

Asymmetric Carbometalation of Unactivated Olefins (‘Negishi Carboalumination’)



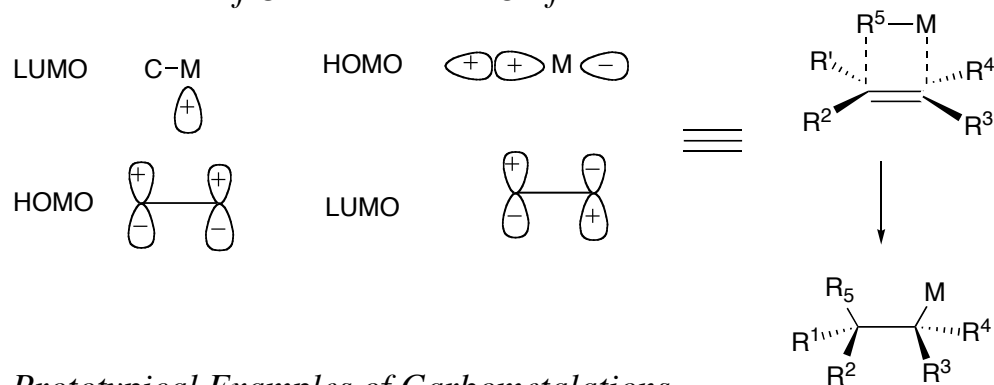
References

- 1] Negishi, E.; Kondakov, D.Y., *J.Am.Chem.Soc.***1995**, *117*, 10771
- 2] Negishi, E.; Kondakov, D.Y., *J.Am.Chem.Soc.***1996**, *118*, 1577
- 3] Negishi, E.;Kondakov, D.Y., *Chem.Soc.Rev.***1996**, 417
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- 7] Negishi,E.; Huo, Shouquan., *Pure and Appl.Chem.***2002**, *74*, *1*, 157
- 8] Negishi, E.; Tan, Ze.; Liang, Bo.; Novak, T., *Proceedings.Natl.Acad.Sci.***2004** “Special Feature Article”*101*, *16*, 7582
- 9] Negishi, E.; Tan, Ze., *Angew.Chem.Int. Ed.***2004**, *43*, 2911
- 10] Negishi, E.; Liang, Bo.; Tan, Ze.; Lachaux, Marina Magnin., *Org.Lett.***2004**, *6*, 1425
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- 12] Wipf, P.; Ribe, S., *Org.Lett.***2001**, *3*, 1503
- 13] Ribe, S.; Kondru, R.K.; Beratan, D.N.; Wipf, P., *J.Am.Chem.Soc.***2002**, *122*, 4608



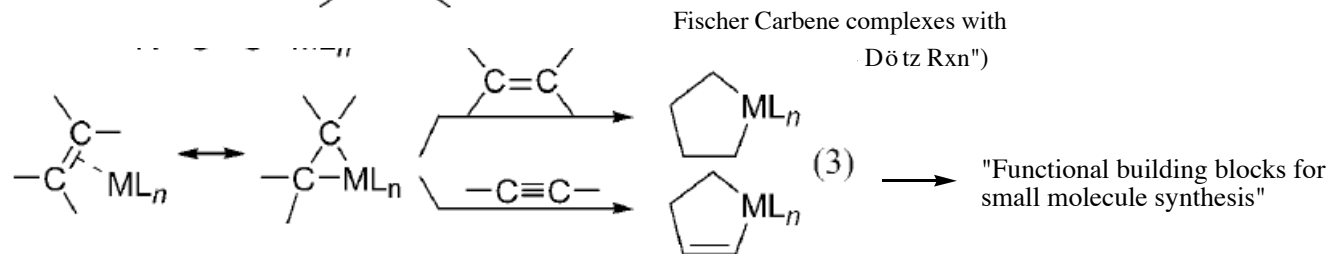
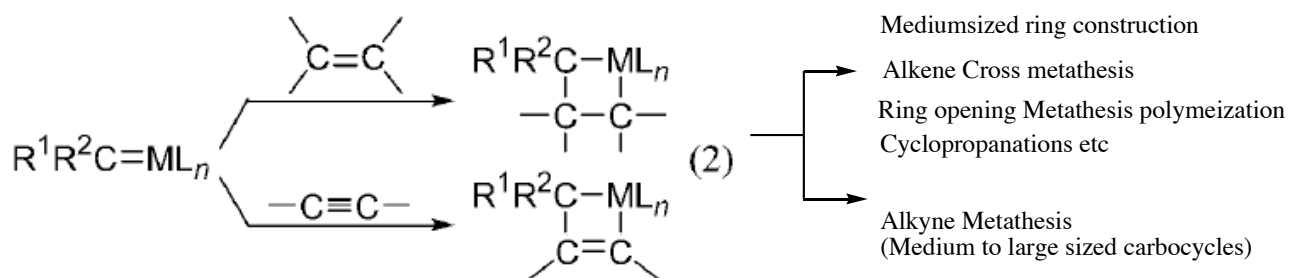
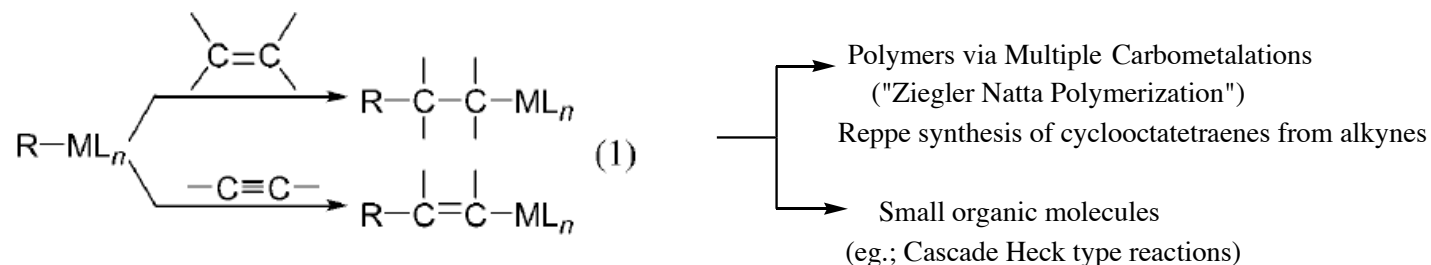
Carbometalation

Interaction of C-M Bond with Olefin



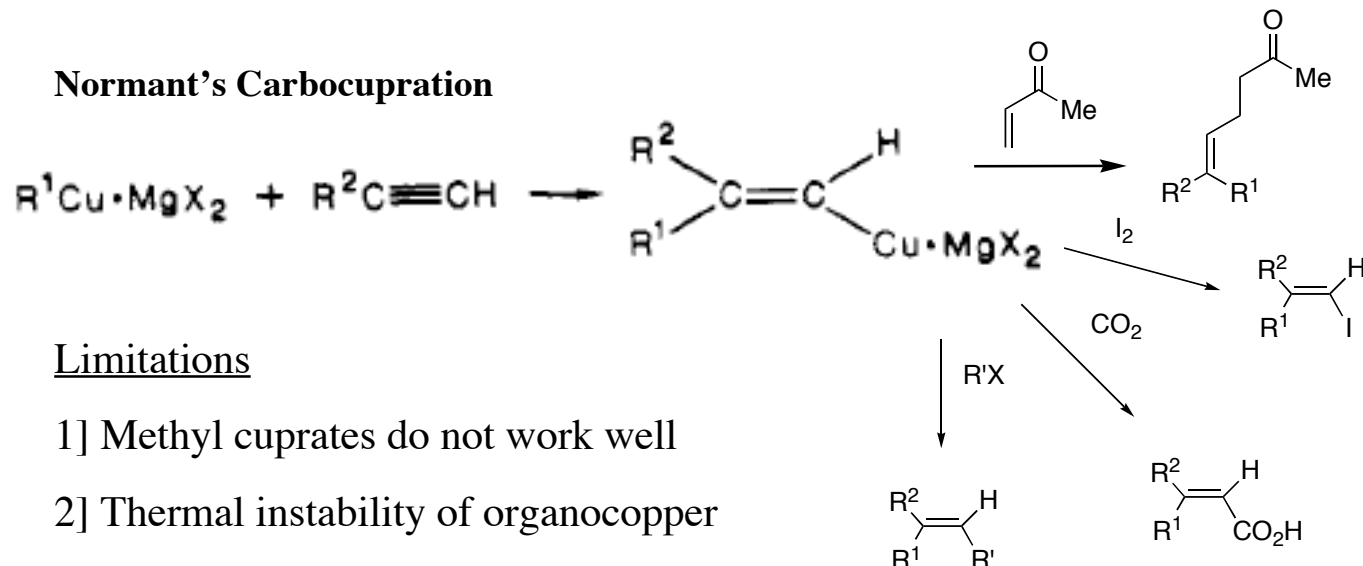
- ❑ 4 center "Cis" addition of R-M to olefin
- ❑ Two contiguous stereocenters are created on planar olefinic bond
- ❑ Same mechanism operative for addition to alkynes and also for Hydrometallations

