Literature Report 12

Organocatalytic Enantioselective Synthesis of Inherently Chiral Calix[4]arenes

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Checker: Gao-Wei Wang
Date: 2024.09.02

Jiang, Y.-K.; Tian, Y.-L.; Feng, J.; Liu, R.-R.* *Angew. Chem. Int. Ed.* **2024**, *63*, e202407752.

CV of Dr. Ren-Rong Liu (刘人荣)

Background:

☐ **2008-2013**	Ph.D., East China Normal University (Prof. Zhang, J.)
☐ **2013-2018**	Associate Prof., Zhejiang University of Technology
☐ **2018-2019**	Postdoc., Colorado State University (Prof. McNally, A.)
☐ **2019-present**	Professor, Qingdao University

Research:

- ✓ **Development of Catalysts/Ligands**
- ✓ **Asymmetric Catalytic Synthesis**
- ✓ **Natural Product and Pharmaceutical Molecule Synthesis**

Contents

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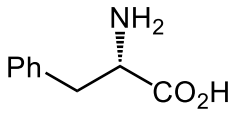
2 Enantioselective Synthesis of Inherently Chiral Calix[4]arenes

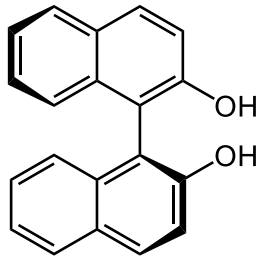
3 Summary

Introduction

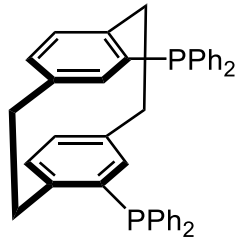
a) Conventional molecular chiral elements



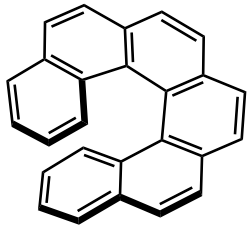
central chirality



axial chirality

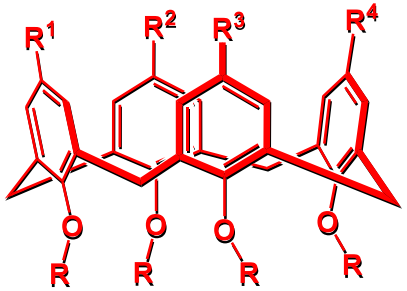


planar chirality

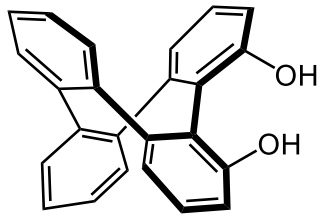


helical chirality

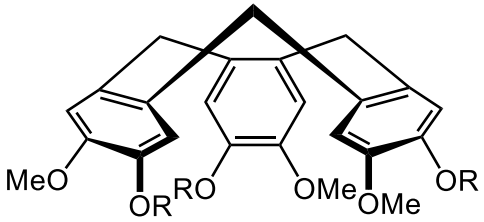
b) Inherent chirality (Böhmer 1994)



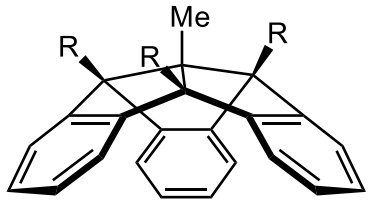
calix[4]arenes



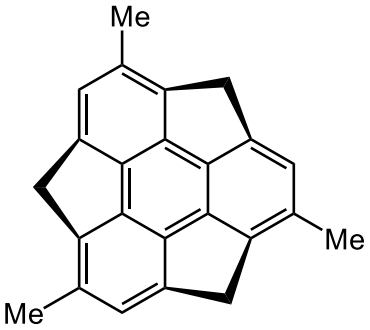
saddle-shaped
eight-membered cycles



cyclotriveratrylenes



tribenzotriquinacenes

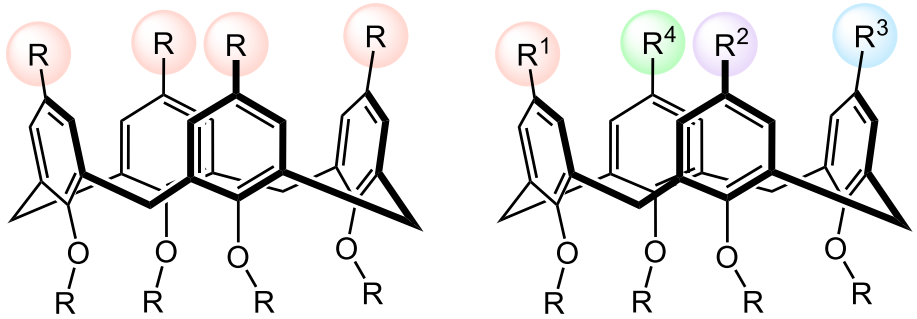


sumanenes

Yang, X. *et al. Eur. J. Org. Chem.* **2023**, *26*, e202300738.

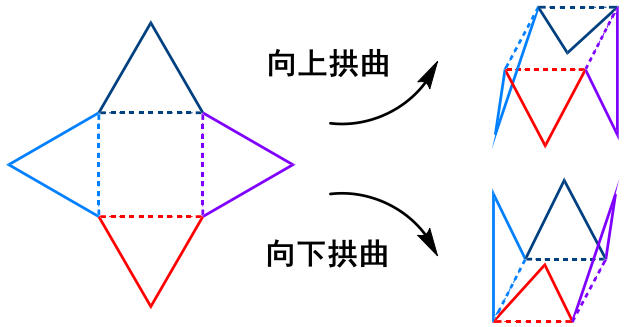
Introduction

不同非手性取代基



非手性杯芳烃　　固有手性杯芳烃

拱曲呈三维结构



非对称二维平面　　固有手性三维物体

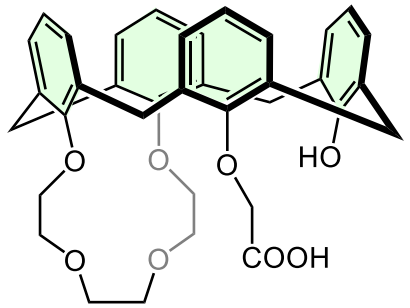
Inherent chirality arises from the introduction of a curvature in an ideal planar structure that is devoid of perpendicular symmetry planes in its bidimensional representation

固有手性来源于拱曲的曲面，该曲面的二维平面结构不含垂直该平面的对称面

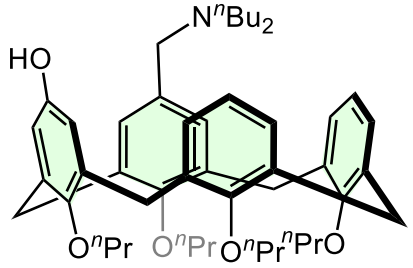
（无垂直对称面的曲面引起的手性）

Szumna, A. *et al. Chem. Soc. Rev.* **2010**, *39*, 4274.

