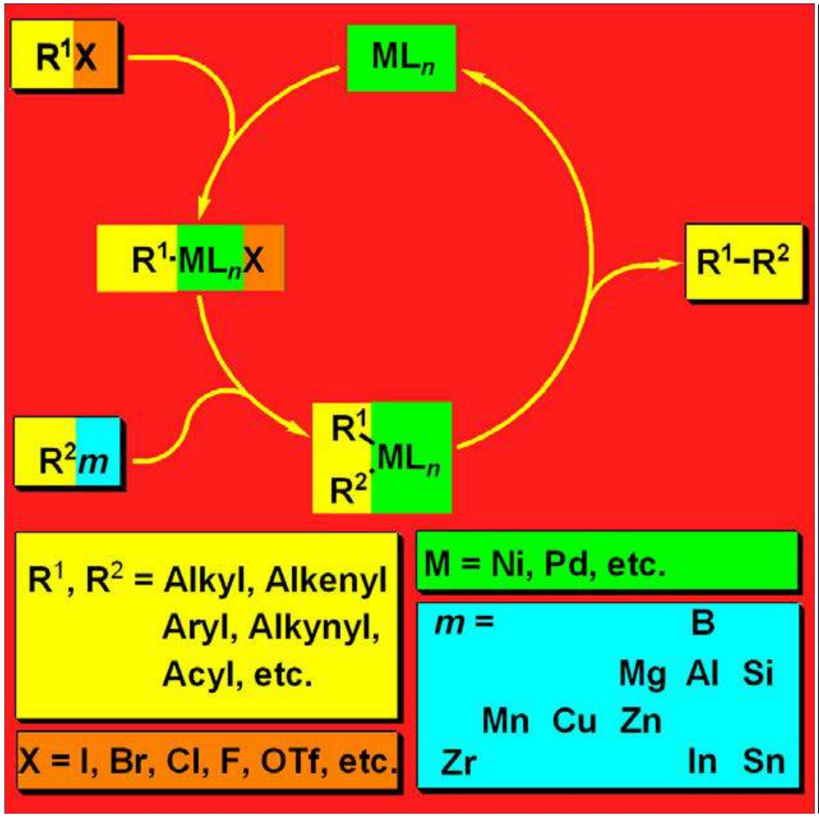
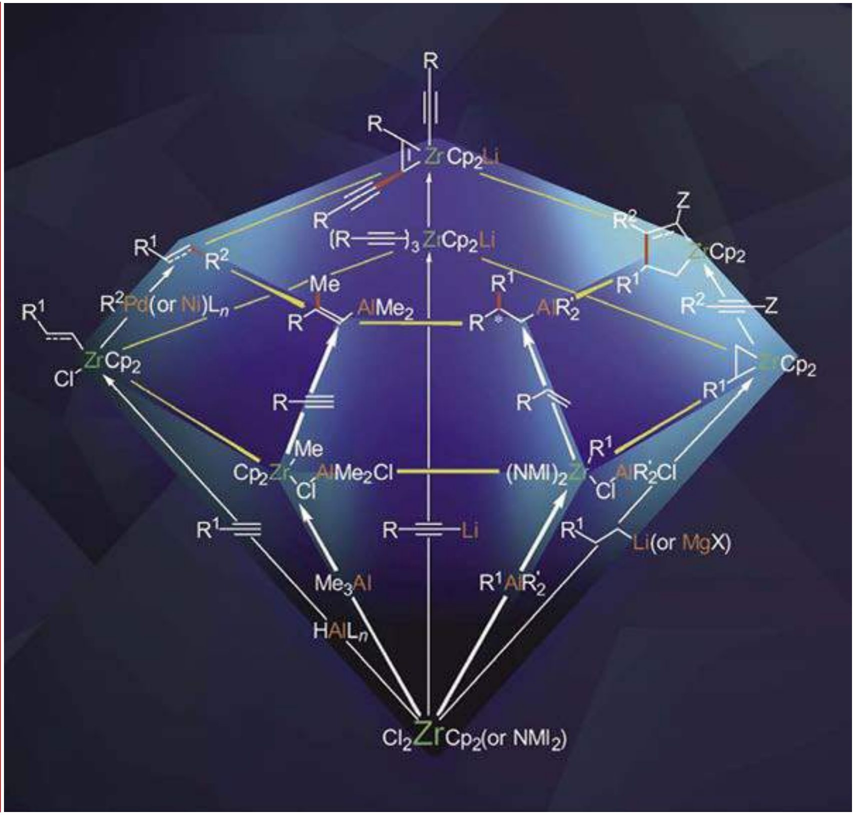
Magical Power of Transition Metals: Past, Present, and Future

Ei-ichi Negishi, Purdue University





How to Synthesize Any Organic Compounds

in High **Y**ields, **E**fficiently, **S**electively, **E**conomically, **S**afely

YES (ES) ! → **Green Chemistry**

1. **Consider all usable elements (ca. 70).**

   Avoid (i) radioactive, (ii) inert, and (iii) inherently toxic elements.

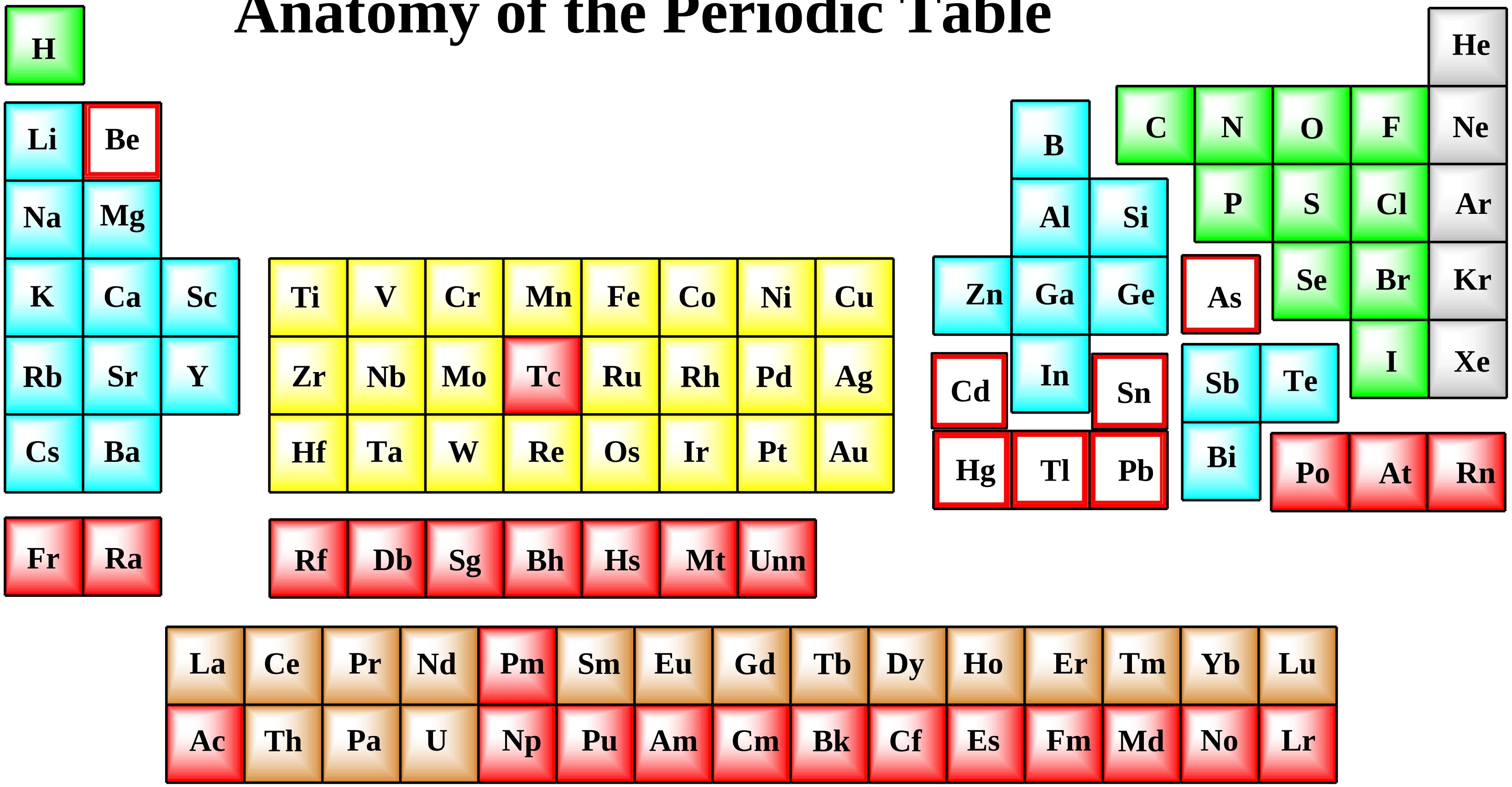
2. If desirable and necessary, **consider their binary combinations** (ca. 5,000). (**Two is Better than One!**)[a]

3. **Use metals for desirable reactivities**.

4. **Use transition metals mainly as catalysts**.

[a] E. Negishi, *CEJ* **1999**, *5*, 411-420.

Anatomy of the Periodic Table



= Radioactive elements (26)

= Organic elements (12 - 1 = 11)

= Main group metals (27 - 6 = 21)

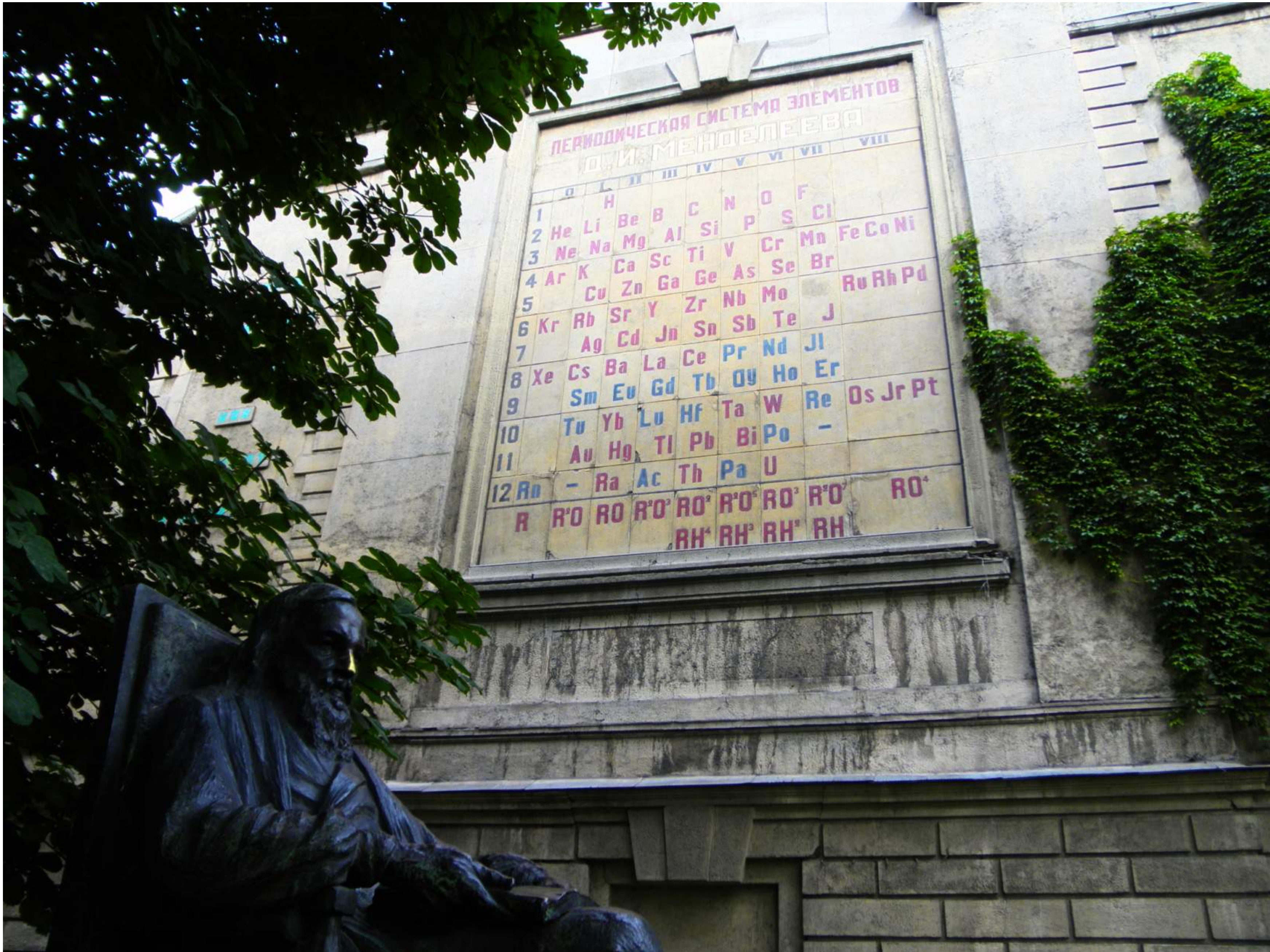
= Intrinsically toxic (?) (7)

= d-Block transtion metals (24 - 1 = 23)

= Inert gases (5)

58 metals usable in Organic Synthesis

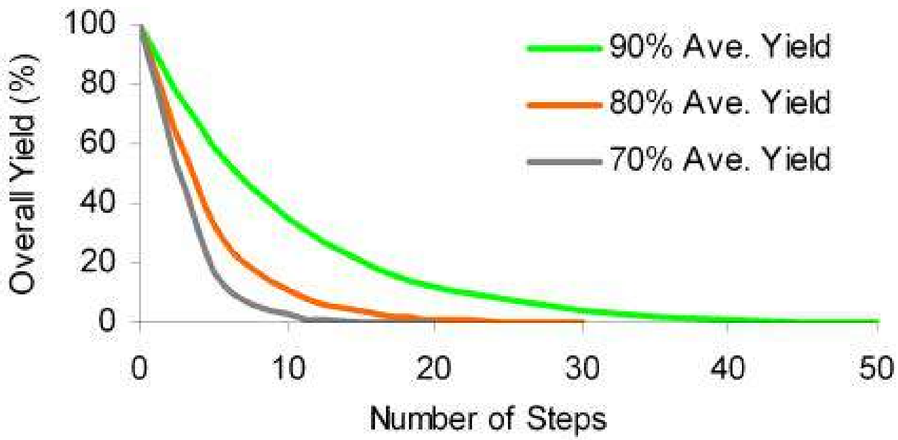
= f-Block transition metals (15 - 1 = 14)


ПЕРИОДИЧЕСКАЯ СИСТЕМА ЭЛЕМЕНТОВ
Д. И. МЕНДЕЛЕЕВА

Effects of Product Yield and Number of Steps on Overall Yield

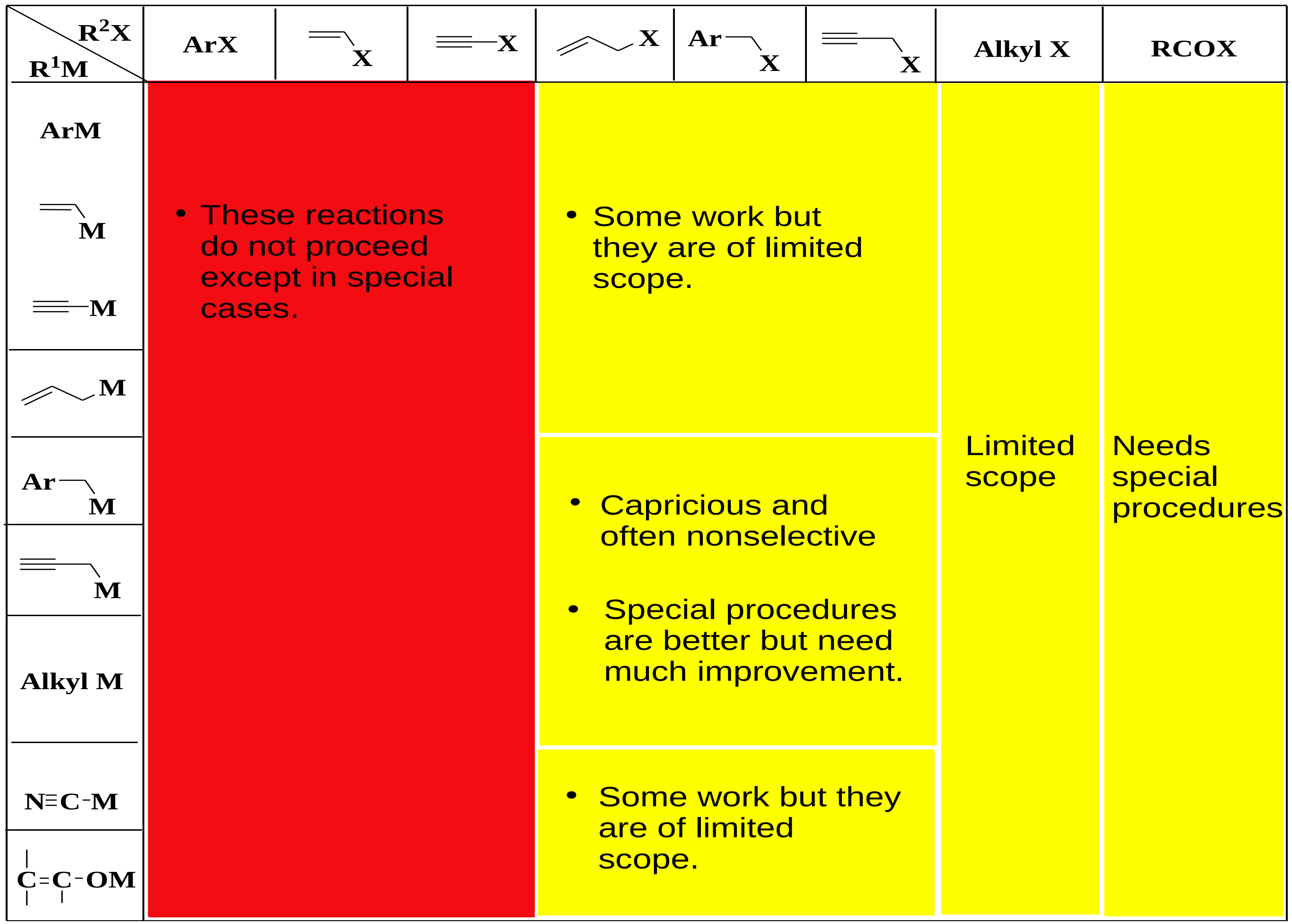
	Overall Yield (%)		
Number of Steps	90% Ave. Yield	80% Ave. Yield	70% Ave. Yield
5	59	33	17
10	35	11	3
15	21	3.6	0.5
20	12	1	0.1
30	4	0.1	
40	1.5		
50	0.5		

"Step-economy" is of utmost importance !



Scope and Limitations of Uncatalyzed Cross-Coupling with Grignard Reagents and Organoalkali Metals

$$R^1M + R^2X \xrightarrow{\text{No Catalyst}} R^1{-}R^2 + M{-}X \quad (M = Mg, Li, etc.)$$



Note: Cu-promoted and Cu-catalyzed reactions have provided some satisfactory procedures.

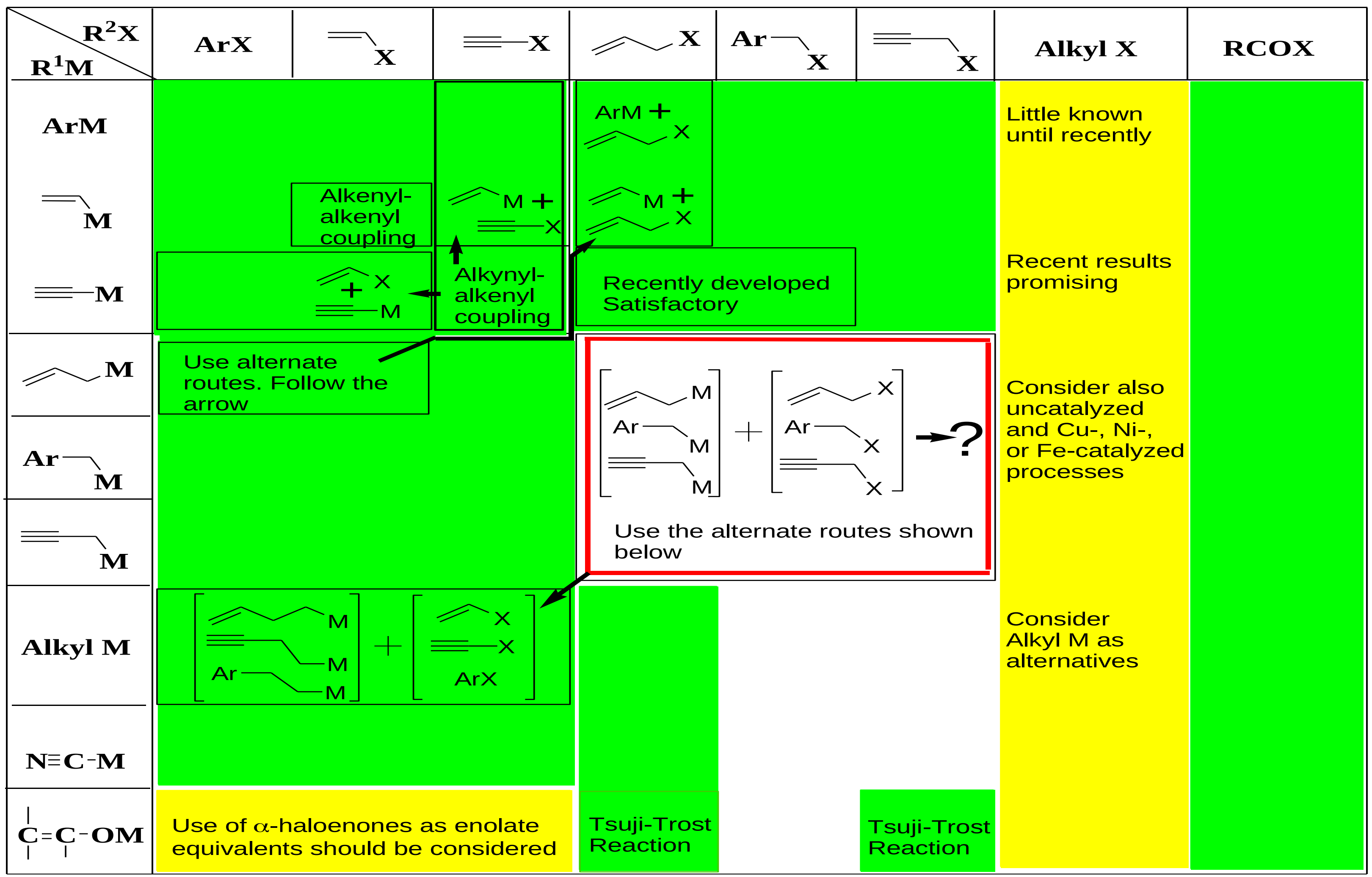
Conventional Wisdom: **Avoid Cross-Coupling! But, should we?**

LEGO Game Approach to C—C Bond Formation via Pd-Catalyzed Cross-Coupling Reactions

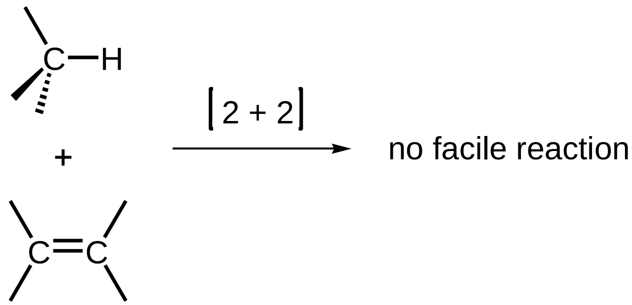
$$R^1\mathbf{M} + R^2\mathbf{X} \xrightarrow{\text{cat. PdL}_n} R^1\text{–}R^2 + \mathbf{M}\text{—}\mathbf{X}$$ (Thermodynamic sink!)

