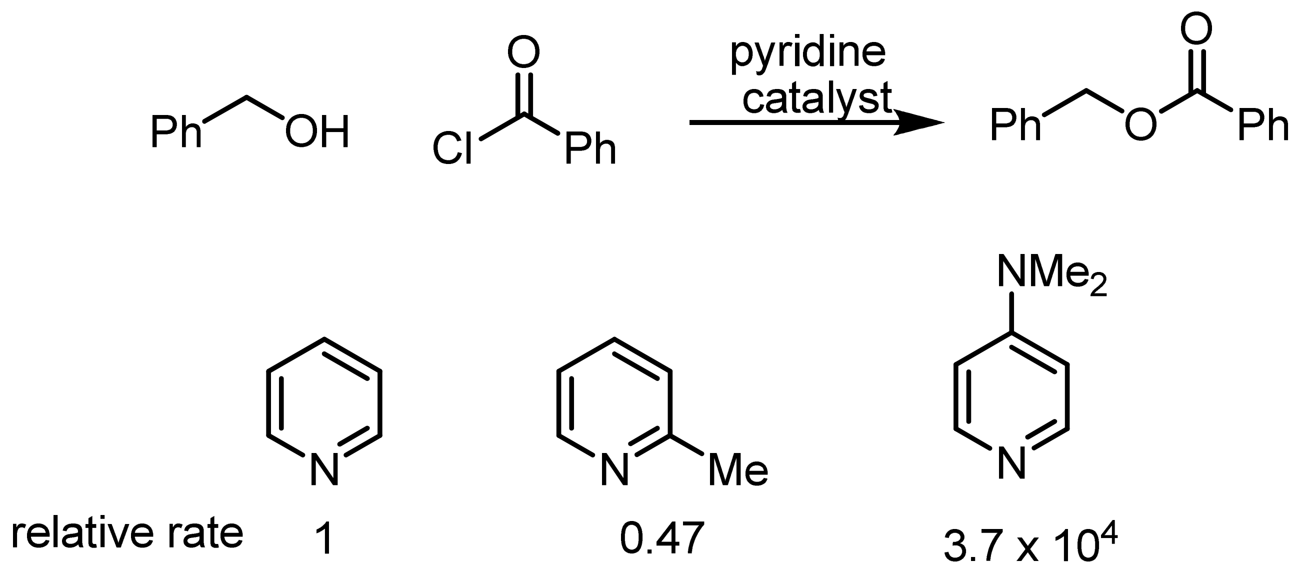
Chiral DMAP Catalysts in Asymmetric Synthesis

Wurz, R.P. *Chem. Rev.* **2007**, *107*, 5570

Outline

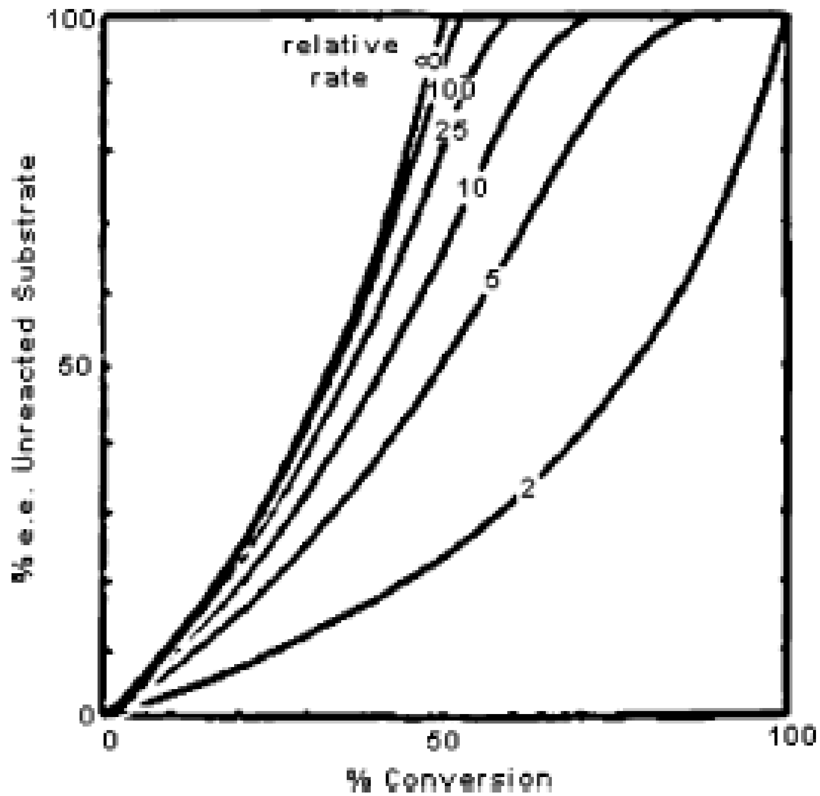
- **Introduction**
- **Kinetic resolutions**
  - Resolutions of alcohols
  - Resolution of amines
- **Cycloadditions**
  - Synthesis of β-lactams
  - Synthesis of β-lactones
  - [3+2] Annulations
- **Asymmetric Protonations of Ketenes**
- **C-Acylation**
  - O-to-C rearrangments of Acyl groups
- **Halogenations**
- **Michael Addition**
- **Conclusion**

Discovery of DMAP



Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk. SSSR* **1967**, *176*, 97.

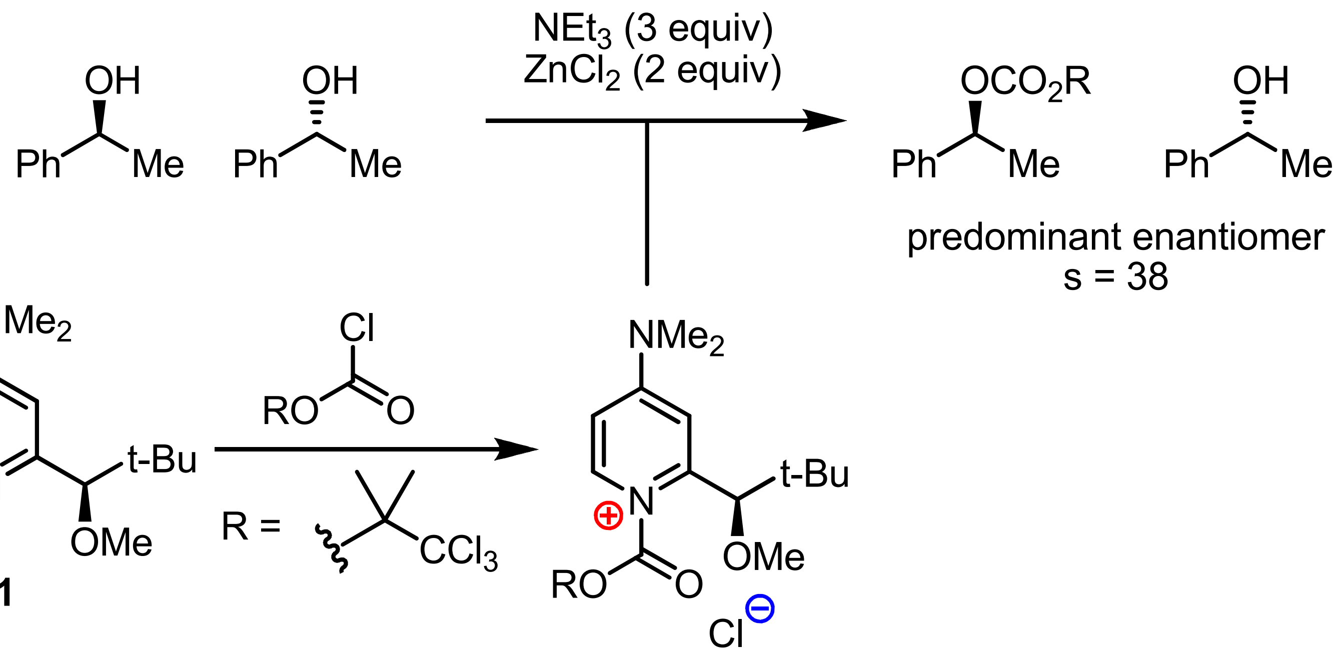
Dependence of Enantiomeric Excess on Relative Rate of Reaction



- s - selectivity factor
- s = 10 treshhold for syntheticaly useful conditions (>90% ee, 62% conversion)
- s > 50 = >99% ee at 55% conversion

