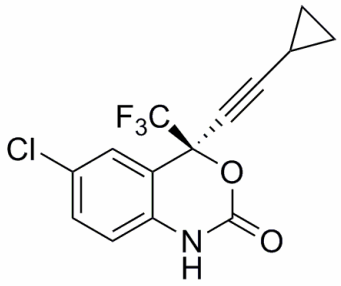
Synthesis of Chiral Tertiary Alcohol: Significant Developments

Nilanjana Majumdar

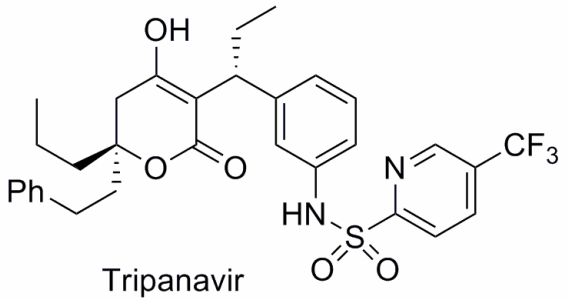
Literature Presentation

03.13.09

Biologically Important Compounds with Chiral Tertiary Alcohol Functionality

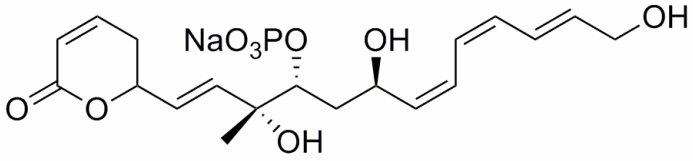


Efavirenz

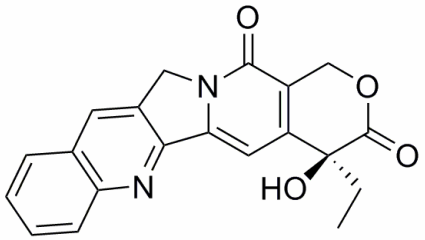


Tripanavir

HIV drugs



Fostriecin



Camptothecin

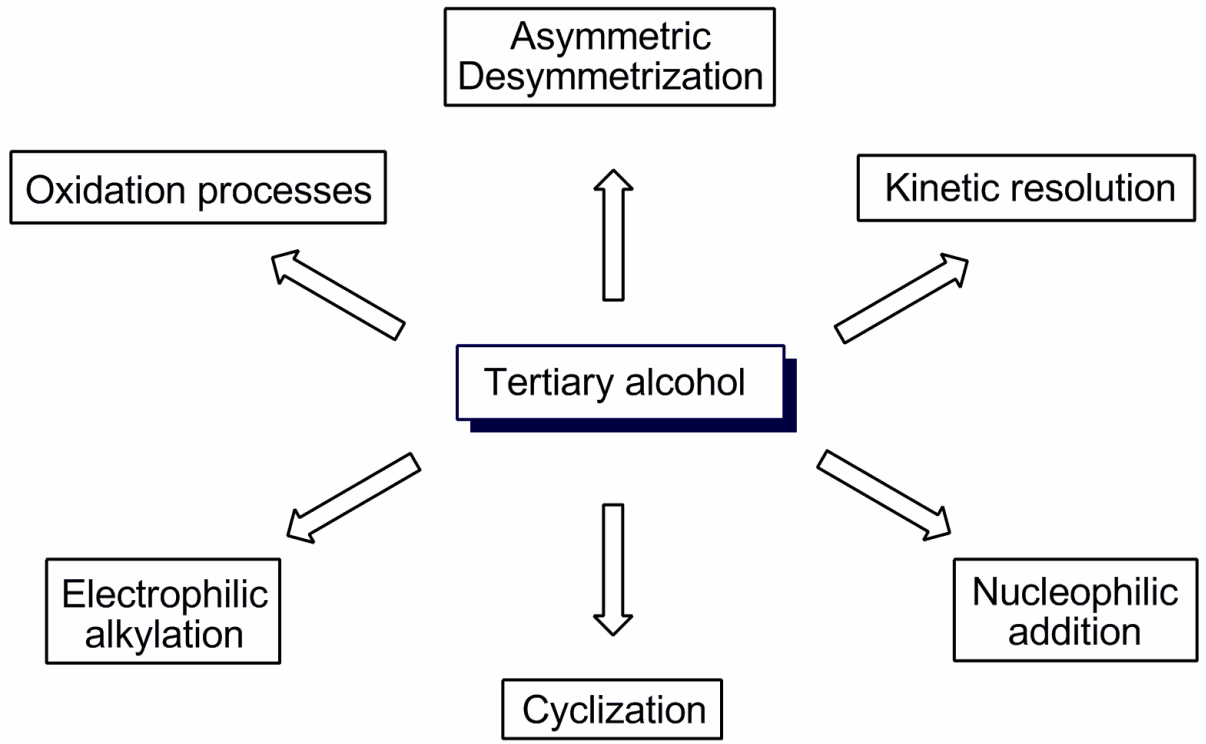
Natural products with cytotoxic activity

Riant, O. & Hannedouche, *J. Org. Biomol. Chem.* **2007**, *5*, 873

Outline

- Challenges and solution
- Different approaches: Organometallic 1, 2-addition
  - Alkynylation
  - Vinylation
  - Allylation
  - Arylation / alkylation
  - Cyanosillylation
- Enantiodivergent conversion of chiral secondary alcohol to chiral tertiary alcohol

Available Methods



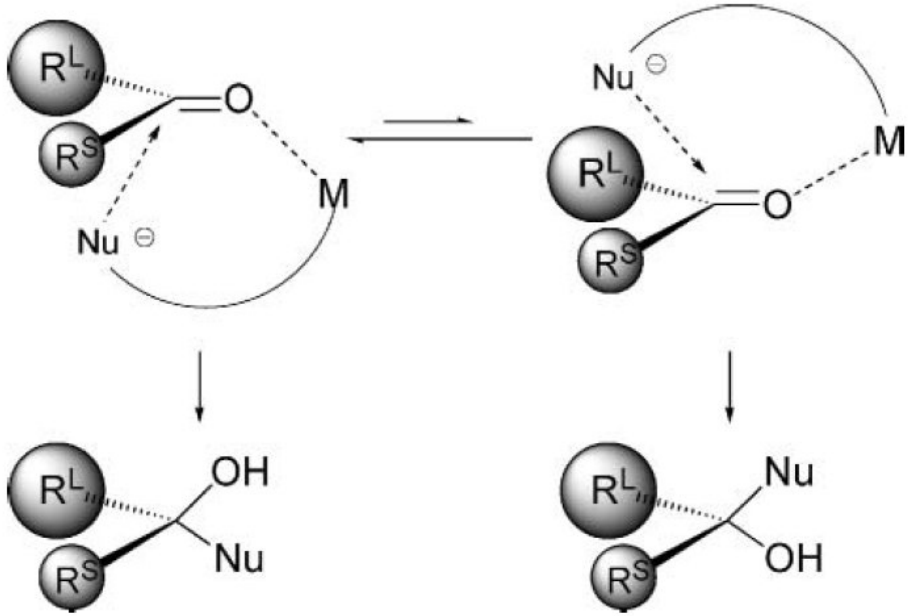
- Method involving stereoselective C-C bond formation is most important
- Simplest approach is the enantioselective 1,2-addition of organometallic reagents to ketones

Shibasaki, M.&Kanai, M. *Chem. Rev.* **2008**, *108*, 2853

Challenges

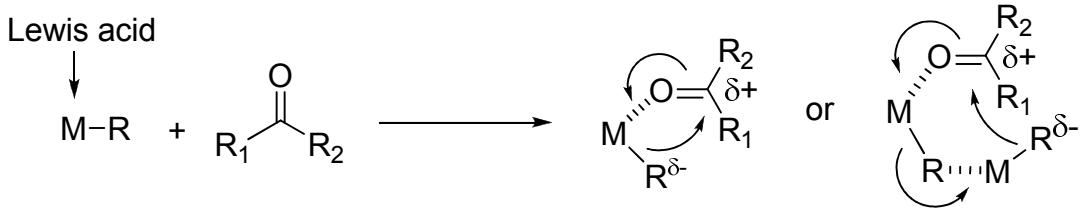
Two main challenges:

- Ketones are significantly less reactive than aldehydes
- Enatio-face differentiation of ketones is more difficult due to smaller steric and electronic differences between the two substituents on prochiral carbons

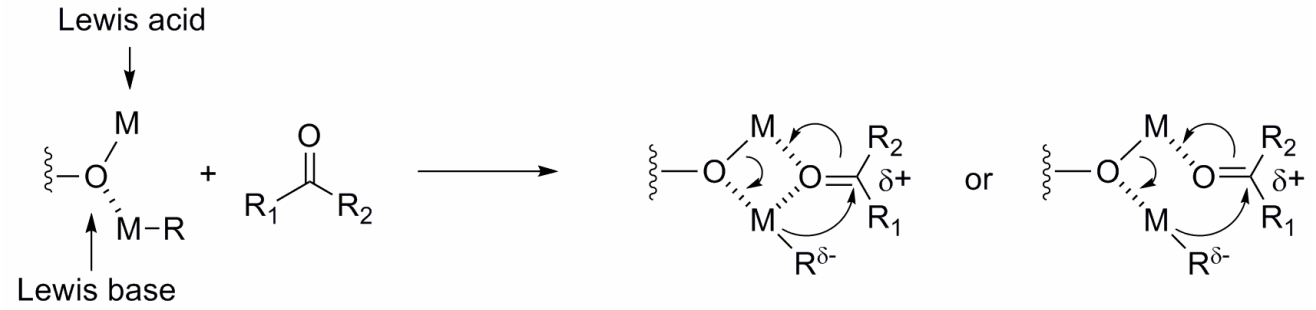


Riant, O. & Hannedouche, *J. Org. Biomol. Chem.* **2007**, *5*, 873

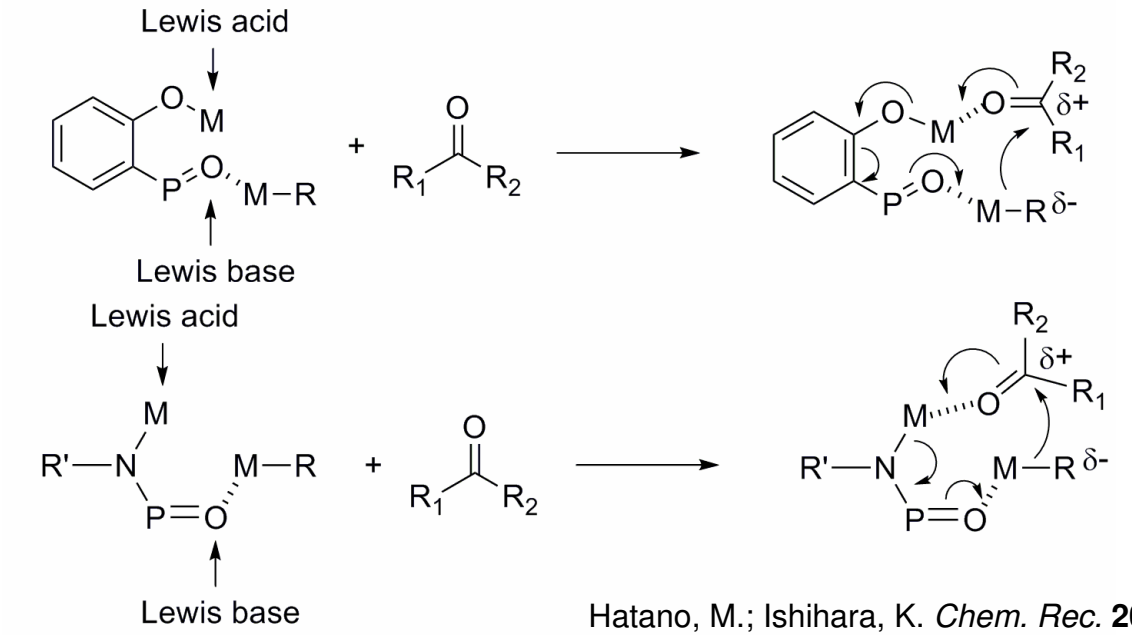
A. Double activation by Lewis acidic organometallic reagent:



