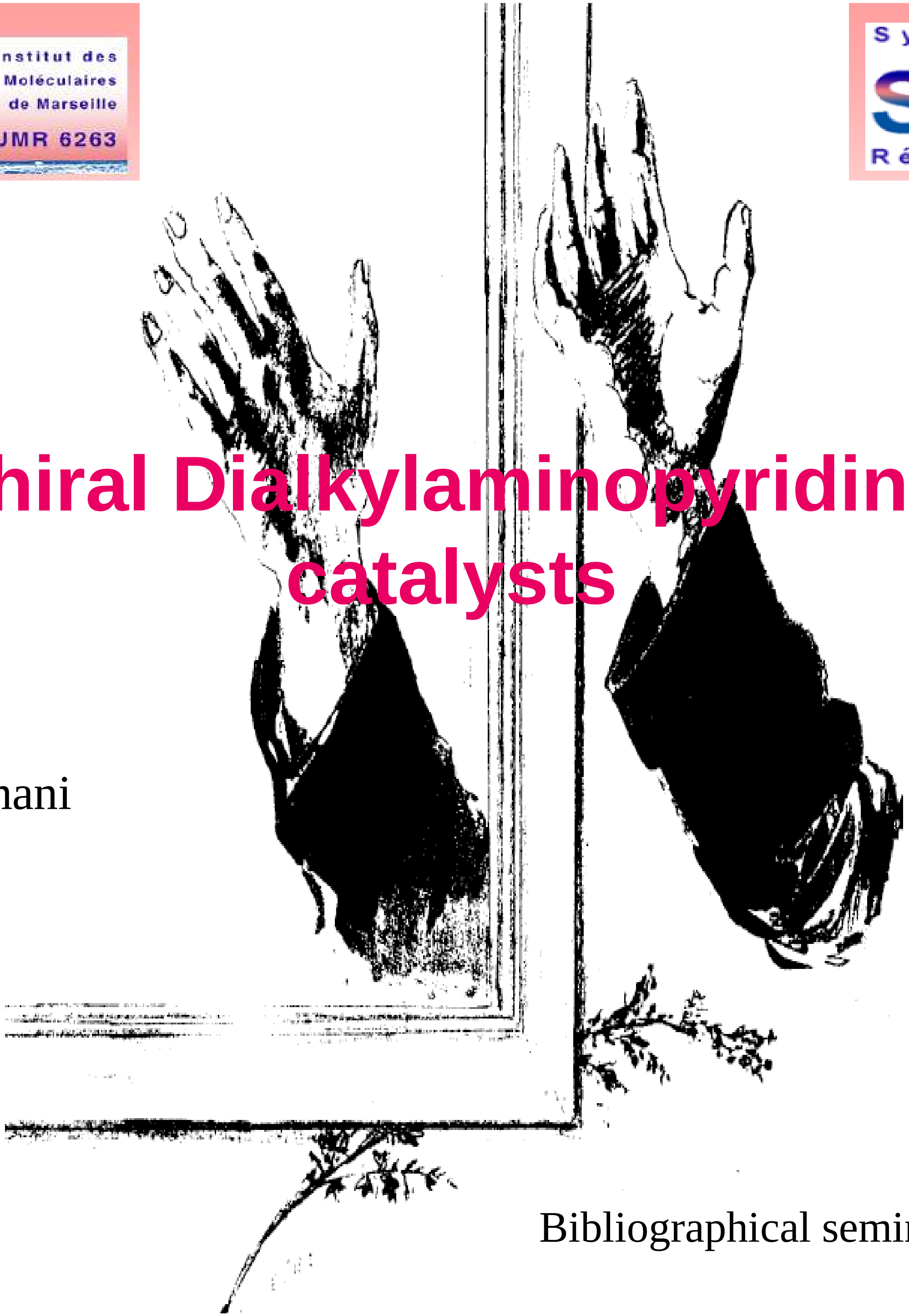
Institut des Sciences Moléculaires de Marseille
UMR 6263

Synthèse Totale et Réactivité Organique
StéRéO



Chiral Dialkylaminopyridine catalysts

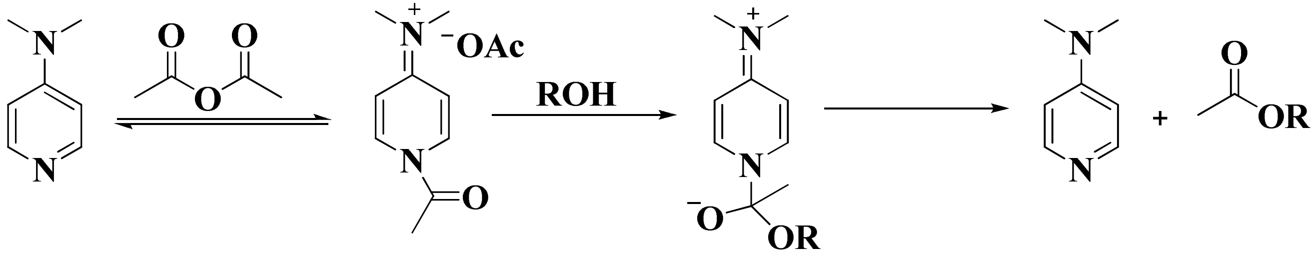
Hadjira Habib Zahmani

Bibliographical seminar, 09 / 12 / 08

DMAP in Chemistry History

- First use in 1967

- First acylation of alcohol in 1969



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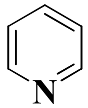
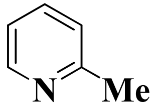
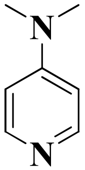
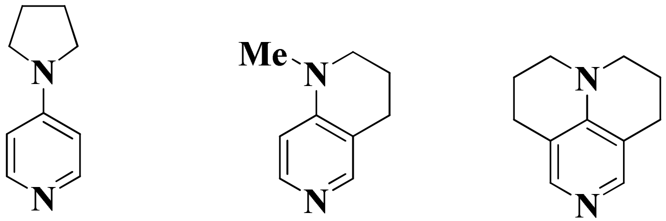
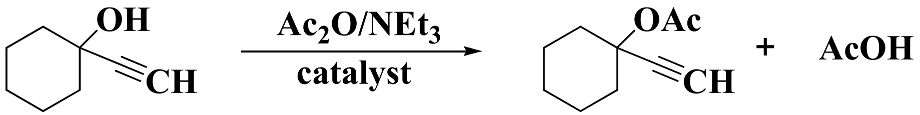
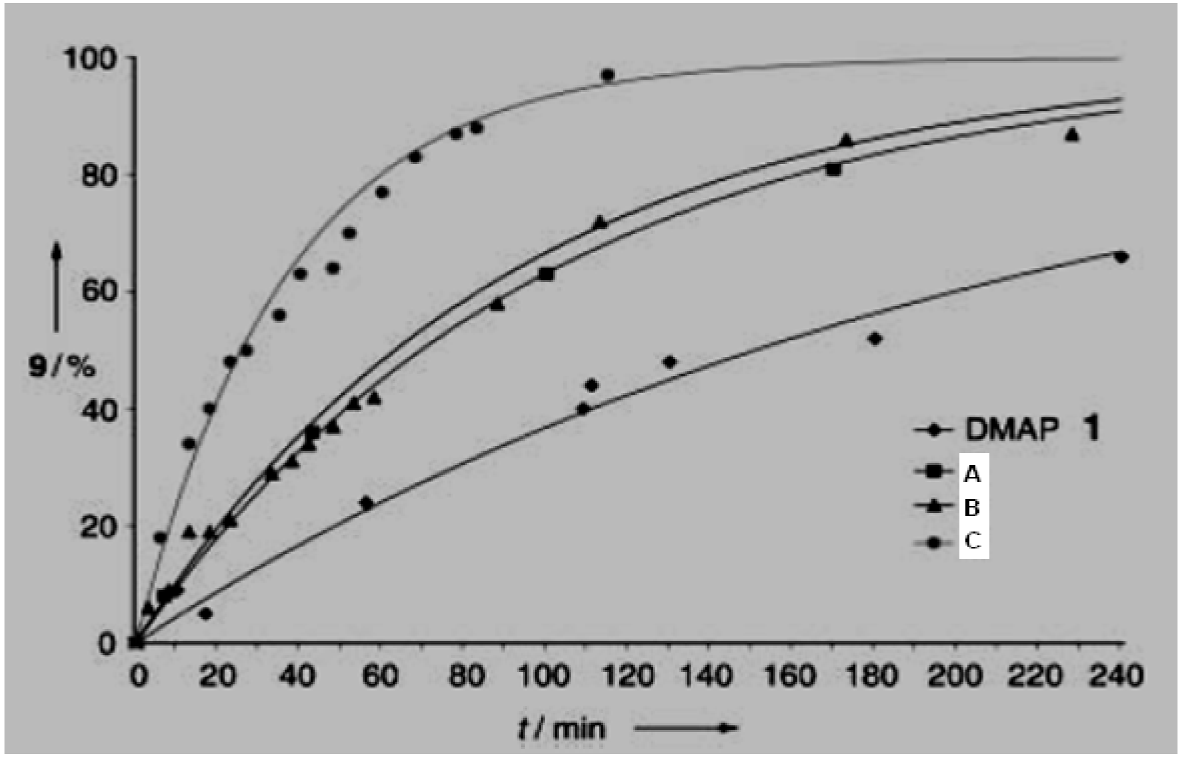
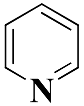
	1
	0,047
	$3{,}7.10^4$

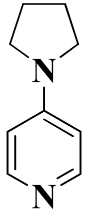


Litvinenko, L. M.; Kirichenko, A.I. *Dokl. Akad. Nauk. SSSR* **1967**, 176, 97.
Steglish, W.; Höfle, G. *Angew. Chem. Int. Ed*. **1969**, 8, 981.
Heinrich, M. R.; Klisa, H. S.; Mayr, H.; Steglish, W.; Zipse, H. *Angew. Chem. Int. Ed*. **2003**, 42, 4827. Singh, S.; Das, G.; Singh, O. V.; Han, H. *Tetrahedron Lett***.** **2007**, 48, 1983.









