

Literature Report 7

Enantioselective Synthesis of “NO₂···NH” Hydrogen Bond-Stabilized C–N Axially Chiral Diarylamines

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Checker: Gao-Wei Wang

2024-05-20

CV of Prof. Xin Li



Research:

- Physical Organic Chemistry
 - Physical-Organic Oriented Asymmetric Catalysis
-

Background:

- **1998-2002** B.S., Nankai University
- **2002-2007** Ph.D., Nankai University (Prof. Jin-Pei Cheng)
- **2007-2010** Postdoc., Institute of Chemistry, CAS (Prof. Sanzhong Luo)
- **2010-Now** Assistant Prof., Associate Prof., Prof., Nankai University

- 1 Introduction**

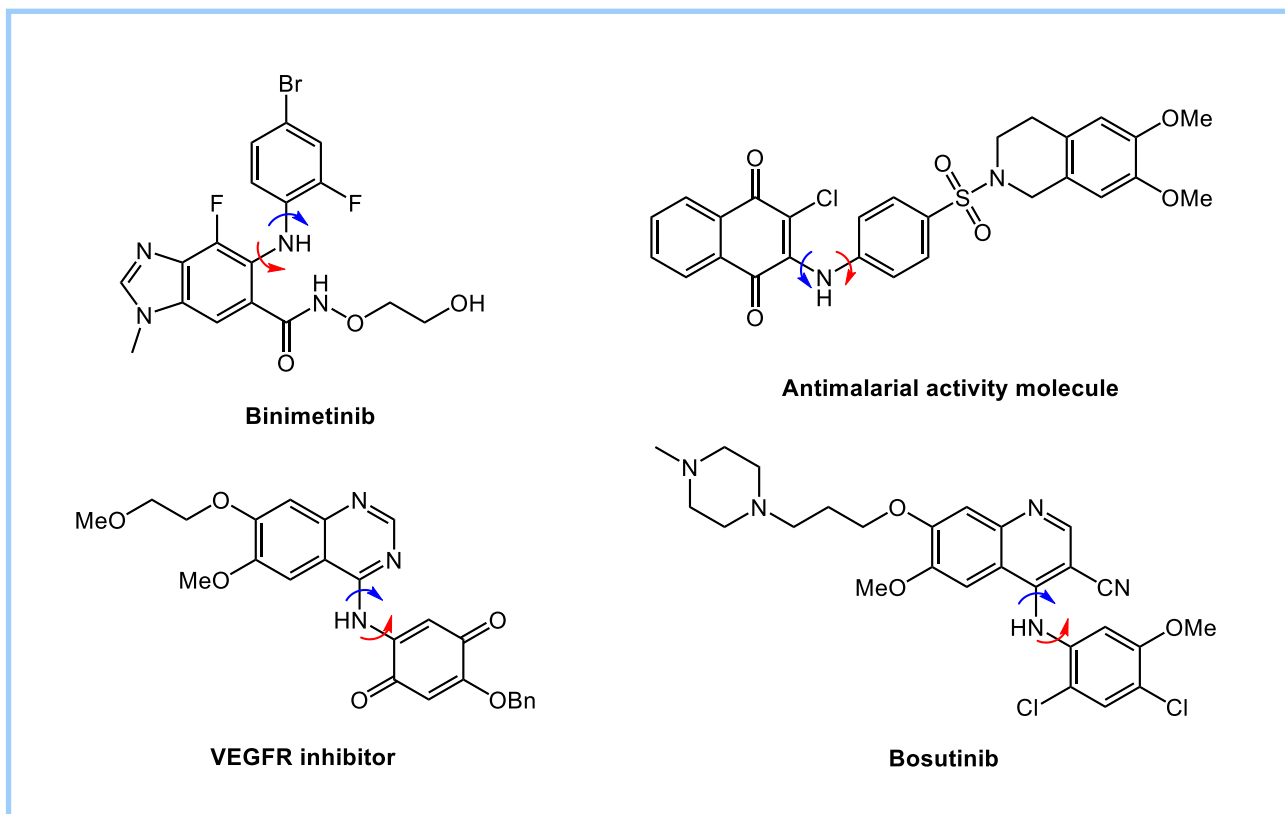
- 2 Atropisomerically Stable Diarylamines**

