香港科技大學
THE HONG KONG UNIVERSITY OF SCIENCE AND TECHNOLOGY

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Organocatalytic Discrimination of Non-Directing Aryl and Heteroaryl Groups: Enantioselective Synthesis of Bioactive Indole-Containing Triarylmethanes

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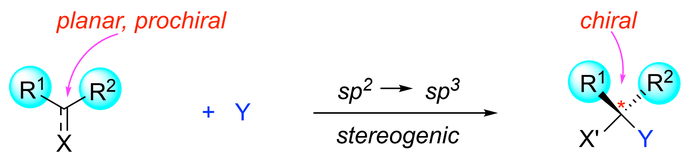
1. Background

a) Asymmetric differentiation in prochiral planar substrates

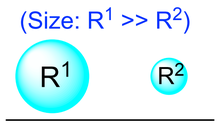


carbocation
radical
C=X bond

key to enantiocontrol:
differentiation between R^1 and R^2

large alkyl	small alkyl / H
aryl	alkyl / H

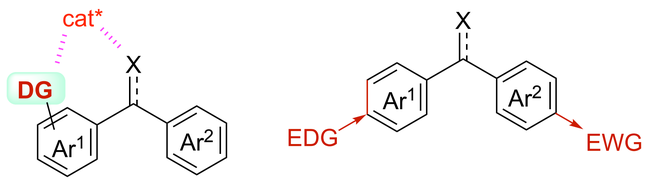
well-established cases
(Size: R^1 >> R^2)



b) Challenges in discrimination between two aryl groups: (Size: $R^1 \neq R^2$)

Almost all the successful examples are based on metal catalysis so far

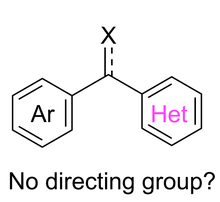
Typical Strategies: Aryl vs Aryl



Directing group (DG)

Electronic difference

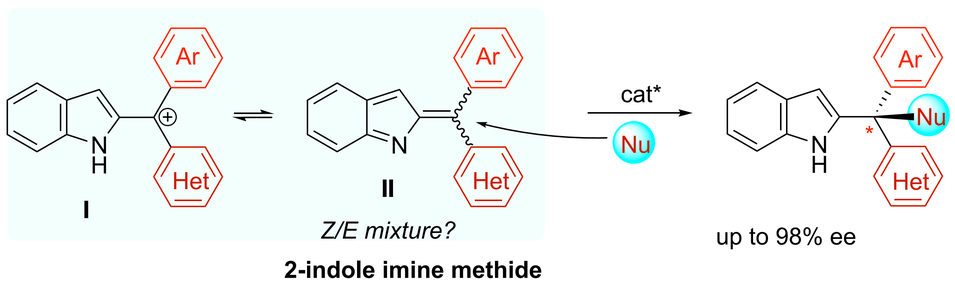
Aryl vs Heteroaryl



No directing group?

Rarely successful

c) *This work:* Organocatalytic differentiation between non-directing aryl and heteroaryl

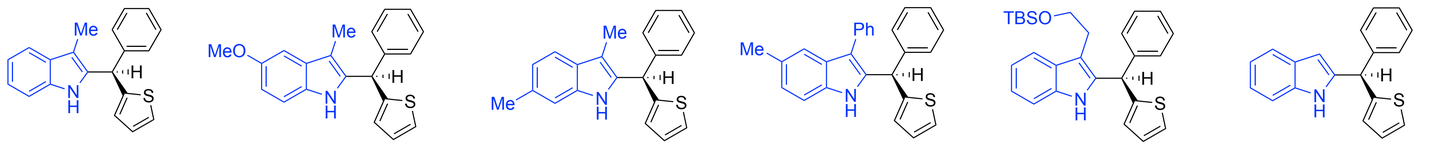


Z/E mixture?