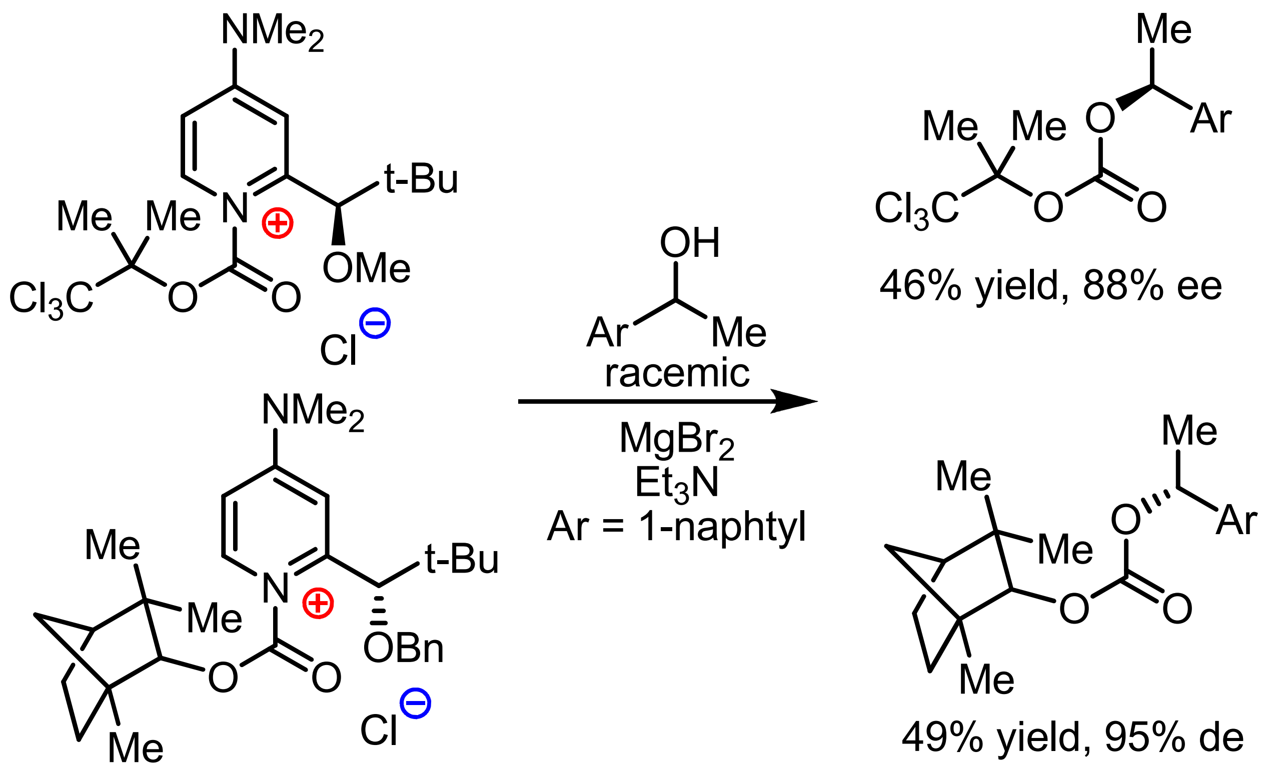
Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.;Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

First Effective Chiral DMAP-based resolution of alcohols by Vedejs and Chen



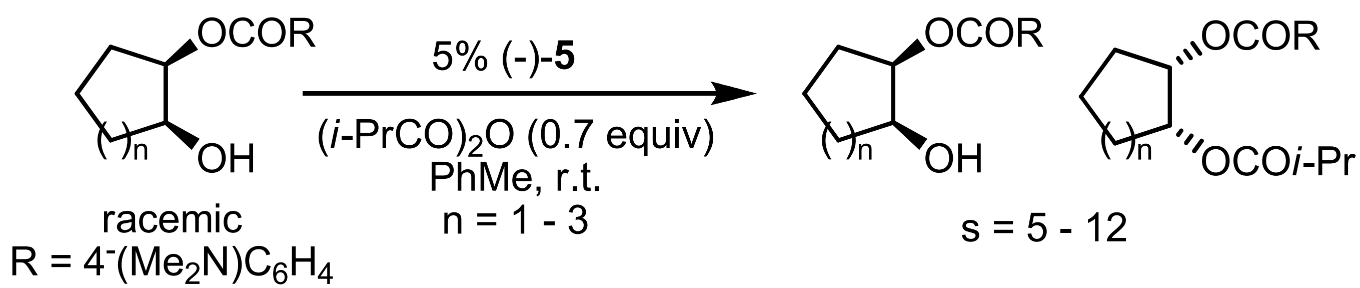
Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809.

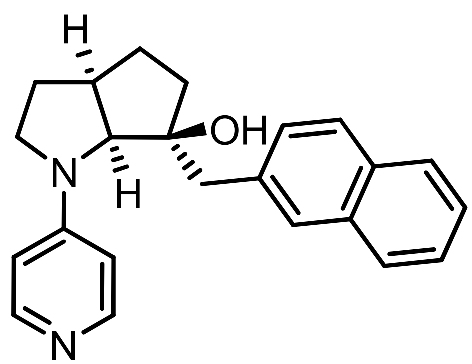
Parallel Kinetic Resolution of Benzylic Alcohols by Vedejs and Chen



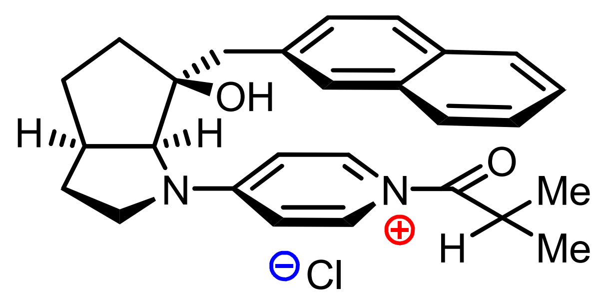
Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1997**, *119*, 2584.

Fuji's Chiral PPY Derivative: Resolution of Secondary Alcohols





(-)-**5**

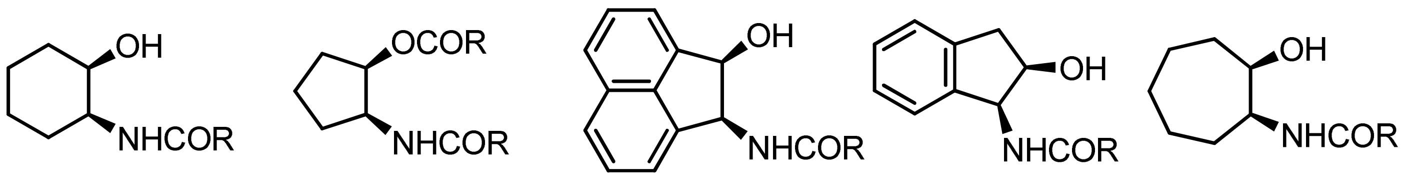


6

- PPY = 4-pyrrolidinopyridine

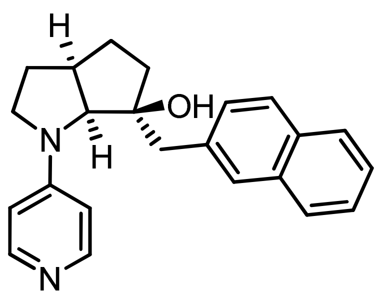
Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc*. **1997**, *119*, 3169.

Fuji's Chiral PPY Derivative: Resolution of *rac*-1,2-aminoalcohols



s >14 >12 21 17 10

R = 4-$(Me_2N)C_6H_4$

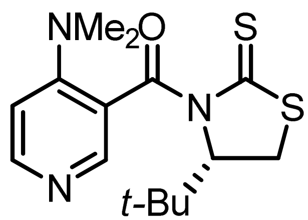


(-)-**5**

Kawabata, T.; Yamamoto, K.; Momose, Y.; Yoshida, H.; Nagaoka, Y.; Fuji, K. *Chem. Commun*. **2001**, 2700.

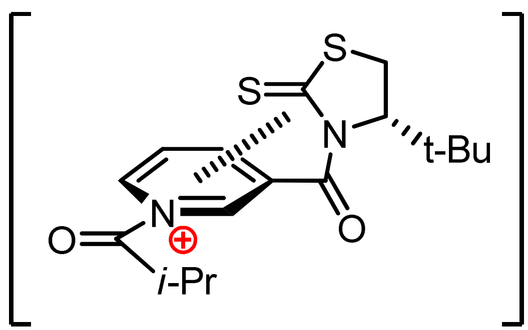
Yamada's Design of a Chiral DMAP: Resolution of Sec-Alcohols

Conditions: 0.5%

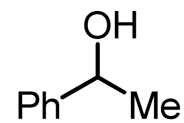
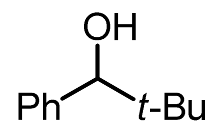
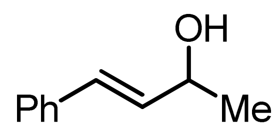
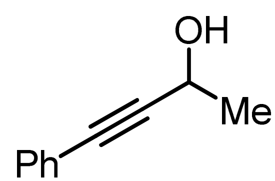


0.8 equiv (i-PrCO)$_2$O
0.9 equiv NEt$_3$
r.t or -30 °C

via



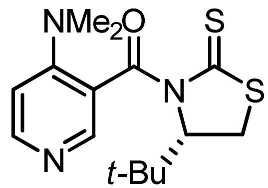
for the sake of clarity,
the NMe$_2$ group has been omitted

substrate	s
	8
	10
	10
	7

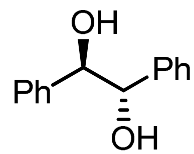
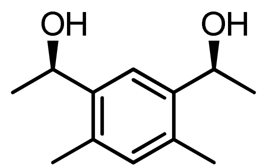
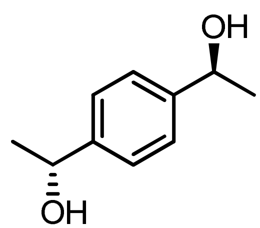
Yamada, S.; Misono, T.; Iwai, Y. *Tetrahedron Lett.* **2005**, *46*, 2239.