- 3 Enantioselective Synthesis of Axially Chiral Diarylamines**

- 4 Summary**

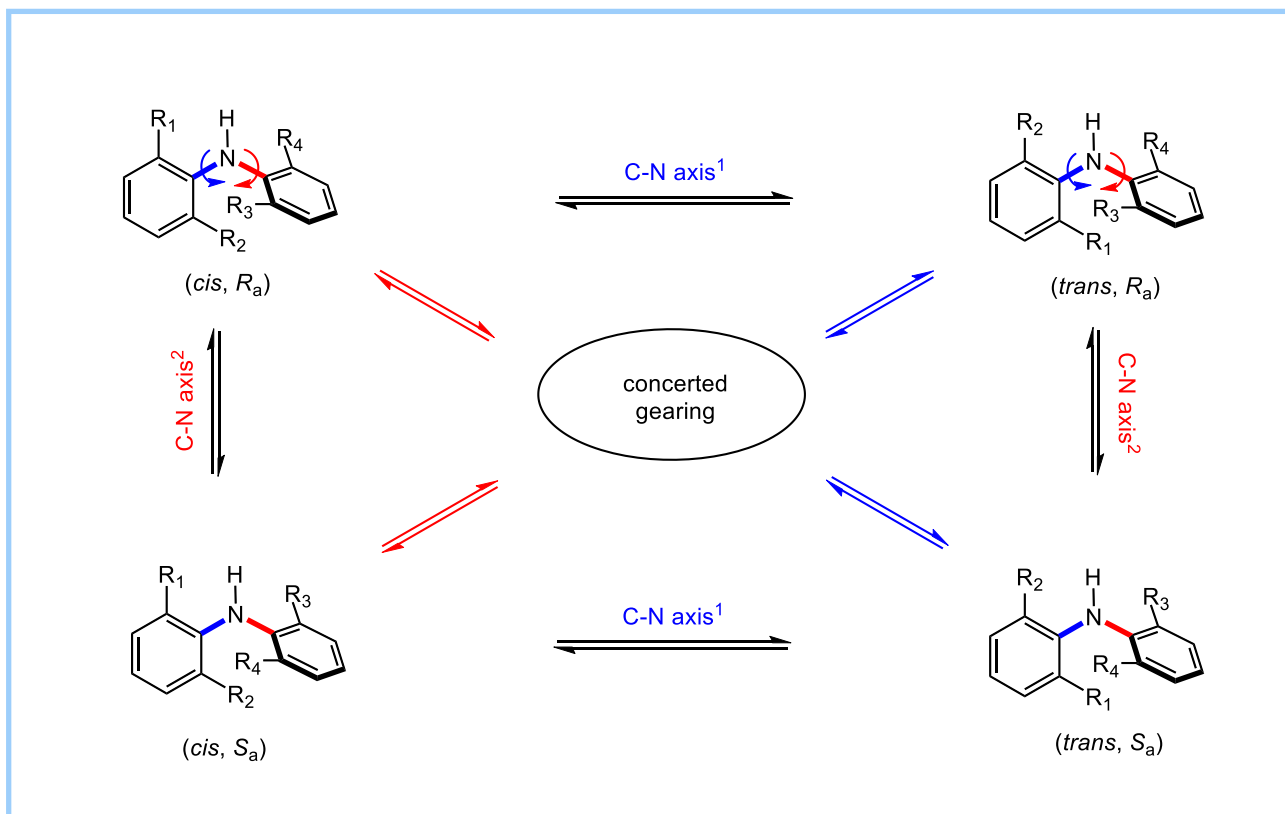
Introduction

Drugs Containing Diarylamine Scaffolds



Vaidya, S. D.; Gustafson, J. L.* *J. Am. Chem. Soc.* **2020**, *142*, 2198–2203

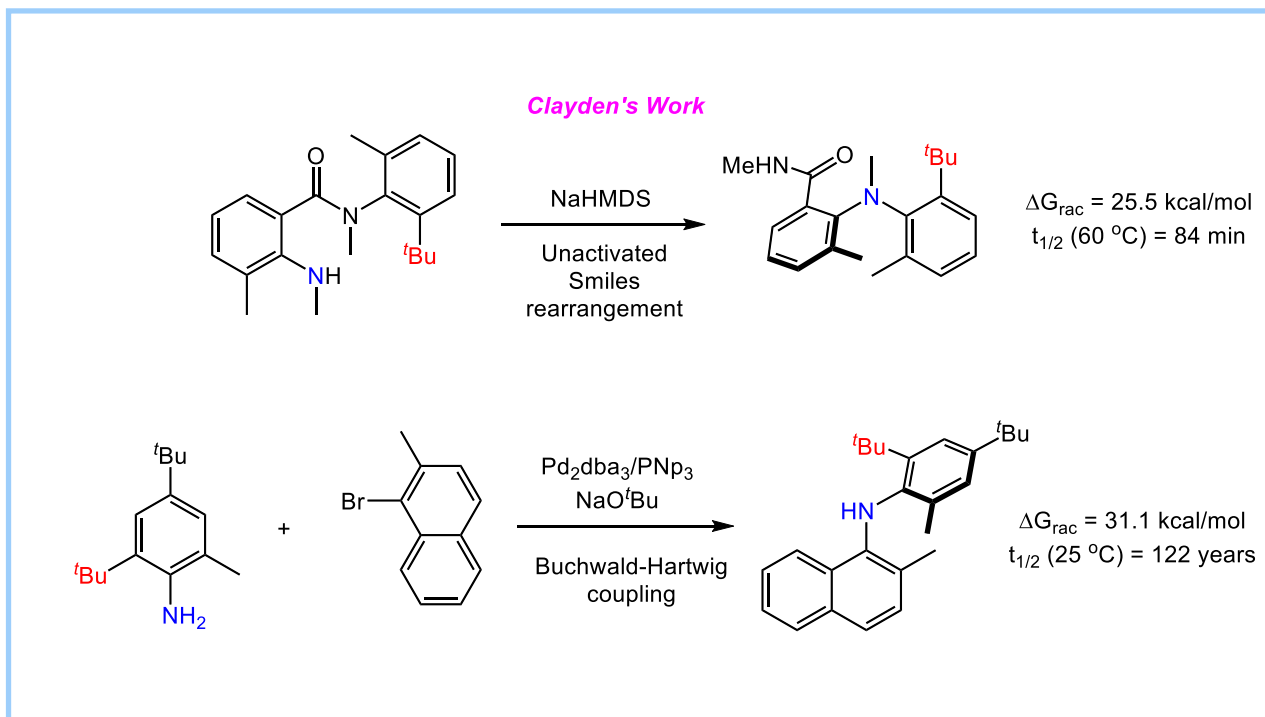
“Concerted Gearing” Mechanisms



Lin, W.; Li, X.* *ACS Catal.* **2024**, *14*, 1183-1192

Atropisomerically Stable Diarylamines

Steric Hindrance in the ortho-Positions of Diarylamines



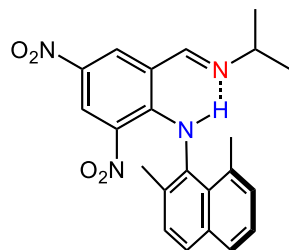
Costil, R.; Clayden, J.* *Angew. Chem. Int. Ed.* **2017**, *56*, 12533-12537

Costil, R.; Clayden, J.* *Angew. Chem. Int. Ed.* **2020**, *59*, 18670-18678

Atropisomerically Stable Diarylamines

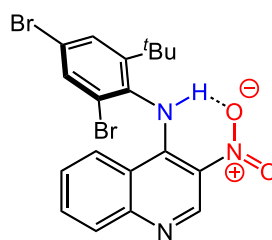
Intramolecular hydrogen bond to lock the C–N bond

Kawabata's Work

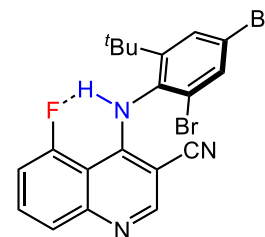


$\Delta G_{\text{rac}} = 28.2 \text{ kcal/mol}$
 $t_{1/2} (20 \text{ }^\circ\text{C}) = 24 \text{ month}$

