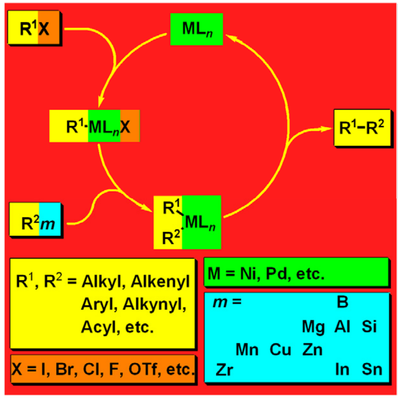
Magical Power of Transition Metals:
Past, Present, and Future

Ei-ichi Negishi, Purdue University

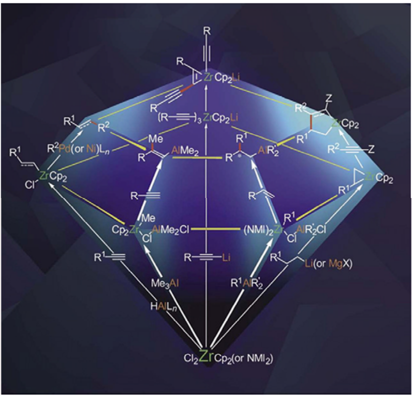


R^1, R^2 = Alkyl, Alkenyl
Aryl, Alkynyl,
Acyl, etc.

X = I, Br, Cl, F, OTf, etc.

M = Ni, Pd, etc.

m = B
Mg Al Si
Mn Cu Zn
Zr In Sn



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.

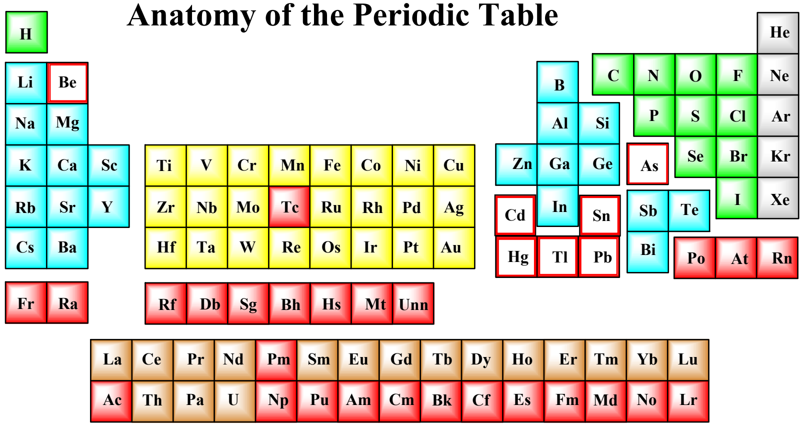
2. If desirable and necessary, **consider their binary combinations** (ca. 5,000). (**Two is Better than One!**)[a]

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)

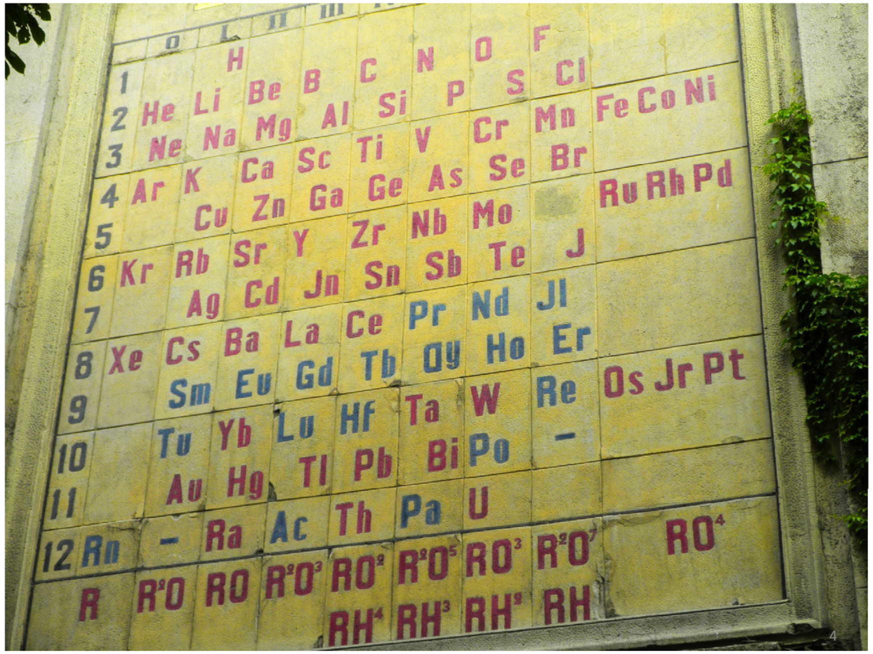
☐ = Intrinsically toxic (?) (7)

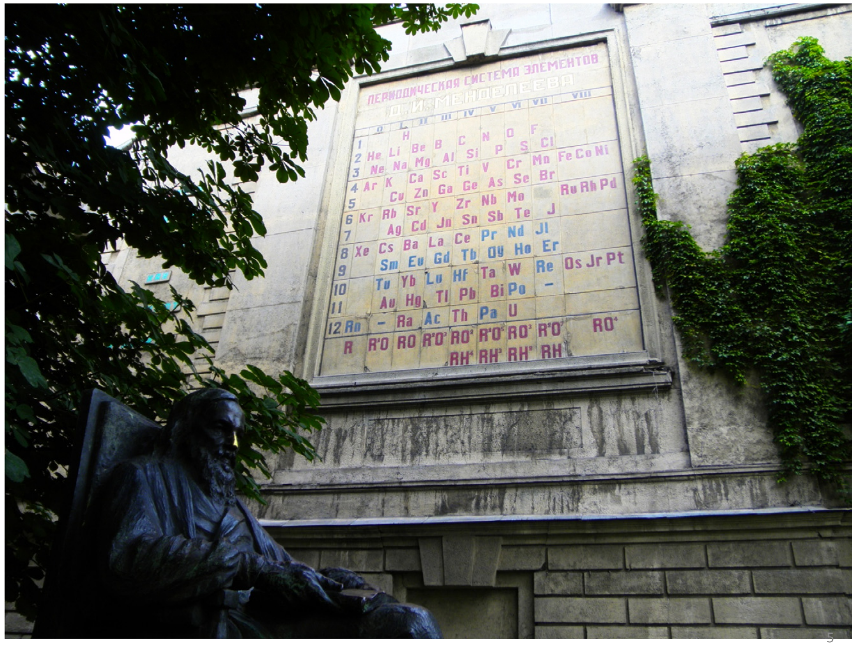
🟨 = d-Block transtion metals (24 - 1 = 23)

⬜ = Inert gases (5)

58 metals usable in Organic Synthesis

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

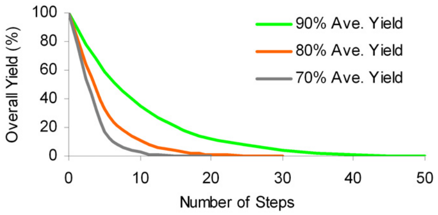




Effects of Product Yield and Number of Steps on Overall Yield

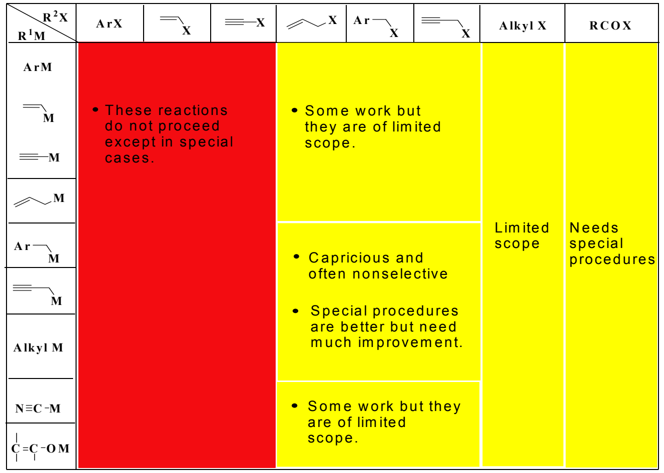
Number of Steps	90% Ave. Yield	80% Ave. Yield	70% Ave. Yield
	Overall Yield (%)		
5	59	33	17
10	35	11	3
15	21	3.6	0.5
20	12	1	0.1
30	4	0.1	
40	1.5		
50	0.5		

"Step-economy" is of utmost importance !



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

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



- These reactions do not proceed except in special cases.
- Some work but they are of limited scope.
- Capricious and often nonselective
- Special procedures are better but need much improvement.
- Some work but they are of limited scope.

Limited scope

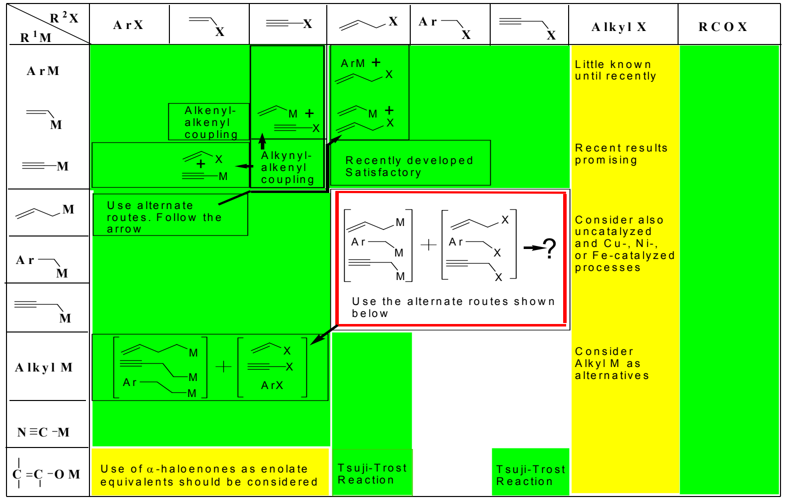
Needs special procedures

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

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

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 ! ! !**



Alkenyl-alkenyl coupling

Alkynyl-alkenyl coupling

Recently developed Satisfactory

Use alternate routes. Follow the arrow

Use the alternate routes shown below

Little known until recently

Recent results promising

Consider also uncatalyzed and Cu-, Ni-, or Fe-catalyzed processes

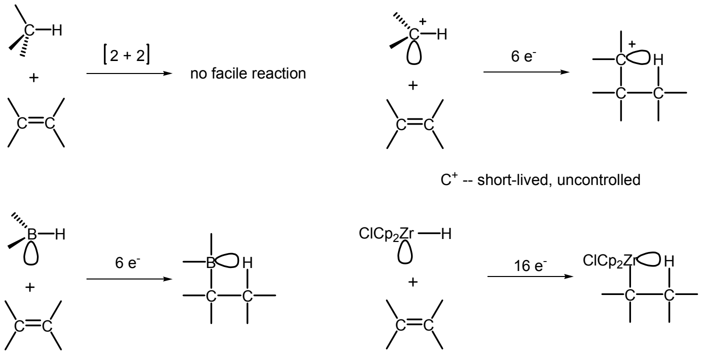
Consider Alkyl M as alternatives

Use of α-haloenones as enolate equivalents should be considered

Tsuji-Trost Reaction

Tsuji-Trost Reaction

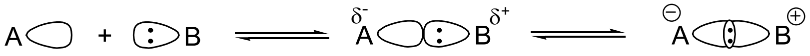
Why Metals?



C⁺ -- short-lived, uncontrolled

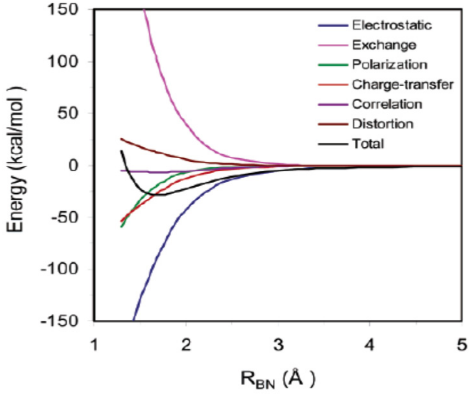
Bottom line:

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.

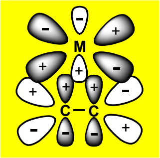
Why d-Block Transition Metals ?