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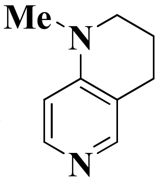

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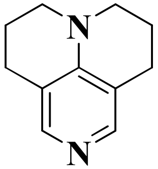

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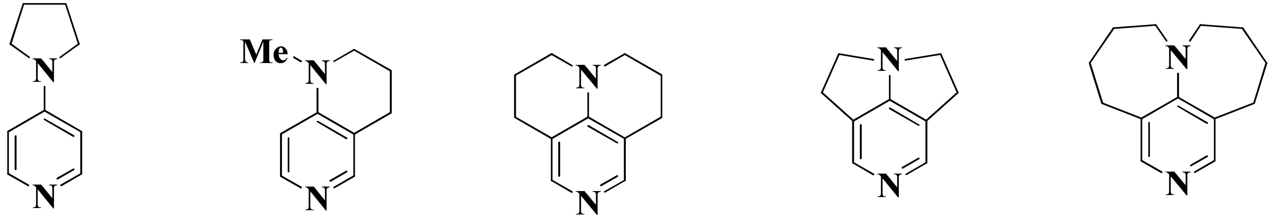
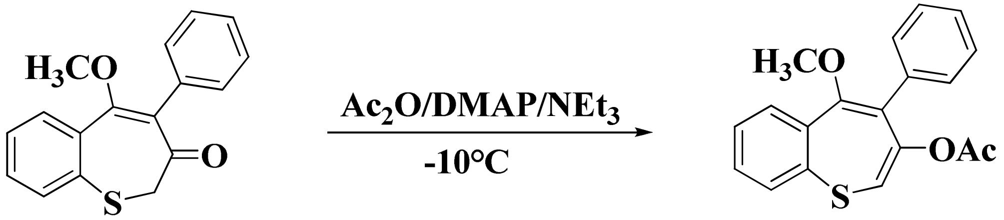


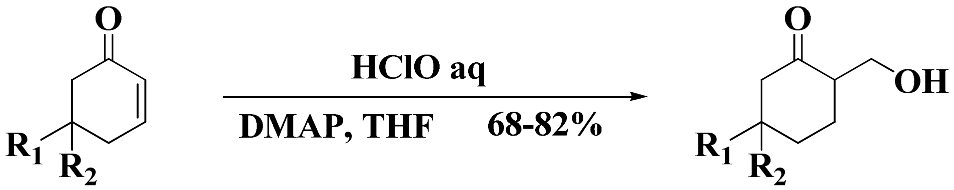
Heinrich, M. R.; Klisa, H. S.; Mayr, H.; Steglish, W.; Zipse, H. *Angew. Chem. Int. Ed*. **2003**, 42, 4827.

DMAP use: examples

- O-Acylation of enolates



- Moritta- Bayllis Hillman reaction

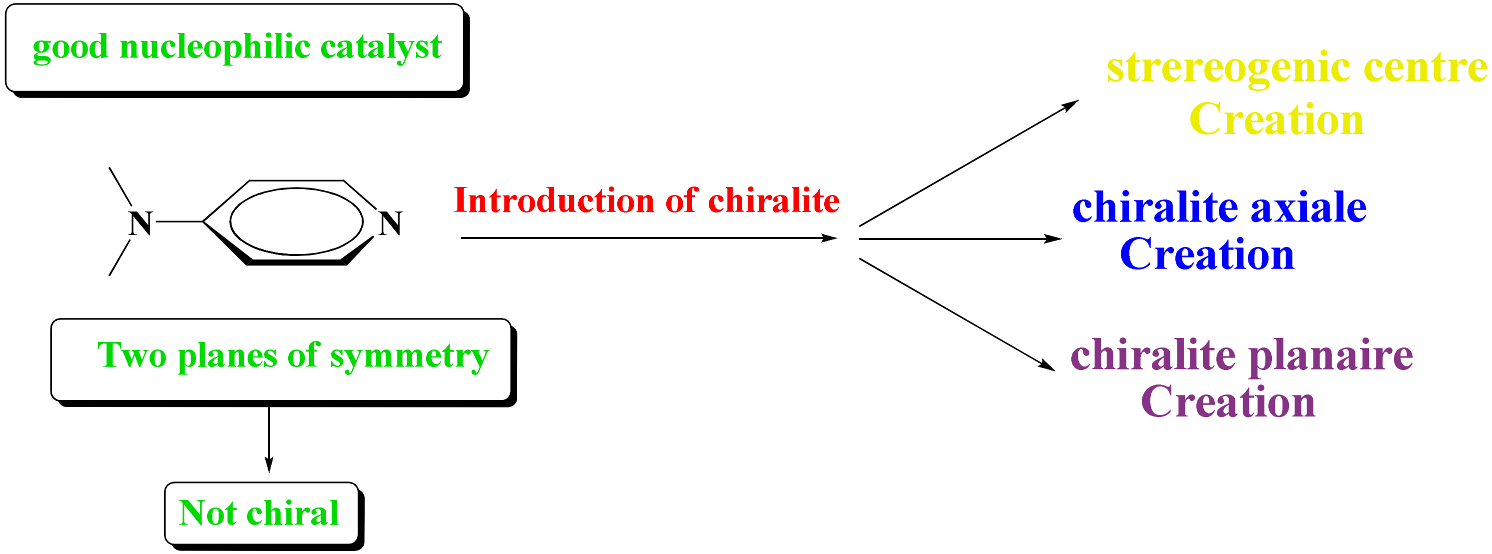


Hofmann, H.; Haberstrosh, H.-J.; Appler, B.; Meyer, B.; Herterich, H. *Chem. Ber*. **1975**, 108, 3596.
Steglish, W.; Höfle, G.*Chem. Ber*. **1972**, 5, 4727.
Rezgui, F.; El Gaied, M. M. *Tetrahedron Lett*. **1998**, 39, 5965.

How to obtain pure enantiomer?

Among usual strategies used in enantiopur synthesis, five different approaches might be found:

1) Use of chiral pool as starting material
2) Resolution of racemic compounds
3) Enzymes use
4) Chiral catalysts use
5) Chiral auxiliaries use



good nucleophilic catalyst

Two planes of symmetry

Not chiral

Introduction of chiralite

strereogenic centre Creation

chiralite axiale Creation

chiralite planaire Creation

France, S.; Guerin, D. J.; Miller, S. J.; Leclka, T.; Herterich, H. *Chem. Rev*. **2003**, 103. 2985.
Wurz, R.P. *Chem. Rev* . **2007**, 107, 5570.

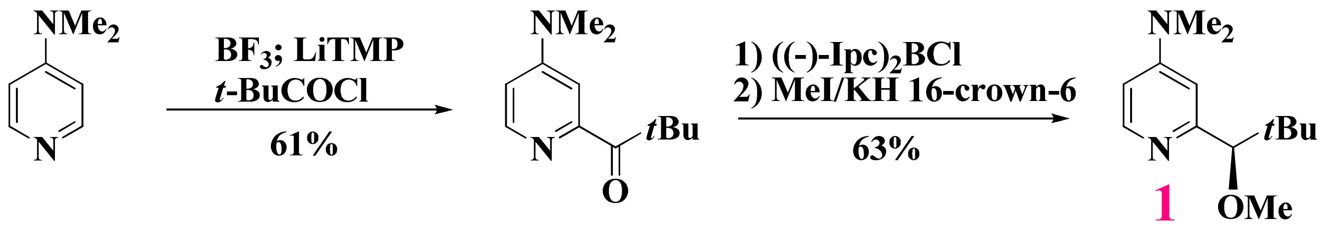
Kinetic resolution

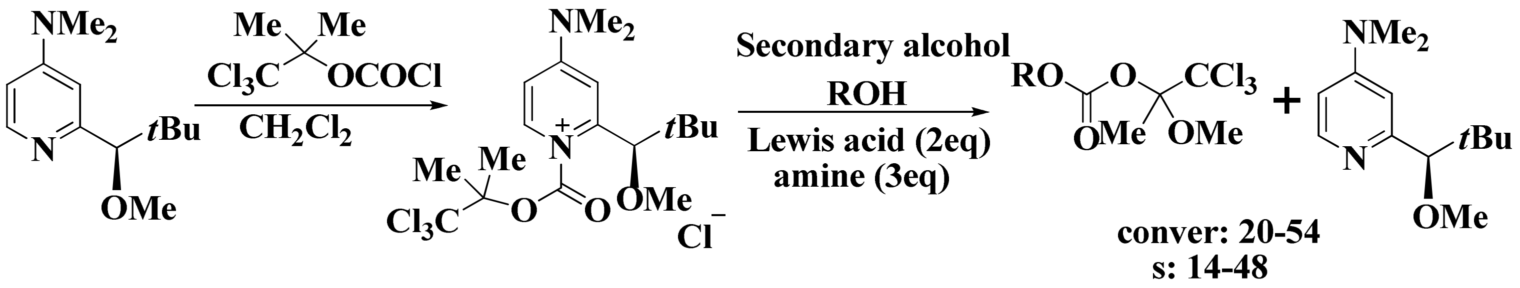
In a kinetic resolution, both enantiomer from racemic substrate react with different speeds to give chiral product or not.
The enantiomer ratio is depending on energy difference between diastereoisomeric transition states.
The kinetic resolution of racemic secondary alcohol has served at the primary testing ground for the design and the development of chiral DMAP derivatives

$$\text{Selectivity factor} = s = K_{\text{fast enantiomer}} / K_{\text{slow enantiomer}}$$

