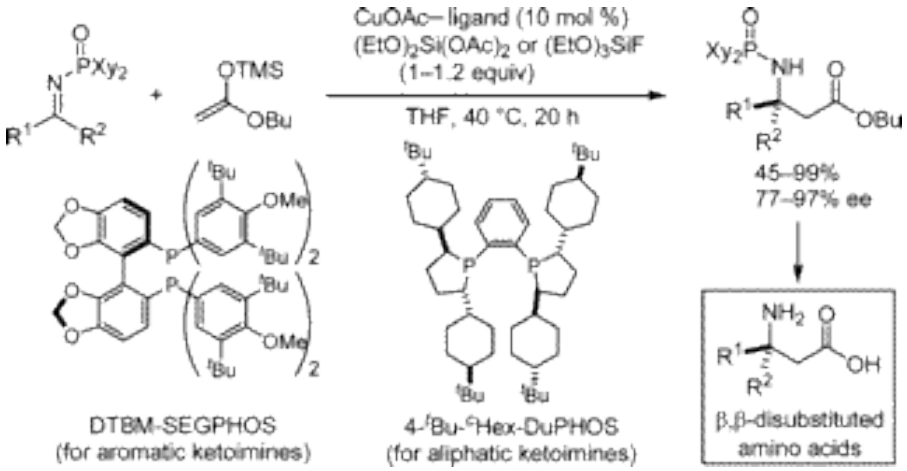
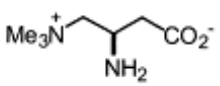
Catalytic Enantioselective Mannich-type Reactions of Ketoimines

Suto, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ASAP.

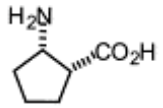


Zhiyong Wang
Wipf Group
Current Literature Presentation
January 6th, 2007

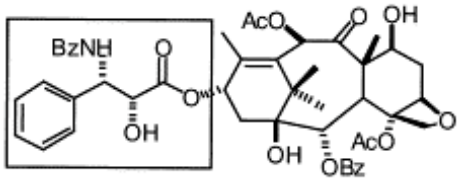
β-Amino Acid-Containing Natural Products



