Literature Report II

Asymmetric Hydrogenation of Racemic 2-Substituted Indoles *via* Dynamic Kinetic Resolution: An Easy Access to Chiral Indolines Bearing Vicinal Stereogenic Centers

Reporter: Sai-Nan Yin
Checker: Kai Xue
Date: 2024-04-08

Rong, N.; Zhou, A.; Liang, M.; Wang, S.-G.; Yin, Q.* *J. Am. Chem. Soc.* **2024**, *146,* 5081

CV of Prof. Qin Yin

Background:

- **2005-2009** B.S., Hunan Normal University
- **2009-2014** Ph.D., Shanghai Institute of Organic Chemistry
- **2014-2017** Postdoc., Technische Universität Berlin
- **2017-2021** Associate Professor, Southern University of Science and Technology
- **2021-now** Professor, Shenzhen Institute of Advanced Technology

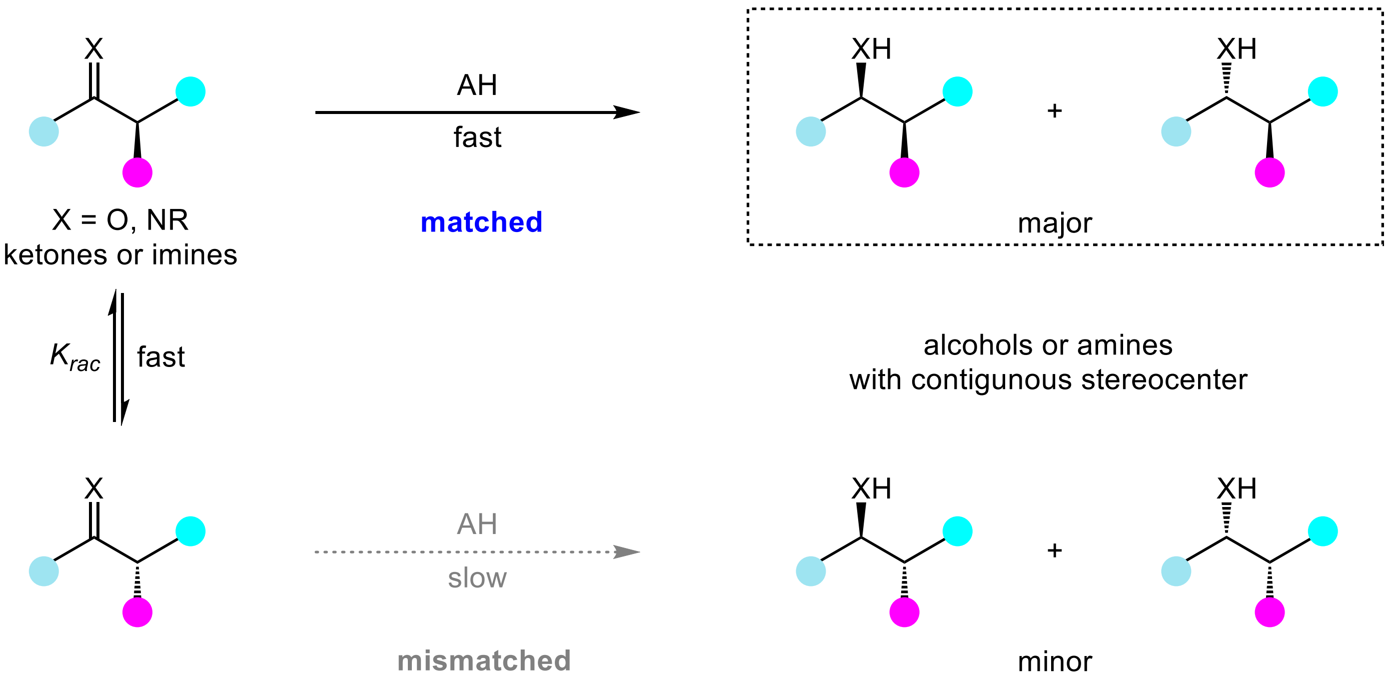
Research:

- **Organic Synthesis Methodology and Total Synthesis**
- **Medicinal Chemistry**
- **Drug Synthesis Process**

Contents

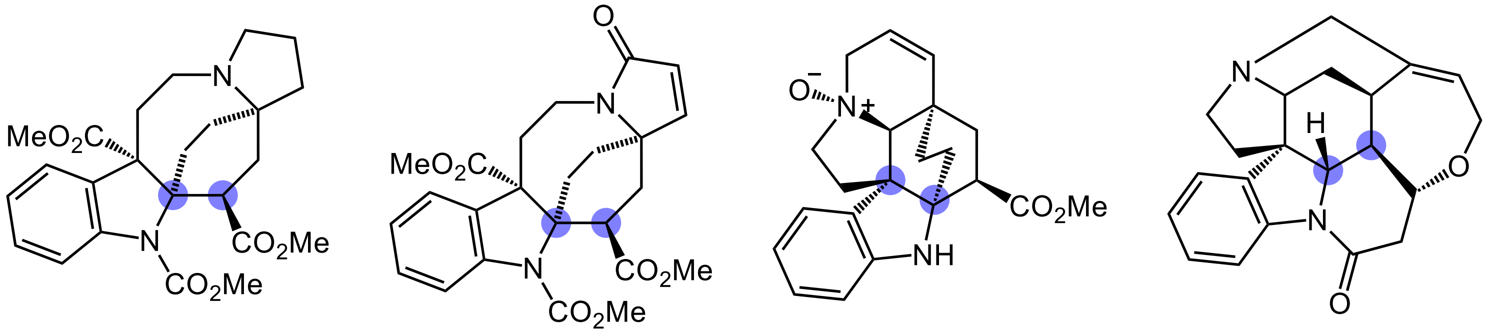
Introduction

DKR via AH (Mainly Limited to Ketones or Imines Bearing a Labile Stereocenter)



