Heterobimetallic Catalysis in Asymmetric 1,4-Addition of *O*-Alkylhydroxylamine to Enones

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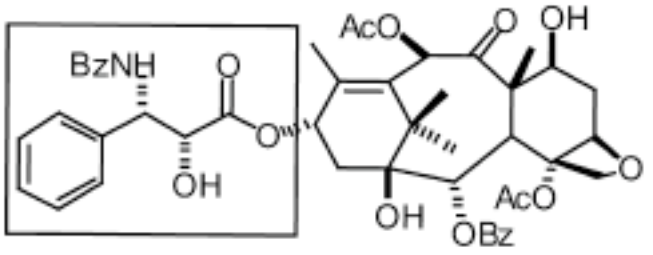
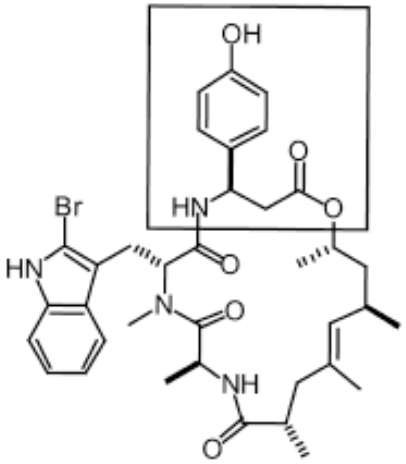
Why make β-amino Carbonyl Compounds?

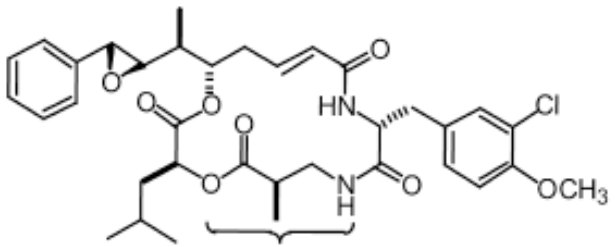
- They are found in a variety of natural products and biologically active compounds.