B. Double activation by Lewis acid-Lewis base complex:



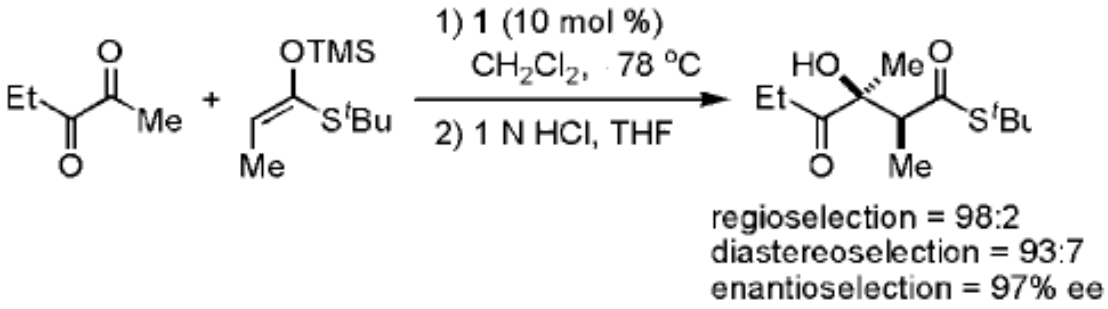
C. Double activation by conjugate Lewis acid-Lewis base complex:

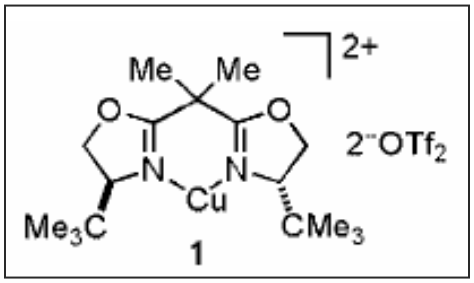


Hatano, M.; Ishihara, K. *Chem. Rec.* **2008**, *8*, 143

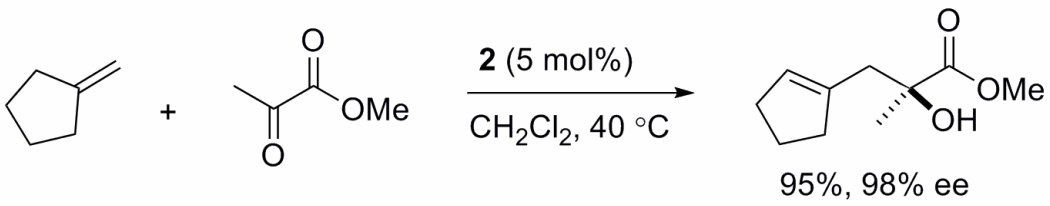
Different Catalytic Approaches to Tertiary Alcohol

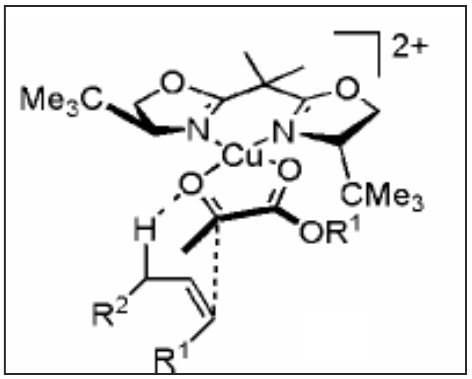
- Asymmetric aldol reaction:





- Enantioselective carbonyl-ene reaction:

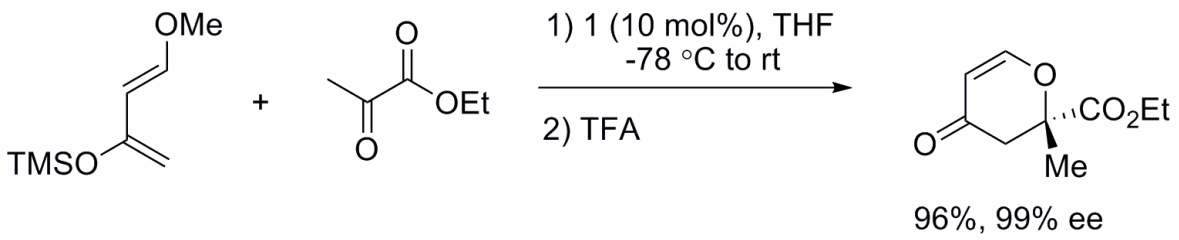


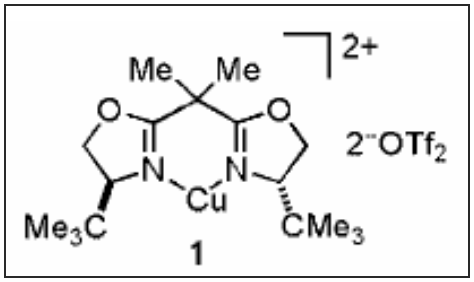


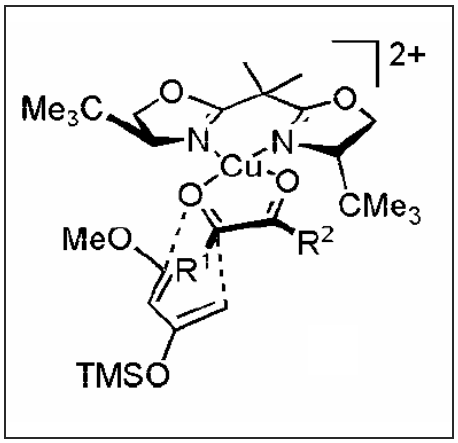
Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893
Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936

Different Catalytic Approaches to Tertiary Alcohol

- Enantioselective hetero-Diels-Alder-type reaction:







Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R. G.;Jørgensen, K. A. *J. Am. Chem. Soc.* **1998**, *120*, 8599

Outline

- Challenges
- Different approaches: Organometallic 1, 2-addition
  - Alkynylation
  - Vinylation
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  - Arylation / alkylation
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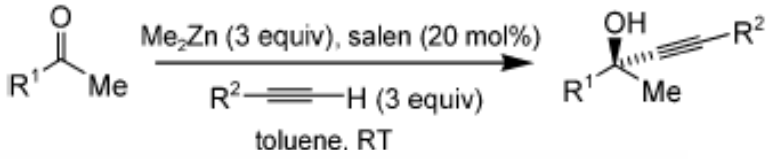
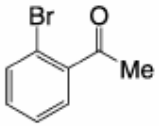
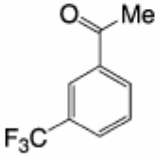
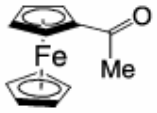
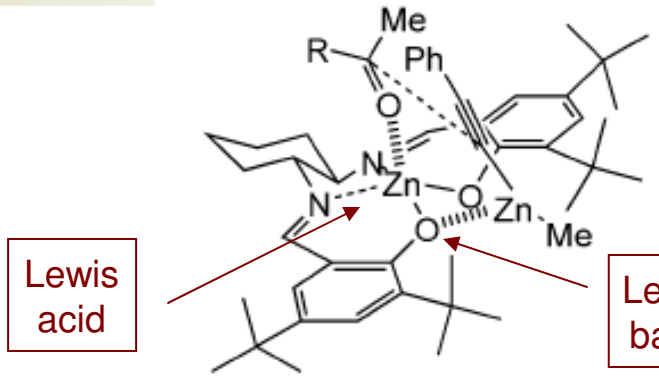
Alkynylation of Ketone

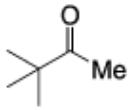
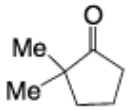
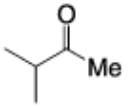
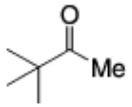
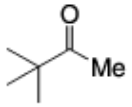


Entry	Ketone	Alkyne	Yield [%][b]	*ee* [%][c]
1	X = F	—≡—Ph	53	57
2	X = Cl	—≡—Ph	55	53
3	X = Br	—≡—Ph	78	53
4	X = NO_2	—≡—Ph	75	53
5	X = *t*Bu	—≡—Ph	45	66
6		—≡—Ph	50	70
7		—≡—Ph	81	61
8		—≡—Ph	40	62



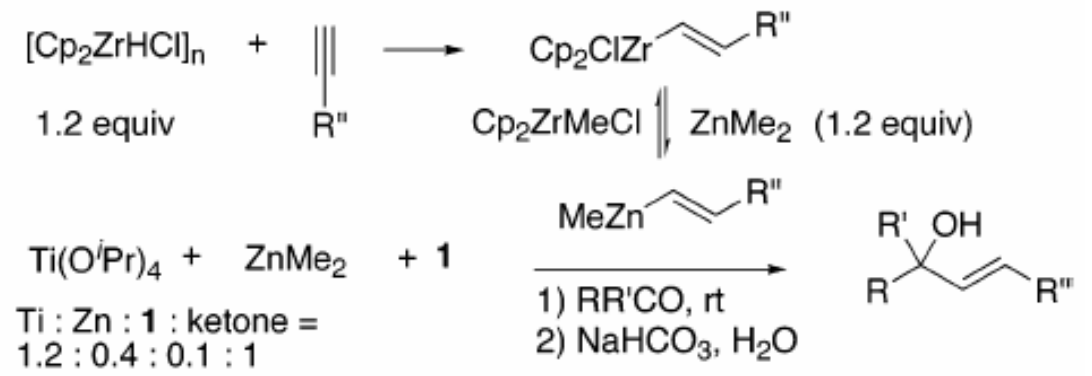
Lewis acid

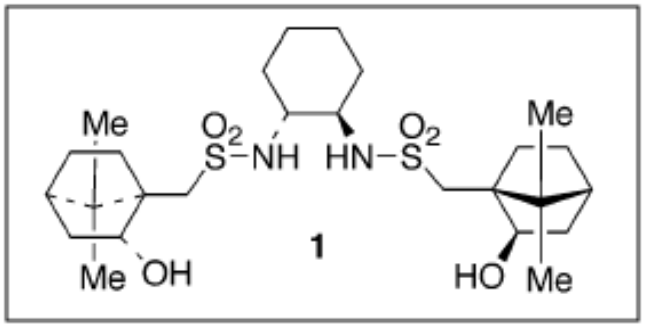
Lewis base

Entry	Ketone	Alkyne	Yield [%][b]	*ee* [%][c]
12		—≡—Ph	89	80
13		—≡—Ph	52	69
14		—≡—$SiMe_3$	75	64
15		—≡—$SiMe_3$	40[d]	81
16		—≡—Cl	40	80