Yamada's Chiral DMAP Catalyst in Desymmetrization of *Meso*-diols

Conditions: 0.5%



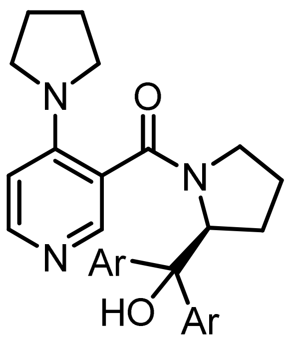
1.1 equiv $(i\text{-PrCO})_2O$
1.1 equiv NEt_3
r.t

substrate	%ee (monoester)	% yield
	72	31
	88	87
	96	69

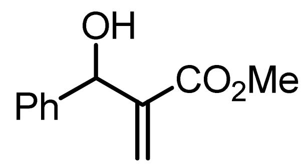
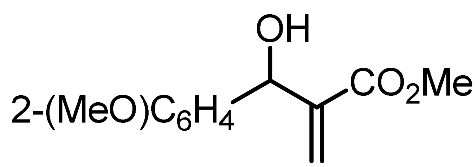
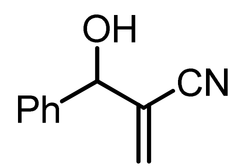
Yamada, S.; Misono, T.; Iwai, Y.; Masumizu, A.; Akiyama, Y. *J. Org. Chem*. **2006**, *71*, 6872.

Connon's chiral PPY derivative: Kinetic Resolution of Baylis-Hillman Adducts

Conditions: 1%

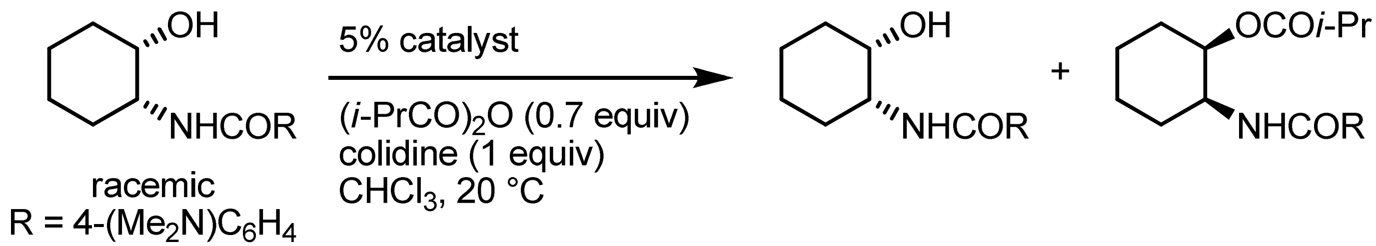


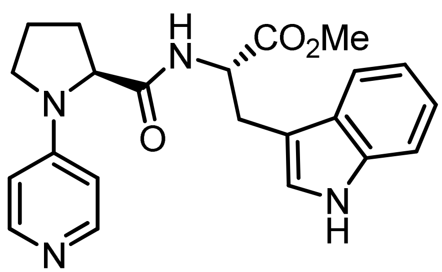
Ar = 3,5-$(CF_3)_2C_6H_3$
1.5 equiv (*i*-PrCO)$_2$O
0.8 equiv NEt_3
CH_2Cl_2, -78 °C

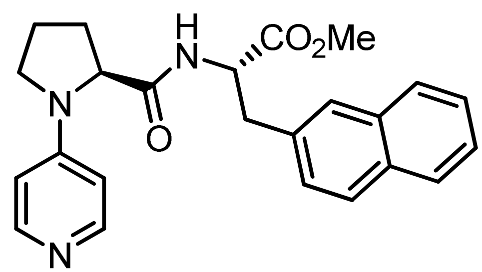
substrate	s
	3.8
	13.1
	3.6

O. Dalaigh, C.; Connon, S. J. *J. Org. Chem*. **2007**, *72*, 7066.

Fuji/Kawabata Proline-derived DMAP catalysts



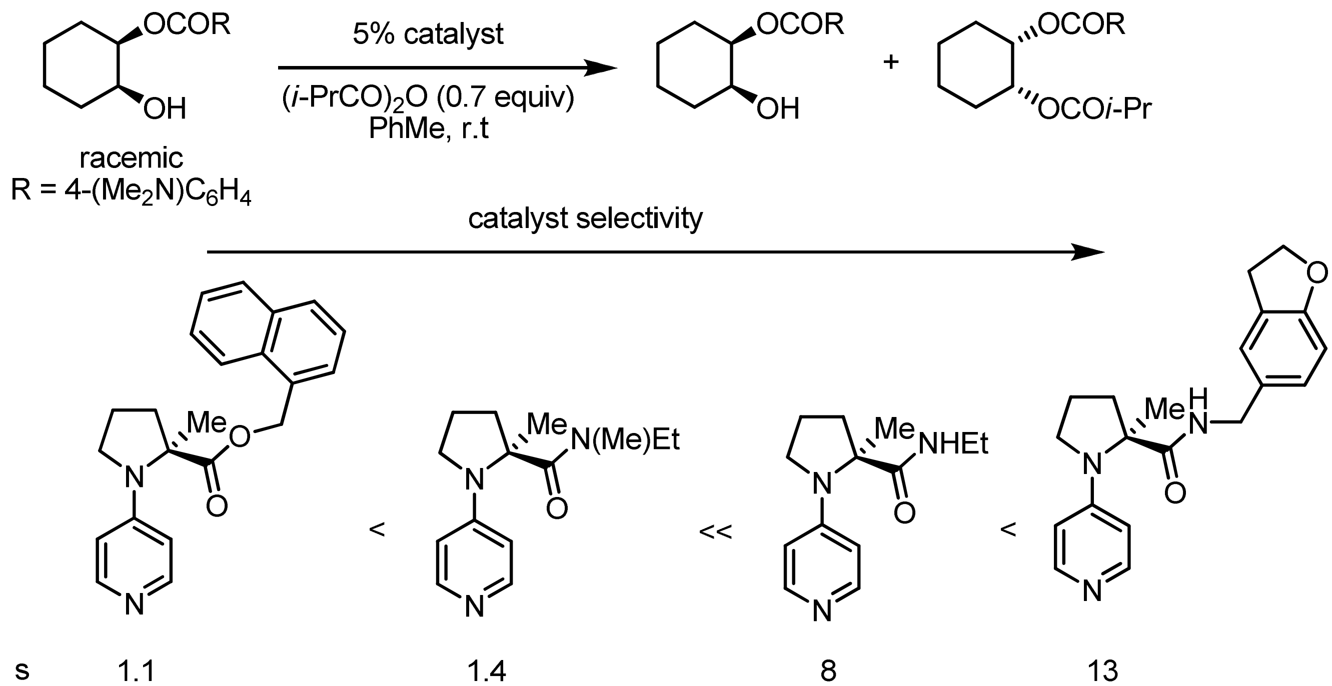




s 8 11

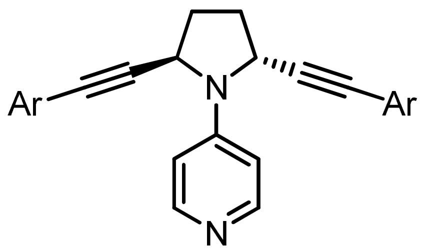
(a) Kawabata, T.; Stragies, R.; Fukaya, T.; Fuji, K. *Chirality* **2003**, *15*, 71.
(b) Kawabata, T.; Stragies, R.; Fukaya, T.; Nagaoka, Y.; Schedel, H.; Fuji, K. *Tetrahedron Lett.* **2003**, *44*, 1545.

Resolution of Monoprotected 1,2-cyclohexanediol with Campbell Catalyst



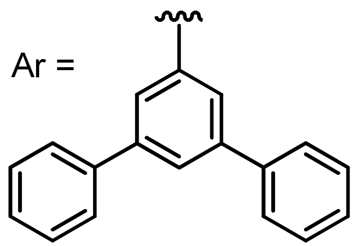
Priem, G.; Pelotier, B.; Macdonald, S. J. F.; Anson, M. S.; Campbell, I. B. *J. Org. Chem.* **2003**, *68*, 3844.

First C2-symmetric PPY Catalyst in Resolution of Sec-alcohols

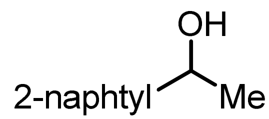
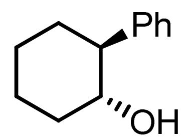
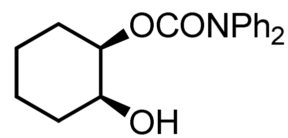


(R,R)-**8**

Ar =

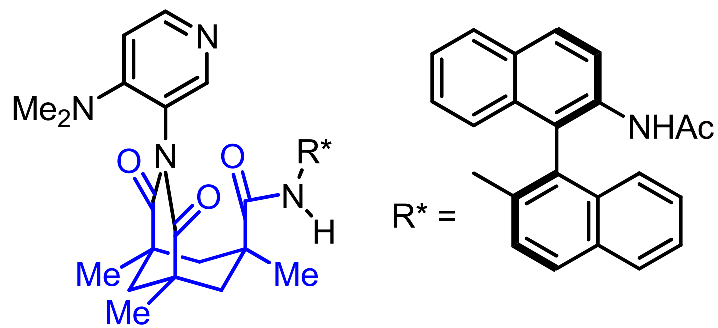


Conditions: 10% catalyst **8**
0.7 equiv $(RCO)_2O$
0.7 equiv NEt_3
PhMe, r.t.

substrate	R	s
	Me	2.4
	Me	2.1
	*i*-Pr	14

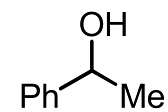
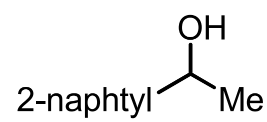
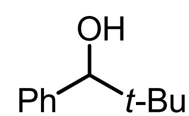
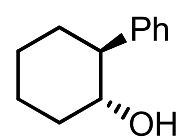
Naraku, G.; Shimomoto, N.; Hanamoto, T.; Inanaga, J. *Enantiomer* **2000**, *5*, 135.