Taxol **3**



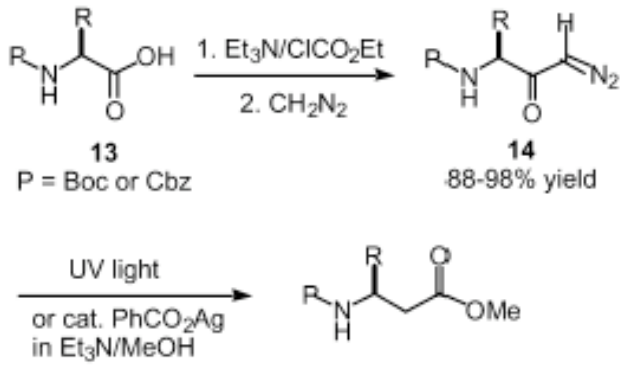
Jasplakinolide **6**



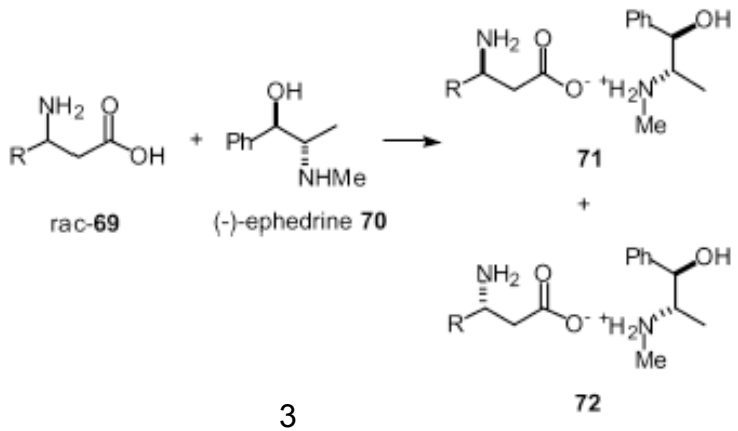
Cryptophycin 1 **7**

Methods for Generation of Enantomerically Enriched α-amino acid derivatives

- α-amino acids as starting materials
