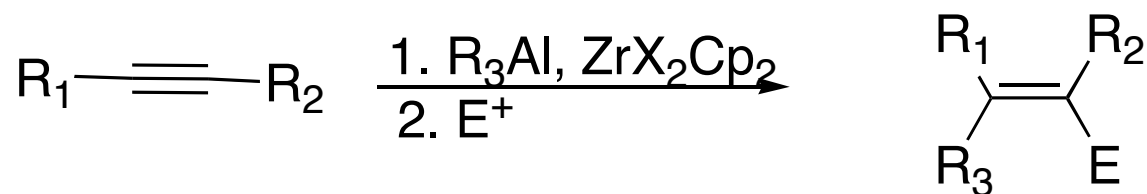


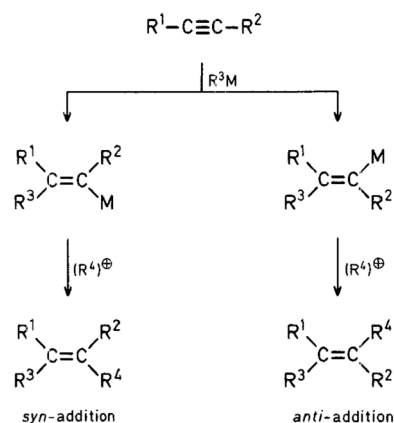
Zirconium Catalyzed Carboalumination of Alkynes: Mechanisms and Applications



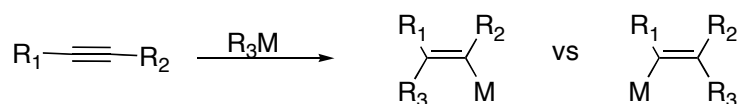
Denmark Group Meeting
Nathan Duncan-Gould
5-31-05

Carbometallation: General Scheme

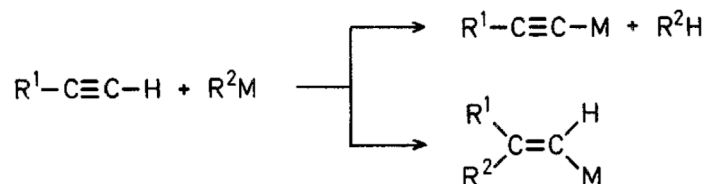
1. Type of Addition



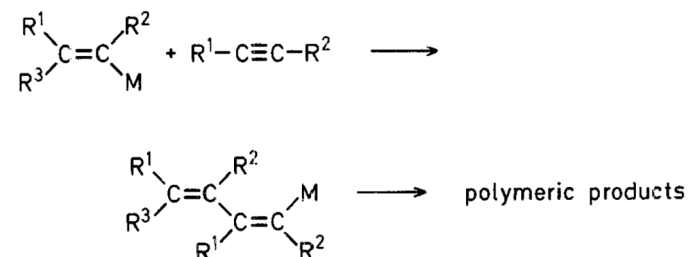
2. Regioselectivity



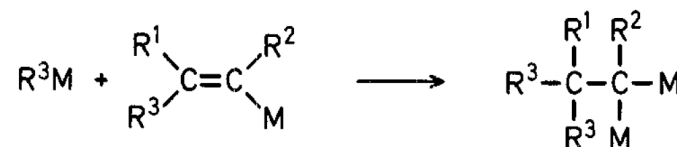
3. Metallation vs Addition



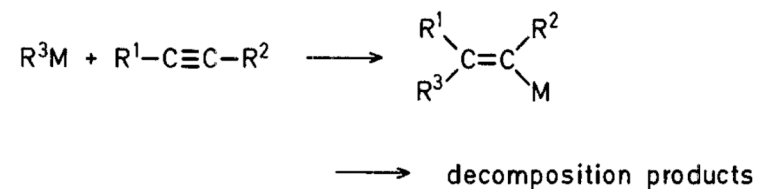
4. Polymerizations



5. Multiple Additions

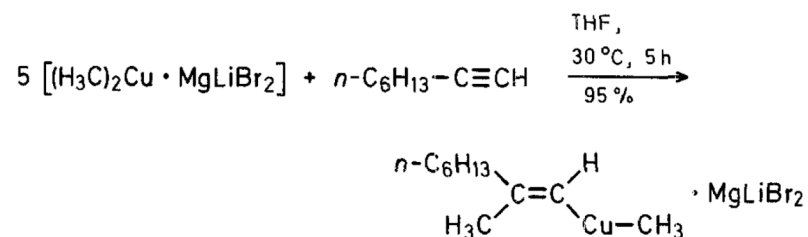
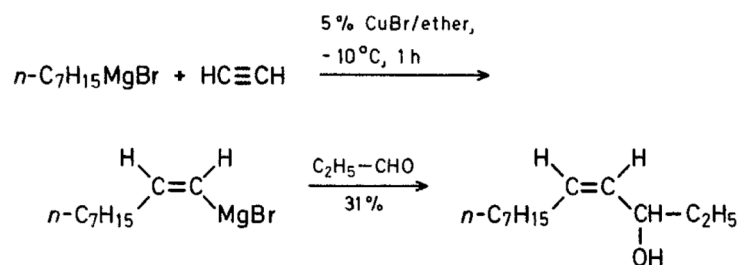


6. Stability of new RM species

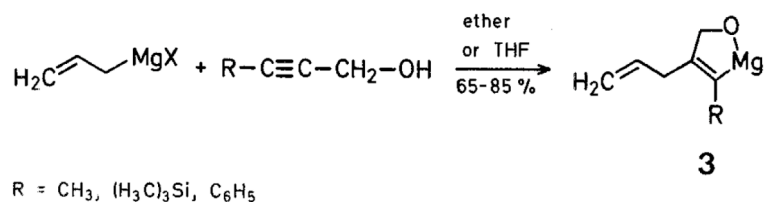


For Comparison: Grignards and Cuprates

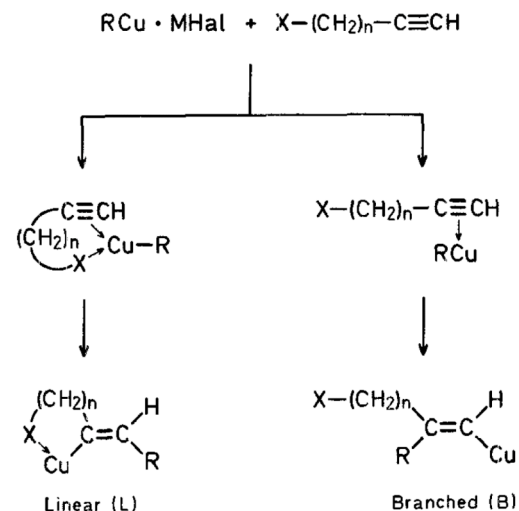
Unfunctionalized



Directed



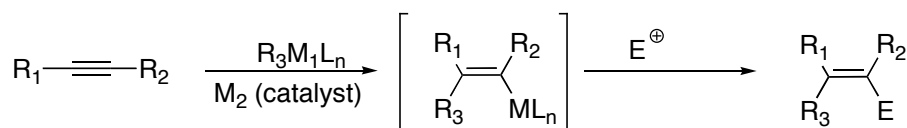
Typically functionalized alkynes
or transition metal catalyzed



n = 0, 1, 2, 3
X = halogen, SR', OR', O[⊖], N(R')₂, OAc

Initial Studies 1: Designing the reaction

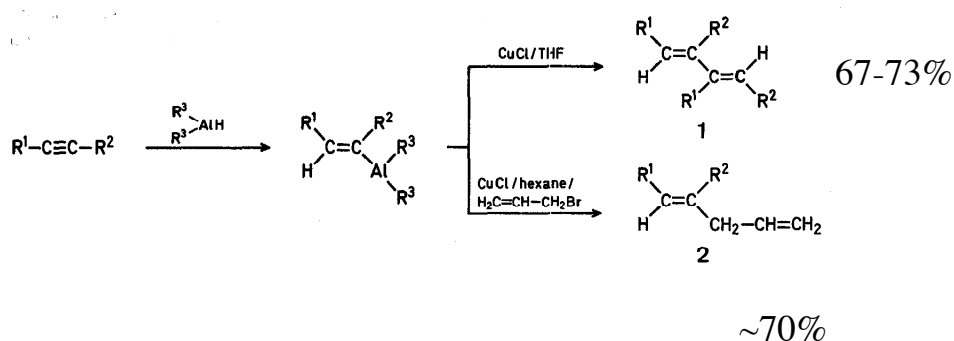
Goal



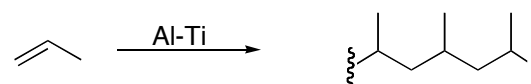
Challenges

1. steric hinderance
2. SM and Product likely have similar reactivity
 - a. polymerization

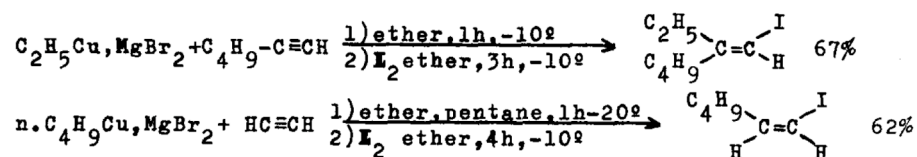
Hydroalumination



Ziegler-Natta Polymerization



Carbocupration



Initial Studies 2: Rational

Alkali and alkaline earth organometallics are too basic

Good Place to Start

May need to be activated in some way

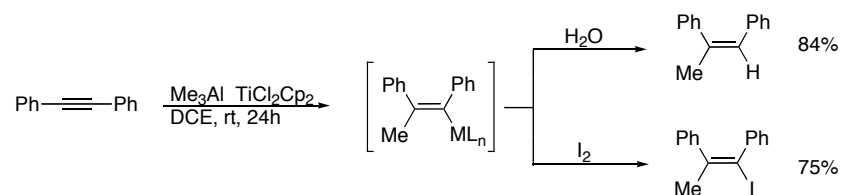
Periodic Table of the Elements

1																	18	
1	H																He	
2	Li	Be											B	C	N	O	F	Ne
3	Na	Mg											Al	Si	P	S	Cl	Ar
4	K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
5	Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
6	Cs	Ba	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
7	Fr	Ra	Ac	Rf	Ha	Sg	Ns	Hs	Mt	Uun	Uuu							
Lanthanide Series			Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu		
Actinide Series			Th	Pa	U	Np	Pu	Am	Cm	Bk	Cf	Es	Fm	Md	No	Lr		

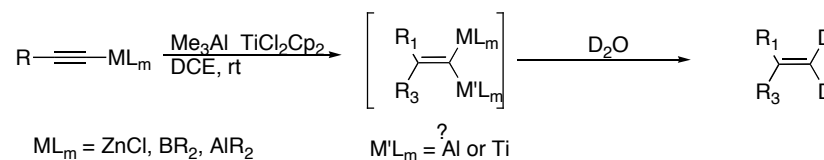
Organoalanes look like a good starting point for a catalytic carbometallation