I- Catalysts with stereogenic center

I.1- Vedejs’s chiral DMAP derivative



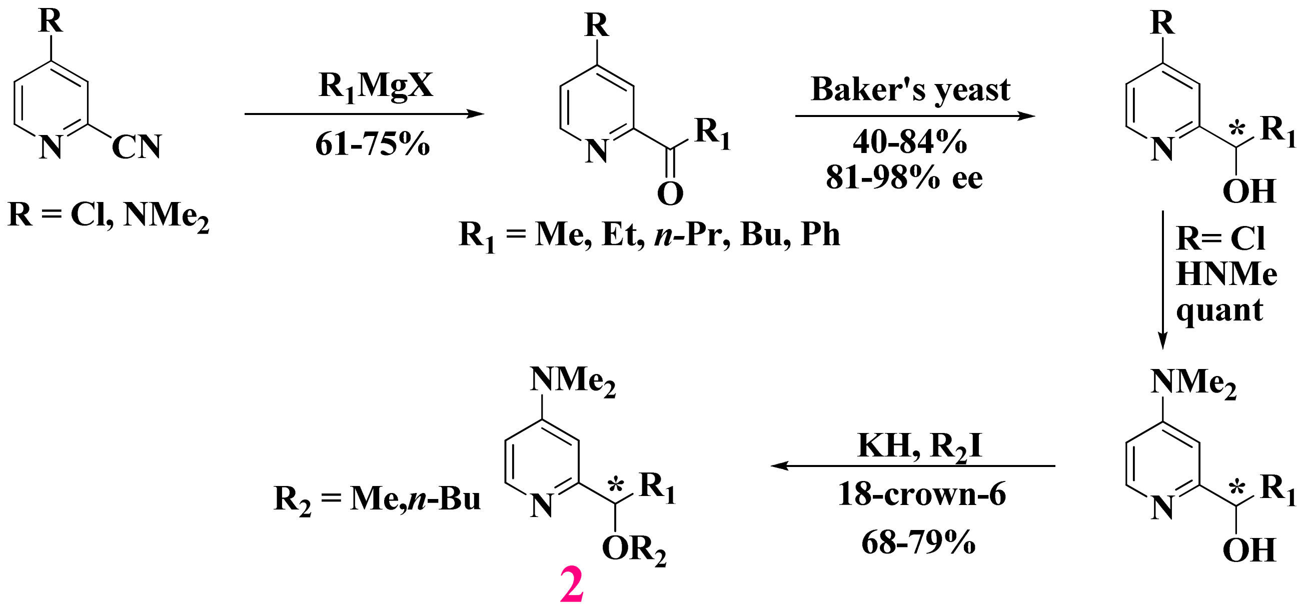


1 is recovered unchanged after aqueous workup, no change in ee after five acylations cycles.

Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, 118, 1809.
Vedejs, E. *Angew. Chem. Int. Ed.* **2005**, 44, 3974.

I- Catalysts with stereogenic center

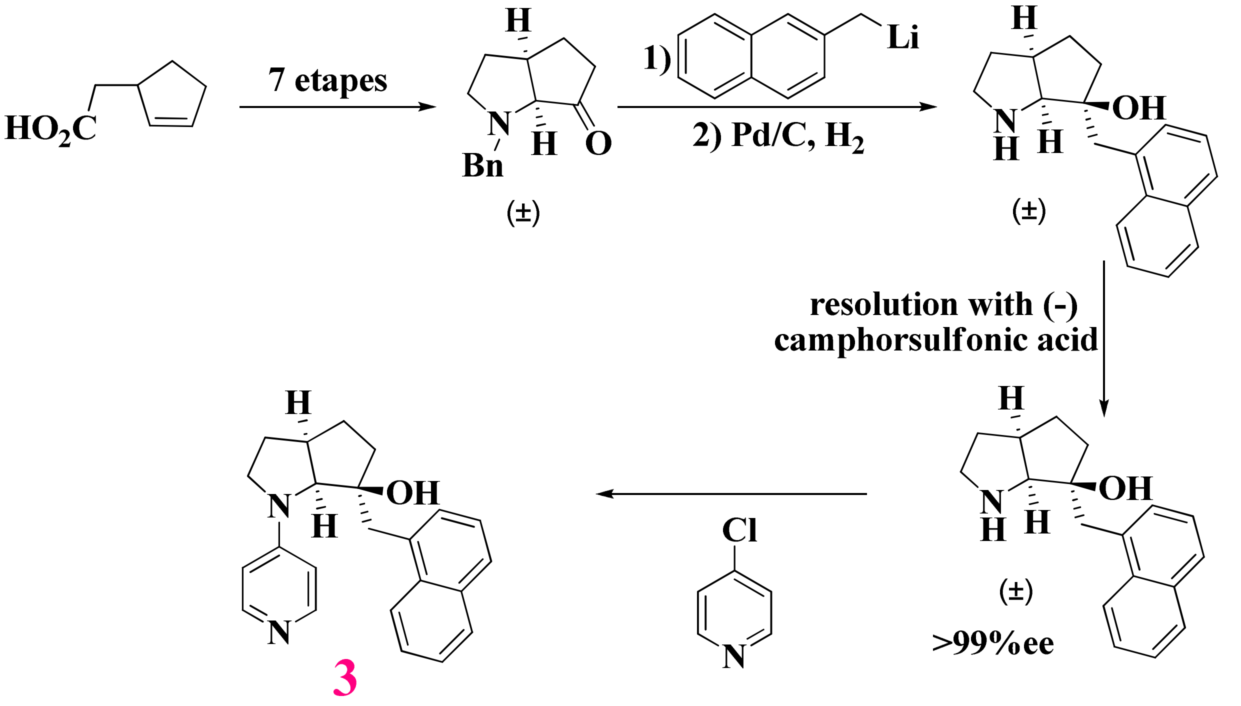
I.2- Gotor’s chiral DMAP derivative

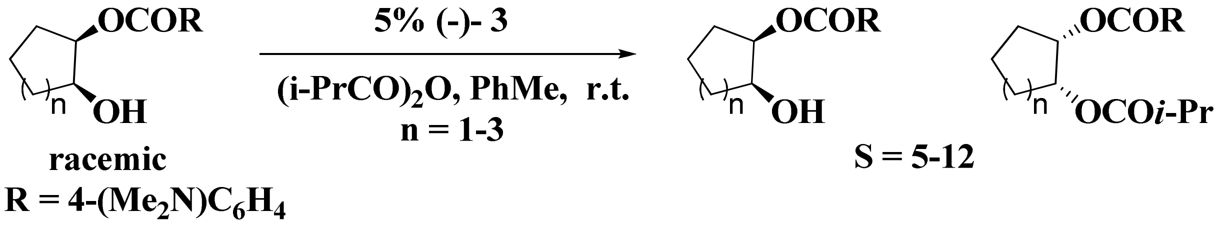


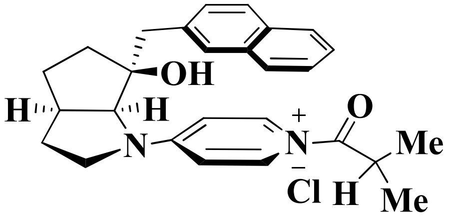
Busto, E.; Gotor-Fernanadez, V.; Gotor, V.; Meyer, B. *Tetrahedron: Asymmetry*, **2005**, 16, 3427.

I- Catalysts with stereogenic center

I.3. - Fuji's chiral PPY derivative





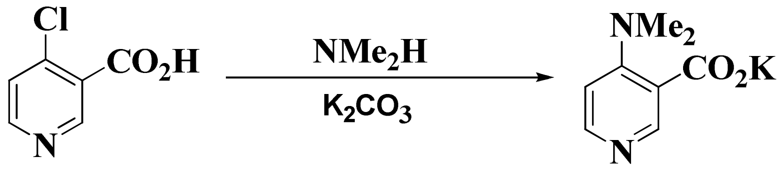


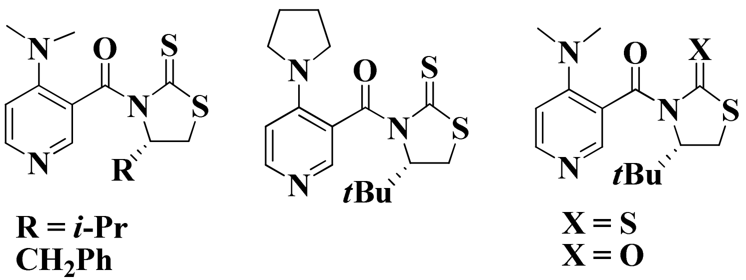
"Closed conformation"

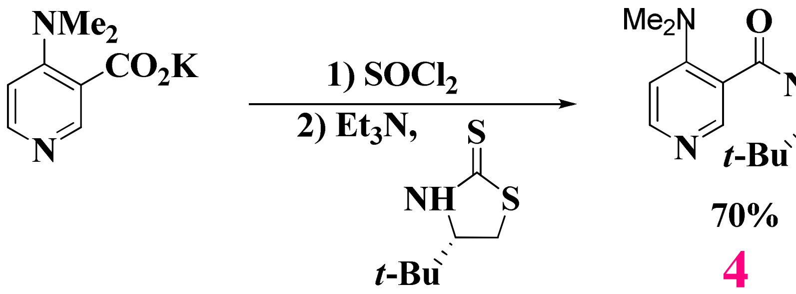
Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, 119, 3169.
Kawabata, T.; Yamamoto, K.; Momose, Y.; Yoshida, H.; Nagaoka, Y.; Fuji, K. *Chem. Commun.* **2001**, 2700.