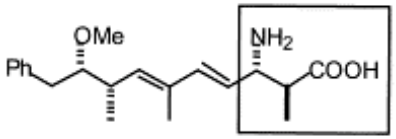
Emeriamine **1**



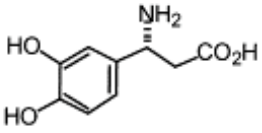
Cispentacin **2**



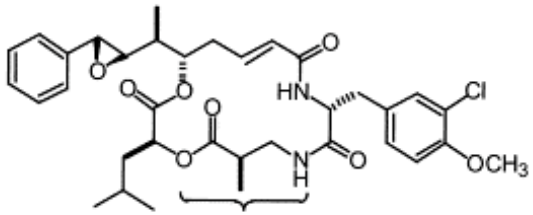
Taxol **3**



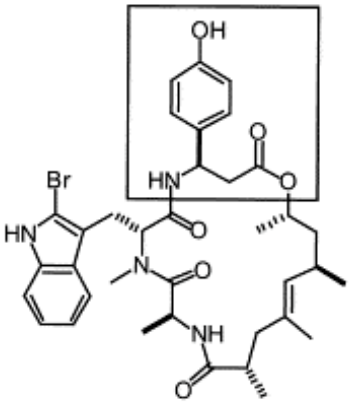
ADDA **4**



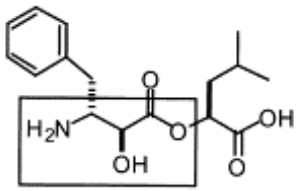
(*R*)-β-Dopa **5**



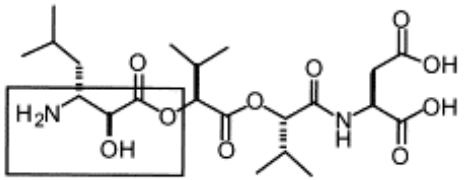
Cryptophycin 1 **7**



Jasplakinolide **6**



Bestatin **8**



Amastatin **9**

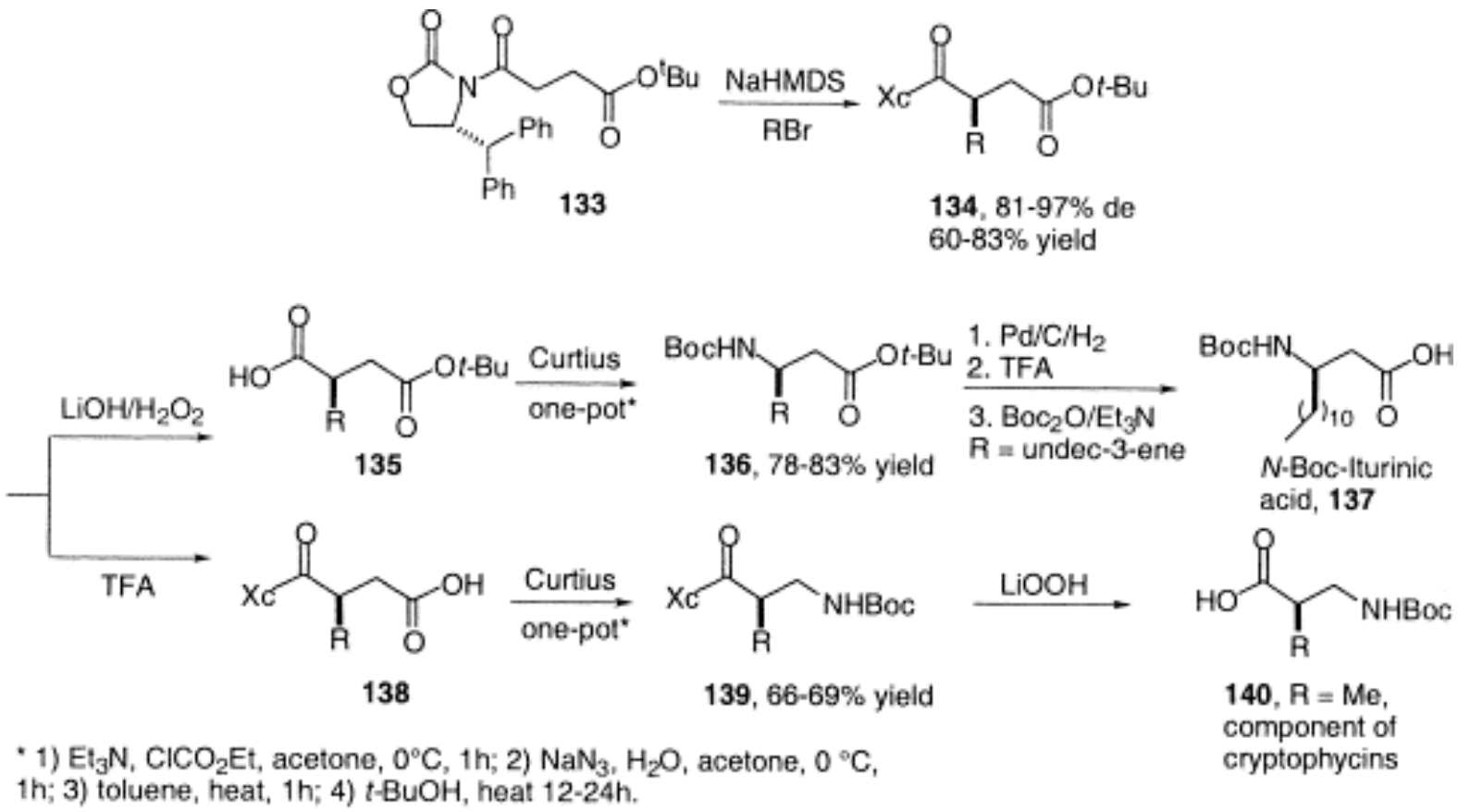
Liu, M., Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991-8035.

Traditional Stereoselective Approaches to Synthesize β-Amino Acids

- Homologation of α-amino acids
- Enzymatic resolution of β-amino acids
- Curtius rearrangement
- Conjugate addition of a nitrogen nucleophile to α,β-unsaturated esters or imides
- Hydrogenation
- Amino hydroxylation and β-lactam synthesis
- Addition of enolates (or equivalents) to imines-indirect Mannich reaction

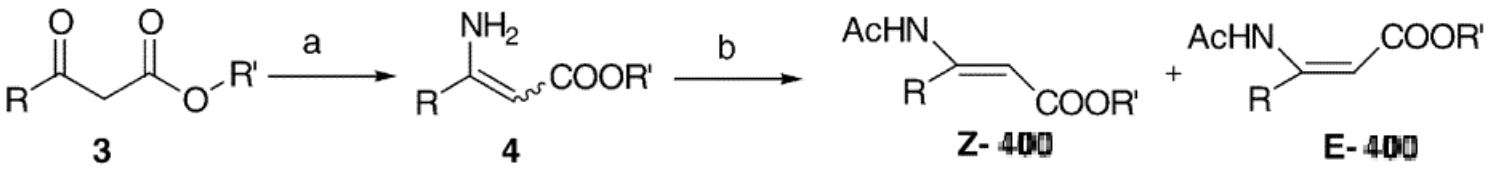
Liu, M., Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991-8035.

Curtius Rearrangement



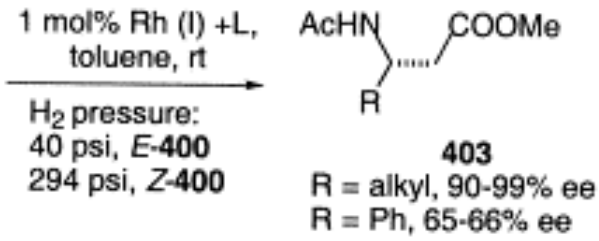
Sibi, M. P., Deshpande, P, K. *J. Chem. Soc., Perkin Trans. 1* **2000**, *1461-1466*.

Catalytic Hydrogenation

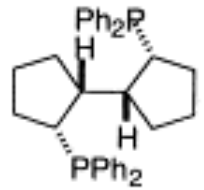


3 4 Z-400 E-400

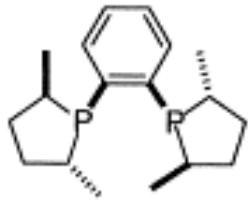
*(a) NH_4OAc, MeOH, rt; (b) Ac_2O, py, THF, reflux.