Cozzi, P. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2895

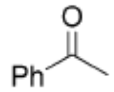
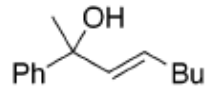
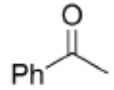
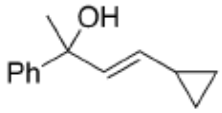
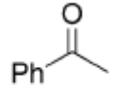
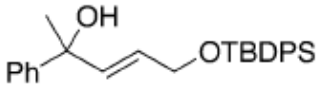
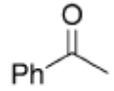
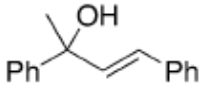
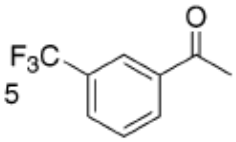
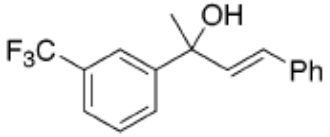
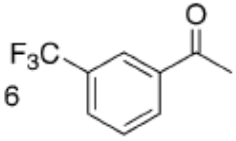
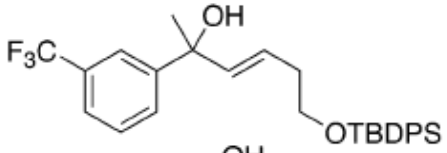
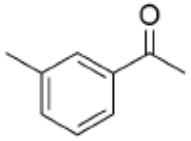
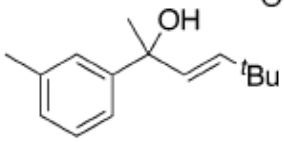
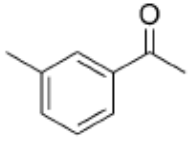
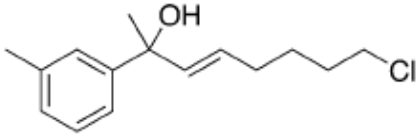
Vinylation of Ketone

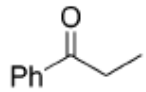
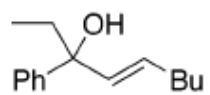
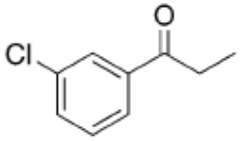
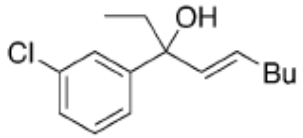
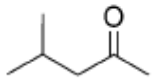
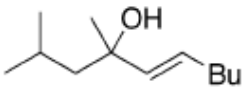




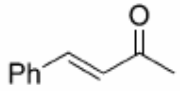
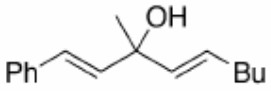
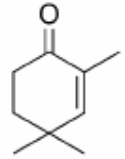
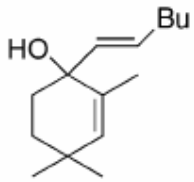
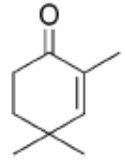
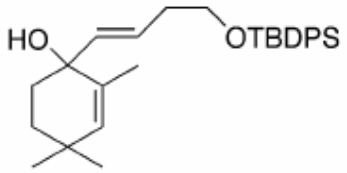
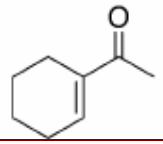
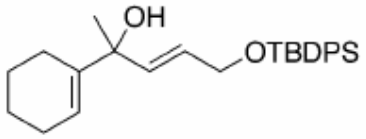
Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538

Substrate Scope

entry	substrate	product	ee (yield)
1			93 (85)
2			95 (90)
3			89 (92)
4			87 (92)
5			88 (84)
6			90 (94)
7			92 (93)
8			90 (98)

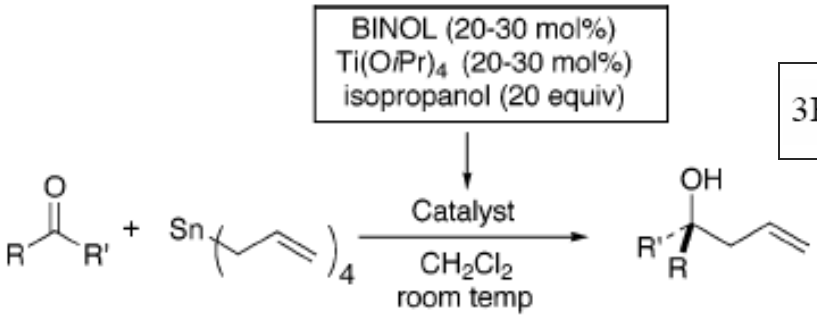
entry	substrate	product	ee (yield)
9			94 (90)
10			93 (93)
11			79 (85)

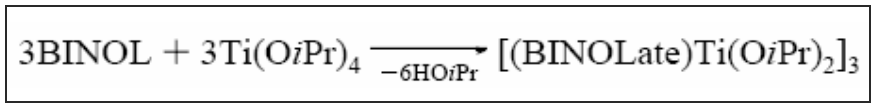
Asymmetric vinylation of enones:

1			92 (87)
2			97 (94)
3			94 (85)
4			92 (98)

Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126*, 6538

Allylation of Ketone





entry	substrate	product	yield (%)[b]	ee (%)[c]
1	3-Me		82	96
2	4-OMe		99	89
3	3-CF_3		93	92
4	2-Me		77[d]	84
5			96	95
6[e]			99	87

entry	substrate	product	yield (%)[b]	ee (%)[c]
7			88	90
8			99	90
9[e]			95	83
10			96	80
11			99	76
12			67	84

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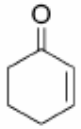
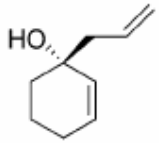
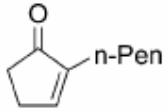
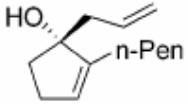
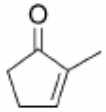
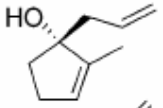
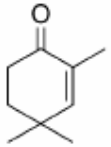
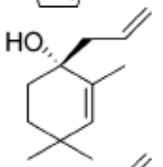
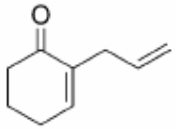
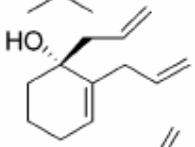
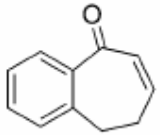
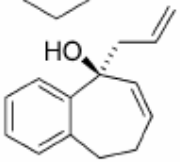
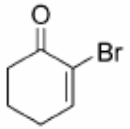
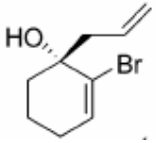
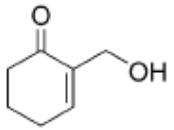
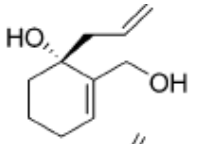
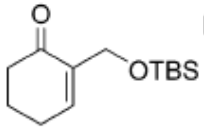
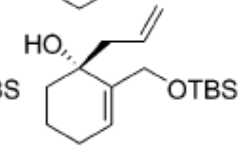
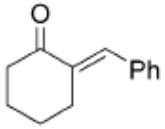
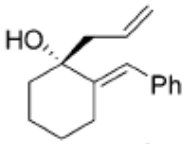
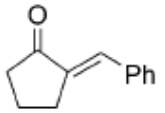
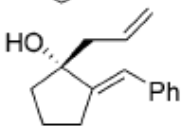
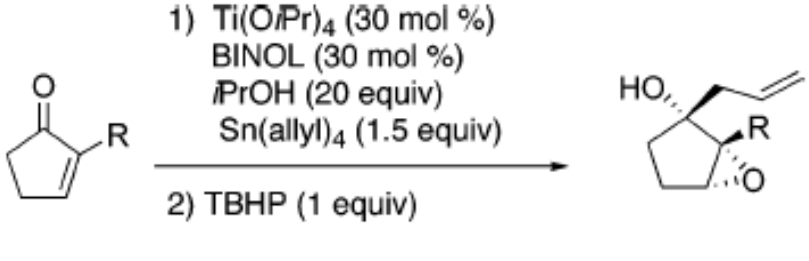
Allylation of Ketone

entry	substrate	product	yield (%)[a]	ee (%)[b]
1			75	11
2			92	94
3			75	87
4			84	96
5			86	90
6			99	88
7			84	84

entry	substrate	product	yield (%)[a]	ee (%)[b]
8			80	50
9			88	85
10			99	96
11			82	91



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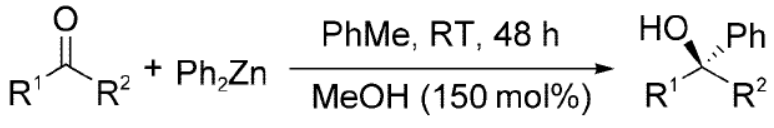
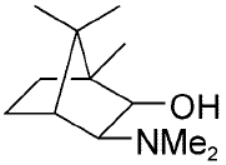
Arylation/Alkylation of Ketone

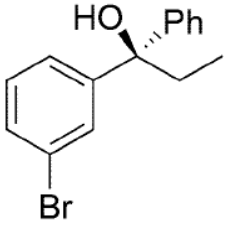
- First example of catalytic asymmetric addition of organometallic reagents on ketones:



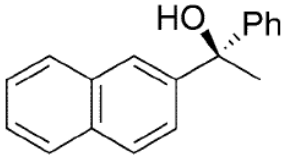


(15 mol%)

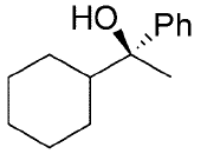
(+)-DAIB = 3-exo-dimethyl amino isoborneol



