Enantioselective Pictet-Spengler Reaction

Tetrahydroisoquinoline Tetrahydro-β-carboline

Daniel Meyer
University of Bern

25.02.2016, Topic Review

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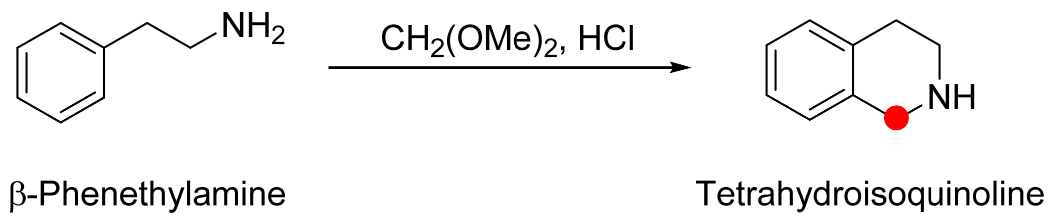
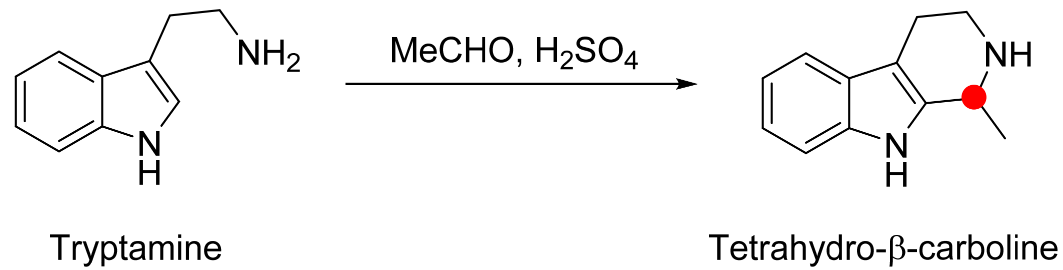
History

> Amé Pictet and Theodor Spengler in 1911
  — Formation of 1,2,3,4-tetrahydroisoquinoline (THIQ)



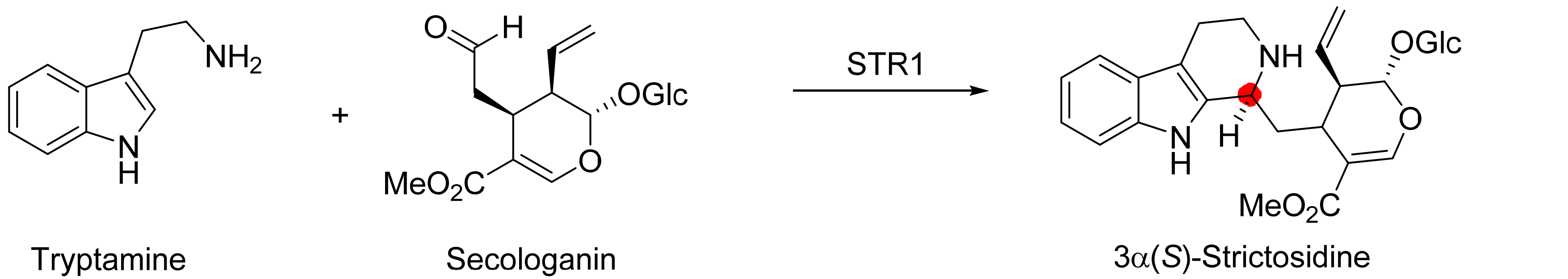
> Tatsui in 1928
  — Formation of 1,2,3,4-tetrahydro-β-carboline (THBC)



Pictet, A.; Spengler T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030. Tatsui. G. J. Pharm. Soc. Jpn. **1928**, *48*, 92.

Enzyme-Catalyzed PSR: Strictosidine Synthase

- Strictosidine synthase was detected in nature in 1977
- Enantioselective synthesis of 3α(*S*)-strictosidine
- Central progenitor of all monoterpenoid indole alkaloids
- Problem: Limited substrate acceptance



Stöckigt, J.; Zenk, M. H. *FEBS Lett.* **1977**, *79*, 233. Stöckigt, J.; Zenk, M. H. *J. Chem. Soc. Chem. Commun.* **1977**, 646.

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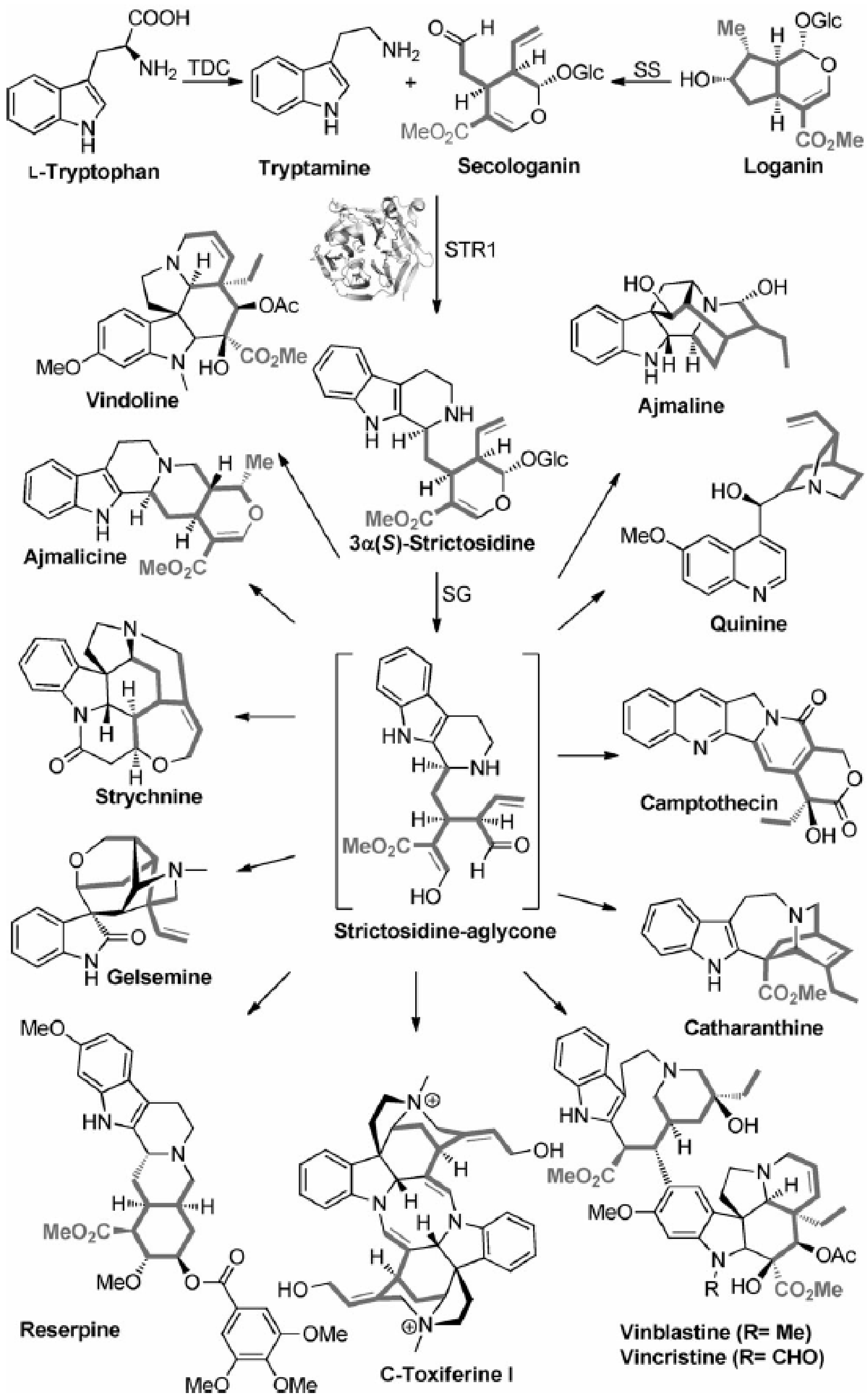
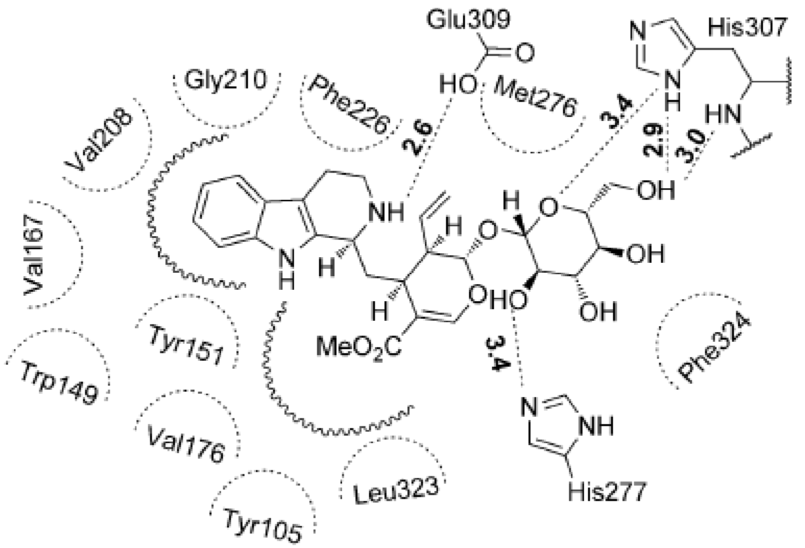
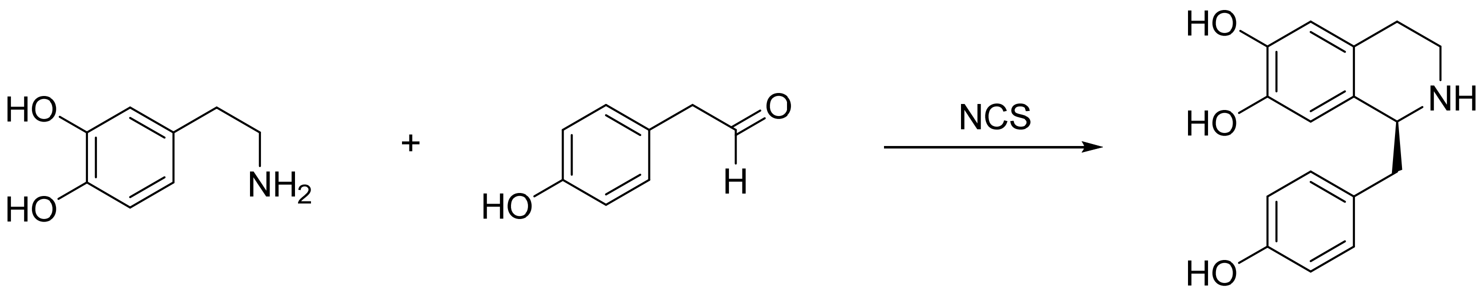