Gustafson's Work



cis conformation
 $\Delta G_{\text{rac}} = 34.5 \text{ kcal/mol}$

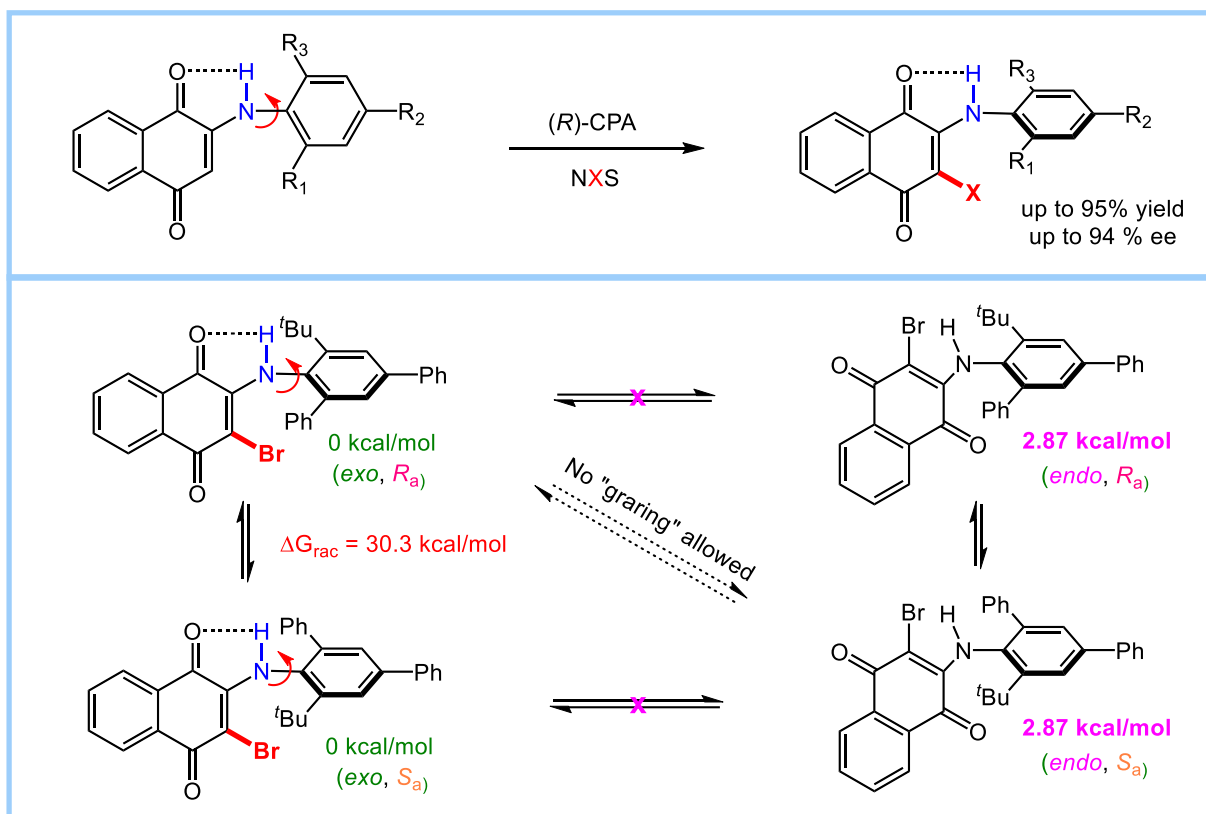


trans conformation
 $\Delta G_{\text{rac}} > 36 \text{ kcal/mol}$

Kawabata, T.*; Jiang, C. J.. *Am Chem. Soc.* **2009**, *131*, 54-55
Vaidya, S. D.; Gustafson, J. L.* *J. Org. Chem.* **2022**, *87*, 6760-6768

Enantioselective Synthesis of Chiral Diarylamine Derivatives

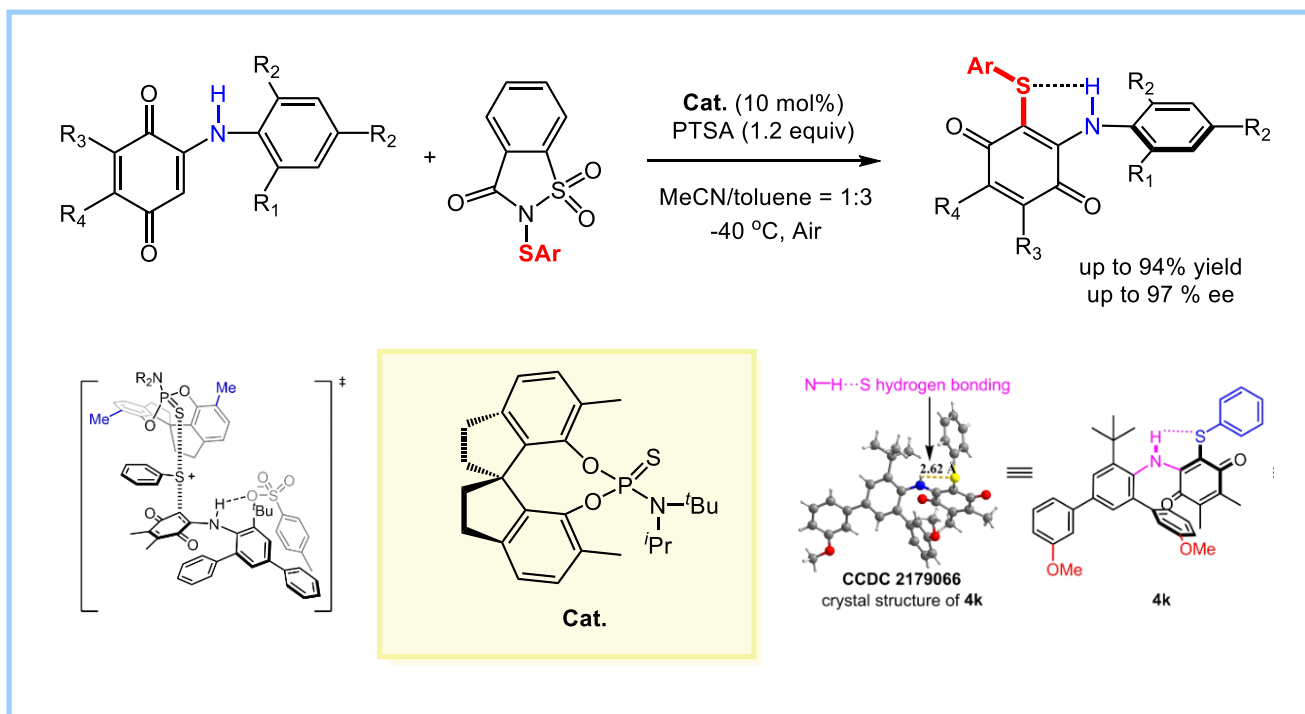
Electrophilic Halogenation of *N*-Aryl Quinoid Compounds



Vaidya, S. D.; Gustafson, J. L.* *J. Am Chem. Soc.* **2020**, 142, 2198–2203

Enantioselective Synthesis of Chiral Diarylamine Derivatives

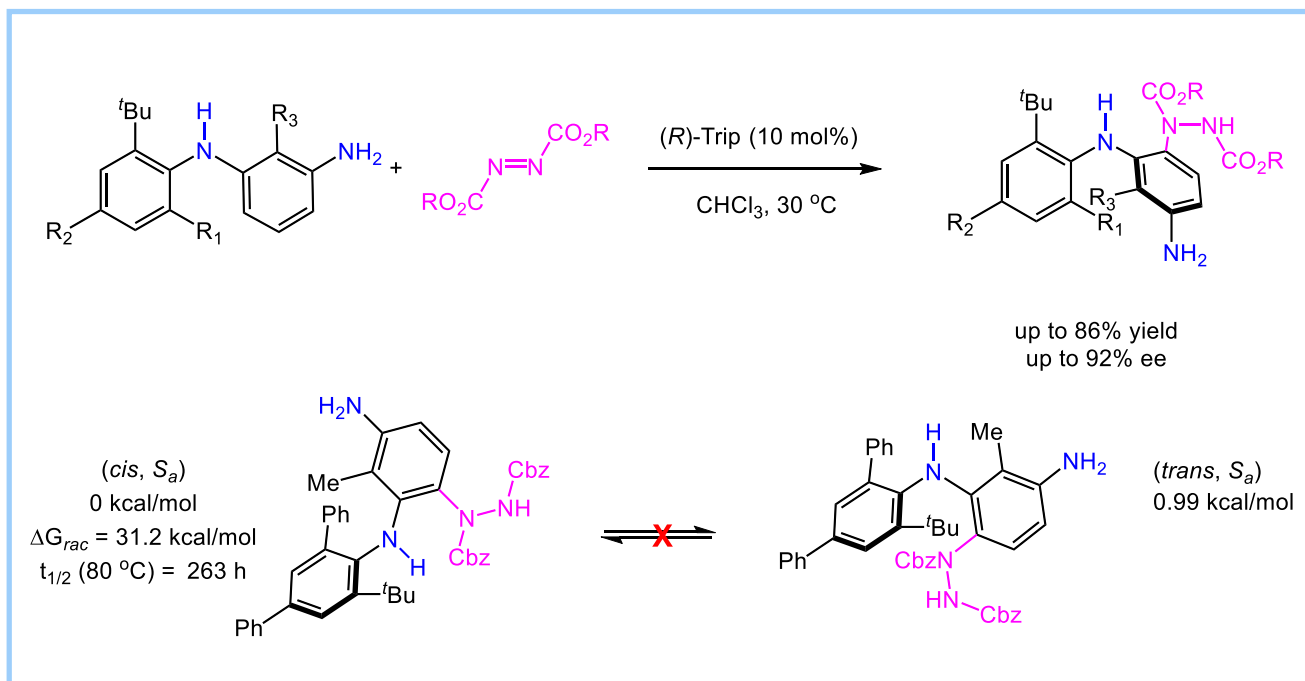
Electrophilic Sulfenylation of *N*-Aryl Quinoid Compounds