91%, 91% *ee*



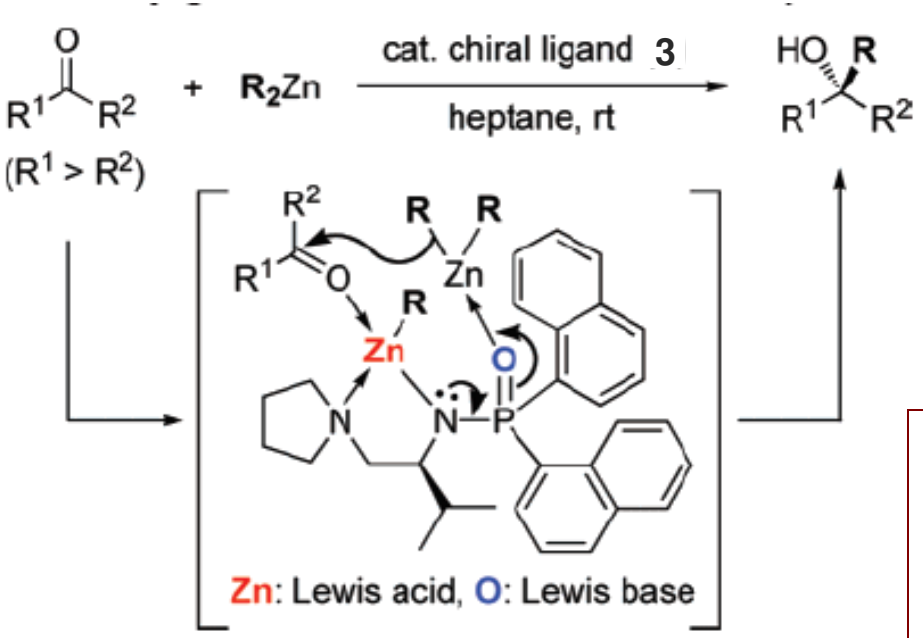
58%, 72% *ee*

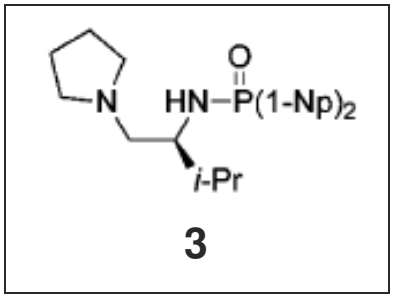


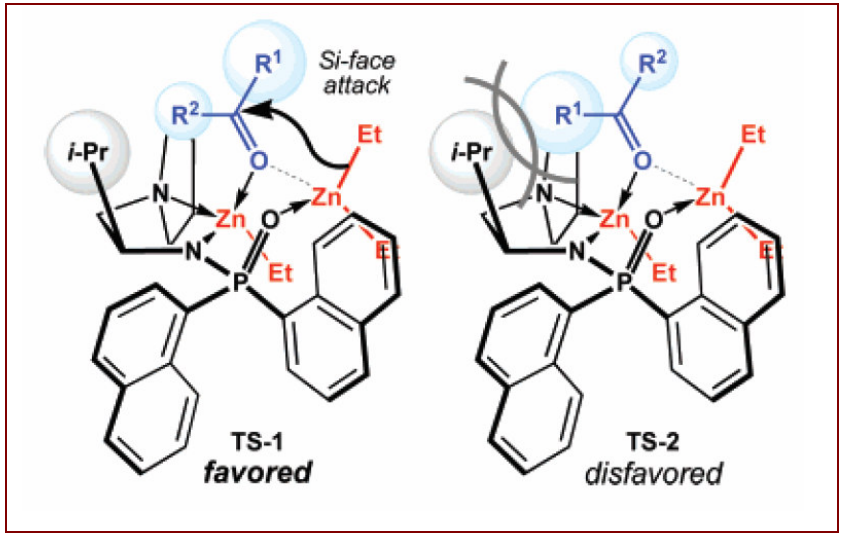
76%, 75% *ee*

Dosa, P. I.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 445

Arylation/Alkylation of Ketone

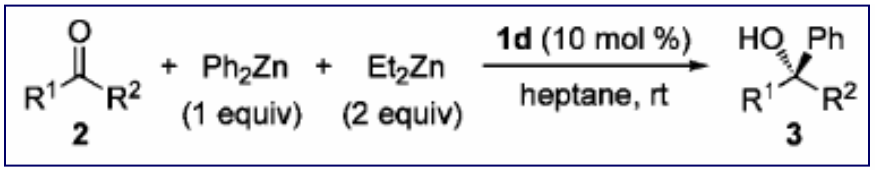




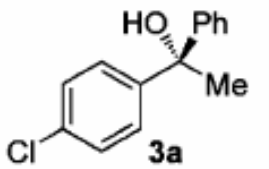


Hatano, M.; Miyamoto, T.; Ishihara, K. *Org. Lett.* **2007**, *9*, 4535

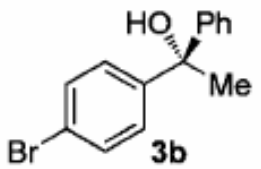
Arylation/Alkylation of Ketone



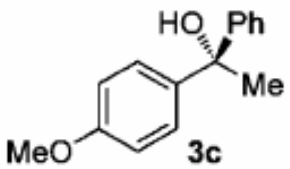
Product (**3**), yield, and enantioselectivity[a]



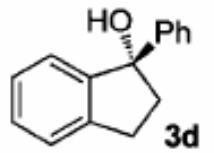
98%, 95% ee (8 h)



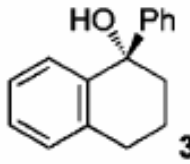
93%, 95% ee (12 h)



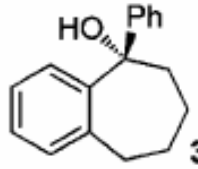
91%, 96% ee (24 h)



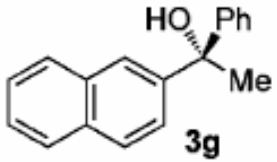
87%, 91% ee (12 h)



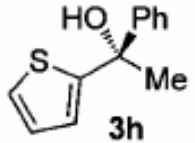
88%, 97% ee (12 h)



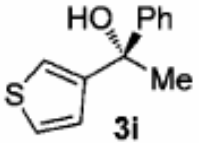
62%, 96% ee (12 h)



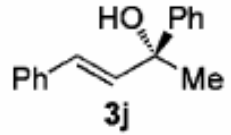
97%, 97% ee (12 h)



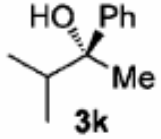
85%, 96% ee (8 h)



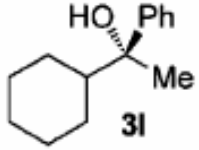
93%, 92% ee (12 h)



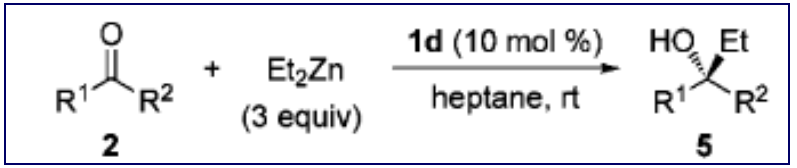
81%, 98% ee (24 h)



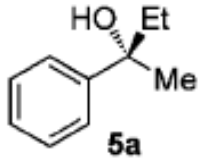
84%, 82% ee (24 h)



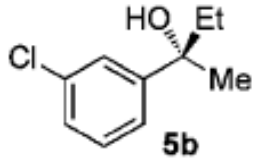
98%, 80% ee (24 h)



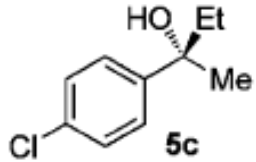
Product (**5**), yield, and enantioselectivity[a]



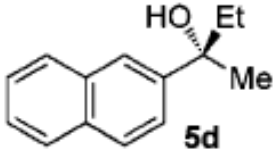
80%, 93% ee (24 h)



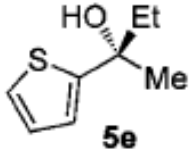
85%, 96% ee (16 h)



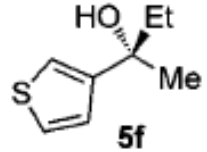
77%, 92% ee (16 h)



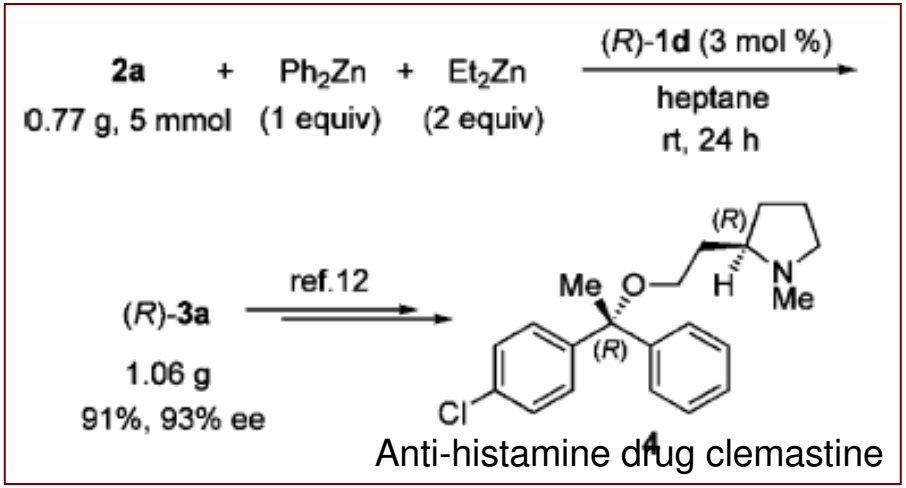
76%, 96% ee (24 h)



85%, 94% ee (24 h)



77%, 91% ee (24 h)



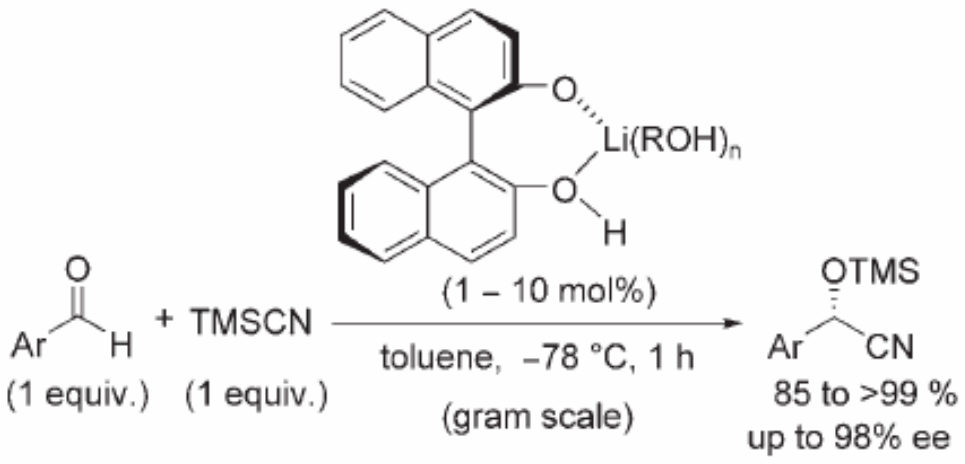
Anti-histamine drug clemastine

Hatano, M.; Miyamoto, T.; Ishihara, K. *Org. Lett.* **2007**, *9*, 4535

Outline

- Challenges
- Different approaches: Organometallic 1, 2-addition
  - Alkynylation
  - Vinylation
  - Allylation
  - Arylation / alkylation
  - Cyanosillylation
- Enantiodivergent conversion of chiral secondary alcohol to chiral tertiary alcohol