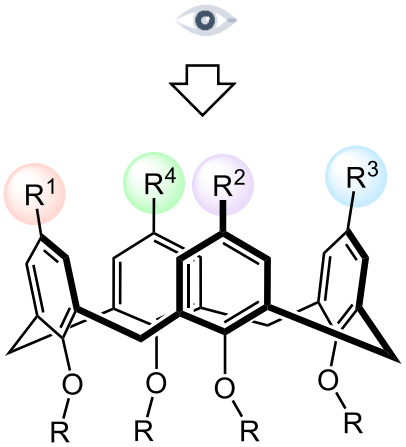
Introduction

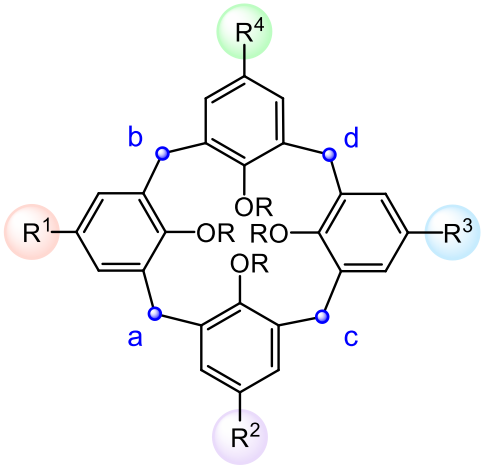


手性识别材料



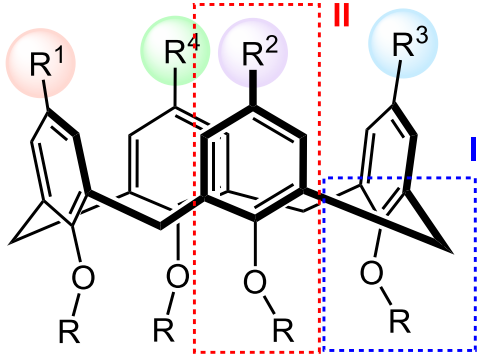
手性催化剂骨架





(*cR*)/(*cS*), *P*/*M*
表示两个对映体
视线从凹面向下看
投影中基团优先级
顺时针为P构型
逆时针为M构型

$R_1>R_2>R_3>R_4$
构型为M

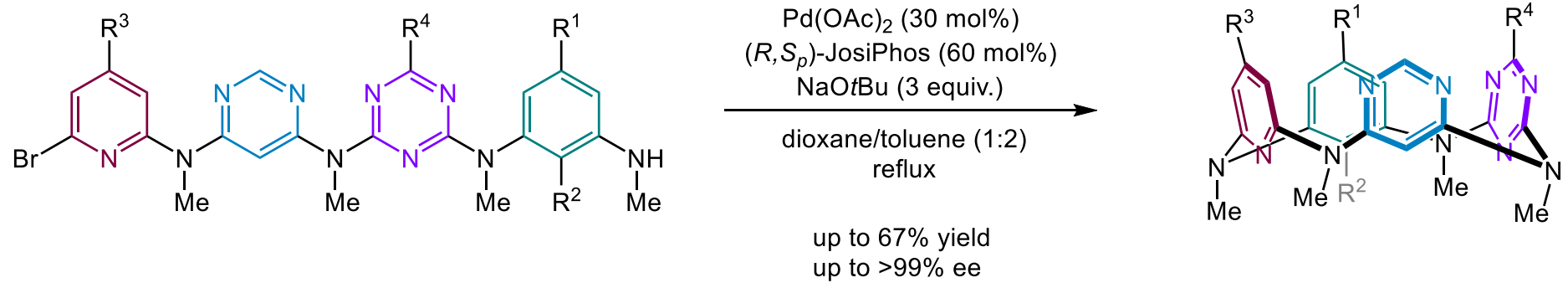


I: 长链底物的环化
常见于含杂原子杯芳烃

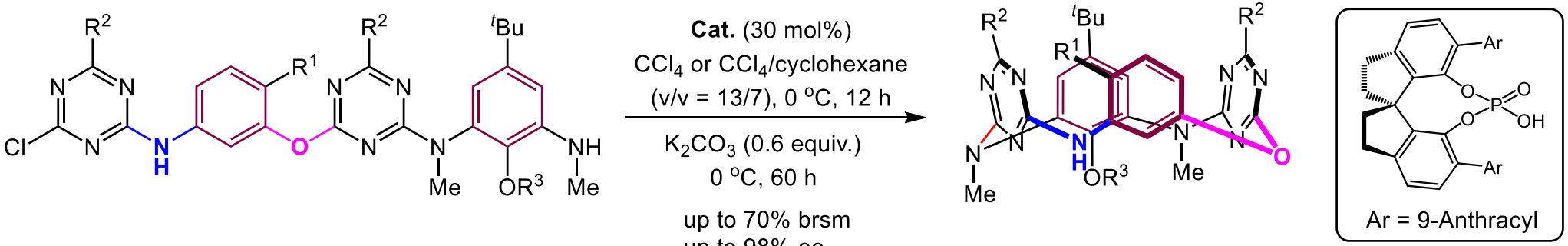
II: 非手性杯芳烃去对称化
常见于全碳骨架杯芳烃

Su, C.-Y. *et al. Int. J. Mol. Sci.* **2011**, *12*, 429.