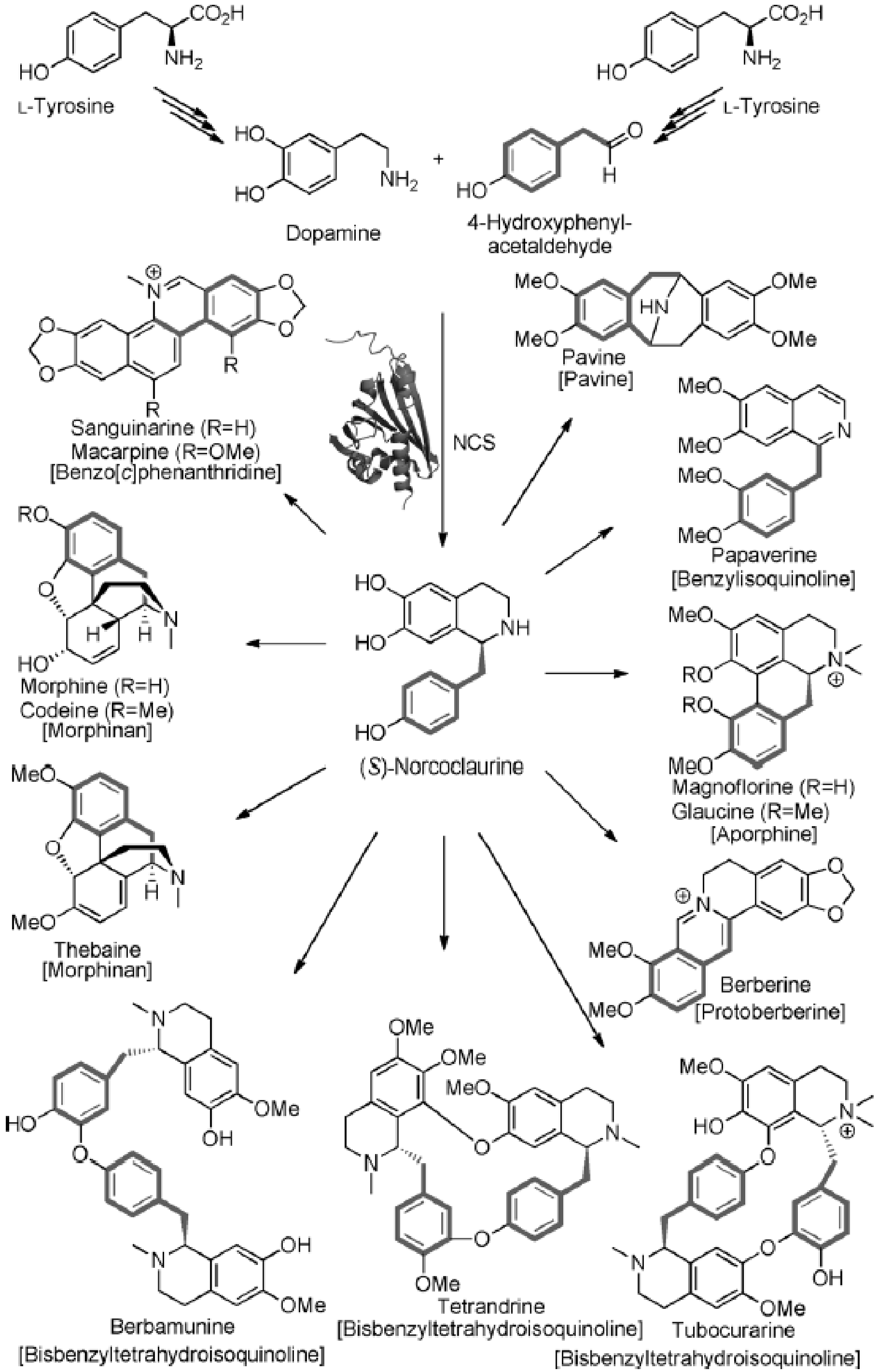
Enzyme-Catalyzed PSR: Norcoclaurine Synthase

- Norcoclaurine synthase was characterized in 1981
- Enantioselective synthesis of (*S*)-Norcoclaurine
- Central progenitor of all benzylisoquinoline alkaloids
- Problem: Limited substrate acceptance



Dopamine | 4-Hydroxyphenyl-acetaldehyde | (*S*)-Norcoclaurine

Rueffer, M. et al. *FEBS Lett.* **1981**, *129*, 5.



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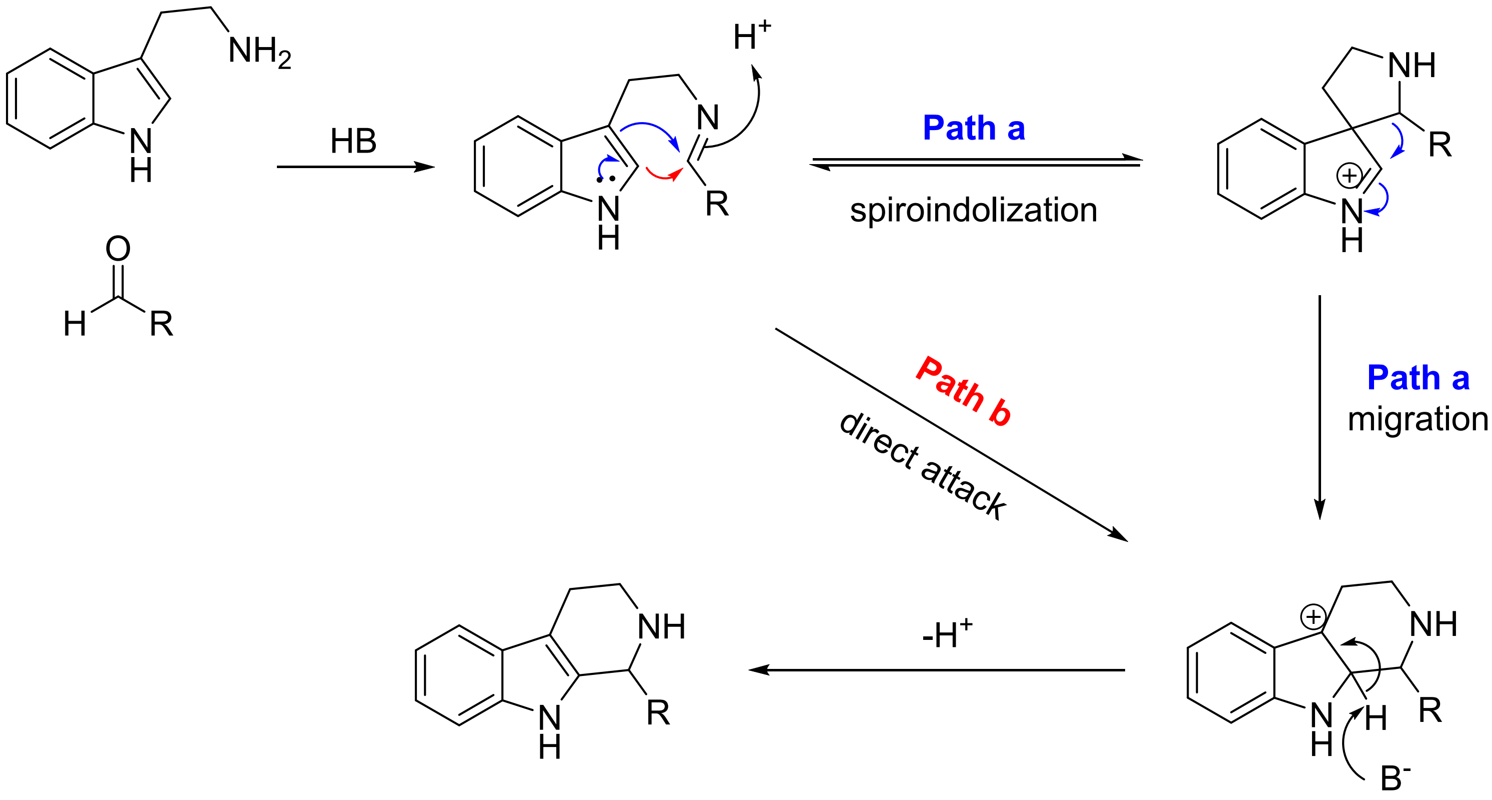
Mechanism of Non-Enzymatic PSR



Stöckigt, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 8538. Shu-Li, Y. *J. Am. Chem. Soc.* **2013**, *135*, 8169.

Diastereoselective PSR

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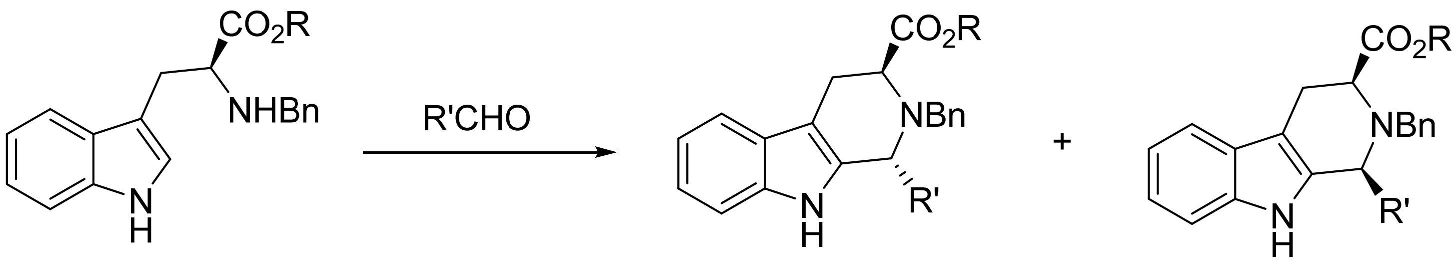
- Tryptophan Derivatives
- Chiral Auxiliary Groups
- Stoichiometric Lewis Acids
- Chiral Carbonyl Compounds

Tryptophan Derivatives: Thermodynamic Control



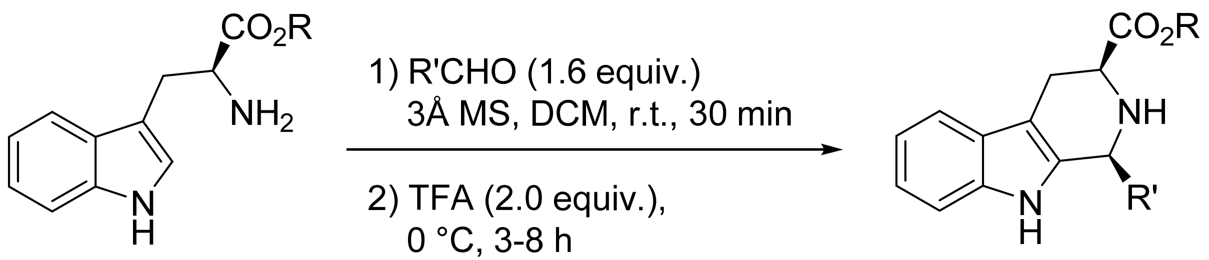
trans (thermodynamic) *cis* (kinetic)

non-acidic cond: benzene, reflux
acidic-cond: excess TFA, benzene, reflux

R	R'	Non-acidic *trans*/*cis*	Acidic *trans*/*cis*
Me	Me	74:26	88:12
Me	*n*Pr	77:23	89:11
Me	*c*-hexyl	100:0	100:0
*i*Pr	Me	77:23	87:13
*i*Pr	*n*Pr	87:13	88:12
*i*Pr	*c*-hexyl	100:0	100:0

Cook, J. M. et al. *Tetrahedron Lett.* **1992**, *33*, 4721. Cook, J. M. et al. *J. Org. Chem.* **1997**, *62*, 44.