Initial Studies 3: Ti

Aromatics

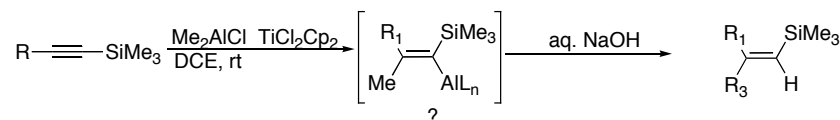
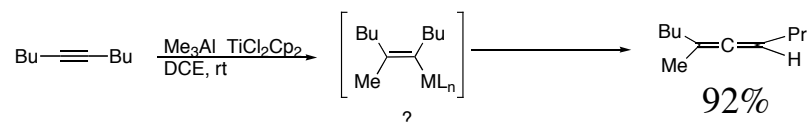


Circumventing Elimination

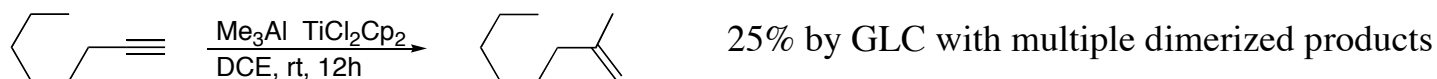


Aliphatics

Internal: Dehydrometallation



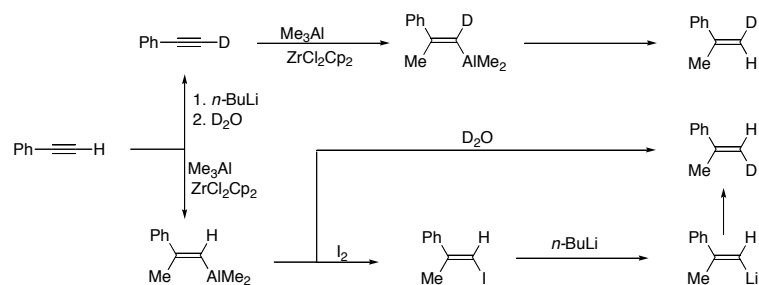
Terminal: Dimerization?



Different Catalyst System Needed?

Initial Studies 4: Zr

Addition is cis



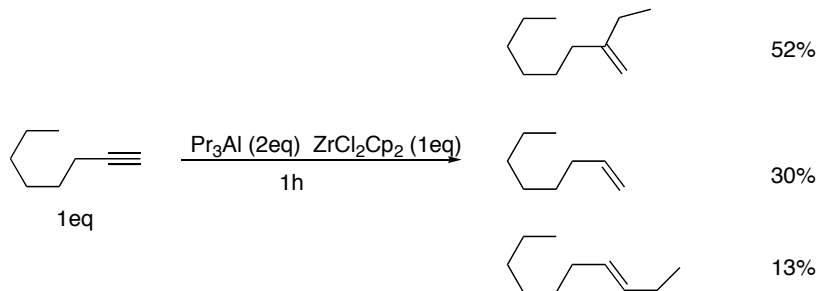
Alkyne Scope

Alkyne	$\text{Me}_3\text{Al} \text{ Cl}_2\text{ZrCp}_2$ rt, 3-6h		methyl alkene	
alkyne	yield of protonolysis product, ^b %	yield of iodinolysis product, ^c %	regio- selectivity ^d	stereo- selectivity
phenylacetylene ^e	98	73 (83)	96	>98
1-hexyne	95-100	85	95	>98
1-heptyne	95-100	83	95	>98
1-octyne	95-100	81	94	>98
2-methyl-1-buten-3-yne ^f	95	70	95	>98
2-methyl-2-hepten-6-yne ^g	95	72 (79)	95	>98
5-decyne ^h	89			97

No allene formation
No dimerization
yne > ene

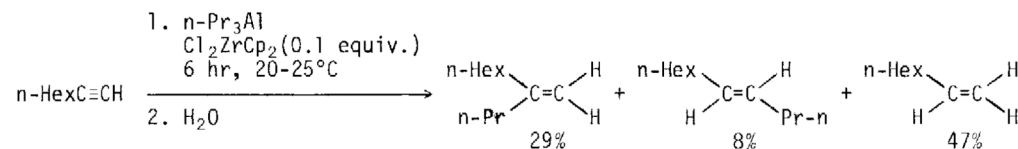
Changing the Aluminane

ethyl



Changing the Aluminane

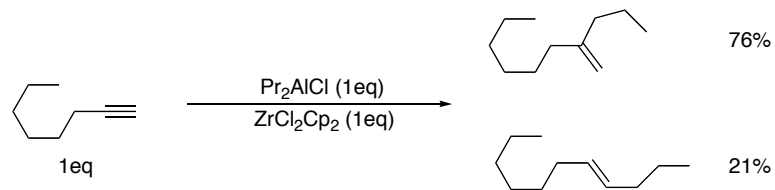
propyl



Regioselectivity ~4:1
Hydrometallation competition

Negishi, et al., *JACS*, **1978**, 100, 2252

Initial Studies 5: Suppressing Hydrometallation



no hydrometallation

Conclusions

Alkylalanes with β -Hydrogens can Hydrometallate

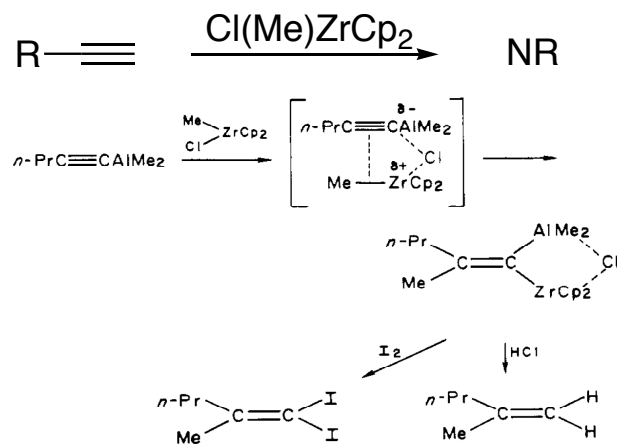
New Hypothesis

Hydrometallation result from alkyl transfer to Zr

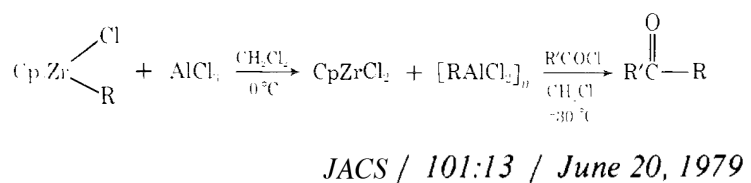
Mechanistic Understanding is Needed

Mechanism 1: Evidence for Zirconation

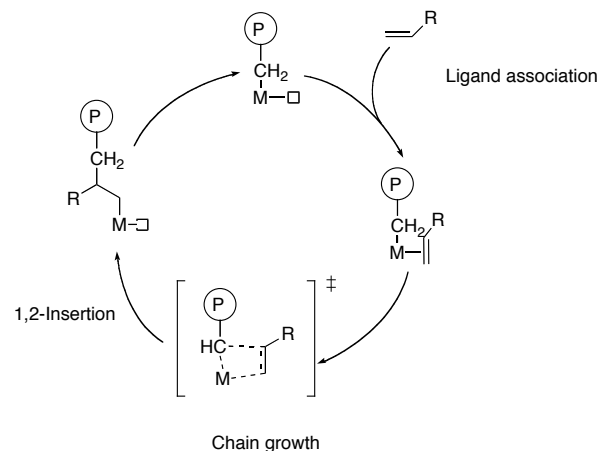
2.a. Analogy: Assisted Carbozirconation



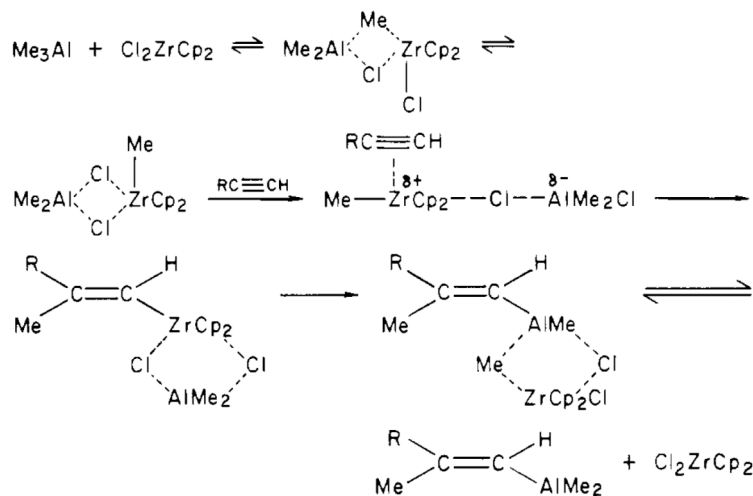
2.b. Analogy : Carbozirconation



2.c. Analogy: Ziegler-Natta



First Proposed Mechanism



Mechanism 2: Evidence for Almination

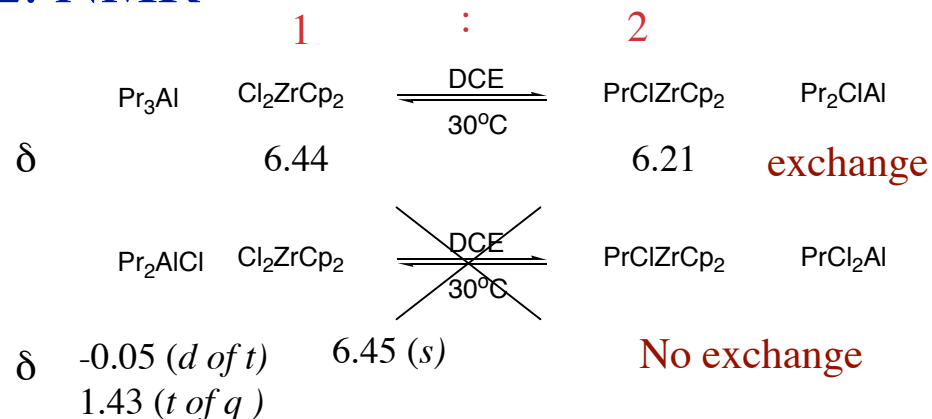
1. Changing the Catalyst System

Reaction of 1-Heptyne with Methylalane-Zirconocene Systems^a

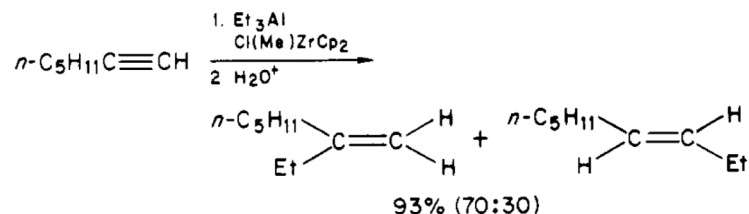
Al-Zr reagent	total protonolysis products ^b (%) formed after indicated time (h)				products obtained after iodinolysis at 24 h, %			
	1	3	6	24	$n\text{-C}_5\text{H}_{11}\text{-C}(\text{Me})=\text{C}(\text{H})\text{-I}$	$n\text{-C}_5\text{H}_{11}\text{-C}(\text{I})=\text{C}(\text{H})\text{-Me}$	$n\text{-C}_5\text{H}_{11}\text{-C}(\text{Me})=\text{CH}_2$	$n\text{-C}_5\text{H}_{11}\text{-C}(\text{H})=\text{C}(\text{Me})\text{-H}$
$\text{Me}_3\text{Al-Me}_2\text{ZrCp}_2$	24	48	70	99 ^c	93	2	2	3
$\text{Me}_3\text{Al-Cl(Me)ZrCp}_2$	95	98			93	2	trace	3
$\text{Me}_3\text{Al-Cl}_2\text{ZrCp}_2$	100				94	2	trace	3
$\text{Me}_2\text{AlCl-Cl}_2\text{ZrCp}_2$	15	35	42	70 ^d	47 ^d	trace ^d	13 ^d	5 ^d
$\text{MeAlCl}_2\text{-Cl}_2\text{ZrCp}_2$	0	0	0	0	0	0	0	0

^a 1-Heptyne (5 mmol) was treated with 5 mmol each of a methylalane and a zirconocene derivative at room temperature in 1,2-dichloroethane. ^b A 95:5 mixture of 2-methyl-1-heptene and (*E*)-2-octene. ^c The yields after 9 and 18 h were 85 and 98%, respectively. ^d The yield figures were taken after 48 h.

