



上海中醫藥大學

Shanghai University of Traditional Chinese Medicine

基于手性磷酸介导的动态动力学 反应在构建轴手性骨架中的应用

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- 1.3 轴手性分子的手性判断

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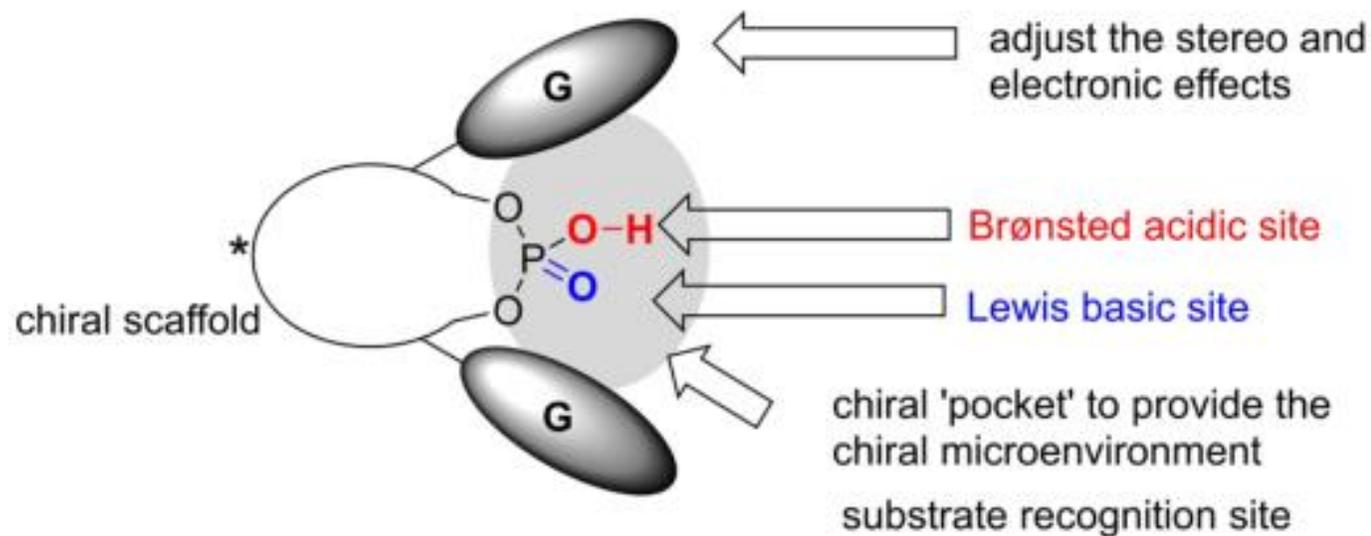
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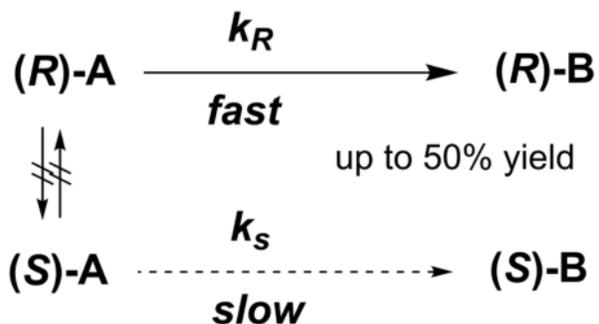
1.1 手性磷酸的结构特征



- 手性磷酸是一种双功能催化剂，由布朗斯特酸性位点（P-OH部分）和Lewis碱性位点（P=O部分）组成
- 手性磷酸的手性骨架通常有对称性，相邻的取代基能够调节手性口袋的立体和电子性质

1.2 动力学拆分和动态动力学拆分

a. kinetic resolution (KR)

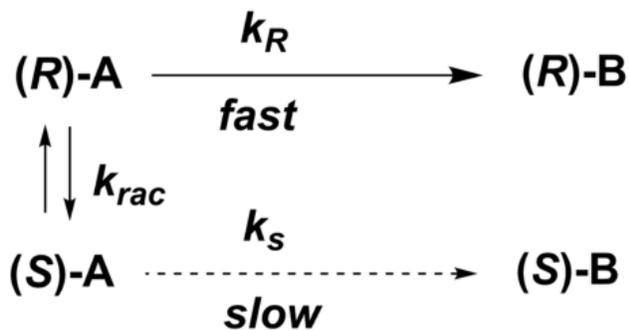


$$\text{s-factor} = k_{\text{fast}}/k_{\text{slow}}$$

$$\text{s-factor} = \frac{\ln[(1-C)(1-ee_{\text{SM}})]}{\ln[(1-C)(1+ee_{\text{SM}})]}$$

C, conversion

b. dynamic kinetic resolution (DKR)

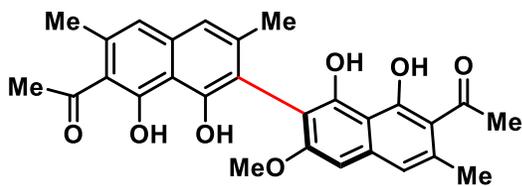


$$k_{\text{rac}} \gg k_{\text{fast}} \gg k_{\text{slow}}$$

up to 100% yield

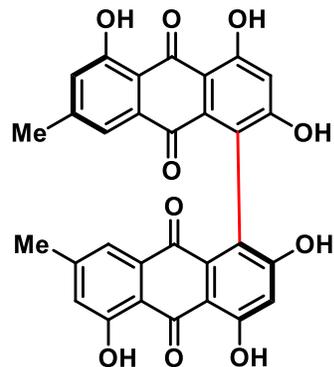
- 理论收益率=50%
 - 需要将产物与剩余原料分离
 - 对映体反应速率的比例 ($k_{\text{R}}/k_{\text{S}}$) 应至少大于20
 - 当反应转化率超过50%时, 产物光学纯度下降
-
- 理论收益率=100%
 - 动态动力学拆分应该是不可逆的, 能确保高对映选择性
 - 对映体反应速率的比例 ($k_{\text{R}}/k_{\text{S}}$) 应至少大于20
 - 外消旋化 (k_{rac}) 应至少等于或大于快速对映体 (k_{R}) 的反应速率

1.3 轴手性分子的手性判断



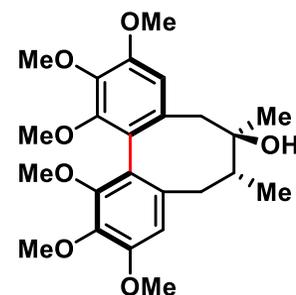
Sporandol

新型杀虫剂



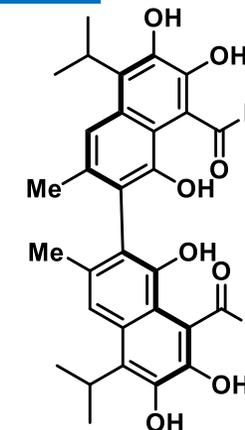
Skyrin

胰高血糖素拮抗剂



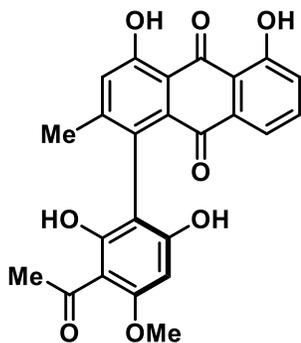
Schizandrin

抗氧化剂



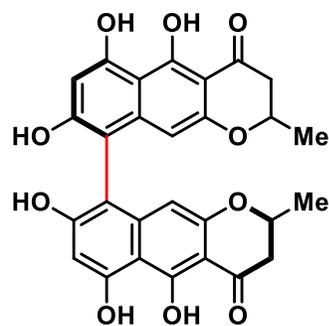
Gossypol

避孕类药物



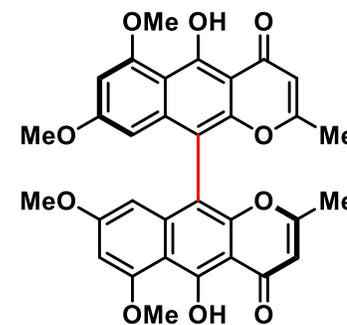
Knipholone

抗疟原虫活性



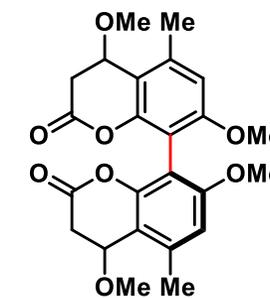
Cephalochromin

抗菌剂



Nigerone

抗肿瘤和抗菌活性

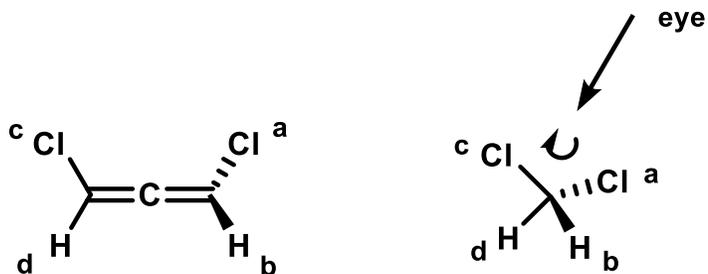


Kotanin

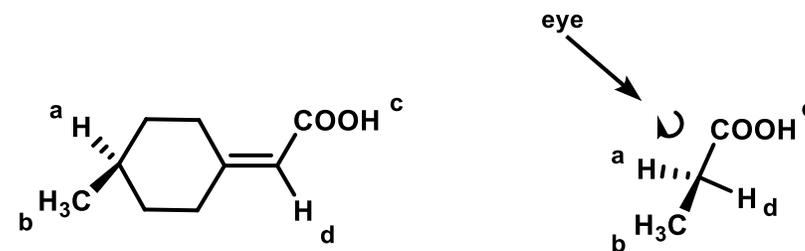
抗真菌活性

1.3 轴手性分子的轴手性判断

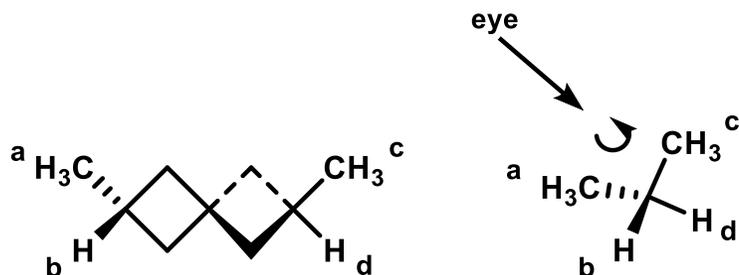
a. 累积烯烃类



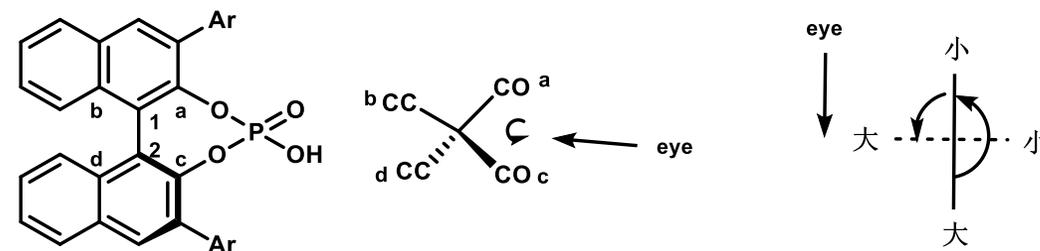
c. 环外双键类



b. 螺环类

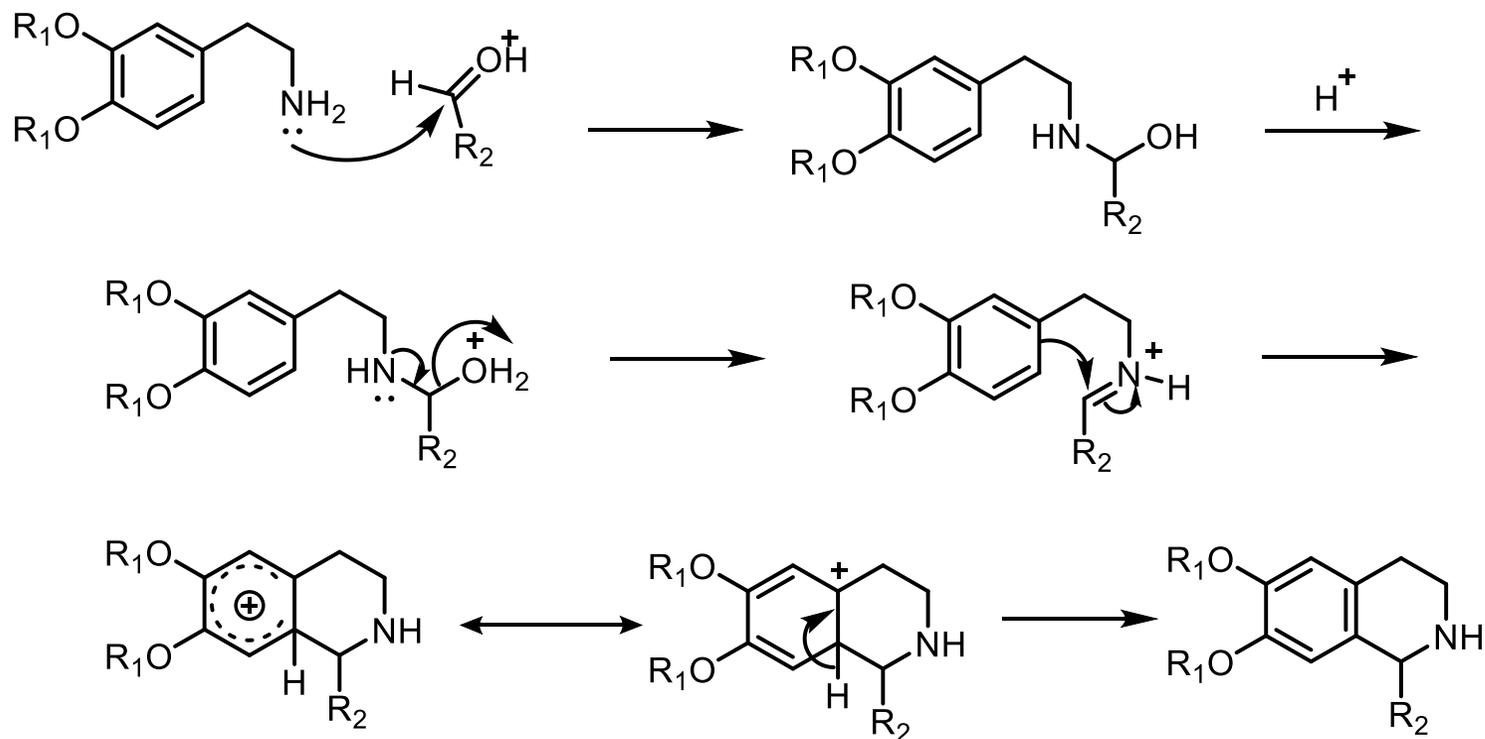


d. 联苯(萘)类



2.1 基于Pictet–Spengler反应构建轴手性骨架

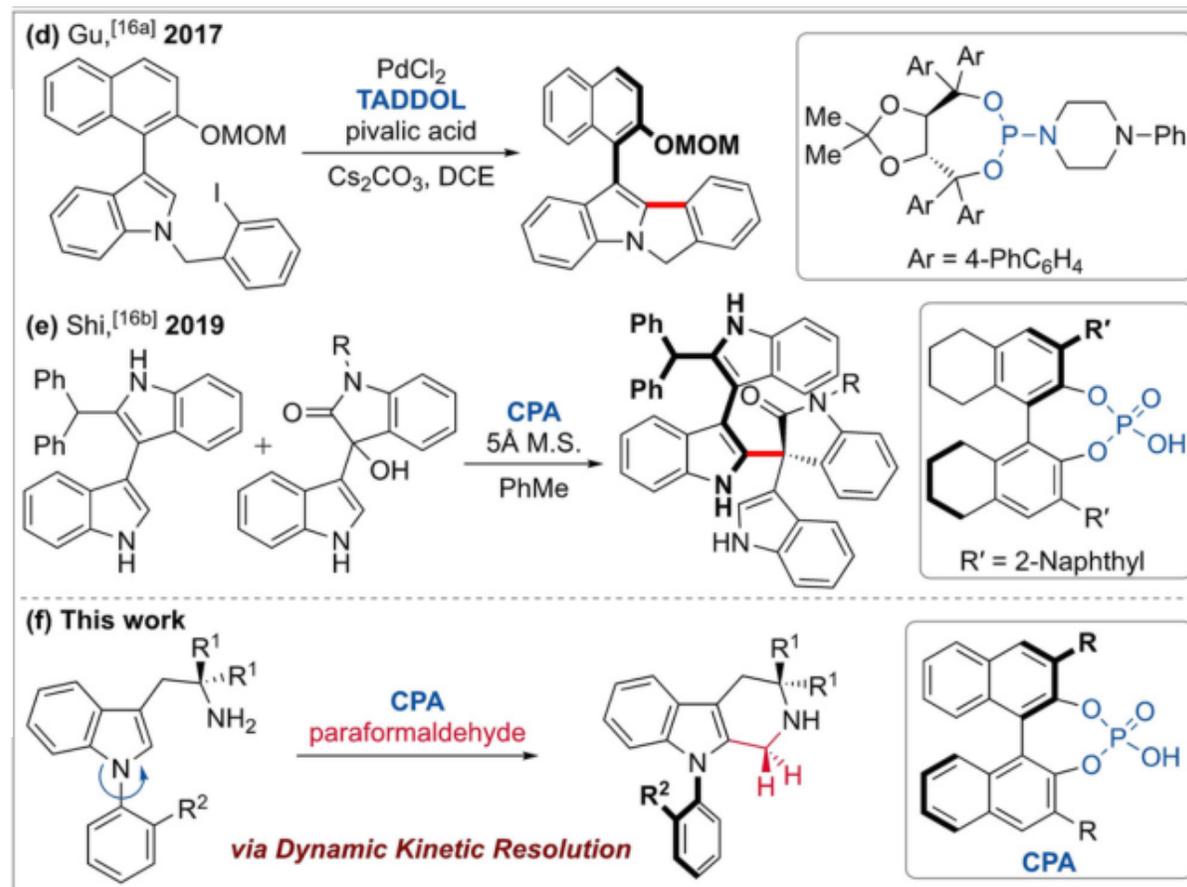
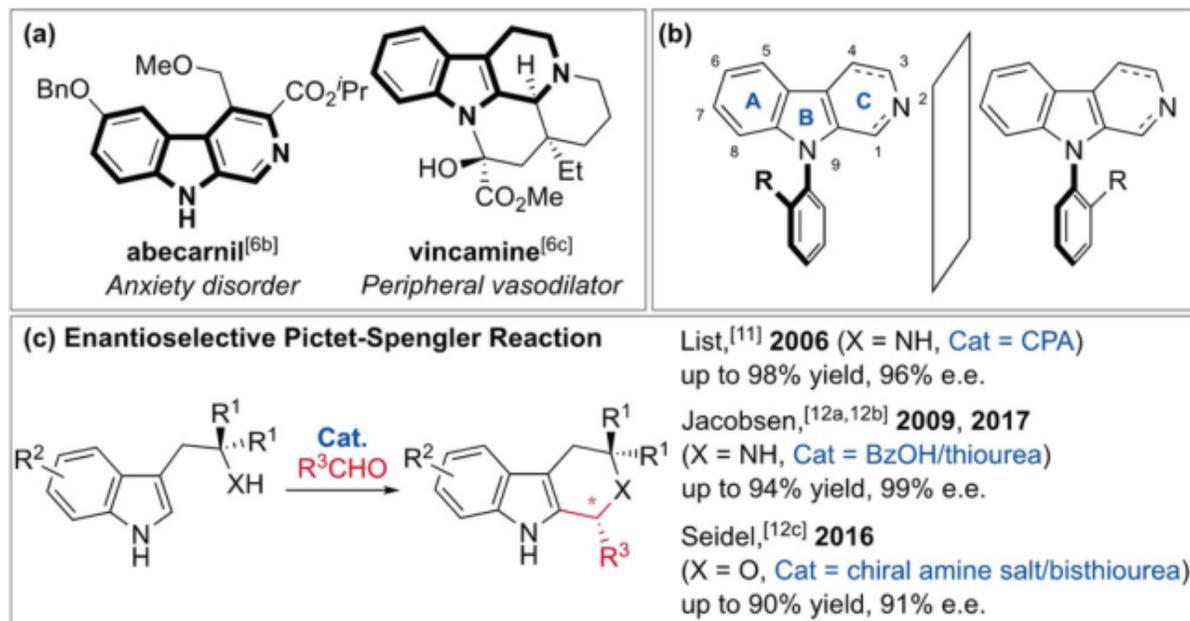
Pictet–Spengler反应是1911年瑞士化学家 Amé Pictet 和 Theodor Spengler 首次报道的 β -芳基乙胺在酸性条件下与羰基化合物（如醛）缩合再环化为1,2,3,4-四氢异喹啉的反应。现在 β -苯乙醇衍生物和 β -色醇衍生物与羰基化合物的相似反应也被称为Pictet–Spengler反应。其反应机理如下：



