

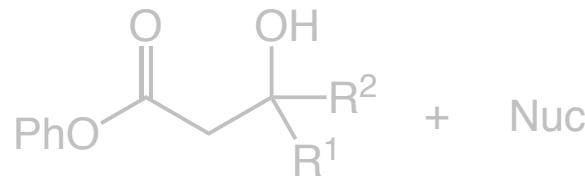
Strategies for the Asymmetric Synthesis of Tertiary Alcohols

Kimberly S. Petersen

Stoltz Group Literature Presentation

March 8th, 2010

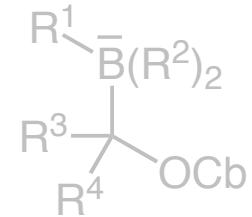
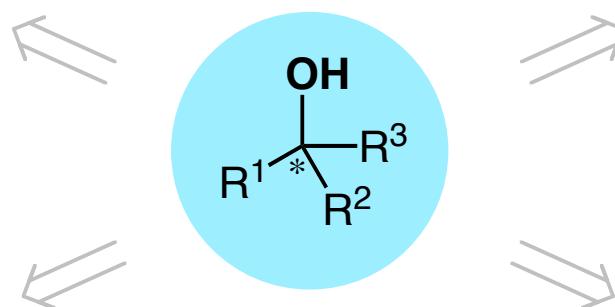
8:30 PM 147 Noyes



kinetic resolution



organozinc addition to ketones

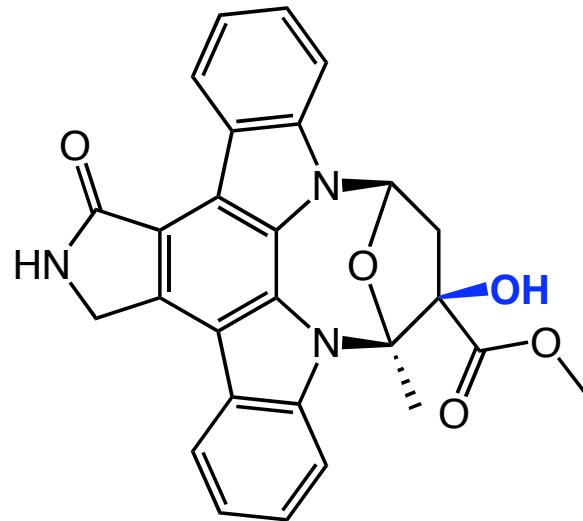


*1,2-metallate
rearrangement of boronate
complexes*

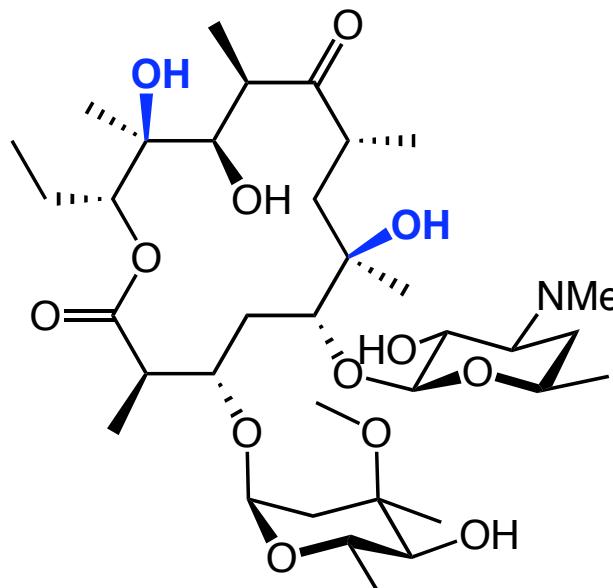


aldol type reactions

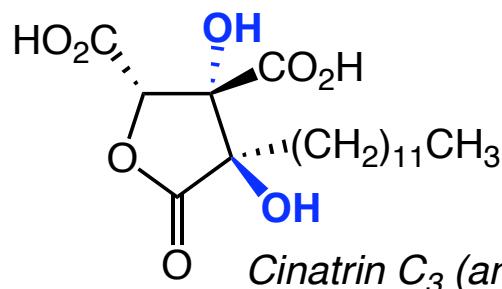
Tertiary Alcohol Containing Natural Products



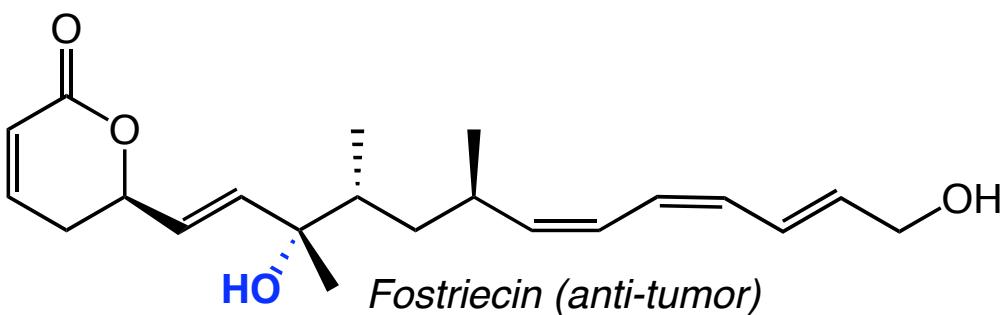
K252a (kinase inhibitor)



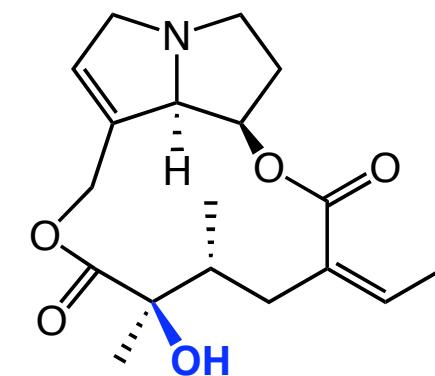
Erythromycin (antibiotic)



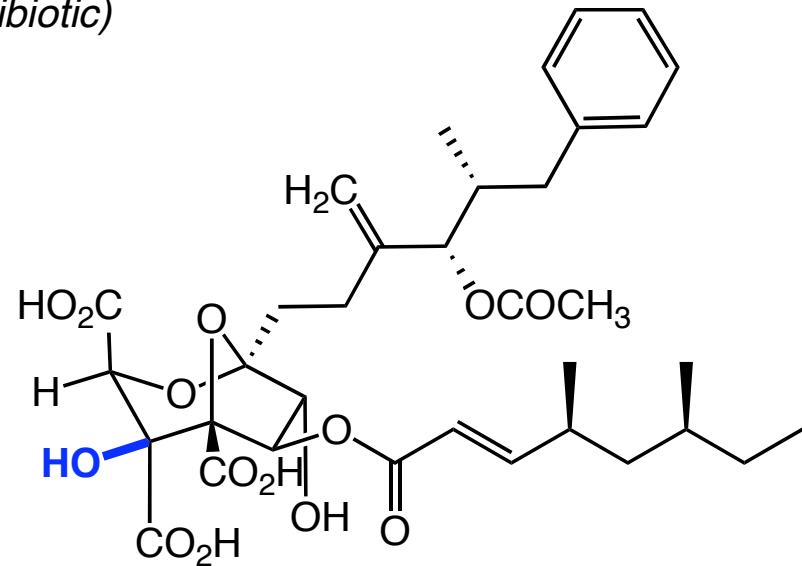
Cinatrin C₃ (anti-inflammatory)



Fostriecin (anti-tumor)



*Integerrimine
(pheromone)*

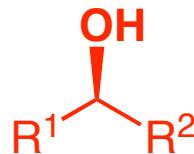


*Zaragozic Acid (squalene synthase
inhibitor)*

Strategies for the Asymmetric Synthesis of Tertiary Alcohols

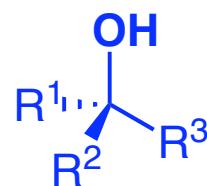
Challenges

2° Alcohols



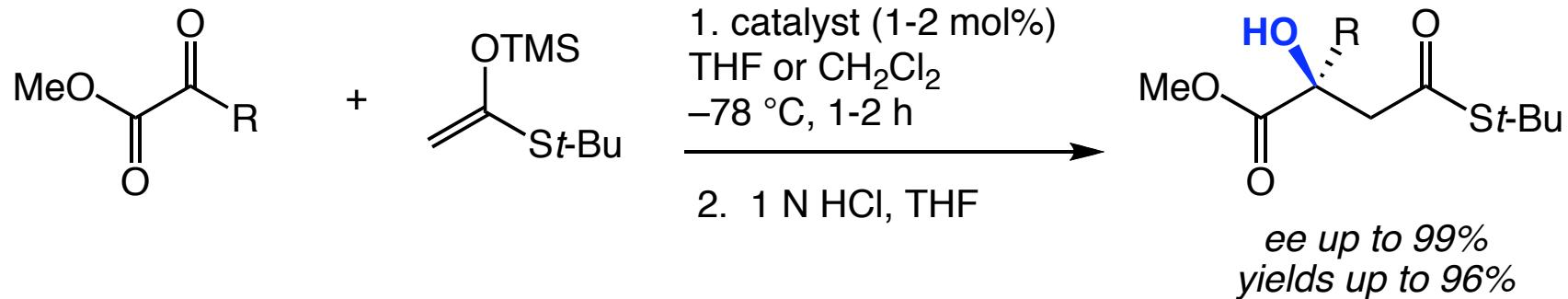
- Kinetic resolution (*i.e. Stoltz Pd catalyzed oxidation*)
- Noyori asymmetric hydrogenation
- Enantioselective additions to aldehydes
- Many are commercially available

3° Alcohols



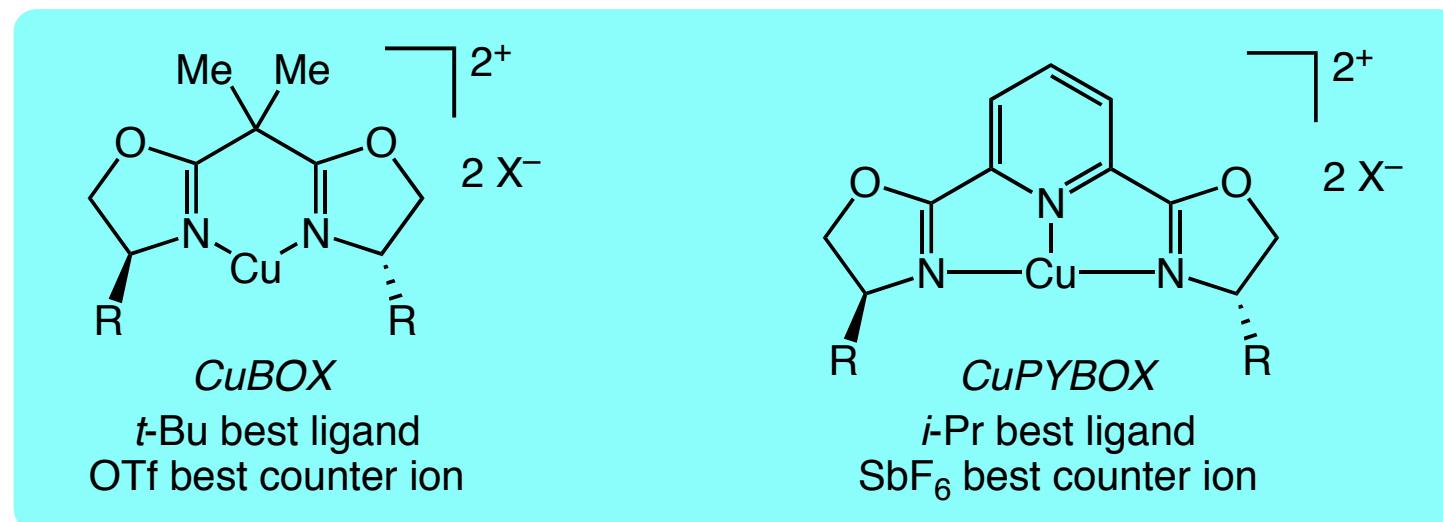
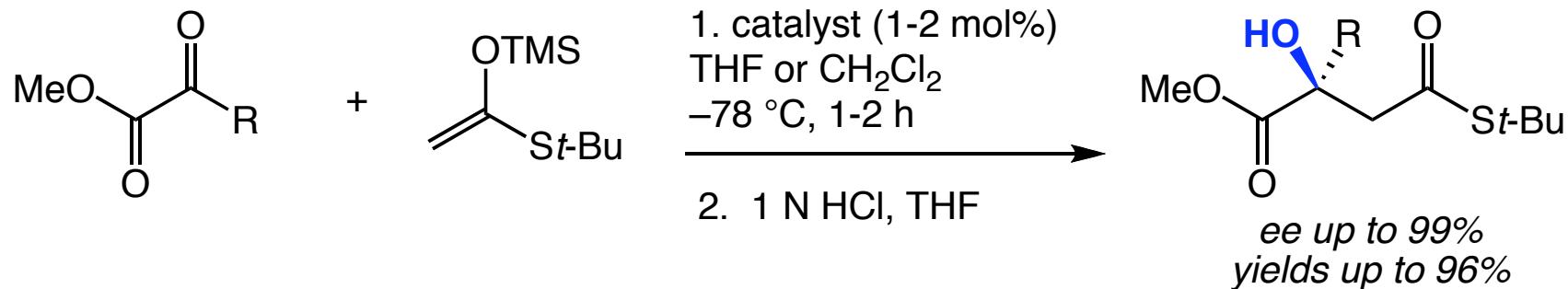
- No oxidation of C-O possible for kinetic resolution
- No hydrogenation of carbonyl possible
- Ketones are less reactive
- Smaller steric and electron differences between prochiral carbons

Copper Catalyzed Enantioselective Aldol Reactions
Additions of Enolsilanes to Pyruvate Esters