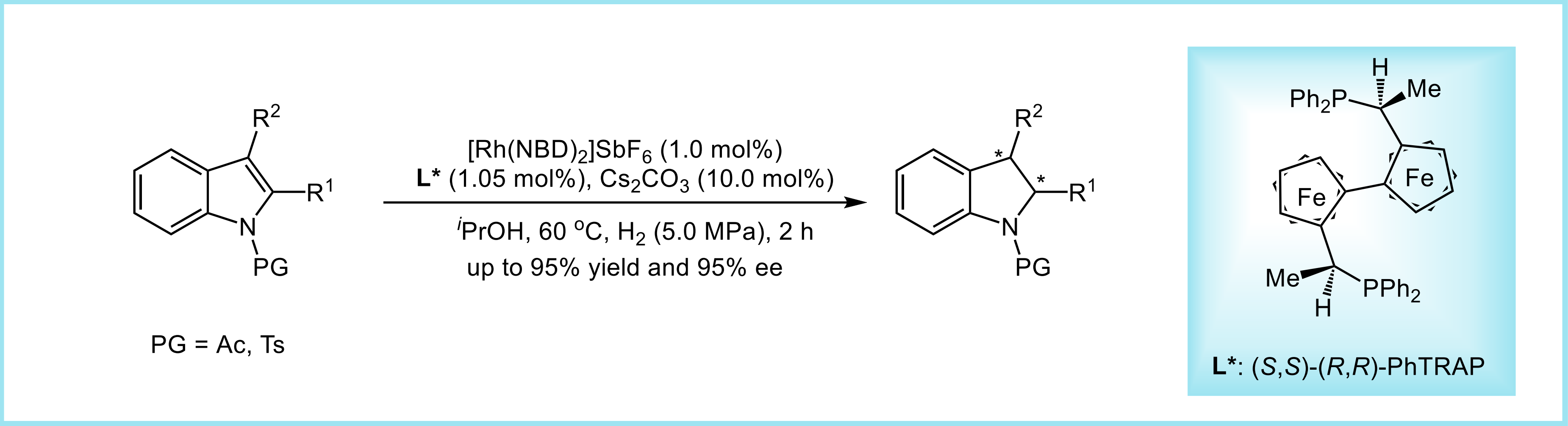
Introduction

Indoline Alkaloids Bearing Vicinal Stereocenters



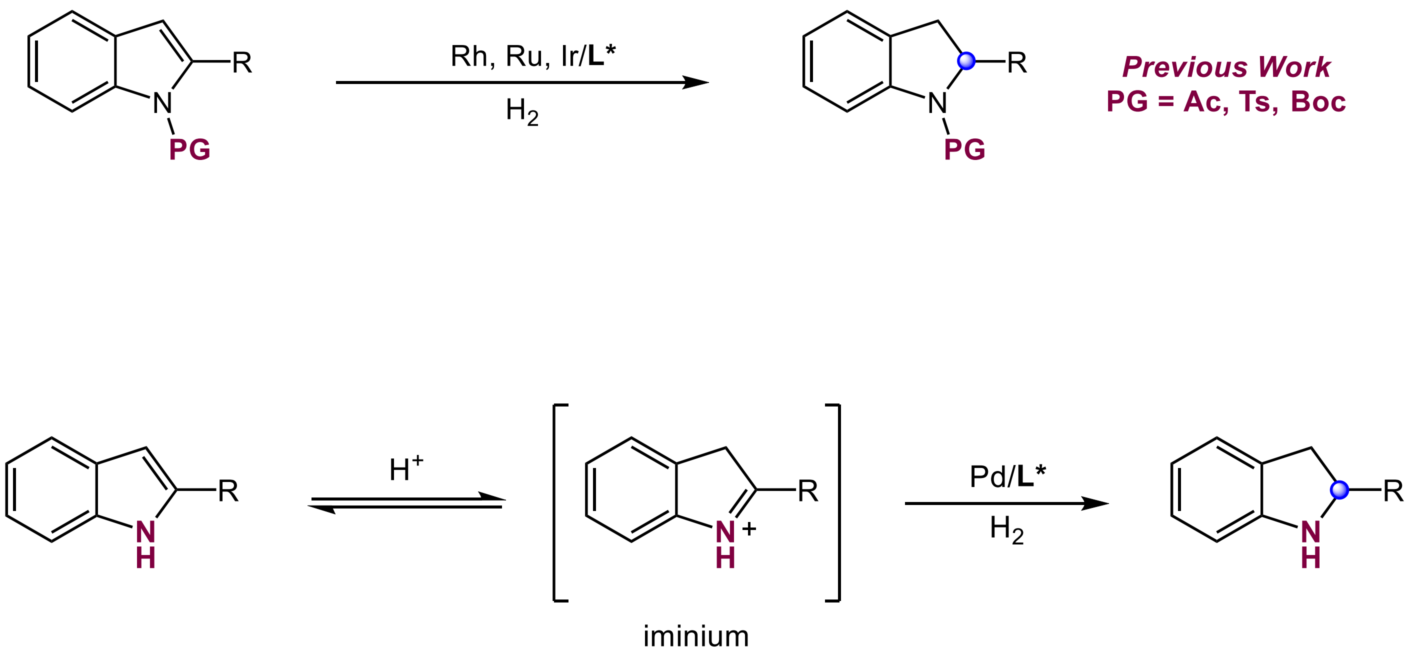
Grandilodine A　　Grandilodine B　　Melodinine L　　Strychine

Introduction

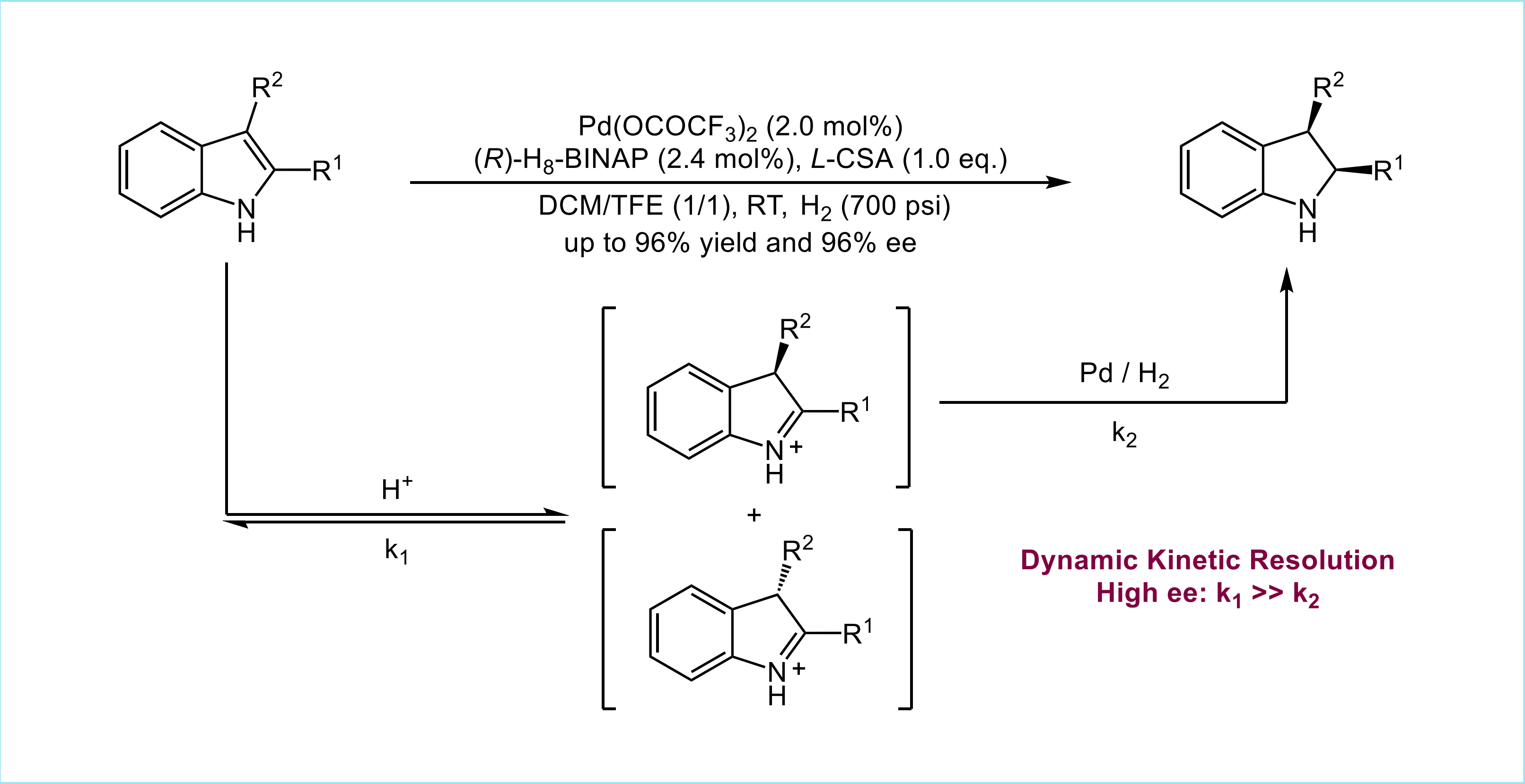


Sato, K.; Kurokawa, T.; Karube, D.; Kuwano, R.; Ito, Y. *J. Am. Chem. Soc.* **2000**, *122*, 7614