2.1 基于Pictet–Spengler反应构建轴手性骨架

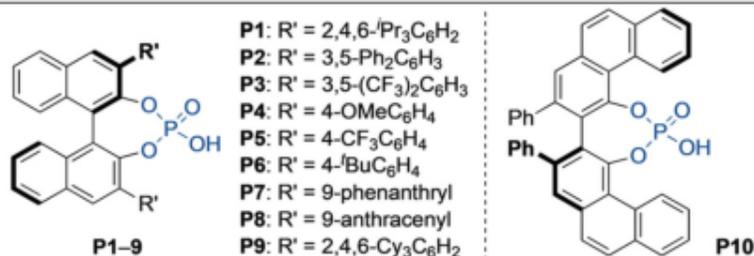
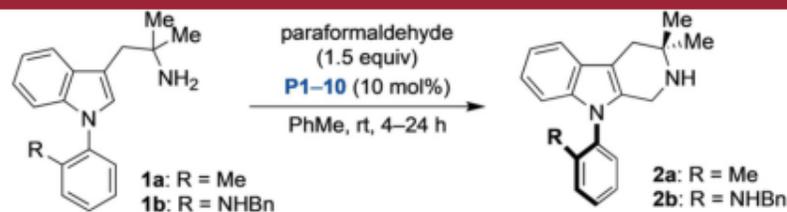
2.1.1 手型磷酸催化的Pictet–Spengler环化反应以高对映选择性实现轴手性*N*-芳基吲哚的构建

I. 研究背景



2.1 基于Pictet–Spengler反应构建轴手性骨架

II. 条件筛选

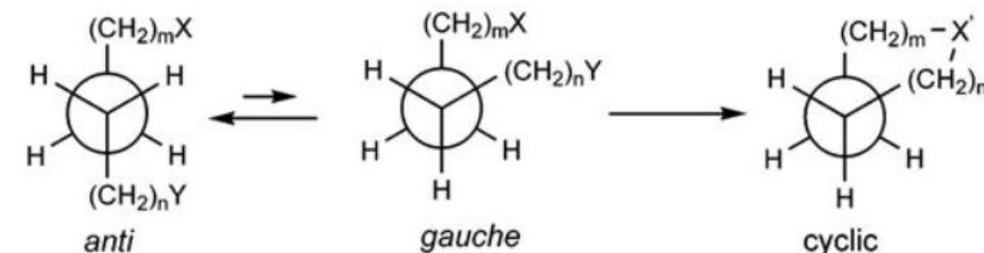


Entry	1	Catalyst	Yield [%] ^[b]	ee [%] ^[c]
1	1a	P1 ((R)-TRIP)	2a, 86	22
2	1b	P1 ((R)-TRIP)	2b, 90	87
3	1b	P2	2b, 91	60
4	1b	P3	2b, 86	48
5	1b	P4	2b, 71	6
6	1b	P5	2b, 81	8
7	1b	P6	2b, 82	4
8	1b	P7	2b, 59	66
9	1b	P8	2b, 98	73
10	1b	P9	2b, 99	94
11	1b	P10	2b, 97	12 ^[d]

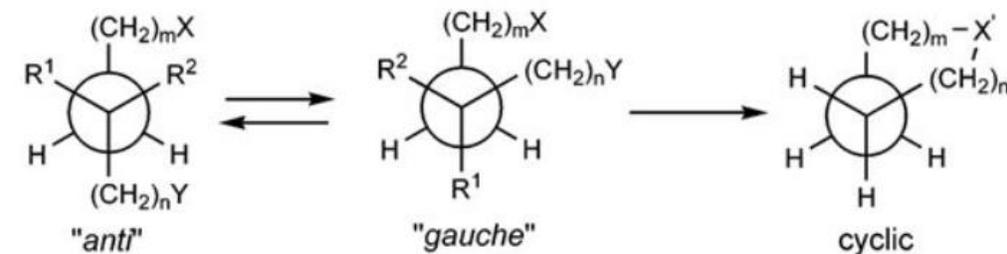
[a] Reaction conditions: **1** (0.050 mmol, 1.0 equiv), paraformaldehyde (0.075 mmol, 1.5 equiv), **P1–10** (0.005 mmol, 10 mol%), PhMe (0.5 mL, 0.1 M). [b] Isolated yields. [c] Enantiomeric excesses were determined by chiral-phase HPLC analysis. [d] The opposite enantiomer was obtained as a major enantiomer.

偕二甲基效应是指当分子链中亚甲基上的氢被大体积烷基取代后，该处键角变小，分子链末端两个反应基团相互靠近，有利于分子内环化反应

a. 取代前

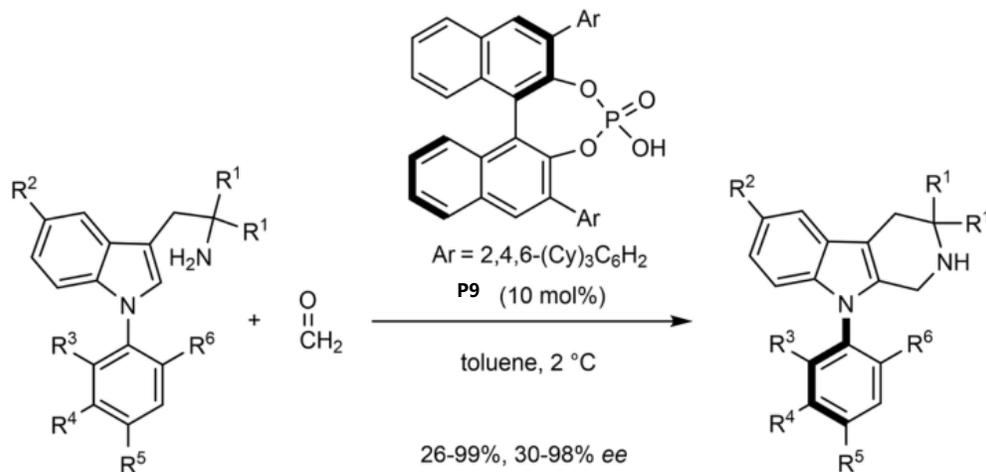


b. 取代后

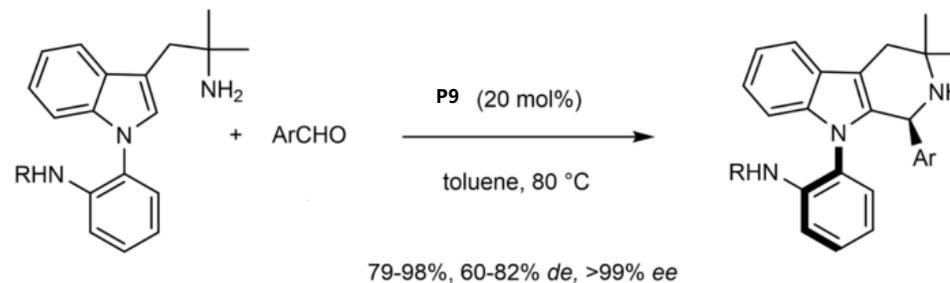


2.1 基于Pictet–Spengler反应构建轴手性骨架

III. 底物拓展



R¹ = Me, H
R¹, R¹ = (CH₂)₅
R² = H, Cl, OMe
R³ = NHBn, NBn₂, NHMe, NHBz, NHCO₂Me, BnHNCH₂
R⁴ = H, Me
R⁵ = H, Me, CF₃
R⁶ = H, OMe



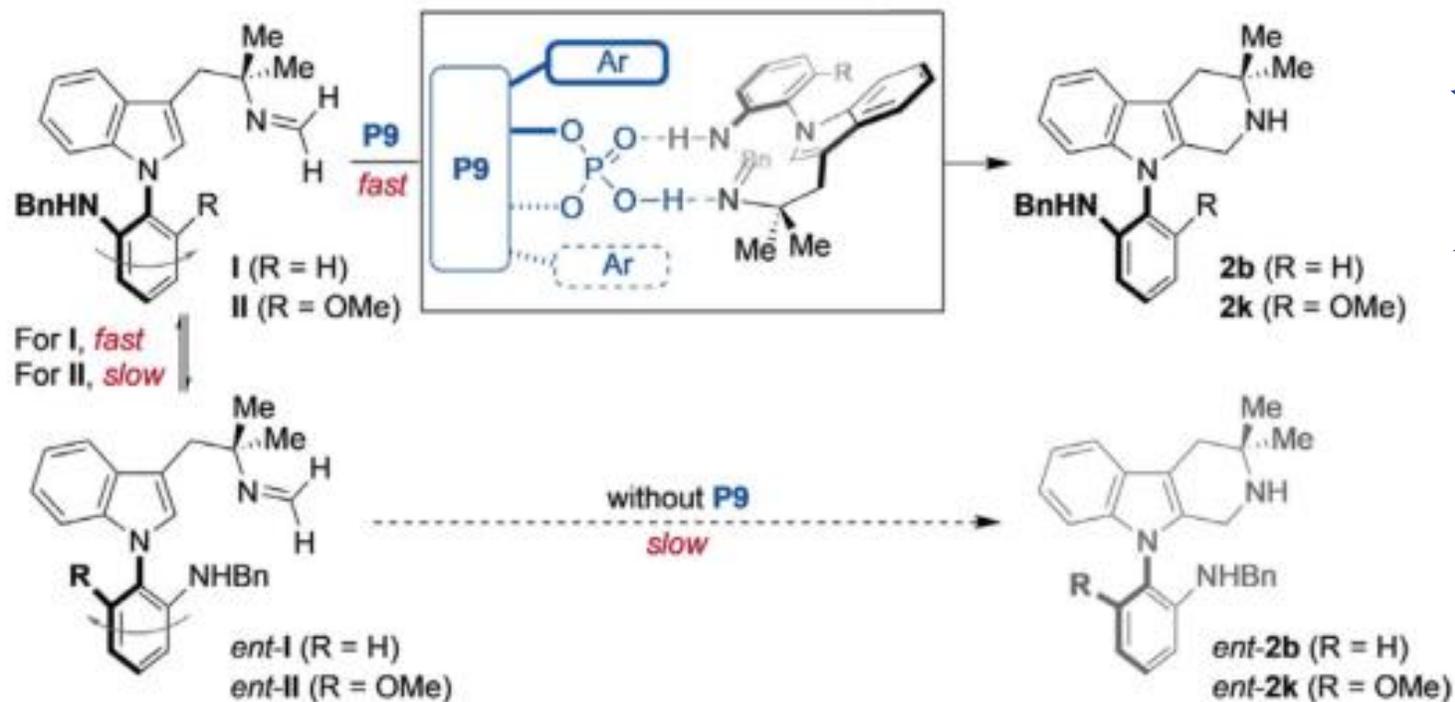
Ar = *p*-O₂NC₆H₄, *p*-F₃CC₆H₄, *p*-NCC₆H₄,
p-MeO₂CC₆H₄, *m*-NCC₆H₄
R = Bn, Bz

- R³=NBn₂ 26% yield, 56% e.e.
- R⁴=Me 90% yield, 30% e.e.
- R⁶=OMe 12h, 45% yield, 93% e.e.
19h, 83% yield, 36% e.e.

- 手性中心
- 手性轴

2.1 基于Pictet–Spengler反应构建轴手性骨架

IV. 机理研究



动态动力学拆分和
动力学拆分的差别

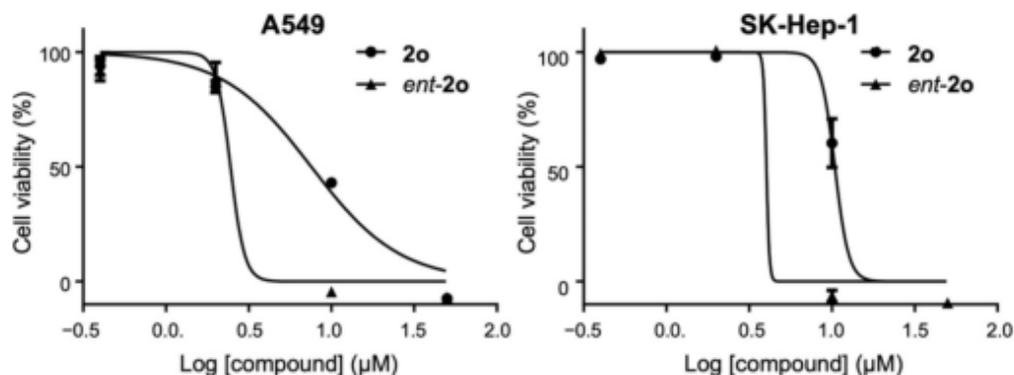
➤ 阻旋能力



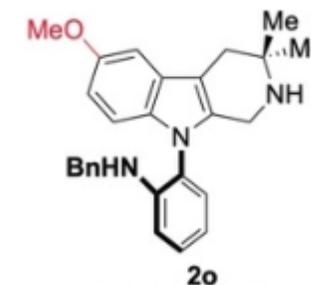
2.1 基于Pictet–Spengler反应构建轴手性骨架

V. 活性测试

Compd.	IC ₅₀ (μM)			
	A549	MDA-MB-231	SK-Hep-1	SNU-638
(±)- 2b	11 ± 2.9	10 ± 3.1	11 ± 1.9	9.4 ± 2.6
(±)- 2d	> 50	> 50	> 50	> 50
(±)- 2e	23 ± 6.3	13 ± 3.3	13 ± 1.8	25 ± 4.1
(±)- 2h	12 ± 3.1	9.5 ± 1.9	10 ± 2.4	5.7 ± 0.94
(±)- 2i	3.4 ± 1.5	2.5 ± 0.78	2.6 ± 0.63	2.4 ± 1.1
(±)- 2m	11 ± 3.3	10 ± 2.8	12 ± 3.9	5.8 ± 1.7
(±)- 2o	2.6 ± 0.67	2.5 ± 0.69	2.5 ± 0.84	2.6 ± 0.88
(±)- 2p	2.6 ± 0.93	3.9 ± 1.3	2.6 ± 0.72	2.7 ± 0.91
Doxorubicin (nM)	24 ± 12	78 ± 16	98 ± 23	36 ± 17



[a] A549: Human lung cancer cell line; MDA-MB-231: Human breast cancer cell line; SK-Hep-1: Human liver cancer cell line; SNU-638: Human stomach cancer cell line. [b] Data are represented as means ± SD. The results are representative of three independent experiments. Measured by the SRB method.^[17]



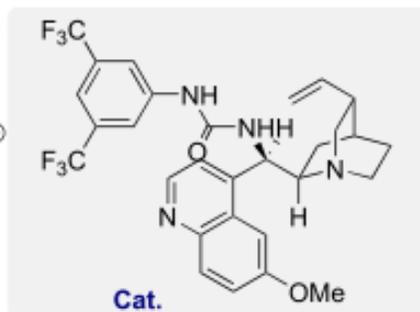
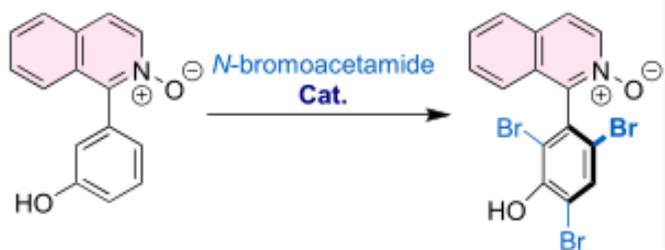
- **2o**的外消旋混合物表现出良好的生物学活性
- 轴手性的 *ent-2o* 相比于 **2o** 的抗肿瘤增殖活性提升了2-3倍

2.1 基于Pictet–Spengler反应构建轴手性骨架

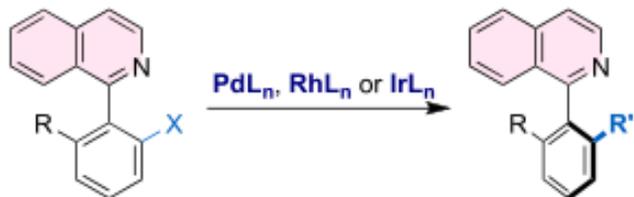
2.1.2 通过动态动力学拆分有机催化合成具有阻旋异构选择性的异喹啉

I. 研究背景

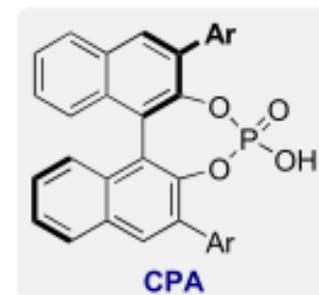
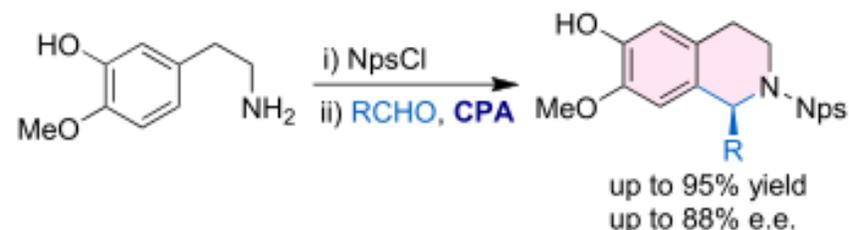
(a) Atroposelective bromination (Asano/Matsubara, 2015)



(b) Atroposelective cross-coupling



(c) Asymmetric control of a stereogenic center (Hiemstra, 2014)