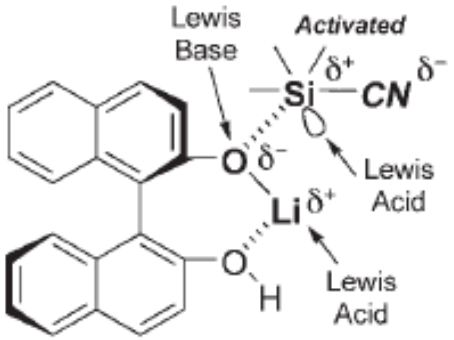
Ishihara Approach



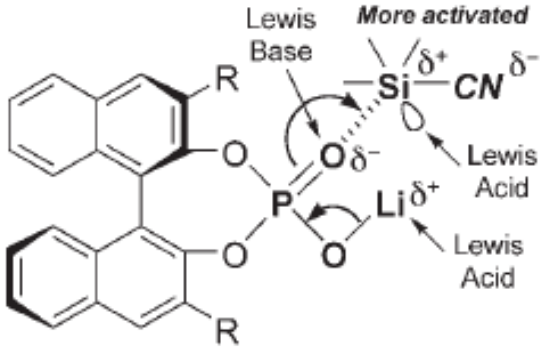
- This catalytic system could not be applied to ketones:
  - The reaction is extremely slow at -78 ℃
  - Higher temperature upto -40 ℃ gives racemates or very low ee
- Lewis basicity of catalyst is inadequate to activate nucleophile

Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *AdV. Synth. Catal.* **2008**, *350*, 1776

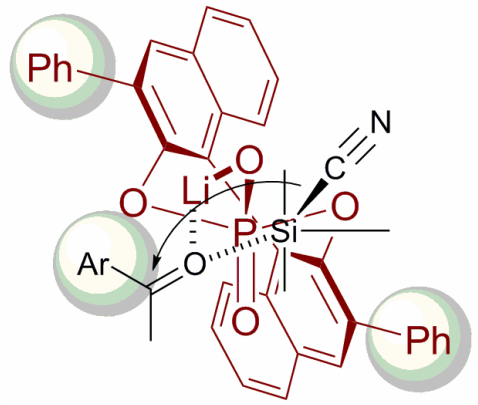
Ishihara Approach

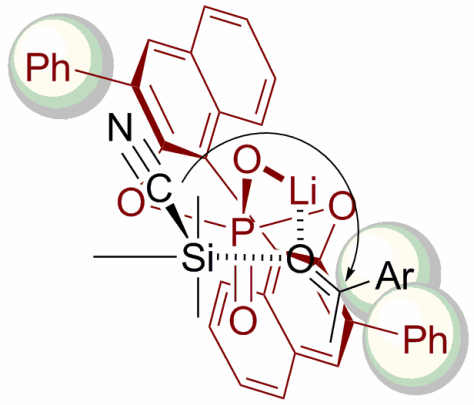


(a) Lithium binaphtolate



(b) Lithium phosphate

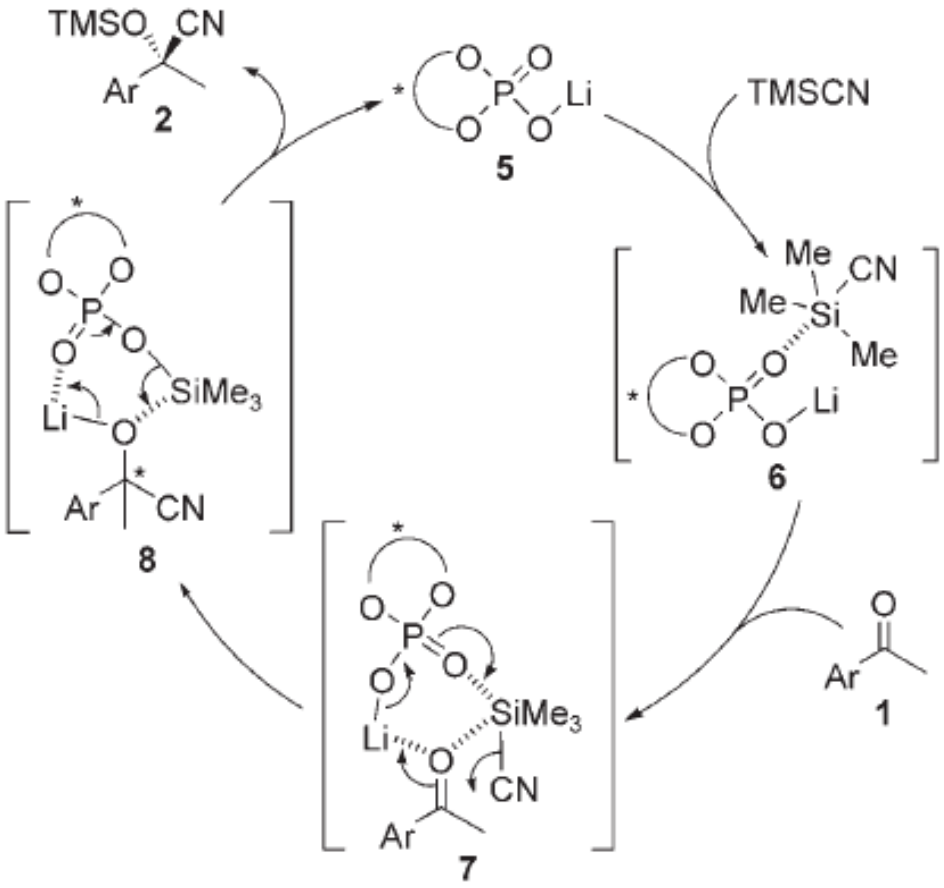




More Favored TS

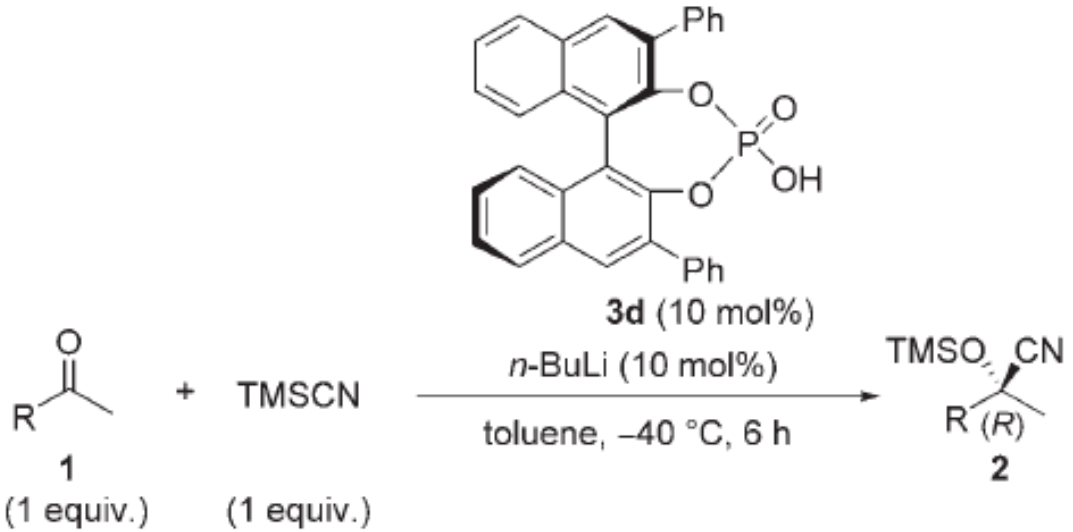
Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *AdV. Synth. Catal.* **2008**, *350*, 1776

Catalytic Cycle



Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *AdV. Synth. Catal.* **2008**, *350*, 1776

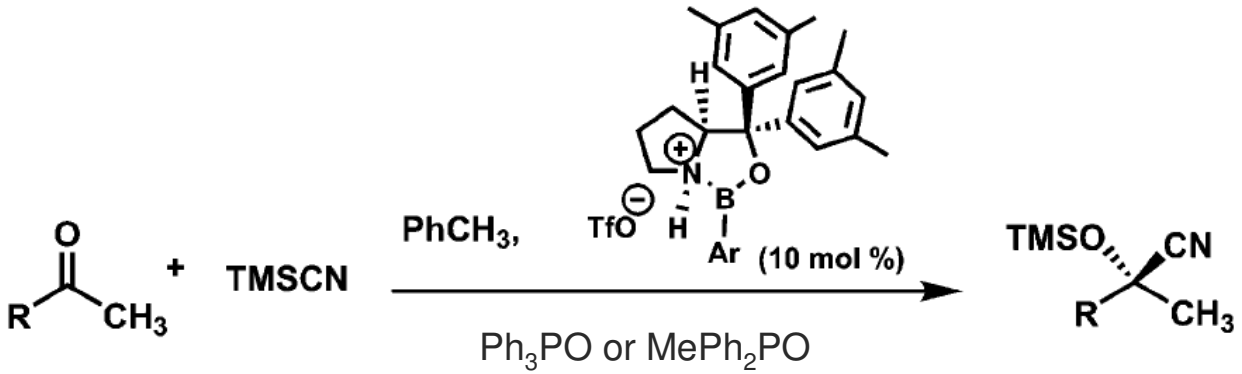
Substrate Scope



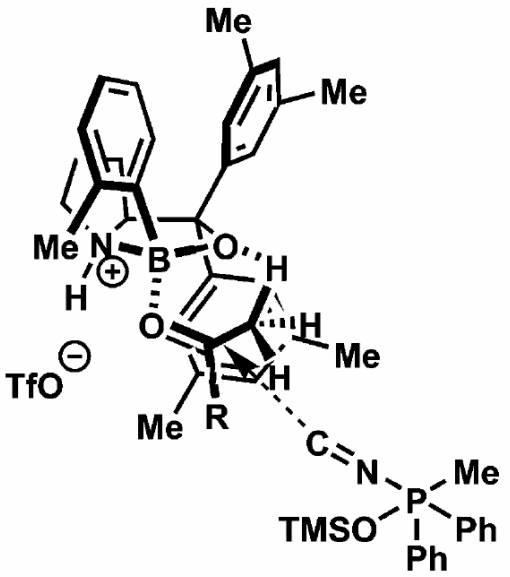
Entry	**1** (R)	Product	Yield [%]	*ee* [%] (Config.)
1[a]	**1a** (Ph)	**2a**	96	86 (*R*)
2	**1b** (2-ClC_6H_4)	**2b**	99	75 (*R*)
3	**1c** (3-ClC_6H_4)	**2c**	99	65
4[a]	**1d** (4-ClC_6H_4)	**2d**	95	68 (*R*)
5[b]	**1e** (2-$MeOC_6H_4$)	**2e**	59	32
6	**1f** (3-$MeOC_6H_4$)	**2f**	91	37 (*R*)
7[a]	**1g** (4-$MeOC_6H_4$)	**2g**	94	63 (*R*)
8	**1h** (2-Naph)	**2h**	96	55 (*R*)
9	**1i** ($Ph(CH_2)_2$)	**2i**	38	2 (*R*)