403
R = alkyl, 90-99% ee
R = Ph, 65-66% ee



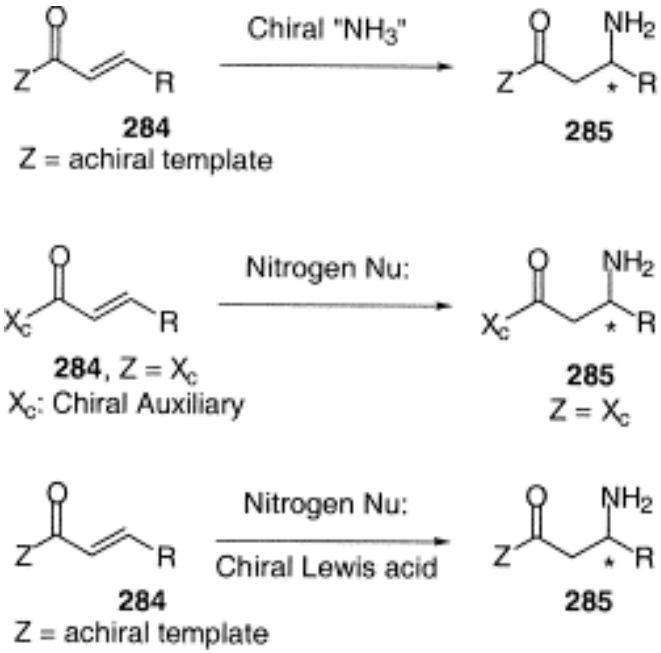
401, (*R,R*)-BICP

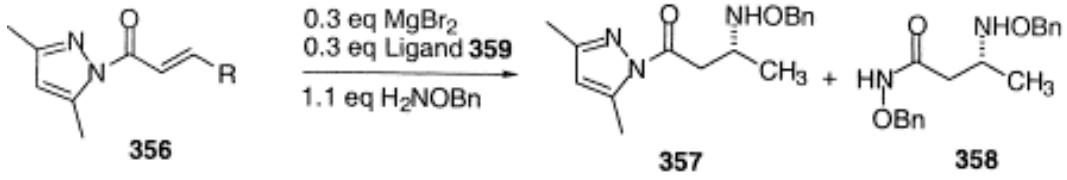


402, (*R,R*)-Me-DuPhos

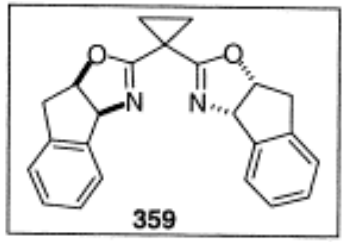
Zhu, G.; Chen, Z.; Zhang, X. *J. Org. Chem.* **1999**, *64*, 6907-6910.

Conjugate Addition





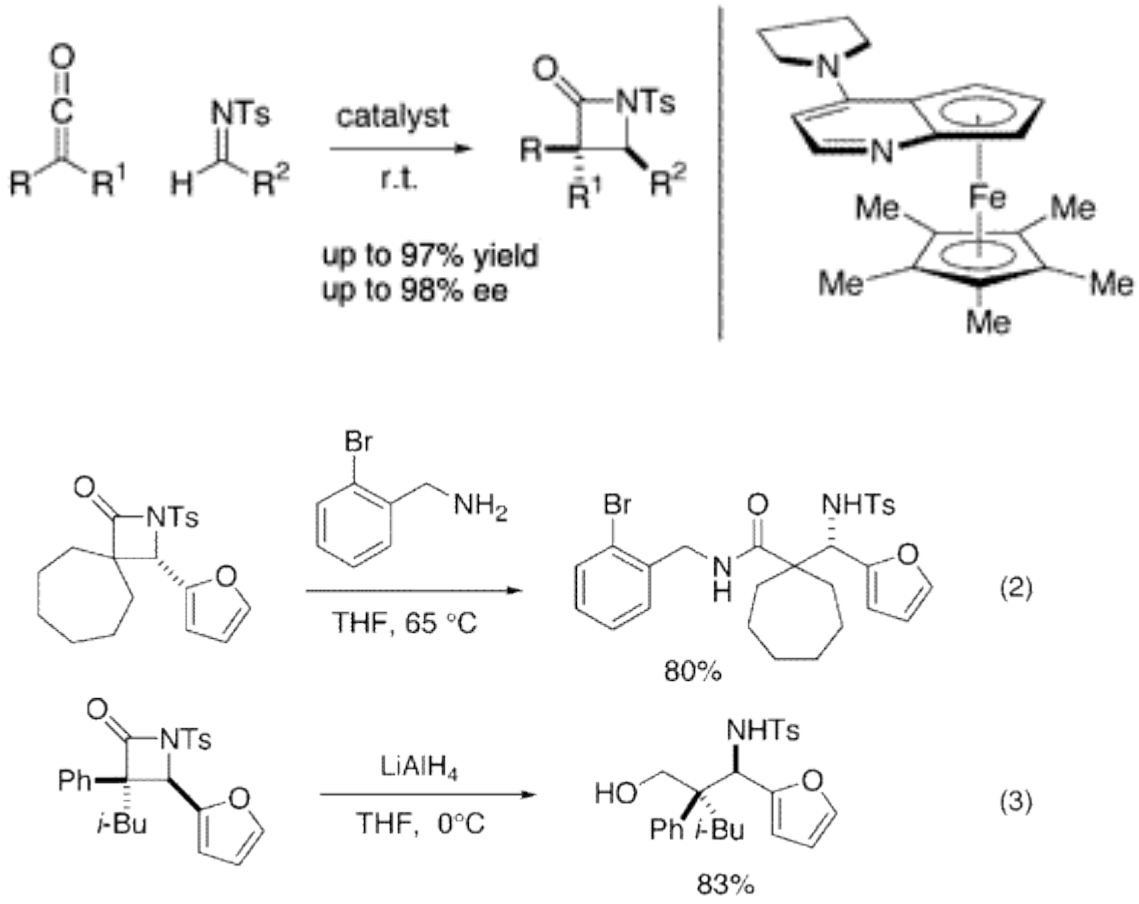
R	yield (%)	ee (%)
Me	80	92 (*R*)
CH_2Ph	80	95 (*R*)
i-Pr	76	87 (*R*)
Me[a]	67	59 (*S*)
Ph[b]	24	83