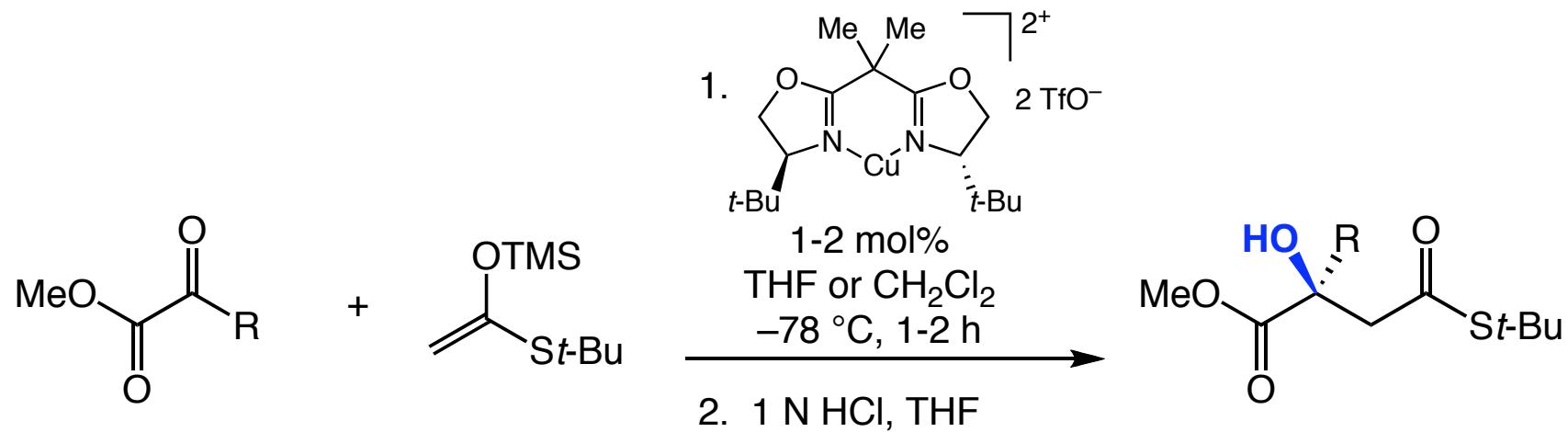


Copper Catalyzed Enantioselective Aldol Reactions

Additions of Enolsilanes to Pyruvate Esters



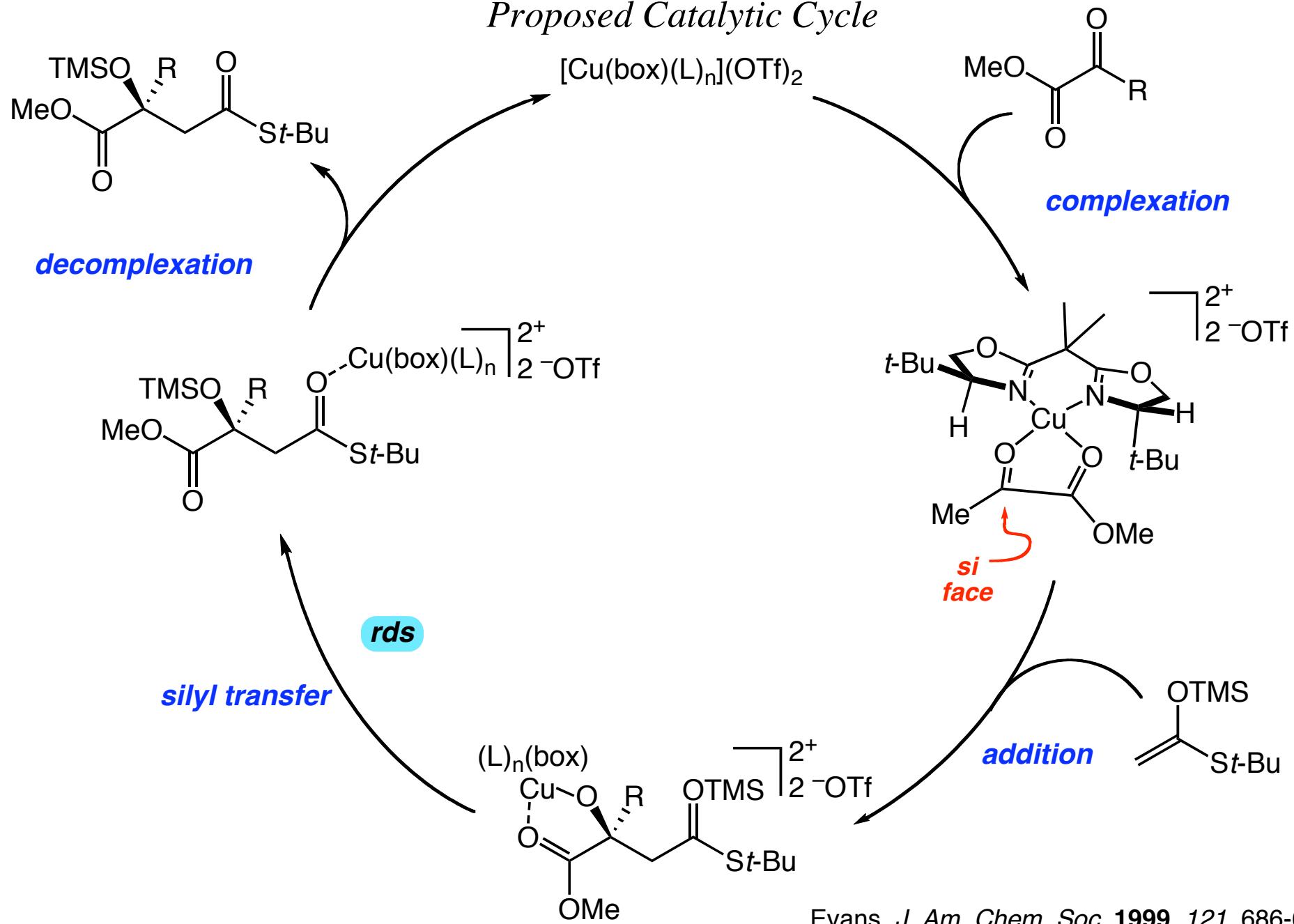
Copper Catalyzed Enantioselective Aldol Reactions
Additions of Enolsilanes to Pyruvate Esters
Reaction Scope



entry	R	yield (%)	ee
1	Me	96	99
2	Et	84	94
3	<i>i</i> -Bu	94	94
4	<i>i</i> -Pr	36	36

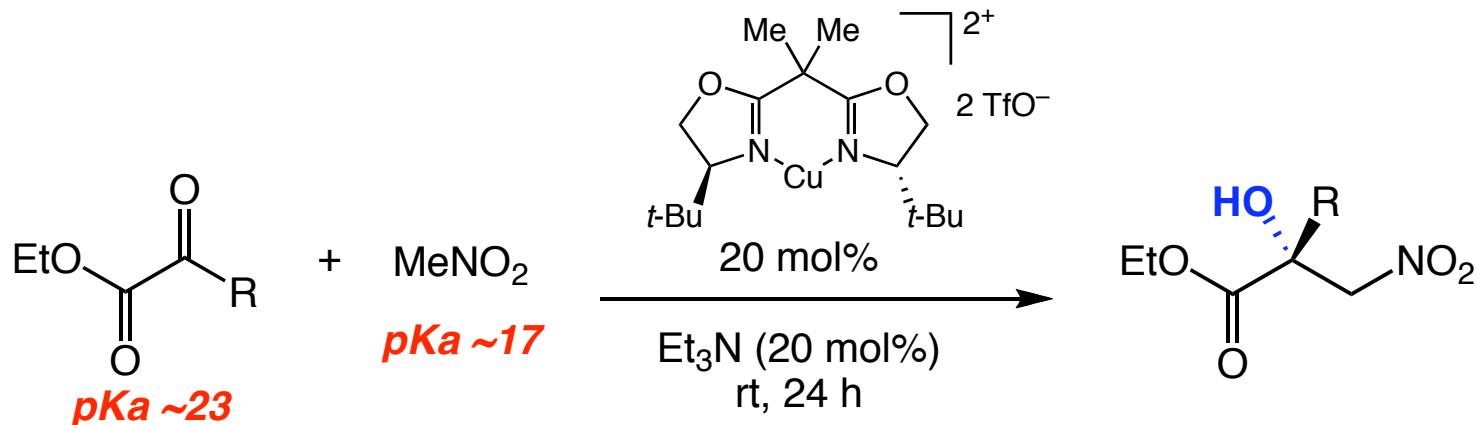
Copper Catalyzed Enantioselective Aldol Reactions

Proposed Catalytic Cycle



Evans, J. Am. Chem. Soc. 1999, 121, 686-699.

Copper Catalyzed Enantioselective NitroAldol Reaction



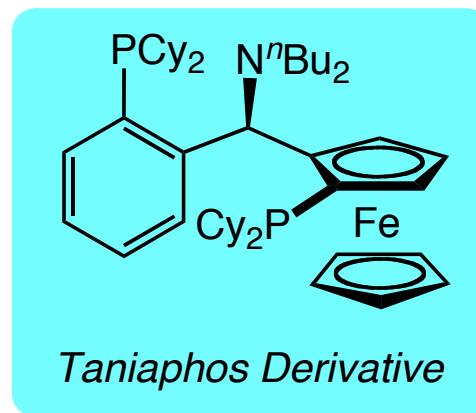
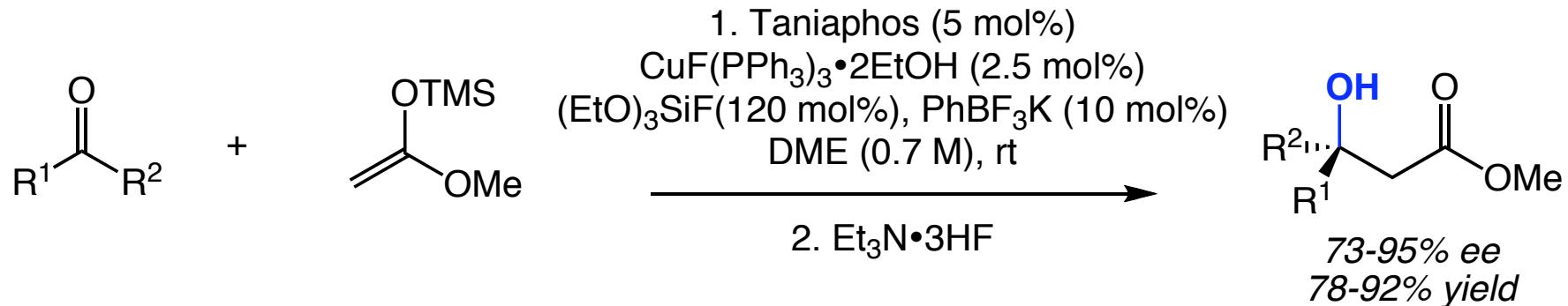
entry	R	yield(%)	ee
1	Me	95	92
2	Et	73	87
3	(CH ₂) ₂ Ph	47	77
4	hexyl	91	93
5	but-3-enyl	97	94
6	pent-4-enyl	92	94
7	3-methylbutyl	90	94
8	<i>i</i> -butyl	99	92
9	Ph	81	86
10	<i>p</i> -ClC ₆ H ₄	91	88
11	<i>p</i> -NO ₂ C ₆ H ₄	99	93
12	<i>p</i> -MeOC ₆ H ₄	68	57

-Nitromethane used as solvent
 and prenucleophile
 -1:1 ratio of Cu and Et₃N critical

Jørgensen, *J. Org. Chem.* **2002**, 67, 4875-4881.

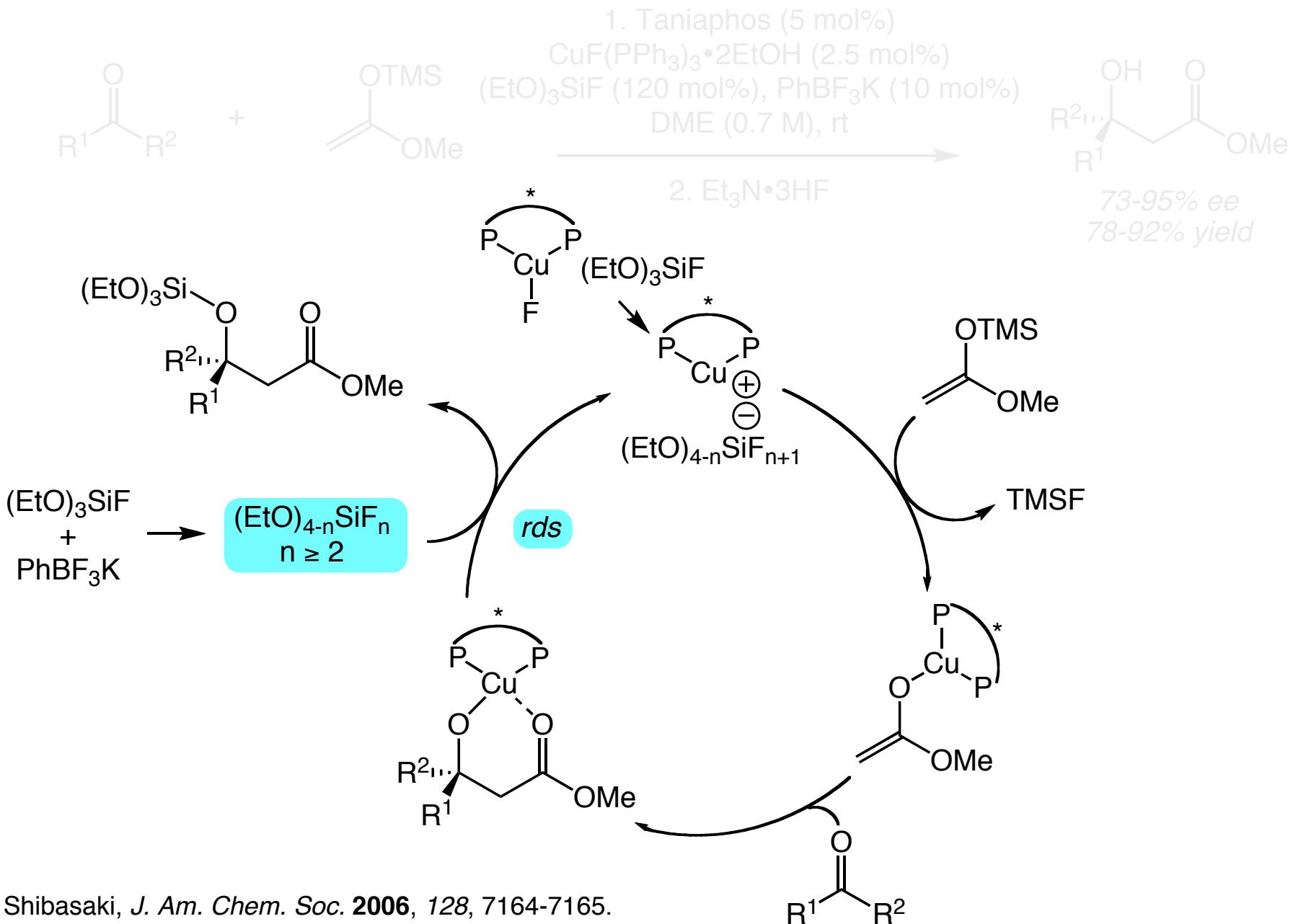
Copper Catalyzed Enantioselective Aldol Reactions

Ketones



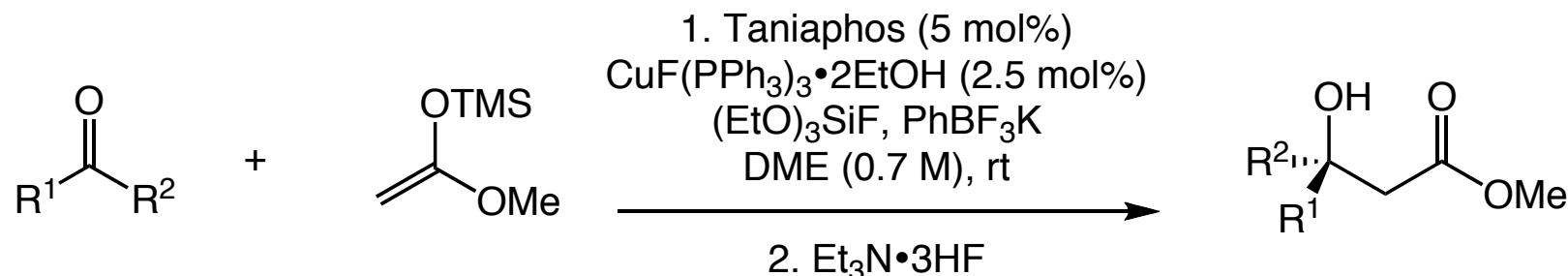
Copper Catalyzed Enantioselective Aldol Reactions

Ketones



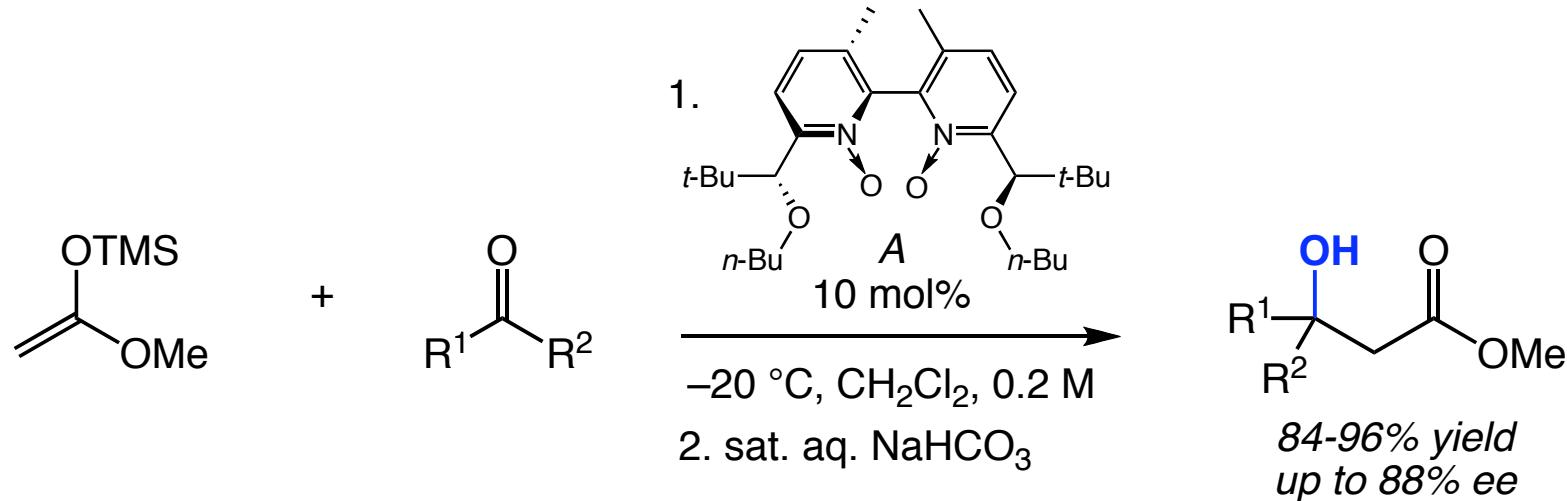
Copper Catalyzed Enantioselective Aldol Reactions

