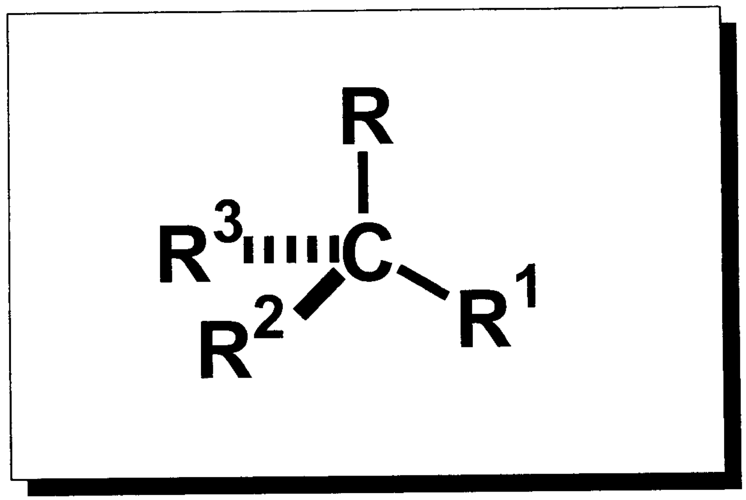
Selected Methods for the Creation of Asymmetric Quaternary Carbon Centers



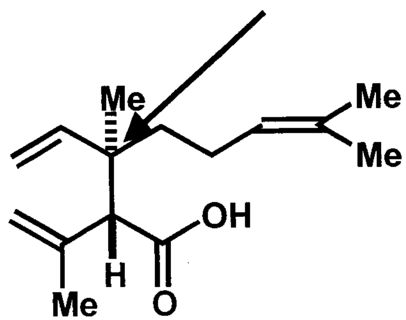
John Baird

October 21, 2003

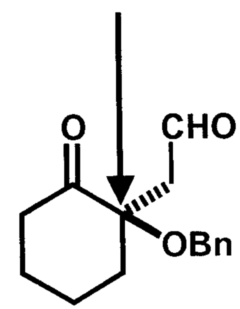
Quaternary Carbon: Definition

Quaternary carbon is a carbon atom bearing four carbon substituents

Quaternary Carbon



Tetrasubstituted carbon

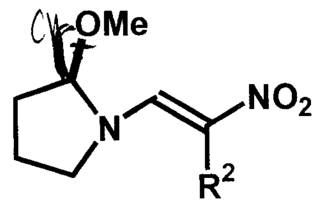


Commonly misidentified
as "quaternary carbon"

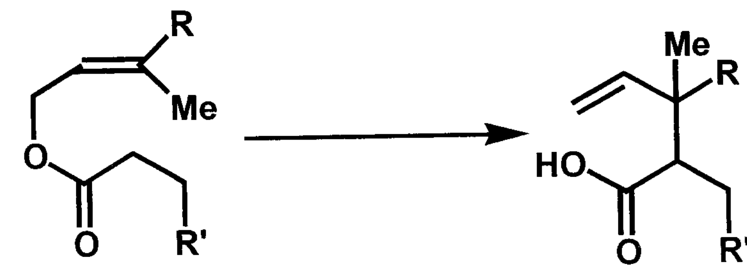
Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.

Some Recent Advances in Asymmetric Quaternary Center Construction

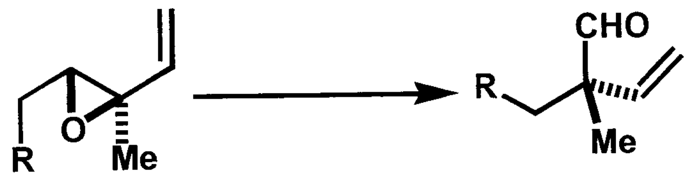
Chiral leaving group



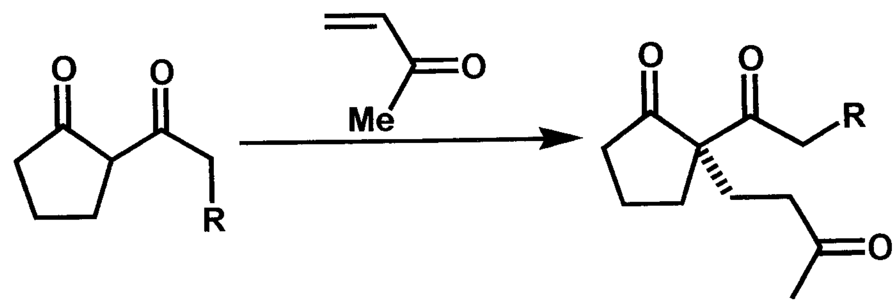
Claisen Rearrangement



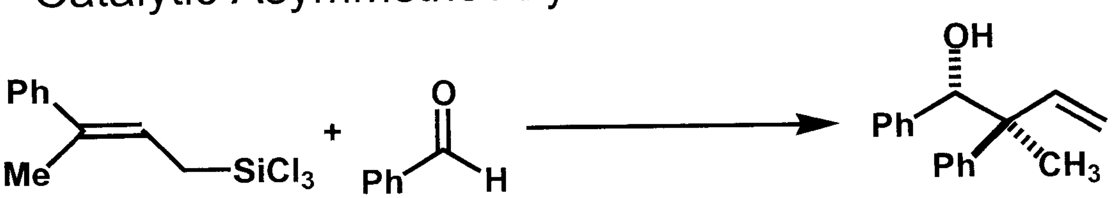
Rearrangement of epoxides



Enantioselective Michael Addition

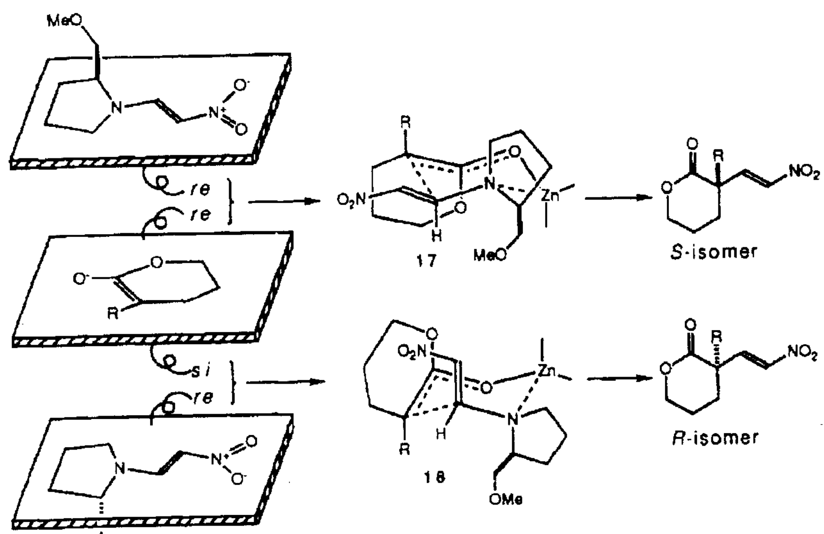


Catalytic Asymmetric Allylation Reaction



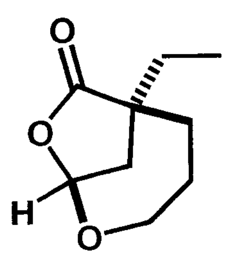
Chiral Leaving Groups

<u>Analysis</u>



entry	R^1	R^2	Yield[a]	%ee[c]
1	CH_3	H	99	86
2	CH_3	CH_3	69	93
3	CH_3	C_2H_5	87	85
4	C_2H_5	H	94	82
5	C_2H_5	CH_3	65	90
6	C_2H_5	C_2H_5	89	96
7	$CH_2CH=CH_2$	H	86	87
8	$CH_2CH=CH_2$	CH_3	54	92
9	$CH_2CH=CH_2$	C_2H_5	69	96