[a] 1 eq $Y(OTf)_3$ used.
[b] 60% of the starting material was recovered

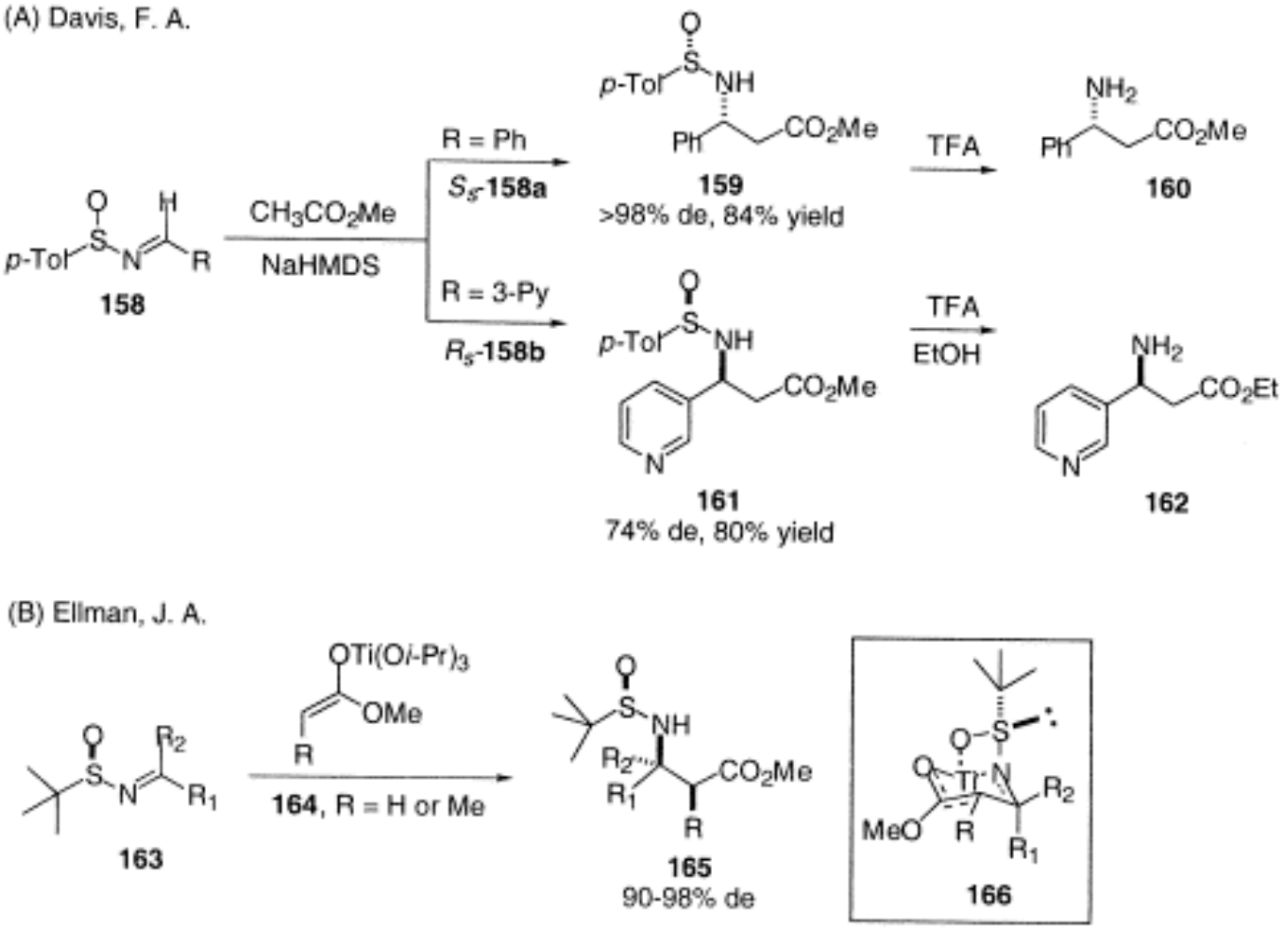
Sibi, M. P. et al. *J. Am. Chem. Soc*. **1998**, *120*, 6615.

From β-Lactam



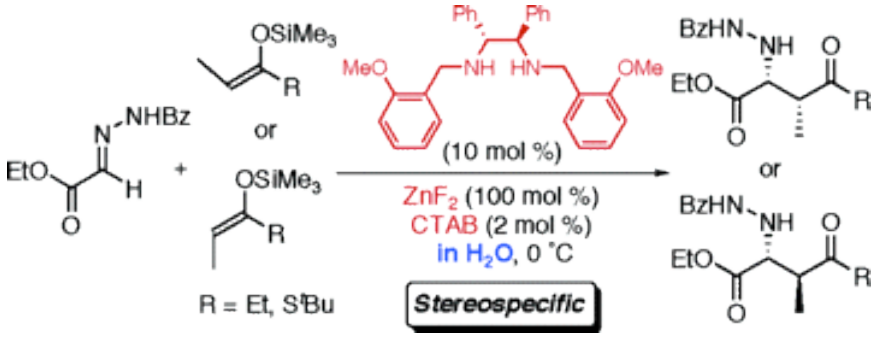
Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc*. **2002**, *124*, 1578-1579.