I- Catalysts with stereogenic center

I.4 - Yamada’s chiral DMAP derivative

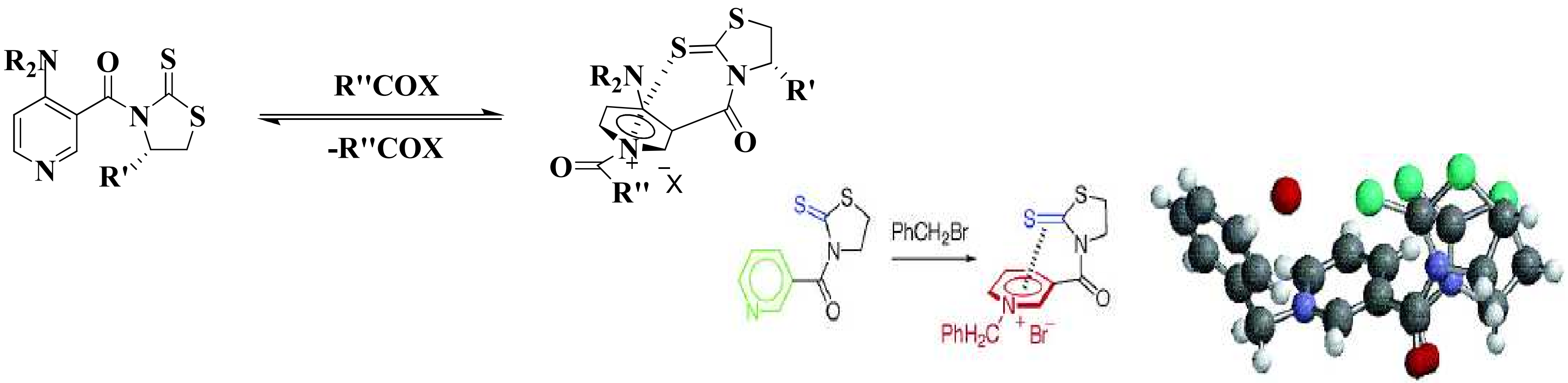






70%

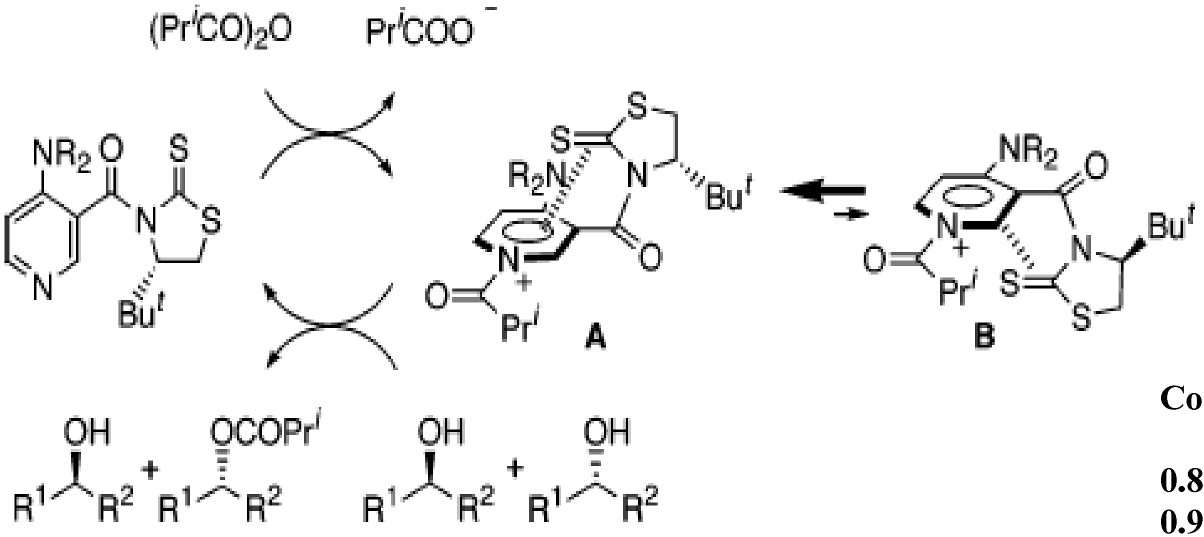
4



Yamada, S.; Katsumata, H. *J. Org. Chem.* **1999**, 64, 9365.

Yamada, S.; Misino, T.; Iwai, Y.; Masumizu, A.; Akiyama, Y. *J. Org. Chem.* **2006**, 71, 6872.

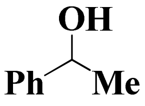
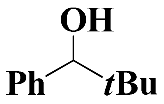
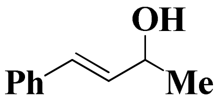
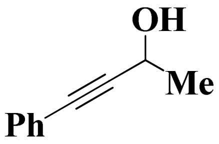
I- Catalysts with stereogenic center



Plausible catalytic cycle for asymmetric acylation of *sec*-alcohols

Conditions : 0.5 of 4

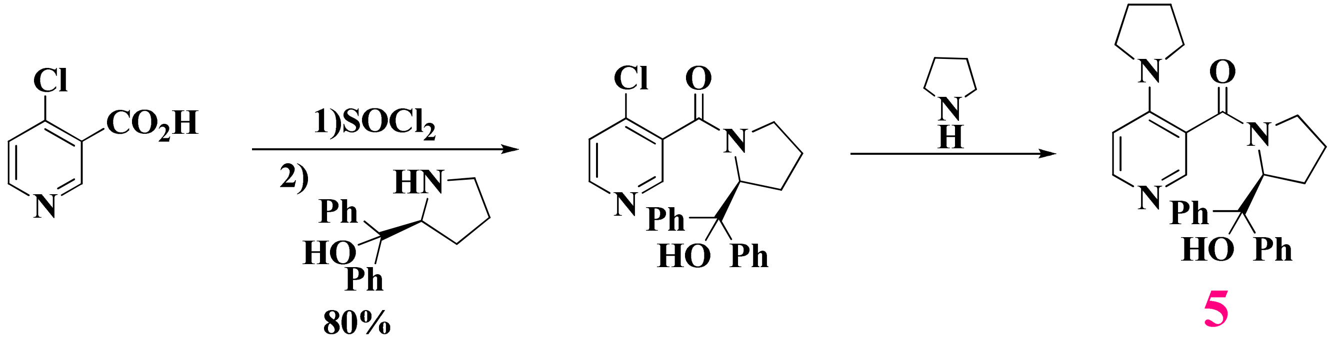
0.8 equiv $(i\text{-}PrCO)_2O$
0.9 equiv NEt_3
r.t. or -30°C

substrate	**S**
	**8**
	**10**
	**10**
	**7**

Yamada, S.; Morita, C. *J. Am. Chem. Soc*. **2002**, 124, 8184.
Yamada, S.; Misino, Tsuzuki, S. *J. Am. Chem. Soc*. **2004**, 126, 9826.

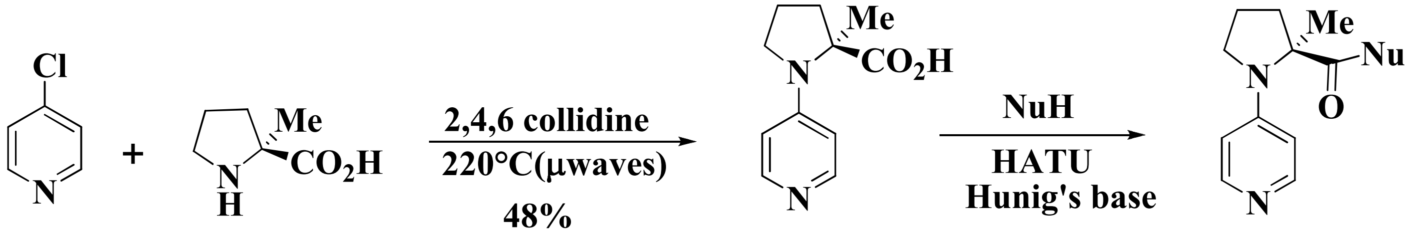
I- Catalysts with stereogenic center

I.5 - Connon's chiral PPY derivative



5

I.6- Campbell's chiral DMAP derivative



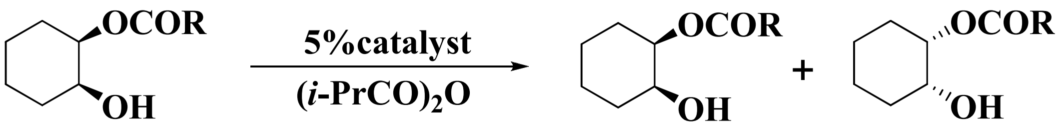
6

HATU : O-(7, Azobenzotriazol-1y) N, N, N', N', tetraméthyluroniumhexafluorophosphate

Ó Dălaigh, C.; Hynes, S. J.; Maher, D. J.; Connon, S. J. *Org. Biomol. Chem.* **2005**, 3, 981.

