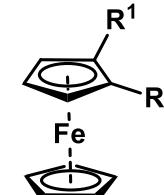
分子手性



中心手性

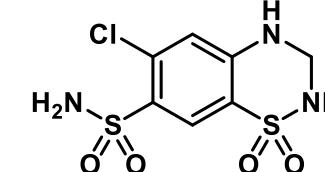


轴手性

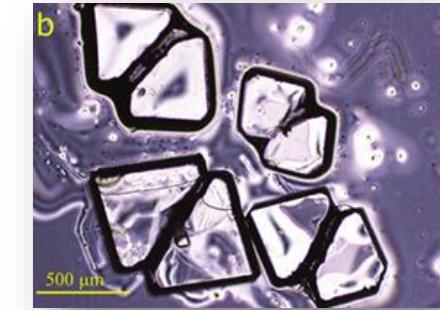


面手性

手性有机晶体



氢氯噻嗪



- ✓ **晶体手性来源:** 分子手性或非对称堆积导致的对称性破缺
- ✓ **晶体手性的描述:** Sohncke空间群
- ✓ **有机化合物常见晶体手性空间群:** $P2_12_12_1$ or $P2_1$

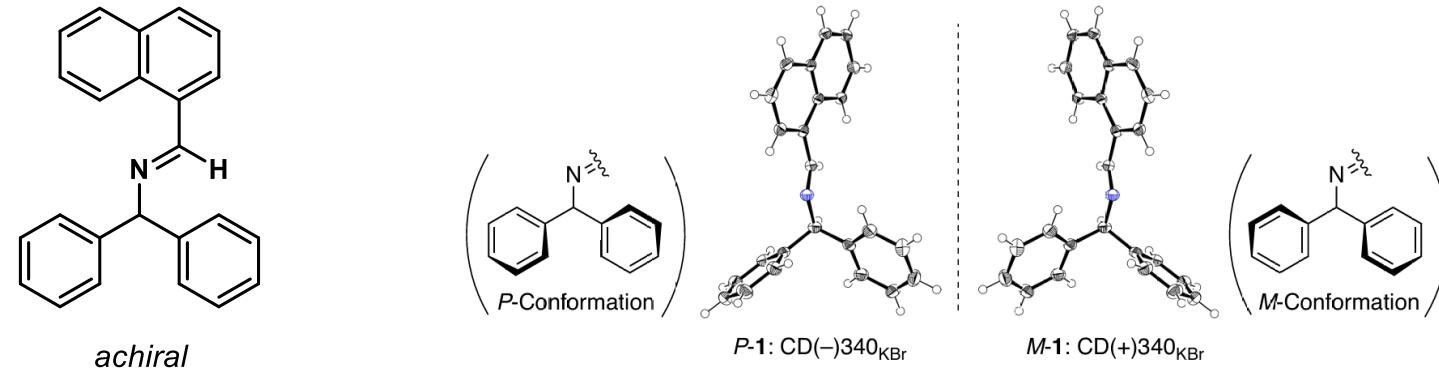
R.M. Hazen and D. S. Sholl, *Nat. Mater.* **2003**, *2*, 367–374.