Hatano, M.; Ikeno, T.; Matsumura, T.; Torii, S.; Ishihara, K. *AdV. Synth. Catal.* **2008**, *350*, 1776

Corey Approach



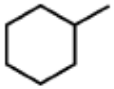
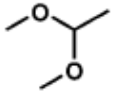
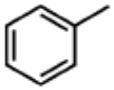
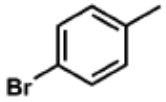
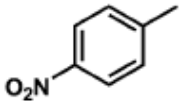
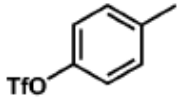
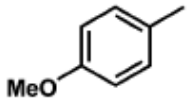
Ar = Ph or *o*-Tolyl

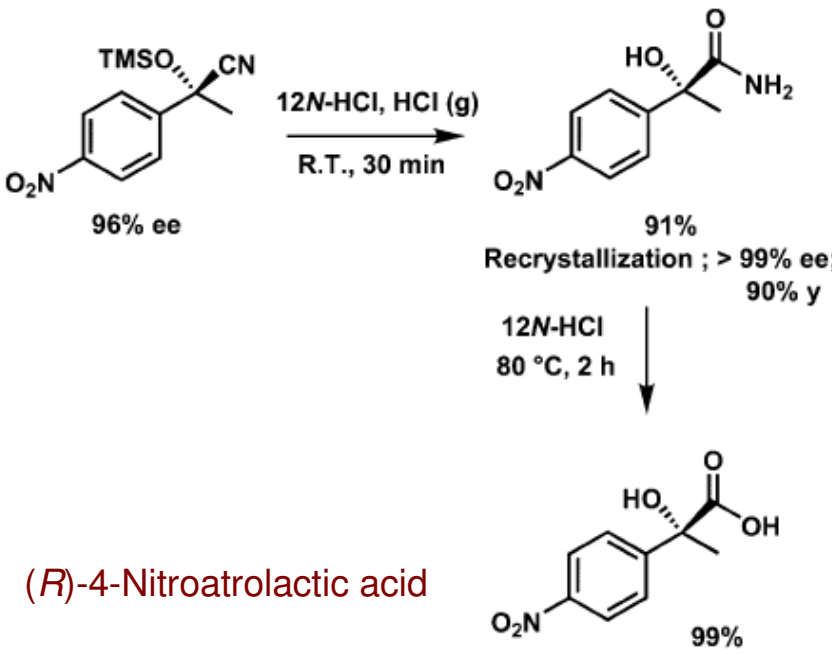


Interaction between partially positively charged carbonyl carbon and neighboring π-electron rich mexyl substituent

Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 5384

Substrate Scope

Entry	Substrate R	Ar	Reaction Condition: Co-reactant (eq.)	Temp. (°C)	Time (day)	% yield, % ee
1		Ph	Ph_3PO (0.2)	25	4	97, 80
		Ph	$MePh_2PO$ (0.11)	25	3	62, 88
		o-Tolyl	$MePh_2PO$ (0.11)	25	3	95, 85
2		Ph	Ph_3PO (0.11)	25	2	92, 96[a]
3		Ph	Ph_3PO (0.1)	25	4	49, 65
		o-Tolyl	$MePh_2PO$ (0.11)	25	14	77, 83
4		*o*-Tolyl	$MePh_2PO$ (0.11)	45	10	73, 81
5		*o*-Tolyl	$MePh_2PO$ (0.11)	45	10	83, 96
6		*o*-Tolyl	$MePh_2PO$ (0.11)	45	10	79, 95
7		*o*-Tolyl	$MePh_2PO$ (0.11)	25	7	45, 32[b]

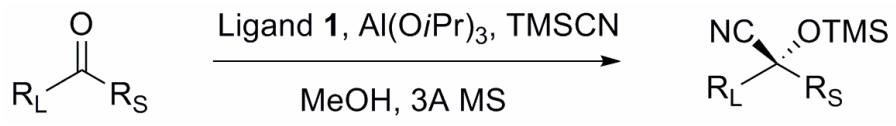


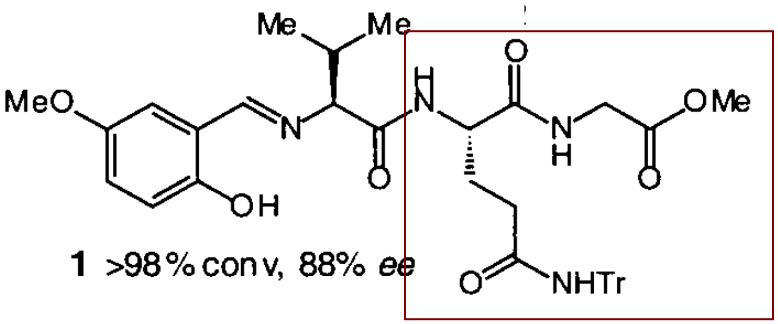
(*R*)-4-Nitroatrolactic acid

α-Hydroxy acids (AHAs) are used in cosmetic products for skin therapy

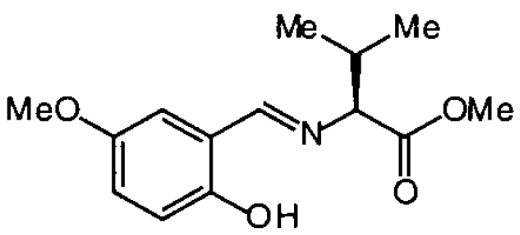
Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 5384

Hoveyda Approach

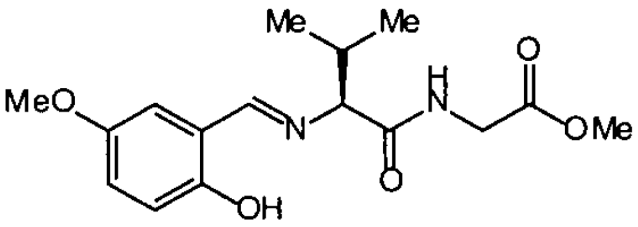




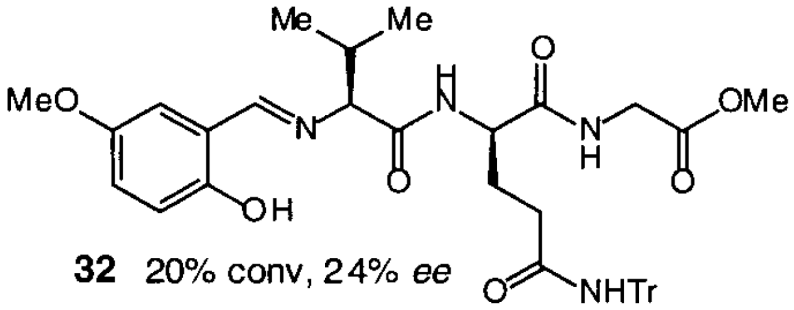
1 >98% conv, 88% *ee*



30 <5% conv



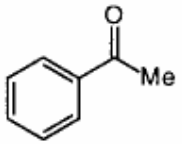
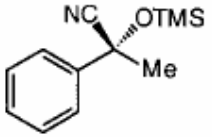
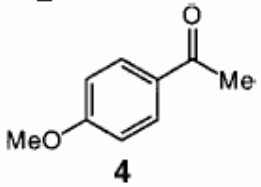
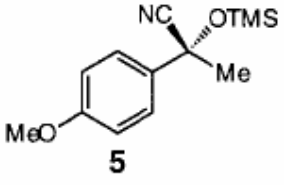
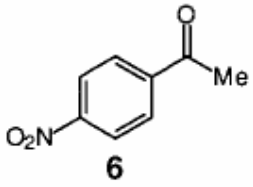
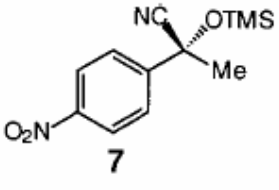
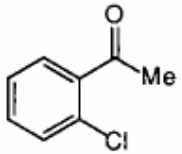
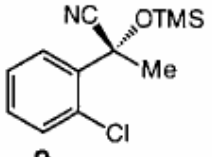
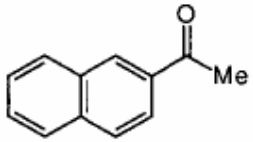
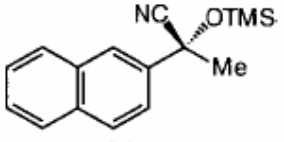
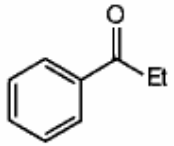
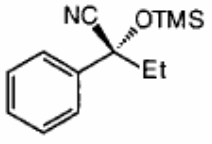
31 <5% conv

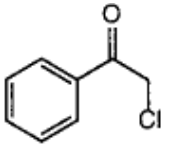
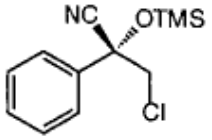
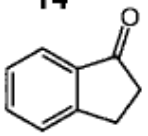
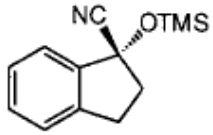
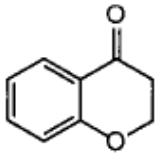
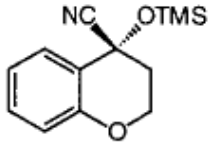
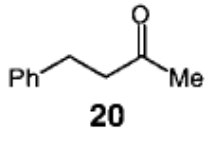
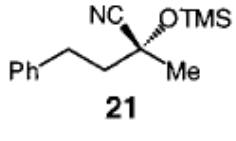
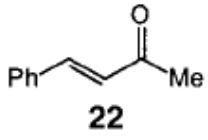
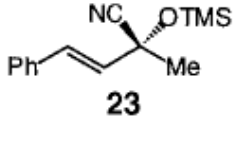
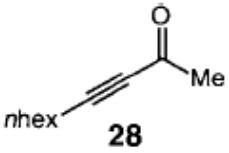
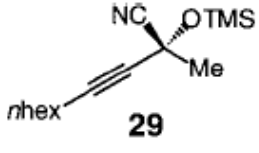


32 20% conv, 24% *ee*

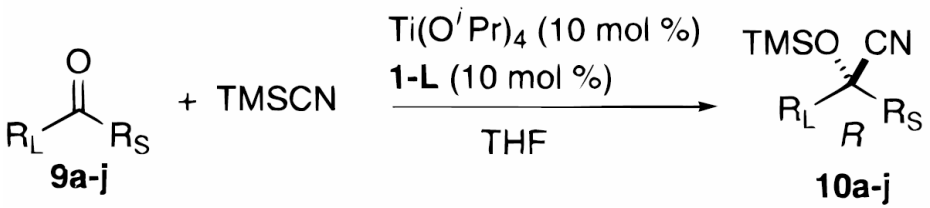
Deng, H.; Isler, M. P.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem.,Int. Ed.* **2002**, *41*, 1009