Introduction

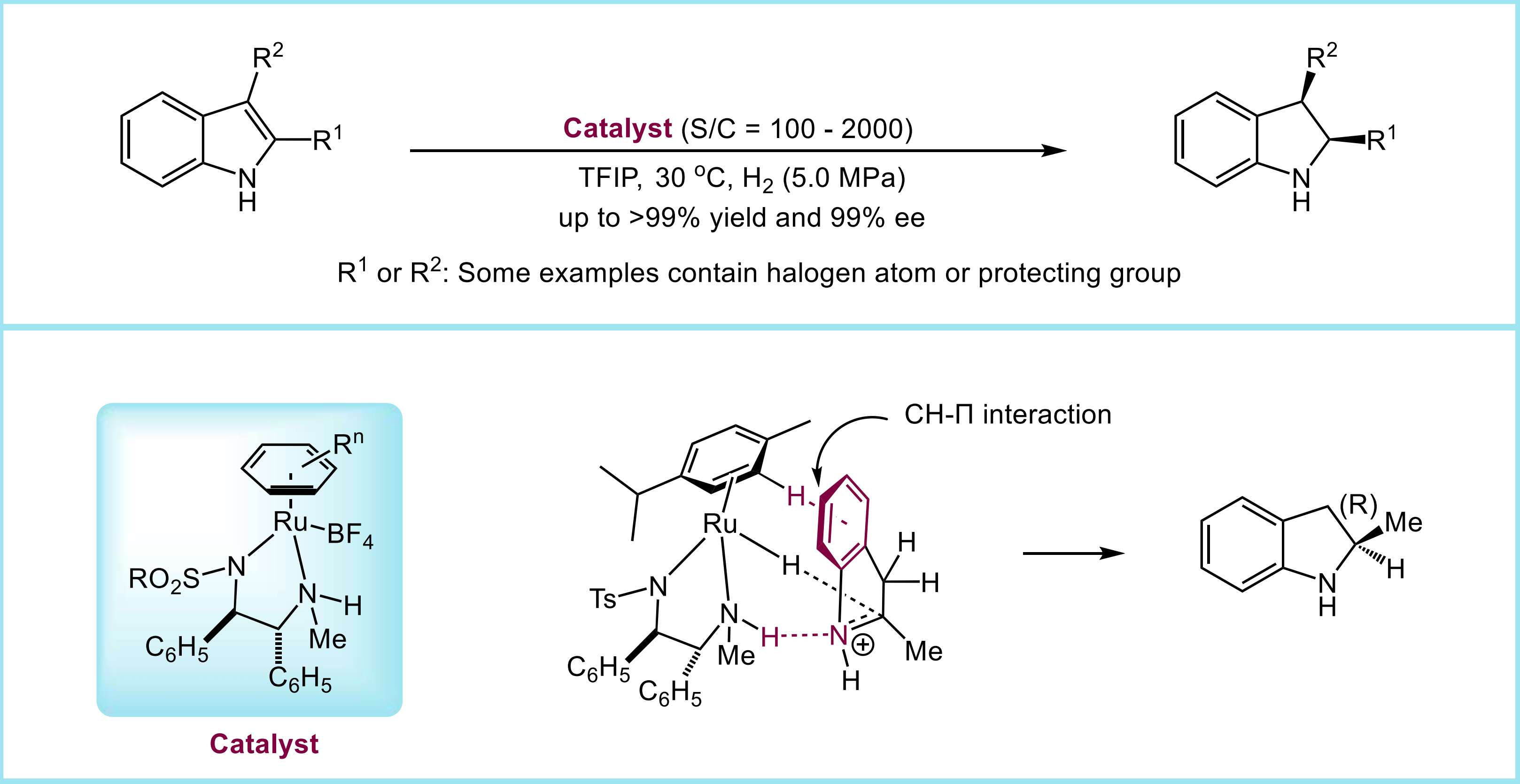


Introduction



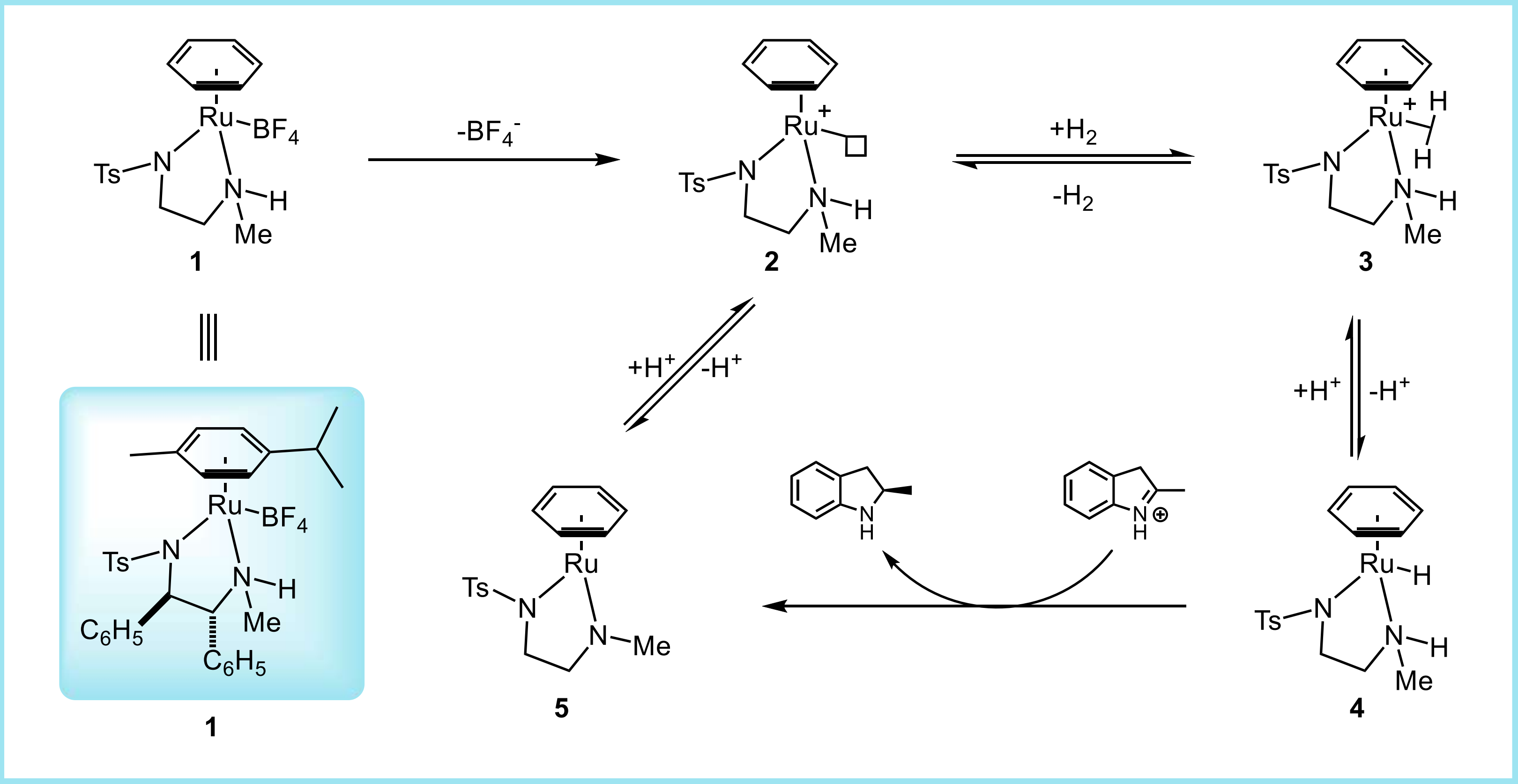
Wang, D.-S.; Chen, Q.-A.; Li, W.; Yu, C.-B.; Zhou, Y.-G.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 8909

Introduction



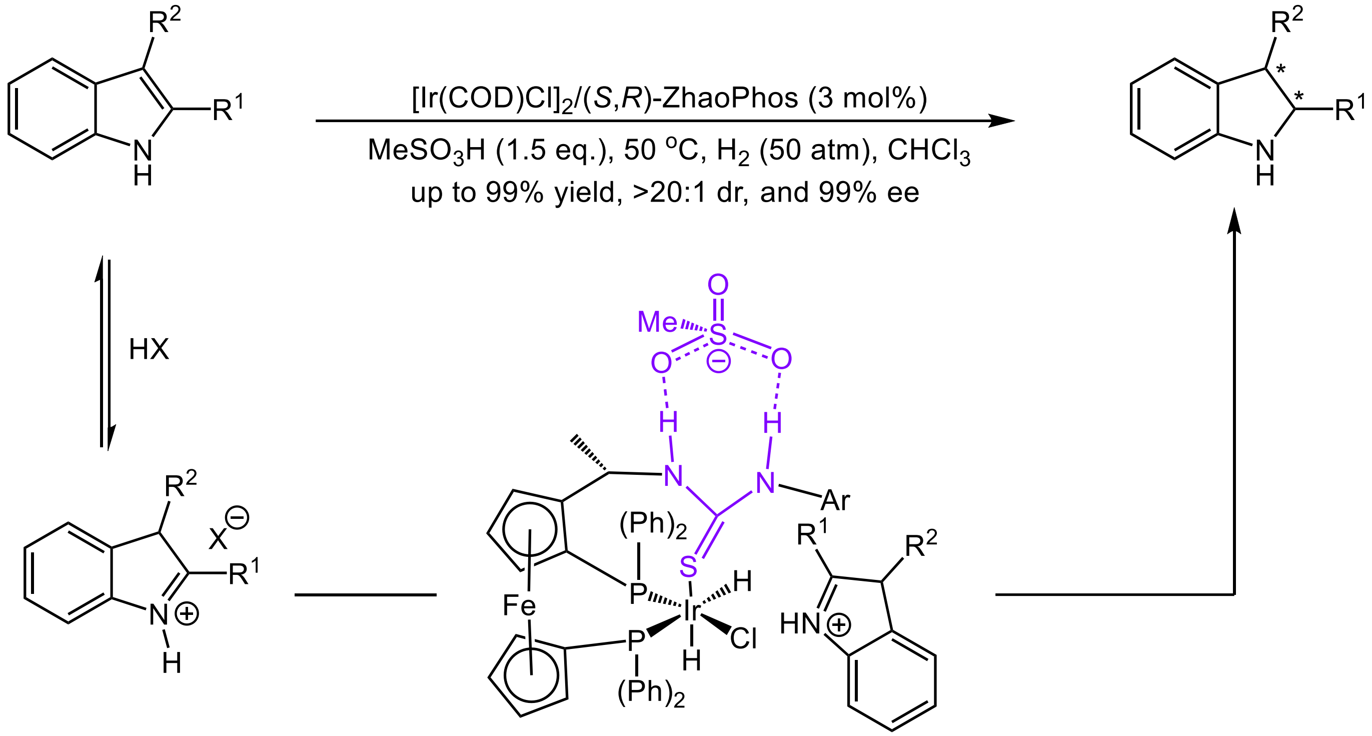
Touge, T.; Arai, T. *J. Am. Chem. Soc.* **2016**, *138*, 11299