Xue, X.-S.*; Chen, Z.-M.* *Angew. Chem. Int. Ed.* **2022**, *61*, e202211782

Enantioselective Synthesis of Chiral Diarylamine Derivatives

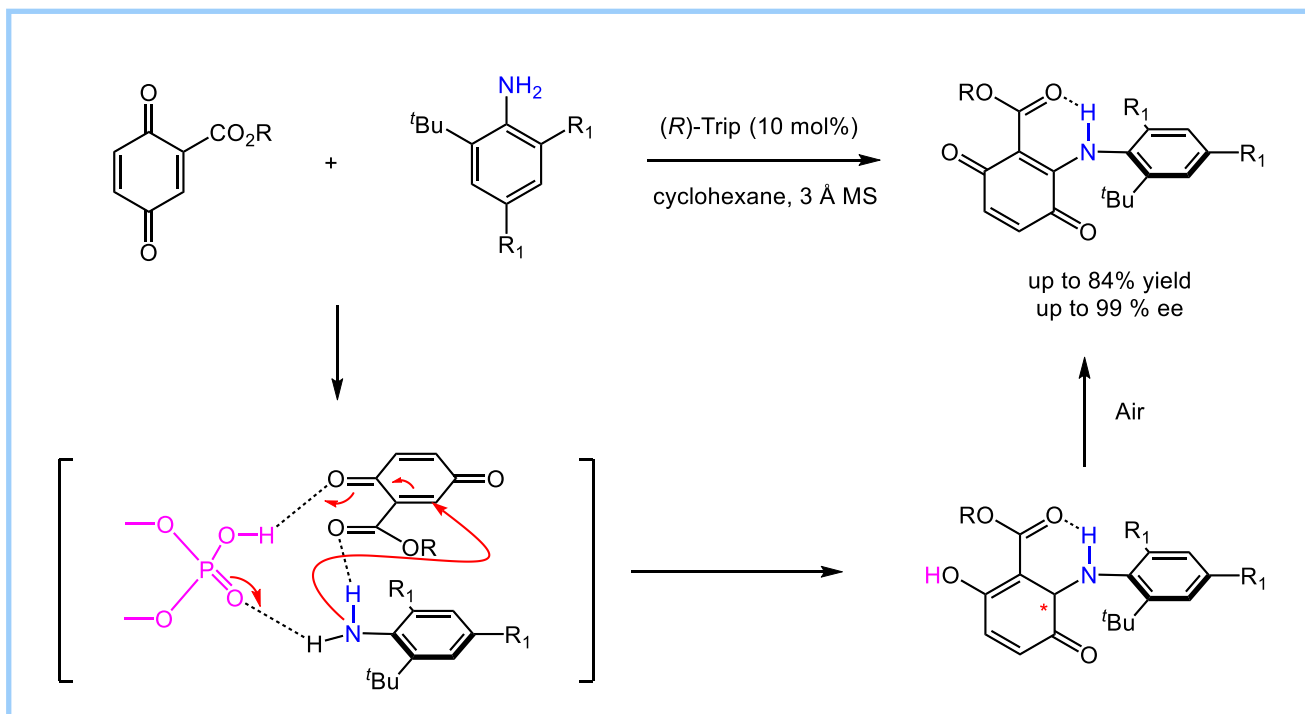
Electrophilic Amination of Diarylamines



Ye, Z.; Yang, X.* *ACS Catal.* **2024**, *14*, 4958-4967

Enantioselective Synthesis of Chiral Diarylamine Derivatives

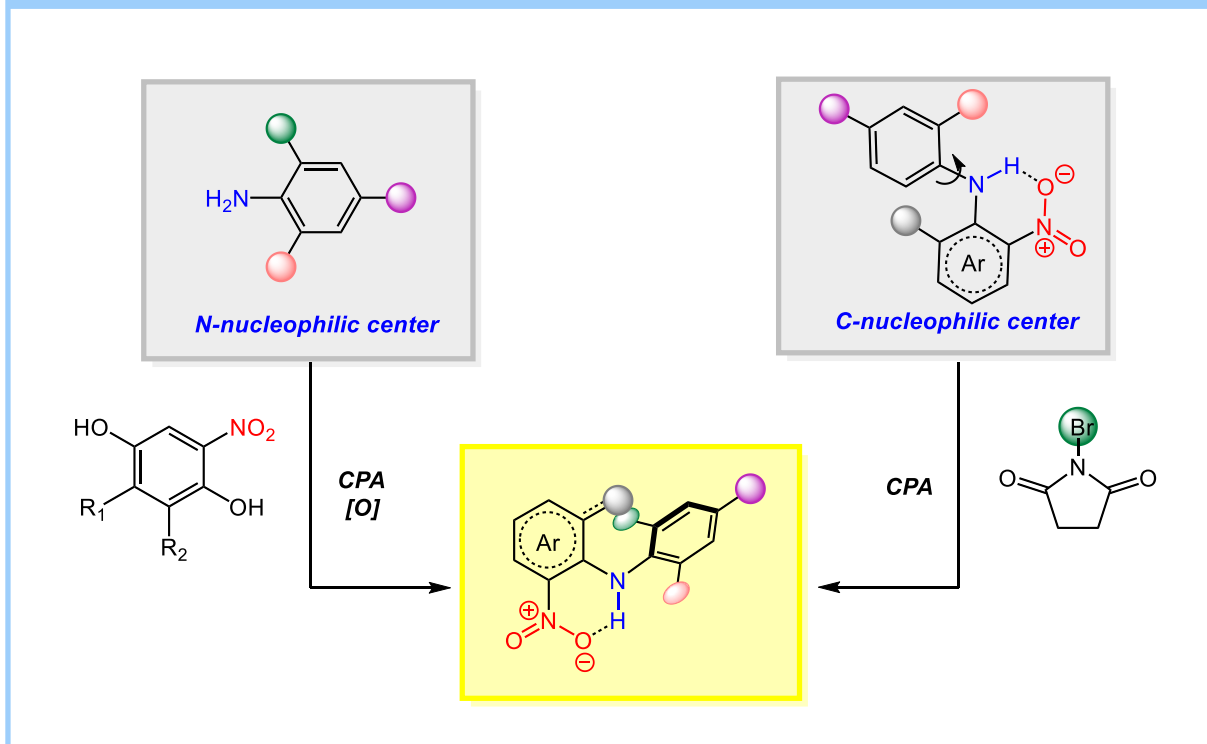
Organocatalytic Tandem *N*-Arylation/Oxidation