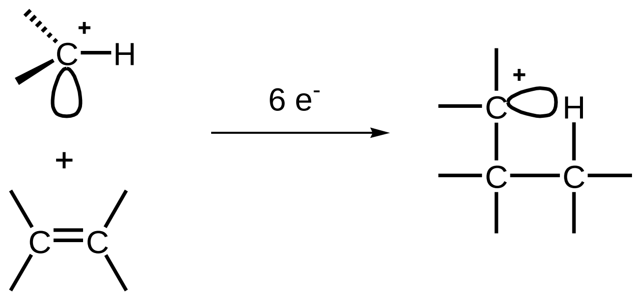
R^1, R^2 = C group. See below. **M** = Mg, Zn, B, Al, In, Si, Sn, Cu, Mn, Zr, etc. **X** = I, Br, Cl, F, OTs, OTf, etc.

M & **X** = **Regio- & stereo-specifiers, which permit a genuine LEGO Game avoiding addition-ELIMINATION ! ! !**

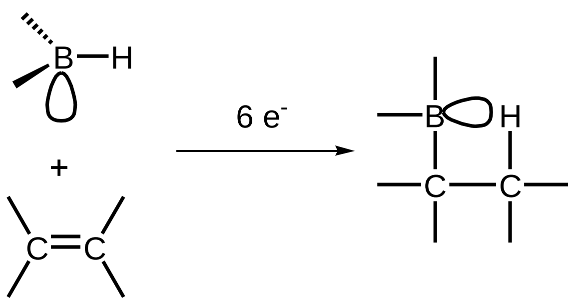


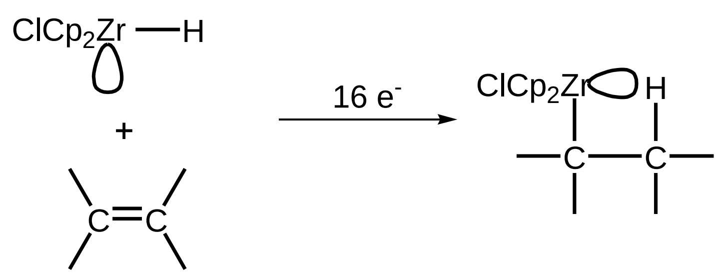
Why Metals?



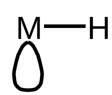


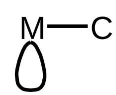
C^+ -- short-lived, uncontrolled



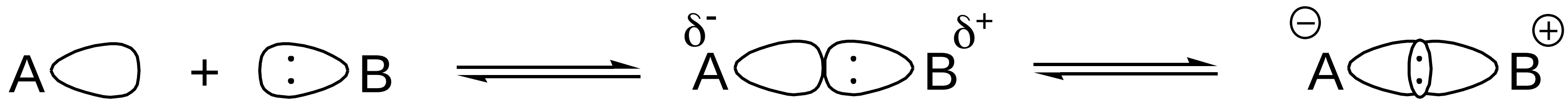


Bottom line:



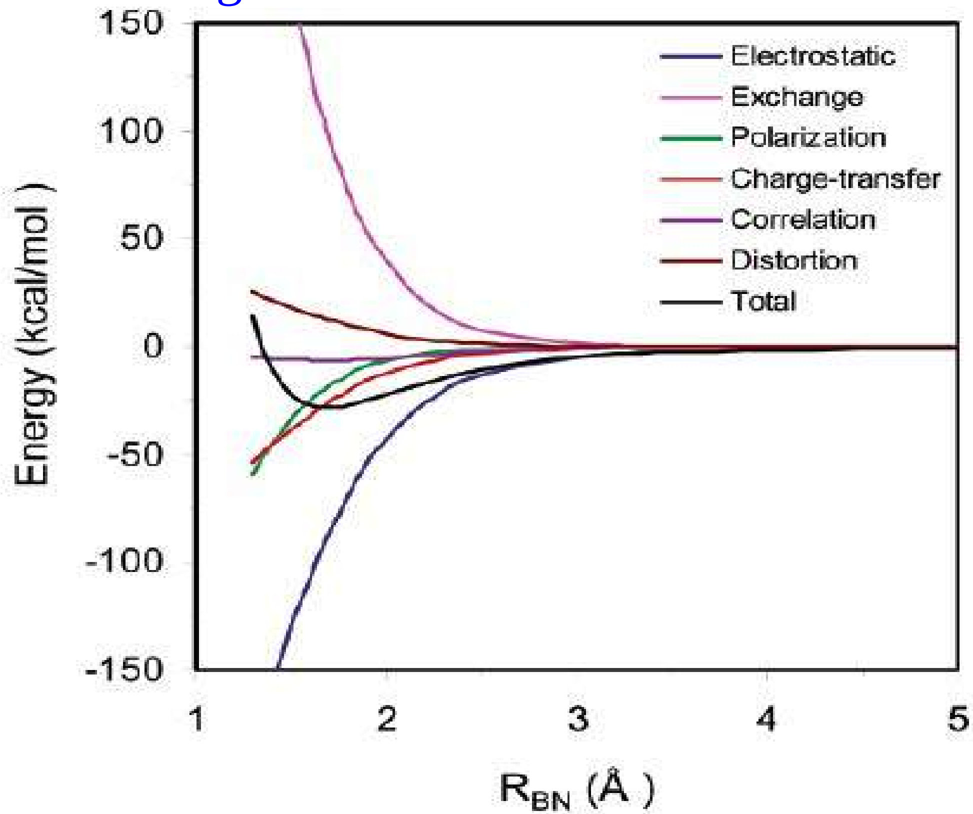


Intermolecular Interaction in Donor-Acceptor Complexes



$$\Delta E_{int} = \Delta E_{es} + \Delta E_{ex} + \Delta E_{pol} + \Delta E_{ct} + \Delta E_{c} + \Delta E_{dist}$$

Interaction = Electrostatic + Exchange Repulsion + Polarization + Charge Transfer + Correlation + Geometry Distortion



Mo, Y.; Song, L.; Wu, W.; Zhang, Q. *J. Am. Chem. Soc.* **2004**, *126*, 3974-3982.

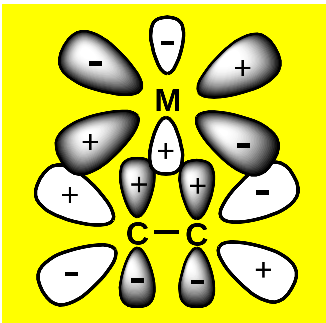
Why d-Block Transition Metals ?

Two Major Reasons (#1)

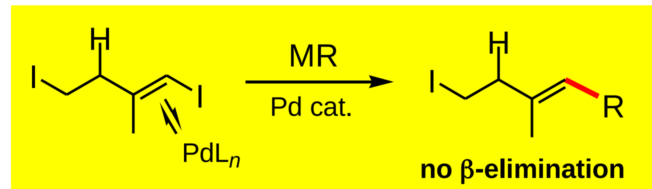
I. Simultaneous Availability of Empty and Filled Non-bonding Orbitals (LUMOs and HOMOs)

Note 1: Strong Affinity toward π-Bonds Explained and Expected.

Note 2: **Highly Reactive** and yet **Stable, and Reversible. ("Super-Carbenoidal")**



- M. J. S. Dewar
- K. Fukui
- R. Hoffmann
- R. B. Woodward

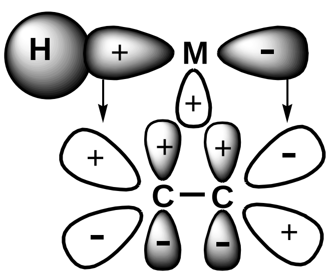


Note: This has been applied to 1,5-diene synthesis as detailed later.

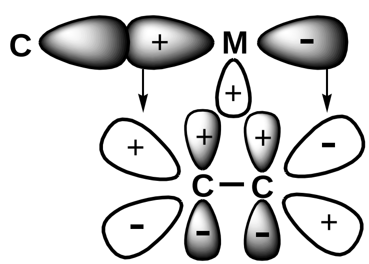
Note 3: **Non-bonding Orbitals** can be substituted with **σ-Orbitals ("Elemento-metalation")**

(These are available to main group metals as well. The only key requirement --- an empty orbital.)

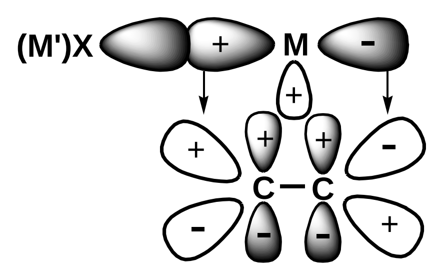
Hydrometalation



Carbometalation

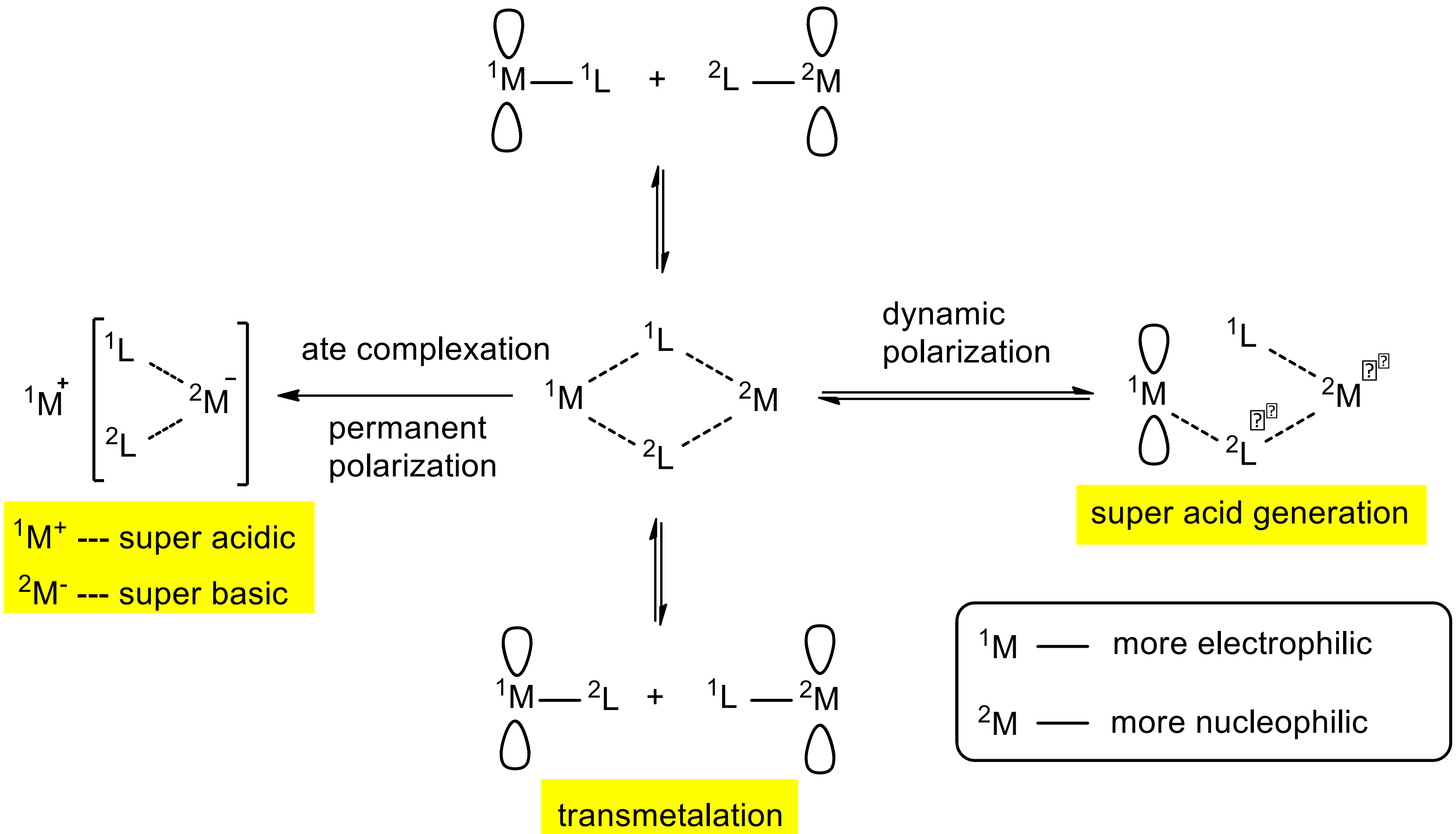


Hetero(Metallo)metalation



The significance of **concerted synergistic** (HOMO-LUMO & HOMO-LUMO) bonding cannot be overemphasized.

Interactions between Two Coordinatively Unsaturated Metal Species



Bottom line: Two is better than one

Genealogy of
Pd-Catalyzed Cross-Coupling

Several Independent Discoveries(1975-1979)

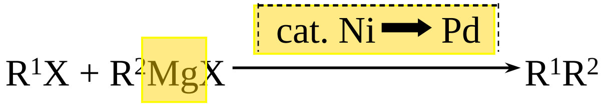
Mg: S. I. Murahashi, N. Ishikawa,
J. F. Fauvarque (1975 & 1976)
(Following **Mg-Ni** version of
Tamao, Kumada and Corriu, 1972)

Al, Zn, Zr: E. Negishi (1976-1977)

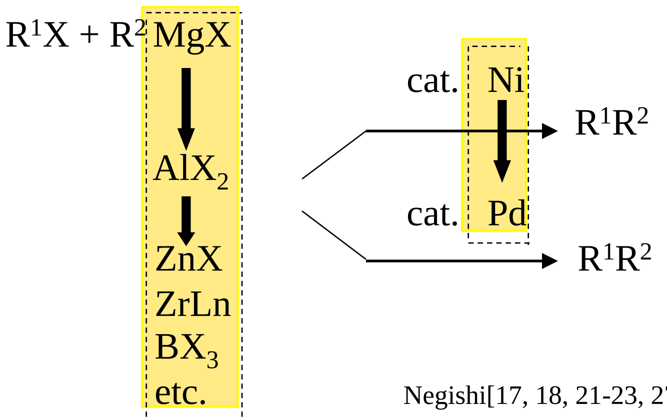
B: E. Negishi (1978) → A. Suzuki (1979)

Sn: M. Kosugi (1977) → J. K. Stille (1978)

Other metals: **Li, Na, K, Cu, In, Si, Mn**



Murahashi[15], Fauvarque[19], Ishikawa[20]



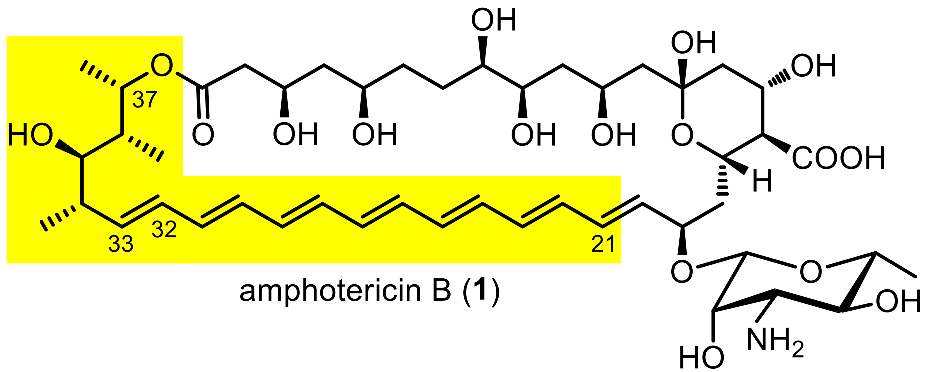
Negishi[17, 18, 21-23, 27-30]

<u>Negishi group contributions</u>:

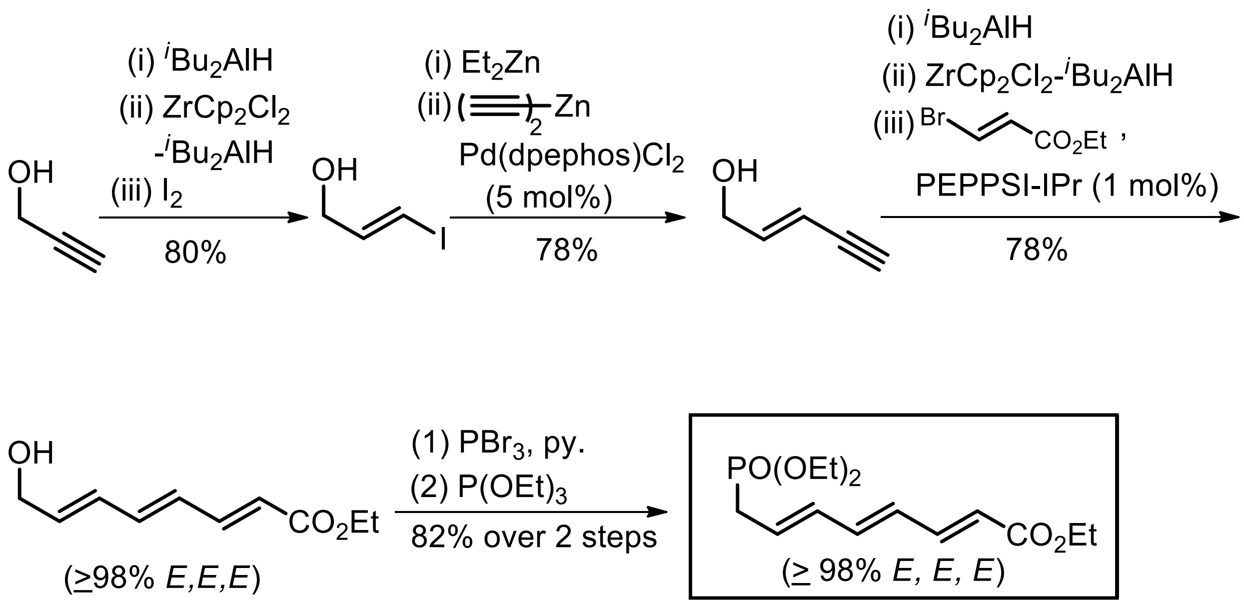
1. Co-discovery of Pd-Catalyzed Cross-Coupling
2. Discovery of Al, B, Zn, Zr, etc. as Effective Metal Countercations
3. Discovery of Hydrometallation—Cross-Coupling & Carbometallation—Cross-Coupling Tandem Reactions
4. Discovery of Double Metal Catalysis, especially with ZnX_2

- Negishi, E., *J. Organomet. Chem*. **2002**, 653, 34.
- Negishi, E., Ed., *Handbook of Organopalladium Chemistry for Organic Synthesis* **2002**, Wiley, Part III, pp 285-1119.