Introduction



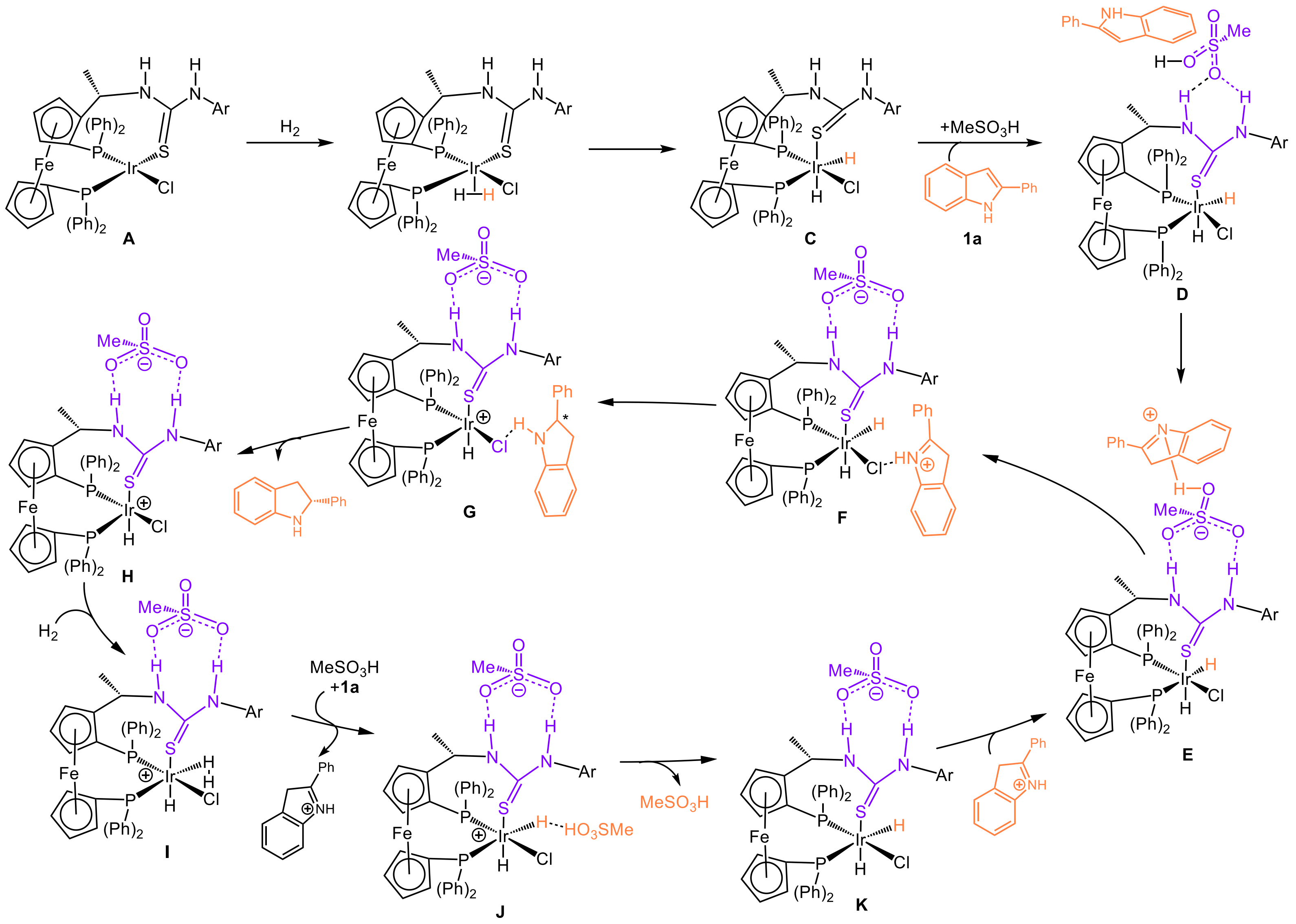
Touge, T.; Arai, T. *J. Am. Chem. Soc.* **2016**, *138*, 11299

Introduction

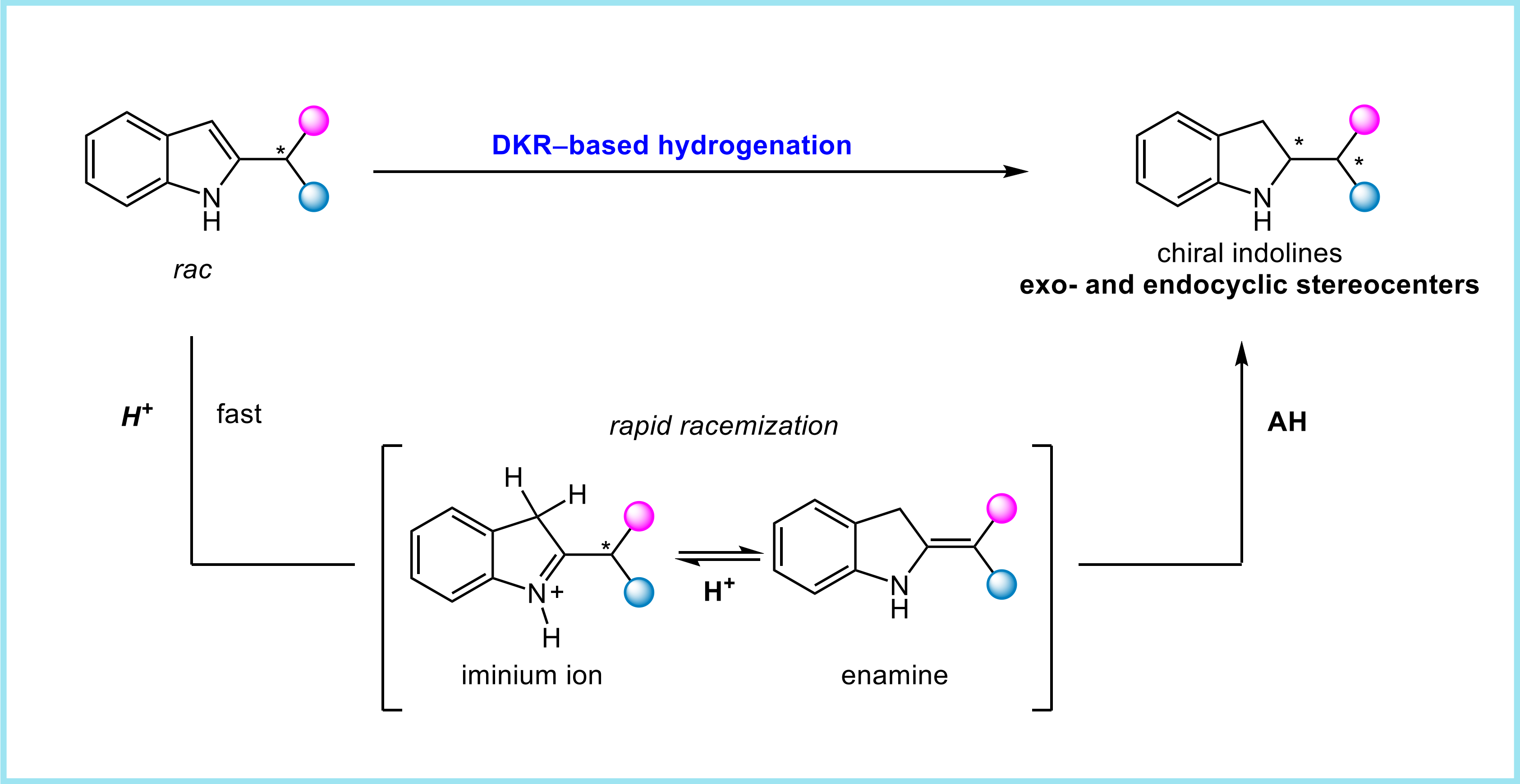


Liu, G.; Zheng, L.; Tian, K.; Wang, H.; Chung, L.; Zhang, X.; Dong, X.-Q. *CCS Chem.* **2023**, *5*, 1398