Asymmetric Addition of Enolates to Imines



Davis, F. A.; Szewczyk, J. M.; Reddy, R. E. *J. Org. Chem.***1996**, *61*, 2222–2225.
Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12–13.

Catalytic Asymmetric Mannich Reaction-Aldimine



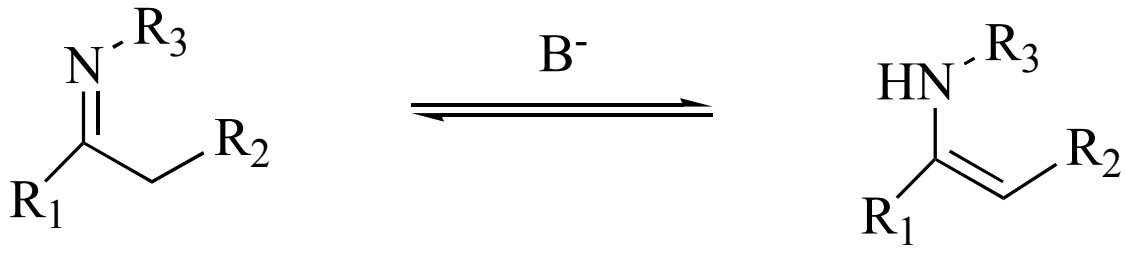
entry	R^1	R^2	R^3	additive (mol %)	yield (%)	syn/anti	ee (%)
1[a]	H	H	4-Me-C_6H_4		91		95
2[a]	H	H	4-MeO-C_6H_4		93		91 (98)[b]
3[a,c]	H	H	4-Cl-C_6H_4		94		95
4[d]	Me	H	Ph		6	91/9	94[e]
5[d]	Me	H	Ph	TfOH (1)	5	91/9	90[e]
6[d]	Me	H	Ph	SDS (5)	9	91/9	78[e]
7[d]	Me	H	Ph	Triton X-405(5)	10	91/9	93[e]
8[d]	Me	H	Ph	CTAB (5)	94	94/6	97[e]
9[d]	Me	H	Ph	CTAB (2)	93	94/6	96[e]
10[d,f]	Me	H	Ph	CTAB (2)	84	93/7	97[e]
11	Et	H	Ph	CTAB (2)	76	96/4 (98.5/1.5)[b]	96[e] (>99.5[e])[b]
12[g,h]	Me	H	Et	CTAB (2)	57	86/14 (98.5/1.5)[b]	97[i] (>99.5[i])[b]
13[h,j]	H	Me	Et	CTAB (2)	94	12/88	94[i]
14[k]	Me	H	StBu	CTAB (2)	39	8/92	94[i]
15[l]	H	Me	StBu	CTAB (2)	51	93/7	67[i]
16[l,m]	H	Me	StBu	CPB (2)	69	92/8	62[i]

[a] **1c** was used instead of **1b**. [b] After one recrystallization. [c] Time = 36 h. [d] E/Z = <1/>99. [e] Ee of syn adduct. [f] Performed with 5 mol % **1b**. [g] E/Z = 2/98. [h] Time = 72 h. [i] Ee of major diastereomer. [j] E/Z = 76/24. [k] E/Z = 98/2. [l] E/Z = 3/97. [m] Time = 48 h.

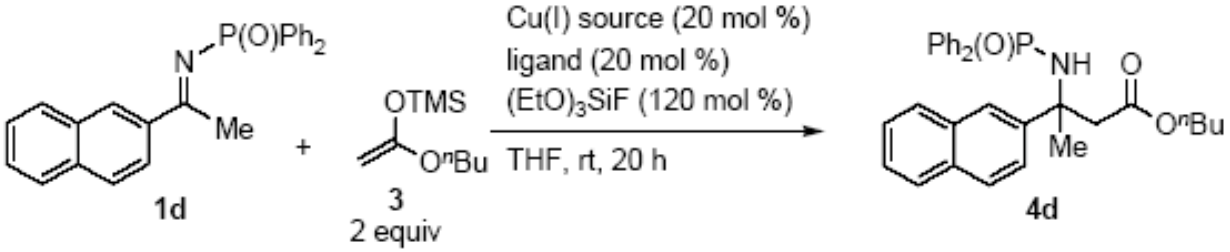
Hamda, T.; Kobayashi, M. S. *J. Am. Chem. Soc*. **2004**, *126*, 7768-7769.