Two Major Reasons (#1)

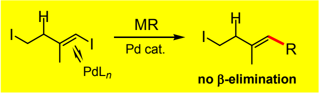
I. Simultaneous Availability of Empty and Filled Non-bonding Orbitals (LUMOs and HOMOs)

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

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

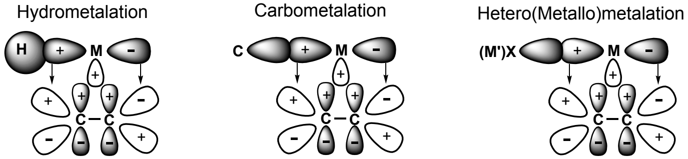


- M. J. S. Dewar
- K. Fukui
- R. Hoffmann
- R. B. Woodward



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.)

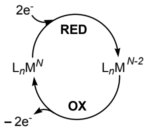


The significance of **concerted synergistic** (HOMO-LUMO & HOMO-LUMO) bonding cannot be overemphasized.

Why d-Block Transition Metals ?

Two Major Reasons (#2)

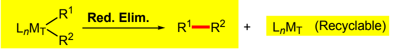
II. Ready and Reversible Reduction and Oxidation under One Set of Reaction Conditions !



- ● **Essential to REDOX Catalysis**
- ● **Very difficult to devise REDOX Catalysis without using transition metals.**

Four Basic Processes of C-C (and C-X) Bond Formation with Transition Metals

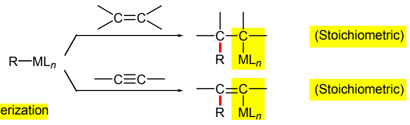
(1) Reductive Elimination



Ex. Pd- or Ni-cat. cross-coupling

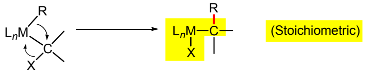
(LEGO Game Approach)

(2) Carbometalation[a,b]



Ex. ●Ziegler-Natta polymerization
●Reppe and Wilke alkyne- and diene cyclooligomerization
●Olefin metathesis

(3) Migratory Insertion[a,b]



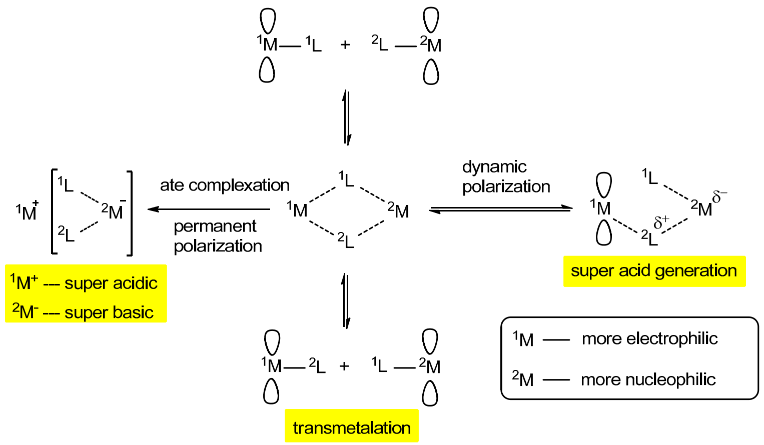
Ex. Oxo and other carbonylation reactions

(4) Nucleophilic and Electrophilic Attack on Ligands [a]

Ex. ●Wacker oxidation
●Tsuji-Trost reaction

Note: (*a*) Missing links must be provided for catalysis.
(*b*) Main group metals also work but not catalytically.

Interactions between Two Coordinatively Unsaturated Metal Species



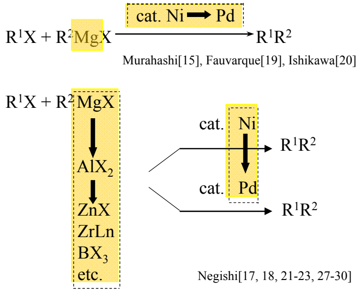
Bottom line: Two is better than one

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**

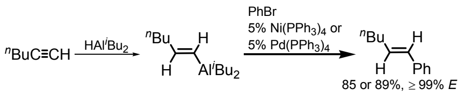


<u>Negishi group contributions</u>:

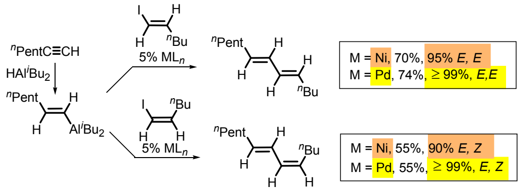
1. Co-discovery of Pd-Catalyzed Cross-Coupling
2. Discovery of Al, B, Zn, Zr, etc. as Effective Metal Countercations
3. Discovery of Hydrometallation—Cross-Coupling & Carbometallation—Cross-Coupling Tandem Reactions
4. Discovery of Double Metal Catalysis, especially with ZnX_2

- 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.

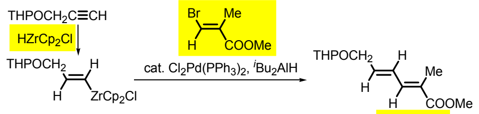
First Highly Selective and General Pd-catalyzed Cross-Coupling Route to Conjugated Dienes (1976-1979)



E. Negishi and S. Baba *CC* **1976**, *596*.



S. Baba and E. Negishi *JACS* **1976**, *98*, 6729.



E. Negishi and D. E. Van Horn *JACS* **1977**, *99*, 3168.
E. Negishi et al. *TL* **1978**, *19*, 1027.

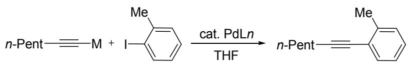
- Pd was used, but no advantage over Ni revealed.
- First Al – Ni or Al – Pd reaction.
- First hydrometallation – cross-coupling tandem process.

- First highly (>98%) selective and general synthesis of conjugated 1,3-dienes.
- Some distinct advantages of Pd over Ni in cross-coupling shown for the first time.

- First Zr – Ni or Zr – Pd reaction

Bottom Line: (a) Superior selectivity associated with Pd over Ni reported for the first time.
(b) Discovery of the hydrometallation–cross-coupling tandem process.

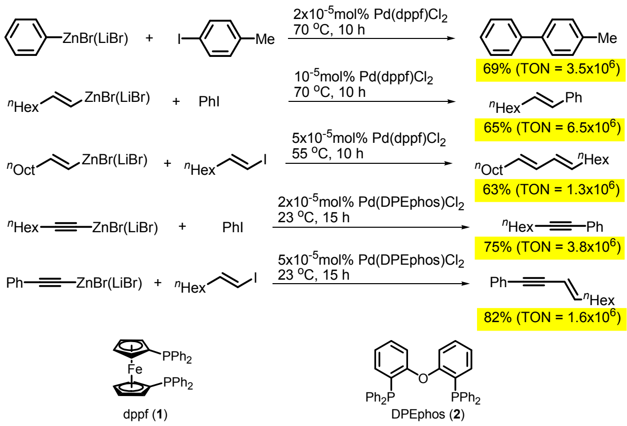
First Systematic Screening of Metal Countercations



Entry	M of n-PentC≡CM	Reaction Cond.^{a} Temp (°C)	Time (h)	Product Yield (%)	Residual Ar-I (%)	
1	Li	22	1	trace	88	
2	Li	22	24	30	80	
3	Na	reflux	24	58	41	
4	MgBr	22	1	29	55	
5	MgBr	22	24	49	33	
6	ZnCl	22	1	91	8	→ **Negishi Coupling**
7	ZnCl	22	3	88	2	
8	HgCl	22	1	trace	92	
9	HgCl	reflux	6	trace	88	
10	BBu3Li	22	3	10	76	
11	BBu3Li	reflux	1	92	5	→ **Suzuki Coupling**
12	AlBu3Li	22	3	4	80	
13	AlBu3Li	reflux	1	38	10	
14	AlBu2	22	3	49	46	
15	SiMe3	reflux	1	trace	94	
16	SnBu3	22	1	75	14	→ **Stille Coupling**
17	SnBu3	22	6	83	6	
18	ZrCp2Cl	reflux	3	0	80	

E. Negishi & A. O. King (**1978**)

High Turnover Numbers Observed in the Pd-Catalyzed Cross-Coupling with Pd(dppf)Cl_2 or Pd(DPEphos)Cl_2 as a Catalyst

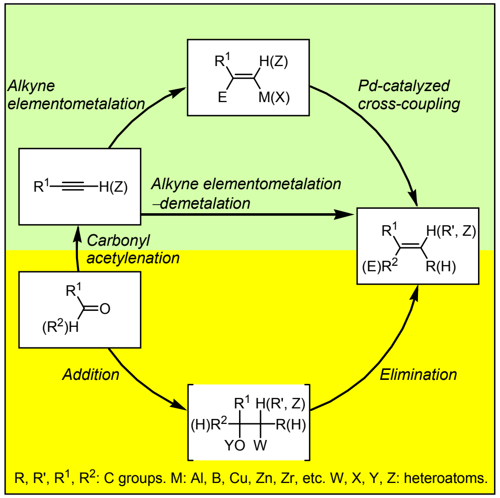


Bottom Line: Use of Zn and chelating ligands can lead to very high TONs.

Z. Huang, M. Qian, D. T. Babinski, and E. Negishi, *Organometallics* **2005**, *24*, 475-478.

How to Synthesize any Alkenes* Efficiently and Selectively

*Mostly acyclic alkenes considered.

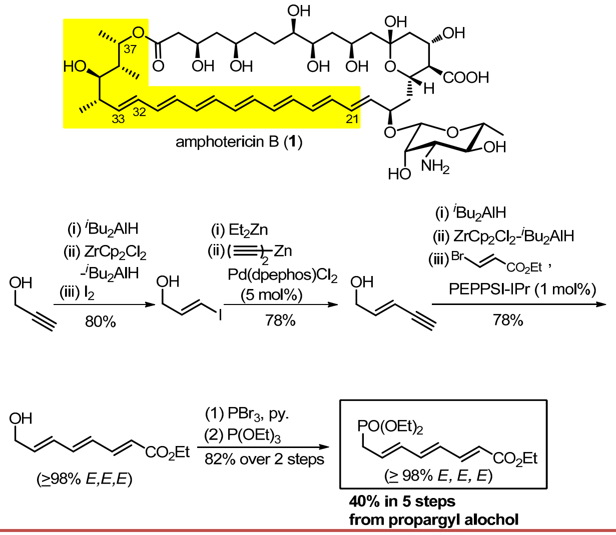


R, R', R^1, R^2: C groups. M: Al, B, Cu, Zn, Zr, etc. W, X, Y, Z: heteroatoms.

It takes Alkynes to make a world.

ACS banner

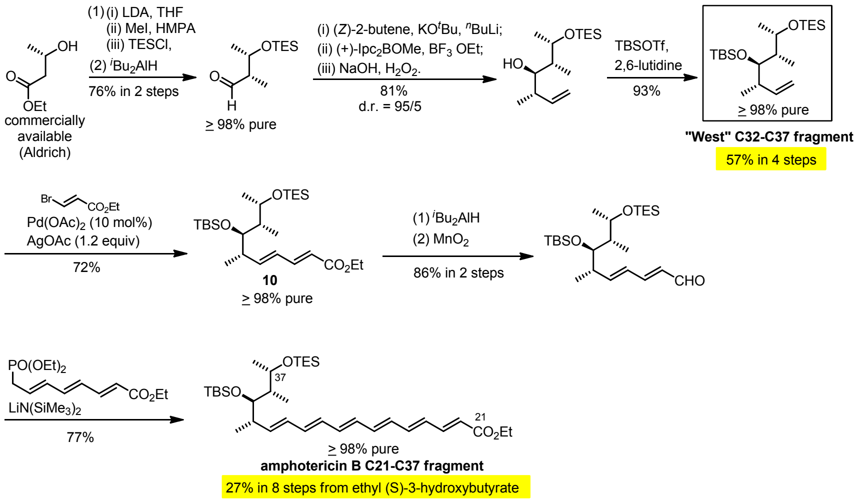
➪ *"Last" Synthesis of Amphotericin B C21-C37 Fragment*



40% in 5 steps from propargyl alochol

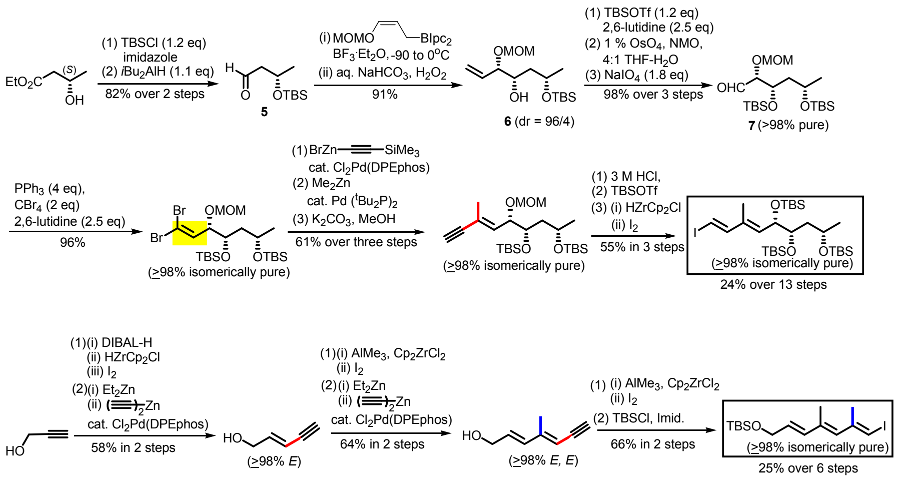
G. Wang, S. Xu, Q. Hu, F. Zeng, E. Negishi, *Chem. Eur. J.* **2013**, *19*, 12938-12942.