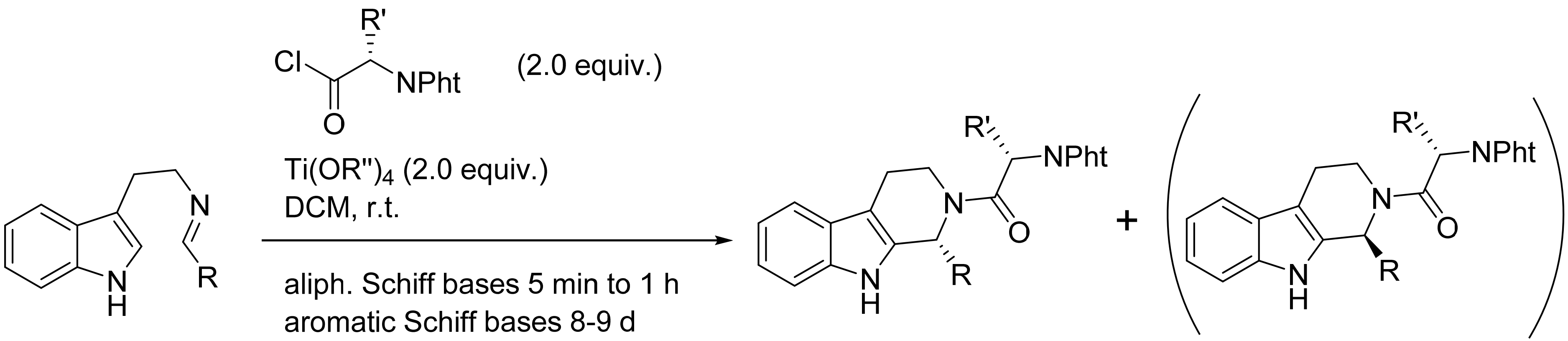
Tryptophan Derivatives: Kinetic Control



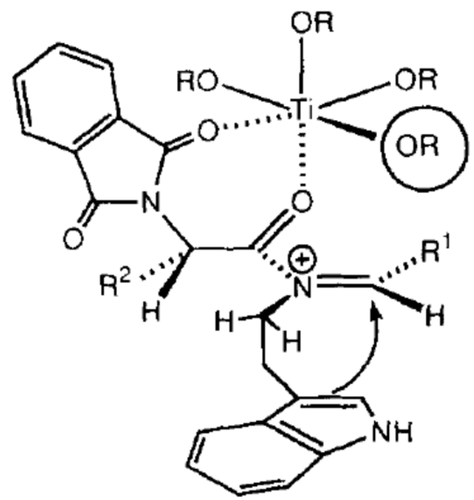
R	R’	yield	*cis*/*trans*
Me	Ph	74	82:18
Me	*c*-hexyl	71	71:29
Me	*n*Pr	75	83:17
allyl	Ph	57	>95:5
allyl	*c*-hexyl	39	75:25
allyl	*n*Pr	67	71:29

Bailey, P. D. et al. *Tetrahedron Lett.* **2009**, *50*, 3645.

Chiral Auxiliary Groups

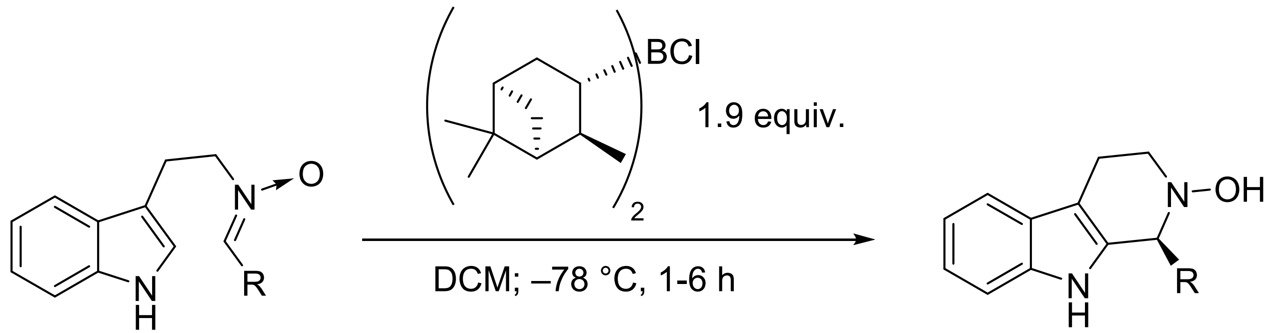


R	R’	R’’	yield (%)	*trans*/*cis*
Me	*t*Bu	*n*Pr	66	96:4
Et	*t*Bu	*n*Pr	59	95:5
*i*Pr	*i*Pr	*n*Pr	99	>99:1
Ph	*t*Bu	*n*Pr	60	>99:1
p-$NO_2C_6H_4$	*t*Bu	*n*Pr	54	93:7
p-ClC_6H_4	*t*Bu	*n*Pr	44	89:11
p-ClC_6H_4	*t*Bu	*i*Pr	60	93:7

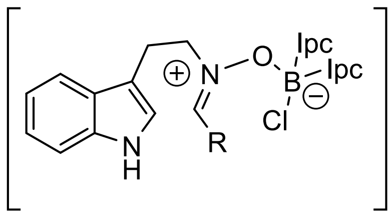


Waldmann, H. et al. *Angew. Chem. Int. Ed.* **1995**, *34*, 2402. Waldmann, H. et al. *Chem. Eur. J.* **1996**, *2*, 1566.

Stoichiometric Lewis Acids



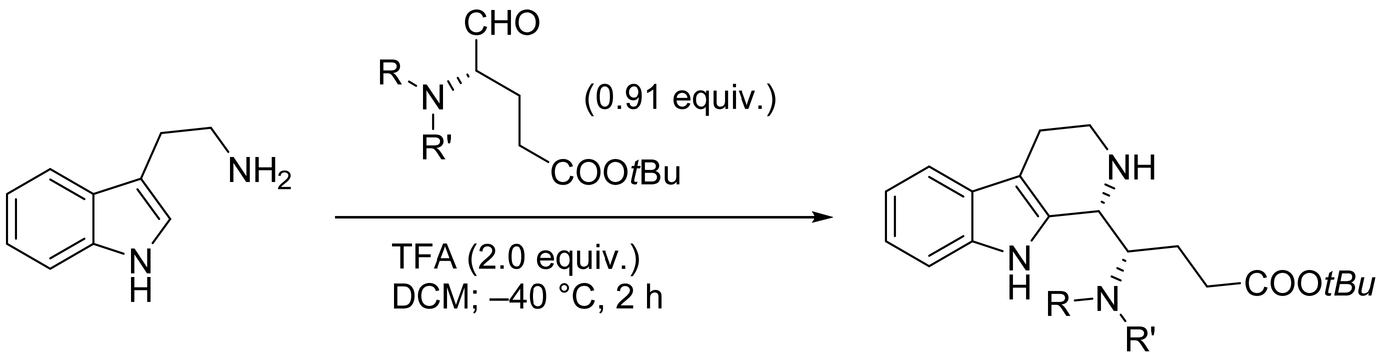
via



R	yield (%)	ee (%)
Me	91	43
*i*Bu	75	35
Ph	92	75
p-MeOC_6H_4	65	90
p-$NO_2C_6H_4$	81	0.6
1-naphthyl	94	86

Nakagawa, M. et al. *J. Org. Chem.* **1998**, *63*, 6348.

Chiral Carbonyl Compounds



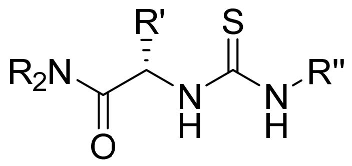
R	R’	yield (%)	*trans*/*cis*
Cbz	H	81	0:100
Boc	H	71	10:90
CO_2Me	H	73	9:91
pyrrole[a]		62	100:0
Pht[b]		68	93:7

a) Reaction temp. = –50 °C
b) r.t. and $CONEt_2$ instead of COO*t*Bu

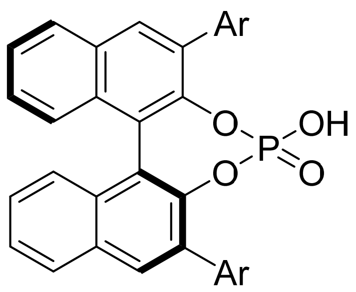
Thal, C. et al. *Tetrahedron* **1993**, *49*, 8589. Thal, C. et al. *Tetrahedron* **2000**, *56*, 2683.

Enantioselective PSR

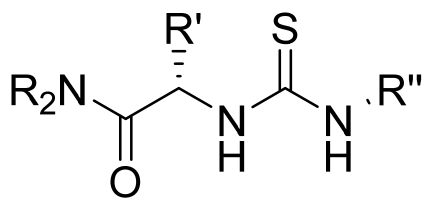
- Thiourea-Catalyzed
  - First enantioselective PSR by Taylor and Jacobsen 2004



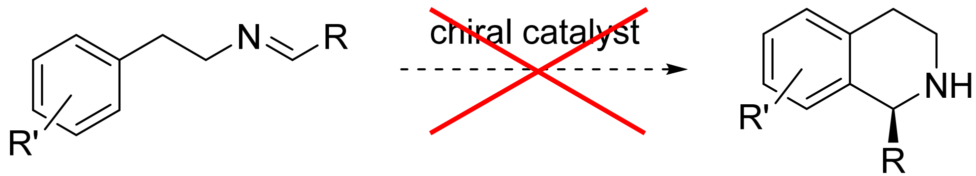
- Strong Brønsted-acid (Phosphoric-Acid)



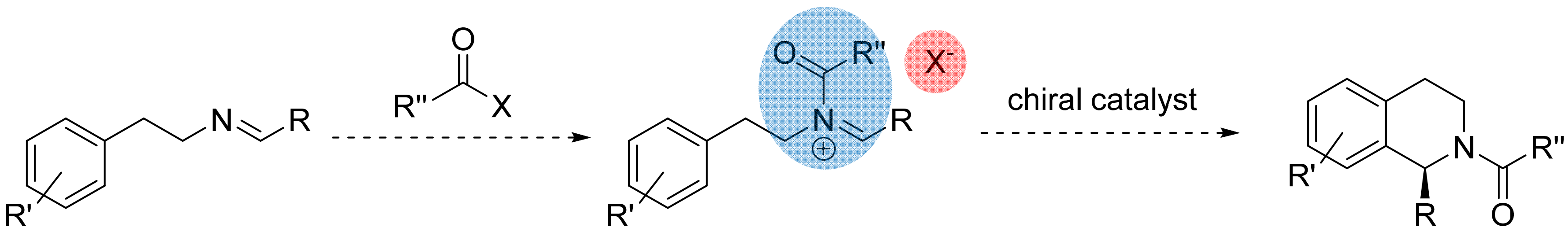
Thiourea Catalyzed PSR



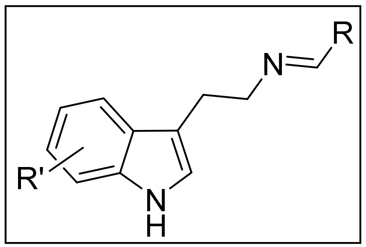
Thiourea-Catalyzed PSR



- Problem: low reactivity of iminium-substrate → strong Brønsted-acid
- high temperature
- → **activation of iminium-part**

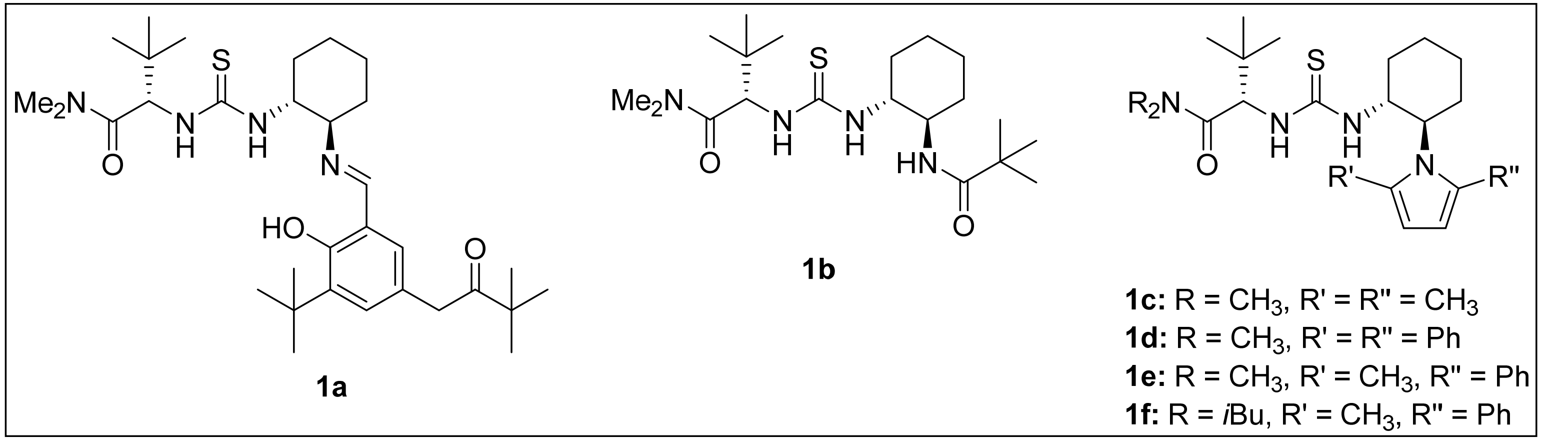


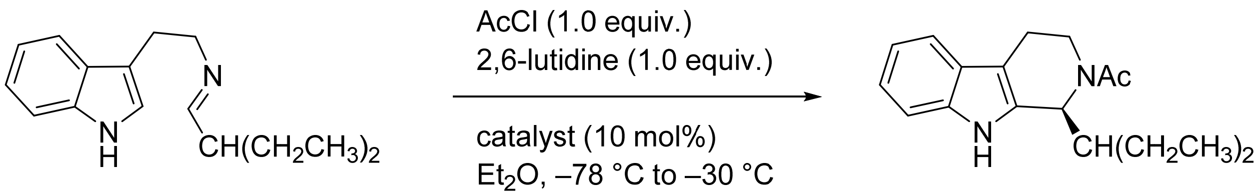
- Reaction works only for tryptamine and -derivatives



Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558

Thiourea-Catalyzed PSR

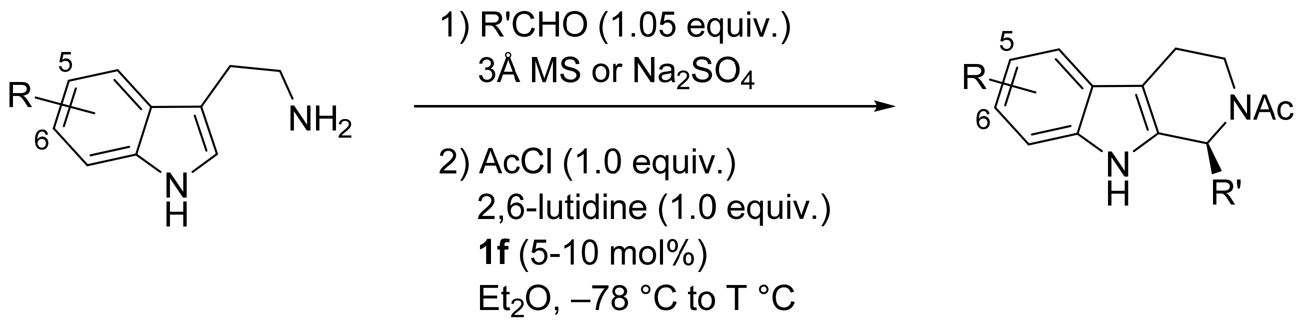




catalyst	yield (%)	ee (%)
1a	65	59
1b	45	61
1c	65	77
1d	55	71
1e	70	93
1f	70	93

Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558

Thiourea-Catalyzed PSR

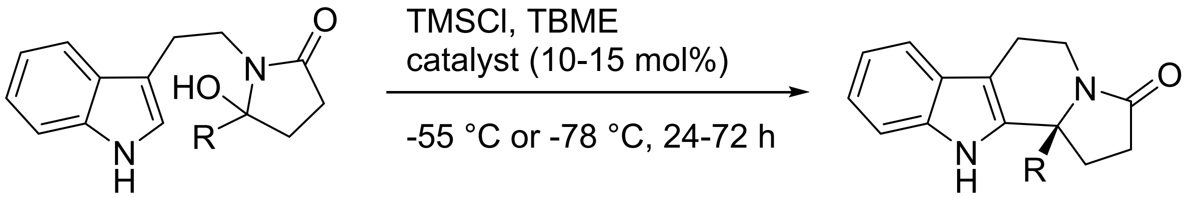


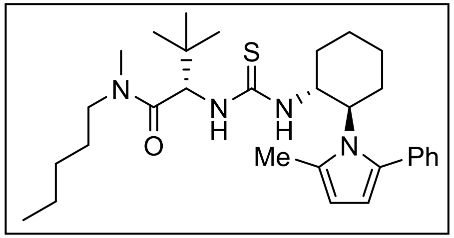
R	R’	T (°C)	yield (%)	ee (%)
H	$CH(CH_2CH_3)_2$	–30	65	93
H	*i*Pr	–40	67	85
H	*n*-Pent	–60	65	95
H	*i*Bu	–60	75	93
H	CH_2CH_2OTBDPS	–60	77	90
5-MeO	$CH(CH_2CH_3)_2$	–40	81	93
6-MeO	$CH(CH_2CH_3)_2$	–50	76	86

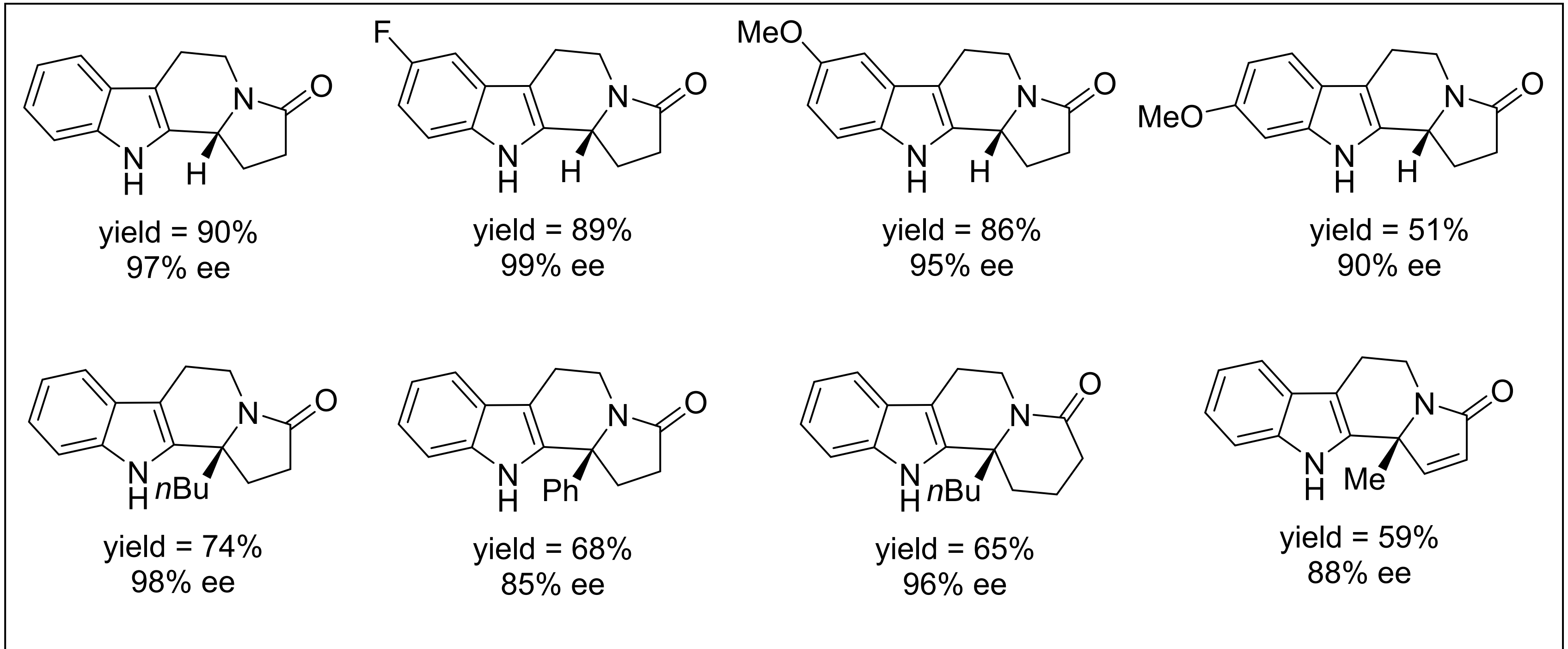
Aromatic aldehydes and trimethyl acetaldehyde display lower reactivity and were not converted.

Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558

Thiourea-Catalyzed PSR: Hydroxylactams

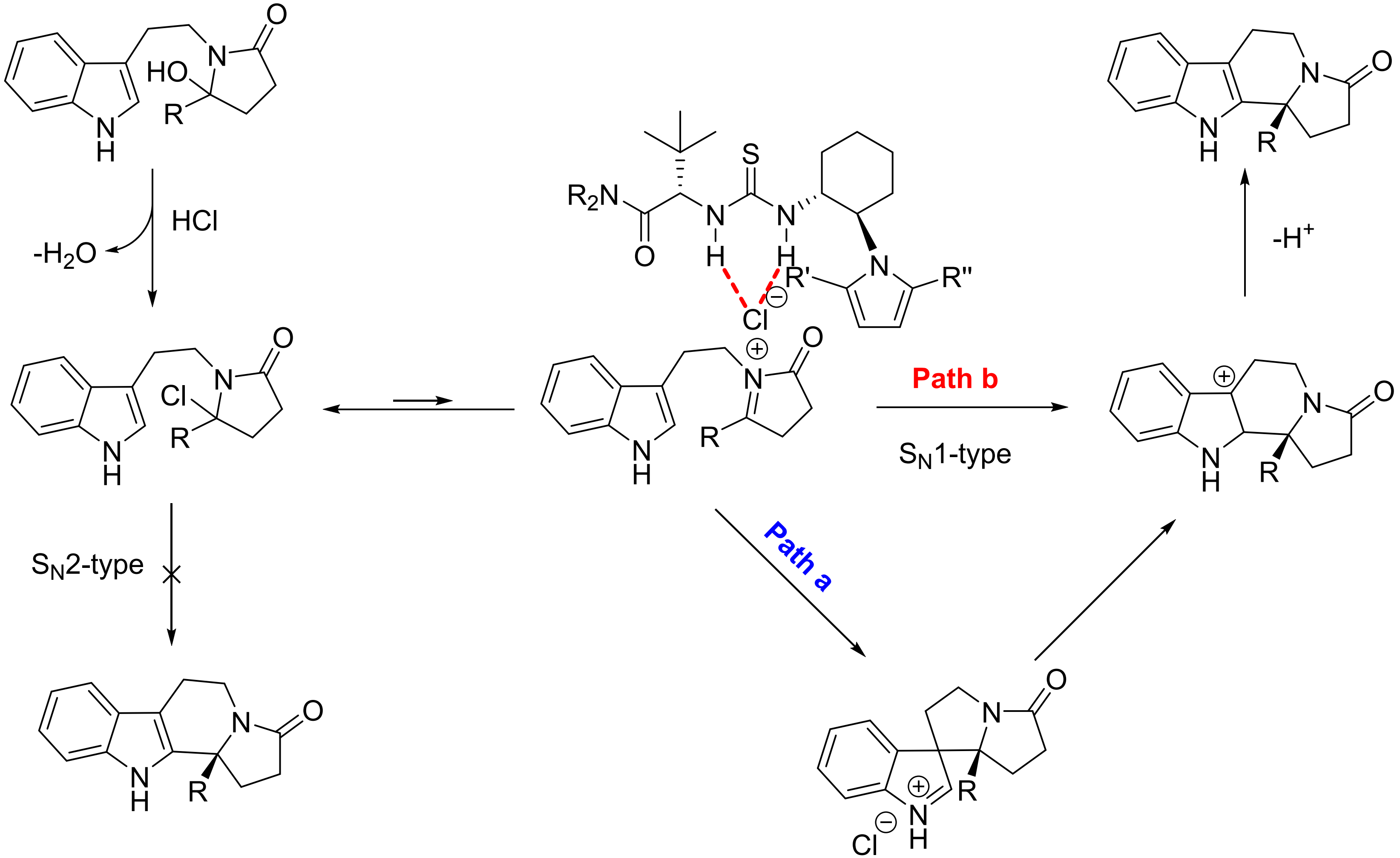






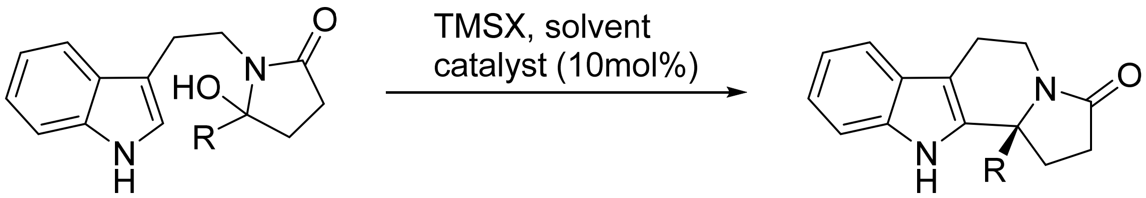
Jacobsen, E. N. et al. *J. Am. Chem. Soc.* **2007**, *129*, 13404.