(d) This work

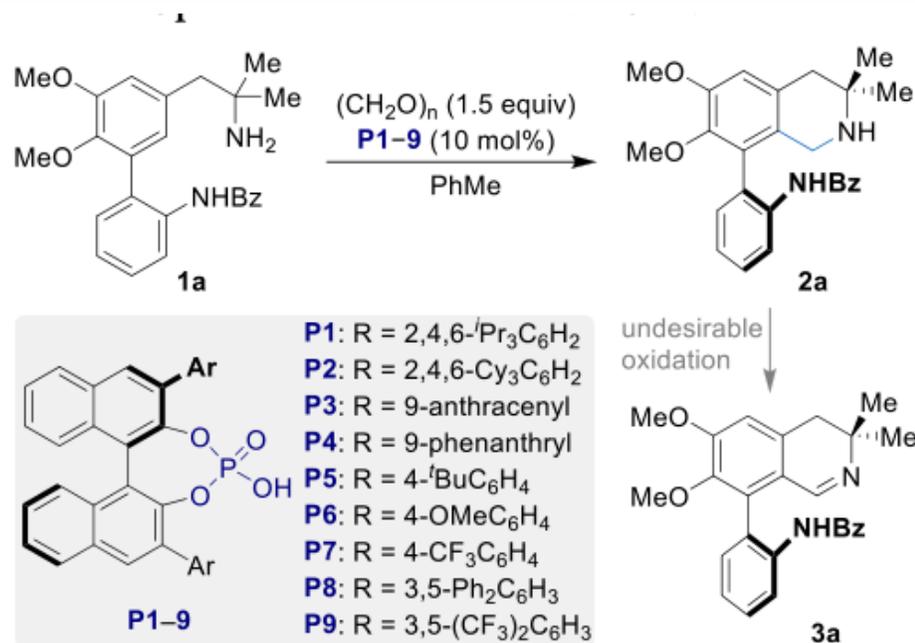


- Excellent enantioselectivity (up to 99% ee)
- Single regioisomer observed
- Dynamic kinetic resolution
- Enantiodivergence

- 异喹啉是一种含氮杂环化合物，常见于天然产物、生物活性化合物和不对称催化剂中
- 多取代的异喹啉及其衍生物可以具有多个立体元素
- 异喹啉和芳环之间的C-C立体定向轴可由催化手性磷酸控制

2.1 基于Pictet–Spengler反应构建轴手性骨架

II. 条件筛选

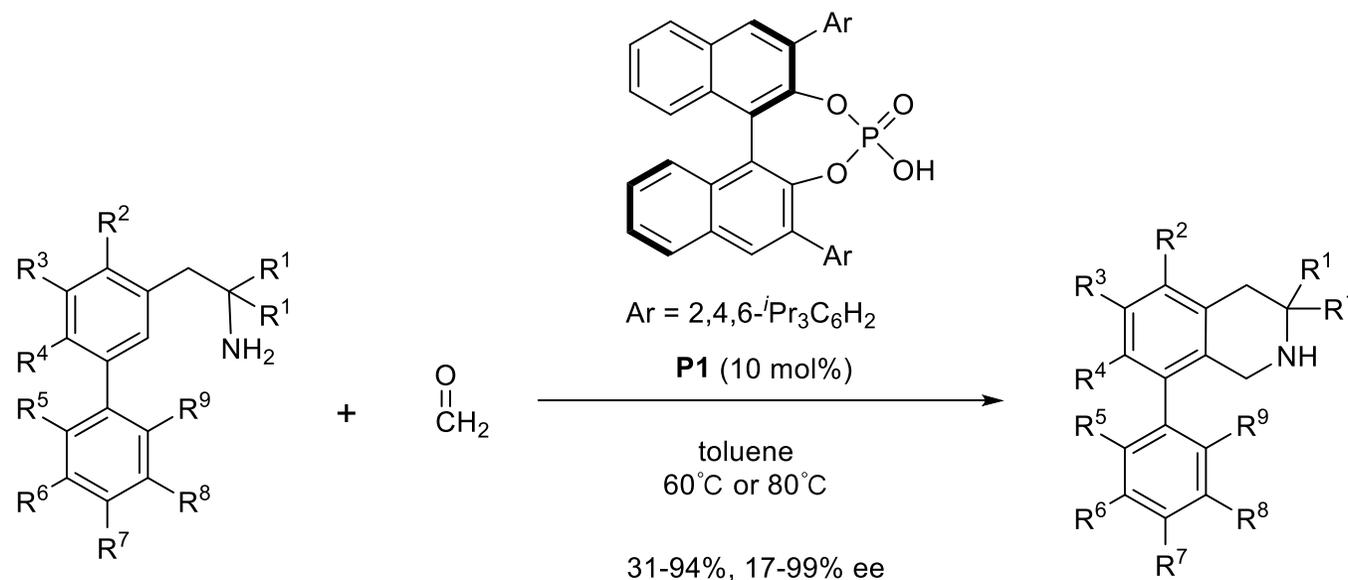


- 对映选择性取决于催化剂苯环上3,3'-邻位取代基，空间要求较低和缺电子的取代基在这种选择性中起着重要作用。
- 环化产物2a可以在高温下借助手性磷酸进行多聚甲醛氧化脱氢生成3a。

entry	catalyst	temp (°C)	conc (M)	yield ^b of 2a (%)	ee ^c of 2a (%)
1	P1	80	0.1	50	96
2	P2	80	0.1	50	95
3	P3	80	0.1	14	70
4	P4	80	0.1	<15	nd ^d
5	P5	80	0.1	18	(31) ^e
6	P6	80	0.1	<15	nd ^d
7	P7	80	0.1	15	(54) ^e
8	P8	80	0.1	24	(24) ^e
9	P9	80	0.1	26	(14) ^e
10	P1	60	0.1	45	97
11	P1 ^f	60	0.1	67	96
12	P1 ^f	60	0.01	83	96

2.1 基于Pictet–Spengler反应构建轴手性骨架

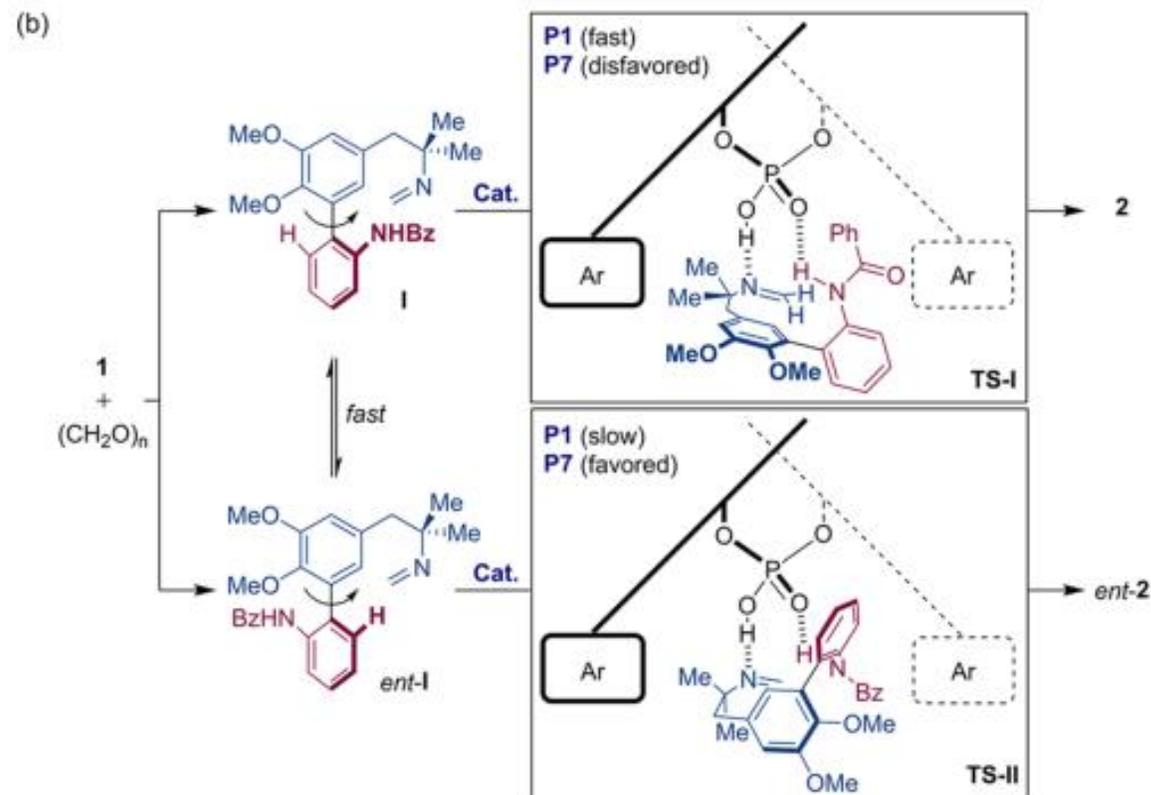
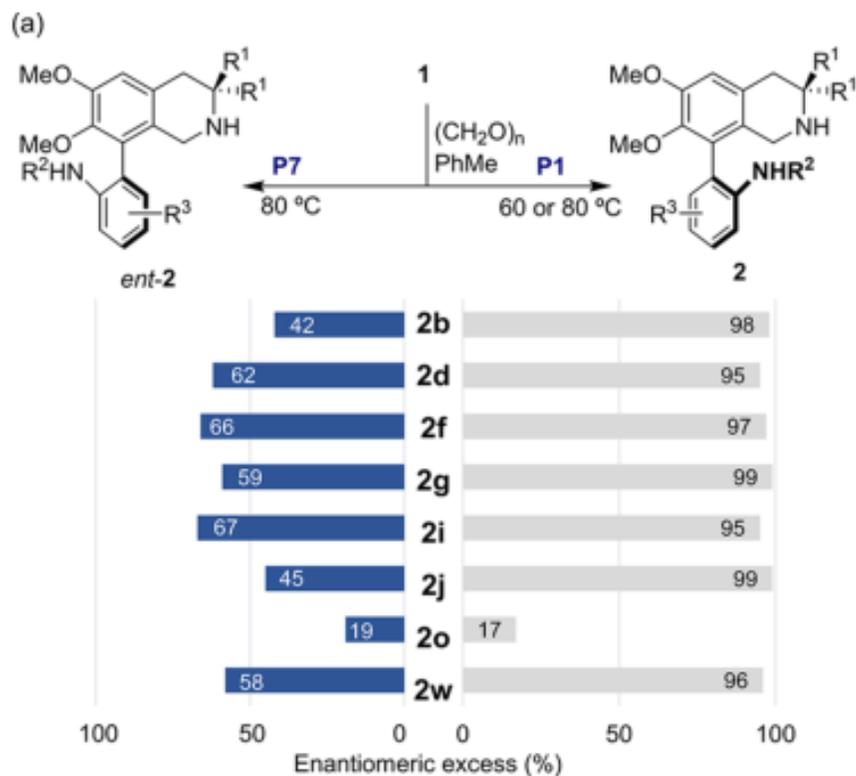
III. 底物拓展



- R¹ = Me, H
- R² = Me, H
- R³ = OMe
- R⁴ = OMe, OBz, O^{*i*}Pr₃
- R⁵ = OMe, H
- R⁶ = Me, Cl, H
- R⁷ = Me, F, CF₃, H
- R⁸ = Me, H
- R⁹ = NHBz, NHCO₂Me, NHMe, NHBn, NMe₂, OH, Me, Ph

2.1 基于Pictet–Spengler反应构建轴手性骨架

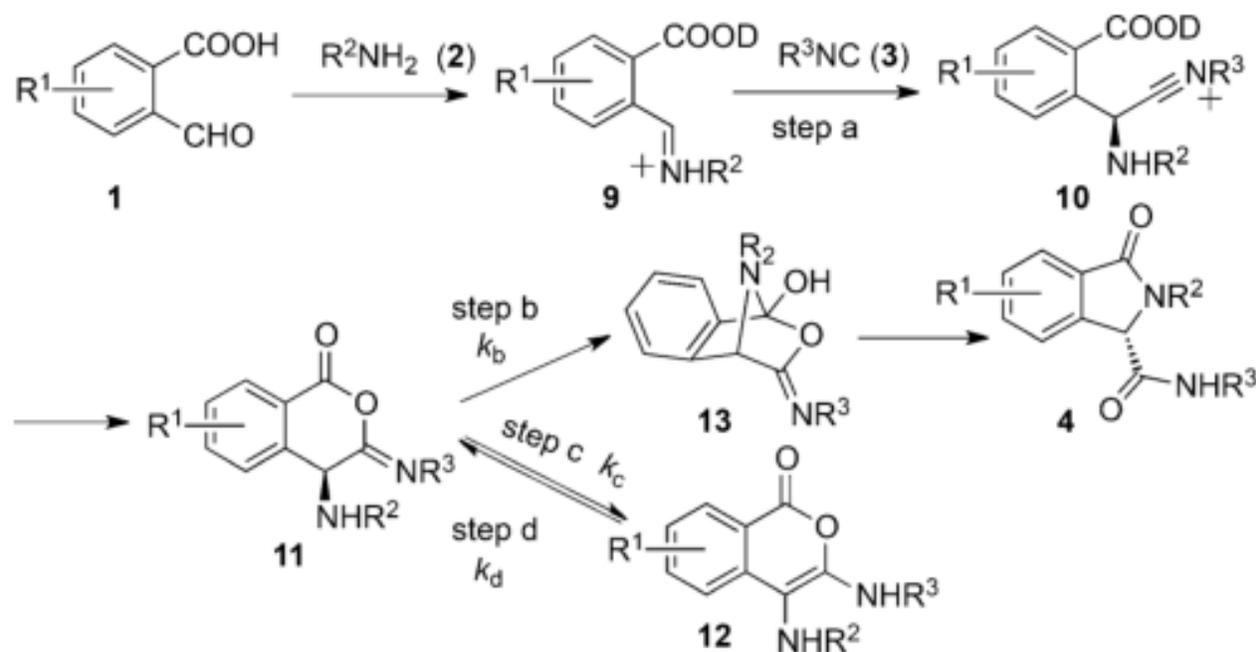
IV. 机理研究



2.2 基于多米诺反应构建轴手性骨架

多米诺反应 顾名思义，像多米洛骨牌一样，不需要分离中间产物，直接进行一锅法合成，具有高度立体选择性，能够构建复杂的分子骨架。与传统的分步反应相比，巧妙的多米诺反应不仅能提高反应效率，还能大大减少溶剂、试剂等的损耗。

祝介平：手性磷酸催化的动态动力学多组分反应



2.2.1 手性布朗斯特酸催化的动态动力学拆分构建阻旋异构邻甲酰基萘酰胺

教育经历

2003年9月,北京大学药学院,本科
2008年7月,中科院上海有机化学研究所,博士
2008年8月至12月在香港大学化学系从事研究助理;
2009年1月-2011年12月,德国马普所Benjamin List课题组从事博士后研究;
2012年1月-至今,兰州化学物理研究所担任研究员

研究领域

导向有机合成和药物化学的有机小分子催化和过渡金属催化
发展新颖的绿色氧化和高原子经济性反应



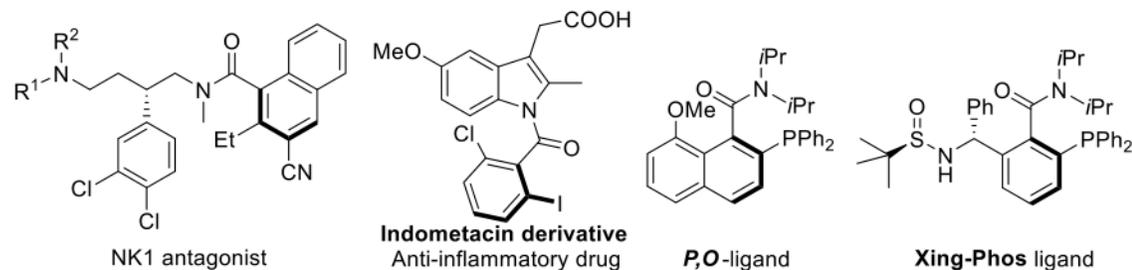
蒋高喜

兰州化学物理研究所

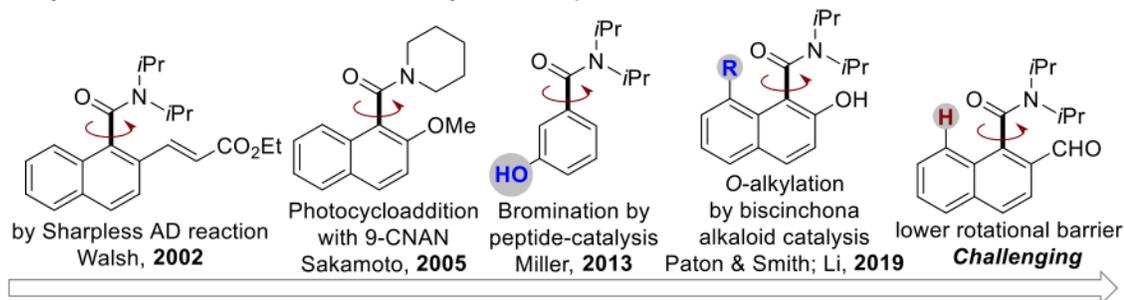
2.2 基于多米诺反应构建轴手性骨架

I. 研究背景

a. Typical axially chiral amides in bioactive molecules and chiral ligands.



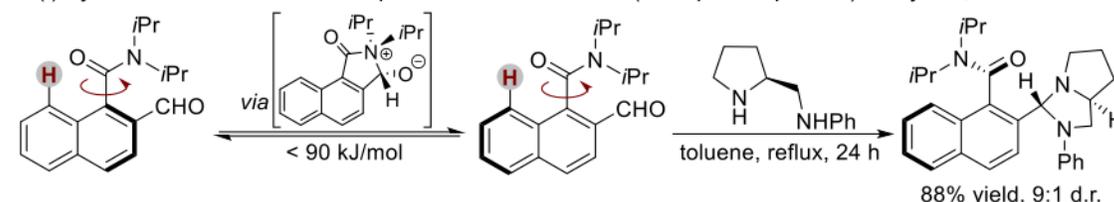
b. Dynamic kinetic resolution of axially chiral naphthamides.