Mannich Reaction with Ketoimines - Challenges

- Low reactivity of ketoimines
- Ketoimine-enamine isomerization
- Differentiation of the two substituents on the prochiral carbon

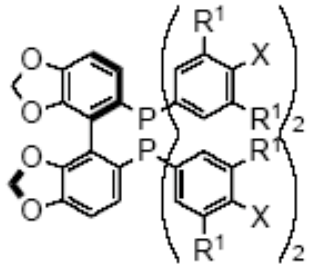


Current Paper: Catalytic Asymmetric Mannich Reaction with Ketoimines

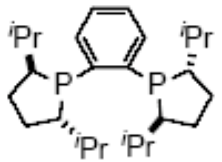


entry	Cu(I)	ligand	yield (%)[a]	ee (%)[b]
1	CuOAc	(*R*)-SEGPHOS	36	46
2	CuOAc	(*R*)-DTBM-SEGPHOS	54	94
3	CuOAc	(*S,S*)-^{i}Pr-Duphos	97	66
4	CuOAc	Taniaphos-Ph	11	N.D.
5	CuOAc	Taniaphos-Cy	11	N.D.
6	CuF•3PPh$_3$•2EtOH	(*R*)-DTBM-SEGPHOS	60	56
7	CuF[c]	(*R*)-DTBM-SEGPHOS	30	6

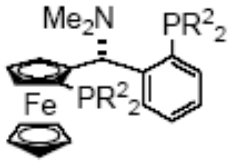
[a] Determined from 1H NMR. [b] Deremined by chiral HPLC
[c] Prepared by reducing $CuF_2•H_2O$ with 2 equiv of chiral phosphine to Cu in situ.



(*R*)-SEGPHOS; R^1 = X =H
(*R*)-DTBM-SEGPHOS; R^1 = ^{t}Bu, X = OMe



(*S,S*)-^{i}Pr-Duphos



Taniaphos-Ph; R^2 = Ph
Taniaphos-Cy; R^2 = Cy

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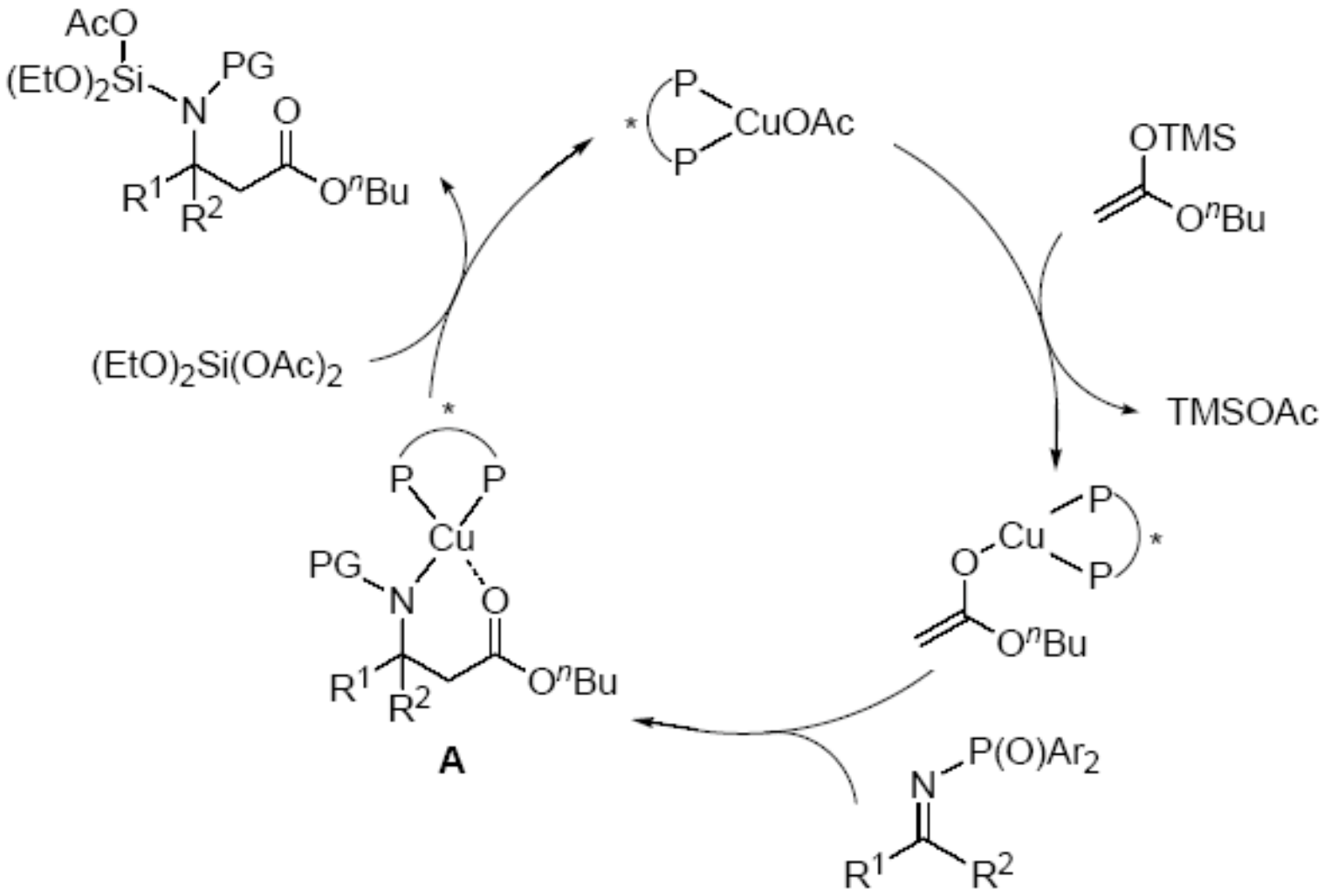
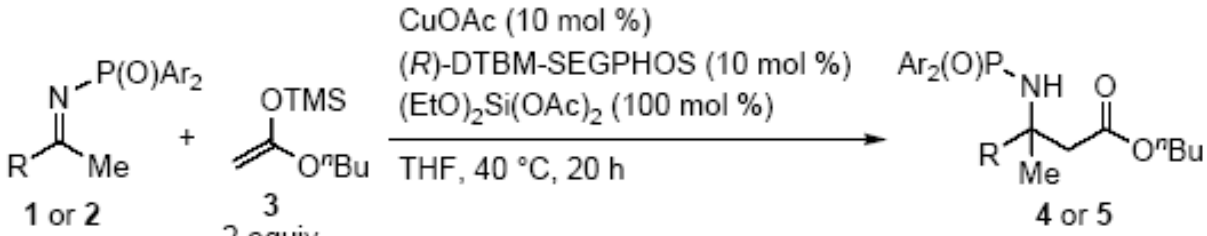
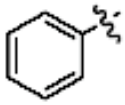
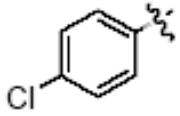
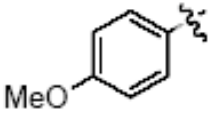
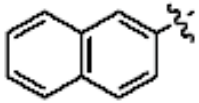
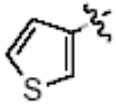
Proposed Reaction Mechanism