Kinetic Resolution of *Sec*-alcohols with Jeong's Catalyst



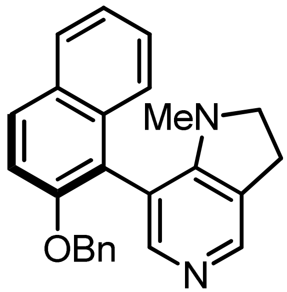
11

Conditions: 1% catalyst **11**
1 equiv Ac2O
t-amylOH, 0 °C

substrate	s
	4.4
	8.3
	13
	21

Jeong, K.-S.; Kim, S.-H.; Park, H.-J.; Chang, K.-J.; Kim, K. S. *Chem. Lett*. **2002**, 1114.

Catalysts with Chiral Axis



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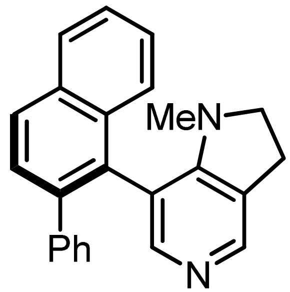

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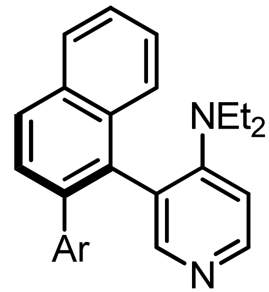

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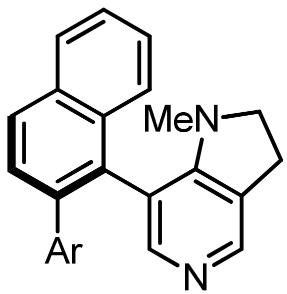

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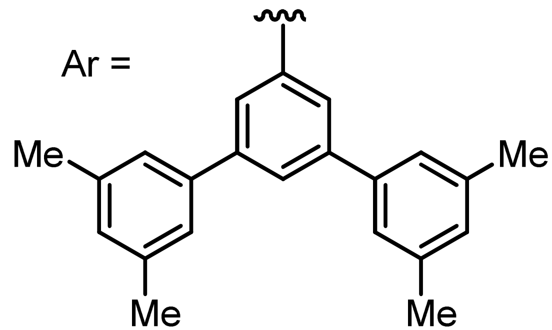
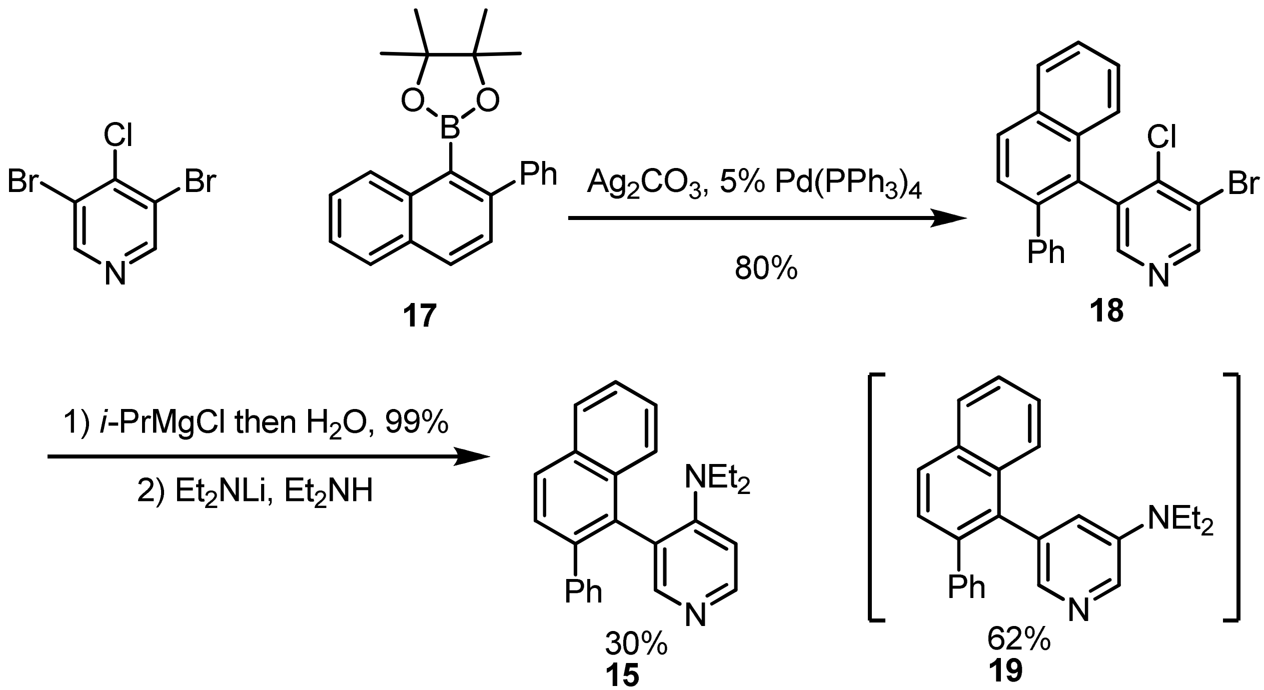


- Spivey's biaryl analogues of DMAP

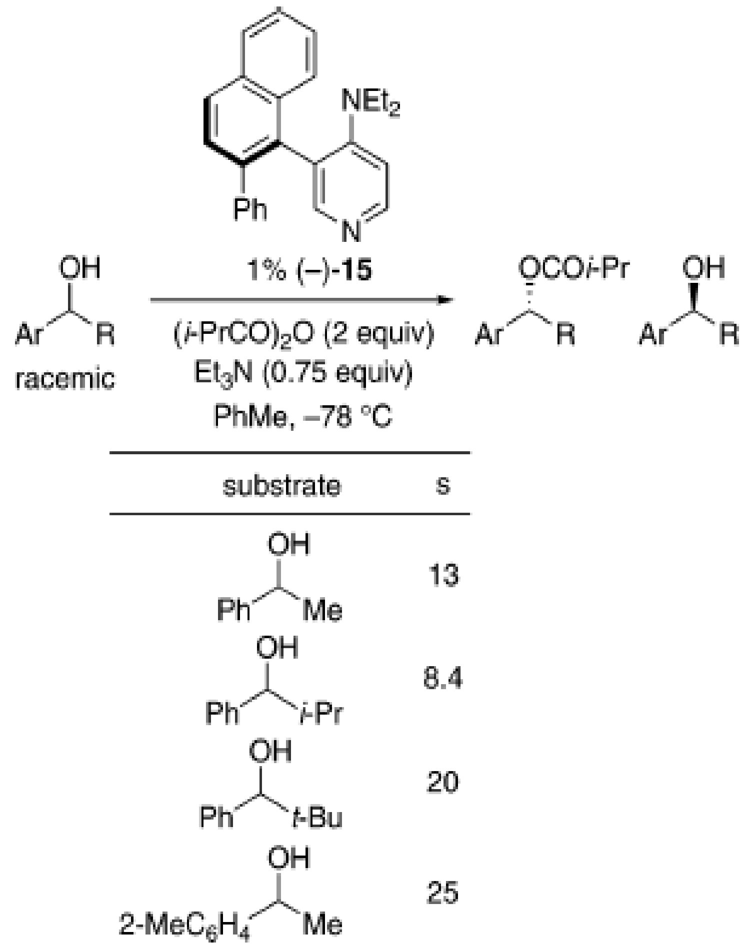
(a) Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. *J. Org. Chem.* **1999**, *64*, 9430.
(b) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154.

Three-step Route to the Atropisomeric-DMAP Derivatives



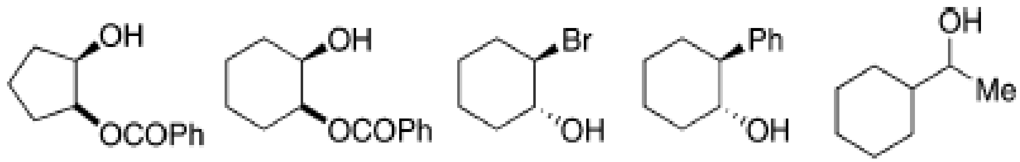
Spivey, A. C.; Zhu, F.; Mitchell, M. B.; Jarvest, R. L. *J. Org. Chem.* **2003**, *68*, 7379.

Resolution of Benzylic Alcohols

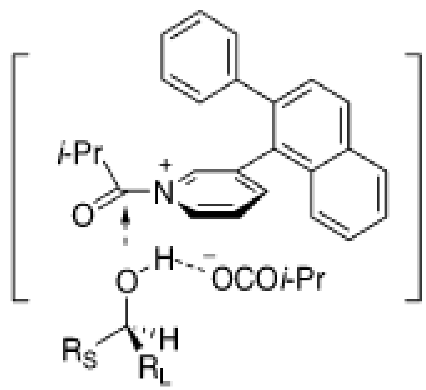


Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154.