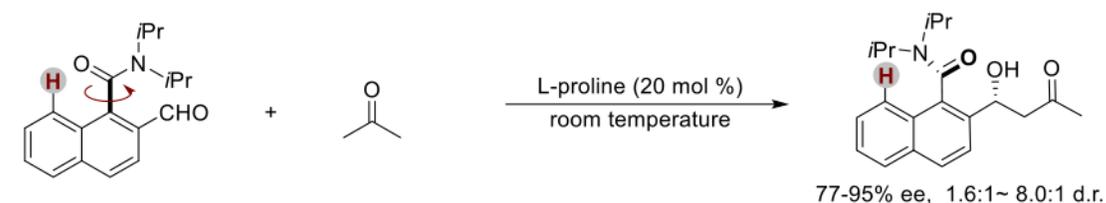
- 轴手性的芳香酰胺是众多生物活性骨架和不对称催化中最重要的骨架之一
- 起始原料的需要多步合成
- 直接动态动力学拆分成功率低
- 固有的醛基不利于阻止芳基的旋转

c. Dynamic kinetic resolution of axially chiral 2-formyl naphthamide

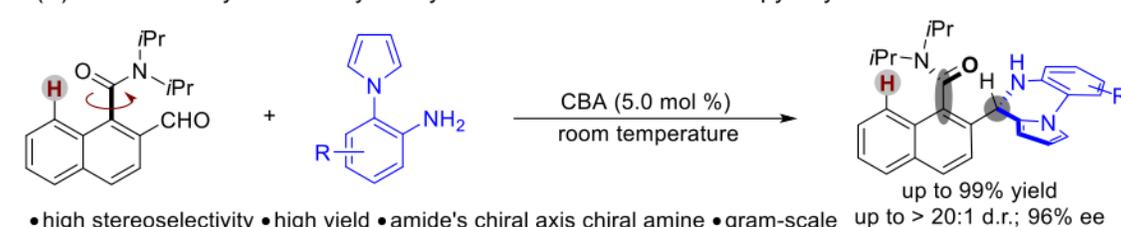
(i) by stoichiometric amount of proline-based diamine (4-step from proline). Clayden, 1999



(ii) by L-proline-catalyzed asymmetric aldol reaction with acetone. Walsh, 2004

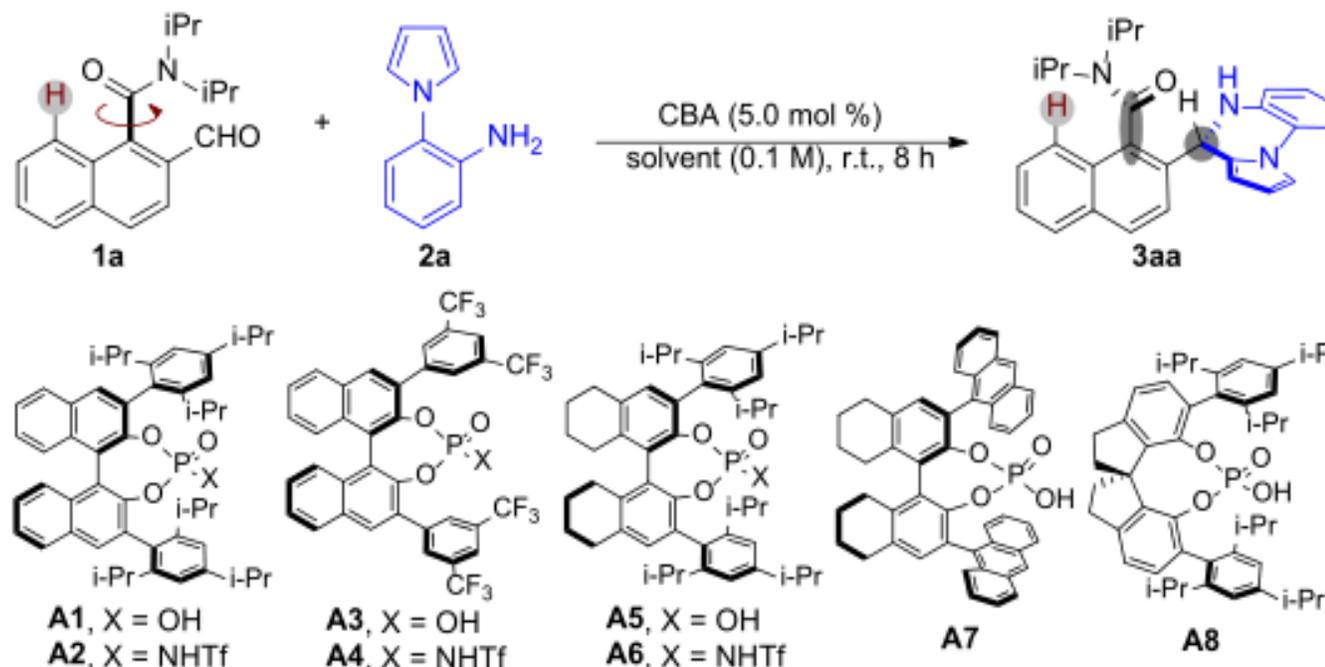


(iii) **This work:** by CBA-catalyzed dynamic kinetic resolution with pyrrolylaniline.



2.2 基于多米诺反应构建轴手性骨架

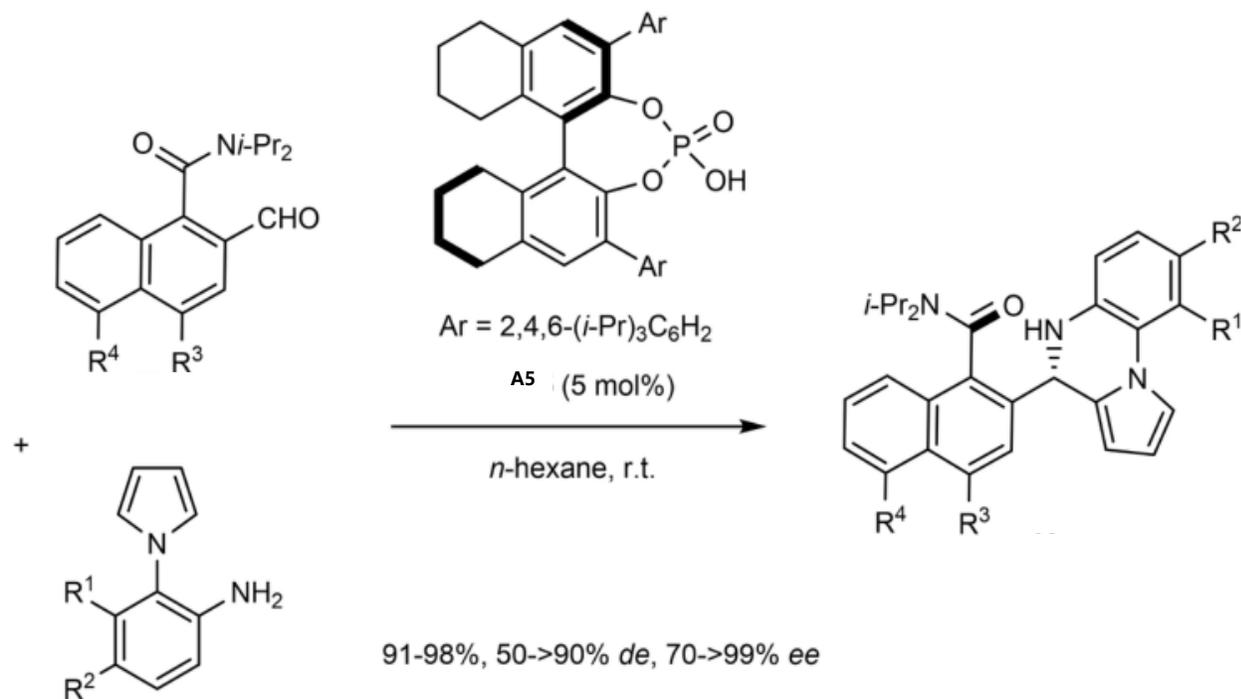
II. 条件筛选



entry	CBA	solvent	yield (%) ^b	d.r. ^c	e.r. ^d
16 ^e	A5	n-hexane	98	>20:1	93:7

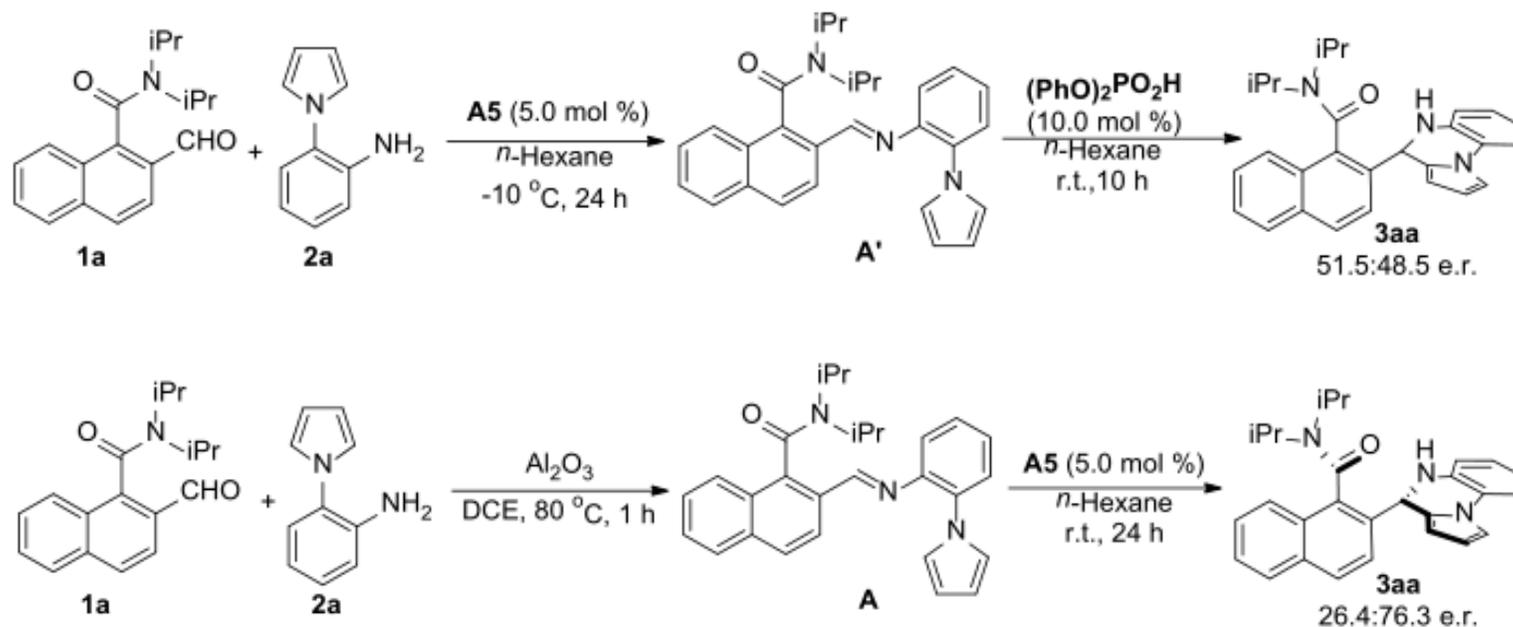
最佳条件: 室温下, 0.1mmol的1a与0.15mmol的2a在正己烷中以5.0 mol%的手型磷酸A5为催化剂, 生成3aa, 产率为98%, d.r>20:1, e.r为93:7

III. 底物拓展



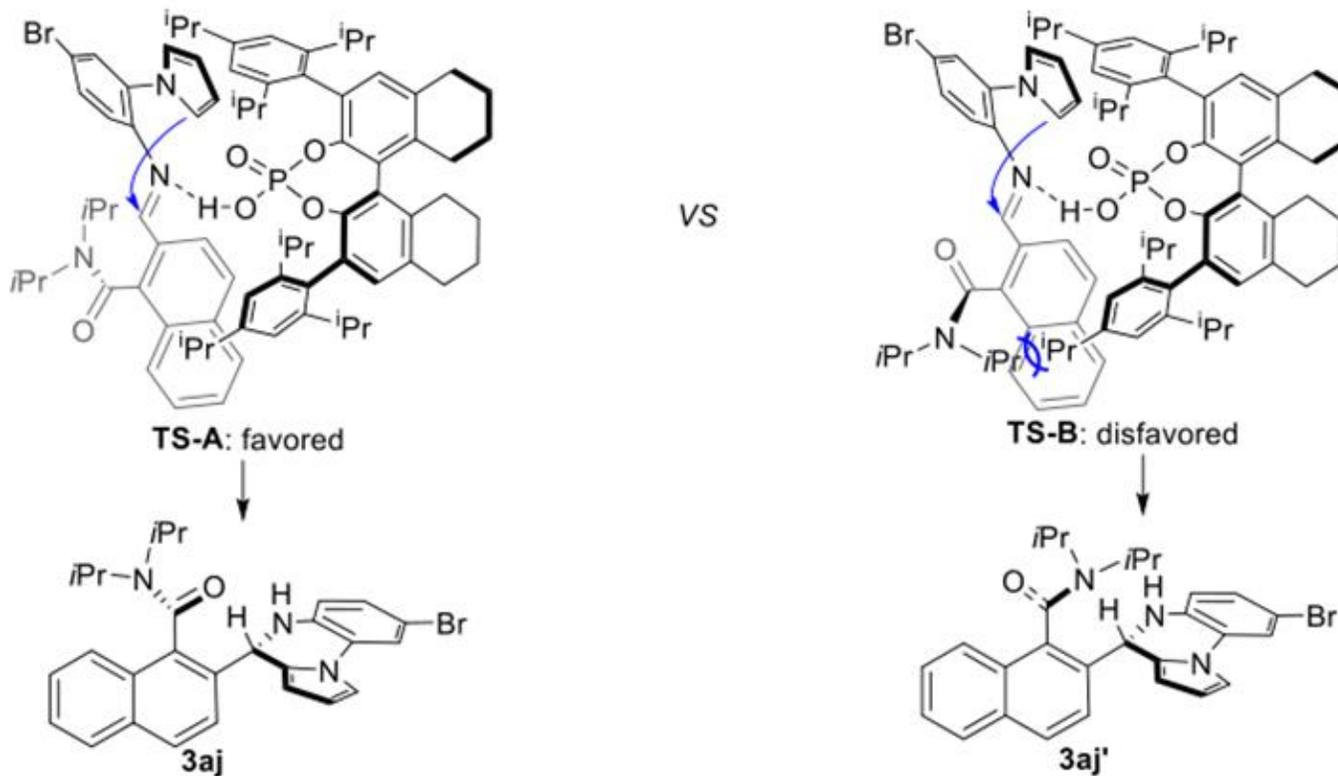
R¹ = H, Me, F, Cl, Br, CF₃
R² = H, Me, F, Cl, Br, CF₃, OMe
R³ = H, Me, F
R³, R⁴ = (CH₂)₂

IV. 机理研究



- 中间体A'由于较低的旋转势垒而经历快速外消旋化
- 手型磷酸催化剂A5对反应的每一步都具有手性识别作用

IV. 机理研究



- TS-A比TS-B更有利，N-异丙基和催化剂骨架之间存在较大的空间冲突

2.3 基于偶联反应构建轴手性骨架

2.3.1 轴向手性萘-吲哚的合成策略：外消旋底物的催化不对称加成反应

教育经历

- 1994.9-1998.7 本科, 江苏师范大学化学系
2001.9-2004.7 硕士, 江苏师范大学化学系
2010.9-2013.7 博士, 苏州大学与中国科学技术大学
联合培养 (导师: 屠树江、龚流柱)
2012.8-2013.2 访问学者, 新加坡南洋理工大学 (导
师: Loh Teck-Peng)
2004.7-2015.7 助教、讲师、副教授, 江苏师范大学
2015.8-至今 教授, 江苏师范大学

研究领域

手性吲哚化学
手性杂环化学
手性杂环骨架的催化不对称构建



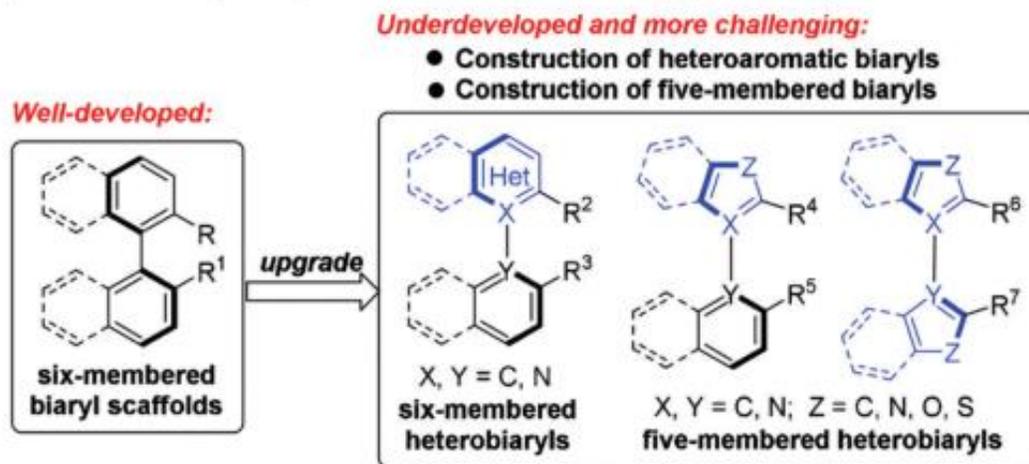
石枫

江苏师范大学

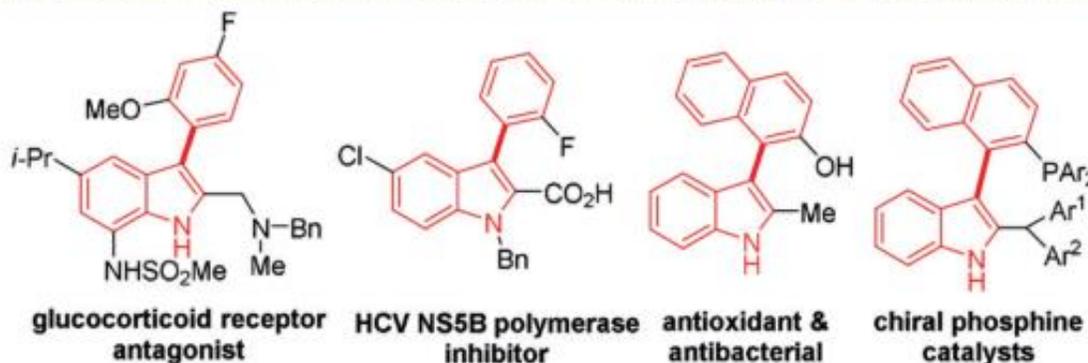
2.3 基于偶联反应构建轴手性骨架

I. 研究背景

a) Profile of catalytic asymmetric construction of axially chiral biaryl scaffolds

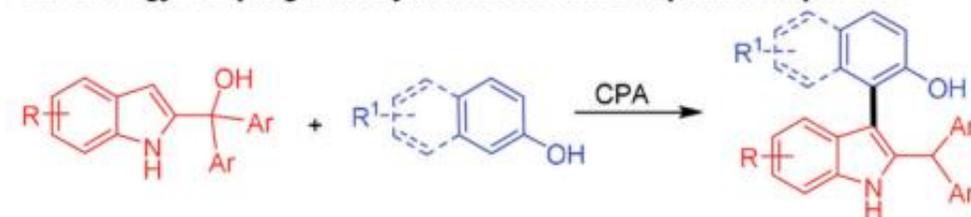


b) Bioactive molecules and chiral catalysts containing naphthyl(phenyl)-indole scaffolds