Enantioselective Cyclization

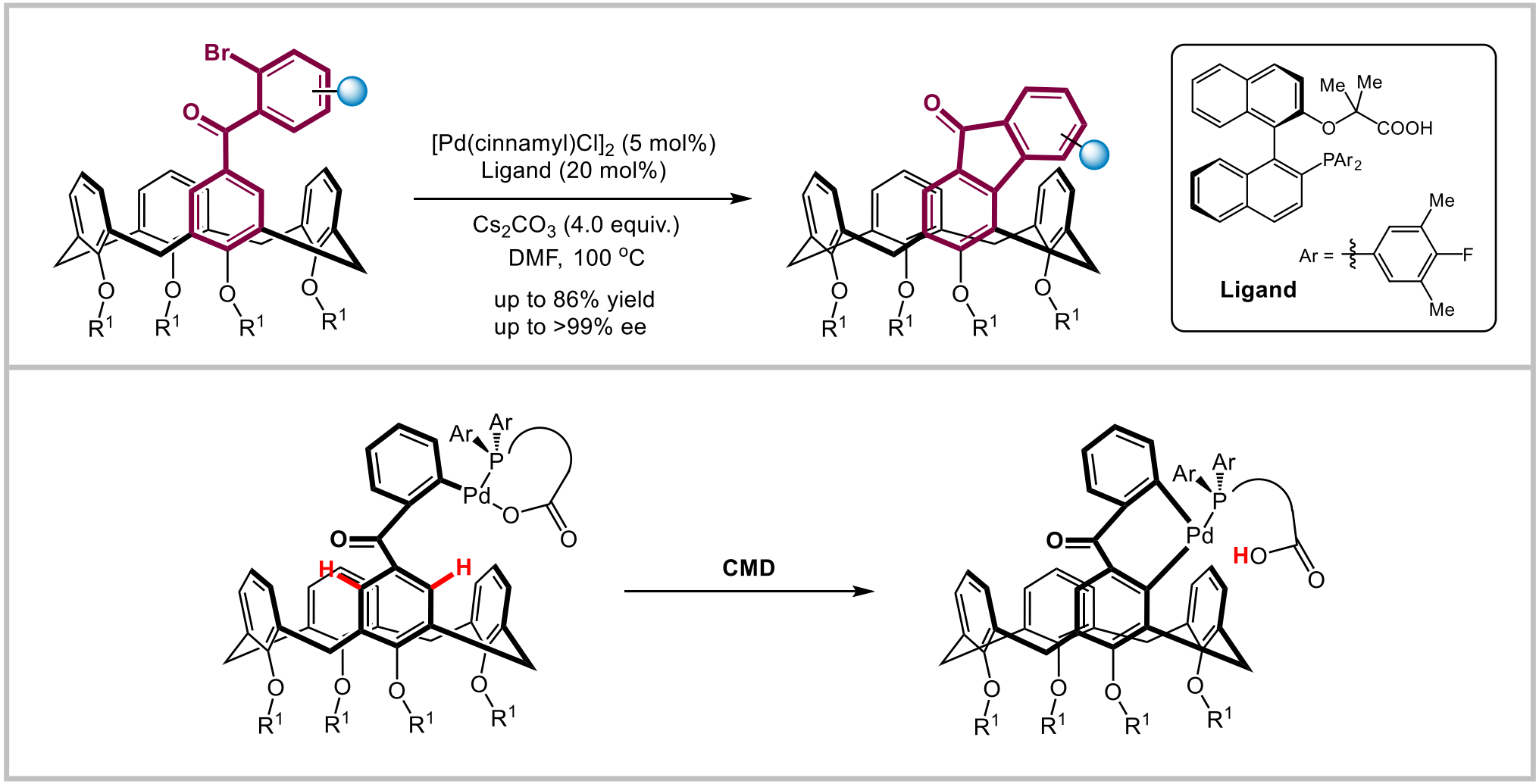


Tong, S.; Wang, M.-X. *et al. J. Am. Chem. Soc.* **2020**, *142,* 14432.



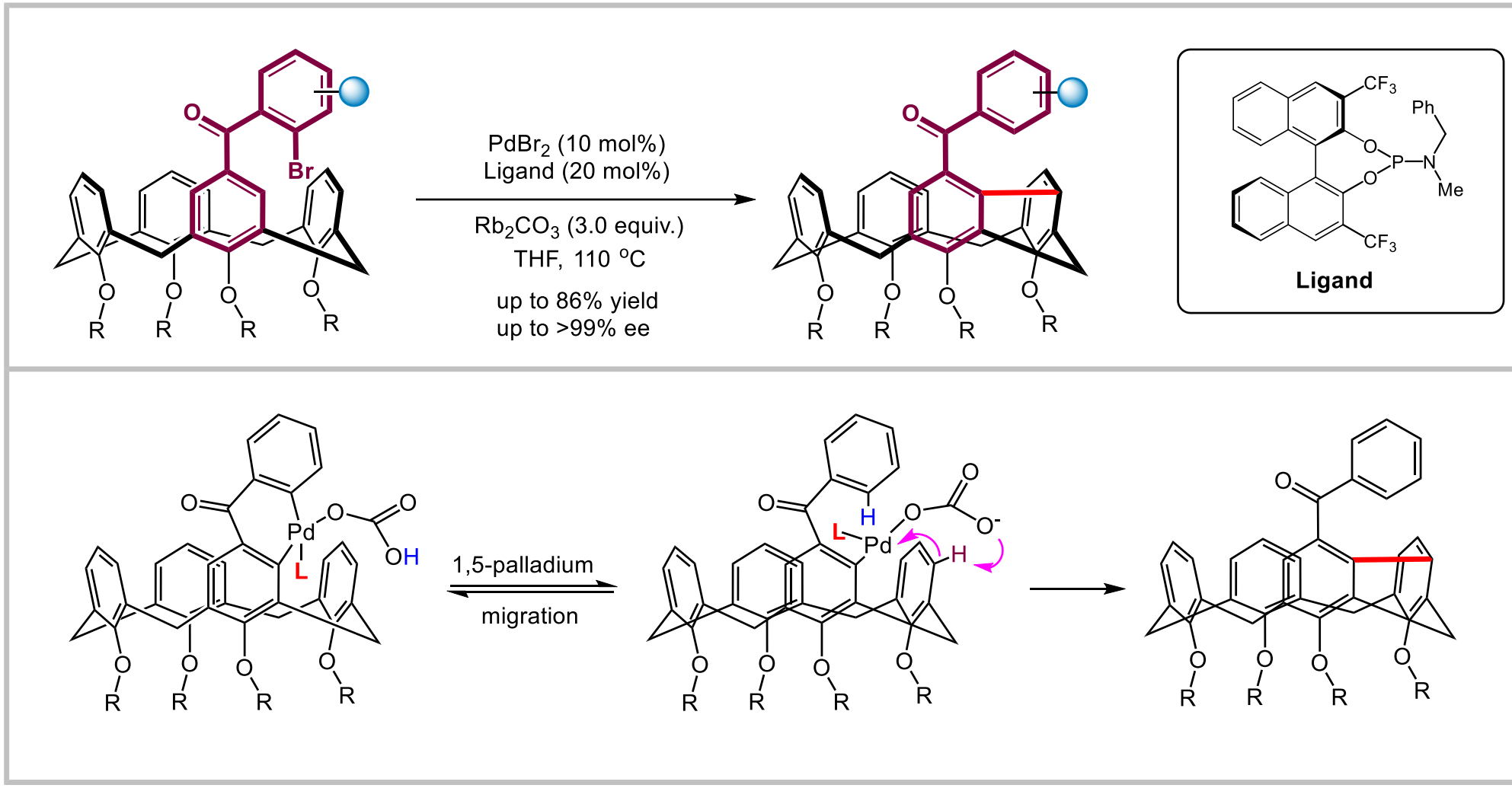
Tong, S.; Wang, M.-X. *et al. Chem. Sci*. **2024**, *15*, 3610.

Desymmetrization



Cai, Q. *et al. J. Am. Chem. Soc.* **2022**, *144*, 22858.

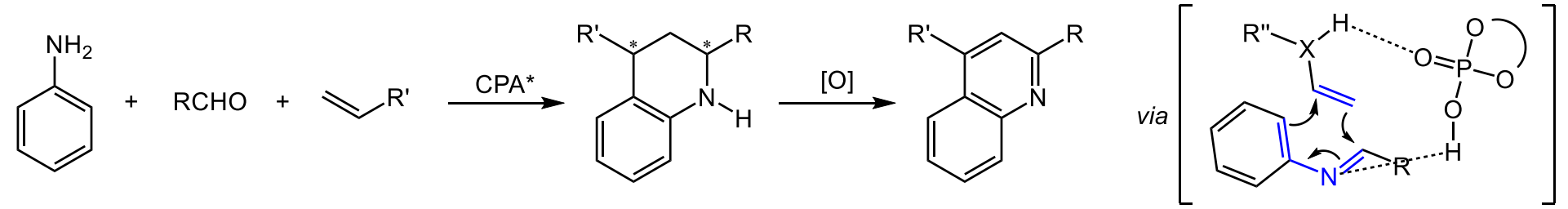
Desymmetrization



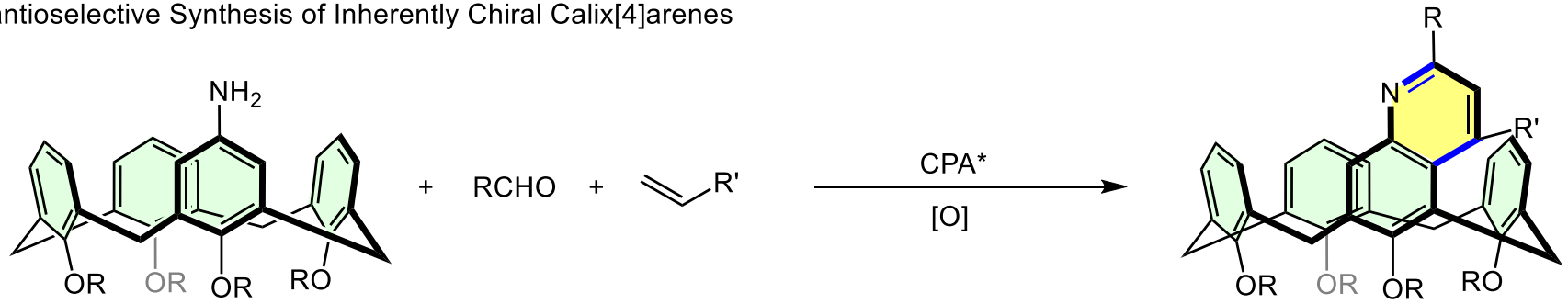
Tong, S. *et al. Chem. Sci*. **2023**, *14, 827*.