2-indole imine methide

up to 98% ee

3. Scope



3a, rt, 16 h
87% yield, 96% ee

3b, 0 °C, 30 h
76% yield, 96% ee

3c, 0 °C, 30 h
73% yield, 94% ee

3d, 0 °C, 30 h
82% yield, 92% ee

3e, rt, 48 h[a]
70% yield, 90% ee

3f, 0 °C, 30 h
78% yield, 89% ee

3g, 0 °C, 30 h
89% yield, 89% ee

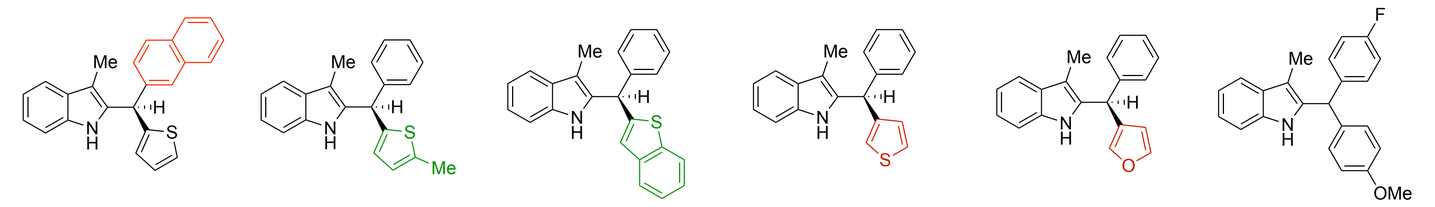
3h, -20 °C, 48 h
85% yield, 93% ee

3i, 0 °C, 30 h
48% yield, 91% ee

3j, -30 °C, 6 d
77% yield, 88% ee

3k, 0 °C, 30 h
89% yield, 95% ee

3l, -20 °C, 48 h
83% yield, 91% ee



3m, 0 °C, 30 h
76% yield, 98% ee

3n, 0 °C, 30 h
82% yield, 98% ee

3o, 0 °C, 72 h
63% yield, 78% ee

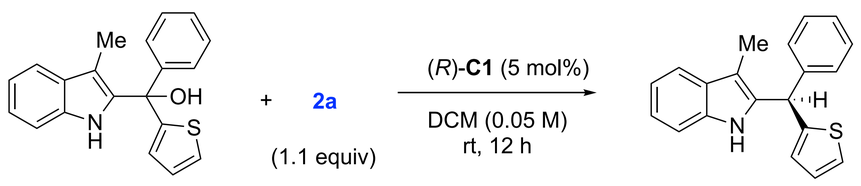
3p, 0 °C, 41 h
85% yield, 92% ee

3q, rt, 12 h
44% yield, 84% ee

3r, 0 °C, 30 h
81% yield, 44% ee

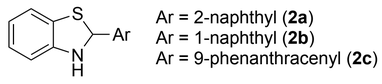
Reaction scale: **1** (0.4 mmol), **2** (0.44 mmol), (*R*)-**C1** (5 mol%), DCM (8.0 mL). [a] Run with 10 mol% of catalyst.

2. Optimization

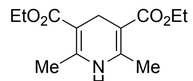


Entry	Deviation from the "standard conditions"	Yield (%)[b]	Ee (%)[b]
1	none	> 95	95
2	(*R*)-**C2** instead of (*R*)-**C1**	> 95	16
3	(*R*)-**C3** instead of (R)-**C1**	> 95	81
4	(*R*)-**A** instead of (*R*)-**C1**	> 95	< 2
5	(*R*)-**B** instead of (*R*)-**C1**	> 95	< 2
6	**2b** instead of **2a**	11[c]	80
7	**2c** instead of **2a**	15[c]	55
8	**2d** instead of **2a**	78[d]	−9
9	Et_2O as solvent	< 5[e]	–
10	Toluene as solvent	87	89
11	EtOAc as solvent	< 5[e]	–
12	Run at 0 °C	84[d]	96
13	*c* = 0.2 M	> 95	93

Hydride source



Ar = 2-naphthyl (**2a**)
Ar = 1-naphthyl (**2b**)
Ar = 9-phenanthracenyl (**2c**)

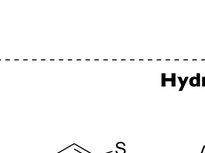


2d

Catalyst

(*R*)-**A**
R = 3,5-$(CF_3)_2C_6H_3$

(*R*)-**B**
R = 3,5-$(CF_3)_2C_6H_3$

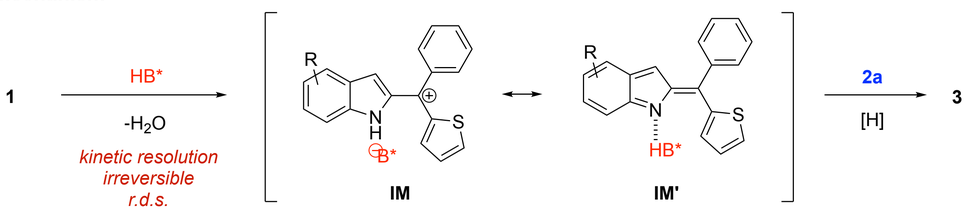


(*R*)-**C1**: R = 3,5-(^{t}Bu)$_2$-4-(OMe)C_6H_2
(*R*)-**C2**: R = 2,4,6-(^{i}Pr)$_3C_6H_2$
(*R*)-**C3**: R = 3,5-$(CF_3)_2C_6H_3$