Prototypical Examples of Carbometalations



Alkyne Carbometalations

Normant's Carbocupration



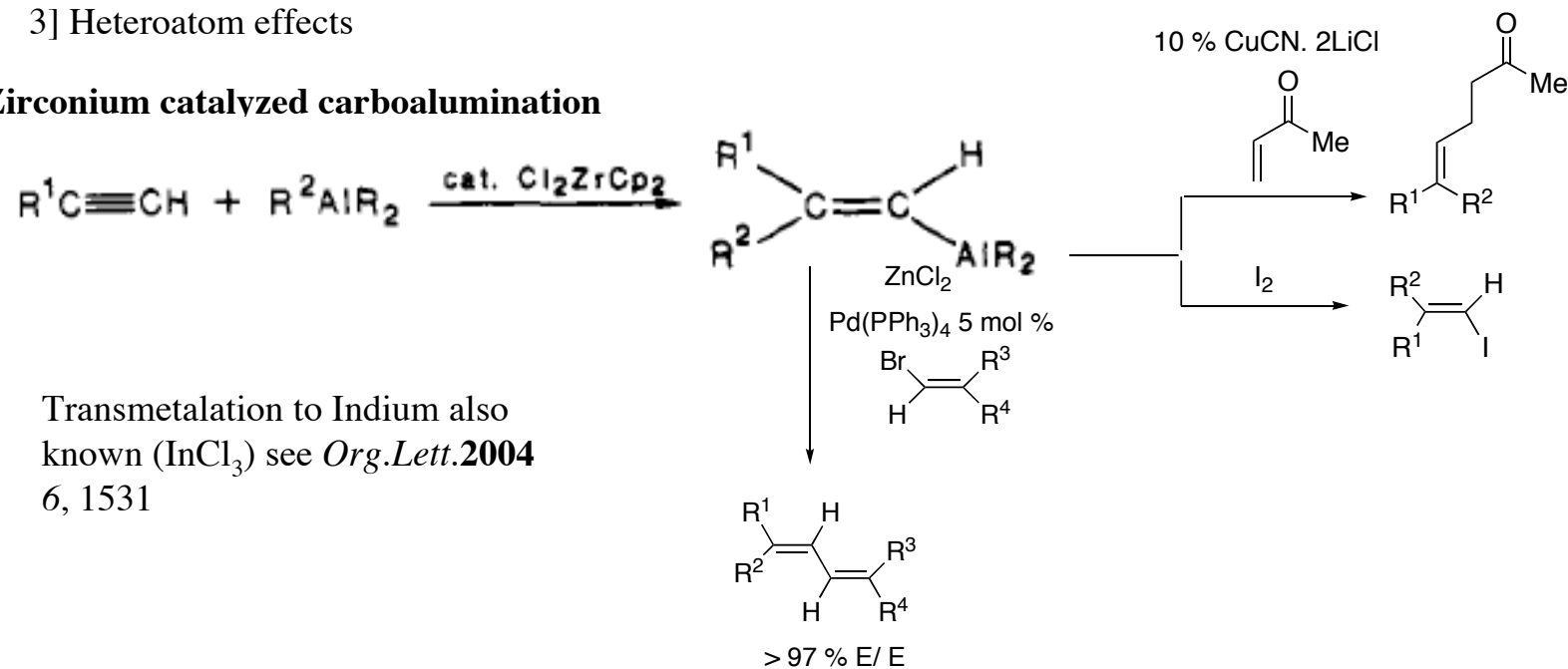
Limitations

- 1] Methyl cuprates do not work well
- 2] Thermal instability of organocopper

Reagents

- 3] Heteroatom effects

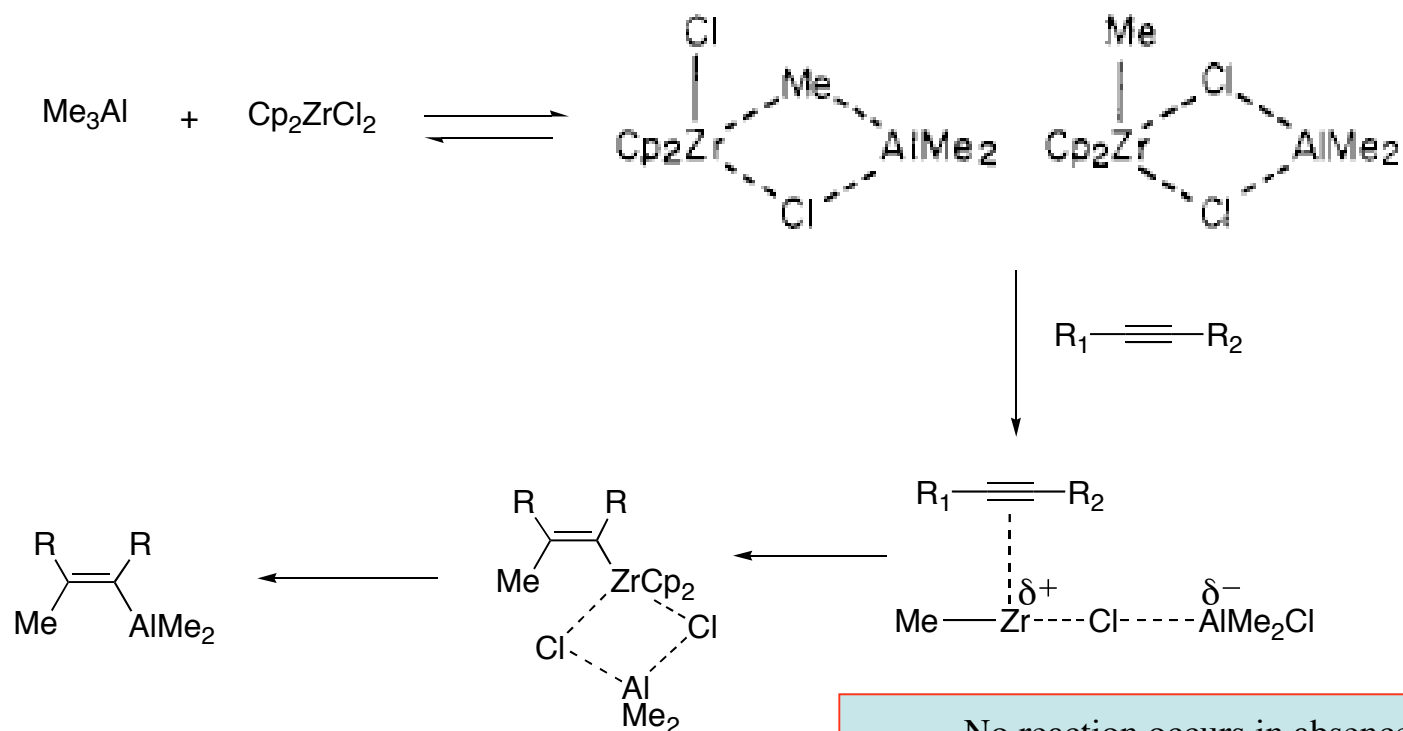
Zirconium catalyzed carboalumination



Transmetalation to Indium also known (InCl₃) see *Org.Lett.* **2004** 6, 1531

Zr catalyzed carboalumination (Bimetallic catalysis)

Zirconium assisted methyl alumination

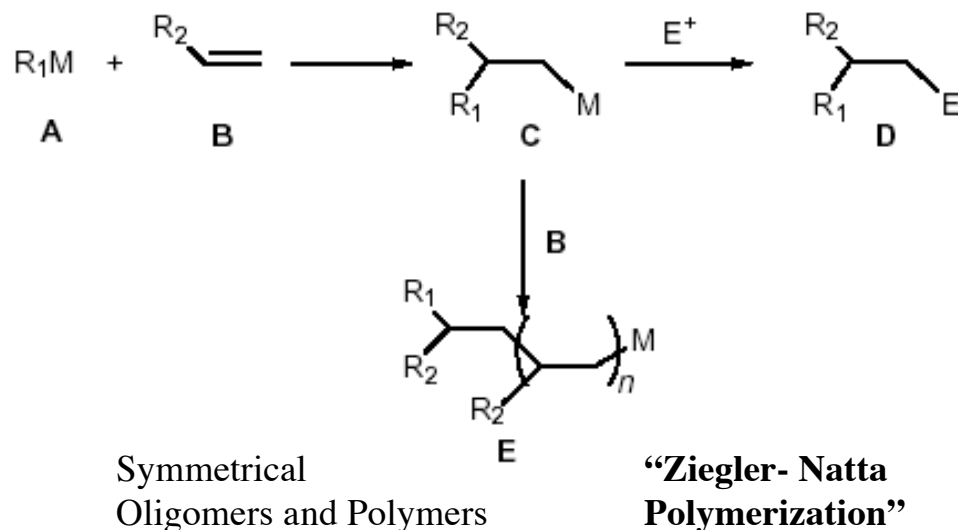


Negishi, E.; Yoshida, T., *J. Am. Chem. Soc.* **103**, 4985

No reaction occurs in absence of either Reagent
 ^1H NMR of (1:1) mixture in 1,2 - DCE at rt δ -0.41(9H), 6.3 ppm (5H) broad
Quenching with THF (THF/ Me_3Al = 1:1) 0.17, -0.81, -1.03 (3H each)
Two Cp signals δ 6.37, 6.14
No Me-Cl exchange occurs between $\text{Me}_2\text{AlCl} + \text{Cp}_2\text{ZrCl}_2$, $\text{Me}_3\text{Al} + \text{Me}(\text{Cl})\text{ZrCp}_2$, $\text{Me}_3\text{Al} + \text{Me}_2\text{ZrCp}_2$