G. H. Fecher et al. *Materials* **2022**, *15*, 5812–5843.

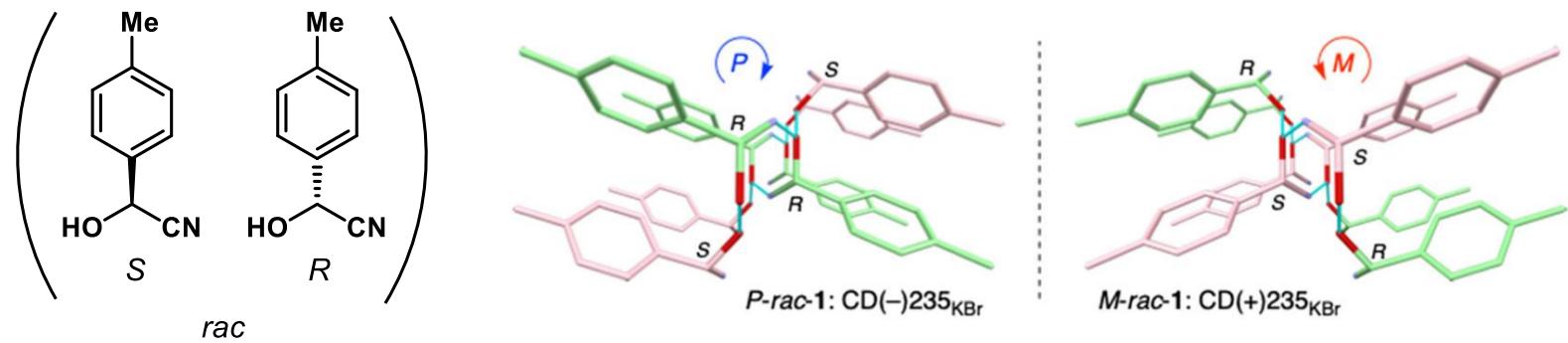


手性有机晶体类型

□ 非手性化合物手性晶体



□ 外消旋化合物手性晶体





背景介绍 — 晶体手性

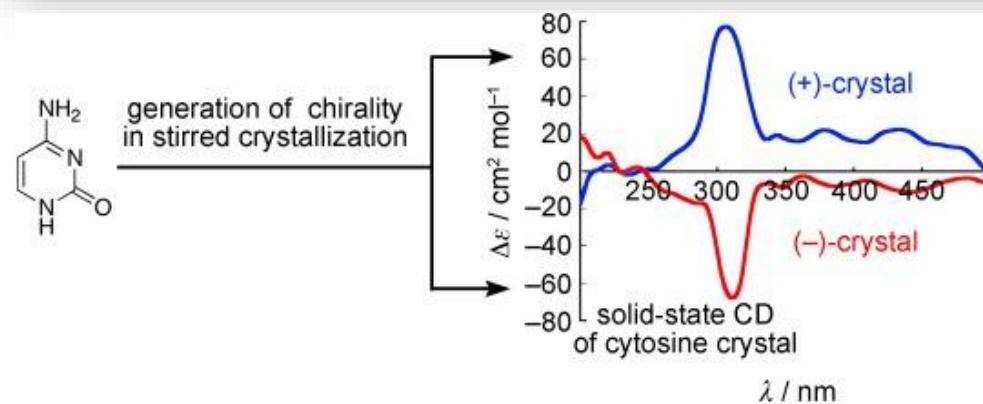


X 射线单晶衍射



- ✓ 晶体绝对构型
- ✓ 晶体空间群

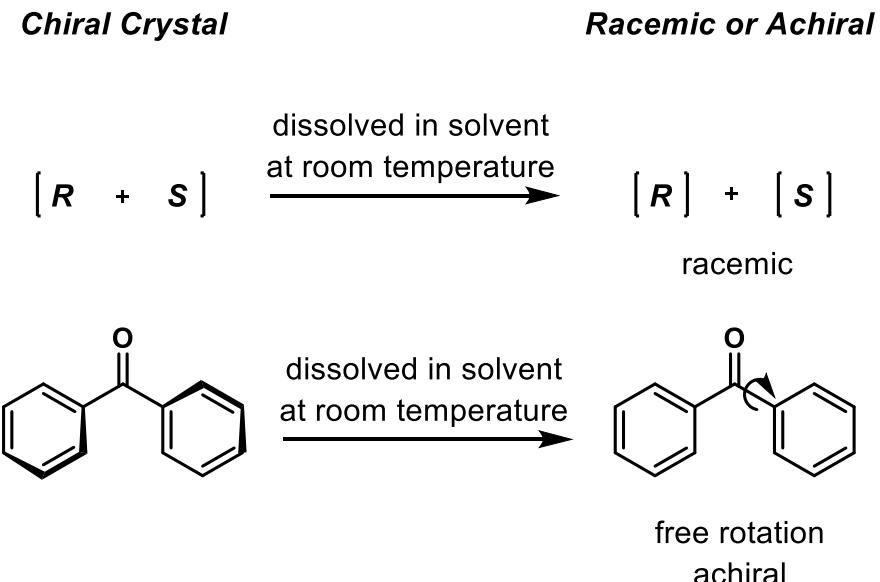
固态圆二色性光谱



- ✓ 手性晶体对左、右圆偏振光的吸收差异
- ✓ 类比旋光仪



快速消旋化



- ✓ 外消旋化合物手性晶体: R: S = 1: 1
- ✓ 非手性化合物手性晶体: 固定的手性构象快速翻转

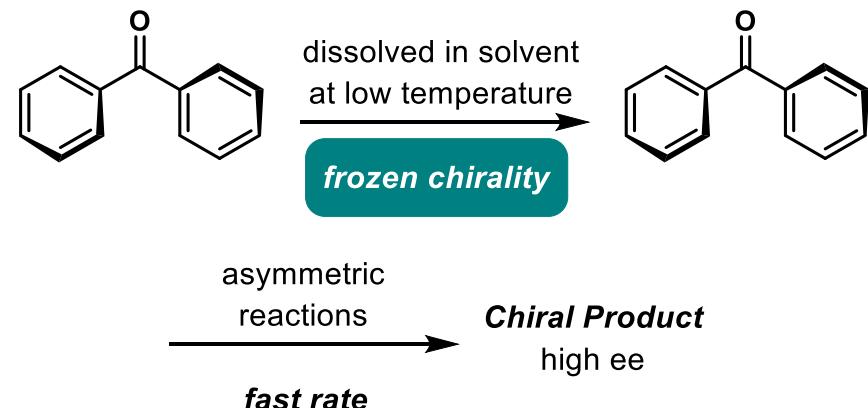
晶体手性保留策略

□ 非均相/固相反应

Gas Reactant *Chiral Product Deposition*

**Chiral Crystals
Reactant**

□ 低温反应



PART TWO
02

手性晶体作反应试剂





手性晶体作反应试剂



1. 固相反应
2. 低温反应



手性晶体作反应试剂

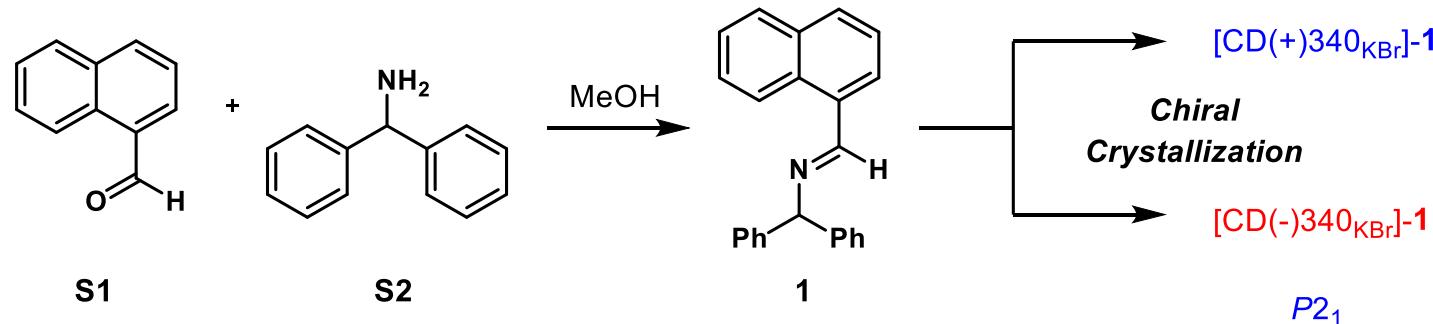


1. 固相反应
2. 低温反应

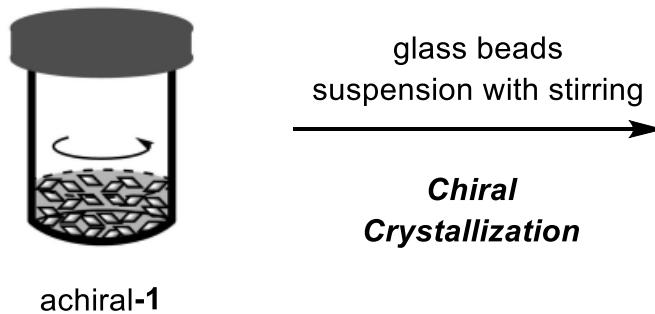


固相反应 — 固-气 Strecker 反应

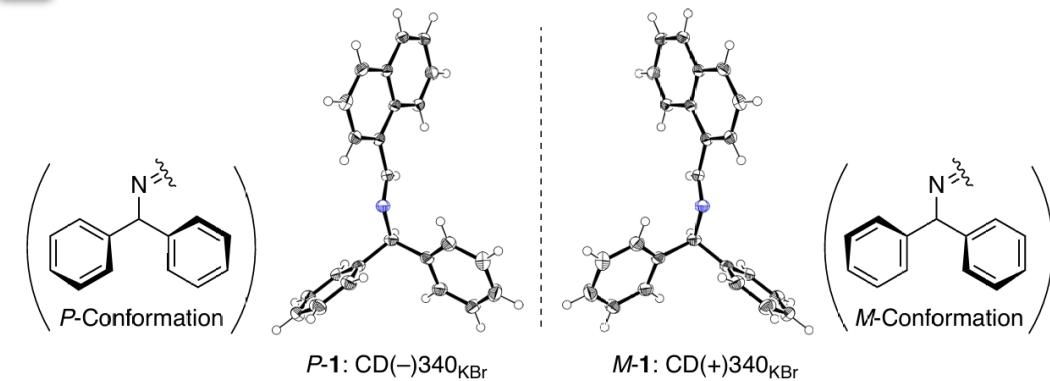
手性晶体制备



手性晶体制备示意图

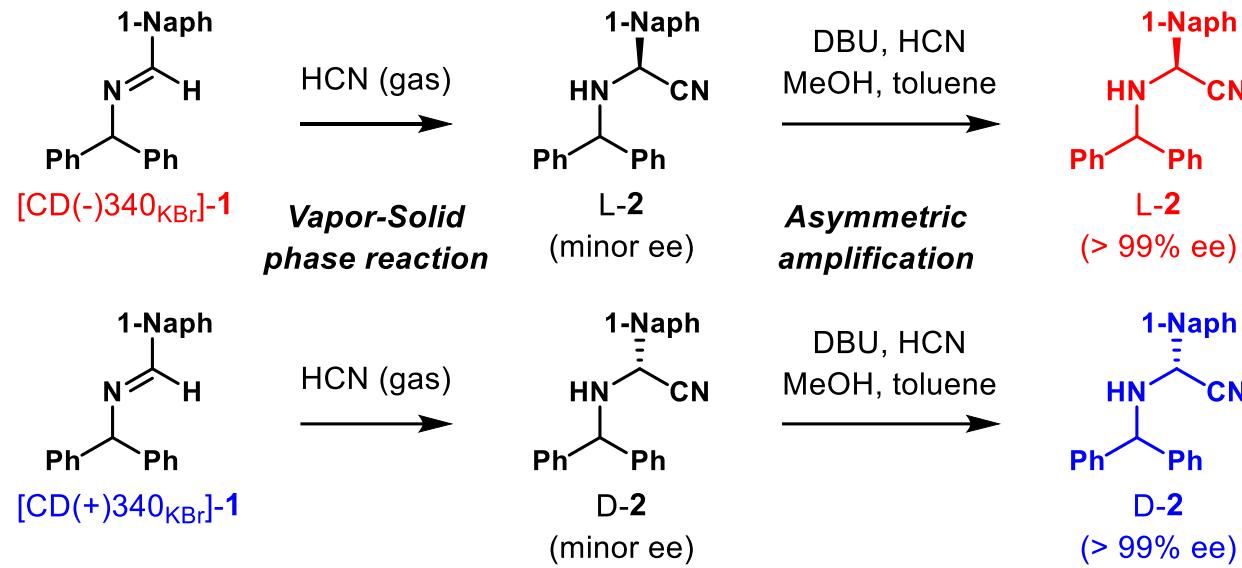


手性晶体结构





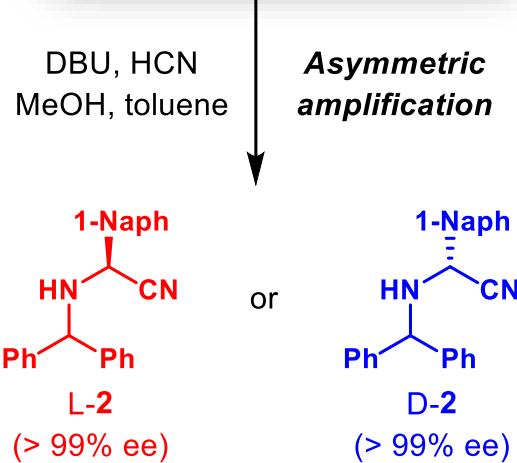
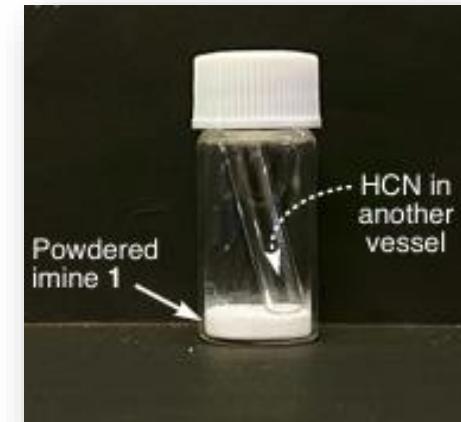
固相反应—固-气 Strecker 反应



Entry	Imine 1	yield	ee/% (config.) of 2
1	$[CD(-)340_{KBr}] \cdot \mathbf{1}$	18%	7% (L)
2	$[CD(+)340_{KBr}] \cdot \mathbf{1}$	23%	7% (D)
3	$[CD(-)340_{KBr}] \cdot \mathbf{1}$	34%	2% (L)
4	$[CD(-)340_{KBr}] \cdot \mathbf{1}$	67%	>99% (L)
5	$[CD(+)340_{KBr}] \cdot \mathbf{1}$	60%	>99% (D)
6	$[CD(-)340_{KBr}] \cdot \mathbf{1}$	53%	>99% (L)
7	$[CD(+)340_{KBr}] \cdot \mathbf{1}$	56%	>99% (D)

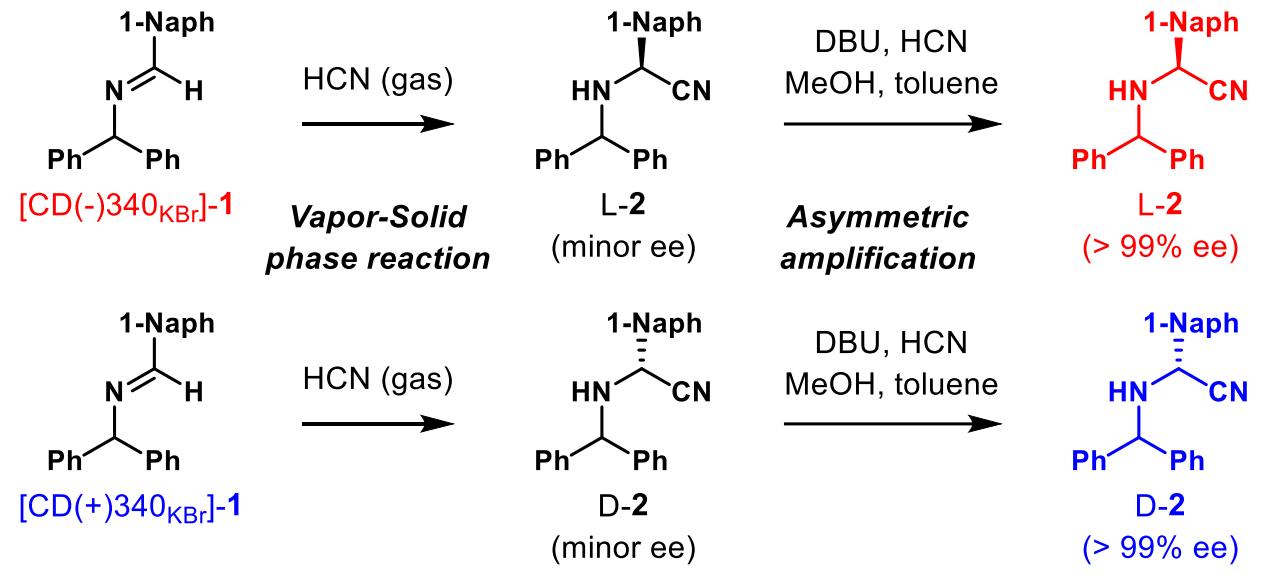
Asymmetric amplification

反应装置示意图





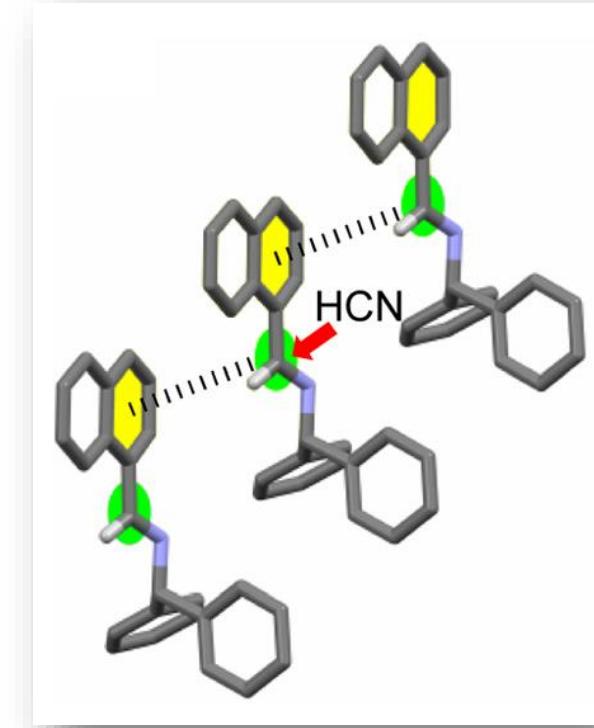
固相反应—固-气 Strecker反应



Entry	Imine 1	yield	ee/% (config.) of 2
1	[CD(-)340 _{KBr}]-1	18%	7% (L)
2	[CD(+)340 _{KBr}]-1	23%	7% (D)
3	[CD(-)340 _{KBr}]-1	34%	2% (L)
4	[CD(-)340 _{KBr}]-1	67%	>99% (L)
5	[CD(+)340 _{KBr}]-1	60%	>99% (D)
6	[CD(-)340 _{KBr}]-1	53%	>99% (L)
7	[CD(+)340 _{KBr}]-1	56%	>99% (D)

