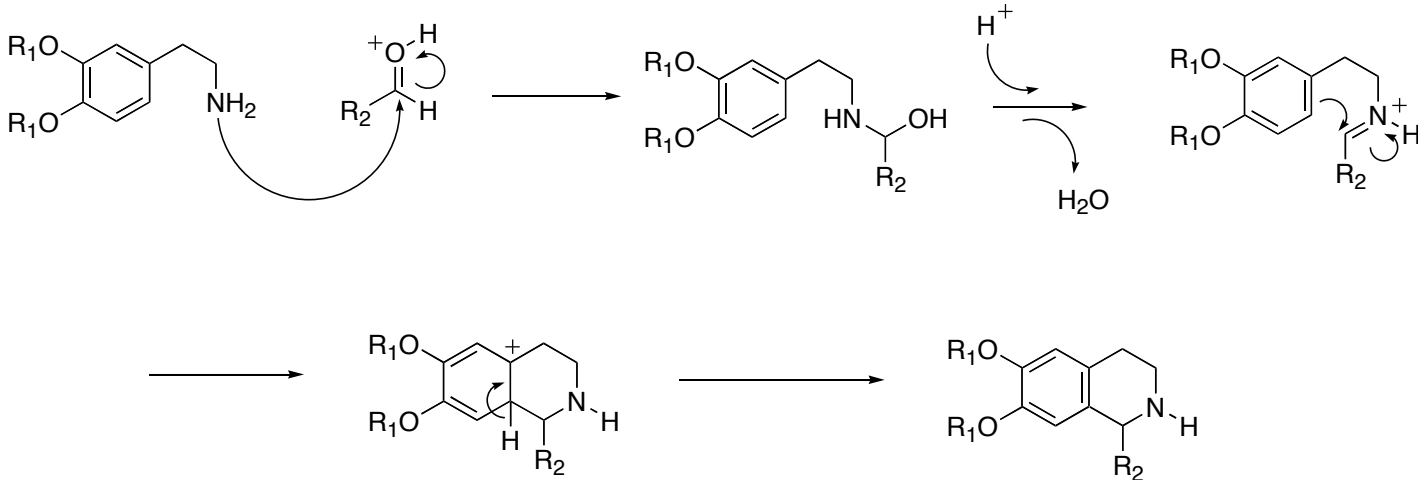
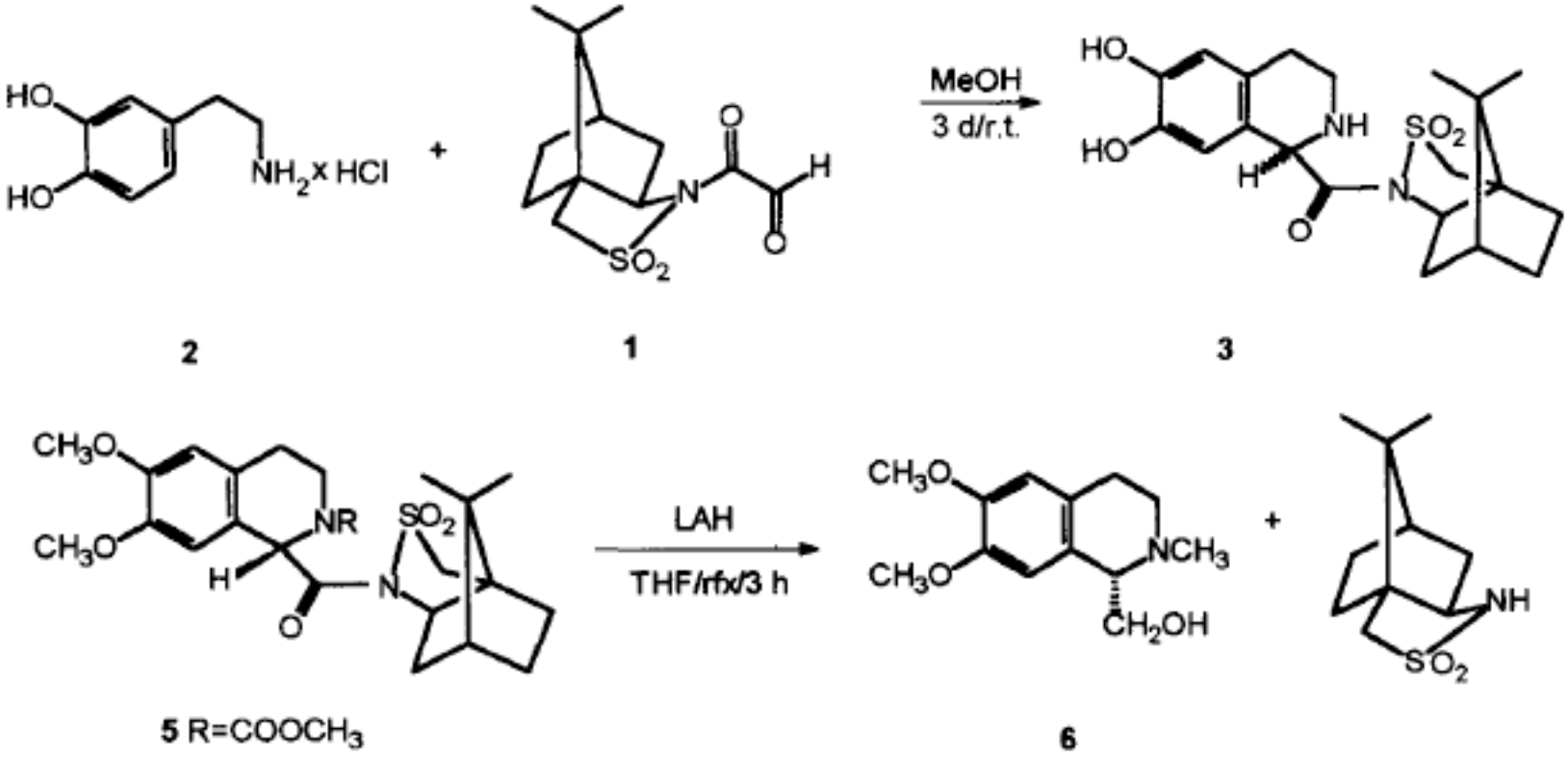
Highly Enantioselective Catalytic Acyl-Pictet-Spengler Reactions