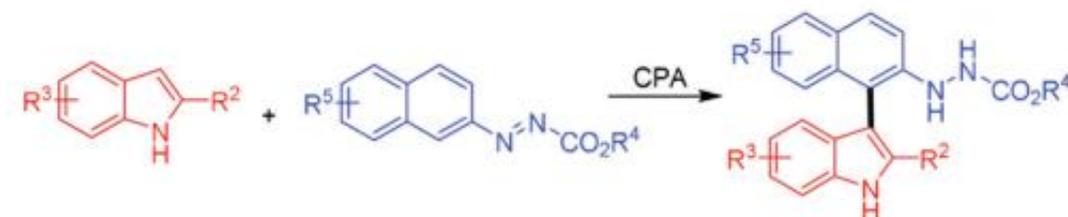


c) Previous strategy: coupling indole ring with naphthyl or phenyl ring

Our strategy: coupling 2-indolylmethanols with 2-naphthols or phenols



Tan's strategy: coupling 2-substituted indoles with azonaphthalenes

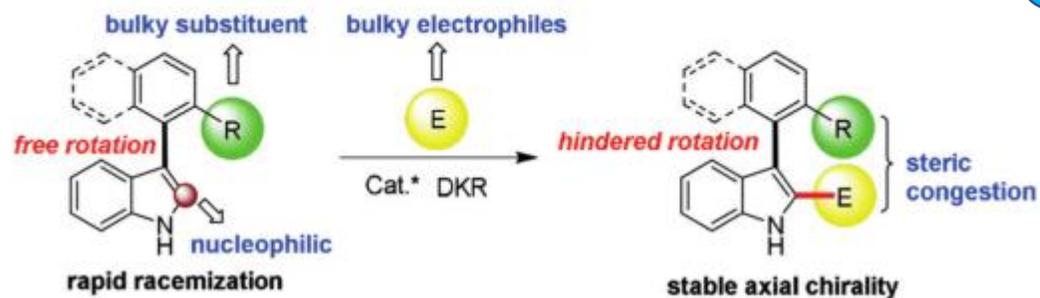


➤ 五元杂环二芳基骨架的构建较为稀少，因为其旋转屏障和构象稳定性远低于六元二芳基骨架

2.3 基于偶联反应构建轴手性骨架

II. 方案设计

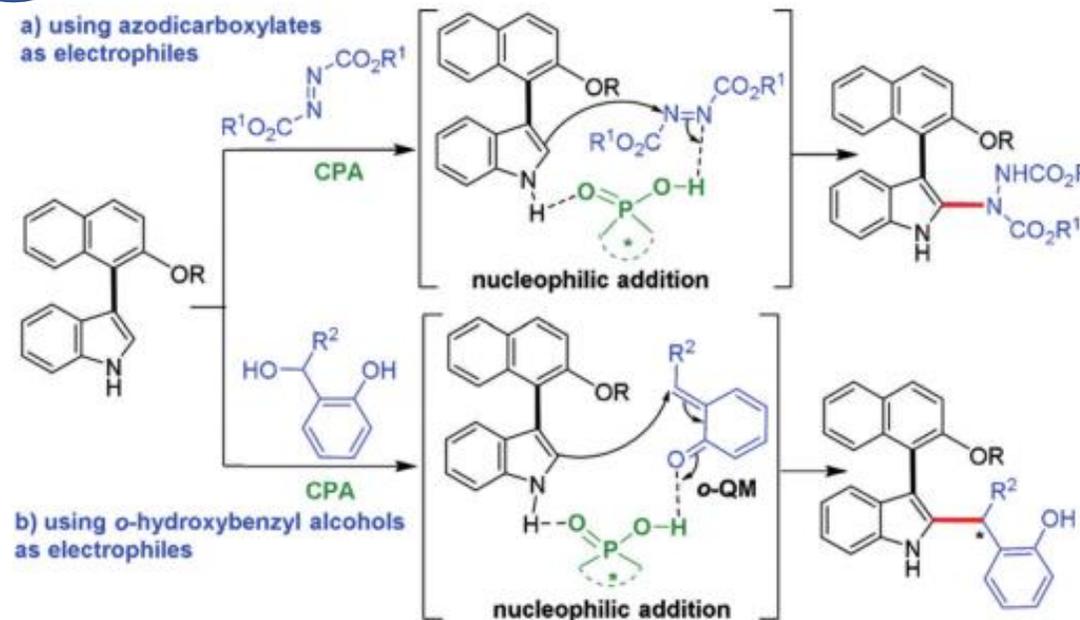
This strategy: nucleophilic addition of racemic naphthyl-indoles



挑战:

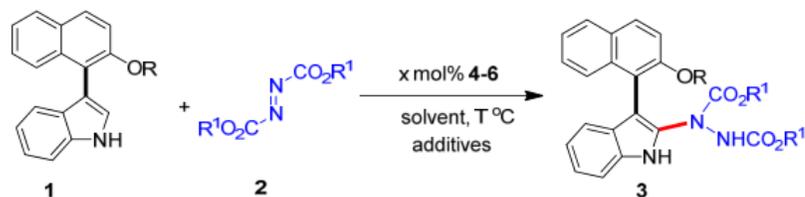
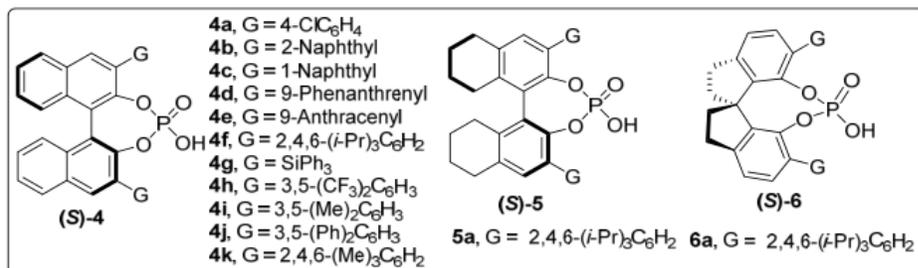
- 1) 寻找位阻大且活性强的亲电试剂
- 2) 选择合适的手性催化剂控制对映选择性
- 3) 利用外消旋亲电试剂同时控制轴向手性和中心手性

方案设计



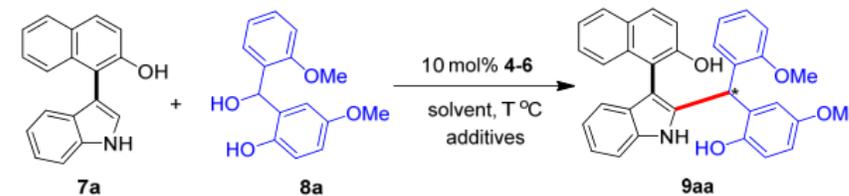
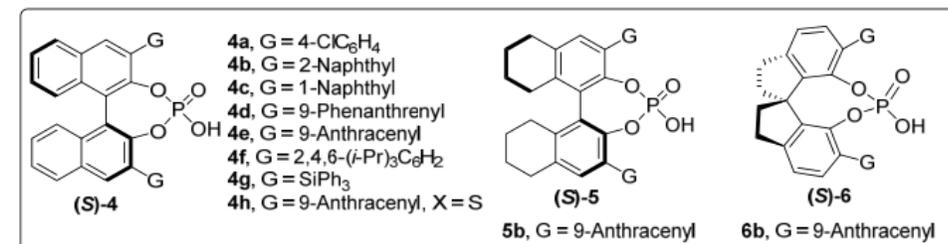
2.3 基于偶联反应构建轴手性骨架

III. 条件筛选



entry	3	R (1)	R ¹ (2)	x	Cat.	solvent	T (°C)	yield (%) ^b	er ^c
44 ^{e,i,k}	3bb	Tf (1b)	Bn (2b)	10	4f	DCM (0.1 M)	25	86	97:3

最佳条件: 温度为25°C, 1b与2b的投料比为1:3, 溶剂为0.1M的二氯甲烷, 催化剂为10 mol%的手型磷酸**4f**, 添加剂为4A分子筛

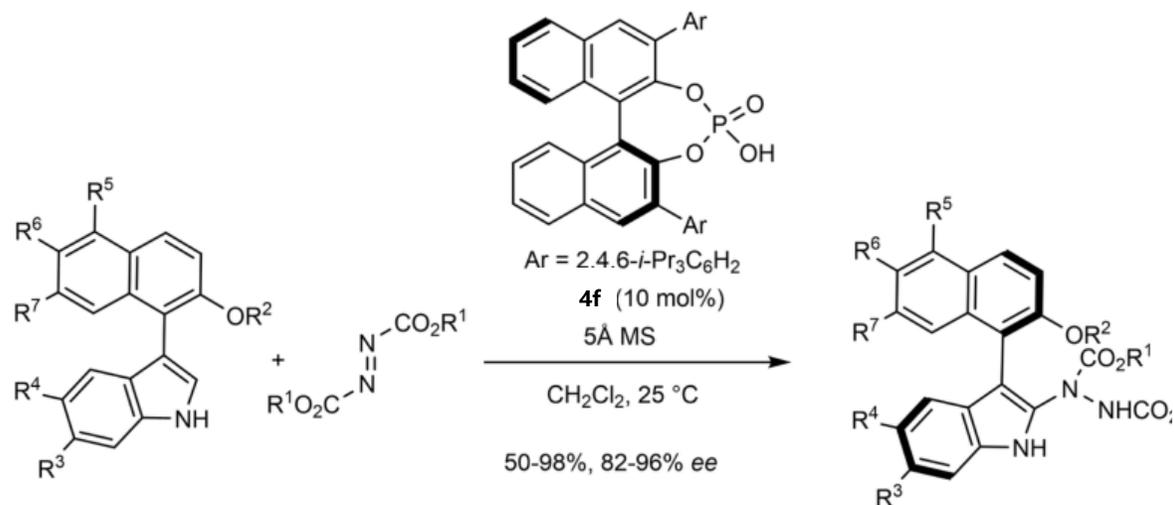


entry	Cat.	solvent	additives	1a:2a	T (°C)	yield (%) ^b	dr ^c	er ^d
38	6b	1:4	5 Å MS	1:1.2	25	93	>95:5	95:5

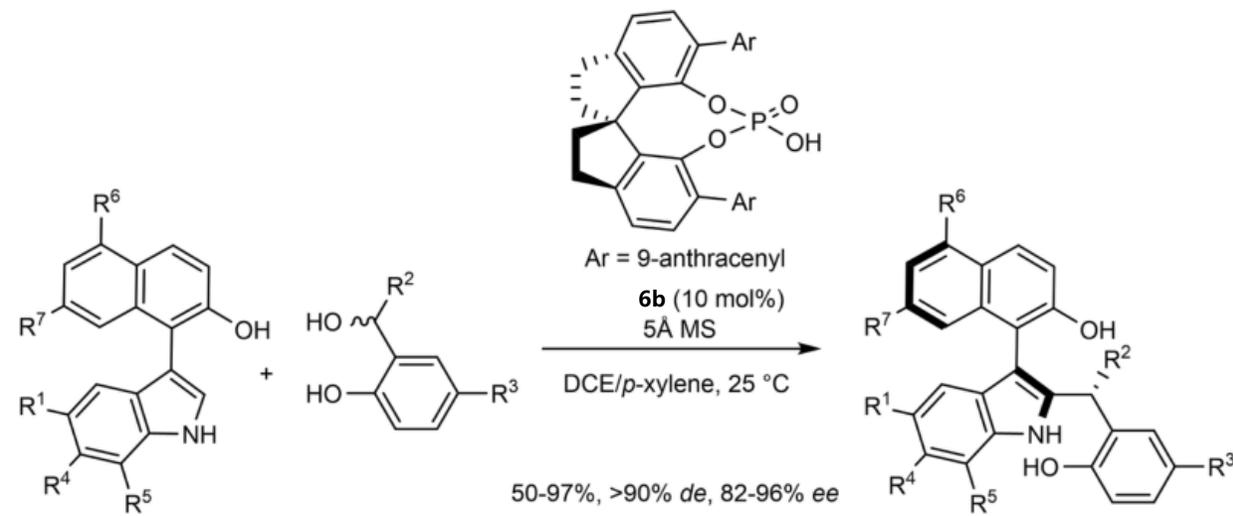
最佳条件: 温度为25°C, 7a与8a的投料比为1:1.2, 溶剂为CHCl₂CHCl₂ / p-xylene = 1:4, 催化剂为10 mol%的手型磷酸**6b**, 添加剂为5A分子筛

2.3 基于偶联反应构建轴手性骨架

IV. 底物拓展



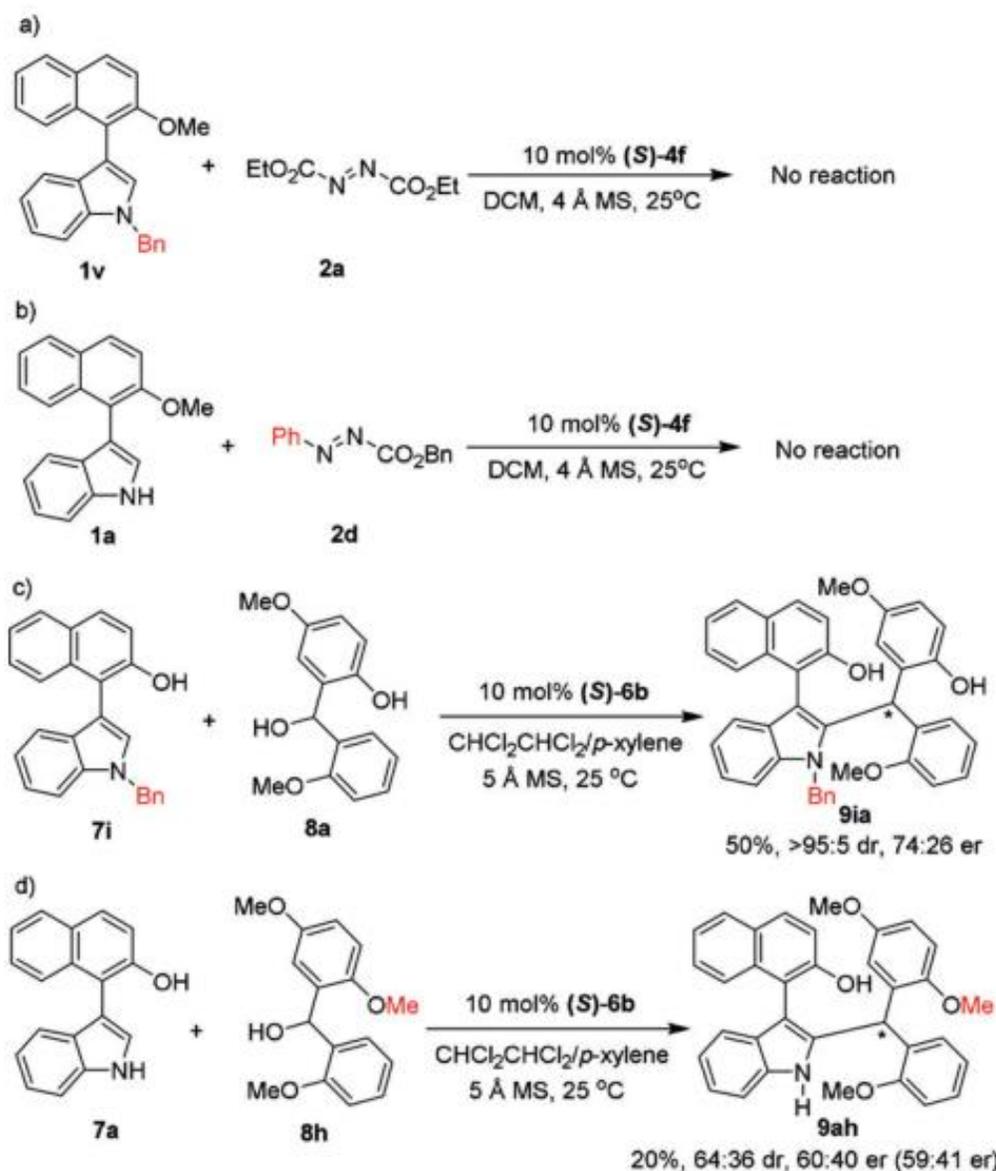
R¹ = Bn, Et, *i*-Pr
R² = Tf, Me, Ts
R³ = H, F, Cl
R⁴ = H, Me, F, Cl, OMe, CO₂Me
R⁵ = H, OMe
R⁶ = H, Br, Me, Ph
R⁷ = H, OMe, Ph



R¹ = H, Cl
R² = *o*-MeOC₆H₄, *m*-MeOC₆H₄, *p*-(*t*-Bu)₂C₆H₃, *p*-MeOC₆H₄, 2-thienyl, Me
R³ = Me, OMe
R⁴ = H, F, Cl
R⁵ = H, F, Me
R⁶ = H, OMe
R⁷ = H, F, Me

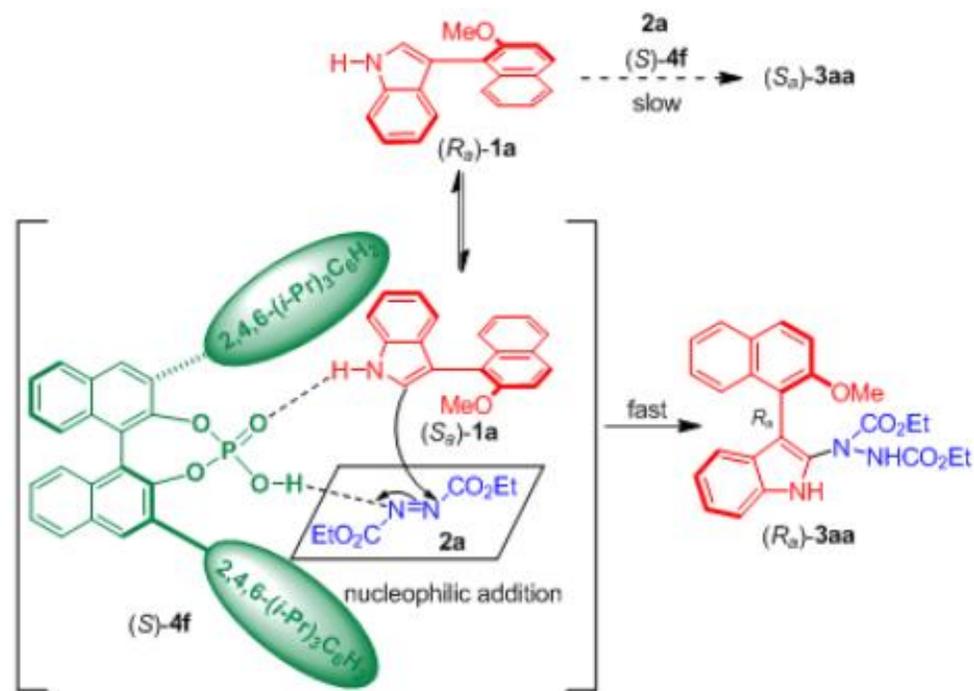
2.3 基于偶联反应构建轴手性骨架

V. 机理研究

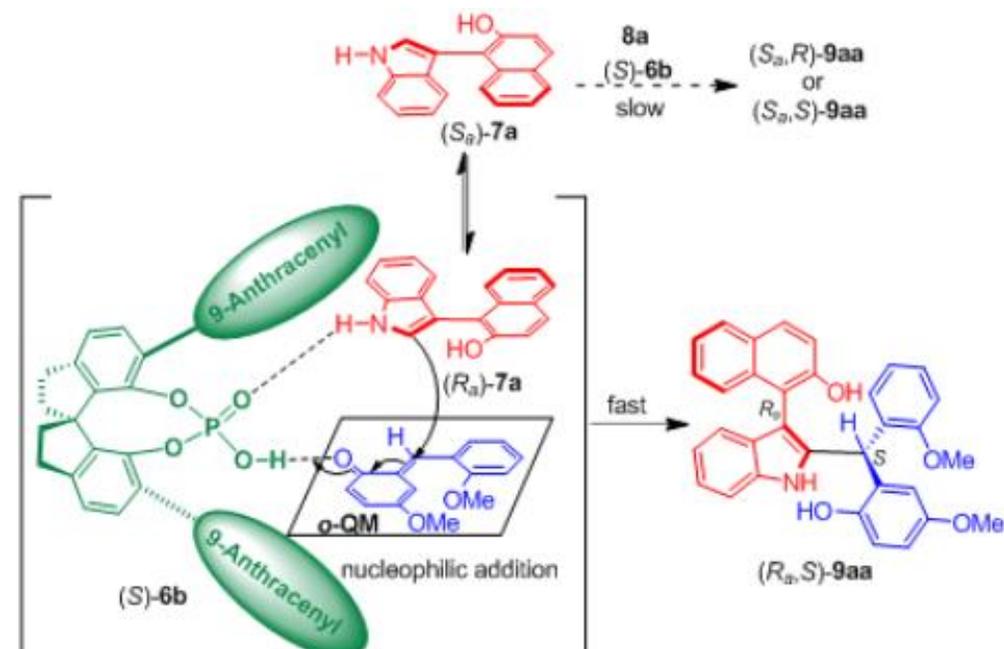


- 底物1中吲哚的N-H基团和底物2中的酯基在控制反应活性中起着关键作用
- 底物7中吲哚的N-H基团和底物8中苯酚的羟基基团可能与手性磷酸形成氢键而对反应活性和对映选择性起着重要的控制作用