Asymmetric amplification

□ 晶体手性对产物手性的控制



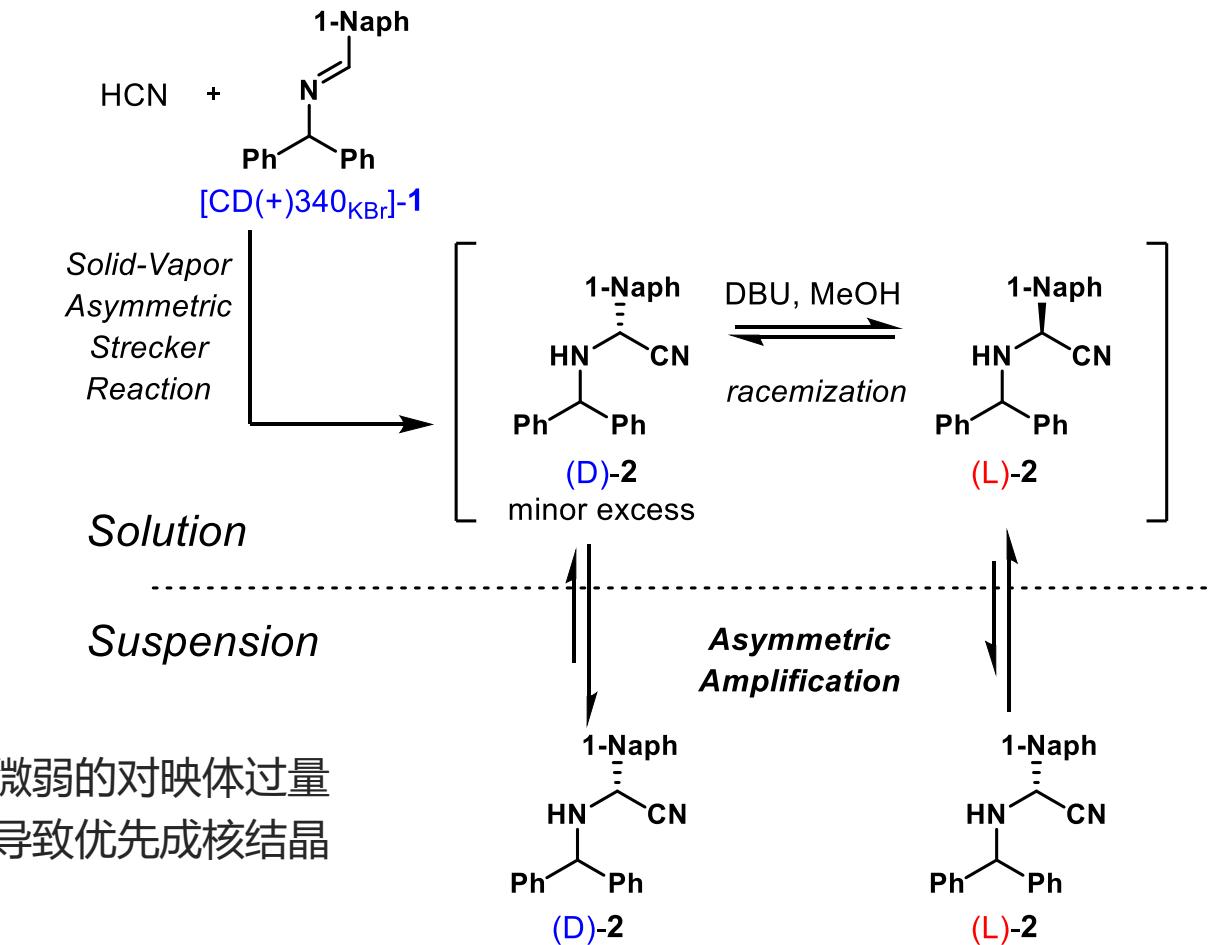
晶体中HCN分子
立体选择性进攻

[CD(+) 340_{KBr}]-1

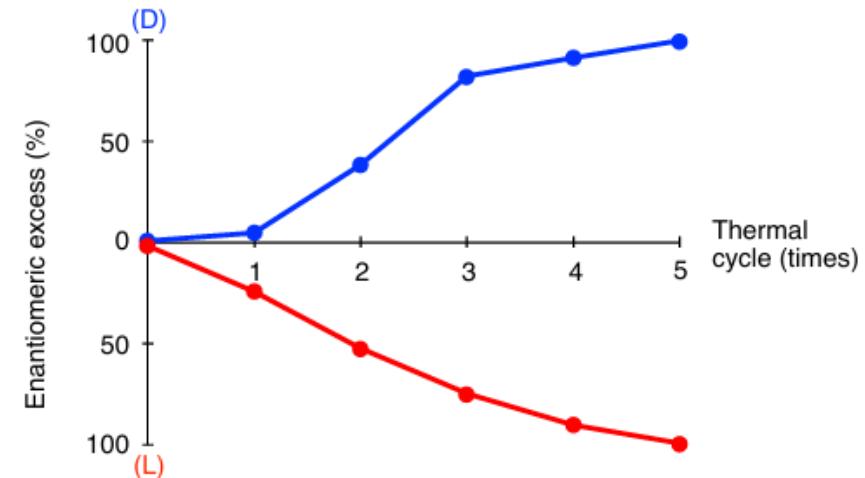


固相反应 — 固-气 Strecker 反应

结晶诱导的对映选择性放大



温度循环强化的手性放大

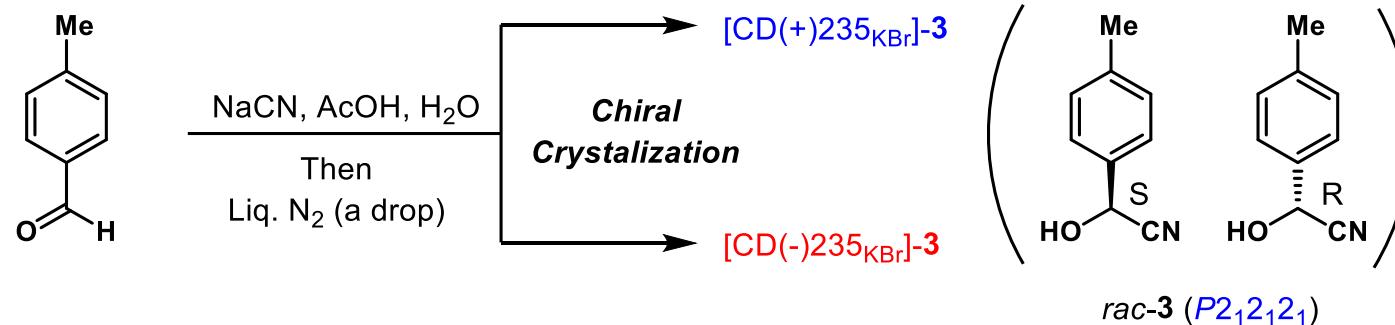


经历5轮温度循环，得到几乎对映纯的产物

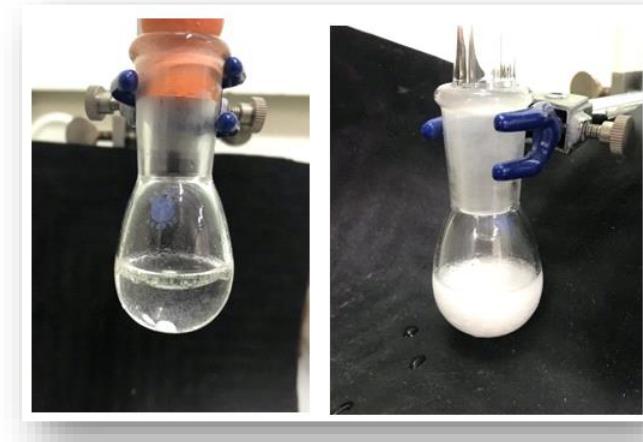


固相反应—固-固 Strecker反应

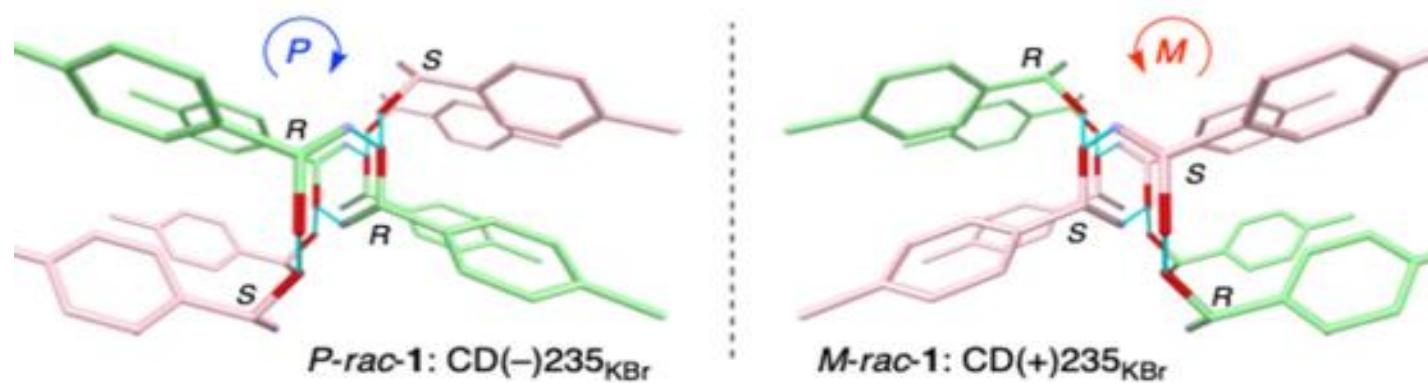
手性晶体制备



手性晶体制备示意图

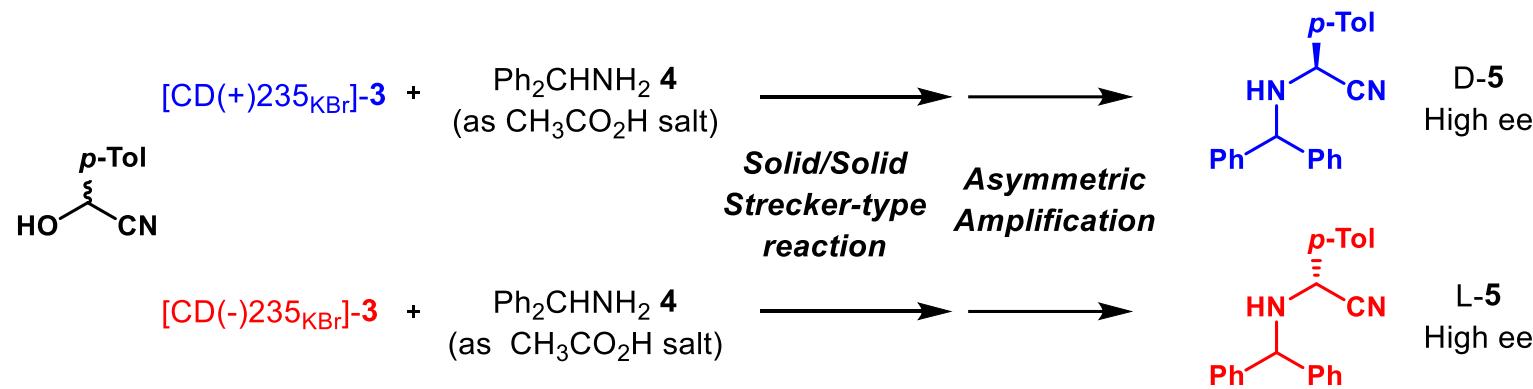


手性晶体结构



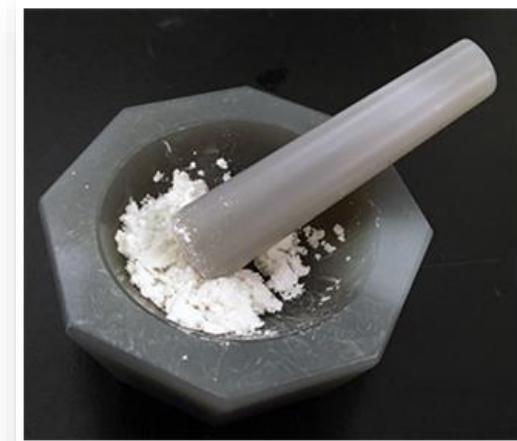


固相反应 — 固-固 Strecker 反应



Entry	rac-1	Solid/solid reaction		Aminonitrile 3	
		T / °C	Time/ day	Yield/ %	ee/ % (config)
1	<chem>[CD(-)235KBr]-3</chem>	r.t.	20 d	49%	> 99% (D)
2	<chem>[CD(+)-235KBr]-3</chem>	r.t.	20 d	53%	92% (L)
3	<chem>[CD(-)235KBr]-3</chem>	r.t.	20 d	55%	99% (D)
4	<chem>[CD(+)-235KBr]-3</chem>	r.t.	20 d	65%	91% (L)
5	<chem>[CD(-)235KBr]-3</chem>	35 °C	4 d	44%	97% (D)
6	<chem>[CD(-)235KBr]-3</chem>	40 °C	2 d	60%	99% (D)
7	<chem>[CD(+)-235KBr]-3</chem>	35 °C	4 d	52%	97% (L)
8	<chem>[CD(+)-235KBr]-3</chem>	40 °C	2 d	58%	92% (L)

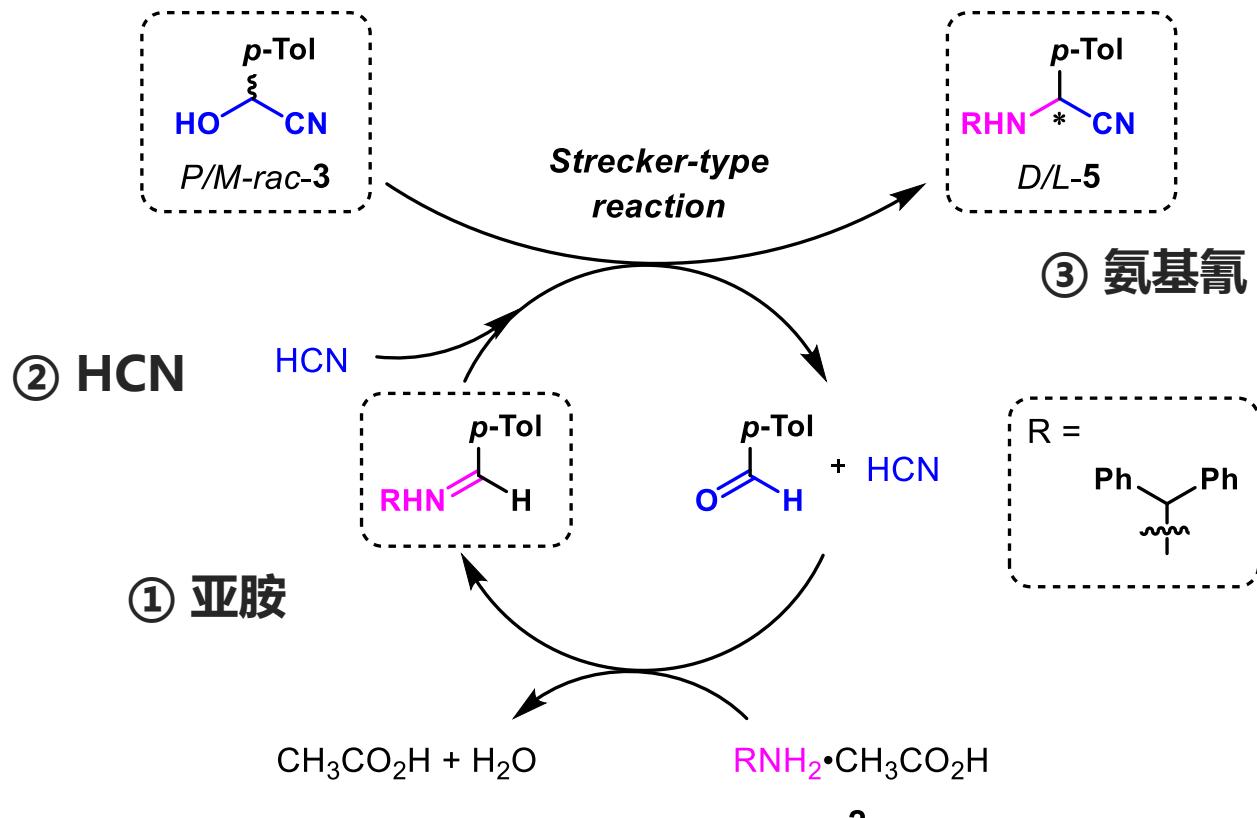
反应装置示意图





固相反应 — 固-固 Strecker 反应

反应机理与对映选择性诱导



亚胺

手性晶体对亚胺的吸附暴露前手性面被进攻的概率存在差异

HCN

手性晶体吸附HCN使其处于手性环境而发生亲核进攻

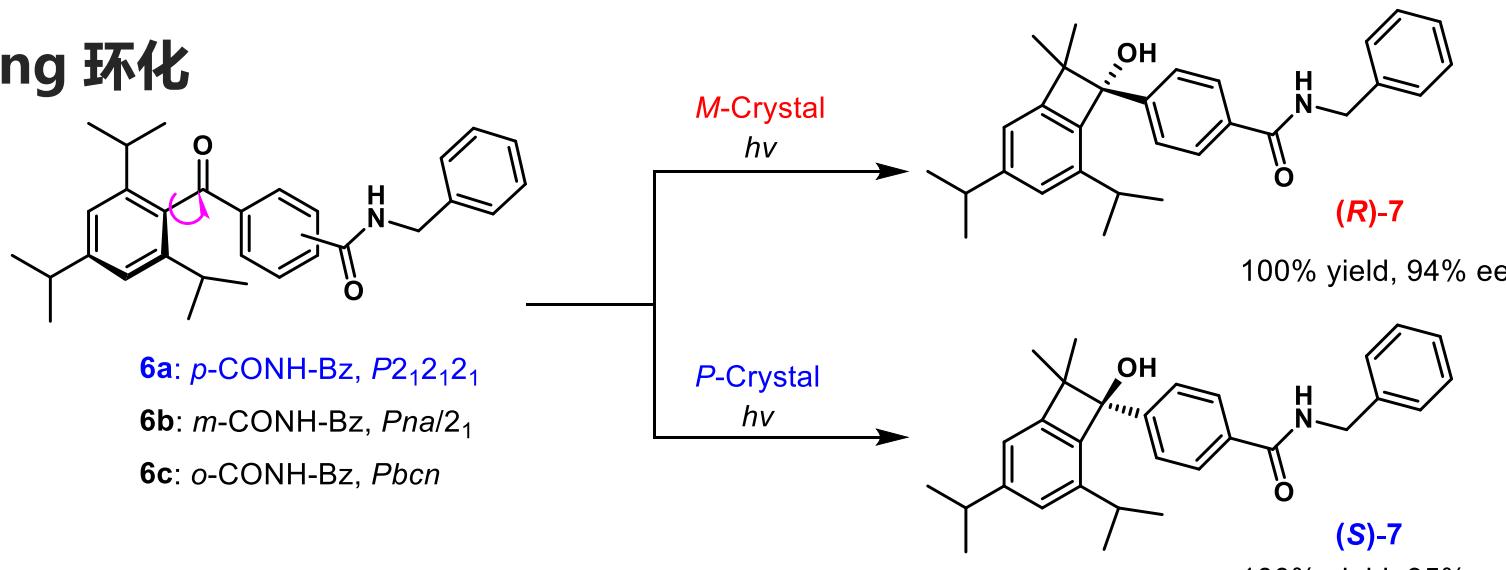
氨基氰

手性晶体对产物氨基氰的手性识别与选择性吸附

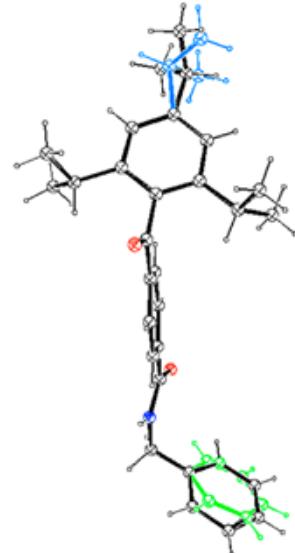


固相反应 — 固相光反应

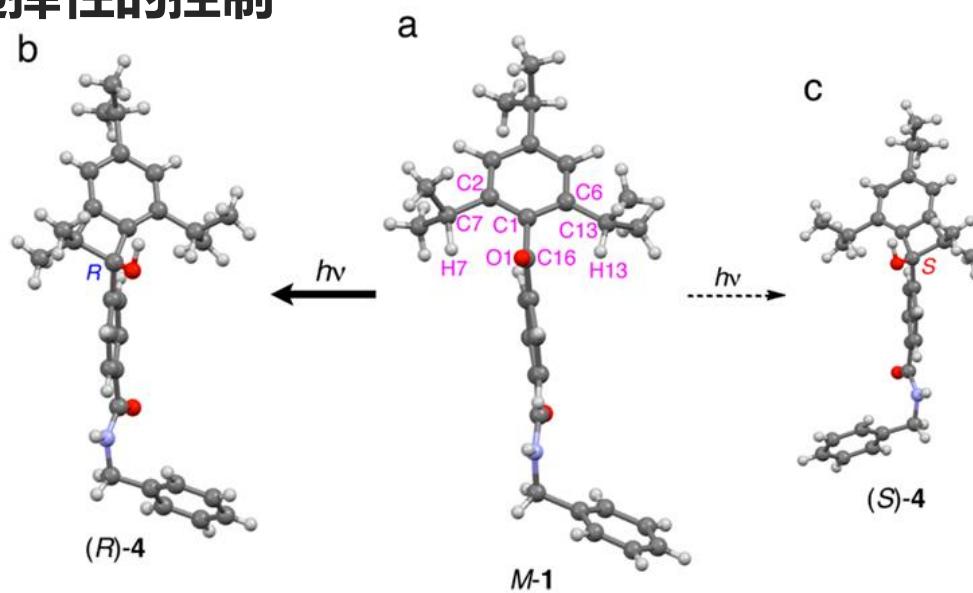
Norrish-Yang 环化



手性晶体结构



立体选择性的控制



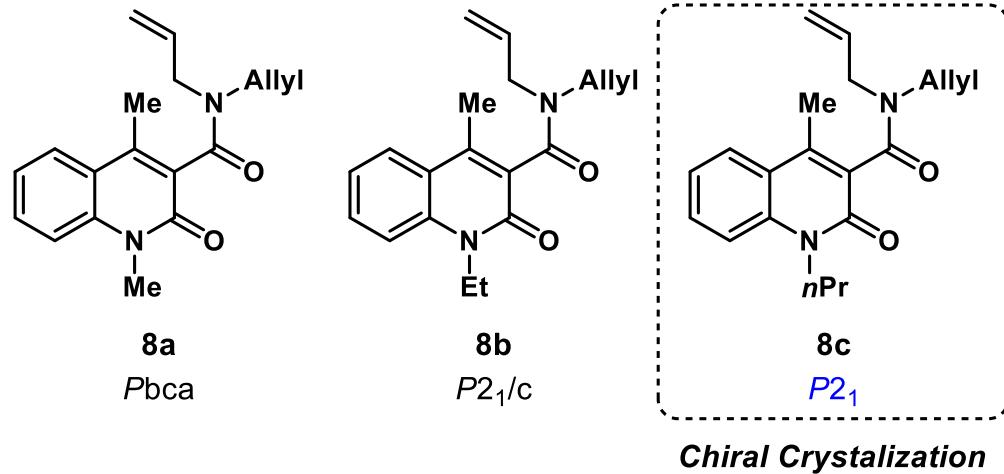
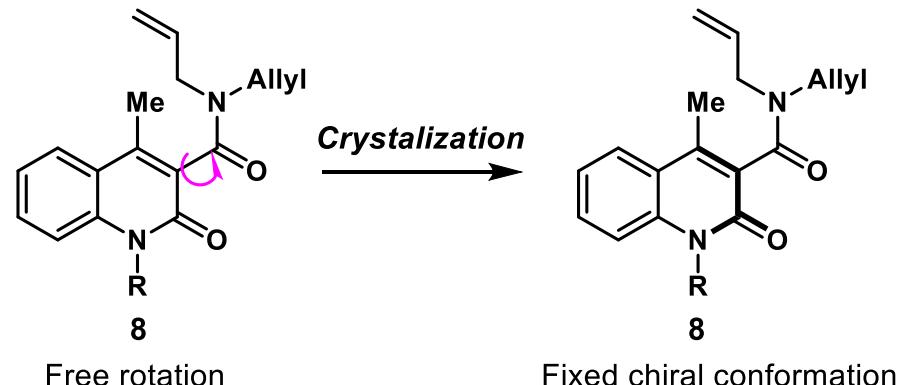
选择性攫取空间位置较近的氢原子