⇨ "Last" Synthesis of Amphotericin B C21-C37 Fragment



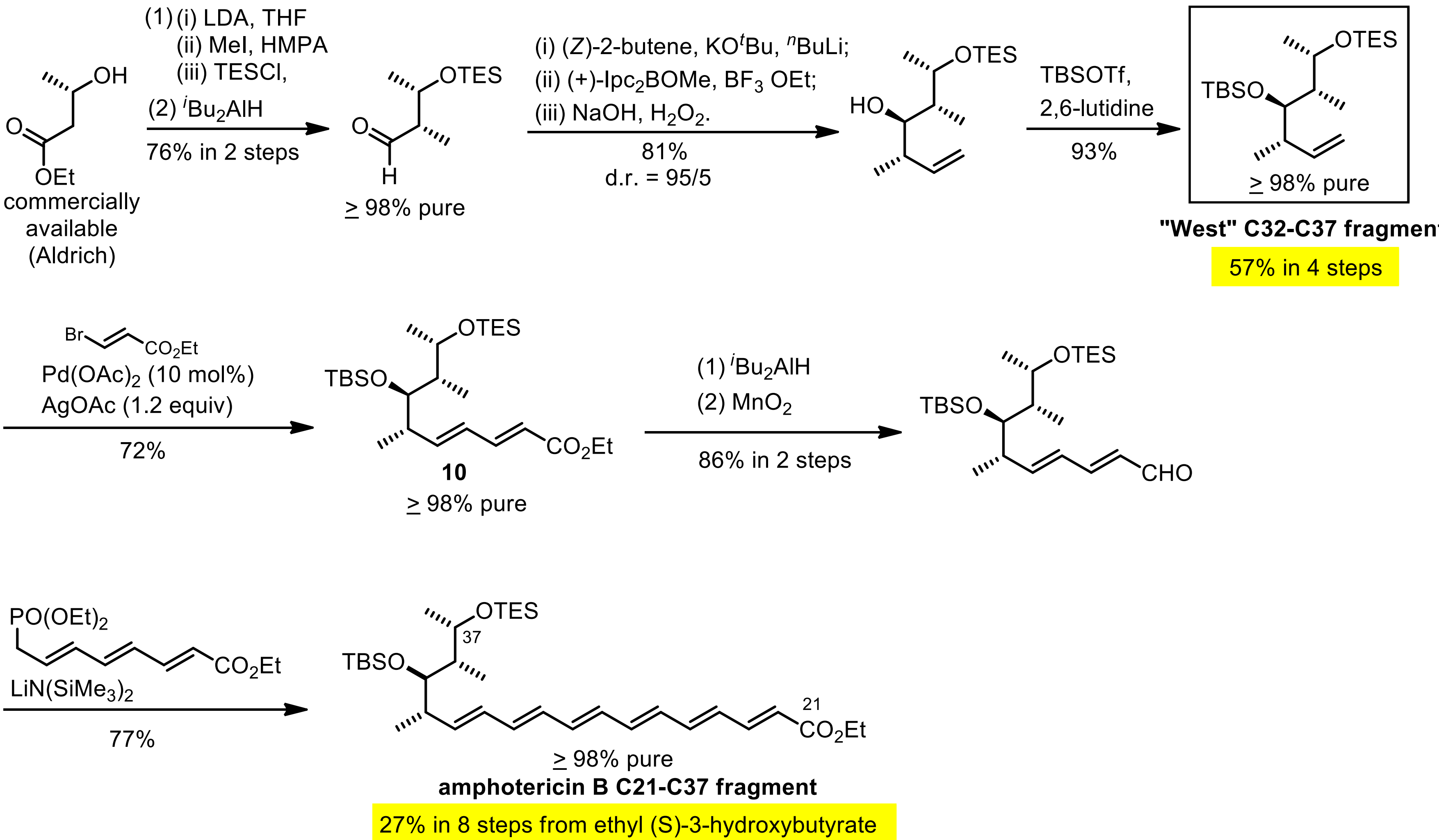
amphotericin B (**1**)



40% in 5 steps
from propargyl alochol

G. Wang, S. Xu, Q. Hu, F. Zeng, E. Negishi, *Chem. Eur. J.* **2013**, *19*, 12938-12942.

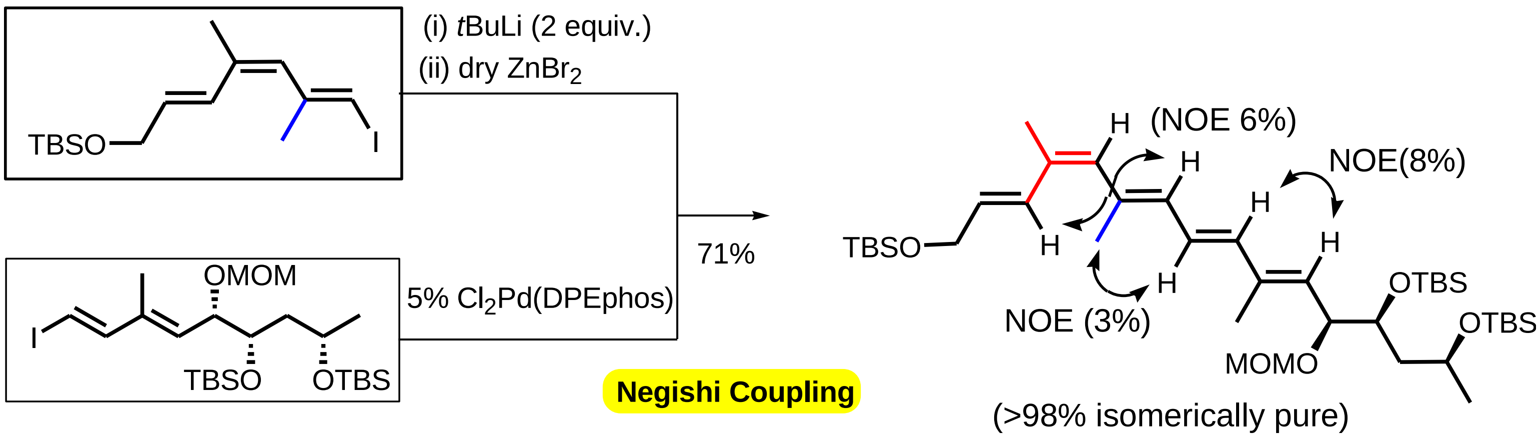
⇨ “Last” Synthesis of Amphotericin B C21-C37 Fragment

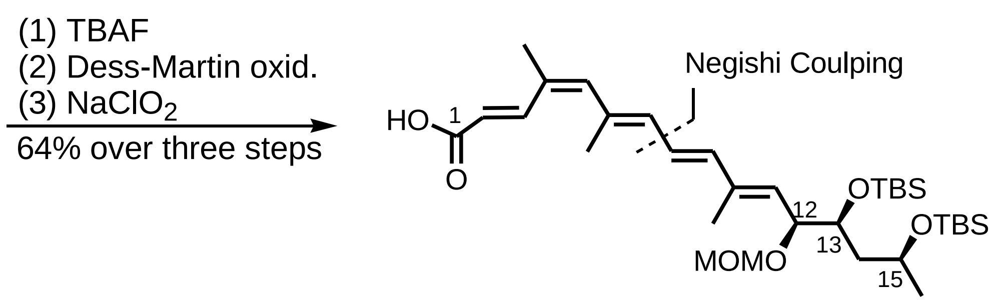


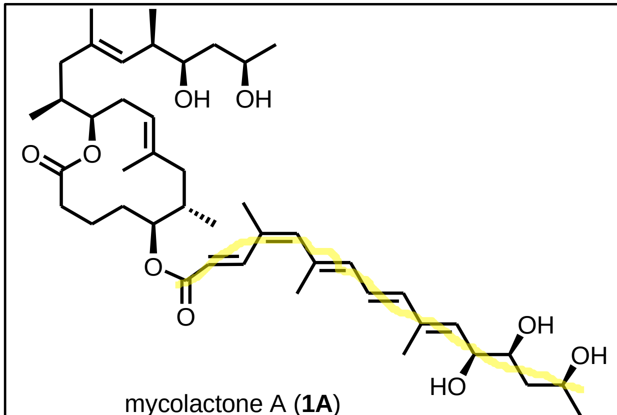
G. Wang, S. Xu, Q. Hu, F. Zeng, E. Negishi, *Chem. Eur. J.* **2013**, *19*, 12938-12942.

Total syntheses of mycolactones A and B

⇨ *Synthesis of Triprotected Side-Chain of Mycolactone A*







mycolactone A (**1A**)

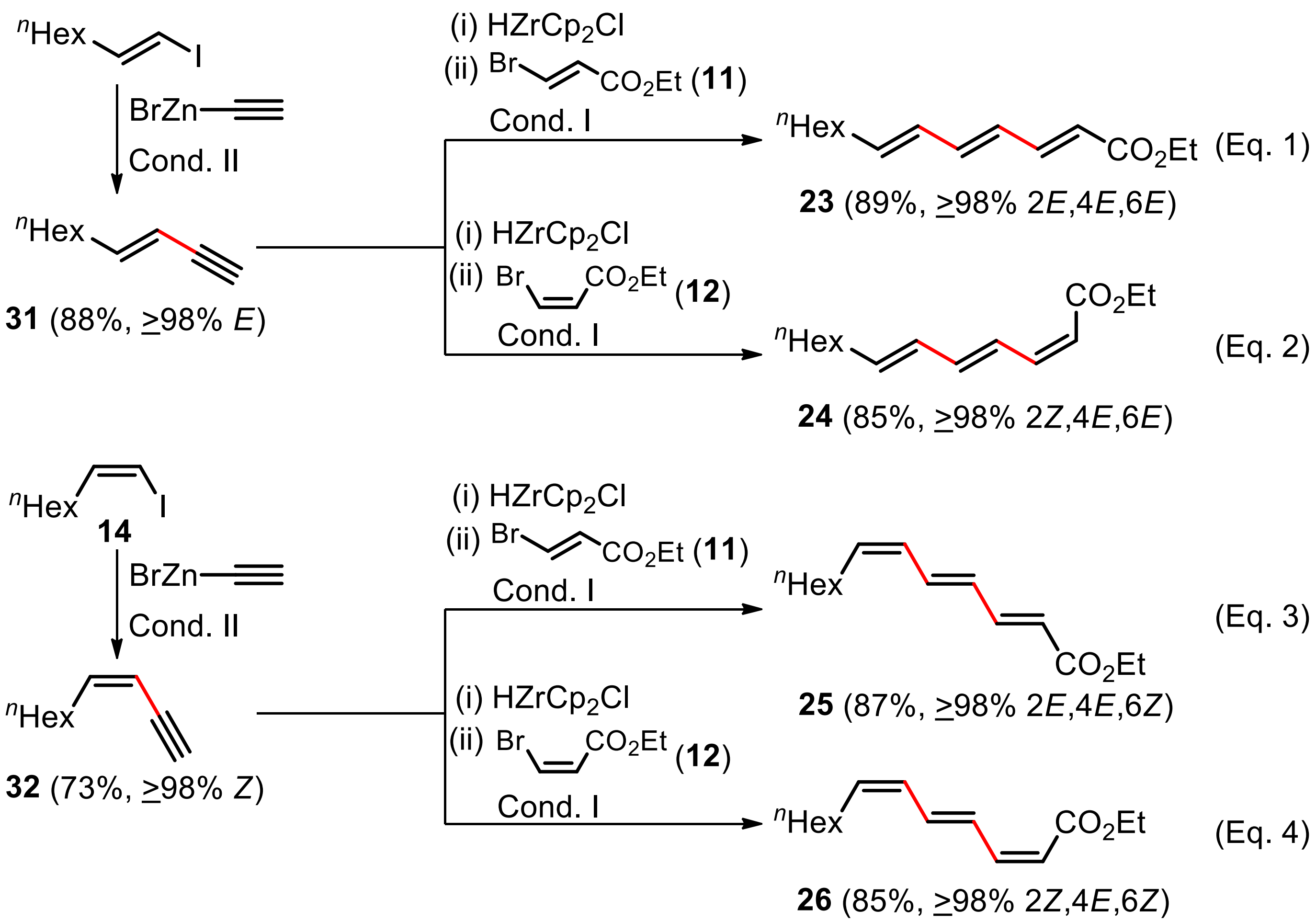
16% overall yield in the longest linear sequence (17 steps)

from ethyl (S)- 3-hydroxybutyrate

G. Wang, N. Yin, E. Negishi, *Chem. Eur. J.* **2011**, *17*, 4118 - 4130.
N. Yin, G. Wang, E. Negishi, *Angew. Chem. Int. Ed.* **2006**, *45*, 2916-2920.

Alkyne Elementometalation–Pd-Catalyzed Negishi Coupling Tandem Processes.

⇨ *Highly (≥98%) Selective Synthesis of All Stereosiomers of 2,4,6-Trienoic Esters*



Cond. I: 1% PEPPSI,THF, 23 °C, 12 h

Cond. II: 5% Pd(DPEphos)Cl_2, THF, 23 °C, 12 h

G. Wang, S. Mohan, E. Negishi. *Proc. Natl. Acad. Sci. USA*, **2011**, *108*, 11344-11349.

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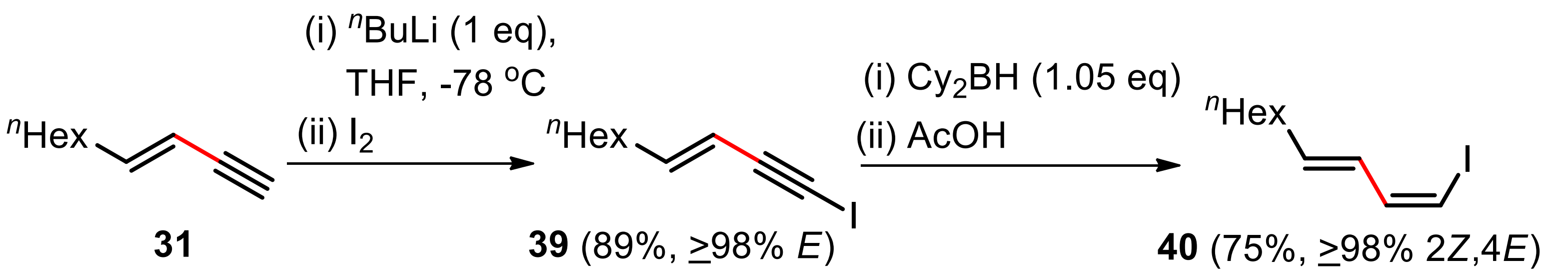

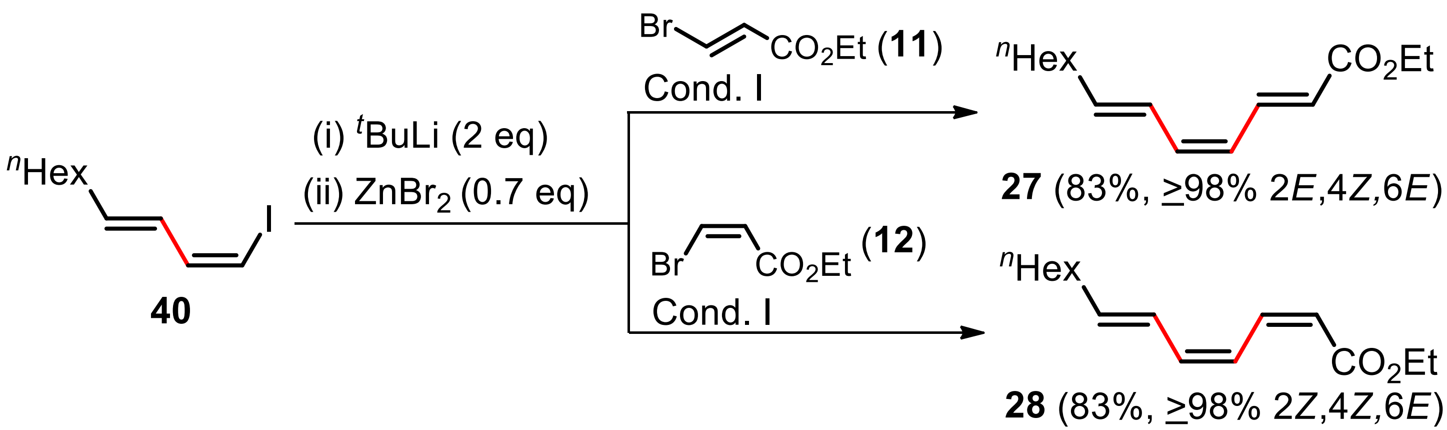

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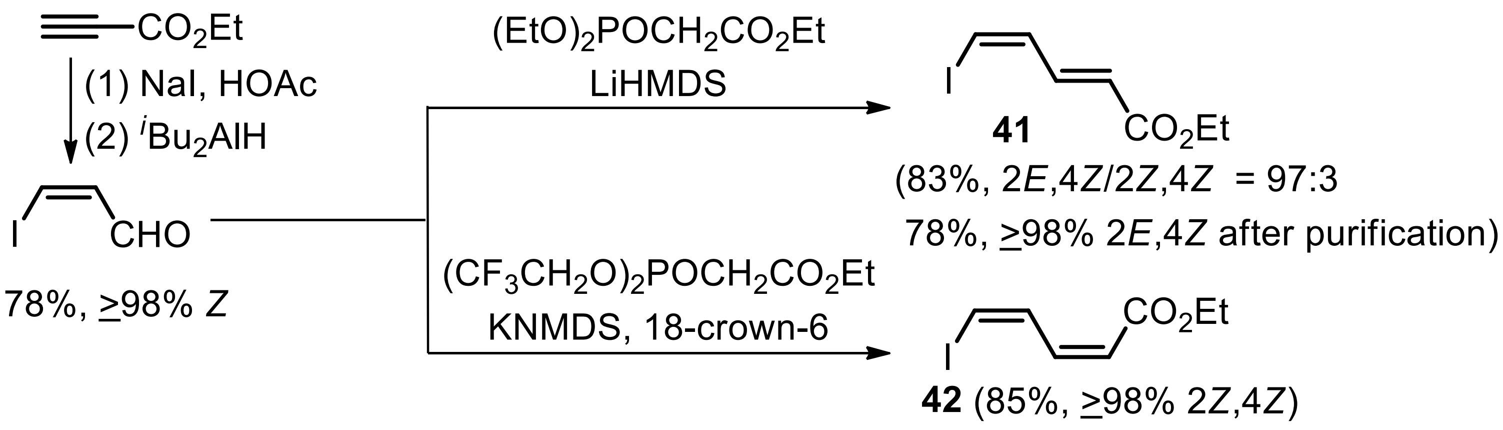
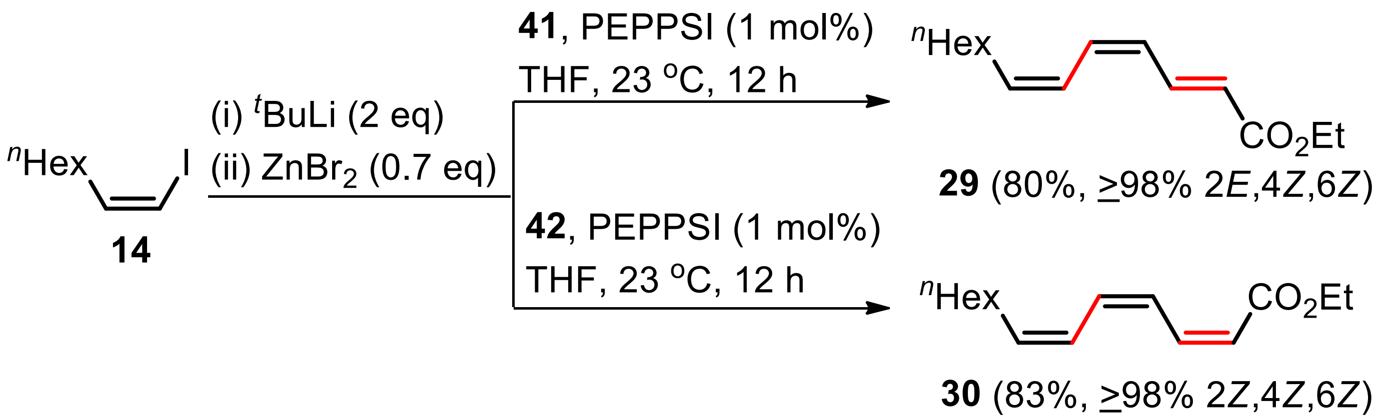
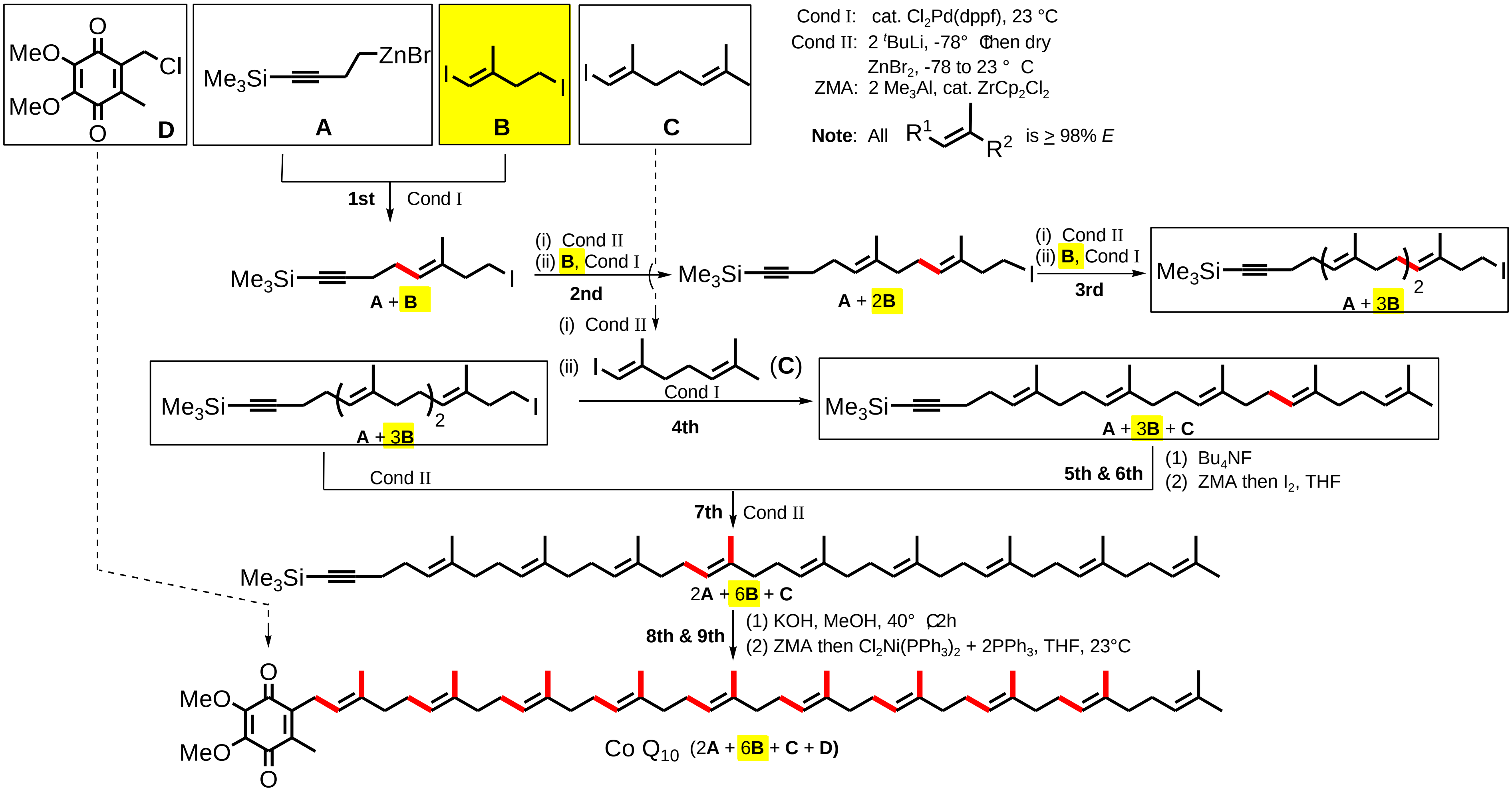




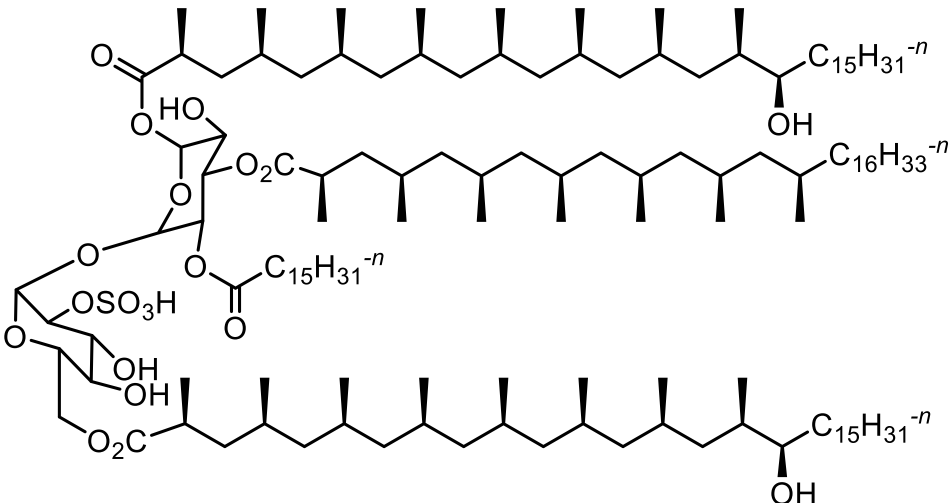
G. Wang, S. Mohan, E. Negishi. *Proc. Natl. Acad. Sci. USA*, **2011**, *108*, 11344-11349.