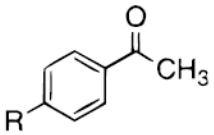
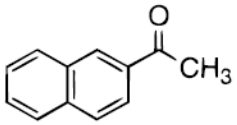
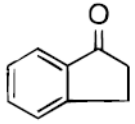
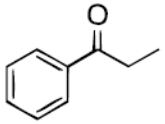
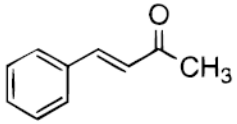
Substrate Scope

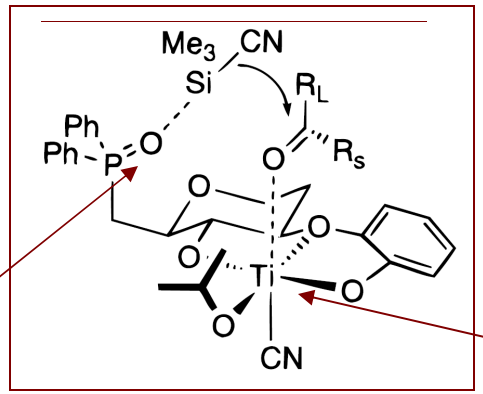
Substrate	Product	mol% **1** and $Al(OiPr)_3$	Yield [%][b]	*ee* [%][c]
 **2**	 **3**	10	84	91
		20	93	88
 **4**	 **5**	20	67	91
 **6**	 **7**	20	>98	88
		10	92	90
 **8**	 **9**	20	87	85
 **10**	 **11**	20	83	94
 **12**	 **13**	20	98	88

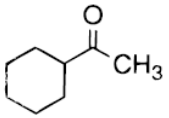
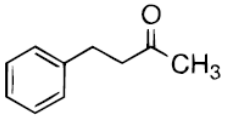
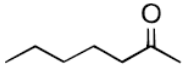
Substrate	Product	mol% **1** and $Al(OiPr)_3$	Yield [%][b]	*ee* [%][c]
 **14**	 **15**	20	87	80
 **16**	 **17**	20	87	88
 **18**	 **19**	20	85	88
 **20**	 **21**	20	93	80
		10	97	82
 **22**	 **23**	20	67	95
 **28**	 **29**	20	78	90
		10	66	91

Shibasaki Approach



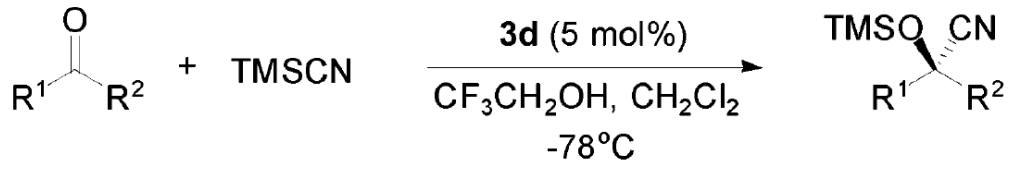
ketone			temp/°C	time/h	yield/%[b]	ee/%[c]
	R = H	**9a**	-30	36	85	92[e]
	R = CH_3	**9b**	-30	84	80	90
	R = Cl	**9c**	-40	80	82	92
		**9d**	-40	80	82	95
		**9e**	-40	96	72	69
		**9f**	-20	64	89	91
		**9g**	-50	88	72	91

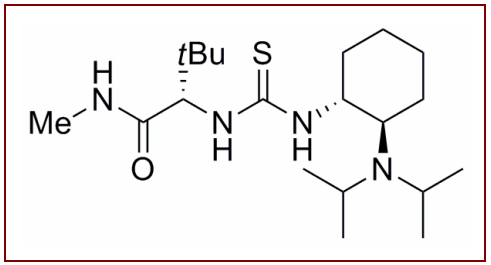


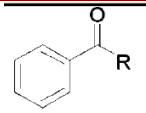
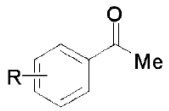
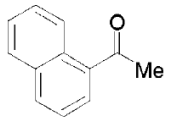
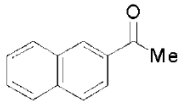
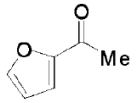
ketone		temp/°C	time/h	yield/%[b]	ee/%[c]
	**9h**	-50	36	86	90[d]
	**9i**	-50	36	92	85
	**9j**	-50	36	88	76[e]

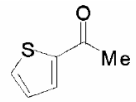
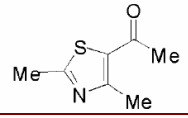
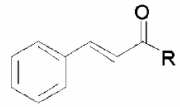
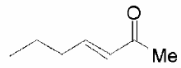
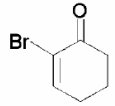
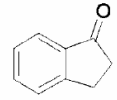
Hamashima, Y.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 7412

Jacobsen Approach





entry	ketone		time (h)	yield (%)[b]	ee (%)
1		R = Me	24	96	97
2		R = Et	24	95	95
3		R = *i*-Pr	24	97	86
4[d]		R = *o*-Me	36	96	98
5		R = *p*-Me	36	97	96
6[e]		R = *m*-OMe	12	97	97
7		R = *p*-OMe	48	93	95
8		R = *p*-Br	12	94	93
9			36	91	95
10			12	98	97
11[e]			48	81	97

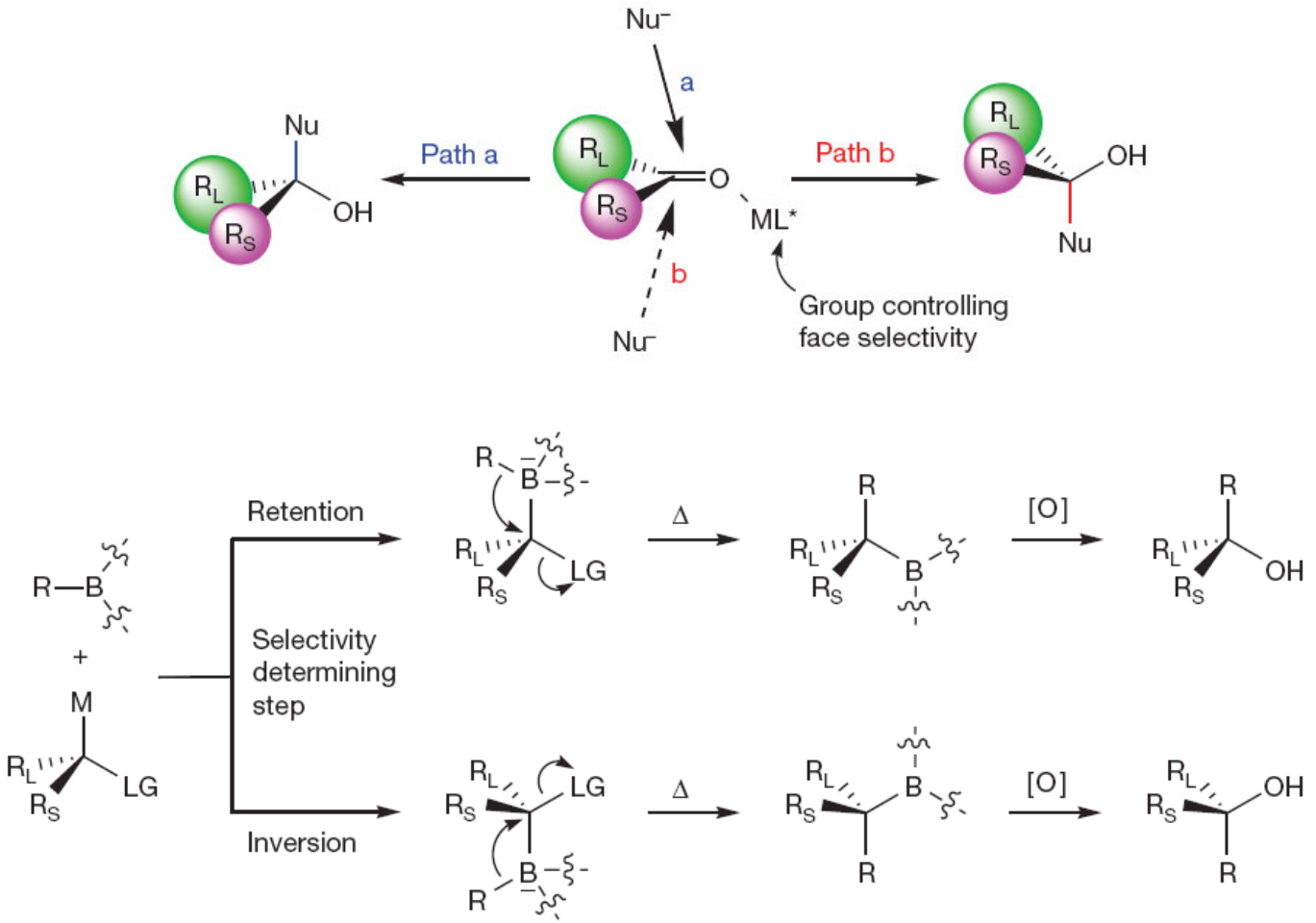
entry	ketone		time (h)	yield (%)[b]	ee (%)[c]
12[e,f]			48	88	98
13[e]			48	87	97
14		R = Me	12	94	96
15		R = *n*-Bu	12	97	93
16			48	95	89
17			12	95	97
18[e]			48	97	91

Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 8964

Outline

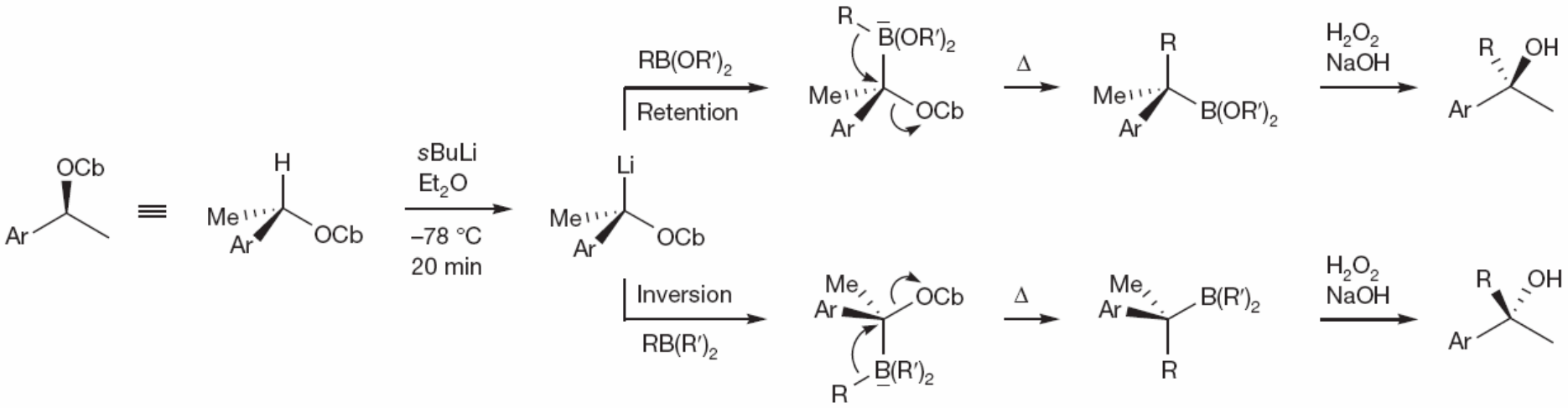
- Challenges
- Different approaches: Organometallic 1, 2-addition
  - Alkynylation
  - Vinylation
  - Allylation
  - Arylation / alkylation
  - Cyanosillylation
- Enantiodivergent conversion of chiral secondary alcohol to chiral tertiary alcohol