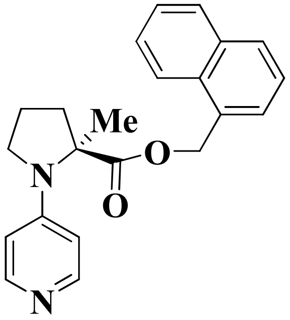
Ó Dălaigh, C.; Hynes, S. J.; O'Brien, J. E.; McCabe, T.; Maher, D.J.; Watson, G. W.; Connon, S. J. *Org. Biomol. Chem.* **2006**, 4, 2785.

I- Catalysts with stereogenic center

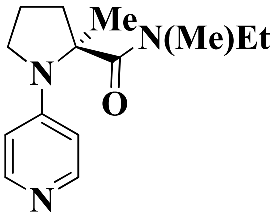


racemic
R = 4-$(Me_2N)C_6H_4$

Catalyst selectivity →



S **1.1**



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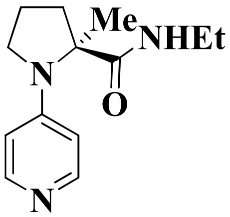

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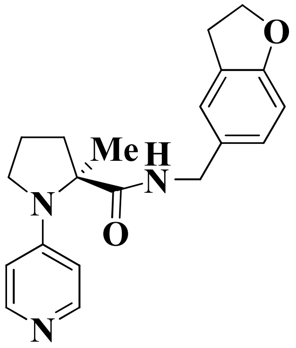

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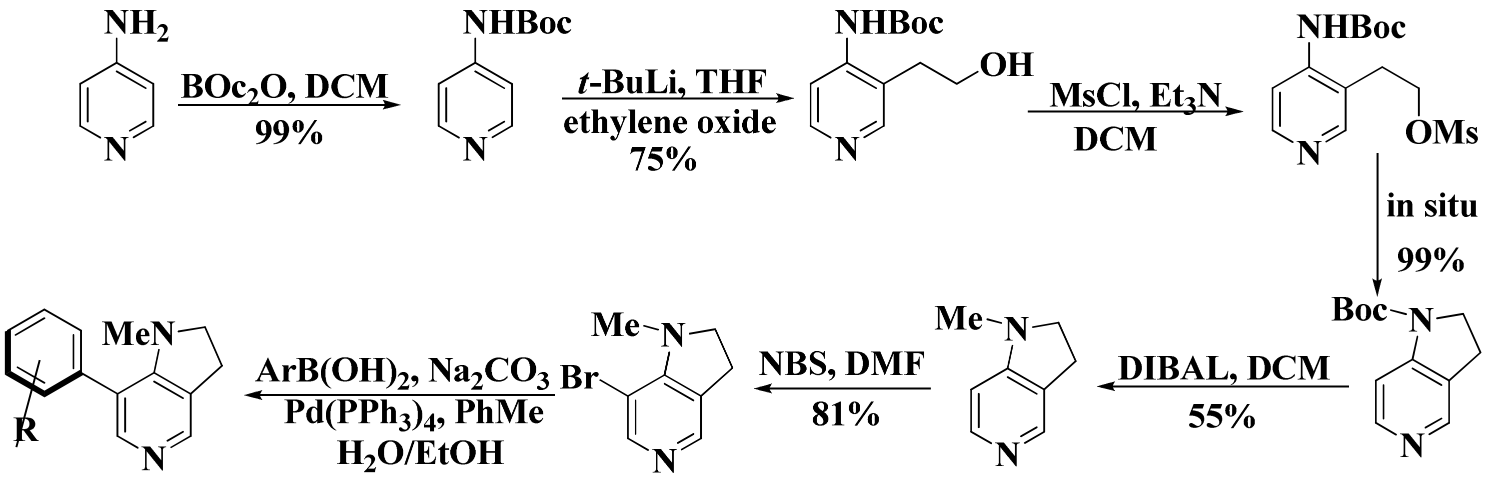
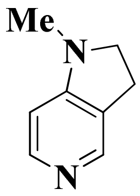
Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem*. **2003**, 68, 3944.

II- Catalysts with axial chirality : Spivey's Work

In 1998 - 1999





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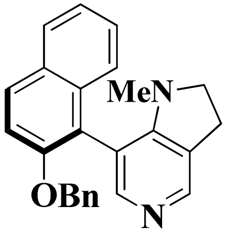

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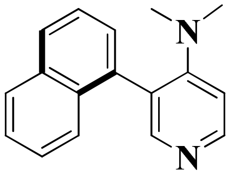

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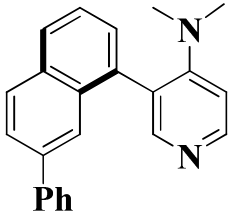
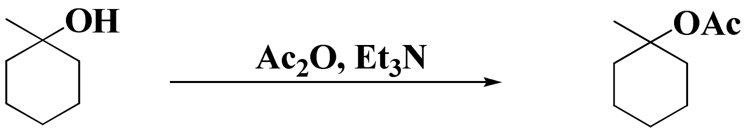


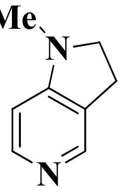
85%

Spivey, A.C.; Fekner, T.; Adams, H. *Tetrahedron Lett.* **1998**, 39, 8919.
Spivey, A.C.; Fekner, T.; Spey, S.E.,;Adams, H. *J. Org. Chem.* **1999,64**, 9430.

II- Catalysts with axial chirality



entry	catalyst	8 : 9 ratios	
		after 10h	after 24h
1	no catalyst	99:1	98:2
2	DMAP	13:87	5:95
3	8	21:79	10:90
4	9	96:4	90:10
5	10	36:64	18:82
6	11	63:37	45:55
7	12	22:78	13:87
8	13	30:70	14:86



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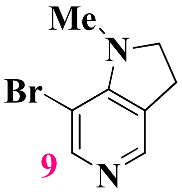

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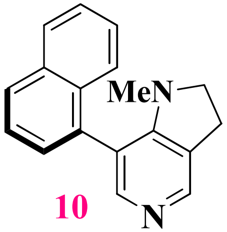

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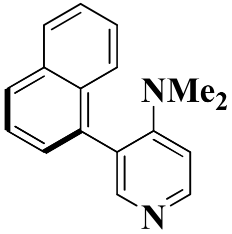

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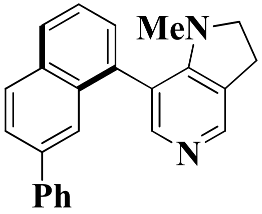

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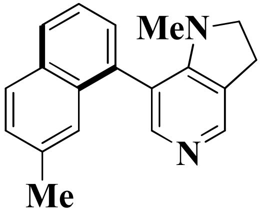

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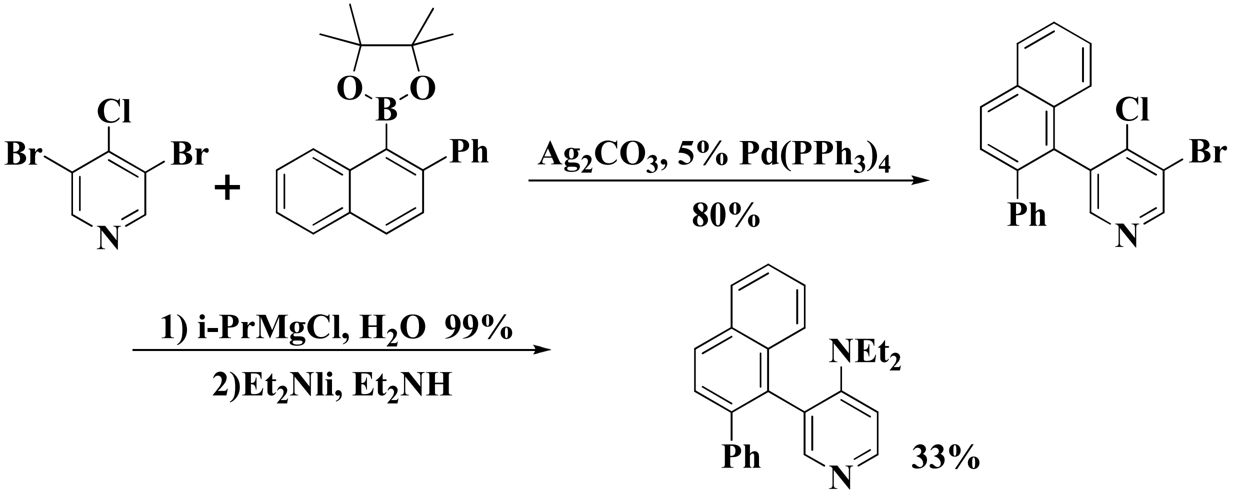
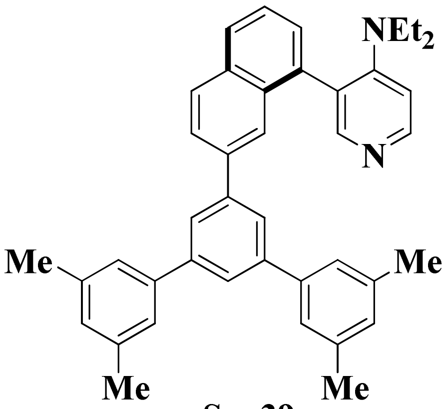
Spivey, A.C.; Charbonneau, P.; Fekner, T.; Hochmuth, D.H.; Maddaford, A.; Adams, H. *J. Org. Chem.* **2001**, 66 , 7394.