- ✓ $O1 \cdots H7$ 距离 (2.65 Å)
- ✓ $O1 \cdots H13$ 距离 (2.99 Å)

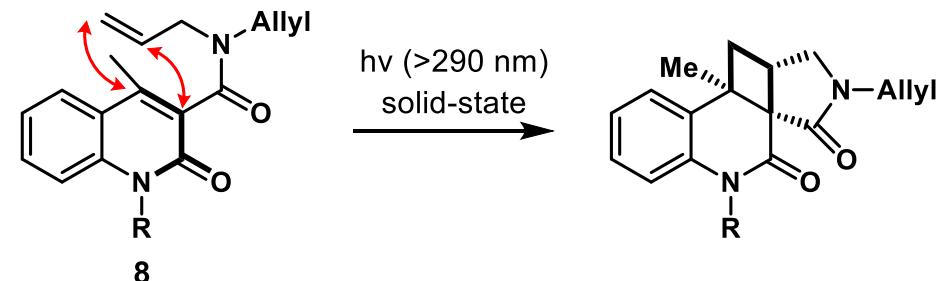


固相反应—固相光反应

制备手性晶体



光致分子内[2+2]环加成



Entry	amide 1	T / °C	conv	yield	ee
1	8a	15 °C	99%	74%	0%
2	8a	40 °C	43%	86%	0%
3	8b	15 °C	95%	62%	0%
4	8b	40 °C	38%	76%	0%
5	8c	15 °C	35%	56%	90%
6	8c	15 °C	59%	43%	88%
7	8c	40 °C	48%	92%	96%
8	8c	40 °C	67%	92%	95%



手性晶体作反应试剂

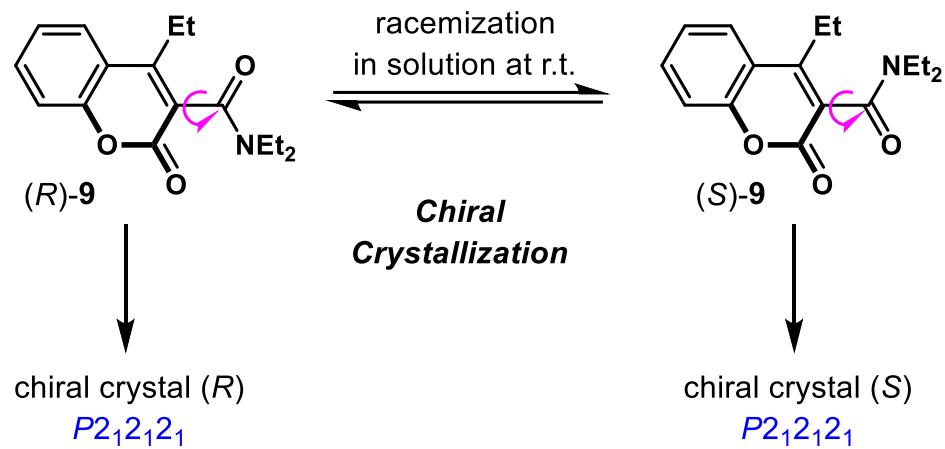


1. 固相反应
2. 低温反应

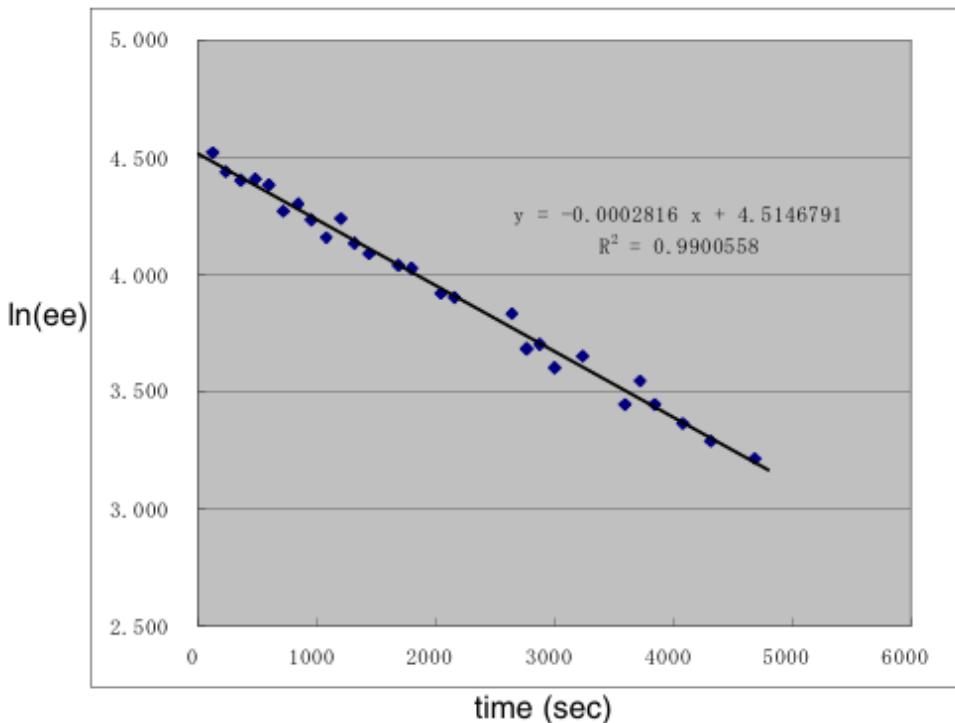


低温反应 — 光致分子间[2+2]环加成

手性晶体



半衰期研究



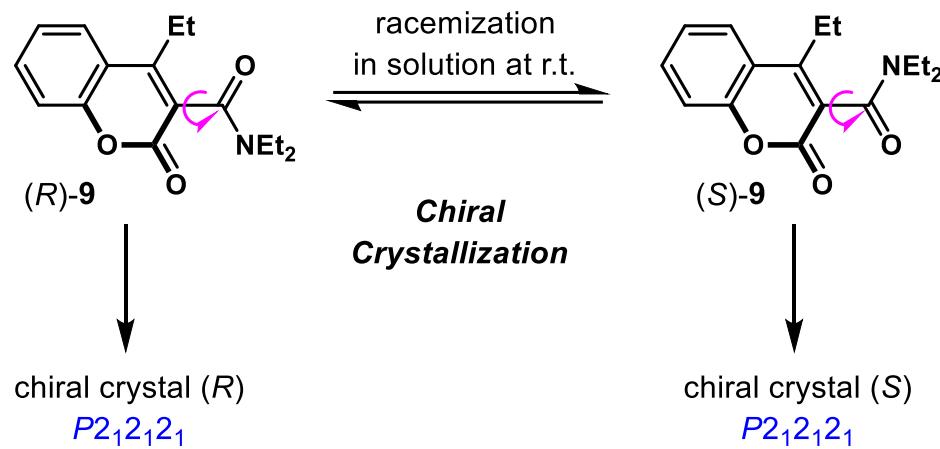
$$\ln(ee) = k_{rac} t$$

$$t_{1/2} = \ln 2 / 2k_{rac}$$

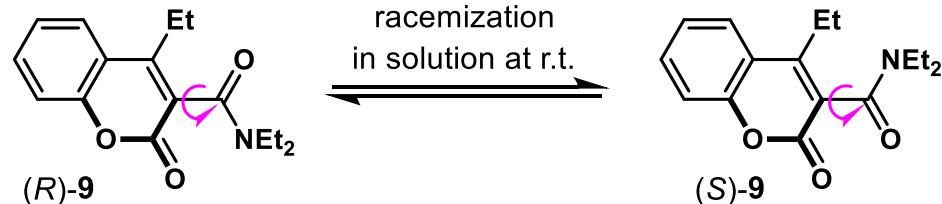


低温反应 — 光致分子间[2+2]环加成

手性晶体



半衰期研究

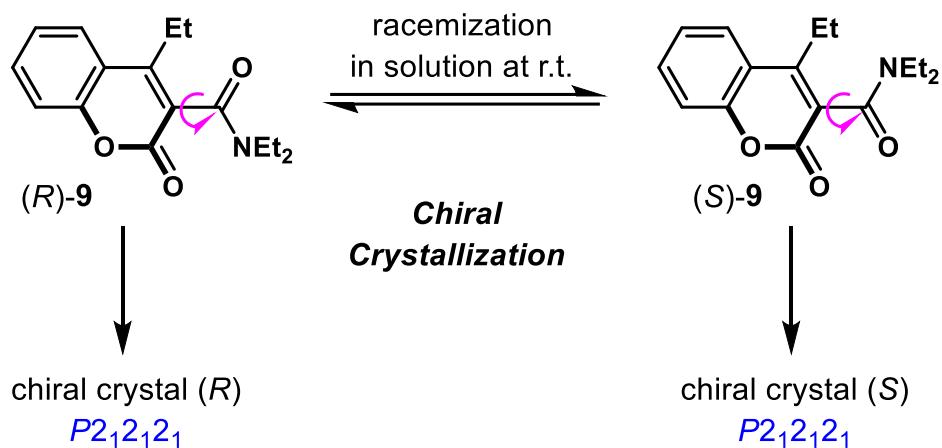


Entry	Solvent	T/ °C	$t_{1/2}/ \text{min}$	$K \times 10^{-4}/ \text{S}^{-1}$
1		-5 °C	82.0	0.704
2	THF	0 °C	30.5	1.89
3		5 °C	11.9	4.85
4		15 °C	84.8	0.681
5	MeOH	20 °C	41.0	1.41
6		25 °C	20.2	2.86
7		15 °C	92.7	0.623
8	DMF	20 °C	45.5	1.27
9		25 °C	23.6	2.44