2.3 基于偶联反应构建轴手性骨架



使用偶氮碳酸酯作为亲电试剂

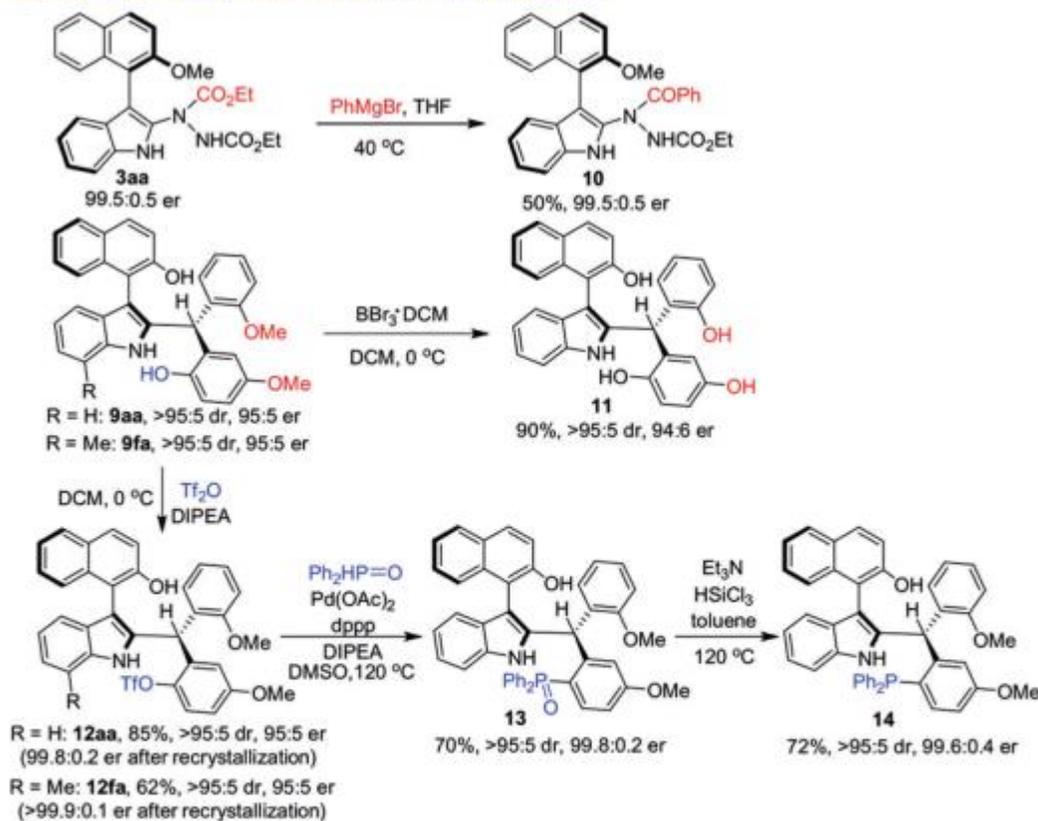


使用邻羟基苯醇作为亲电试剂

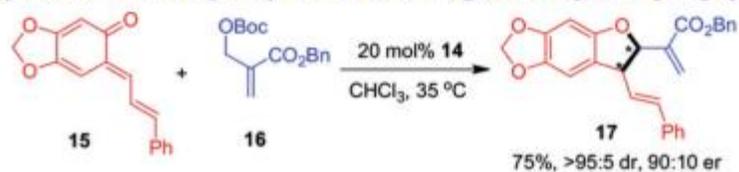
2.3 基于偶联反应构建轴手性骨架

e. 转化应用

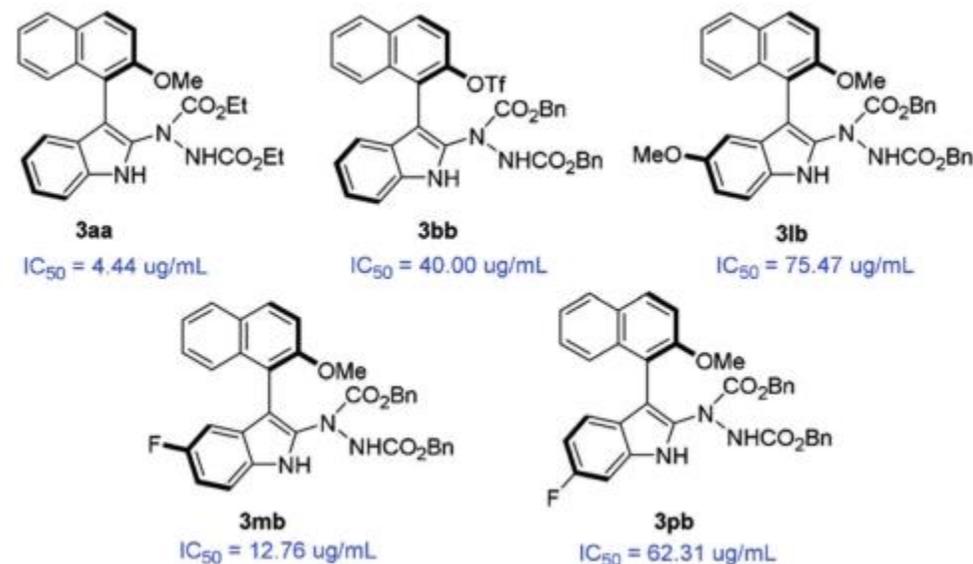
Derivation of axially chiral naphthyl-indole products:



Application of chiral phosphine **14** as an organocatalyst for [4+1] cyclization:



f. 活性测试

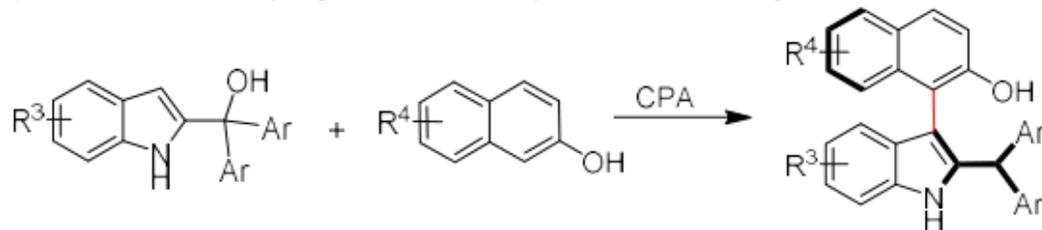


3aa对MCF-7乳腺癌细胞的具有较高细胞毒性

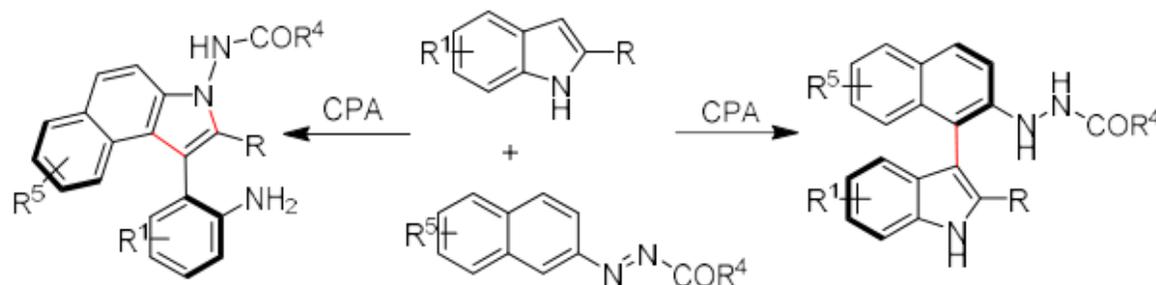
2.3.2 轴向手性3,3'-双吲哚骨架的设计与催化不对称构建

I. 研究背景

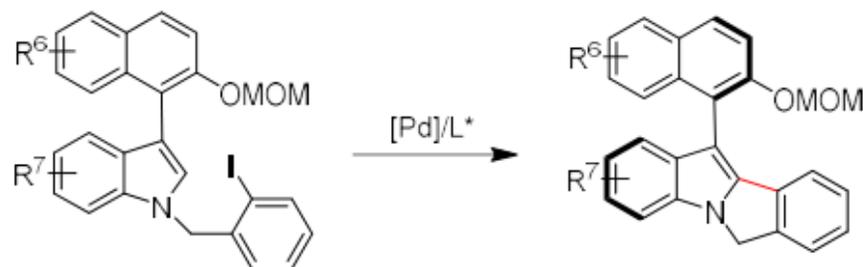
a) CPA-catalyzed coupling reaction of 2-naphthols with 2-indolylmethanols



b) CPA-catalyzed coupling and rearrangement reactions of indoles with azonaphthalenes

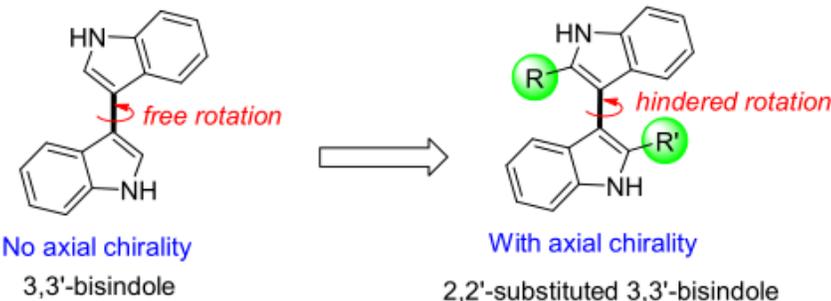


c) Palladium-catalyzed dynamic kinetic intramolecular C-H cyclization

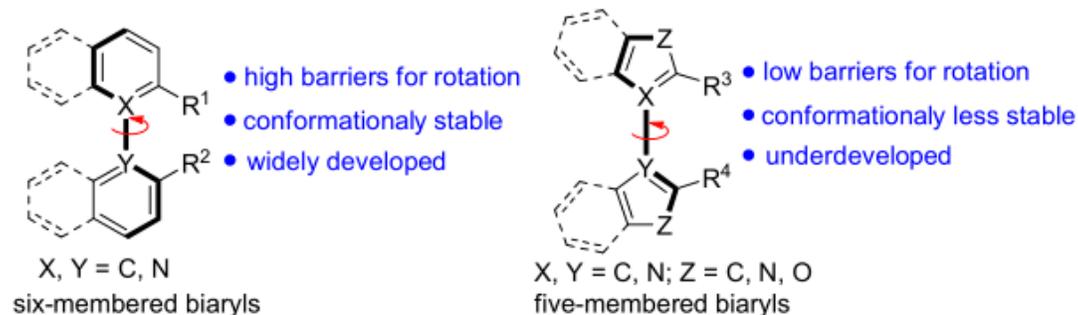


II. 骨架设计

a) Design of new indole-based axially chiral biaryl backbones

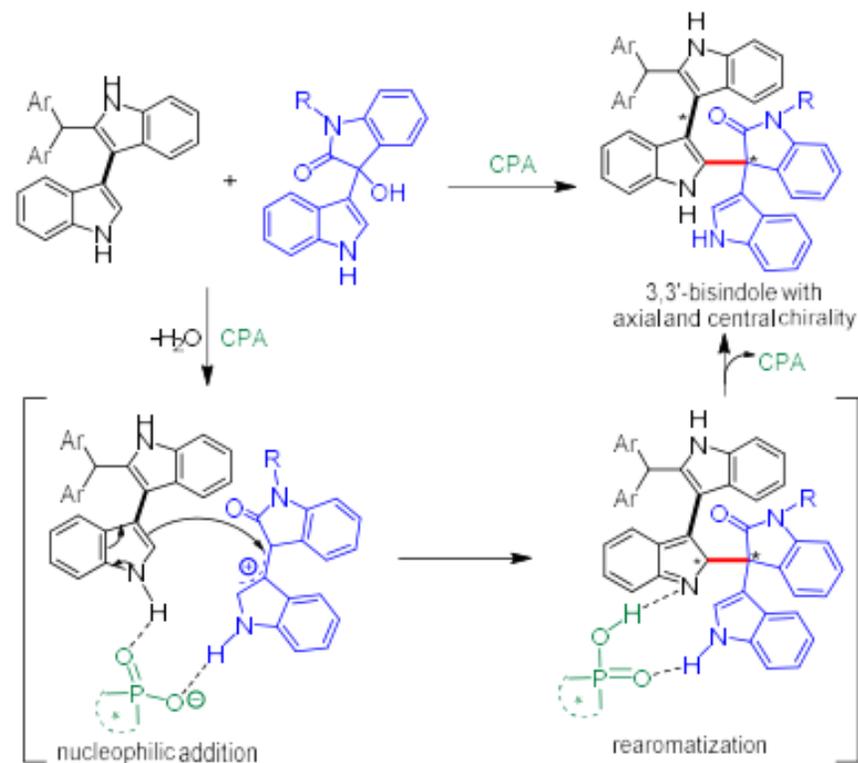
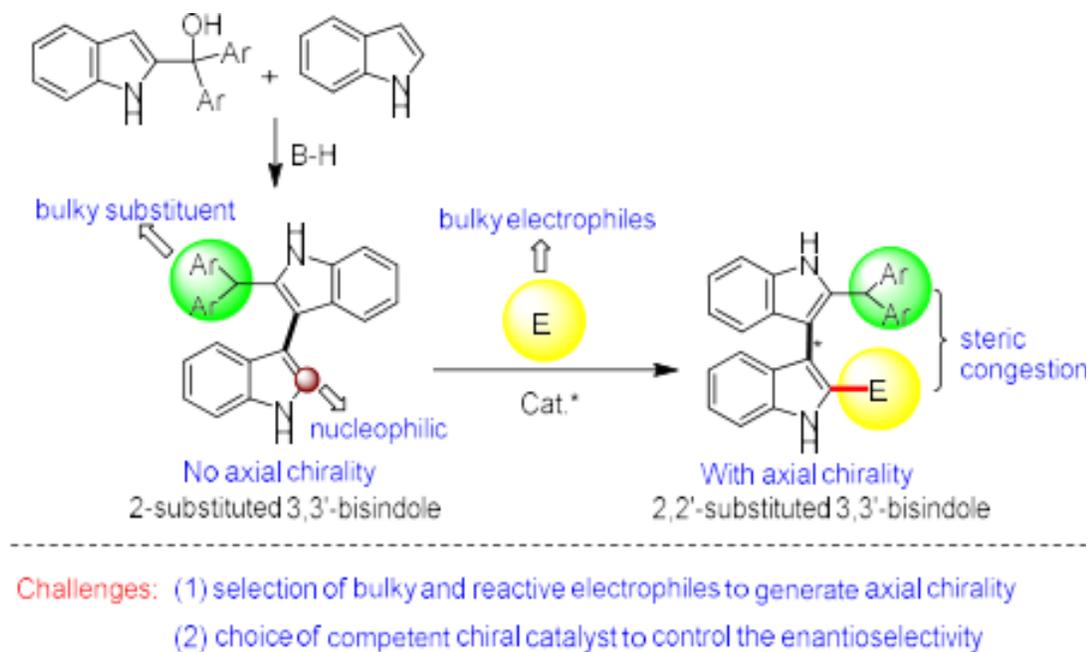


b) Challenges in constructing five-membered axially chiral biaryl skeletons



- 在3,3'-双吲哚骨架的2,2'-位置引入两个大的R和R'基团能够增大空间位阻，两个吲哚环不能自由旋转
- 与经典的六元轴向手性双芳基化合物相比，五元轴向手性双芳基骨架邻位取代基围绕轴的距离增加，导致较低的旋转势垒和较弱的构象稳定性

III. 方案设计

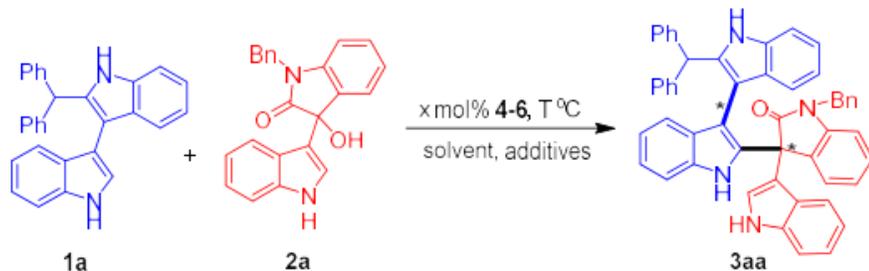
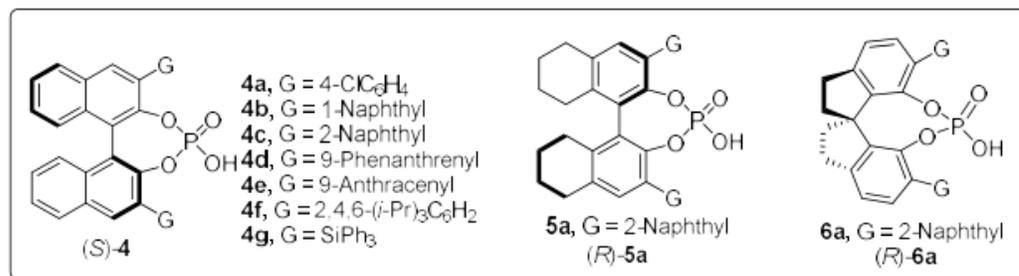


挑战:

- 1) 选择位阻大、活性强的亲电试剂，以增加旋转屏障和构象稳定性
- 2) 选择合适的手性催化剂来控制反应的活性和立体选择性

2.3 基于偶联反应构建轴手性骨架

IV. 条件筛选

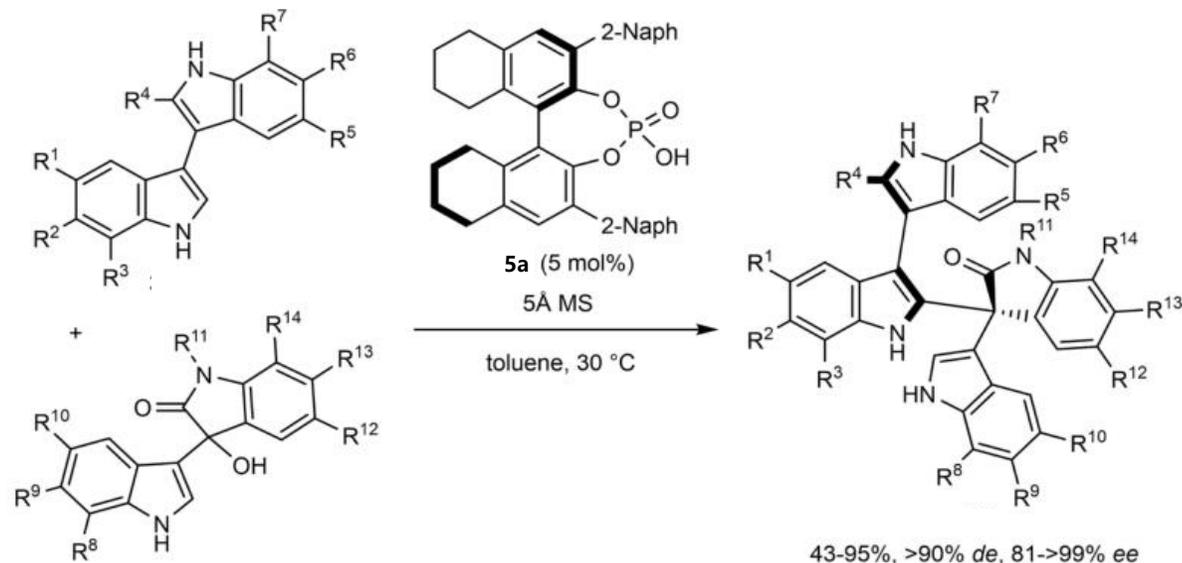


entry	Cat.	solvent	additives ^[b]	T (°C)	x	yield (%) ^[c]	dr ^[d]	ee ^[e]
22	(R)-5a	toluene	5 Å M.S.	30	5	93	>95:5	97