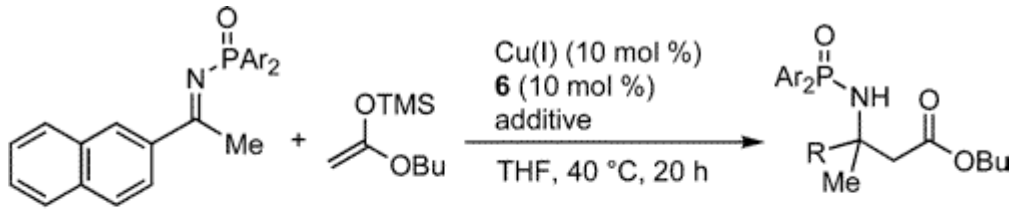
Effects of *N*-Phosphinoyl Moiety



entry	substrate R	substrate Ar		yield[a] (%)	ee[b] (%)
1		Ph	**1a**	69	94
2		3,5-Xy	**2a**	81	95
3		Ph	**1b**	73	93
4		3,5-Xy	**2b**	82	97
5[c]		Ph	**1c**	59	94
6[c]		3,5-Xy	**2c**	87	97
7		Ph	**1d**	82	92
8		3,5-Xy	**2d**	74	96
9		Ph	**1f**	69	93
10		3,5-Xy	**2f**	92	97

[a] Isolated yield. [b] Determined by chiral HPLC.
[c] 4 equiv of 3 was used.

Optimization for Aromatic Ketoimines

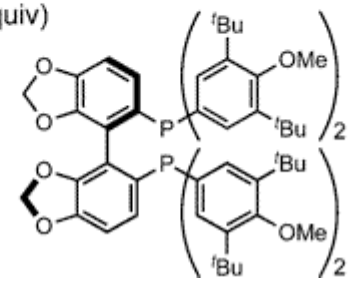


1d: Ar = Ph
2d: Ar = 3,5-xylyl

3 (2 equiv)

4d: Ar = Ph
5d: Ar = 3,5-xylyl
(R = 2-naphthyl)

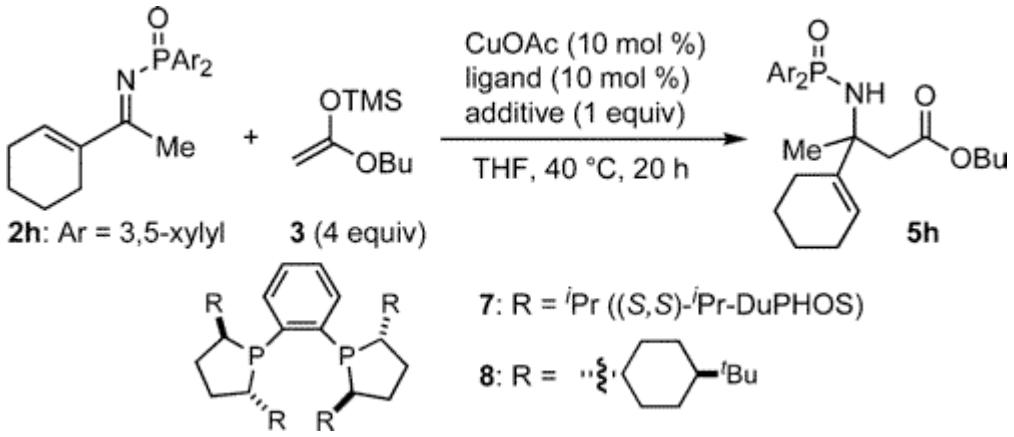
(*R*)-DTBM-SEGPHOS (**6**) =



entry	ketoimine	Cu source	additive[a]	yield[b] (%)	ee[c] (%)
1	**1d**	CuF[d]	$(EtO)_3SiF + PhBF_3K$	60	60
2	**1d**	CuOAc	$(EtO)_3SiF + PhBF_3K$	58	85
3	**1d**	CuOAc	$(EtO)_3SiF$	54	94
4	**1d**	CuOAc	$(MeO)_2SiF_2$	85	93
5	**1d**	CuOAc	$Me_2Si(OAc)_2$	68	78
6	**1d**	CuOAc	$EtSi(OAc)_3$	60	80
7	**1d**	CuOAc	$(EtO)_2Si(OAc)_2$	82	92
8	**2d**	CuOAc	$(EtO)_2Si(OAc)_2$	74	96

[a] In entries 1 and 2, 1 equiv of $(EtO)_3SiF$ and 10 mol % of $PhBF_3K$ were used. In other entries, 1 equiv of additive was used. [b] Isolated yield. [c] Determined by chiral HPLC. [d] $CuF \cdot 3PPh_3 \cdot 2EtOH$.

