Literature Report V

Construction of Chiral Tetrahydro-*β*-Carbolines: Asymmetric Pictet–Spengler Reaction of Indolyl Dihydropyridines

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Checker：Xin-Wei Wang

Date：2018-04-02

You, S.-L. *et al*. *Angew. Chem. Int. Ed.* **2017**, *56*, 7440.
You, S.-L. *et al. Angew. Chem. Int. Ed.* **2018**, *57*, 2653.

Contents

CV of Shu-Li You

Education:

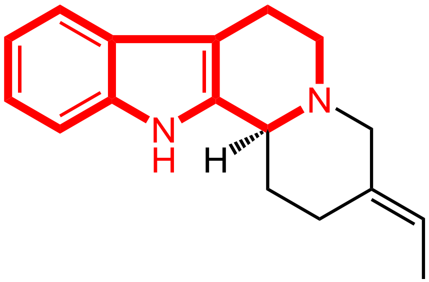
- **1992–1996** B.S., Nankai University
- **1996–2001** Ph.D., SIOC (Prof. Li-Xin Dai)
- **2001–2004** Postdoc., The Scripps Research Institute (Prof. Jeffery W. Kelly)
- **2004–2006** Principal Investigator, Genomics Institute of the Novartis Research Foundation, San Diego
- **2006–Present** Professor, SIOC

Research:

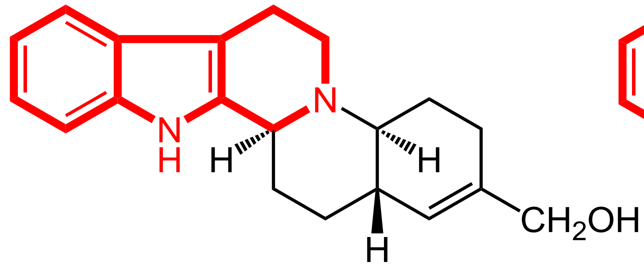
★ Enantioselective C-H bond direct functionalization processes

★ Catalytic asymmetric dearomatization reactions

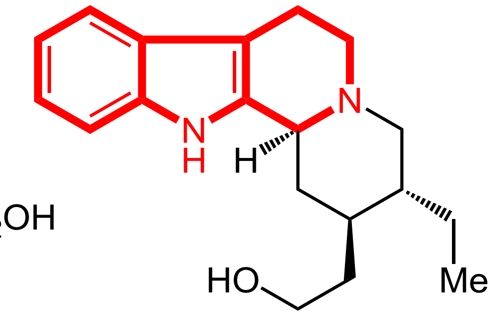
Introduction



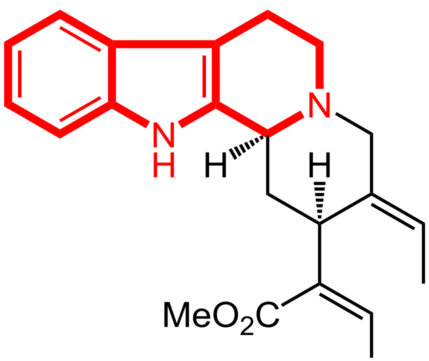
Deplancheine



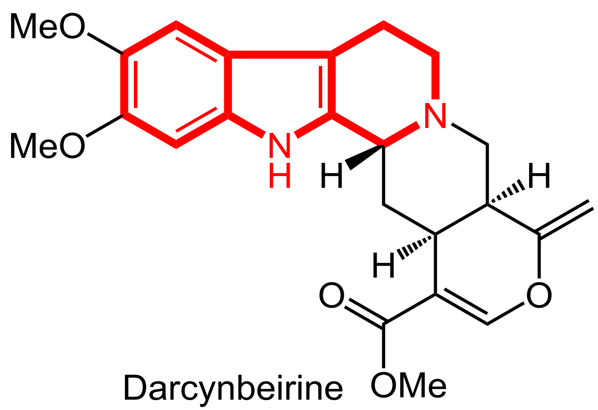
Tangutorine



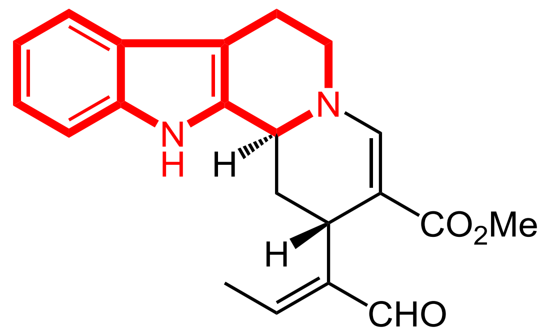
Dihydrocorynantheol



Geissochizine



Darcynbeirine

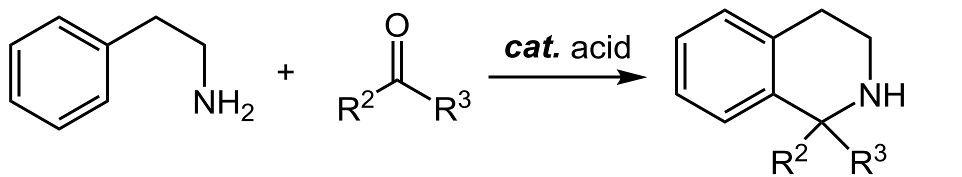


Vallesiachotamine

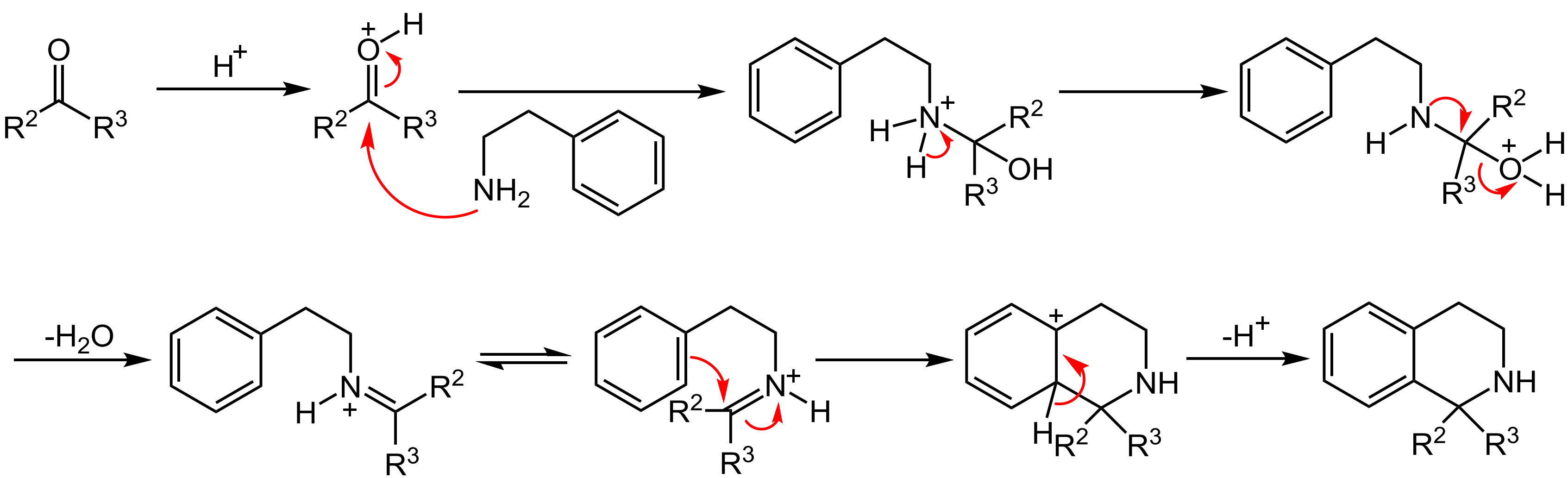
Higuchi. K. *et al*. *Nat. Prod. Rep.* **2005**, *22*, 761.
Yamada. F. *et al. Nat. Prod. Rep.* **2004**, *21*, 278.

Pictet-Spengler reaction

The Pictet-Spengler reaction is an organic reaction used to convert a β-arylenylamine and an aldehyde or ketone to a tetrahydroisoquinoline using an acid catalyst.