Kinetic Resolution of Diverse Alcohols by Spivey's Catalyst



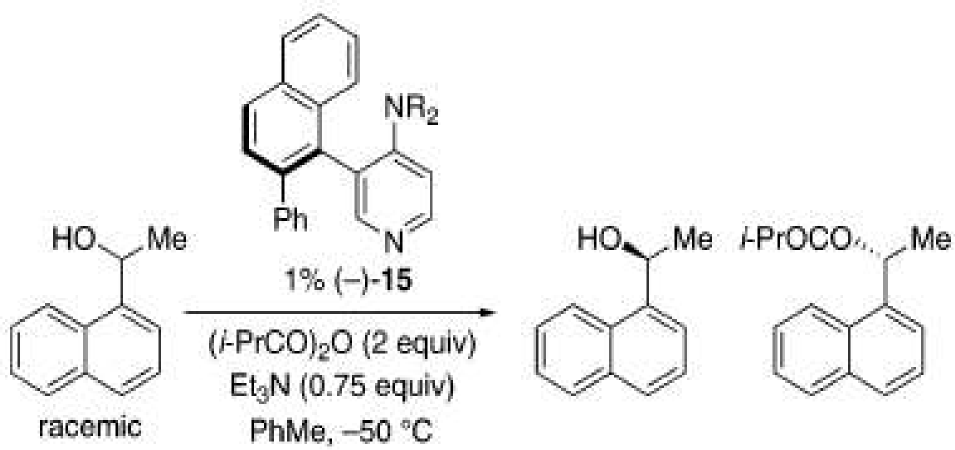
s	14	20	5.9	9.3	8.4



for the sake of clarity,
the NEt_2 group has been omitted

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

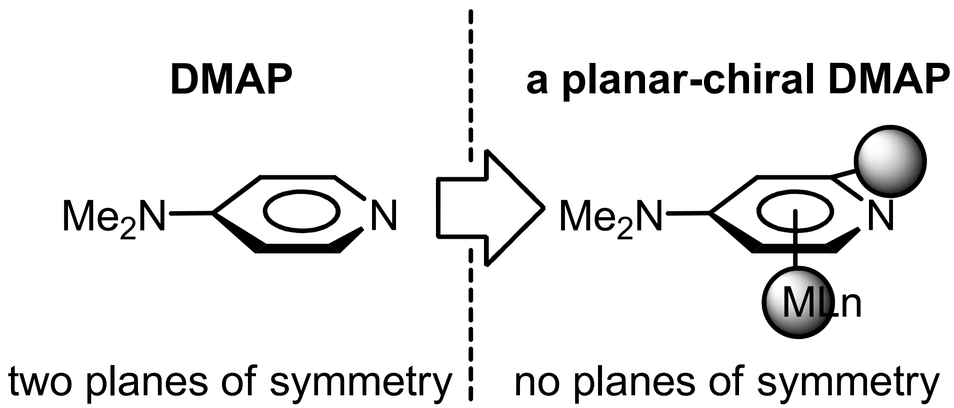
Kinetic Resolution of *rac*-1-1-(Naphtyl)ethanol



NR_2	s
pyrrolidino	3.5
NMe_2	10
NEt_2	24
N*n*-Pr_2	25
N*i*-Pr_2	15
N*n*-Bu_2	31
N*n*-$pent_2$	30
N*n*-hex_2	9

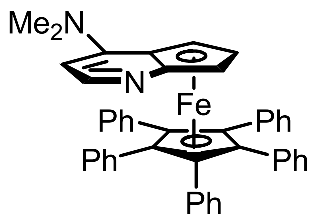
Spivey, A. C.; Leese, D. P.; Davey, S. G.; Jarvest, R. L. *Tetrahedron* **2004**, *60*, 4513.

Planar-Chiral Catalysts by Fu

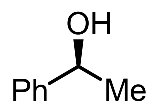
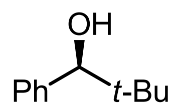
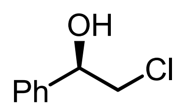
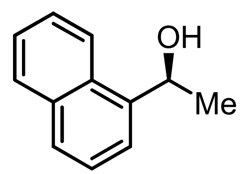


Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230.

Resolution of Arylalkylcarbinols by (-)DMAPC_5Ph_5

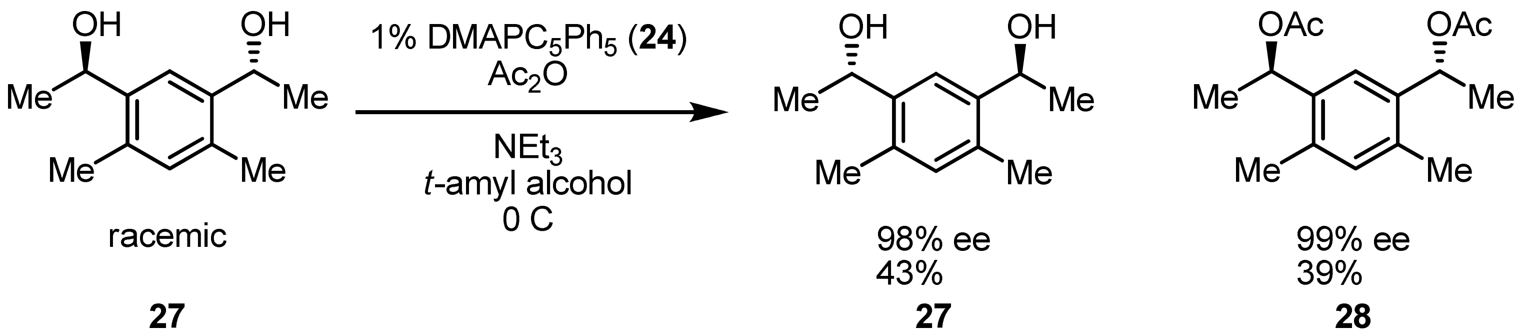


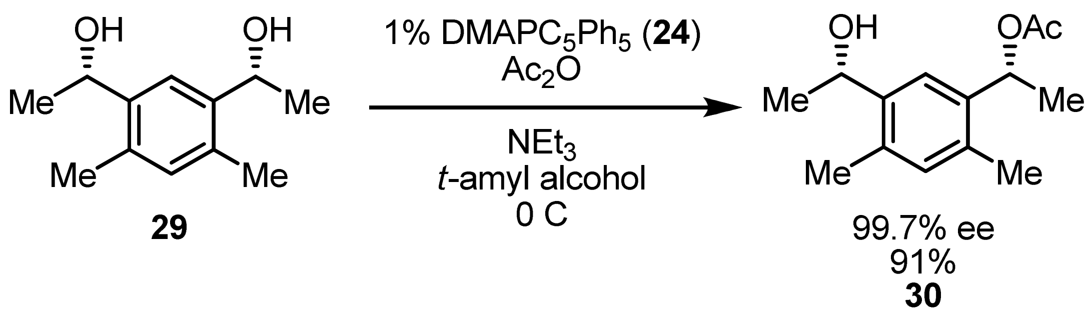
24 (DMAPC_5Ph_5)

Unreacted alcohol, Major enantiomer	s (selectivity factor)	
	Et_2O 2% catalyst r.t.	*t*-amyl alcohol 1% catalyst 0 °C
	14	43
	52	95
	12	32
	22	65

Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492.

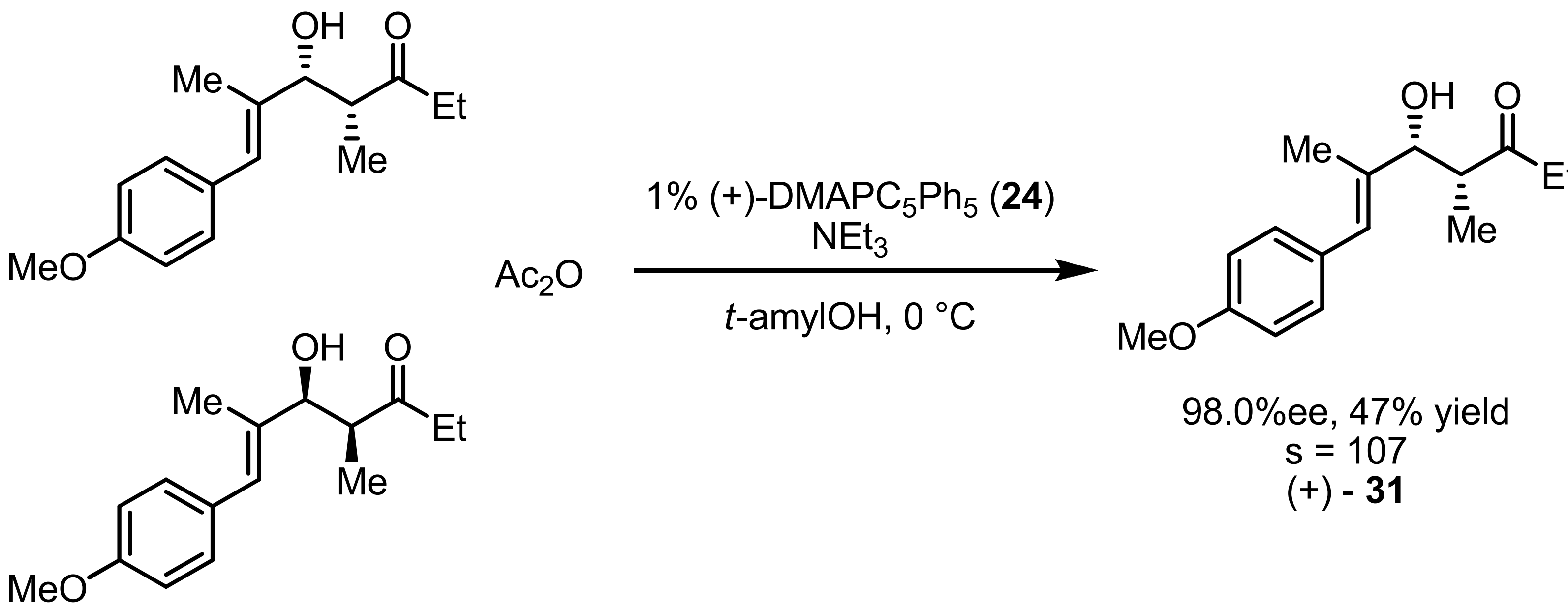
Resolution of Racemic and *meso*-diols





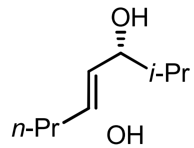
Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794.