Taylor, M. S.; Jacobsen, E. N. *JACS asap*, **2004**.



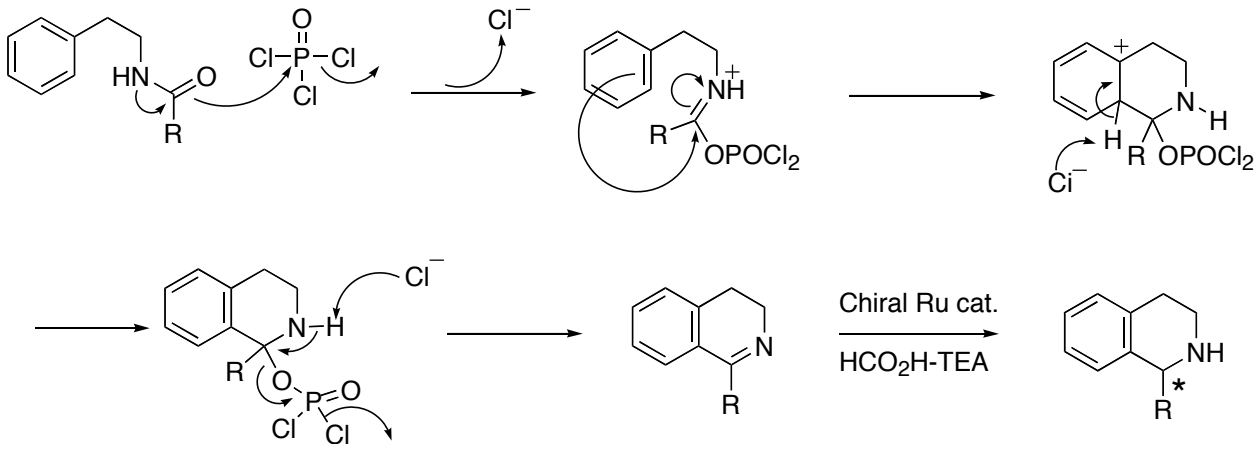
Previous enatioselective Pictet-Spengler Reactions