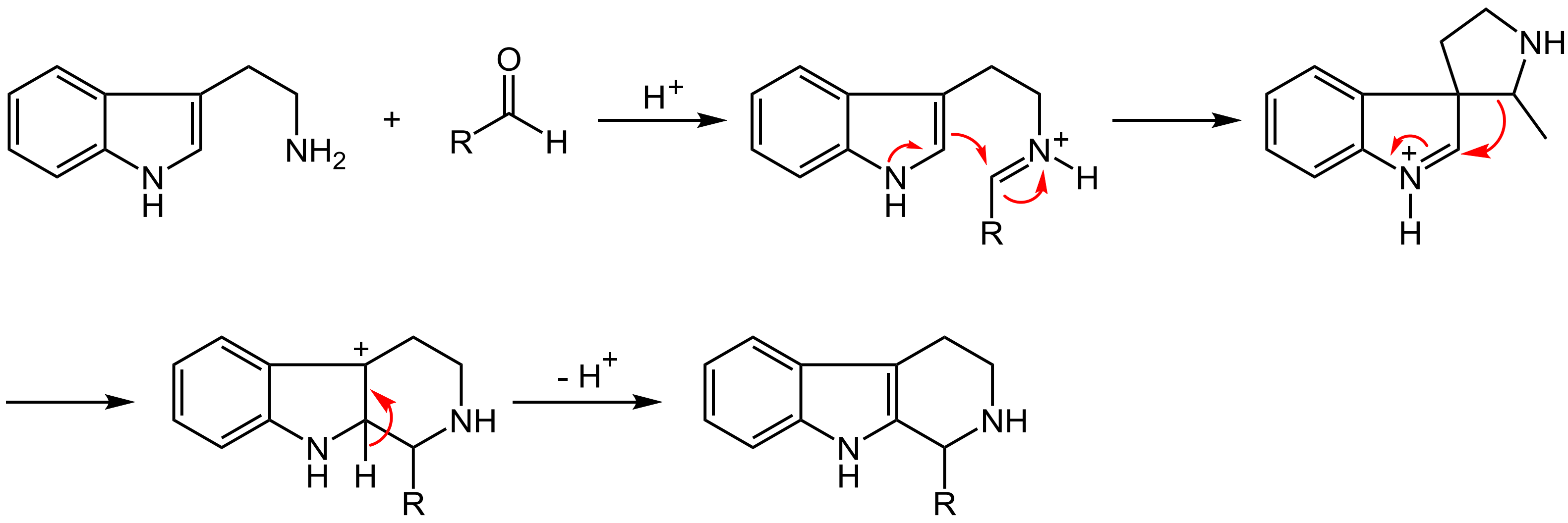


β-arylethylamine aldehyde or ketone tetrahydroisoquinoline



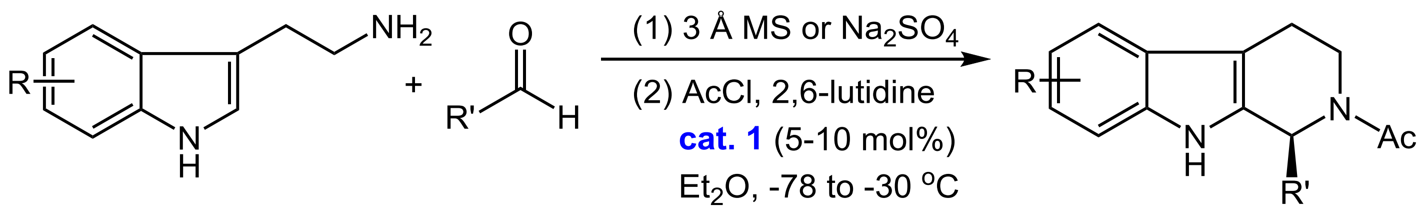
Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030.

Pictet-Spengler reaction-Second Mechanism



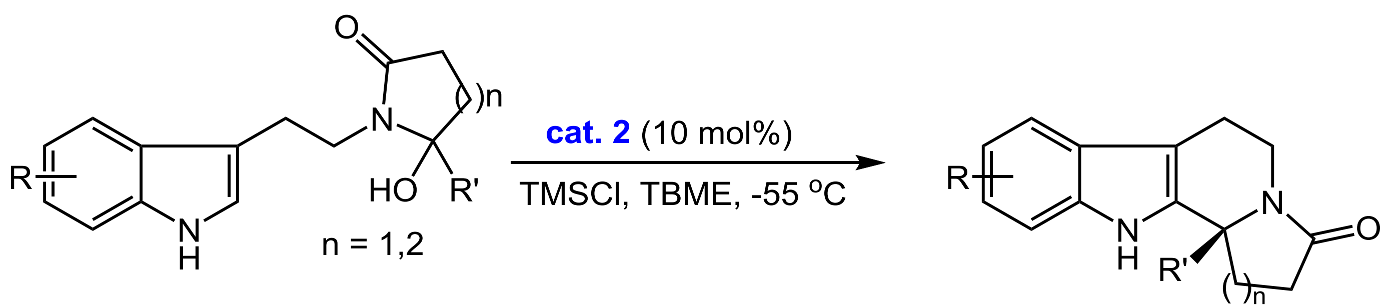
From Wikipedia

Thiourea derivatives catalyzed asymmetric PS reactions



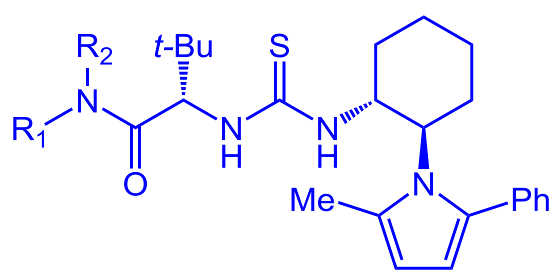
65-81% yield, 86-95% *ee*

Jacobsen, E. N. *et al. J. Am. Chem. Soc*. **2004**, *126*, 10558.



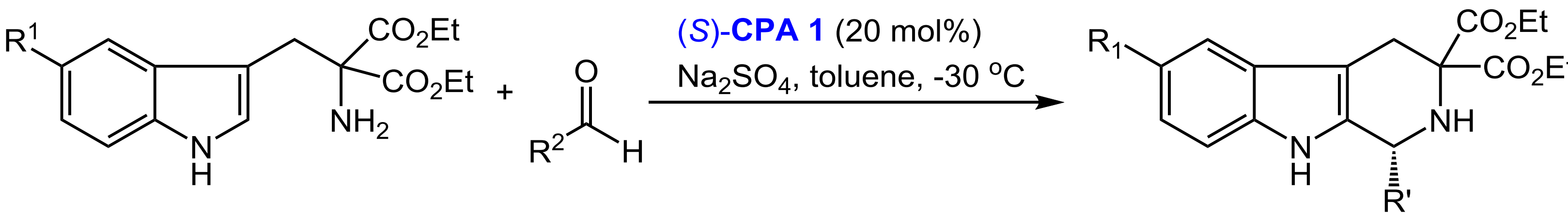
51-94% yield, 85-99% *ee*

Jacobsen, E. N. *et al. J. Am. Chem. Soc.* **2007**, *129*, 13404.



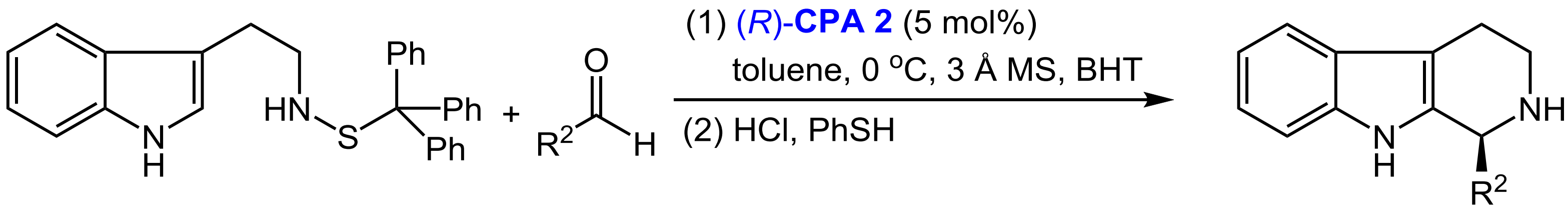
cat. 1: $R_1 = R_2 =$ *i*-Bu
cat. 2: $R_1 = CH_3$, $R_2 =$ *n*-C_5H_{11}

CPA catalyzed asymmetric PS reactions



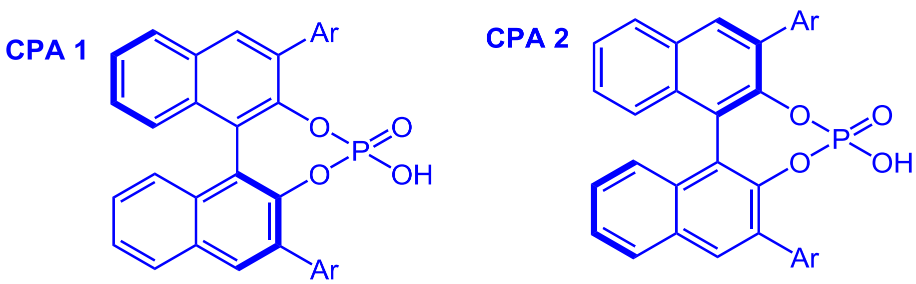
40-98% yield, 62-96% *ee*

List, B. *et al*. *J. Am. Chem. Soc.* **2006**, *128*, 1086.



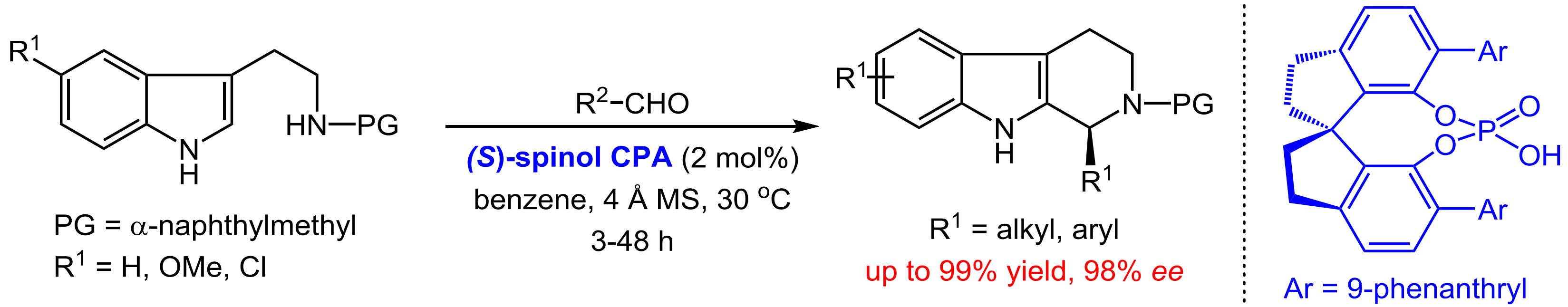
77-90% yield, up to 87% *ee*

Hiemstra, H. *et al*. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485.