Resolution as a Key Step in the Sinha-Lerner Synthesis of Epothilone A



Sinha, S. C.; Barbas, C. F. , III; Lerner, R. A. *Proc. Natl. Acad. Sci.U.S.A.* **1998**, *95*, 14603.

Resolution of Allylic Alcohols by (+)-DMAPC$_5$Ph$_5$

<table>
<tr><th>unreacted alcohol</th><th>selectivity factor</th></tr>
<tr><td>
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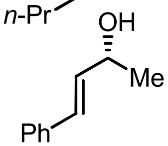
<tr><td>
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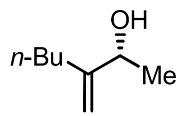
<tr><td>
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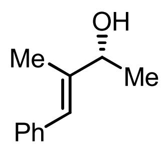
<tr><td>
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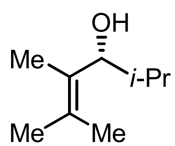
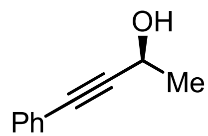
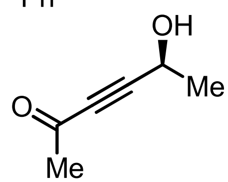
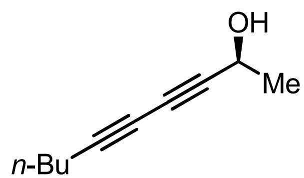
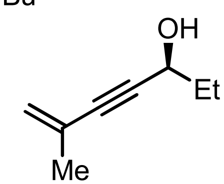
<tr><td>
</td><td>29</td></tr>
</table>

Conditions: 1-2.5% catalyst; 0.59 equiv of NEt_3;
0.59 equiv of Ac_2O;
tert-amylOH, 0 °C

Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun*. **2000**, 1009.

Resolution of Propargylic Alcohols by (+)-DMAPC_5Ph_5

unreacted alcohol	selectivity factor
	20
	12
	10
	7.9

Conditions: 1% catalyst; 0.75 equiv of Ac_2O; *tert*-amylOH, 0 °C

(a) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091.
(b) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 10452.

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- **Kinetic resolutions**
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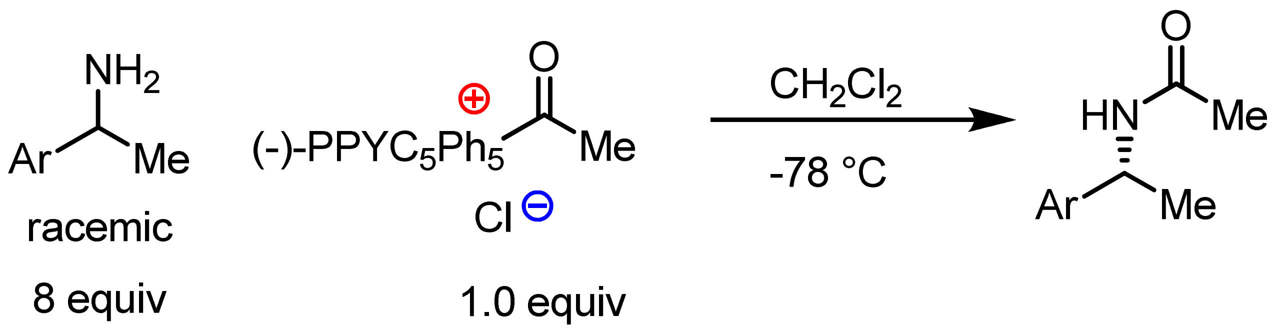
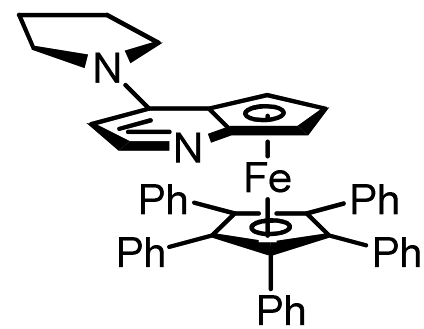
- **Conclusion**

Enantioselective Acylation of Amines by (-)-PPYC_5Ph_5



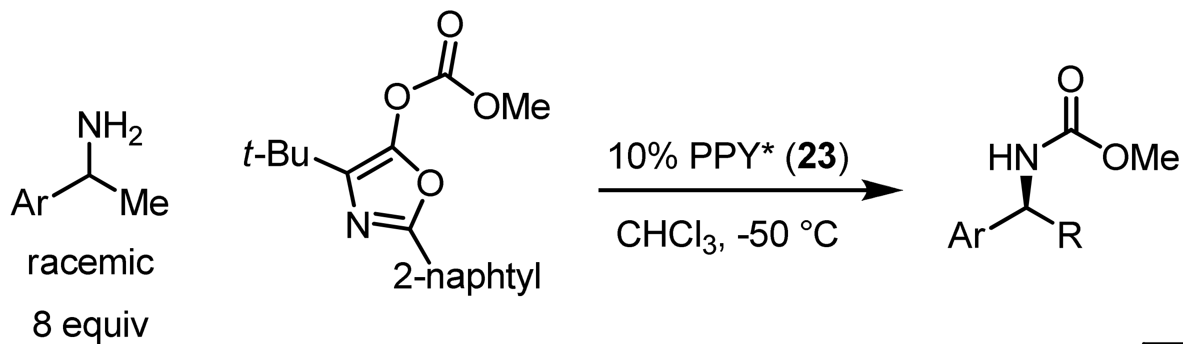
entry	Ar	% ee of amide
1	Ph	87
2	1-naphtyl	90
3	2-MeC_6H_4	91



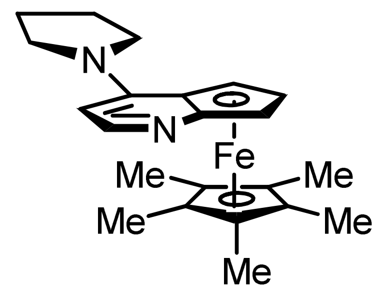
PPYC_5Ph_5

Ie, Y.; Fu, G. C. *Chem. Commun.* **2000**, 119.

Kinetic Resolution of Amine Catalyzed by (-)-PPY



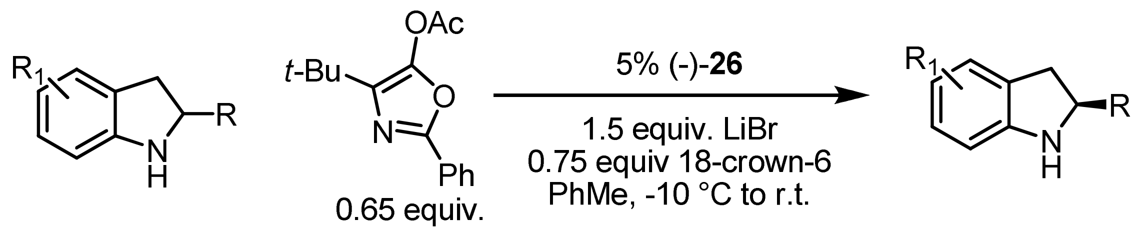
entry	Ar	R	selectivity factor
1	Ph	Me	12
2	1-naphtyl	Me	27
3	4-(MeO)C_6H_4	Me	11
4	4-(CF_3)C_6H_4	Me	13
5	Ph	Et	16

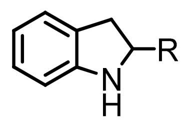
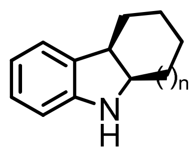
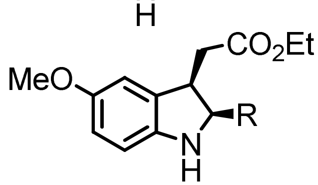


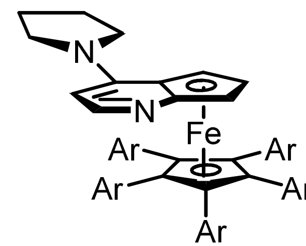
23 (PPY*)

Arai, S.; Bellemin-Laponnaz, S.; Fu, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 234.

Kinetic Resolution of Indolines by (-)-26



entry	indoline	R	selectivity factor
1		R = Me	25
2		*n*-Pr	26
3		CH_2CH_2Ph	18
4		CH_2OTBS	14
5		n = 1	9.8
6		2	31
7			19



26 (PPYC_5Ar_5)
Ar = 3,5-Me(C_6H_3)

Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264.