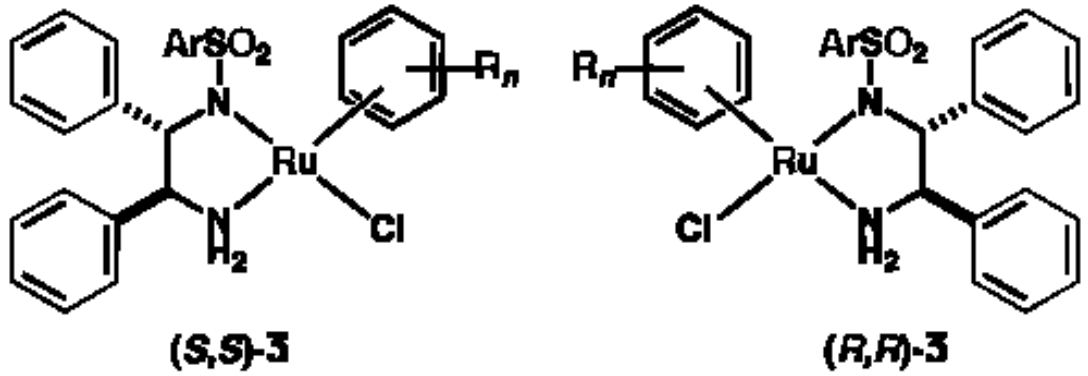
1. Czarnocki, Z. et al. *Tetrahedron; Asymmetry* **1995**, 2899.
2. Substrate-controlled Pictet-Spengler cyclization.
3. Compound 3 (89:11, major isomer in 57 % yield).
4. 79 % yield, 92 %ee from 3 to 6.
5. Chiral auxiliary was recovered in 92 % yield.



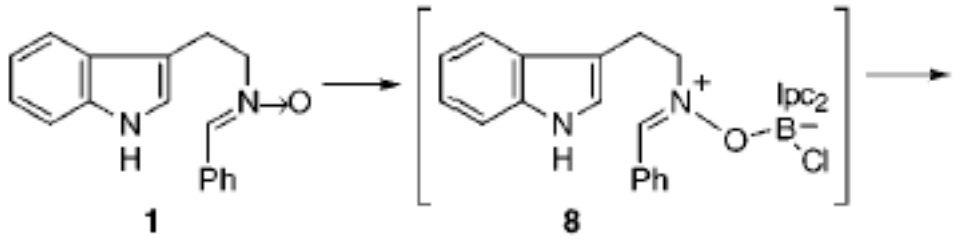
Catalytic approach

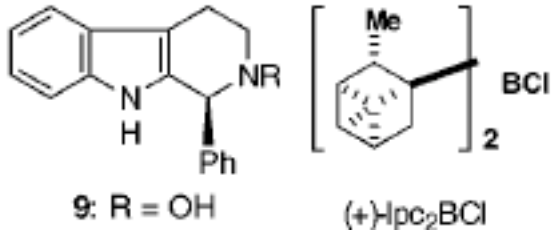
1. Noyori, R. et al. *JACS*, **1996**, 4916.
2. Cyclic imines accessed by Bischler-Napieralski reaction.
3. Asymmetric hydrogenation of cyclic imines.
4. 77~97 %ee in 72~99 % yield.
5. 0.4 mol% loading of Ru catalyst.





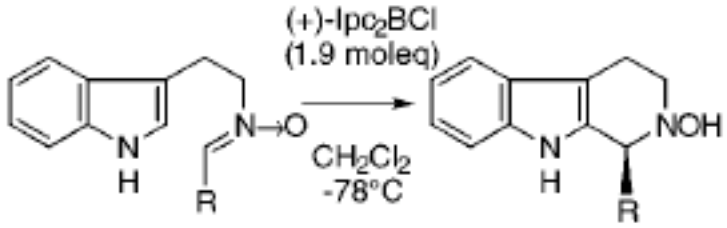
Chiral Lewis acid-mediated enatioselective Pictet-Spengler reactions of N_β-Hydroxytryptamin with aldehydes





