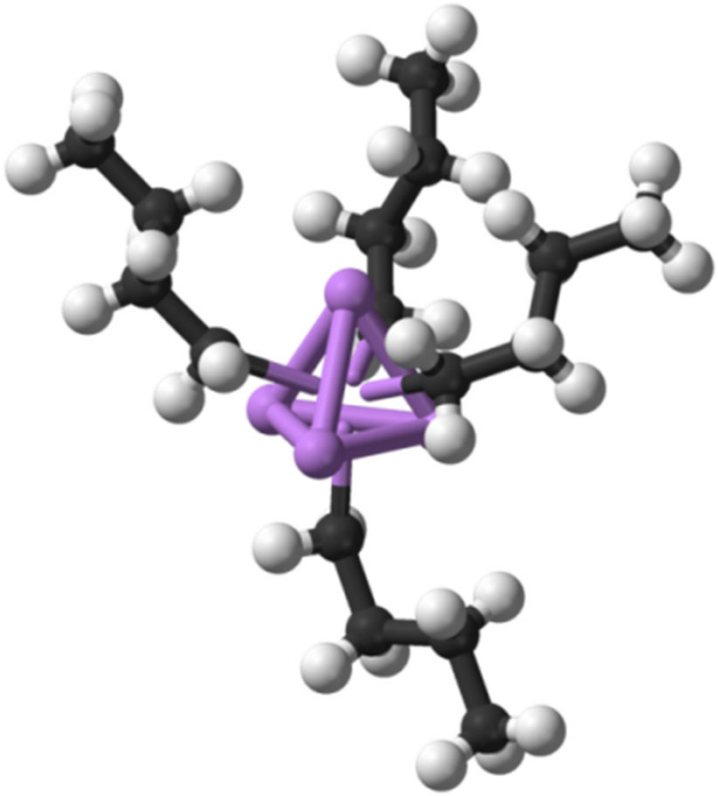
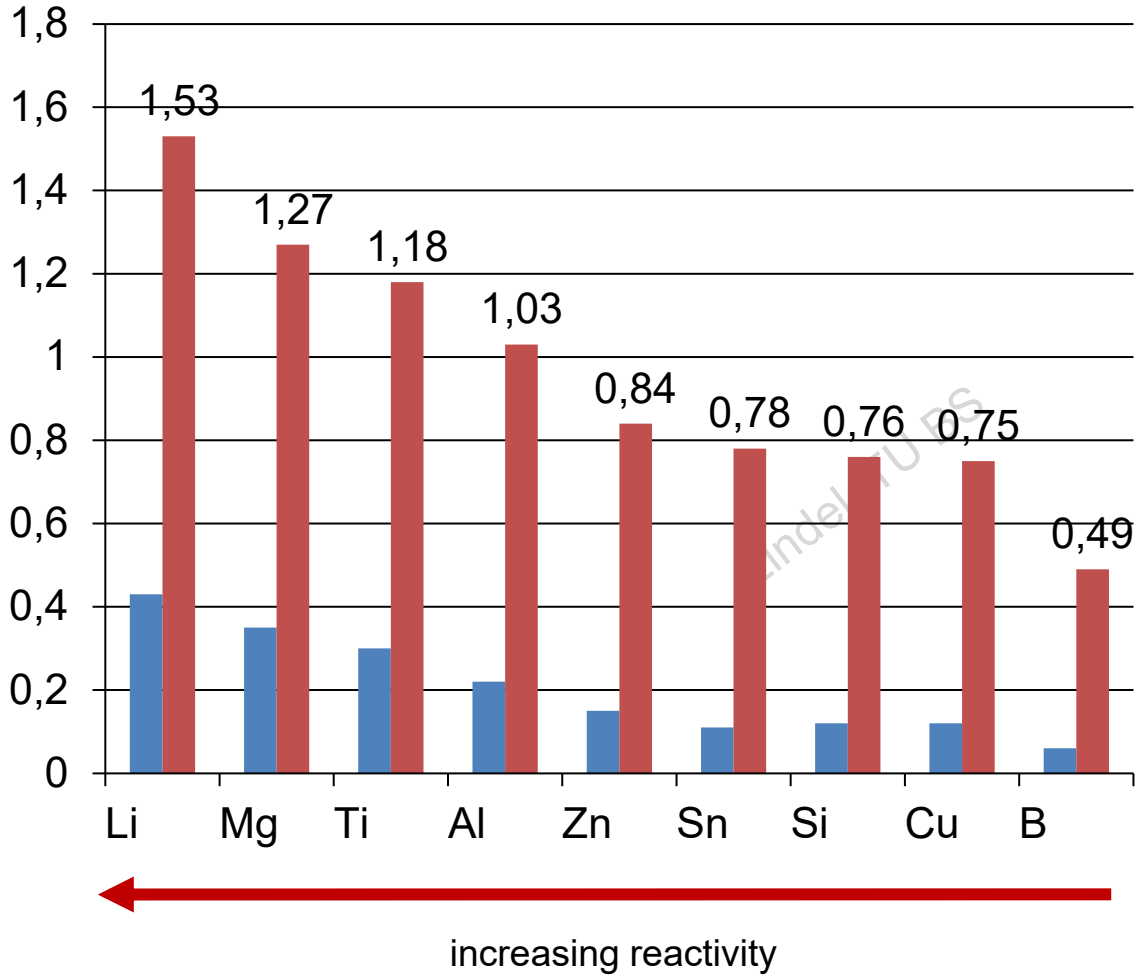
Prof. Dr. Thomas Lindel,
TU Braunschweig, Institute of Organic Chemistry
Class *„Organometal reagents in synthesis"*



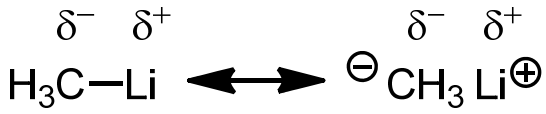
A. Organolithium reagents
B. Organomagnesium reagents
C. Organozinc reagents
D. Organotitanium and organozirconium reagents
E. Organosamarium reagents
F. Organosilicon reagents

Pd-, Ru-, Au-, and Cu-catalyzed reactions already have been subject of the class "Reaction Mechanisms".

The larger the electronegativity difference, the more reactive is a carbon-metal bond.



z. B.

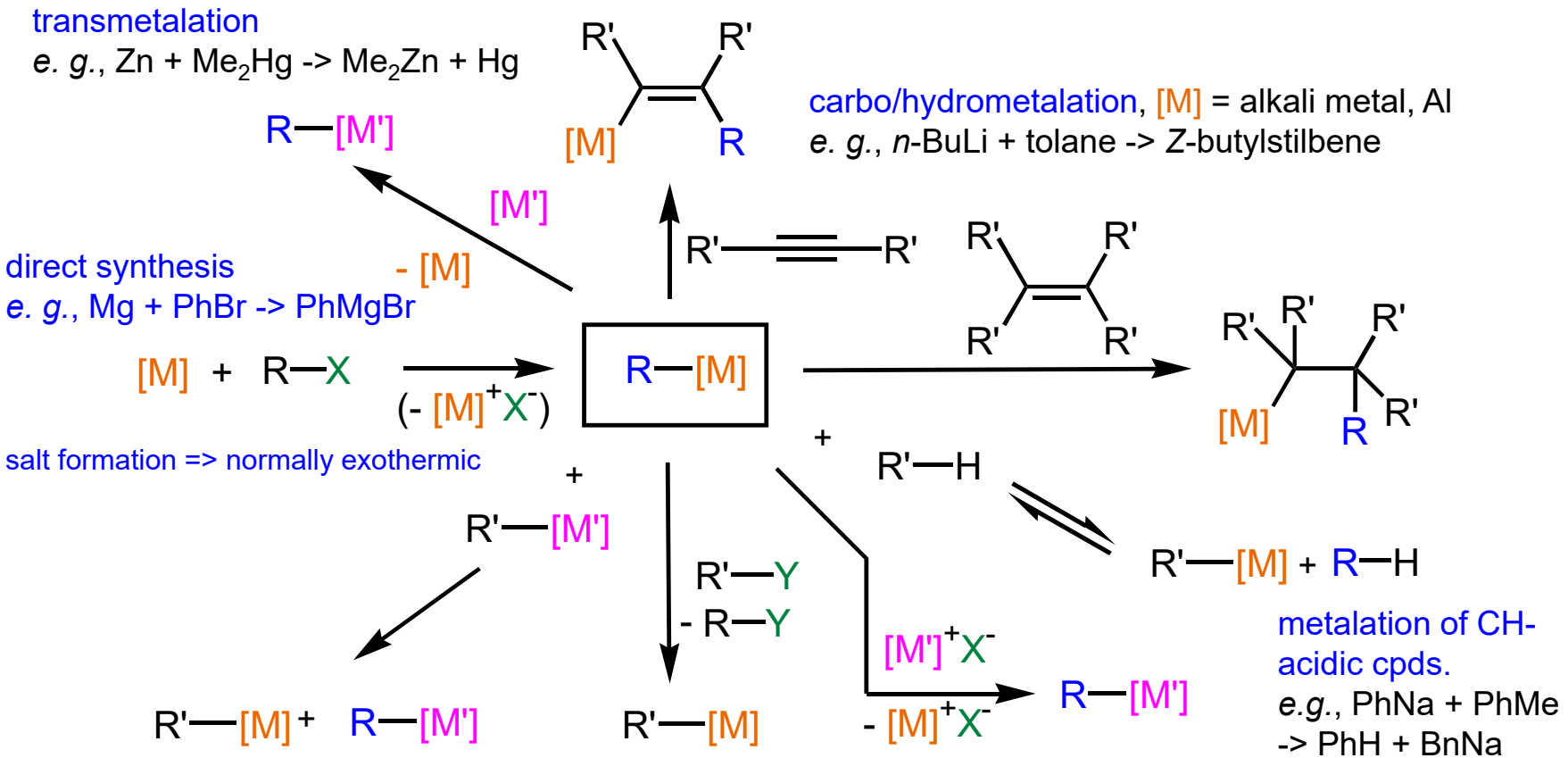


ionic char.

Diff EN (C)

carbon is partially negatively charged (Allred-Rochow electronegativity 2.5)

Overview of most important reaction types



[M]: metal, coordinated by ligands or solvent, or as cluster

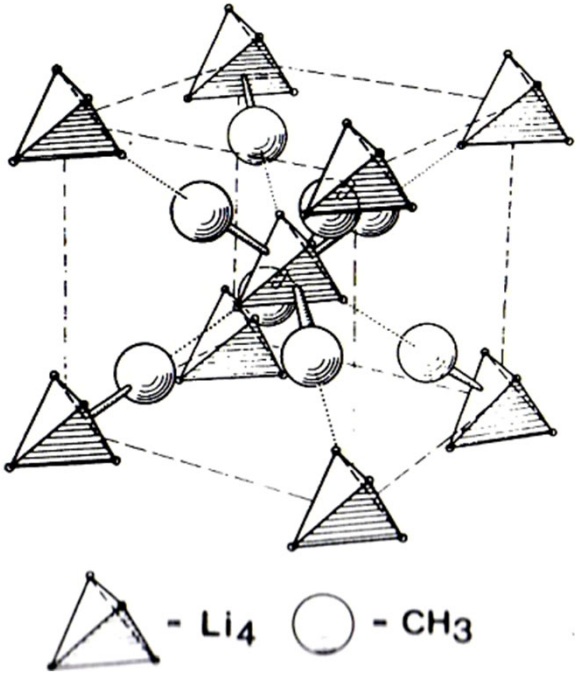
Methyllithium

2 Li + MeCl –(in Et_2O)→ MeLi + LiCl (precipitates)

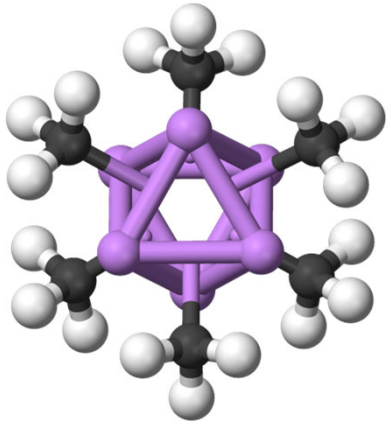
Radical reaction (which?)!

MeLi is stable up to 150 °C (no β-elimination of LiH possible).

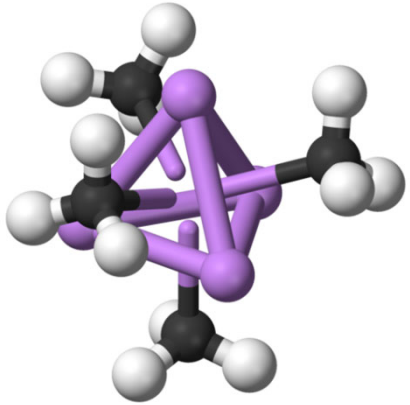
Solid state, etheral solutions: tetramer $[CH_3Li]_4$
(distorted cube, tetra-μ_3-methyl-tetralithium);
$d_{Li\text{-}Li}$ 236 pm



Benzene solution: hexamer



4 center 2 electron bondings with both electrons contributed by CH_3^-



Ethyllithium

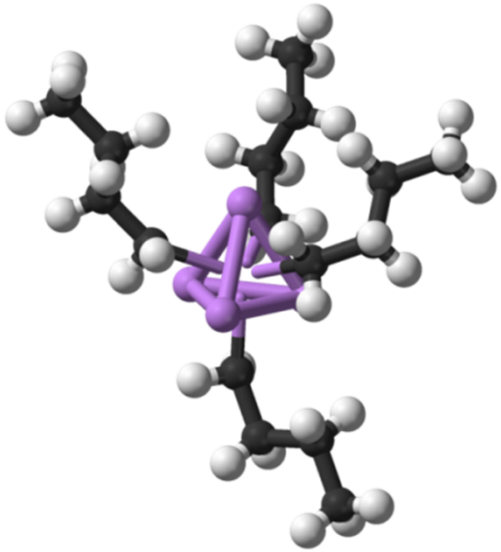
2 Li + EtCl –(in PhH, 40-45 °C)→ EtLi (mp ca. 90 °C, sublim. possible) + LiCl (precip.)

β-Elimination: EtLi –(> 90 °C)→ ethene + LiH (residue)

from Karl Ziegler, H.-G. Gellert, *Ann. Chem.* **1950**, *567*, 179:

Das Lithiumäthyl war in üblicher Weise aus Lithiumschnitzeln in Benzol durch Einleiten von Äthylchlorid unter Rühren bei 40—45° (außen Wasser von 20°) hergestellt. Die etwa 1 molare gesättigte Lösung wird nach dem Dekantieren von Lithiumchlorid i. V. auf etwa $^1/_4$ konzentriert. Dann scheidet sich beim langsamen Abkühlen das Lithiumäthyl schön kristallisiert aus. Man gießt die Restlösung von dem an den Wänden festsitzenden Kristallisat ab und vertreibt das letzte Benzol i. V. bei 45°.

n-Butyllithium



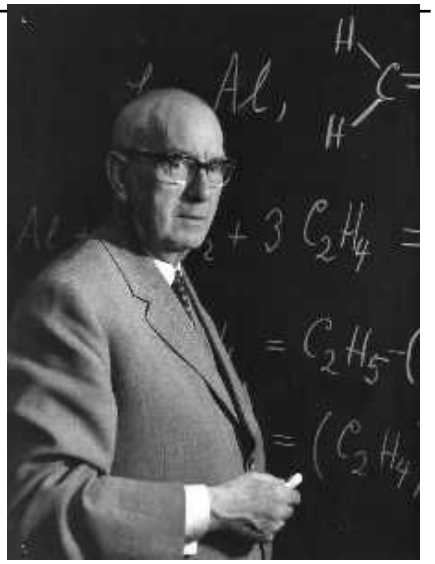
Preparation:

$2\ Li + C_4H_9Cl \rightarrow C_4H_9Li + LiCl$ (precip.)

tetrameric in ethers, hexameric in hexanes

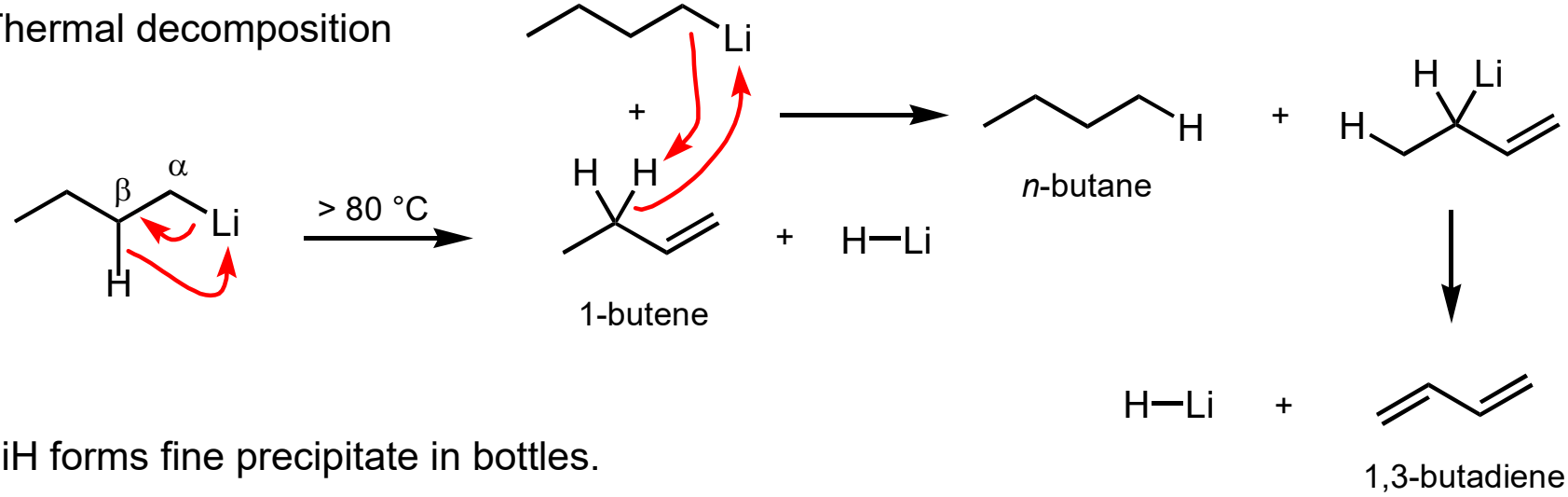
solutions in hexanes commercially available, but not in ethers

m. p. -76 °C; b. p. decomposition



Karl Ziegler (1898-1973)
Nobel Prize 1963

Thermal decomposition

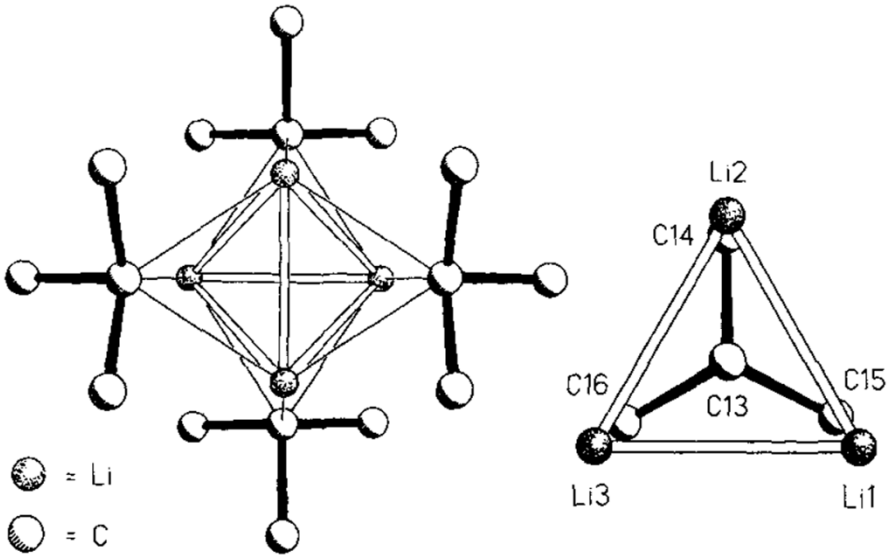


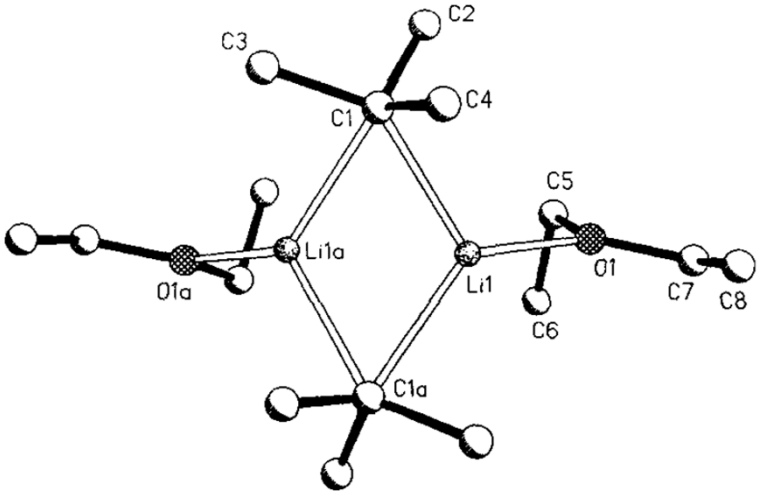
$H—Li$ +

1,3-butadiene

LiH forms fine precipitate in bottles.

t-Butyllithium





Stalke et al., *Angew. Chem.* **1993**, *105*, 619: [*t*BuLi-OEt_2]$_2$

"Bei allen drei Verbindungen wurden zunächst aus den handelsüblichen Lösungen (in Hexan oder Pentan) das Lösungsmittel im Vakuum entfernt. *n*BuLi: 2.9 g (46 mmol) *n*BuLi wurden bei - 80 "C unter ständigem Rühren tropfenweise mit vorgekühltem Pentan versetzt, bis eine homogene Lösung entstand (ca. 20 mL). Aus der Probe kristallisierten bei -90 °C nach einer Woche farblose Kristallblöcke rnit einem Schmelzpunkt von - 34(2) °C. *t*BuLi: 2.2 g (34 mmol) *t*BuLi wurden, wie für *n*BuLi beschrieben, mit Pentan versetzt (ca. 18 mL). Kristallisation über eine Woche bei -90 °C ergab farblose längliche Blöcke."