[a]Isolated yield, [b]Determined by ^1H NMR with $Eu(hfc)_3$

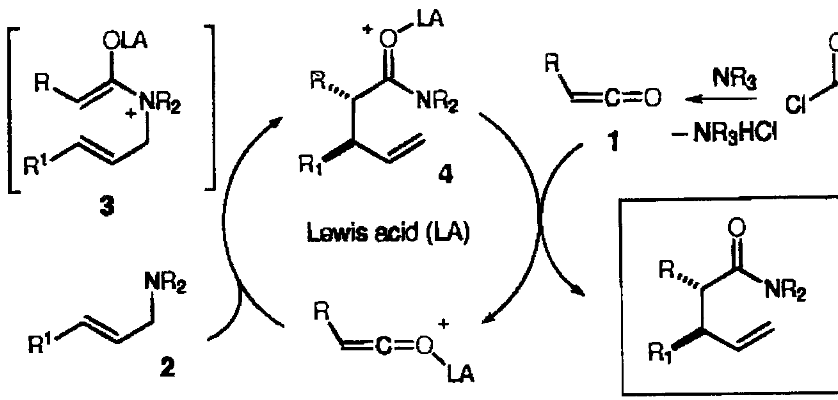


74% in 2 steps from entry 4 product

Other metals examined including Li and Cu, but Zn was found to be superior in yield and selectivity

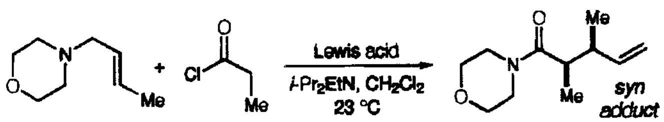
Fuji, K. et. al. *J. Am. Chem. Soc.* **1989**, *111*, 7921

Lewis Acid-Catalyzed Claisen Rearrangement



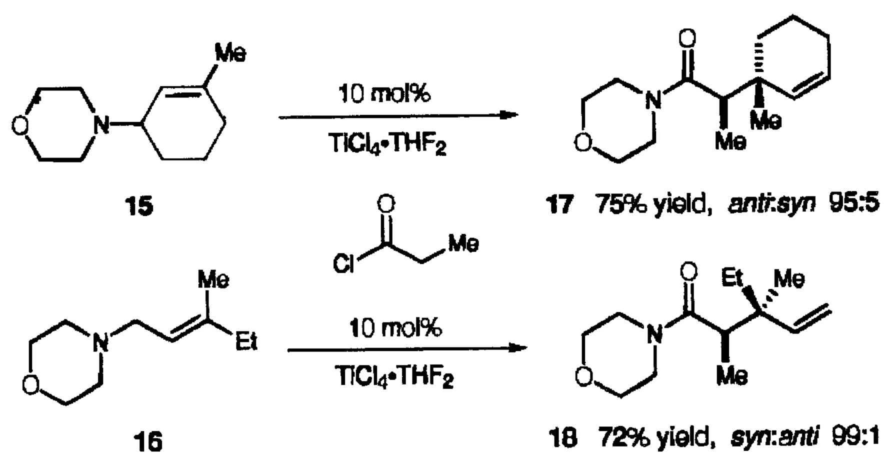
Proposed Catalytic Cycle

Catalyst Optimization



entry	Lewis acid	mol% cat	% yield	*syn:anti*[a]
1	--	--	NR	--
2	$Yb(OTf)_3$	10	80	>99:1
3	$AlCl_3$	10	90	>99:1
4	$Ti(O\textit{i}\text{-}Pr)_2Cl_2$	10	76	>99:1
5	$TiCl_4{\cdot}THF_2$	5	92	>99:1

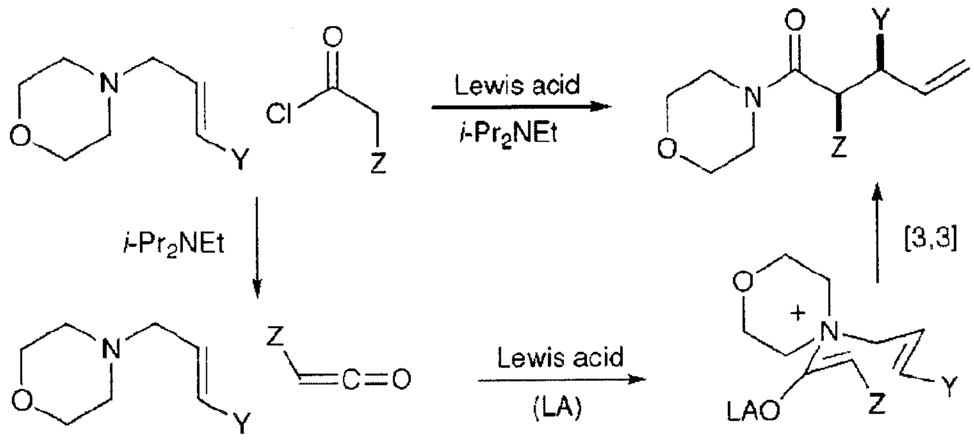
[a] Product ratios determined by GLC using a Bodman CC1701 column.



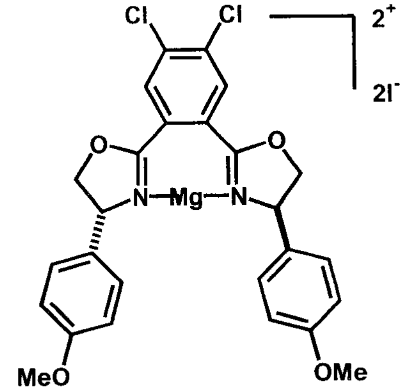
Reaction proceeds in high yields with excellent diastereoselectivity