最佳条件: 温度为30°C, 1a与2a的投料比为1:1.2, 溶剂为甲苯, 催化剂为5 mol%的手型磷酸5a, 添加剂为5A分子筛

2.3 基于偶联反应构建轴手性骨架

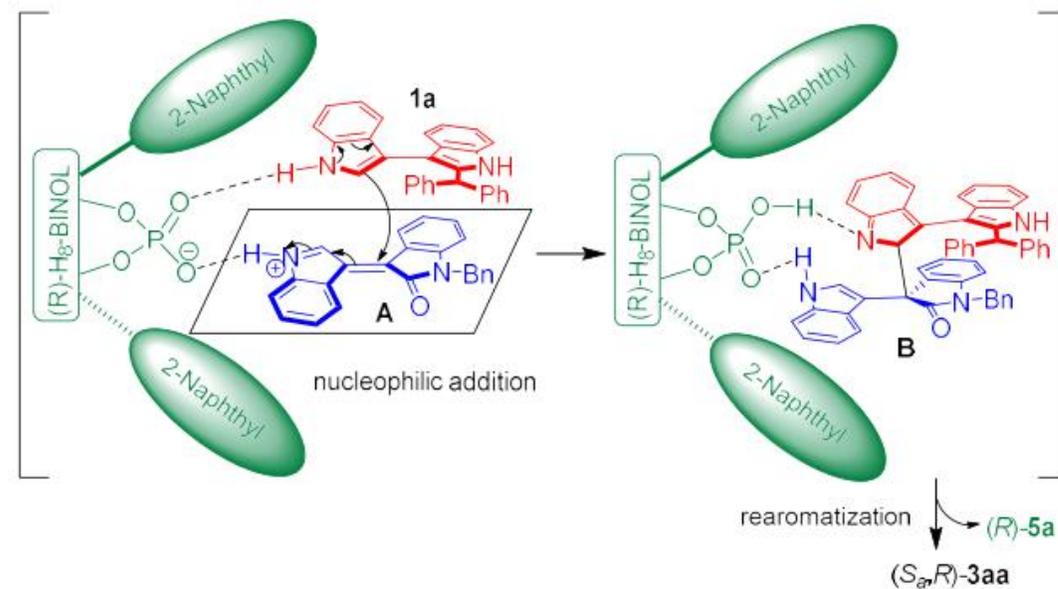
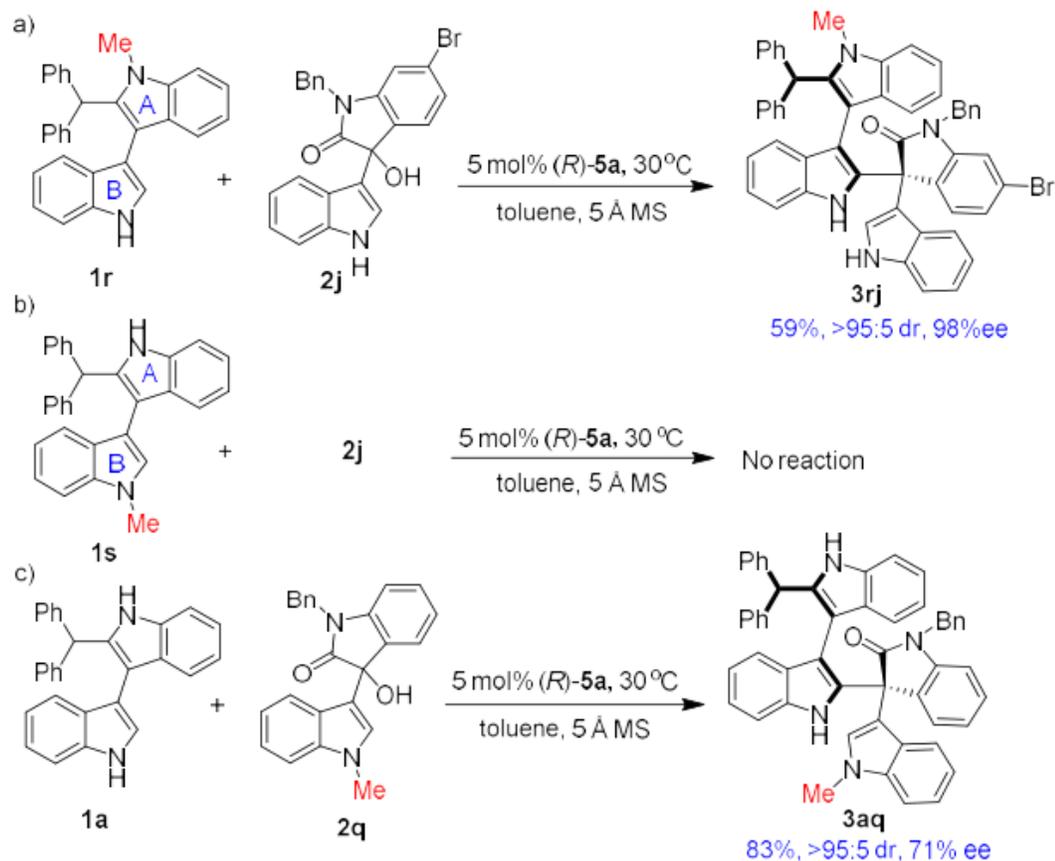
V. 底物拓展



R¹ = H, Cl, OMe
R² = H, Cl, OMe
R³ = H, Me
R⁴ = Ph₂CH, (*p*-FC₆H₄)₂CH, (*p*-*t*-BuC₆H₄)₂CH, (*p*-Tol)₂CH,
(*m*-FC₆H₄)₂CH, (*o*-Tol)₂CH, (*m*-MeOC₆H₄)₂CH
R⁵ = H, Cl, OMe
R⁶ = H, Br, OMe
R⁷ = H, Br
R⁸ = H, F, Me
R⁹ = H, F
R¹⁰ = H, OMe, F, Cl
R¹¹ = Bn, Ph, Me, H
R¹² = H, OMe, Me
R¹³ = H, Br, OMe
R¹⁴ = H, F, Me

2.3 基于偶联反应构建轴手性骨架

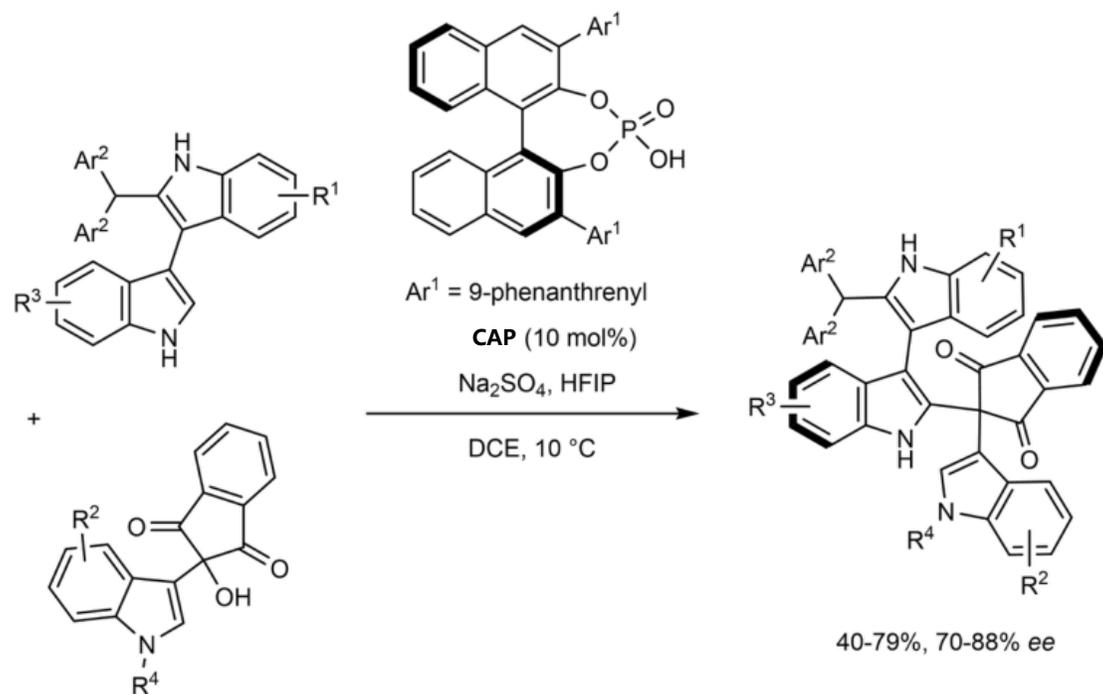
VI. 机理研究



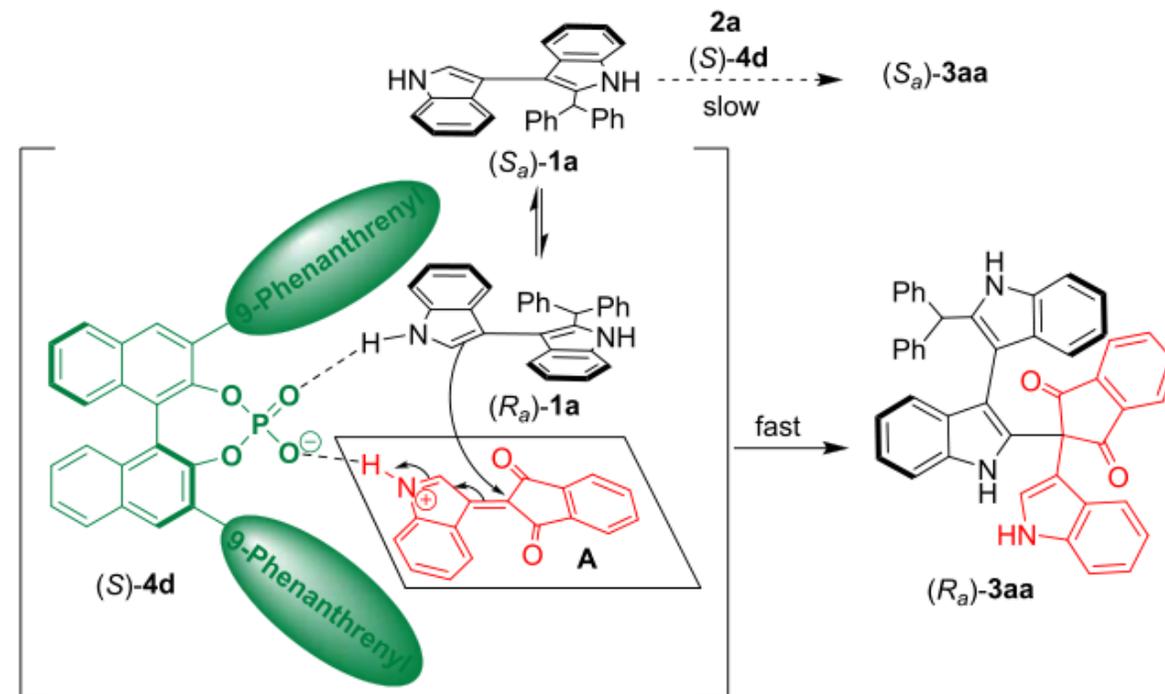
- 氢键作用
- 离子对作用

2.3 基于偶联反应构建轴手性骨架

2.3.3 单轴手性3,3'-双吲哚的催化不对称合成

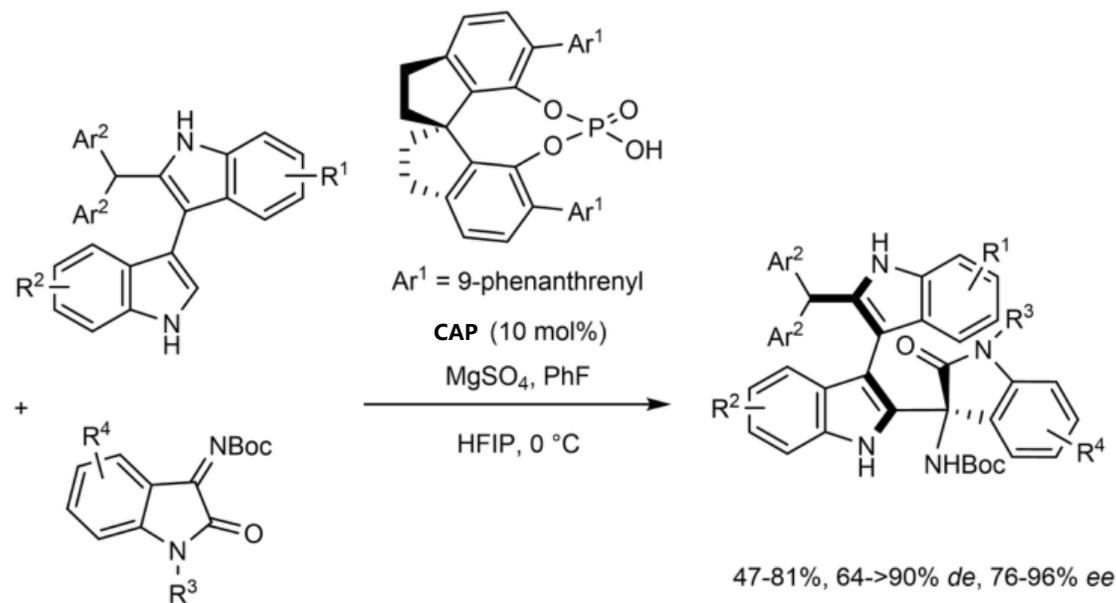


Ar² = Ph, *m*-MeOC₆H₄, *m*-FC₆H₄, *p*-FC₆H₄
R¹ = H, 5'-Br, 5'-Me, 5'-OMe
R² = H, 5-Cl, 5-Me, 5-OMe, 6-Br, 7-Me
R³ = H, 5-F, 5-Cl, 5-Br, 5-Me, 5-OMe
R⁴ = H, Me

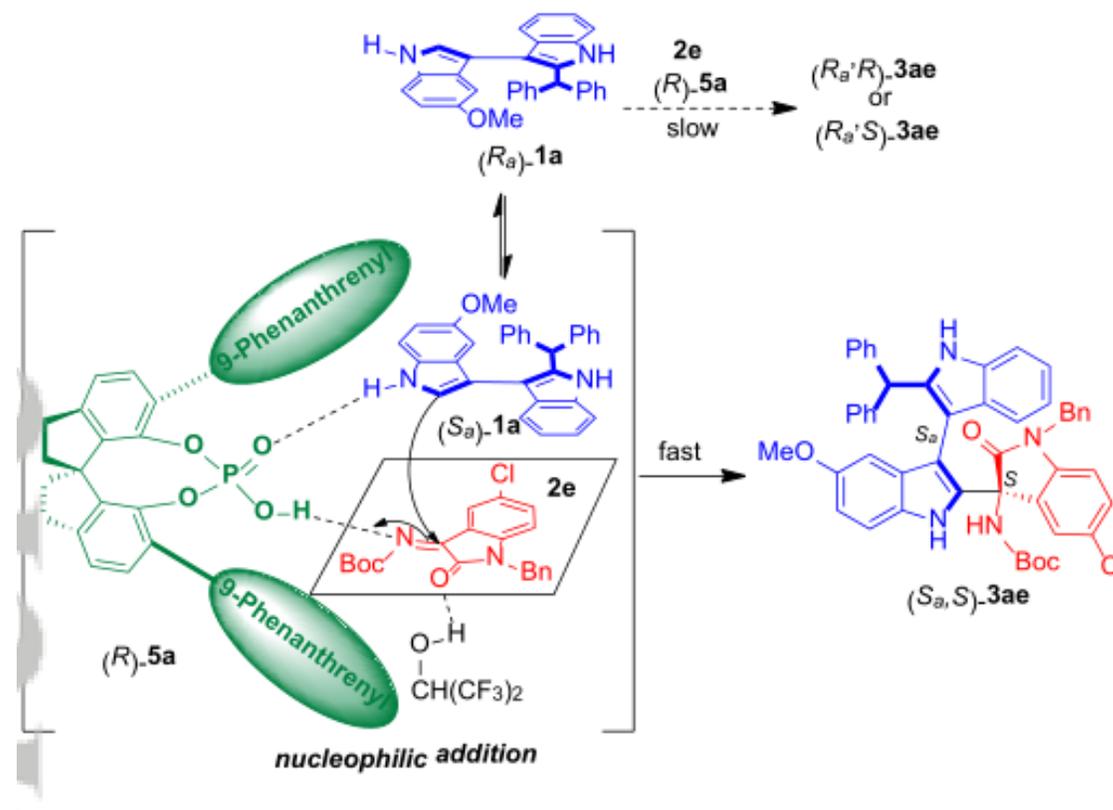


2.3 基于偶联反应构建轴手性骨架

2.3.4 具有轴向和中心手性的3,3'-双吲哚的阻旋异构选择性合成：以靛红衍生的亚胺为亲电试剂



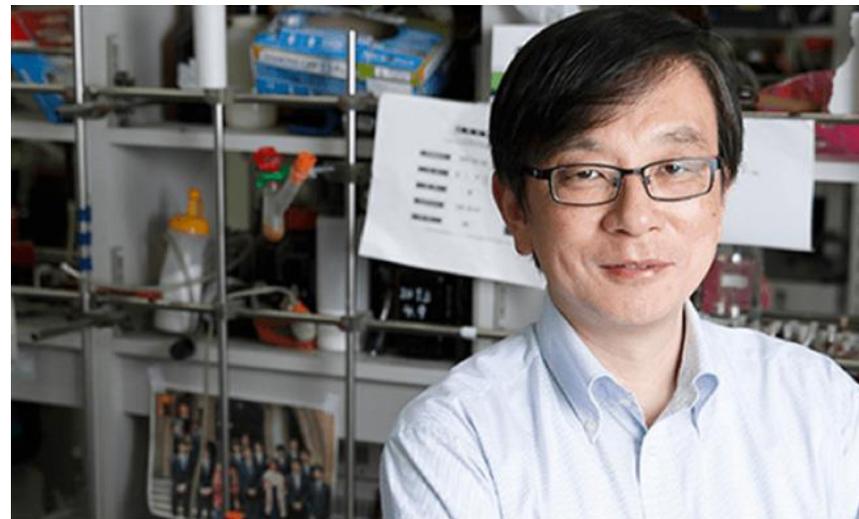
Ar² = Ph, *p*-FC₆H₄, *m*-FC₆H₄, *p*-Tol, *m*-Tol, *o*-Tol
R¹ = H, 7-Br, 6-Cl, 6-OMe, 5-Cl, 5-Me
R² = 5'-OMe, 6'-Me, 7'-Me
R³ = Bn, Me, allyl, Ph
R⁴ = H, 7-Cl, 6-Br, 6-OMe, 5-Cl, 5-Me