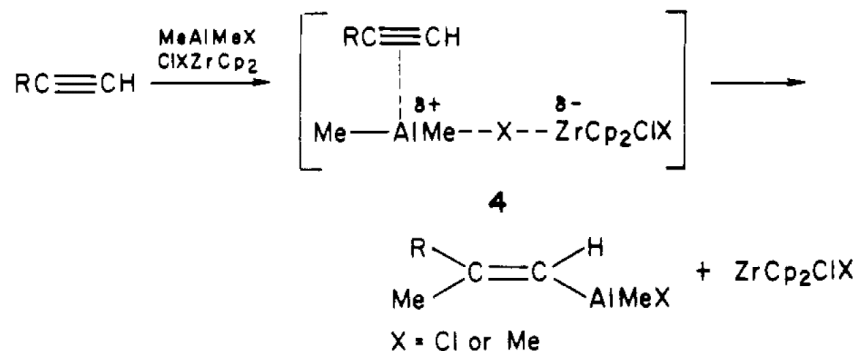
2. NMR



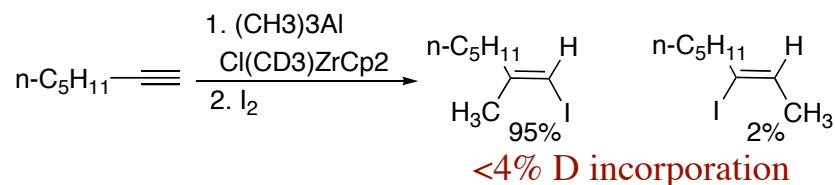
3.a. Competition: Et vs Me



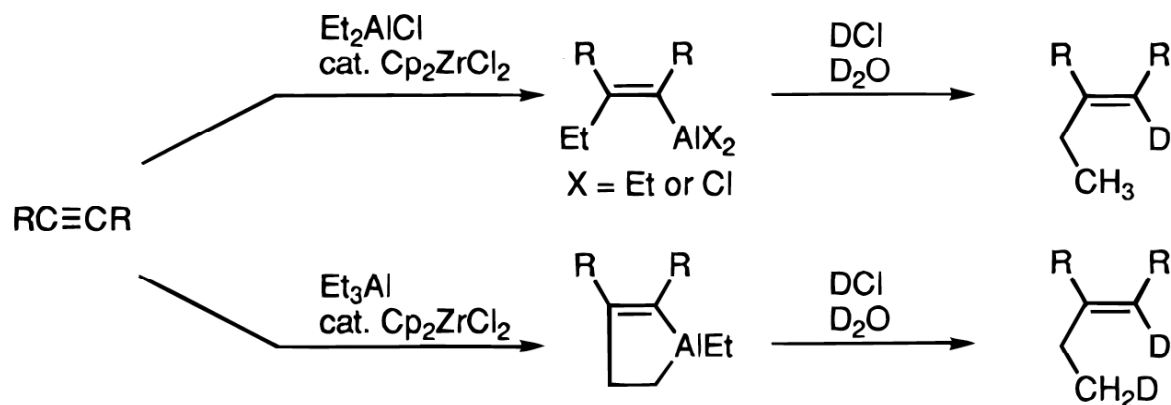
New Mechanism Proposal



3. b. Competition: CH₃ vs CD₃

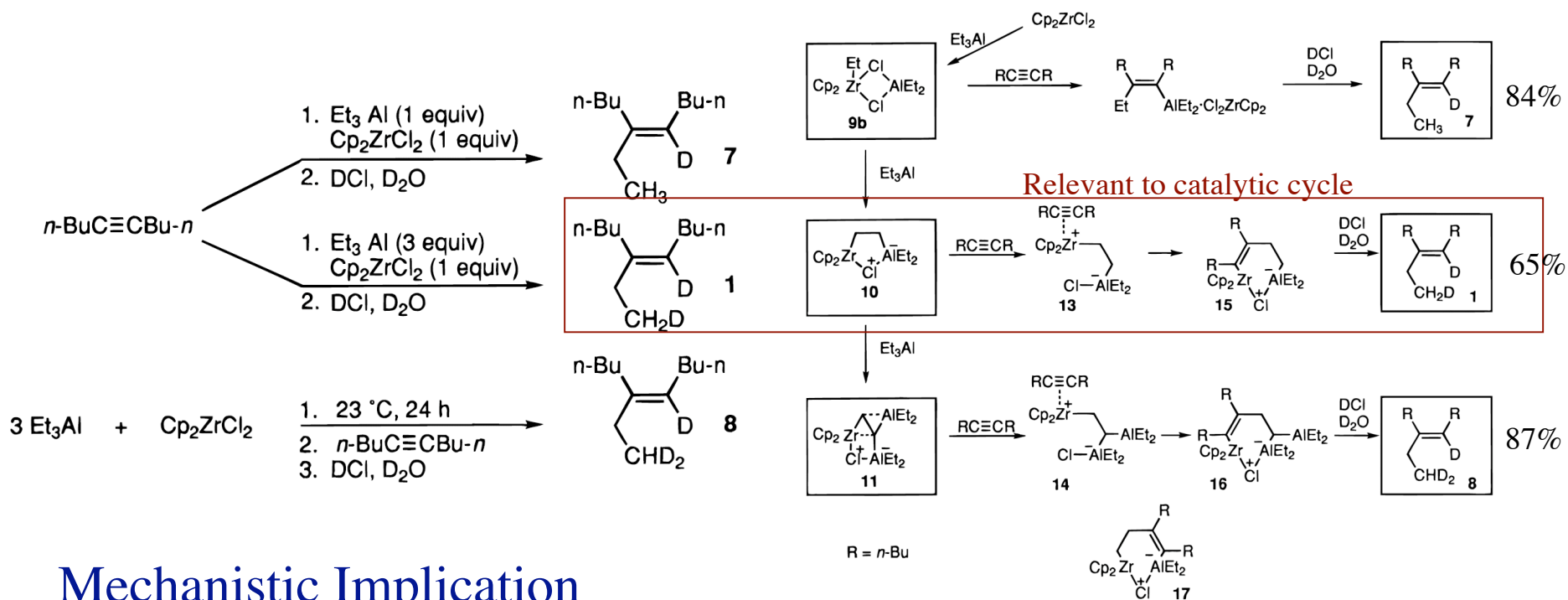


Multiple Mechanisms Operating

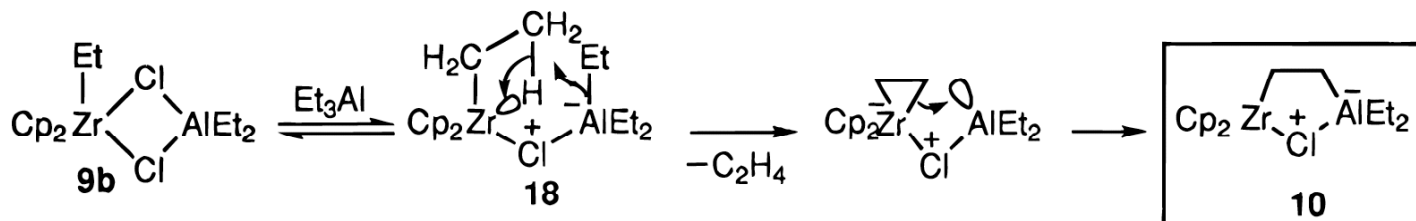


To decipher the mechanism the organoalane, catalyst system, Solvent and alkyne were varied systematically.