Yoon, T.; Dong, V.; MacMillan, D. *J. Am. Chem. Soc.* **1999**, *121*, 9726

Enantioselective Acyl-Claisen

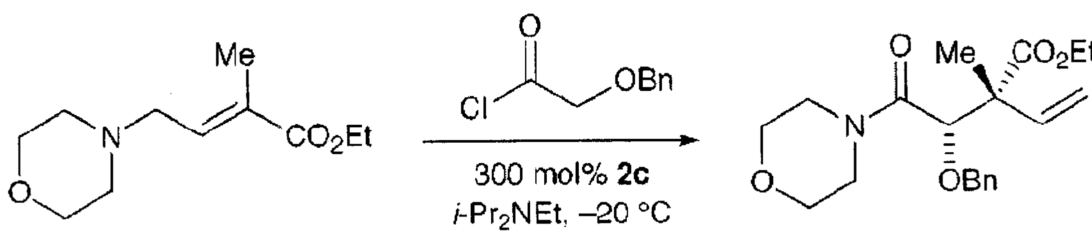


Lewis Acid



[(R,R) Mg-Arbox](I)$_2$

Catalytic version is still being developed

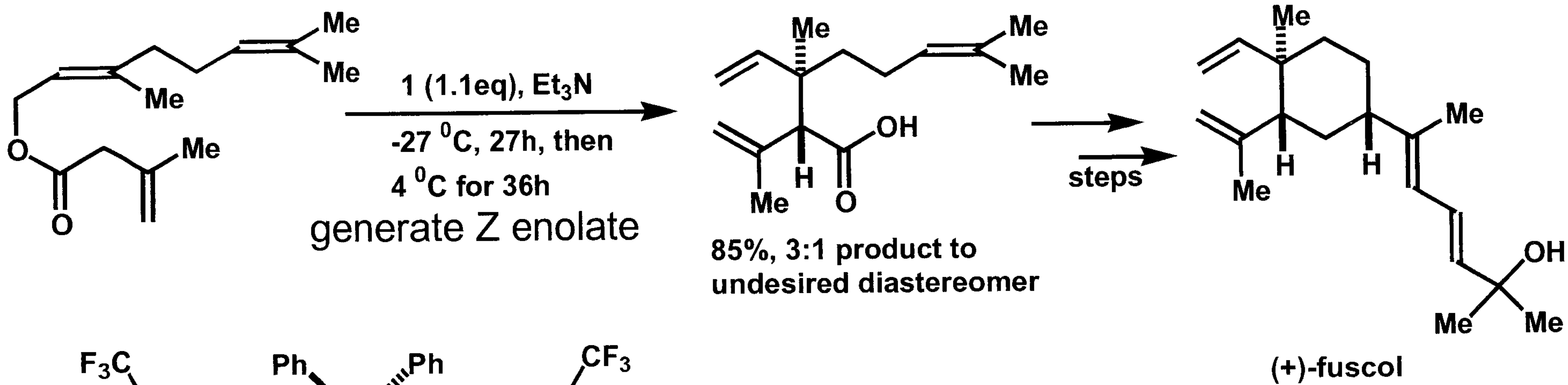


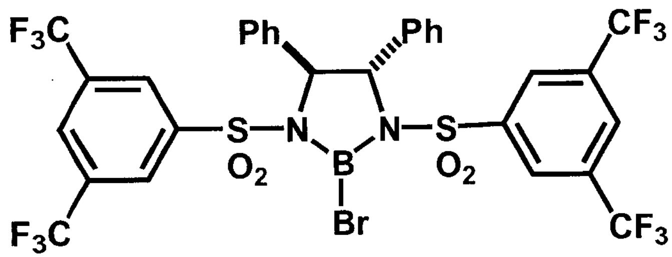
94:6 syn:anti, 97% ee
75% yield

Although high enantioselectivities were demonstrated, 3 equivalents of chiral Lewis Acid were required

Yoon, T.; MacMillan, D. *J. Am. Chem. Soc.* **2001**, *123*, 2911.

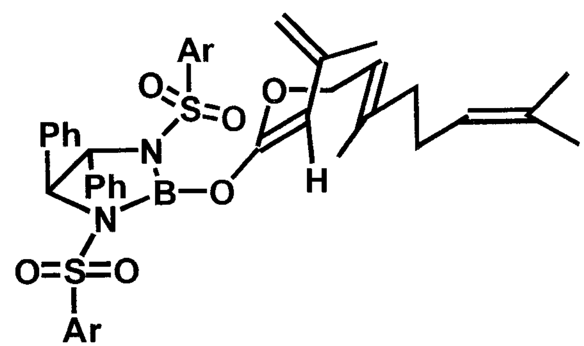
Ireland-Claisen Rearrangement





1

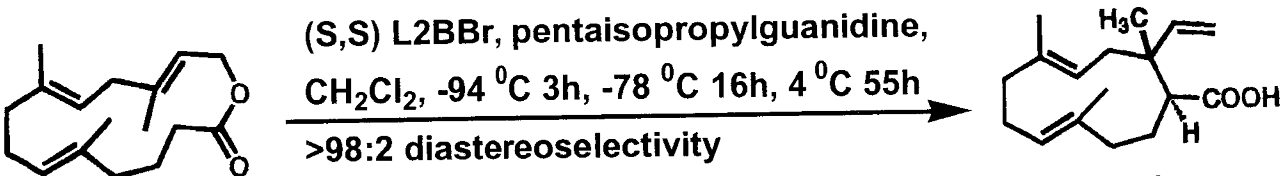
- -recyclable
- -gives very high ee's (generally >97%)
- -can change enolate preference by adjusting amine base



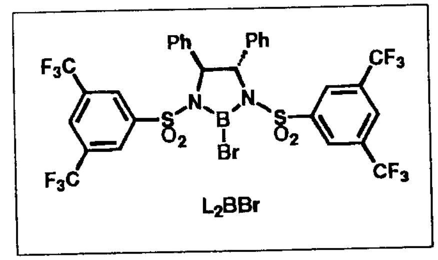
Via chair arrangement

Corey, E. J et. al. *J. Am. Chem. Soc.* **1995**, *117*, 193.

Ireland-Claisen Rearrangement- Dolabellane

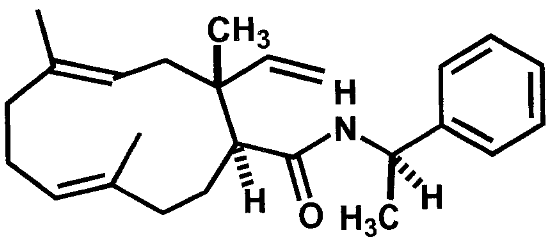


9 (86%)