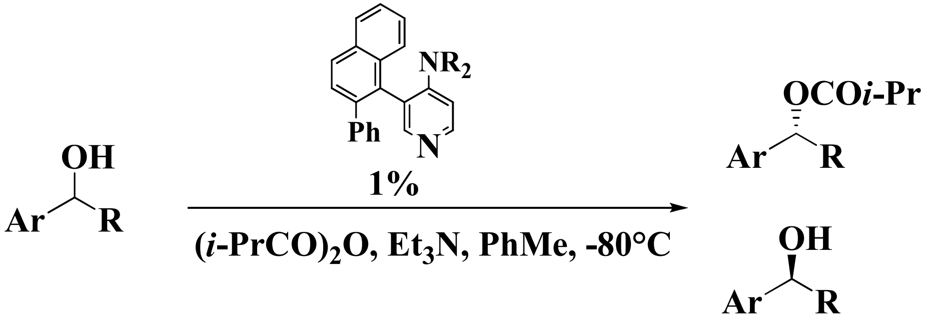
II- Catalysts with axial chirality

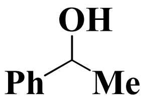
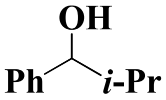
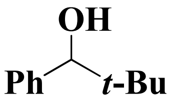
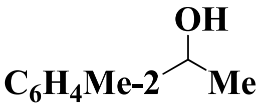
In 2001





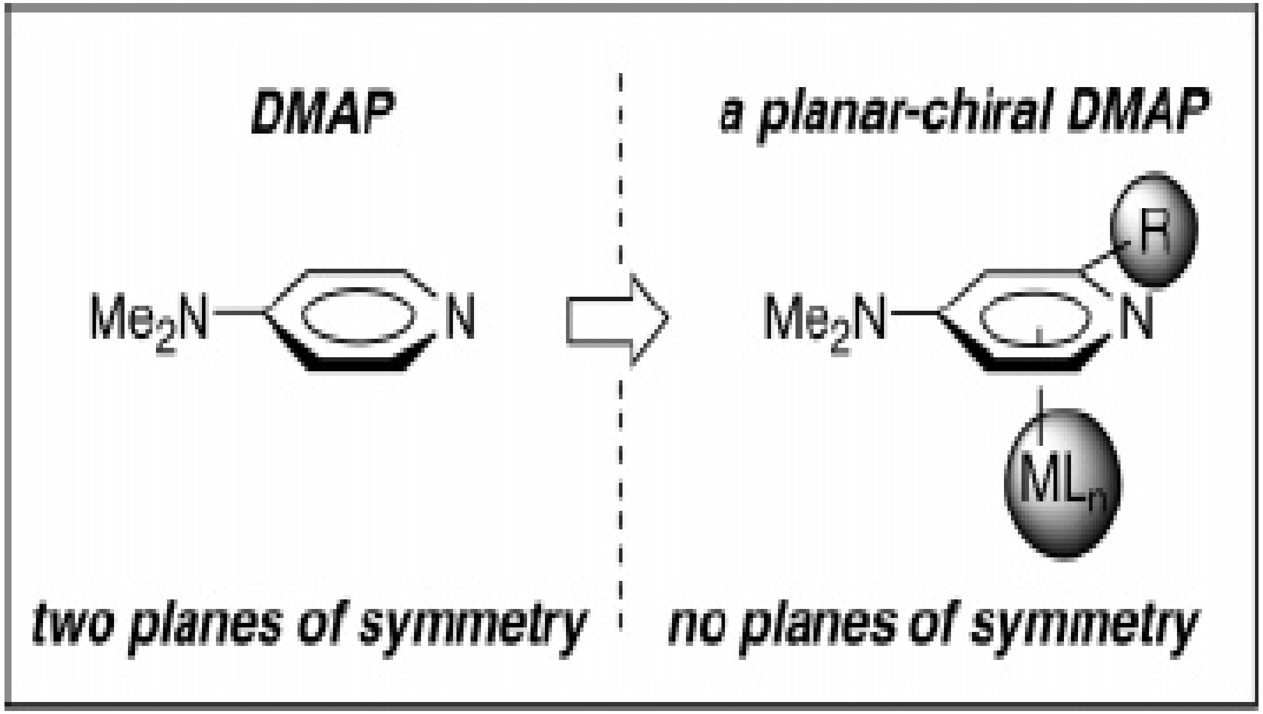
S = 39



Substrate	S
	13
	8.4
	20
	25

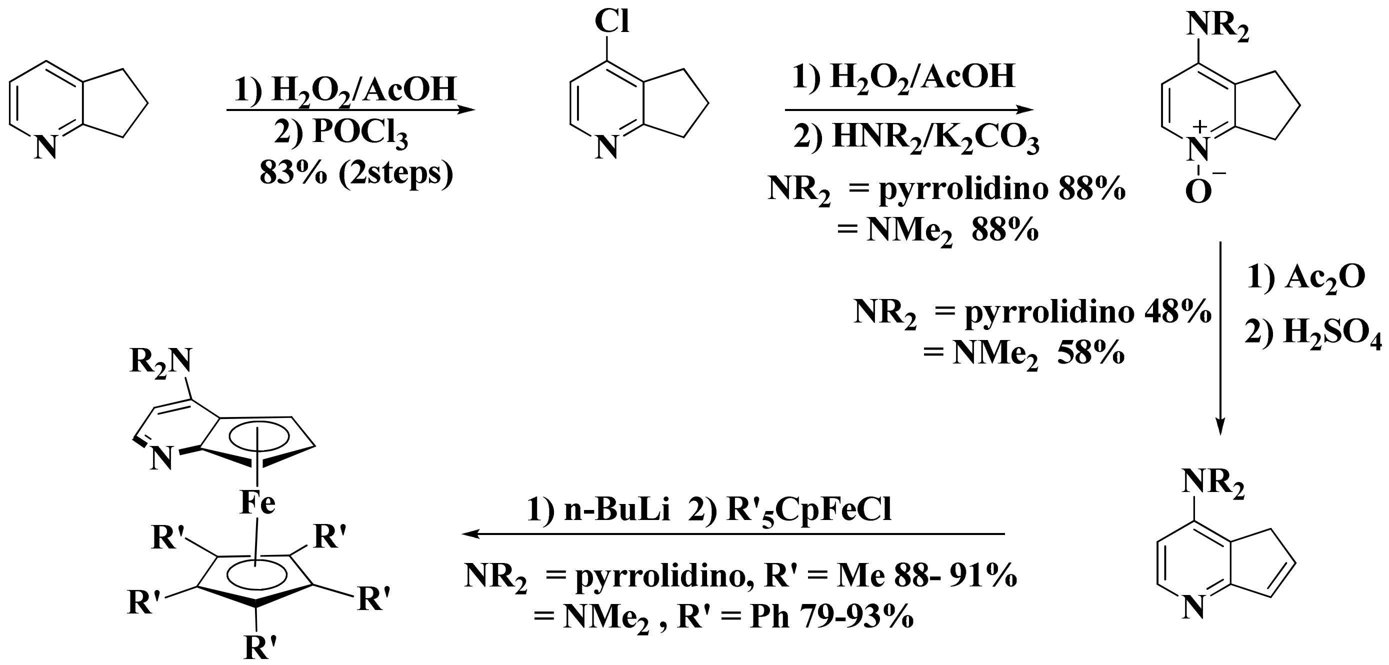
Spivey, A.C.; Zhu, F.; Mitchell, M. B.; Davey, S. G.; Jarvest, R. L. *J. Org. Chem.* **2003**, 68, 7379.

III- Catalysts with planar chirality



III- Catalysts with planar chirality

Fu’s Work



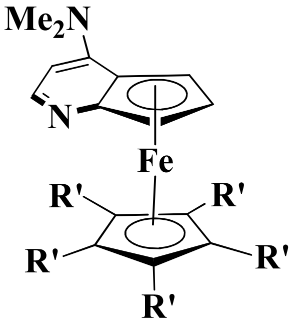
1) H_2O_2/AcOH
2) $POCl_3$
83% (2steps)

1) H_2O_2/AcOH
2) HNR_2/K_2CO_3
NR_2 = pyrrolidino 88%
= NMe_2 88%

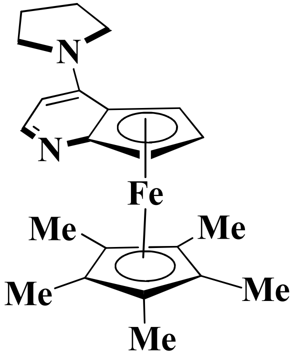
1) Ac_2O
2) H_2SO_4
NR_2 = pyrrolidino 48%
= NMe_2 58%

1) n-BuLi 2) $R'_5CpFeCl$
NR_2 = pyrrolidino, R' = Me 88- 91%
= NMe_2 , R' = Ph 79-93%

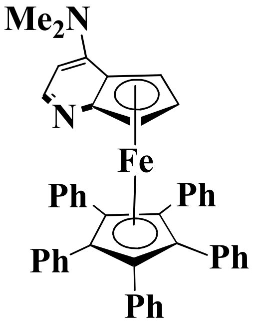
resolved via two crystallizations
of the appropriate tartaric acid salt