i-Propyllithium at -108 °C: equilibrium between two species

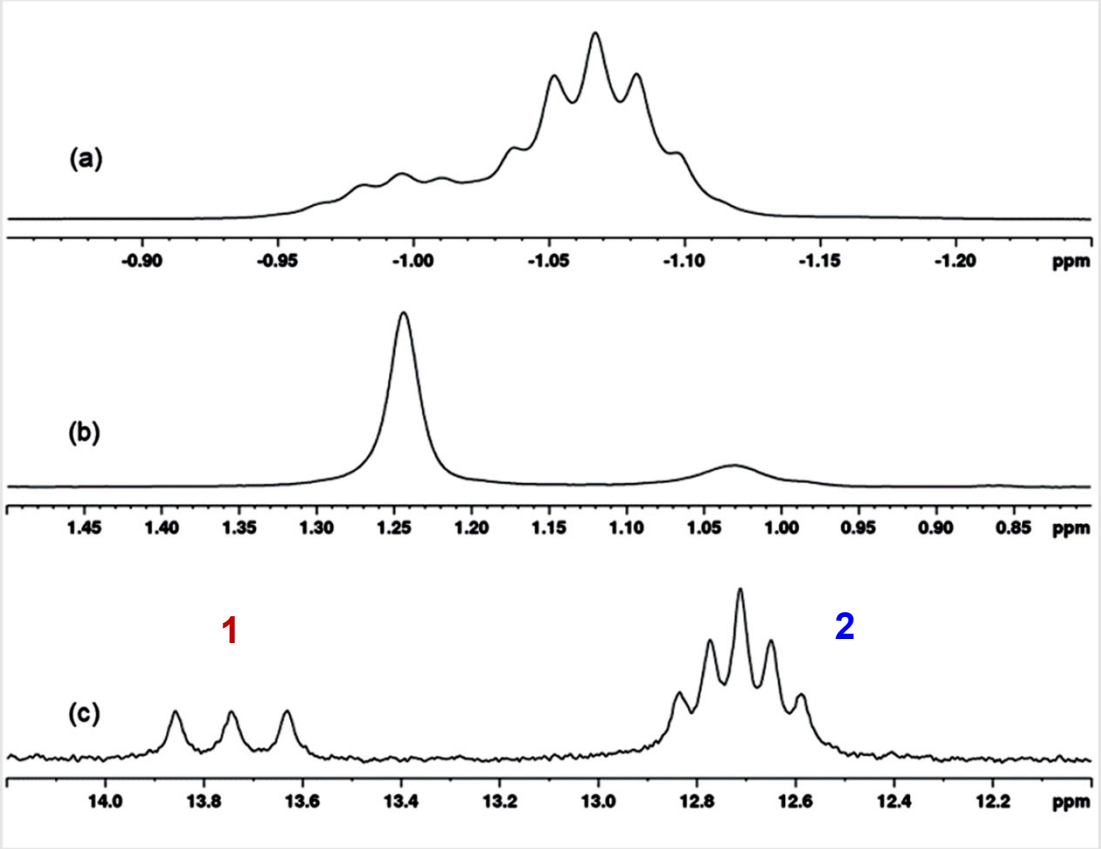
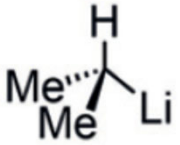
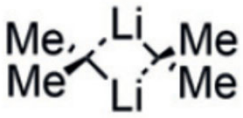


Figure 14 (a) ^{1}H NMR, (b) ^{6}Li NMR, and (c) $^{13}C\{^{1}H\}$ NMR spectra of *i*-Pr^{6}Li in THF-d_8 at 165 K. The ^{1}H NMR and $^{13}C\{^{1}H\}$ NMR spectra are restricted to the CH–Li signals zone. Reprinted with permission from ref. 38. Copyright 2017 Wiley.

determined by ^{6}Li-DOSY (diffusion-ordered spectroscopy) experiments



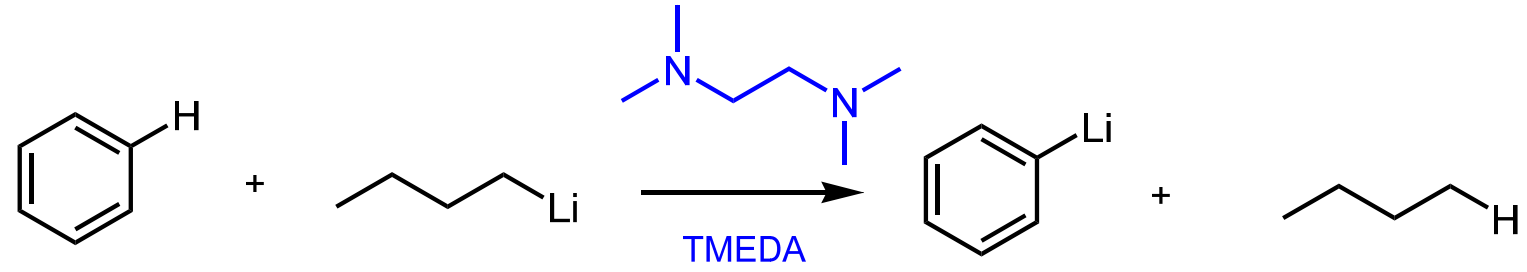
[*i*-PrLi]
1



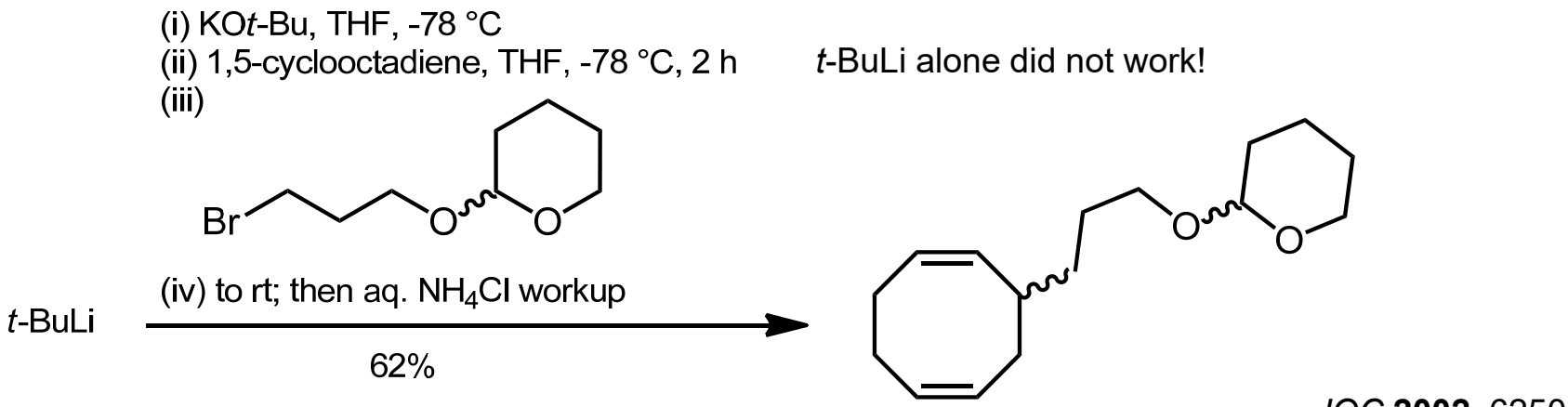
[*i*-PrLi]$_2$
2

from (review): H. Ouliyadi, *Synthesis* **2018**, *50*, 3603

Deprotonation of PhH by *n*-BuLi: thermodynamically possible, but kinetically inhibited.
Addition of TMEDA enables deprotonation of PhH by *n*-BuLi by changing the cluster leading to faster action of Bu^-.

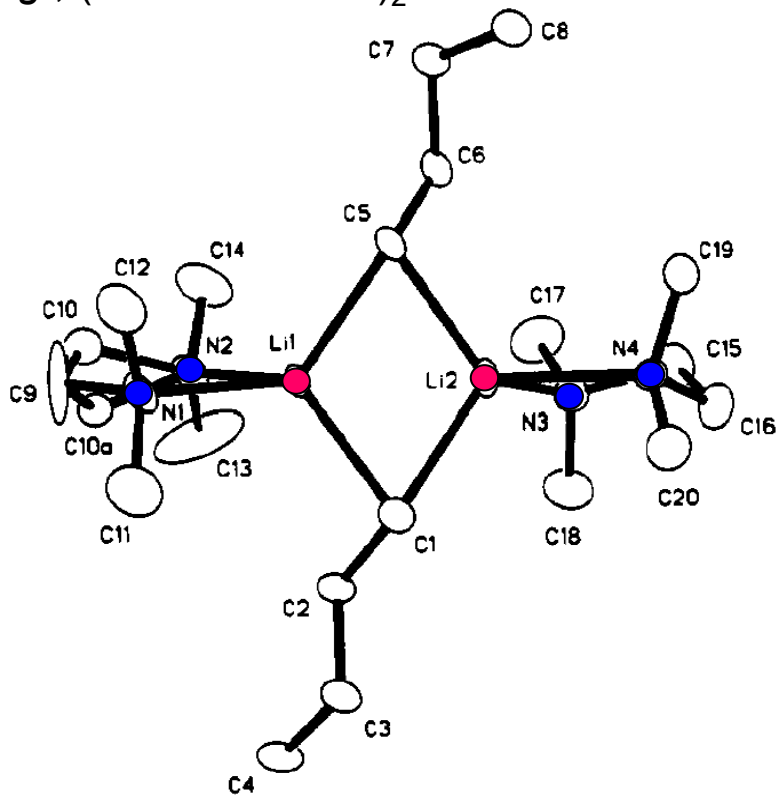


Addition of 1 eq. KO*t*-Bu (leading to the *Schlosser* base ("LICKOR base"), 1967) breaks up *t*-BuLi clusters (formation of more basic *t*-BuK; LiOtBu more stable than KOtBu):



JOC **2002**, 6250

E. g., (*n*-BuLi·TMEDA)$_2$



Four milliliters of a 2.5 M *n*-BuLi-hexanes solution was added to a septum-capped test tube and cooled to 0 or -78 °C.

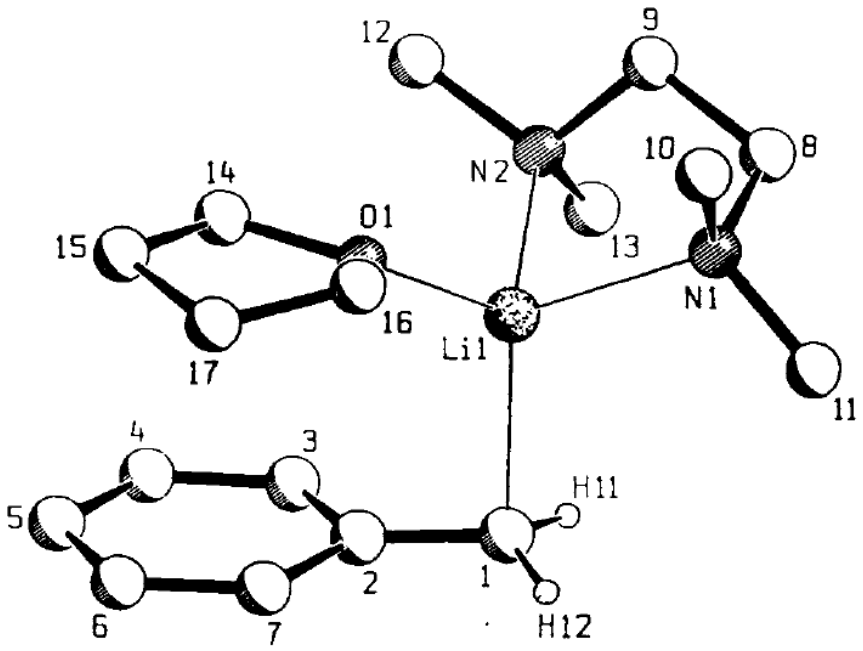
The (*n*-BuLi-TMEDA)$_2$ complex ... was prepared ... with 1.5 equiv (1.65 mL) of pure TMEDA added via syringe. The solution was frozen by immersing in liquid nitrogen, and the frozen solution was placed into a refrigerated bath at -92 °C overnight. Colorless, square crystals were isolated and mounted on the X-ray diffractometer at -110 °C.

These crystals are extremely air- and temperature-sensitive.

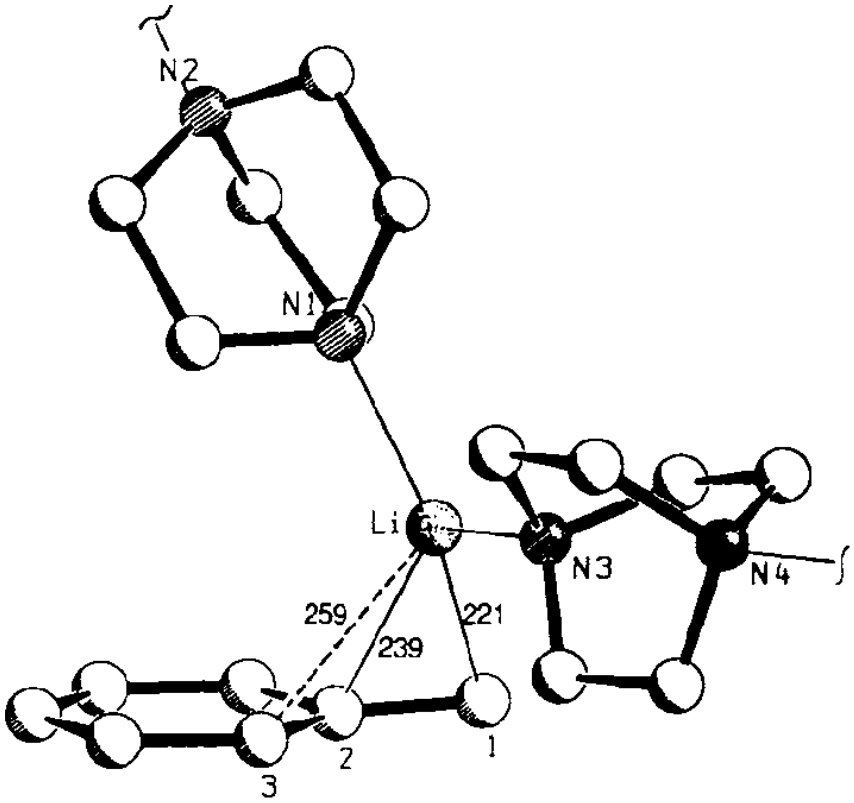
$$(n\mathrm{BuLi})_6 \underset{\text{TMEDA}}{\overset{\text{0.50 Equiv}}{\rightleftharpoons}} (n\mathrm{BuLi})_4 \cdot \mathrm{TMEDA}_2 \underset{\text{TMEDA}}{\overset{\text{0.25 Equiv}}{\rightleftharpoons}} (n\mathrm{BuLi})_4 \cdot \mathrm{TMEDA}_3 \underset{\text{TMEDA}}{\overset{\text{0.25 Equiv}}{\rightleftharpoons}} (n\mathrm{BuLi} \cdot \mathrm{TMEDA})_2$$

from: Nichols, Williard, *J. Am. Chem. Soc.* **1993**, 1568

Deprotonation of benzyl-H: benzyllithium from PhMe (pK_a 43) and *n*-BuLi



BnLi-TMEDA-THF: η^1

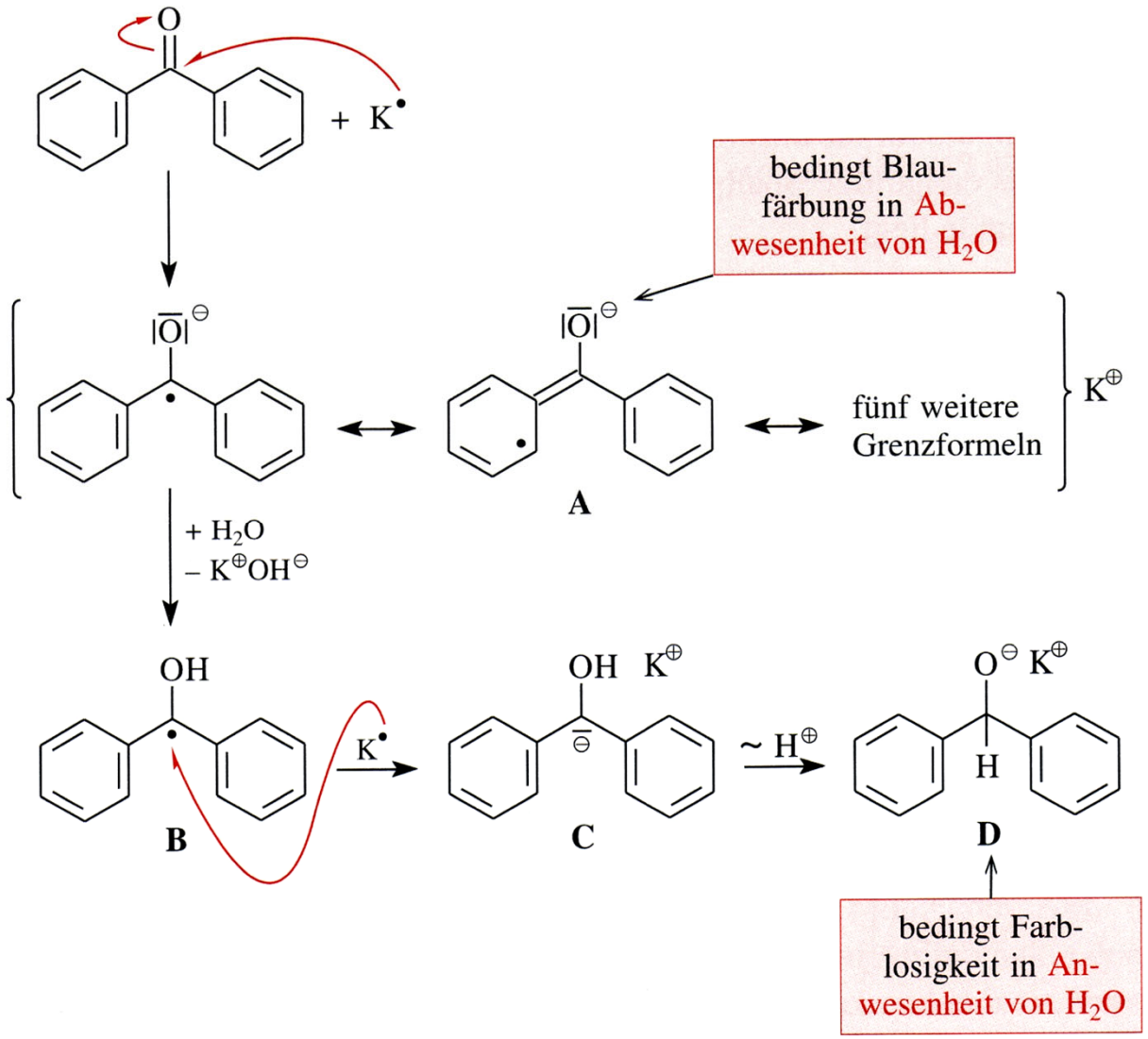


BnLi-DABCO$_\infty$: η^2
(259 pm too long for C-Li)

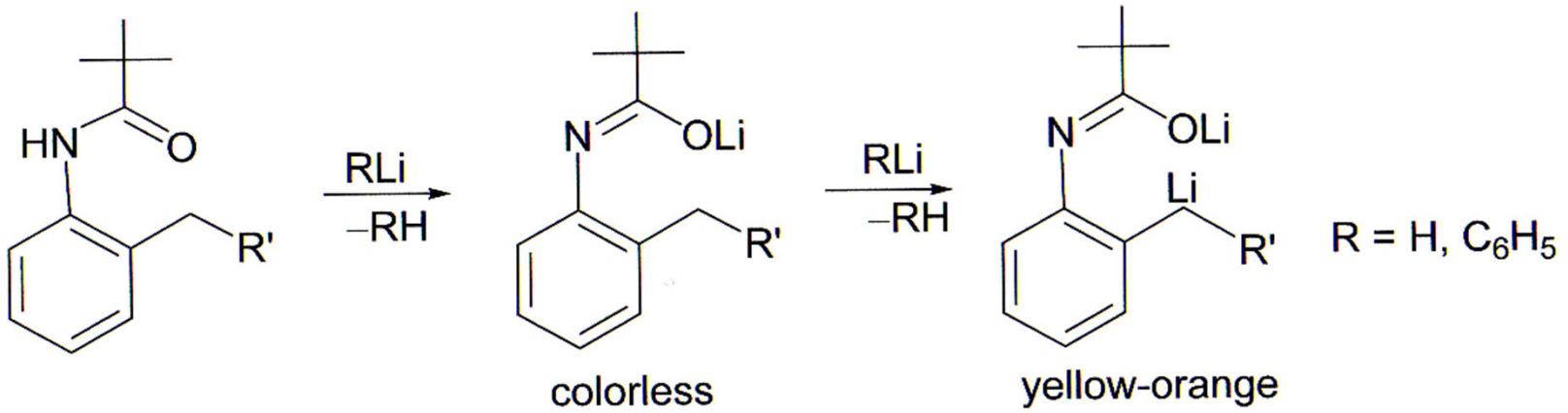
Boche et al., *Chem. Ber.* **1989**, *122*, 2303

Testing for water in THF

a ketyl radical (anion)



Titration of a BuLi solution with *N*-pivaloyl-*o*-toluidine (R'=H):



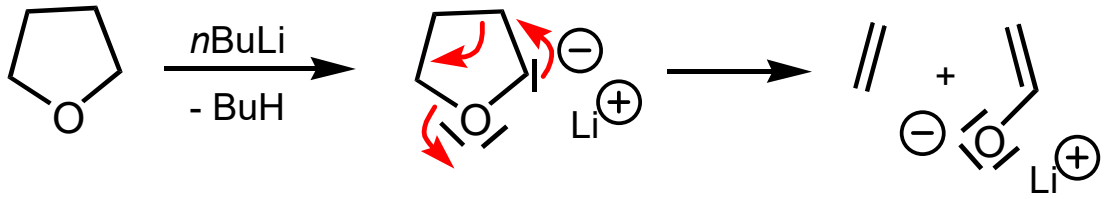
Simple hydrolysis of BuLi would include decomposition products LiOH or LiH.

The sterically hindered amide is not attacked by the nucleophile "Bu^-".

Titration of less basic PhLi with more acidic *N*-pivaloyl-*o*-benzylanilin (R'=Ph)
=> sharper end point.

J. Suffert, *J. Org. Chem.* **1989**, *54*, 509.

Deprotonation of ether α-H:
In ethers, butyllithium reagents are usually handled at low temperatures (-78 °C), because otherwise partial decomposition occurs, *e. g.* in THF:



Temperature/solvent combinations for which organolithium reagents have half lives > 100 h for ether cleavage.