  - Arndt-Eistert

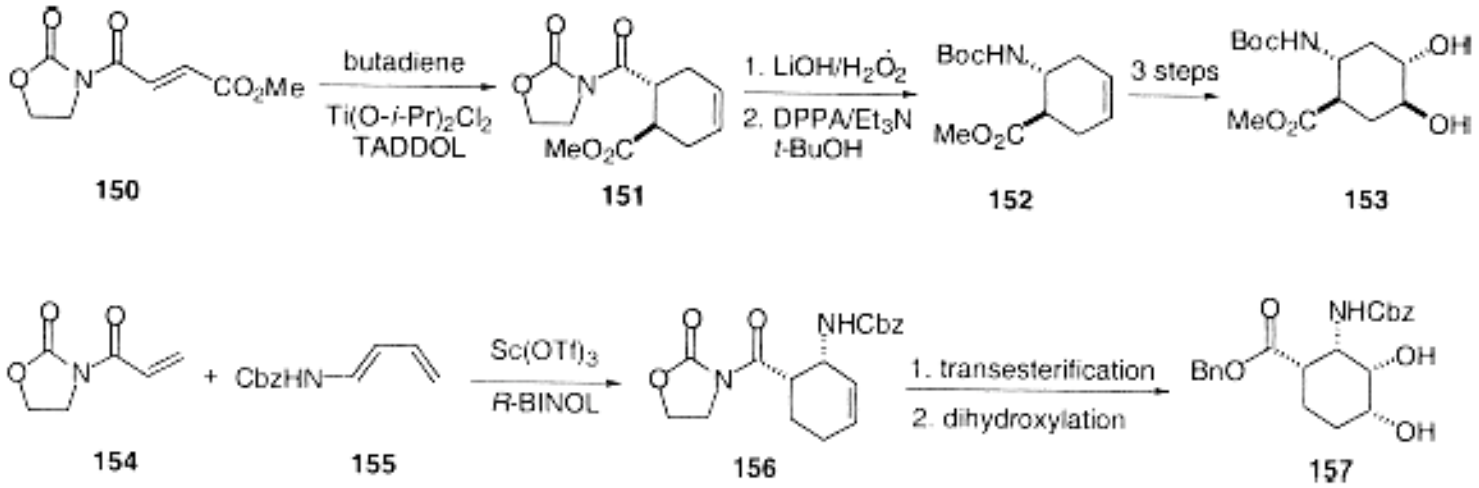


- β-amino acids as starting materials
  - Resolution



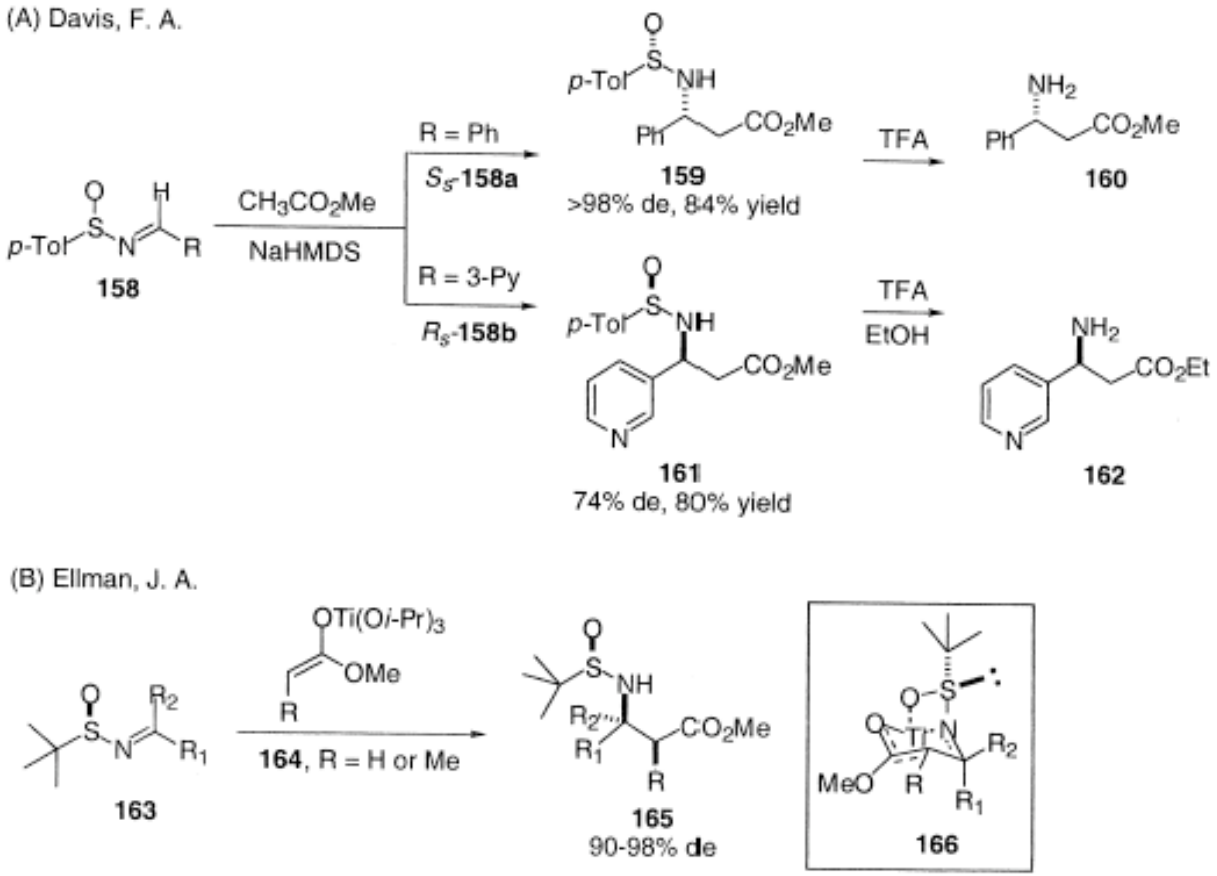
Methods for Generation of Enantomerically Enriched □-amino acid derivatives