Guo, C.-Q.*; Liu, R.-R.* *Angew. Chem. Int. Ed.* **2022**, 61, e202212846

Project Synopsis

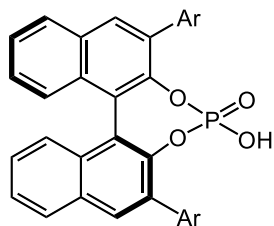
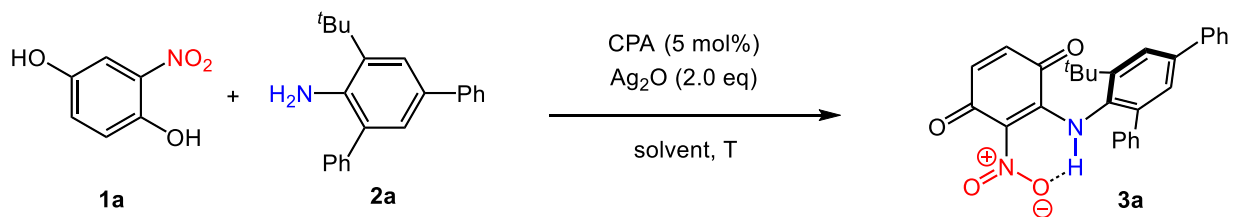
This Work: Enantioselective Synthesis of NO₂--NH Hydrogen Bond-Stabilized Diarylamines



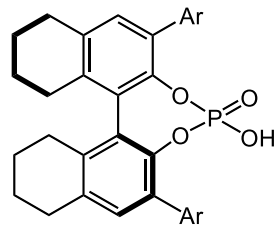
Lin, W.; Shao, Y.-B.; Hao, Z.; Huang, Z.; Chen, L*, Li, X.* *ACS Catal.* **2024**, *14*, 1183-1192

Optimization of Reaction Conditions

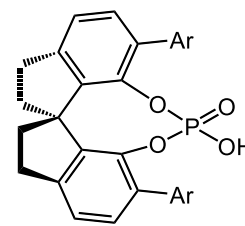
Optimization of the Reaction Conditions



(S)-A1: Ar = 2,4,6-*i*-Pr₃C₆H₂
(S)-A2: Ar = 2,4,6-Me₃C₆H₂

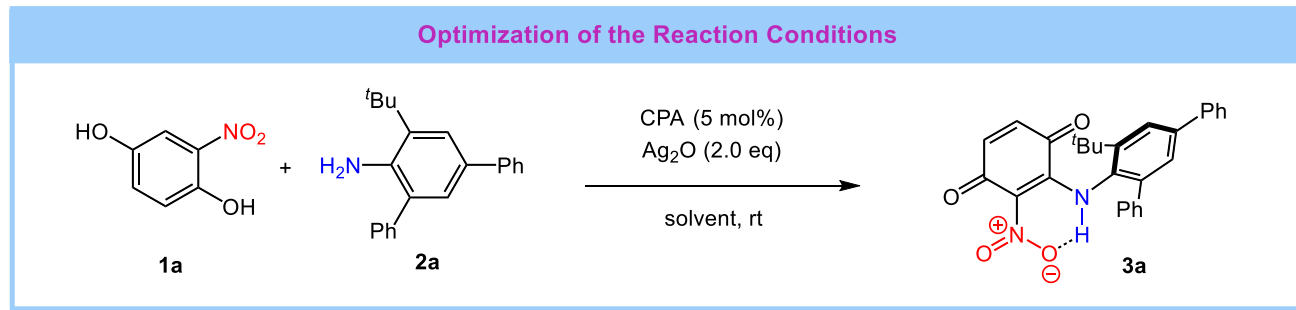


(S)-B1: Ar = 2,4,6-*i*-Pr₃C₆H₂
(S)-B2: Ar = 9-phenanthrenyl



(S)-C1: Ar = 9-anthryl
(S)-C2: Ar = 3,5-Ph₂C₆H₃

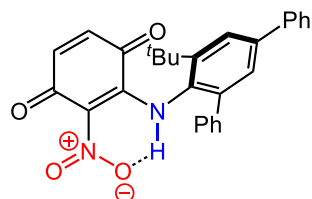
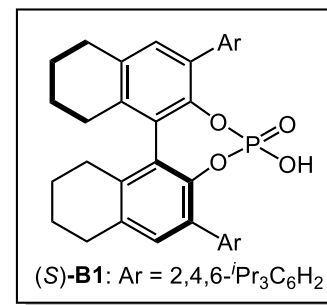
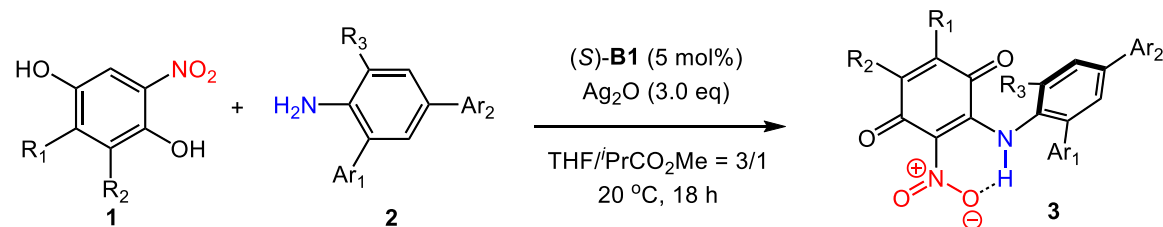
Optimization of Reaction Conditions



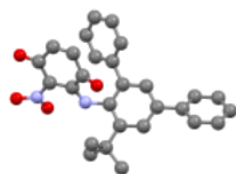
Entry ^a	CPA	Solvent	Yield of 3a (%)	E.r. of 3a (%)
1	A1	DCM	16	70.5:29.5
2	A2	DCM	62	63.5:36.5
3	B1	DCM	44	73:27
4	B2	DCM	61	58:42
5	C1	DCM	38	30.5:69.5
6	C2	DCM	47	33:67
7	B1	THF	50	92.5:7.5
8	B1	toluene	47	80:20
9	B1	EA	70	90.5:9.5
10	B1	<i>i</i> PrCO ₂ Me	97	91.5:8.5
11 ^b	B1	THF/ <i>i</i> PrCO ₂ Me = 3:1	78	96:4
12 ^{c,d}	B1	THF/ <i>i</i> PrCO ₂ Me = 3:1	83	96.5:3.5
13 ^{c,d,e}	B1	THF/ <i>i</i> PrCO ₂ Me = 3:1	88	0

^aReaction conditions: a mixture of 1a (0.1 mmol), 2a (0.12 mmol), Ag₂O (2.0 equiv), and CPA (5 mol %) in solvent (1.0 mL) was stirred at room temperature for 12 h; ^b10 °C; ^c20 °C; ^d3.0 eq. Ag₂O; ^eDDQ instead of Ag₂O

Substrate Scope

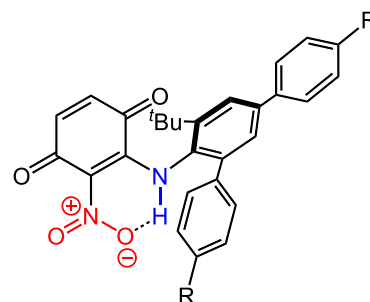


3a, 83%, 96.5:3.5 e.r.



CCDC: 2242982

$\Delta G_{\text{rac}} = 28.66\text{ kcal/mol}$
 $t_{1/2}$ (102 °C in toluene) = 4.06 h



3b, R = F, 74%, 95.5:4.5 e.r.

3c, R = Cl, 72%, 95.5:4.5 e.r.

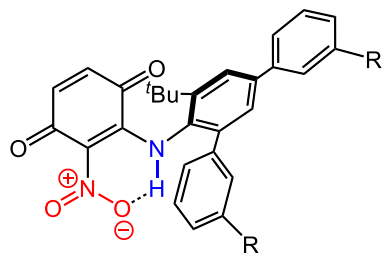
3d, R = Me, 99%, 96.5:3.5 e.r.