Substrate Scope

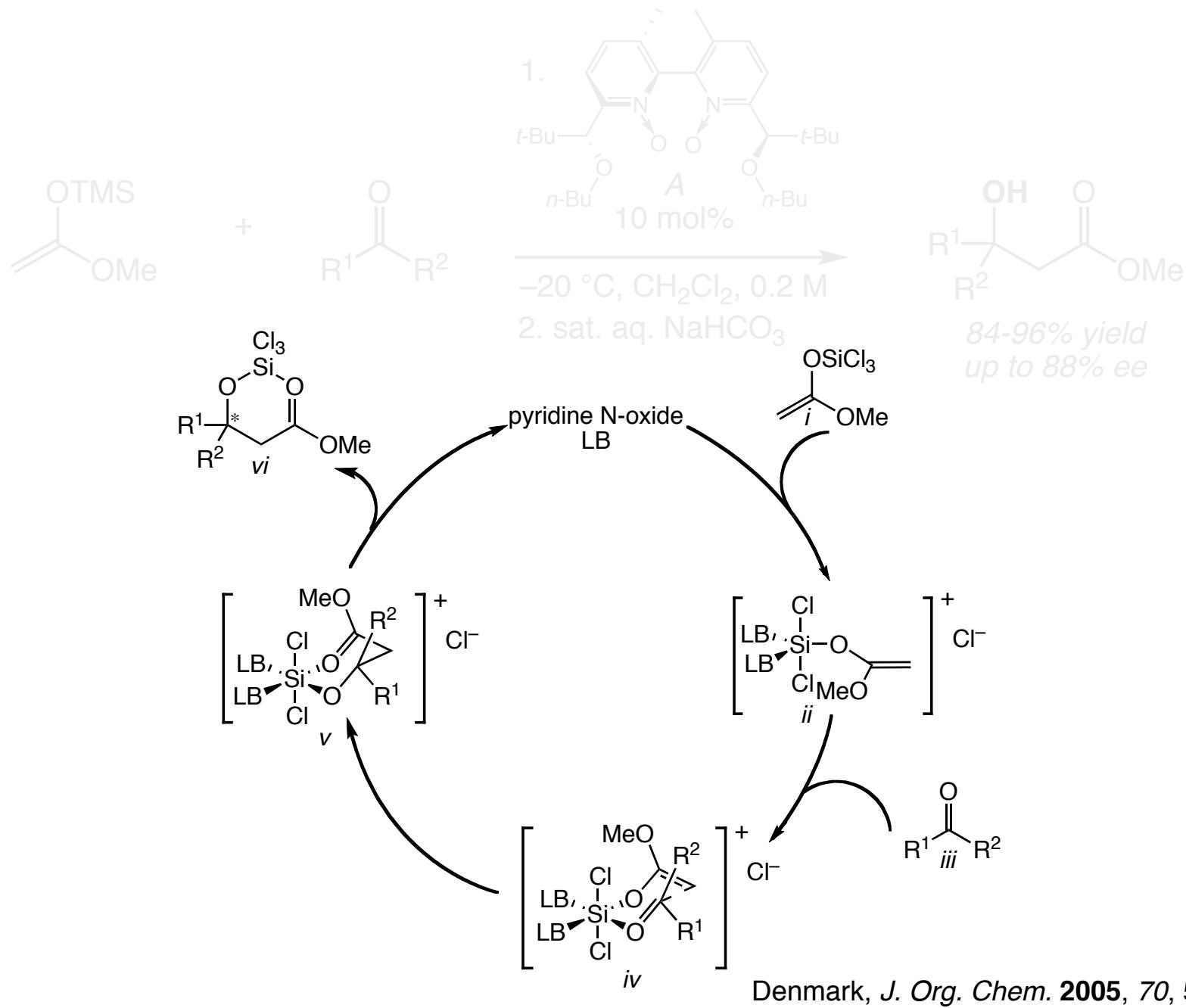


entry	ketone	temp (°C)	time (h)	yield (%)	ee
1		R = H -20	19	93	92
2		R = OMe -20	42	95	91
3		R = Cl -20	38	85	87
4		-20	40	88	83
5		-20	42	92	90
6		-20	42	73	84
7		-20	37	93	79

Lewis Base Catalyzed Enantioselective Aldol Reactions

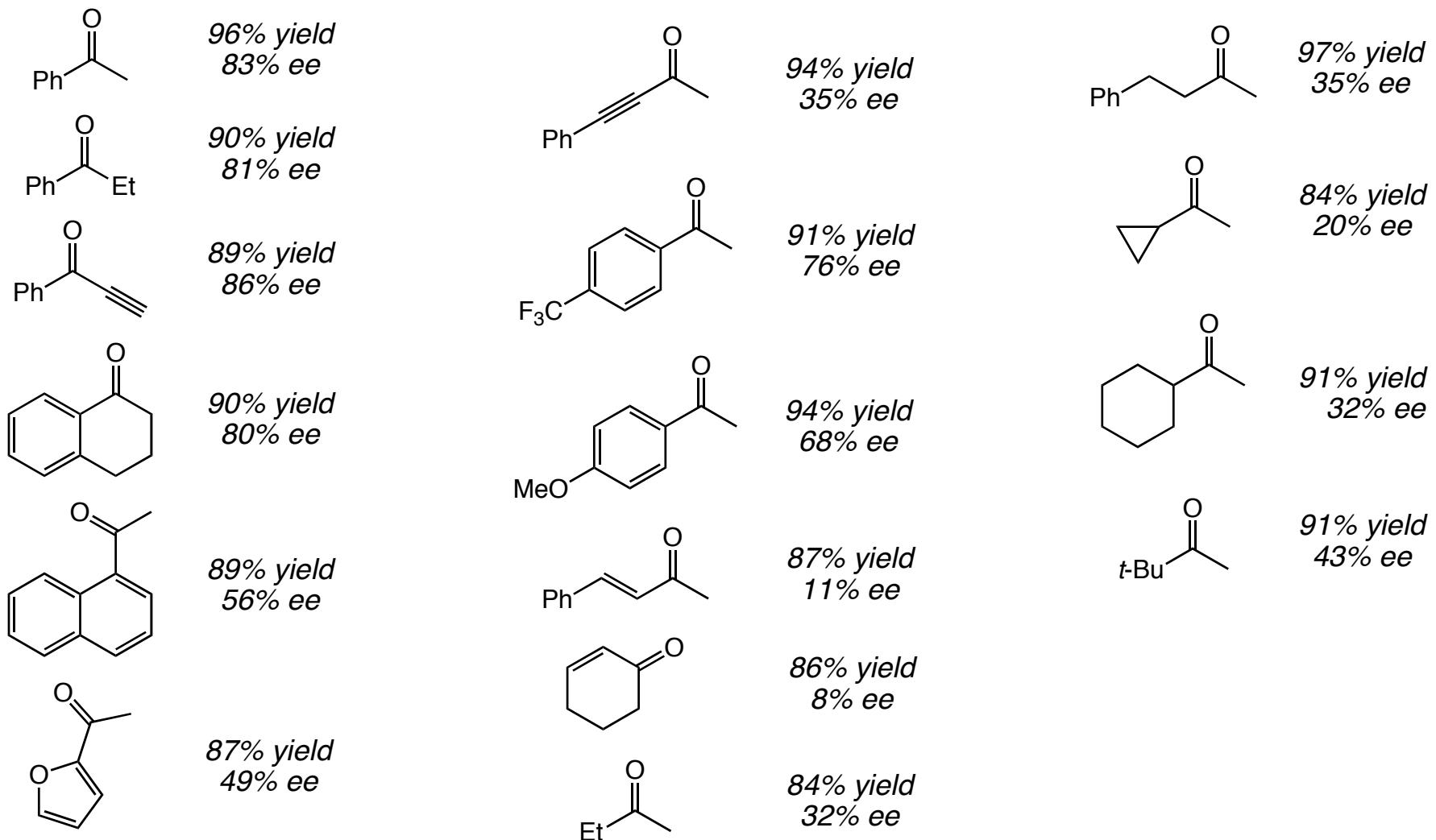


Lewis Base Catalyzed Enantioselective Aldol Reactions



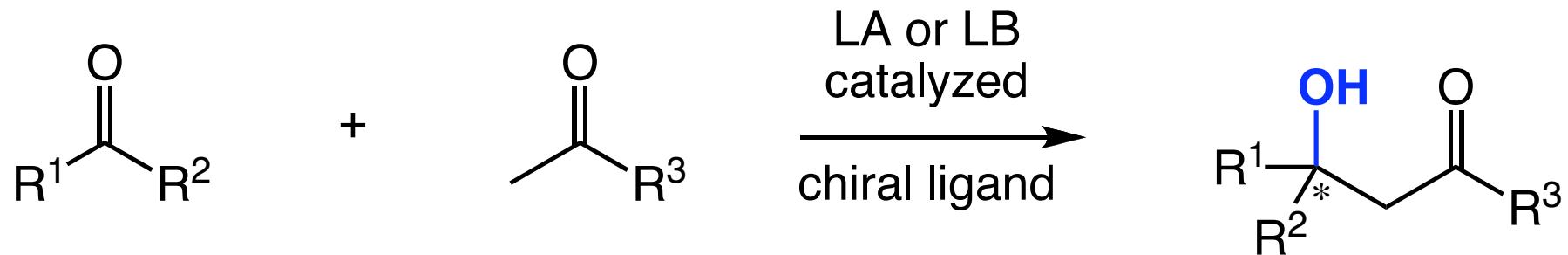
Lewis Base Catalyzed Enantioselective Aldol Reactions

Substrate Scope



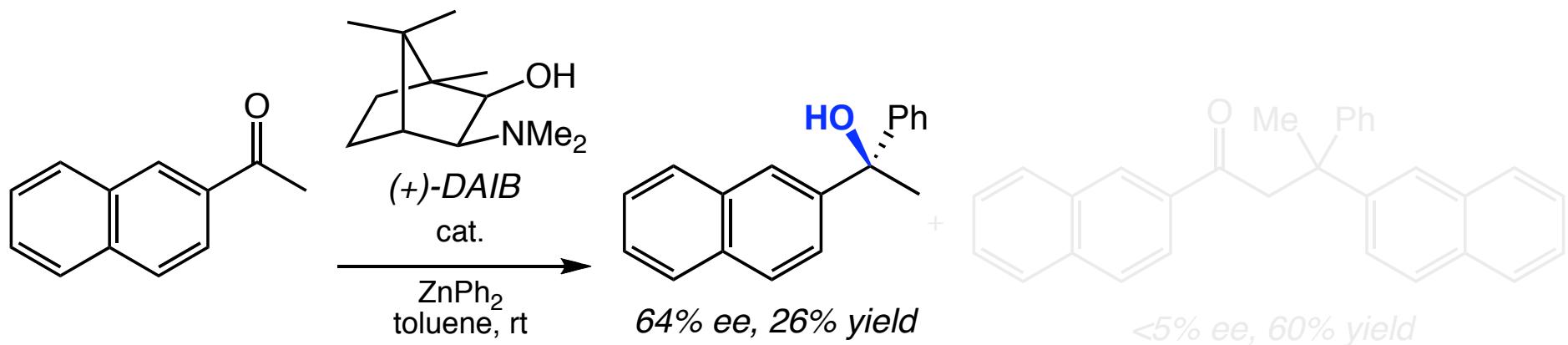
Catalytic Asymmetric Aldol Reactions

Summary

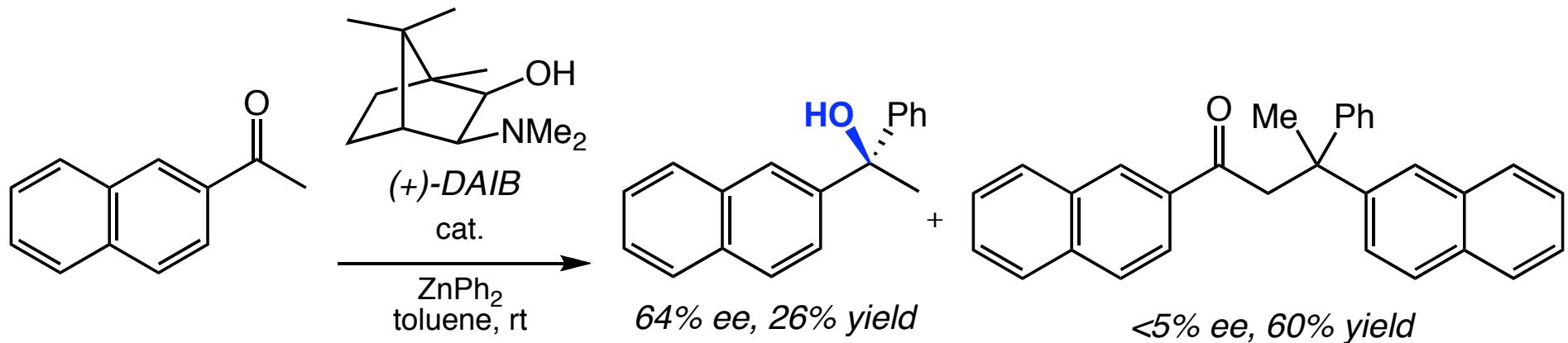


- Can give high yields and good enantioselectivities
- Usually use a prenucleophile
- Often need activated ketones

Asymmetric Addition of Diphenylzinc to Ketones

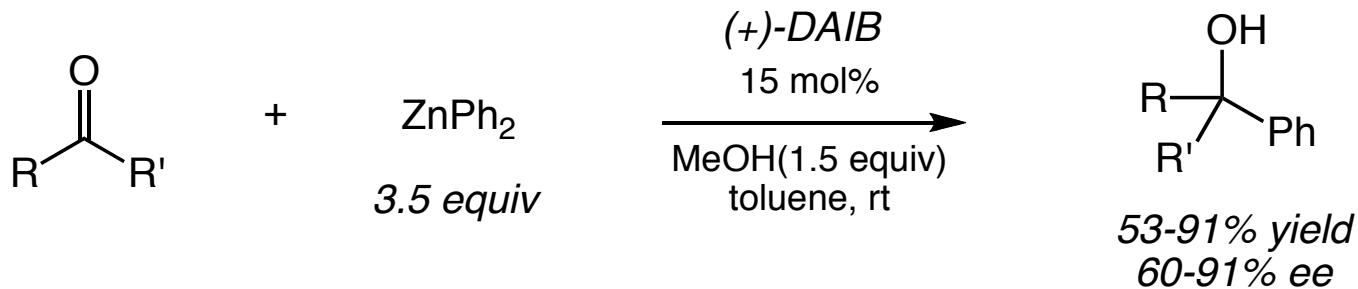
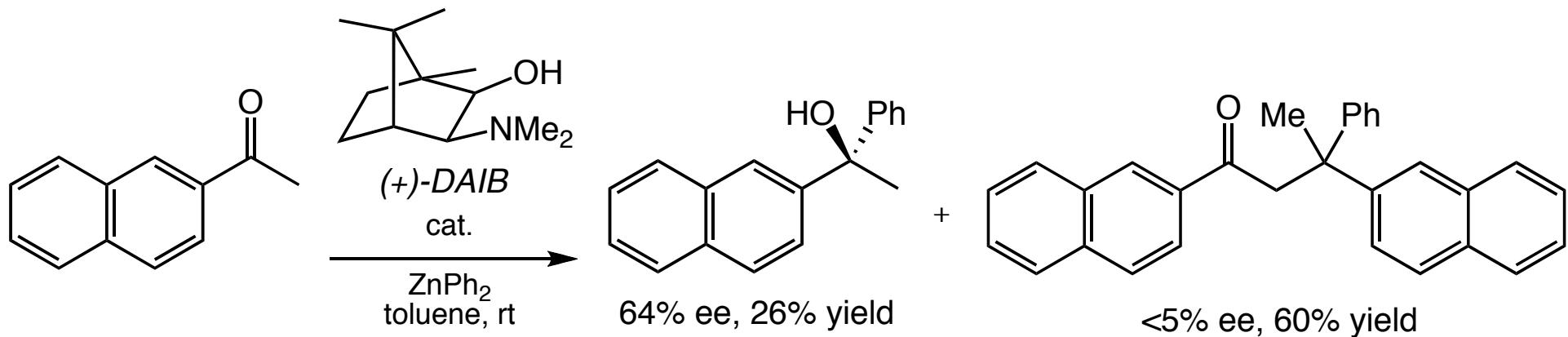


Asymmetric Addition of Diphenylzinc to Ketones



product arises from
aldol/dehydration/conjugate
addition

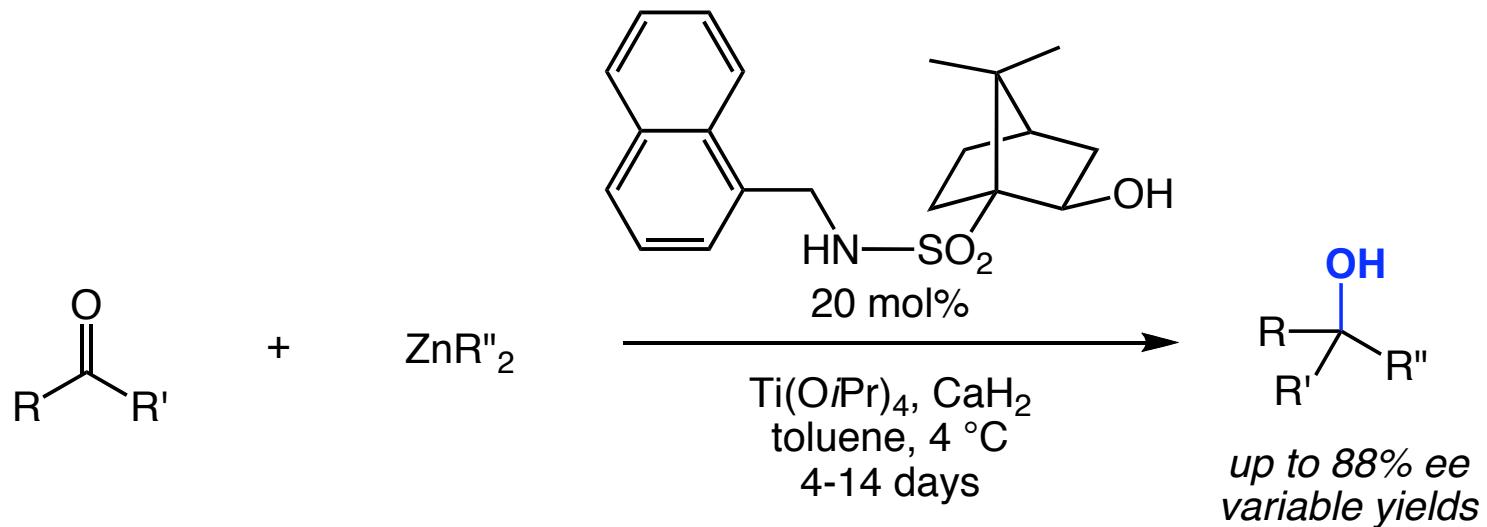
Asymmetric Addition of Diphenylzinc to Ketones