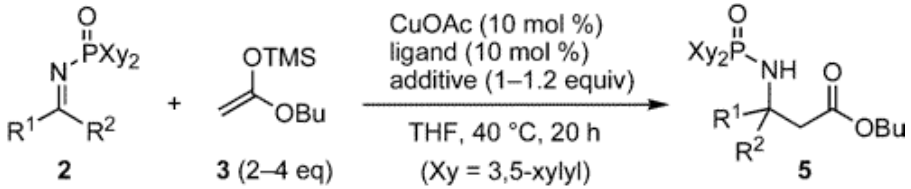
Optimization for Aliphatic Ketoimines



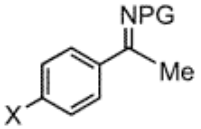
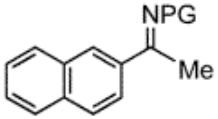
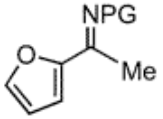
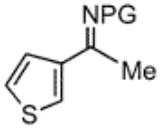
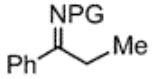
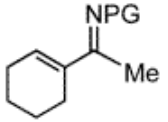
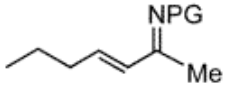
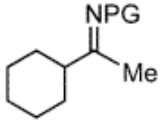
entry	ligand	additive	yield[a] (%)	ee[b] (%)
1	**6**	$(EtO)_2Si(OAc)_2$	29	87
2	**6**	$(EtO)_3SiF$	58	86
3	**7**	$(EtO)_3SiF$	90	75
4	**8**	$(EtO)_3SiF$	99	81

[a] Isolated yield. [b] Determined by chiral HPLC.

Reaction Scope

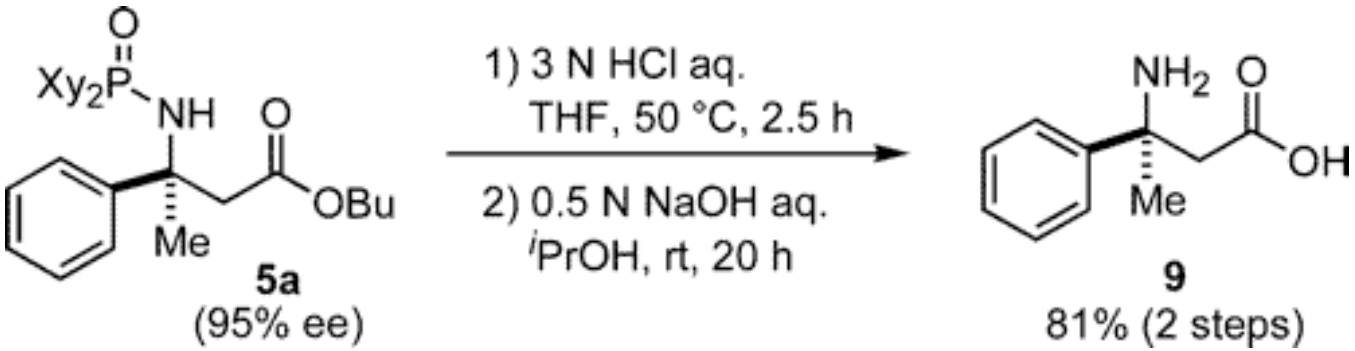


2 + **3** (2–4 eq) → **5**

entry	substrate		conditions[a]	yield (%)[b]	ee (%)[c]
1		X = H (**2a**)	A	81	95[g]
2		X = Cl (**2b**)	A	82	97
3[d]		X = OMe (**2c**)	A	87	97
4		**2d**	A	74	96
5[d]		**2e**	A	74	96
6		**2f**	A	92	97
7[d]		**2g**	A	61	91
8[e]		**2h**	B	99	75
9[f]			B	99	81
10[e]		**2i**	B	74	58
11[f]			B	65	77
12[e]		**2j**	B	81	75
13[f]			B	45	80

[a]Condition A: **3** = 2 equiv, ligand = 6, additive = $(EtO)_2Si(OAc)_2$ (1 equiv). Condition B: **2** = 4 equiv, ligand = DuPHOS (**7** or **8**), additive = $(EtO)_3SiF$ (1.2 equiv). [b]Isolated yield. [c]Determined by chiral HPLC. [D]4 equiv of **3** were used. [e]Ligand = **7**. [f]Ligand = **8**. [g]Absolute configuration was determined to be (*S*).

Conversion to β,β-Disubstituted Amino Acid



Summary

- The first catalytic enantioselective Mannich reaction of simple ketoimines is developed, providing a general way to synthesize chiral β,β-disubstituted amino acids.
- Excellent enantioselectivity is achieved with aromatic ketoimines.
- Further ligand optimization is need to improve the enantioselectivity of aliphatic ketoimines.