3e, R = OMe, 57%, 95:5 e.r.

3f, R = iPr , 55%, 94:6 e.r.

3g, R = tBu , 99%, 95:5 e.r.

3h, R = CF_3 , 68%, 93:7 e.r.



3i, R = F, 66%, 95:5 e.r.

3j, R = Cl, 68%, 94:6 e.r.

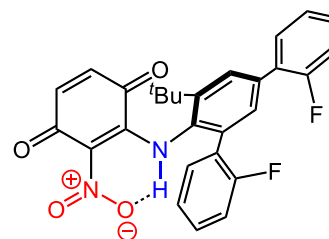
3k, R = Me, 62%, 96:4 e.r.

3l, R = OMe, 80%, 95:5 e.r.

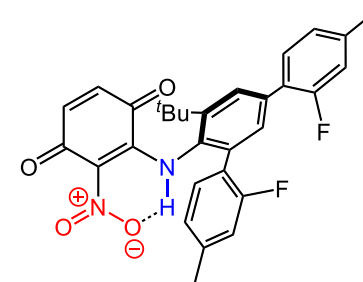
3m, R = iPr , 57%, 94:6 e.r.

3n, R = tBu , 64%, 92.5:7.5 e.r.

3o, R = Ph, 50%, 94.5:5.5 e.r.

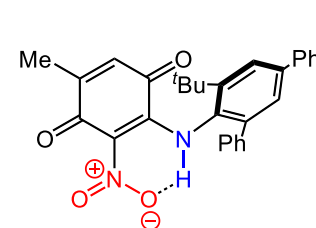
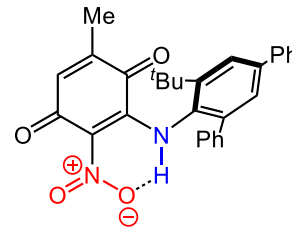
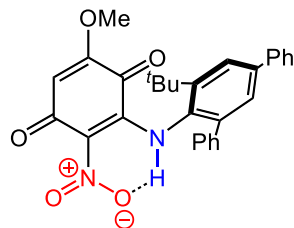
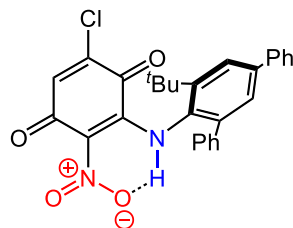
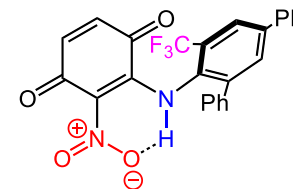
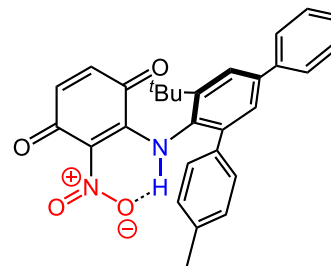
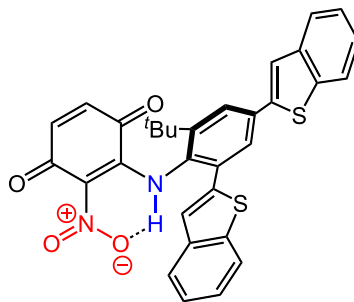
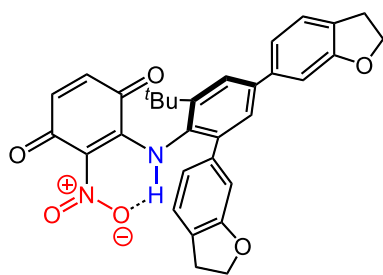
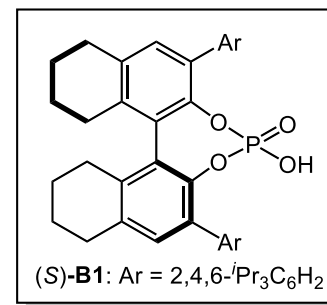
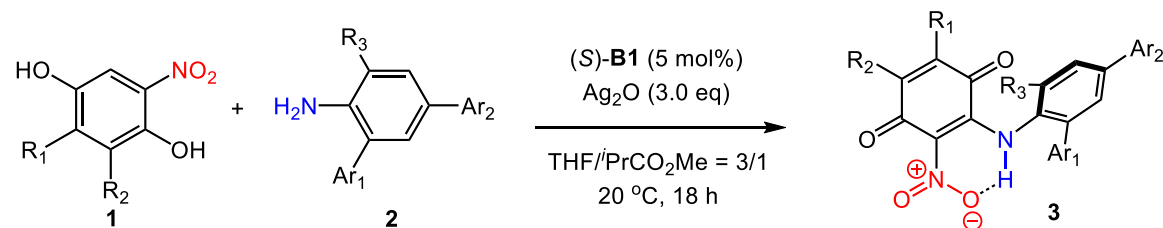


3p, 74%, 97.5:2.5 e.r.

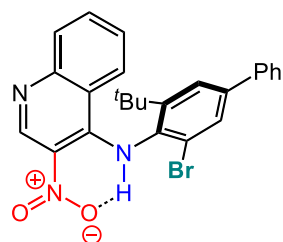
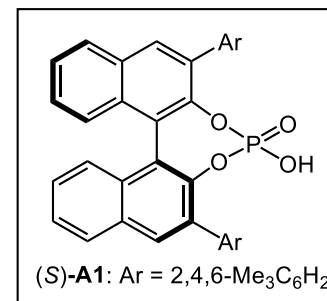
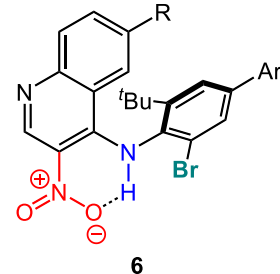
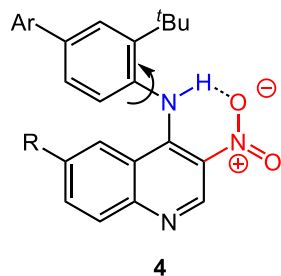


3q, 72%, 97:3 e.r.

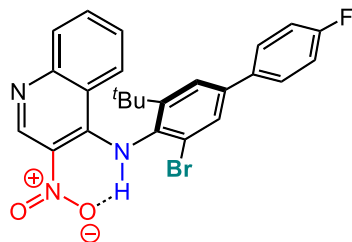
Substrate Scope



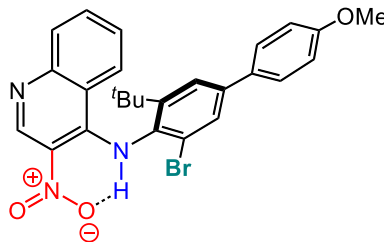
C-Nucleophilic Bromination Reaction



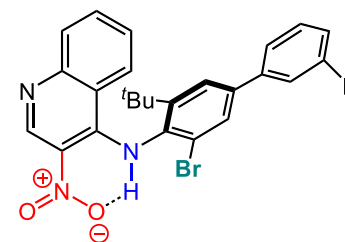
6a, 99%, 99:1 e.r.



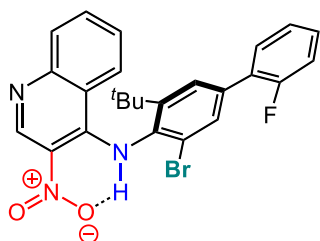
6b, 74%, 99.5:0.5 e.r.