Chiral Tertiary Alcohol from Chiral Secondary Alcohol



Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778

Chiral Tertiary Alcohol from Chiral Secondary Alcohol

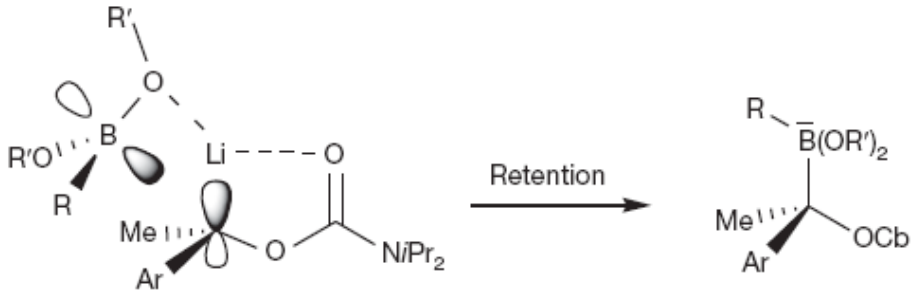


- Boronic esters retains the stereochemistry
- Boranes inverts the stereochemistry
- In case of boranes when 9-BBN derivatives were used boracycle doesn't migrate

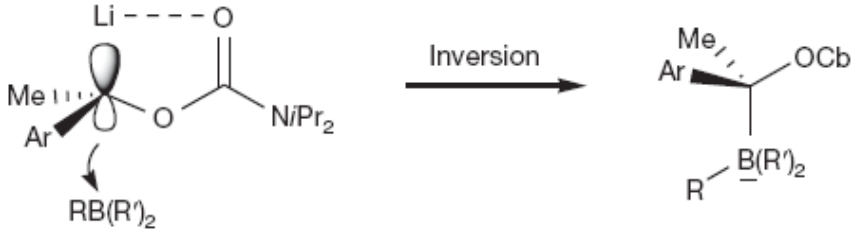
Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778

Rationalization of Sterechemistry

Boronic esters with aryl ketone:



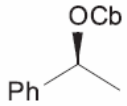
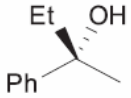
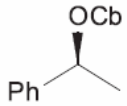
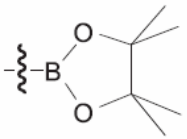
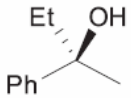
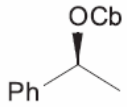
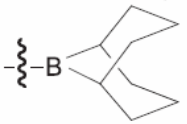
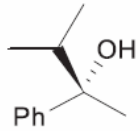
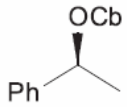
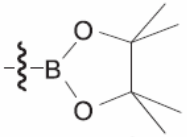
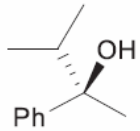
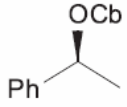
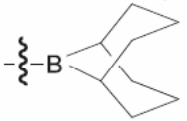
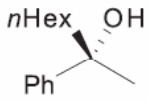
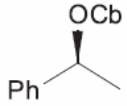
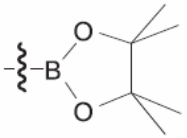
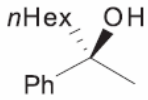
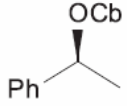
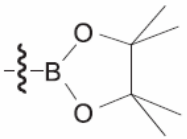
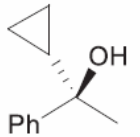
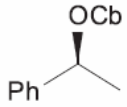
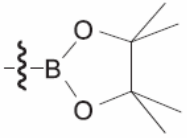
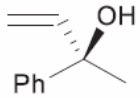
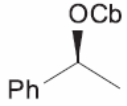
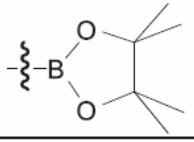
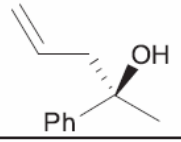
Boranes with aryl ketone:



Boranes and boronic esters with alkyl ketone:

Stymiest, J. L.; Bagutski, V.; French, R. M.; Aggarwal, V. K. *Nature* **2008**, *456*, 778

Substrate Scope

Entry	Carbamate (e.r.)	Migrating group, R	Borane/boronic ester component	Product	Yield (%) (e.r., S:R)
1	 (99:1)	Et			91 (99:1)
2	 (99:1)	Et			95 (1:99)
3	 (99:1)	*i*Pr			91 (98:2)*
4	 (99:1)	*i*Pr			80 (4:96)
5	 (99:1)	*n*Hex			60 (98:2)*
6	 (99:1)	*n*Hex			85 (4:96)
7	 (99:1)	*c*Pr			85 (3:97)
8	 (99:1)	vinyl			75 (2:98)
9	 (99:1)	allyl			95 (1:99)†

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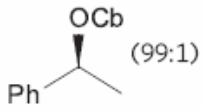
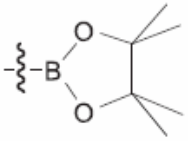
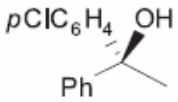
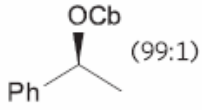
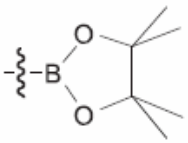
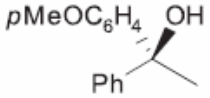
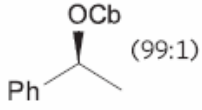
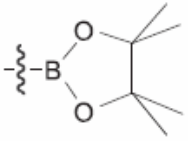
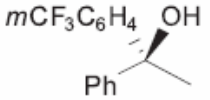
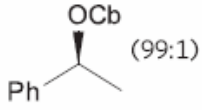
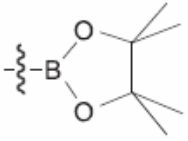
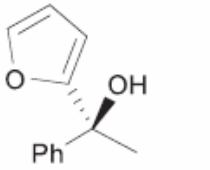
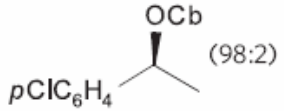
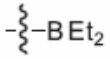
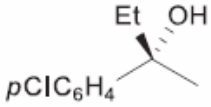
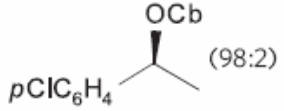
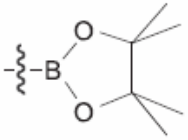
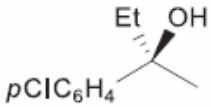
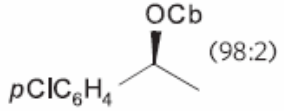
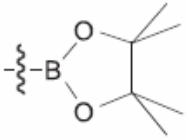
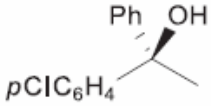
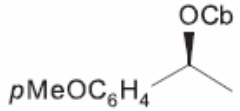
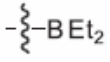
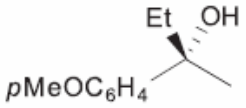
Substrate Scope

Entry	Carbamate (e.r.)	Migrating group, R	Borane/boronic ester component	Product	Yield (%) (e.r., S:R)
10	 (99:1)	*p*Cl-C_6H_4-			97 (99:1)‡
11	 (99:1)	*p*MeO-C_6H_4-			92 (98:2)‡
12	 (99:1)	*m*CF_3-C_6H_4-			92 (99:1)‡
13	 (99:1)	2-furyl			94 (98:2)‡
14	 (98:2)	Et			82 (95:5)
15	 (98:2)	Et			92 (4:96)§
16	 (98:2)	Ph			89 (4:96)†
17		Et			87 (96:4)‖

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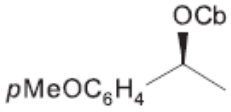
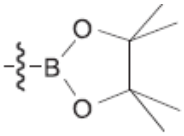
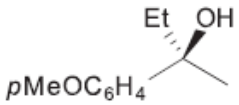
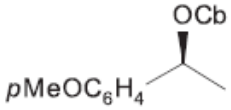
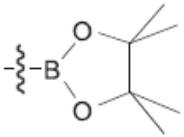
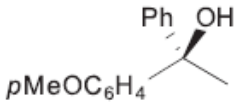
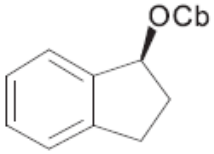
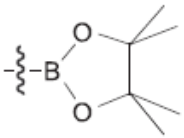
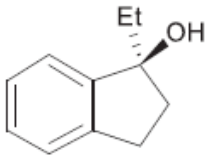
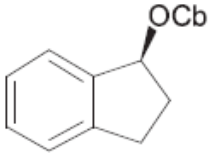
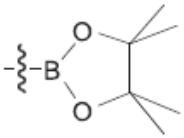
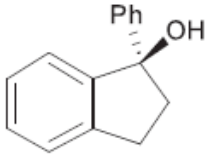
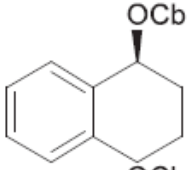
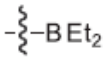
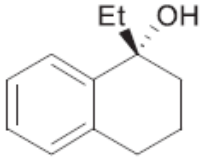
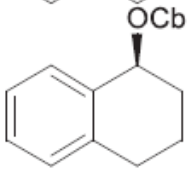
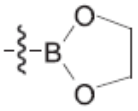
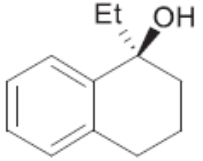
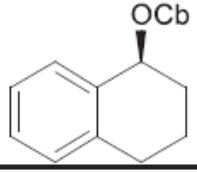
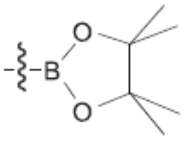
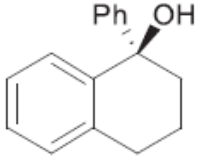
Substrate Scope

Entry	Carbamate (e.r.)	Migrating group, R	Borane/boronic ester component	Product	Yield (%) (e.r., S:R)
18		Et			97 (2:98)‖
19		Ph			81 (4:96)‡‖
20		Et			69 (99:1)§‖
21		Ph			73 (6:94)‡‖
22		Et			90 (5:95)‖
23		Et			98 (91:9)§‖¶
24		Ph			97 (4:96)†‖

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Conclusion

- Enantiodivergent synthesis of tertiary alcohol from chiral secondary alcohol broadens the scope
- Still more work is needed in this area specially for alkyl ketones for the synthesis of di-/tri-alkyl substituted tertiary alcohols