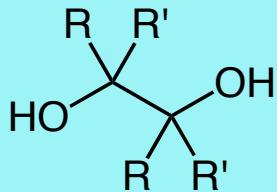
- Addition of MeOH increases yield and enantioselectivity
- Works best when R = aryl and R' = methyl (2-pentanone reacts in 74% yield and 36% ee)
- Only more reactive diphenylzinc adds to ketones (dialkylzincs do not work)

Asymmetric Addition of Alkylzinc Reagents to Ketones

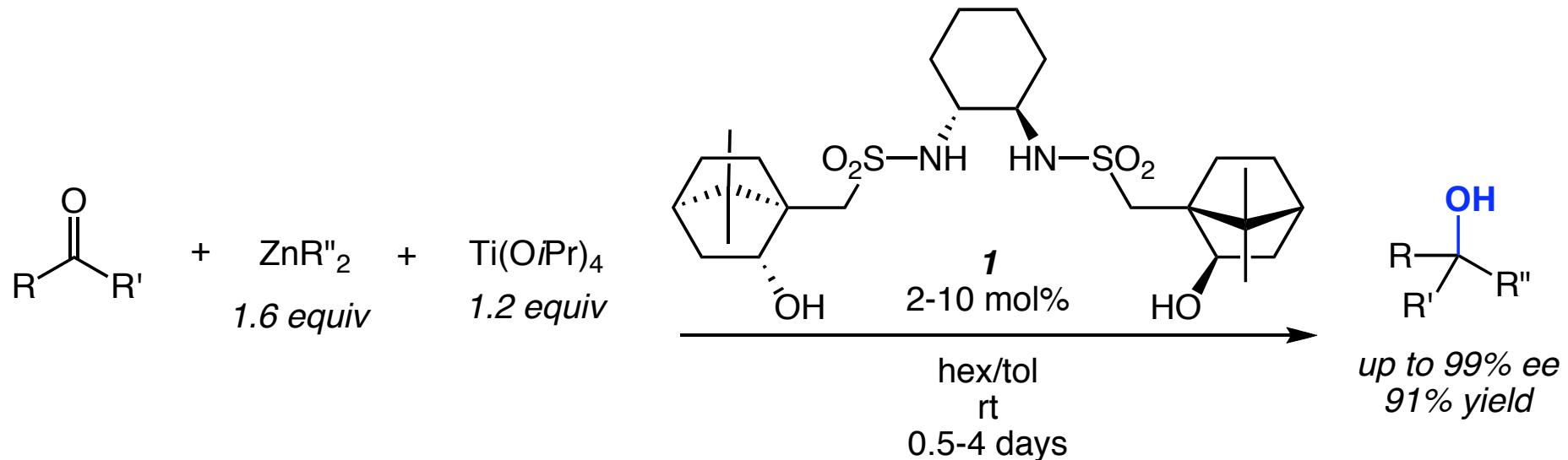
Early Work



Major side product:



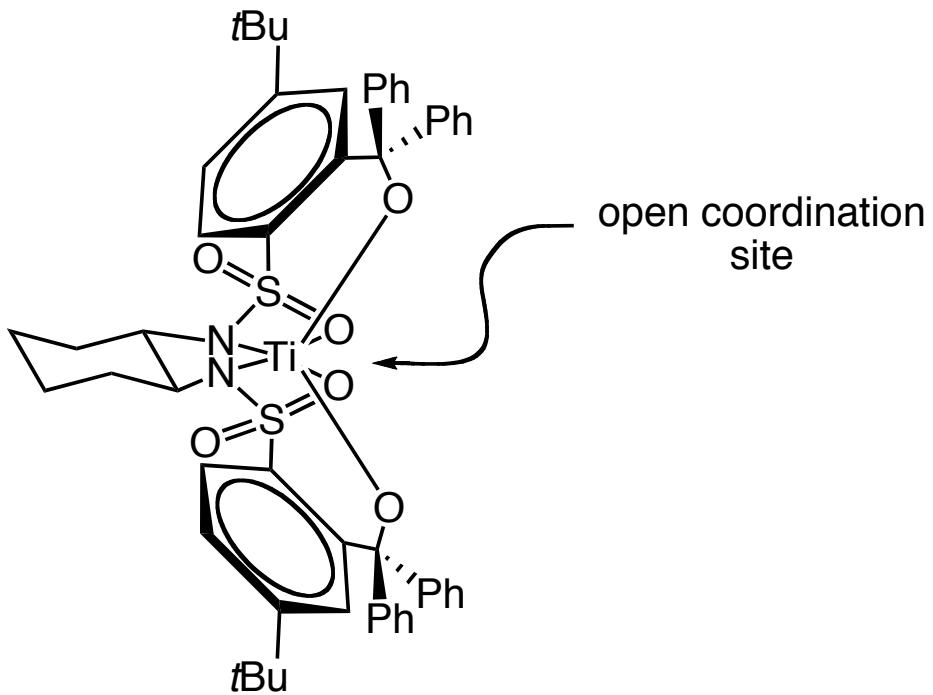
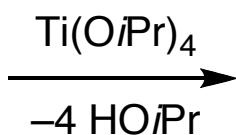
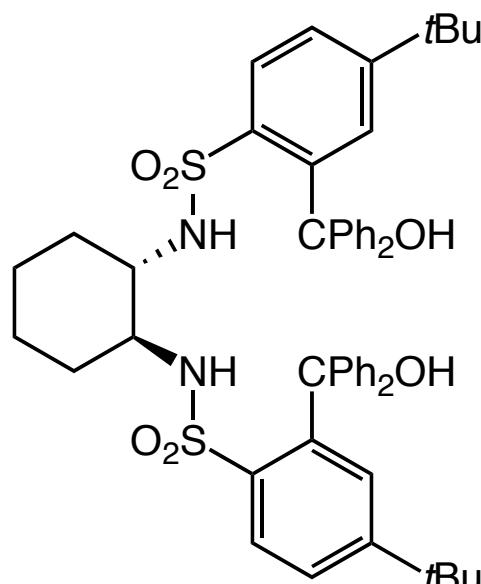
Asymmetric Addition of Alkylzinc Reagents to Ketones



- Process is more general than previous reports
- Generally high yields and enantioselectivities
- Both simple and functionalized zinc reagents work
- Reasonable reaction time
- Low catalyst loading for more active substrates

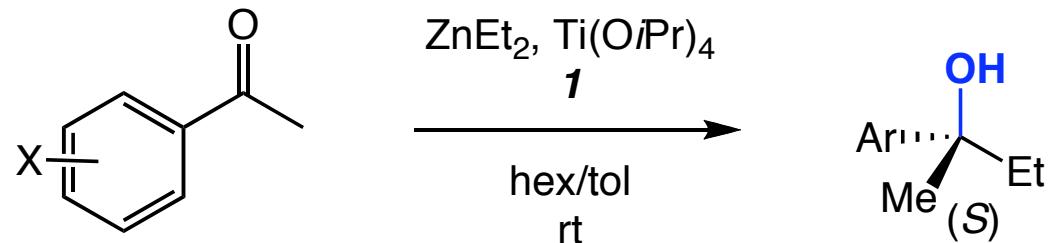
Asymmetric Addition of Alkylzinc Reagents to Ketones

Catalyst



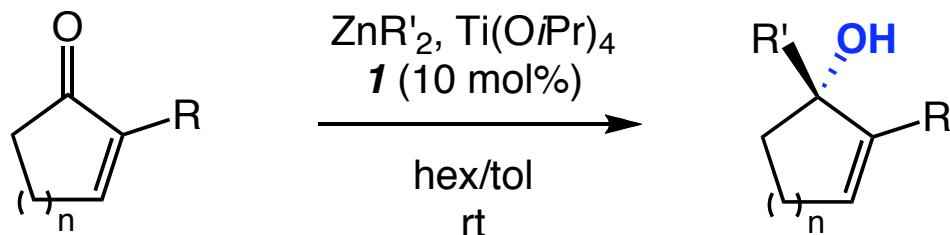
constrained geometry gives larger binding pocket to accommodate the bulky ketone

Asymmetric Addition of Alkylzinc Reagents to Acetophenone Derivatives

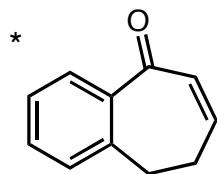


entry	substrate	mol% 1	time (h)	yield (%)	ee
1	X = H	2	29	71	96
2	X = 3-Me	10	12	82	99
3	X = 3-Me	2	24	78	99
4	X = 4-OMe	10	111	85	94
5	X = 3-CF ₃	2	14	56	98
6	X = 2-Me	10	48	24	96

Asymmetric Addition of Alkylzinc Reagents to Conjugated Enones



entry	R	n	R'	time (h)	yield (%)	ee
1	H	2	Et	19	75	52
2	Ph	2	Me	40	84	99
3	CH ₂ OTBS	2	Et	40	81	>99
4	CH ₃	1	Et	37	65	96
5	pentyl	1	Me	40	62	99
6	H*	3*	Et	40	70	96

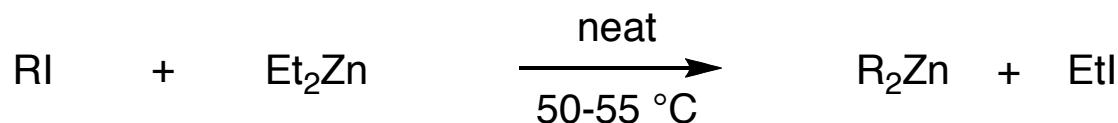


Walsh, *J. Org. Chem.* **2005**, *70*, 448-455.

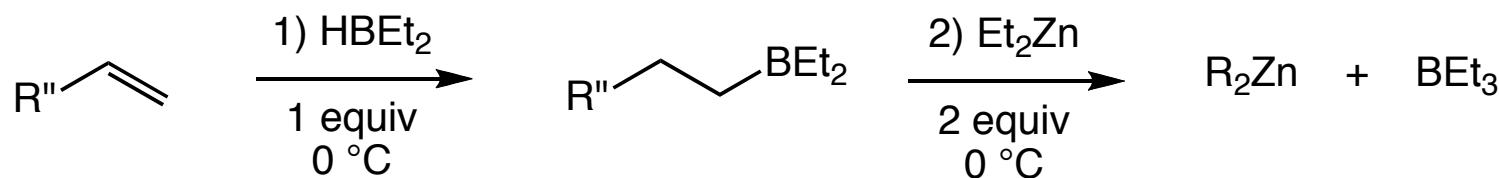
Asymmetric Addition of Functionalized Dialkylzinc Reagents to Ketones

Preparation of Reagents

Method A



Method B

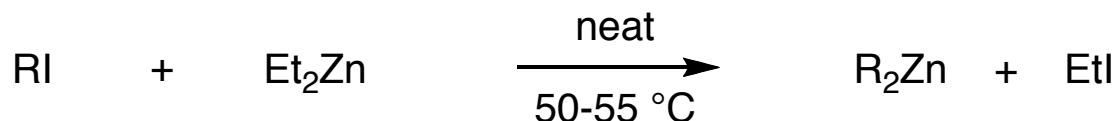


Knochel, *J. Org. Chem.* **1992**, *57*, 1956-1958.
Knochel, *J. Org. Chem.* **1996**, *61*, 8229-8243.
Walsh, *J. Org. Chem.* **2005**, *70*, 448-455.

Asymmetric Addition of Functionalized Dialkylzinc Reagents to Ketones

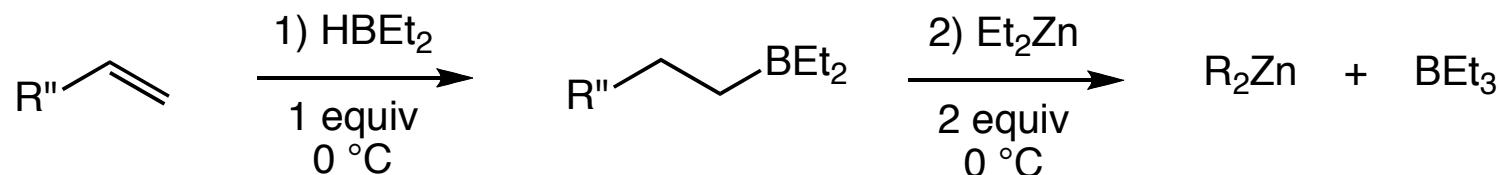
Preparation of Reagents

Method A



Reaction driven to the right by removal of volatile materials

Method B



Knochel, *J. Org. Chem.* **1992**, *57*, 1956-1958.
Knochel, *J. Org. Chem.* **1996**, *61*, 8229-8243.
Walsh, *J. Org. Chem.* **2005**, *70*, 448-455.

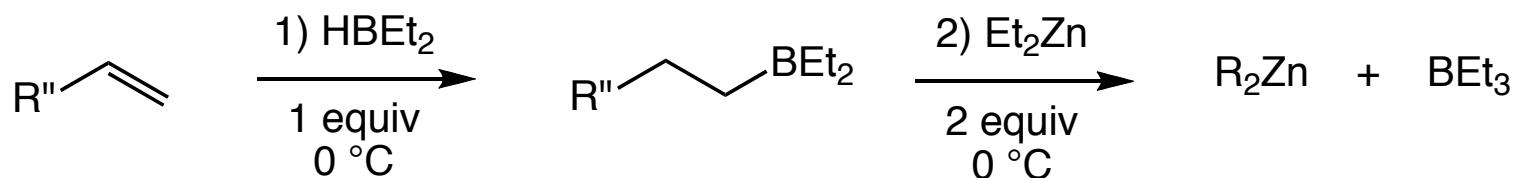
Asymmetric Addition of Functionalized Dialkylzinc Reagents to Ketones

Results using *Method A*

entry	substrate	RI + Et ₂ Zn	neat 50-55 °C	R ₂ Zn + EtI	time (h)	yield (%)	ee (%)
1		ZnOct ₂			40	91	98
2		Zn((CH ₂) ₄ Cl) ₂			40	95	99
3		Zn((CH ₂) ₄ OPiv) ₂			40	58	96
4		ZnOct ₂			40	70	99
5		Zn((CH ₂) ₄ Cl) ₂			40	83	99
6		ZnOct ₂			40	83	97
7		Zn((CH ₂) ₄ Cl) ₂			40	62	96
8		Zn((CH ₂) ₄ OPiv) ₂			40	53	97
9		ZnOct ₂			40	70	>99

Asymmetric Addition of Functionalized Dialkylzinc Reagents to Ketones

Results using *Method B*

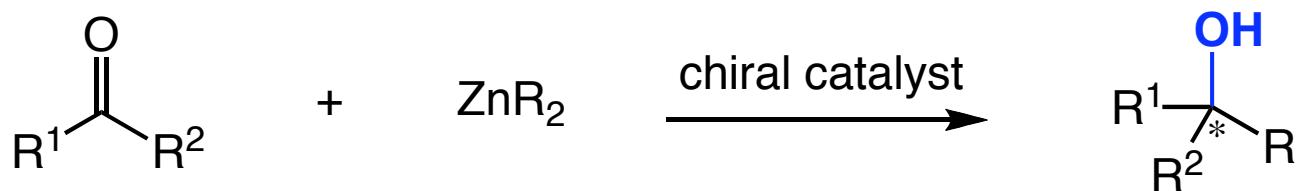


entry	substrate	ZnR_2	time (d)	yield (%)	ee (%)
1		$\text{Zn}((\text{CH}_2)_3\text{CHMe}_2)_2$	3	77	96
2		$\text{Zn}((\text{CH}_2)_4\text{OTBS})_2$	3	89	98
3		$\text{Zn}((\text{CH}_2)_4\text{OPiv})_2$	3	47	96
4		$\text{Zn}((\text{CH}_2)_5\text{Br})_2$	3	89	96
5		$\text{Zn}((\text{CH}_2)_3\text{CHMe}_2)_2$	3	75	90
6		$\text{Zn}((\text{CH}_2)_4\text{OTBS})_2$	5	52	98
7		$\text{Zn}((\text{CH}_2)_5\text{Br})_2$	3	55	94
9		$\text{Zn}((\text{CH}_2)_4\text{OPiv})_2$	3	88	87

Walsh, *J. Org. Chem.* **2005**, *70*, 448-455.