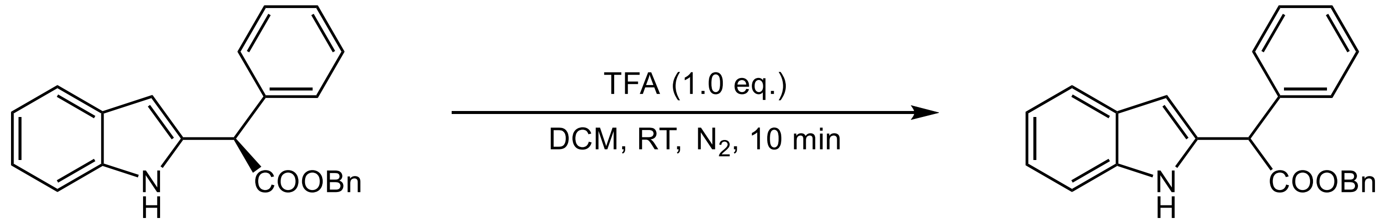
Introduction



Project Synopsis



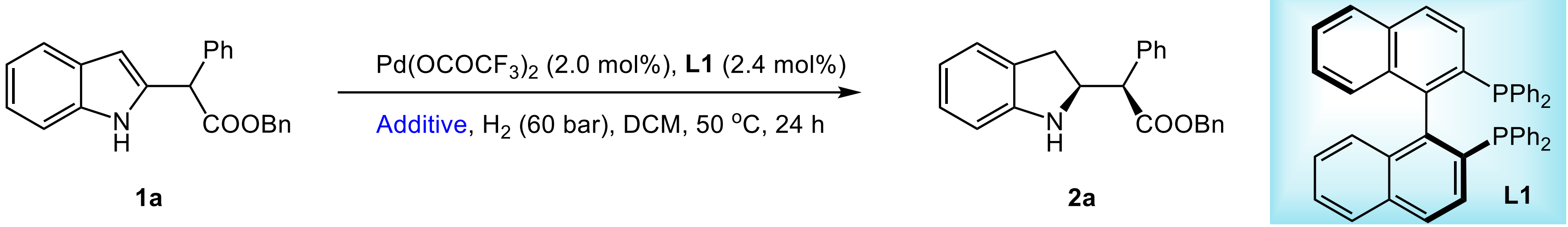
The Racemization Experiment of 1a



R-**1a**, > 99% ee

rac-**1a**

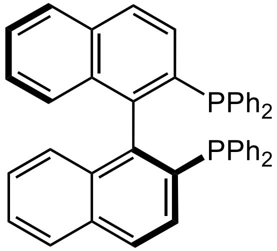
Condition Optimization-Additive Screening



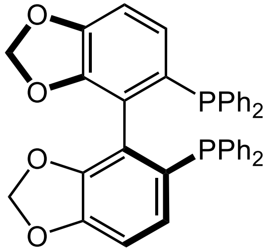
Entry[a]	ligand	Additive (eq.)	Conv. (%)	yield (%)[b]	dr	ee (%)
1	**L1**	HOAc (1.0)	<5	-	-	-
2	**L1**	TsOH (1.0)	87	86	8:1	45
3	**L1**	HCl (1.0)	>99	-	-	-
4	**L1**	TfOH (1.0)	>99	-	-	-
5	**L1**	H_2SO_4 (1.0)	70	-	-	-
6	**L1**	TFA (1.0)	60	58	>20:1	81
7	**L1**	TFA (2.0)	78	60	>20:1	85
8	**L1**	**TFA (6.0)**	**95**	**81**	**>20:1**	**89**
9	**L1**	TFA (10.0)	98	76	>20:1	89

[a]Reaction conditions: **1a** (0.1 mmol), $Pd(CF_3CO_2)_2$ (2 mol %), **L** (2.4 mol %), acid, 1.0 mL of DCM, 50 °C, 24 h. [b]Isolated yield. Diastereomeric ratios (dr) and enantiomeric excesses (ee) were determined by HPLC analysis using a chiral stationary phase.

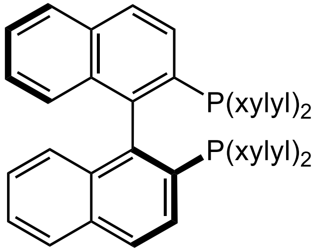
Condition Optimization-Other Ligands Screening



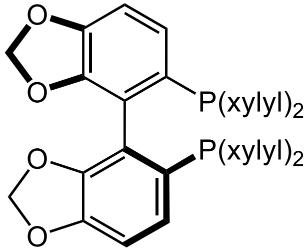
L1
95% conv., 81% yield
>20:1 dr, 89% ee



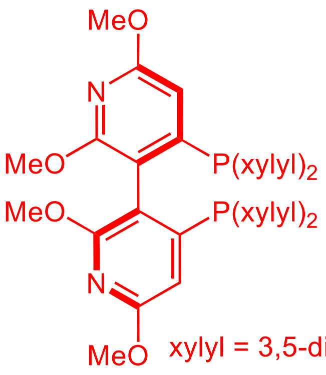
L2
84% conv., 70% yield
7:1 dr, 47% ee



L3
90% conv., 81% yield
>20:1 dr, 89% ee

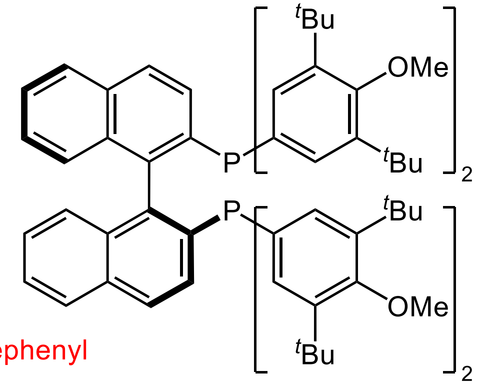


L4
98% conv., 85% yield
>20:1 dr, 89% ee

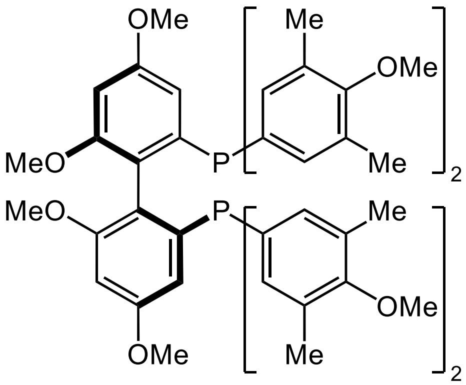


xylyl = 3,5-diMephenyl

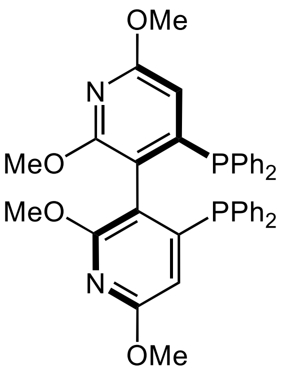
L5
98% conv., 82% yield
>20:1 dr, 91% ee



L6
65% conv., 46% yield
>20:1 dr, 62% ee

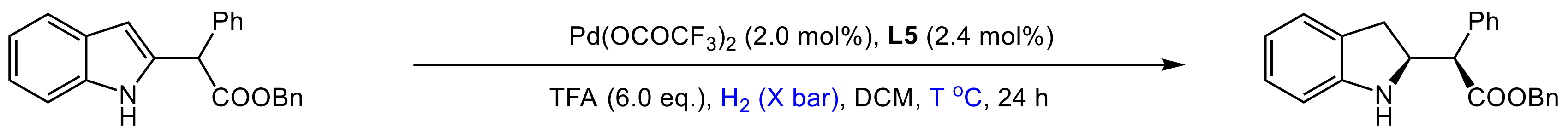


L7
58% conv., 42% yield
6:1 dr, 5% ee



L8
79% conv., 77% yield
>20:1 dr, 84% ee

Condition Optimization-Temperature and Pressure



1a   2a

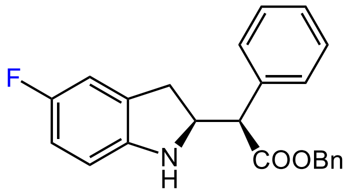
Entry[a]	T (°C)	H_2 (bar)	Conv. (%)	yield (%)[b]	dr	ee (%)
1	50	60	98	82	>20:1	91
2	rt	60	98	89	>20:1	94
3	rt	40	95	86	>20:1	94

[a]Reaction conditions: **1a** (0.1 mmol), $Pd(CF_3CO_2)_2$ (2 mol %), **L** (2.4 mol %), acid, 1.0 mL of DCM, 50 °C, 24 h. [b]rt. [c]H_2 (40 bar). [b]Isolated yield. Diastereomeric radios (dr) and enantiomeric excesses (ee) were determined by HPLC analysis using a chiral stationary phase.