Mechanism 4: Stoichiometry

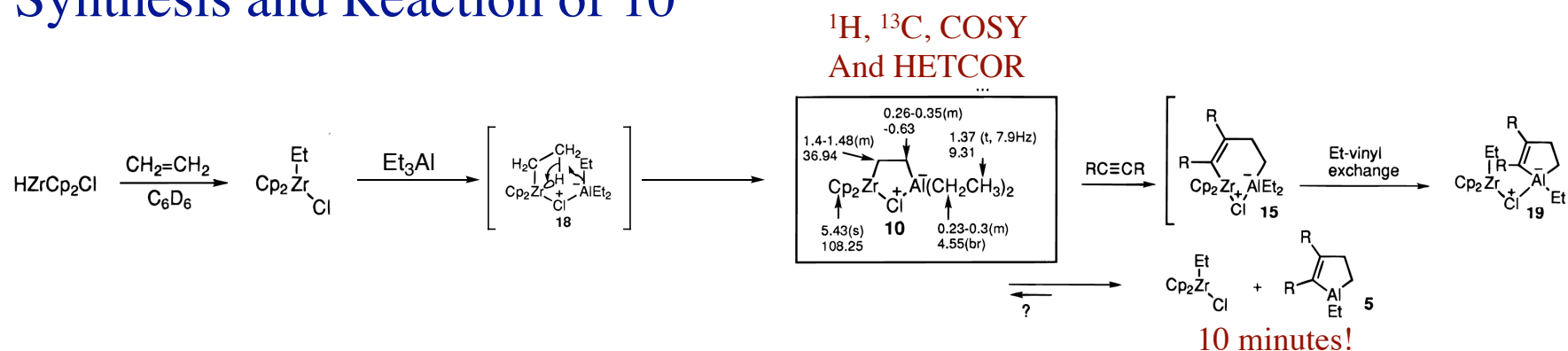


Mechanistic Implication

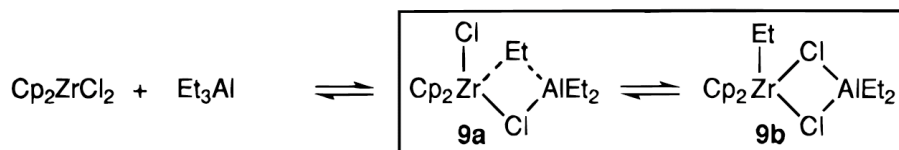


Mechanism 5: Investigation of 10

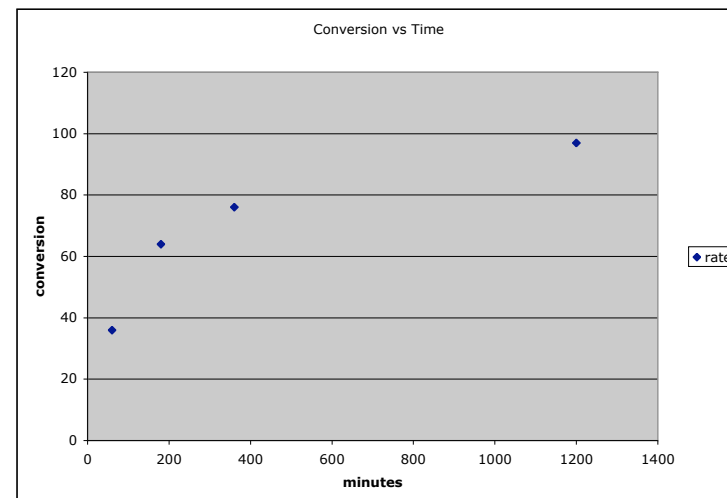
Synthesis and Reaction of 10



Accounting for drastic rate difference



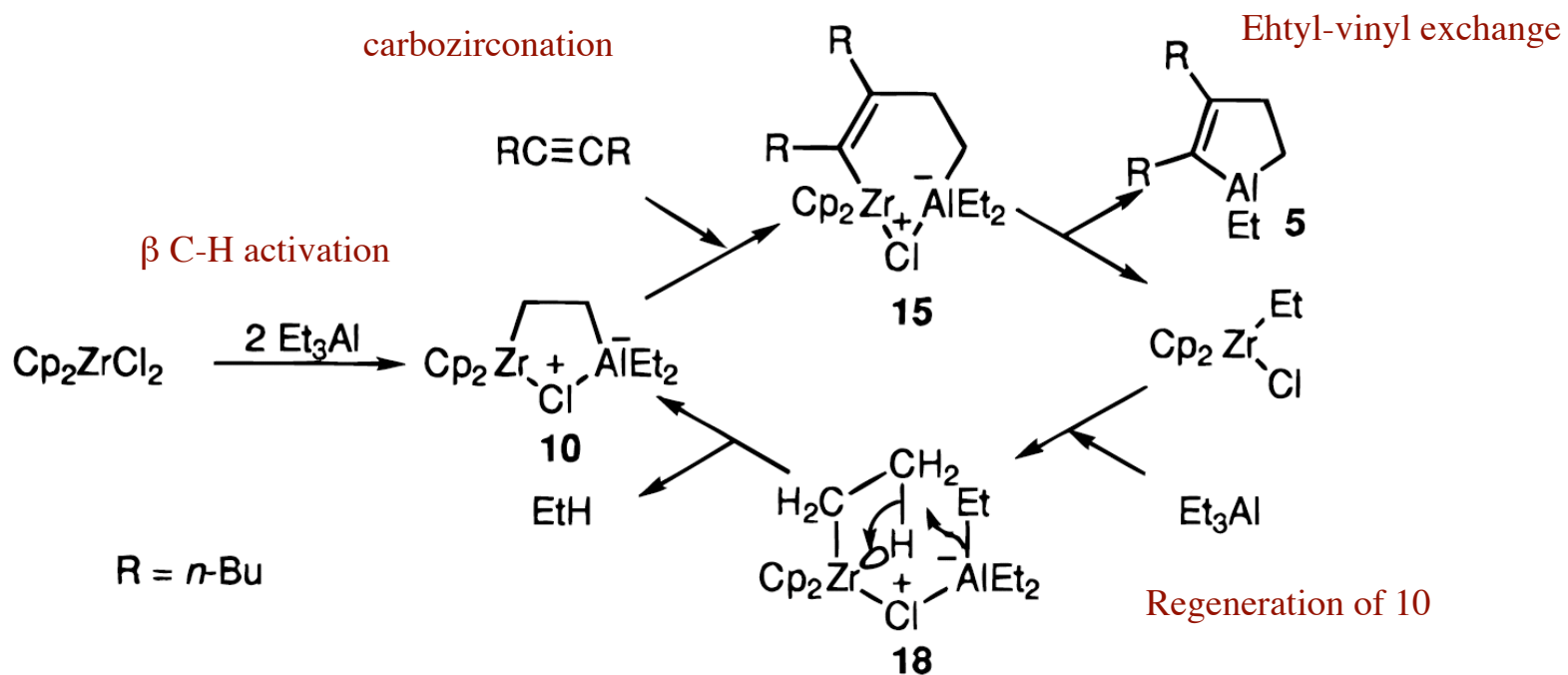
Inhibitory effect of Et_2AlCl ?



Rxn stalling? Product inhibition?
 No data on distribution of products during reaction

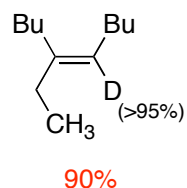
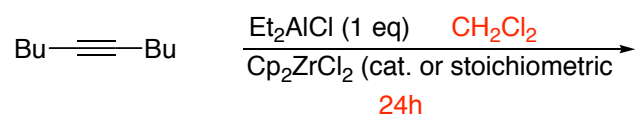
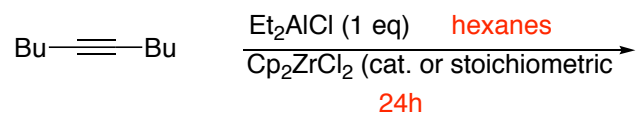
Mechanism 6: 1st mechanistic extreme

Excess Et_3Al , Cat. Cp_2ZrCl_2

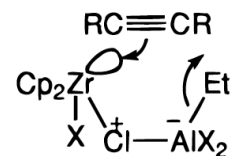


Mechanism 7: Second Mech. Extreme

Solvent Effect

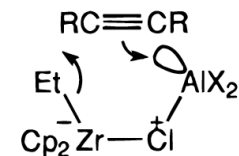


6-Centered TS



X = Cl and/or Et

(6 - C - Zr)



X = Cl and/or Et

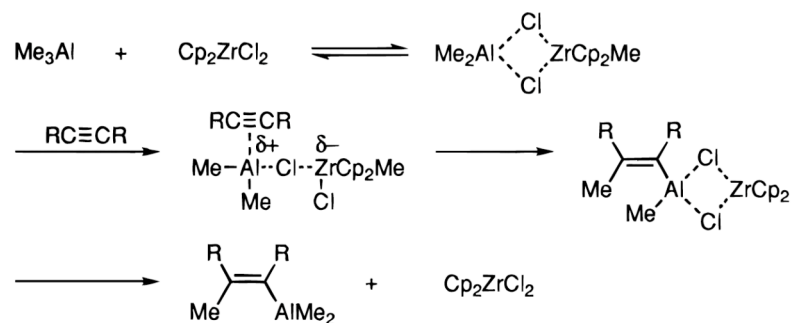
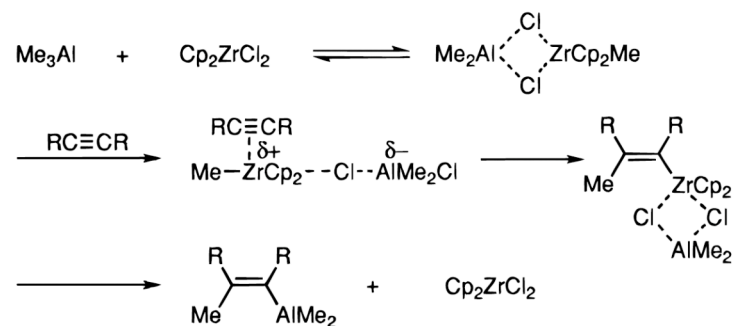
(6 - C - Al)

Rate and solvent effects
similar to methylalumination

No C-H activation

Dialkylalumanes do not exchange
alkyl groups with zirconium (remember
NMR studies)

4-Centered TS



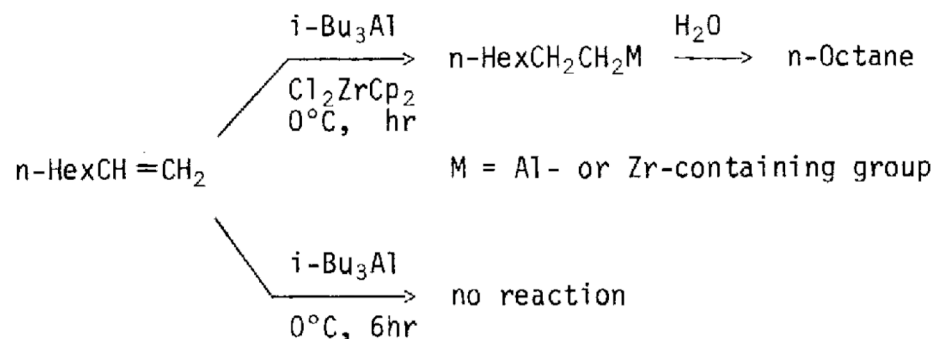
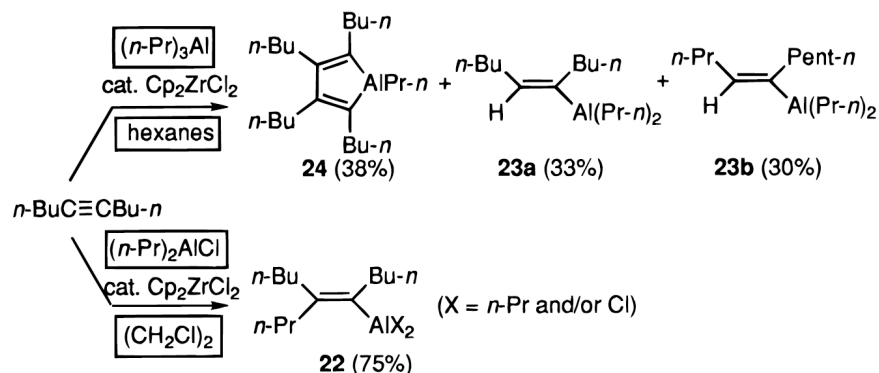
Mechanism 8: Mixture of Mechanisms

Table 1. Reaction of Alkynes with Et₃Al and Et₂AlCl in the Presence of 10 mol % of Cp₂ZrCl₂

alkyne	ethylalane (equiv)	solvent	temp. °C	time h	deuterolysis products (yield, ^a %)		
							others
<i>n</i> -BuC≡CBu- <i>n</i>	Et ₃ Al (3)	hexanes	23	6		<i>b</i>	<i>b</i>
<i>n</i> -BuC≡CBu- <i>n</i>	Et ₃ Al (3 or 6)	(CH ₂ Cl) ₂	23	72		<i>b</i>	<i>c</i>
PhC≡CPh	Et ₃ Al (3)	benzene	55	19		<i>b</i>	
<i>n</i> -OctC≡CH	Et ₃ Al (3)	benzene	23	17			<i>b</i>
PhC≡CH	Et ₃ Al (3)	hexanes	55	7			<i>b</i>
<i>n</i> -BuC≡CBu- <i>n</i>	Et ₂ AlCl (3)	(CH ₂ Cl) ₂	55	20	<i>b</i>		
PhC≡CPh	Et ₂ AlCl (3)	(CH ₂ Cl) ₂	70-75	36-40	<i>b</i>		<i>b</i>
<i>n</i> -OctC≡CH	Et ₂ AlCl (3)	(CH ₂ Cl) ₂	23	5	<i>b</i>		