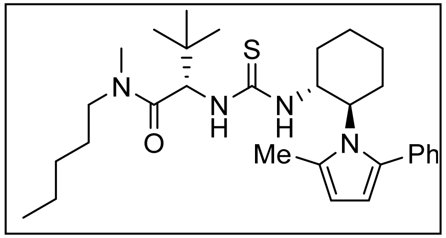
Thiourea-Catalyzed PSR: Hydroxylactams Mechanism



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

Thiourea-Catalyzed PSR: Hydroxylactams Mechanism

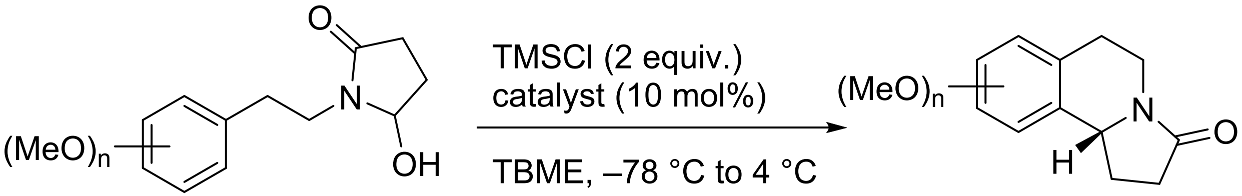




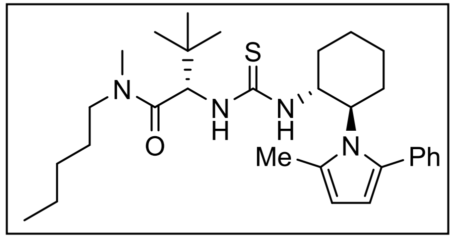
solvent	X	R	T (°C)	t (h)	conv. (%)	ee (%)
TBME	Cl	H	–78	8	12	99
TBME	Cl	CH_3	–78	8	94	96
TBME	Cl	H	–55	23	80	97
TBME	Br	H	–55	23	82	68
TBME	I	H	–55	23	75	<5
TBME	Cl	H	–55	8	65	97
THF	Cl	H	–55	8	>95	34
DCM	Cl	H	–55	8	>95	<5

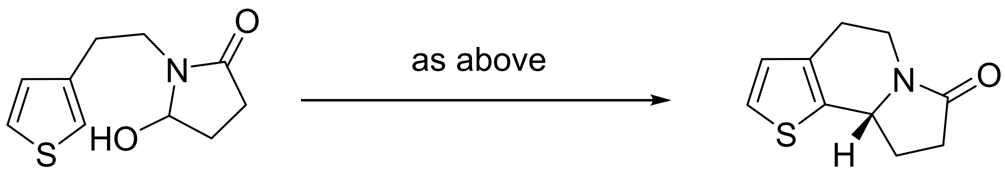
Jacobsen, E. N. et al. *J. Am. Chem. Soc.* **2007**, *129*, 13404.

Thiourea-Catalyzed PSR: Other Aromatic Substrates

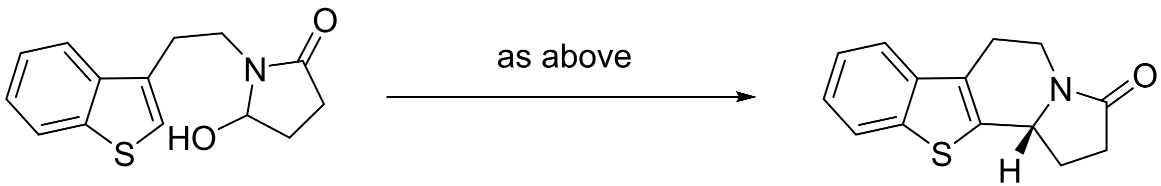


0-40% conv., 0% ee

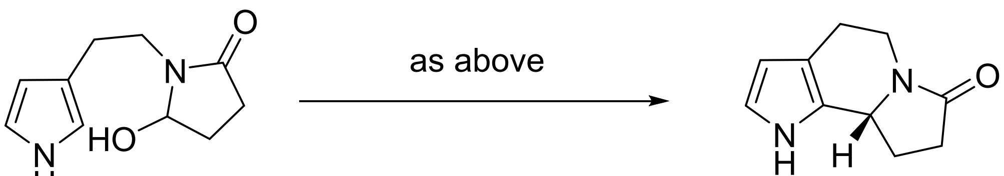




up to 30% ee



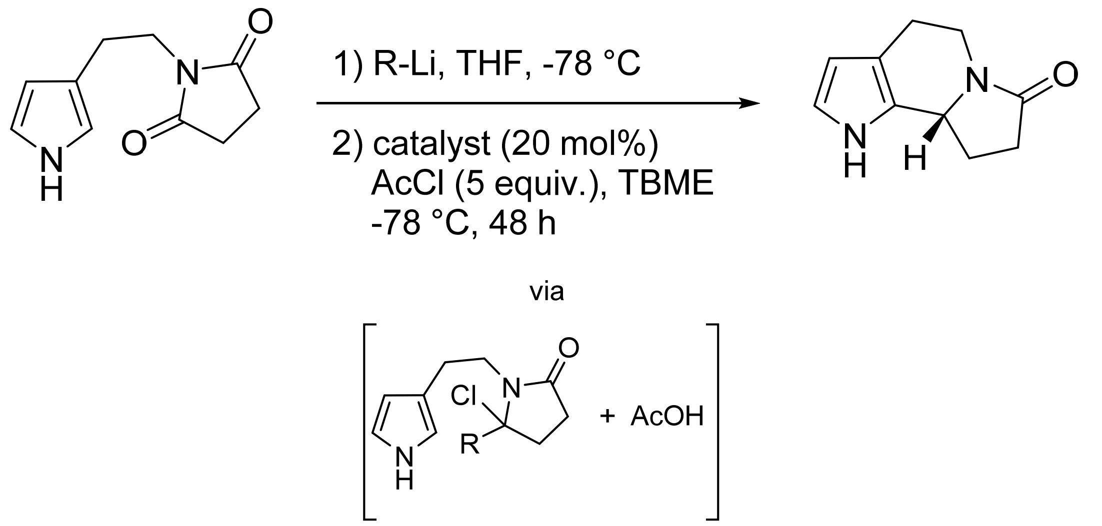
up to 15% ee

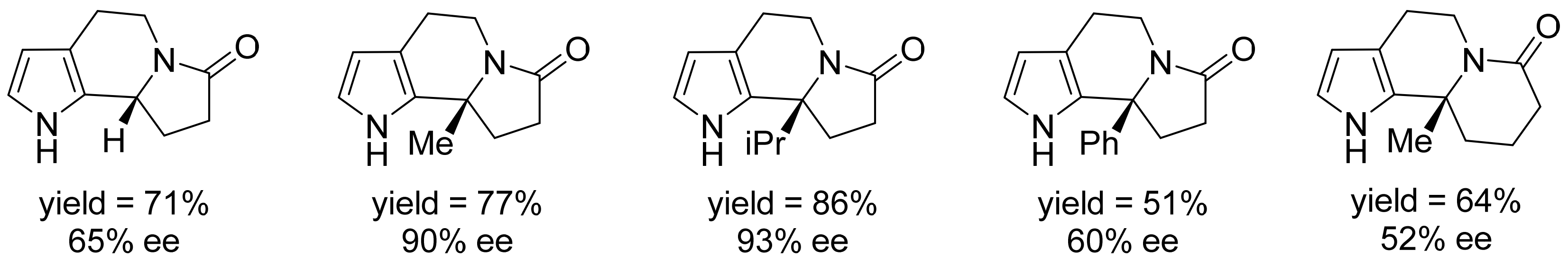


51% yield, 60% ee

Jacobsen, E. N. et al. *Org. Lett.* **2008**, *10*, 1577.

Thiourea-Catalyzed PSR: C2-Cyclization of Pyrroles

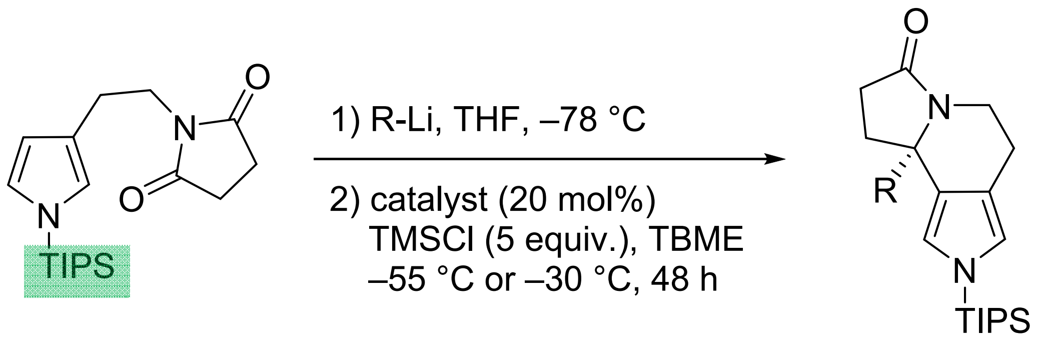


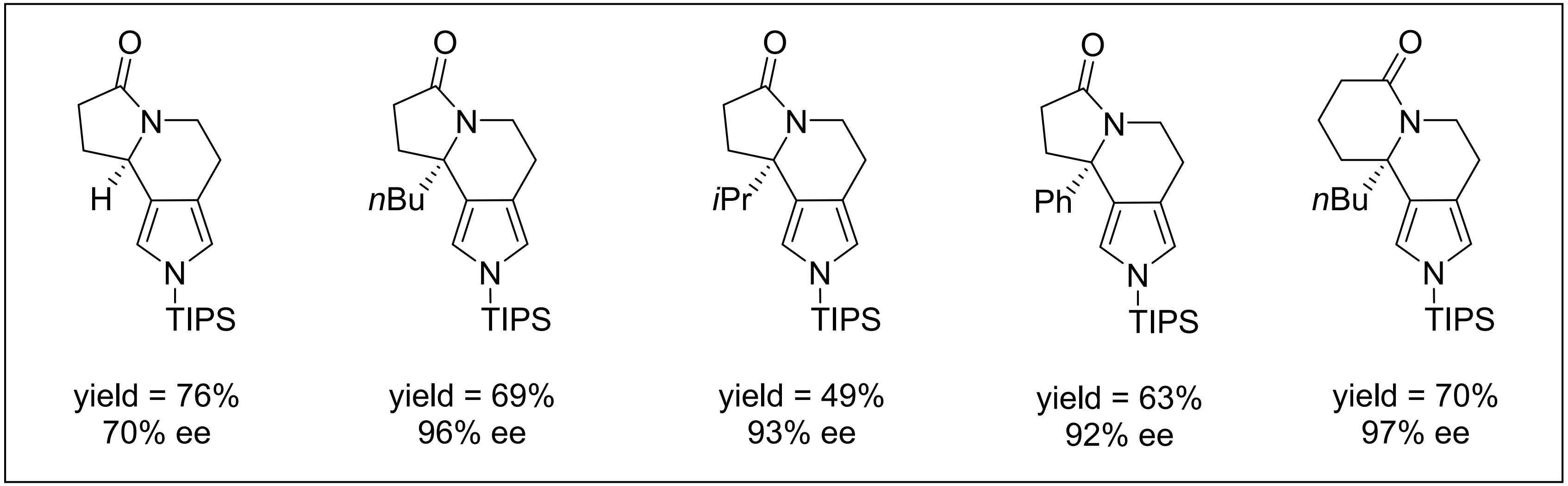


Yield for second step.