➪ *"Last" Synthesis of Amphotericin B C21-C37 Fragment*



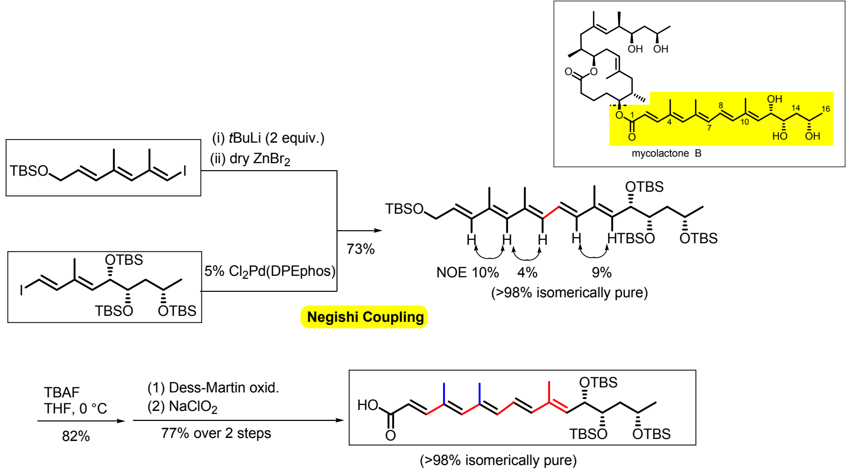
G. Wang, S. Xu, Q. Hu, F. Zeng, E. Negishi, *Chem. Eur. J.* **2013**, *19*, 12938-12942.

⇨Synthesis of Triprotected Side-Chain of Mycolactone B



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.

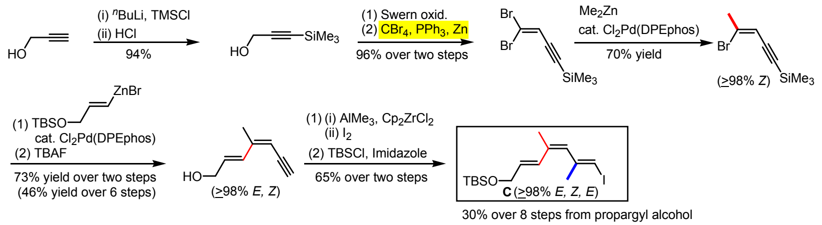
⇨Synthesis of Triprotected Side-Chain of Mycolactone B



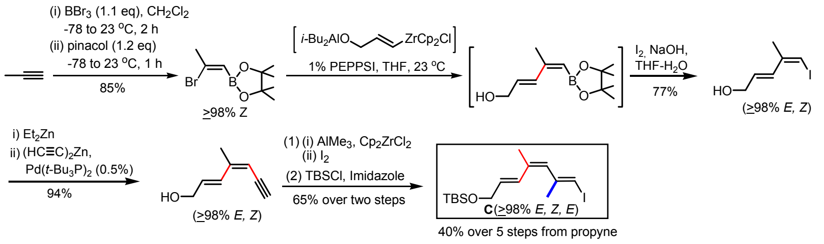
15% overall yield in the longest linear sequence (17 steps) from ethyl (S)- 3-hydroxybutyrate

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.

⇨Synthesis of Triprotected Side-Chain of Mycolactone A

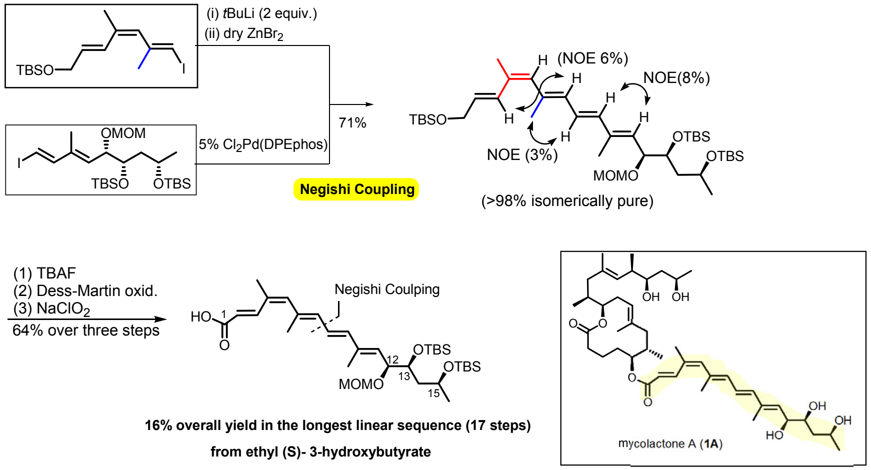


Alternative route to ***C***



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.

⇨Synthesis of Triprotected Side-Chain of Mycolactone A



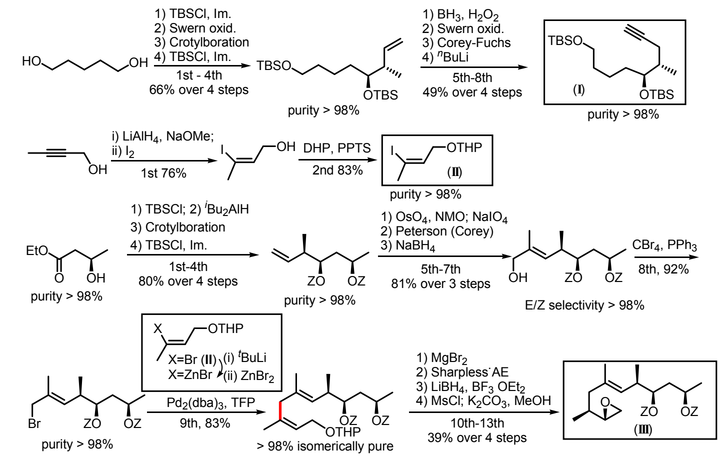
16% overall yield in the longest linear sequence (17 steps)

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.

Total syntheses of mycolactones A and B

➪*Synthesis of the Core of Mycolactones A and B*

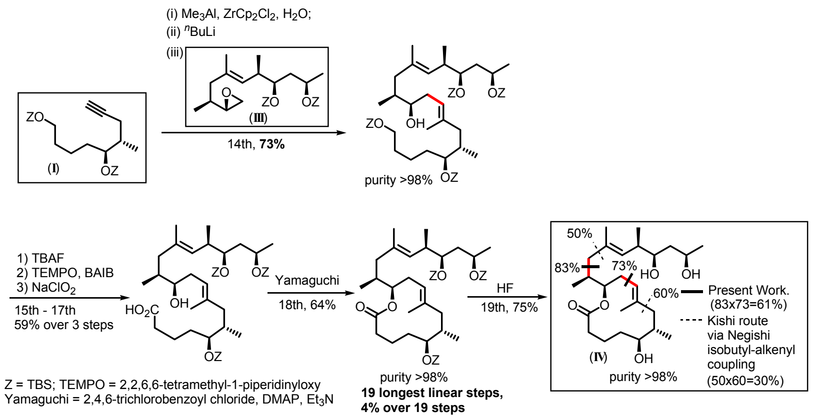


Z=TBS; Sharpless AE = ^tBuOOH, (-)-DET, $Ti(O^iPr)_4$; Peterson (Corey) = ^sBuLi, $CH_3CH(Et_3Si)CH{=}NCy$, TFA, H_2O
Crotylboraton = (*Z*)-2-butene, KO^tBu, ^nBuLi, (+)-Ipc_2BOMe, BF_3 OEt_2; H_2O_2, NaOH

G. Wang, N. Yin, E. Negishi, *Chem. Eur. J.* **2011**, *17,* 4118 - 4130.

Total syntheses of mycolactones A and B

➪*Synthesis of the Core of Mycolactones A and B*

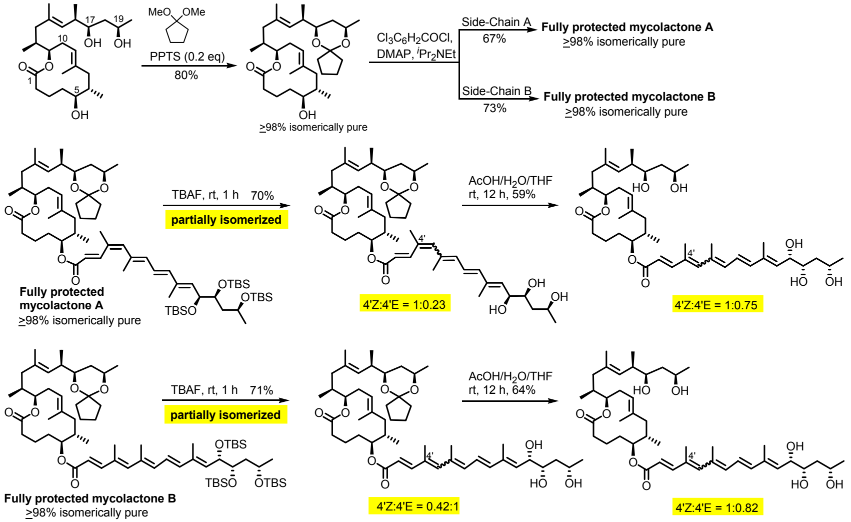


Z = TBS; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy
Yamaguchi = 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N

G. Wang, N. Yin, E. Negishi, *Chem. Eur. J.* **2011**, *17,* 4118 - 4130.

Total syntheses of mycolactones A and B

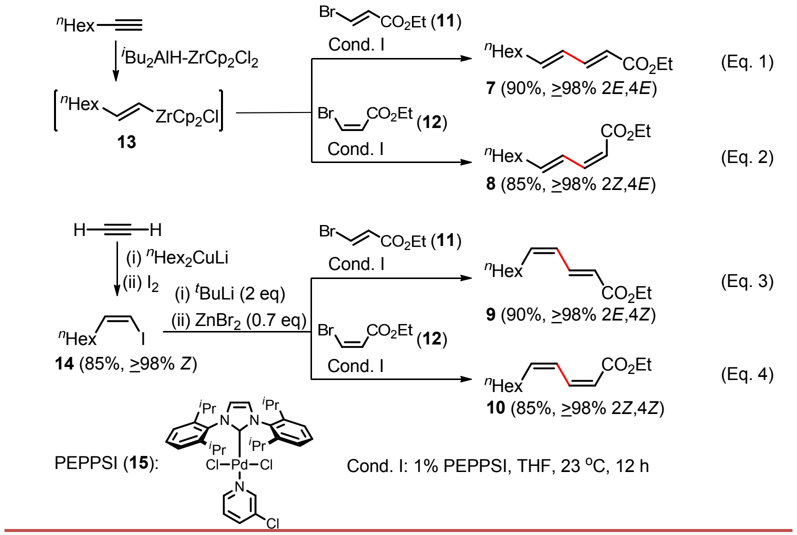
➪*Final Assembly of Mycolactones A and B*



G. Wang, N. Yin, E. Negishi, *Chem. Eur. J.* **2011**, *17,* 4118 - 4130.

Alkyne Elementometalation–Pd-Catalyzed Negishi Coupling Tandem Processes.