Prospect

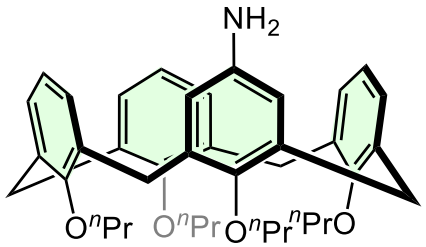
CPA-catalyzed Enantioselective Povarov Reactions



Enantioselective Synthesis of Inherently Chiral Calix[4]arenes



Optimization of the Reaction Conditions

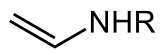


1a

+

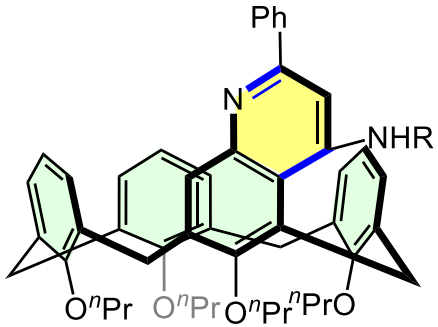
PhCHO

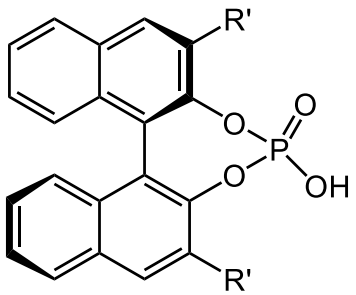
2a



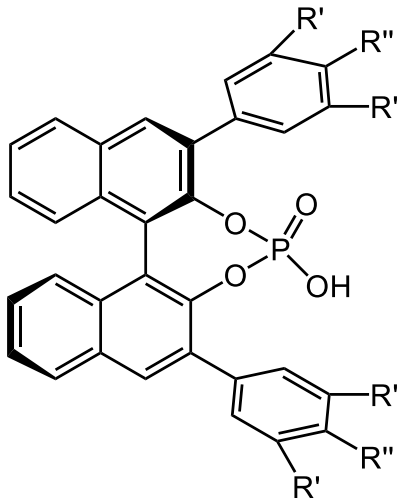
3a' R = Boc
3a R = Cbz

CPA (5 mol%)
3 Å MS, solvent, T °C
then DDQ (3.0 equiv.)
MeCN, -20 °C

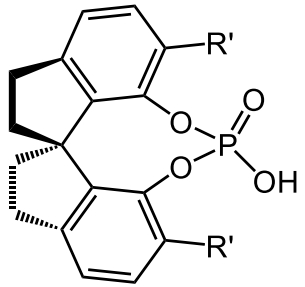




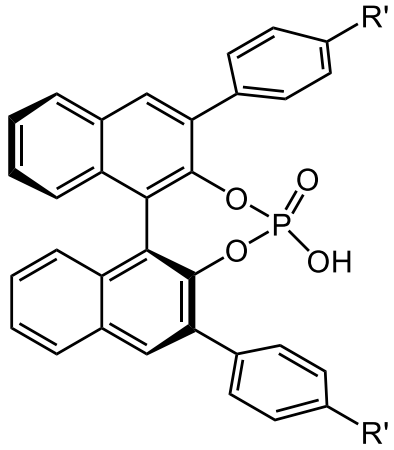
(*R*)-**A1**: R' = H;
(*R*)-**A2**: R' = 9-Anthranyl;
(*R*)-**A3**: R' = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$;



(*R*)-**A4**: R' = R'' = F;
(*R*)-**A5**: R' = ^{t}Bu, R'' = H;

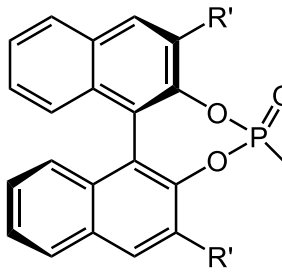


(*R*)-**A6**
R' = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$;

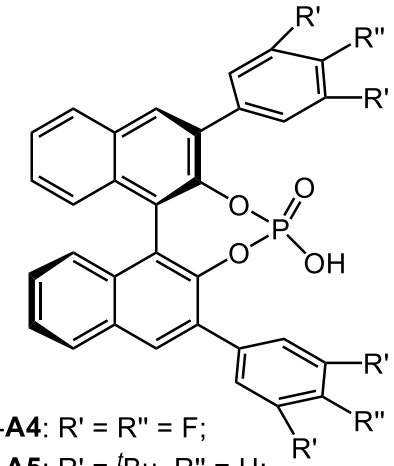


(*S*)-**A7**: R' = Ph;
(*S*)-**A8**: R' = CF_3;
(*S*)-**A9**: R' = NO_2
(*S*)-**A10**: R' = 2-Naphthyl;
(*S*)-**A11**: R' = Cl;

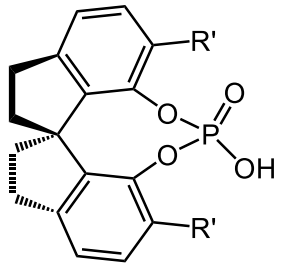
Optimization of the Reaction Conditions



(*R*)-**A1**: R' = H;
(*R*)-**A2**: R' = 9-Anthranyl;
(*R*)-**A3**: R' = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$;



(*R*)-**A4**: R' = R'' = F;
(*R*)-**A5**: R' = ^{t}Bu, R'' = H;

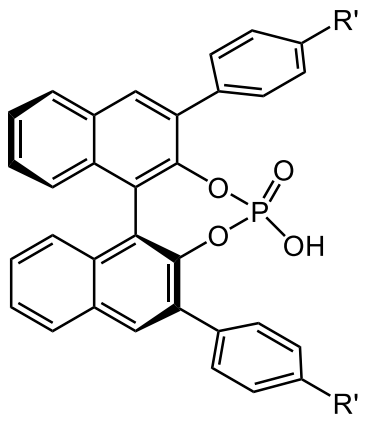


(*R*)-**A6**
R' = 2,4,6-(^{i}Pr)$_3$C$_6$H$_2$;

Entry[a]	3	CPA	Yield [%]	Ee [%]
1	**3a'**	(*R*)-**A1**	65	13
2	**3a'**	(*R*)-**A2**	62	50
3	**3a'**	(*R*)-**A3**	31	40
4	**3a'**	(*R*)-**A4**	60	43
5	**3a'**	(*R*)-**A5**	13	43
6	**3a'**	(*R*)-**A6**	trace	-
7	**3a'**	(*S*)-**A7**	72	51

[a] **1a** (0.1 mmol), **2a** (0.2 mmol), **3** (0.2 mmol), CPA (0.005 mmol) and 3 Å MS (50 mg) in DCM (1.0 mL) at 25 °C for 24 h. Then DDQ (0.3 mmol) in MeCN (0.25 mmol) was added at -20 °C for 12 h.