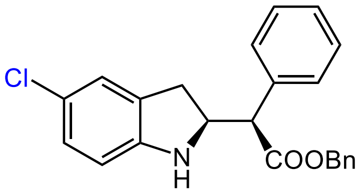
Optimal conditions: $Pd(CF_3CO_2)_2$/$\mathbf{L_5}$ as the catalyst, TFA (6.0 equiv) as the additive, DCM as the solvent, and 60 bar of H_2 at rt

Substrate Scope of 2- Substituted Indoles

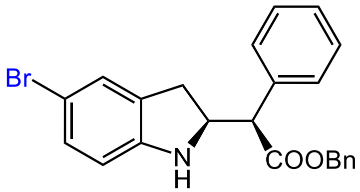
Scope of the Indole Side



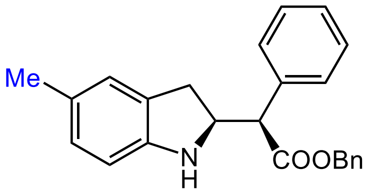
2b, 88% yield
dr > 20:1, 93% ee



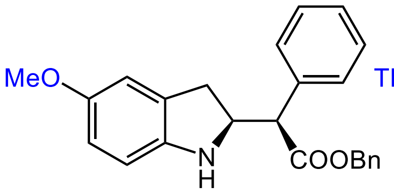
2c, 89% yield
dr > 20:1, 89% ee



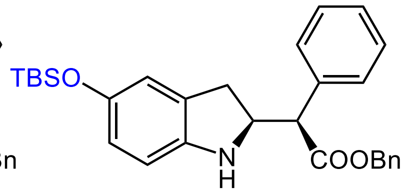
2d, 90% yield
dr > 20:1, 86% ee



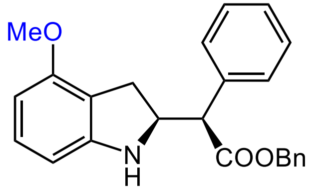
2e, 89% yield
dr > 20:1, 90% ee



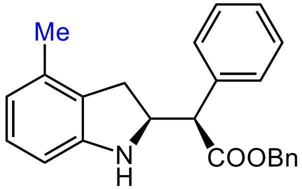
2f, 90% yield
dr > 20:1, 92% ee



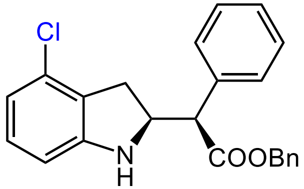
2g, 88% yield
dr > 20:1, 91% ee



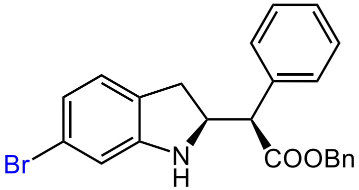
2h, 91% yield
dr > 20:1, 88% ee



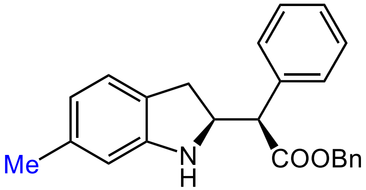
2i, 94% yield
dr > 20:1, > 99% ee



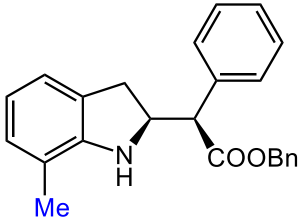
2j, 90% yield
dr > 20:1, 93% ee



2k, 92% yield
dr > 20:1, 87% ee



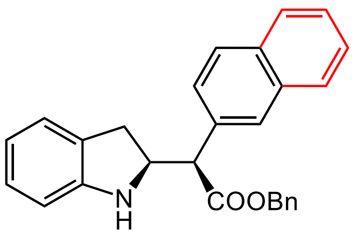
2l, 89% yield
dr > 20:1, 94% ee



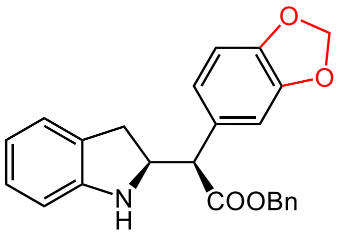
2m, 89% yield
dr > 20:1, 94% ee

Substrate Scope of 2- Substituted Indoles

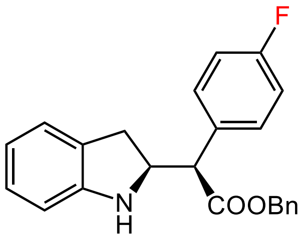
Scope of the Aryl Group



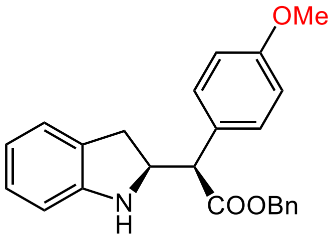
2n, 89% yield
dr > 20:1, 98% ee



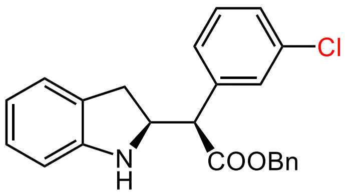
2o, 89% yield
dr > 20:1, 94% ee



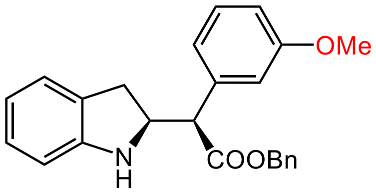
2p, 90% yield
dr > 20:1, 94% ee