Outline

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  - Acylations of silyl ketene imines
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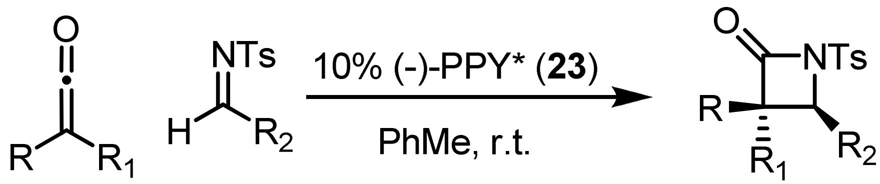
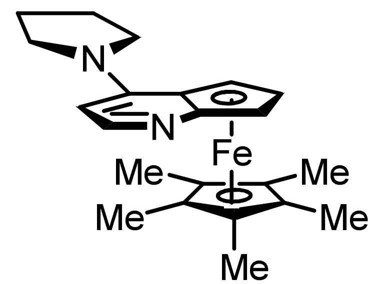
Synthesis of *cis*-*β*-Lactams from Ketene and *N*-Ts Imines



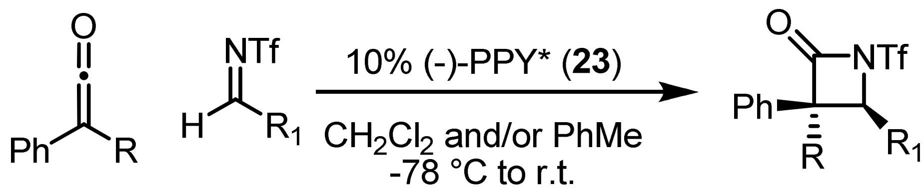
entry	R	R_1	R_2	%ee	%yield
1	-$(CH_2)_6$-		Ph	81	84
2	Et	Et	2-furyl	92	93
3	-$(CH_2)_6$-		cyclopropyl	94	89
4	Ph	*i*-Bu	Ph	98 (8:1 dr)	88
5	Ph	Et	cyclopropyl	98 (10:1 dr)	98



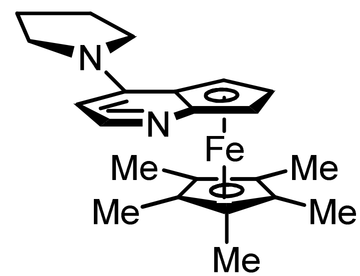
23 (PPY*)

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

Synthesis of *trans*-*β*-Lactams from Ketene and *N*-Tf Imines



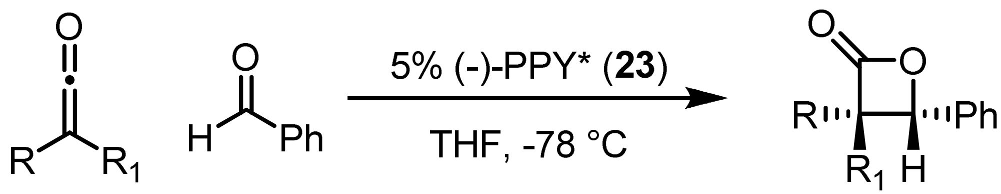
entry	R	R_1	trans:cis	%ee	%yield
1	Me	Ph	98:2	81	83
2	Et	Ph	86:14	63	60
3	*i*-Bu	Ph	97:3	63	72
4	Me	4-FC_6H_4	96:4	85	84
5	Me	4-(MeO)C_6H_4	81:19	82	76
6	Me	*o*-tolyl	81:19	99	89

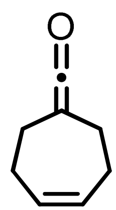


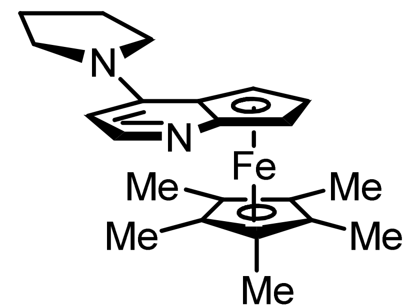
23 (PPY*)

Lee, E. C.; Hodous, B. L.; Bergin, E.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11586.

Synthesis of β-Lactones



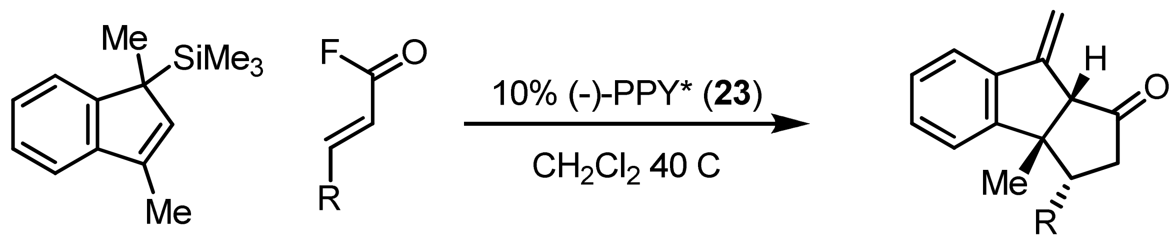
entry	R	R_1	%ee	%yield
1	Ph	Et	91	92
2			82	71
3	*i*-Pr	Me	91	48
4	Cyclopentyl	Me	88	53



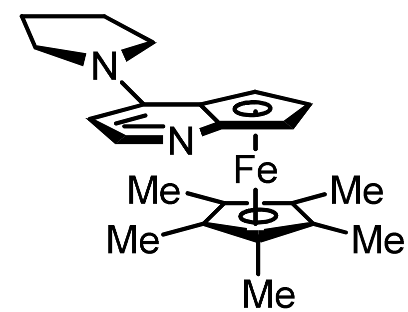
23 (PPY*)

Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6358.

Catalytic Asymmetric [3+2] Annulations



entry	R	dr	%ee	%yield
1	Ph	12:1	78	60
2	3-F-C_6H_4	7:1	58	51
3	3,5-(MeO)C_6H_3	8:1	70	61
4	1-naphthyl	9:1	70	42
5	3-furyl	9:1	70	48



23 (PPY*)

Bappert, E.; Mu¨ller, P.; Fu, G. C. *Chem. Commun*. **2006**, 2604.

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  - Acylations of silyl ketene imines
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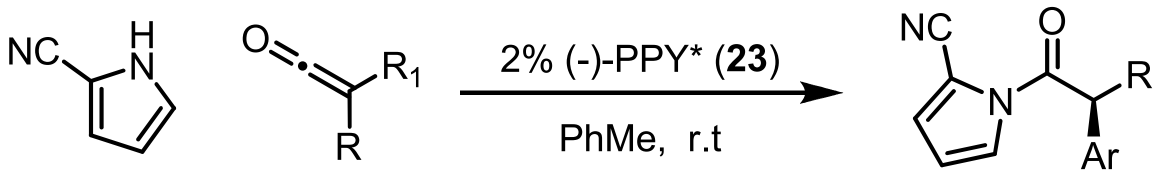
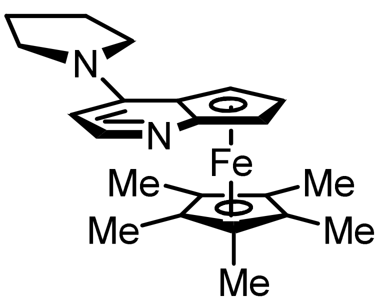
Enantioselective Addition of 2-Cyanopyrrole to Ketenes



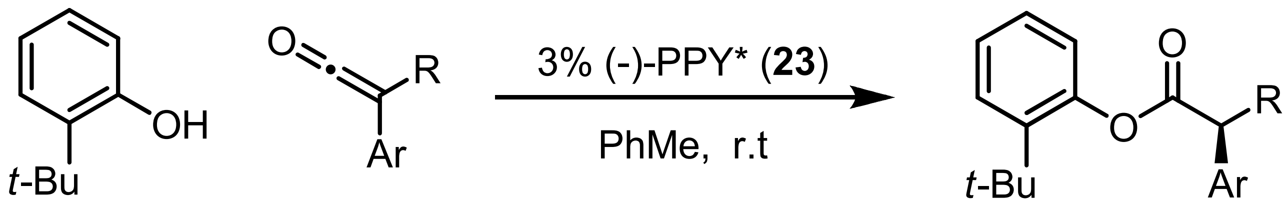
entry	Ar	R	%ee	%yield
1	Ph	Et	90	93
2	Ph	*i*-Pr	95	96
3	Ph	t-Bu	81	90
4	*o*-tolyl	Et	98	95
5	3-(*N*-methylindolyl)	Bn	86	80



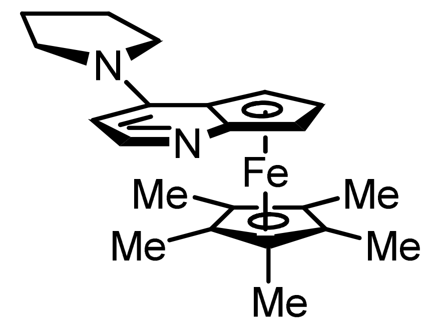
23 (PPY*)

Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10006.

Catalytic Enantioselective Synthesis of Esters from Ketenes



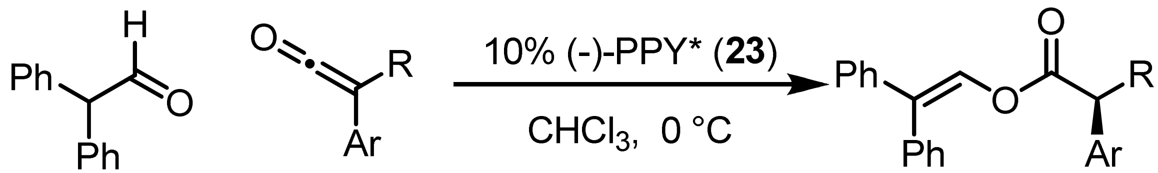
entry	Ar	R	%ee	%yield
1	Ph	Et	91	93
2	Ph	Me	79	87
3	Ph	*i*-Pr	91	66
4	*o*-tolyl	Et	92	84
5	3-thienyl	*i*-Pr	79	94



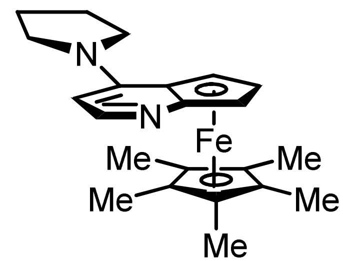
23 (PPY*)

Wiskur, S. L.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 6176.