Optimization of the Reaction Conditions

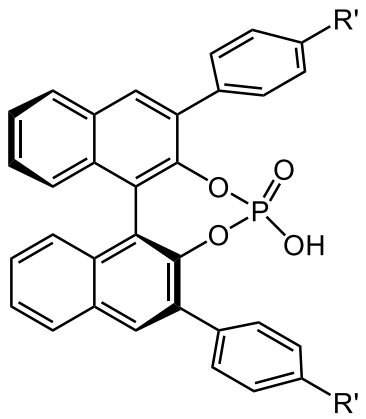


(*S*)-**A7**: R' = Ph;
(*S*)-**A8**: R' = CF_3;
(*S*)-**A9**: R' = NO_2
(*S*)-**A10**: R' = 2-Naphthyl;
(*S*)-**A11**: R' = Cl;

Entry[a]	3	CPA	T [°C]	Yield [%]	Ee [%]
1	**3a'**	(*S*)-**A7**	25	72	51
2	**3a**	(*S*)-**A7**	25	75	75
3	**3a**	(*S*)-**A7**	-20	73	89
4	**3a**	(*S*)-**A8**	-20	82	91
5	**3a**	(*S*)-**A9**	-20	72	92
6	**3a**	(*S*)-**A10**	-20	82	99
7	**3a**	(*S*)-**A11**	-20	70	96

[a] **1a** (0.1 mmol), **2a** (0.2 mmol), **3** (0.2 mmol), CPA (0.005 mmol) and 3 Å MS (50 mg) in DCM (1.0 mL) at the designed temperature for 24 h. Then DDQ (0.3 mmol) in MeCN (0.25 mmol) was added at -20 °C for 12 h.

Optimization of the Reaction Conditions

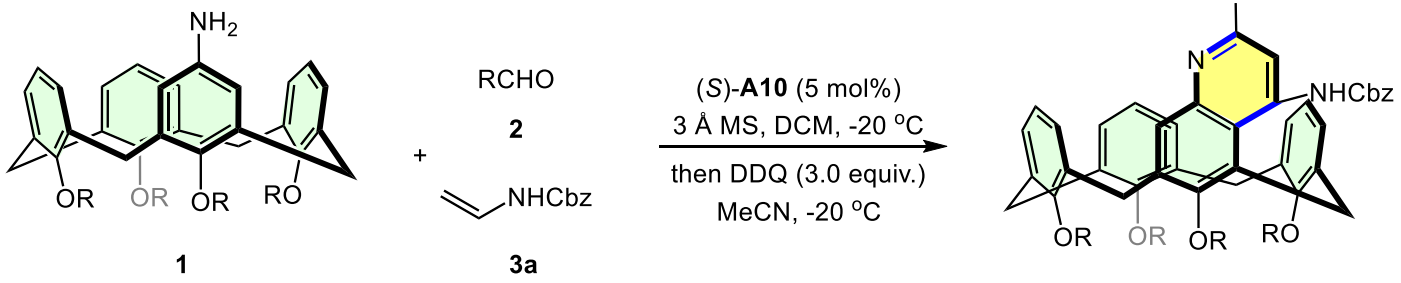


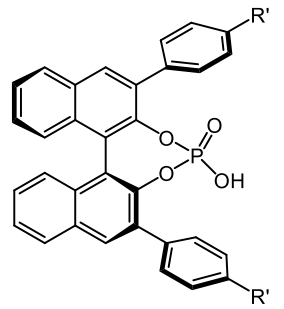
(*S*)-**A10**: R' = 2-Naphthyl;

Entry[a]	3	Additives	Solvent	Yield [%]	Ee [%]
1	**3a**	3 Å MS	DCM	82	99
2	**3a**	4 Å MS	DCM	70	97
3	**3a**	5 Å MS	DCM	75	84
4	**3a**	No MS	DCM	78	88
5	**3a**	3 Å MS	Toluene	72	94
6	**3a**	3 Å MS	THF	65	95

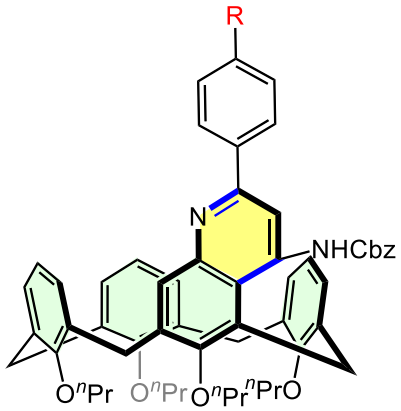
[a] **1a** (0.1 mmol), **2a** (0.2 mmol), **3** (0.2 mmol), (*R*)-**A10** (0.005 mmol) and molecular sieve (50 mg), solvent (1.0 mL) at -20 °C for 24 h. Then DDQ (0.3 mmol) in MeCN (0.25 mmol) was added at -20 °C for 12 h.