Extent of operating mechanisms depends on the system

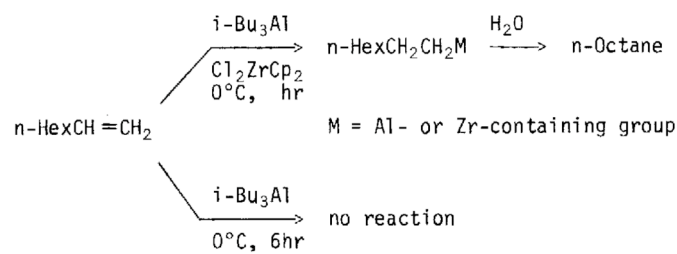
Mechanism 9: Higher Alkyls



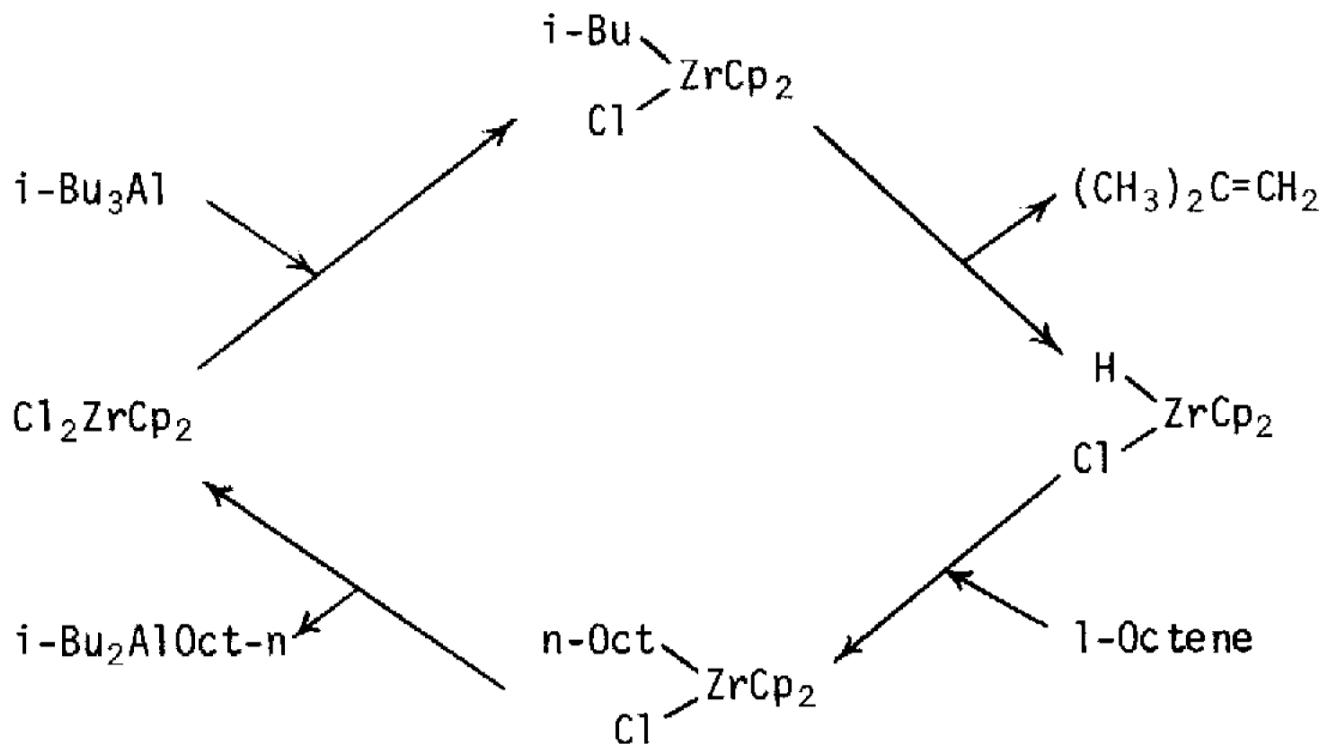
Hydrometallation “Problem” Again

Reaction Course depends strongly on alumane and solvent

Proposed Hydrometallation Mech.



Stoichiometry 1:2:0.1

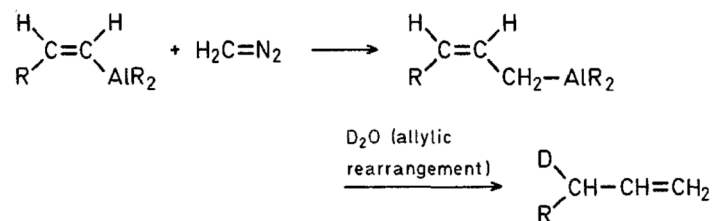


Mechanistic Conclusions

1. Three Different Mechanisms are operative:
 - (i) Direct C-M bond addition
 - (ii) C-H activation
 - (iii) Hydrometallation
2. Using R_2AlCl and polar solvents increases the direct C-M bond addition
3. C-H activation pathway is dominant with $Alkyl_3Al$ and nonpolar solvents
4. Exclusive Hydrometallation results when $(i-Bu)_3Al$ is used

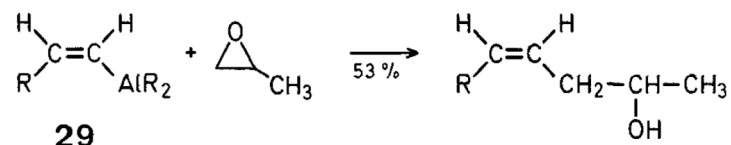
Electrophiles

Diazomethane



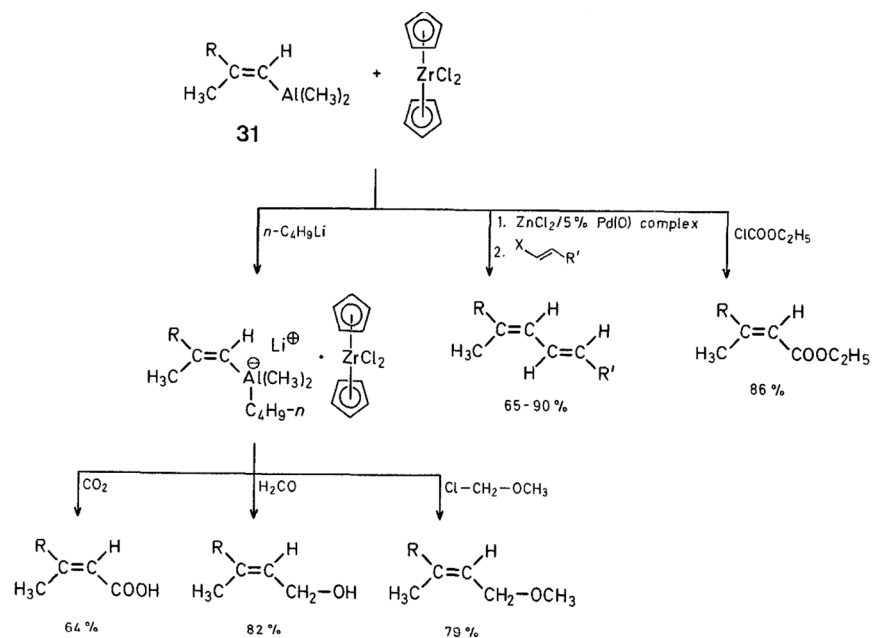
ACIE, 1966, 5, 513

Epoxides



JOC, 1977, 42, 2712

One-pot procedures: Almination-electrophilic attack



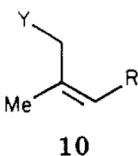
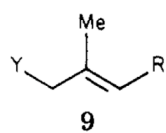
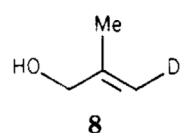
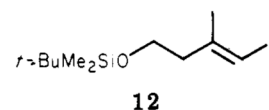
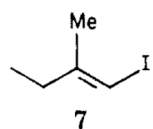
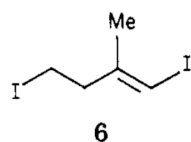
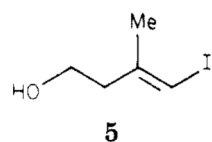
Synthesis, 1981, 853

Applications: Difunctional Alkenes

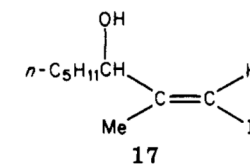
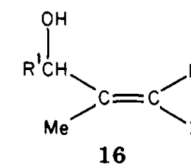
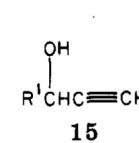
Table I. Preparation of Heterofunctional Trisubstituted (*E*)-Alkenes via Zirconium-Catalyzed Carboalumination of Alkynes ^a

alkyne	product	meth- od ^b	% yield, isolated (GLC)	regiose- lectivity of carbomet- alation, %	¹³ C NMR chemical shift of the allylic methyl carbon, ppm
3-butyn-1-ol	5	A	62 (85)	92	
	12	A	87	94	
	methyl (<i>E</i>)-5-hydroxy- 3-methyl-2-pentenoate	B	(63)	94	18.83
3-butyloxy- <i>tert</i> - butyldimethylsilane	12	A	52	94	
4-iodo-1-butyne	ethyl (<i>E</i>)-iodo- 3-methyl-2-pentenoate	B	74 (89)	>98	16.65
3-butyryl phenyl sulfide	6	A	60	>98	
	(<i>E</i>)-3-methyl-5-(thiophenoxy)- 2-pentenoic acid	C	62	83 (>98) ^c	16.26
	(<i>E</i>)-3-methyl-5-(thiophenoxy)- 2-penten-1-ol	D	78	83 (>98) ^c	
2-propyn-1-ol	8	E	41	94	
1-octyn-3-ol ^d	17	A	60 (77)	>98	10.94 ^e
2-propynyl phenyl sulfide	(<i>E</i>)-1-iodo-2-methyl-3- (thiophenoxy)-1-propene	A	75	>98	
	(<i>E</i>)-3-methyl-4-(thiophenoxy)- 2-buten-1-ol	D	78	>98	15.42

A = I₂
 B = ClCO₂Et
 C = ate
 complexatin
 the CO₂
 D = ate, then
 paraformalde
 hyde
 E = D₂O



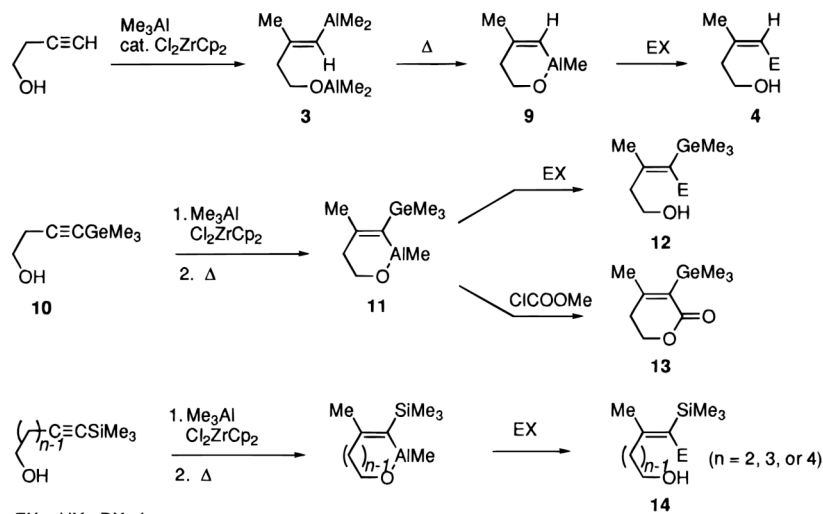
Alumination is not
directed



Y = carbon or heteroatom group, R = carbon group

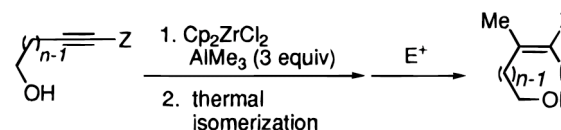
Difunctional Alkenes: E to Z

Isomerization



Mechanism?