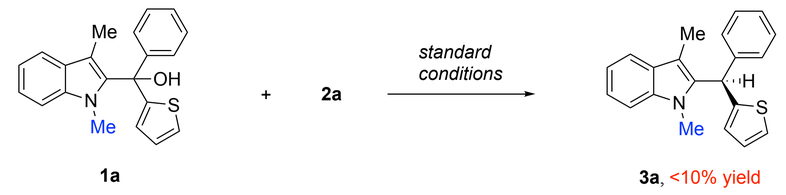
[a] Reaction scale: **1a** (25 μmol), hydride source (27.5 μmol), catalyst (2.5 μmol), solvent (0.5 mL).
[b] Yield was determined by analysis of the ^{1}H NMR spectrum of the crude reaction mixture with CH_2Br_2 as internal standard. Ee was determined by HPLC analysis on a chiral stationary phase.
[c] A mixture of unidentifiable products was formed.
[d] Clean conversion. The starting material accounts for the remainder of the mass balance.
[e] Conversion < 5%.

4. Proposed Mechanism

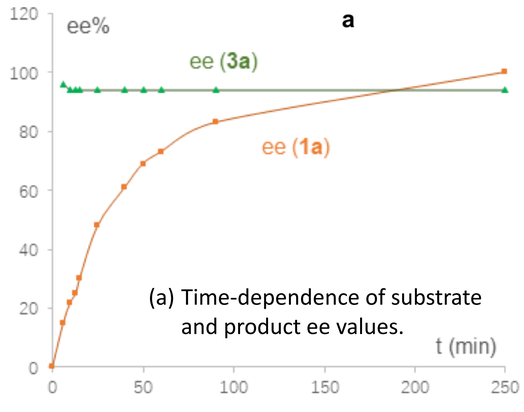
(a) Proposed mechanism

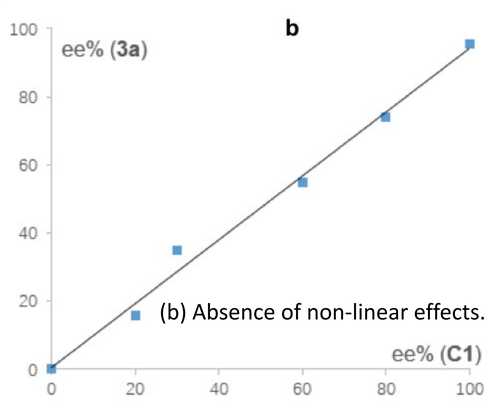


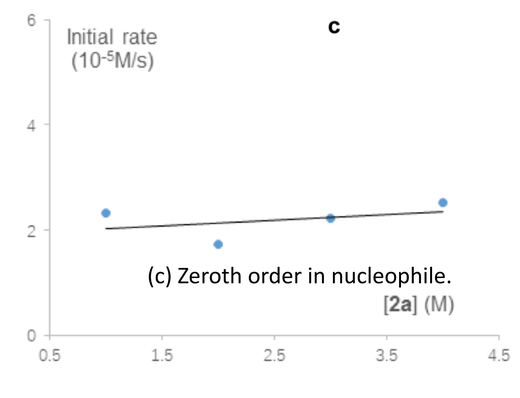
(b) Control experiment

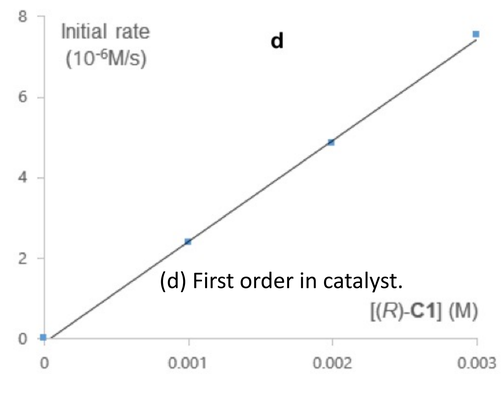


5. Mechanistic Experiments









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