Reaction Scope





(*S*)-**A10**: R' = 2-Naphthyl



4b, R = Me, 65%, 99% ee

4c, R = OBn, 63%, 96% ee

4d, R = OMe, 61%, 98% ee

4e, R = SMe, 62%, 98% ee

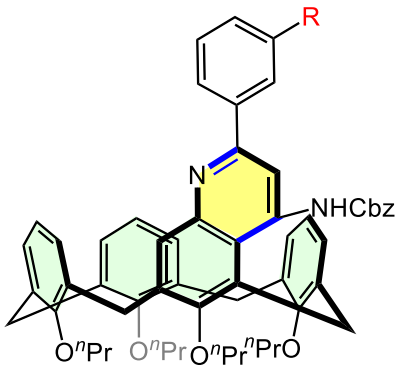
4f, R = Ph, 71%, 99% ee

4g, R = CF_3, 72%, 97% ee

4h, R = NO_2, 80%, 94% ee

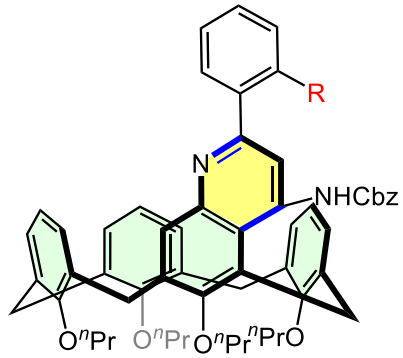
4i, R = F, 74%, 97% ee

4j, R = Br, 70%, 97% ee



4k, R = Me, 71%, 93% ee

4l, R = Br, 80%, 98% ee



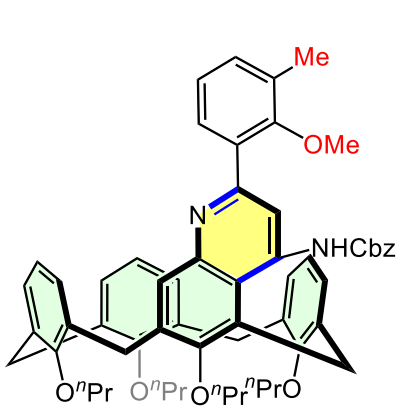
4m, R = Me, 42%, 95% ee

4n, R = OMe, 47%, 91% ee

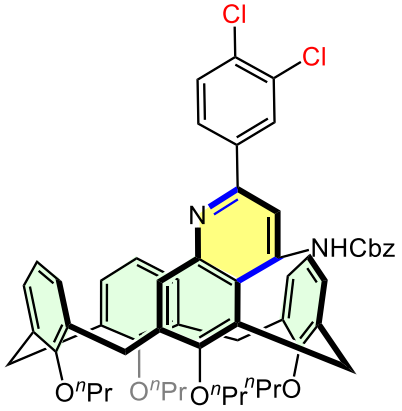
4o, R = NO_2, 51%, 84% ee

4p, R = Br, 50%, 91% ee

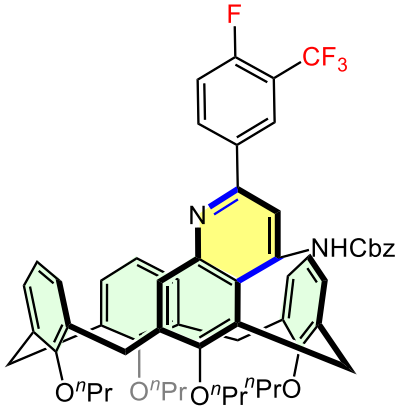
Reaction Scope



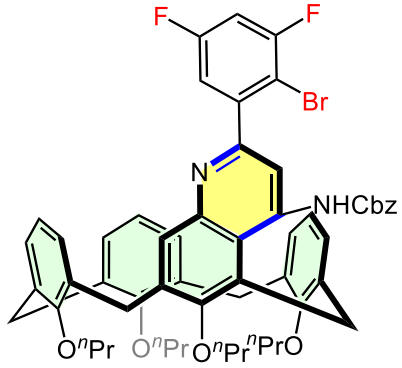
4q, 43%, 95% ee



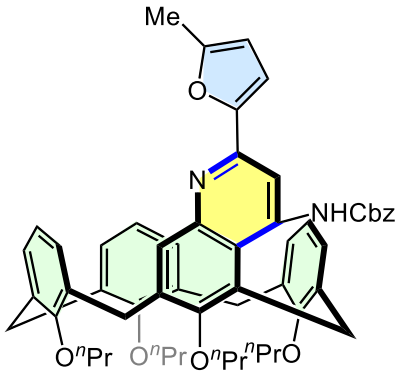
4r, 68%, 94% ee



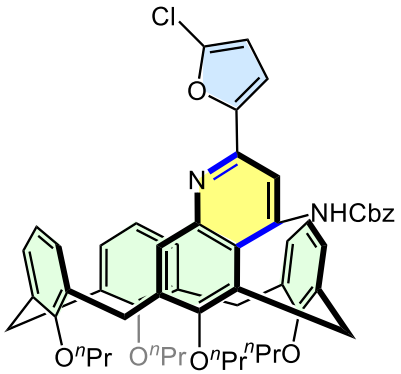
4s, 61%, 92% ee



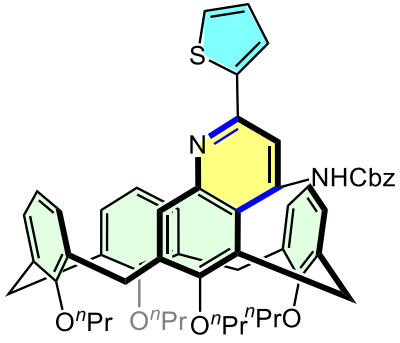