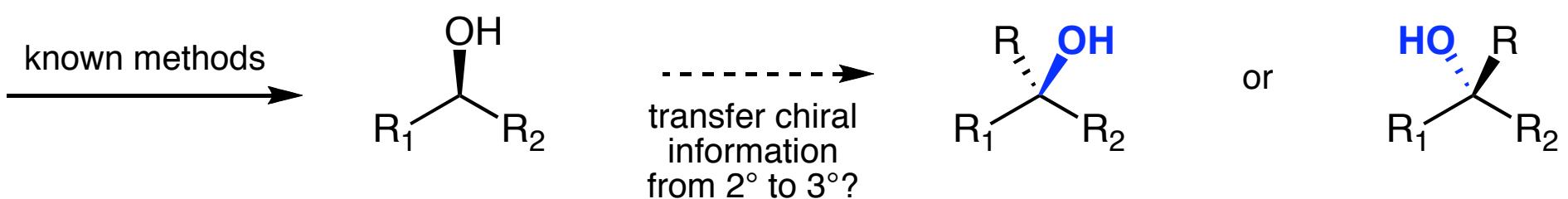
Asymmetric Addition of Diorganozinc Reagents to Ketones

Summary



- Reasonable substrate scope
- Both alkyl and aryl zinc reagents work
- Good yields and generally high enantioselectivity
- 1 Step process
- Branched alkyl, vinyl and heteroaryl groups not accessible
- Lack of commercially available diorganozinc reagents available
(Synthesis of functionalized reagents seems tricky)

Enantiodivergent Synthesis of Tertiary Alcohols through Conversion of Chiral Secondary Alcohols

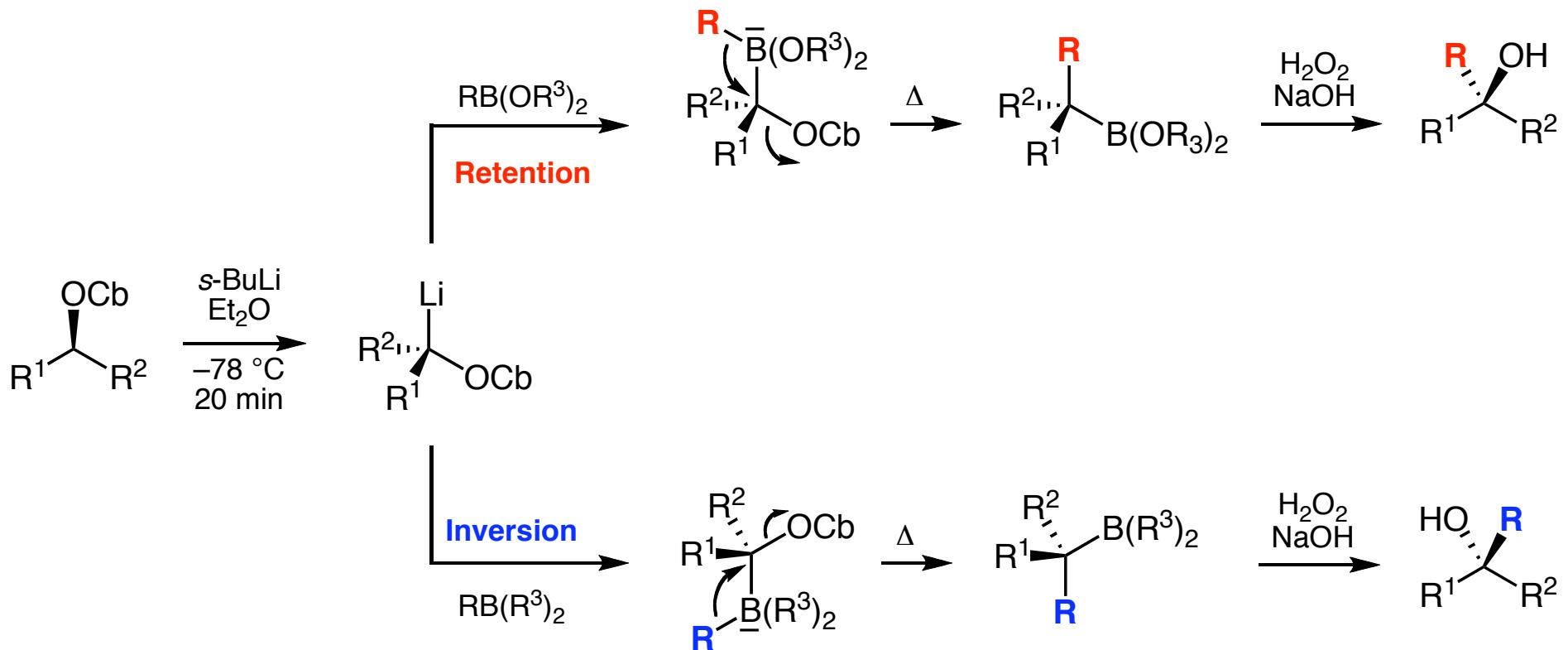


-2° Alcohols are easily accessed through known methods (Noyori hydrogenation, resolution, etc.)

-Potentially access either isomer through a "retention" or "inversion" event

Enantiodivergent Synthesis of Tertiary Alcohols through Conversion of Chiral Secondary Alcohols

Lithiation-Borylation of Chiral Secondary Carbamates



- Deprotonation of carbamate
- Addition of borane (inversion) or boronic ester (retention)
- 1,2-Metallate rearrangement
- Oxidation

Lithiation-Borylation of (*S*)-1-Phenylethanol

Entry	Substrate	Migrating group, R	Borane/boronic ester	Product	Yield (%) (e.r., S:R)
1		Et			91 (99:1)
2		Et			95 (1:99)
3		iPr			91 (98:2)
4		iPr			80 (4:96)
5		nHex			60 (98:2)
6		nHex			85 (4:96)
7		cPr			85 (3:97)
8		vinyl			75 (2:98)
9		allyl			95 (1:99)

*Cb = *N,N*-diisopropylcarbamoyl (99:1 e.r.)

Aggarwal, *Nature* **2008**, *456*, 778-781.

Lithiation-Borylation of (*S*)-1-Phenylethanol

Entry	Substrate	Migrating group, R	Borane/boronic ester	Product	Yield (%) (e.r., S:R)
1		Et			91 (99:1)
2		Et			95 (1:99)
3		iPr			91 (98:2)
4		iPr			80 (4:96)
5		nHex			60 (98:2)
6		nHex			85 (4:96)
7		cPr			85 (3:97)
8		vinyl			75 (2:98)
9		allyl			95 (1:99)

*Cb = *N,N*-diisopropylcarbamoyl (99:1 e.r.)

Aggarwal, *Nature* **2008**, *456*, 778-781.

Lithiation-Borylation of (*S*)-1-Indanol and (*S*)-1-Tetralol

Entry	Substrate	Migrating group, R	Borane/boronic ester	Product	Yield (%) (e.r., S:R)
10		Et			69 (99:1)
11		Ph			73 (6:94)
12		Et			90 (5:95)
13		Et			98 (91:9)
14		Ph			97 (4:96)

Lithiation-Borylation of (*S*)-1-Indanol and (*S*)-1-Tetralol

Entry	Substrate	Migrating group, R	Borane/boronic ester	Product	Yield (%) (e.r., S:R)
10		Et			69 (99:1)
11		Ph			73 (6:94)
12		Et			5:95
13		Et			91:9
14		Ph			97 (4:96)

-They don't give an example, but they mention in the text that reaction of indanol-derived carbamate with triethylborane gives the same enantiomer (so retention instead of the usual inversion)

-Result of increased pyramidalization of the geometrically constrained carbanion

-Need to start with (*R*)-indanol to get opposite enantiomer

Lithiation-Borylation of (*S*)-1-Indanol and (*S*)-1-Tetralol

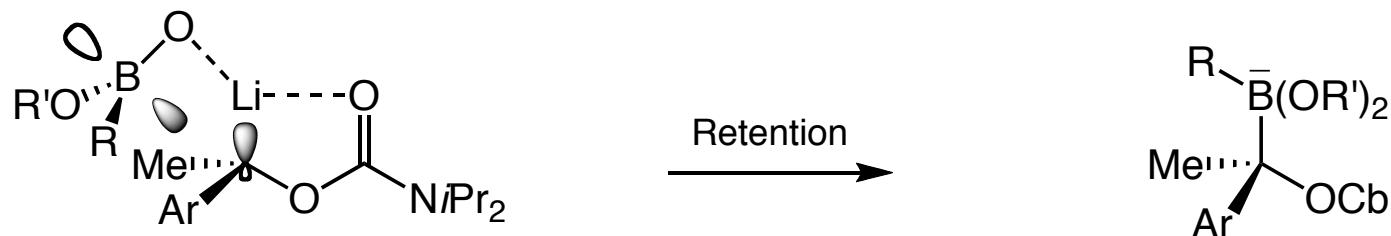
Entry	Substrate	Migrating group, R	Borane/boronic ester	Product	Yield (%) (e.r., S:R)
10		Et			69 (99:1)
11		Ph			73 (6:94)
12		Et			90 (5:95)
13		Et			98 (91:9)
14		Ph			97 (4:96)

-Entry 13 used 1 equiv of $\text{LaCl}_3 \cdot 2\text{LiCl}$

-EtB(pin) gave ~80:20 e.r. (with or without $\text{LaCl}_3 \cdot 2\text{LiCl}$)

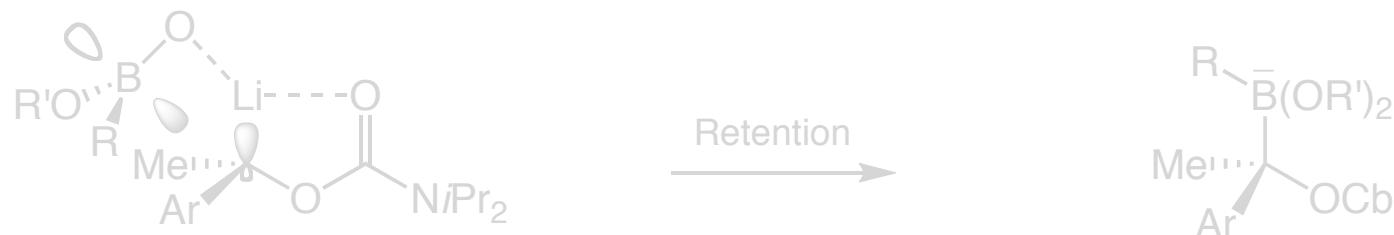
Rationalization of Stereochemistry

Boronic Esters

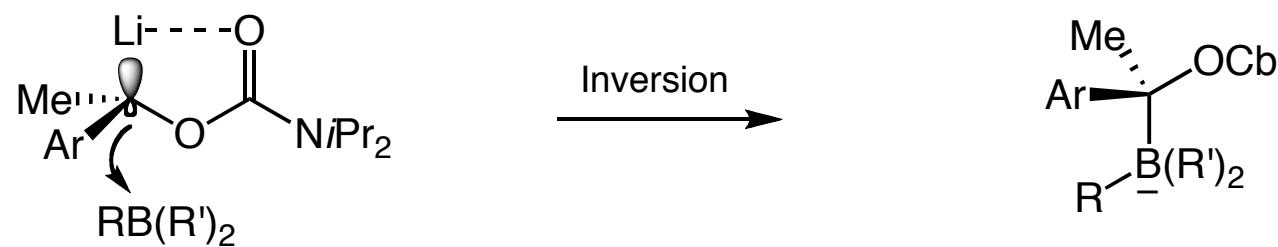


Rationalization of Stereochemistry

Boronic Esters

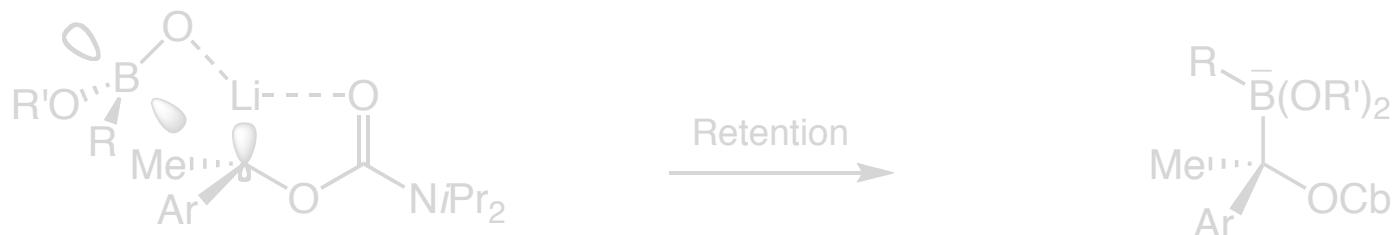


Boranes

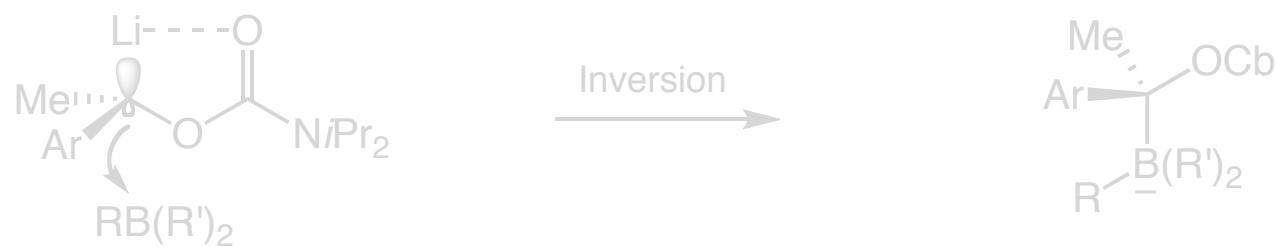


Rationalization of Stereochemistry

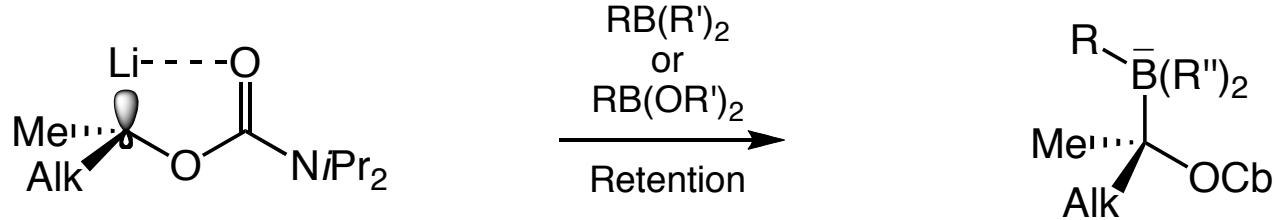
Boronic Esters



Boranes

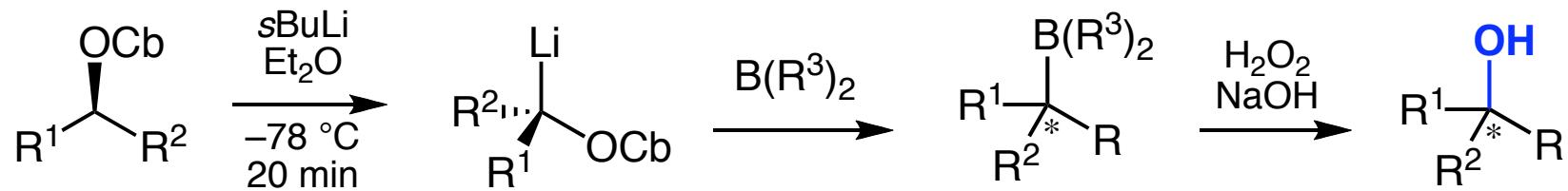


However...