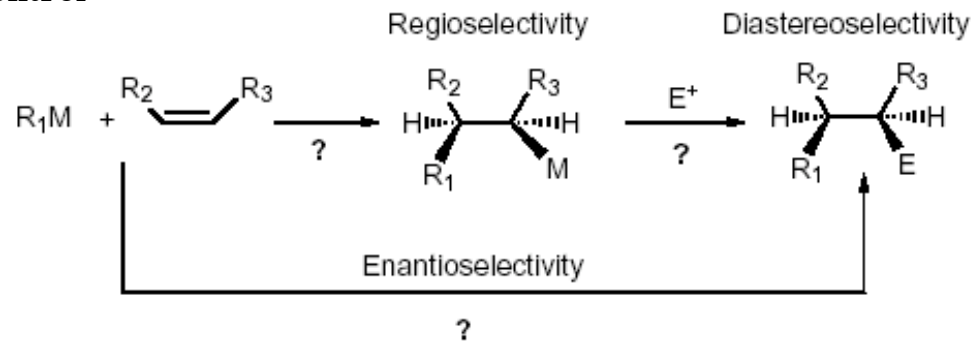
Controlled Olefin Carbometalation as Useful Tool in Natural Product Synthesis

Principle



The reactivity of the new σ - alkyl metal species C must be lesser than A to avoid undesired polymerization
 Proper choice of metal and ligands essential


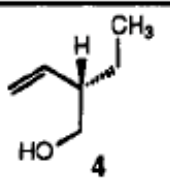

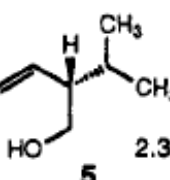
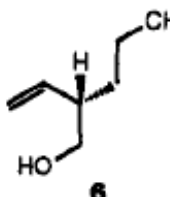
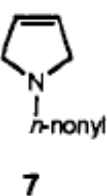
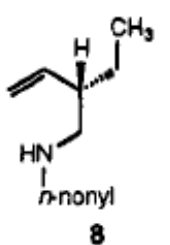
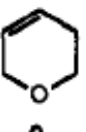
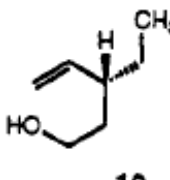
Regio and Stereocontrol



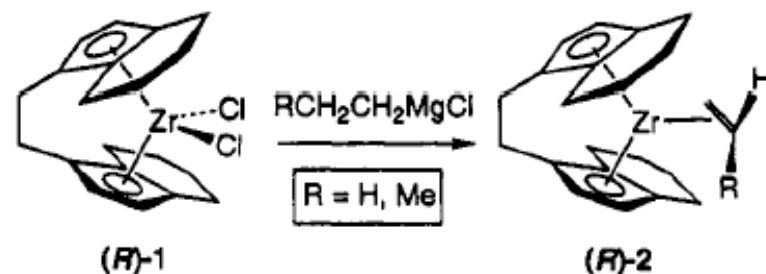
Scheme 2

Enantioselective Ethyl Magnésation of Allyl ethers

Table I. Enantioselective Carbomagnesation of Cyclic Alkenes^a

entry	substrate	Grignard reagent	product	ee (%) ^b	yield (%) ^c
1		EtMgCl		>97	65
2		<i>n</i> -PrMgCl	  2.3 : 1	>95	40
3		EtMgCl ^d		>95	75
4		EtMgCl		95	73 ^e

^a Reaction conditions: 10 mol % (*R*)-1, 5.0 equiv of alkylMgCl, THF, 25 °C, 6–12 h. ^b Enantiomeric excess determined by GLC (BETA-DEX 120 chiral column by Supelco, entries 1, 4–6) or analysis of the 300-MHz ¹H NMR spectrum of the derived (*S*)-MPTA esters in comparison with authentic enantiomers and authentic racemic material (see supplementary material). ^c Isolated yields of purified products. ^d Reaction run at 4 °C for 12 h. ^e In addition, 10–15% of starting material was recovered.

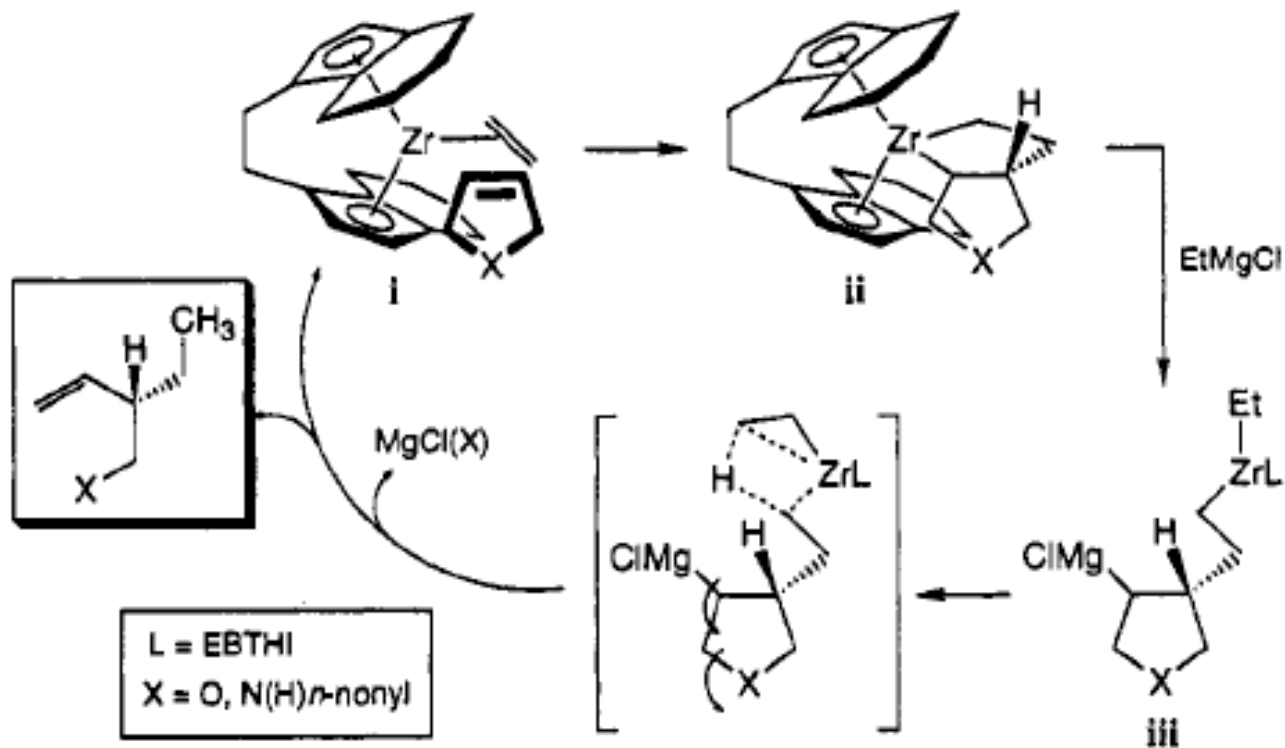


(*R*)-1 = Ethylene- bis-(tetrahydroindenyl zirconium Dichloride (ETBHI))

Morken, J.P.; Didiuk, M.T.; Hoveyda, A.H., *J. Am. Chem. Soc.* **1993**, *115*, 6997

Mechanism

Scheme I



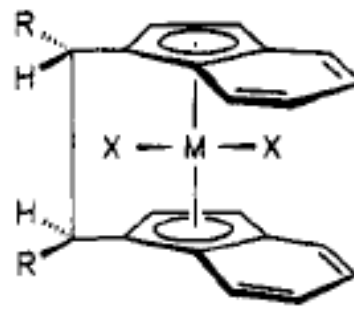
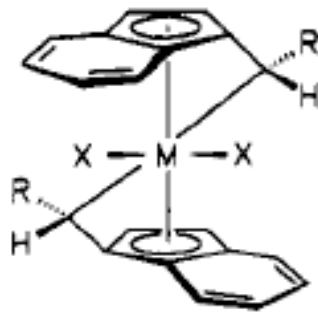
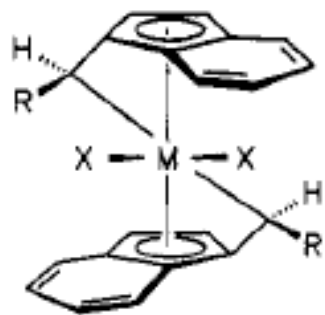
Long chain alkyl magnesium halides can also be used but afford products with varying levels of regio and diastereoselectivity. Diastereoselectivity arises due to two isomeric forms of metal olefin complex (syn or anti)

Also employed in kinetic resolution of unsaturated heterocycles. % ee at 56-63 % conversion = 94 - 99%

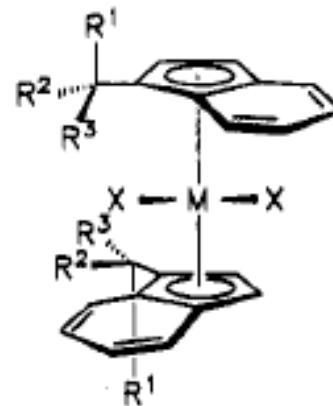
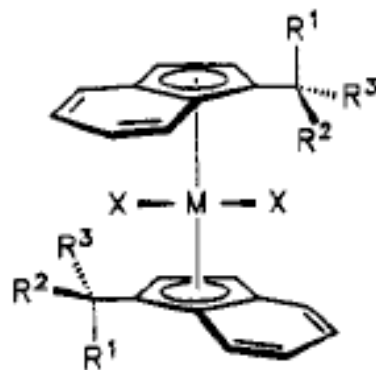
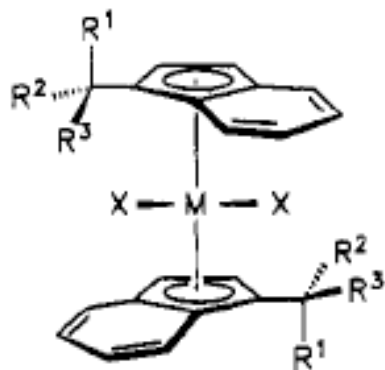
Morken, J.P.; Didiuk, M.T.; Hoveyda, A.H., *J.Am.Chem.Soc.* **1993**, *115*, 6997