➪*Highly (≥98%) Selective Synthesis of All Stereosiomers of 2,4-Dienoic Esters*

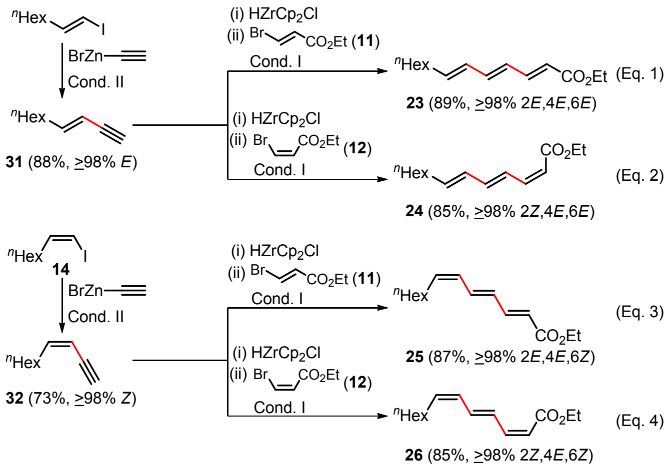


Cond. I: 1% PEPPSI, THF, 23 °C, 12 h

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

Alkyne Elementometalation–Pd-Catalyzed Negishi Coupling Tandem Processes.

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

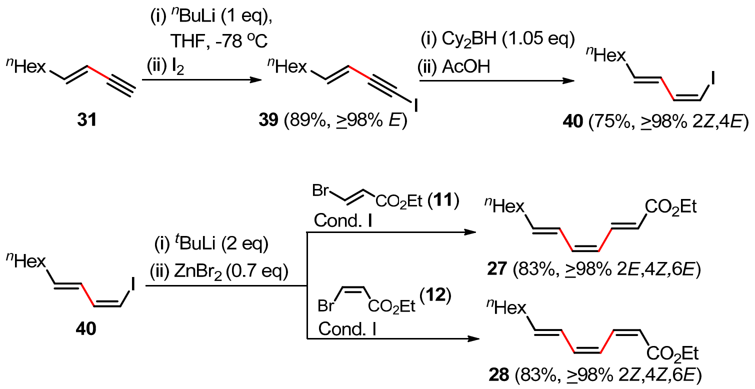


Cond. I: 1% PEPPSI,THF, 23 °C, 12 h
Cond. II: 5% Pd(DPEphos)Cl_2, THF, 23 °C, 12 h

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

Alkyne Elementometalation–Pd-Catalyzed Negishi Coupling Tandem Processes.

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

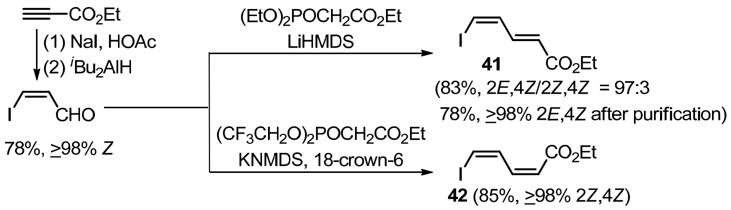


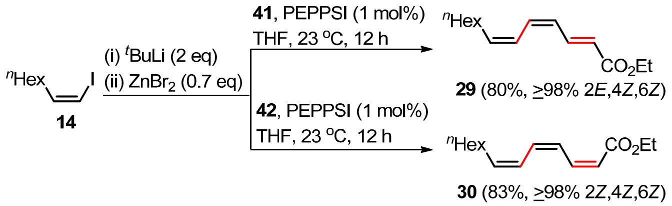
Cond. I: 1% PEPPSI, THF, 23 °C, 12 h

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

Alkyne Elementometalation–Pd-Catalyzed Negishi Coupling Tandem Processes.

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

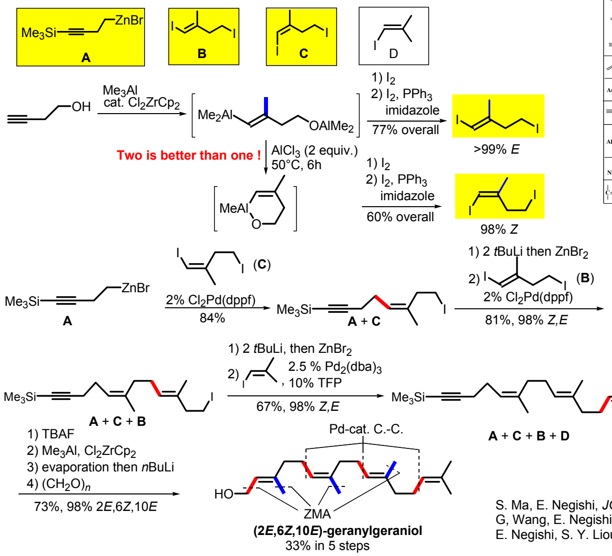


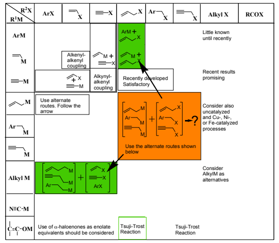


G. Wang, S. Mohan, E. Negishi. *Proc. Natl. Acad. Sci. USA,* **2011**, *108*, 11344-11349.

LEGO Game Route to 1,5-Diene-Containing Terpenoids

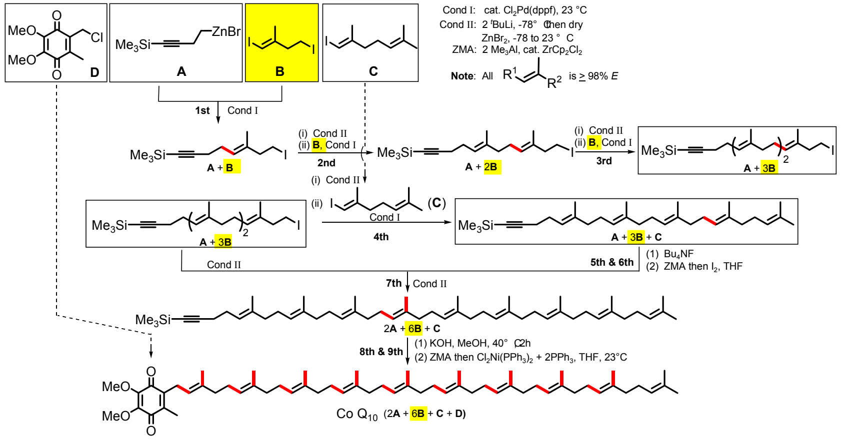
Avoid Allyl-Allyl Coupling !





S. Ma, E. Negishi, *JOC* **1997**, *62*, 784
G, Wang, E. Negishi, *EJOC* **2009**, *11*, 1679
E. Negishi, S. Y. Liou, C. Xu, S. Huo, *Org. Lett.* **2002**, *4*, 261

ALKYNE ZMA–Pd-CATALYZED ALKYL–ALKENYL COUPLING: LEGO GAME ROUTE TO Co Q_{10}

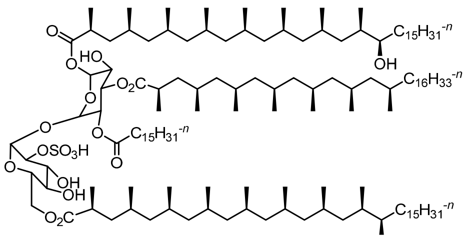


Cond I: cat. $Cl_2Pd(dppf)$, 23 °C
Cond II: 2 ^tBuLi, -78° C then dry $ZnBr_2$, -78 to 23 ° C
ZMA: 2 Me_3Al, cat. $ZrCp_2Cl_2$

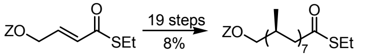
Note: All R^1–R^2 is ≥ 98% *E*

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

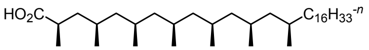
CAN WE POSSIBLY SYNTHESIZE THESE NATURAL POLYOLEFINS BY THE ZIEGLER-NATTA POLYMERIZATION?



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



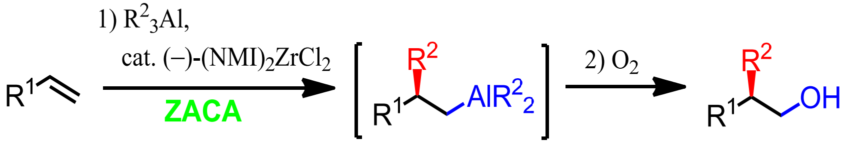
- Key reagents: MeMgBr, 1% Josiphos-CuBr
- For a recent synthesis of **phthioceranic acid (1)**, see:
  ter Horst, B.; Feringa, B. L.; Minnaard, A. J. *OL*, **2007**, *9*, 3013



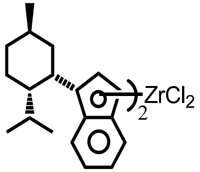
phthioceranic acid (1)

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

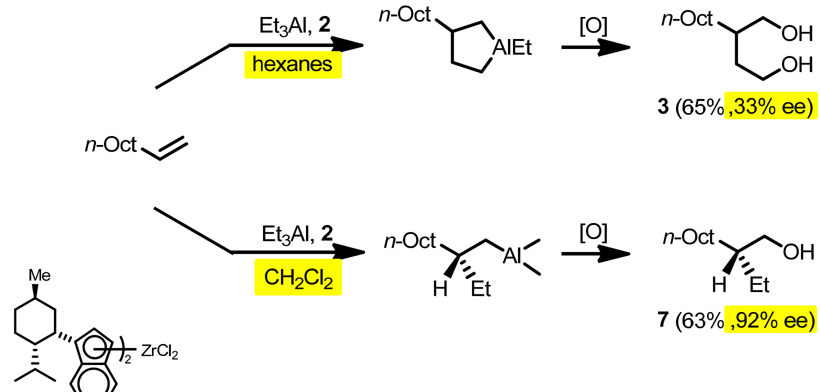
Early Contributions

- 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 al*. 1993 *JACS* 4590
- Wipf, P.; Ribe, S. 2000 *OL* 1713

Zr-Catalyzed Asymmetric Carboalumination of Alkenes (Solvent Effect)



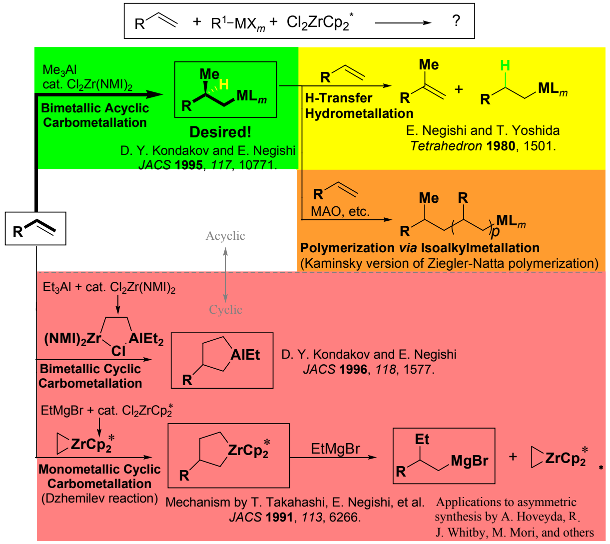
3 (65%,33% ee)

7 (63%,92% ee)

2

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

WHAT CAN HAPPEN IN THE FOLLOWING REACTIONS?



D. Y. Kondakov and E. Negishi *JACS* **1995**, *117*, 10771.

E. Negishi and T. Yoshida *Tetrahedron* **1980**, 1501.

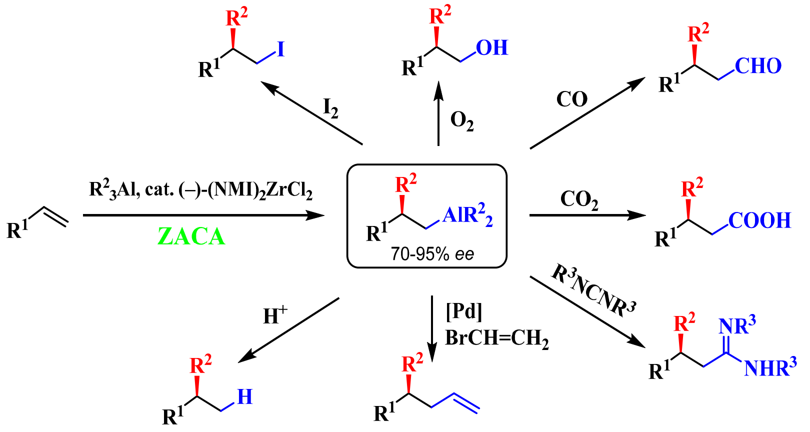
D. Y. Kondakov and E. Negishi *JACS* **1996**, *118*, 1577.

Mechanism by T. Takahashi, E. Negishi, et al. *JACS* **1991**, *113*, 6266.