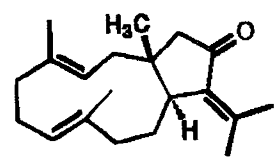


(E) form of boron enolate required

steps



Crystal structure of amide derivative

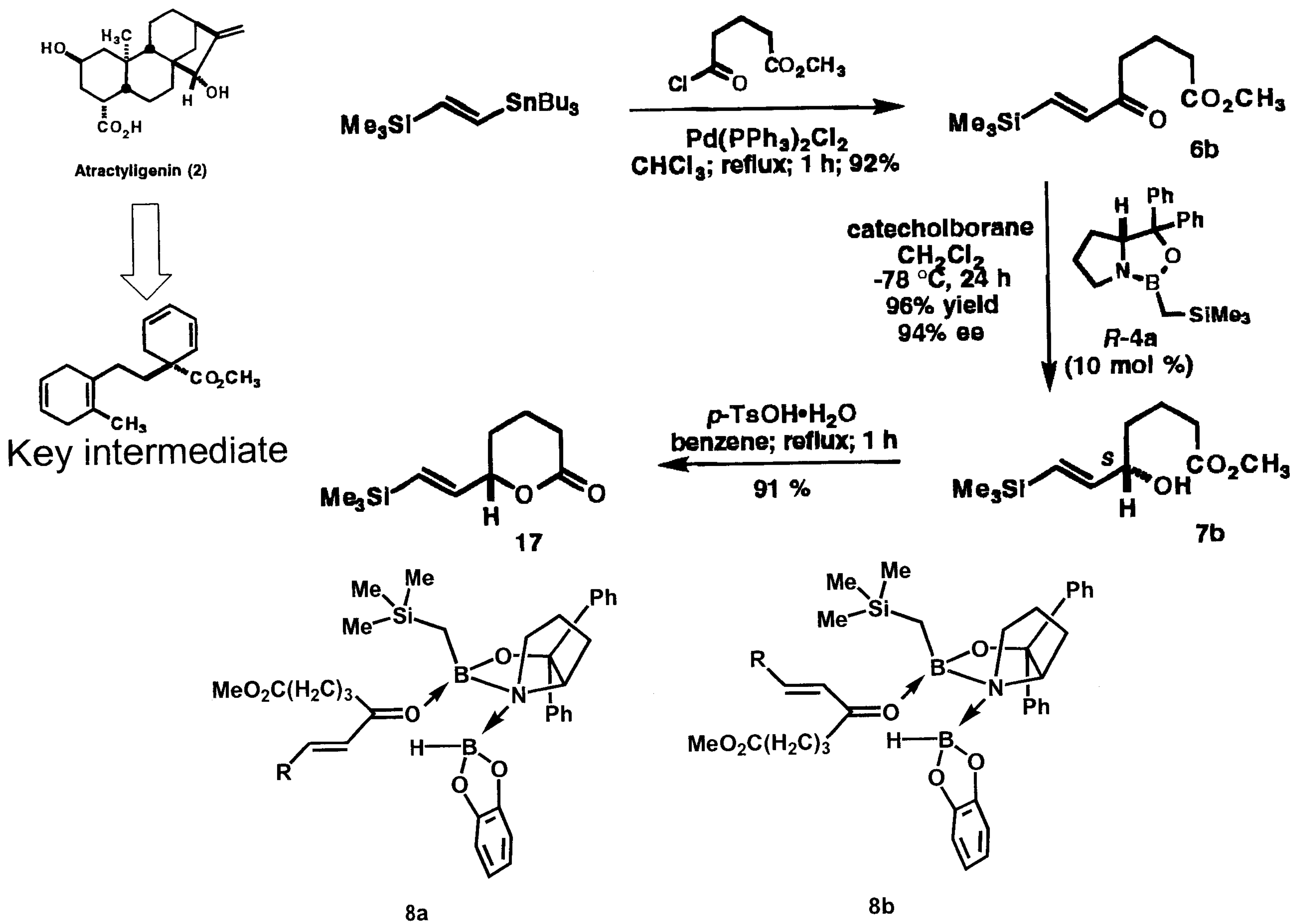


Correct structure of dolabellane established

Both enantiomers were prepared to confirm the need for structural revision

Corey, E. J; Kania, R. *J. Am. Chem. Soc.* **1996**, *118*, 1229.

Selective Reduction

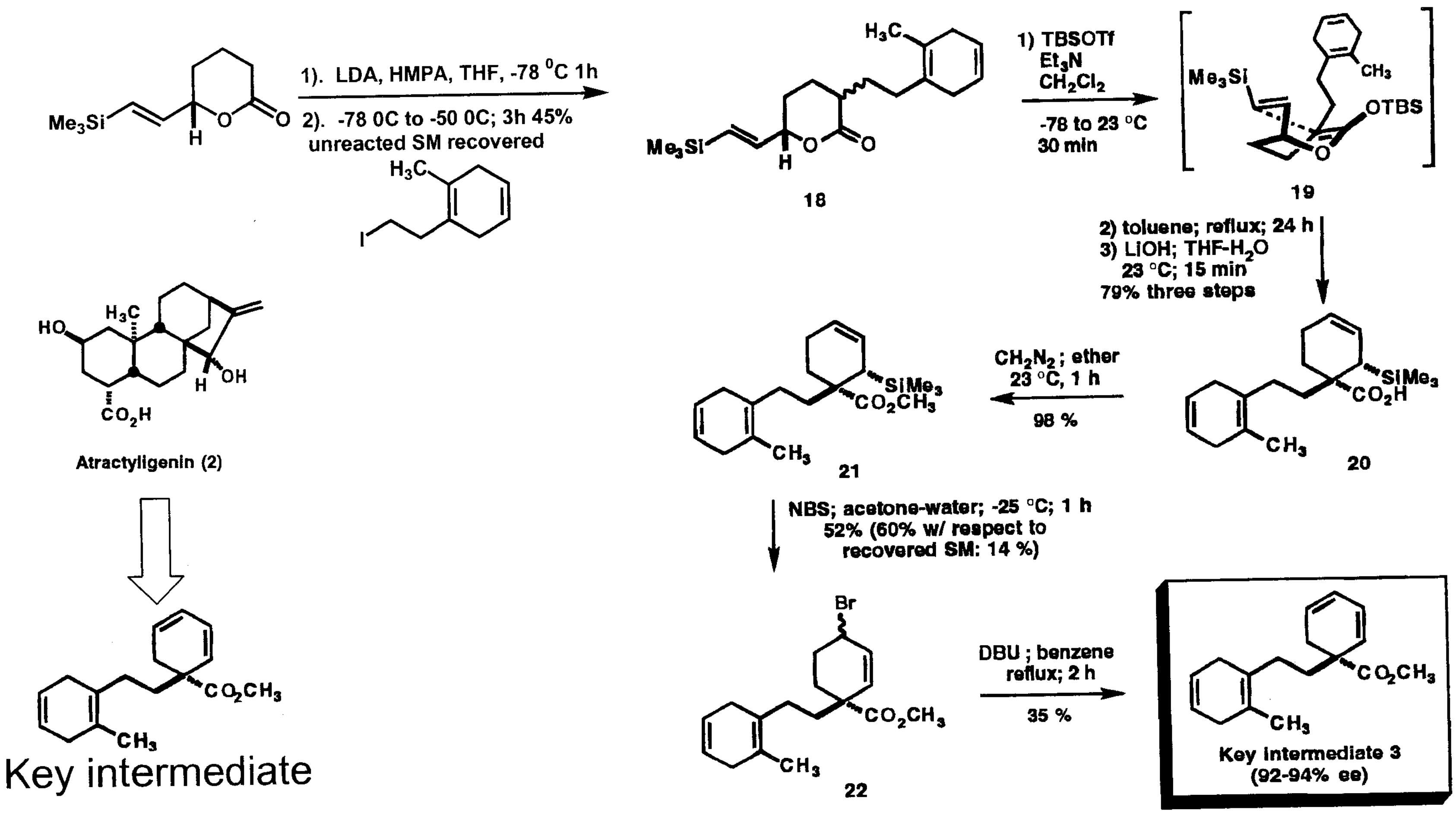


Key intermediate

Adding TMS (R) increased steric bulk to favor 8a

Corey, E. J et. al. *J. Am. Chem. Soc.* **1997**, *119*, 11769.