Alkyne ZMA–Pd-Catalyzed Alkyl–Alkenyl Coupling: LEGO Game Route to Co Q_{10}

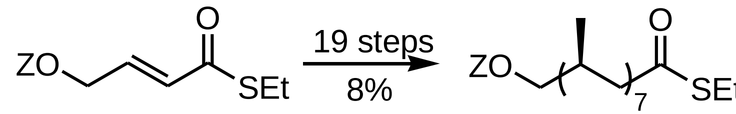


S.-Y. Liou, C. Xu, S. Huo & EN. *OL*, **2002**, 261
B. Lipshutz, G. Bulow, F. Fernandez-Lazaro, S.-K. Kim, R. Lowe, P. Mollard, K. Stevens. *J. Am. Chem. Soc.* **1999,** 11664

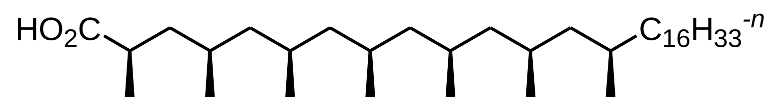
CAN WE POSSIBLY SYNTHESIZE THESE NATURAL POLYOLEFINS BY THE ZIEGLER-NATTA POLYMERIZATION?



Sulfolipid-□, a virulence factor in *Mycobacterium tuberculosis*



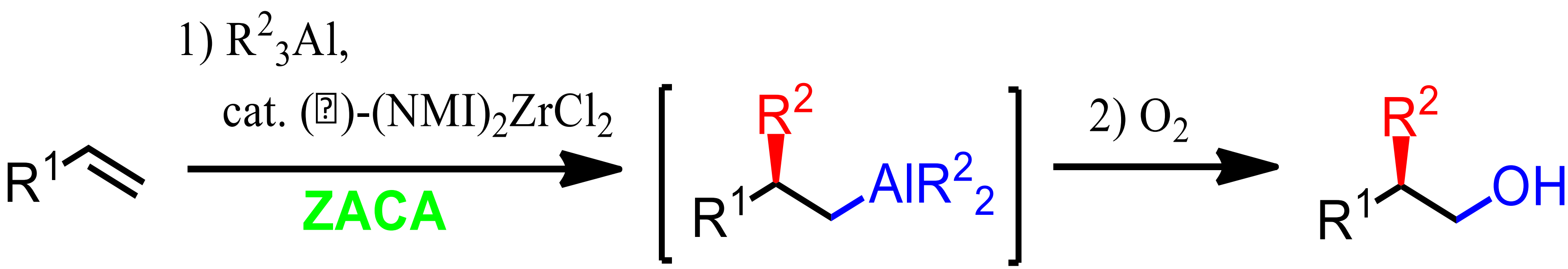
- Key reagents: MeMgBr, 1% Josiphos-CuBr
- For a recent synthesis of **phthioceranic acid (1)**, see: ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *OL*, **2007**, *9*, 3013



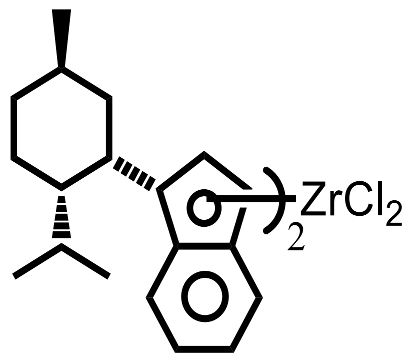
phthioceranic acid (1)

Nature does it, but……

Zr-Catalyzed Asymmetric Carboalumination of Alkenes (ZACA Discovery)



(-)-$(NMI)_2ZrCl_2$=



R^2 = Me, 68-92% yield, 70-90% ee

R^2 = Et, 56-90% yield, 85-95% ee

R^2 = Higher primary alkyl groups, 74-85% yield, 90-95% ee

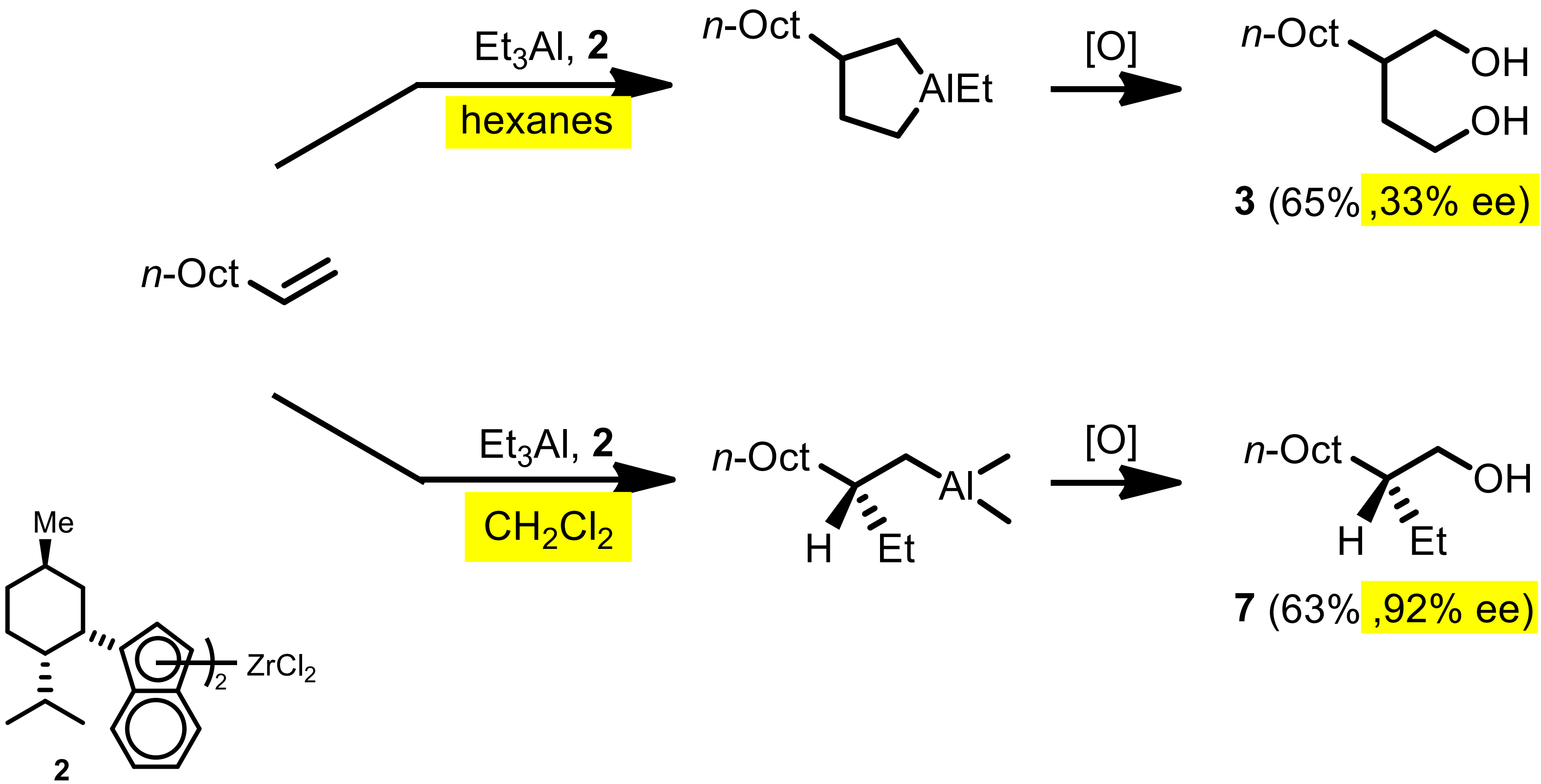
Early Contributions

- Kondakov, D. Y.; Negishi, E., 1995 *JACS* 10771, 1996 *JACS* 1577.
- Huo, S.; Negishi, E., 2001 *OL* 3253.
- Huo, S.; Shi, J.; Negishi, E., 2002 *ACIE* 2141.

Contributions by Others

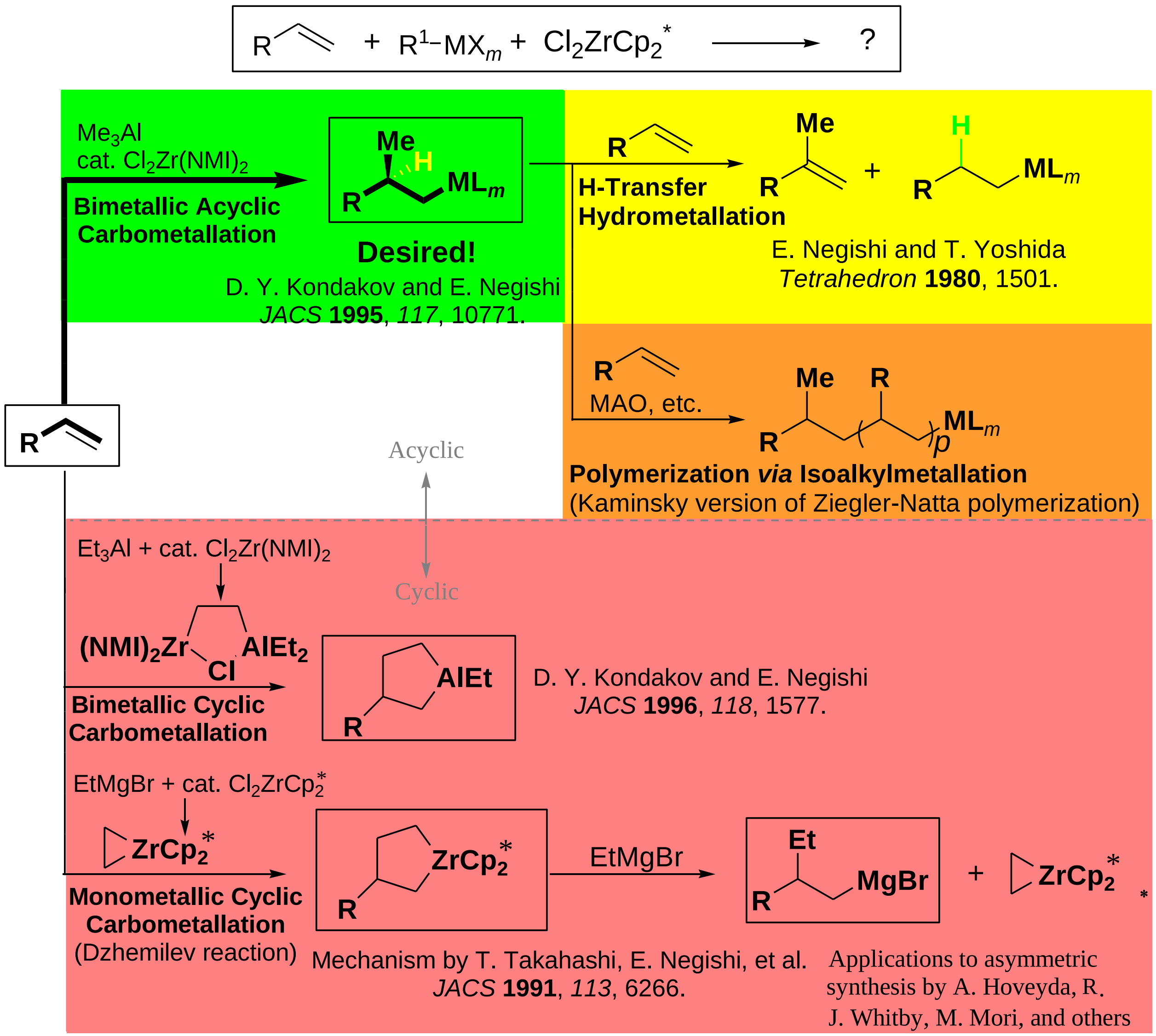
- Erker, G. *et a*l. 1993 *JACS* 4590
- Wipf, P.; Ribe, S. 2000 *OL* 1713

Zr-Catalyzed Asymmetric Carboalumination of Alkenes (Solvent Effect)



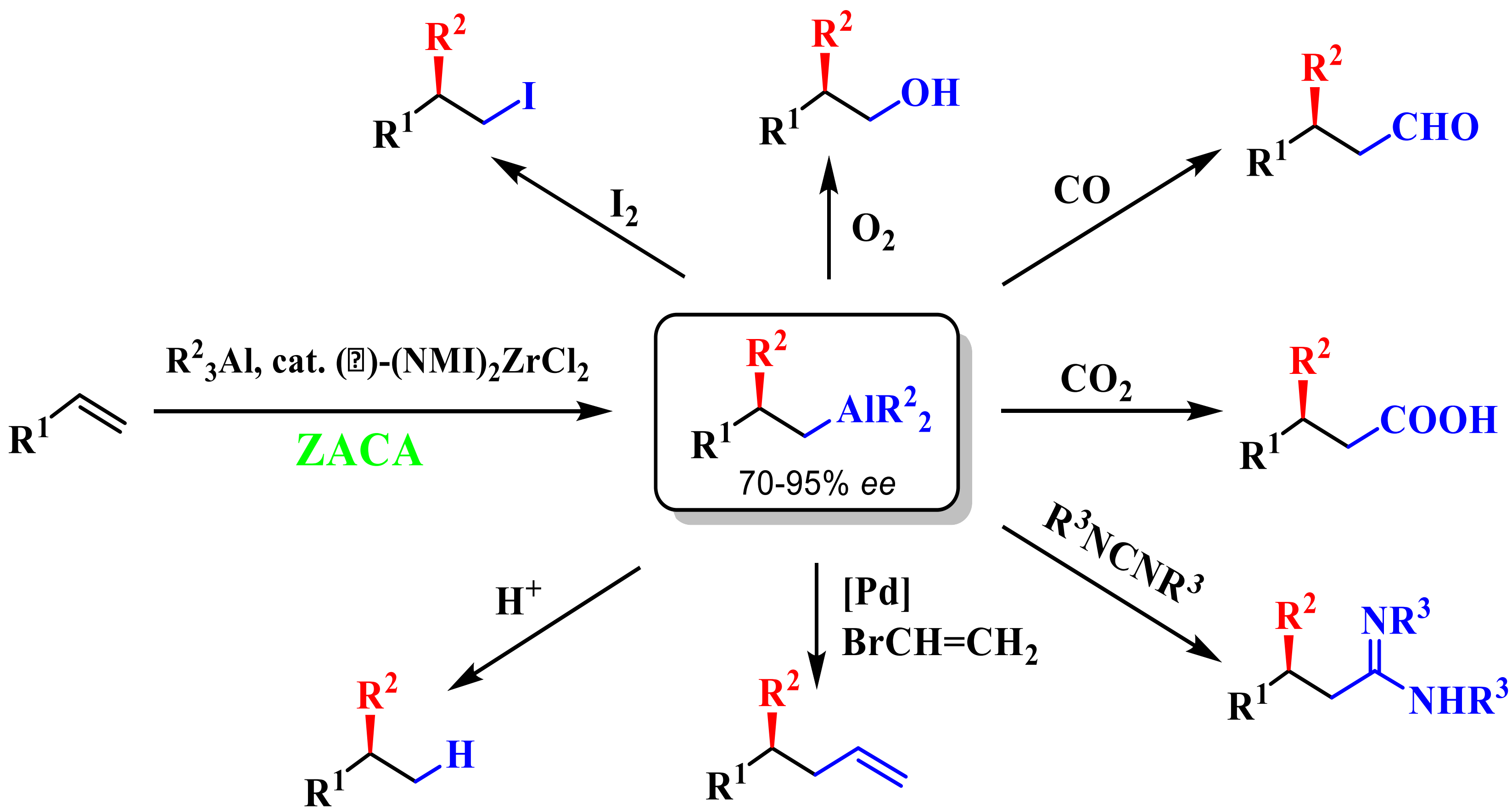
Kondakov, D. Y.; Negishi, E. *J. Am. Chem. Soc*. **1996**, *118*, 1577-1578.

WHAT CAN HAPPEN IN THE FOLLOWING REACTIONS?



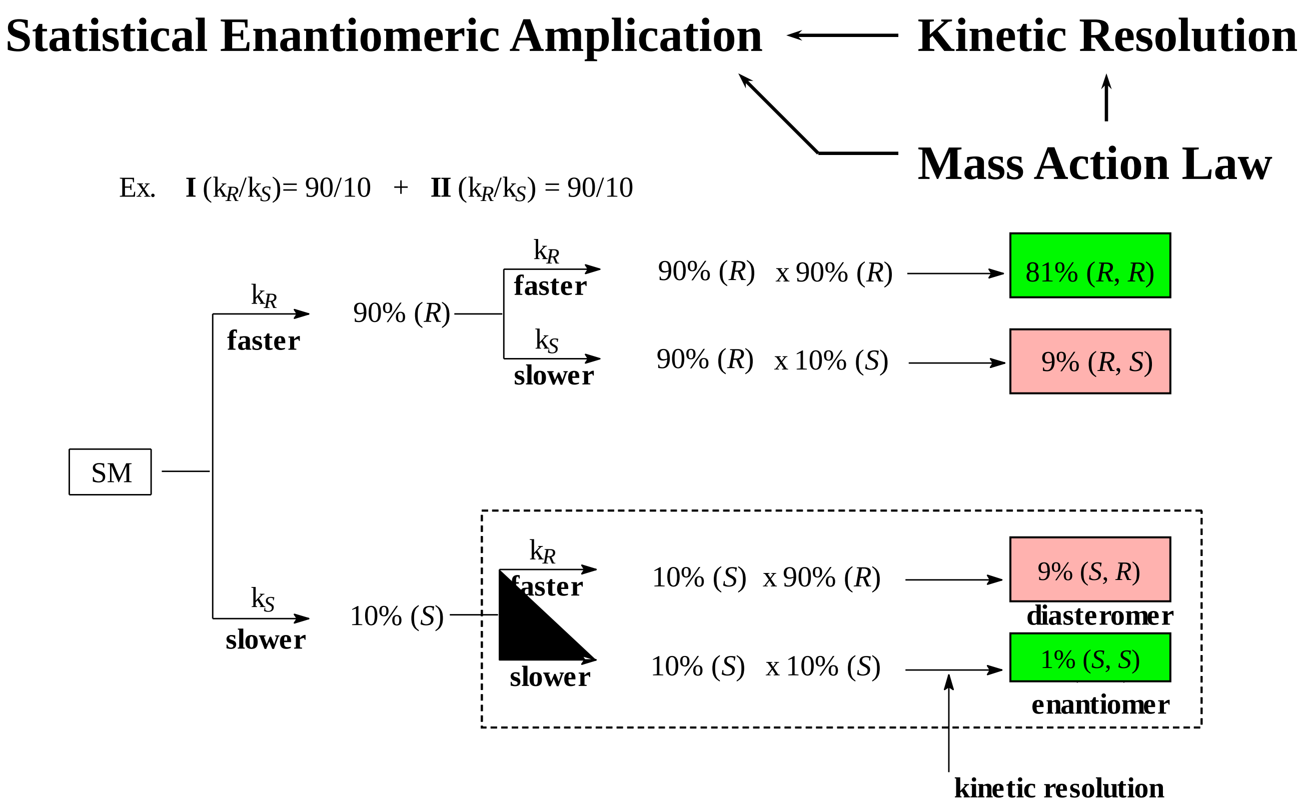
Bottom Line (No. 1): Avoid (i) H-transfer hydrometallation
(ii) Polymerization
(iii) Cyclic carbozirconation

The Importance of Organometallic Functionality



- Catalytic asymmetric C–C bond formation
- One-point-binding without requiring any other functional groups
- ***Organometallic functionality*** with many potential transformations

STATISTICAL ENANTIOMERIC AMPLIFICATION



Overall ee for **I + II** $= \frac{81-1}{81+1} \times 100 = \frac{80}{82} \times 100 =$ 97.6%

Note: If another round III is added the overall ee will be 99.7%

Bottom Line (No. 3): (a) Cleverly exploit the statistical enantiomeric amplication principle.