Also see Hoveyda, A.H.; Heron, N.M., “*Comprehensive Asymmetric Catalysis*”
Vol.1, **1999**, Chapter 13, 431-452

Isomers of Bridged and non bridged ansa-metallocenes



Bridged ansa metallocenes
very rigid and rotation
about metal -Cp axis leading
to torsional deformation very
restricted



Open-bridged metallocenes
Low torsional energy barriers
rotation about metal -indenyl
vector unhindered

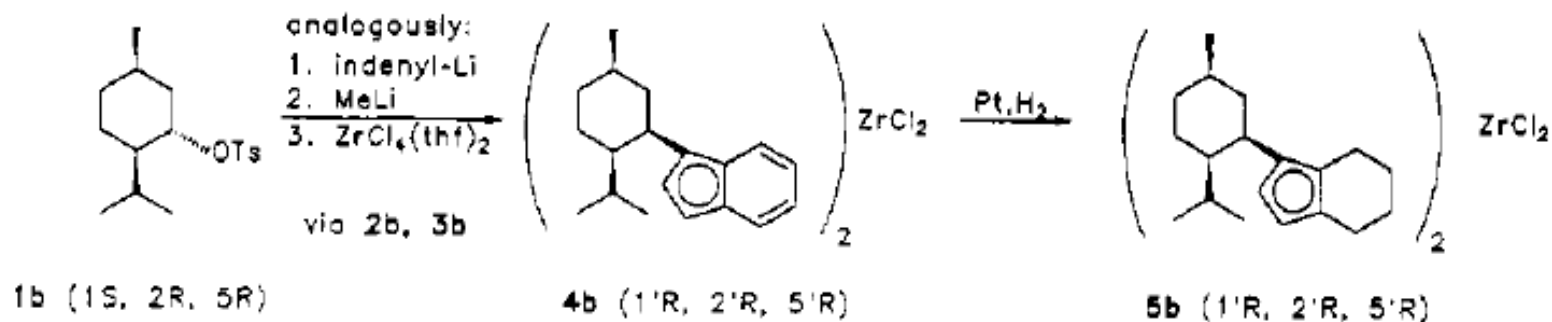
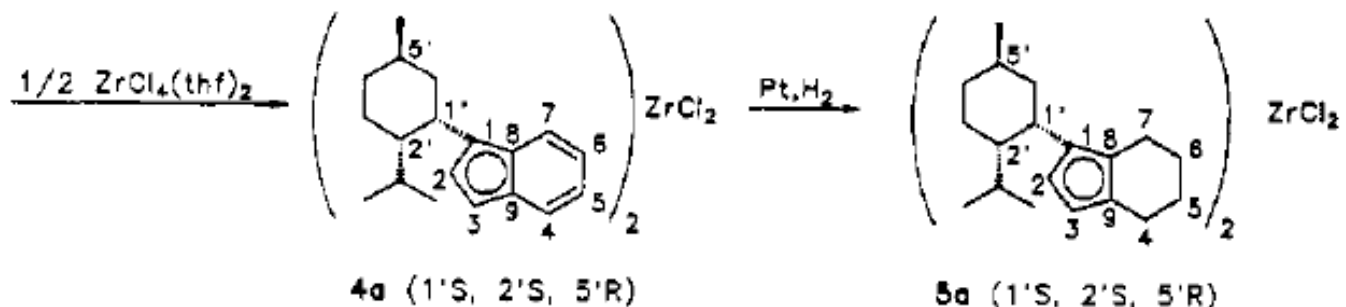
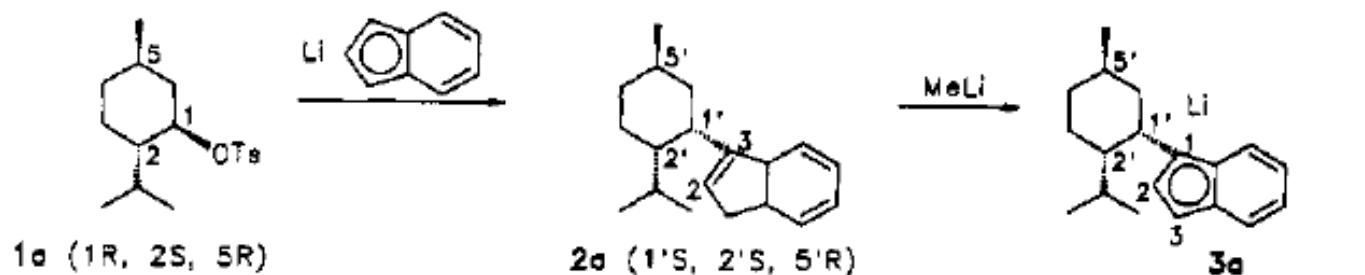
$R^*, p-R^*, p-R^*, R^*$
 (*racem-like-A*)

$R^*, p-S^*, p-S^*, R^*$
 (*racem-like-B*)

$R^*, p-R^*, p-S^*, R^*$
 (*meso-like-C*)

For nomenclature of Cp rings see Schlögl, K in "Topics in Stereochemistry" **1967**, *1*, 39
 Erker, G.; Aulbach, M.; Knickmeier, M.; WingberMühle, D.; Krüger, C.; Nolte, M.; Werner, S., *J. Am. Chem. Soc.* **1993**,
115, 4590

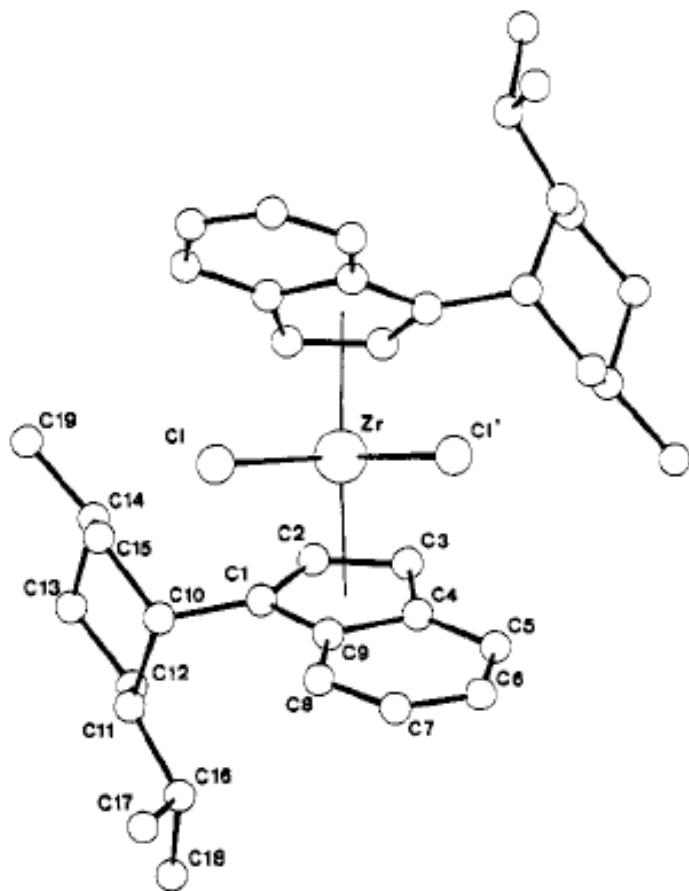
Bis-(1-neomenthylindenyl) and Bis-(1-neoisomenthyl indenyl)-zirconium dichloride (Erker's Catalysts) - Preparation



Ratio of 4a-A / 4a-B / 4a-C = 93/2/5 After crystallization 60 % yield of 4a-A

Ratio 4b-A / 4b-B / 4b-C = 82 / 7 / 11 After crystallization 25 % yield of 4b - A

X-ray Structure



Zr - pseudo tetrahedral geometry (Cl - Zr - Cl angle = 91.6°, Cp - Zr - Cp = 129.6°)

Zr atom at two fold rotation axis

All metal-sp² carbon bond lengths not equidistant

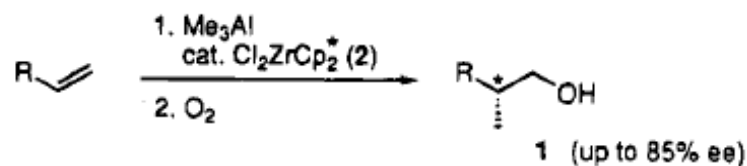
All C-C bond lengths in Cp higher than typical bond lengths of 1.32 Å

Large group at C1 and coordination of bulky M-center to Cp ring results overall in distortion of bond lengths

Indenyl ligand oriented axially at cyclohexane chair of substituent, *i*-Pr and methyl groups in equatorial position

C₂ - symmetric bent metallocene conformation. Neomenthyl substituents oriented toward lateral sectors of bent metallocene

Zr-catalyzed Asymmetric Methyl almination of alkenes



Stereochemical Model

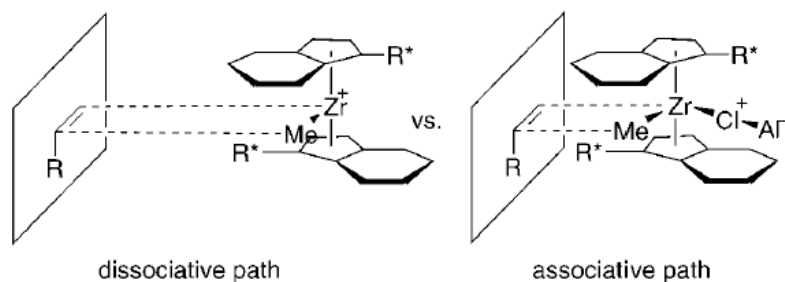


Table 1. Zirconium-Catalyzed Methylalmination of Monosubstituted Alkenes^a

substrate	time, h	product	yield, ^b %	ee, %
	12		88	72
	12		92	74
	12		80	65
	24		77	70
	528		30	85
	12		81	74
	12 ^c		79	75
	96 ^d		68	71

^a The reactions were run using 8 mol % of **2** and 1 equiv of Me₃Al in 1,2-dichloroethane at 22 °C. ^b Isolated yields. ^c Three-fold excess of Me₃Al was used. ^d Two-fold excess of Me₃Al was used.