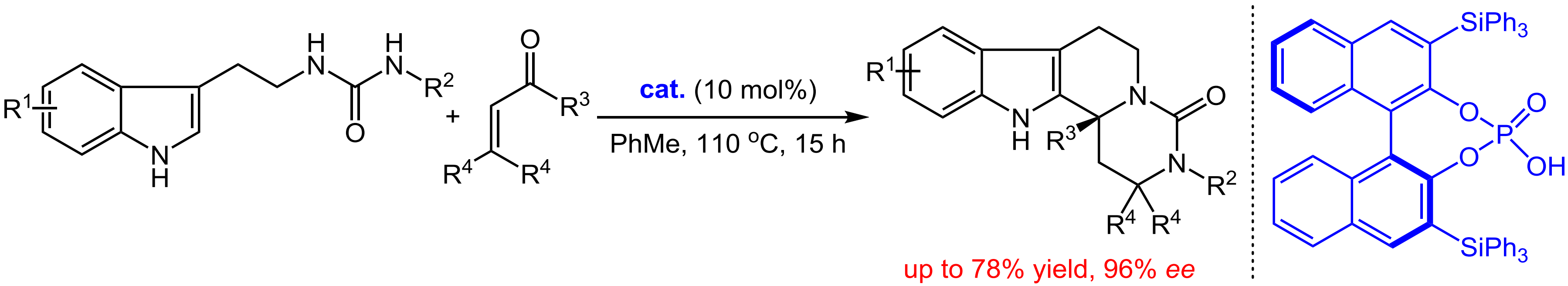


Ar^1 = 2,4,6-(^{i}Pr)$_3C_6H_2$ Ar^2 = 3,5-(CF_3)$_2C_6H_3$

CPA catalyzed asymmetric PS reactions

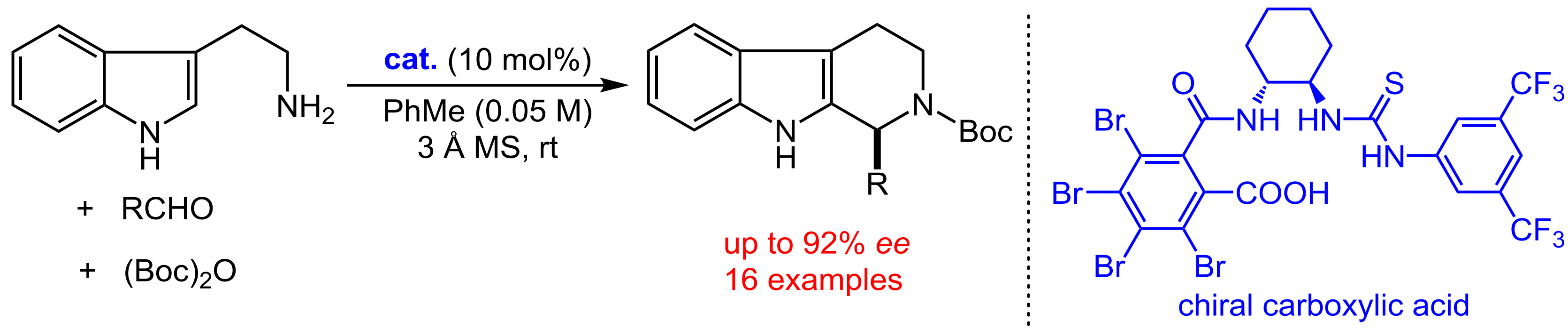


Wang, Y. *et al. Chem. Eur. J.* **2012**, *18*, 3148.

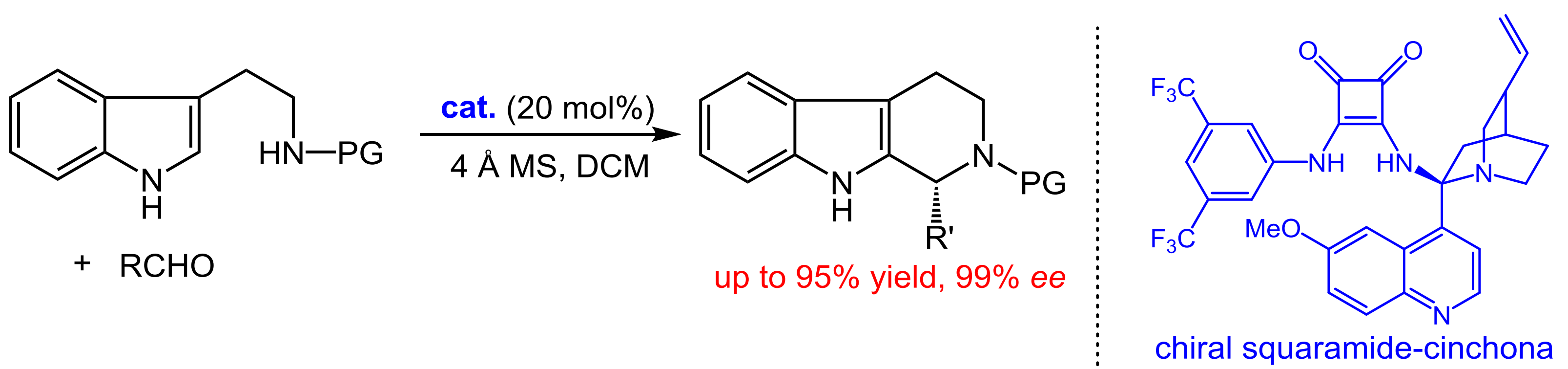


Dixon, D. J. *et al. Org. Lett.* **2013**, *15*, 2946.

Chiral Carboxylic Acids and Squaramide-Cinchona

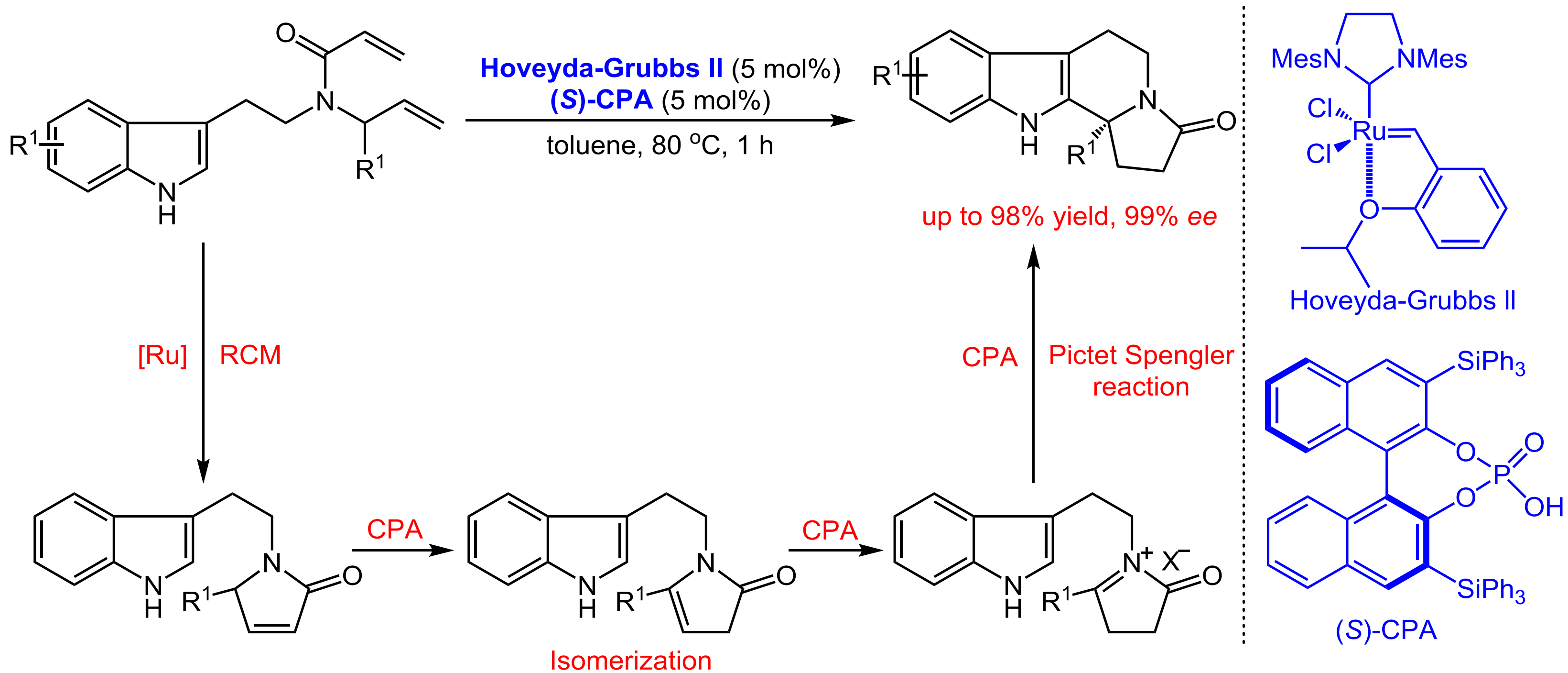


Seidel, D. *et al. Org. Lett.* **2014**, *16*, 1012.