It's mathematical (or statistical)

If each step is 80%ee (90/10),

$$(9R + 1S)(9R + 1S) = \underbrace{81R,R + 18\,R,S\,(S,R) + 1S,S}$$

Enantiomers: 81R,R and 1S,S

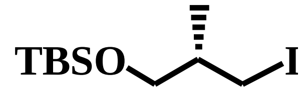
Diastereomers: R,S (S,R)

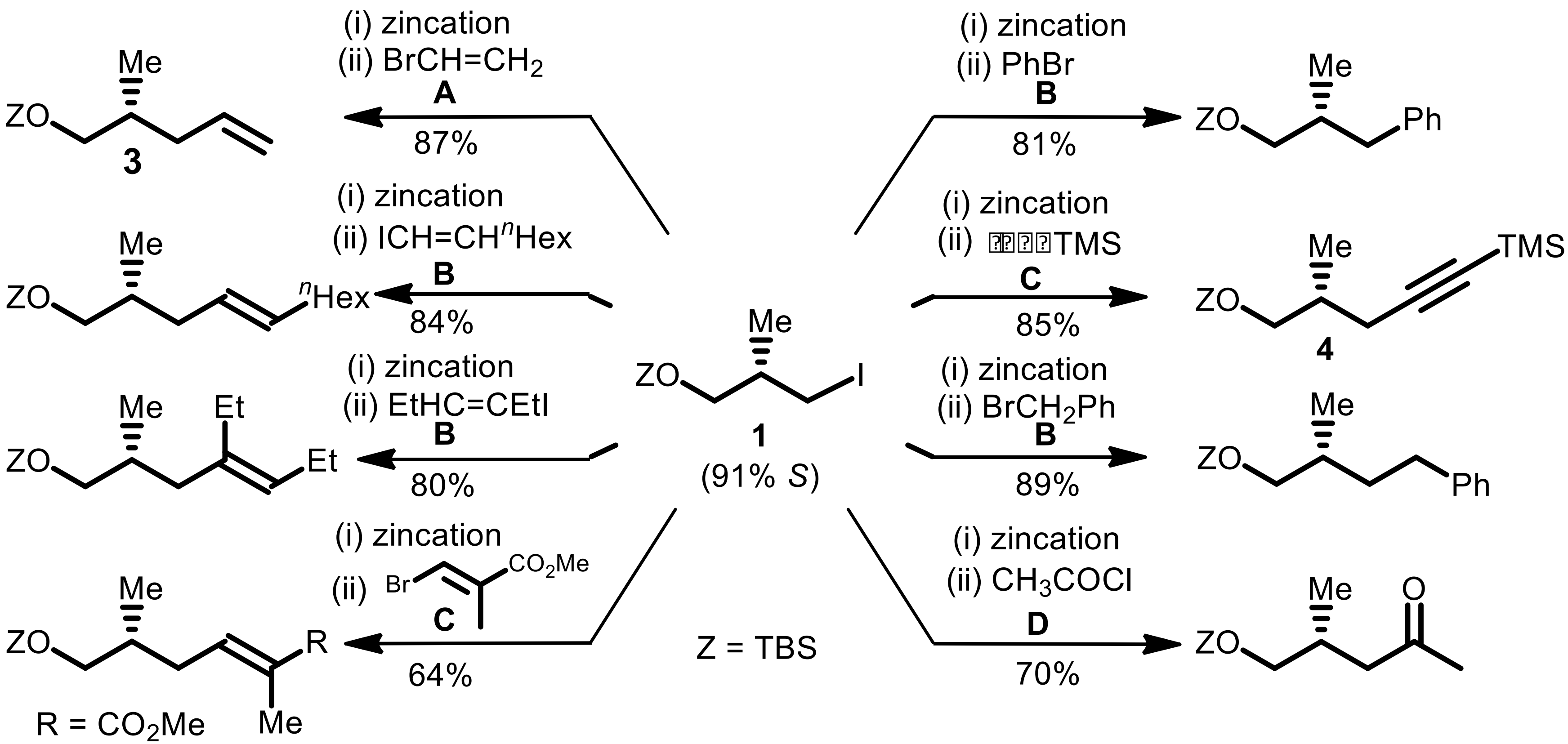
$$\frac{R,R}{S,S} = \frac{81}{1} \quad \therefore \text{ Enantiomeric Excess} = \frac{81-1}{81+1} = \frac{80}{82} = 0.976 \approx 98\%ee$$

$$(9R + 1S)^n = 9^n \times R^n + \sum(\text{All Cross Terms}) + 1^n \times S^n$$

Diastereomers: $\sum$(All Cross Terms)

n	ee (%)
1	80
2	98 (= 97.6)
3	99.7
4	99.97
5	99.997

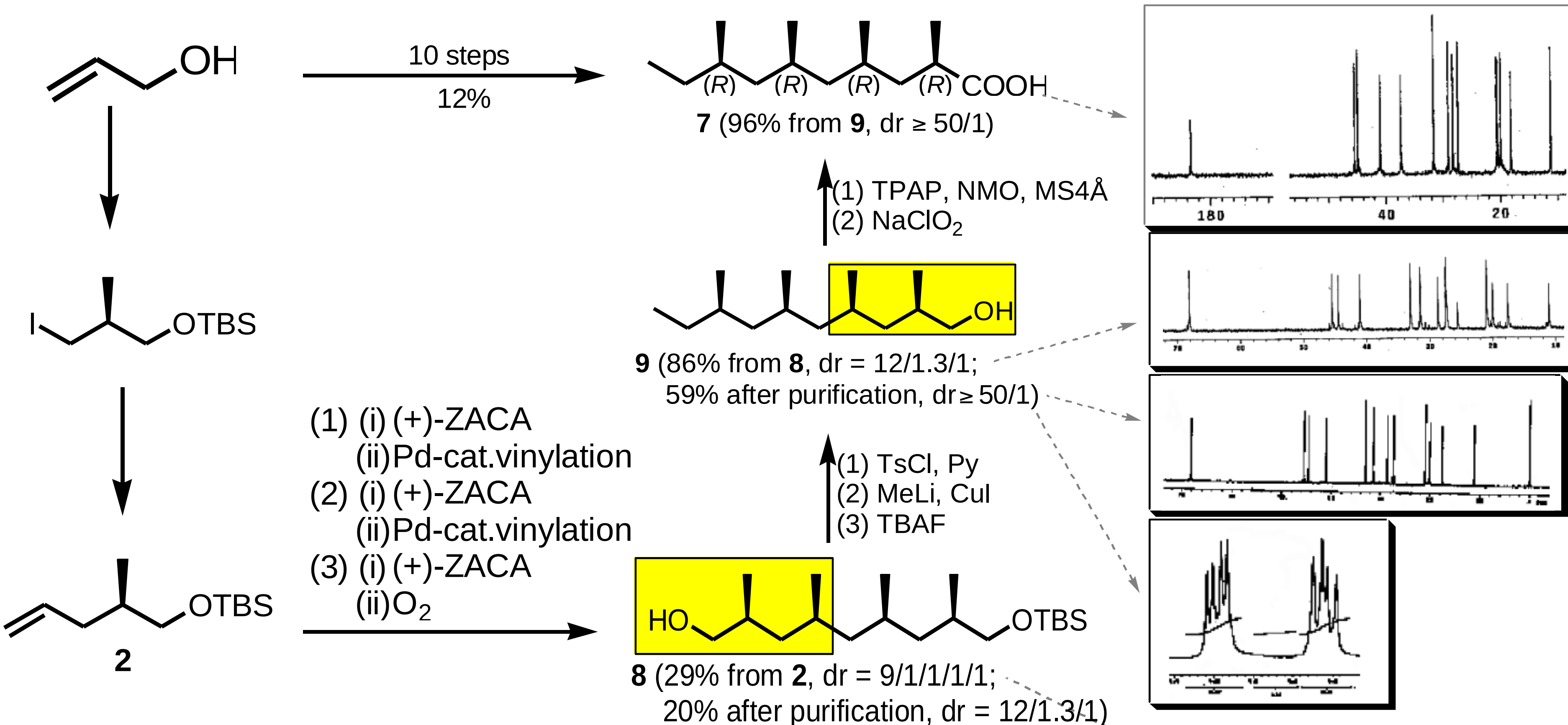
Pd-Catalyzed Cross-Coupling Reaction of 

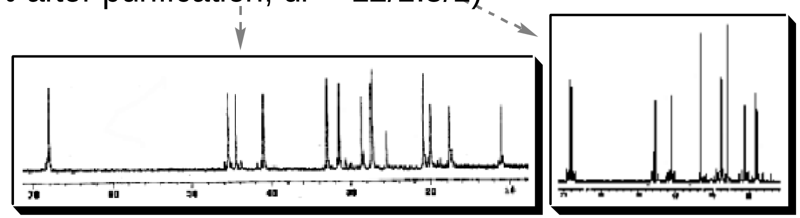


[a]**A**: 5% Pd(DPEphos)Cl_2, 10% DIBAL-H, THF-ether, 23 °C, 12 h; **B:** 5% $Pd(PPh_3)_4$, THF-ether, 23 °C, 12 h; **C:** 5% Pd(DPEphos)Cl_2, DMF-THF-ether, 23 °C, 12 h; **D**: 5% Pd(DPEphos)Cl_2, THF, 23 °C, 12 h. [b]Zincation: ^{t}BuLi (2.1 equiv), and then dry $ZnBr_2$ (0.6 equiv)

B. Liang, T. Novak, Z. Tan, E. Negishi, *J. Am. Chem. Soc.* , **2006**. *128*, 2770-2771.

Synthesis of (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-Tetramethyldecanoic Acid, The Acid Component of Preen-Gland Wax of Graylag Goose, *Anser Anser*

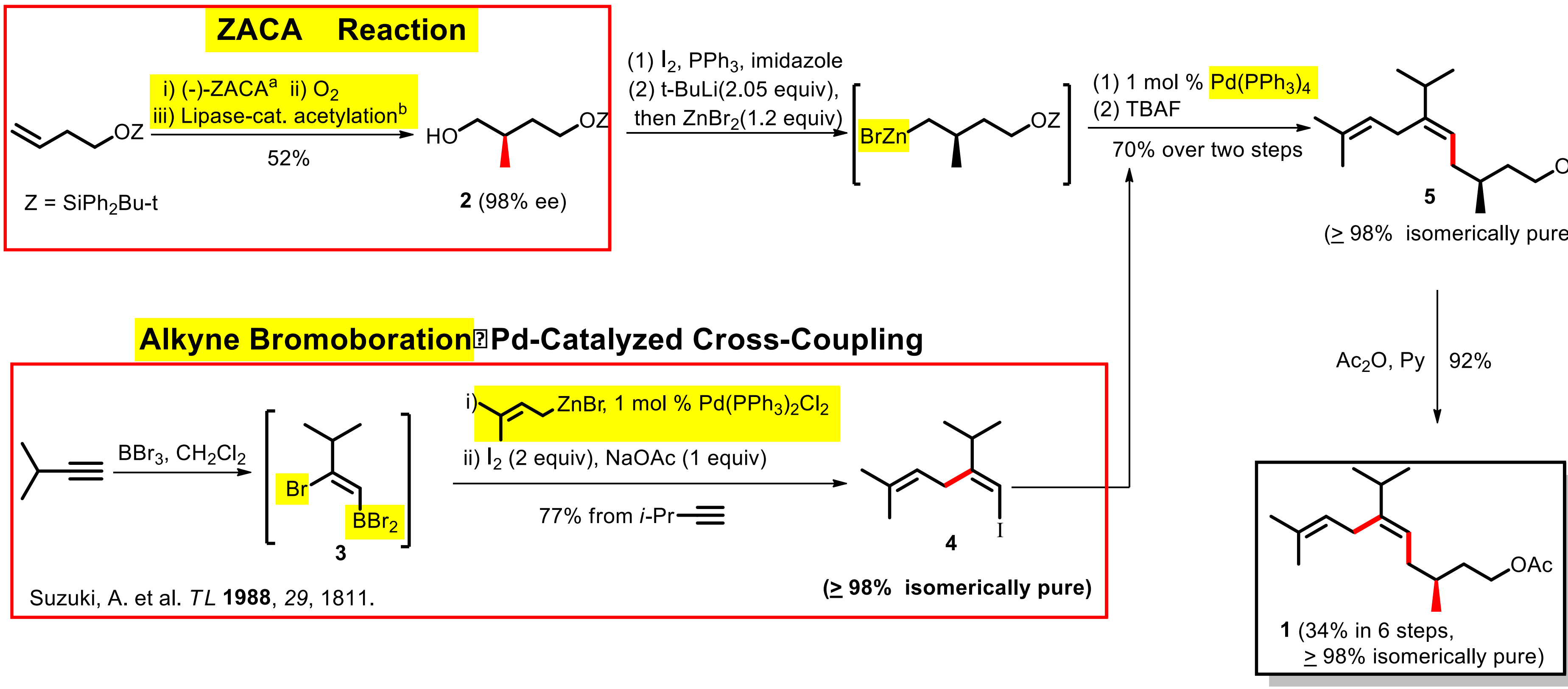




Py = pyridine; TBAF = $n\mathrm{Bu_4NF}$.
TPAP = tetrapropylammonium perruthenate;
NMO = 4-methylmorpholine *N*-oxide;
MS4Å = molecular sieves, 4Å; TsCl = Tosyl chloride;

B. Liang, T. Novak, Z. Tan, E. Negishi, *J. Am. Chem. Soc.* **2006,** *128,* 2770 – 2771.

LEGO Game Route to Yellow Scale Pheromone

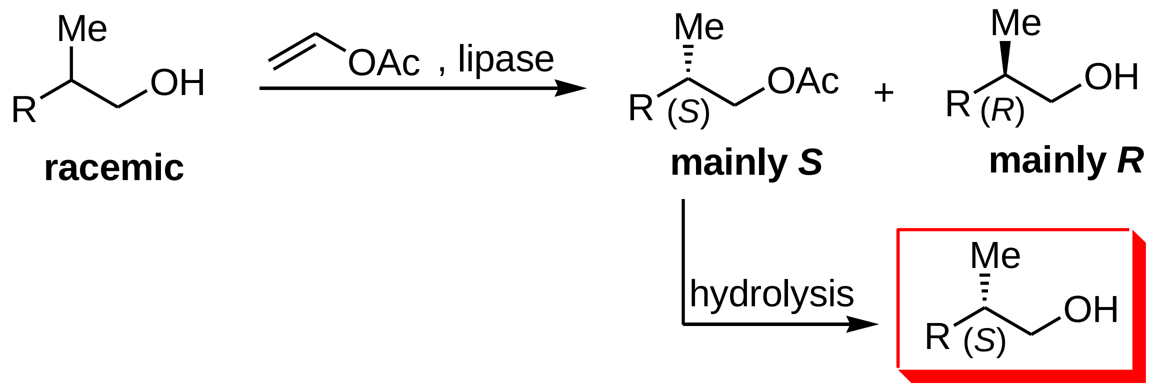


[a] (-)-ZACA = Me_3Al(3.0 equiv), 1 mol % (-)-$(NMI)_2ZrCl_2$, H_2O(0.5 equiv), CH_2Cl_2, 23 °C, 5 h

[b] OAc(5 equiv), Amano PS lipase (30 mg/ mmol)

Z. Xu, E. Negishi, *Org. Lett*. **2008**, *10*, 4311-4314.

⇨ Lipase-Catalyzed Kinetic Resolution of Enantiomeric Mixtures



Preparation of (*S*)-2-Methyl-1-alcohols (≥98% *ee*) from Enantiomeric Mixtures

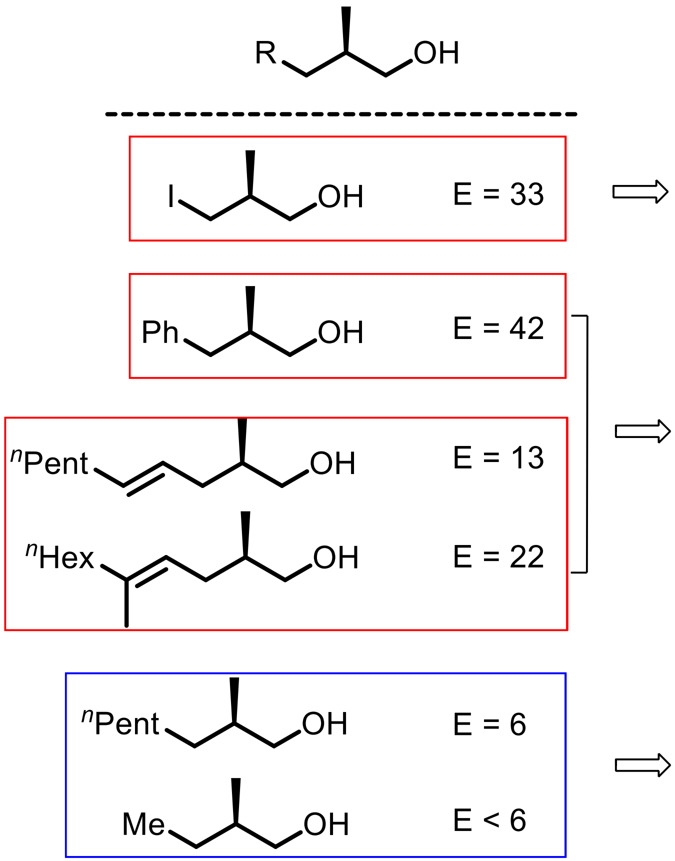
Initial ee$_o$ (%)	*E*[a]	Max. yield (%)[a,b]
0 (racemic)	100	≤2
	90	0
20	100	≤35
	80	~20
	60	0
50	100	≤70
	50	~55
	40	~25
	30	0
60	100	≤80
	50	~65
	30	~25
	20	0

Initial ee$_o$ (%)	*E*[a]	Max. yield (%)[a,b]
70	100	≤85
	50	~80
	30	~60
	20	~25
	10	0
80	100	≤90
	30	~85
	20	~70
	10	0
90	100	≤95
	20	≤95
	10	80
	5	0

(adopted from C. J. Sih's paper: *JACS*, **1982**, *104*, 7294)

Huang, Z.; Tan, Z.; Novak, T.; Zhu, G.; Negishi, E., *Adv. Synth. Catal*. **2007**, *349*, 539-545.

➩ *E Factors*



E Factors:

proximal hetereoatoms
(halogen, oxygen, etc.)

proximal ?-bonds
(aromatic groups, double bonds, etc.)

alkyl groups
(increasing the difference of R and Me)

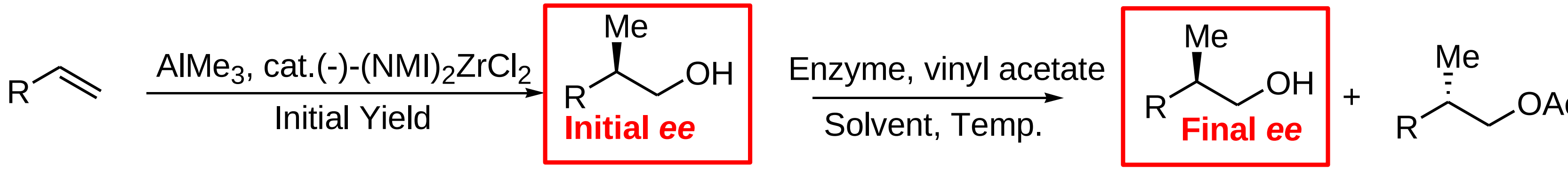
E (enantiomeric ratio): $E = \dfrac{\ln(A/A_o)}{\ln(B/B_o)} = \dfrac{V_A/K_A}{V_B/K_B}$ = ln [(1-*C*)(1-ee)] / ln [(1-*C*)(1+ee)]

C = conversion
ee = ee of the unreacted alcohol

(adopted from C. J. Sih's paper: *JACS*, **1982**, *104*, 7294)

Huang, Z.; Tan, Z.; Novak, T.; Zhu, G.; Negishi, E., *Adv. Synth. Catal.* **2007**, *349*, 539-545.

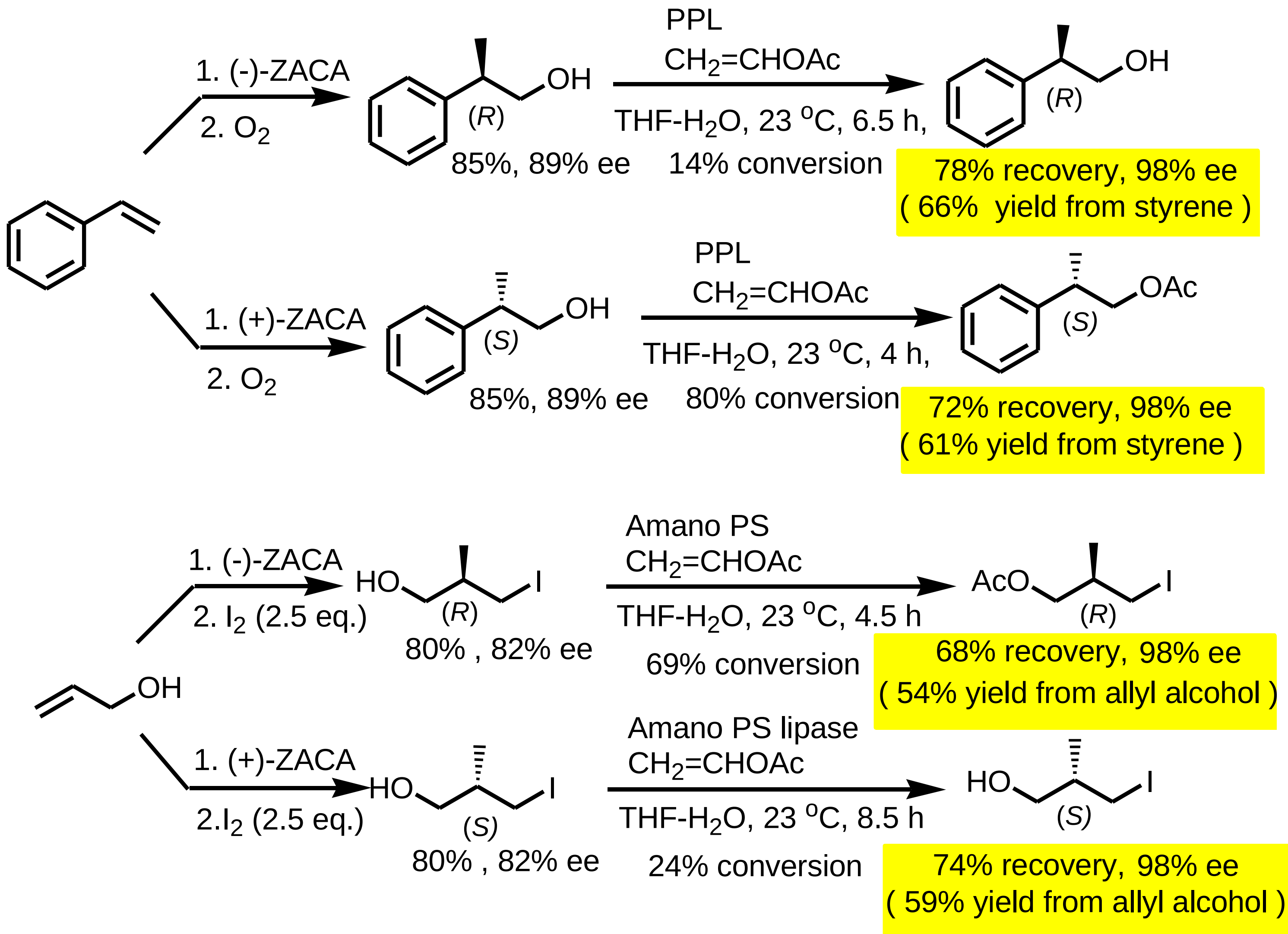
⇨ Lipase-Catalyzed Kinetic Resolution of ZACA Products



R	Initial Yield (%)	Intial *ee* (%)	Enzyme	Solvent	Temp.(°C)	Conversion (%)	Recovery (%)	Final *ee* (%)
Ph	85	89	Amano PS	THF/H_2O	23	22	68	93
			Amano PS	THF/H_2O	23	50	43	96
			PPL	THF/H_2O	23	31	62	99
$PhCH_2$	85	76	PPL	THF/H_2O	23	48	51	77
			Amano PS	THF/H_2O	23	40	59	99
$Ph(CH_2)_2$	84	76	PPL	THF/H_2O	23	30	64	99
			Amano PS	THF/H_2O	23	38	56	99
^{n}Hex	71	72	Amano PS	CH_2Cl_2	0	44	52	98
$CH_2=CHCH_2$	NA	82	Amano PS	CH_2Cl_2	0	19	76	98

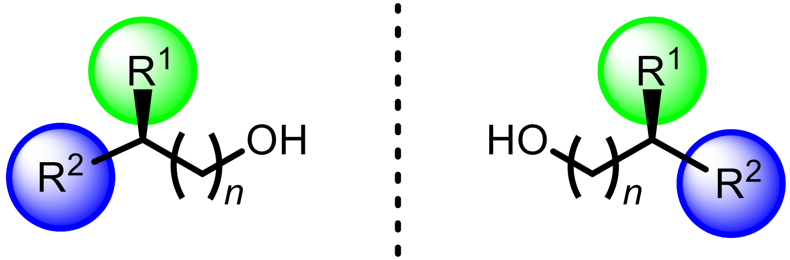
Huang, Z.; Tan, Z.; Novak, T.; Zhu, G.; Negishi, E., *Adv. Synth. Catal.* **2007**, *349*, 539-545.