The observed ee's are consistent with Zr catalyzed methyl almination than direct carboalumination

Other catalysts such as Neoisomenthyl indenyl zirconium dichloride, Neomenthyl tetrahydroindenyl zirconium dichloride, Neoisomenthyl Tetrahydroindenyl zirconium dichloride, Neoisomenthyl zirconium BINOL gave low ee's.

Negishi, E.; Kondakov, D.Y.,
J. Am. Chem. Soc. **1995**, *117*, 10771

Solvent and Temperature effects in Alkyl aluminations

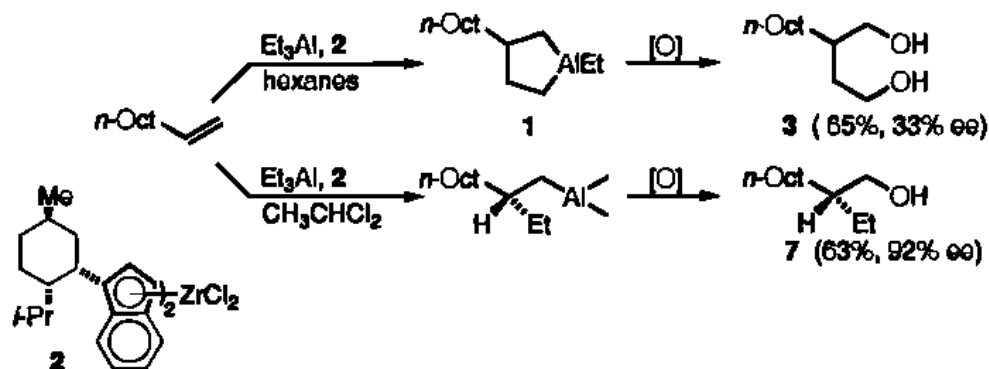


Table 1. Zirconium-Catalyzed Alkylaluminumation of Monosubstituted Alkenes^a




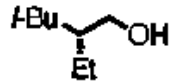

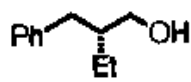

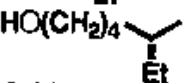

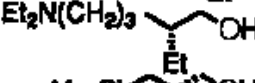



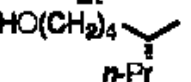

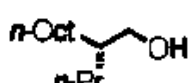

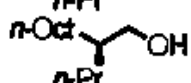
substrate	R of R_3Al	solvent	temp °C	time h	quenching agent	product	yield ^b %	%ee
<i>n</i> -Bu	Et	$(\text{CH}_2\text{Cl}_2)_2$	25	4	O_2	<i>n</i> -Bu-CH(OH)-CH ₂ -Et	65	68
<i>n</i> -Bu	Et		25	4	O_2	<i>n</i> -Bu-CH(OH)-CH ₂ -Et	70	68
<i>n</i> -Bu	Et		25	4	O_2	<i>n</i> -Bu-CH(OH)-CH ₂ -Et	72	67
<i>n</i> -Bu	Et	CH_2Cl_2	25	6	O_2	<i>n</i> -Bu-CH(OH)-CH ₂ -Et	57	81
<i>n</i> -Bu	Et	CH_2Cl_2	0	6	O_2	<i>n</i> -Bu-CH(OH)-CH ₂ -Et	63	92
<i>n</i> -Bu	Et	CH_2Cl_2	-25	6	O_2	<i>n</i> -Bu-CH(OH)-CH ₂ -Et	60	94
<i>n</i> -Bu	Et	CH_3CHCl_2	25	6	O_2	<i>n</i> -Bu-CH(OH)-CH ₂ -Et	70	86
<i>n</i> -Bu	Et	CH_3CHCl_2	0	24	O_2	<i>n</i> -Bu-CH(OH)-CH ₂ -Et	74	93

^a The reactions were run using 8 mol % of **2** and 1 equiv of R_3Al , unless otherwise stated. ^b Isolated yields. ^c Three-fold excess of R_3Al was used. ^d Two-fold excess of R_3Al was used.

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*J.Am.Chem.Soc.***1996**, *118*, 1577

Higher Alkyl aluminations

Table 1. Zirconium-Catalyzed Alkylaluminumation of Monosubstituted Alkenes^a

substrate	R of R ₃ Al	solvent	temp °C	time h	quenching agent	product	yield ^b %	%ee
<i>n</i> -Oct 	Et	CH ₃ CHCl ₂	0	12	O ₂	<i>n</i> -Oct 	64	92
<i>t</i> -Bu 	Et	CH ₃ CHCl ₂	0	24	O ₂	<i>t</i> -Bu 	77	90
Ph 	Et	CH ₃ CHCl ₂	0	24	O ₂	Ph 	69	93
HO(CH ₂) ₄ 	Et ^c	CH ₃ CHCl ₂	10	24	HCl	HO(CH ₂) ₄ 	88	90
Et ₂ N(CH ₂) ₃ 	Et ^d	CH ₃ CHCl ₂	25	72	O ₂	Et ₂ N(CH ₂) ₃ 	56	95
	Et	CH ₃ CHCl ₂	0	24	O ₂		56	96
HO(CH ₂) ₄ 	<i>n</i> -Pr ^e	CH ₃ CHCl ₂	10	24	HCl	HO(CH ₂) ₄ 	90	91
<i>n</i> -Oct 	<i>n</i> -Pr	CH ₃ CHCl ₂	0	12	O ₂	<i>n</i> -Oct 	62	91
<i>n</i> -Pr 	<i>n</i> -Oct	CH ₃ CHCl ₂	0	12	O ₂	<i>n</i> -Pr 	59	85

^a The reactions were run using 8 mol % of **2** and 1 equiv of R₃Al, unless otherwise stated. ^b Isolated yields. ^c Three-fold excess of R₃Al was used. ^d Two-fold excess of R₃Al was used.

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Water as Additive in Alkene Carbometalations

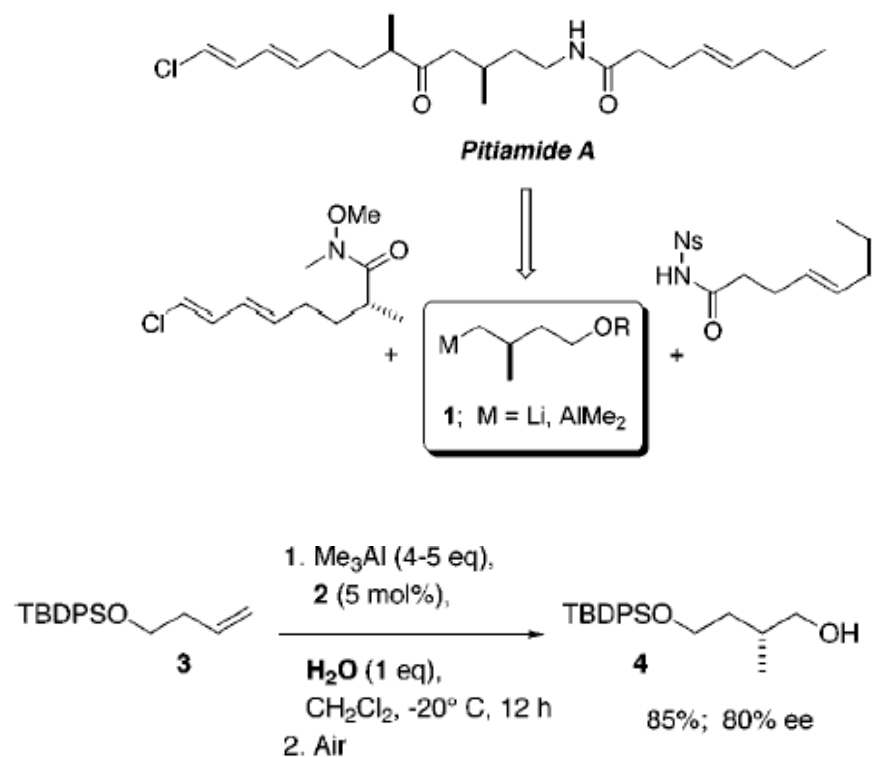
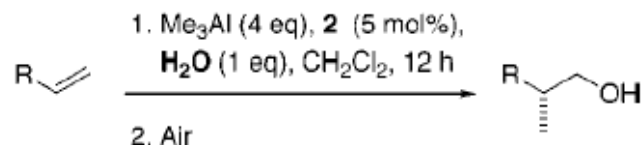


Table 1. Water-Accelerated Methylalumination of α -Olefins⁸



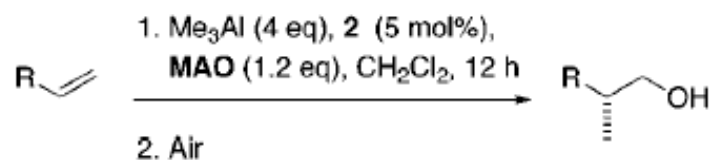
entry	<i>T</i> (°C)	product, R	yield ^a (%)	ee (%)
1	-20	5 , TBDPSO(CH ₂) ₄	73	75 ^c
2	-20	6 , CH ₃ (CH ₂) ₅	35	76 ^d
3	-20	7 , HO(CH ₂) ₄	45	86 ^d
4	-20	8 , <i>c</i> -C ₆ H ₁₁	94	55 ^d
5	-20	9 , Ph	20	89 ^d
6	-5	9 , Ph	73	89 ^d
7	0	10 , 4-Cl-Ph	76 ^b	90 ^c

^a Isolated yields. ^b Yield obtained after 24 h. ^c Determined by chiral HPLC (Chiralcel OD). ^d Determined by Mosher ester analysis (¹H NMR).