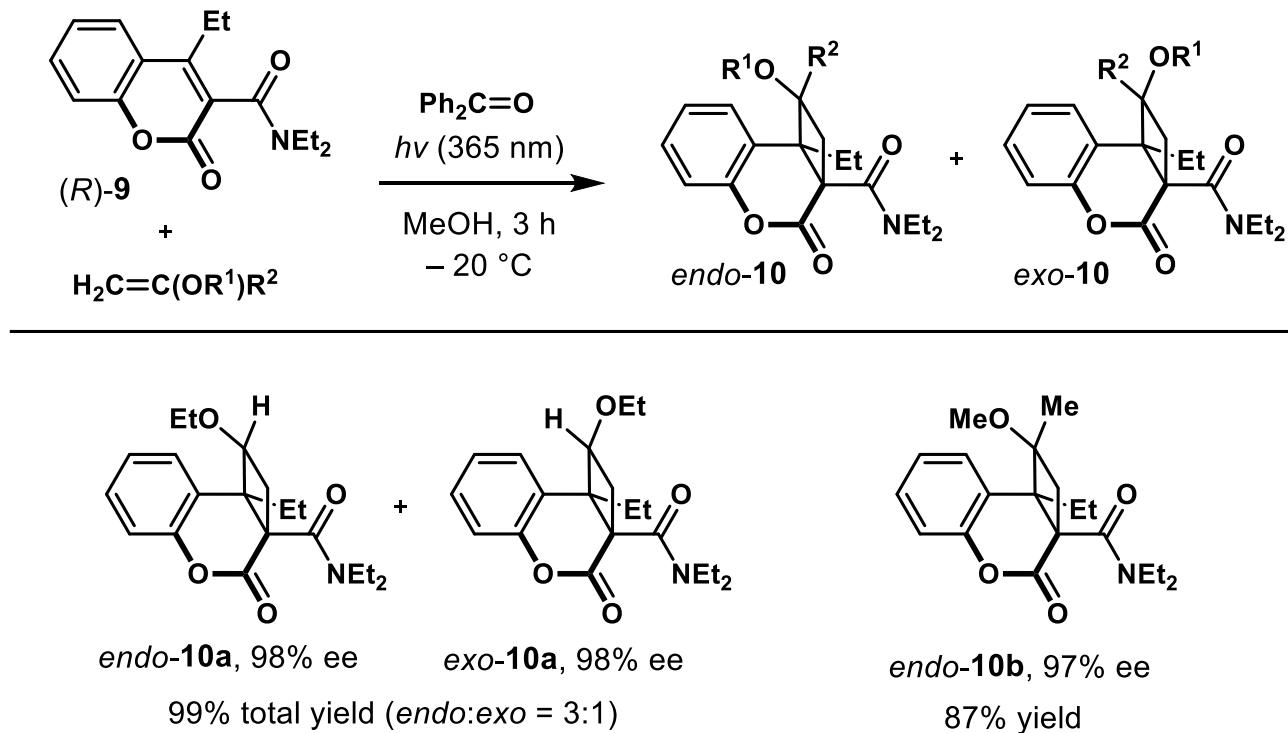


低温反应 — 光致分子间[2+2]环加成

手性晶体



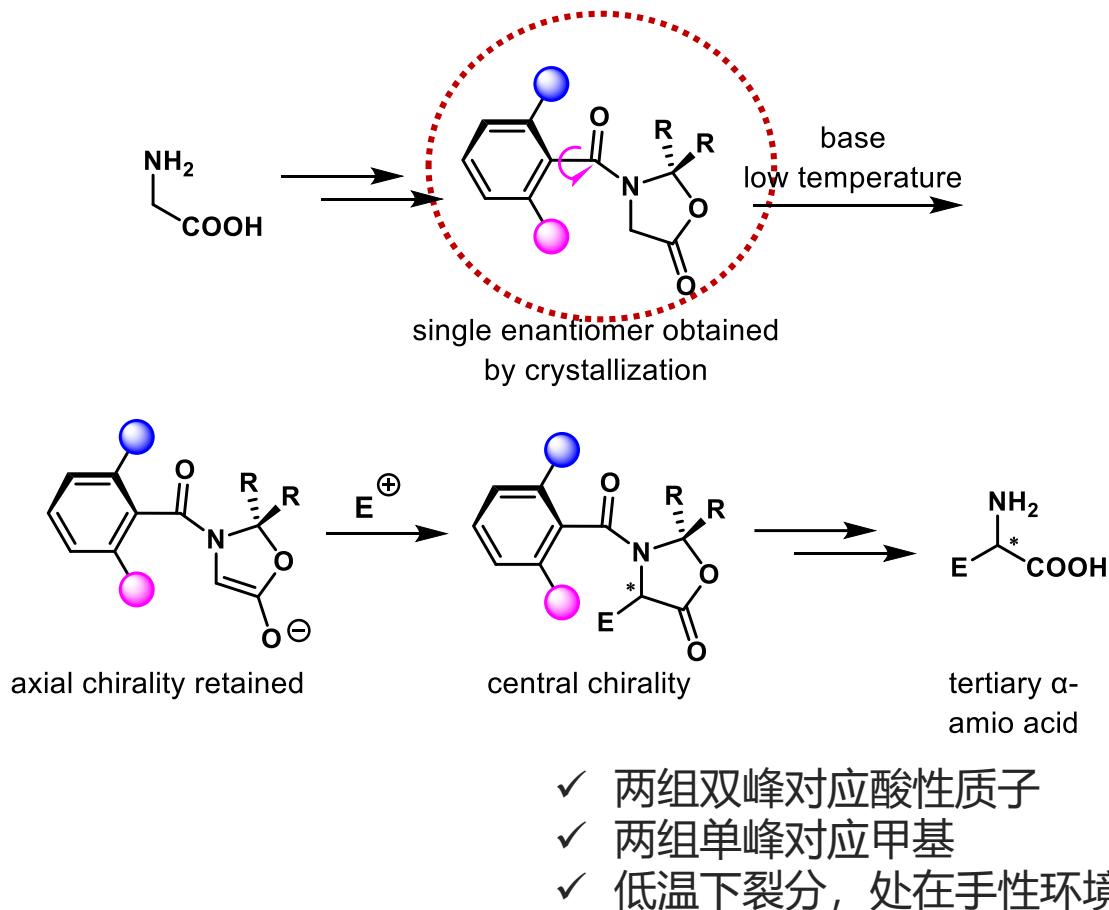
底物范围





低温反应 — 非天然氨基酸的合成

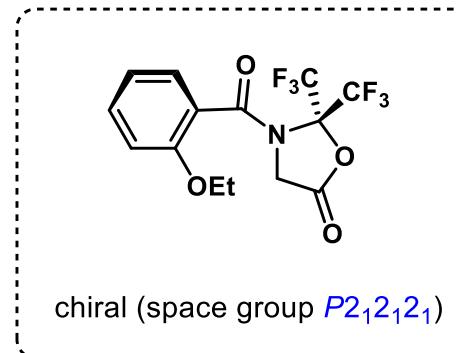
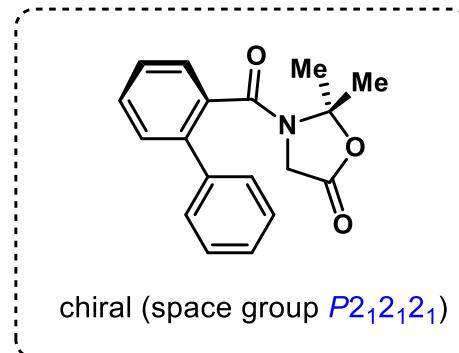
非天然氨基酸的绝对不对称合成设计



V. Alezra et al. *Angew. Chem. Int. Ed.* 2012, 51, 4981–4984.

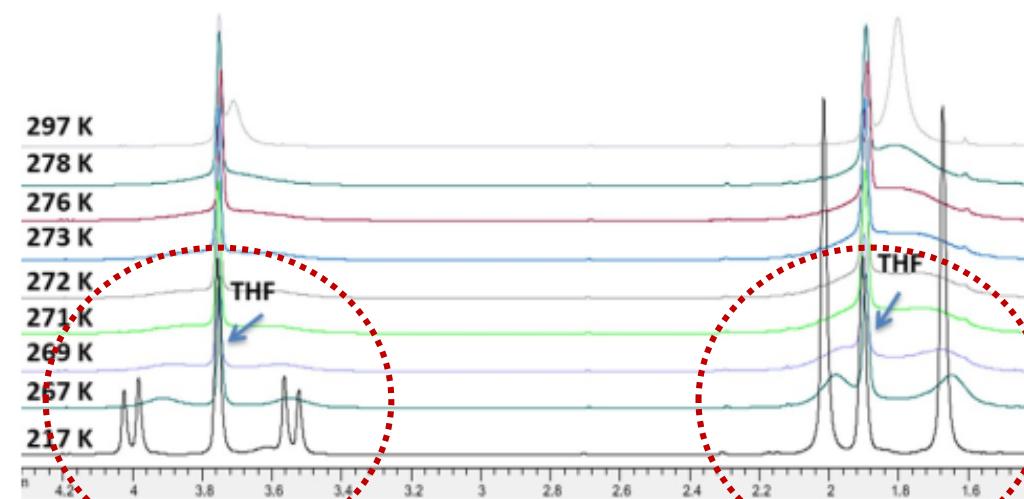
V. Alezra et al. *Chem. Eur. J.* 2017, 23, 5787–5798.