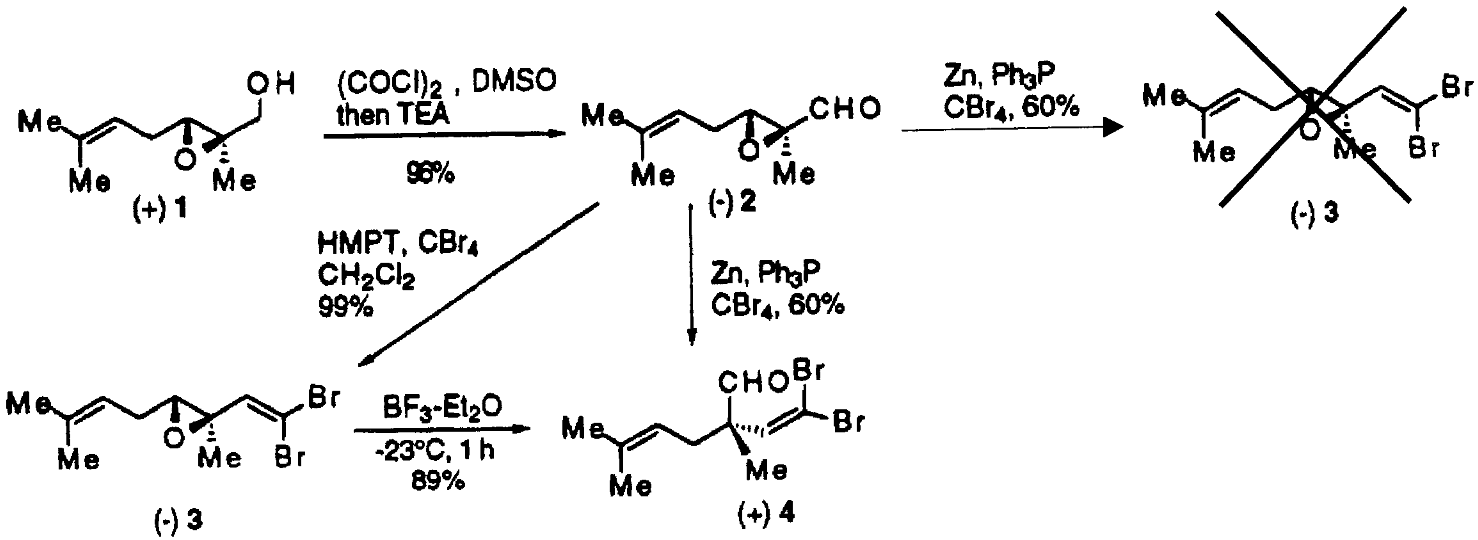
Claisen Reaction

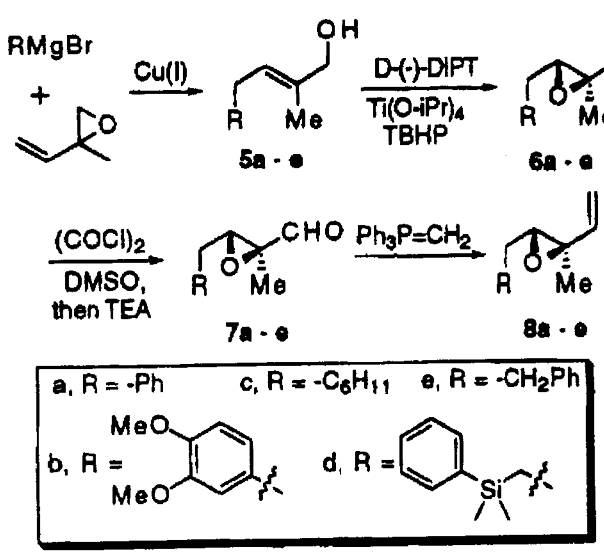


CBS reduction followed by Claisen enables the synthesis of either enantiomer

Corey, E. J et. al. *J. Am. Chem. Soc.* **1997**, *119*, 11769.

Stereospecific Rearrangement of Allylic Epoxides



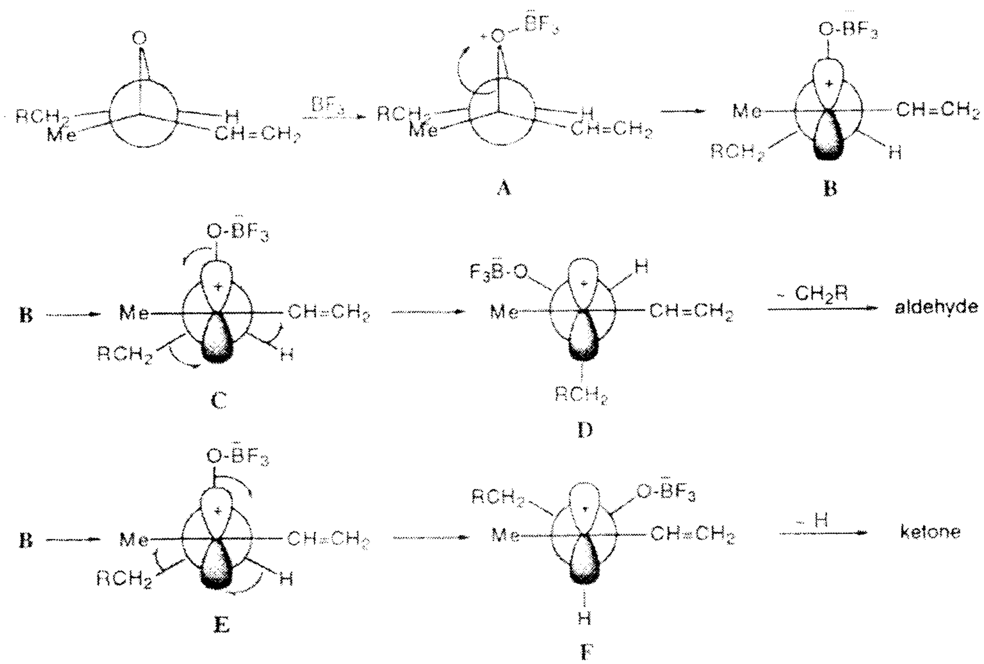


	% **5** (*E/Z*)	% **6** (% ee)	% **7**	% **8**
a	79 (94/6)	93 (92)	82	96
b	68 (95/5)	98 (94)	96	87
c	68 (96/4)	67 (90)	97	97
d	88 (96/4)	91 (96)	84	79[a]
e	87 (95/5)	89 (96)	83	88

[a] Isolated 14% of rearranged aldehyde **9d**.

Jung, M.E.; D'Amico, D. *J. Am. Chem. Soc.* **1995**, *117*, 7379.

Rearrangement Mechanism



Aldehyde product experiences H eclipsing vinyl group

Ketone product experiences alkyl eclipsing methyl group

Rearrangement proceeds well for epoxyalkenes with allylic, benzylic and silylethyl substituents >90%

Simple alkyl substituents remain problematic

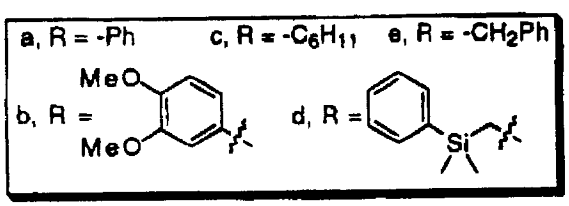
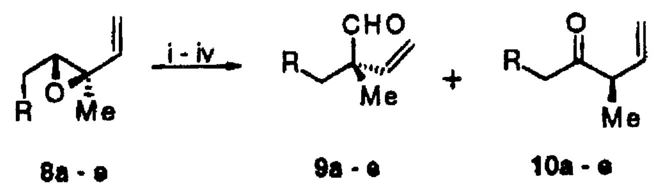