No reaction occurs in the absence of water as additive

Methyl aluminumoxane as additive - Comparison of MAO vs Water in Rate Acceleration

Table 2. MAO-Accelerated Methylalumination of α -Olefins¹⁴



entry	<i>T</i> (°C)	product, R	yield ^a (%)	ee (%)
1	-20	4 , TBDPSO(CH ₂) ₂	46	79 ^c
2	-20	4 , TBDPSO(CH ₂) ₂	88 ^b	80 ^c
3	-20	5 , TBDPSO(CH ₂) ₄	50	82 ^c
4	0	5 , TBDPSO(CH ₂) ₄	83	81 ^c
5	-20	6 , CH ₃ (CH ₂) ₅	78 ^b	81 ^d
6	-20	8 , <i>c</i> -C ₆ H ₁₁	82 ^b	74 ^d

^a Isolated yields. ^b Yield obtained after 24 h. ^c Determined by chiral HPLC (Chiralcel OD). ^d Determined by Mosher ester analysis (¹H NMR).

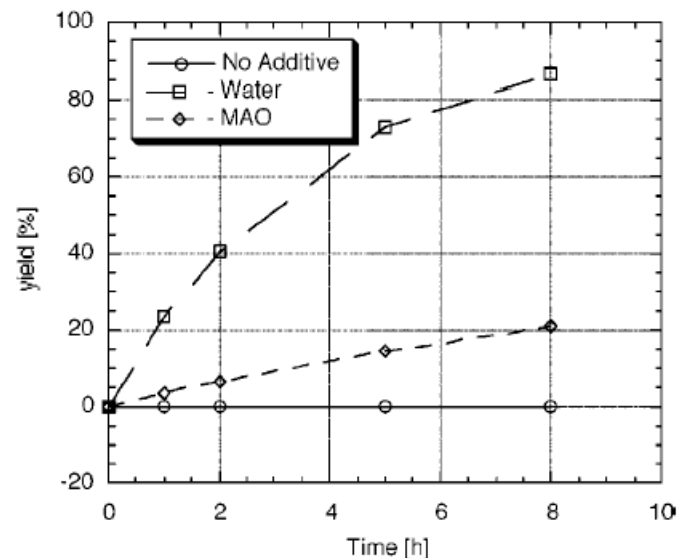
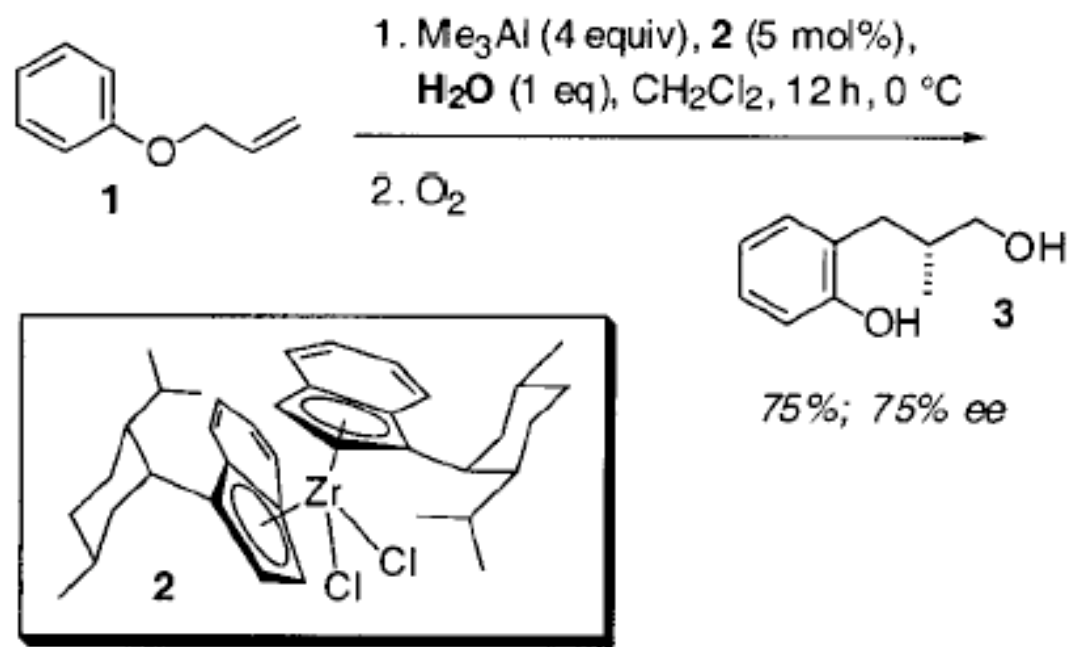


Figure 1. Kinetic analysis of the Zr-catalyzed methylalumination of styrene using no additive, 1.2 equiv of MAO, and 1.0 equiv of water, respectively. Reactions were performed at 0 °C using 4–5 equiv of Me₃Al and 5 mol % of **2**, and data were obtained by GC analysis of quenched samples with dodecane as internal standard. The concentration of styrene was kept constant at 0.17 M.

Addition of water to trialkyl alane is exothermic accompanied by the evolution of gas and not suitable for Scale up. Addition of MAO doesn't pose safety hazards.

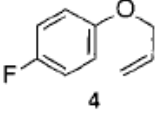
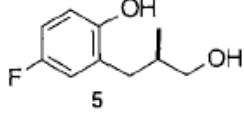
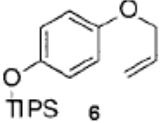
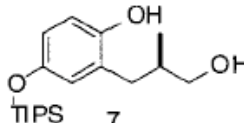
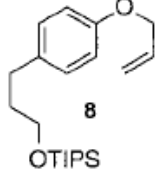
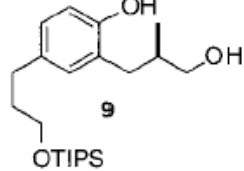
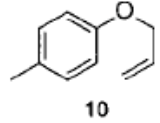
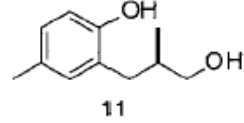
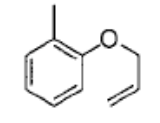
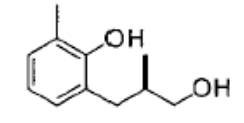
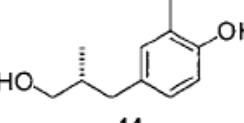
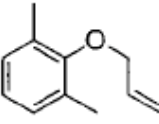
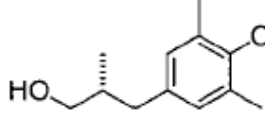
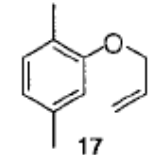
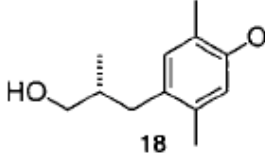
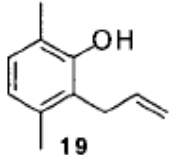
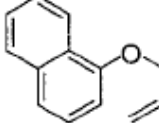
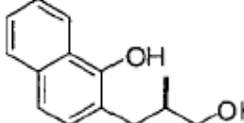
Water Accelerated Tandem Claisen Alkene Carbometalation



Wipf, P.; Ribe, S., *Org.Lett.* **2001**, 3, 1503

Substrate scope

Table 1. H₂O-Accelerated Tandem Claisen Rearrangement–Methylalumination

entry	substrate	product	yield (<i>ee</i>) ^a
1			78% (78%)
2			51% (74%)
3			60% (73%)
4			74% (76%)
5			51% (74%)
			29% (70%)
6			78% (75%)
7			39% (60%)
			55%
8			75% (80%)

^a Determined by Mosher ester analysis (¹H NMR).