Applications to asymmetric synthesis by A. Hoveyda, R. J. Whitby, M. Mori, and others

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

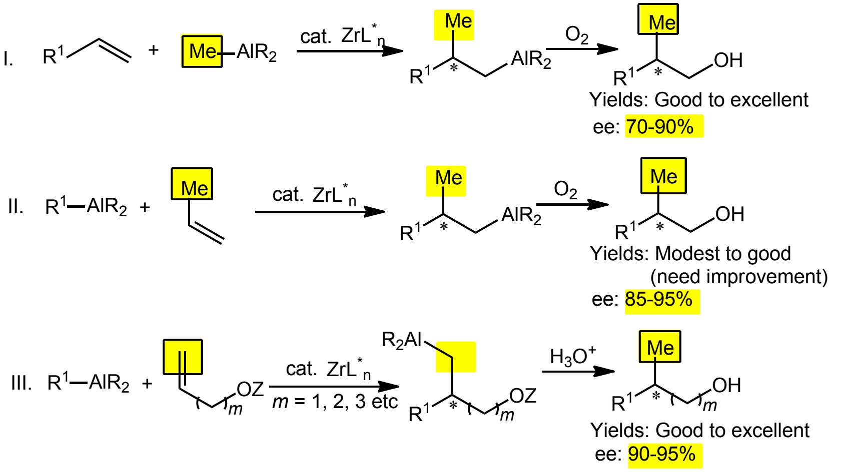
The Importance of Organometallic Functionality



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

---

THREE PROTOCOLS FOR ENANTIOSELECTIVE SYNTHESIS OF METHYL-SUBSTITUTED 1-ALKANOLS



I. Yields: Good to excellent
ee: 70-90%

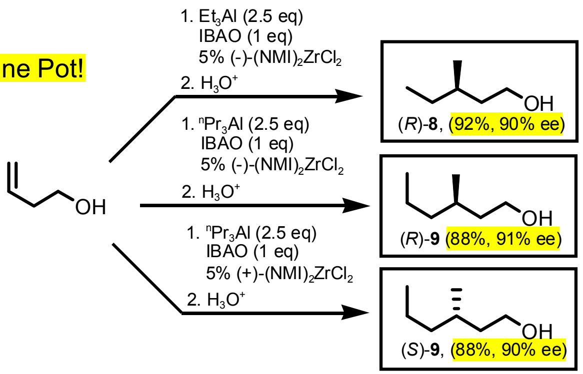
II. Yields: Modest to good
(need improvement)
ee: 85-95%

III. Yields: Good to excellent
ee: 90-95%

Bottom Line (No. 2): (a) 3 discrete protocols are available.
(b) Minimize methylalumination.

SYNTHESIS OF 3-METHYL-1-ALKANOLS VIA Zr-CATALYZED ASYMMETRIC CARBOALUMINATION OF 3-BUTEN-1-OL

One Pot!



(*R*)-**8**, (92%, 90% ee)

(*R*)-**9** (88%, 91% ee)

(*S*)-**9**, (88%, 90% ee)

Negishi, E.; Tan, Z.; Liang, B.; Novak, T. *Proc. Natl. Acad. Sci.* **2004**, 5782-5787.

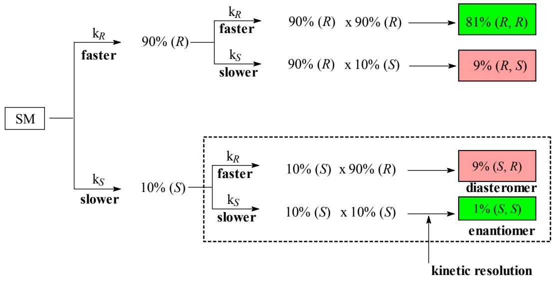
STATISTICAL ENANTIOMERIC AMPLIFICATION

Statistical Enantiomeric Amplication ← **Kinetic Resolution**

↑

Mass Action Law

Ex. **I** (k_R/k_S)= 90/10 + **II** (k_R/k_S) = 90/10



SM

k_R **faster** 90% (*R*)

k_R **faster** 90% (*R*) x 90% (*R*) → 81% (*R*, *R*)

k_S **slower** 90% (*R*) x 10% (*S*) → 9% (*R*, *S*)

k_S **slower** 10% (*S*)

k_R **faster** 10% (*S*) x 90% (*R*) → 9% (*S*, *R*) **diasteromer**

k_S **slower** 10% (*S*) x 10% (*S*) → 1% (*S*, *S*) **enantiomer**

kinetic resolution

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

Note: If another round III is added the overall ee will be $\boxed{99.7\%}$

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),

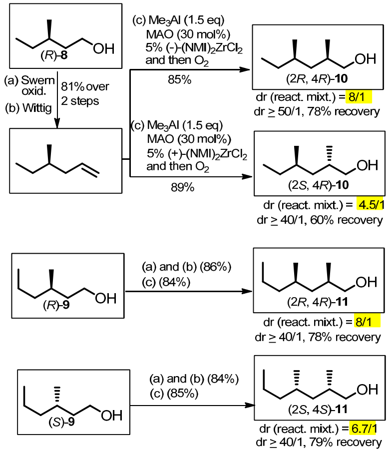
$$(9R + 1S)\,(9R + 1S) = \overbrace{\boxed{81R,R} + 18\underset{\uparrow\ \text{Diastereomers}}{\boxed{R,S\ (S,R)}} + \boxed{1S,S}}^{\text{Enantiomers}}$$

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

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

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

SYNTHESIS OF 2,4-DIMETHYL-1-ALKANOLS VIA Zr-CATALYZED ASYMMETRIC CARBOALUMINATION



dr (react. mixt.) = 8/1
dr ≥ 50/1, 78% recovery

49% over 4 (3-isolation) steps (dr ≥50/1)

dr (react. mixt.) = 4.5/1
dr ≥ 40/1, 60% recovery

40% over 4 (3-isolation) steps (dr ≥40/1)

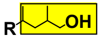
dr (react. mixt.) = 8/1
dr ≥ 40/1, 78% recovery

50% over 4 (3-isolation) steps (dr ≥40/1)

dr (react. mixt.) = 6.7/1
dr ≥ 40/1, 79% recovery

40% over 4 (3-isolation) steps (dr ≥40/1)

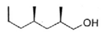
Negishi, E.; Tan, Z.; Liang, B.; Novak, T. *Proc. Natl. Acad. Sci.* **2004**, 5782-5787
For use of MAO, see Wipf, P.; Ribe, S. *Org. Lett.* **2000**, *2*, 1713.

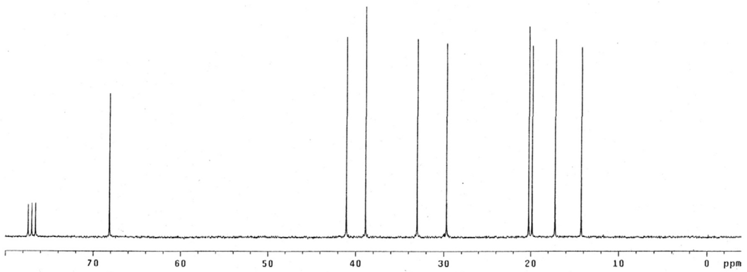
Bottom Line (No.4):  **Can be readily purifiable by a single round of chromatography (Silica gel, EtOAc-hexanes).**

---

^{13}C NMR SPECTRUM OF (2*R*,4*R*)-2,4-DIMETHYL-1-HEPTANOL

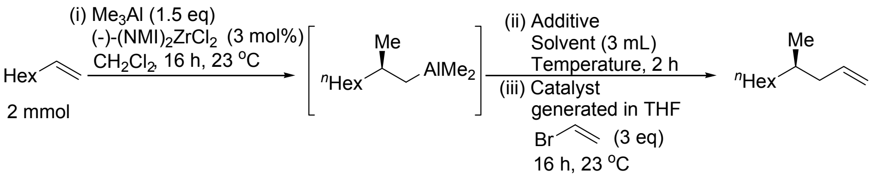
INDEX	FREQUENCY	PPM	HEIGHT
1	5138.970	68.134	49.2
2	3095.738	41.044	68.4
3	2932.613	38.881	78.9
4	2489.558	33.007	67.8
5	2239.261	29.689	66.3
6	1525.482	20.225	72.0
7	1496.712	19.844	65.4
8	1298.776	17.219	67.7
9	1076.961	14.279	64.9





S/N >100/1

OPTIMALIZATION OF THE ONE-POT CARBOALUMINATION—CROSS-COUPLING TANDEM PROCESS

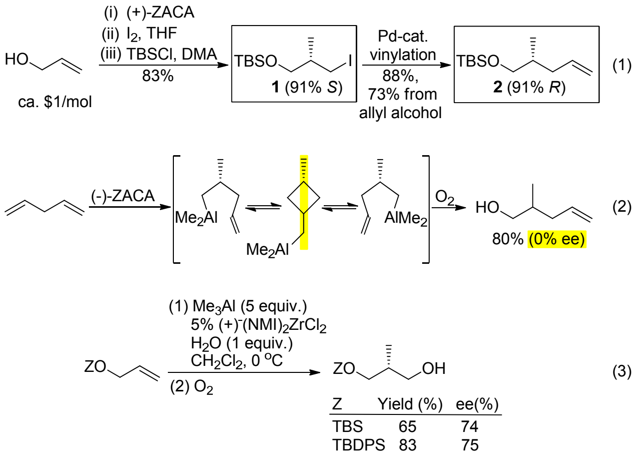


Transmetallation Conditions			Cross-Coupling Conditions	
Additive (eq)	Solvent	Temp., °C	Catalyst	Yield, %
ZnBr$_2$ (1)	THF	60	Pd(PPh$_3$)$_4$ (5%)	14
ZnBr$_2$ (1)	DMF	120	Cl$_2$Pd(DPEphos) (5%) + DIBAL-H (10%)	36
ZnBr$_2$ (3)	DMA	120	Cl$_2$Pd(DPEphos) (5%) + DIBAL-H (10%)	12
ZnBr$_2$ (3)	NMP	120	Cl$_2$Pd(DPEphos) (5%) + DIBAL-H (10%)	36
ZnBr$_2$ (3)	DMSO	120	Cl$_2$Pd(DPEphos) (5%) + DIBAL-H (10%)	30
ZnBr$_2$ (3)	**DMF**	**120**	**Cl$_2$Pd(DPEphos) (5%) + DIBAL-H (10%)**	**63**
Zn(OTf)$_2$ (1)	**DMF**	**70**	**Cl$_2$Pd(DPEphos) (3%) + DIBAL-H (6%)**	**71**

T. Novak, Z. Tan, B. Liang, E. Negishi, *J. Am. Chem. Soc*. **2005**, *127*, 2838.

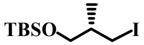
Bottom Line (No. 5): One-pot homologation by one propylene unit.

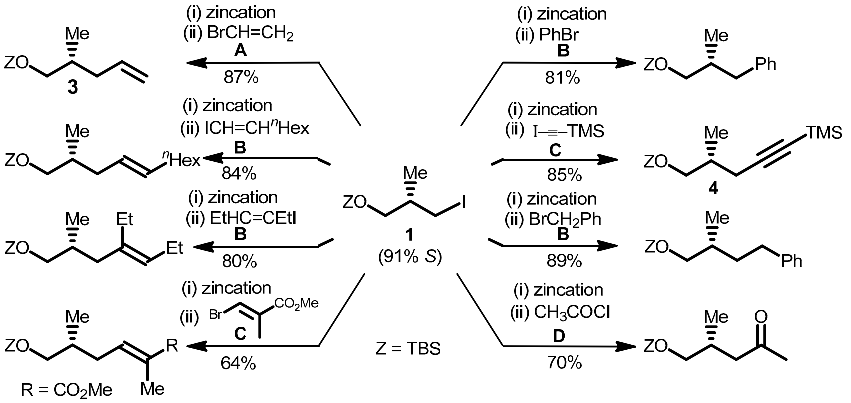
ZACA REACTION OF ALLYL ALCOHOL AND ITS SI-PROTECTED DERIVATIVES AS WELL AS 1,4-PENTADIENE



Z	Yield (%)	ee(%)
TBS	65	74
TBDPS	83	75

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

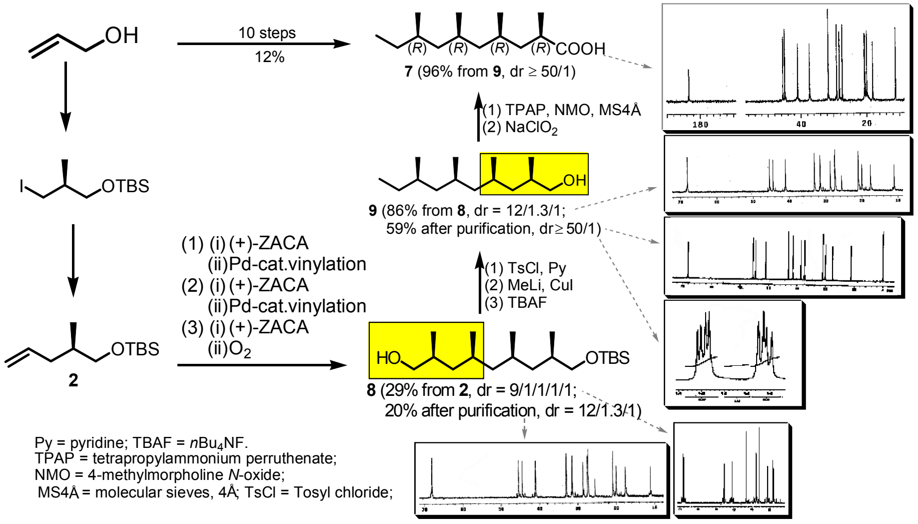
Pd-Catalyzed Cross-Coupling Reaction of 



[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.