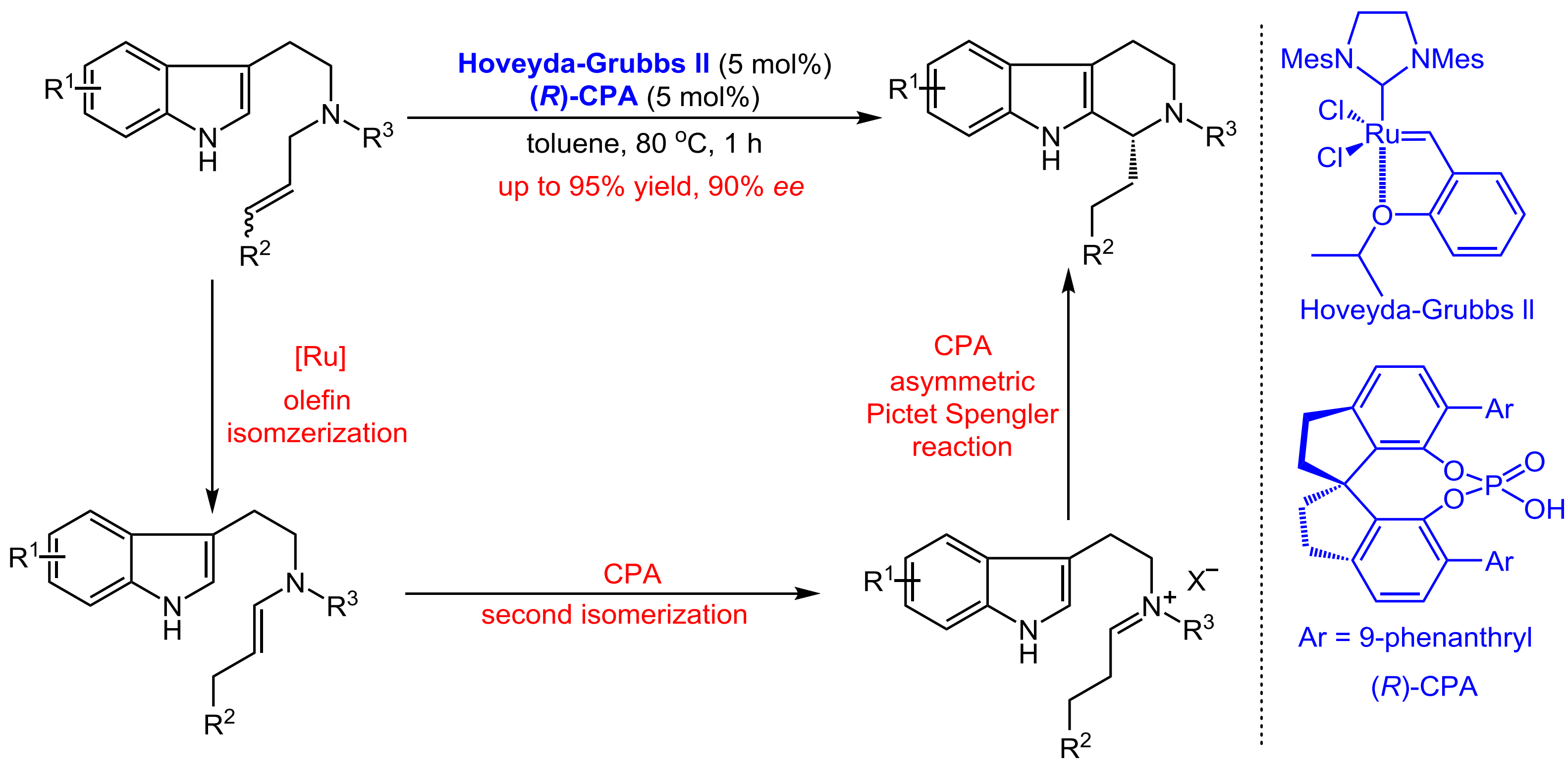
Zhong, W.-H. *et al. Org. Biomol. Chem.* **2018**, *16*, 566.

RCM/Isomerization/PS Cascade



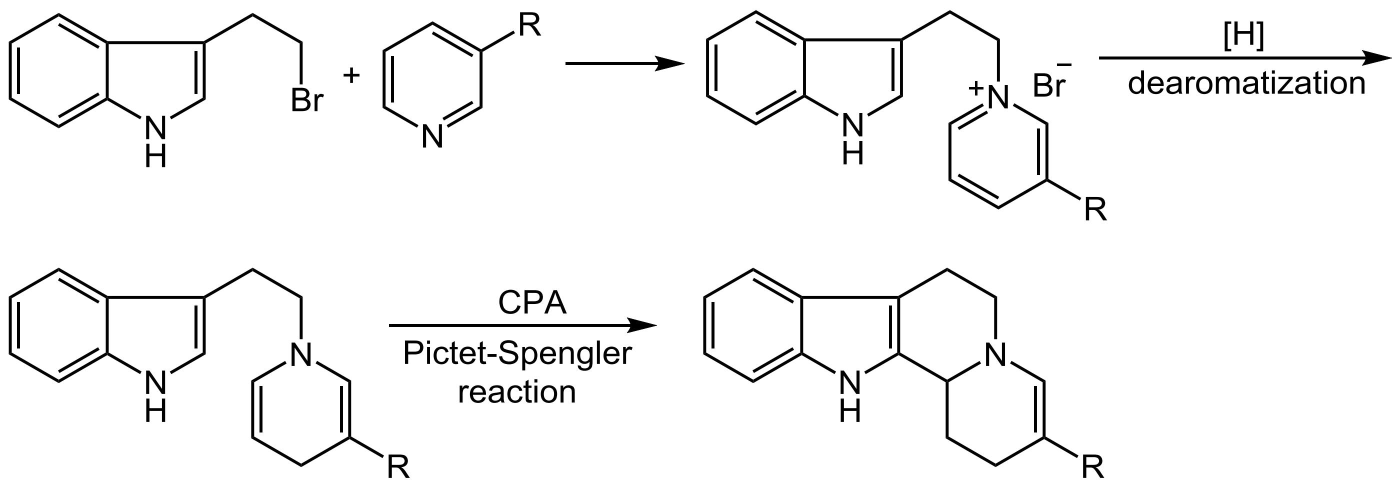
You, S.-L. *et al*. *Org. Lett.* **2012**, *14*, 5022.

Isomerization/asymmetric PS cascade



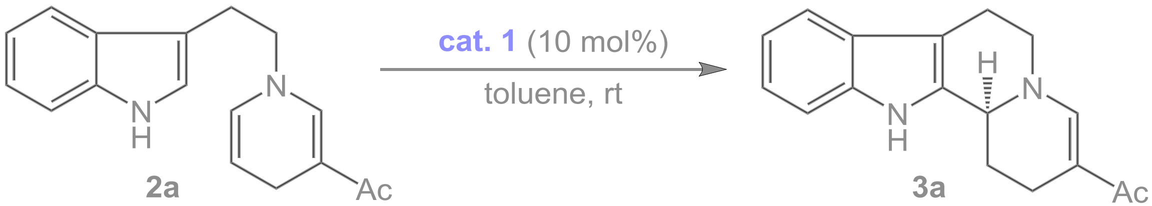
You, S.-L. *et al. Org. Biomol. Chem.* **2013**, *11*,1602.

Asymmetric Pictet-Spengler Reaction of Indolyl Dihydropyridines



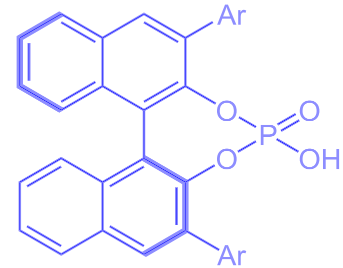
You, S.-L. *et al*. *Angew. Chem. Int. Ed.* **2017**, *56*, 7440.

Condition Optimization



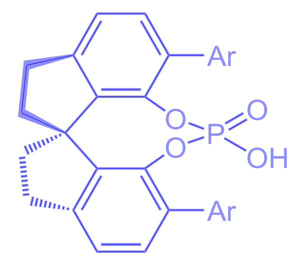
Entry[a]	Catalyst	*t* (h)	Yield (%)	*ee* (%)
1	**1a**	3.5	66	38
2	**1b**	10	42	10
3	**1c**	3.5	56	31
4	**1d**	3.5	10	14
5	**1e**	3.5	81	25
6	**1f**	3.5	80	11
7	**1g**	3.5	70	35
8	**1h**	3.5	80	62
9	**1i**	3.5	69	20
10	**1j**	3.5	81	40

[a] Reaction conditions: **2a** (0.1 mmol), **1** (10 mol%), additives (50 mg), solvent (2.0 mL), room temperature.