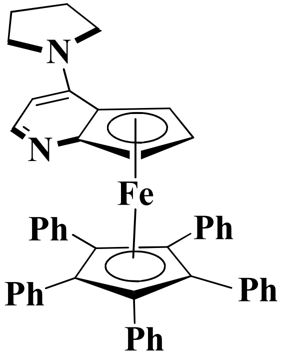
DMAP*



PPY*



$DMAPC_5Ph_5$

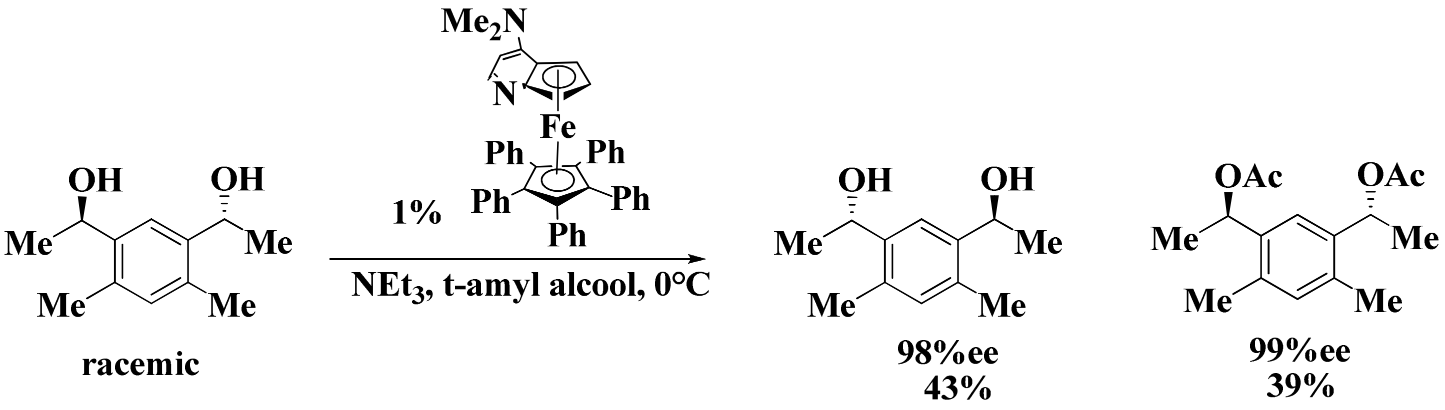


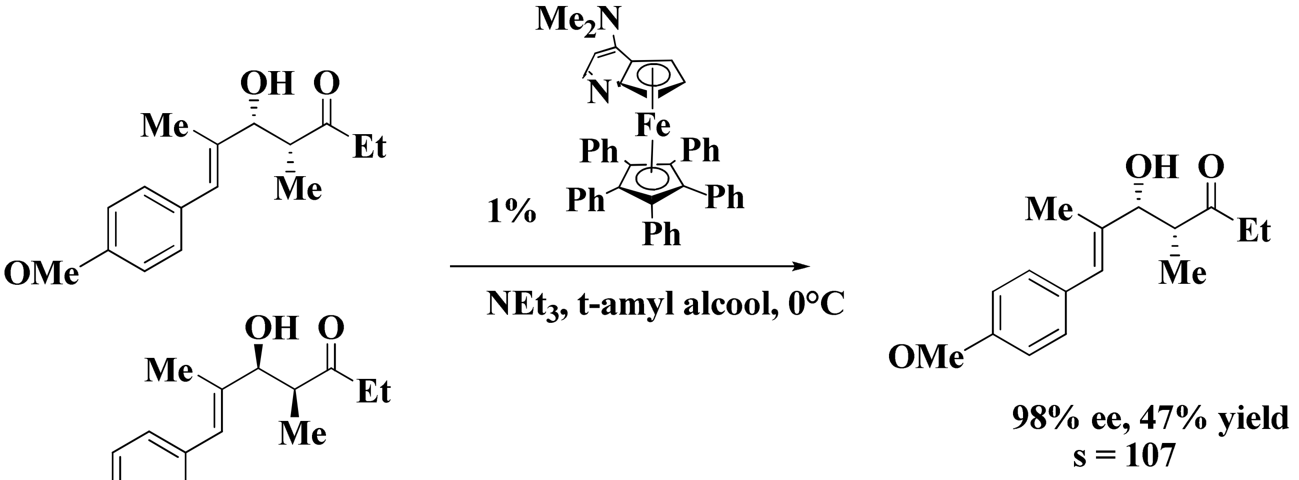
$PPYC_5Ph_5$

Craig Ruble, J.; Fu, G. C. *J. Org. Chem.* **1996**, 61, 7230.

III- Catalysts with planar chirality

Fu’s Work





racemic

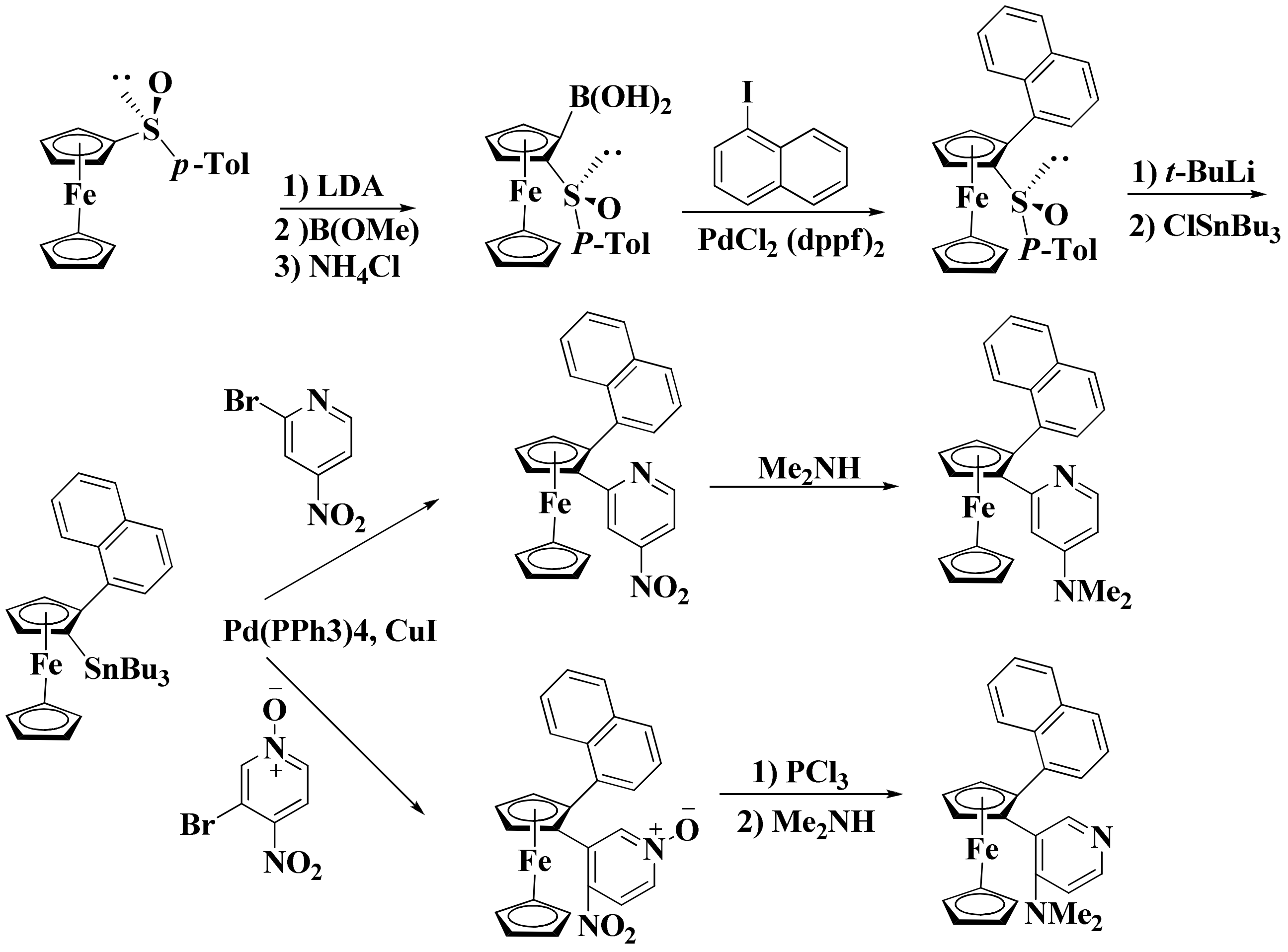
98% ee, 47% yield
s = 107

key intermediate in
the Sinha-Lerner synthesis of epothilone

Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J.C.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009.
Wurz, R.P.; Lee, E. C.; Ruble, J. C.; Fu, G. C. *Adv. Synth. Catal*. **2007**, 349, 2345.