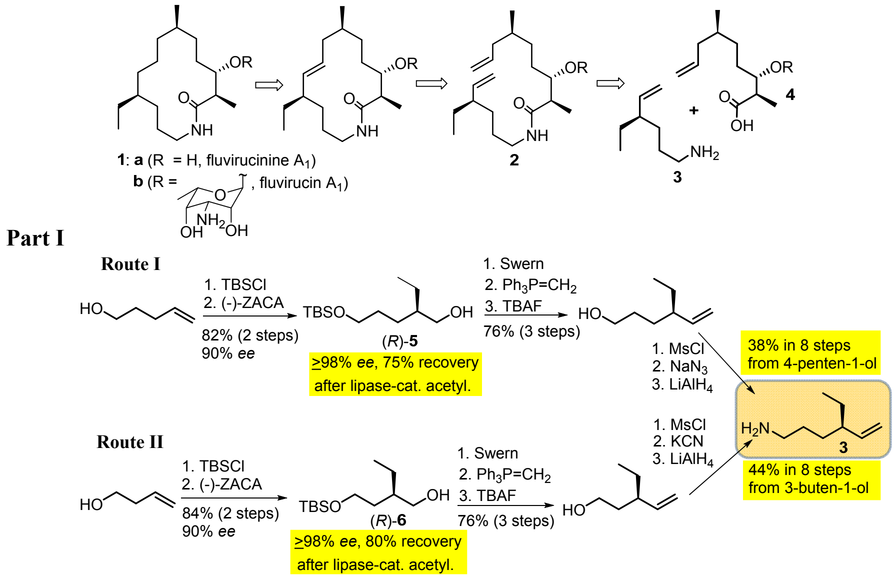
Synthesis of (2*R*,4*R*,6*R*,8*R*)-2,4,6,8-Tetramethyldecanoic Acid, The Acid Component of Preen-Gland Wax of Graylag Goose, *Anser Anser*



Py = pyridine; TBAF = *n*Bu$_4$NF.
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.

Total Synthesis of Fluvirucinine A_1



≥98% *ee*, 75% recovery after lipase-cat. acetyl.

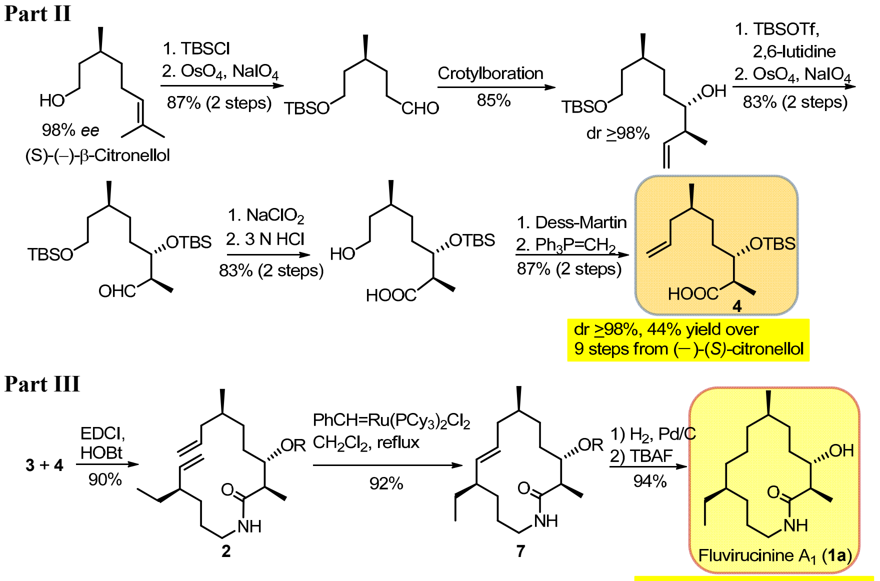
38% in 8 steps from 4-penten-1-ol

44% in 8 steps from 3-buten-1-ol

≥98% *ee*, 80% recovery after lipase-cat. acetyl.

Liang, B.; Negishi, E. *Org. Lett.* **2008**, *10*, 193-195.

Total Synthesis of Fluvirucinine A_1

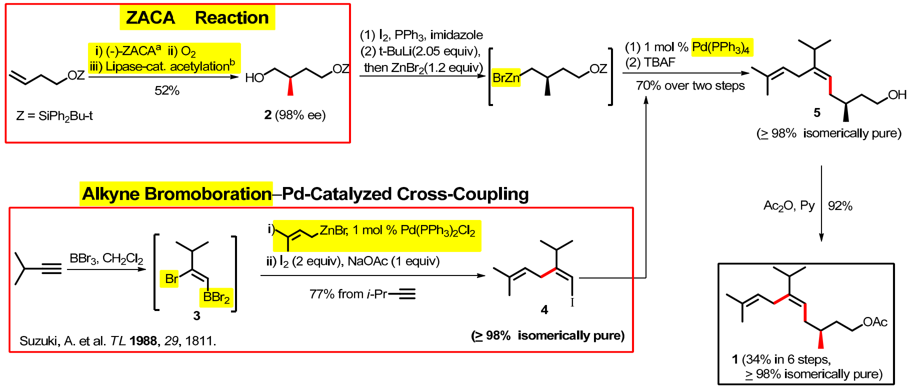


dr ≥98%, 44% yield over 9 steps from (–)-(*S*)-citronellol

≥99% pure, 34% yield over 13 steps from (–)-(*S*)-citronellol

Liang, B.; Negishi, E. *Org. Lett.* **2008**, *10*, 193-195.

LEGO Game Route to Yellow Scale Pheromone

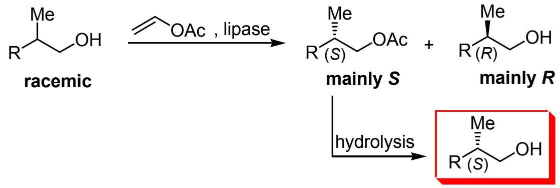


[a] (-)-ZACA = Me_3Al(3.0 equiv), 1 mol % (-)-$(NMI)_2ZrCl_2$, H_2O(0.5 equiv), CH_2Cl_2, 23 °C, 5 h

[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*



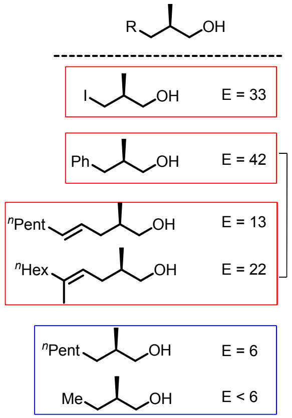
Preparation of (*S*)-2-Methyl-1-alcohols (≥98% *ee*) from Enantiomeric Mixtures

Initial ee$_o$ (%)	$E^{[a]}$	Max. yield (%)$^{[a,b]}$	Initial ee$_o$ (%)	$E^{[a]}$	Max. yield (%)$^{[a,b]}$
0 (racemic)	100	≤2	70	100	≤85
	90	0		50	~80
20	100	≤35		30	~60
	80	~20		20	~25
	60	0		10	0
50	100	≤70	80	100	≤90
	50	~55		30	~85
	40	~25		20	~70
	30	0		10	0
60	100	≤80	90	100	≤95
	50	~65		20	≤95
	30	~25		10	80
	20	0		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 π-bonds
(aromatic groups, double bonds, etc.)

⇨ alkyl groups
(increasing the difference of R and Me)

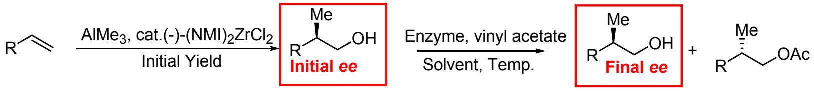
E (enantiomeric ratio): $E = \dfrac{\ln(A/A_o)}{\ln(B/B_o)} = \dfrac{V_A/K_A}{V_B/K_B} = \ln[(1-C)(1-ee)] / \ln[(1-C)(1+ee)]$

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.

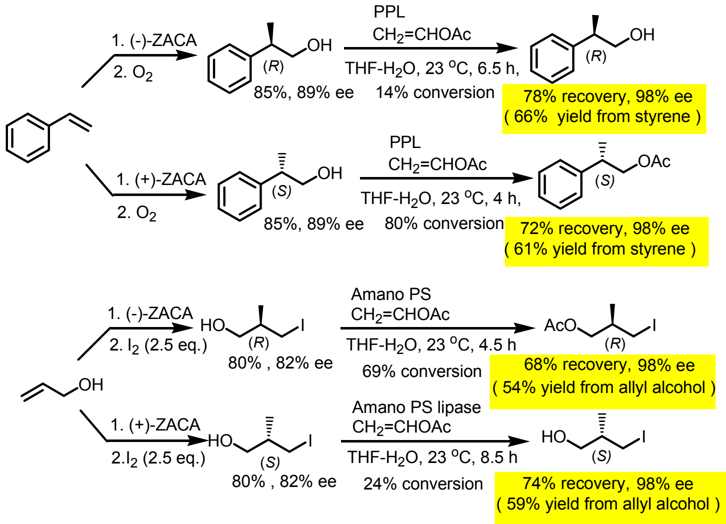
➪Lipase-Catalyzed Kinetic Resolution of ZACA Products



R	Initial Yield (%)	Intial ee (%)	Enzyme	Solvent	Temp.(^oC)	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



78% recovery, 98% ee
(66% yield from styrene)

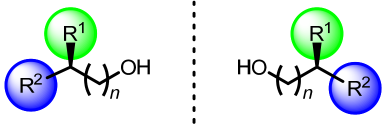
72% recovery, 98% ee
(61% yield from styrene)

68% recovery, 98% ee
(54% yield from allyl alcohol)

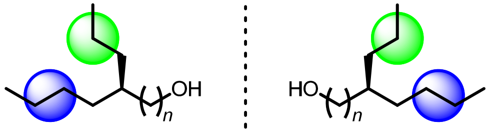
74% recovery, 98% ee
(59% yield from allyl alcohol)

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

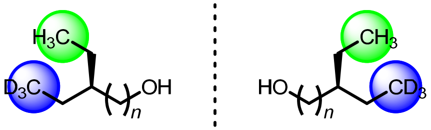
➪How to Prepare Feebly Chiral Compounds of ≥99% ee