手性晶体



degradation

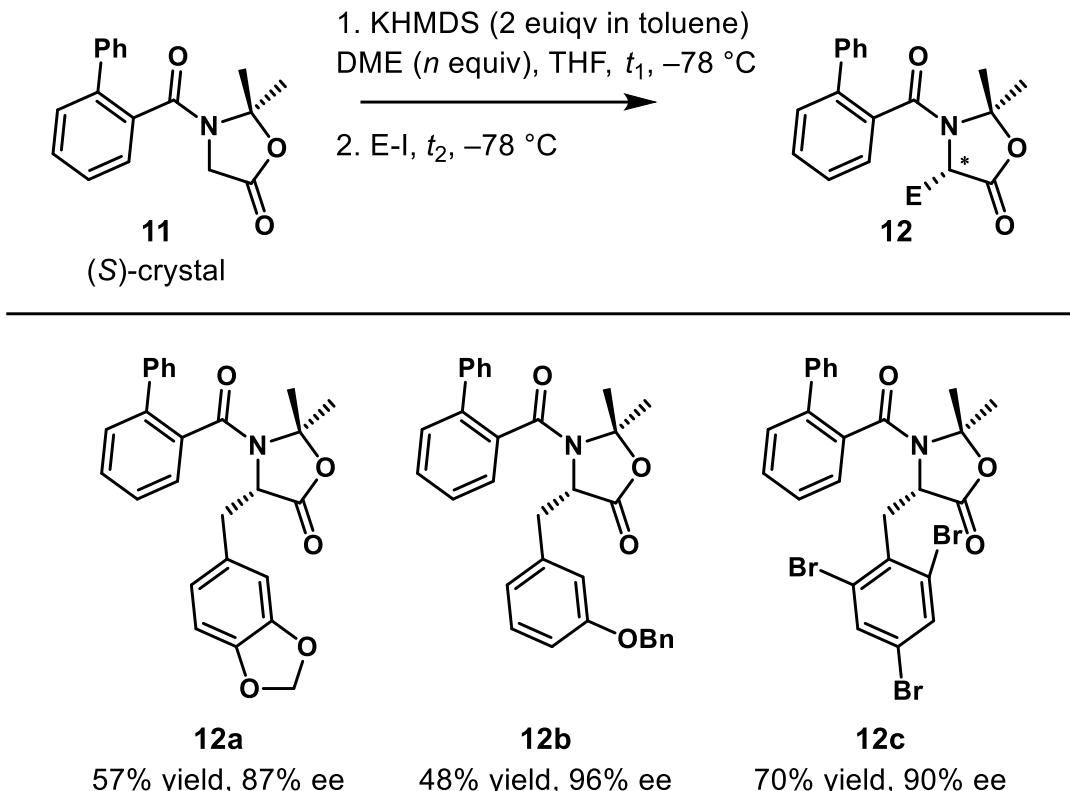
变温核磁



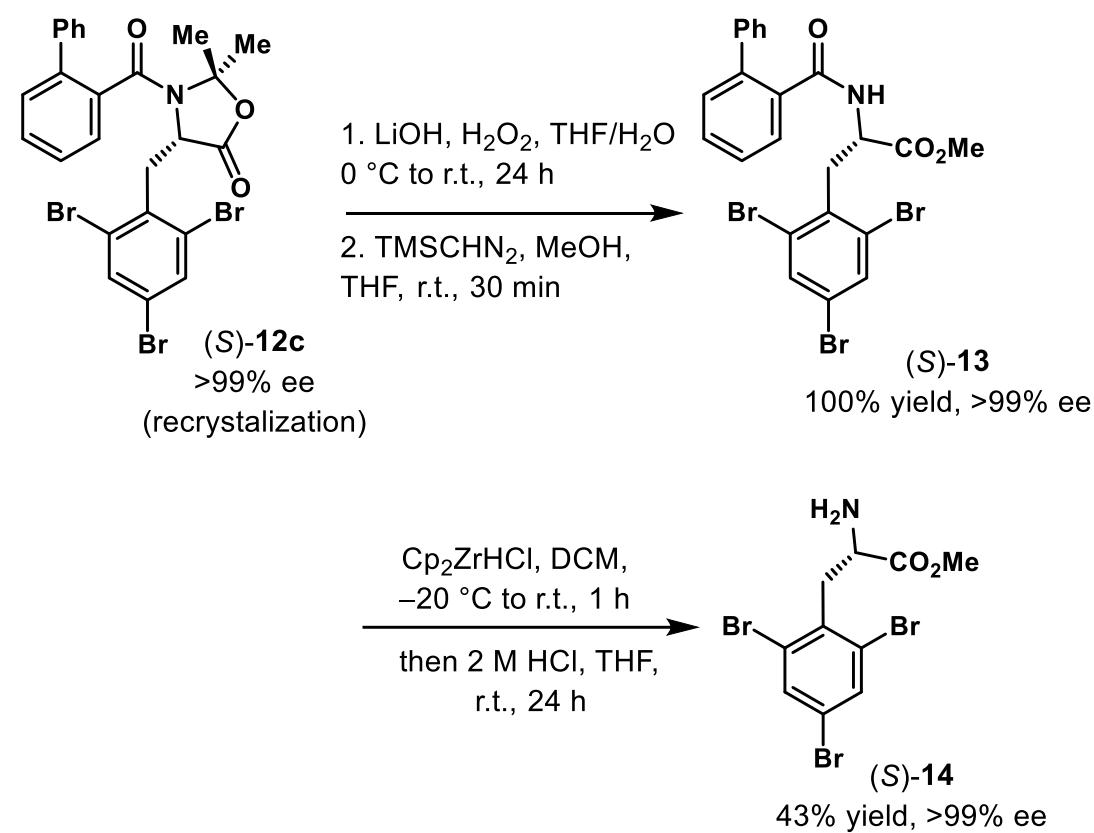


低温反应 — 非天然氨基酸的合成

底物范围



脱保护合成非天然氨基酸





手性晶体作手性催化剂或引发剂



1. 低温策略合成手性催化剂
2. 非均相策略引发的Soai反应



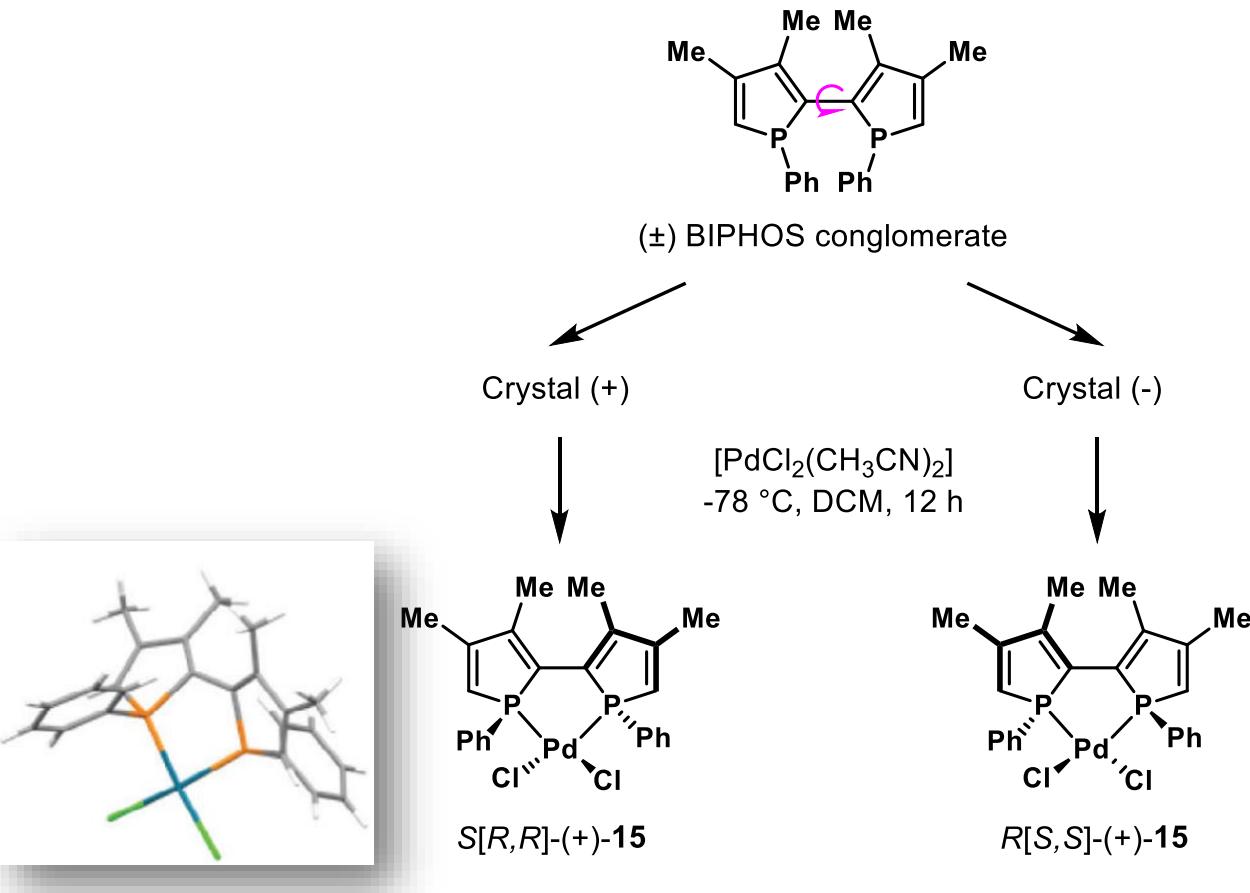
手性晶体作手性催化剂或引发剂



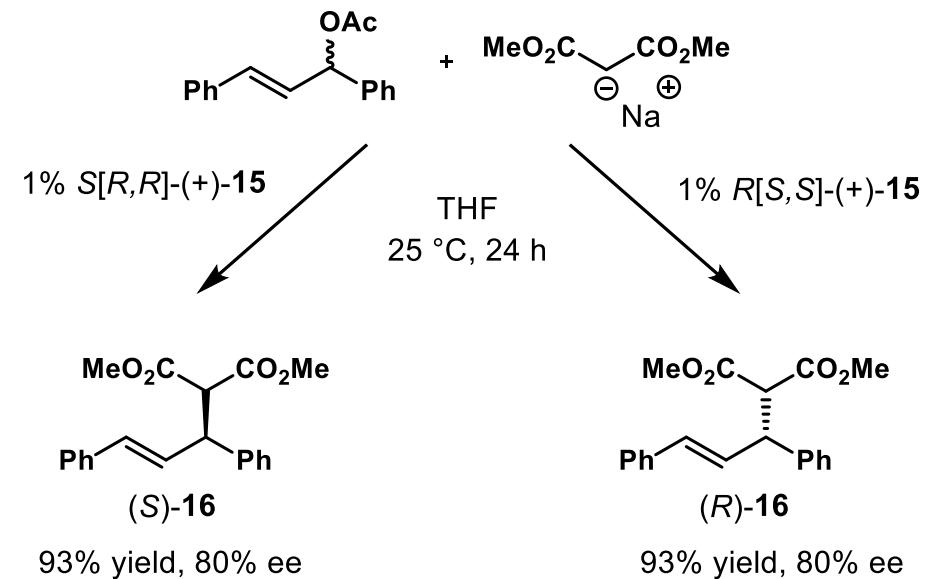
1. 低温策略合成手性催化剂
2. 非均相策略引发的Soai反应



手性钯络合物



在烯丙基取代反应中的应用





手性晶体作手性催化剂或引发剂



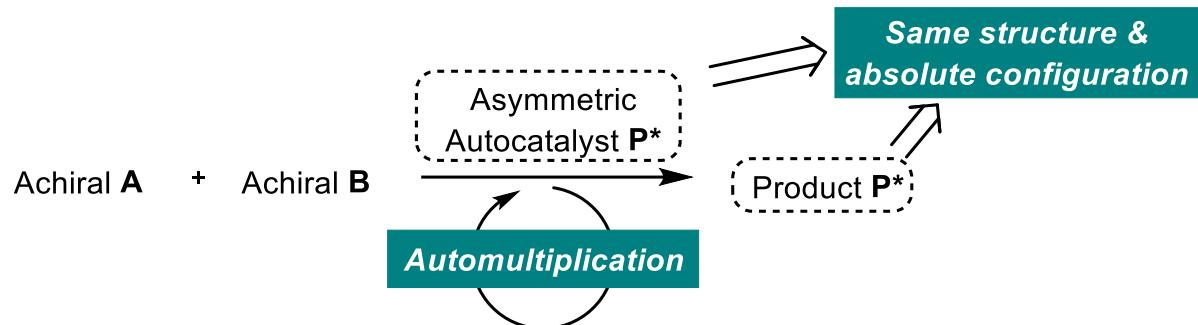
1. 低温策略合成手性催化剂
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Soai 反应

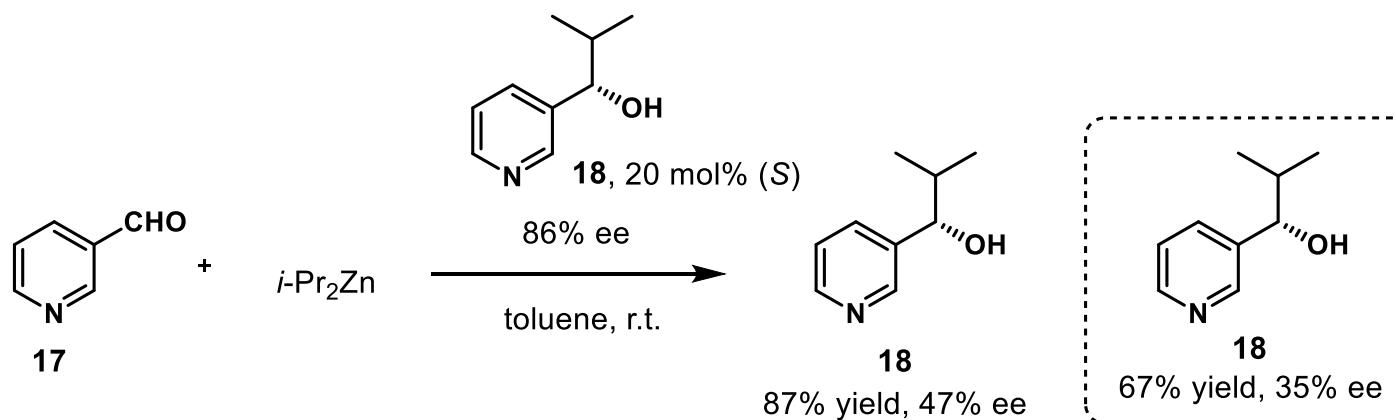
不对称自催化：Soai 反应—最具代表性的绝对不对称合成

□ 不对称自催化概念图



- ✓ 对映体的自我增殖
- ✓ 产物即催化剂
- ✓ 产物与催化剂绝对构型相同

□ 第一例不对称自催化：Soai反应



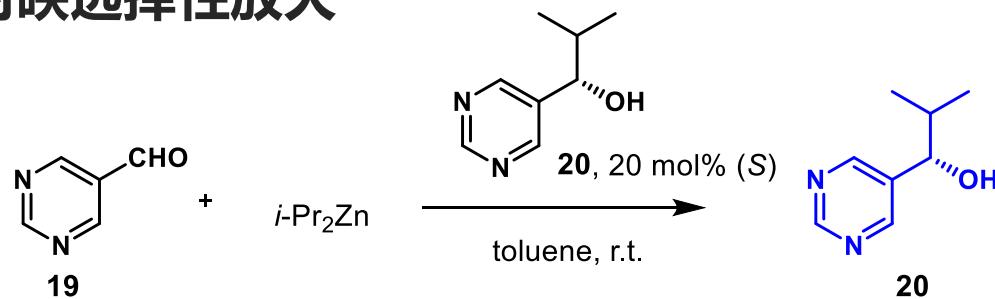
- ✓ 产物ee值小于催化剂
- ✓ 产物ee值如何实现大于催化剂，即正向非线性效应(**challenge!!!**)

K. Soai et al. *Acc. Chem. Res.* **2014**, *47*, 3643–3654.

K. Soai et al. *J. Chem. Soc., Chem. Commun.* **1990**, 982–983.

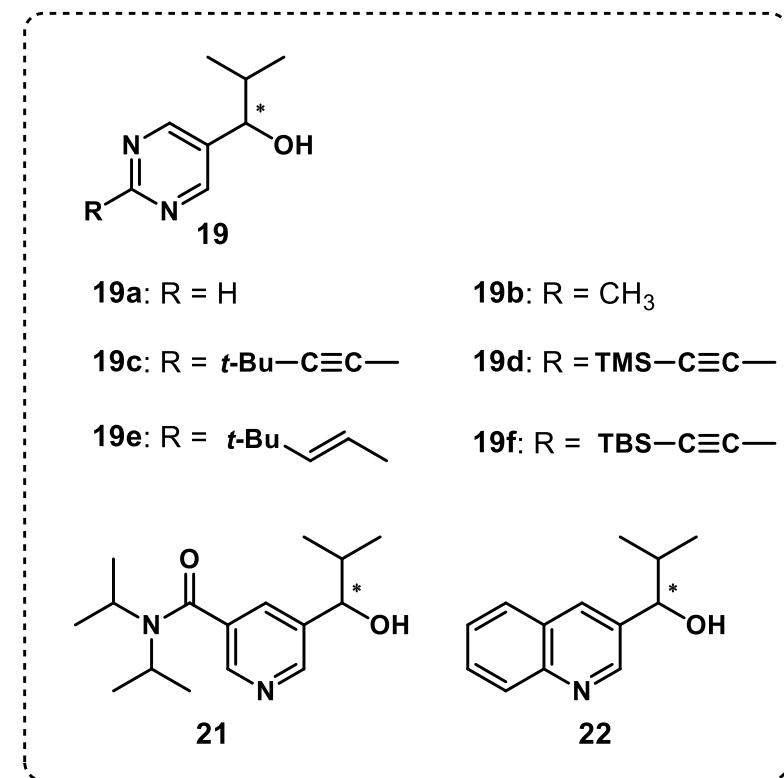


自催化对映选择性放大



Run	Catalyst 20 (ee/ %)	Mixture of cat. and product 20		Factor by which the amount of (S)-1 has increased	Newly formed product 20	
		yield/ %	ee/ %		yield/ %	ee/ %
A1	5% (S)	62%	39% (S)	4.1	42%	55% (S)
A2	39% (S)	86%	76% (S)	22	46%	87% (S)
A3	76% (S)	80%	85% (S)	94	60%	88% (S)
A4	85% (S)	86%	89% (S)	413	66%	90% (S)
A5	89% (S)	81%	89% (S)	1674	61%	90% (S)

底物范围



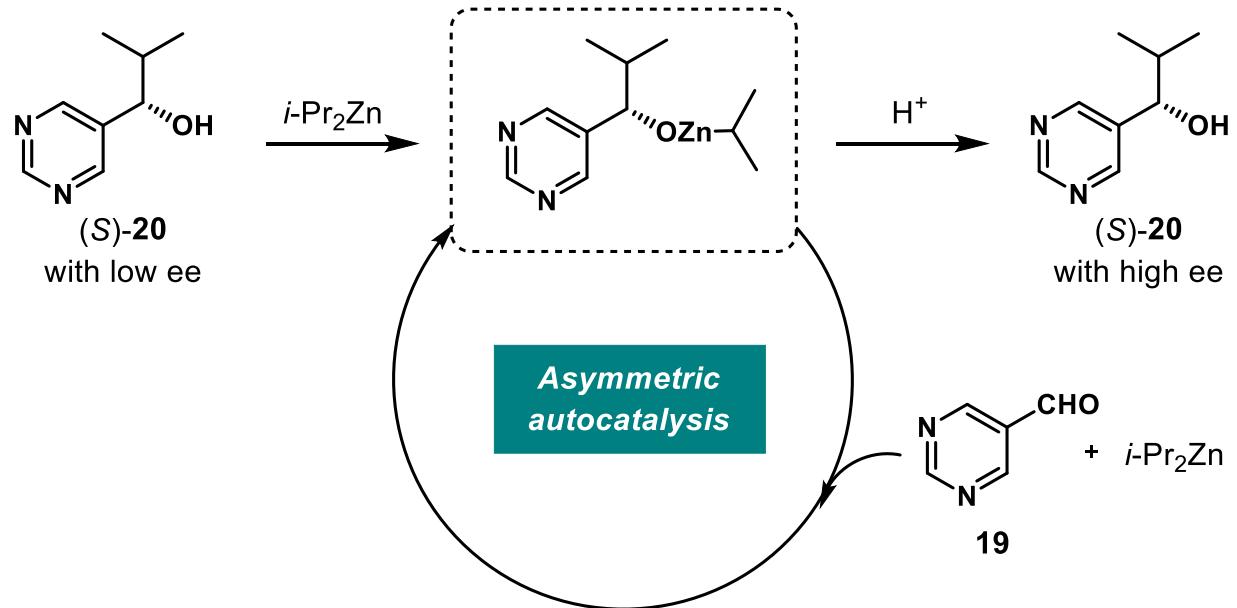
K. Soai et al. *Nature* **1995**, 378, 767–768.