Table 2. Isolated Yields of Carbonyl Compounds

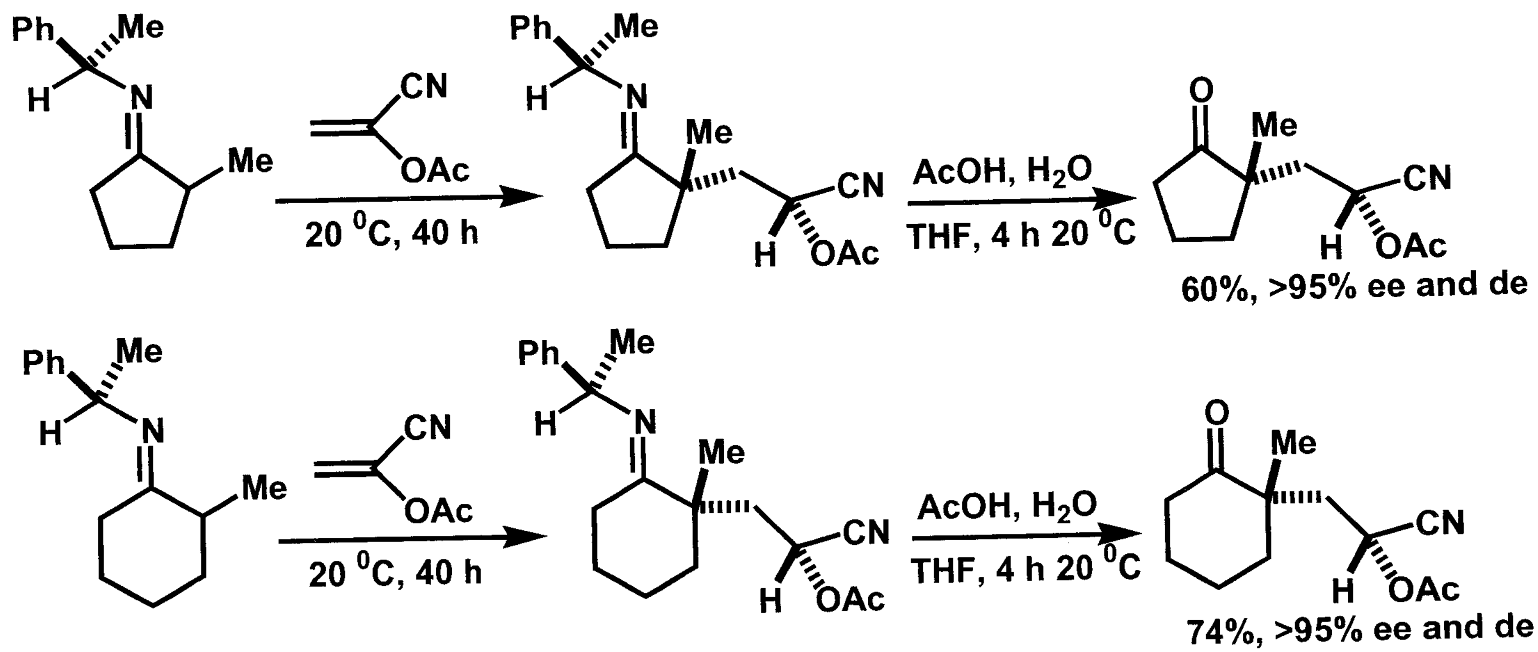


	conditions[a]	% 9	% 10
a	i	quant.	
b	i	51	
	ii	91	
c	i	53	
	iii	36	31
	iv	40	31
d	i	98	
e	i	26	21
	iv	30	48

[a] (iv) $BF_3 \cdot Et_2O$, −78 °C, 120 s. (ii) 5 M $LiClO_4$ in Et_2O, reflux. (iii) Et_2AlCl, CH_2Cl_2, −78 °C. (iv) SiO_2, sonication.

Jung, M.E.; D'Amico, D. *J. Am. Chem. Soc.* **1995**, *117*, 7379.

Enantioselective Michael Reactions



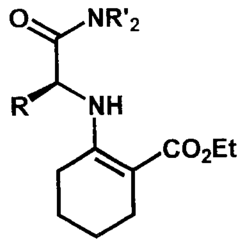
Proposed Model for Selectivity

Excellent enatio- and diastereo-selectivities afford quaternary center in moderate to good yields

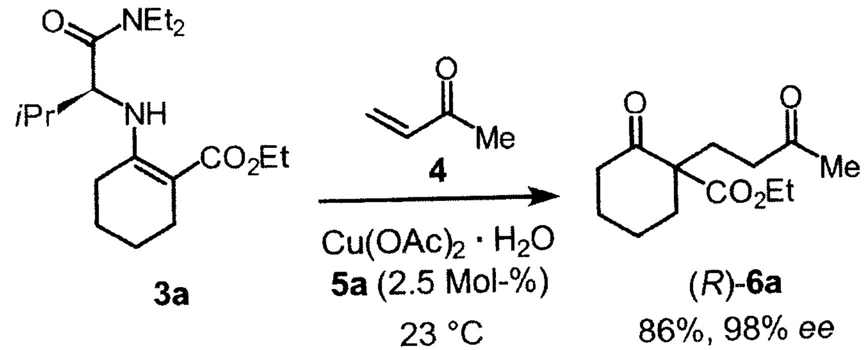
Synclinal approach
Cyano group facilitates H transfer

D'Angelo, J. et al. *Tetrahedron Lett.* **2001**, *42*, 381.

Chiral α-Amino Amide Auxiliaries



Enamine screen



enamine	R	R'
3c	*i*Pr	Allyl
3d	*i*Pr	$(CH_2)_5$
3e	*i*Bu	$(CH_2)_4$
3g	*t*Bu	Me
3h	*i*Bu	Me
3i	*s*Bu	Me

Table 1. Selected results for the screening of enaminoesters **3** with MVK (**4**) in the presence of different metal salts **5**.[a]

Enamine	*ee* (**6a**) [%][b] without metal salt	Metal salt (mol %)	*ee* (**6a**)[b] [%]	Metal salt (mol %)	*ee* (**6a**)[b] [%]
3c	28	$Cu(OAc)_2 \cdot H_2O$ (10)	59	$SnCl_2$ (5)	43
3d	47	$Cu(OAc)_2 \cdot H_2O$ (5)	57	$FeCl_3$ (5)	59
3e	53	$Cu(OAc)_2 \cdot H_2O$ (10)	73	$FeCl_3$ (5)	50
3g	78	$Cu(OAc)_2 \cdot H_2O$ (20)	86	$Cu(OTf)_2$[c] (10)	68
3h	72	$Cu(OAc)_2 \cdot H_2O$ (5)	76	$FeCl_3$ (5)	77
3i	66	$Cu(OAc)_2 \cdot H_2O$ (20)	86	$FeCl_3 \cdot 6H_2O$ (10)	73

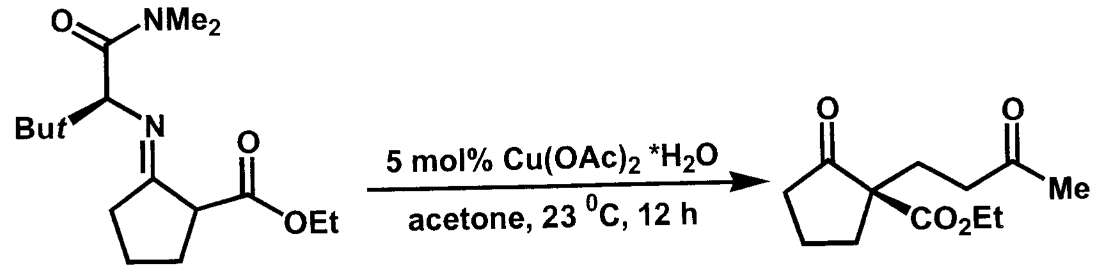
[a] Reaction conditions: Scale = approximately 0.20 mmol of **3**; **3**:**4** = 1:2; solvent = CH_2Cl_2. [b] The *ee* value of **6a** was determined by GC on a chiral phase.[15] The yields were not determined. [c] Tf = F_3CSO_2.

Copper-Catalyzed Process gives good yields and excellent enantioselectivites at rt

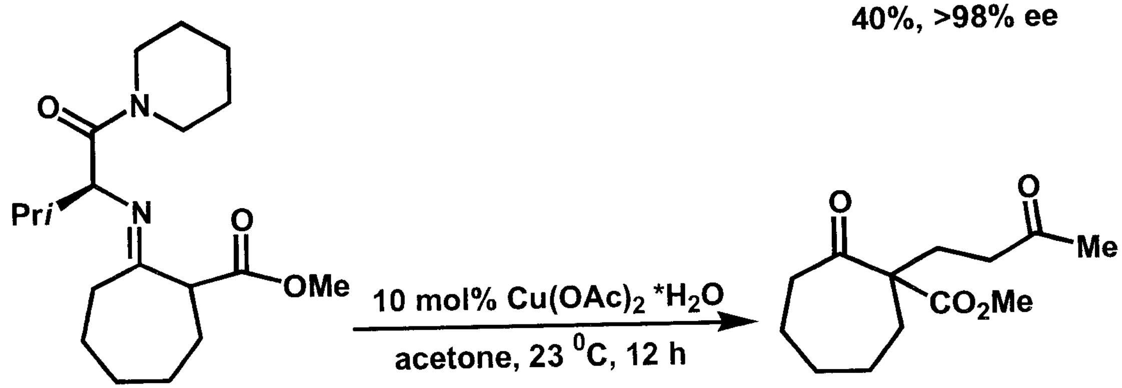
Christoffers, J.; Mann, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2753.