(*S*)-BINOL-CPA

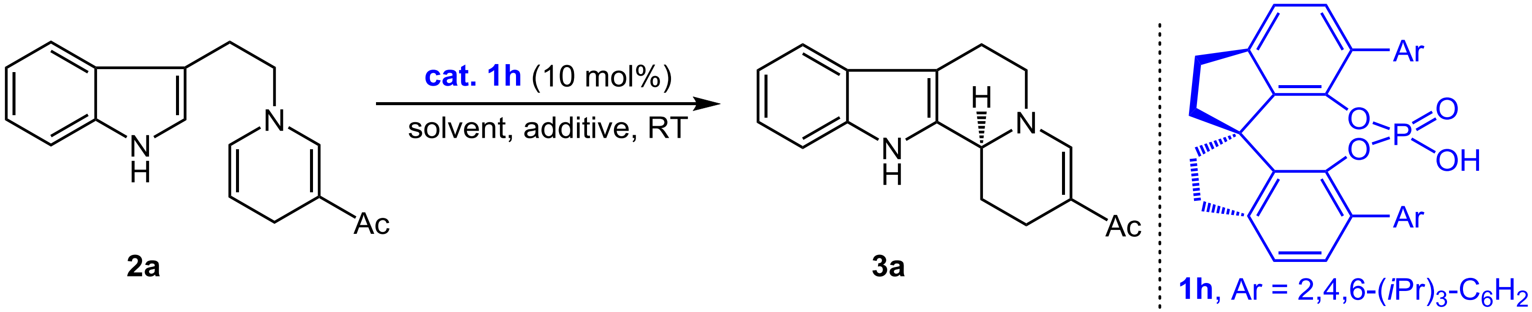
1a, Ar = 2,4,6-(iPr)$_3$-C_6H_2
1b, Ar = 2-naphthyl
1c, Ar = $SiPh_3$
1d, Ar = 4-Ph-C_6H_4
1e, Ar = 9-anthryl
1f, Ar = 3,5-$(CF_3)_2$-C_6H_3



(*R*)-SPINOL-CPA

1g, Ar = 1-naphthyl
1h, Ar = 2,4,6-(iPr)$_3$-C_6H_2
1i, Ar = 4-Cl-C_6H_4
1j, Ar = 3,5-$(CF_3)_2$-C_6H_3

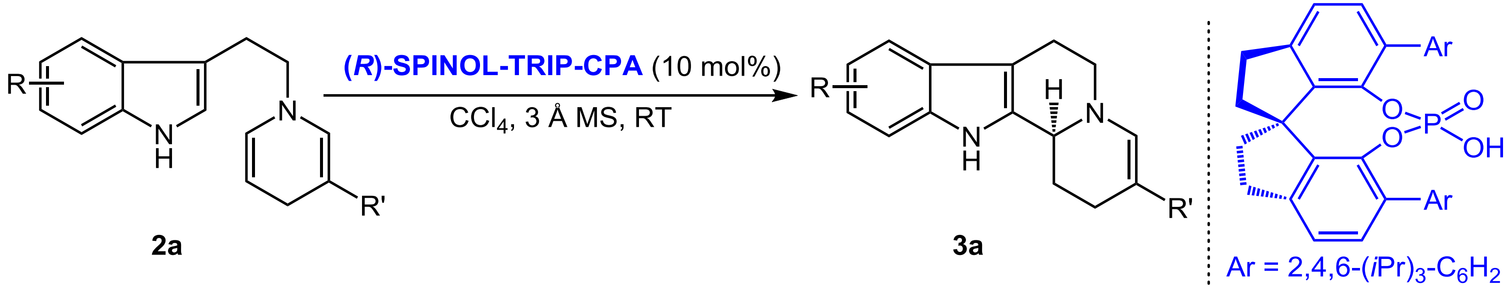
Condition Optimization

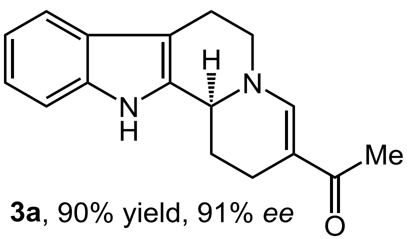


Entry[a]	Solvent	*t* (h)	Additive	Yield (%)	*ee* (%)
1	toluene	3.5	-	80	62
2	benzene	3.5	-	77	62
3	DCM	3.5	-	83	55
4	$CHCl_3$	3.5	-	95	47
5	CCl_4	3.5	-	85	72
6	CCl_4	12	3 Å MS	90	91
7	CCl_4	12	4 Å MS	90	89
8	CCl_4	8	5 Å MS	82	74
9[b]	CCl_4	36	3 Å MS	45	92

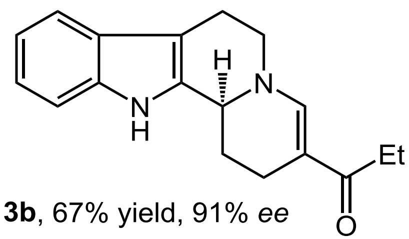
[a] Reaction conditions: **2a** (0.1 mmol), **1** (10 mol%), additives (50 mg), solvent (2.0 mL), room temperature. [b] The reaction mixture was stirred at 0 ^{o}C.

Substrate Scope

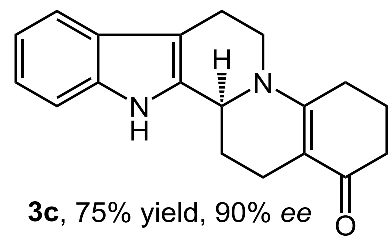




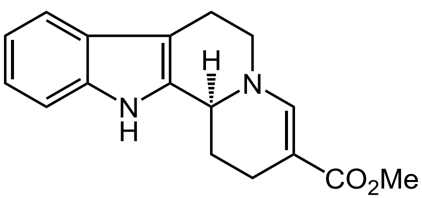
3a, 90% yield, 91% *ee*



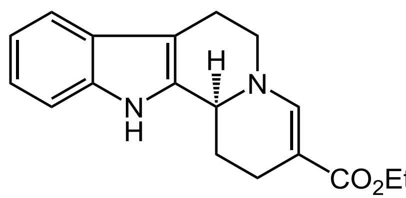
3b, 67% yield, 91% *ee*



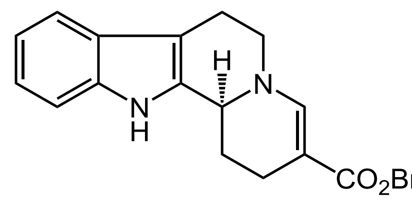
3c, 75% yield, 90% *ee*



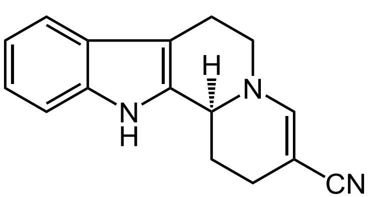
3d, 95% yield, 96% *ee*



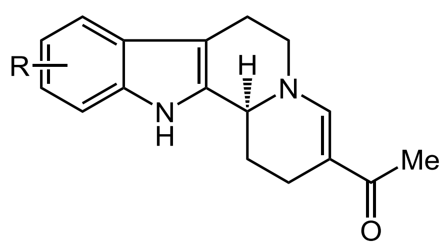
3e, 68% yield, 90% *ee*



3f, 89% yield, 88% *ee*

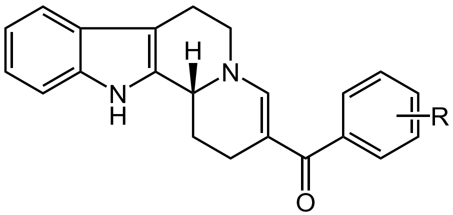


3g, 85% yield, 89% *ee*



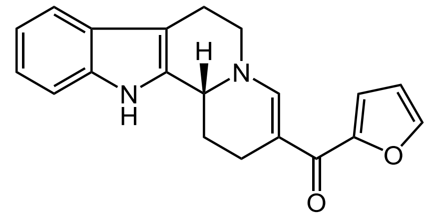
3h, R = 6-Me, 94% yield, 89% *ee*
3i, R = 7-Me, 86% yield, 91% *ee*
3j, R = 5-OMe, 66% yield, 92% *ee*
3k, R = 6-OMe, 67% yield, 87% *ee*
3l, R = 6-F, 61% yield, 89% *ee*

Substrate Scope and Transformations of Products

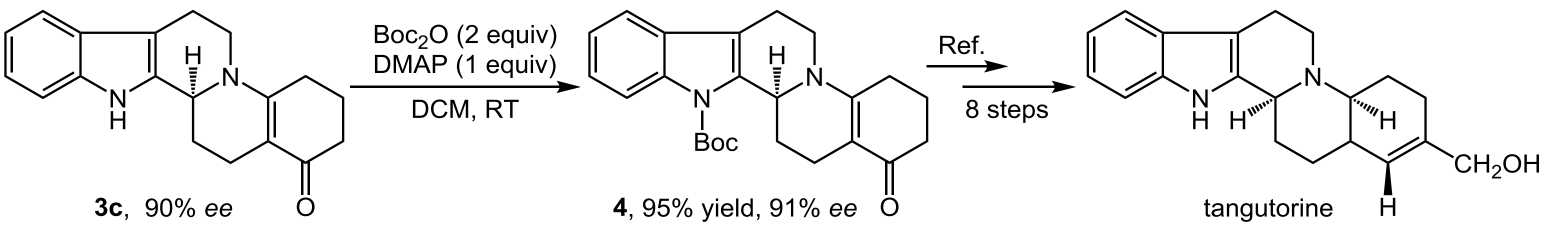


3m, R = H, 92% yield, 94% *ee*
3n, R = *p*-OMe, 92% yield, 77% *ee*
3o, R = *p*-Me, 94% yield, 66% *ee*

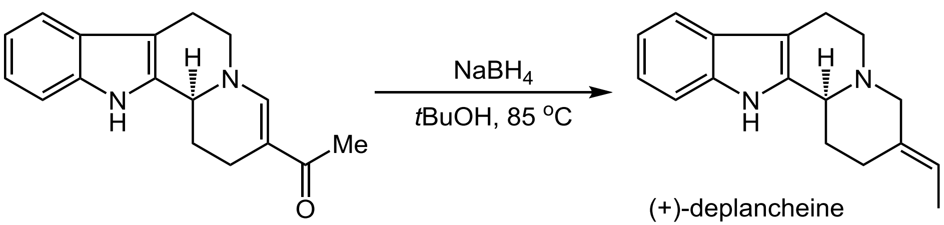
3p, R = *o*-Me, 91% yield, 80% *ee*
3q, R = *p*-*n*Bu, 85% yield, 72% *ee*
3r, R = *p*-*t*Bu, 95% yield, 92% *ee*
3s, R = *m,m*-(tBu)$_2$, 89% yield, 84% *ee*
3t, R = *p*-Ph, 90% yield, 83% *ee*
3u, R = *p*-CF_3, 95% yield, 87% *ee*
3v, R = *p*-F, 91% yield, 99% *ee*
3w, R = *p*-Cl, 92% yield, 97% *ee*
3x, R = *p*-Br, 90% yield, 98% *ee*
3y, R = *p*-I, 91% yield, 87% *ee*