4t, 51%, 91% ee



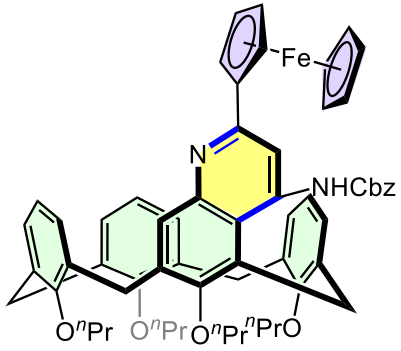
4u, 67%, 97% ee



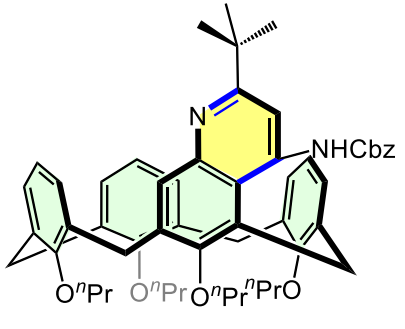
4v, 62%, 95% ee



4w, 65%, 97% ee

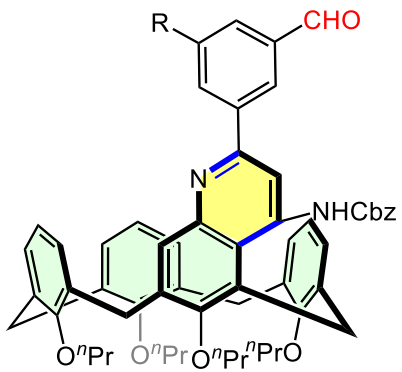


4x, 71%, 99% ee



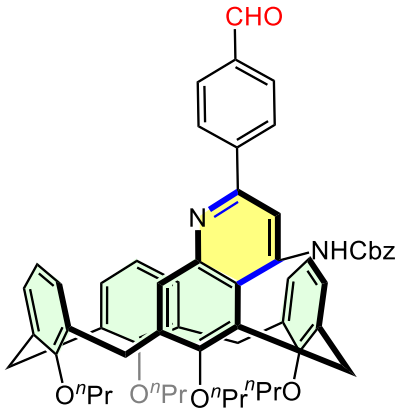
4y, 43%, 95% ee

Reaction Scope

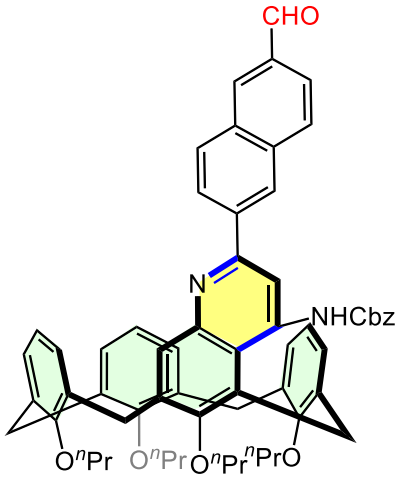


4z, R = H, 75%, 98% ee

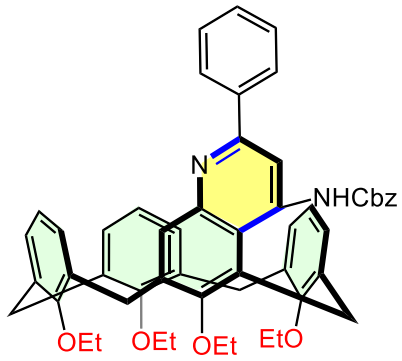
4aa, R = Br, 90%, 98% ee



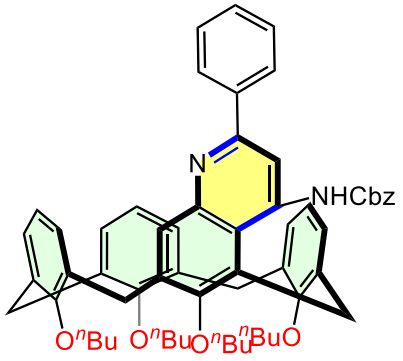
4ab, 82%, 98% ee



4ac, 67%, 97% ee



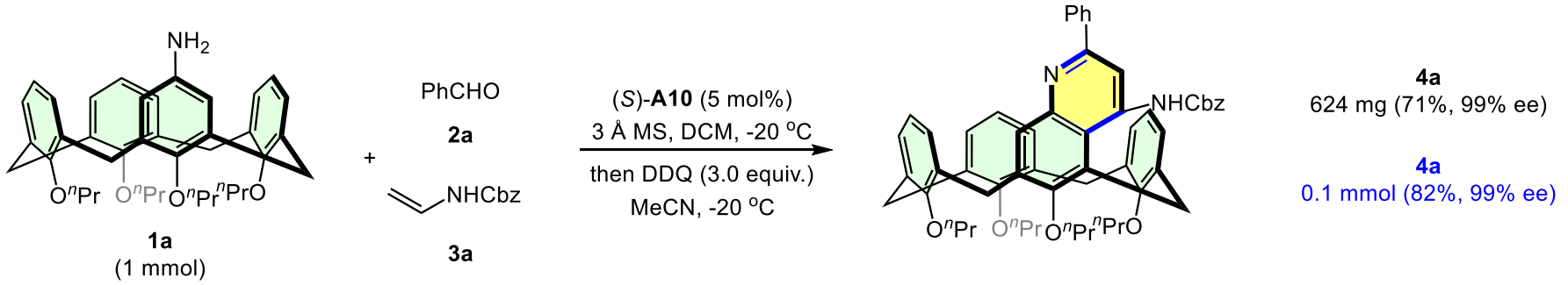
4ad, 67%, 96% ee



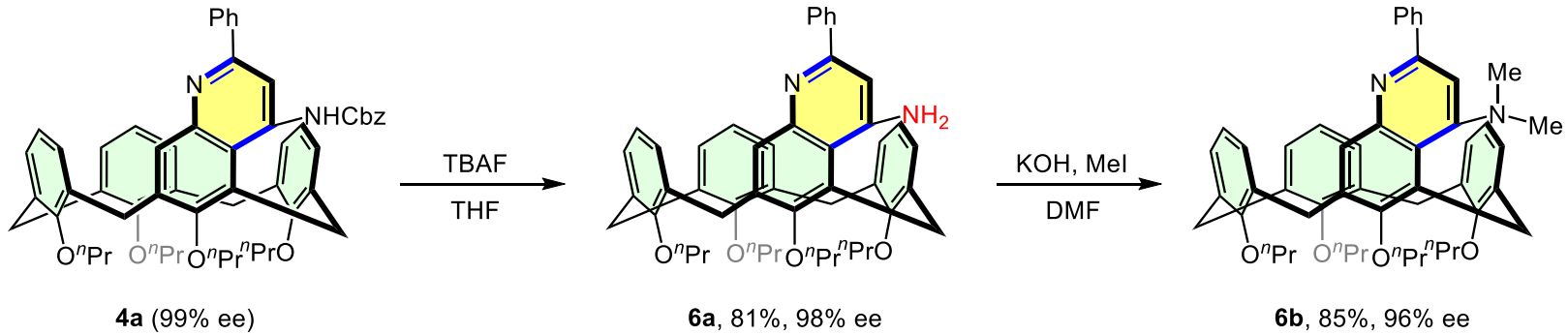
4ae, 75%, 95% ee

Scale-up Reaction and Synthetic Application

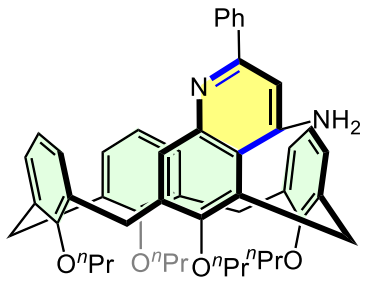
a) Scale-up reaction



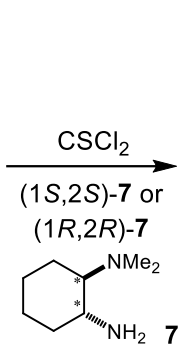
b) Synthetic application



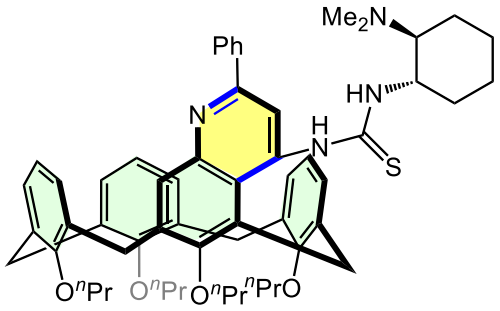
Calix[4]arenes as Chiral Organocatalysts