1. Nakagawa, M. et al. *JOC*, **1998**, 6348.
2. The use of superstoichiometric quantaties of boron reagents.
3. Restricted to N_β-hydroxytryptamine-derieved nitrones.
4. Up to 90 %ee

Table 2. Pictet–Spengler Reaction of Nitrones Catalyzed by (+)-Ipc₂BCl



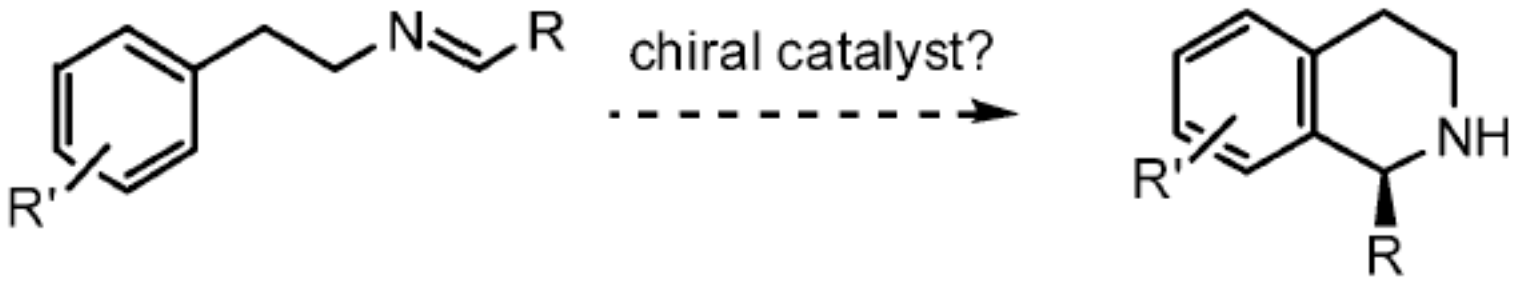
1: R = Ph
2: R = *p*-MeO-C_6H_4
3: R = *p*-NO_2-C_6H_4
4: R = 1-Naphthyl
5: R = Me
6: R = *i*-Bu

9: R = Ph
15: R = *p*-MeO-C_6H_4
16: R = *p*-NO_2-C_6H_4
17: R = 1-Naphthyl
18: R = Me
19: R = *i*-Bu

			β-carboline	
entry	nitrone	time (h)	yield (%)	% ee
1	**1**	6	**9** (92)	75 (*S*)
2	**2**	3	**15** (65)	90 (*S*)
3	**3**	1	**16** (81)	0.6
4	**4**	1	**17** (94)	86 (*S*)
5	**5**	3	**18** (91)	43 (*S*)
6	**6**	4	**19** (75)	35 (*S*)