R^1 and R^2 are structrually very similar

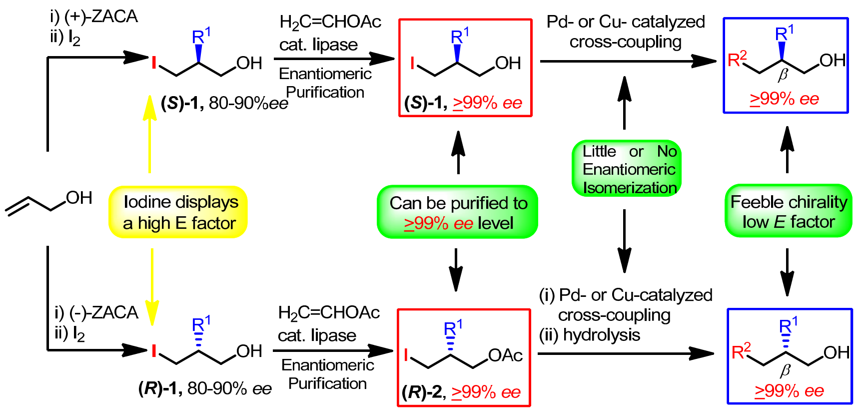


Two very similar groups
of low chirality



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

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



i) (+)-ZACA
ii) I_2

(*S*)-1, 80-90%*ee*

$H_2C{=}CHOAc$
cat. lipase
Enantiomeric Purification

(*S*)-1, ≥99% *ee*

Pd- or Cu- catalyzed cross-coupling

≥99% *ee*

Iodine displays a high E factor

Can be purified to ≥99% *ee* level

Little or No Enantiomeric Isomerization

Feeble chirality low *E* factor

i) (-)-ZACA
ii) I_2

(*R*)-1, 80-90% *ee*

$H_2C{=}CHOAc$
cat. lipase
Enantiomeric Purification

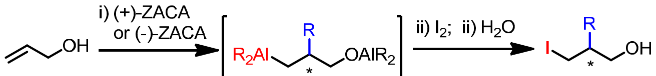
(*R*)-2, ≥99% *ee*

(i) Pd- or Cu-catalyzed cross-coupling
(ii) hydrolysis

≥99% *ee*

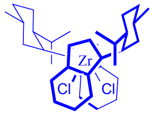
ZACA Reaction of Allyl Alcohol

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



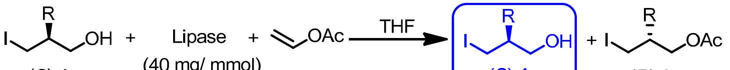
(-)-$(NMI)_2ZrCl_2$
or (+)-$(NMI)_2ZrCl_2$

[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



(*S*)-**1** (40 mg/ mmol) (*S*)-**1** (*R*)-**2**

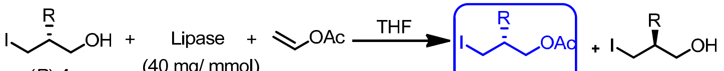
Major **Minor**

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



(*R*)-**1** (40 mg/ mmol) (*R*)-**2** (*S*)-**1**

Major **Minor**

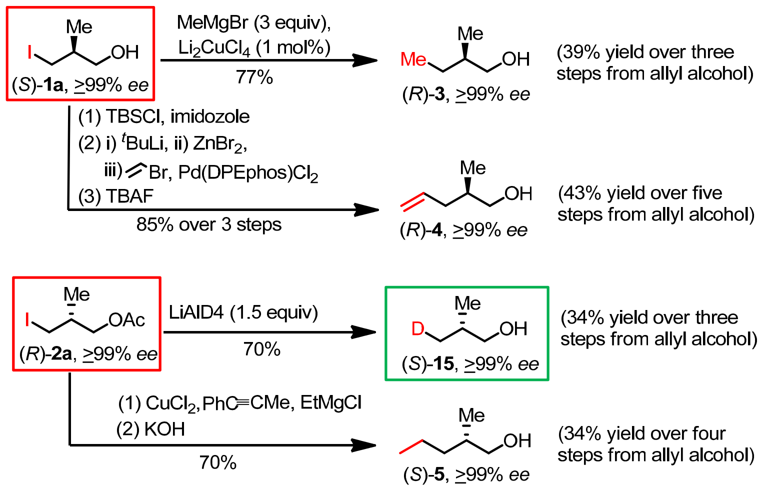
R = Me (**1a**), Et (**1b**), ^{n}Pr(**1c**)

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



(*S*)-**1a**, ≥99% *ee*

MeMgBr (3 equiv), Li_2CuCl_4 (1 mol%)
77%

(*R*)-**3**, ≥99% *ee*
(39% yield over three steps from allyl alcohol)

(1) TBSCl, imidozole
(2) i) ^{t}BuLi, ii) $ZnBr_2$,
iii) Br, $Pd(DPEphos)Cl_2$
(3) TBAF
85% over 3 steps

(*R*)-**4**, ≥99% *ee*
(43% yield over five steps from allyl alcohol)

(*R*)-**2a**, ≥99% *ee*

LiAlD4 (1.5 equiv)
70%

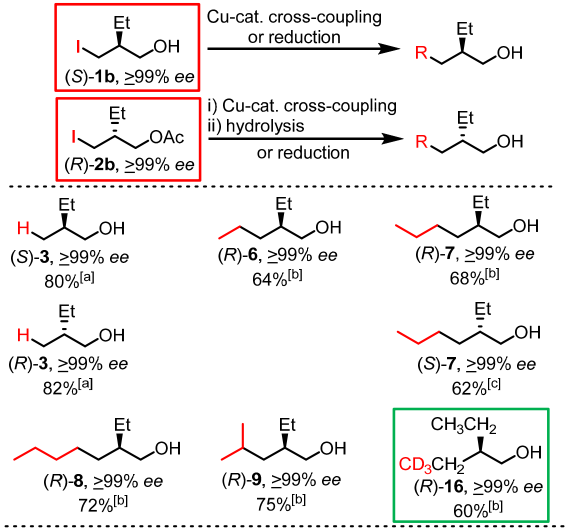
(*S*)-**15**, ≥99% *ee*
(34% yield over three steps from allyl alcohol)

(1) $CuCl_2$, PhC≡CMe, EtMgCl
(2) KOH
70%

(*S*)-**5**, ≥99% *ee*
(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



(*S*)-**1b**, ≥99% *ee*

Cu-cat. cross-coupling
or reduction

(*R*)-**2b**, ≥99% *ee*

i) Cu-cat. cross-coupling
ii) hydrolysis
or reduction

(*S*)-**3**, ≥99% *ee*
80%[a]

(*R*)-**6**, ≥99% *ee*
64%[b]

(*R*)-**7**, ≥99% *ee*
68%[b]

(*R*)-**3**, ≥99% *ee*
82%[a]

(*S*)-**7**, ≥99% *ee*
62%[c]

(*R*)-**8**, ≥99% *ee*
72%[b]

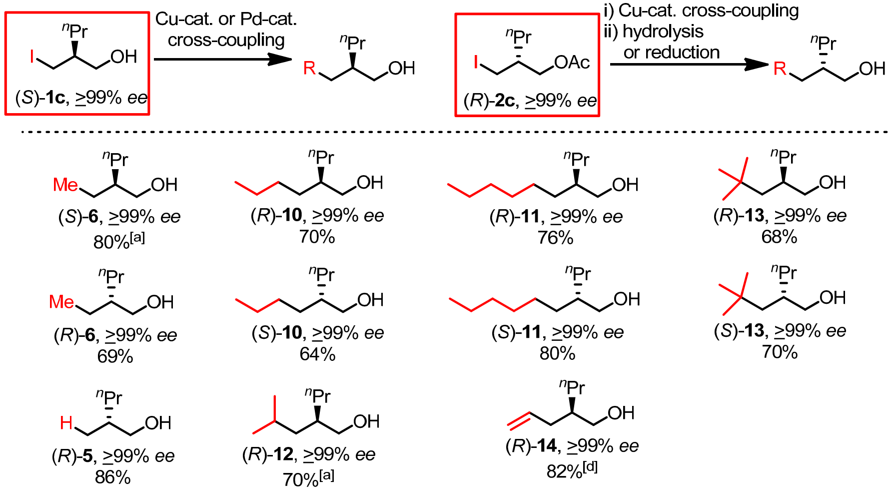
(*R*)-**9**, ≥99% *ee*
75%[b]

(*R*)-**16**, ≥99% *ee*
60%[b]

[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



(*S*)-**1c**, ≥99% *ee*

Cu-cat. or Pd-cat.
cross-coupling

(*R*)-**2c**, ≥99% *ee*

i) Cu-cat. cross-coupling
ii) hydrolysis
or reduction

(*S*)-**6**, ≥99% *ee*
80%[a]

(*R*)-**10**, ≥99% *ee*
70%

(*R*)-**11**, ≥99% *ee*
76%

(*R*)-**13**, ≥99% *ee*
68%

(*R*)-**6**, ≥99% *ee*
69%

(*S*)-**10**, ≥99% *ee*
64%

(*S*)-**11**, ≥99% *ee*
80%

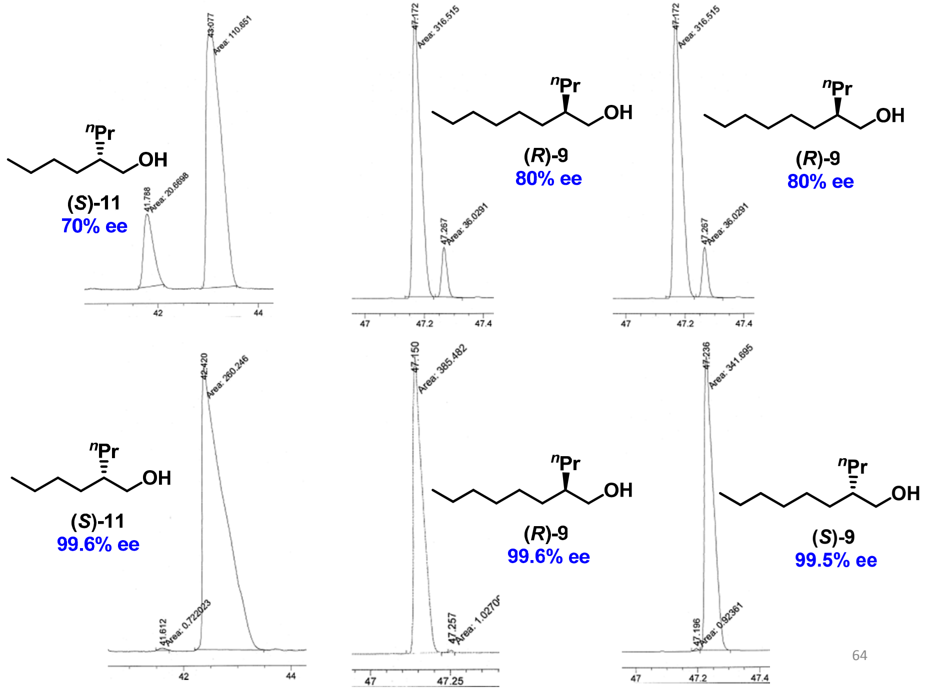
(*S*)-**13**, ≥99% *ee*
70%

(*R*)-**5**, ≥99% *ee*
86%

(*R*)-**12**, ≥99% *ee*
70%[a]

(*R*)-**14**, ≥99% *ee*
82%[d]

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



(*S*)-11
70% ee

(*R*)-9
80% ee

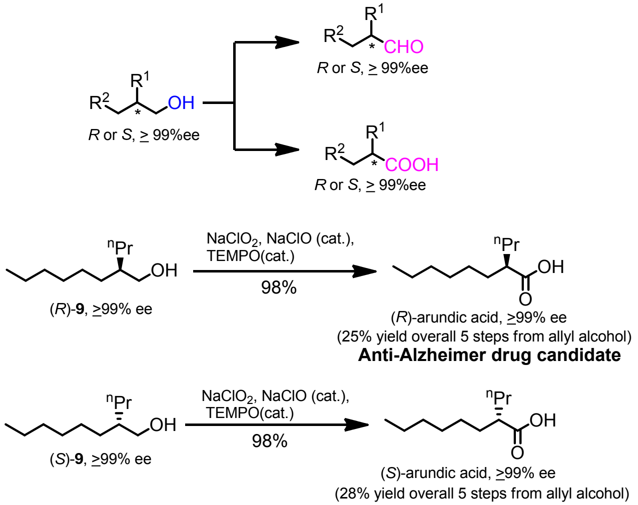
(*R*)-9
80% ee

(*S*)-11
99.6% ee

(*R*)-9
99.6% ee

(*S*)-9
99.5% ee

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



(*R*)-**9**, ≥99% ee

(*R*)-arundic acid, ≥99% ee
(25% yield overall 5 steps from allyl alcohol)