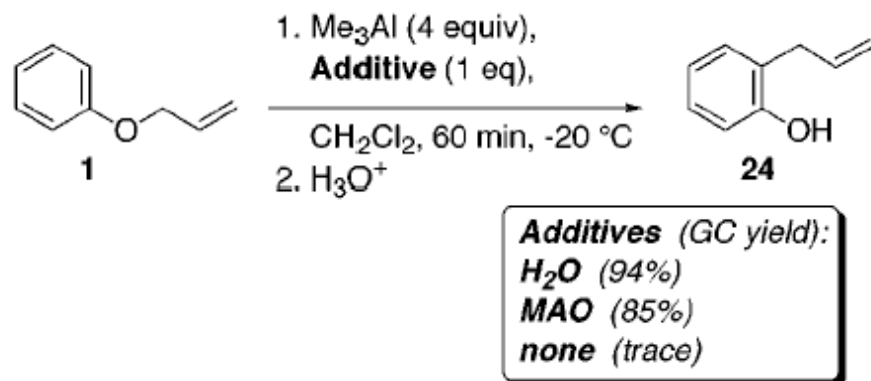
Wipf, P.; Ribe, S., *Org.Lett.* **2001**, 3, 1503

MAO Accelerated Tandem Process and Role of Additive

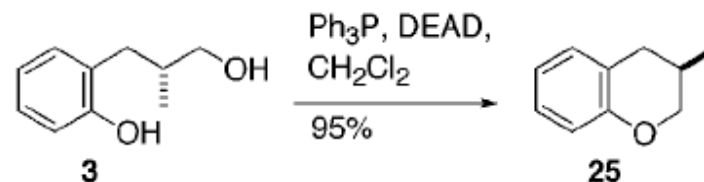
Table 2. MAO-Accelerated Tandem Claisen Rearrangement–Methylalumination

entry	substrate	product	yield, % (ee, %) ^a
1	1	<i>ent</i> - 3	71 (75)
2	4	<i>ent</i> - 5	80 (76)
3	6	<i>ent</i> - 7	58 (75)
4	8	<i>ent</i> - 9	55 (74)
5	10	<i>ent</i> - 11	75 (74)
6	12	<i>ent</i> - 13	60 (77)
		<i>ent</i> - 14	25 (73)
7	15	<i>ent</i> - 16	78 (72)
8	17	<i>ent</i> - 18	34 (69)
		19	59
9	20	<i>ent</i> - 21	74 (76)

^a Determined by Mosher ester analysis (¹H NMR).

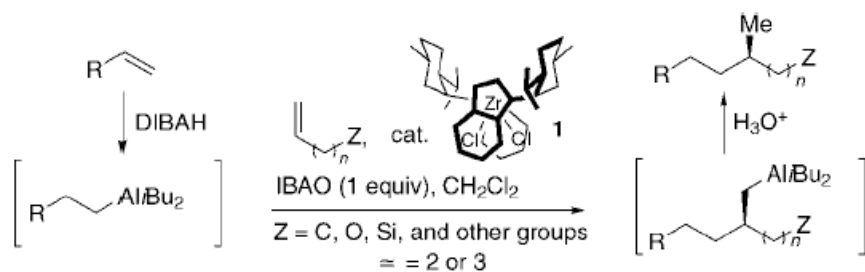


Asymmetric synthesis of chromans



Wipf, P.; Ribe, S., *Org.Lett.* **2001**, 3, 1503

Hydroalumination - Alkyl alumination Tandem Process



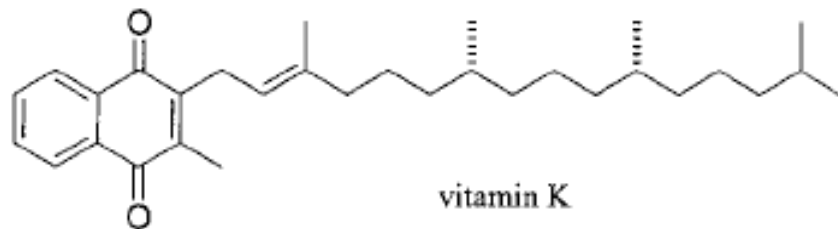
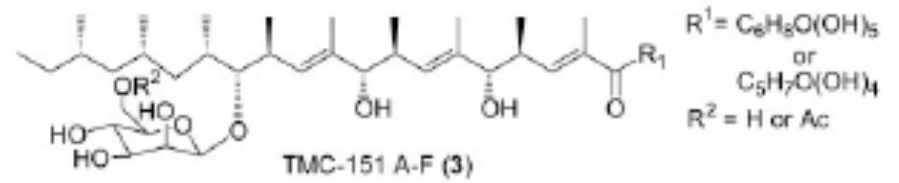
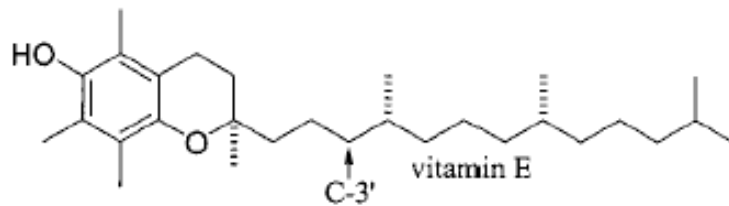
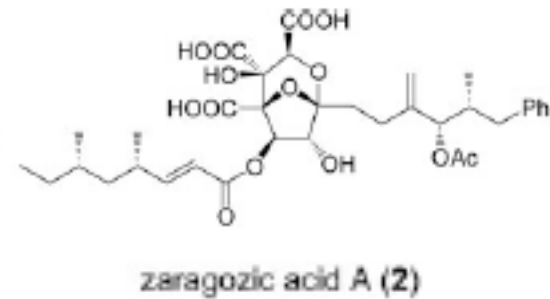
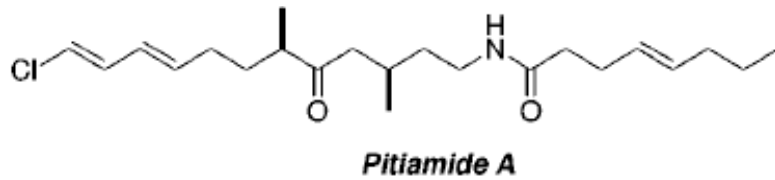
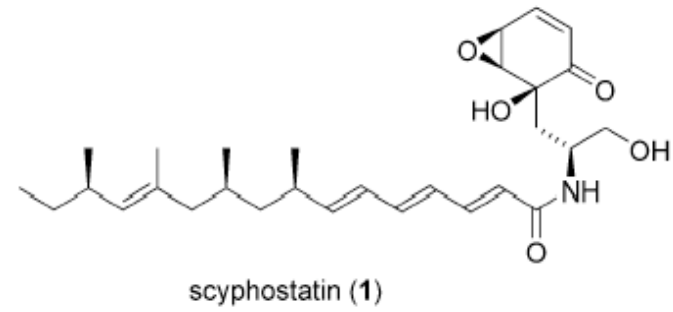
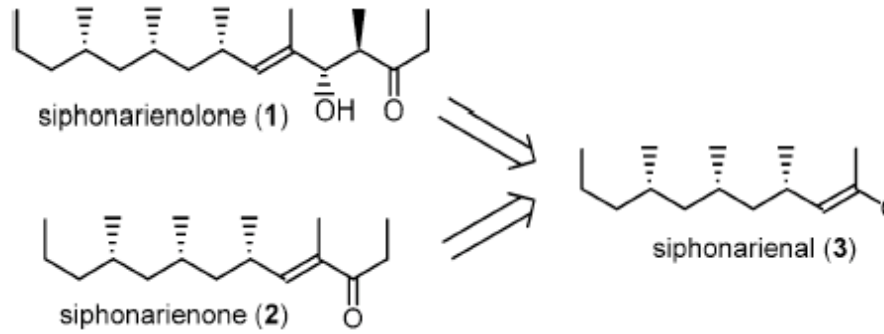
Scheme 1. Hydroalumination/Zr-catalyzed enantioselective carboalumination/hydrolysis process for the synthesis of methyl-substituted alkanols. IBAO = isobutylaluminoxane.

Table 1. Zr-catalyzed enantioselective alkylaluminum of ω -alkenyl silyl ethers with alkyl-diisobutylalanes.^[a]

Entry	$\text{R-CH}_2\text{-CH}_2\text{-AlBu}_2$	$\text{H}_2\text{C=CH(CH}_2)_n\text{OTBS}$	t [h]	Yield ^[b] [%]	ee ^[c] [%]
	R	n			
1	<i>n</i> -pentyl	2	3	74	92 ^[d]
2	<i>n</i> -hexyl	2	3	77	91 ^[d]
3	2-methylpropyl	2	3	82	93 ^[d]
4	4-methylpentyl	2	3	66	91 ^[e]
5	cyclohexyl	2	3	81	91 ^[e]
6	PhMe ₂ SiCH ₂	2	3	85	90 ^[e]
7	<i>n</i> -hexyl	3	6	83	92 ^[f]
8	2-methylpropyl	3	3	78	91 ^[f]
9	<i>n</i> -hexyl	4	4	76	90 ^[g]

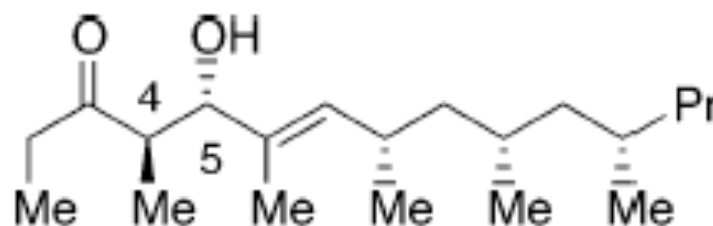
[a] Unless otherwise stated, the reaction was carried out at 23 °C in CH₂Cl₂ in the presence of **1** (5 mol %) and IBAO (1 equiv). RCH=CH₂/DIBALH/H₂C=CH(CH₂)_{*n*}OTBS = 1.5:1.5:1. [b] Yield based on the protected enols after protonolysis and deprotection. [c] Determined by HPLC analysis of a derivative of the alcohol (see below) on a CHIRALCEL OD-H or AD (hexane/2-propanol 95:5 or 90:10 v/v). [d] The alcohol was treated successively with COCl₂ and (*R*)-1-(1-naphthyl)ethylamine to give the corresponding urethane. [e] The alcohol was oxidized to the corresponding carboxylic acid and then treated with (*R*)-1-(1-naphthyl)ethylamine to give the corresponding amide. [f] As above, except that (*S*)-1-(1-naphthyl)ethylamine was used to produce the amide. [g] This *ee* determination was less accurate than in the other cases (90 ± 2 %). TBS = *tert*-butyldimethylsilyl.