- Curtius Rearrangement



Methods for Generation of Enantomerically Enriched α-amino acid derivatives

- Additions to imines

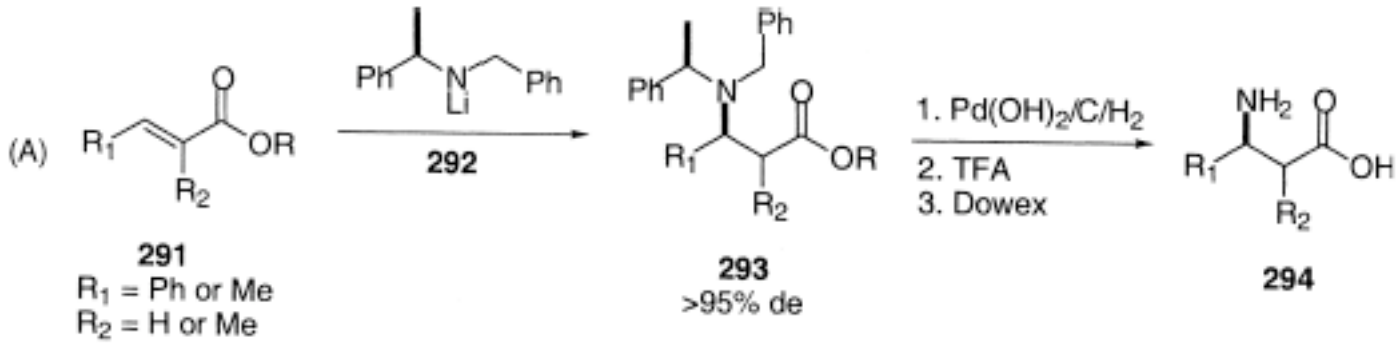


Methods for Generation of Enantomerically Enriched □-amino acid derivatives

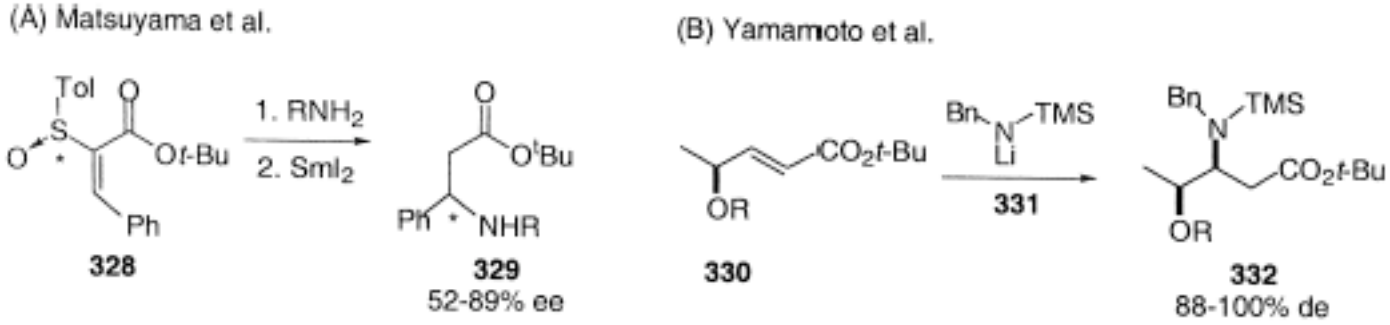
- Conjugate Additions
  - Addition of "Chiral Ammonia" equivalent
  - Addition of Nitrogen nucleophile to chiral enone
  - Asymetric catalysis

Conjugate Additions

- Chiral Ammonia equivalent

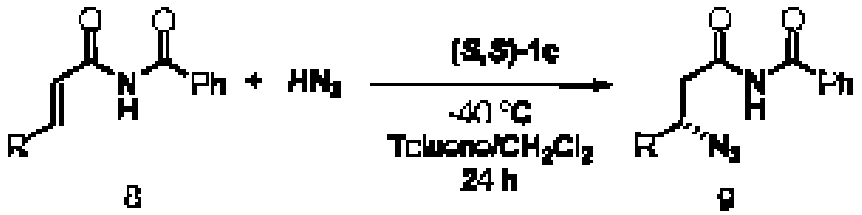


- Chiral Enone



Conjugate Additions

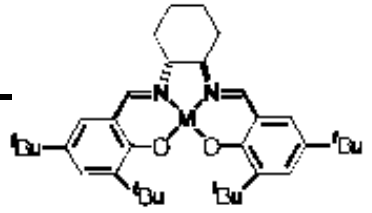
- Asymmetric Catalysis



8 9

	R	ee (%)[d]	yield (%)[e]		R	ee (%)[d]	yield (%)[e]
8a	Me	96	96	**8e**	*t*-Bu[b]	97	99
8b	Et	97	97	**8f**	Bn	95	97
8c	*n*-Pr	95	97	**8g**	CH_2OBn	96	93
8d	*i*-Pr	97	98	**8h**	Ph[c]	58	60