Jacobsen, E. N. et al. *Org. Lett.* **2008**, *10*, 1577.

Thiourea-Catalyzed PSR: C4-Cyclization Pyrroles



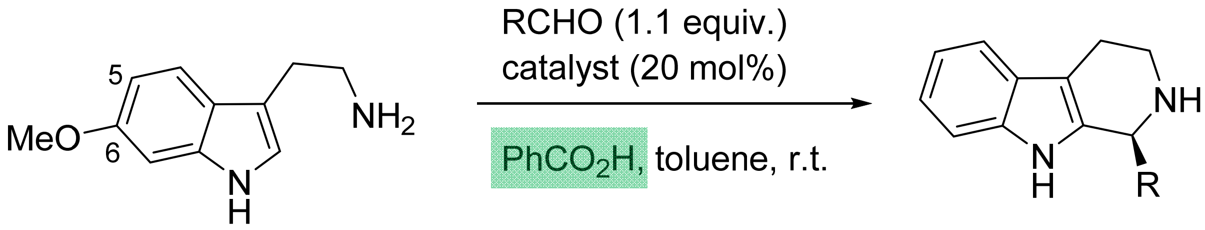


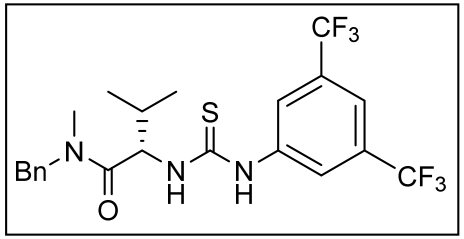
First product 1.7:1 mixture of C4:C2, only one regioisomer was detected for the others.

Yield for second step.

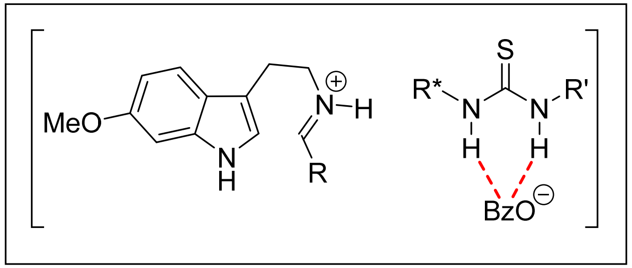
Jacobsen, E. N. et al. *Org. Lett.* **2008**, *10*, 1577.

Thiourea-Catalyzed PSR: benzoic acid cocatalyzed





R	$PhCO_2H$ (%)	time (h)	yield (%)	ee (%)
Ph	20	70	94	86
p-BrC_6H_4	20	74	79	94
p-$MeOC_6H_4$	20	91	78	85
o-BrC_6H_4	20	11	74	95
o-BrC_6H_4[a]	40	87	82	99
o-BrC_6H_4[b]	100	240	45	95
*i*Pr	20	4	60	88
*i*Pr	0	88	90	94
n-pentyl	0	18	74	86
*i*Pr[a]	20	36	39	88



a) 5-MeO-tryptamine, T = 35 °C
b) non substituated tryptamine; T = 35 °C

Jacobsen, E. N. et al. *Org. Lett.* **2009**, *11*, 887.

Thiourea-Catalyzed Iso-PSR

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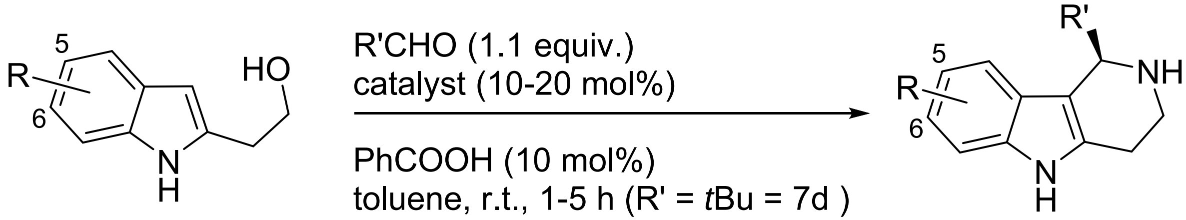
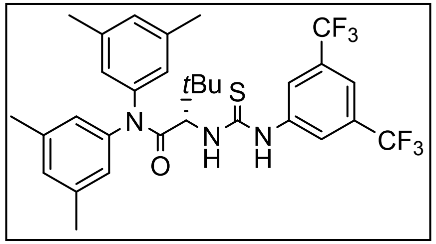
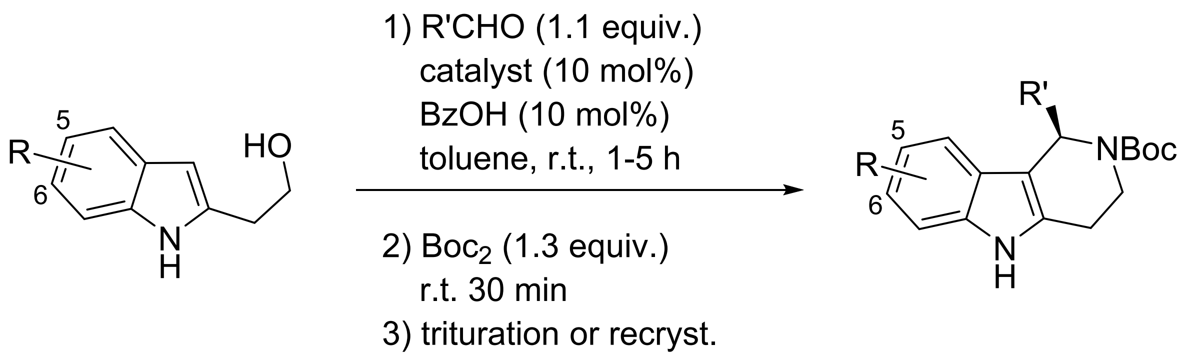
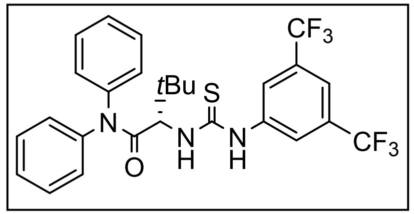


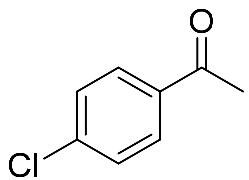


R = 5-F; 6-F; 5-MeO; 6-MeO; 5-Me; 5-vinyl
R' = *i*Bu; *c*-Hex; $CH(Et)_2$; *t*Bu; *o*-MeC_6H_4, 1-naph

83-99% yield
79% to 95% ee







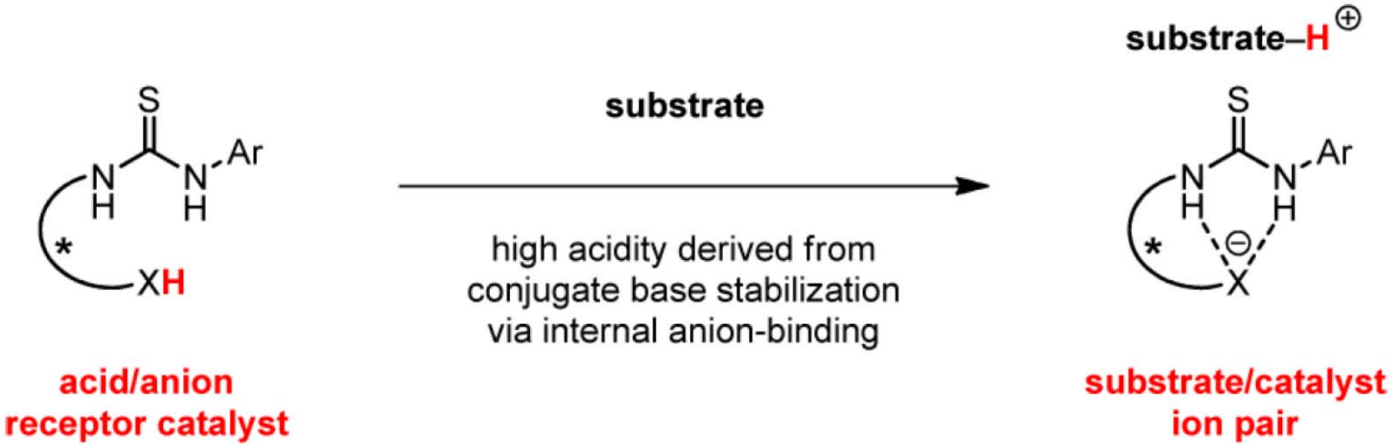
R = 5-F; 6-F; 5-MeO; 6-MeO; 5-Me; 5-vinyl
R' = *n*-pent; *i*Bu; *i*Pr; *c*-Hex; $CH(Et)_2$; Ph; *o*-MeC_6H_4,
p-FC_6H_4; p-ClC_6H_4; p-BrC_6H_4;

45-81% yield
98% to >99% ee

53% yield; 98% ee

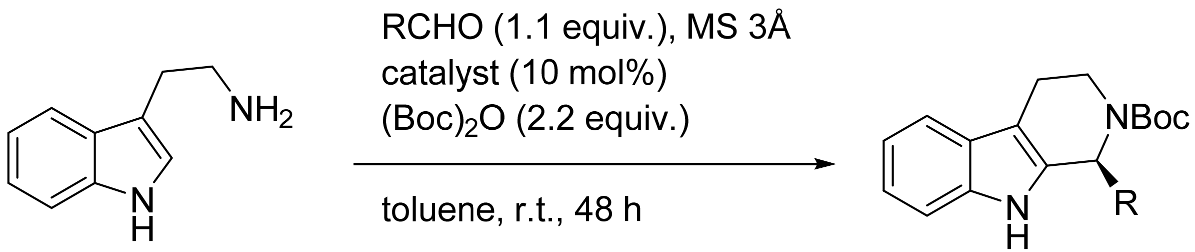
Jacobsen, E. N. et al. *Org. Lett.* **2011**, *13*, 5564.