⇨Enantiomeric Purification of (R) and (S) Isomers of 2-Methyl-1-alkanols

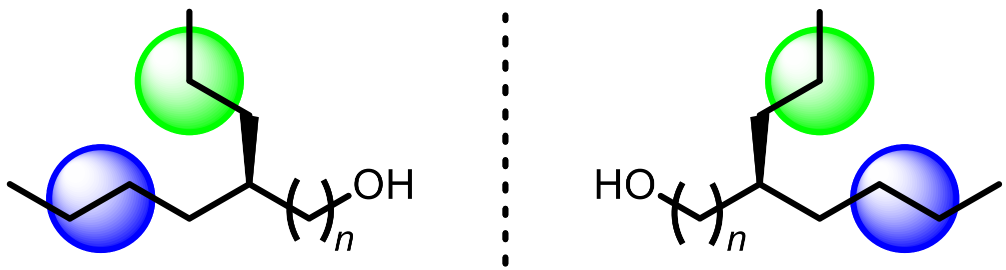


Huang, Z.; Tan, Z.; Novak, T.; Zhu, G.; Negishi, E., *Adv. Synth. Catal.* **2007**, *349*, 539-545.

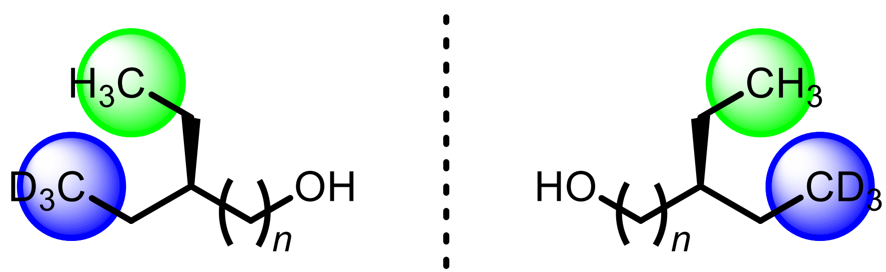
⇨ *How to Prepare Feebly Chiral Compounds of ≥99% ee*



R^1 and R^2 are structrually very similar

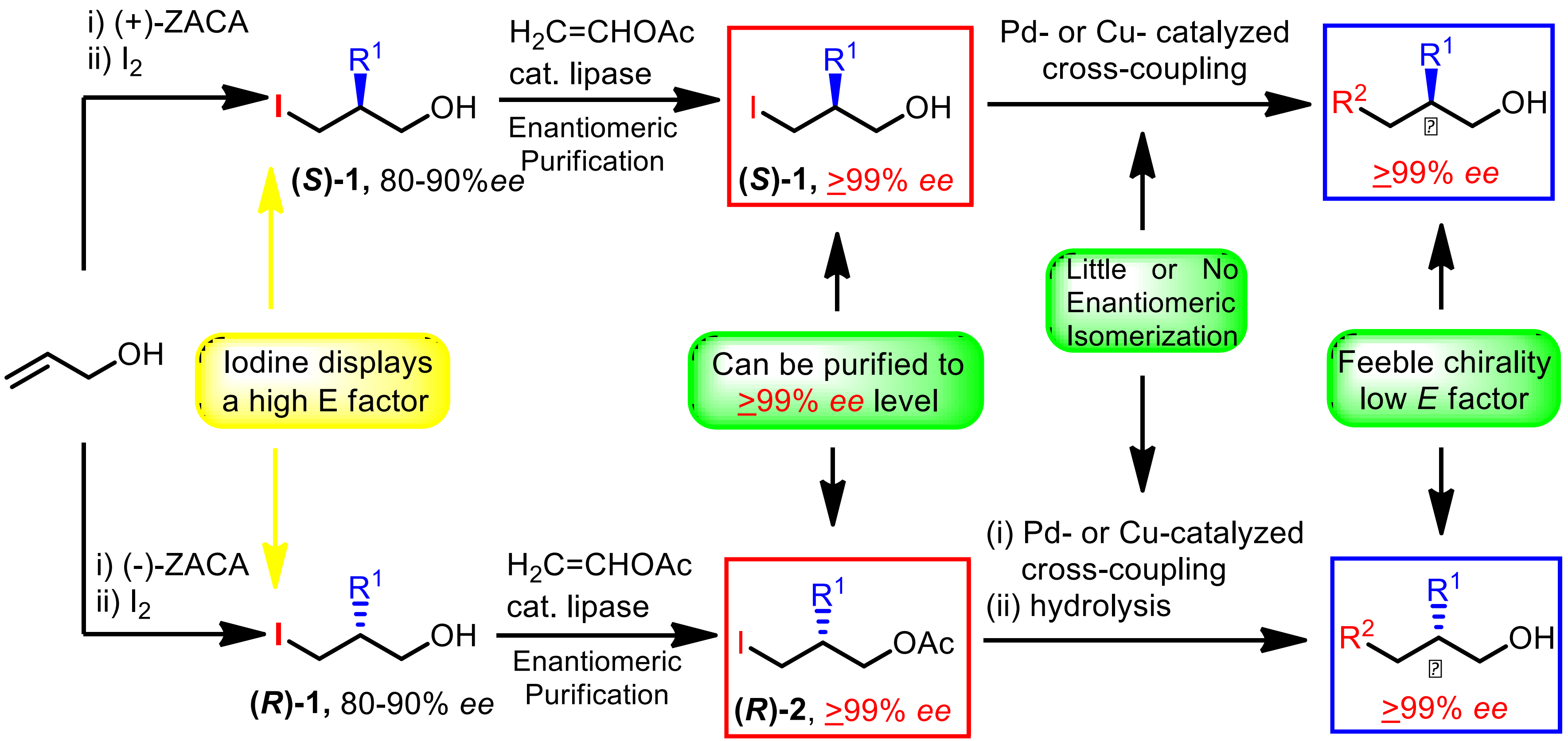


Two very similar groups of low chirality



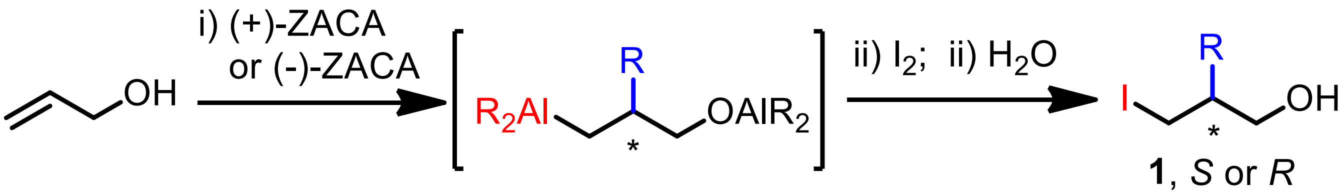
Isotopomers:
Ultimately feeble chirality!
$[\alpha]_D^{23} \approx 0^o$

General Strategy for Synthesis of Feebly Chiral 2-Alkyl-1-Alkanols of ≥99% *ee*



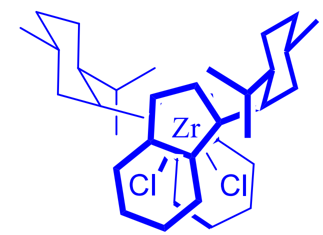
ZACA Reaction of Allyl Alcohol

Asymmetric synthesis of (*R*)- and (*S*)-3-iodo-2-alkyl-1- alkanols 1



1, *S* or *R*

Entry	R	Protocol[a]	Product	Yield[b] (%)	Purity of 1 (% ee[c])
1	Me	I	(*S*)-1a	80	82
2	Me	II	(*R*)-1a	81	84
3	Et	III	(*S*)-1b	60	87
4	Et	IV	(*R*)-1b	62	88
5	^{n}Pr	III	(*S*)-1c	59	82
6	^{n}Pr	IV	(*R*)-1c	60	80

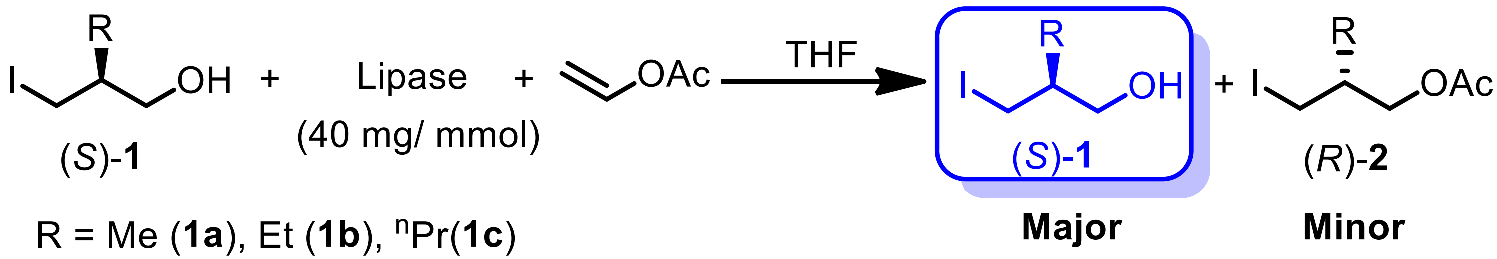


(-)-$(NMI)_2ZrCl_2$
or (+)-$(NMI)_2ZrCl_2$

[a] Protocol I: i) Me_3Al (2.5 eq), MAO (1 eq), 5%(+)-$(NMI)_2ZrCl_2$ ii) I_2 (2.5 eq), THF
Protocol II: i) Me_3Al (2.5 eq), MAO (1 eq), 5%(-)-$(NMI)_2ZrCl_2$ ii) I_2 (2.5 eq), THF
Protocol III: i) R_3Al (3.0 eq), IBAO (1 eq), 5%(+)-$(NMI)_2ZrCl_2$ ii) I_2 (6 eq), Et_2O
Protocol IV: i) R_3Al (3.0 eq), IBAO (1 eq), 5%(-)-$(NMI)_2ZrCl_2$ ii) I_2 (6 eq), Et_2O
[b] Isolated yield [c] Enantiomeric excess

Xu, S.; Lee, CT.; Wang, G.; Negishi, E., *Chem. Asian J.* **2013**, *8*, 1829–1835.

Lipase-Catalyzed Acetylation of (*S*)-3-Iodo-2-Alkyl-1-Alkanols

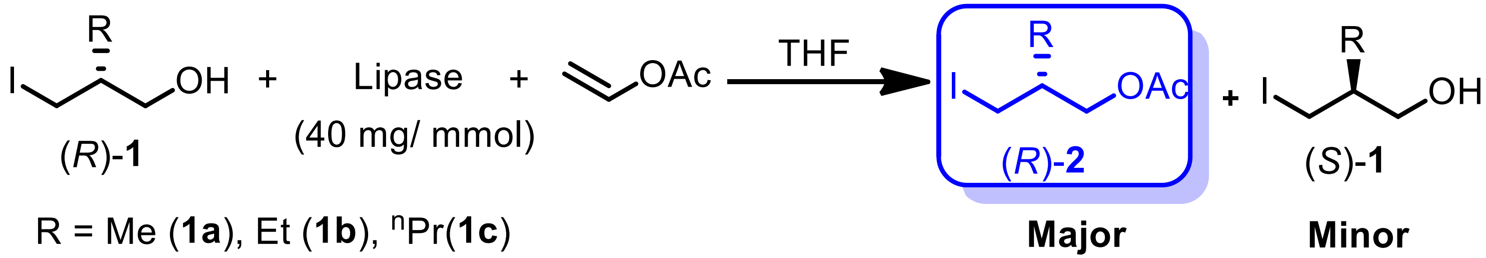


R = Me (**1a**), Et (**1b**), ^{n}Pr(**1c**)

Entry	Substrate	Initial purity of (*S*)-**1** (% *ee*)	Lipase	Recovery of (*S*)-**1** (%)	Purity of (*S*)-**1** (% *ee*)	
1	(*S*)-**1a**	82	**Amano PS**	**63**	**≥99**	→ **50% yield from allyl alcohol**
2	(*S*)-**1b**	87	Amano PS	72	96	
3	(*S*)-**1b**	87	Amano AK	74	96	
4	(*S*)-**1b**	87	**Amano AK**	**60**	**≥99**	→ **36% yield from allyl alcohol**
5	(*S*)-**1c**	82	PPL	35	85	
6	(*S*)-**1c**	82	Amano AK	74	94	
7	(*S*)-**1c**	82	**Amano AK**	**58**	**≥99**	→ **34% yield from allyl alcohol**
8	(*S*)-**1c**	82	Amano PS	74	92	
9	(*S*)-**1c**	82	Lipase from *Rhizomucor Miehei*	34	80	
10	(*S*)-**1c**	82	Lipase from *Candida rugosa*	59	83	

Xu, S.; Lee, CT.; Wang, G.; Negishi, E., *Chem. Asian J.* **2013**, *8*, 1829–1835.

Lipase-Catalyzed Acetylation of (*R*)-3-Iodo-2-Alkyl-1-Alkanols

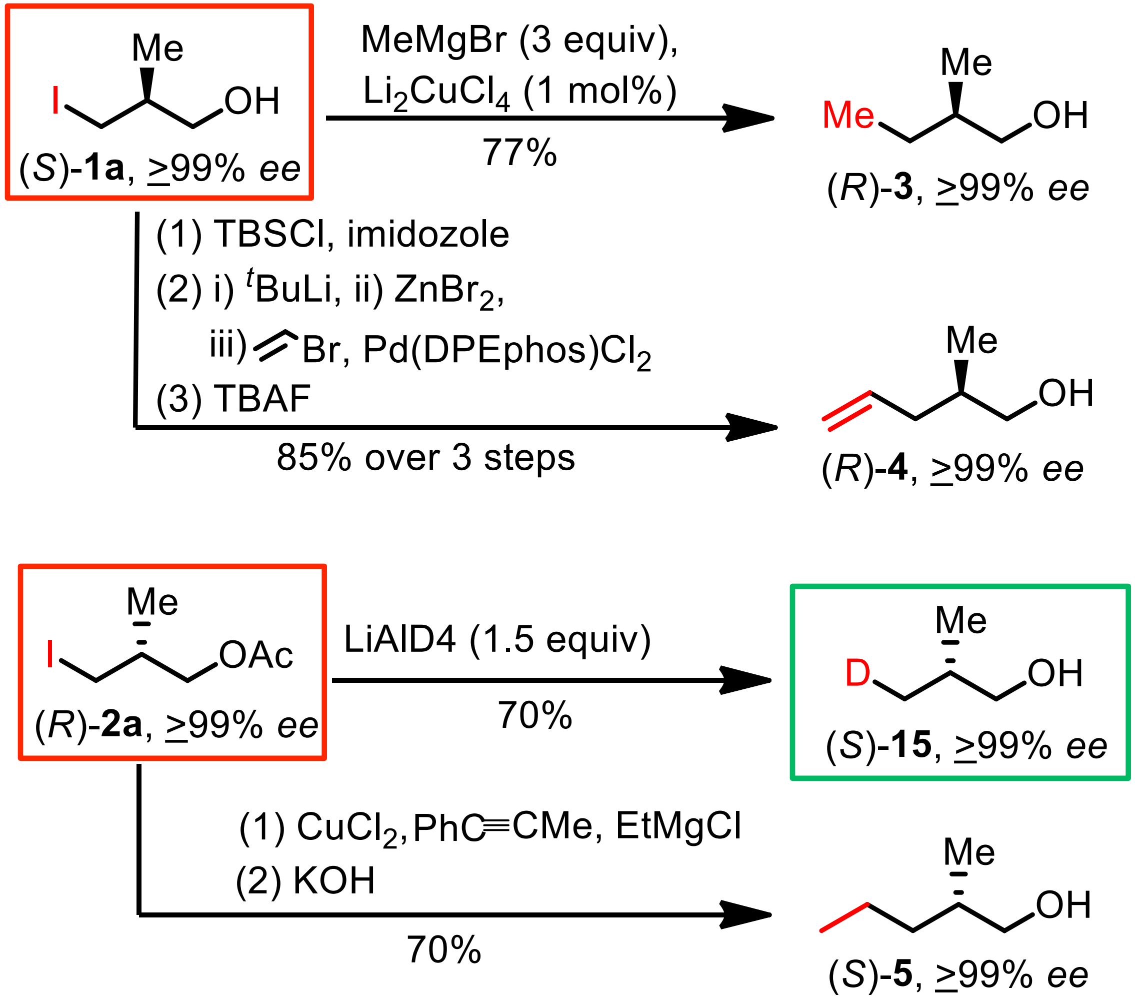


Entry	Substrate	Inital purity of (*R*)-**1** (% *ee*)	Lipase	Yield of (*R*)-**2** (%)	Purity of (*R*)-**2** (% *ee*)	
1	(*R*)-**1a**	84	**Amano PS**	**60**	**≥99**	→ **49% yield from allyl alcohol**
2	(*R*)-**1b**	88	**Amano PS**	**52**	**≥99**	
3	(*R*)-**1b**	88	Amano PS	64	98	
4	(*R*)-**1b**	88	Amano PS	81	96	
5	(*R*)-**1b**	96	**Amano PS**	**62**[a]	**≥99**	→ **38% yield from allyl alcohol**
6	(*R*)-**1c**	80	**Amano AK**	**50**	**≥99**	
7	(*R*)-**1c**	80	Amano AK	60	98	
8	(*R*)-**1c**	80	Amano AK	79	94	
9	(*R*)-**1c**	94	**Amano AK**	**60**[b]	**≥99**	→ **36% yield from allyl alcohol**

[a] Overall yield in two rounds of lipase-catalyzed purification (entry 4+5).
[b] Overall yield in two rounds of lipase-catalyzed purification (entry 8+9).

Xu, S.; Lee, CT.; Wang, G.; Negishi, E., *Chem. Asian J.* **2013**, *8*, 1829–1835.