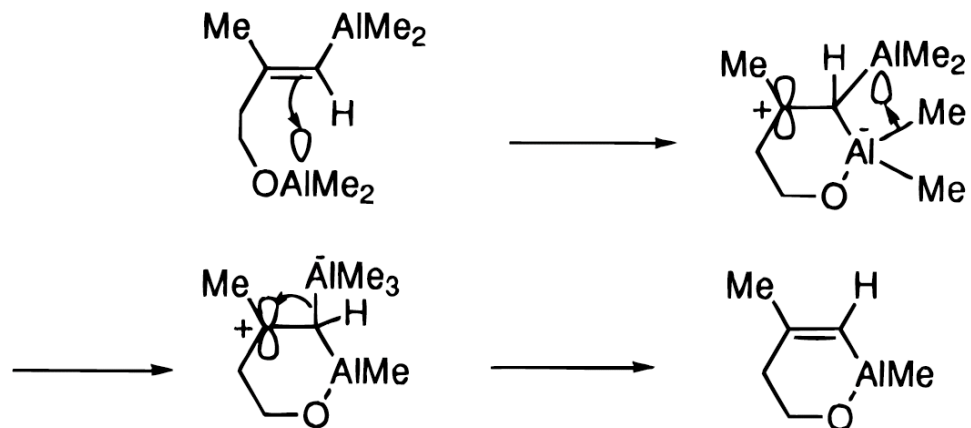
Utility Limited by chain length



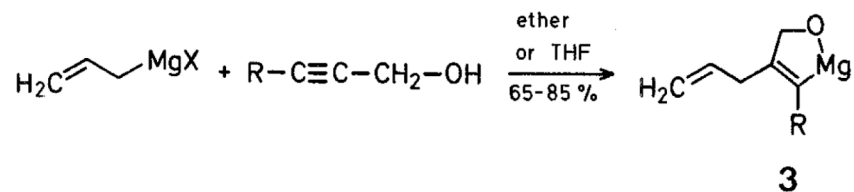
entry	alkynol		cond for isomerization		product		
	n	Z	temp, °C	time, d	E	yield, ^b %	anti/syn ^c
1 ^d	2	H	reflux	3	I (4a)	60	>98:2
2 ^d		5 ^e	reflux	5	I (7)	61	>98:2
3 ^d		6 ^f	reflux	5	I (8)	50	>98:2
4	2	SiMe ₃	25	3	I (14a)	73 (77)	>98:2
5 ^d	2	SiMe ₃	50	3	I (14a)	52 (52)	>98:2
6	2	SiMe ₃	25	3	H (14b)	64 (70)	>98:2
7		19 ^g	45	4	I (14c)	60 (60)	>98:2
8	3	SiMe ₃	25	3.5	I (14d)	59 (66)	>97:3
9	4	SiMe ₃	45	0.7	I (14e)	60 (65)	88:12
10	4	SiMe ₃	25	3.5	H (14f)	80 (82)	86:14
11	5	SiMe ₃	45	0.5	I (14g)	54 (64)	60:40
12	9	SiMe ₃	25	3	I (14h)	h (62)	47:53
13	2	GeMe ₃	25	1.5	I (12b)	73 (84)	>95:5
14	2	GeMe ₃	25	1.5	H (12a)	77 (84)	>98:2

Same reagents: E or Z selectively

E to Z Isomerization Mechanism

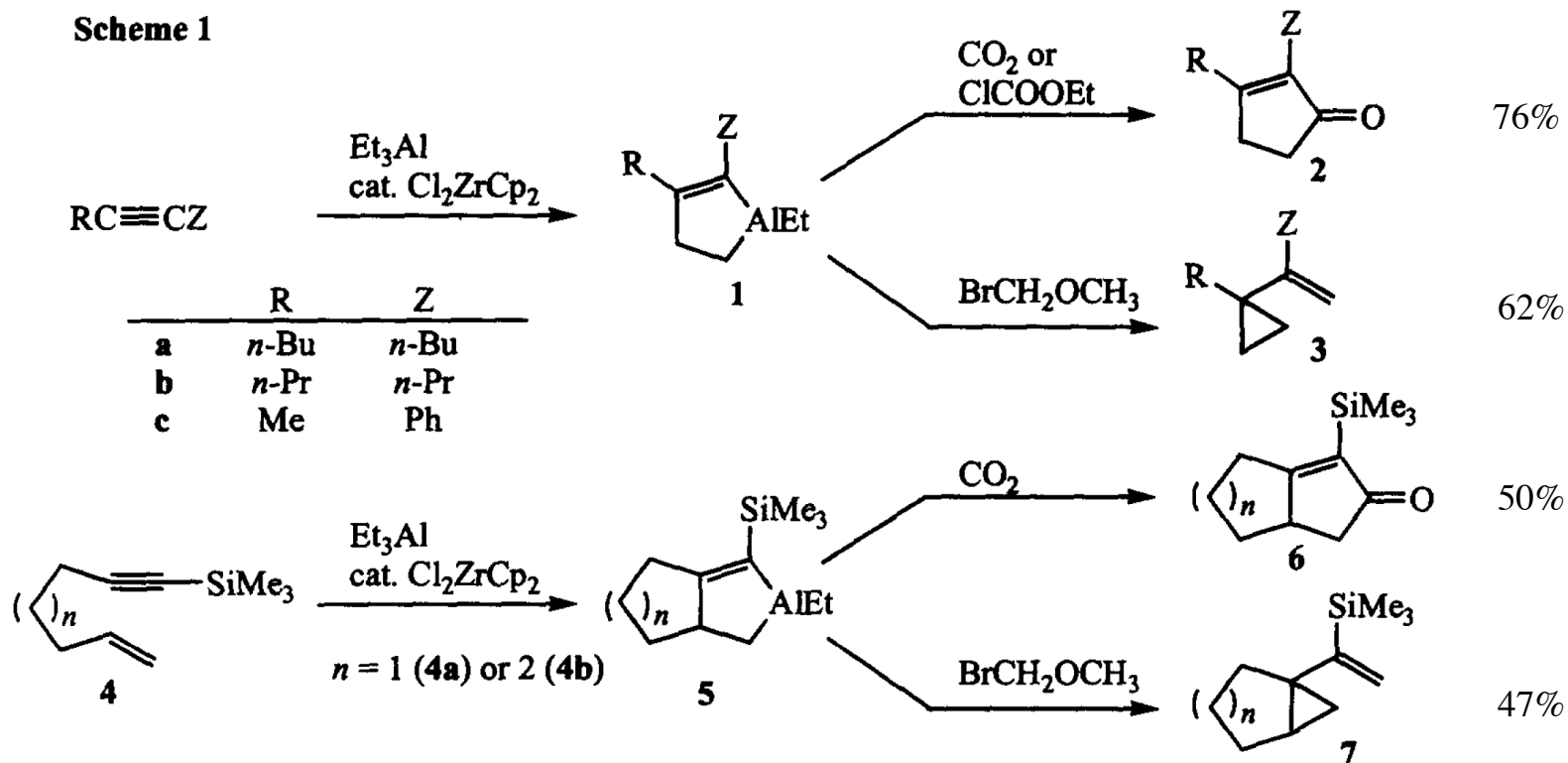


Comparable anti-selective carbometallation



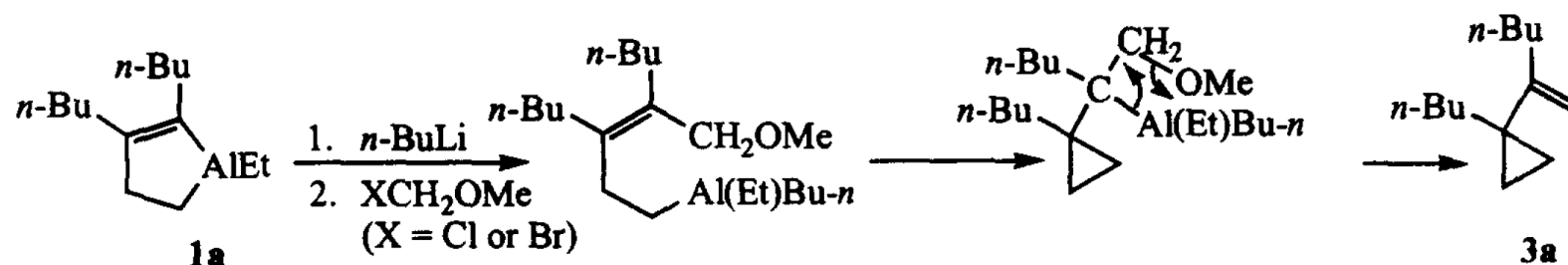
R = CH₃, (H₃C)₃Si, C₆H₅

Cyclic Systems via aluminacycles



Mechanism?