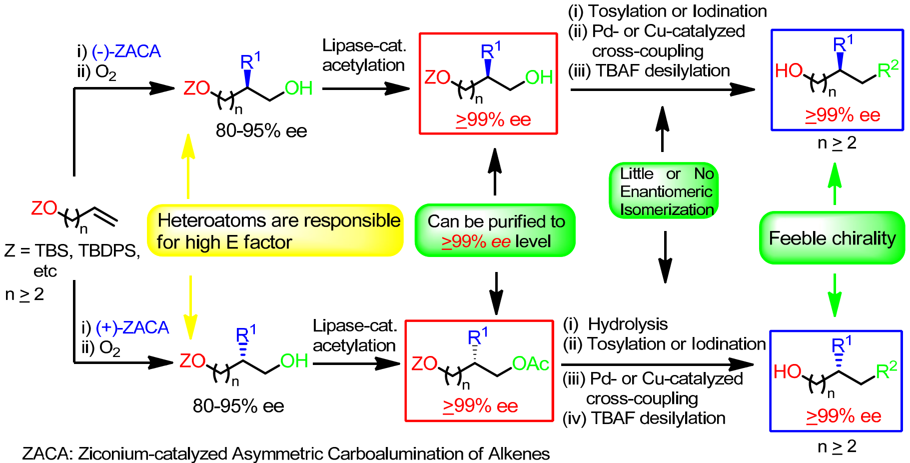
Anti-Alzheimer drug candidate

(*S*)-**9**, ≥99% ee

(*S*)-arundic acid, ≥99% ee
(28% yield overall 5 steps from allyl alcohol)

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

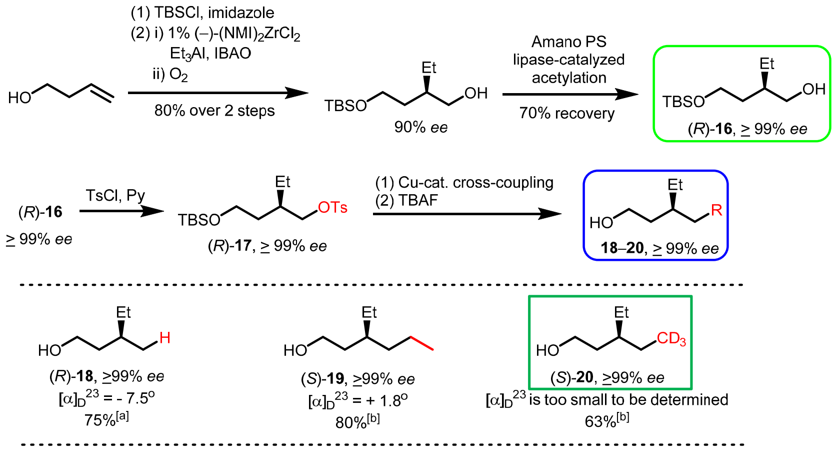
General Strategy for the Synthesis of Remotely Chiral (n+1)-alkyl-1-alkanols of ≥*99% ee*, where n ≥ 2



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



(*R*)-**18**, ≥99% *ee*
$[\alpha]_D^{23}$ = - 7.5°
75%[a]

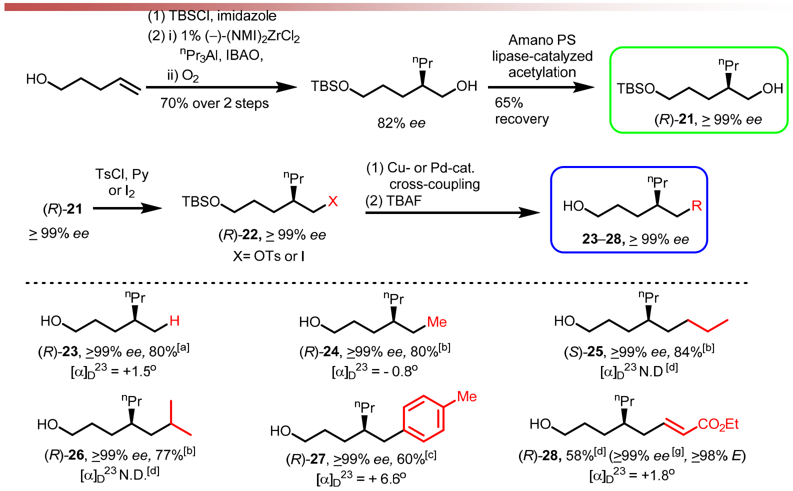
(*S*)-**19**, ≥99% *ee*
$[\alpha]_D^{23}$ = + 1.8°
80%[b]

(*S*)-**20**, ≥99% *ee*
$[\alpha]_D^{23}$ is too small to be determined
63%[b]

[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.

Synthesis of Feebly Chiral 4-Alkyl-1-alkanols



(*R*)-**23**, ≥99% *ee*, 80%[a]
$[\alpha]_D^{23}$ = +1.5°

(*R*)-**24**, ≥99% *ee*, 80%[b]
$[\alpha]_D^{23}$ = - 0.8°

(*S*)-**25**, ≥99% *ee*, 84%[b]
$[\alpha]_D^{23}$ N.D [d]

(*R*)-**26**, ≥99% *ee*, 77%[b]
$[\alpha]_D^{23}$ N.D.[d]

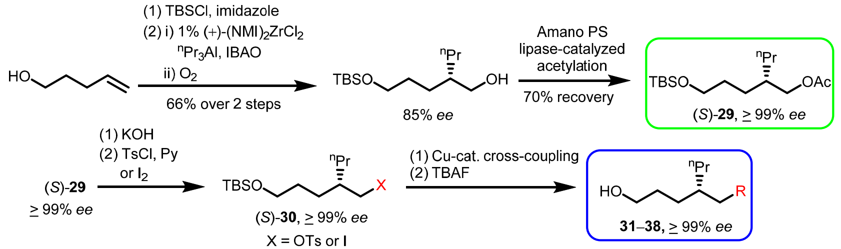
(*R*)-**27**, ≥99% *ee*, 60%[c]
$[\alpha]_D^{23}$ = + 6.6°

(*R*)-**28**, 58%[d] (≥99% *ee*[g], ≥98% *E*)
$[\alpha]_D^{23}$ = +1.8°

[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) ^tBuLi, ii) ZnBr$_2$, iii) PEPPSI (1 mol%), RX; 2) TBAF [d] $[\alpha]_D^{23}$ is too small to be determined

Xu, S.; Oda, A.; Kamada, H.; Negishi, E., *Proc. Natl. Acad. Sci. USA*, **2014**, *111*, 8368-8373.

Synthesis of Feebly Chiral 4-Alkyl-1-alkanols


(1) TBSCl, imidazole
(2) i) 1% (+)-$(NMI)_2ZrCl_2$
$^nPr_3Al$, IBAO
ii) O_2
66% over 2 steps

85% *ee*

Amano PS
lipase-catalyzed
acetylation
70% recovery

(*S*)-**29**, ≥ 99% *ee*

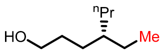
(*S*)-**29**
≥ 99% *ee*

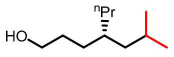
(1) KOH
(2) TsCl, Py
or I_2

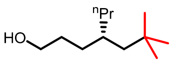
(*S*)-**30**, ≥ 99% *ee*
X = OTs or I

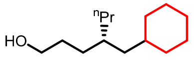
(1) Cu-cat. cross-coupling
(2) TBAF

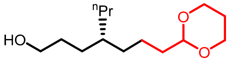
31–**38**, ≥ 99% *ee*

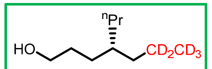

(*S*)-**31**, ≥99% *ee*, 60%[a]
$[\alpha]_D^{23}$ = + 0.9°

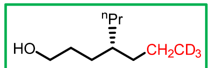

(*S*)-**32**, ≥99% *ee*, 70%[a]
$[\alpha]_D^{23}$ N.D.[b]

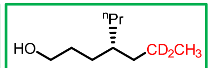

(*S*)-**33**, ≥99% *ee*,72%[a]
$[\alpha]_D^{23}$ N.D.[b]


(*S*)-**34**, ≥99% *ee*, 70%[a]
$[\alpha]_D^{23}$ = - 0.28°


(*R*)-**35**, ≥99% *ee*, 58%[a]
$[\alpha]_D^{23}$ = - 0.56°


(*R*)-**36**, ≥99% *ee*, 60%[a]
$[\alpha]_D^{23}$ N.D.[b]

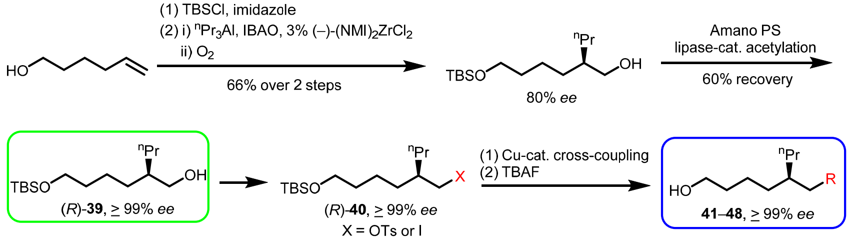

(*R*)-**37**, ≥99% *ee*, 50%[a]
$[\alpha]_D^{23}$ N.D.[b]


(*R*)-**38**, ≥99% *ee*, 54%[a]
$[\alpha]_D^{23}$ N.D.[b]

[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.

Synthesis of Feebly Chiral 5-Alkyl-1-alkanols


(1) TBSCl, imidazole
(2) i) $^nPr_3Al$, IBAO, 3% (–)-$(NMI)_2ZrCl_2$
ii) O_2
66% over 2 steps

80% *ee*

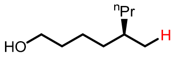
Amano PS
lipase-cat. acetylation
60% recovery

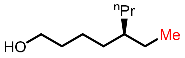
(*R*)-**39**, ≥ 99% *ee*

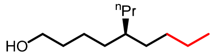
(*R*)-**40**, ≥ 99% *ee*
X = OTs or I

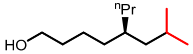
(1) Cu-cat. cross-coupling
(2) TBAF

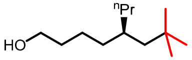
41–**48**, ≥ 99% *ee*

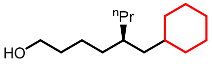

(*R*)-**41**, ≥ 99% *ee*, 75%
$[\alpha]_D^{23}$ = - 0.65°

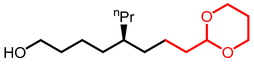

(*R*)-**42**, ≥ 99% *ee*, 72%[a]
$[\alpha]_D^{23}$ = + 0.41°

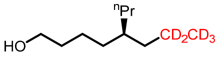

(*S*)-**43**, ≥ 99% *ee*, 66%[a]
$[\alpha]_D^{23}$ N.D [b]


(*R*)-**44**, ≥ 99% *ee*, 71%[a]
$[\alpha]_D^{23}$ N.D [b]


(*R*)-**45**, ≥ 99% *ee*, 88%[a]
$[\alpha]_D^{23}$ = + 1.2°


(*R*)-**46**, ≥ 99% *ee*, 85%[a]
$[\alpha]_D^{23}$ = + 0.57°

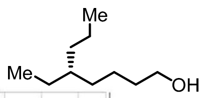

(*R*)-**47**, ≥ 99% *ee*, 61%[a]
$[\alpha]_D^{23}$ = + 0.63°

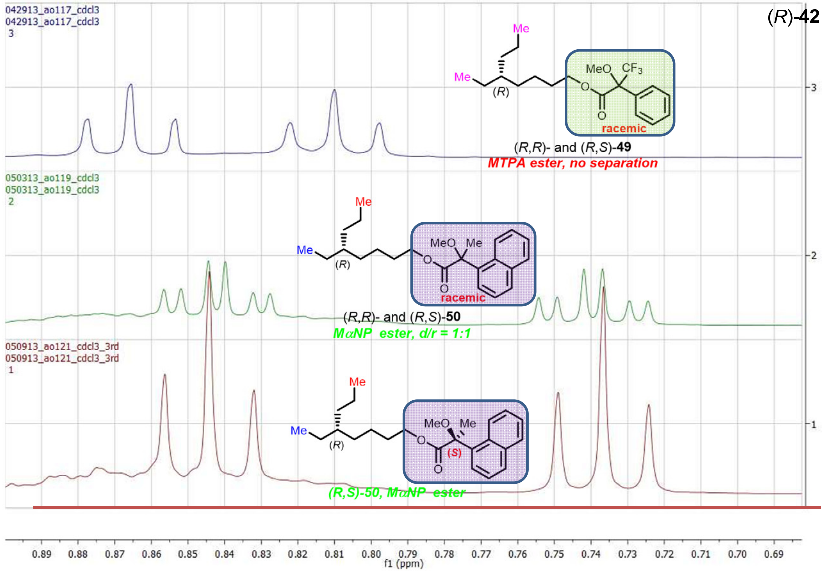

(*R*)-**48**, 51%
$[\alpha]_D^{23}$ N.D [b]

[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.

Determination of *ee* by MαNP ester


(*R*)-**42**



a) A. Ichikawa, *Chirality*, **1999**, *11*,70–74; b) N. Harada, etal, *Tetrahedron: Asymmetry*, **2000**, *11*, 1249–1253.