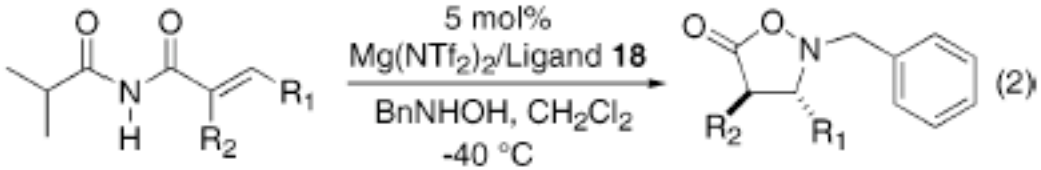
- JACS, **1999**, *121*, 8959



(1)

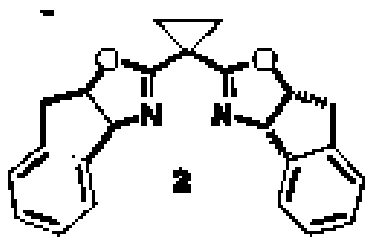
(*R*,*R*)-1a M = H, H
(*R*,*R*)-1b M = AlN3
(*R*,*R*)-1c M = AlMe

Conjugate Additions



17, 20-30 **19, 31-41**

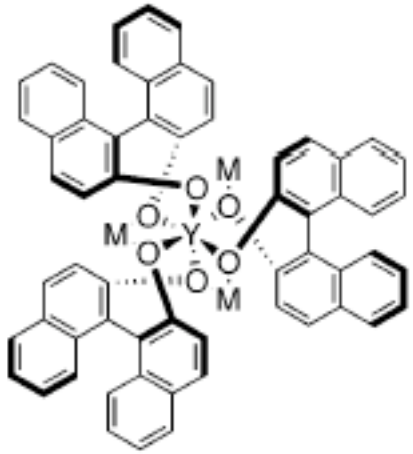
entry	SM	R_1	R_2	product	yield (%)[a]	de[b]	ee %[c]
1[d]	**17**	methyl	methyl	**19**	95	96	96
2	**20**	methyl	ethyl	**31**	70	98	86
3	**21**	methyl	bromo	**32**	76	99	76
4	**22**	methyl	phenyl	**33**	90	95	90
5	**23**	ethyl	methyl	**34**	82	96	90
6	**24**	*n*-propyl	methyl	**35**	92	95	89
7[e]	**25**	isopropyl	methyl	**36**	28	95	81
8[f]	**26**	isobutyl	methyl	**37**	64	95	77
9	**27**	*n*-heptyl	methyl	**38**	73	96	87
10	**28**	ethyl	ethyl	**39**	72	96	60
11[e]	**29**	phenyl	methyl	**40**	38	95	76
12[e]	**30**	phenyl	phenyl	**41**	49	93	84



- JACS, **2003**, *125*, 11796

Conjugate Additions using Heterobimetallic Catalysis

- Heterobimetallic catalysts exhibit both Lewis acidity and Bronsted basicity.



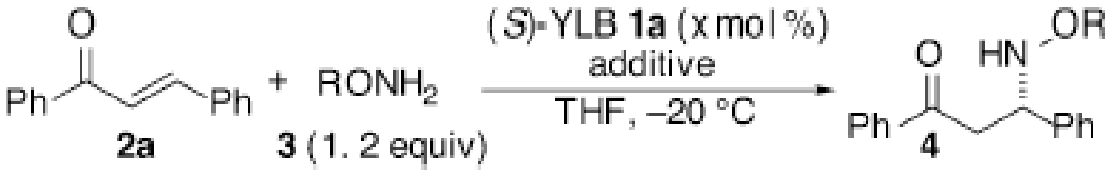
M = Li

YLi_3tris(binaphthoxide) (YLB **1a**)

M = K

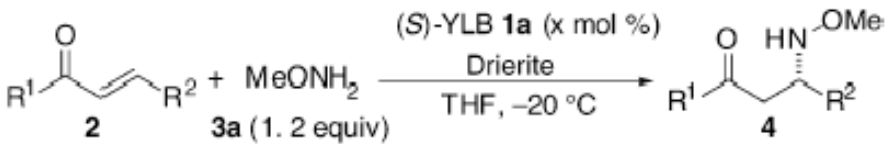
YK_3tris(binaphthoxide) (YPB **1b**)