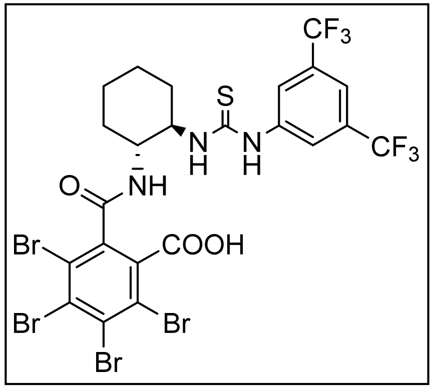
Thiourea Catalyzed PSR: Internal Anion-Binding



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

Thiourea Catalyzed PSR: Internal Anion-Binding





R	yield (%)	ee (%)
*t*Bu	23	62
Ph	86	87
o-BrC_6H_4	87	79
m-BrC_6H_4	92	89
p-BrC_6H_4	78	92
p-Me	28	64
p-MeO	12	32
p-$NO_2C_6H_4$	90	89

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

Thiourea Catalyzed PSR

b UNIVERSITÄT BERN

> Acetyl-PSR
  — Good for aliphatic aldehydes; *N*-protected products

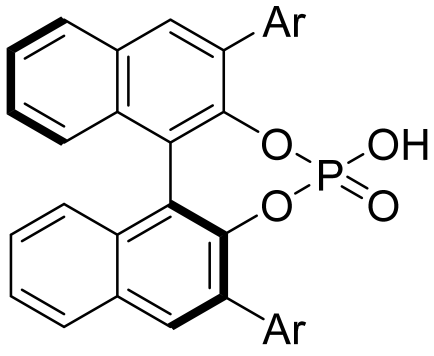
> Hydroxylactam-PSR
  — Good for aliphatic and aromatic aldehydes; *N*-protected products

> Weak Brønsted acid PSR
  — Good for aliphatic and aromatic aldehydes; no *N*-protected products; low conversion rates for unsubstituted tryptamines with aromatic aldehydes

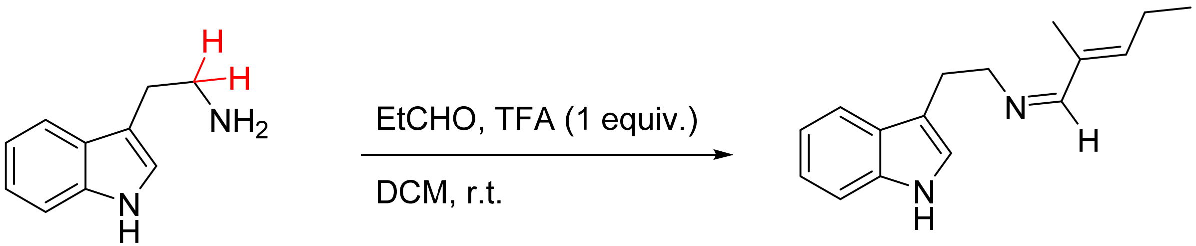
> Internal anion-binding PSR
  — Good for aromatic aldehydes; no *N*-protected products

> **NO SOLUTION FOR TETRAHYDROISOQUINOLINES**

Chiral Phosphoric Acid Catalyzed PSR

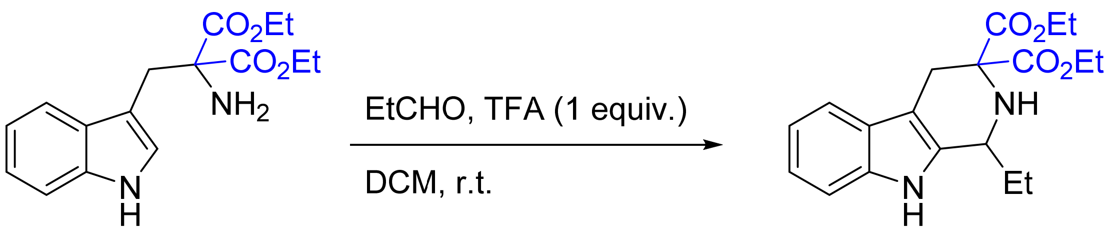


BINOL-Phosphoric Acid PSR



>90%

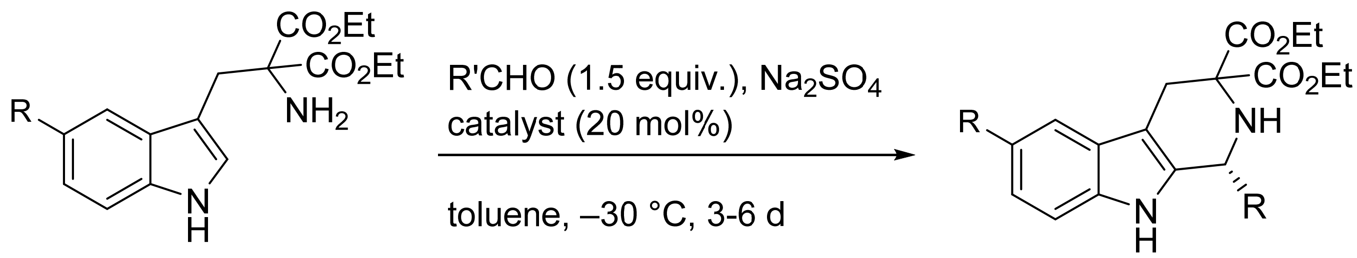
homo-aldol cond.
iminium formation



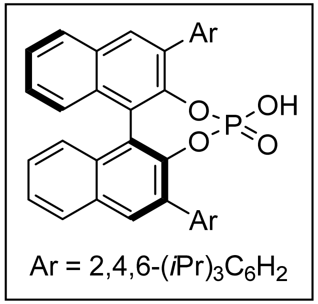
>90%

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

BINOL-Phosphoric Acid PSR



R = H or OMe

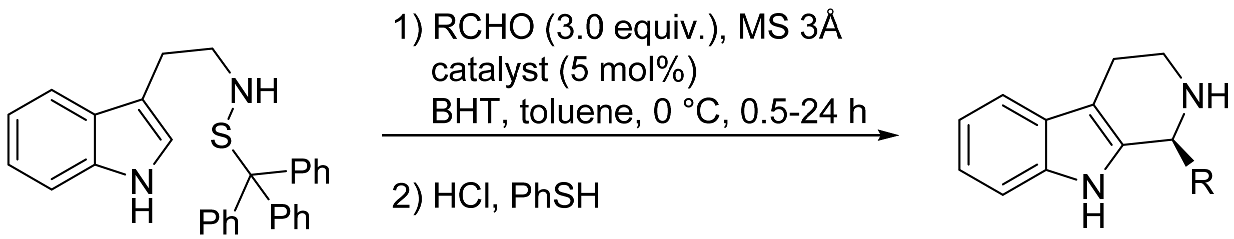


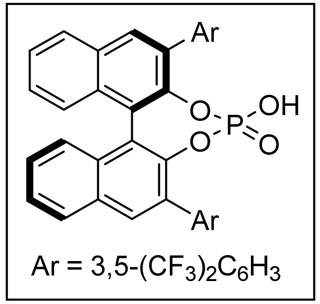
R	R'	yield (%)	ee (%)
H	Et	76	88
OMe	Et	96	90
H	*n*Bu	91	87
OMe	*n*Bu	90	87
OMe	*i*Pr	85	81
OMe	Cy	64	94
OMe[a]	Ph	82	62
OMe[a]	*p*-NO_2-C_6H_4	98	96

a) At -10 °C in DCM

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

BINOL-Phosphoric-Acid PSR: Sulfenyliminium Ions



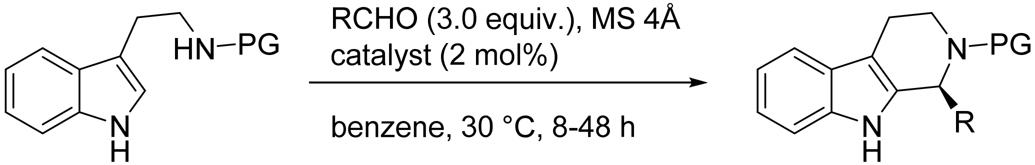


R	time (h)	yield (%)	ee (%)
Me	1	88	30
n-pentyl	2	87	84
*i*Pr	24	77	78
Bn	4	90	87
Ph	24	77	82
p-$NO_2C_6H_4$	24	78	82

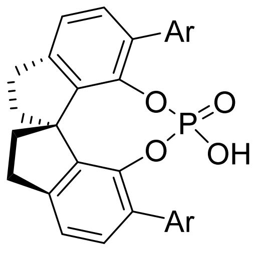
3 g scale-up experiment with *n*-hexanal showed the same selectivity.

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

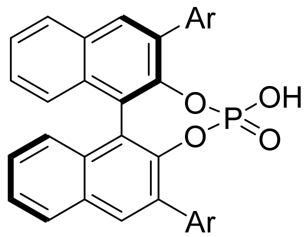
SPINOL-Phosphoric Acid PSR



PG = 1-naphthylmethyl
R = p-BrC_6H_4



1a: Ar = Ph
1b: Ar = 4-biphenyl
1c: Ar = 3,5-$(CH_3)_2C_6H_3$
1d: Ar = 3,5-$(CF_3)_2C_6H_3$
1e: Ar = 1-naphthyl

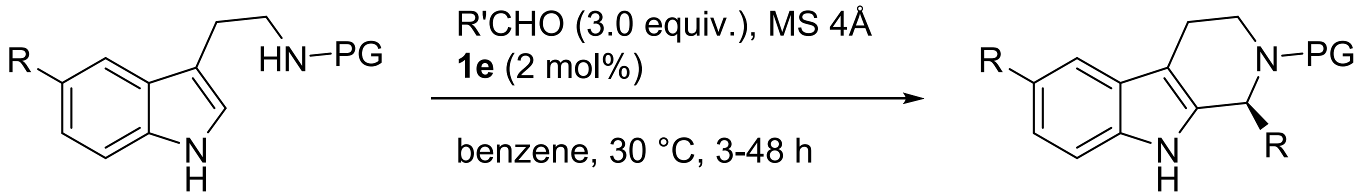


2a: Ar = 3,5-$(CF_3)_2C_6H_3$
2b: Ar = 1-naphthyl

catalyst	t (h)	yield (%)	ee (%)
1a	48	72	87
1b	24	80	75
1c	24	79	87
1d	8	99	96
1e	24	96	98
2a	24	70	79
2b	24	56	44

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

SPINOL-Phosphoric Acid PSR



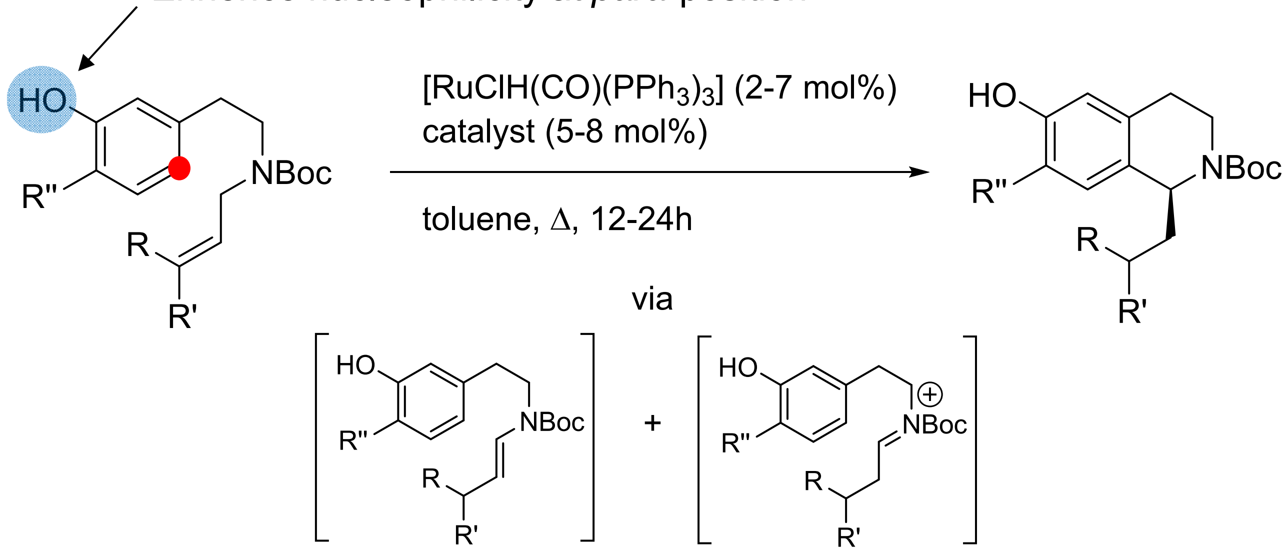
R = H; OMe; Cl
R' = Et; *i*Pr; *n*-pentyl; Ph; *p*-BrC_6H_4; *m*-BrC_6H_4; *p*-$NO_2C_6H_4$; *p*-$MeOC_6H_4$; furyl; piperonyl
PG = 1-naphthylmethyl