3z, 93% yield, 76% *ee*



3c, 90% *ee*
4, 95% yield, 91% *ee*
tangutorine

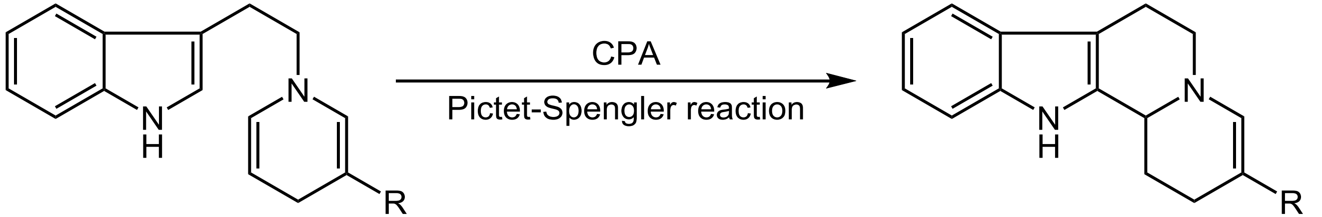


3a, 91% *ee*
(+)-deplancheine
81% yield, *E/Z* = 13:1, 93% *ee*

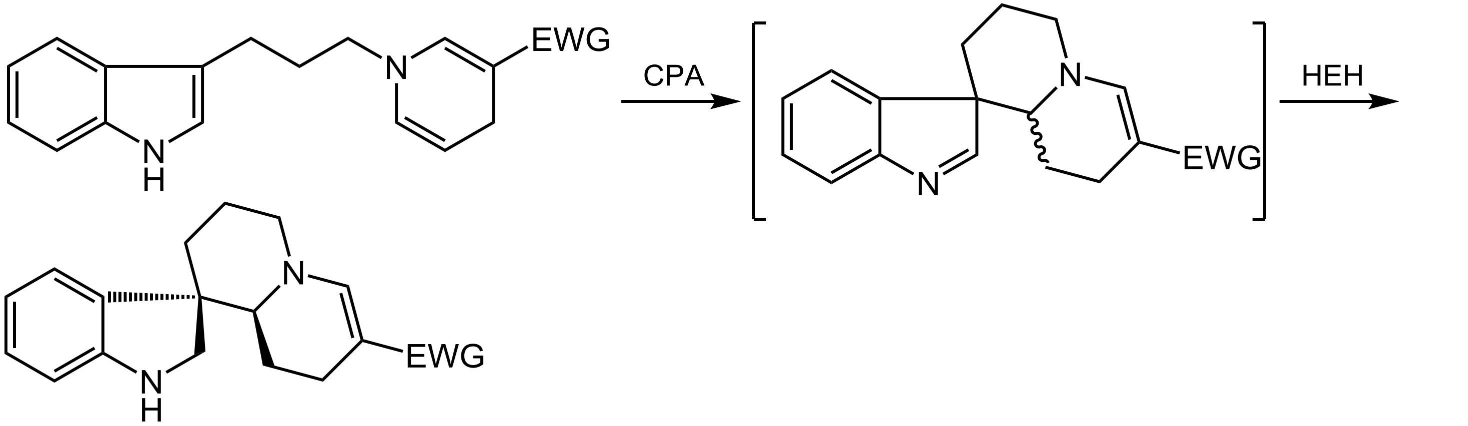
Hsung, R. P. *et al. Org. Lett.* **2003**, *5*, 4709.

Catalytic Asymmetric Dearomatization of Indolyl Dihydropyridines

Previous work

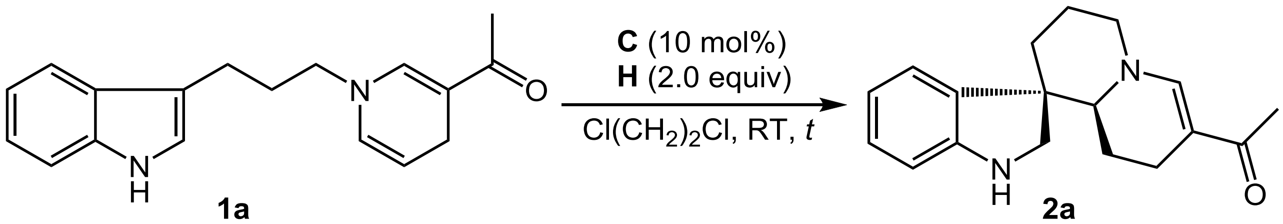


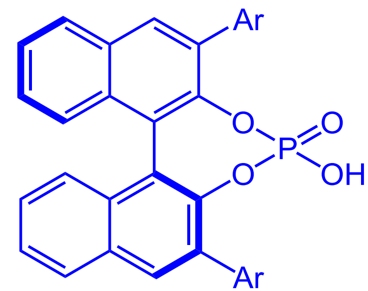
This work



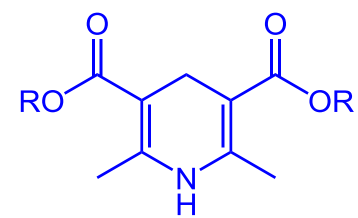
You, S.-L. *et al*. *Angew. Chem. Int. Ed.* **2018**, *57*, 2653.

Condition Optimization





C1, Ar = 9-phenanthryl
C2, Ar = 2,4,6-(iPr)$_3$-C$_6$H$_2$
C3, Ar = 9-anthryl
C4, Ar = 1-naphthyl
C5, Ar = SiPh$_3$
C6, Ar = 3,5-(CF$_3$)$_2$-C$_6$H$_3$
C7, Ar = 4-NO$_2$-C$_6$H$_4$

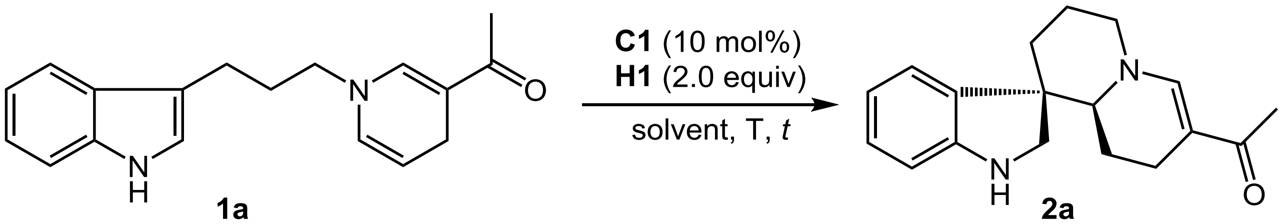


H1, R = Et
H2, R = Me
H3, R = t-Bu

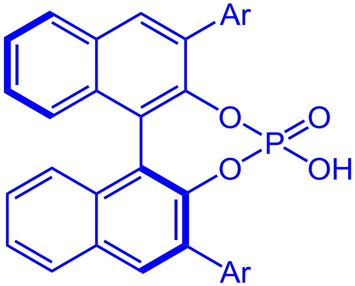
Entry[a]	C	H	t (h)	Yield (%)	*ee* (%)
1	**C1**	**H1**	24	83	81
2	**C2**	**H1**	24	53	59
3	**C3**	**H1**	24	70	70
4	**C4**	**H1**	24	79	72
5	**C5**	**H1**	24	31	43
6	**C6**	**H1**	24	45	22
7	**C7**	**H1**	24	68	51
8	**C1**	**H2**	36	37	74
9	**C1**	**H3**	48	18	77

[a] Reaction conditions: **1a** (0.1 mmol), **C** (10 mol%), **H** (0.2 mmol), solvent (2.0 mL).

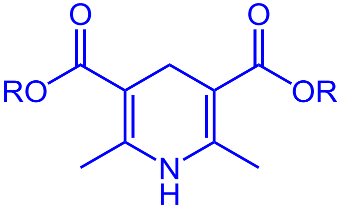
Condition Optimization



Entry[a]	Solvent	*t* (h)	*T* (ºC)	Yield (%)	*ee* (%)
1	$Cl(CH_2)_2Cl$	24	RT	83	81
2	EtOAc	24	RT	72	85
3	THF	24	RT	57	84
4	1,4-dioxane	24	RT	66	84
5	toluene	24	RT	62	69
6	EtOAc	12	40	76	85
7	EtOAc	12	60	62	81
8[b]	EtOAc	36	40	82	93



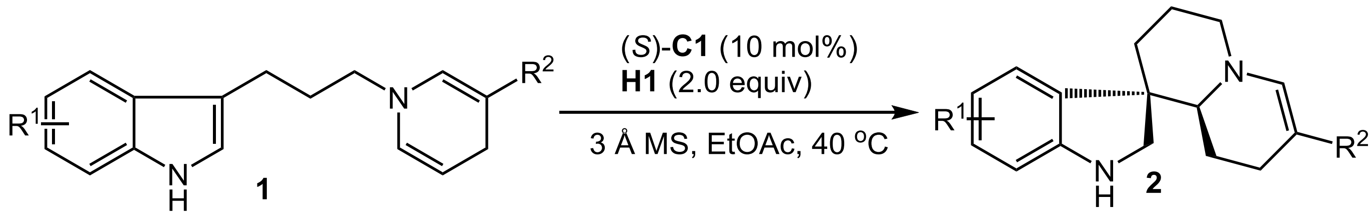
C1, Ar = 9-phenanthryl

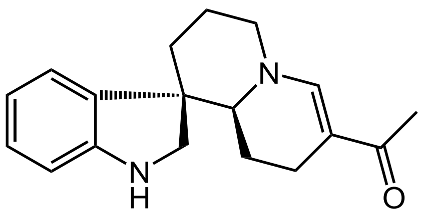


H1, R = Et

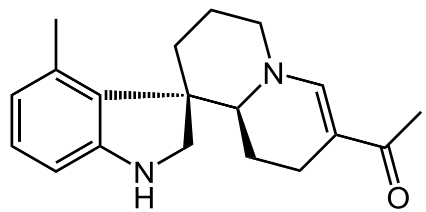
[a] Reaction conditions : **1a** (0.1 mmol), **C** (10 mol%), **H** (0.2 mmol), solvent (2.0 mL). [b] 50 mg 3 Å MS were added and 6 mL of EtOAc were used.