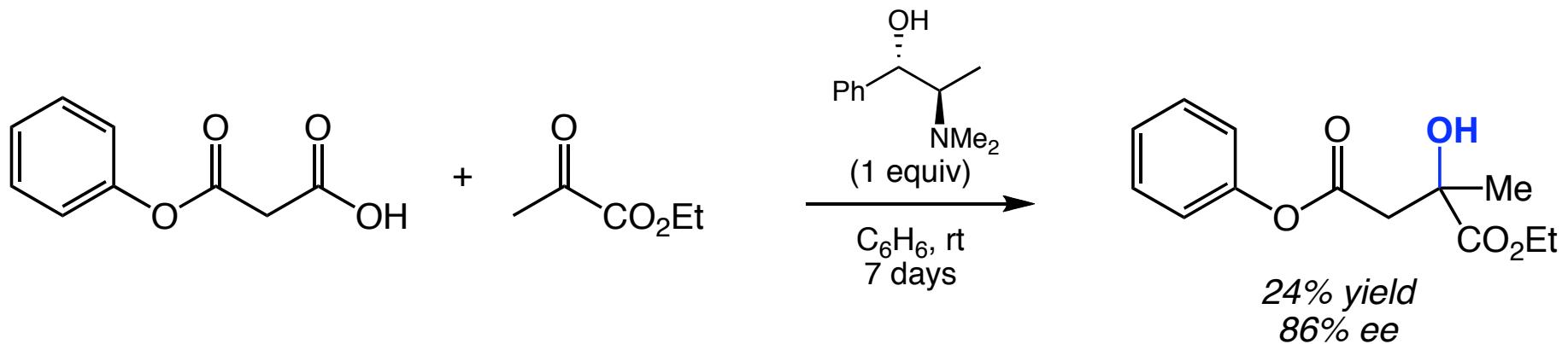
Enantiodivergent Synthesis of Tertiary Alcohols through Conversion of Chiral Secondary Alcohols

Summary

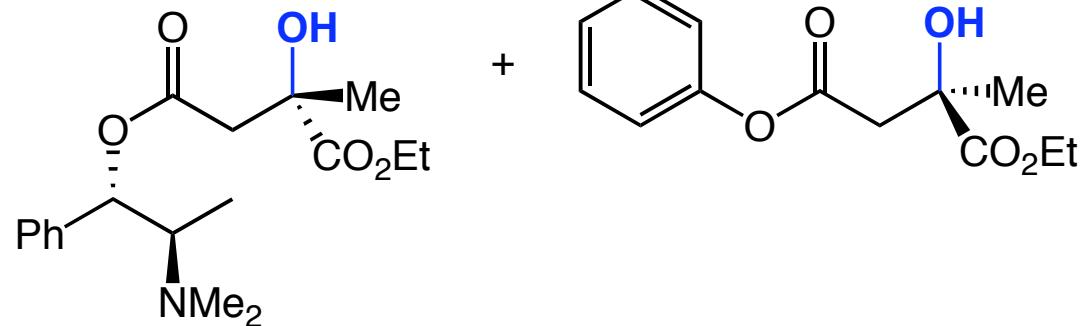


- High yields and enantioselectivities
- Good substrate scope within the migrating group
(*vinyl and heteroaryl group work fine*)
- Limited to aryl ketones
- Can access either enantiomer of tertiary alcohol from the same chiral secondary alcohol
- 3 Step process (1 pot)

*Kinetic Resolution of Tertiary Alcohols using (1*S*,2*R*)-*N*-methylephedrine*

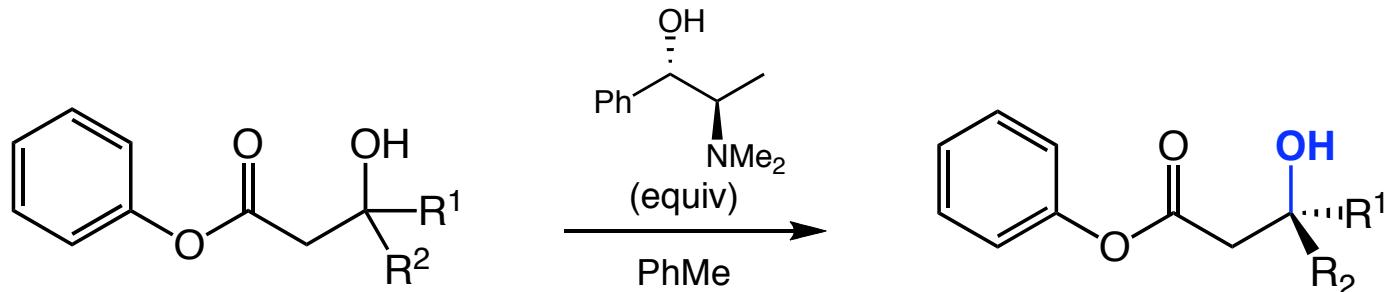


attempted amine catalyzed asymmetric decarboxylative ketone aldol reaction
actually kinetic resolution of racemic product!



Kinetic Resolution of Tertiary Alcohols

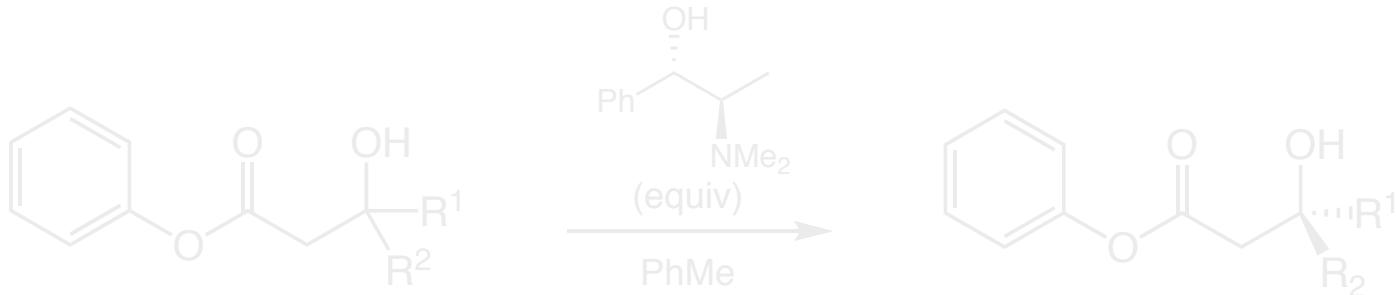
Scope



entry	substrate	equiv	T (°C)	conv (%)	ee	s
1		2	60	51	88	38
2		2	80	58	96	21
3		1	rt	28	34	21
4		1	60	51	70	10
5		0.7	60	46	8	1.3

Kinetic Resolution of Tertiary Alcohols

Scope



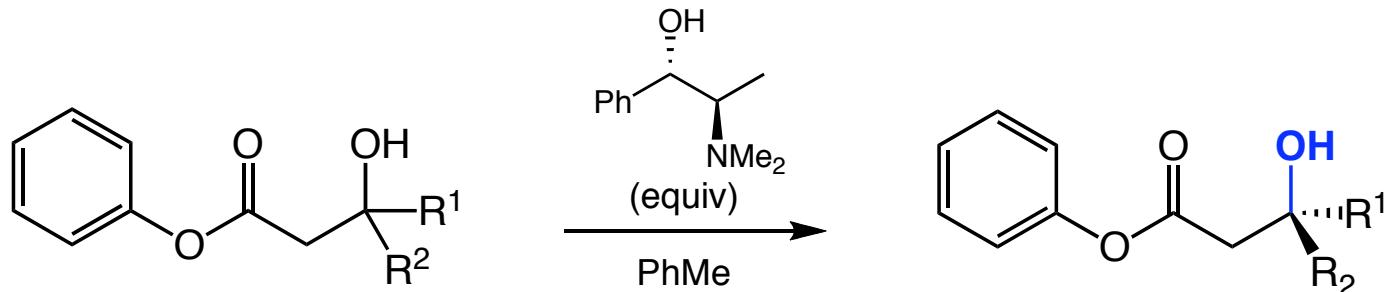
entry	substrate	equiv	T (°C)	conv (%)	ee	s
1				1	88	38
2				3	96	21
3		1	rt	28	34	21
4		1	60	51	70	10
5		0.7	60	46	8	1.3

$$s = \frac{\ln[(1-c)(1-ee_s)]}{\ln[(1-c)(1+ee_s)]}$$

Kagan, *Topics in Stereochemistry*, Vol 18 1998, 249-330.

Kinetic Resolution of Tertiary Alcohols

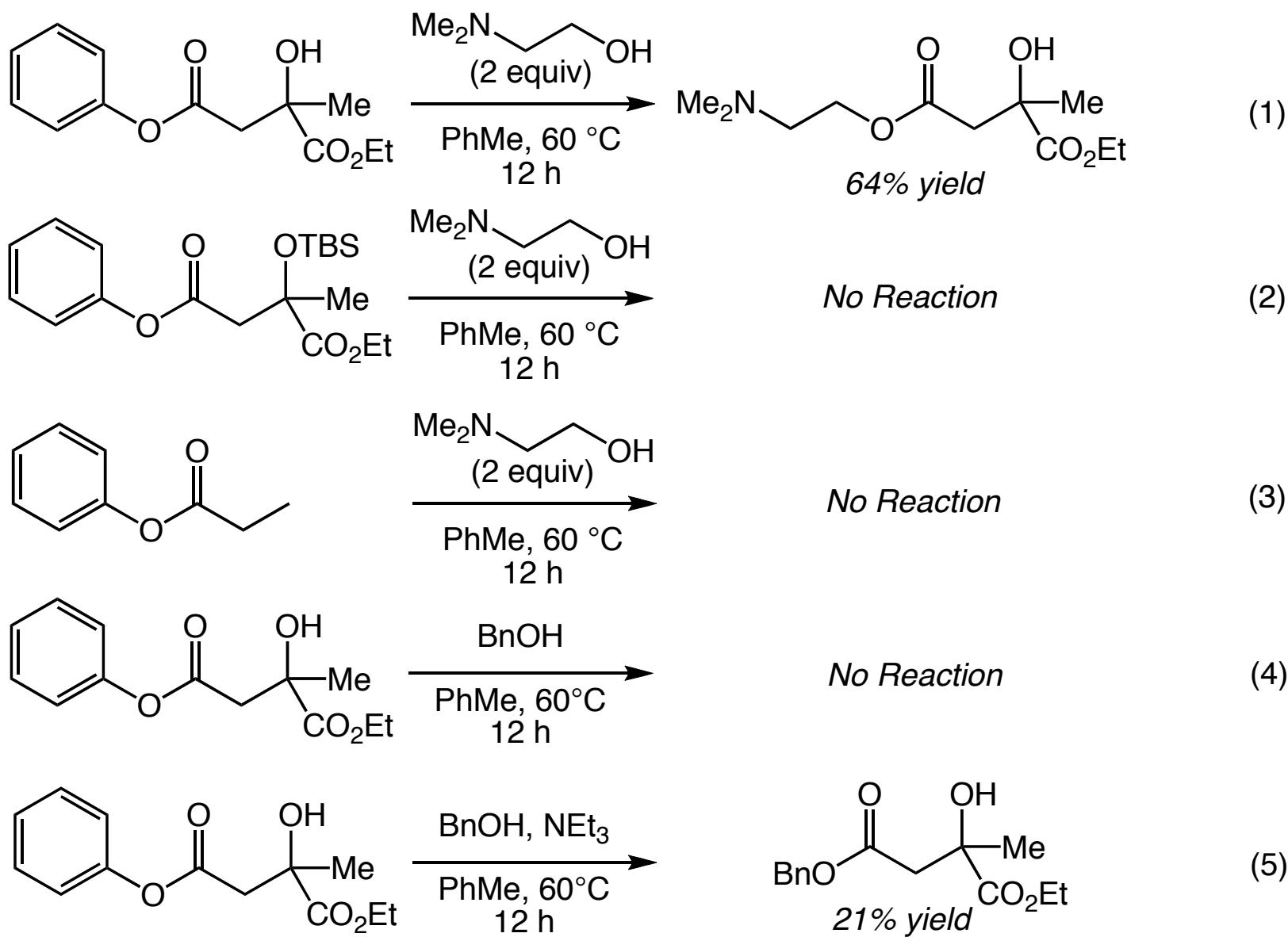
Scope



entry	substrate	equiv	T (°C)	conv (%)	ee	s
1		2	60	51	88	38
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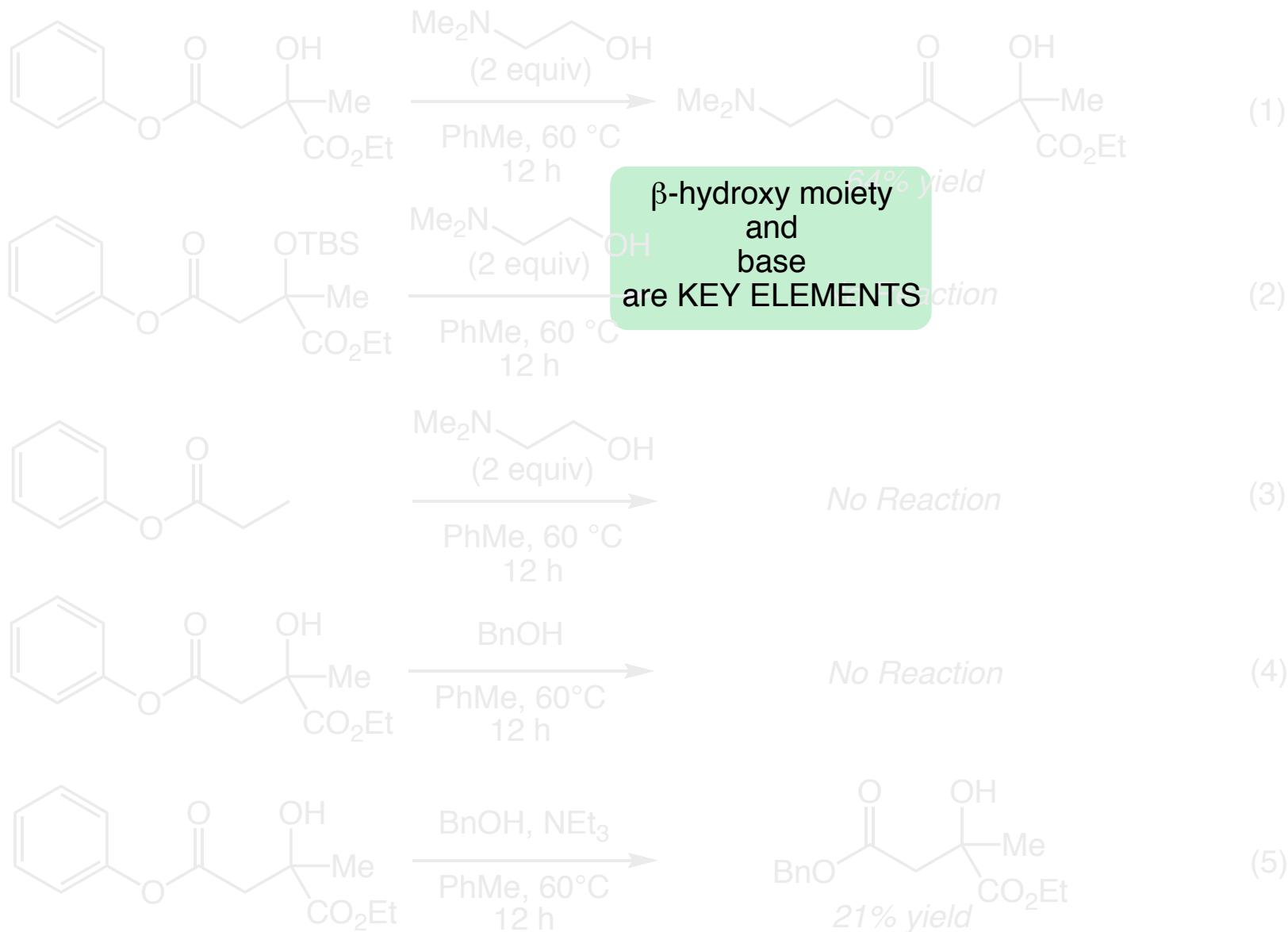
Kinetic Resolution of Tertiary Alcohols