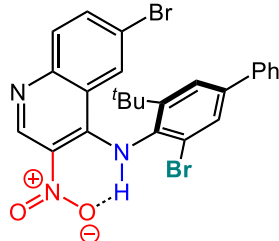
6c, 91%, 91:9 e.r.



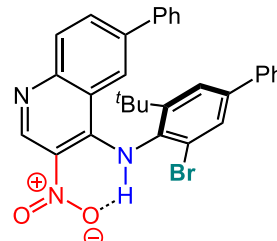
6d, 97%, 96:4 e.r.



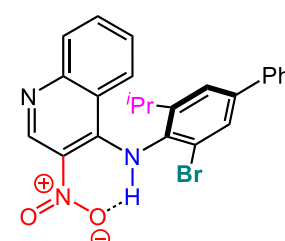
6e, 95%, 93.5:6.5 e.r.



6f, 95%, 97:3 e.r.

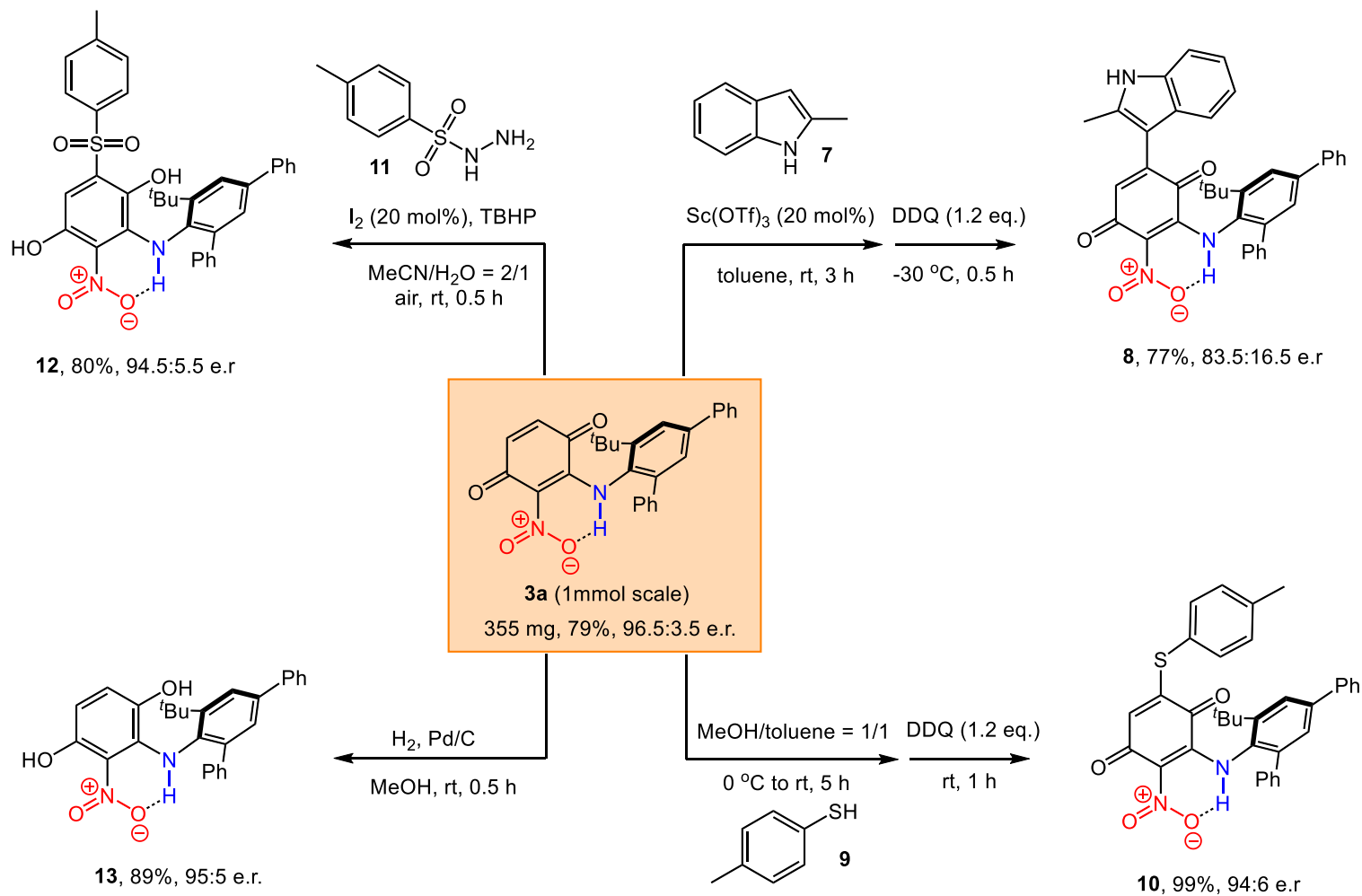


6g, 79%, 94.5:5.5 e.r.



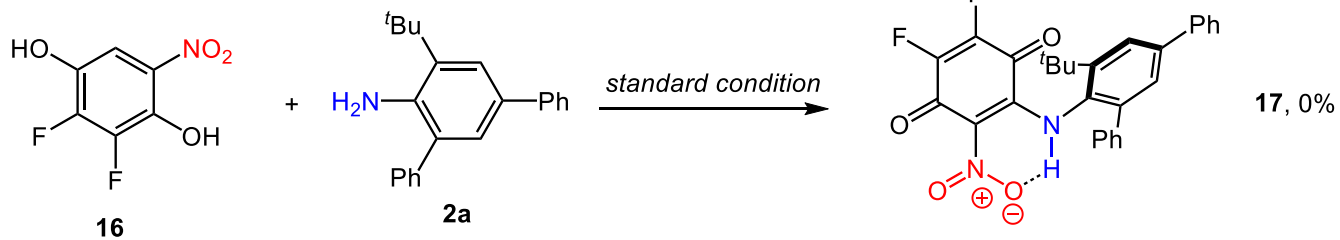
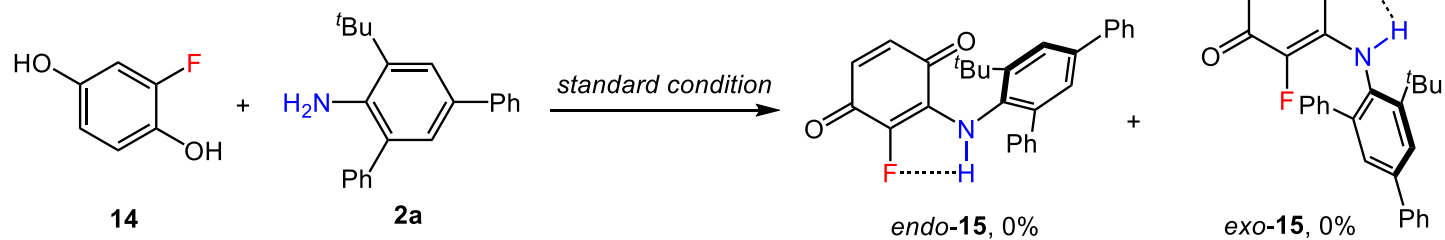
6h, 77%, 96.5:3.5 e.r.