Substrate Scope

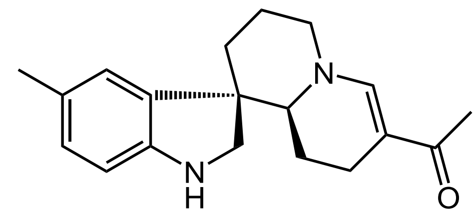




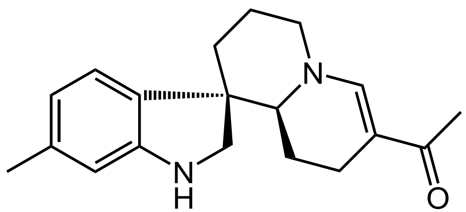
2a, 82% yield, 93% *ee*



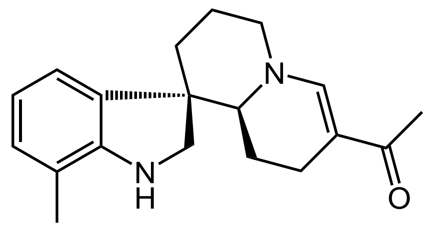
2b, 87% yield, 95% *ee*



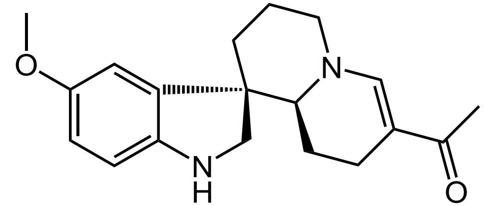
2c, 78% yield, 92% *ee*



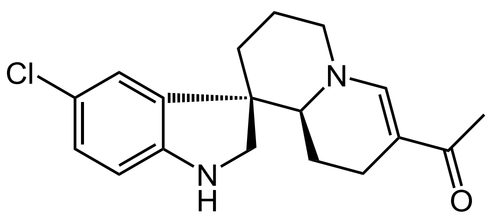
2d, 73% yield, 8:1 *dr*, 87% *ee*



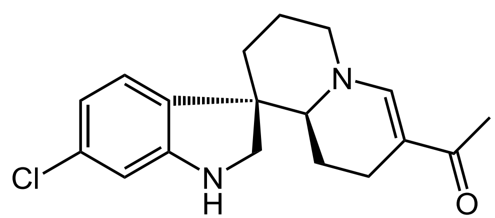
2e, 73% yield, 97% *ee*



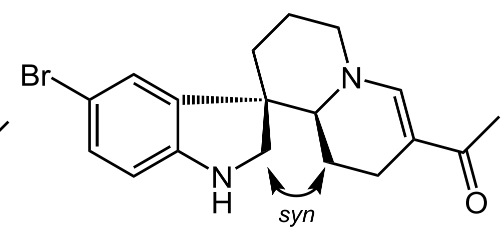
2f, 88% yield, 89% *ee*



2g, 74% yield, 91% *ee*

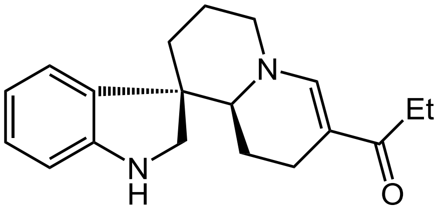


2h, 58% yield, 6:1 *dr*, 82% *ee*

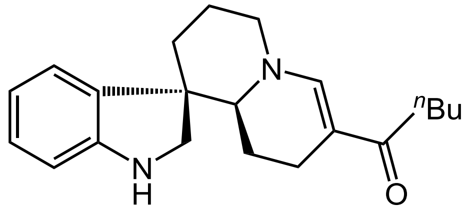


2i, 70% yield, 93% *ee*

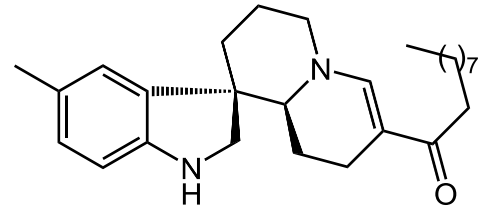
Substrate Scope



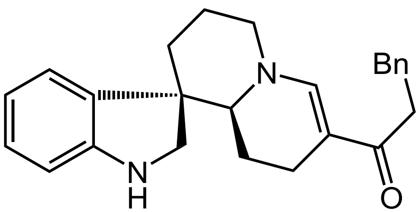
2j, 87% yield, 94% *ee*



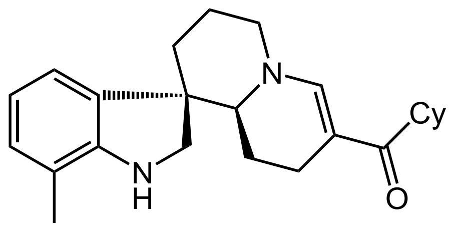
2k, 78% yield, 95% *ee*



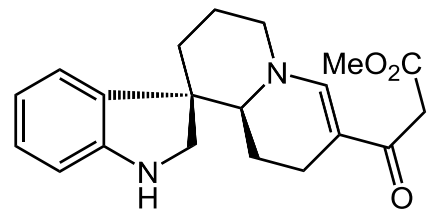
2l, 63% yield, 95% *ee*



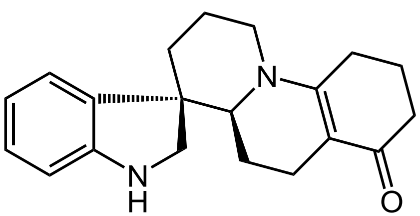
2m, 78% yield, 95% *ee*



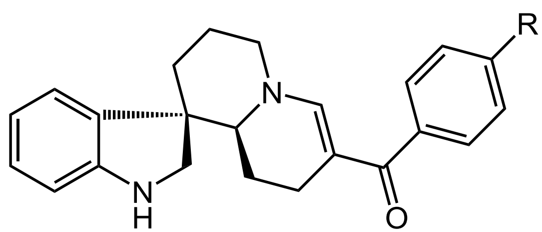
2n, 72% yield, 95% *ee*



2o, 65% yield, 94% *ee*

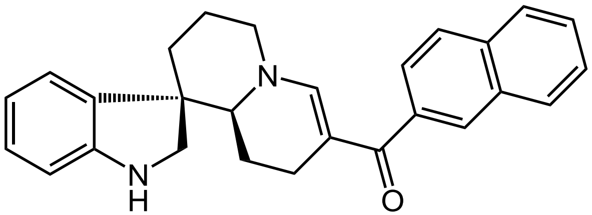


2p, 52% yield, 91% *ee*

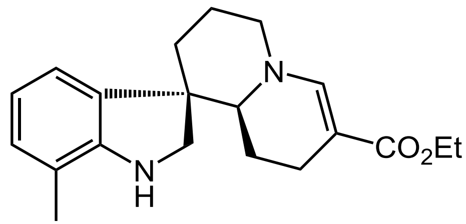


2q, R = H 79% yield, 93% *ee*
2r, R = Me 77% yield, 95% *ee*
2s, R = OMe 86% yield, 95% *ee*
2t, R = *t*-Bu 75% yield, 94% *ee*
2u, R = F 55% yield, 93% *ee*
2v, R = Br 54% yield, 92% *ee*