Synthesis of Feebly Chiral 2-Alkyl-1-alkanols



(39% yield over three steps from allyl alcohol)

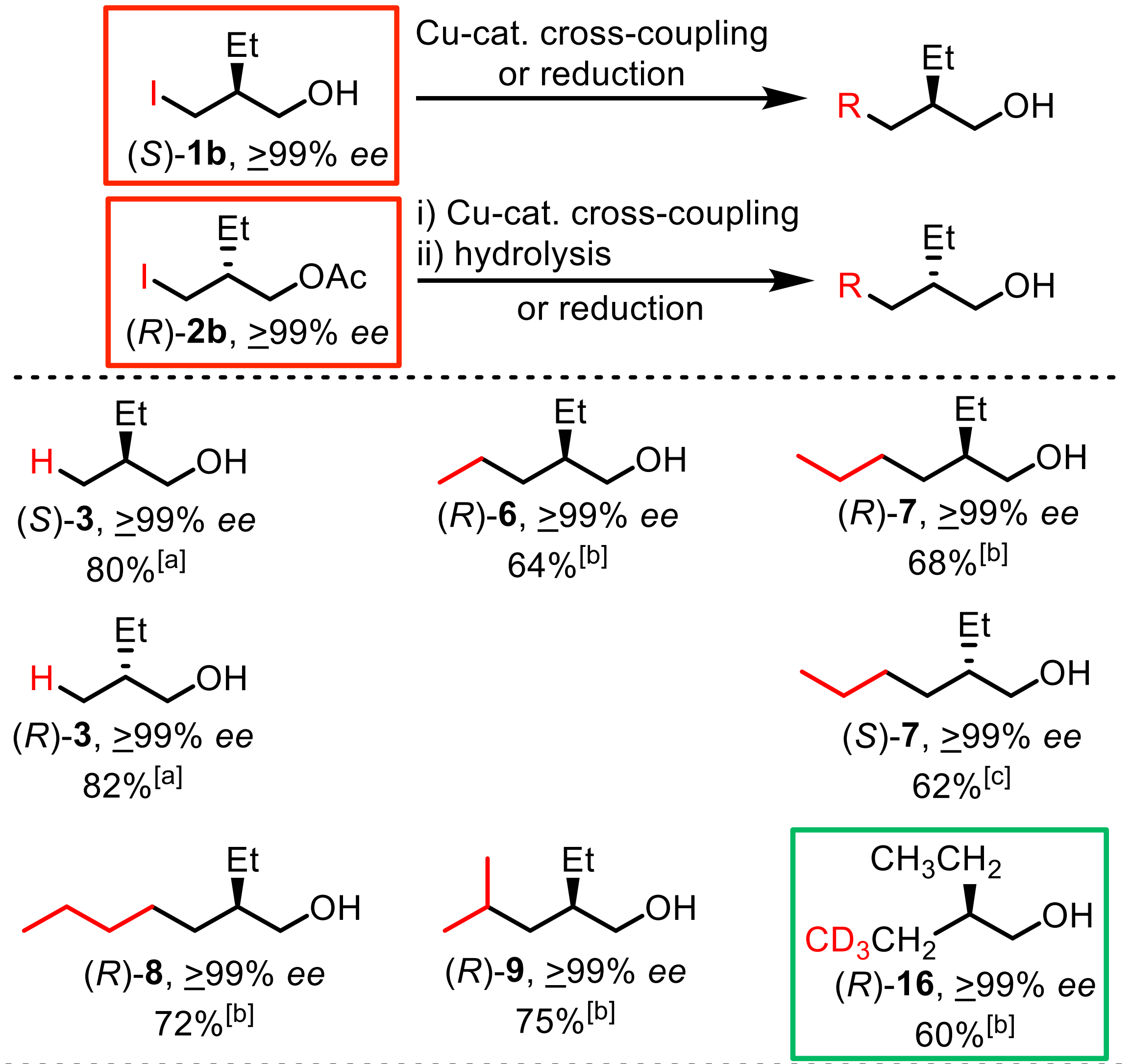
(43% yield over five steps from allyl alcohol)

(34% yield over three steps from allyl alcohol)

(34% yield over four steps from allyl alcohol)

Xu, S.; Lee, CT.; Wang, G.; Negishi, E., *Chem. Asian J.* **2013**, *8*, 1829–1835.

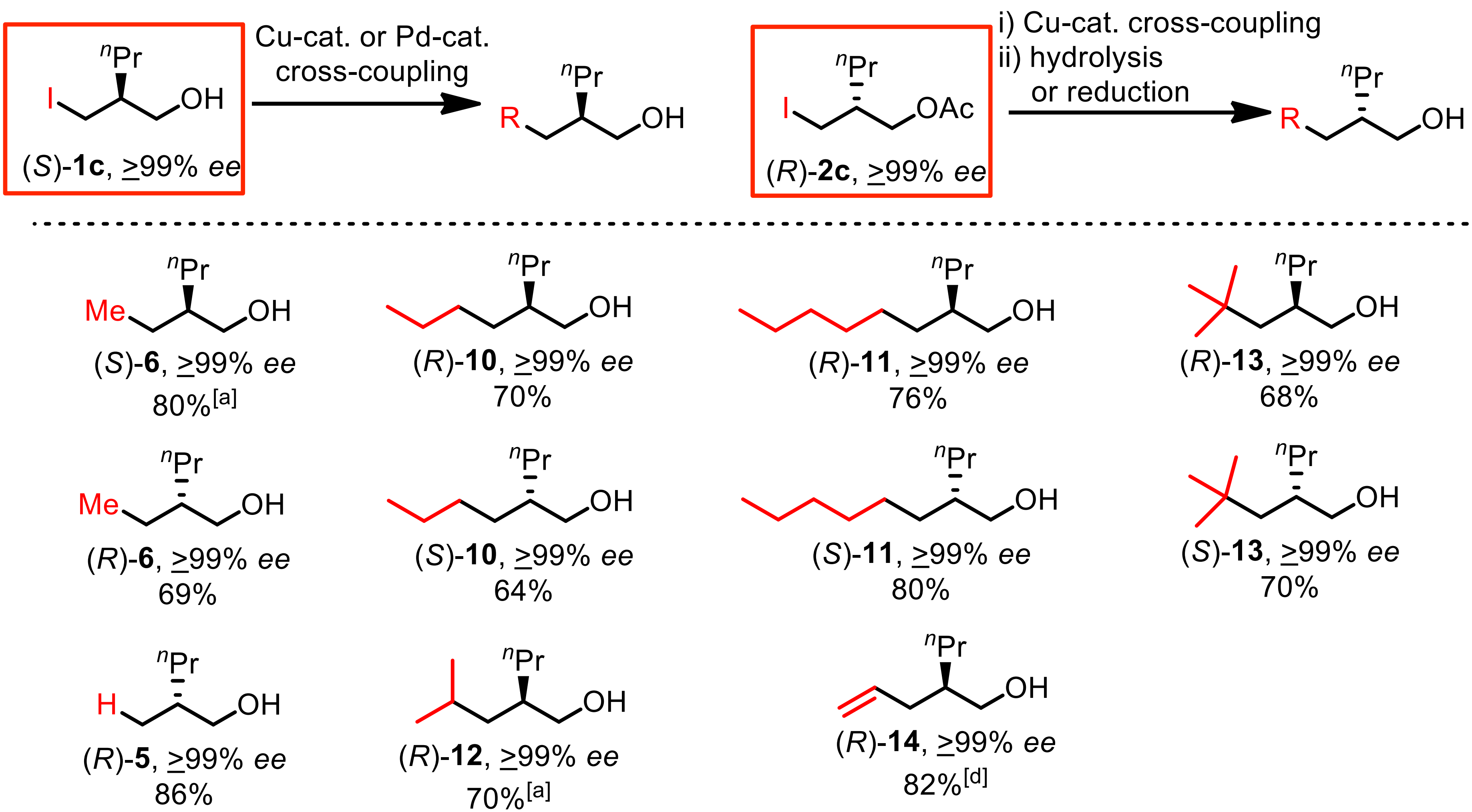
Synthesis of Feebly Chiral 2-Alkyl-1-alkanols



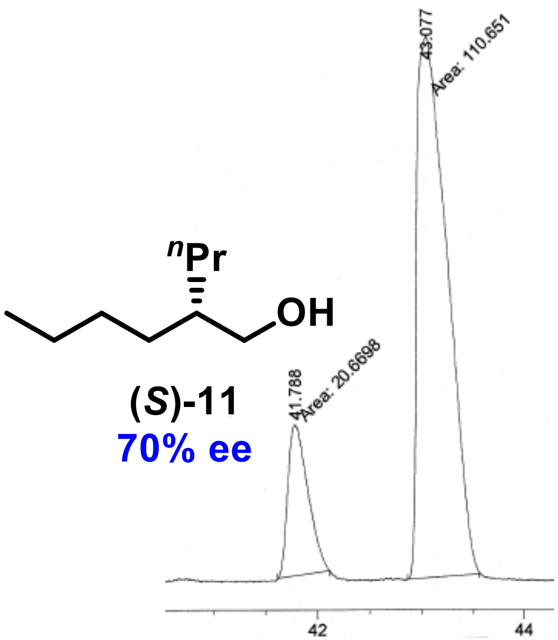
[a] $LiAlH_4$ [b] Con. I: $CuCl_2$ (5 mol%), PhC≡CMe (15 mol%), RMgCl [c] i) Con. I; ii) KOH

Xu, S.; Lee, CT.; Wang, G.; Negishi, E., *Chem. Asian J.* **2013**, *8*, 1829–1835.

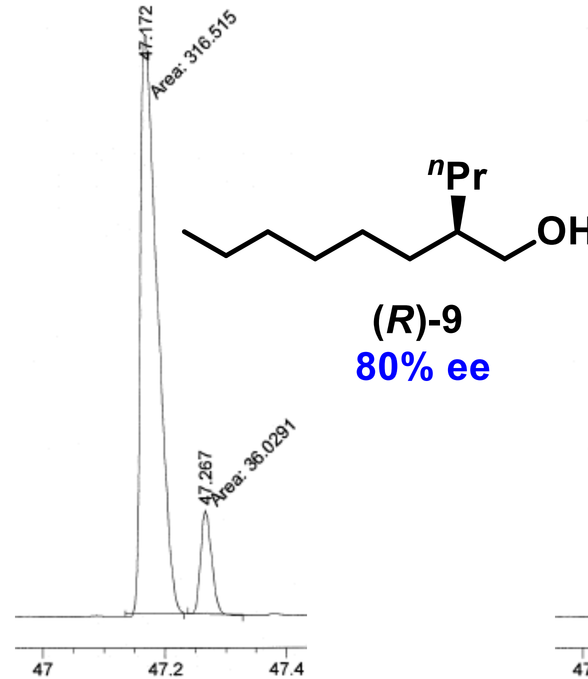
Synthesis of Feebly Chiral 2-Alkyl-1-alkanols



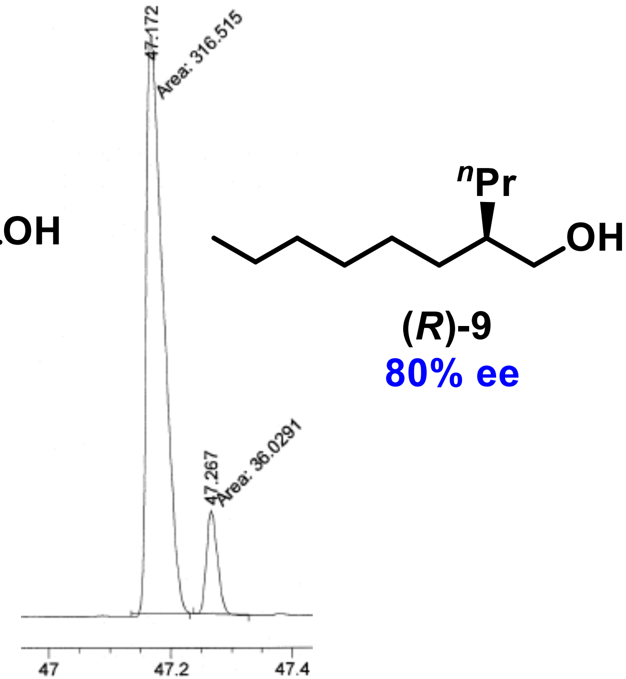
Xu, S.; Lee, CT.; Wang, G.; Negishi, E., *Chem. Asian J.* **2013**, *8*, 1829–1835.



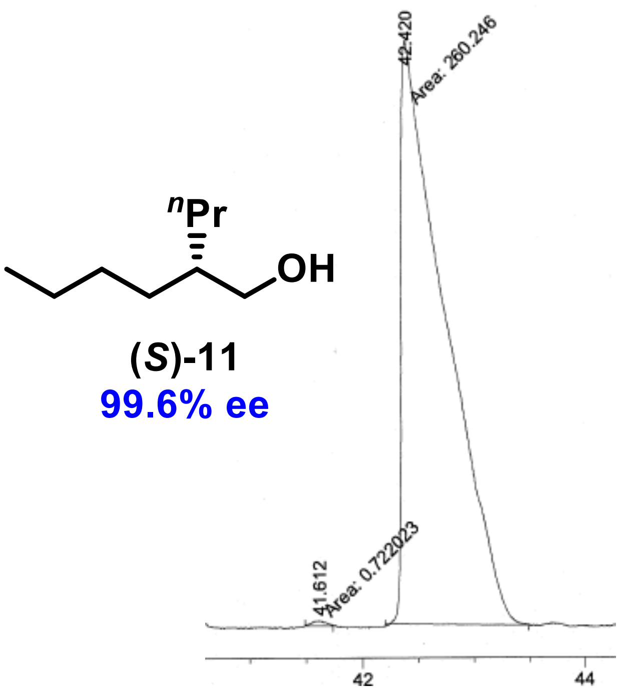
(*S*)-11
70% ee



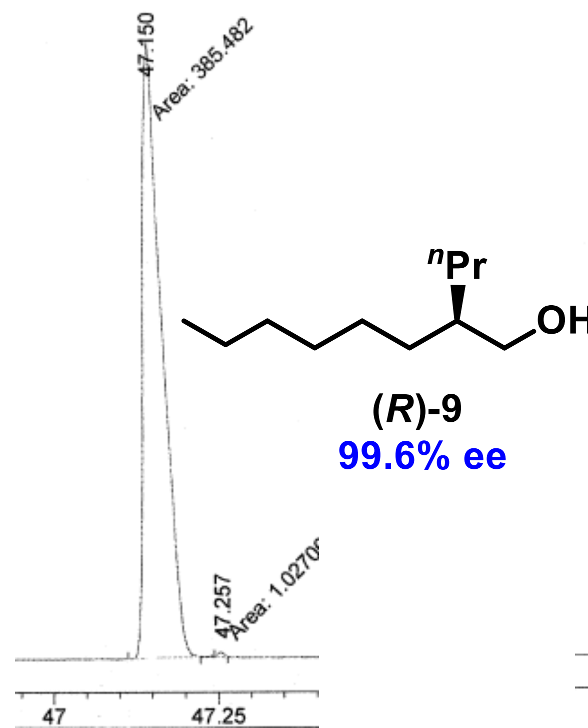
(*R*)-9
80% ee



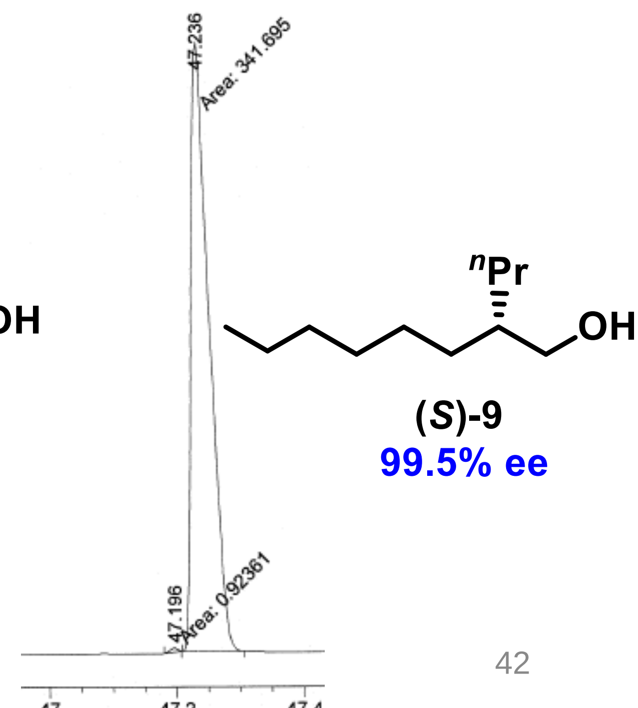
(*R*)-9
80% ee



(*S*)-11
99.6% ee

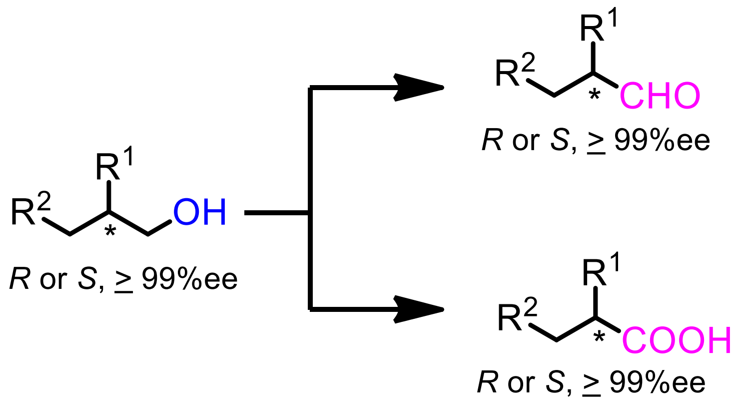


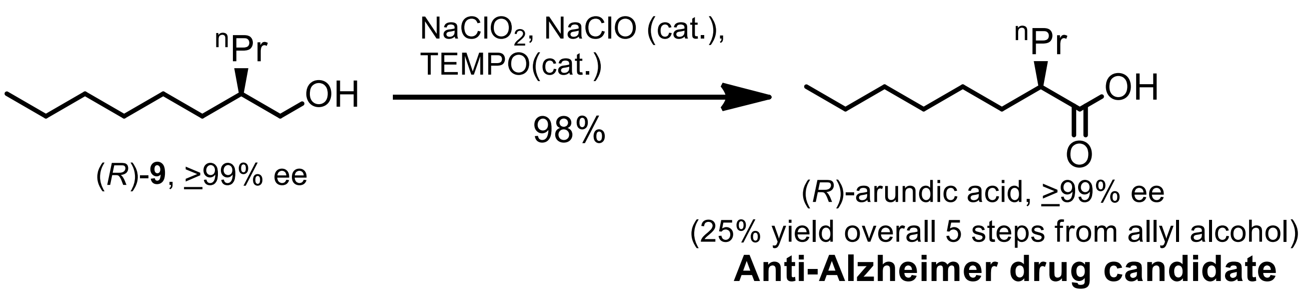
(*R*)-9
99.6% ee

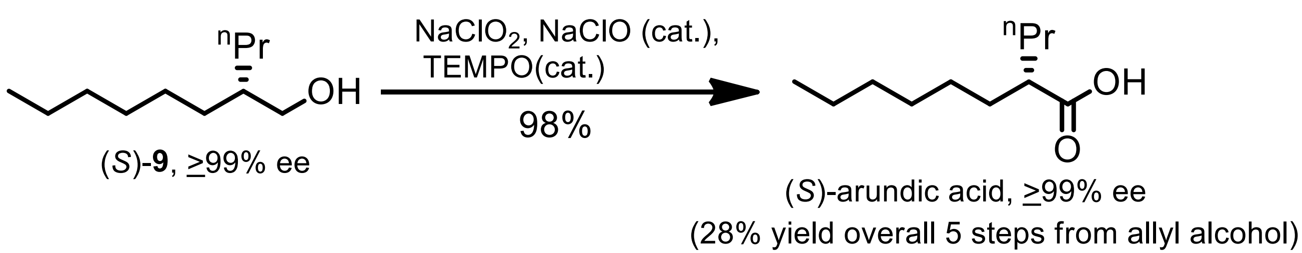


(*S*)-9
99.5% ee

Synthesis of (*R*)- and (*S*)-Arundic Acids

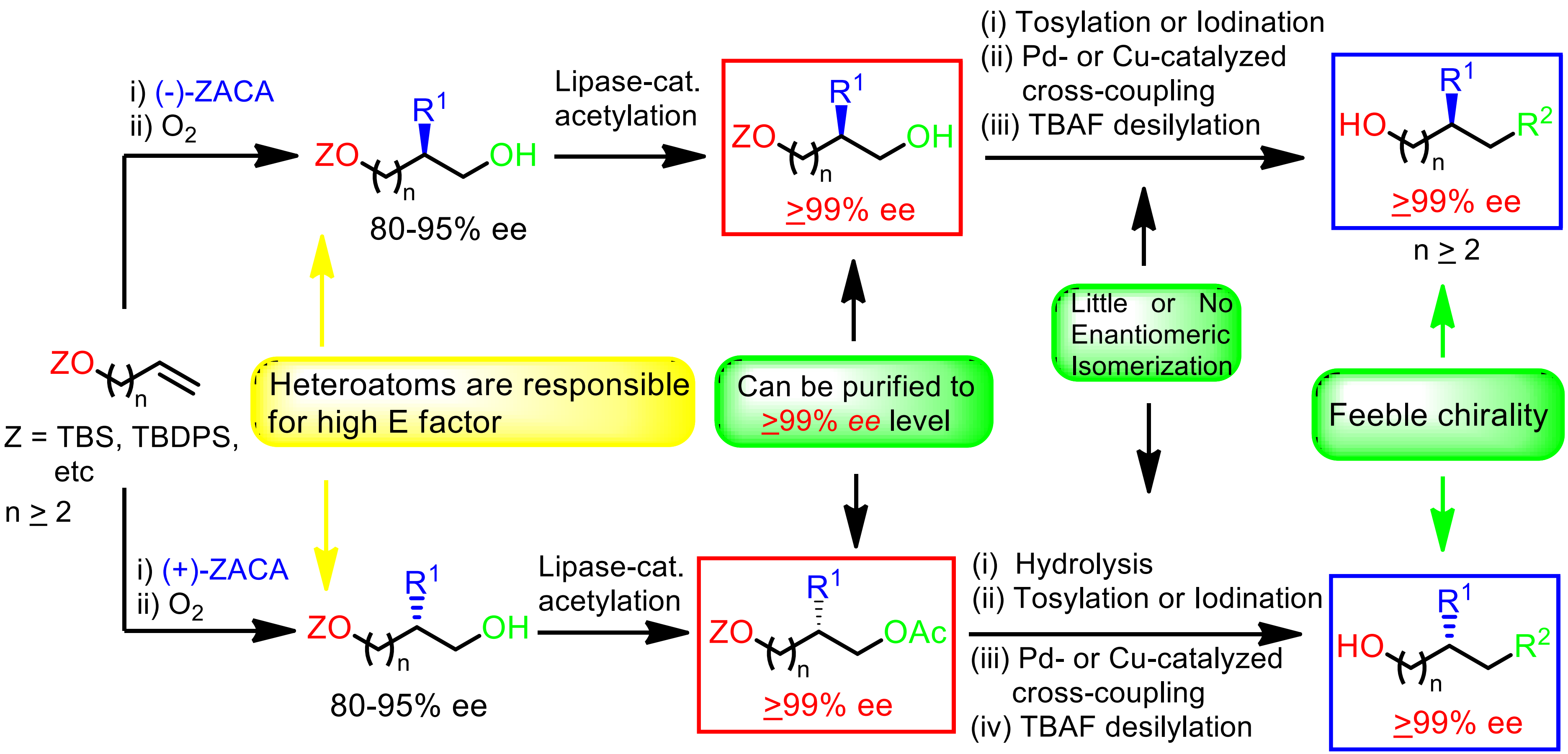






Xu, S.; Lee, CT.; Wang, G.; Negishi, E., *Chem. Asian J.* **2013**, *8*, 1829–1835

General Strategy for the Synthesis of Remotely Chiral (n+1)-alkyl-1-alkanols of ≥99% *ee*, where n ≥ 2