Chiral α-Amino Amide Auxiliaries

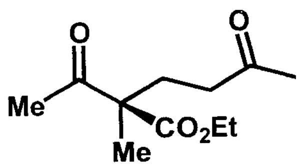
Method has been extended to 5 and 7 membered cyclic enamines



40%, >98% ee

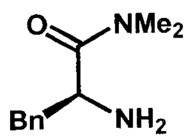


76%, 90% ee



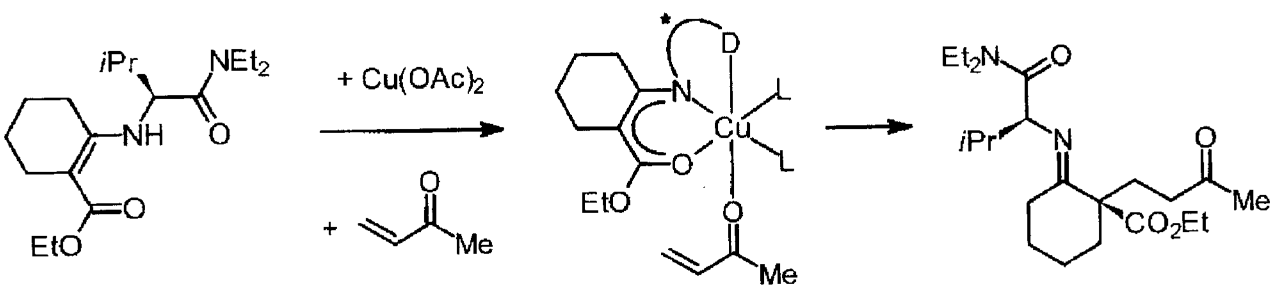
74%, 96% ee

Acyclic case as well



via

Proposed Mechanism



3db

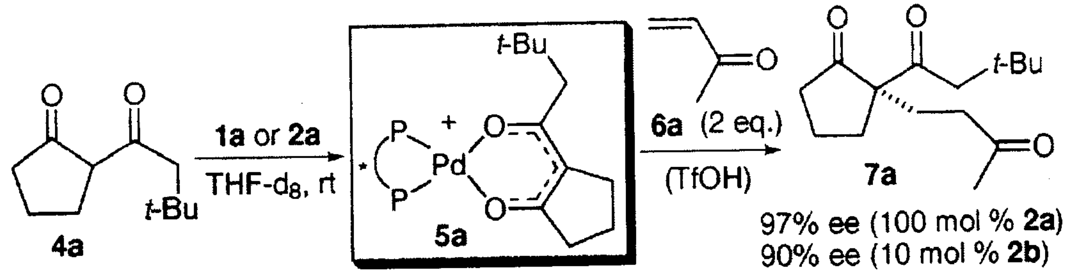
4

Tridentate ligand formed

Amide nitrogen forms chelate ring

Christoffers, J.; Mann, A. *Chem. Eur. J.* 2001, 7, 1014.

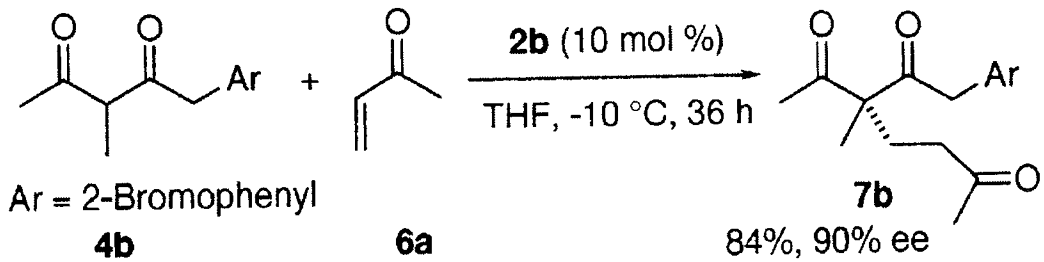
Chiral Pd Enolate Michael Addition



eq. 1

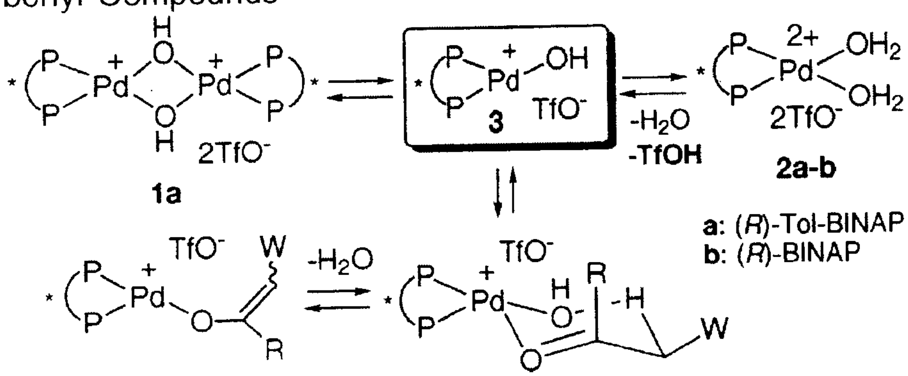
1,3 diketones used initially- not reported as a nucleophile for this reaction

TfOH required for reactivity



eq. 2

Scheme 1. Generation of PdOH and Direct Enolate Formation of Carbonyl Compounds



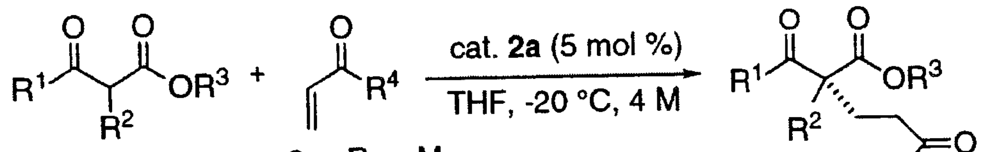
Monomeric Pd hydroxo complex with dual functions-

Lewis Acidity and Bronsted basicity

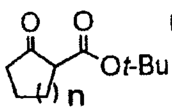
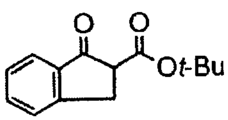
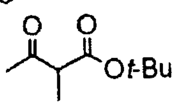
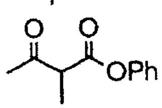
Sodeoka, M. et al. *J. Am. Chem. Soc.* **2002**, *124*, 11240.

Catalytic Enantioselective Michael Reaction With Enones- Scope

Table 1. Michael Reaction Using Various β-Ketoesters



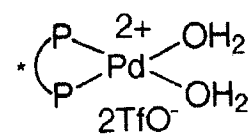
8a-e + **6a** : R_4 = Me, **6b** : R_4 = Et → **9a-g**

entry	ketoester		enone	time (h)	product	yield (%)	ee (%)	conf.
1		n = 1 : **8a**	**6a**	24	**9a**	92	92	*R*
2[a,b]		n = 2 : **8b**	**6a**	72	**9b**	92	90	*R*
3[c,d]		**8c**	**6a**	48	**9c**	88	89	-
4[a,b,c]		**8d**	**6a**	72	**9d**	88	90	-
5[b,c]		**8e**	**6a**	72	**9e**	69	93	*R*
6[e]	**8a**		**6a**	40	**9a**	93	93	-
7[a]	**8a**		**6b**	20	**9f**	84	88	-
8[a,b]	**8b**		**6b**	72	**9g**	89	86	-

[a] Catalyst **2b** was used. [b] The reaction was conducted at 0 °C. [c] 10 mol % of Pd catalyst was used. [d] 1 M **8c**. [e] 2 mol % of catalyst **2b** was used.