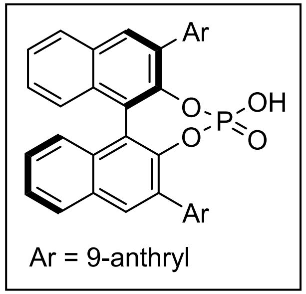
76-99% yield
90% to 98% ee

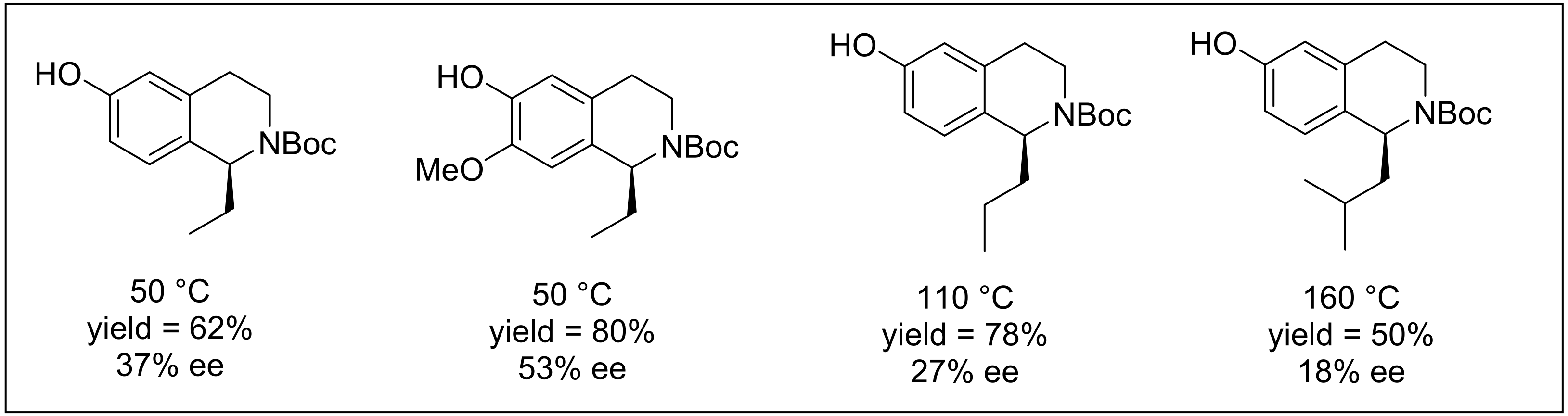
Wang, Y. et al. *Chem. Eur. J.* **2012**, *18*, 3148.

Ruthenium Complex/BINOL-Phosphoric Acid PSR: Tetrahydroisoquinolines

Enhence nucleophilicity at *para*-position

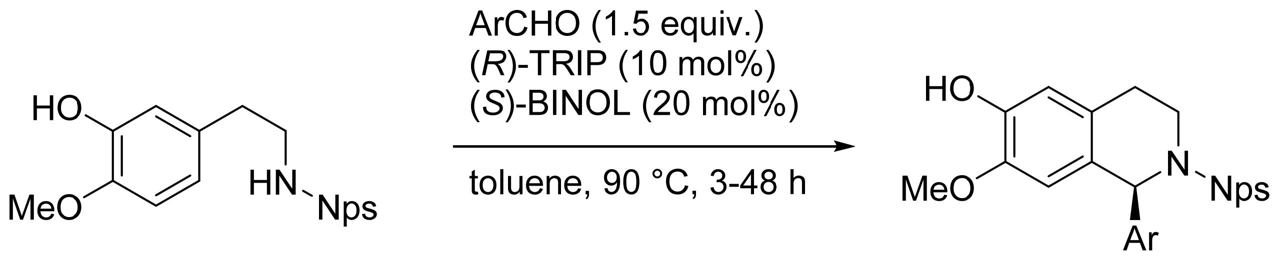


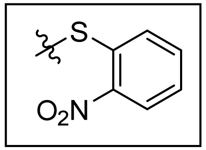


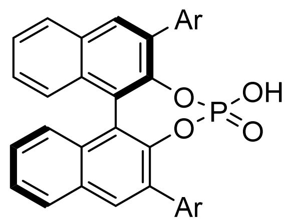


Toda, Y.; Terada, M. *Synlett* **2013**, *24*, 752.

BINOL-Phosphoric Acid PSR: Tetra-hydroisoquinolines







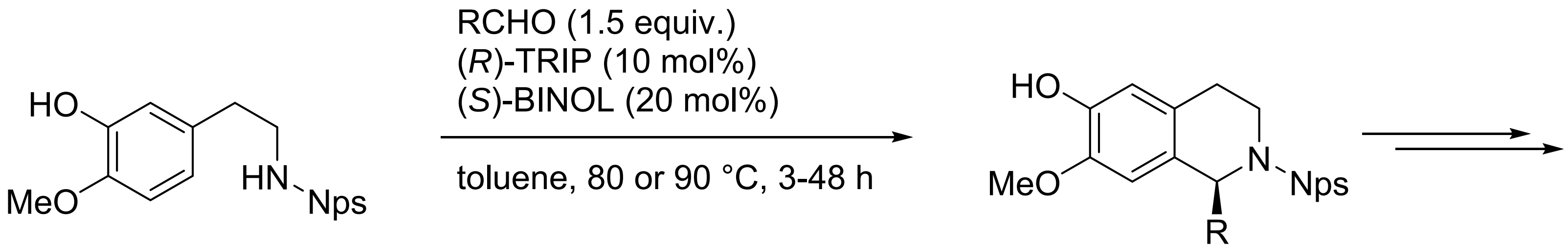
Ar = 2,4,6-(iPr)$_3$C$_6$H$_2$

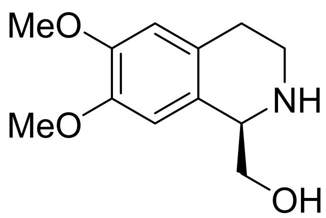
R	yield (%)	ee (%)
n-pentyl[a]	88	70
p-$MeOC_6H_4CH_2CH_2$[a]	84	72
$AcOCH_2$[a]	92	58
Ph	75	26
o-ClC_6H_4	83	0
m-ClC_6H_4	75	47
p-ClC_6H_4	83	71
p-$MeOC_6H_4$	63	0
p-$CF_3C_6H_4$	79	86
p-$NO_2C_6H_4$	51	68

a) **Aliphatic aldehydes:** Other enantiomer is formed.
5 mol% (*R*)-TRIP, 20-50 mol% AcOH and 80 °C.

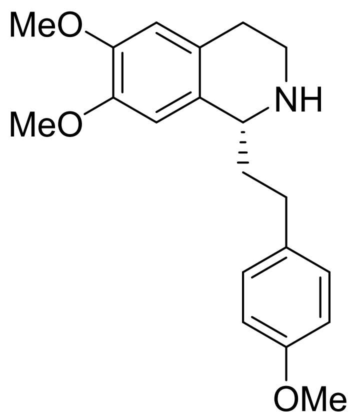
Hiemstra, H. et al. *J. Org. Chem.* **2014**, *79*, 7380.

BINOL-Phosphoric Acid PSR: Tetra-hydroisoquinolines

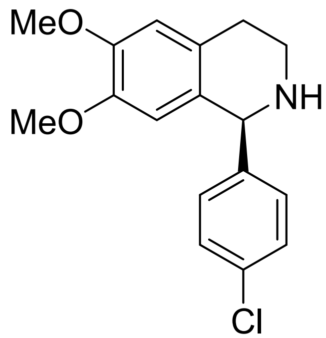




(*R*)-(-)-calycotomine
(97% ee)



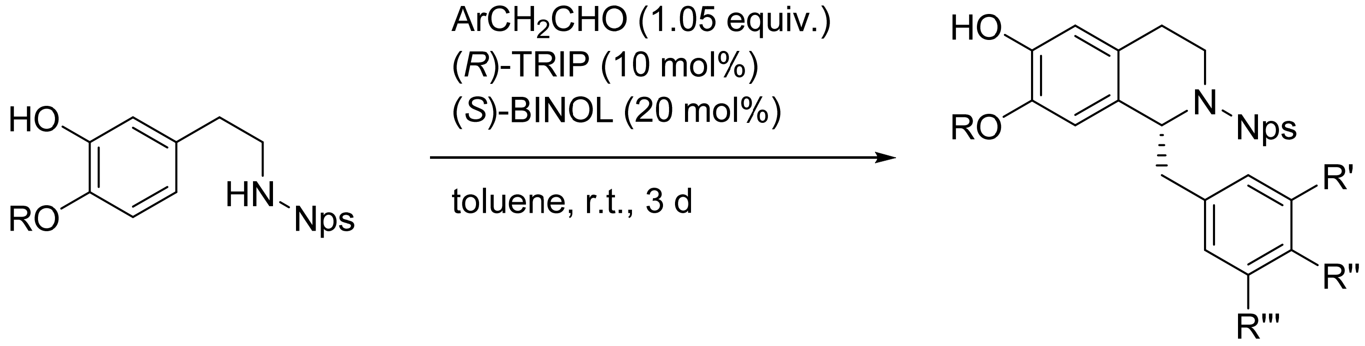
(*R*)-(+)-colchietine
(98% ee)



(*S*)-(+)-AMPA-
antagonist (99% ee)

Hiemstra, H. et al. *J. Org. Chem.* **2014**, *79*, 7380.

BINOL-Phosphoric Acid PSR: Tetra-hydroisoquinolines



R = Me or MOM
R', R'', R''' = H or OTBS or OMe

70-85% yield
86-92% ee

Hiemstra, H. et al. *J. Org. Chem.* **2015**, *80*, 5125.

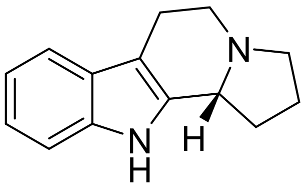
Chiral Phosphoric Acid Catalyzed PSR

- Similar ee with tryptamine(derivatives) compared to thiourea catalyzed process

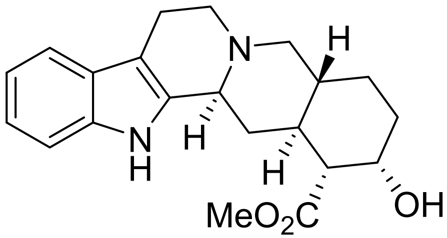
- Alkyl-, aryl- and benzylic aldehydes used as substrates

- **Possibility of converting β-phenethylamine to tetrahydro-isoquinolines**
  - Activation of aromatic moiety with *para*-hydroxyl-group

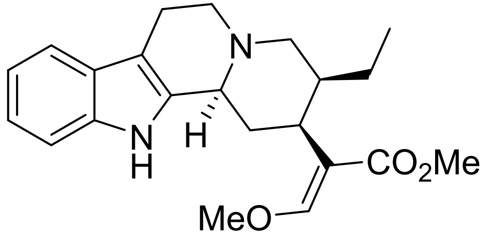
Selection of Alkaloids synthesized by enantioselective PSR



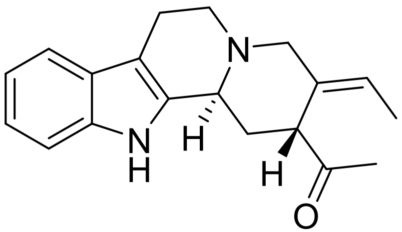
(+)-hermicine



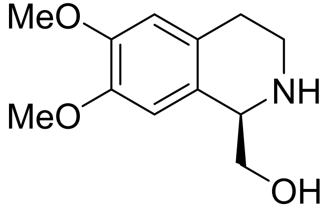
(+)-yohimbine



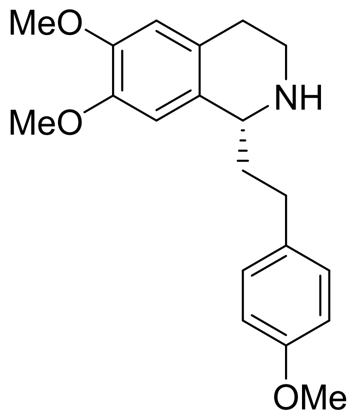
(-)-corynantheidine



(+)-arboricine



(-)-calycotomine



(+)-colchietine

Thank you for your attention