Scheme 1. Approaches to Catalysis of Enantioselective Pictet–Spengler Reactions

A. The Pictet-Spengler reaction

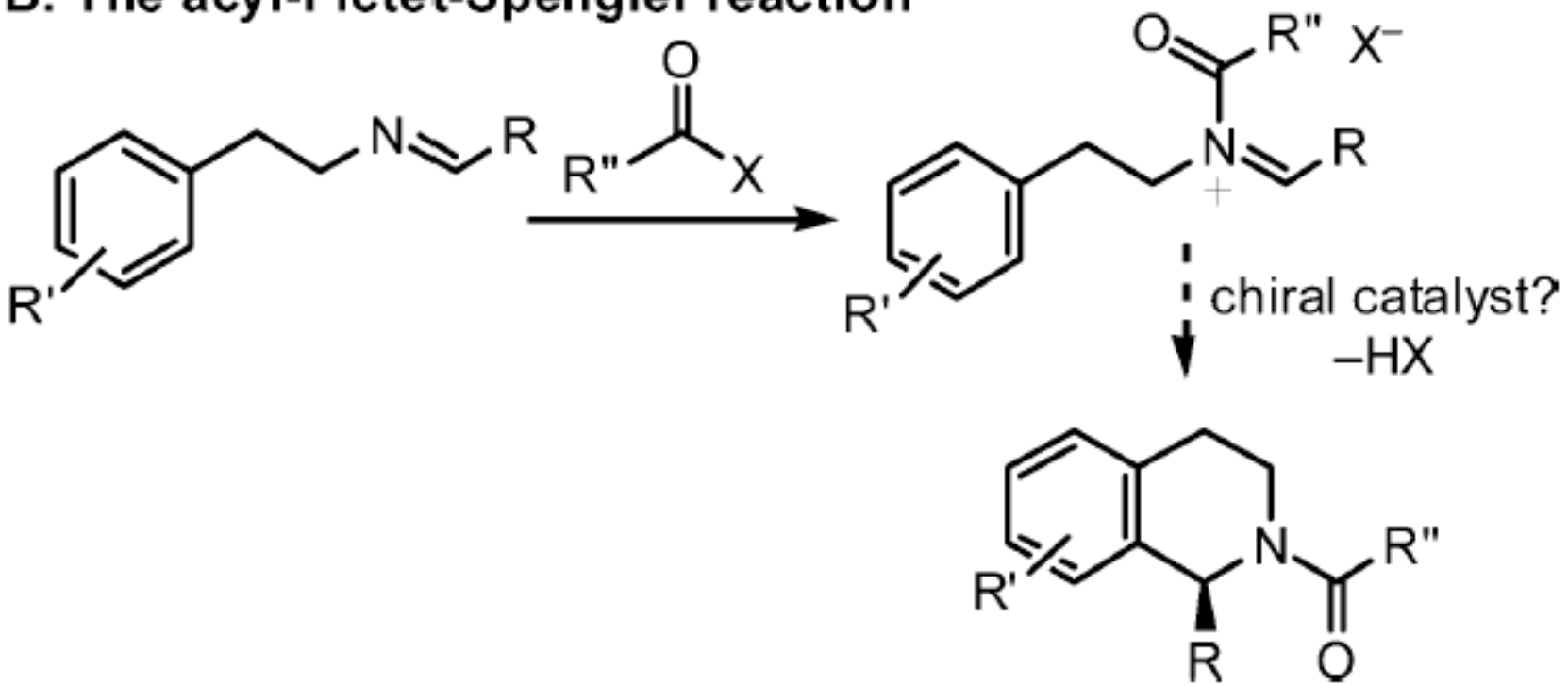


1. The challenge of an asymmetric catalytic Pictet-Spengler reaction
   ; the low reactivity of the imime substrates
2. Strong Bronsted acids; racemic pathway.
   Lewis acid catalysis; highly reactive reagents, high temperature often.
3. A screen of potential chiral catalysts didn't afford any useful leads.

⇓

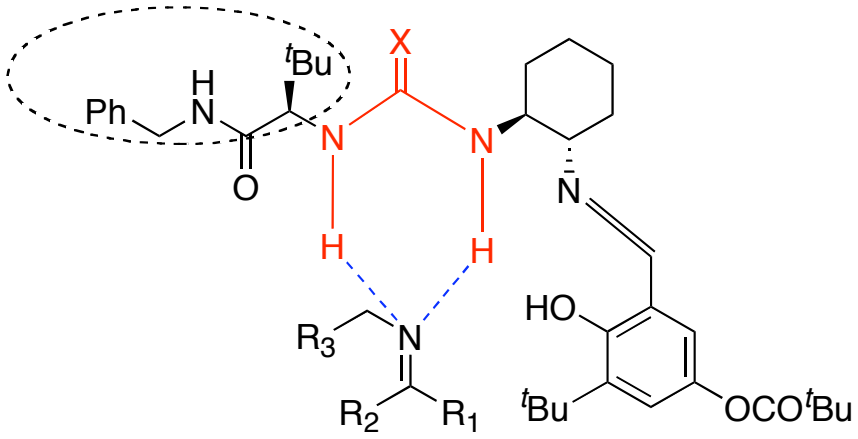
More reactive imtermidiates; under relatively mild conditions