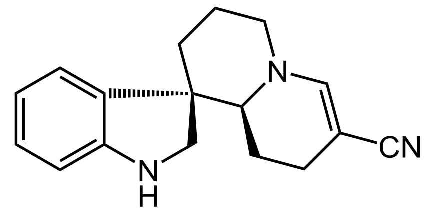
Substrate Scope



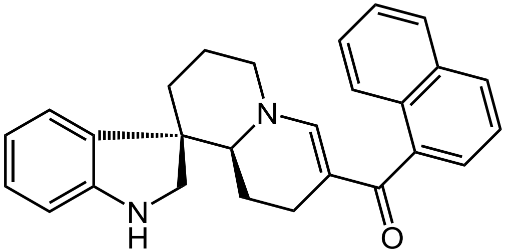
2w, 65% yield, 93% *ee*



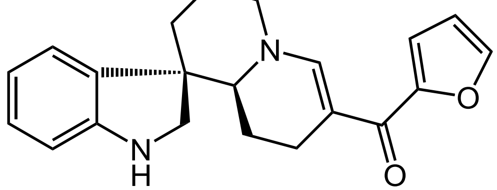
2x, 51% yield, 93% *ee*



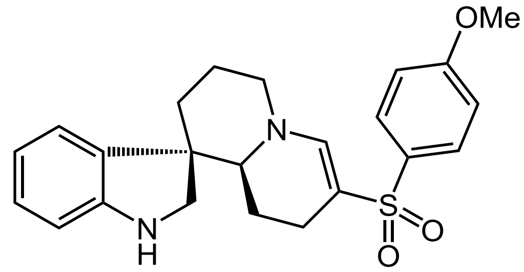
2y, 51% yield, 93% *ee*



2z, 59% yield, 84% *ee*

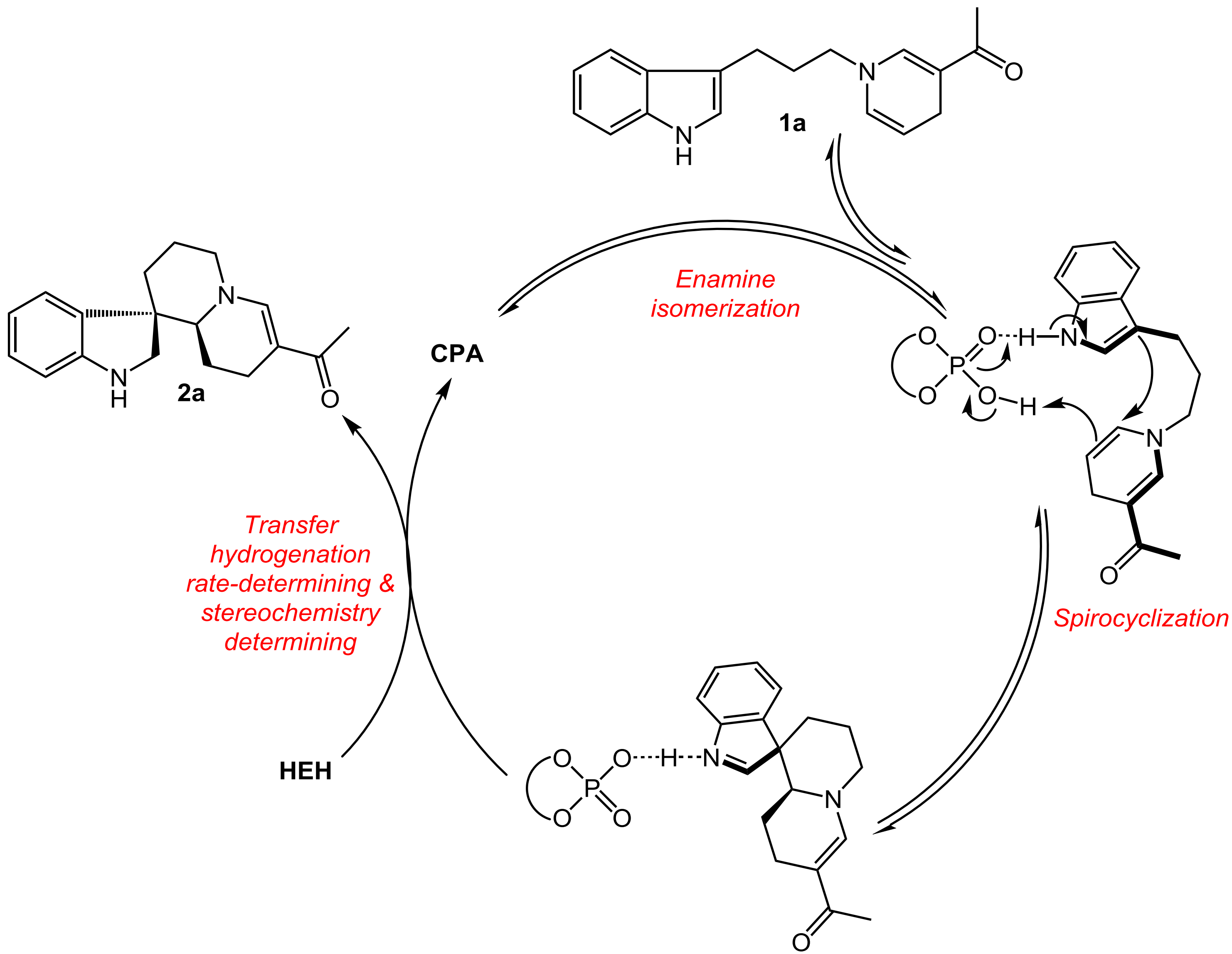


2aa, 60% yield, 95% *ee*

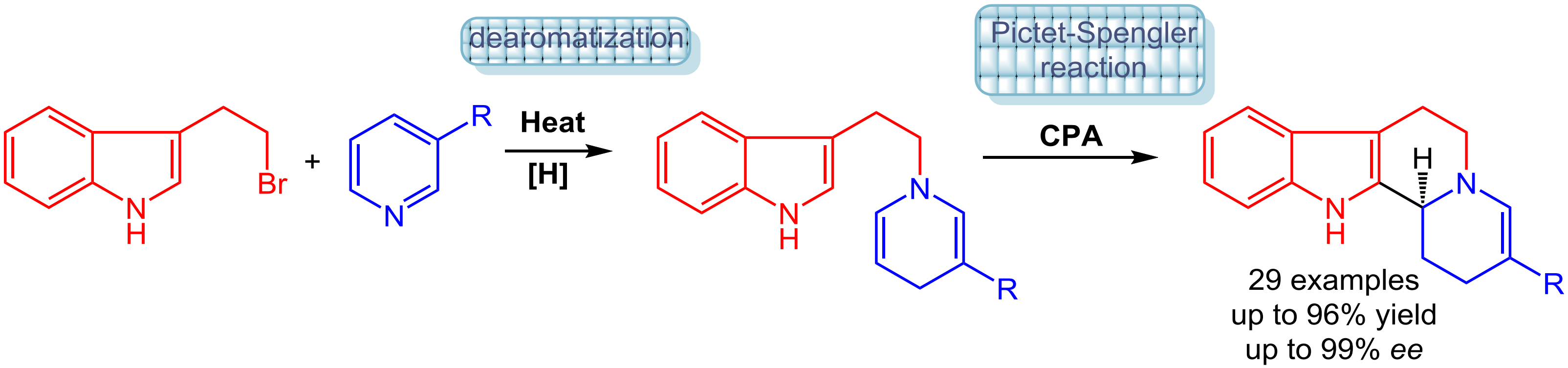


2ab, 54% yield, 88% *ee*

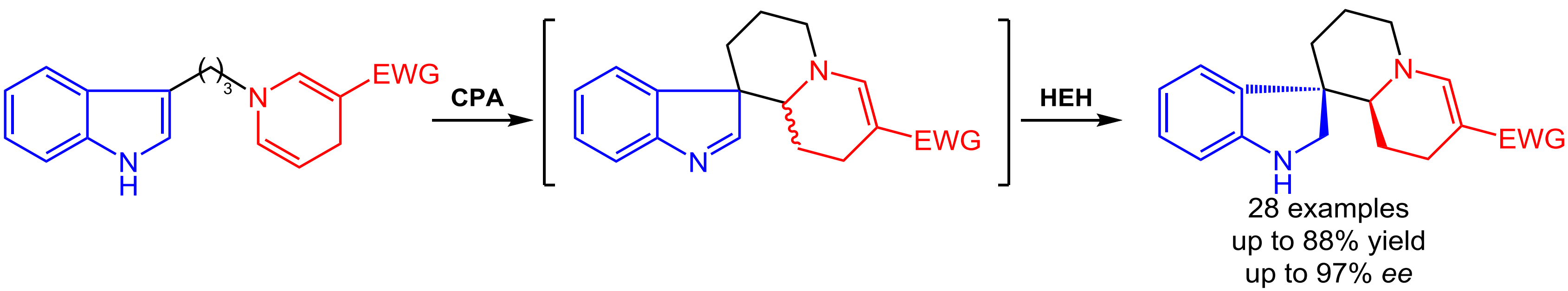
Proposed catalytic cycle



Summary



You, S.-L. *et al*. *Angew. Chem. Int. Ed.* **2017**, *56*, 7440.



You, S.-L. *et al*. *Angew. Chem. Int. Ed.* **2018**, *57*, 2653.

The First Paragraph

Synthetic studies of polycyclic indole derivatives have attracted plenty of research interests due to the widespread occurrence of such structural cores in natural products as well as their biological activities. Pictet–Spengler reactions are widely recognized as one of the most efficient and straightforward methods to afford tetrahydro-*β*-carbolines. Traditionally, tryptamine derivatives and carbonyl compounds are employed as the substrates of Pictet–Spengler reactions. As part of our ongoing research on catalytic asymmetric dearomatization (CADA) reactions, we recently developed an efficient asymmetric synthesis of tetrahydro-*β*-carbolines through chiral phosphoric acid (CPA)-catalyzed sequential enamine isomerization/Pictet–Spengler reaction of indolyl dihydropyridines **1**.

The First Paragraph

Spiroindolenine has been generally regarded as a key intermediate in Pictet–Spengler reactions. To capture and further manipulate the spiroindolenine species would allow unprecedented access to novel polycyclic indole derivatives. In this regard, we envisioned that the analogous reaction of indolyl dihydropyridine, which bears a one-methylene prolonged tether, would afford spiroindolenine, from which an in situ transfer hydrogenation with Hantzsch ester might lead to tetrahydrospiro[indoline-3.1'-quinolizine]. Herein, we report the results of the study on this cascade reaction catalyzed by a chiral phosphoric acid.

The Last Paragraph

In summary, we have developed a highly efficient synthesis of enantioenriched spiroindolines through a chiral phosphoric acid catalyzed enamine isomerization/spirocyclization/transfer hydrogenation sequence. This reaction proceeds under mild reaction conditions to afford novel spiroindolines in good yields (up to 88%) with excellent enantioselectivity (up to 97% *ee*). Further exploration on the reactivity of spiroindolenines is currently underway in our laboratory.

Acknowledgement

Thanks

for your attention