Chemical reactions are usually faster, allowing the handling of organolithiums at higher temperatures.

in °C	Et_2O	THF	DME
MeLi	50	0	-50
PhLi	25	-25	
n-BuLi	0	-50	-100
s-BuLi	-25	-75	-125
t-BuLi	-50	-100	-150

n-Butyllithium is the most important organolithium reagent (> 1000 t/a)

- initiator of anionic polymerizations as a nucleophile
- lithiation by deprotonation, except of some other alkanes (such as *t*-BuH)
- lithiation by halogen-metal exchange (faster than deprotonation)
- lithiation is frequently followed by transmetalation to more selective organometallics
- in situ generation of LDA (lithium diisopropylamide)

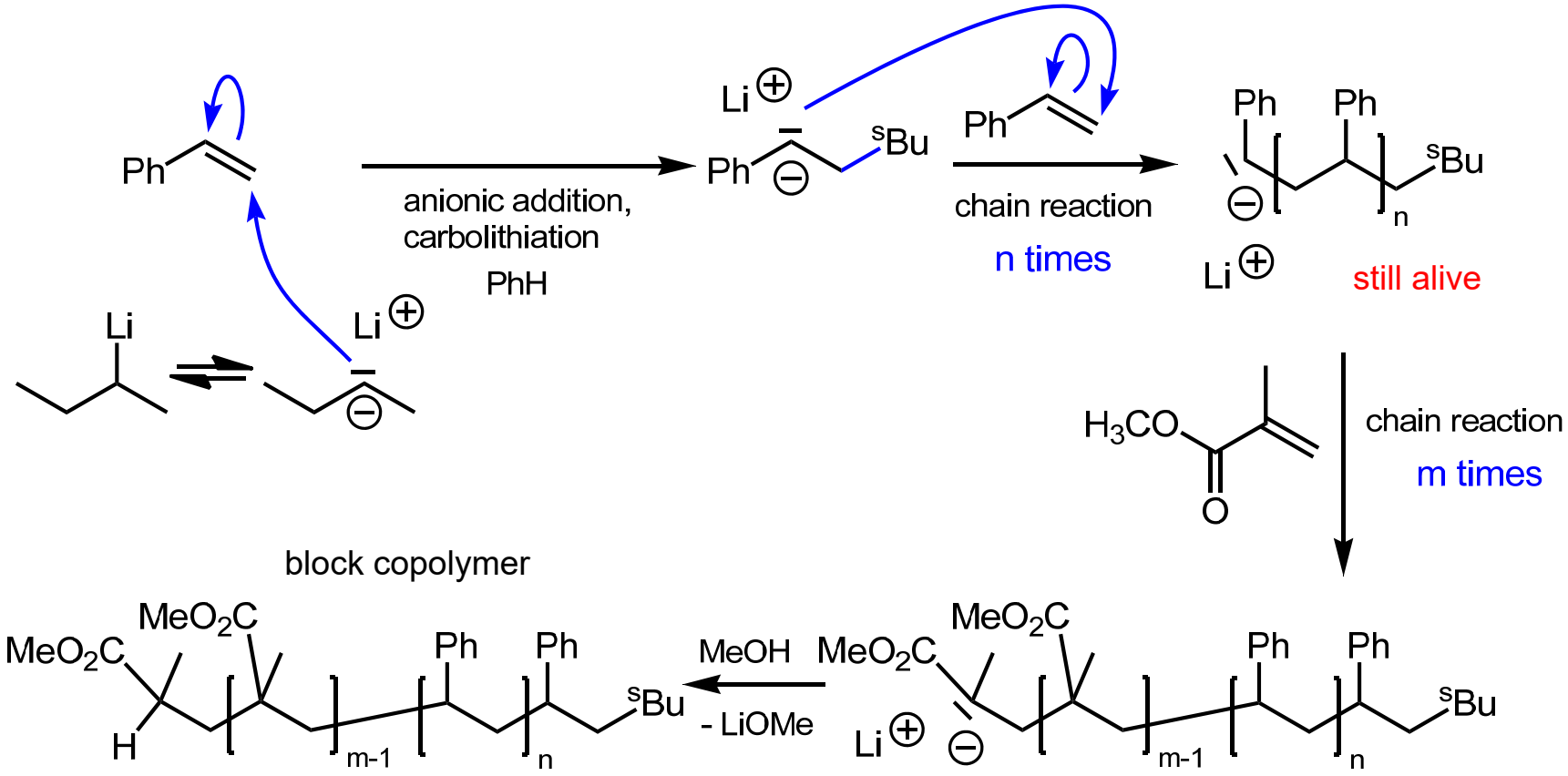
s-BuLi and *t*-BuLi are more basic than *n*-BuLi. *s*-BuLi looses LiH already at 0 °C!

***Caution**:* hydrolysis of *t*-BuLi is highly exothermic, leading to ignition of organic solvents!

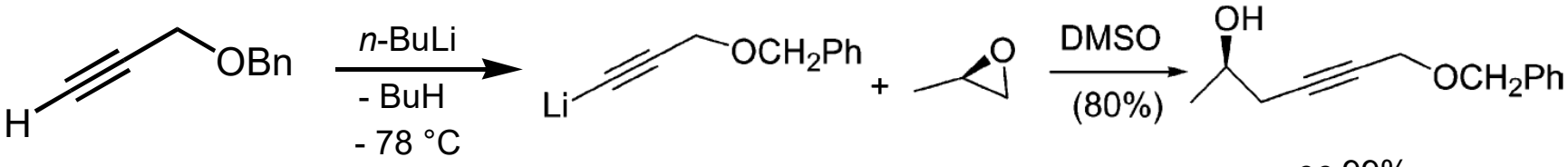
t-BuLi immediately burns on contact with air with a red flame.

Butyllithiums are the most important organolithium reagents (> 1000 t/a) and used as initiators of anionic polymerizations

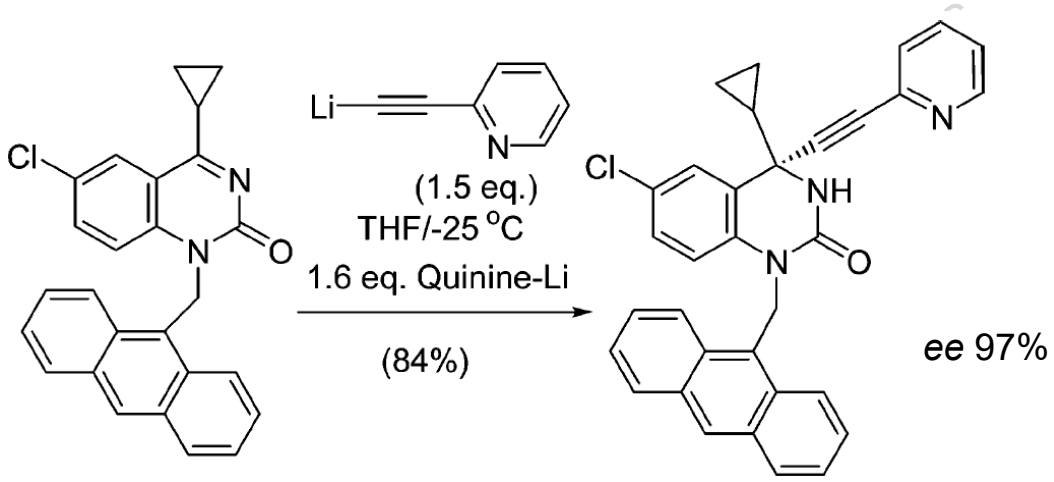
"Living polymerization":
chain ends remain active, polymerization continues after addition of new monomer.



Deprotonation of alkynyl-H with BuLi or LDA or LiHMDS.

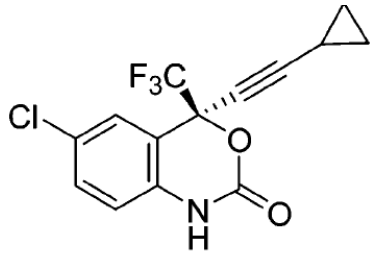


ee 99%

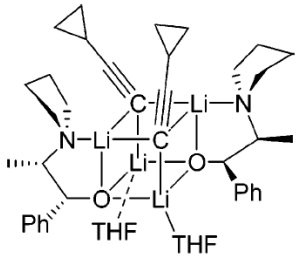


ee 97%

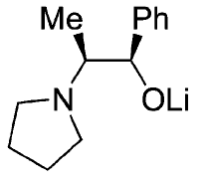
How would you make the HIV reverse transcriptase inhibitor?



Efavirenz



2:2 tetramer

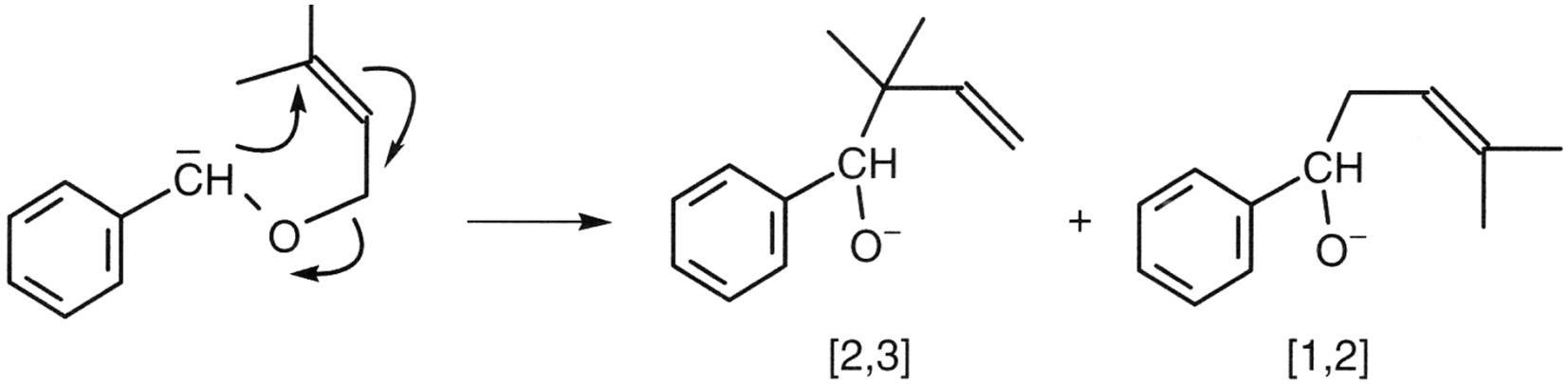


chiral catalyst

Acidities in DMSO (pK_a 35.1):

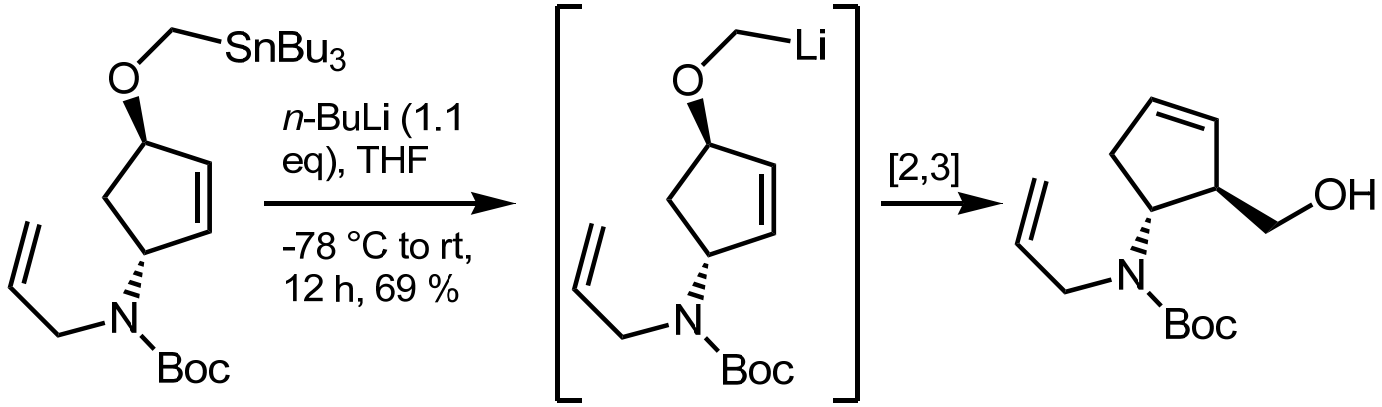
Species[b]	pK_a	
CH_3NO_2	17.2	
$CH_3C(O)CH_3$	26.5	
$CH_3C(O)OEt$[c]	27.4	
$CH_3SO_2CH_3$	31.1	
$CH_3C{\equiv}N$	31.3	
$CH_3S(O)CH_3$	35.1	
Cyclopentadiene	18.0	
Indene[d]	20.1	
Fluorene[d]	22.6	
$PhC{\equiv}CH$	28.7	
Ph_3CH	30.6	
Ph_2CH_2	32.2	
$PhCH_3$	43[e]	(estimated)

Wittig-[2,3] rearrangement of allyloxycarbanions



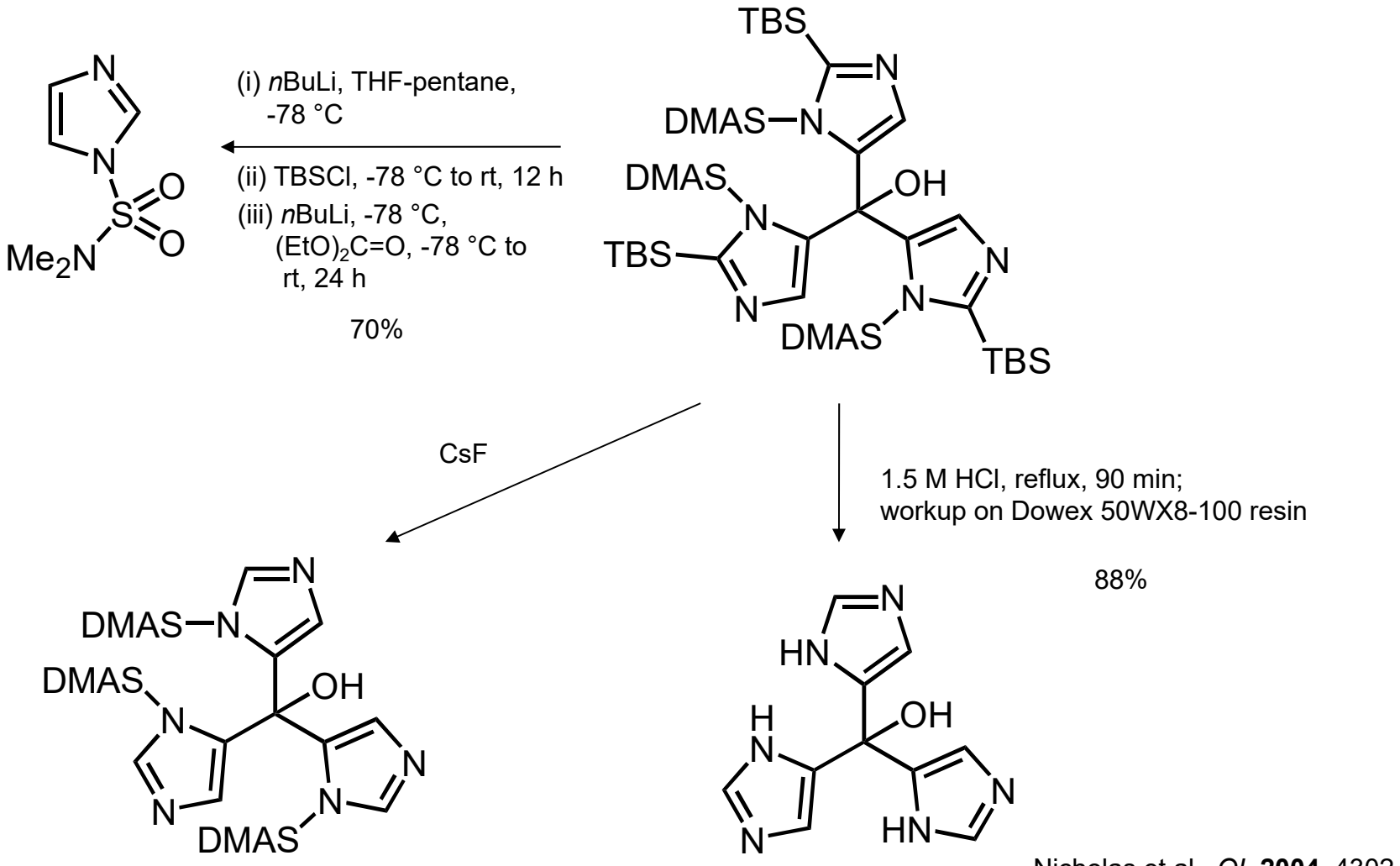
Driving force: oxyanion more stable than carbanion

e.g.



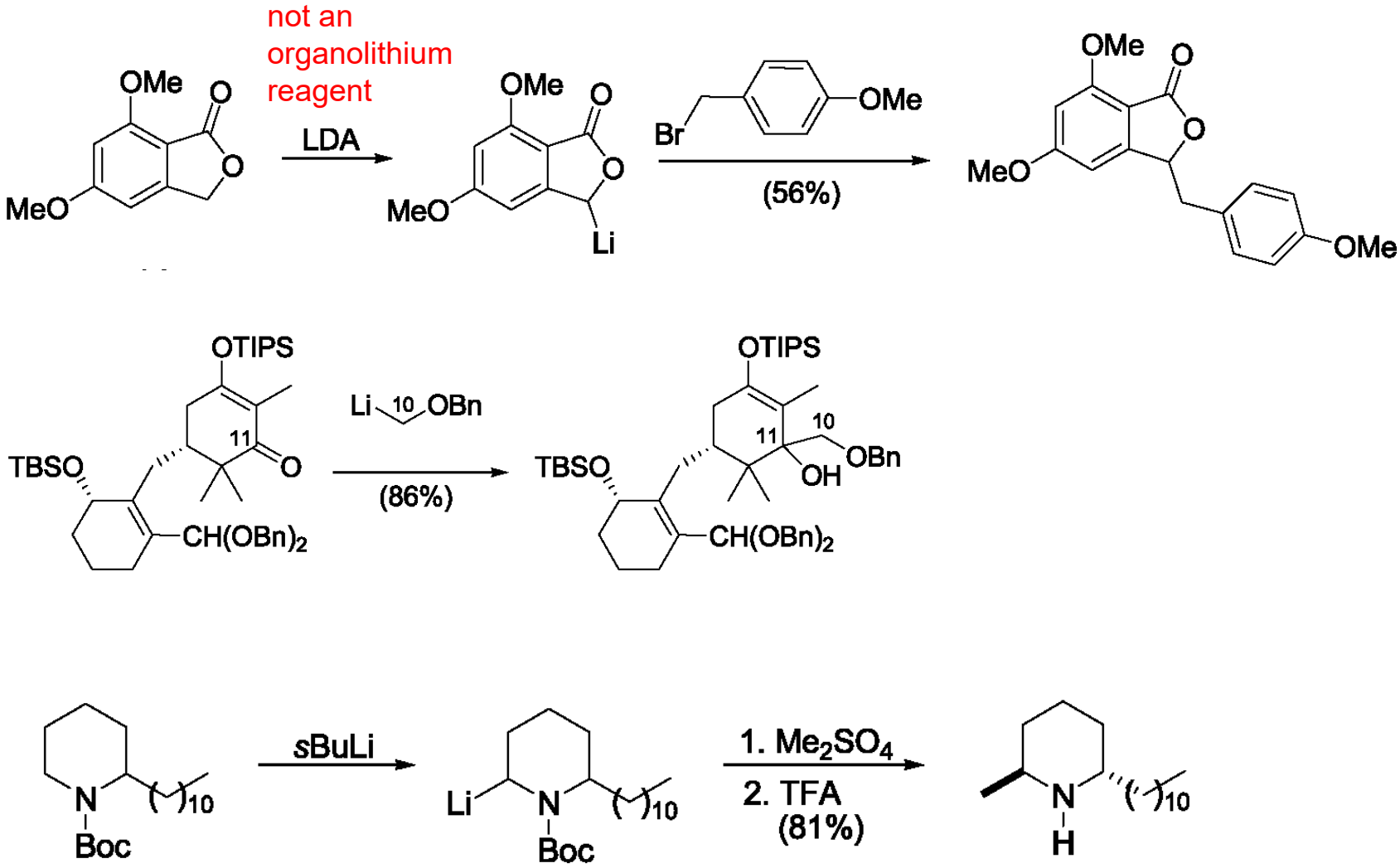
Sn/Li-Austausch (*Still*-Variante)

Regioselective deprotonation of the more acidic aryl-H:

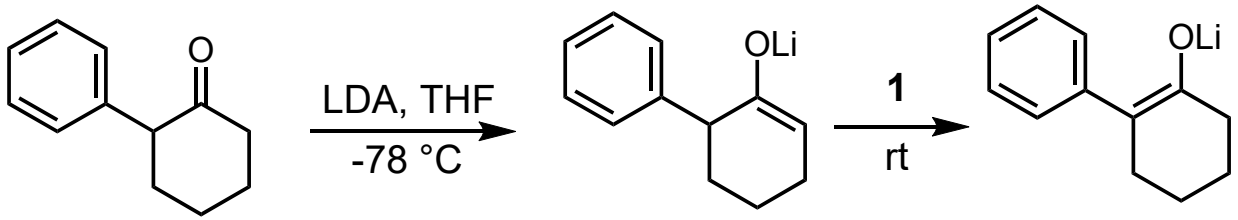


Nicholas et al., *OL* **2004**, 4302

Deprotonation of ether or amine α-H:



Flashback: kinetic and thermodynamic control with LDA

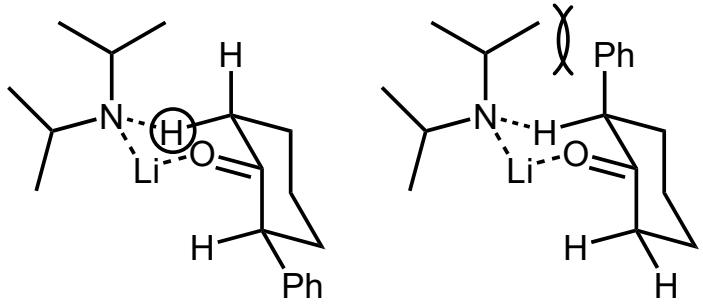


1 "kinetic" thermodyn.

< 1 equiv. LDA

higher substituted double bond in the thermodynamically more stable enolate; here also in conjugation

Zimmerman-Traxler-TS (chair)



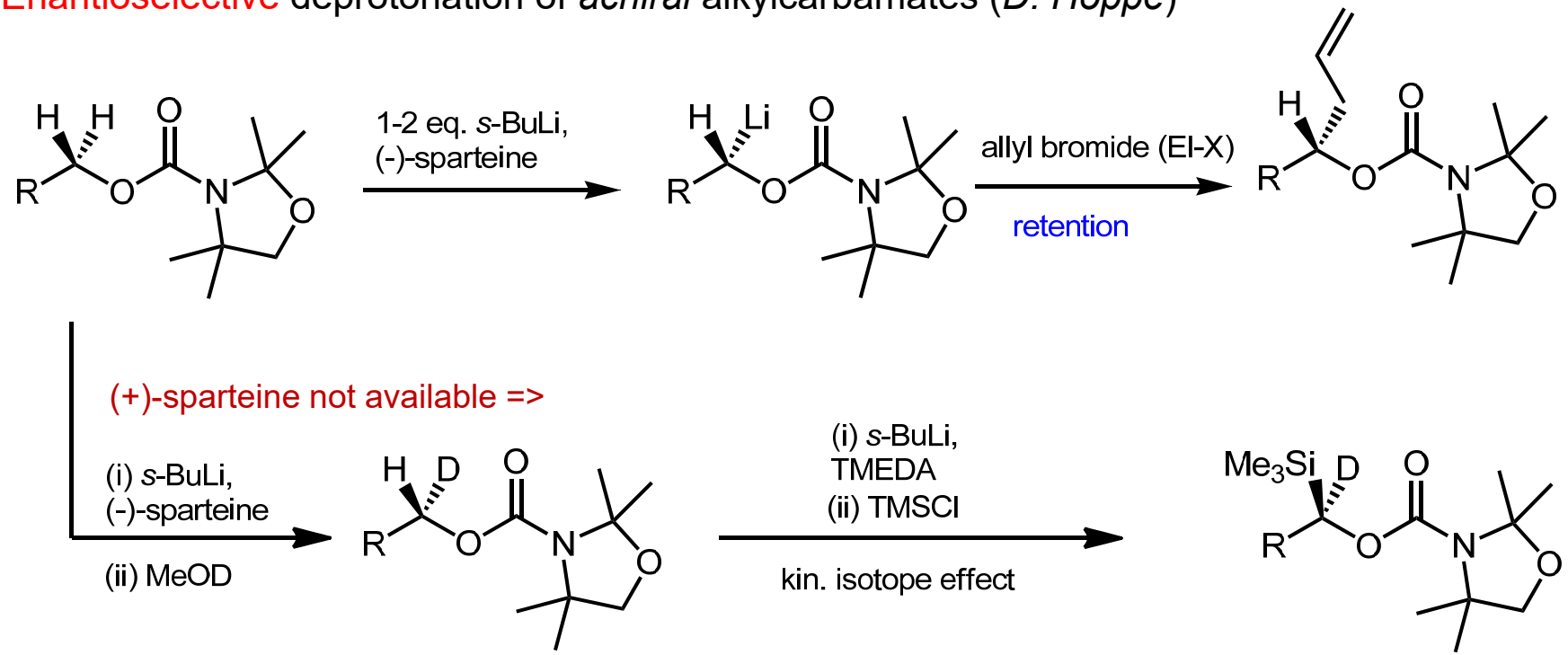
preferred

Ireland model

"kinetic enolate" formed via energetically favored, less hindered TS

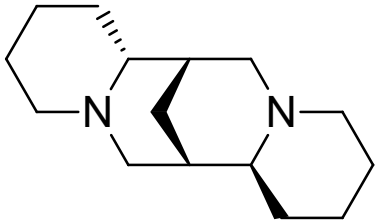
also: diastereoselective deprotonation "*trans*" to the phenyl group because of favored $\sigma_{C\text{-}H}/\pi^*_{C=O}$-overlap