Synthetic Applications

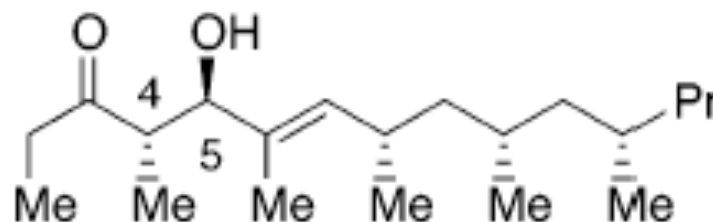


Total Synthesis of Siphonarienolone

- Member of Siphonarienes a class of polypropionates produced by mollusks of genus siphonaria
- Norté reported the isolation in **1988** and tentatively assigned structure as **3**
- Displays moderate activity against cancer cell lines as single epimer
- Calter synthesized and reassigned the structure as **1**(**2002**)

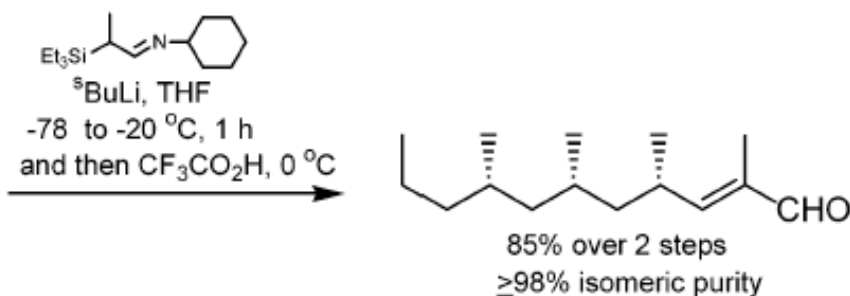
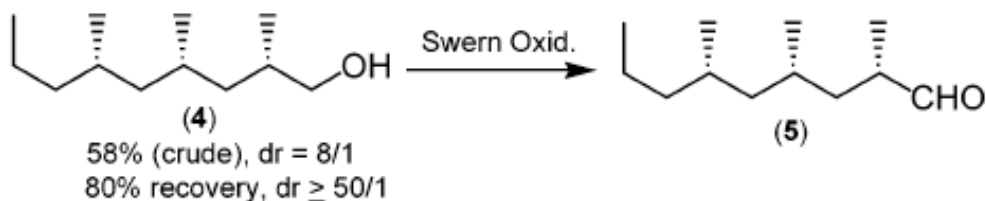
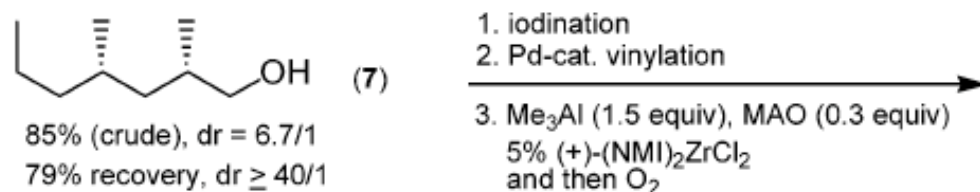
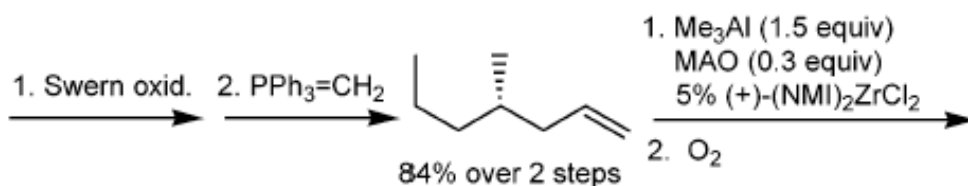
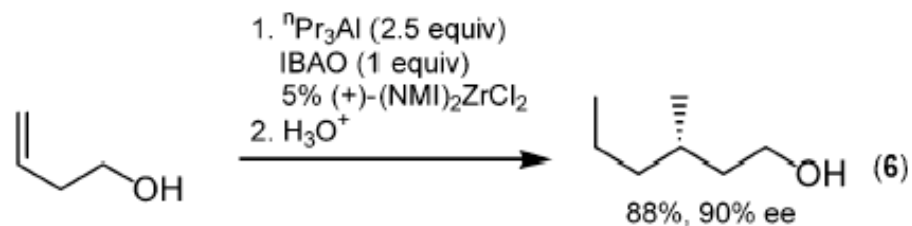


1, siphonarienolone (revised)



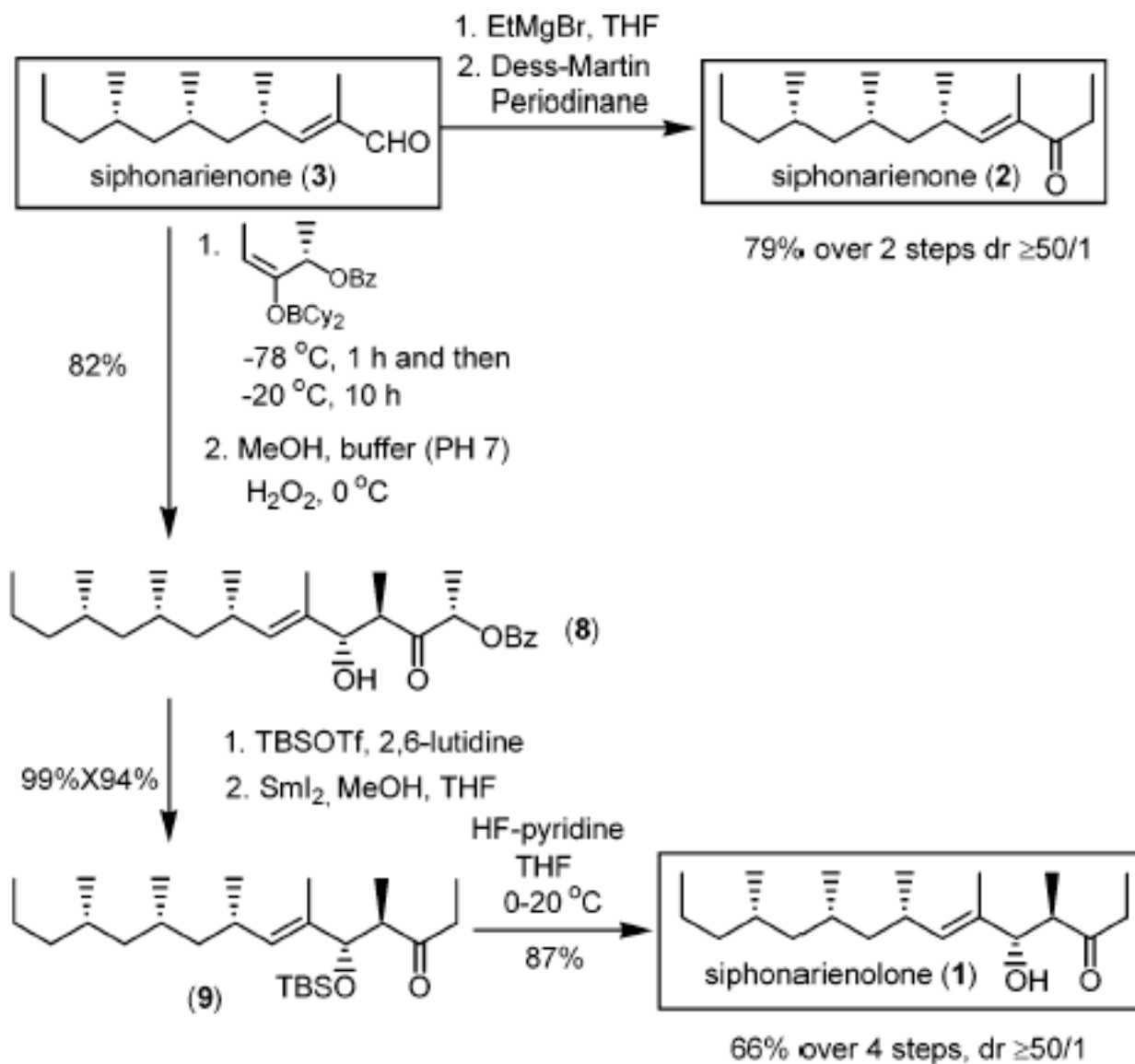
3, siphonarienolone (proposed)

Iterative Approach to 3



Negishi, E.; Liang, Bo.; Tan, Ze.; Lachaux,
 Marina Magnin., *Org.Lett.***2004**,
 6, 1425

Completion of Synthesis



Negishi, E.; Liang, Bo.; Tan, Ze.; Lachaux, Marina Magnin., *Org.Lett.* **2004**, 6, 1425

Conclusions

- Zirconium catalyzed alkyl alumination of alkenes has been developed into extremely powerful synthetic process.
- Mechanistic role of water and methyl aluminoxane as additive needs to be examined in detail.
- Tandem Claisen alkene carbometalation is versatile approach to poly-functionalized building blocks.
- Hydroalumination, alkene carbometalation tandem process enables the preparation of methylated adducts in high enantioselectivities.
- Asymmetric amplification has also been developed as fairly useful method of enantioenrichment of primary alcohols.
- Further exploitations of alkene carbometalation in synthesis of several natural products are conceivable.