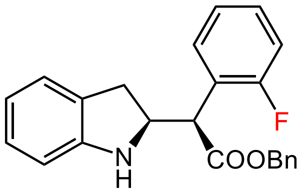
2q, 90% yield
dr > 20:1, 94% ee



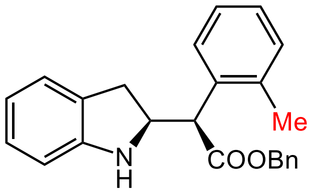
2r, 90% yield
dr > 20:1, 94% ee



2s, 91% yield
dr > 20:1, 94% ee

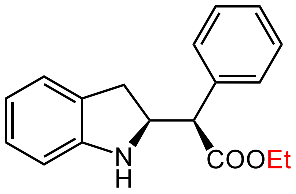


2t, 90% yield
dr = 9:1, 88% ee

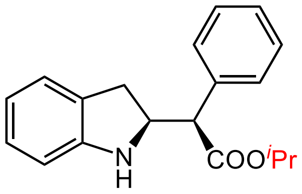


2u, 91% yield
dr > 20:1, 76% ee

Scope of the ester group



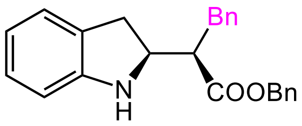
2v, 89% yield
dr > 20:1, 93% ee



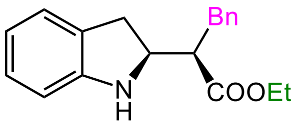
2w, 90% yield
dr > 20:1, 94% ee

Substrate Scope of 2- Substituted Indoles

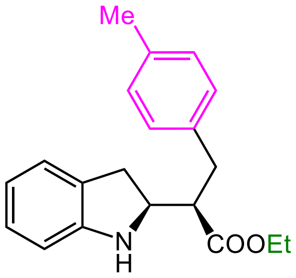
Scope of the Alkyl Group



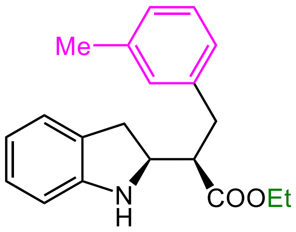
2x, 89% yield
dr > 13:1, 96% ee



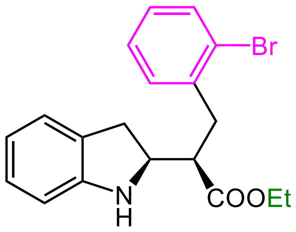
2y, 91% yield
dr > 20:1, 98% ee



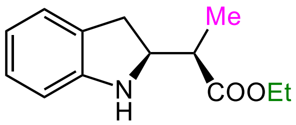
2z, 90% yield
dr > 20:1, 94% ee



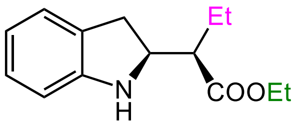
2aa, 91% yield
dr > 20:1, 94% ee



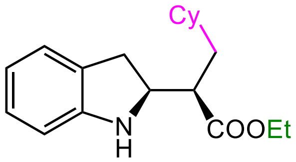
2ab, 91% yield
dr > 20:1, 92% ee



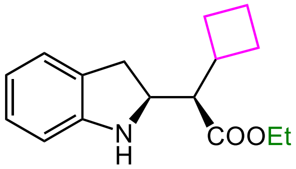
2ac, 89% yield
dr > 20:1, 86% ee



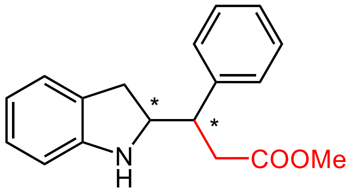
2ad, 89% yield
dr > 20:1, 89% ee



[b]**2ae**, 89% yield
dr > 20:1, 92% ee



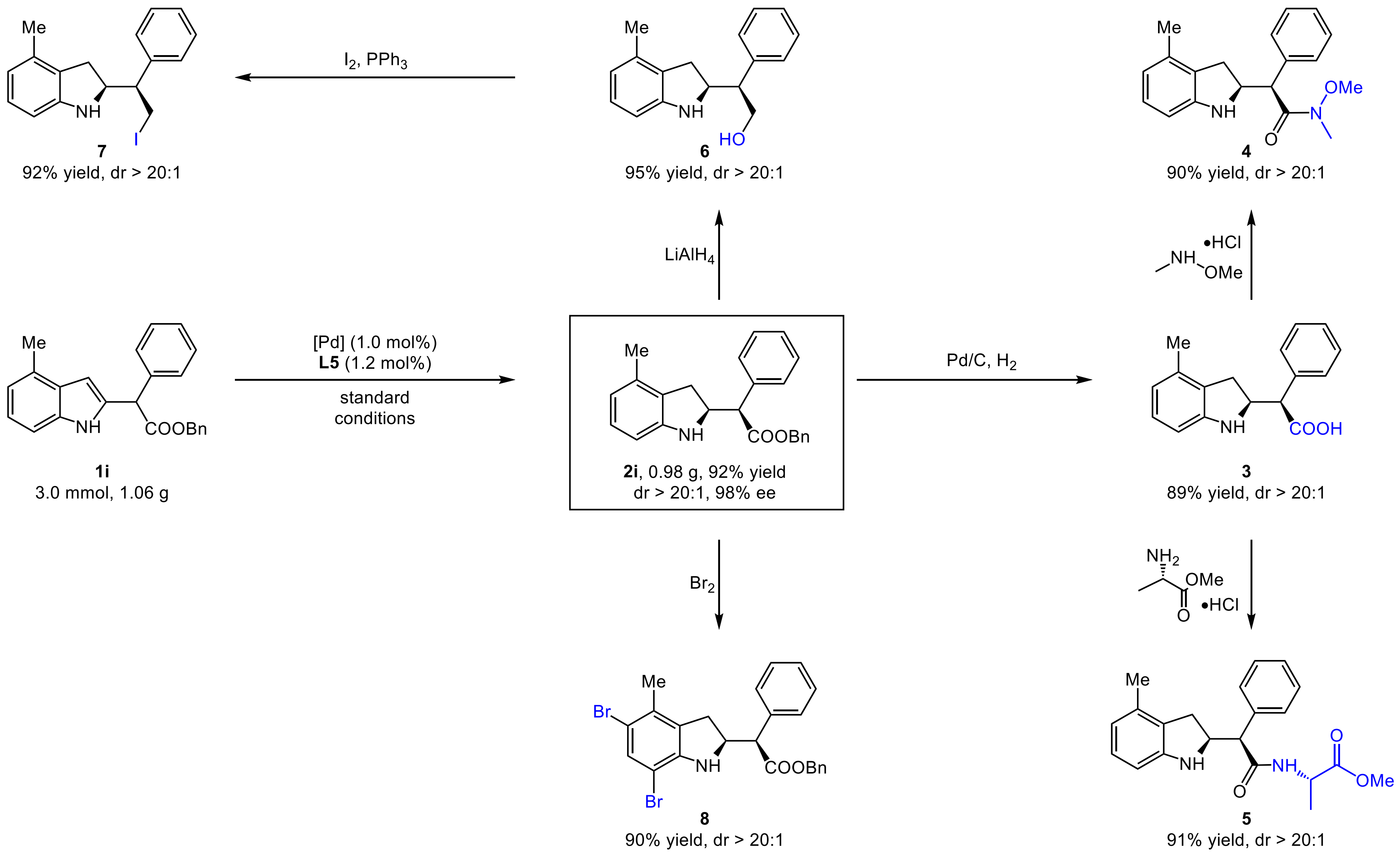
2af, 91% yield
dr > 20:1, 90% ee



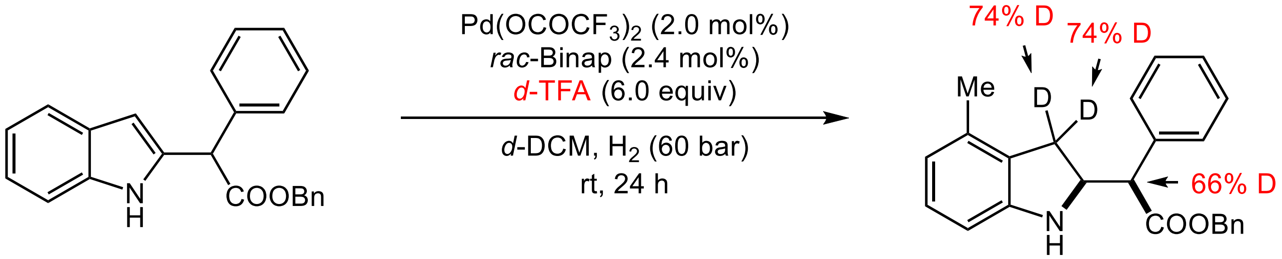
[c]**2ag**, 89% yield
dr > 20:1, > 91% ee

[b]48 h. [c]with (*S*)-H8-Binap.

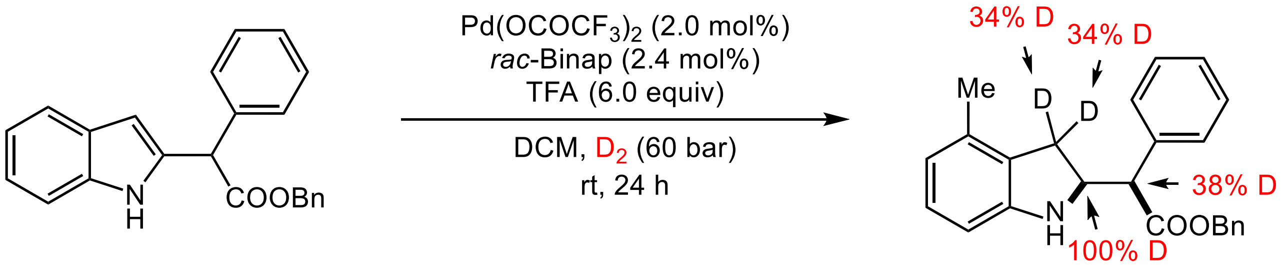
Scale-up Reaction and Synthetic Transformations