Enantioselective deprotonation of *achiral* alkylcarbamates (*D. Hoppe*)



(–)-sparteine:

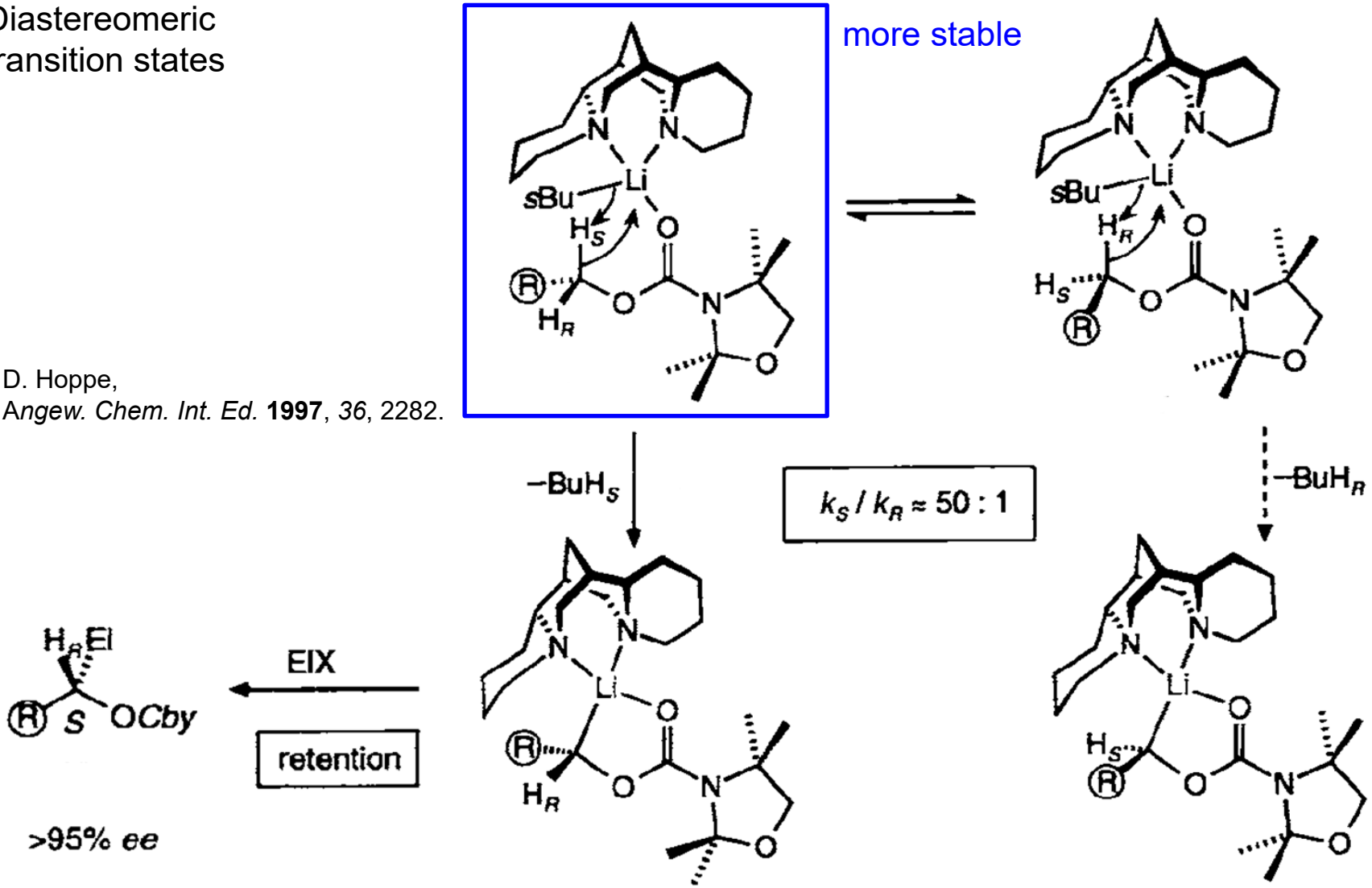
breaks Li clusters
(like TMEDA)



Cytisus scoparius
(Scotch broom, Besenginster)

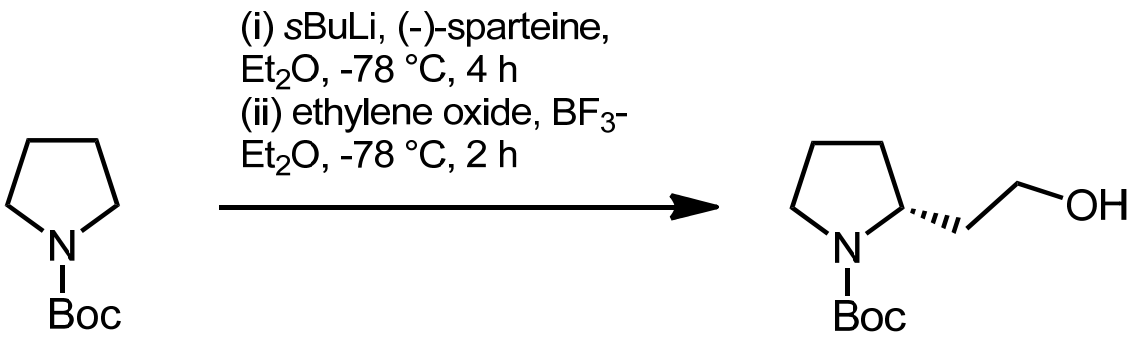
D. Hoppe, A*ngew. Chem. Int. Ed.* **1997**, *36*, 2282

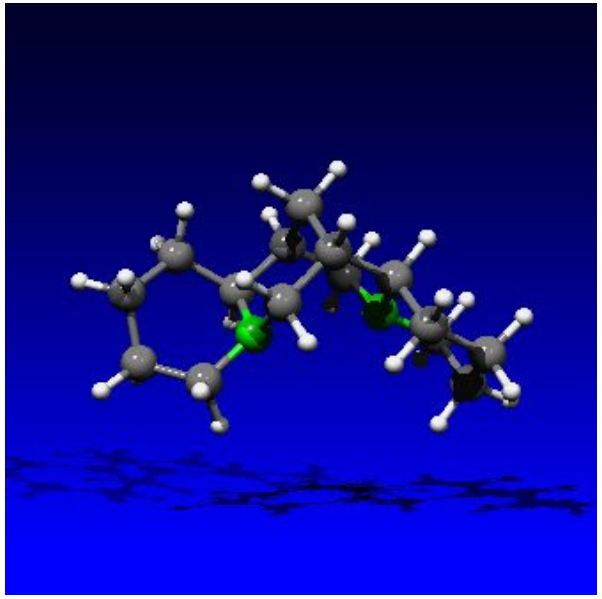
Diastereomeric transition states

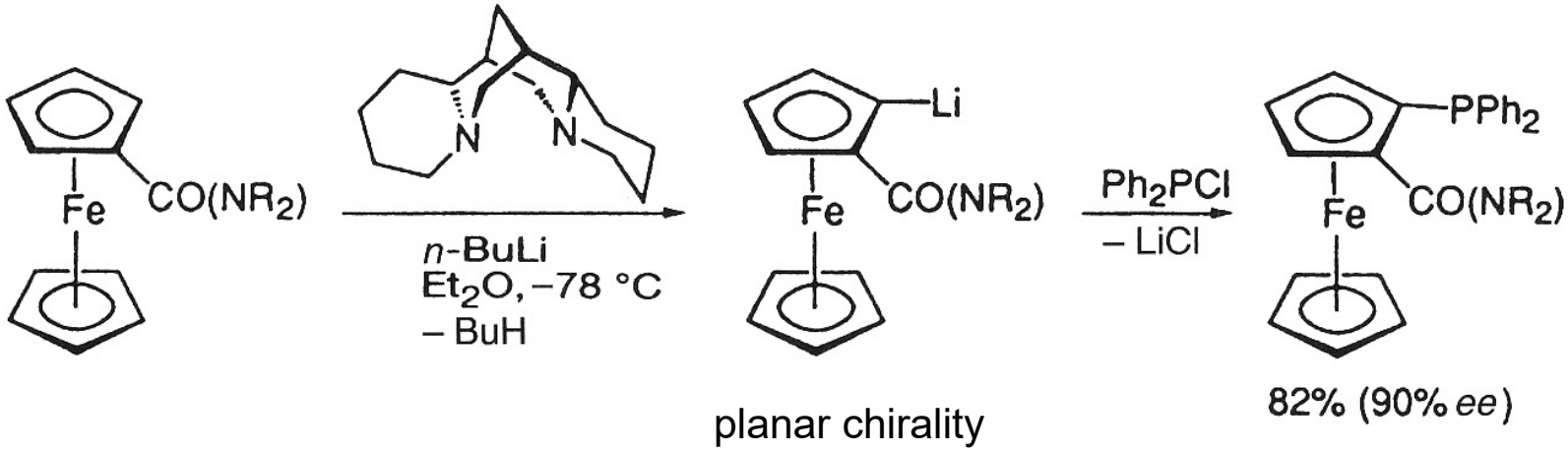


D. Hoppe,
Angew. Chem. Int. Ed. **1997**, *36*, 2282.

Enantioselective deprotonation of *N*-Boc-pyrrolidine (a carbamate, too):

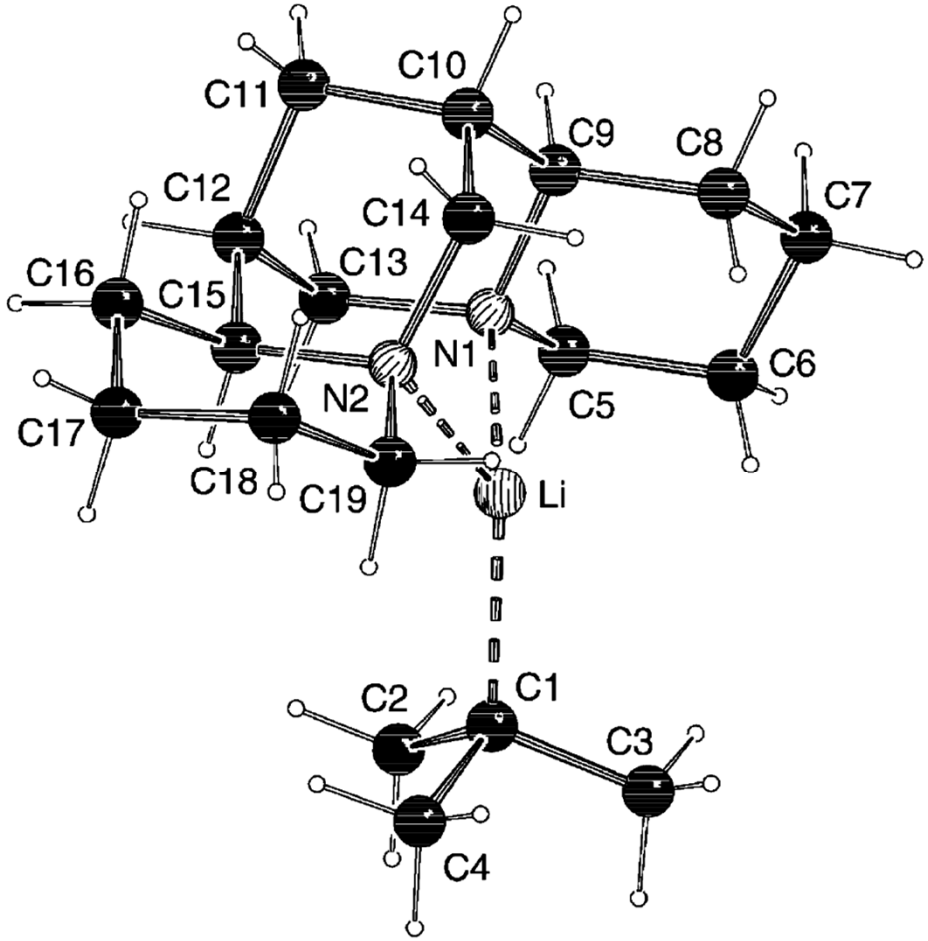




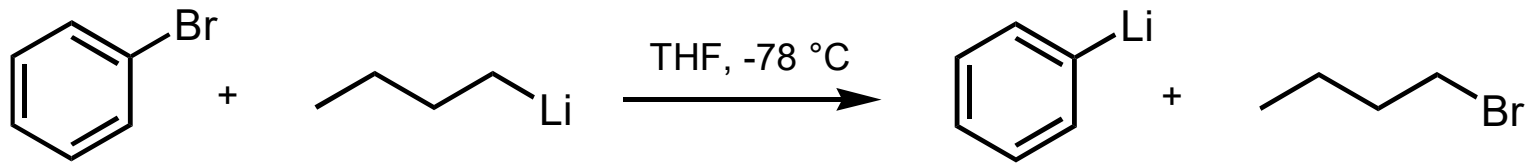


planar chirality

X-ray analysis of *t*BuLi-sparteine (Strohmann et al., *ACIE* **2003**, *42*, 4531)

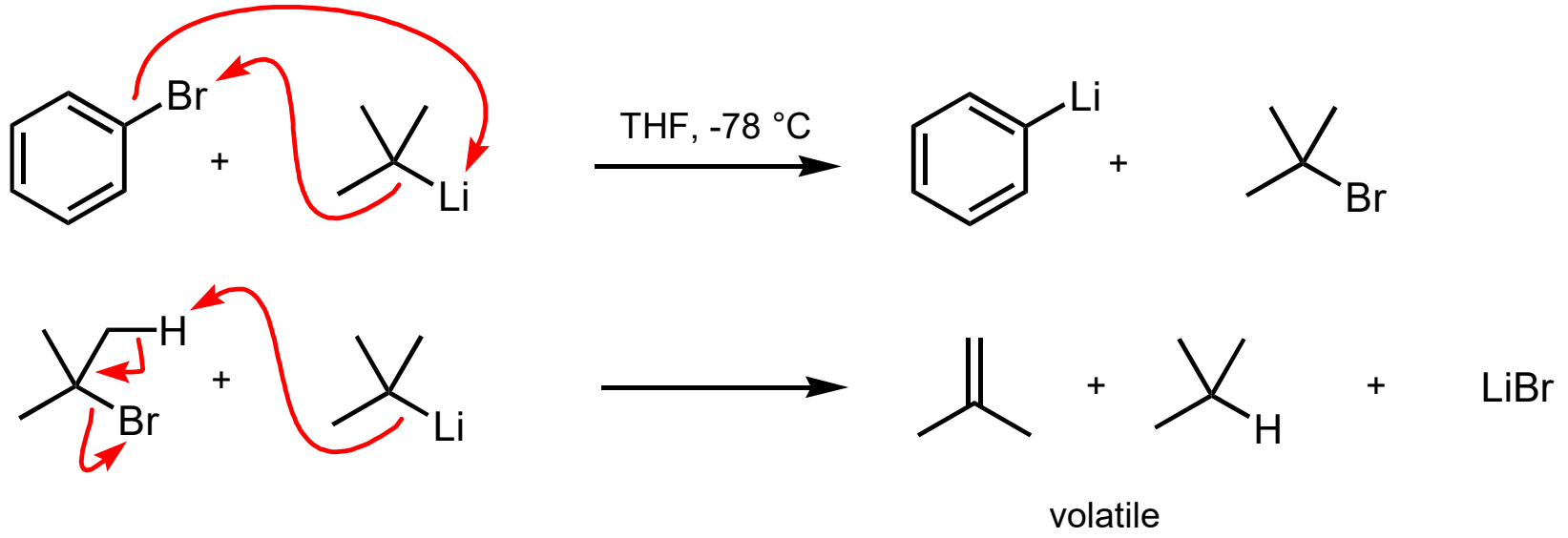


Halogen-metal exchange easier than deprotonation:



Problem: *n*-BuLi reacts with *n*-BuBr forming non-volatile products.

Solution: use 2 equivalents of *t*-BuLi (caution!)



Alkyl halides inert against alkyl-Li at low temperatures.

Half lives of *n*-BuX in the presence of *n*-BuLi (each reactant 0.5 M, 25 °C, in hours):

	in benzene	in Et_2O
X = Cl	> 100	40
X = Br	40	0.5
X = I	3	< 0.1

BuBr reacts rapidly with BuLi above 0 °C

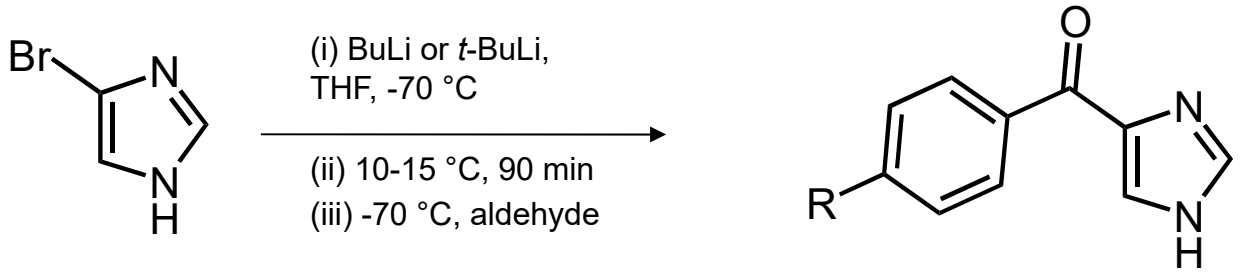
Make *n*-BuLi from *n*-BuCl !

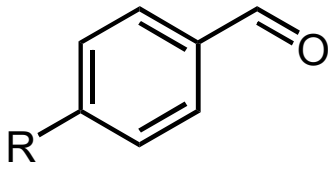
PhLi can be made from PhBr (less reactive).

Table 1 Bond dissociation energies of aryl halides

Bond	Dissociation energy (kJ mol^{-1})
Ph–F	533
Ph–Cl	407
Ph–Br	346
Ph–I	280

Sheppard , *OBC* **2009**, 1043



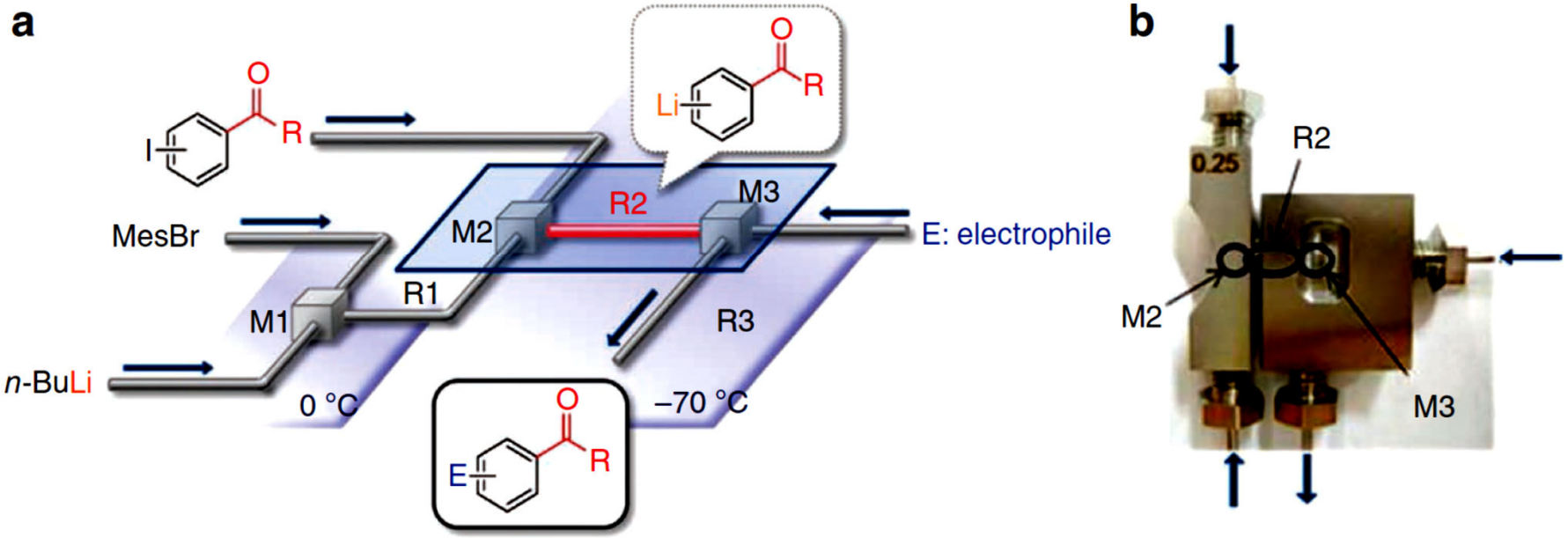


R = H (54%)
R = Me (36%)
R= OMe (61%)
R=Cl (37%)

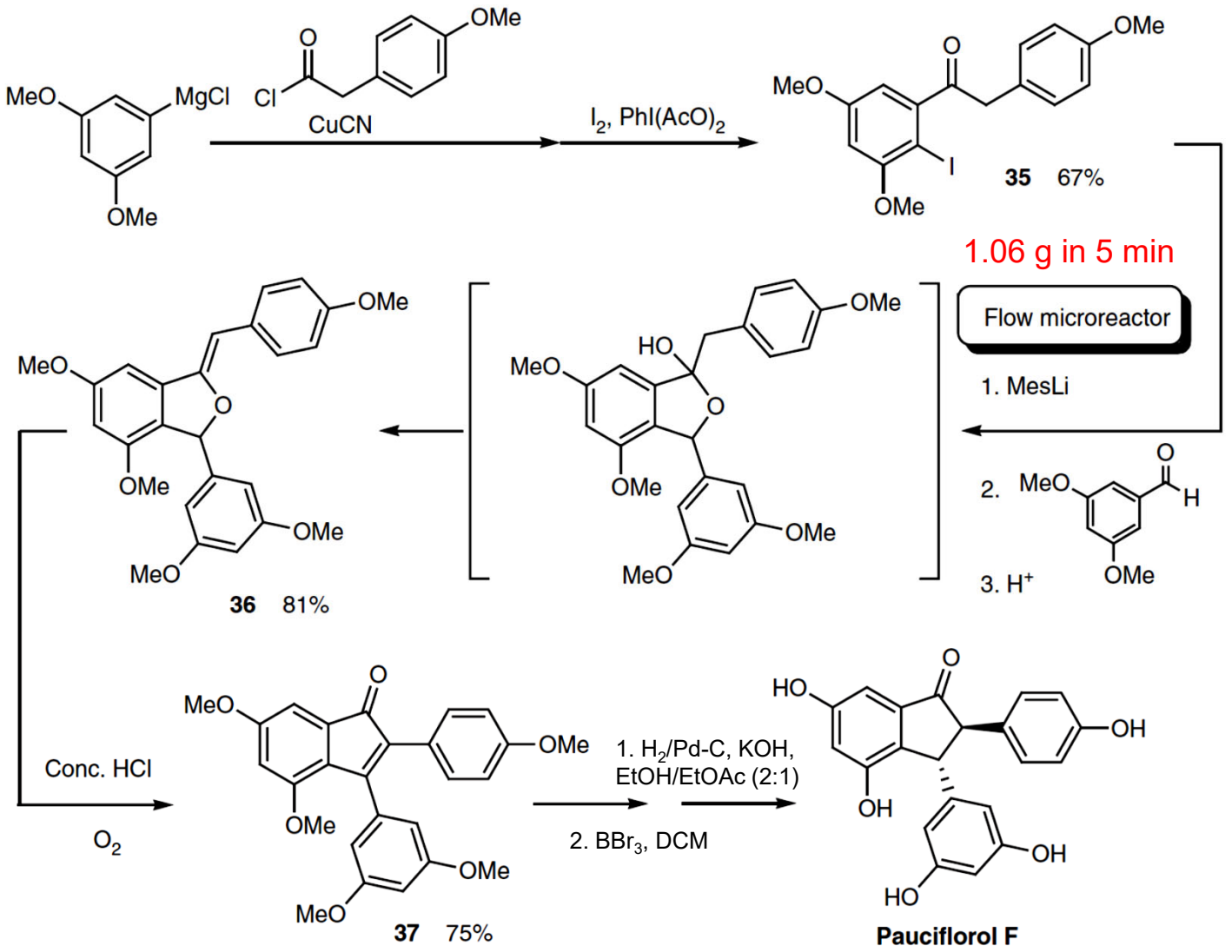
(iv) O_2

22%

Katritzky et al., *JCSP1* **1989**, 1139



Jun-ichi Yoshida et al., *Nature Commun.* **2011**, DOI: 10.1038/ncomms1264

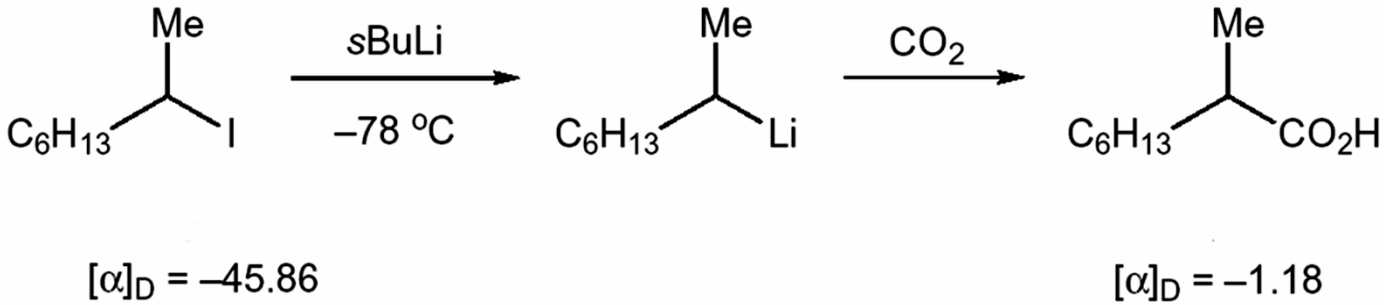


Jun-ichi Yoshida et al., *Nature Commun.* **2011**, DOI: 10.1038/ncomms1264

Stereochemistry (review: *Angew. Chem. Int. Ed.* **2002**, *41*, 716)

Alkyllithium compounds have the highest covalent character among the organolithiums. LiCp exhibits the highest ionic character (Li^+ resides over Cp^-).