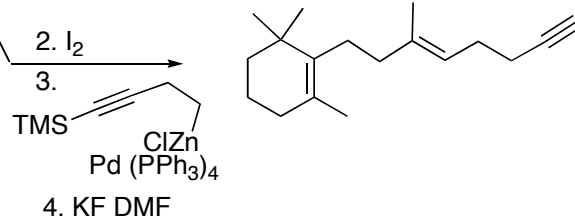
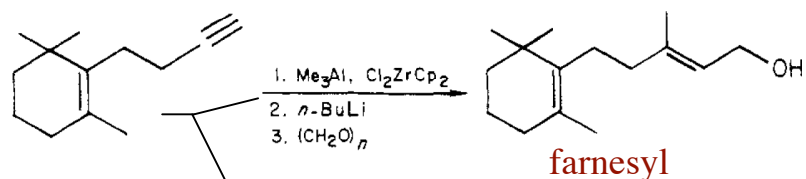
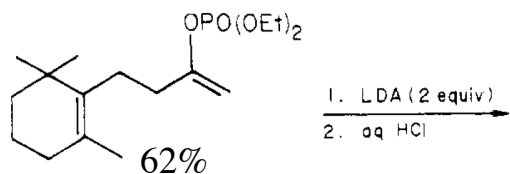
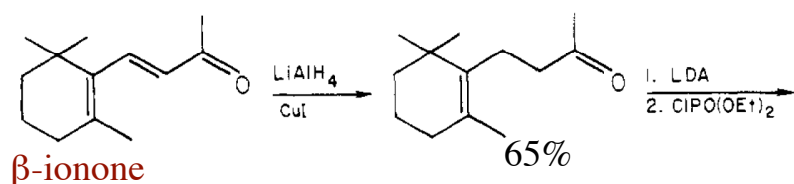
Aluminacycle Mechanism



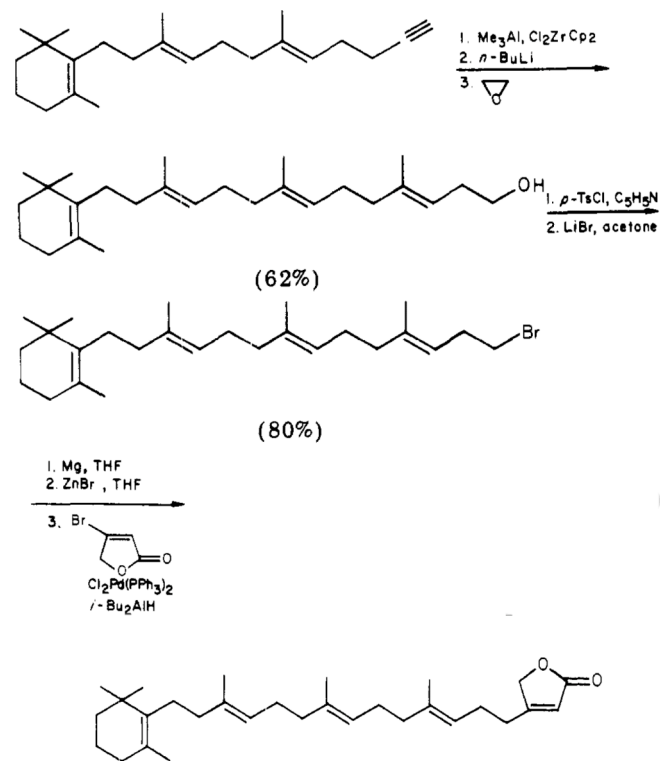
Applications 1: 1,5 dienes

Monocyclofarnesol

Mokupalide

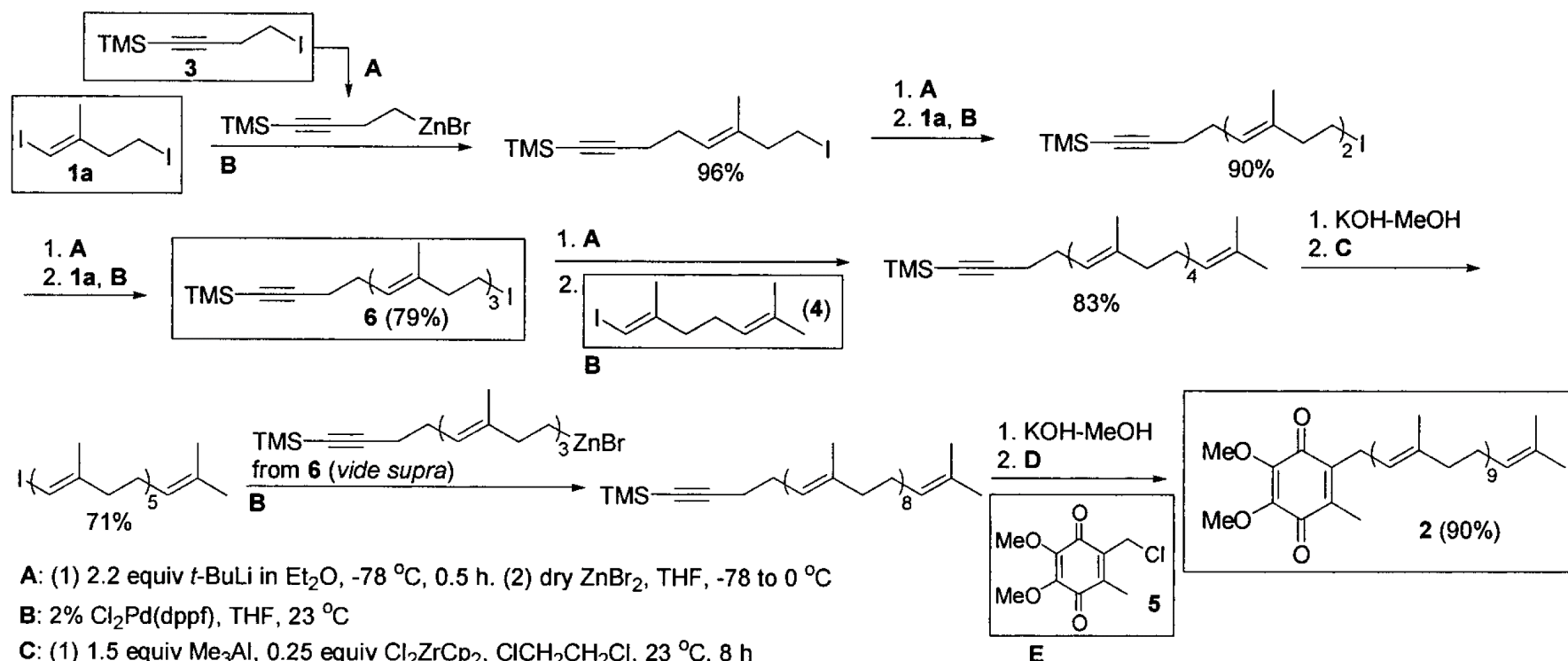


Iteration \rightarrow



Applications 2: 1,5 dienes continued

Coenzyme Q₁₀



A: (1) 2.2 equiv *t*-BuLi in Et₂O, -78 °C, 0.5 h. (2) dry ZnBr₂, THF, -78 to 0 °C

B: 2% Cl₂Pd(dppf), THF, 23 °C

C: (1) 1.5 equiv Me₃Al, 0.25 equiv Cl₂ZrCp₂, ClCH₂CH₂Cl, 23 °C, 8 h

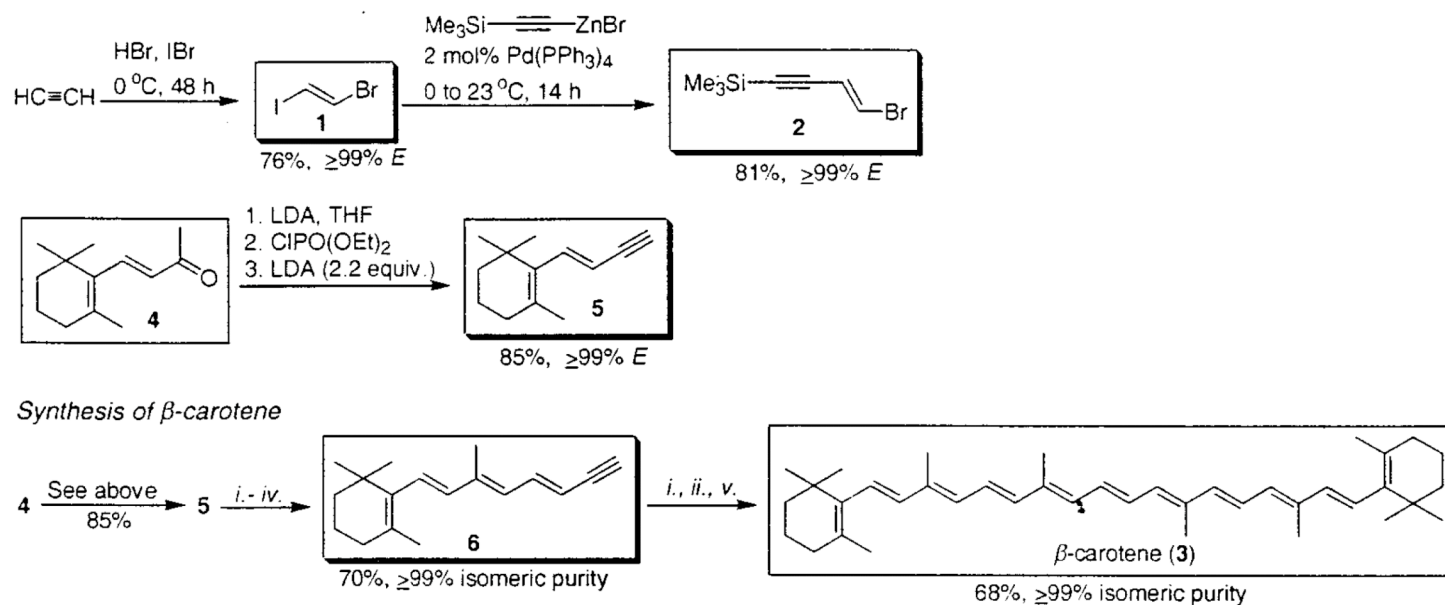
(2) I₂ (1.2 equiv), THF, -78 to 23 °C

D: (1) 1.5 equiv Me₃Al, 0.25 equiv Cl₂ZrCp₂, ClCH₂CH₂Cl, 23 °C, 8 h. (2) solvent evaporation, extraction with hexanes, evaporation, and addition of THF

E: 4% Cl₂Ni(PPh₃)₂, 8% *n*-BuLi, 8% PPh₃, THF, 23 °C

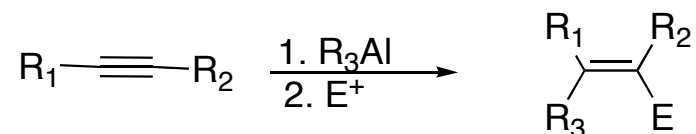
Applications 3: Conjugated systems

β -carotene



^a i. Me_3Al (2 equiv), Cp_2ZrCl_2 (1 equiv), $(\text{CH}_2\text{Cl})_2$, 23°C , 4 h; ii. evaporation at 50°C and <0.5 mmHg; iii. **2** (1.05 equiv), ZnCl_2 (1 equiv) in THF, 2.5 mol % of $\text{Pd}_2(\text{dba})_3$, 10 mol % of TFP [= tri(2-furyl)phosphine], DMF, 23°C , 6 h; iv. K_2CO_3 , MeOH, 23°C , 3 h; v. **1** (0.5 equiv), ZnCl_2 (1 equiv) in THF, 2.5 mol % of $\text{Pd}_2(\text{dba})_3$, 10 mol % of TFP, DMF, 23°C , 8 h;

Synthetic Conclusions



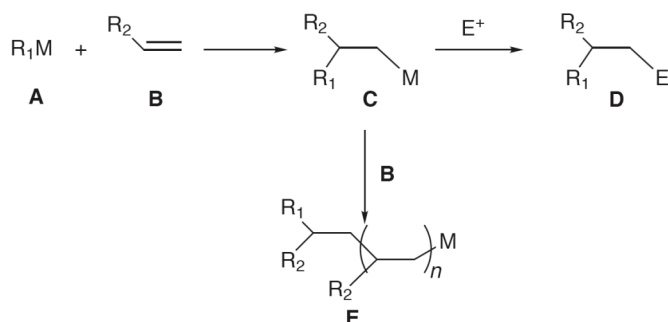
- R_3 groups are limited to small alkyls (by the mechanism).
- Regiochemically most synthetically useful with terminal alkynes.
- Electrophiles are more general: epoxides, aldehydes, cross coupling
- Highly functionalized (with 2 or more FG's), stereochemically defined alkenes can be made in one step.
- Often, it is more synthetically facile to do a second step in tandem than to isolate the product.
- A wide variety of “unfunctionalized alkenes” can be made...often from the same starting material (ie: 1,5-dienes and highly conjugated dienes).
- If the molecule has a coordinating group either E or Z alkenes can be made selectively. Note opposite regioselectivity of Cu reagents.