III- Catalysts with planar chirality

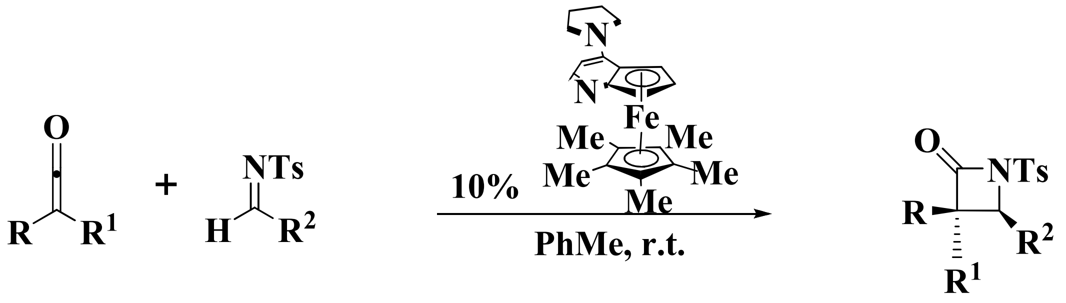
Johannsens' Work



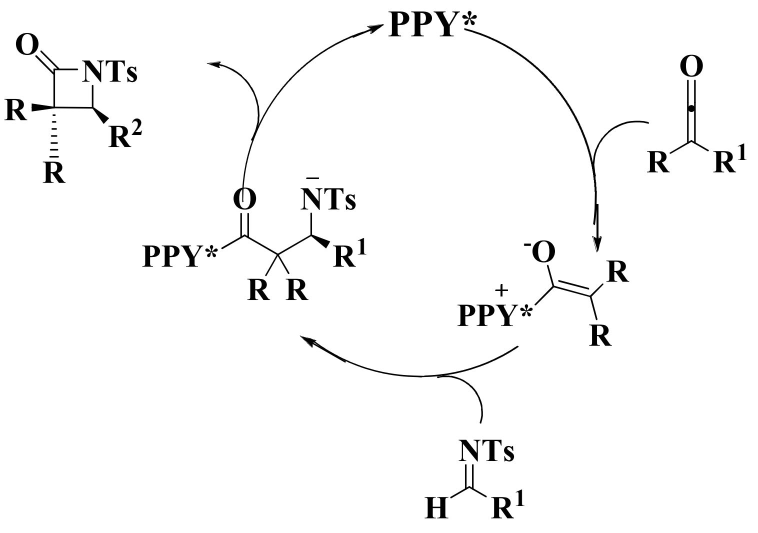
Seitzberg, J. G.; Dissing, C.; Sotofte, I.; Norrby, P. O.; Johannsen, M. *J. Org. Chem* **2005**, 70. 10890.
Seitzberg, J. G.; Dissing, C.; Sotofte, I.; Norrby, P. O.; Johannsen, M. *J. Org. Chem* **2005**, 70. 8332.

Some Applications of Chiral DMAP

Catalytic Staudinger cycloaddition



entry	R	R^1	R^2	%ee	% Yield
1	-$(CH_2)_6$-		Ph	81	84
2	Et	Et	2-furyl	92	93
3	-$(CH_2)_6$-		cyclopropyl	94	89
4	Ph	*i*-Bu	Ph	98	88
5	Ph	Et	cyclopropyl	98	



Hodous, B. L.; Fu, J. C. *J. Am. Chem.Soc.* **2002**, 124. 1578.

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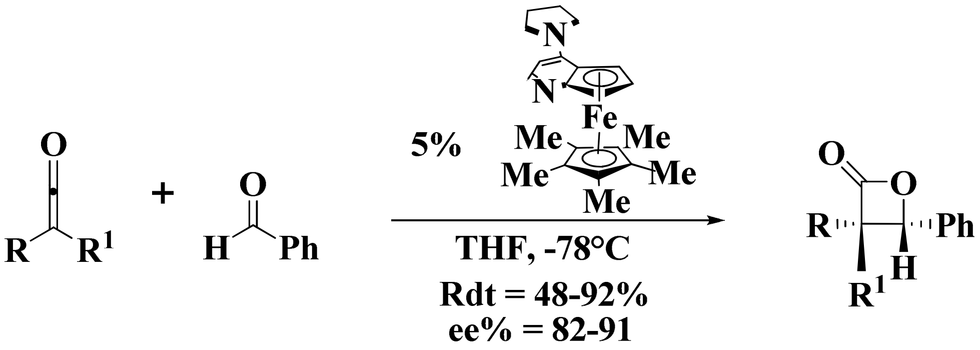
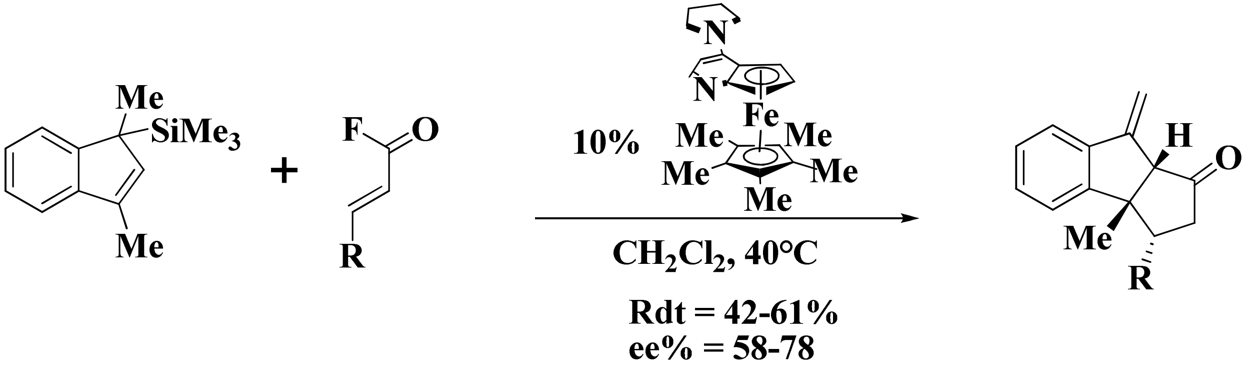
Some Applications of Chiral DMAP

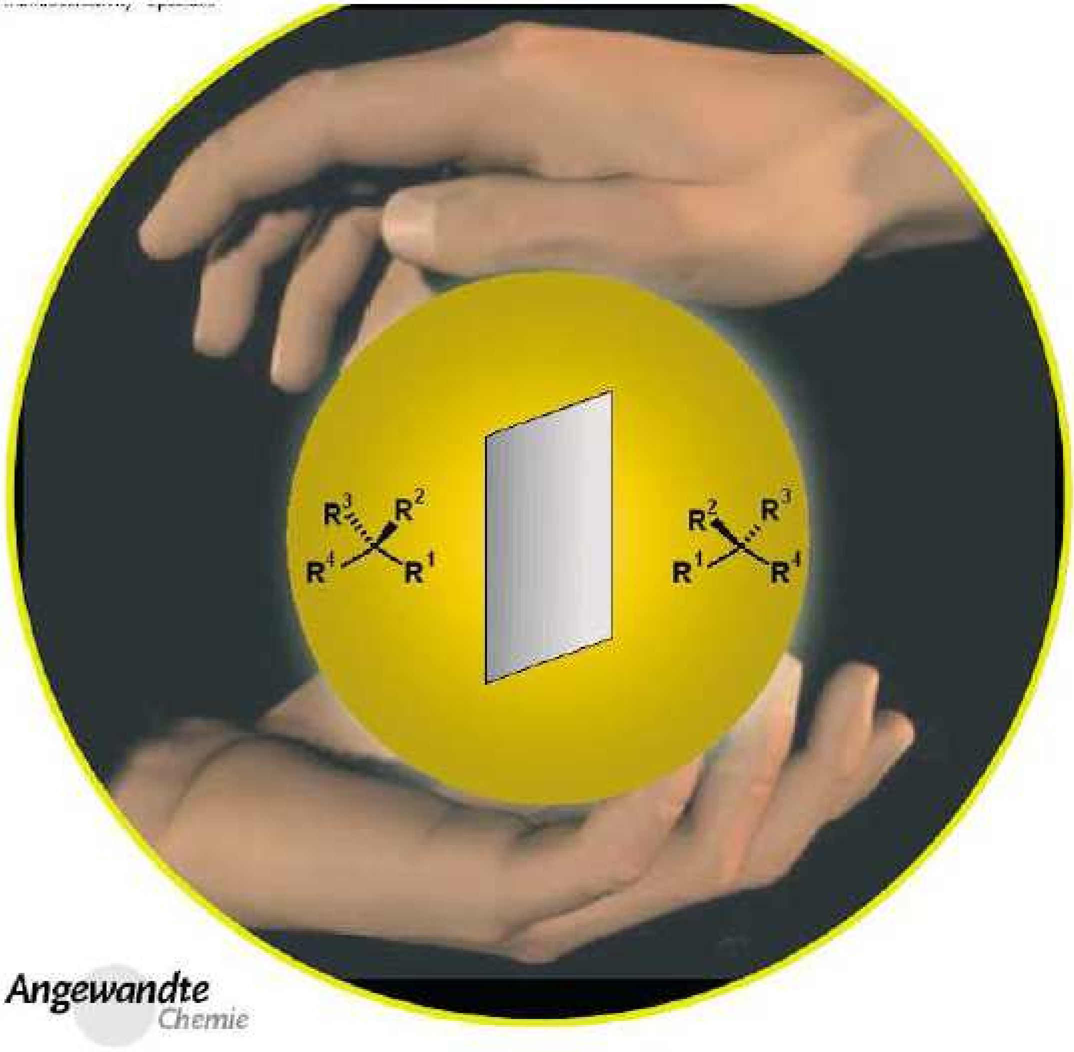
Catalytic Asymmetric Synthesis of β-Lactones



Catalytic Asymmetric [3+2] Annulations



Bappert, E.; Muller, P.; Fu, J. C. *Chem. Commun.* **2006**, 2604.


R^3
R^2
R^4
R^1
R^2
R^3
R^1
R^4
Angewandte
Chemie