Control Reactions



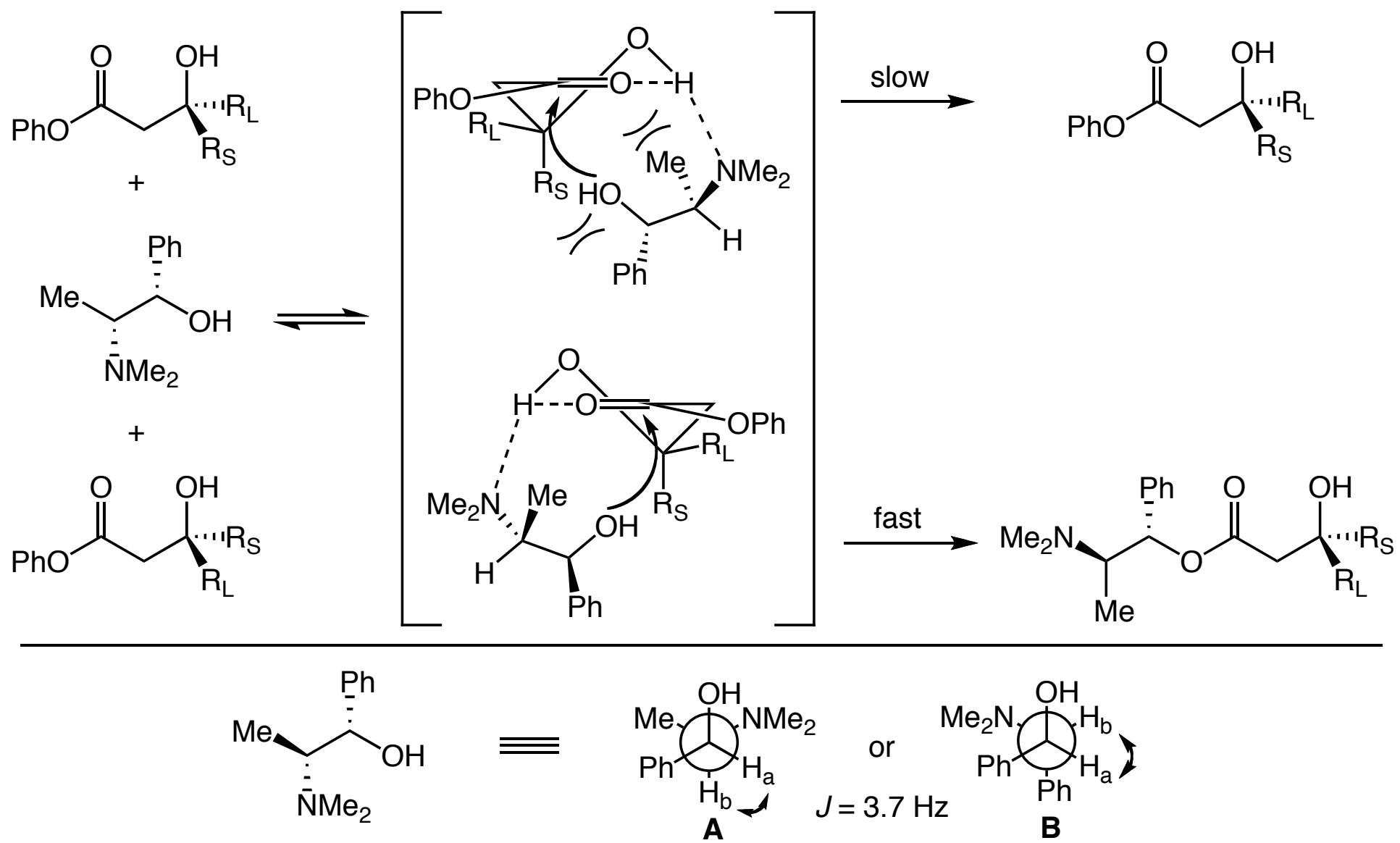
Kinetic Resolution of Tertiary Alcohols

Control Reactions



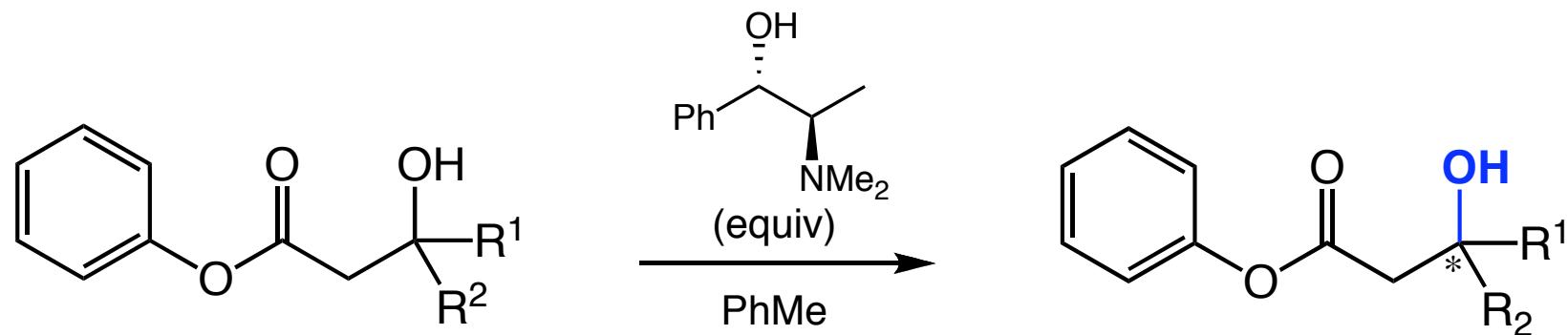
Kinetic Resolution of Tertiary Alcohols

Proposed Origin of Selectivity



*Kinetic Resolution of Tertiary Alcohols Using (1*S*,2*R*)-*N*-Methylephedrine*

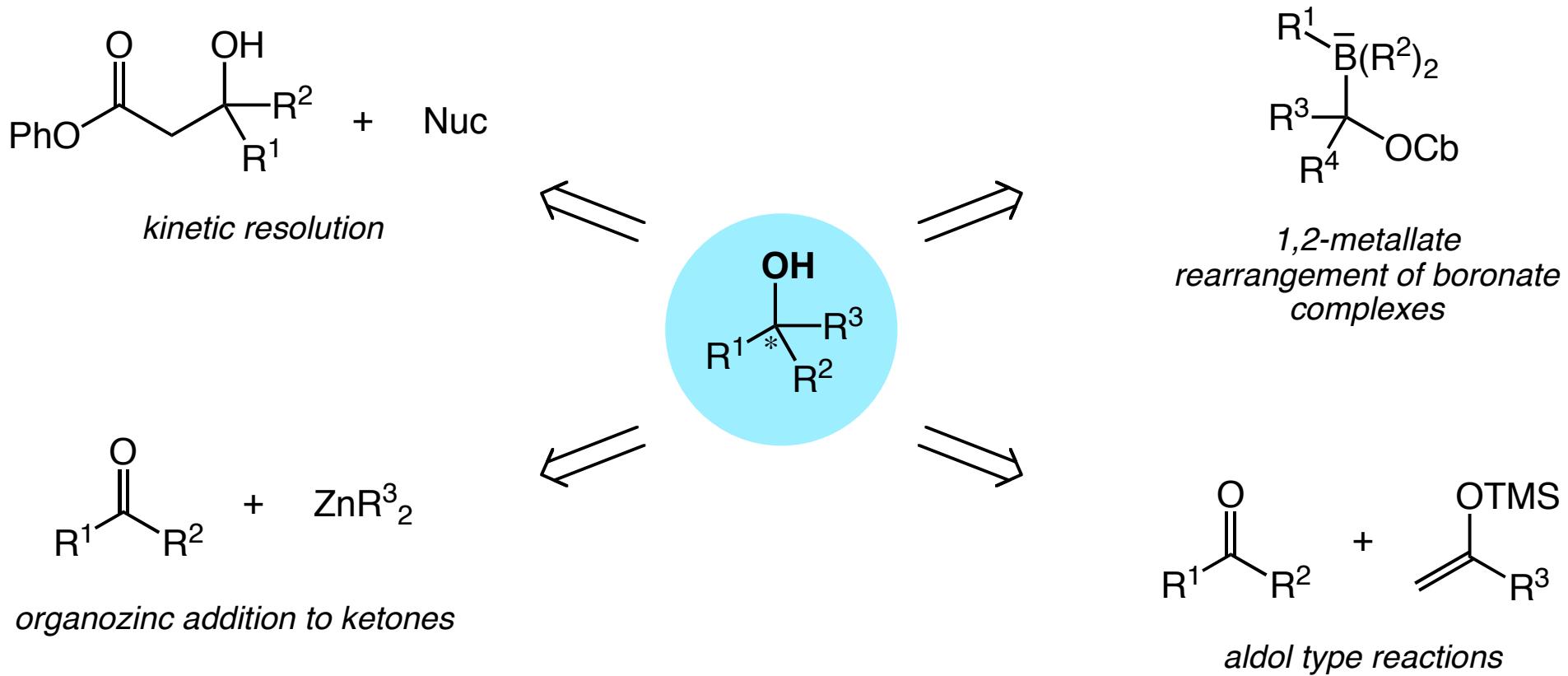
Summary



- Good selectivities for select substrates
- 50% yield maximum
- Not catalytic

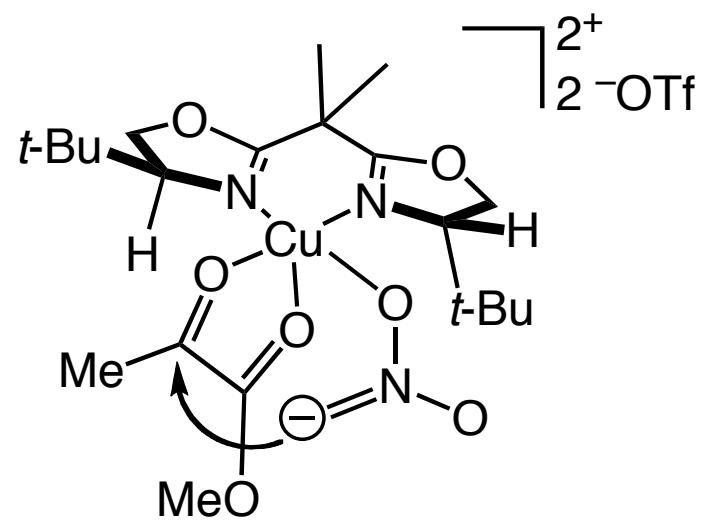
Strategies for the Asymmetric Synthesis of Tertiary Alcohols

Summary

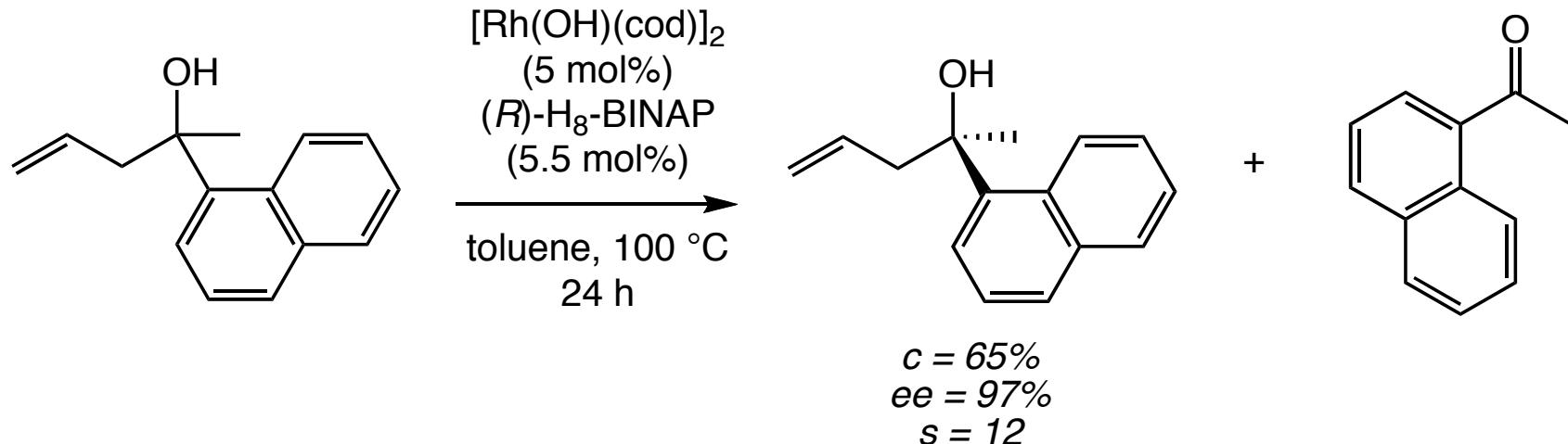


- Many strategies have been developed to allow for access of tertiary alcohols in good yields and enantiopurity
- Most require some sort of specialized substrate and are not very general
- Continued work will lead to further development

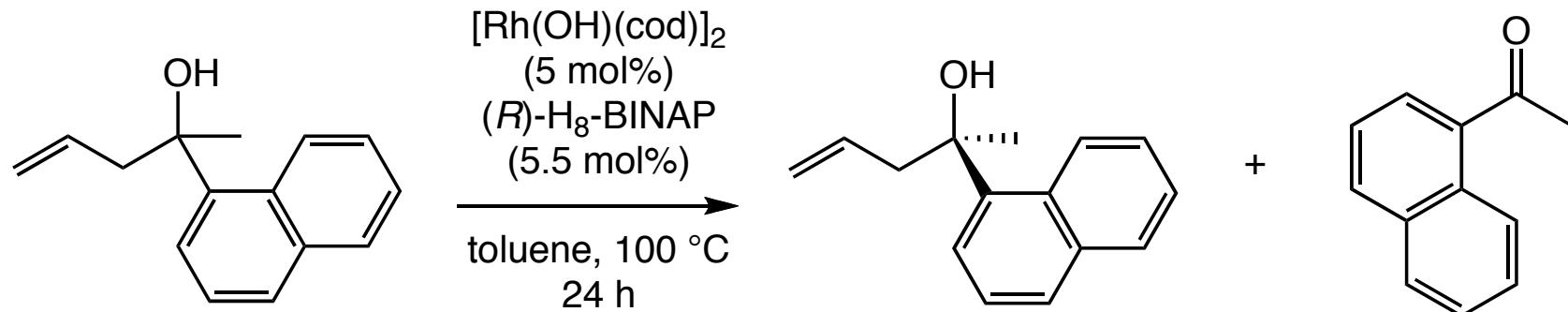
Copper Catalyzed Enantioselective NitroAldol Reaction



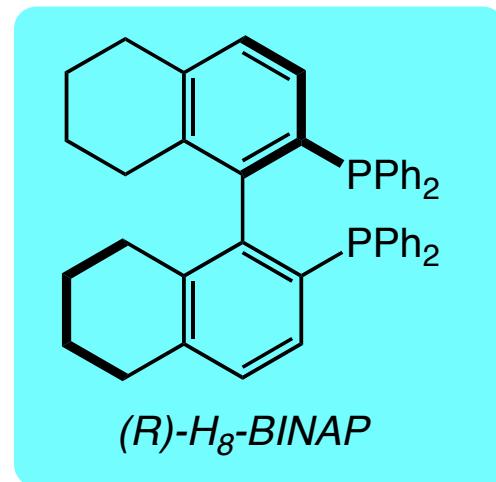
Rhodium Catalyzed Kinetic Resolution of Tertiary Homoallyl Alcohols



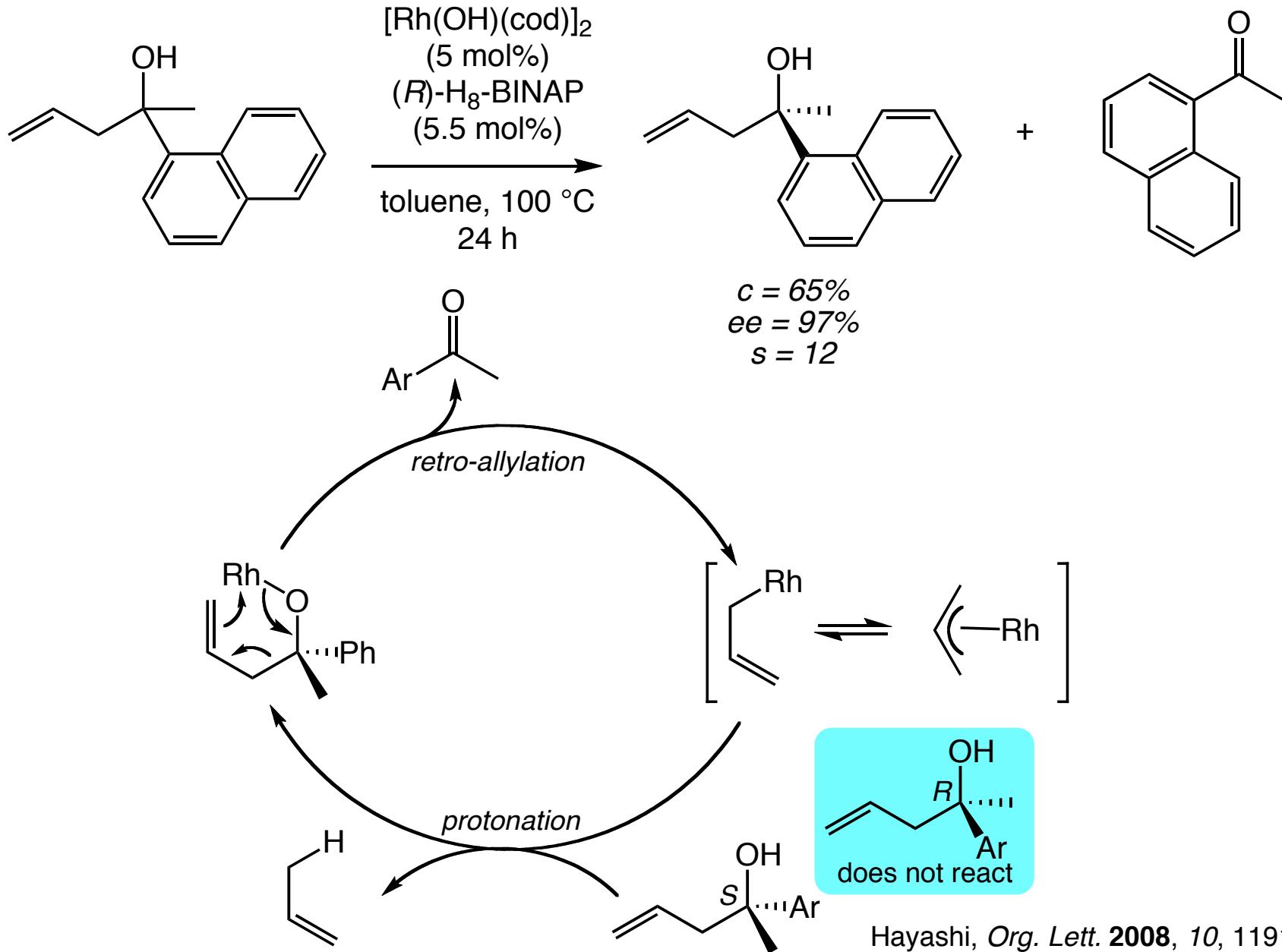
Rhodium Catalyzed Kinetic Resolution of Tertiary Homoallyl Alcohols



c = 65%
ee = 97%
s = 12



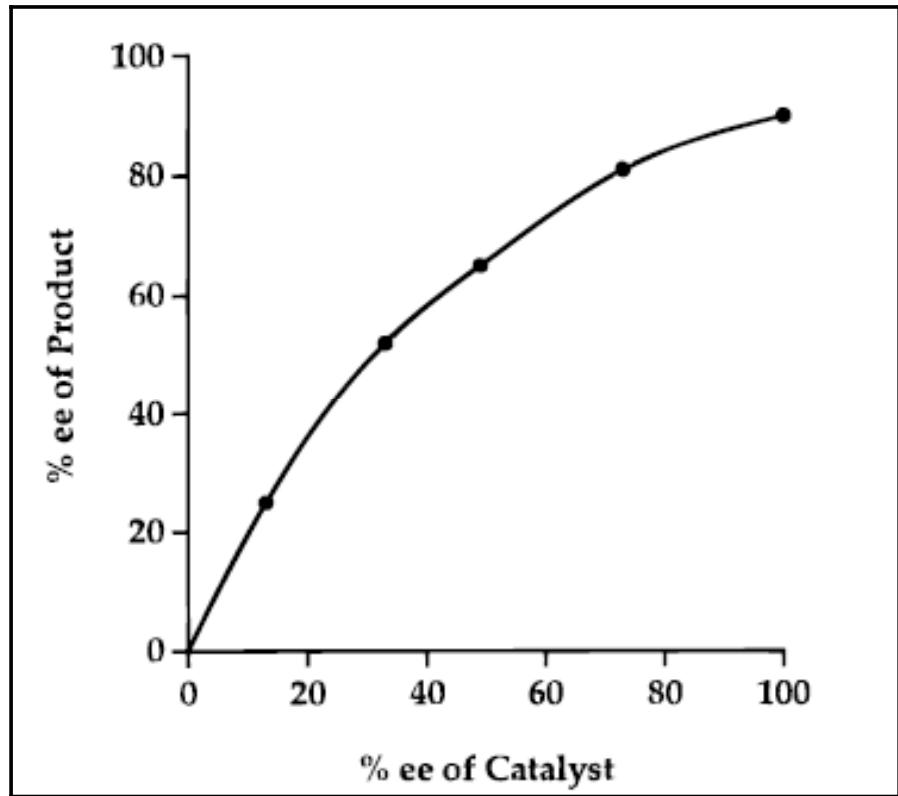
Rhodium Catalyzed Kinetic Resolution of Tertiary Homoallyl Alcohols



Hayashi, *Org. Lett.* **2008**, *10*, 1191-1193.