Extension to Alkenes

Direct comparison to Ziegler-Natta

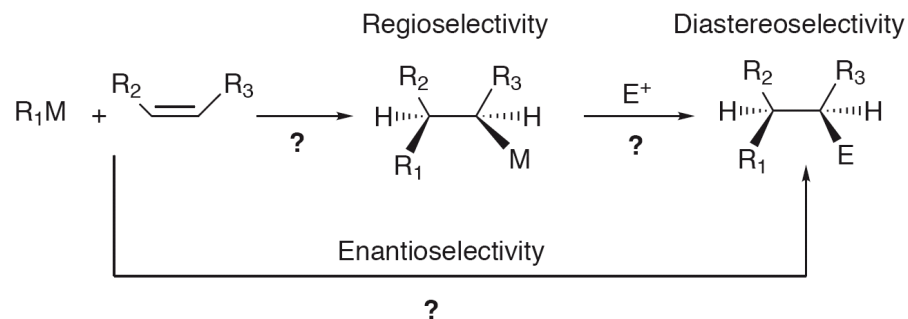
General Scheme

Mechanistic Requirements

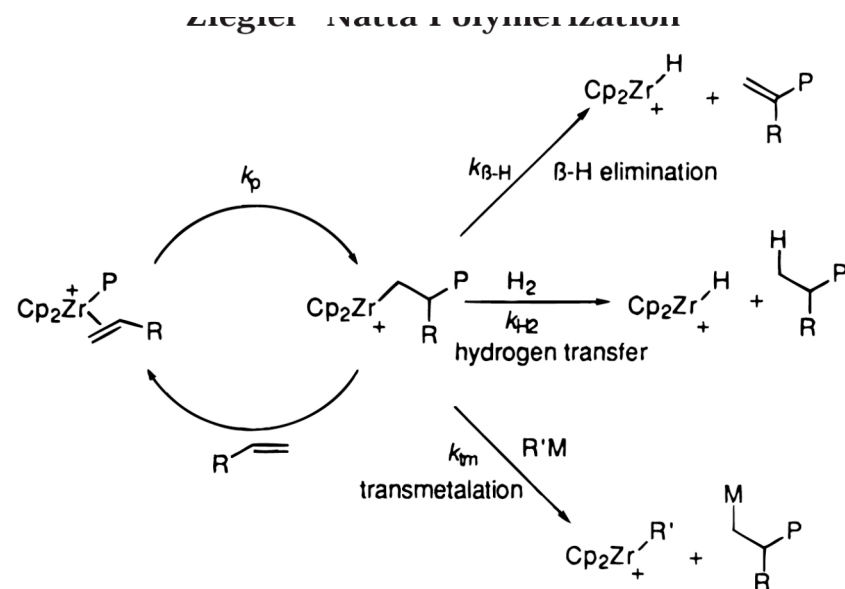


Anionic Polymerization (Ziegler)

Selectivity Issues



Metals used
 Mg, Al, Li, Cu, Zn
Catalyst Systems
 Ti, Zr, Pd, Ni

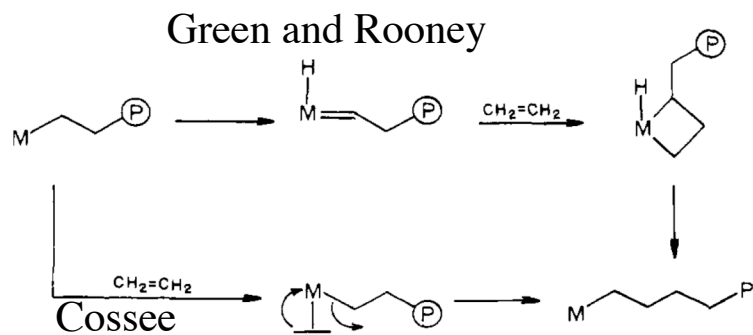


Ziegler-Nata Mechanism

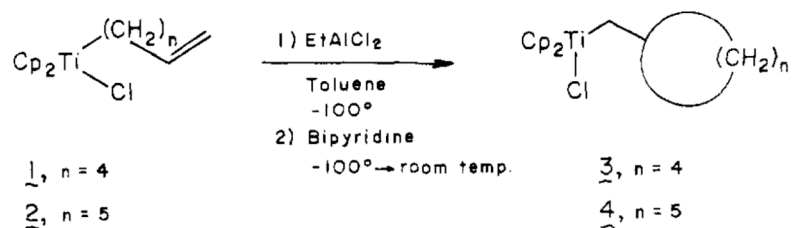
Cossee Proposed, Grubbs provided evidence

There is not a Ti - C double bond

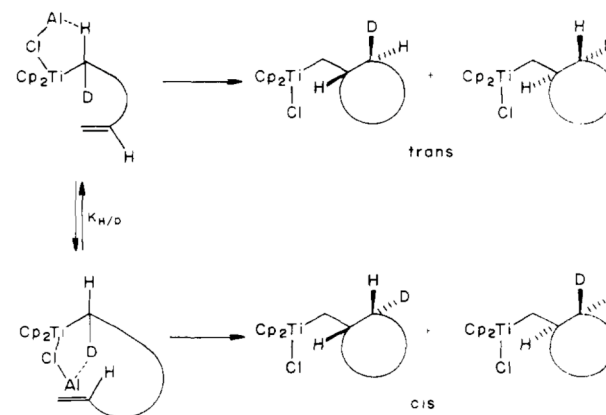
1. Proposed Mechanisms



2. Experiment



3. Observations

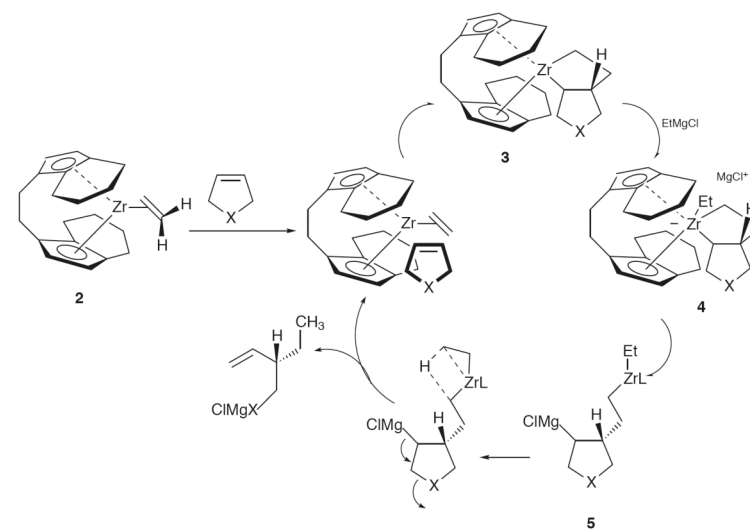
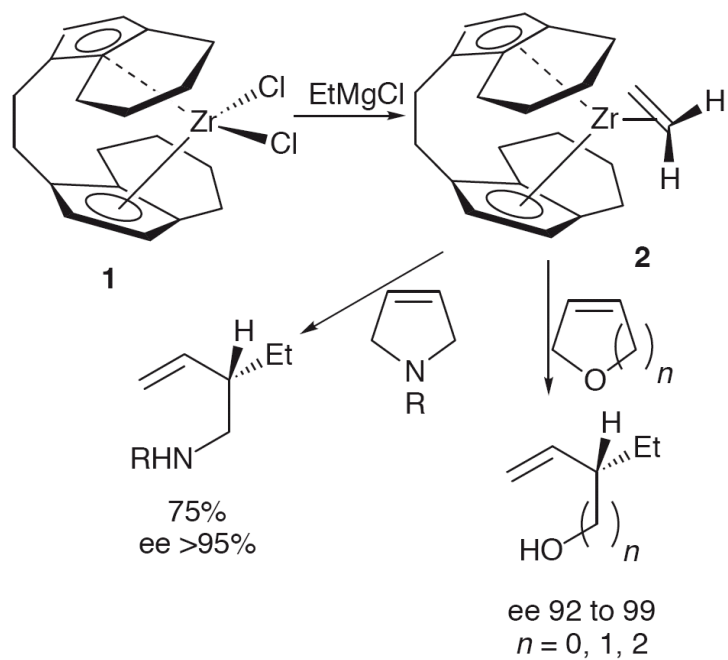


cis:trans = 1:1

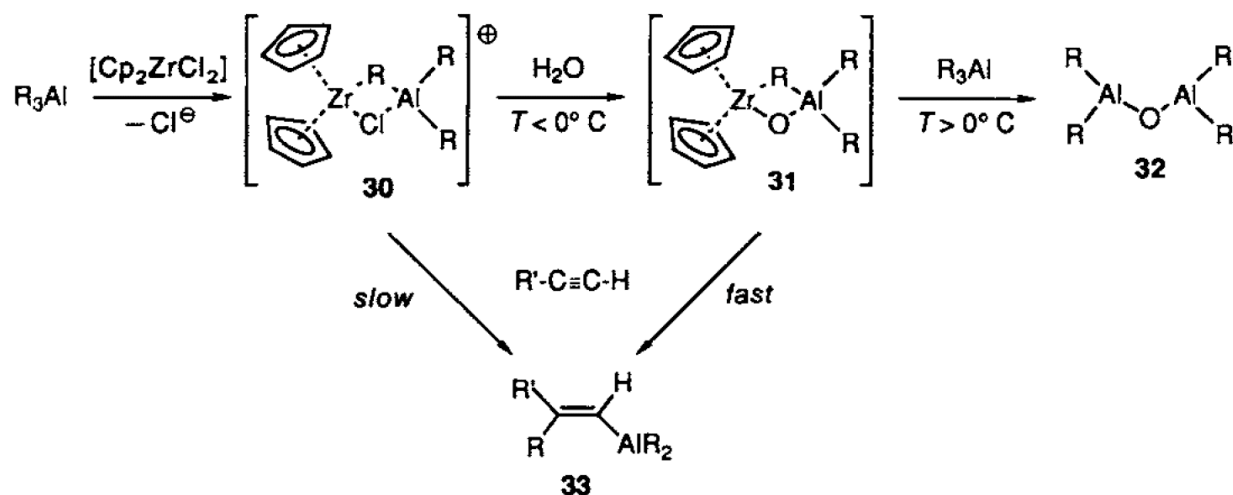
No α -H activation involved

Carbomagnesiation

Catalytic Cycle



Add water: Rapid Rate Enhancement



Without water: 4-12h
With water: minutes