Reaction shows broad scope with many β-ketoesters

Tolerates cyclic as well as acylic cases all with good yields and selectivities



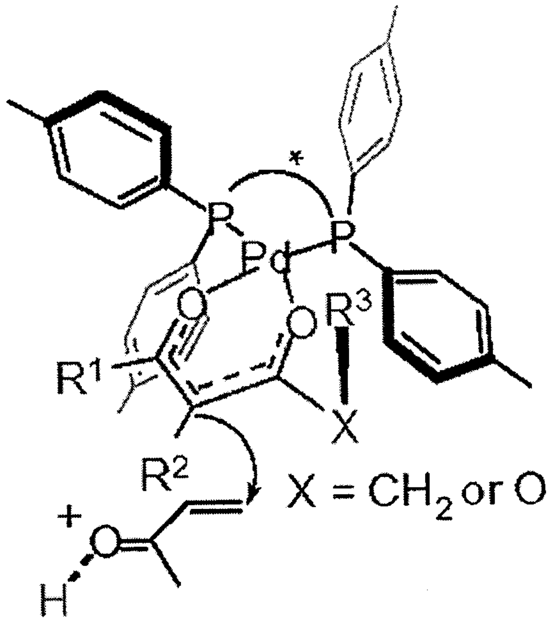
2a-b

a: (*R*)-Tol-BINAP
b: (*R*)-BINAP

catalyst

Sodeoka, M. et al. *J. Am. Chem. Soc.* **2002**, *124*, 11240.

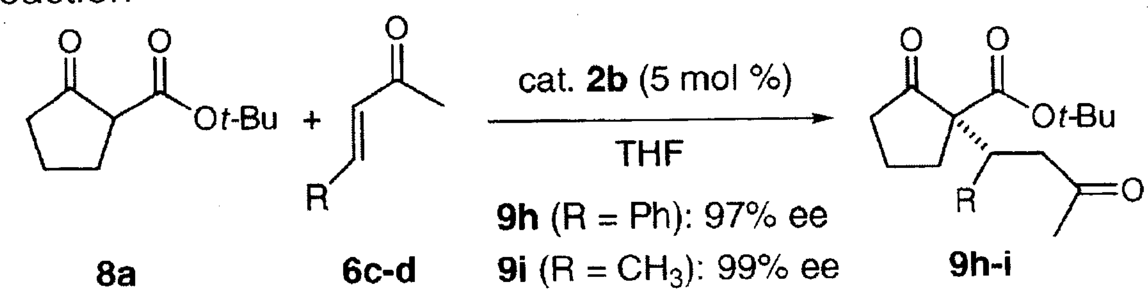
Proposed Transition State



Bulky ester group was essential for high enantioselectivity

Preferential blocking of the si face of enolate

Scheme 2. Catalytic Diastereo- and Enantioselective Michael Reaction



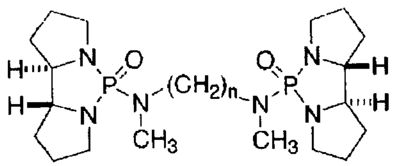
9h 83% yield dr (3.6/1) 36h

9i 89% yield dr (8/1) 24h

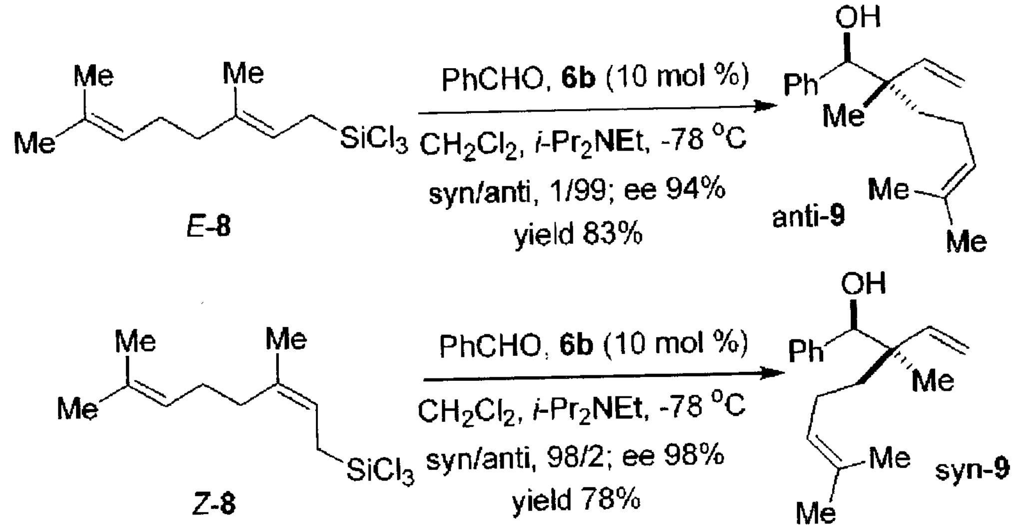
Sodeoka, M. et al. *J. Am. Chem. Soc.* **2002**, *124*, 11240.

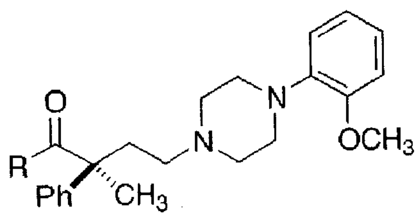
Chiral Lewis-Base Method

Chiral Catalyst



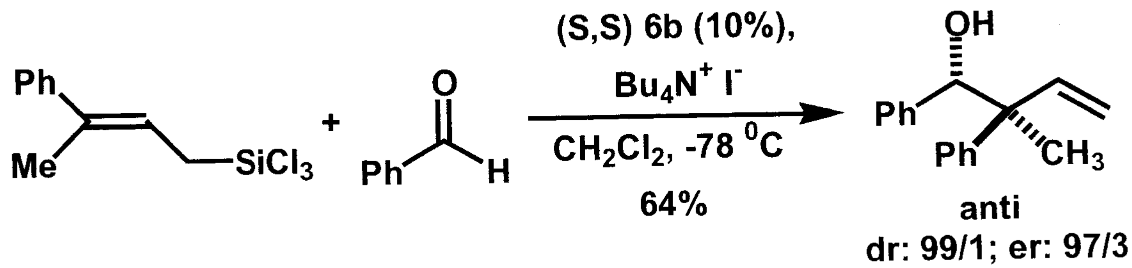
R,R Bisphosphoramide





LY426965

Synthesis of Seratonin Antagonist LY426965:



Denmark, S. E.; J et. al. *J. Am. Chem. Soc.* **2001**, *123*, 9488.

Conclusions

- The use of chiral nucleofuges can provide good yields and selectivities, but requires stoichiometric chiral material not encorporated in the final product.

The Claisen rearrangement remains a useful way to establish a quaternary center and has been demonstrated with many examples.

Sharpless Asymmetric Epoxidation coupled with the LA catalyzed rearrangement affords good yields of aldehydes with α-quaternary centers.

Much progress has been made very recently in the enantioselective Michael Reaction.

Catalytic enantioselective allylation to form quaternary centers has been demonstrated to proceed with good yields and selectivities.