B. The acyl-Pictet-Spengler reaction



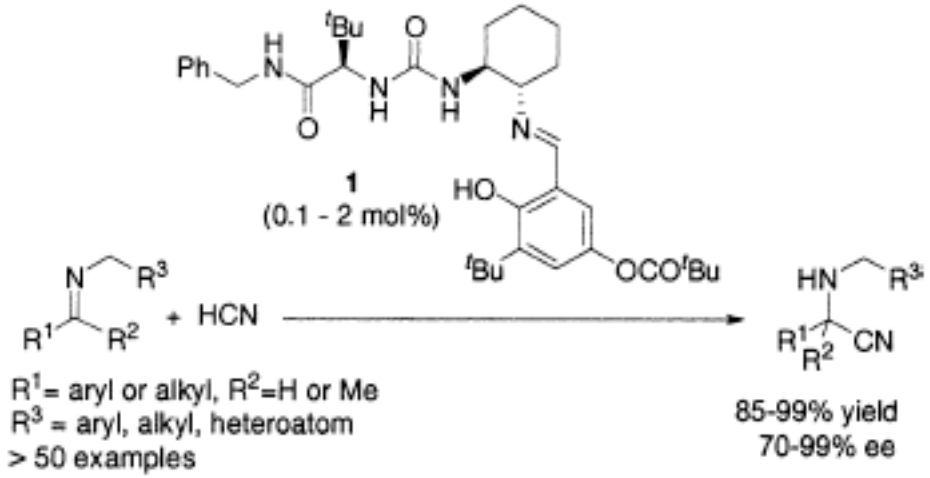
1. How to enhance the reactivity of imine or iminium intermediates ;N-acyliminium intermediates; highly active electrophiles.
2. ? by a relatively mild Lewis or Bronsted acid catalyst.
3. Chiral thiourea catalyst.
   ; activate a weakly Lewis bsaic N-acyliminium ion using a chiral hydrogen bond donor.

Thiourea catalyst



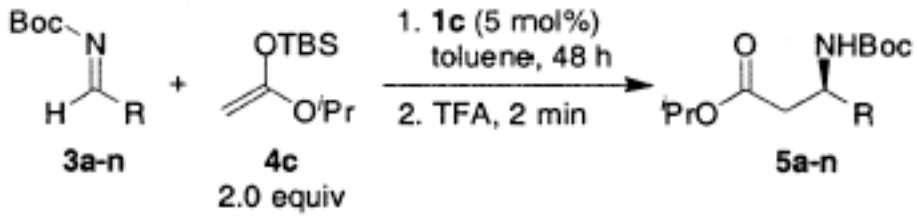
1. Jacobsen, E. N. et al. *JACS*, **2002**, 10012.
2. Reversible formation of an imine-catalyst complex, presumably through a hydrogen bond between the imine nitrogen and an acidic proton of the catalyst.
3. Only the two urea hydrogens of the catalyst is essential for catalyst activity.
4. Increasing the steric bulk of the amino acid side chain had a beneficial effect.
5. A thiourea group improve enantioselectivity.
6. Wider range of substrate in Strecker reaction.

Scheme 1. Asymmetric Strecker Reaction Catalyzed by **1**



JACS, **2002**, 10013

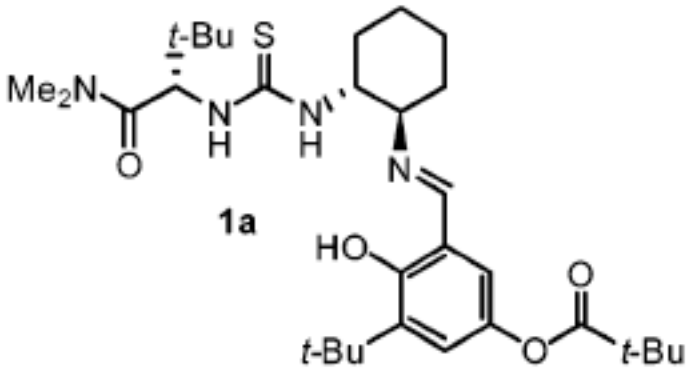
Table 2. Mannich Reactions Catalyzed by **1c**



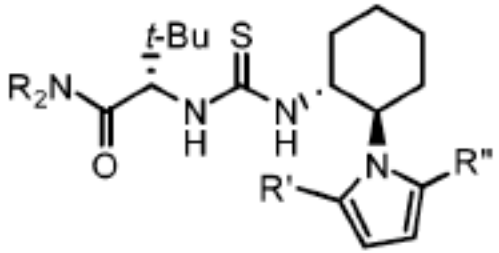
-40 °C, 48 h
R =aryl, >90 % yield, >90 %ee