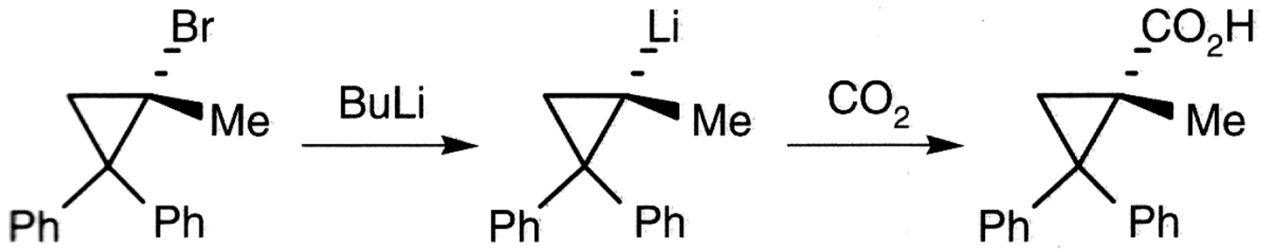
However, the stereochemical integrity of organolithium compounds is generally very low.



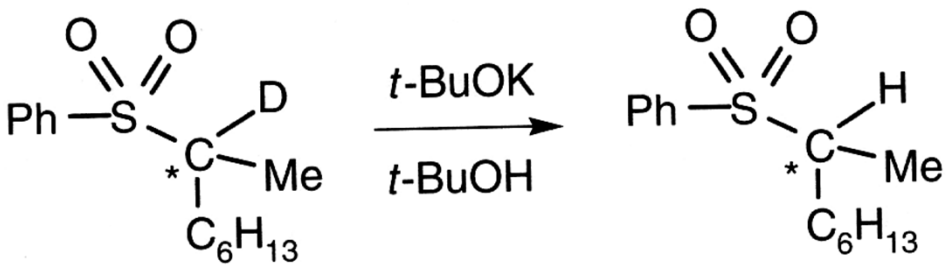
Letsinger et al., 1950: 80% of the optical purity of the starting alkyl iodide was lost!

Tetrahedral CH_3^- isoelectronic to NH_3.
Very low inversion barrier 9 kJ/mol, compared to 25 kJ/mol

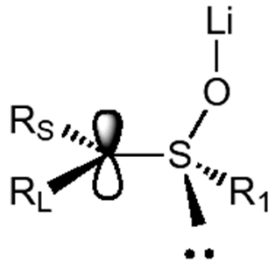
Higher inversion barriers, if carbanion embedded in strained rings
(inversion barrier of the cyclopropyl carbanion 68 kJ/mol):



Higher inversion barriers, if rotation restricted (58 kJ/mol for $DMSO^{-}$):

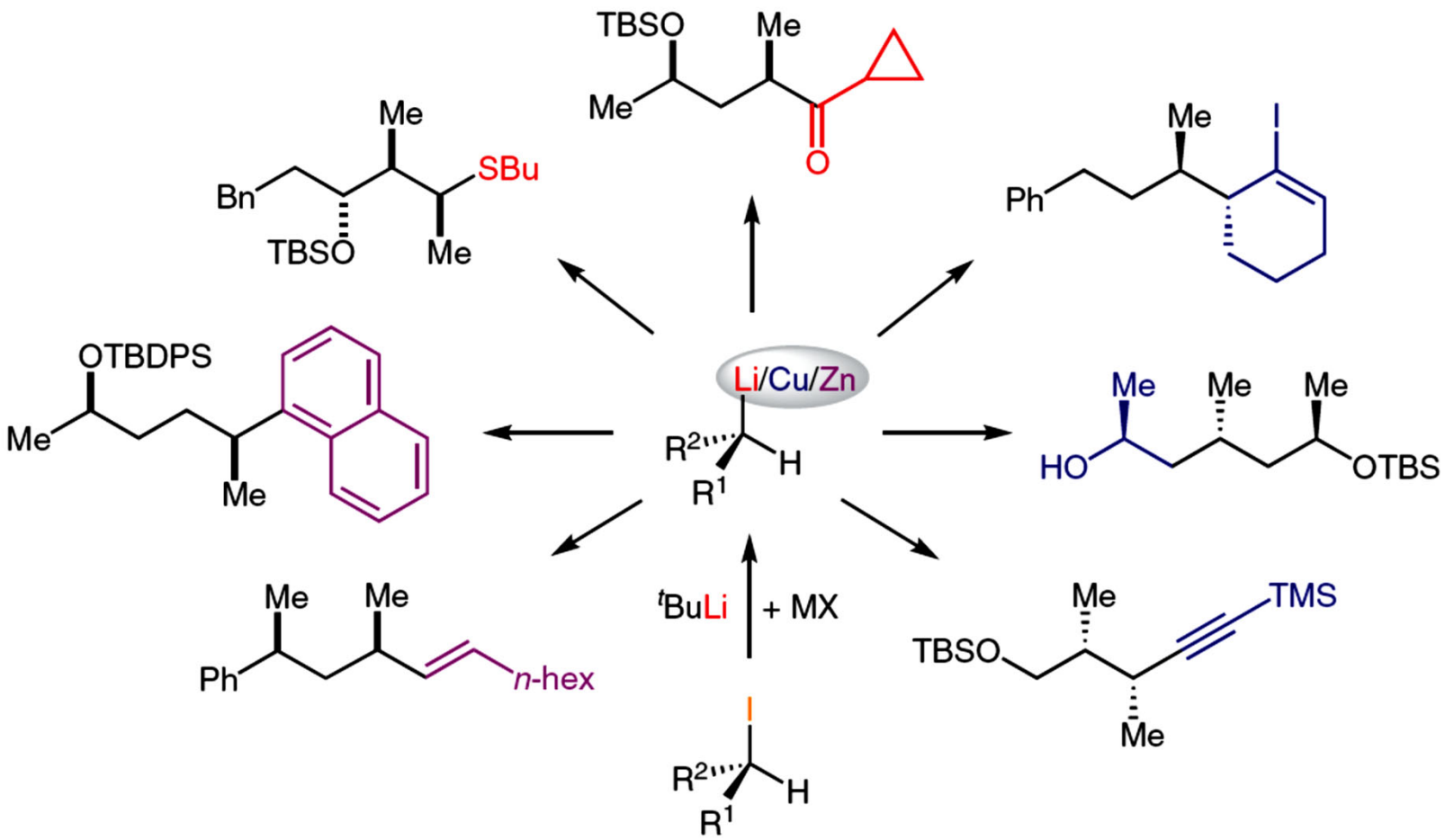


k_{exc}/k_{rac} = 139 (25 °C)



planar α-lithio sulfoxides
permit stereodivergent
electrophilic substitution

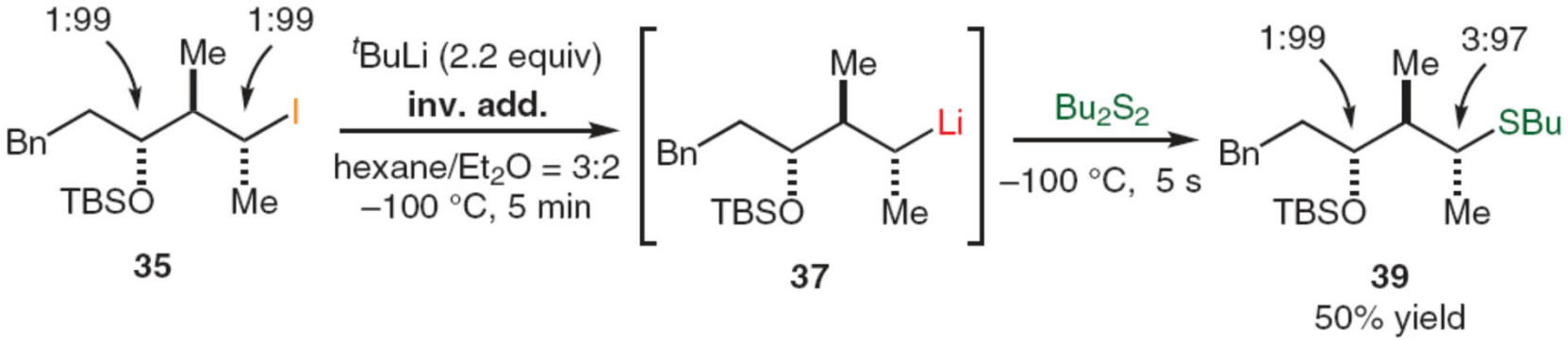
What is possible with chiral secondary organolithium compounds?

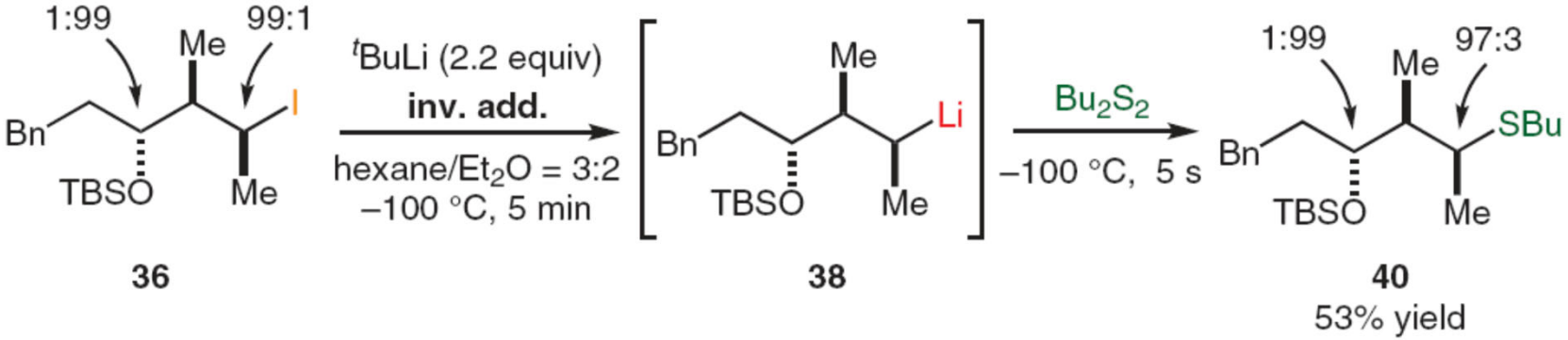


from: Knochel et al., *Synthesis* **2020**, *52*, 189

It has to be cold enough (-100 °C), *t*-BuLi has to be used in the inverse addition mode.
Lithiated products are almost as reactive as *t*-BuLi itself.

Starting material chiral iodoalkanes: retention of configuration





from: Knochel et al., *Synthesis* **2020**, *52*, 189

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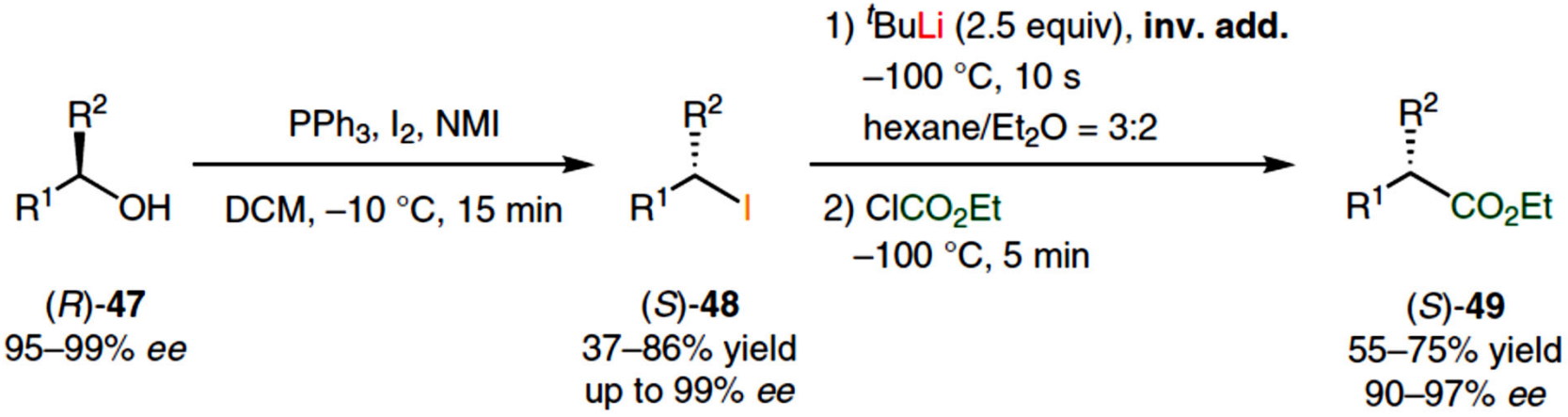


(*R*)-**47**
95–99% *ee*

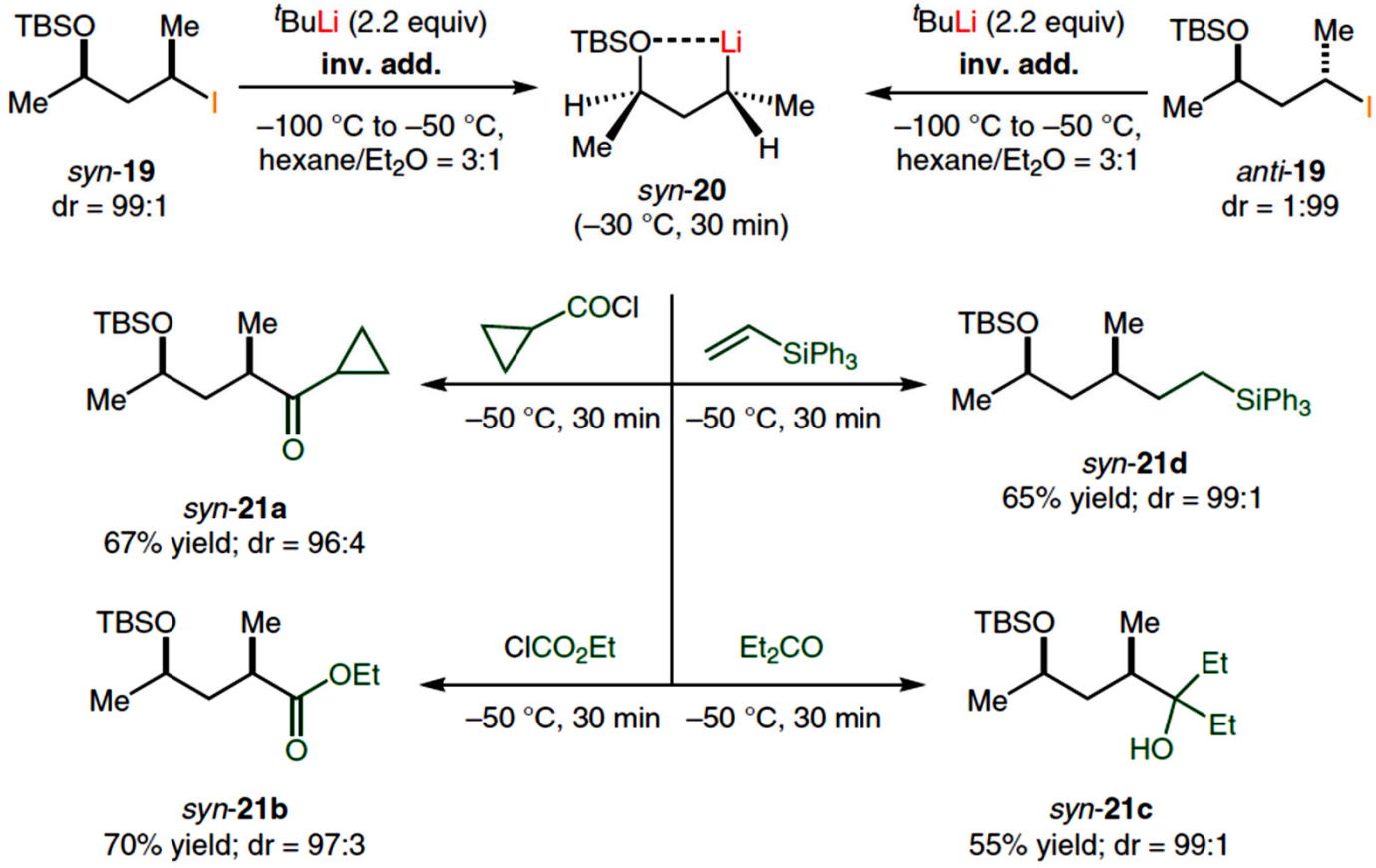
(*S*)-**48**
37–86% yield
up to 99% *ee*

(*S*)-**49**
55–75% yield
90–97% *ee*

from: Knochel et al., *Synthesis* **2020**, *52*, 189

It has to be cold enough (-100 °C), *t*-BuLi has to be used in the inverse addition mode.
Lithiated products are almost as reactive as *t*-BuLi itself.

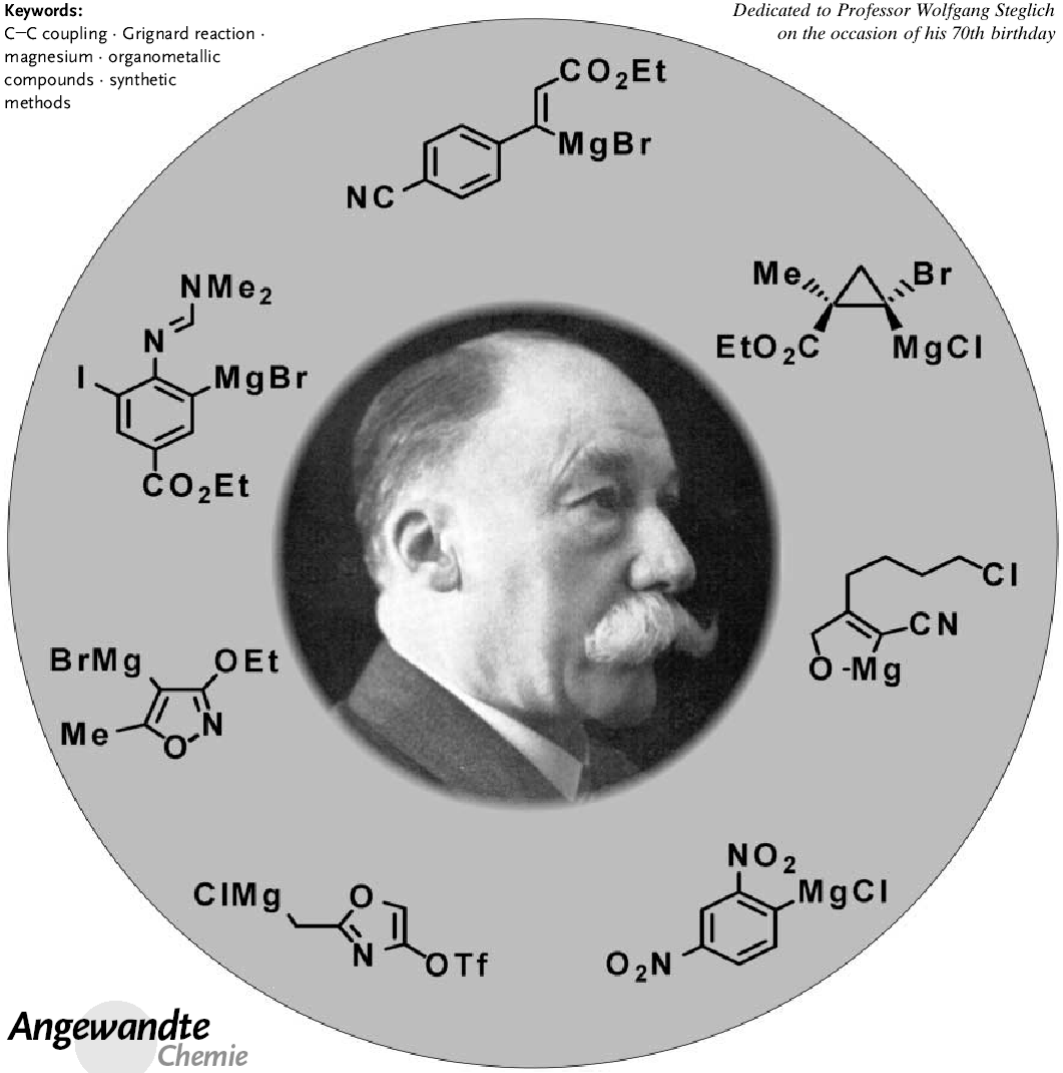
Stereoconvergent preparation of a chelate-stabilized secondary alkyllithium:



from: Knochel et al., *Synthesis* **2020**, *52*, 189

Keywords:
C–C coupling · Grignard reaction · magnesium · organometallic compounds · synthetic methods