Transformations of Products

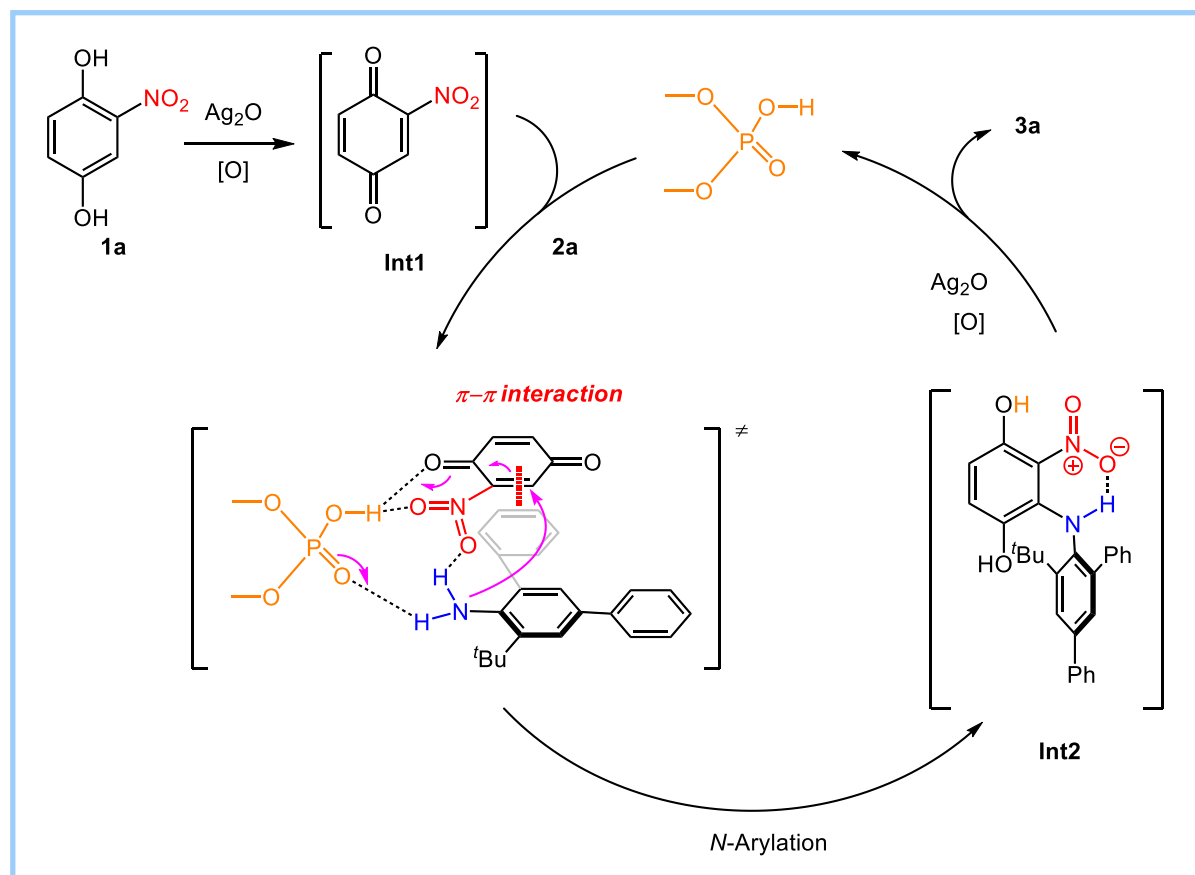


Mechanism Studies

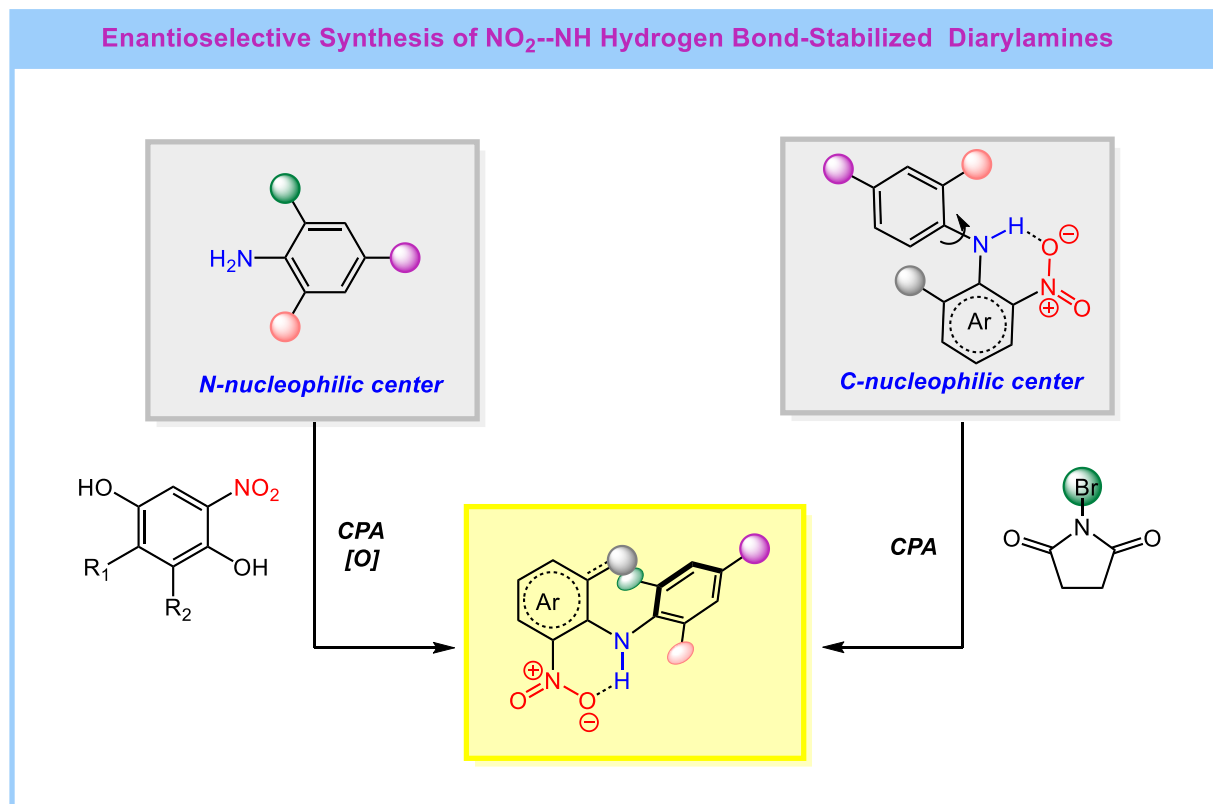
Control Experiment



Mechanism Studies

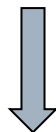


Summary

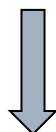


写作思路

阻转异构体具有重要意义



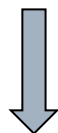
二芳基仲胺阻转异构体合成的挑战



近年来科学家做出的努力

写作思路

总结工作：CPA催化合成二芳胺阻转异构体



工作亮点：硝基与仲氨基形成氢键稳定一个C-N轴

Representative Examples

- This **innovative** design provided a foundation for subsequent studies. (**innovative**: 创新的, 革命性的, 用于赞美前人研究)
- Ester groups were **strategically** incorporated into intramolecular hydrogen bonds, effectively locking the configuration of the planar C–N. (**strategically**: 策略性地)
- Therefore, nitro compounds have always been **a focal point** in pharmaceutical and organic chemistry research. (**a focal point**: 焦点)

Acknowledgement

Thanks for Your Attention