Conjugate Additions using Heterobimetallic Catalysis



entry	additive	amine: R	catalyst (×mol %)	time (h)	yield (%)	ee (%)
1	none	**3a** (Me−)	10	24	94	97
2	MS 3A	**3a**	10	24	85	96
3	MS 4A	**3a**	10	24	67	96
4	MS 5A	**3a**	10	24	44	97
5	Drierite	**3a**	10	24	94	97
6	Drierite	**3b** (Bn−)	10	26	91	91
7	Drierite	**3a**	5	42	94	96
8	Drierite	**3a**	3	42	97	95
9	Drierite	**3a**	1	48	95	96
10	Drierite	**3a**	0.5	80	96	96
11[a]	Drierite	**3a**	1	48	98	95

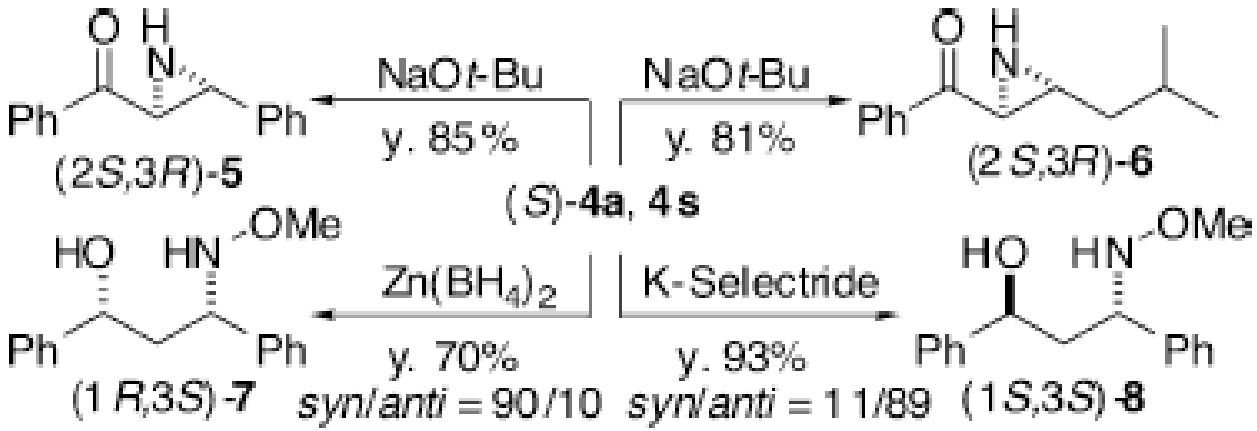
Conjugate Additions using Heterobimetallic Catalysis