Catalytic Asymmetric Coupling of Aldehydes with Ketenes



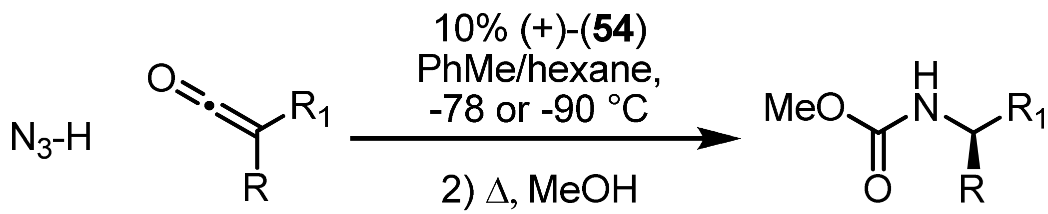
entry	Ar	R	%ee	%yield
1	Ph	Et	91	84
2	Ph	Me	78	74
3	Ph	*i*-Pr	98	95
4	Ph	Et	88	96
5	*o*-tolyl	*i*-Pr	98	99



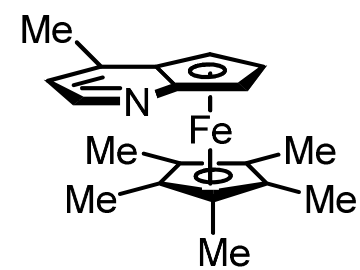
23 (PPY*)

Schaefer, C.; Fu, G. C. *Angew. Chem., Int. Ed.* **2005**, *44*, 4606.

Catalytic Asymmetric Addition of HN_3 to Ketenes



entry	R	R	%ee	%yield
1	Ph	i-Pr	96	94
2	Ph	cyclohexyl	96	93
3	Ph	t-Bu	76	94
4	o-tolyl	Et	91	93
5	Ph	Et	4	89



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Dai, X.; Nakai, T.; Romero, J. A. C.; Fu, G. C. *Angew. Chem., Int. Ed*. **2007**, *46*, 4367.

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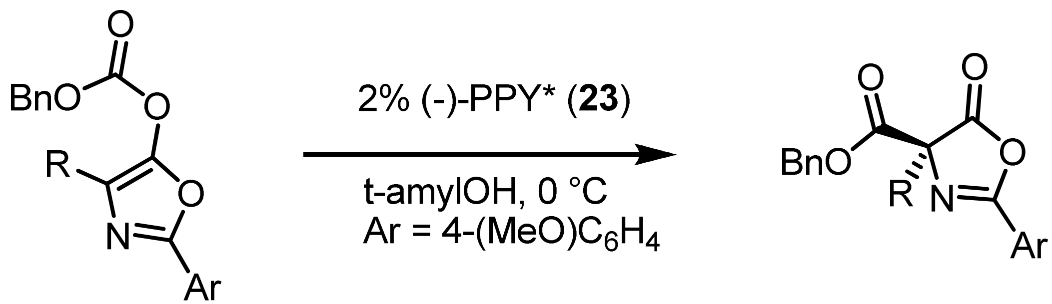
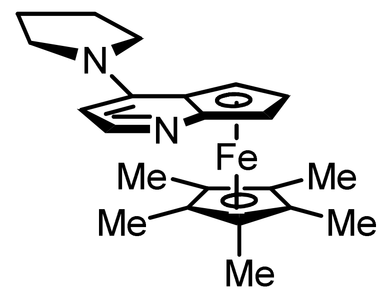
Rearrengment of O-Acylated Azlactones



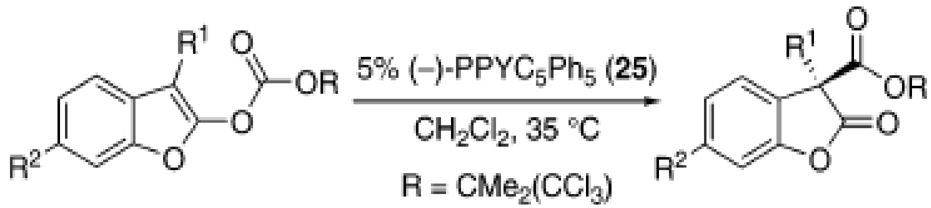
entry	R	%ee	%yield
1	Me	91	94
2	Et	90	93
3	CH_2Ph	90	93
4	allyl	91	93
5	CH_2CHMe_2	92	95
6	CH_2CH_2SMe	88	94



23 (PPY*)

Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc*. **1998**, *120*, 11532.

Rearrangement of Benzofuranone Derivatives

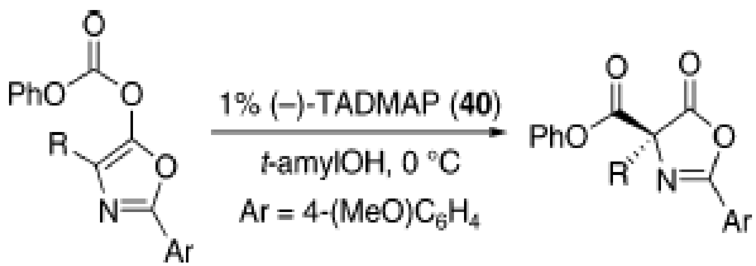


entry	R^1	R^2	% ee	% yield
1	Ph	H	97	81
2	Bn	H	88	95
3[a]	Me	Me	90	93

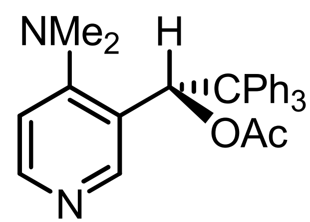
[a] This reaction was run at −12 °C with 10% catalyst.

Hills, I. D.; Fu, G. C. *Angew. Chem., Int. Ed*. **2003**, *42*, 3921.

Steglish Rearrangment by (-)-TADMAP



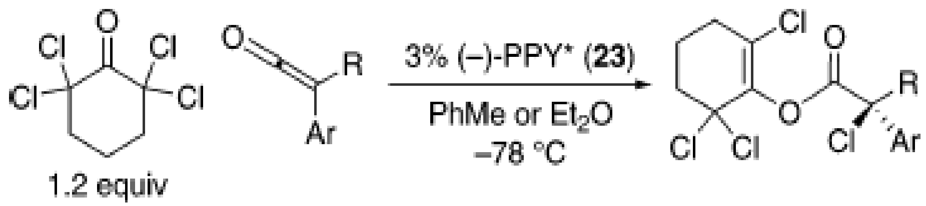
R	% ee	% yield
Me	91	95
CH_2Ph	95	99
allyl	91	90
CH_2CHMe_2	91	90
Ph	58	95



TADMAP

(a) Shaw, S. A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368.
(b) Shaw, S. A.; Aleman, P.; Kampf, J. W.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925.

Halogenation

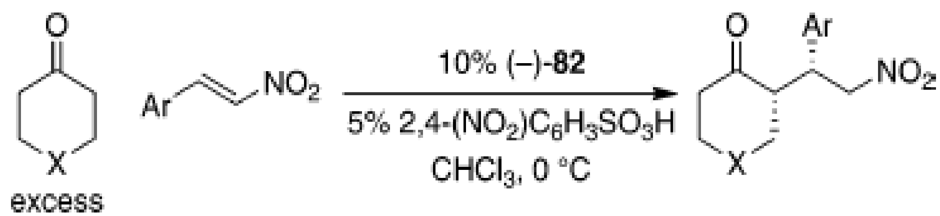


entry	Ar	R	% ee	% yield
1	Ph	Me	91	74
2	Ph	Et	94	86
3	Ph	*i*-Bu	85	76
4	*o*-tolyl	Et	67	84
5[a]	Ph	cyclopentyl	65	79

[a] Reaction conducted at −78 °C at room temperature.

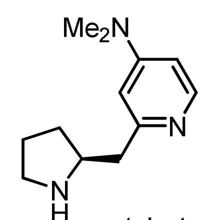
Lee, E. C.; McCauley, K. M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 977.

Michael reaction



entry	catalyst	X	Ar	syn:anti	% ee[a]	% yield
1	**82a**	CH_2	Ph	98:2	95	98
2	**82b**	CH_2	Ph	98:2	99	95
3	**82a**	CH_2	1-naphthyl	97:3	98	92
4	**82b**	CH_2	1-naphthyl	97:3	93	100
5	**82a**	CH_2	2-thienyl	94:6	88	92
6	**82b**	CH_2	2-thienyl	93:7	90	98
7	**82a**	S	Ph	99:1	96	95
8	**82b**	S	Ph	98:2	92	98

[a] Enantiomeric excess of the syn diastereomer.



catalyst

Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc*. **2004**, *126*, 9558.

Conclusion

- Chiral DMAP promising area of application:
  - Resolution of alcohols, amines
  - Catalyst for β-lactam, β-lactone, rearrangements, halogenations, annulations reaction
- Central, axial and planar chiral DMAP expand the area of imagination in the design of catalysts