JACS, **2002**, 12964

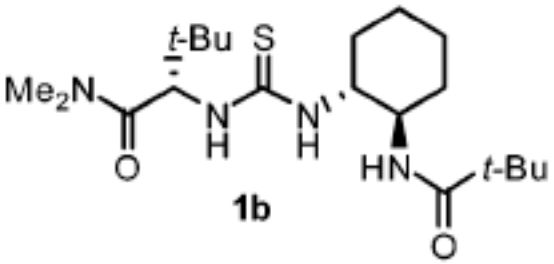
Table 1. Optimization of Catalyst Structure



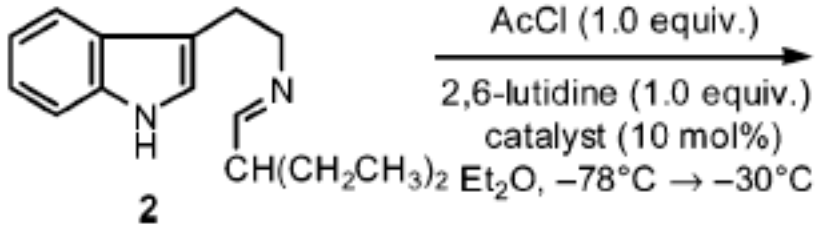
1a



1c: R = CH_3, R = R" = CH_3
1d: R = CH_3, R' = R" = Ph
1e: R = CH_3, R' = CH_3, R" = Ph
1f: R = *i*-Bu, R' = CH_3, R" = Ph



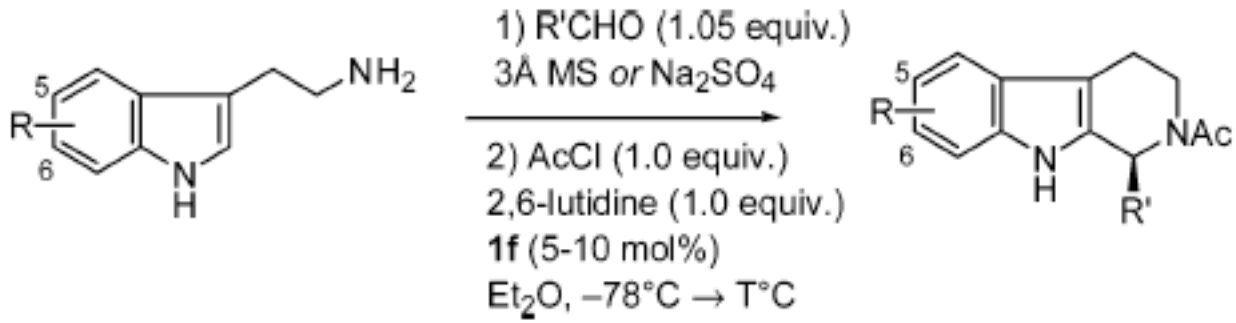
1b



2 **3a**

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

Table 2. Asymmetric Acyl-Pictet–Spengler Reactions Catalyzed by **1f**



product	R	R′	*T* (°C)	yield (%)[a]	ee (%)[b]
3a	H	$CH(CH_2CH_3)_2$	−30	65[c]	93
3b	H	$CH(CH_3)_2$	−40	67[d]	85
3c	H	*n*-C_5H_{11}	−60	65[d]	95
3d	H	$CH_2CH(CH_3)_2$	−60	75[d]	93
3e	H	CH_2CH_2OTBDPS	−60	77[d]	90
3f	5-MeO	$CH(CH_2CH_3)_2$	−40	81[c]	93
3g	6-MeO	$CH(CH_2CH_3)_2$	−50	76[d]	86

Limitation; The substrates derived from aromatic aldehydes or trimethylacetaldehyde display low activity.

1. Access to a range of substituted tetrahydro-β-carboline in high ee.
2. Enantioselective transformation using a chiral H-bond donor.

3. Examination of the mechanism of this transformation.
4. Application in alkaloid synthesis.