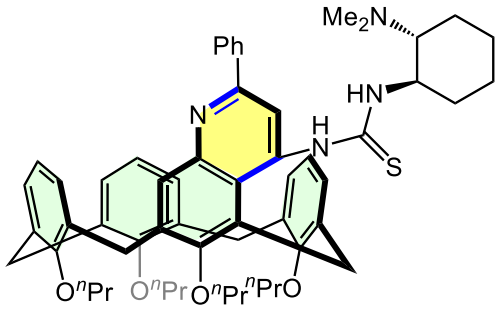
6a, 98% ee



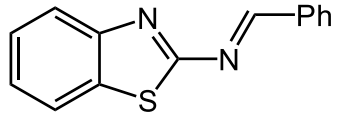
7



8, 52%

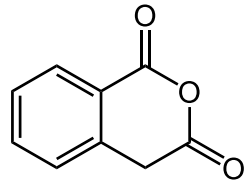


9, 53%

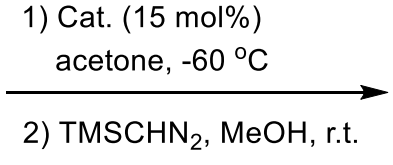


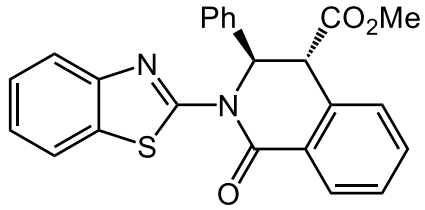
10

\+



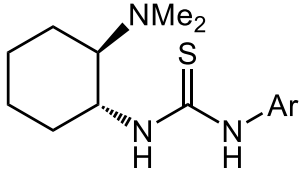
11





12

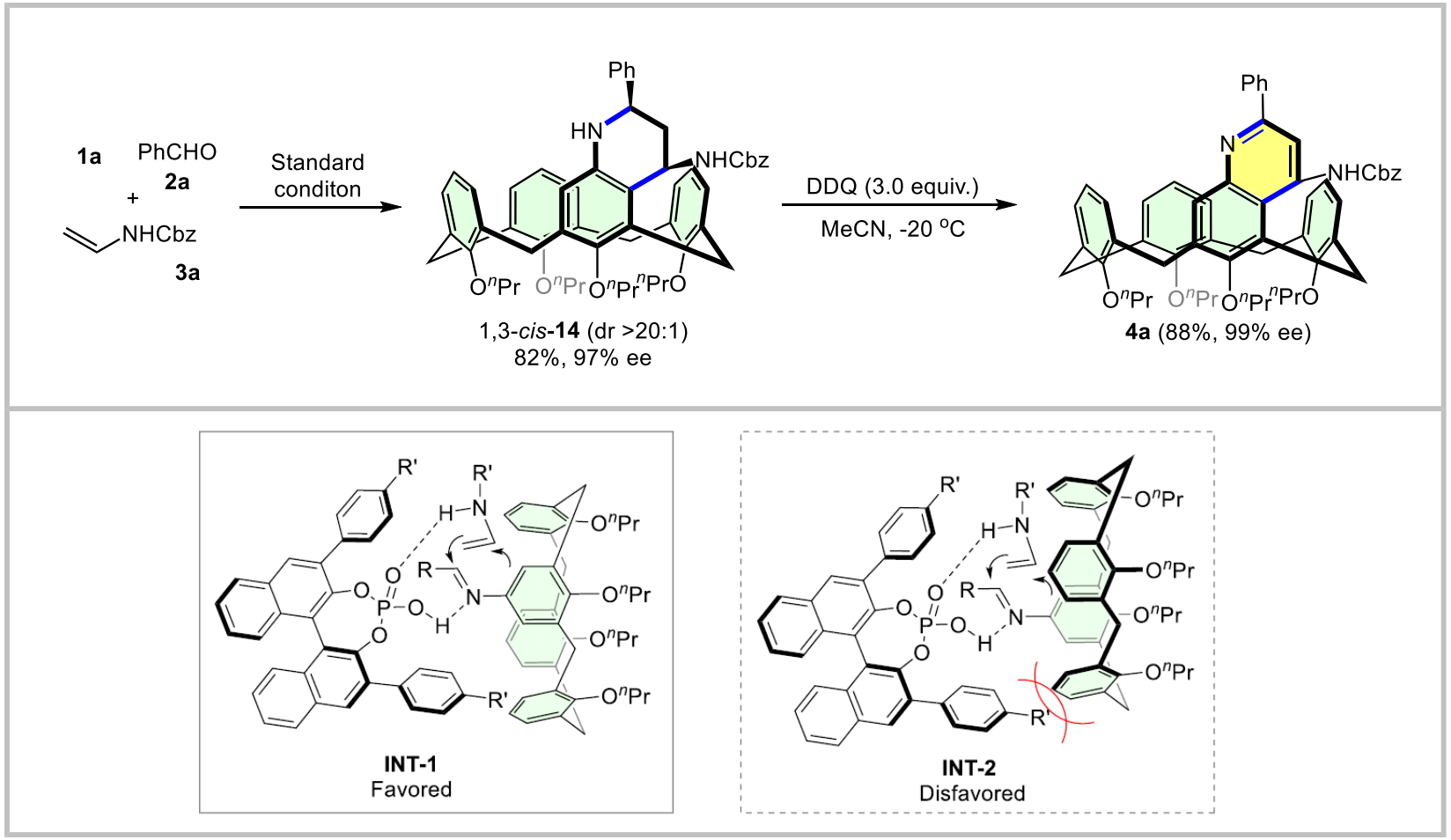
Entry[a]	Cat.	Yield [%]	Ee [%]	Dr
1	**8**	75	82	>20:1
2	**9**	72	46	>20:1
3	**13**	68	68	>20:1



13

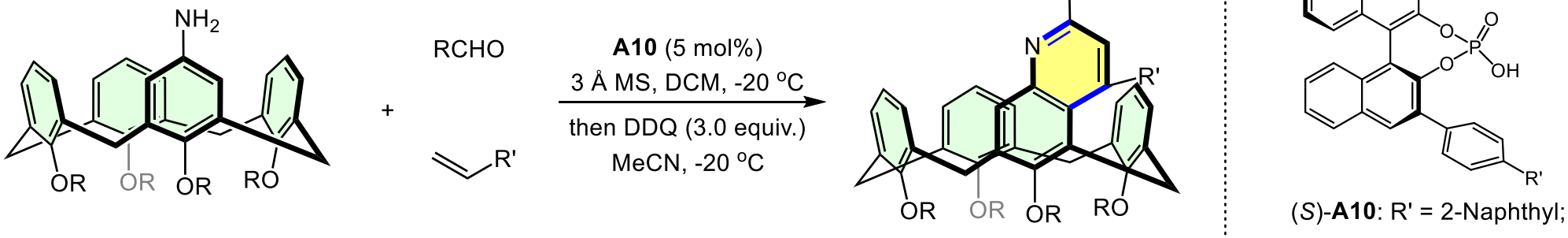
Ar = 3,5-$(CF_3)_2C_6H_3$

Study of Mechanism



Summary

Organocatalytic Enantioselective Synthesis of Inherently Chiral Calix[4]arenes



(*S*)-**A10**: R' = 2-Naphthyl;

- Organcatalytic synthesis of chiral calix[4]arenes;
- Intermolecular synthesis of inherent chiral calix[4]arenes;
- Enantioselective Povarov reaction in inherent chirality;
- Excellent enantioselectivity and remarkable luminescence properties.

Writing Strategy

➢The First Paragraph

固有手性和
固有手性杯芳烃
的发展和重要性

固有手性杯芳烃
合成的局限挑战

- In general, chirality is classified into central, axial, planar, and helical chirality. Inherent chirality was first coined by Böhmer in 1994 to describe the chirality arising from calixarene scaffolds. During the last decade, tremendous efforts have been devoted to constructing inherent chirality. As a remarkable framework for achieving inherent chirality, calix[4]arene has developed into a privileged molecular structure in the fields of enantio-selective catalysis, chiral recognition and sensing, and circularly polarized luminescence.
- Although inherently chiral calix[4]arenes have broad applications in chiral functional materials and devices, their enantioselective synthesis is still in its infancy. The main method for obtaining enantioenriched calix[4]arenes heavily relies on chiral high performance liquid chromatography (HPLC) separation or diastereoselective synthesis with the aid of chiral auxiliaries, which significantly restrict their applicable research.

Writing Strategy

➢The Last Paragraph

总结工作
（手性Povarov反应）

↓

产物实用性
（克级规模&光致发光）

- In conclusion, we have achieved an enantioselective three-component cyclization to access inherently chiral calix[4]arenes bearing a π-extended structure. The sequent enantioselective Povarov reaction/oxidation process proceeded smoothly to give structurally diverse calix[4]arenes with excellent enantioselectivity.
- Both the gram-scale synthesis and synthetic transformation of calix[4]arene-based chiral catalysts have demonstrated their potential applications. In addition, the investigation of the photophysical and optical properties of the synthesized calix[4]arenes showed that they have remarkable fluorescence luminescence and CPL bearing a $|g_{lum}|$ value of up to 1.2×10^{-3}.

Representative Examples

- Inherent chirality was first **coined** by Böhmer in 1994 to describe the chirality arising from calixarene scaffolds. (vt. 铸币，创造)
- In addition, introducing substituents **ranging from** furan to thiophene gave inherently chiral calix[4]arenes in moderate to good yields with excellent enantioselectivity. (从……排列)
- Stepwise reactions were conducted to **elucidate** the stereo-control mechanism of this enantioselective synthesis. (vt. 阐明，说明，解释)

Acknowledgement

Thanks
for your attention