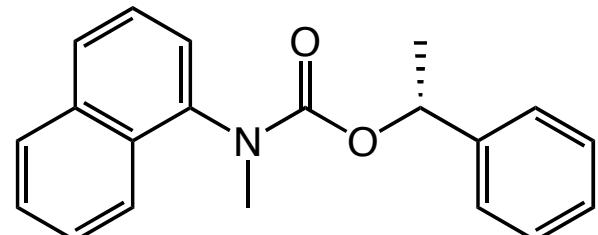
Asymmetric Addition of Diphenylzinc to Ketones

Nonlinear Dependence of Product ee on catalyst ee



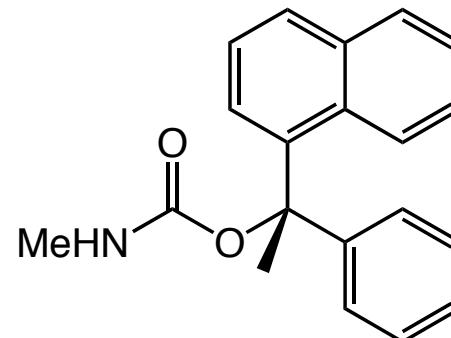
Due to relatively unreactive dinuclear zinc complex that sequesters a 1:1 mixture of DAIB enantiomers?

N to *C* Aryl Migration in Lithiated Carbamates to form Tertiary Alcohols

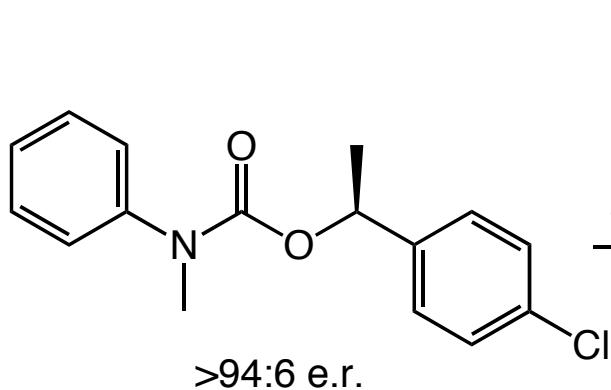


>99:1 e.r.

1. *s*BuLi (2.5 equiv),
*Et*₂O, -78 °C, 4 h
 2. MeOH

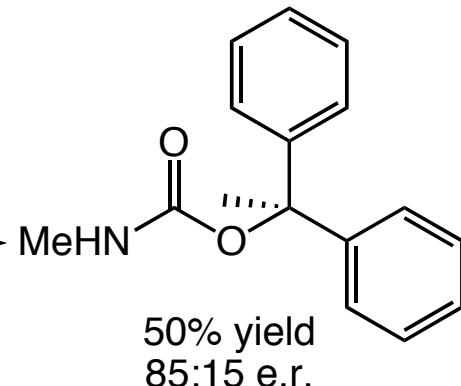


50% yield
 75:25 e.r.

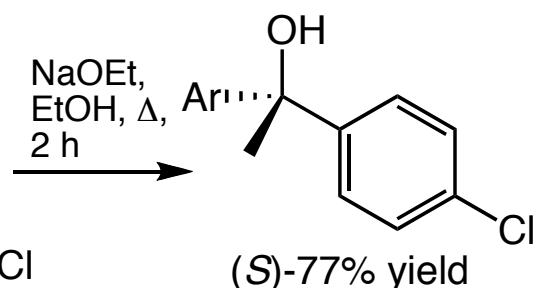


>94:6 e.r.

1. LDA
 (2.5 equiv),
*Et*₂O, -78-
 -35 °C, 24 h
 2. MeOH



50% yield
 85:15 e.r.



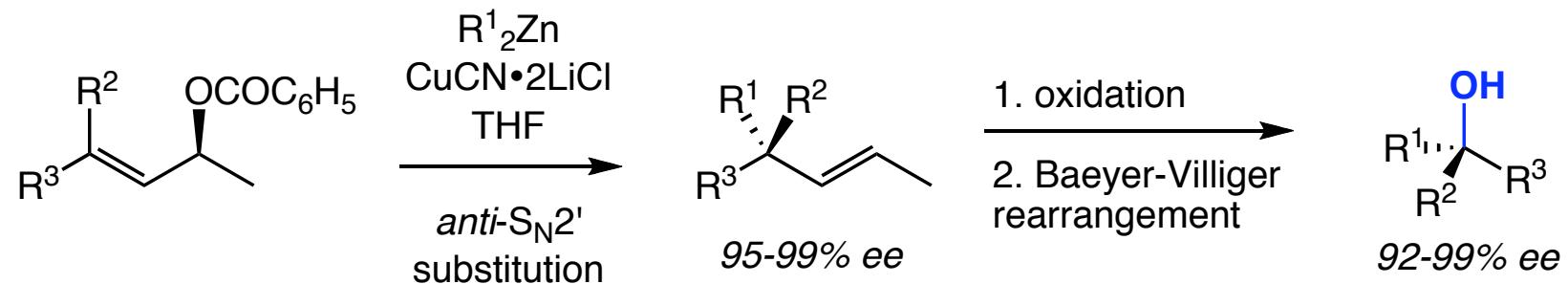
(S)-77% yield

-*N* to *C* aryl transfer with inversion at the lithium-bearing center

-Theoretical studies suggest attack on aromatic ring is a significantly lower energy pathway than the expected 1,2-acyl transfer

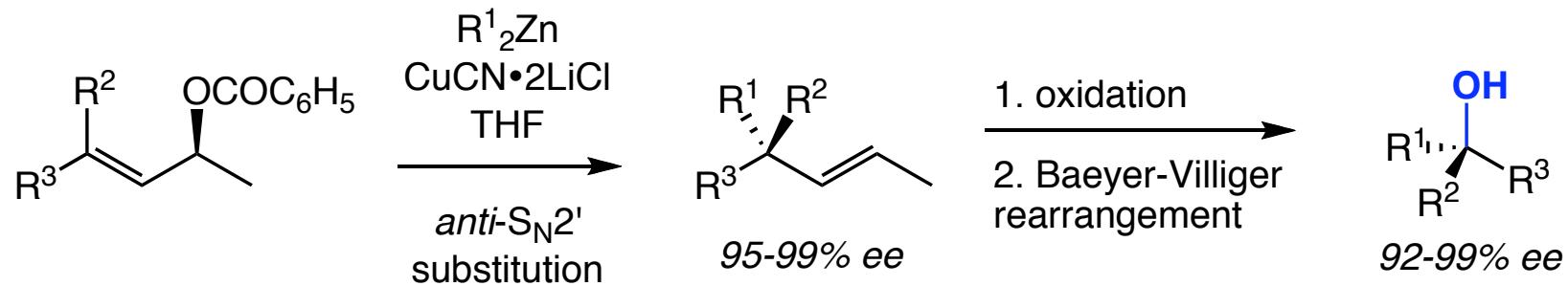
-THF and DMPU which they use as additives in the racemic version lower e.r.

Enantioselective Preparation of Tertiary Alcohols by Copper-Mediated Diastereoselective Allylic S_N2' Substitutions

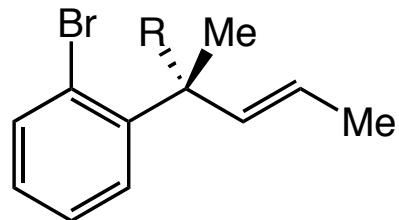


Knochel, *Angew. Chem. Int. Ed.* **2005**, *44*, 4627-4631.
Knochel, *Org. Lett.* **2003**, *5*, 2111.

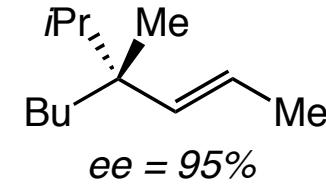
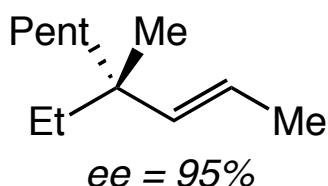
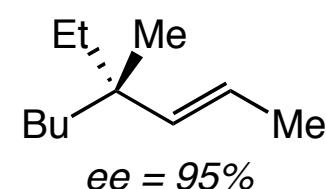
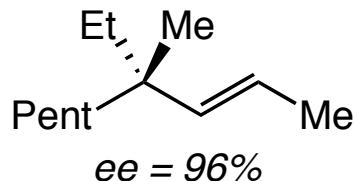
Enantioselective Preparation of Tertiary Alcohols by Copper-Mediated Diastereoselective Allylic S_N2' Substitutions



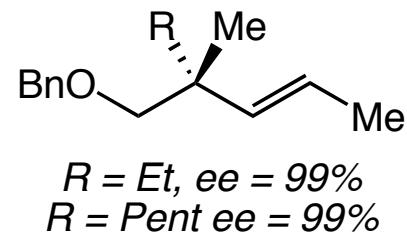
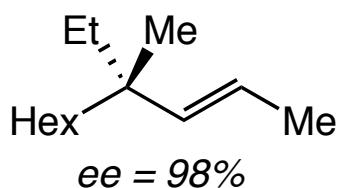
They have shown you can make these allylic quaternary centers with high almost complete transfer of chiral information



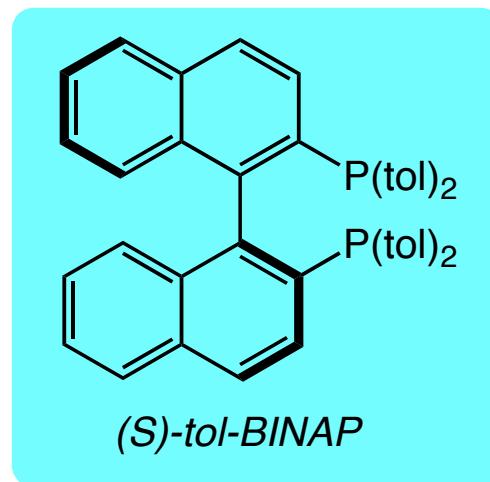
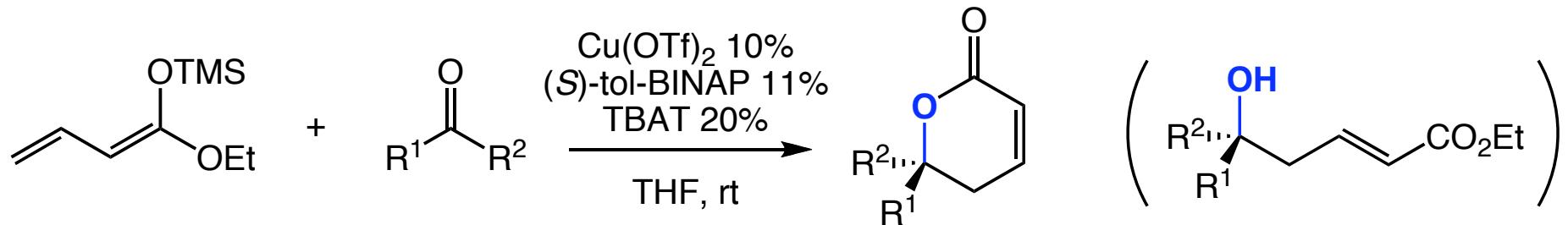
$R = \text{Pent, ee} = 96\%$
 $R = (\text{CH}_2)_3\text{CO}_2\text{Et, ee} = 96\%$



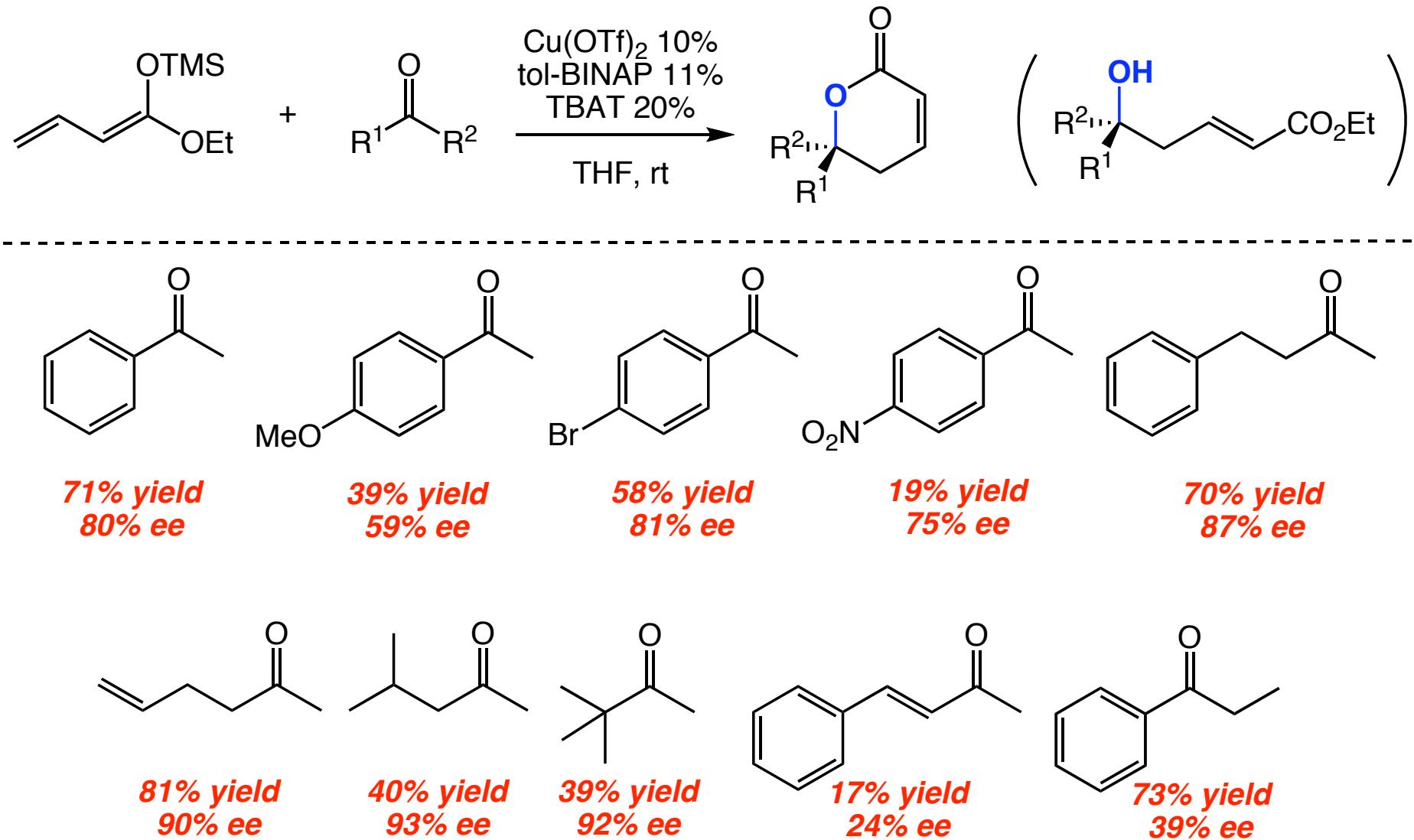
$R = \text{Pent, ee} = 98\%$
 $R = (\text{CH}_2)_3\text{CO}_2\text{Et, ee} = 96\%$



Catalytic and Asymmetric Vinylogous Mukaiyama Reaction



Catalytic and Asymmetric Vinylogous Mukaiyama Reaction



Enantioselective Preparation of Tertiary Alcohols by Copper-Mediated Diastereoselective Allylic S_N2' Substitutions

entry	alkene	intermediate	yield (%)	ee (%)	product	yield (%)	ee (%)
1			85	98		70	97
2			63	96		76	92
3			65	98		68	93
4			62	99		70	99
5			66	99		77	98
6			71	99		93	96

Enantioselective Preparation of Tertiary Alcohols by Copper-Mediated Diastereoselective Allylic S_N2' Substitutions

Conclusions

- Access to certain tertiary alcohols that might not be available otherwise
- Good yields and high fidelity of enantiopurity of starting reagents
- 3-Steps
- Requires synthesis of allylic pentafluorobenzoates