Dedicated to Professor Wolfgang Steglich on the occasion of his 70th birthday



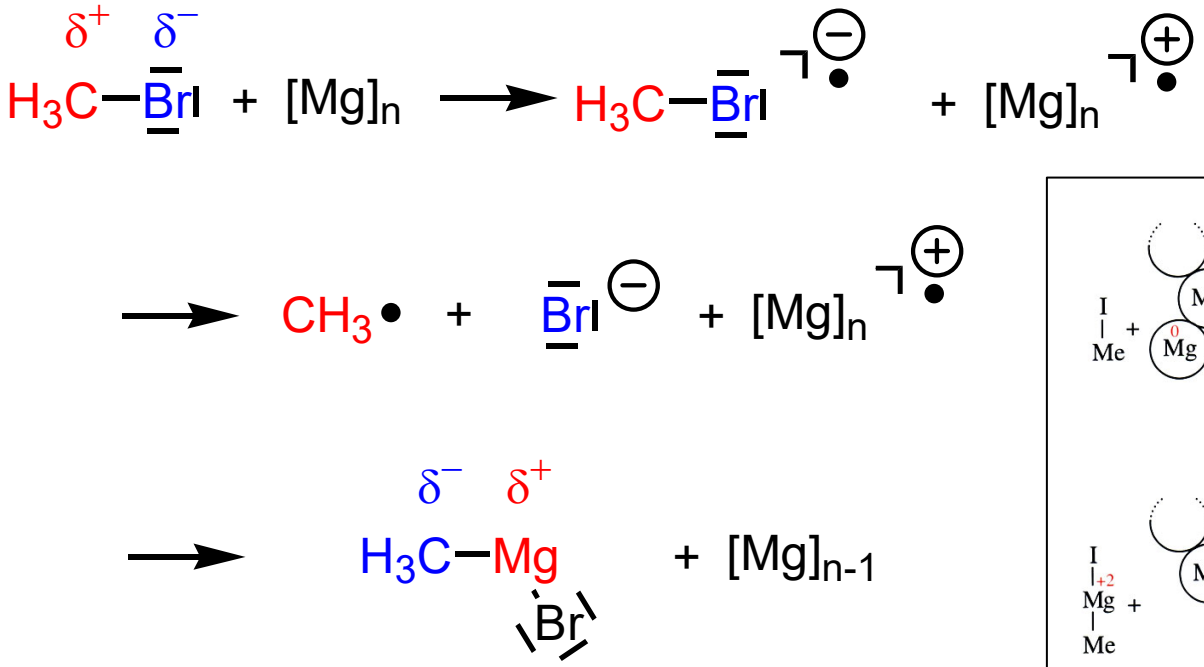
Angewandte Chemie

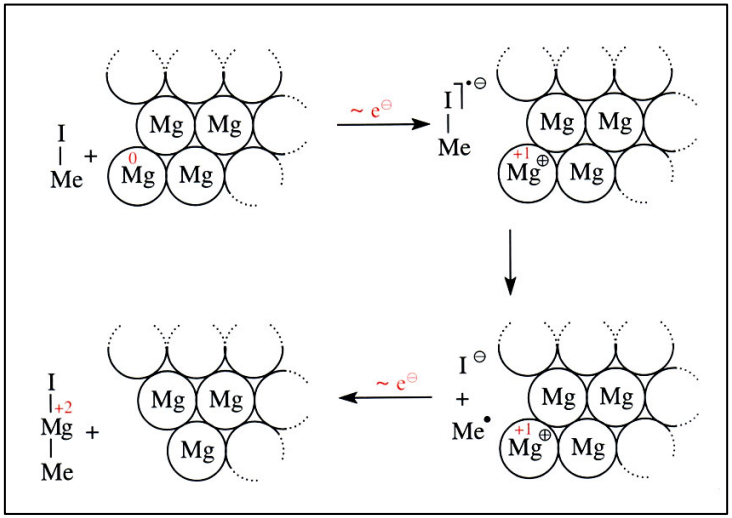
Victor Grignard
(1871-1935,
Nobelpreis 1912)

aus: Knochel et al., *ACIE* **2003**, 4302.

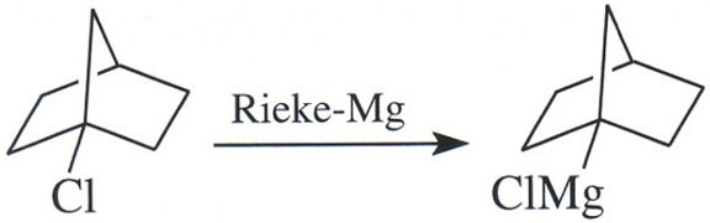
Formation of a *Grignard* reagent from RX and metallic Mg by **halogen/Mg exchange**:
2 one-electron steps

Mechanism for organolithium compounds?





Use of *Rieke*-Mg (generated by reduction of a suspension of $MgCl_2$ in THF with K) in sterically demanding cases:



Schlenk equilibrium in solution:

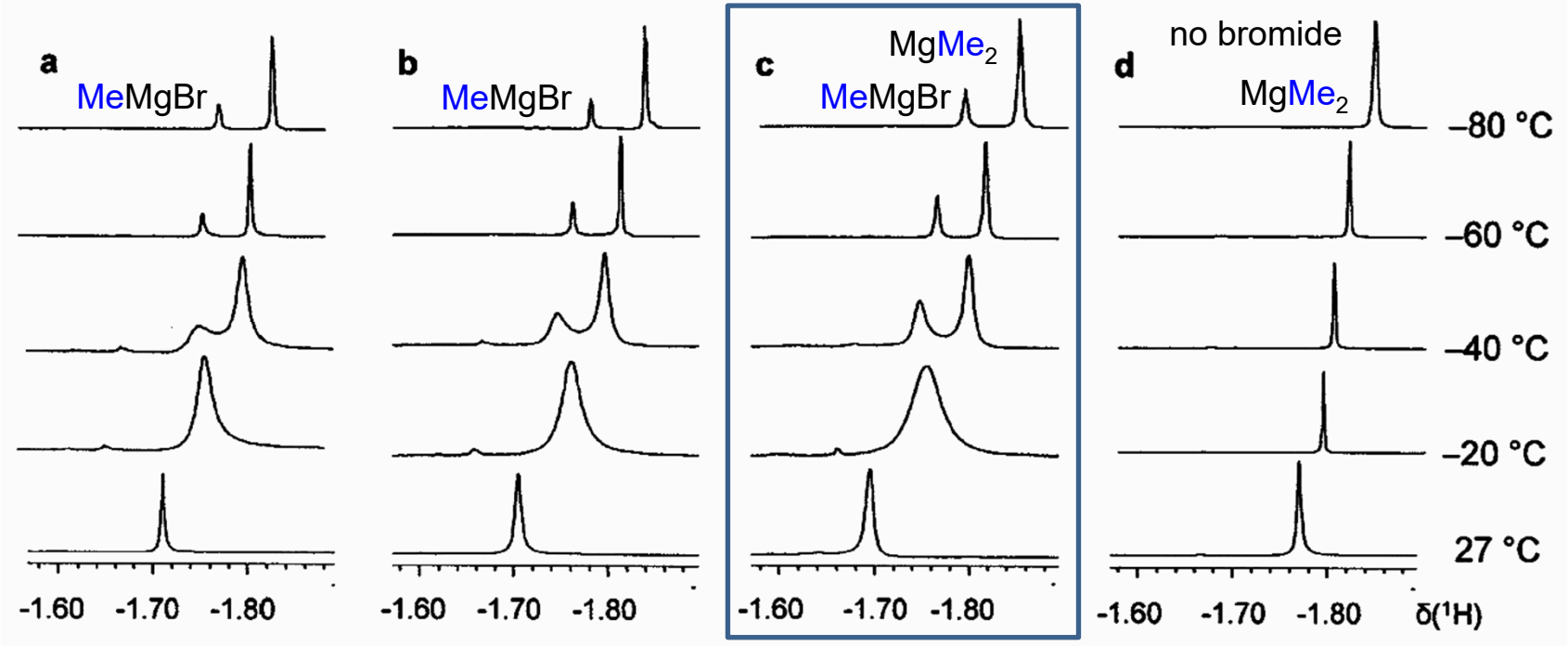
aus: Youssef et al., *J. Organomet. Chem.* **2005**, 1178.

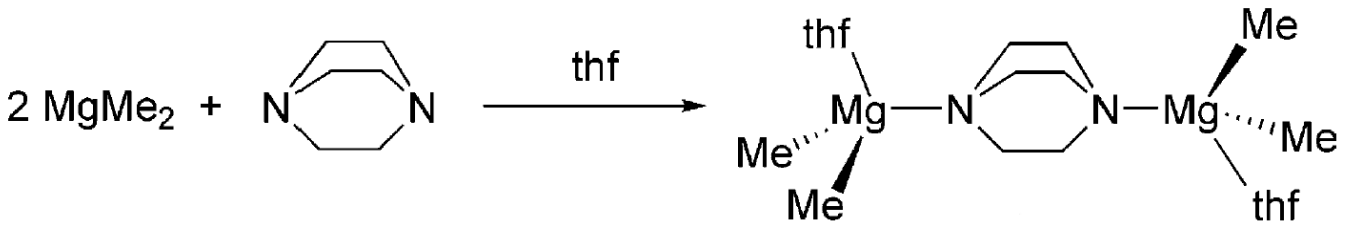
$$(RMgX)_2 \rightleftharpoons 2RMgX \rightleftharpoons R_2Mg + MgX_2 \rightleftharpoons R_2Mg{\cdot}MgX_2$$

Temperatur

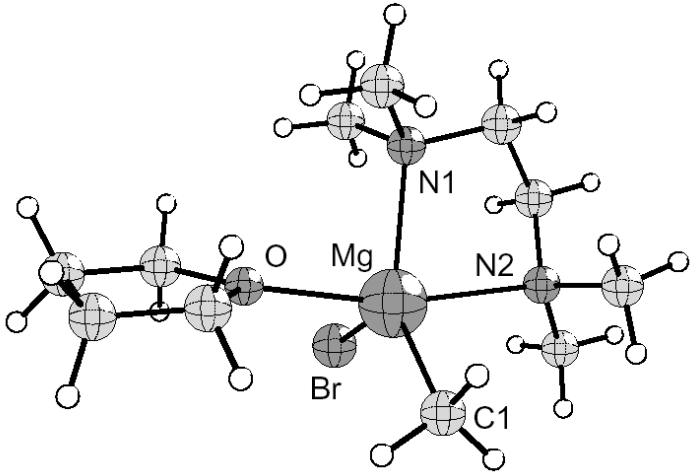
Low-temperature ^{1}H NMR spectra of methyl protons for
(a) MgMeBr(diglyme), (b) MgMeBr(NEt_3), (c) MgMeBr(thf),
(d) $MgMe_2$ in THF-d_8 (concentration: 0.04 M).

synthesis of $MgMe_2$: precipitation from an Et_2O solution of MeMgBr by addition of dioxane at -40°C, 1 d

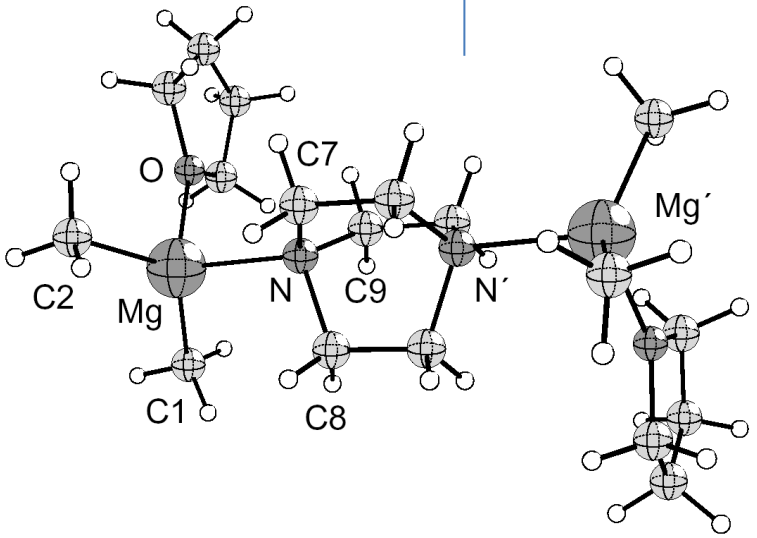




Synthesis of $[\{MgMe_2(thf)\}_2(\mu\text{-dabco})]$

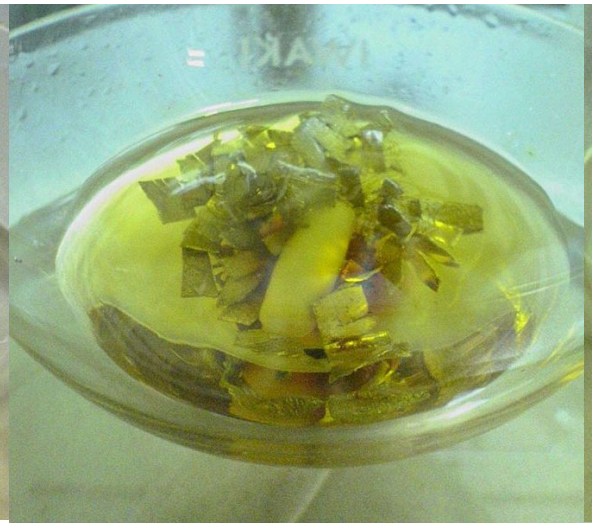


Molecular structure of [MgMeBr(thf)(tmeda)]



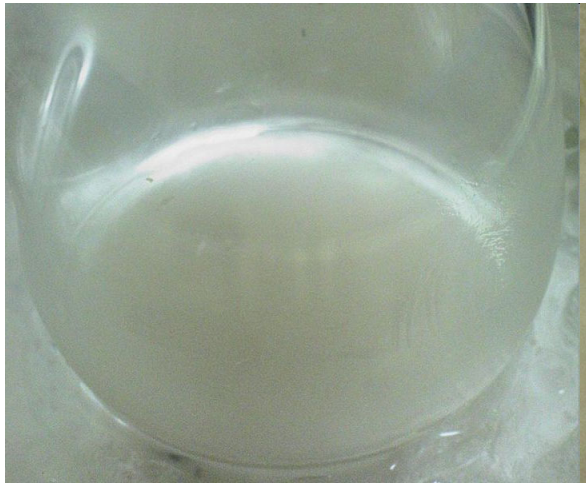
aus: Youssef et al., *J. Organomet. Chem.* **2005**, 1178.

Mg-Späne

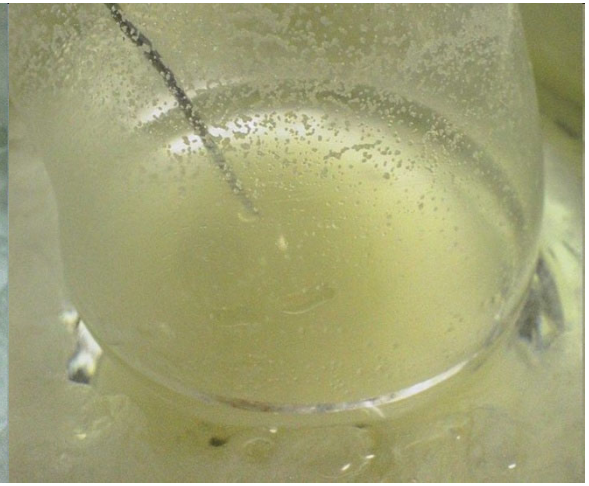


Mg-Späne + THF + Spuren Iod

Erhitzen nach Addition des Bromoalkans



Nach Abkühlung auf 0 °C

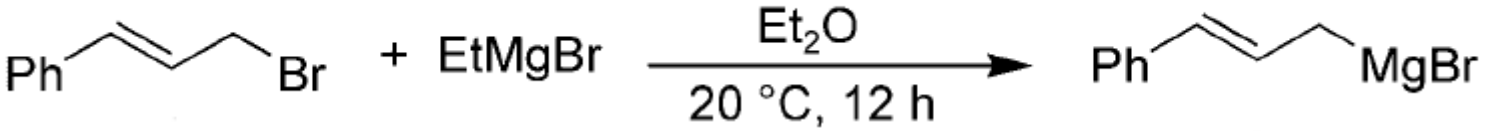


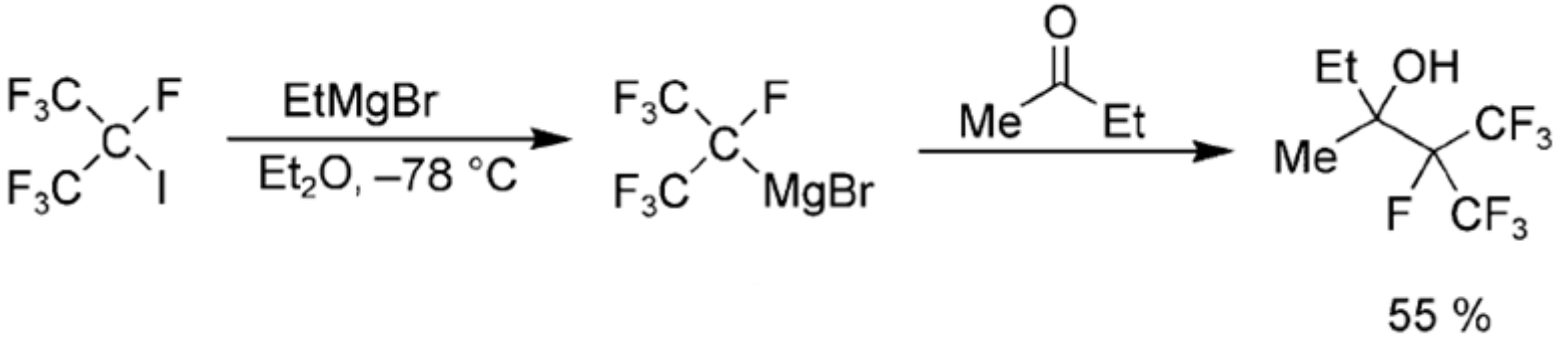
+ Carbonylverbindung bei 0°C

Aufarbeitung fehlt noch.

Convenient formation of a *Grignard* reagent from another, less stable *Grignard* reagent by halogen/Mg exchange

First example (1931):

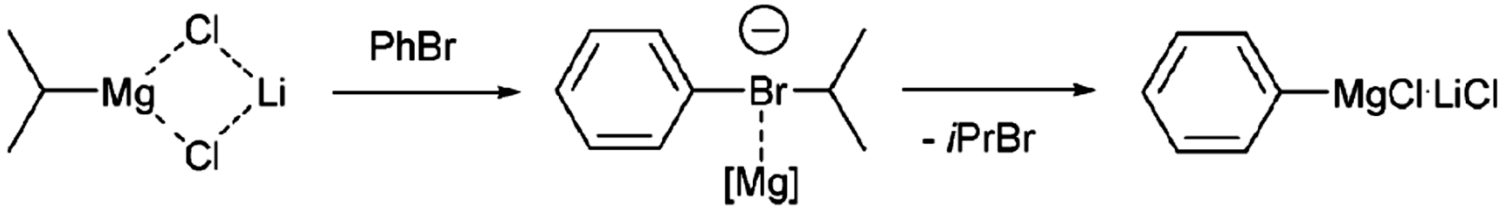




iPrMgCl-LiCl: LiCl assists the deaggregation of oligomeric organo-Mg halides

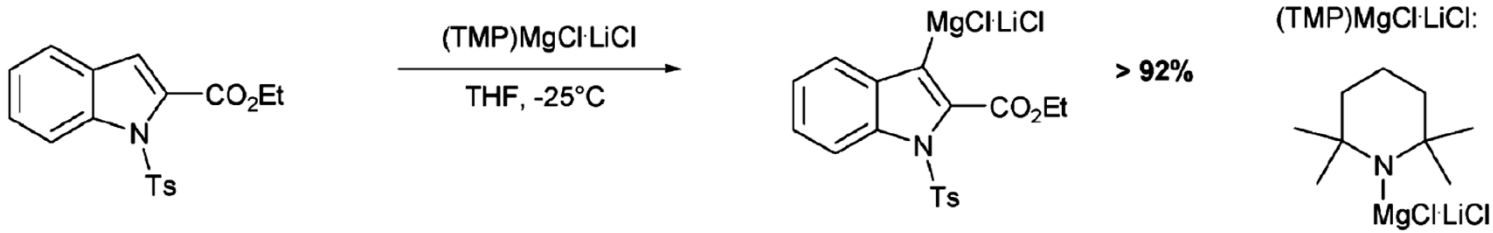
equilibrium!

stability: **sp > sp^2(vinyl) > sp^2(aryl) > sp^3(1°) > sp^3(2°) > RLi**



[Mg] = $MgCl_2$(solv) or *i*-PrMgCl(solv)

(TMP)MgCl-LiCl (TMP = 2,2,6,6-tetramethylpiperidin-1-yl, Hauser base): selective deprotonation of heteroarenes



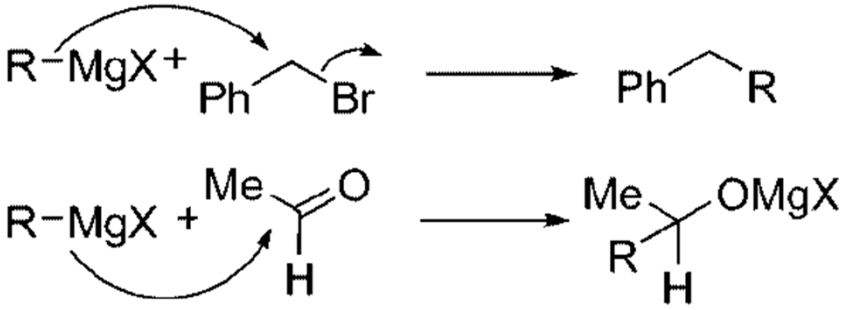
from: Jacobi von Wangelin, *Chem. Soc. Rev.* **2011**, 4948

Principle reactions of Grignard compounds

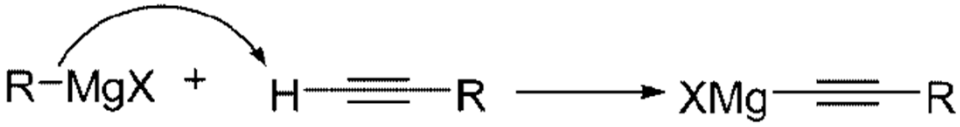
RMgX less basic than RLi

=>
formation of Grignard reagents by deprotonation possible only for acidic protons, such as in terminal alkynes or hetero-H compounds

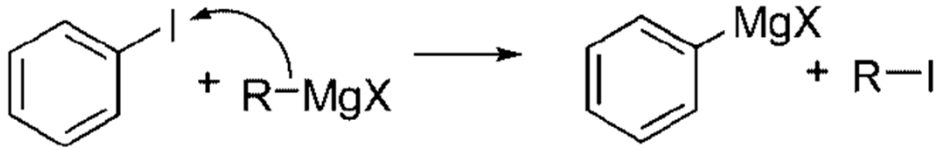
(1) Nucleophilic Addition and Substitution



(2) Base



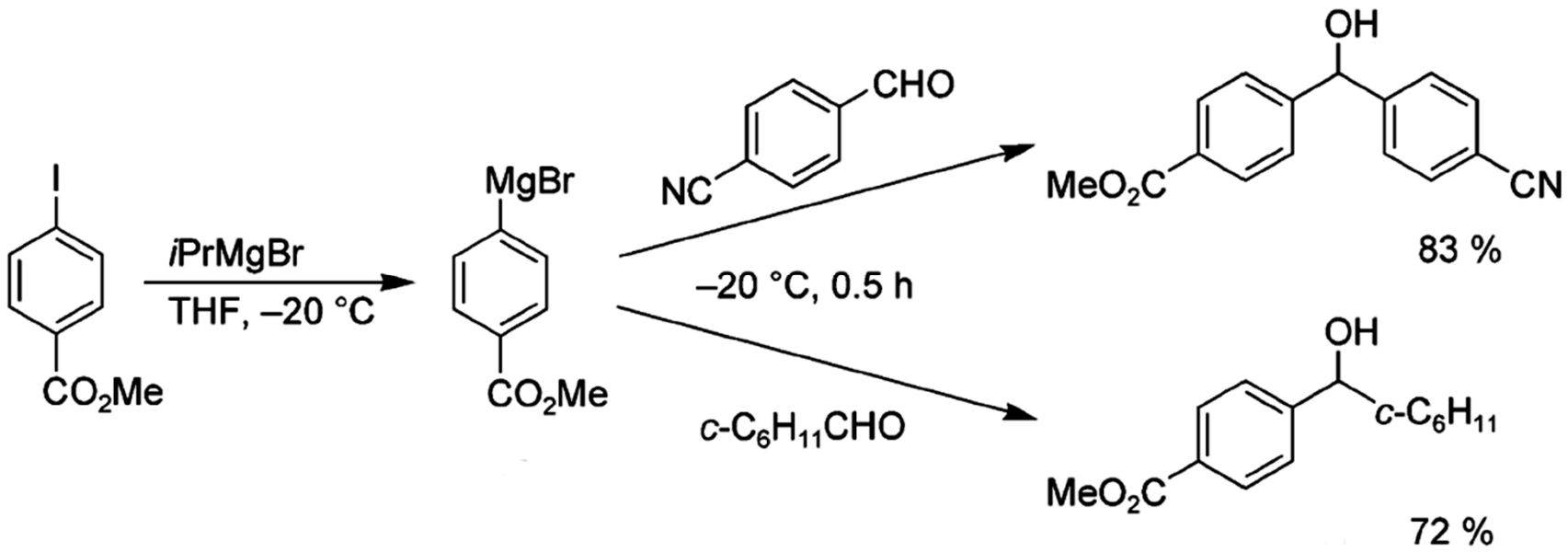
(3) Magnesium–Halogen Exchange



X = Cl, Br, I

reaction and formation

Microreview: Shinokubo et al., *Eur. J. Org. Chem.* **2004**, 2081.