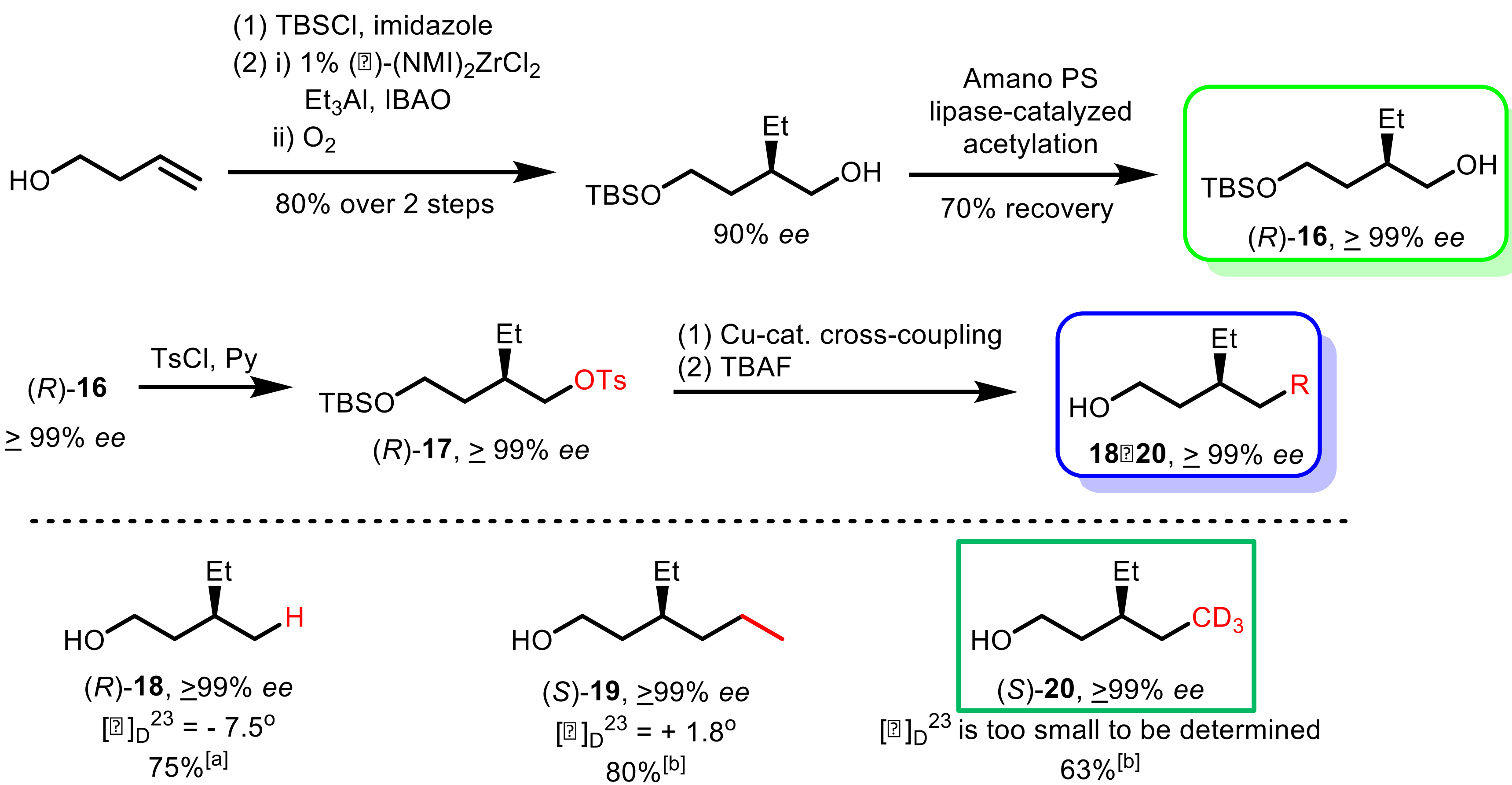


ZACA: Ziconium-catalyzed Asymmetric Carboalumination of Alkenes

R^1 = alkyl group, R^2 = alkyl, alkenyl, alkynyl, or aryl group

R^1 and CH_2R^2 may be very similar

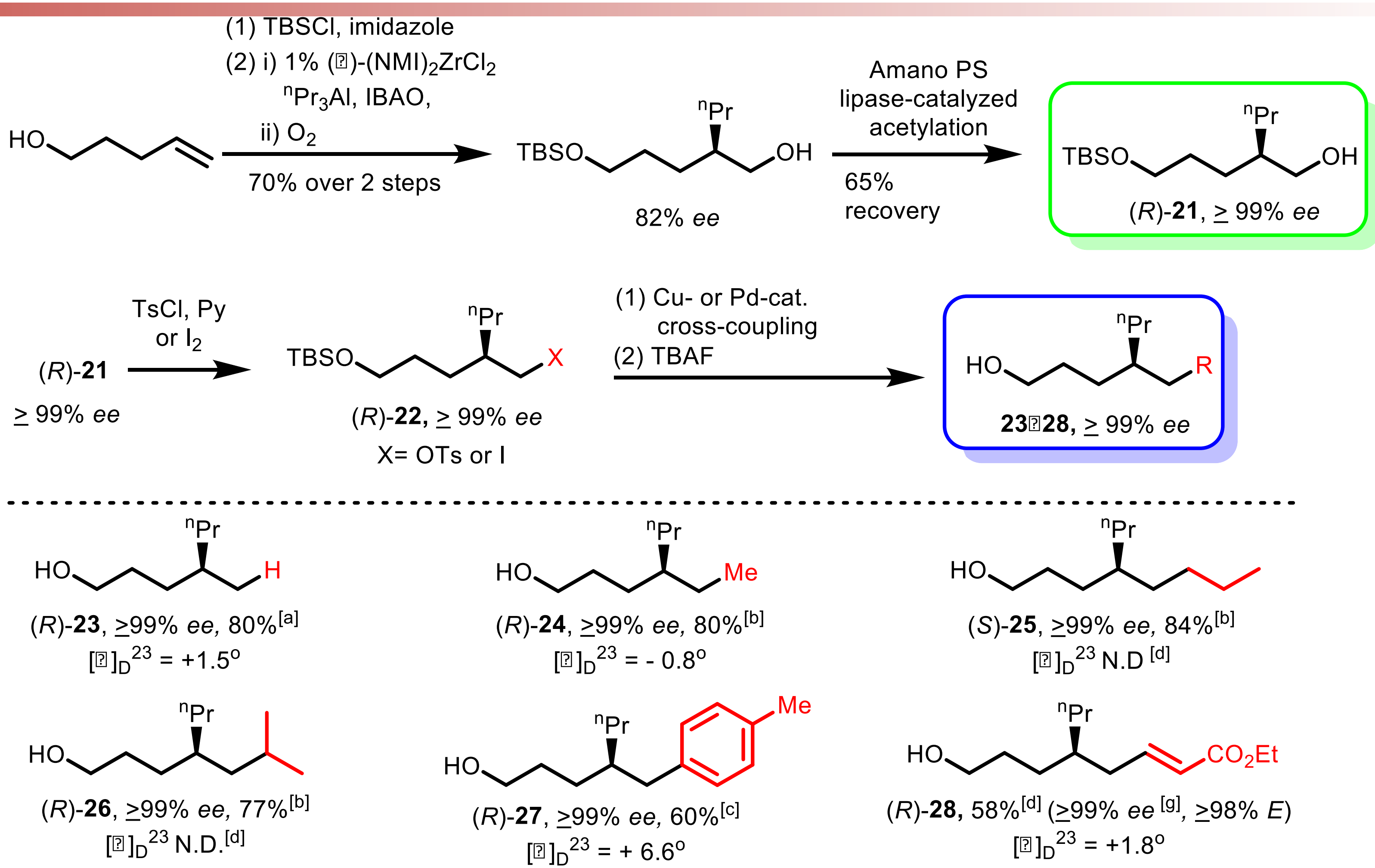
Synthesis of Feebly Chiral 3-Alkyl-1-alkanols



[a] $LiAlH_4$ (1.5 equiv); 2) TBAF [b] 1) $CuCl_2$ (5 mol%), PhC≡CMe (15 mol%), RMgX (2 equiv); 2) TBAF

Xu, S.; Oda, A.; Kamada, H.; Negishi, E., *Proc. Natl. Acad. Sci. USA*, **2014**, *111*, 8368-8373.
Xu, S.; Oda, A.; Negishi, E., *Chem. Eur. J.* **2014**, 20, 16060-16064.

Synthesis of Feebly Chiral 4-Alkyl-1-alkanols

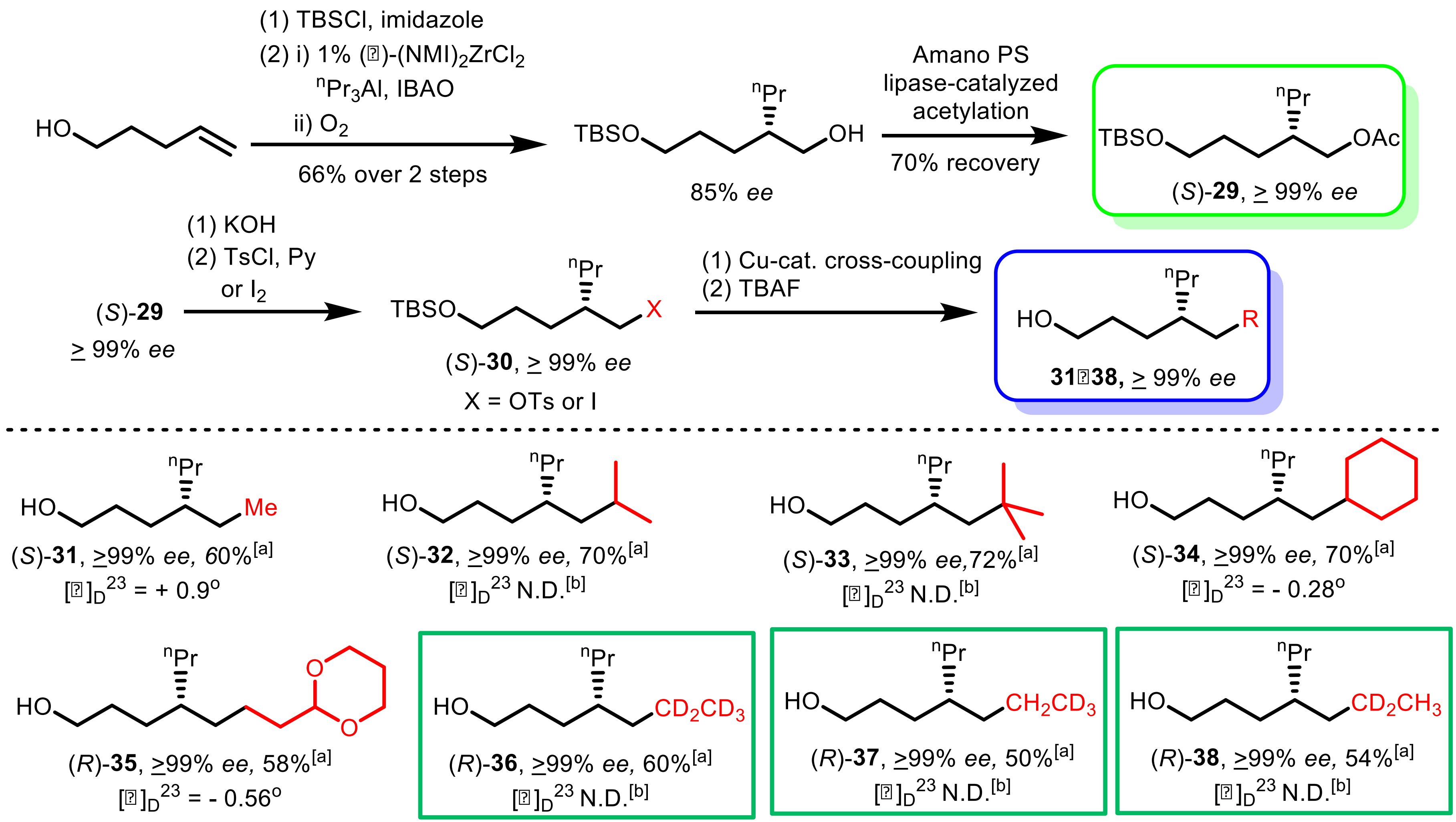


[a] LiAlH$_4$ (1.5 equiv); 2) TBAF [b] 1) CuCl$_2$ (5 mol%), PhC≡CMe (15 mol%), RMgX (2 equiv); 2) TBAF

[c] 1) i) ^{t}BuLi, ii) ZnBr$_2$, iii) PEPPSI (1 mol%), RX; 2) TBAF [d] [⍰]$_D^{23}$ is too small to be determined

Xu, S.; Oda, A.; Kamada, H.; Negishi, E., *Proc. Natl. Acad. Sci. USA*, **2014**, *111*, 8368-8373.
Xu, S.; Oda, A.; Negishi, E., *Chem. Eur. J.* **2014**, 20, 16060-16064.

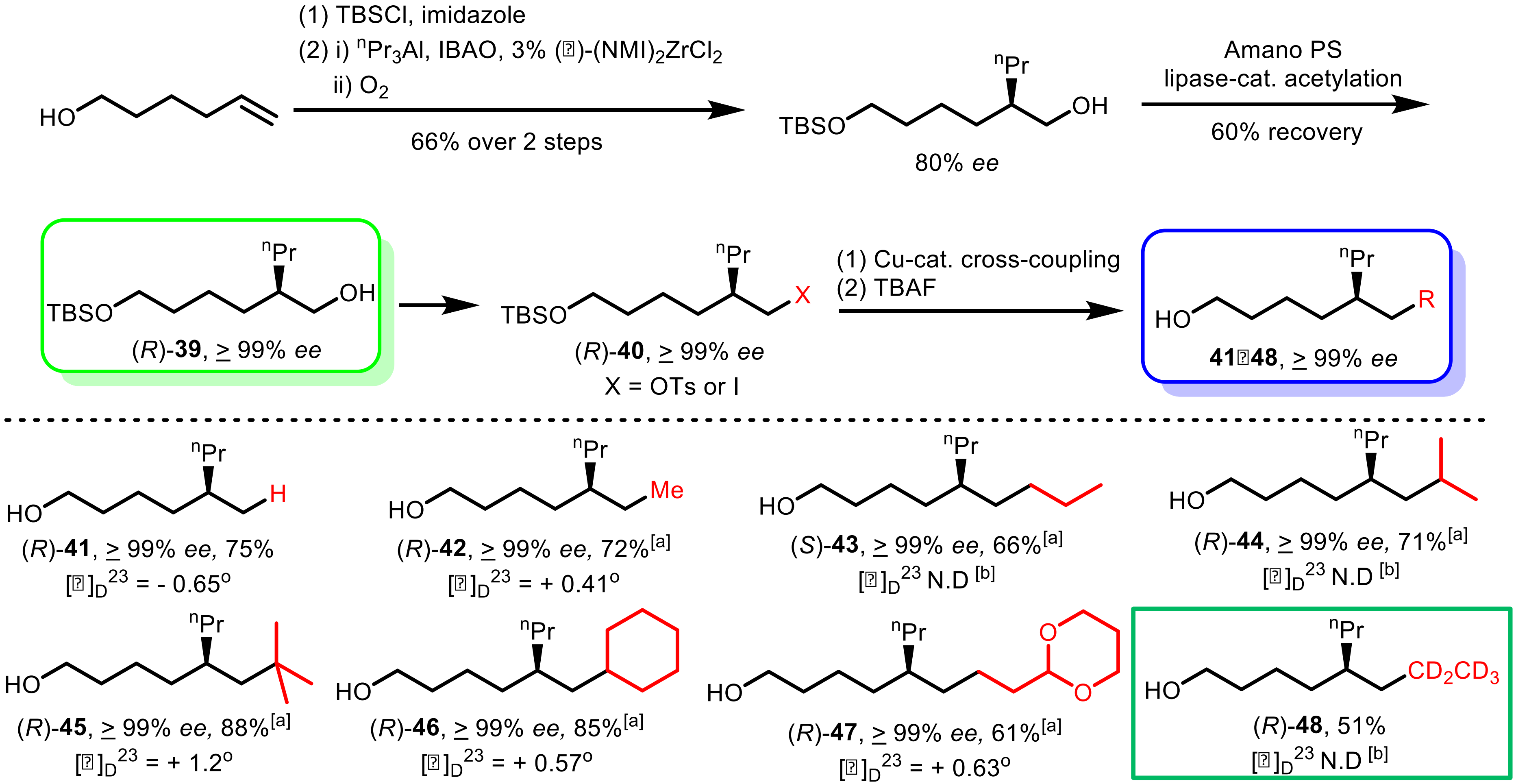
Synthesis of Feebly Chiral 4-Alkyl-1-alkanols



[a] 1) $CuCl_2$ (5 mol%), PhC≡CMe (15 mol%), RMgX (2 equiv); 2) TBAF [b] $[⍰]_D^{23}$ is too small to be determined

Xu, S.; Oda, A.; Kamada, H.; Negishi, E., *Proc. Natl. Acad. Sci. USA*, **2014**, *111*, 8368-8373.
Xu, S.; Oda, A.; Negishi, E., *Chem. Eur. J.* **2014**, 20, 16060-16064.

Synthesis of Feebly Chiral 5-Alkyl-1-alkanols

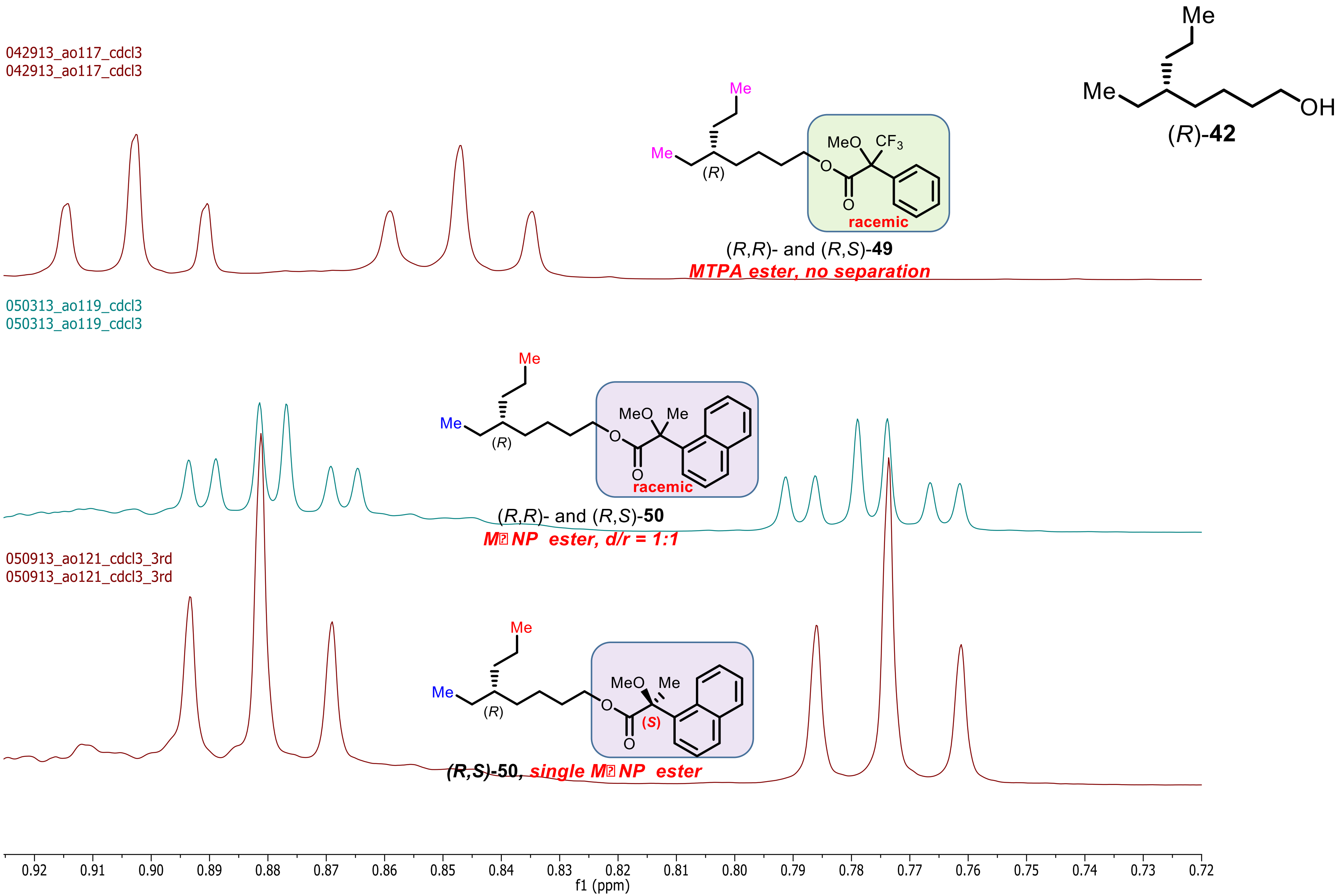


[a] 1) $CuCl_2$ (5 mol%), PhC≡CMe (15 mol%), RMgX (2 equiv); 2) TBAF

[b] $[\alpha]_D^{23}$ is too small to be determined

Xu, S.; Oda, A.; Kamada, H.; Negishi, E., *Proc. Natl. Acad. Sci. USA*, **2014**, *111*, 8368-8373.
Xu, S.; Oda, A.; Negishi, E., *Chem. Eur. J.* **2014**, 20, 16060-16064.

Determination of ee by MαNP Ester



1) Xu, S.; Oda, A.; Kamada, H.; Negishi, E., *Proc. Natl. Acad. Sci. USA*, **2014**, *111*, 8368-8373.
2) Ichikawa, A.; *Chirality*, **1999**, *11*,70; 3) Harada, N.; etal, *Tetrahedron: Asymmetry*, **2000**, *11*, 1249.

Acknowledgments

Pd- or Ni-Catalyzed C–C Bond Formation

1976-1980	Baba, S. King, A. O. Okukado, N. Kobayashi, M. Van Horn, D. E.	Valente, L. F. Silveira, A. Jr. Villani, F. J. Klima, W. L. Spiegel, B. I.	
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