Mechanistic Studies: Isotope Labeling Reaction

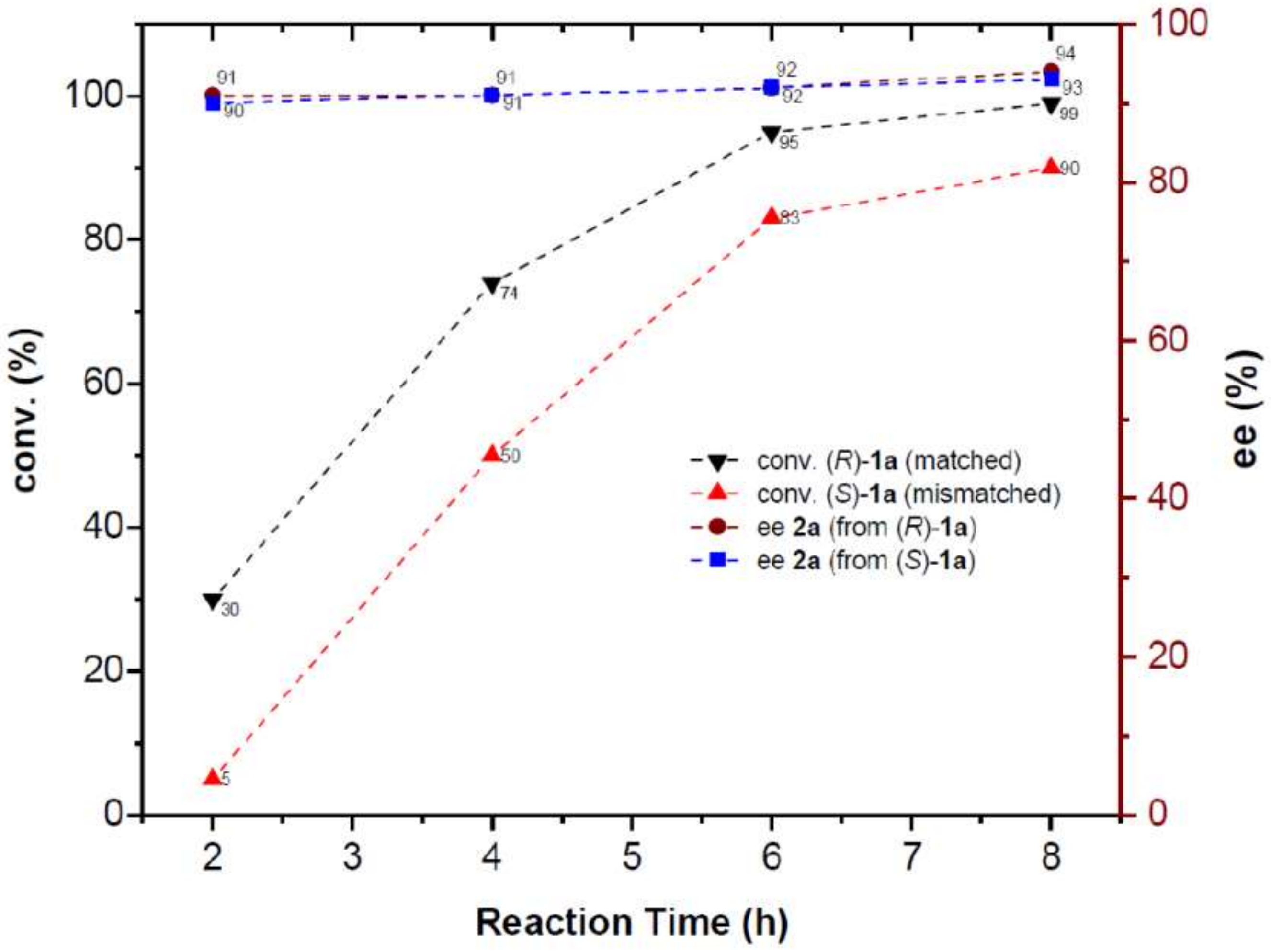


1a full conv. *rac*-**2a** dr > 20:1

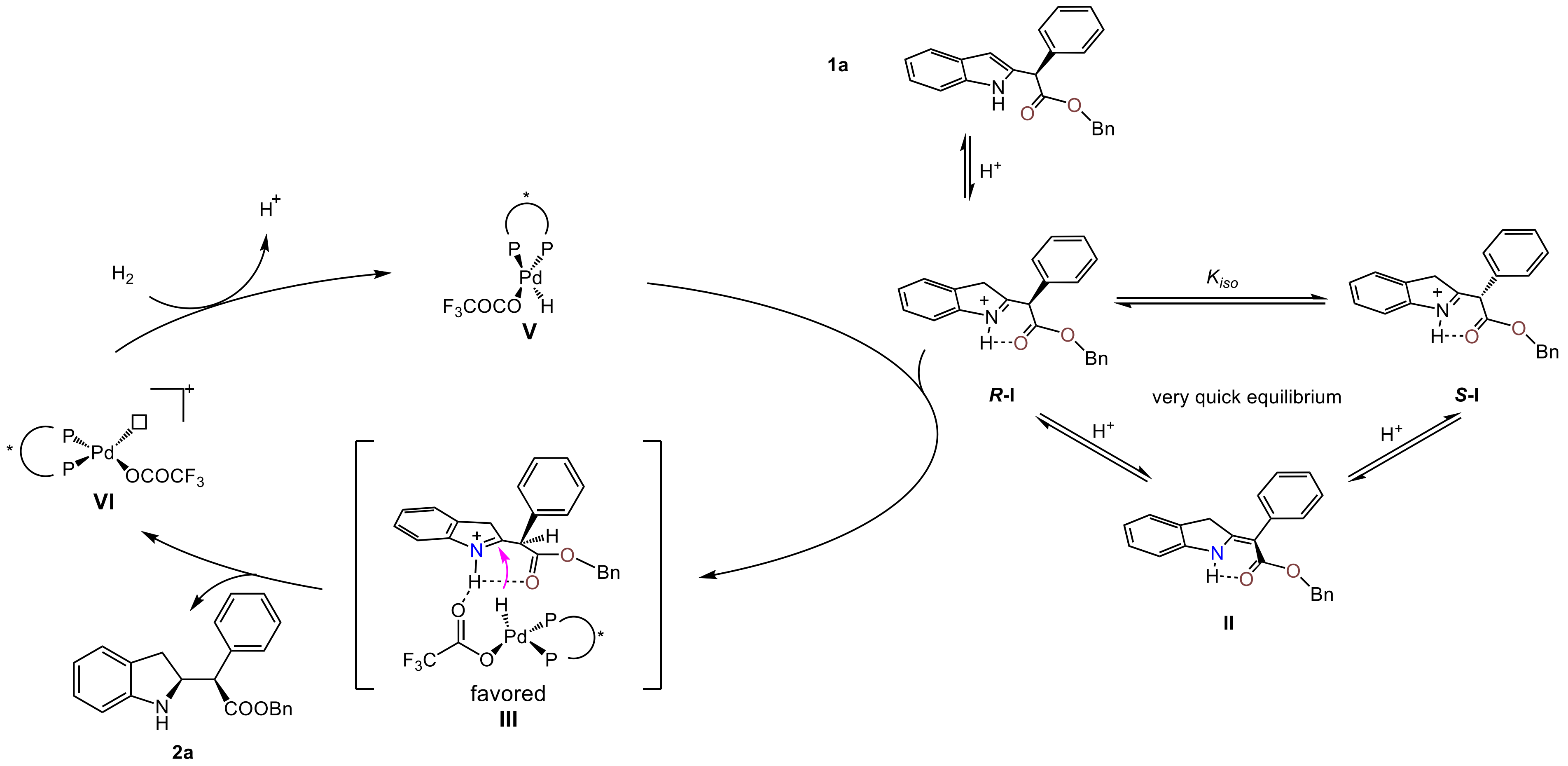


1a full conv. *rac*-**2a** dr > 20:1

Mechanistic Studies: Profile of Enantiopure 1a

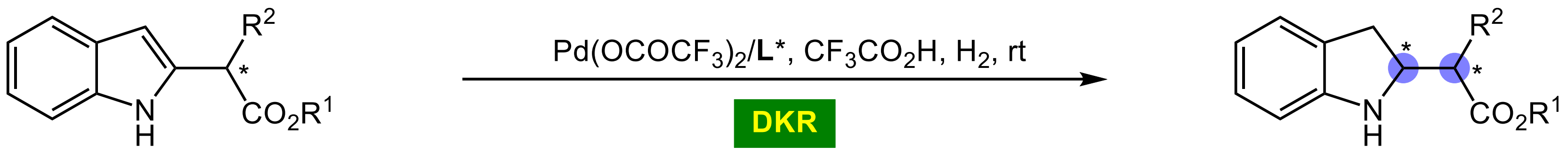


Plausible Mechanism and Stereoinduction Model



Summary

AH of racemic indoles via DKR



rac

β-amino esters

up to 99% ee and >20:1 dr

- *a unique DKR mode via AH of indoles*
- *exocyclic/vicinal stereocenters*
- *broad scope with over 30 examples*
- *gram scale and synthetic applications*

Strategy for Writing The First Paragraph

DKR在构建具有多个立体中心的手性分子方面具有很大的潜力

DKR, which converts both enantiomers of a racemic substrate into a single enantiopure product, has become a desirable method in asymmetric synthesis.. Hence, DKR has found great potential in constructing chiral molecules with multiple stereogenic centers.

↓

基于DKR的AH是合成手性醇/胺的重要手段

AH has been broadly studied and established as an important means to synthesize chiral alcohols or amines with contiguous stereocenters.

↓

其他类型的底物需要被探索，因此引出本文工作

However, this useful method is mainly limited to enolizable ketones or activated imines, while other types of substrates are rarely explored and thus highly desirable.

Strategy for Writing The Last Paragraph

总结工作

In summary, we have disclosed a Pd-catalyzed DKR-based hydrogenation of racemic α-alkyl or aryl-substituted indole-2-acetates with excellent yields, enantioselectivities and diastereoselectivities.

↓

提出展望

We hope our discovery will open a new window for further expanding the chiral N-heterocycle libraries by using this novel DKR model.

Representative Examples

- We chose … as the model substrate since it could be one-step synthesized from commercially available … via … (解释选择模板底物的原因：可由商业可得的原料一步得到)

- To probe the mechanistic information, isotopic labeling experiments were carried out. (carry out 执行；开展；完成，可代替 take、perform、conduct)

Acknowledgement

Thanks for your attention