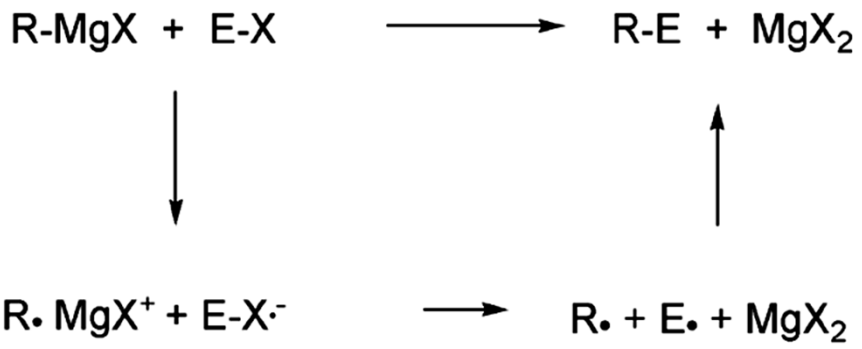


Below 0 °C, only aldehydes and some ketones react with *Grignard* reagents.
=> ester-(or nitrile-, amide-) functionalized *Grignard* reagents can be handled at -20 °C.

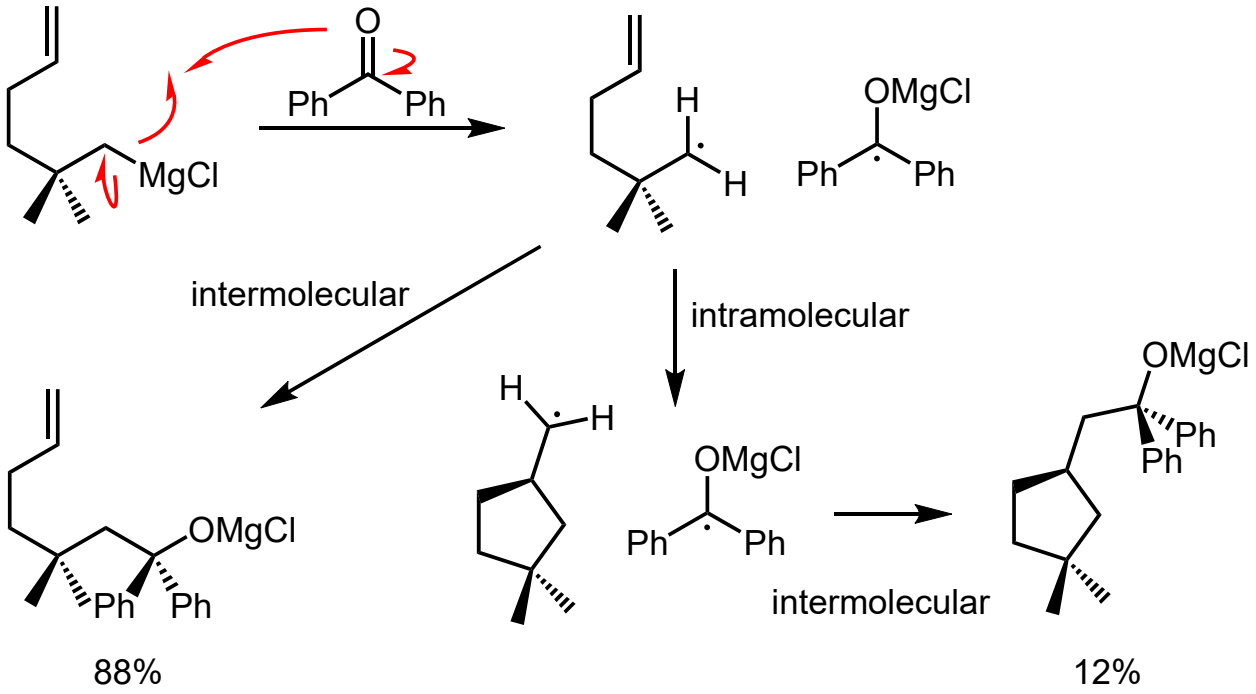
*i*PrMgCl, *i*PrMgBr are the reagents of choice for halogen magnesium exchange.

from: Knochel et al., *ACIE* **2003**, 4302.

Reaction of *Grignard* reagents



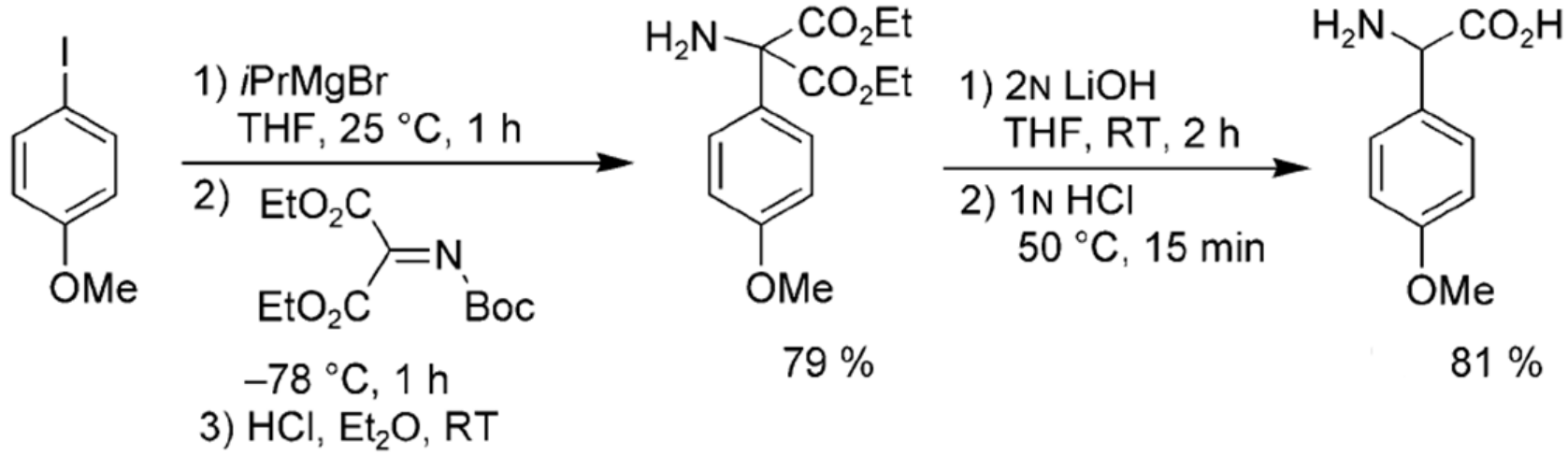
a) transfer of one electron to the electrophile forming the radical anion
b) formation of R• and E• (and X^-)
c) reaction of R• and E•

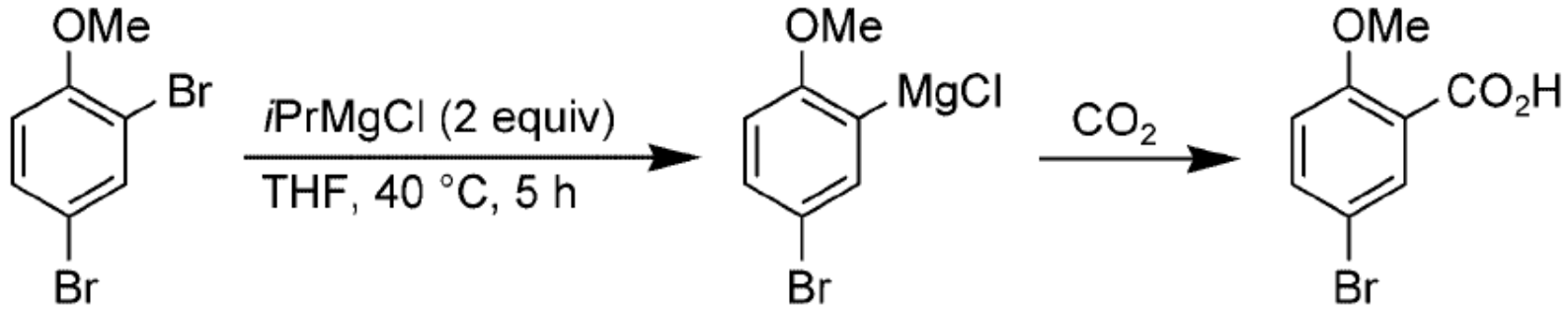


intramolecular competition proves participation of radical intermediate

R. W. Hoffmann, *CSR* **2003**, 225.

Aryl halides with electron-donating groups: halogen/Mg exchange only at higher temperatures (> 25 °C)

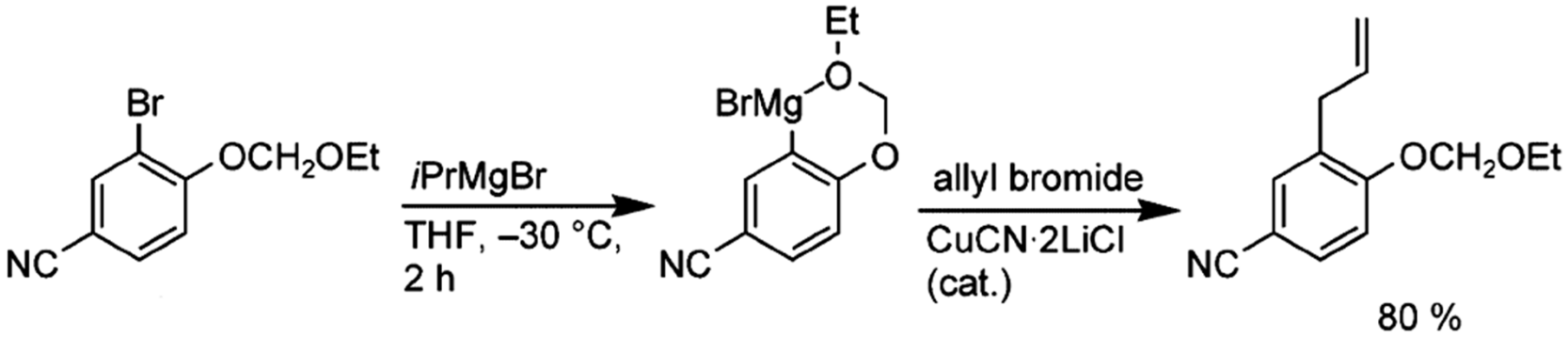




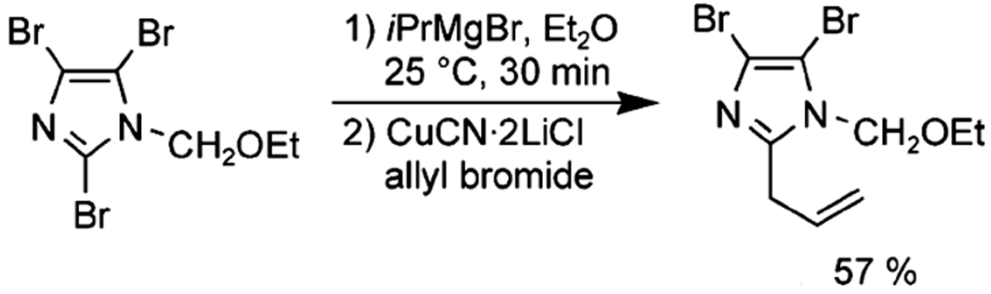
Comparison:
pentafluorobromobenzene undergoes Br/Mg exchange at -78 °C within 30 min.

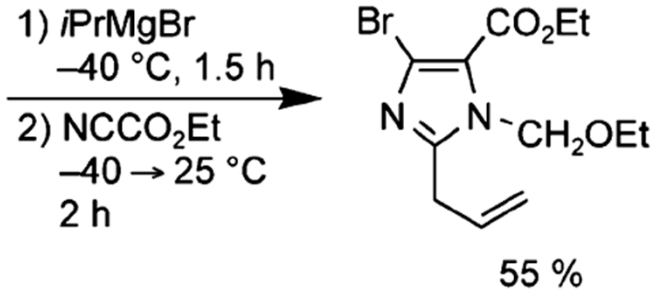
from: Knochel et al., *ACIE* **2003**, 4302.

Mg-coordinating *ortho* substituent: lower temperatures possible



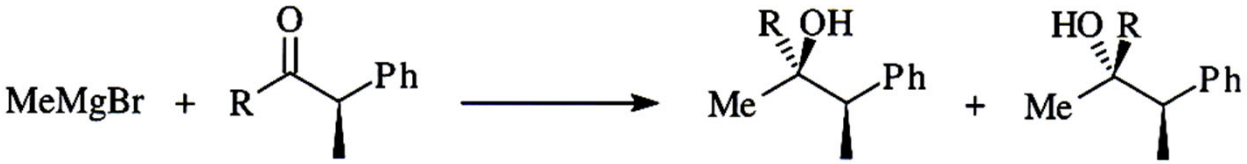
***ortho* effect:** X/M exchange preferably in the *o*-position of a coordinating substituent



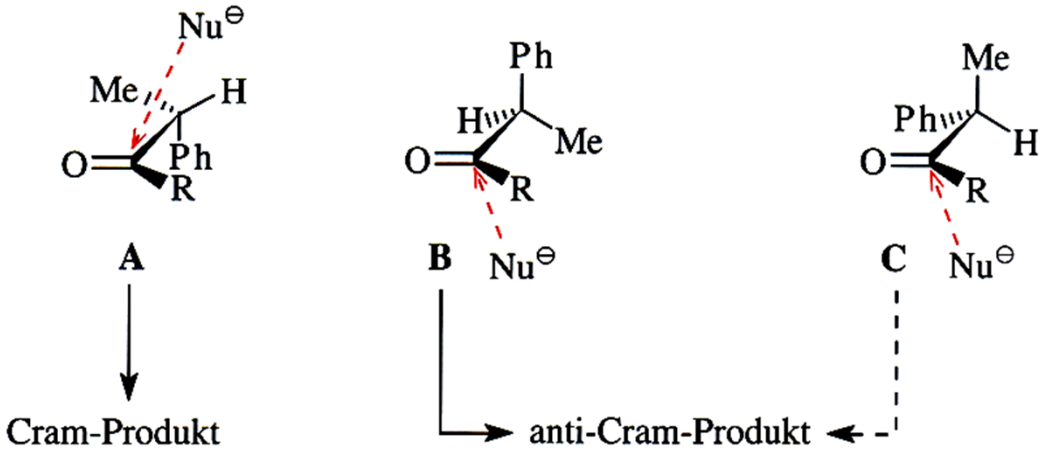


from: Knochel et al., *ACIE* **2003**, 4302.

Diastereoselective addition to α-chiral carbonyl compounds

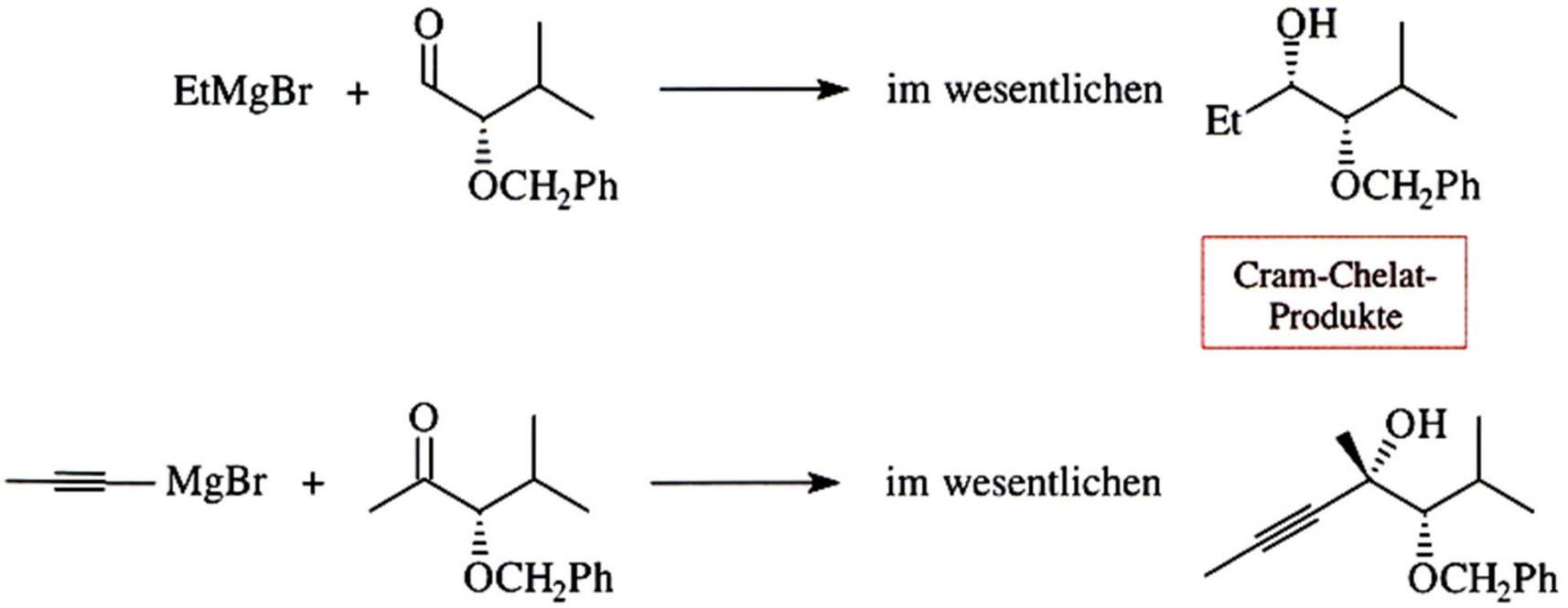


R	Cram-Produkt	anti-Cram-Produkt
H	71	29
Et	86	14
*i*Pr	90	10
tert-Bu	96	4



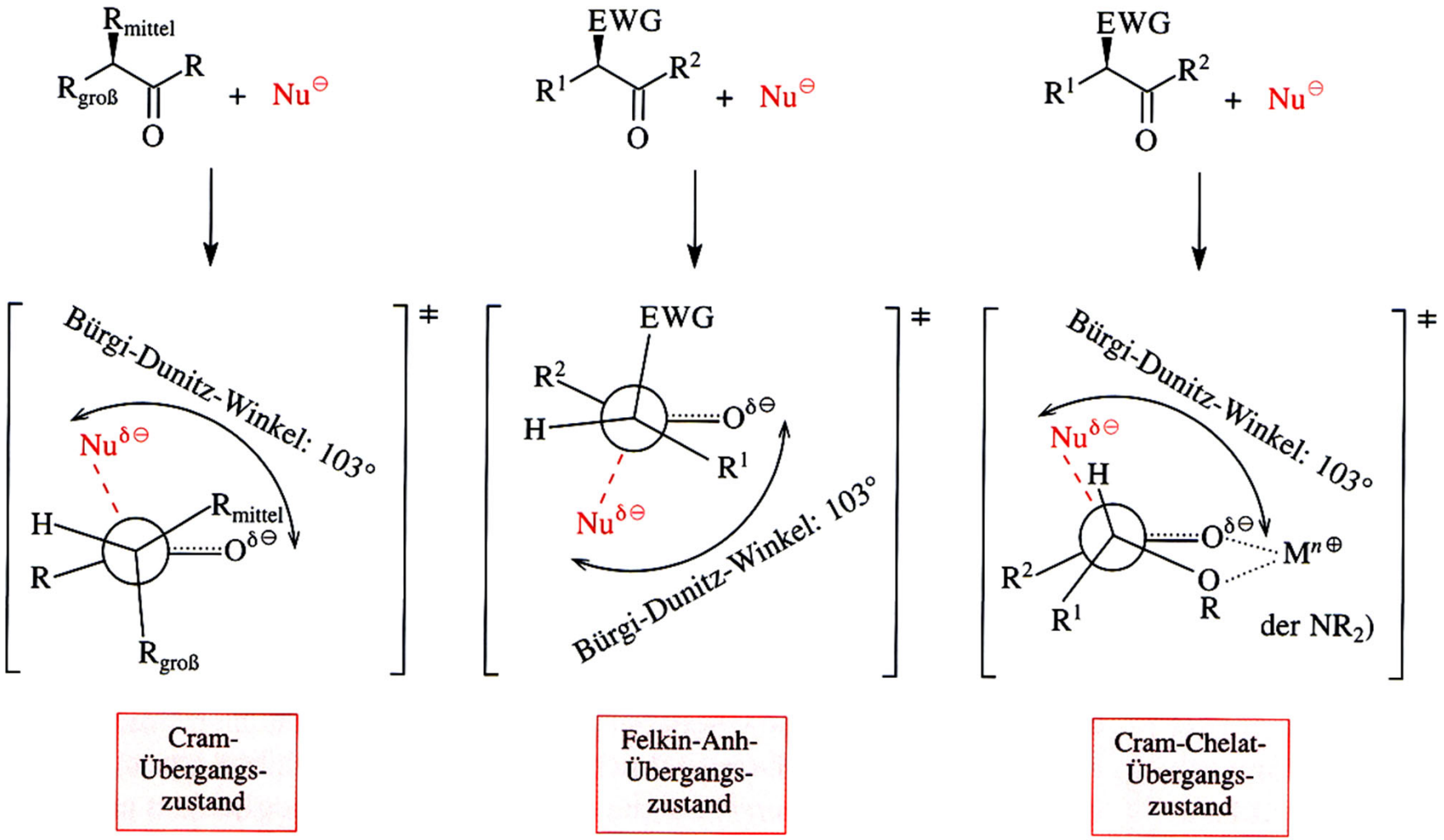
from: Brückner, Reaktionsmechanismen

Diastereoselective addition to α-chiral carbonyl compounds



from: Brückner, Reaktionsmechanismen

Diastereoselective addition to α-chiral carbonyl compounds

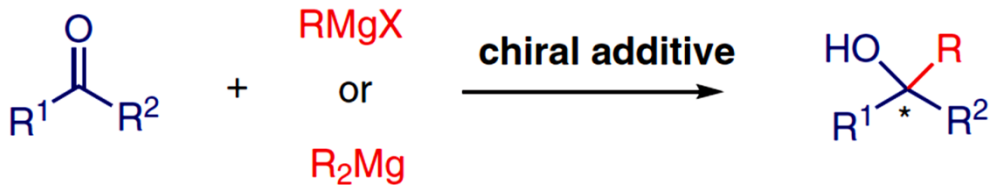


from: Brückner, Reaktionsmechanismen

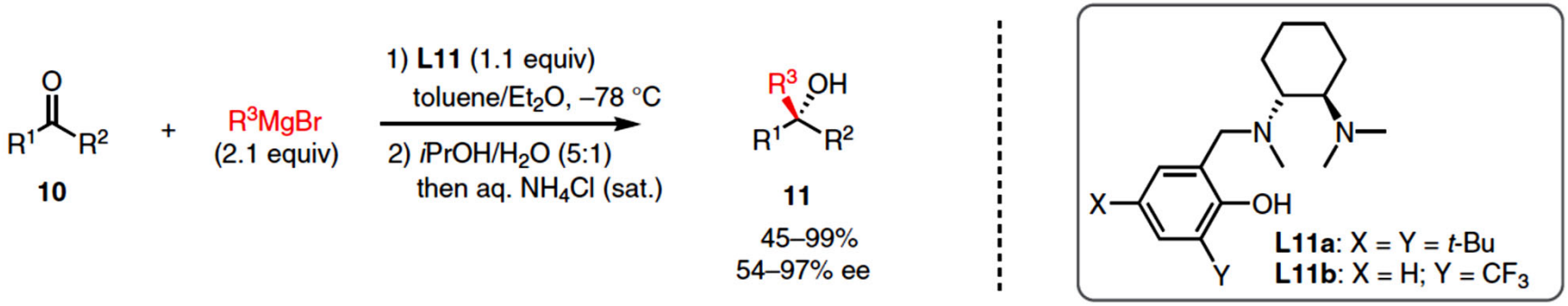
Enantioselective addition to carbonyl compounds