2.4 基于转移氢化法构建轴手性骨架

教育经历

1980, 本科, 东京大学
1985, 博士, 东京大学
1988, 助理教授, 爱媛大学
1992, 访问学者, 斯坦福大学
1994, 副教授, 学习院大学
1985, 教授, 学习院大学



研究领域

手性磷酸催化的不对称反应

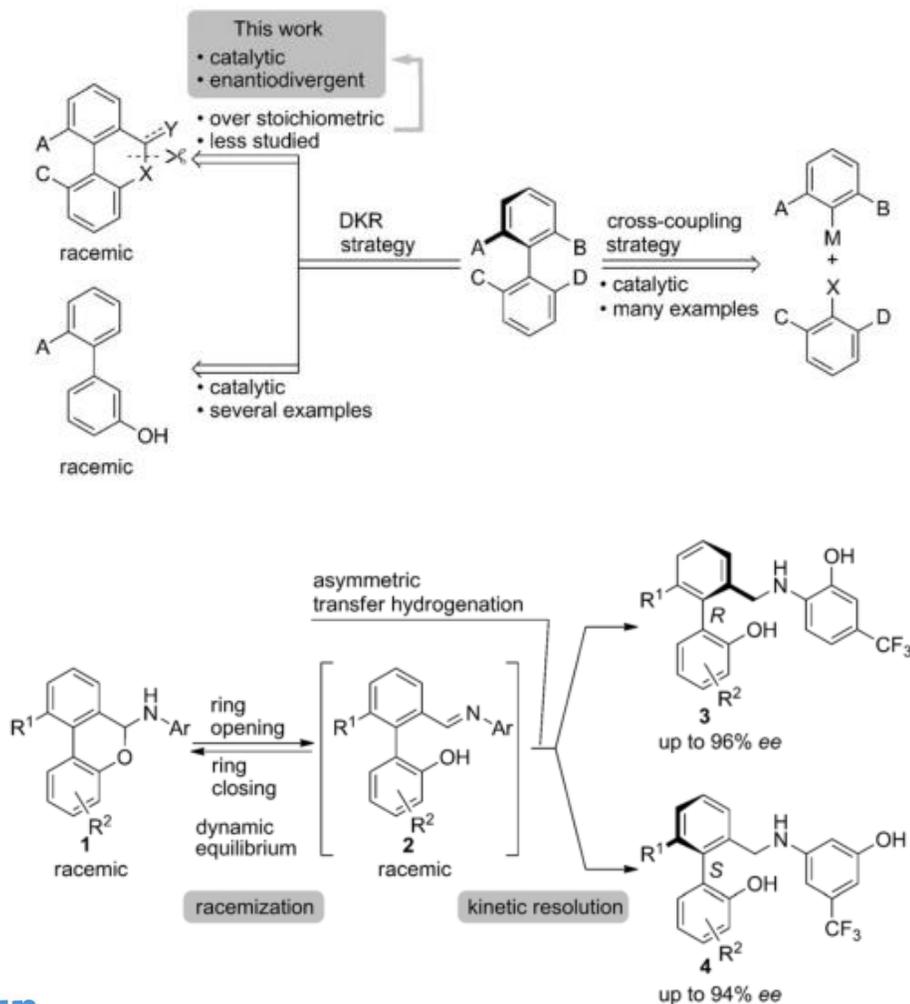
Takahiko Akiyama

学习院大学

2.4 基于转移氢化法构建轴手性骨架

2.4.1 不对称转移氢化法合成手性二芳基：手性磷酸催化的动态动力学拆分

I. 研究背景

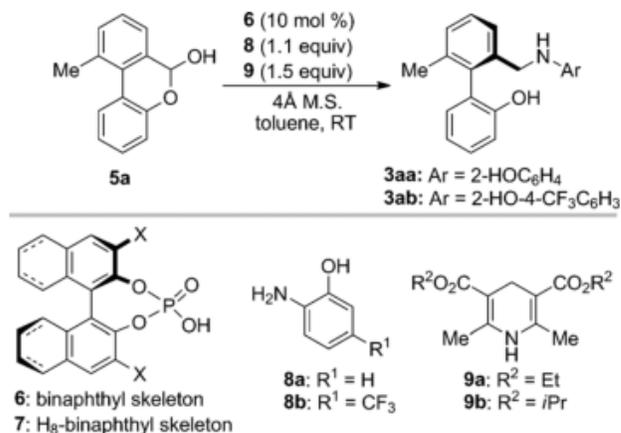


底物特点:

- 易于开环形成二芳基亚胺
- 二芳基亚胺与手性磷酸催化剂有高亲和力
- 苯胺部分的芳环易于修饰，这一特性能够严重影响反应活性和对映选择性

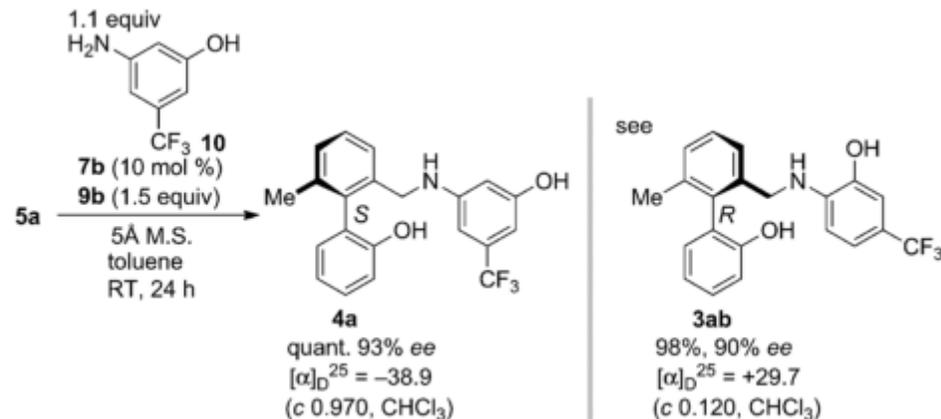
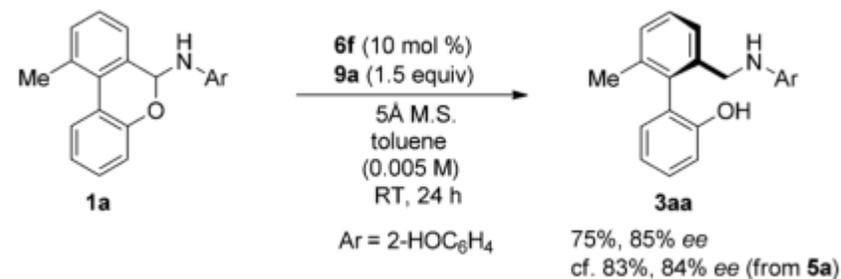
2.4 基于转移氢化法构建轴手性骨架

II. 条件筛选



Entry	Catalyst (X)	Yield [%]	ee [%] ^[b]
1	2,4,6- <i>(i</i> Pr) ₃ C ₆ H ₂ (6a)	75	33
2	9-anthryl (6b)	80	30
3	2,4-(CF ₃) ₂ C ₆ H ₃ (6c)	86	47
4	4-PhC ₆ H ₄ (6d)	74	13
5	SiPh ₃ (6e)	91	59
6	Si(3-FC ₆ H ₄) ₃ (6f)	75	73
7 ^[c,d]	Si(3-FC ₆ H ₄) ₃ (6f)	72	81
8 ^[c,e]	Si(3-FC ₆ H ₄) ₃ (6f)	83	84
9 ^[c,e,f]	Si(3-FC ₆ H ₄) ₃ (6f)	98	90

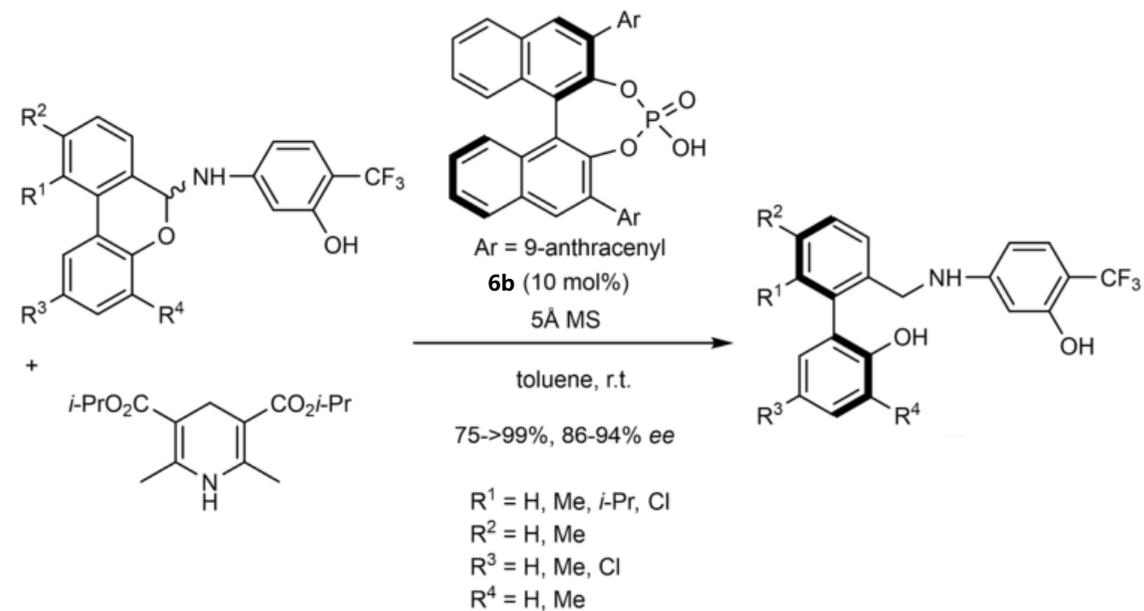
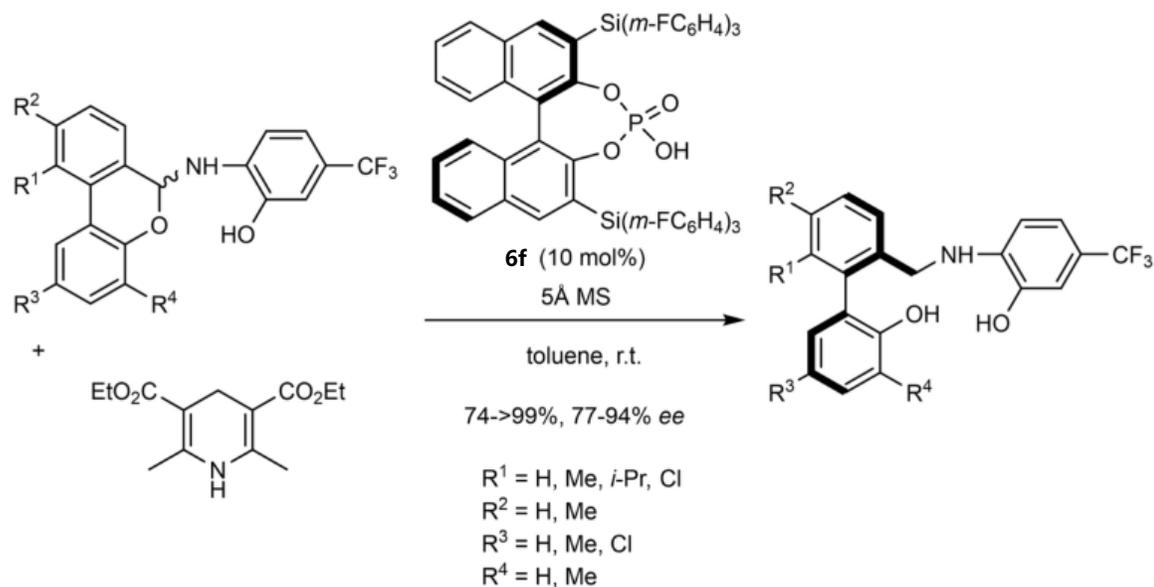
[a] Unless otherwise noted, all reactions were conducted with the lactol **5a** (0.10 mmol), hydroxyaniline **8a** (0.11 mmol), and Hantzsch ester **9a** (0.15 mmol) in the presence of 10 mol% **6** and 4Å M.S. in toluene (1.0 mL) at room temperature. [b] Enantiomeric ratio was determined by HPLC analysis using a chiral stationary phase. [c] 5Å M.S. was employed instead of 4Å M.S. [d] 0.01 M. [e] 0.005 M. [f] 2-Amino-5-(trifluoromethyl)phenol (**8b**) was employed instead of **8a**. M.S. = molecular sieves.



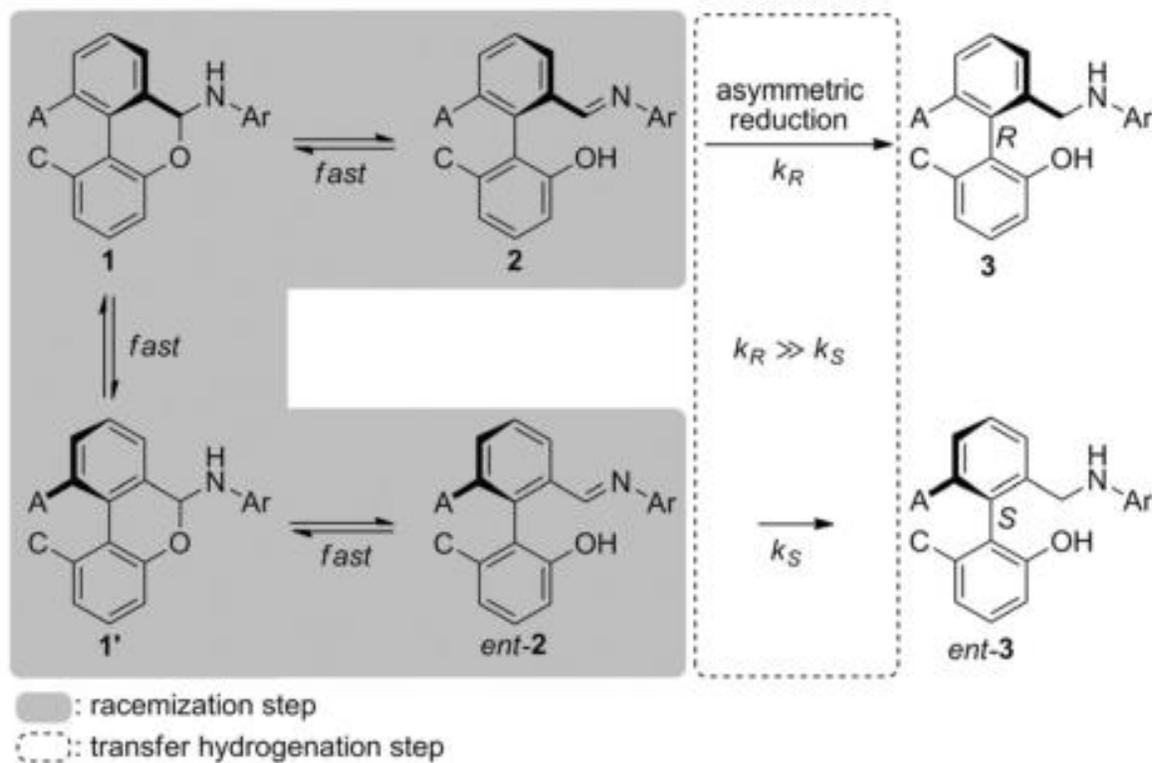
- 5a与1a在相同的反应条件下，生成3aa的产率和ee值几乎相同
- 阻旋异构选择性有苯胺的羟基位置控制

2.4 基于转移氢化法构建轴手性骨架

III. 底物拓展

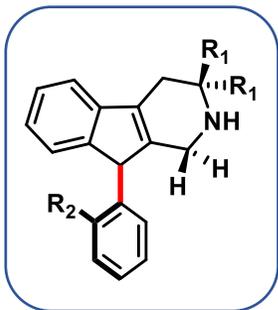


IV. 机理研究

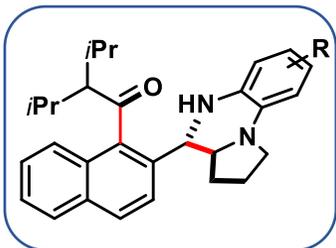


- 二芳基亚胺2的不对称转移氢化反应具有显著的动态动力学特征
- 2与对映体 $ent-2$ 的平衡和转移氢化之间有适当的反应速率差

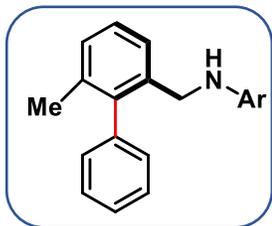
3 总结—轴手性骨架的构建



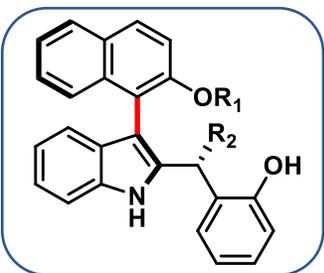
- 轴手性骨架是许多天然产物、生物活性分子和特殊手性催化剂的核心结构。近年来以手型磷酸介导的动态动力学反应在构建轴手性骨架的领域被广泛应用



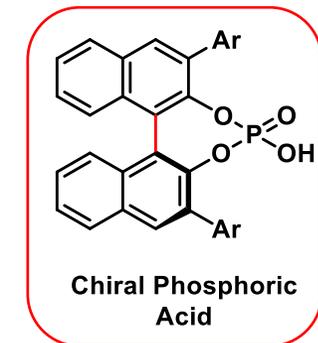
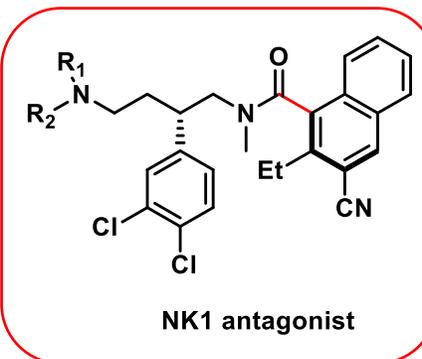
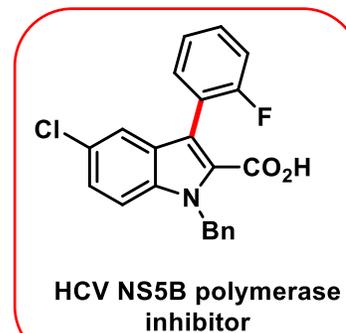
- 通过Pictet-Spengler反应、多米诺反应、偶联反应、转移氢化一系列的方法完成了C-N轴手性骨架、邻甲酰基萘酰胺骨架、双吲哚骨架、二芳基骨架等轴手性骨架的构建



- 在轴手性骨架的构建过程中，研究了各取代基对轴手性的影响，大位阻的取代基可以增加旋转势垒和构象稳定性



- 探究了手性磷酸对于不对称构建轴手性骨架的作用，发现其在反应历程中与底物通过氢键、离子对、空间位阻等作用来控制对映选择性



敬请大家批评指正!

汇报人：刘西良（硕士二年级）

日期：2022年05月25日