K. Soai et al. *Acc. Chem. Res.* **2014**, 47, 3643–3654.



Soai 反应

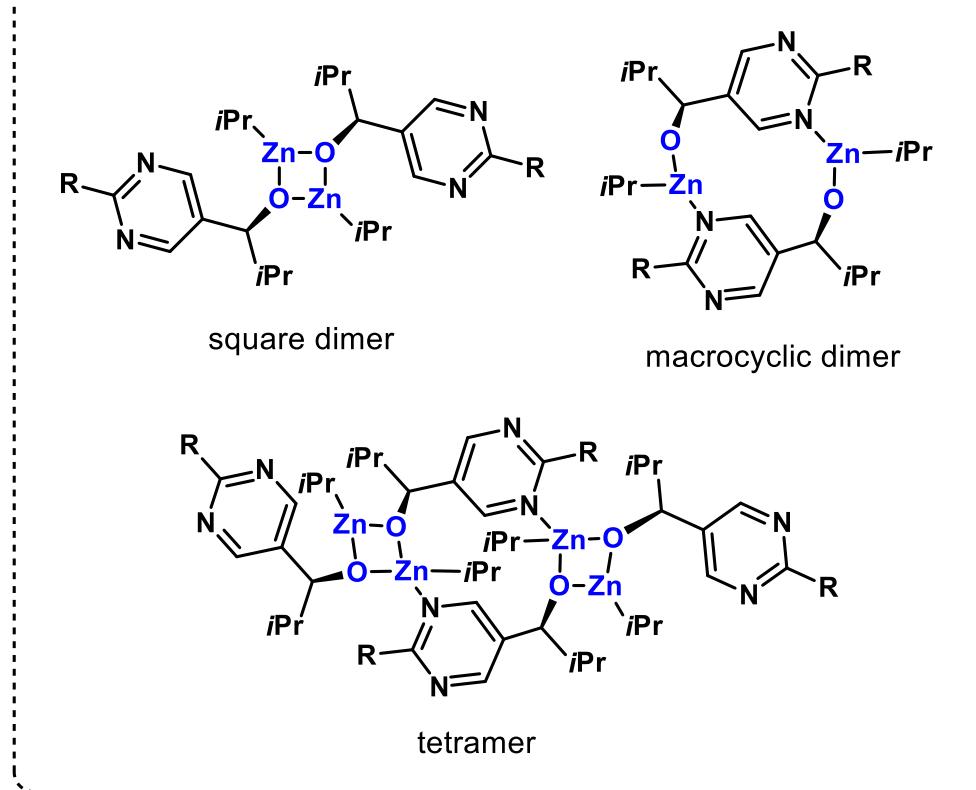
Soai 反应机理



K. Soai et al. *Acc. Chem. Res.* **2014**, *47*, 3643–3654.

D. G. Blackmond, *Chem. Rev.* **2020**, *120*, 4831–4847.

可能存在的催化剂多聚体



R^*R^* or S^*S^*
(dimer)
active

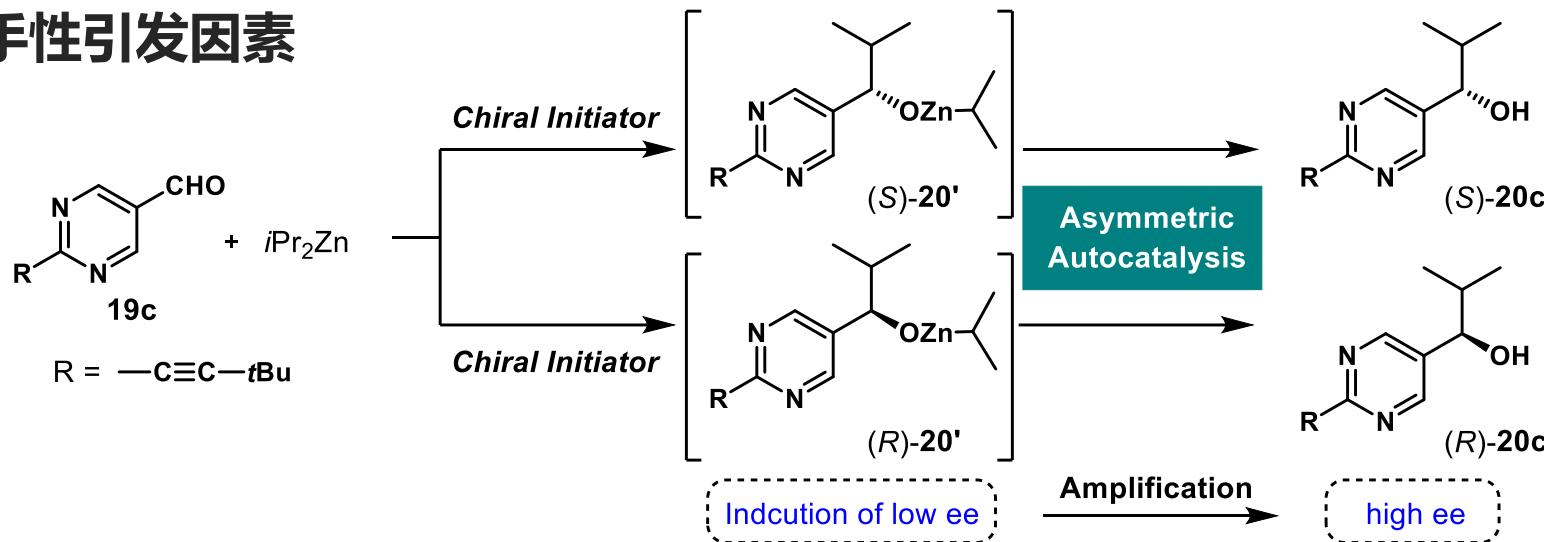
R^*S^*
(dimer)
inactive

- ✓ 同手性：自我复制
- ✓ 异手性：相互拮抗

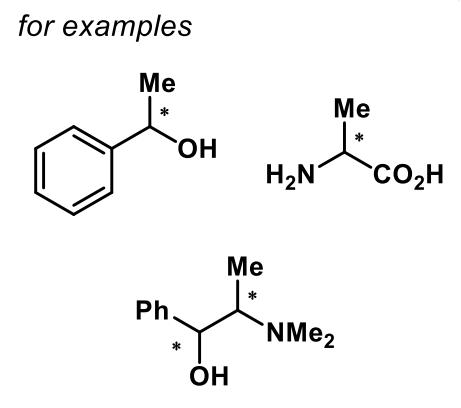


Soai 反应

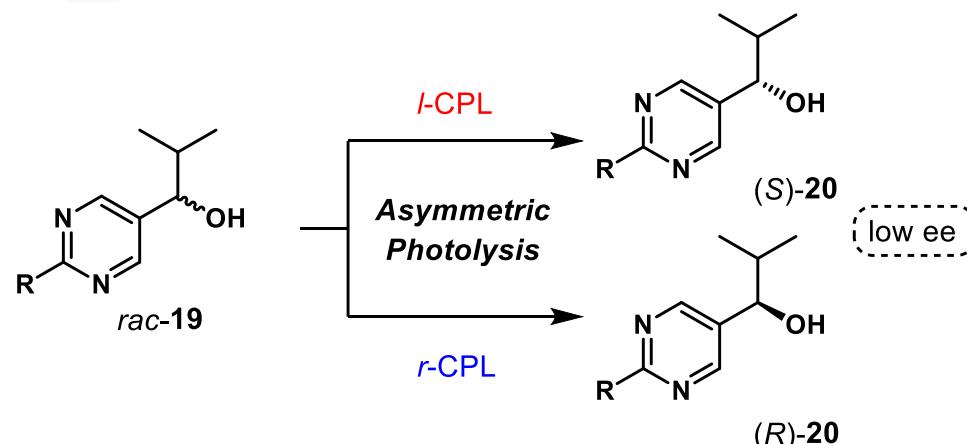
Soai 反应手性引发因素



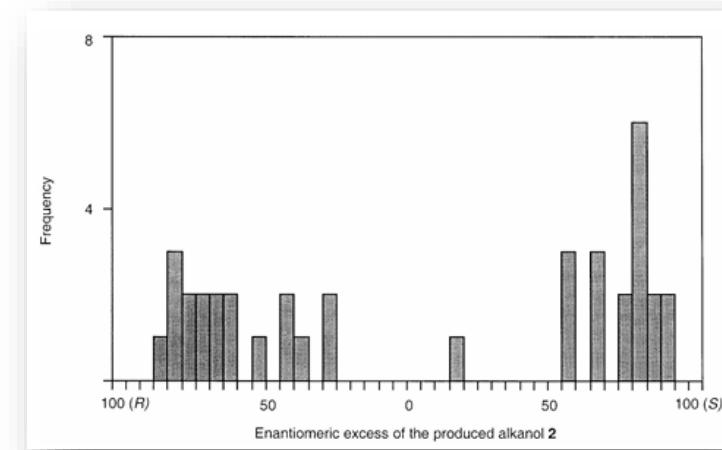
手性化合物



偏振光



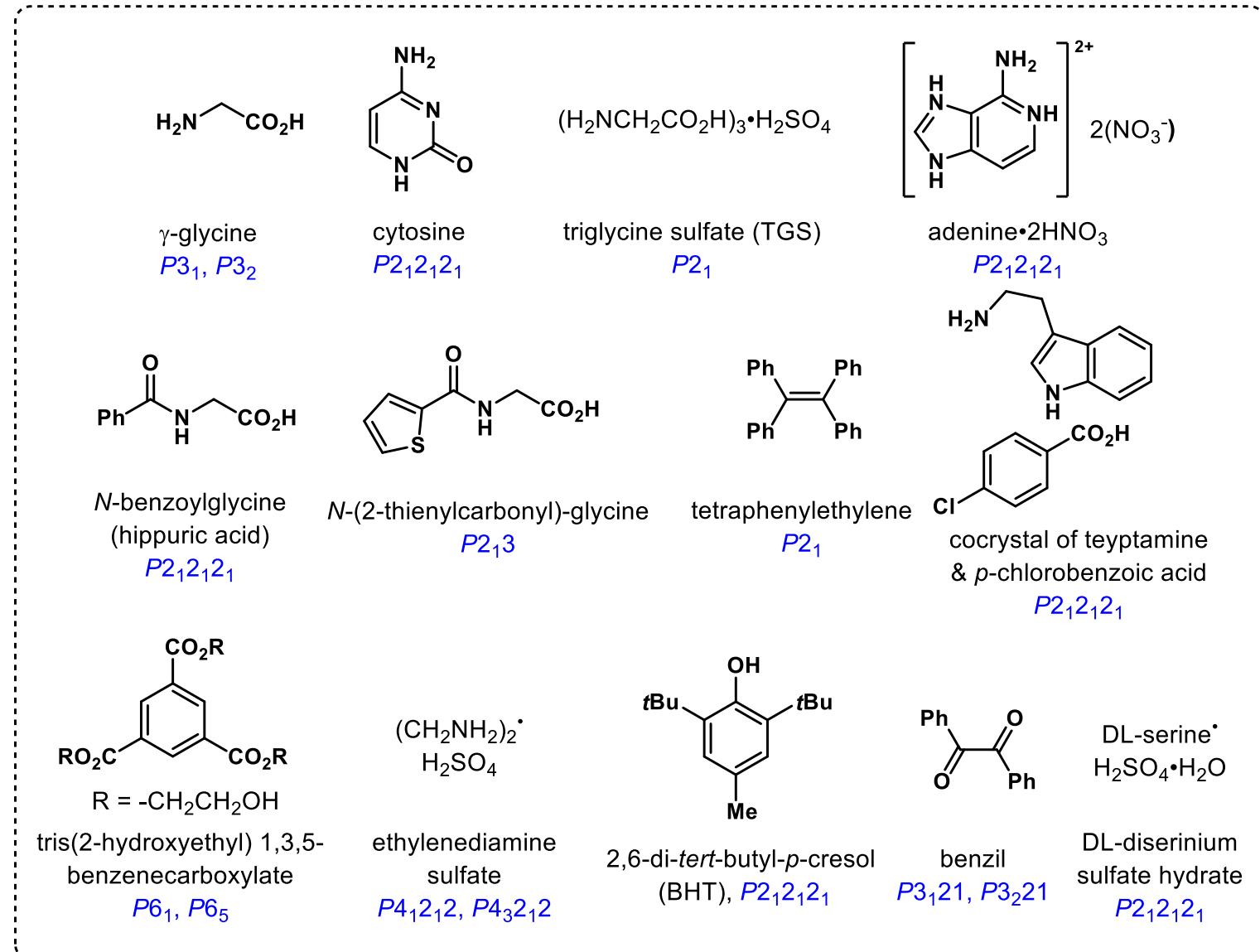
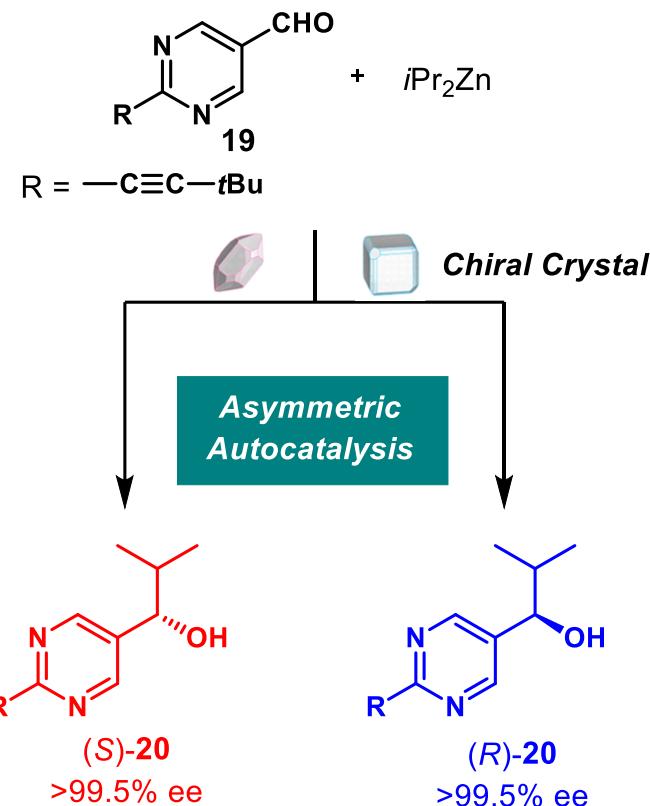
统计学波动





非均相引发的Soai反应

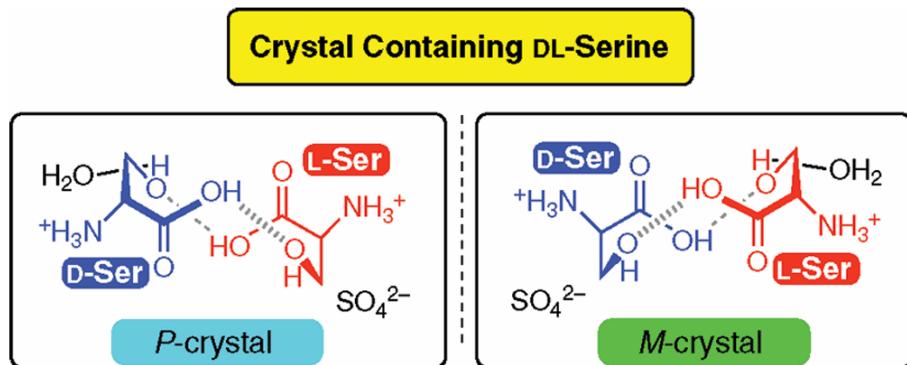
手性有机晶体作为Soai反应的手性引发剂



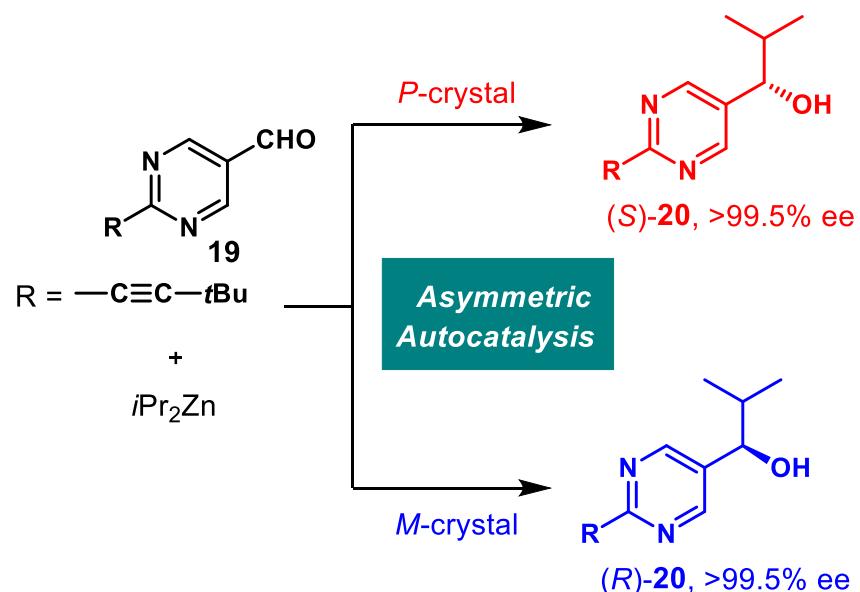


非均相引发的Soai反应—以丝氨酸为例

丝氨酸手性晶体引发的Soai反应



solvent → Suspension $\xrightarrow{i\text{Pr}_2\text{Zn in toluene}}$ heterogeneous → Product with low ee