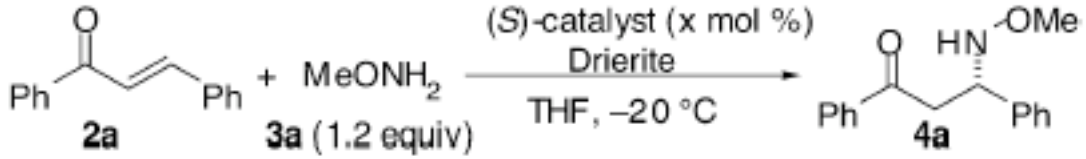
entry	enone R¹	enone R²		product	YLB (mol %)	time (h)	yield (%)	ee (%)
1	Ph	Ph	**2a**	**4a**	3	42	97	95
2	Ph	Ph	**2a**	**4a**	1	48	95	96
3	4-Cl-C_6H_4	Ph	**2b**	**4b**	3	42	96	96
4	4-Cl-C_6H_4	Ph	**2b**	**4b**	1	46	92	96
5	4-F-C_6H_4	Ph	**2c**	**4c**	3	54	97	96
6[a]	4-F-C_6H_4	Ph	**2c**	**4c**	1	65	91	96
7	4-Me-C_6H_4	Ph	**2d**	**4d**	3	48	96	94
8[a]	4-MeO-C_6H_4	Ph	**2e**	**4e**	3	74	91	96
9	3-Me-C_6H_4	Ph	**2f**	**4f**	3	48	96	92
10[a]	2-furyl	Ph	**2g**	**4g**	3	48	95	94
11[a]	2-thienyl	Ph	**2h**	**4h**	3	78	96	93
12	Ph	4-Cl-C_6H_4	**2i**	**4i**	3	48	92	92
13	Ph	4-Cl-C_6H_4	**2i**	**4i**	1	78	97	93
14	Ph	4-Me-C_6H_4	**2j**	**4j**	3	48	96	96
15[a]	Ph	4-MeO-C_6H_4	**2k**	**4k**	3	82	85	95
16[a]	Ph	4-MeO-C_6H_4	**2k**	**4k**	1	74	85	95
17	Ph	3-NO_2-C_6H_4	**2l**	**4l**	3	42	98	81
18	Ph	3-Cl-C_6H_4	**2m**	**4m**	3	48	95	92
19[a]	Ph	2-Cl-C_6H_4	**2n**	**4n**	3	122	92	82
20[a]	Ph	2-furyl	**2o**	**4o**	3	84	80	92
21	Ph	2-thienyl	**2p**	**4p**	3	48	96	95
22[a]	Ph	4-pyridyl	**2q**	**4q**	3	60	91	85
23[a]	Ph	*n*-C_5H_{11}	**2r**	**4r**	3	84	96	84
24[a]	Ph	*i*-$PrCH_2$	**2s**	**4s**	3	48	95	93
25	Ph	*i*-Pr	**2t**	**4t**	3	78	97	86
26	Ph	*cyclo*-hexyl	**2u**	**4u**	3	48	98	82
27[a]	Ph	*t*-Bu	**2v**	**4v**	3	96	57	82
28[b]	Ph	*trans*-PhCH=H	**2w**	**4w**	3	84	91	95

[a] 2 equiv of **3a** was used. [b] 3 equiv of **3a** was used.

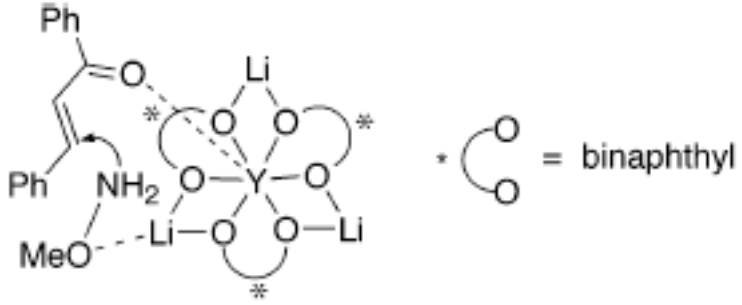
Functionalization of Products



Possible Mechanism of Addition using Heterobimetallic Catalyst



entry	catalyst (×mol %)	time (h)	yield (%)	ee (%)	config
1	none	42	trace		
2	BuLi/BINOL (9/9)	42	11	12	*R*
3	$Y(HMDS)_3$/BINOL (3/9)	42	29	16	*R*
4	YPB **1b** (3)	42	19	12	*R*
5	YLB **1a** (3)	42	97	95	*S*



Conclusion

- Shibasaki reports a method for the generation of □-amino carbonyl compounds using a cheap nitrogen source with the lowest catalyst loading reported to date.
- Work needs to be done to improve the substrate scope, hopefully toward compounds that can easily be converted to □-amino acid derivatives.
- More mechanistic studies need to be carried out to better define the role of the Lithium in the complex.