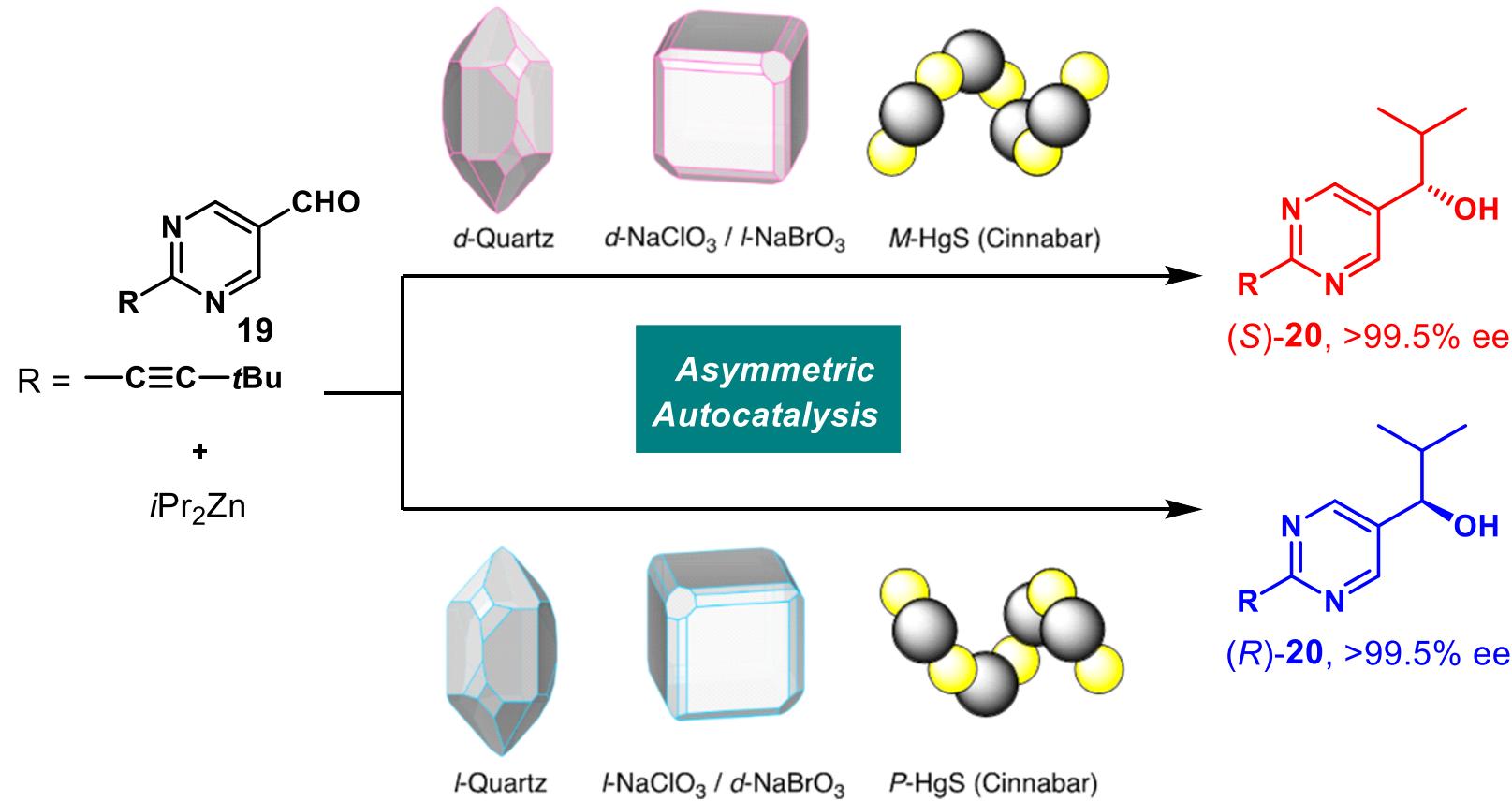
Entry	crystal of rac-serine	rounds of amplification	5-pyrimidylalkanol 1	
			yield/ %	ee/ % (config.)
1	<i>M</i>	2 rounds	88%	92% (<i>R</i>)
2	<i>P</i>	2 rounds	87%	85% (<i>S</i>)
3	<i>M</i>	2 rounds	87%	90% (<i>R</i>)
4	<i>P</i>	2 rounds	89%	92% (<i>S</i>)
5	<i>M</i>	5 rounds	92%	>99.5% (<i>R</i>)
6	<i>P</i>	5 rounds	92%	>99.5% (<i>S</i>)

- ✓ 晶体手性与产物手性存在对应关系
- ✓ 5轮放大后, >99.5% ee



非均相引发的Soai反应

手性无机晶体作为Soai反应的手性引发剂

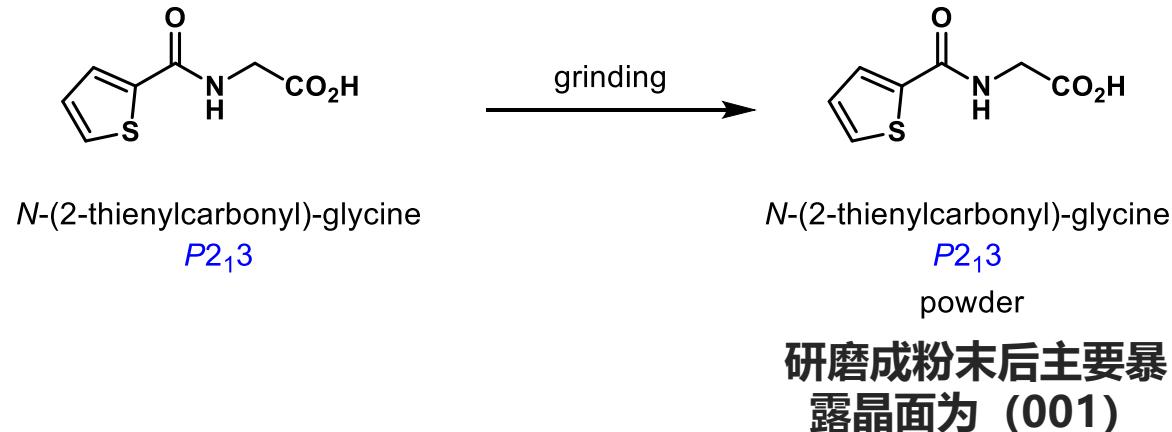




非均相引发的Soai反应—晶体表面立体选择性解释



模板手性晶体

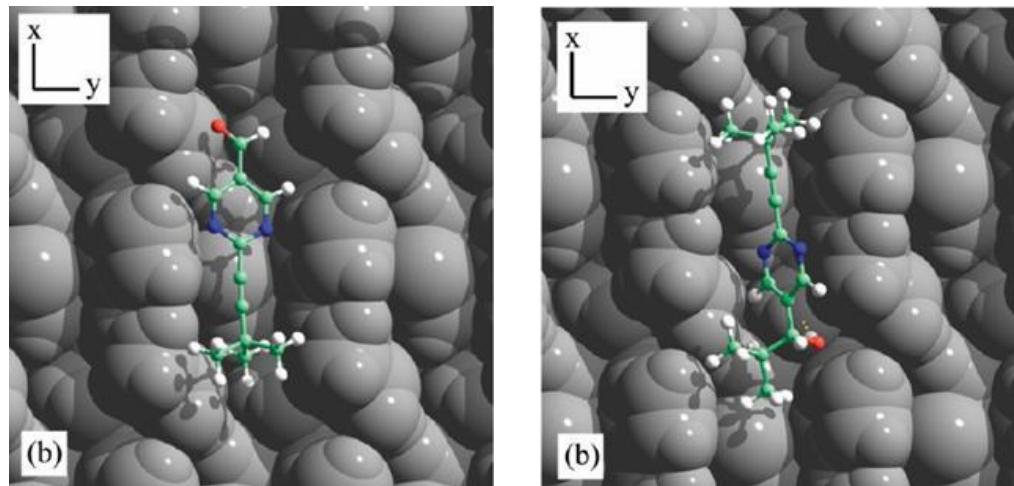


(M)型手性晶体对前手性醛的吸附

surface	configuration	E_b (kcal/mol)	enantiomer
(100)	1	-24.845	S
	2	-23.848	S
	3	-23.388	S
(001)	1	-27.171	S
	2	-25.756	S
	3	-25.062	S
(110)	1	-24.534	R
	2	-22.429	R
	3	-21.982	S

吸附构型决
定暴露的前
手性面

(001) 晶面对前手性醛(左)与手性醇 (右) 的吸附行为



(M)型手性晶体对手性醇的吸附

surface	configuration	E_b (kcal/mol)	enantiomer
(100)	1	-29.848	R
	2	-29.321	S
	3	-28.930	S
(001)	1	-30.244	R
	2	-29.908	S
	3	-29.863	R
(110)	1	-26.630	R
	2	-25.568	S
	3	-25.467	S

吸附构型影
响溶液中的
对映体失衡

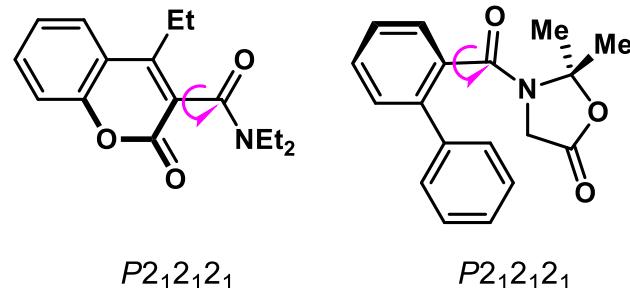
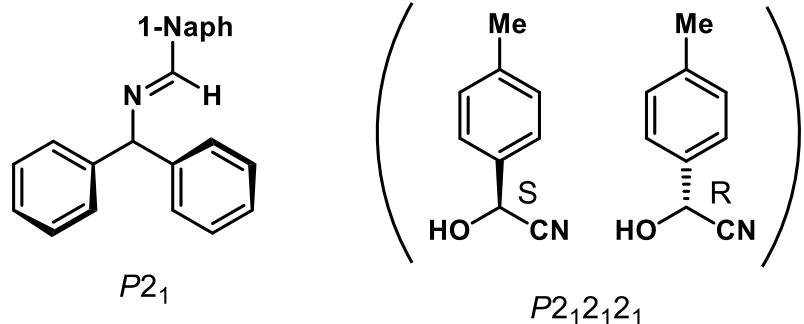
04
PART TWO

总结与展望

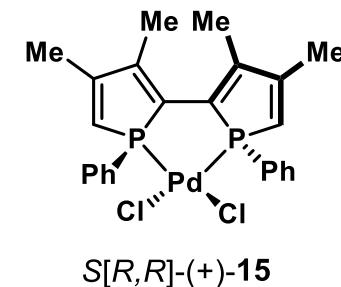




手性晶体作反应试剂

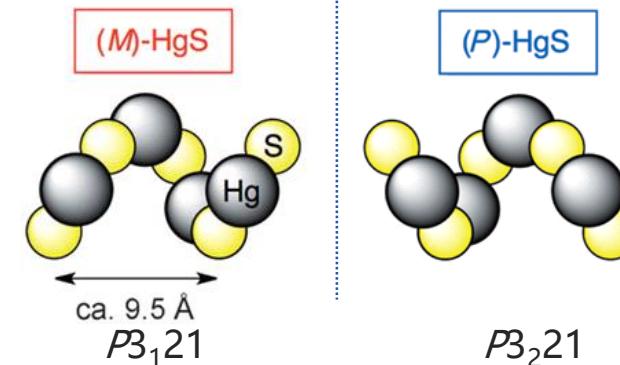


手性晶体作手性催化剂或手性引发剂



DL-serine[•]
H₂SO₄•H₂O

DL-diserinium
sulfate hydrate
P2₁2₁2₁



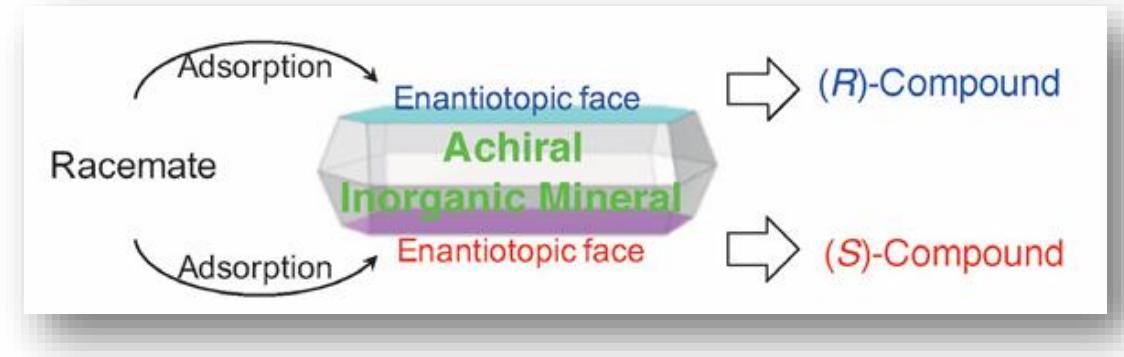
- ✓ 固相反应, 非均相反应
- ✓ “frozen chirality”, 低温反应
- ✓ 结晶诱导对映选择性放大

- ✓ 低温策略合成手性钯络合物
- ✓ 非均相条件下引发的Soai反应



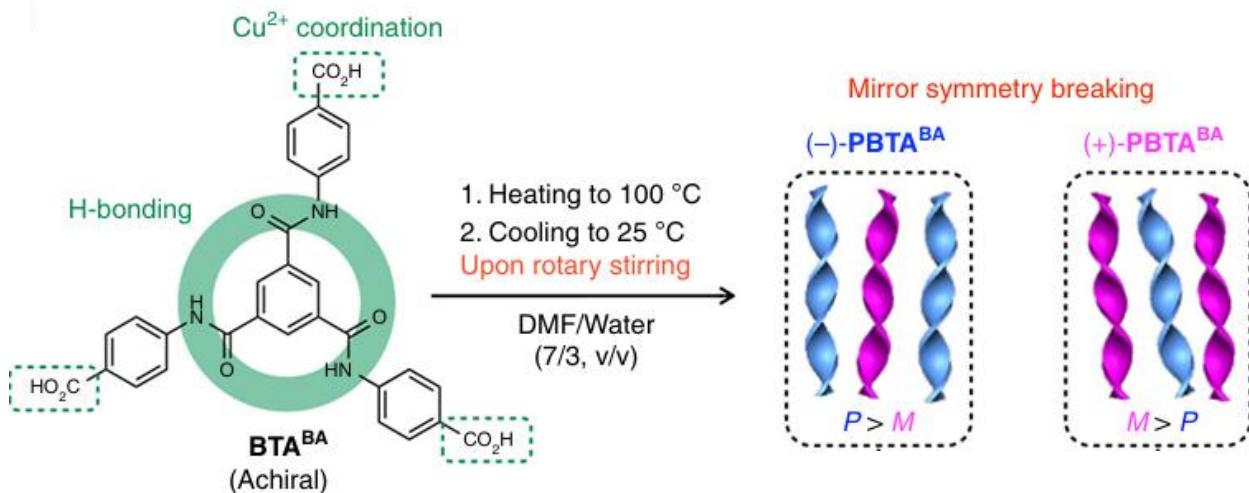
非手性晶体的对映异位面反应

非手性的晶体，其对映异位面也可诱导手性产生



超分子化学的螺旋结构

非手性化合物形成超分子螺旋结构时，宏观上的对称性破缺，形成手性



T. Kawasaki et al. *Angew. Chem. Int. Ed.* **2017**, *56*, 1055–1058.

M. Liu et al. *Nat. Commun.* **2019**, *10*, 3976–3983.



THANKS
恳请各位老师同学批评指正