Transition metal-free (Review: Boussonnière, Castanet, *Synthesis* **2018**, 3589)

to C=O bonds:

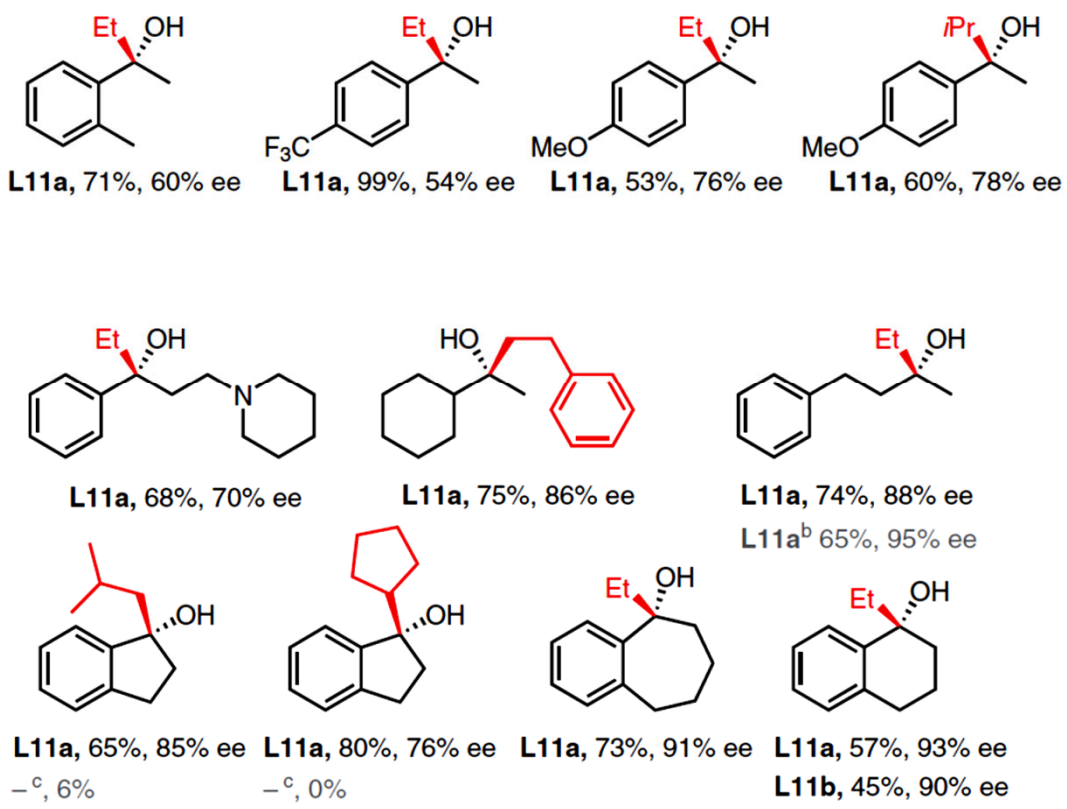


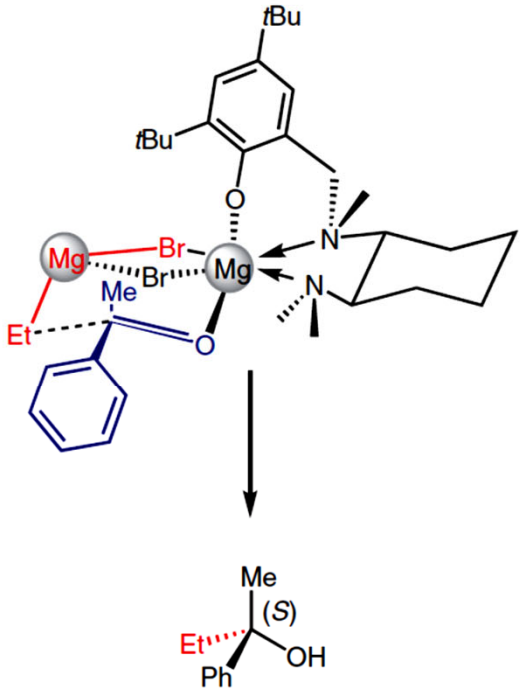
tridentate diamine/phenol ligand (Bieszczard, Gilheany, *ACIE* **2017**, 4272): for ketones



to C=O bonds: ligands before 2009 (from *Synthesis* **2018**, 3589)

For every new ligand, there will be a proposed mechanism
(here: tridentate diamine/phenol ligand):

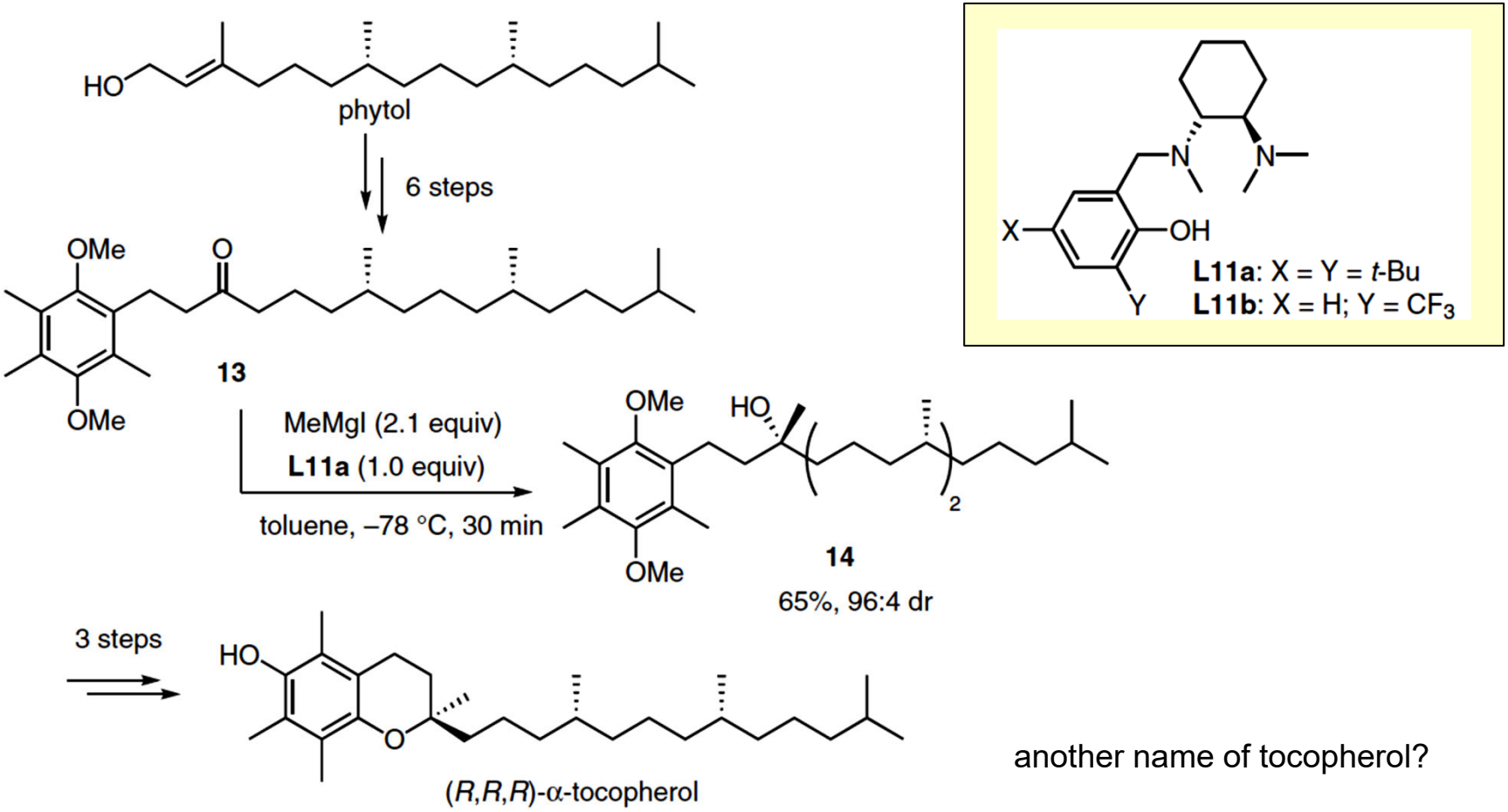




proposed transition state

to C=O bonds: ligands before 2009 (from *Synthesis* **2018**, 3589)

Application in natural product synthesis:

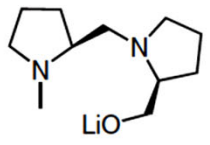


another name of tocopherol?

to C=O bonds: ligands before 2009 (from *Synthesis* **2018**, 3589)

TADDOL (where is it?): efficient for arylmethylketones

Lithium alkoxides

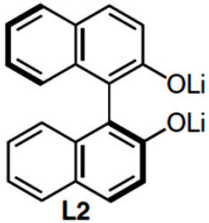


L1

Mukaiyama, 1979

56–94%, 22–92% ee

PhCHO; primary Alk_2Mg[a]



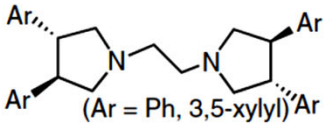
L2

Noyori, 1988

40–99%, 4–92% ee

AlkCHO, ArCHO; primary Alk_2Mg[a]

Tertiary diamines

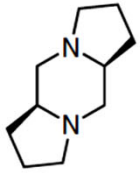


L3

Tomioka, 1987

68–96%, 36–75% ee

PhCHO; NaphthylMgBr[a]



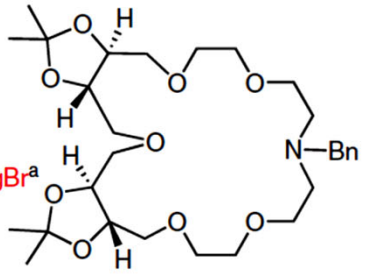
L4

Breitmaier, 1994

59–87%, 47–98% ee

ArCHO, PhCOMe; Alk_2Mg, AlkMgBr[a]

Crown ethers



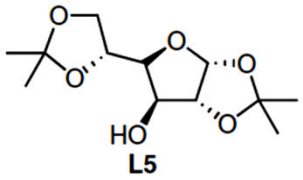
L8

Luk'yanenko, 2004

90–98%, 9–86% ee

PhCHO, PhCOMe; EtMgBr[a]

Alcohols

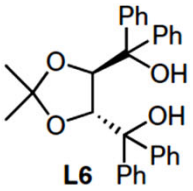


L5

Inch, 1969

45–95%, 10–70% ee

ArCOAlk; CH_3MgX[a]



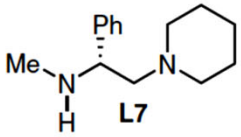
L6

Seebach, 1992

7–99%, 24–92% ee

ArCOMe; primary AlkMgBr[a]

Secondary amines



L7

Chong, 2002

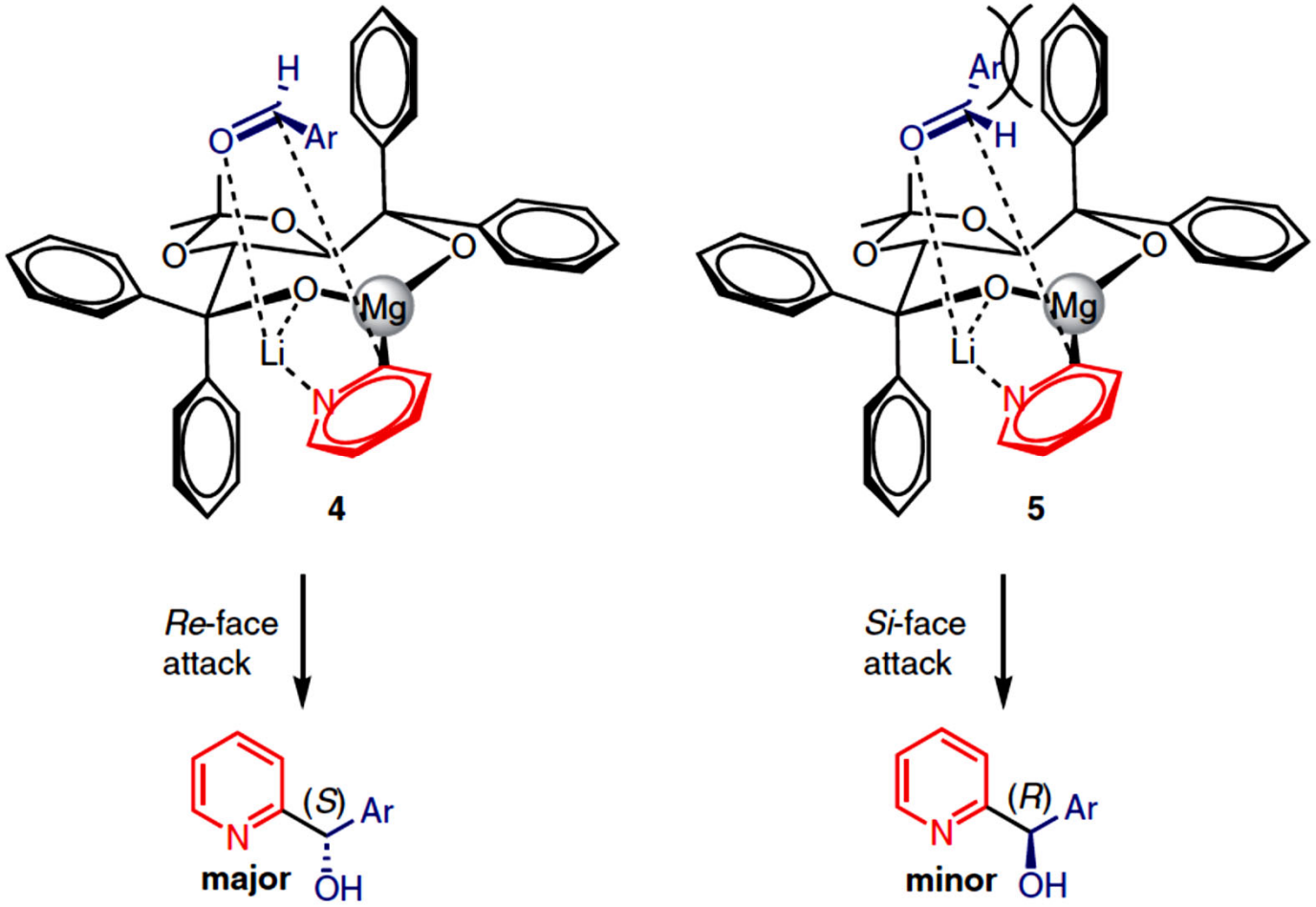
34–77%, 44–82% ee

ArCHO; primary Alk_2Mg[a]

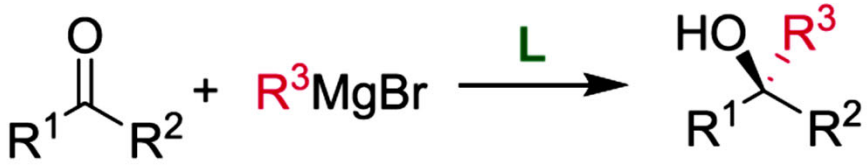
[a] substrates and reagents affording yield > 50% and ee ≥ 70%

to C=O bonds: ligands before 2009 (from *Synthesis* **2018**, 3589)

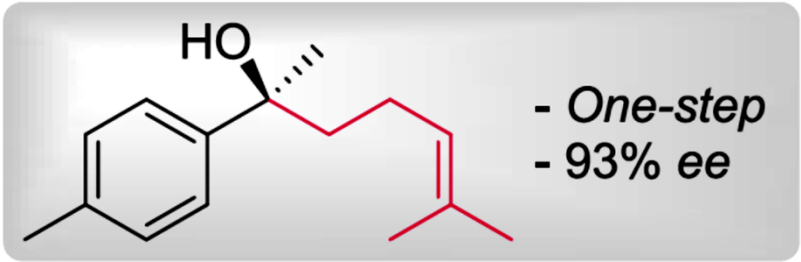
For every new ligand, there will be a proposed mechanism (here: TADDOL):

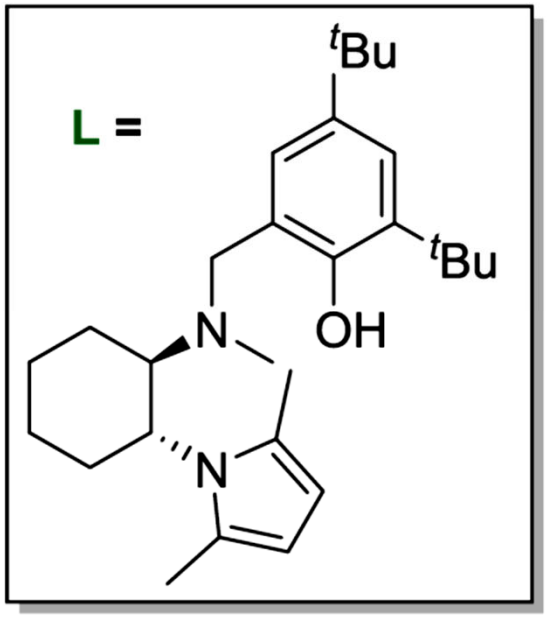


Asymmetric Grignard reaction affording tertiary alcohols



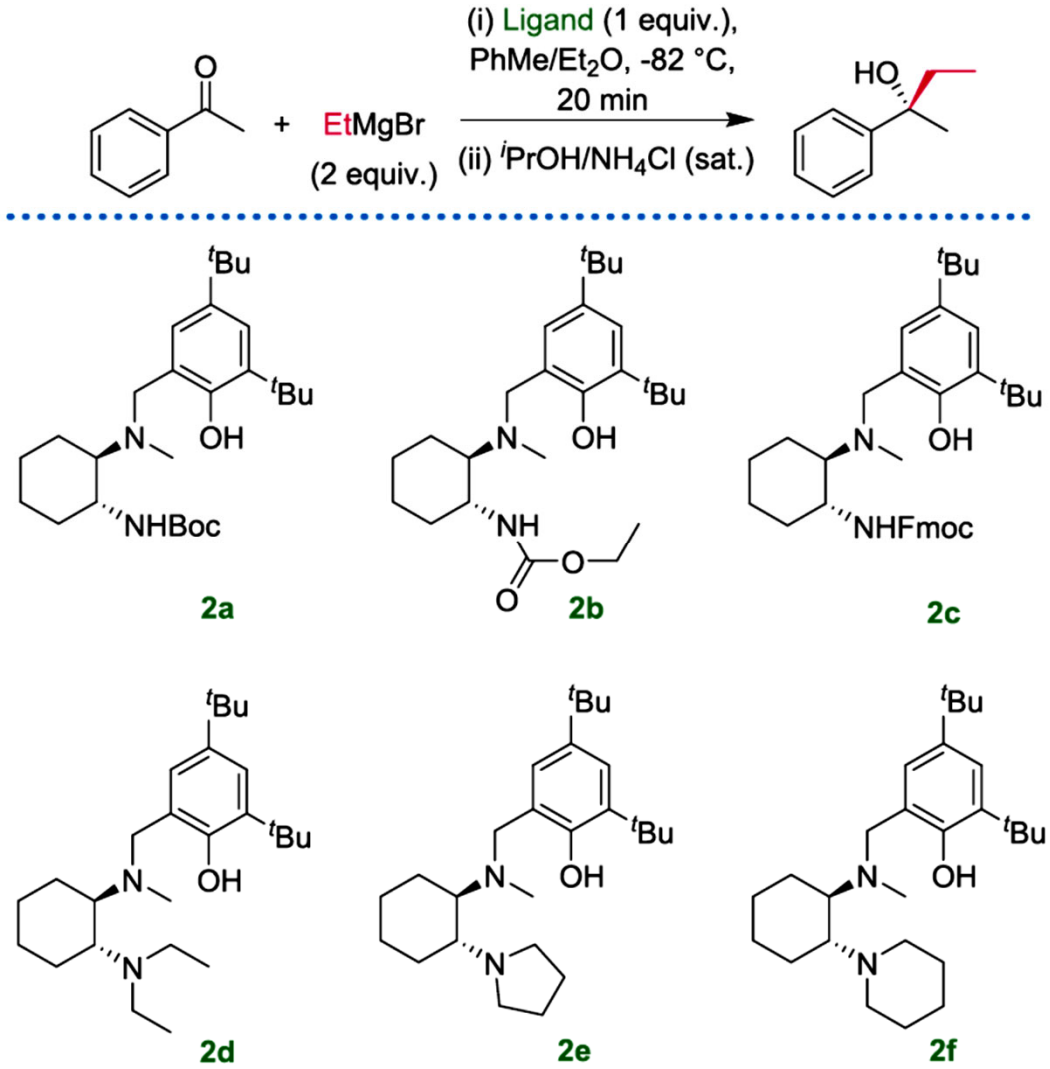
- ✔ Highly enantioselective additions to acetophenones
- ✔ Heteroaryl substrate tolerance
- ✔ Shortest possible highly selective synthesis of (*S*)-gossonorol





Kavanagh, Gilheany, https://dx.doi.org/10.1021/acs.orglett.0c02629, *Org. Lett.* **2020**, *22*, 8198−8203

Asymmetric Grignard reaction affording tertiary alcohols



Ligand Screening!

Kavanagh, Gilheany, https://dx.doi.org/10.1021/acs.orglett.0c02629, *Org. Lett.* **2020**, *22*, 8198−8203

Asymmetric Grignard reaction affording tertiary alcohols

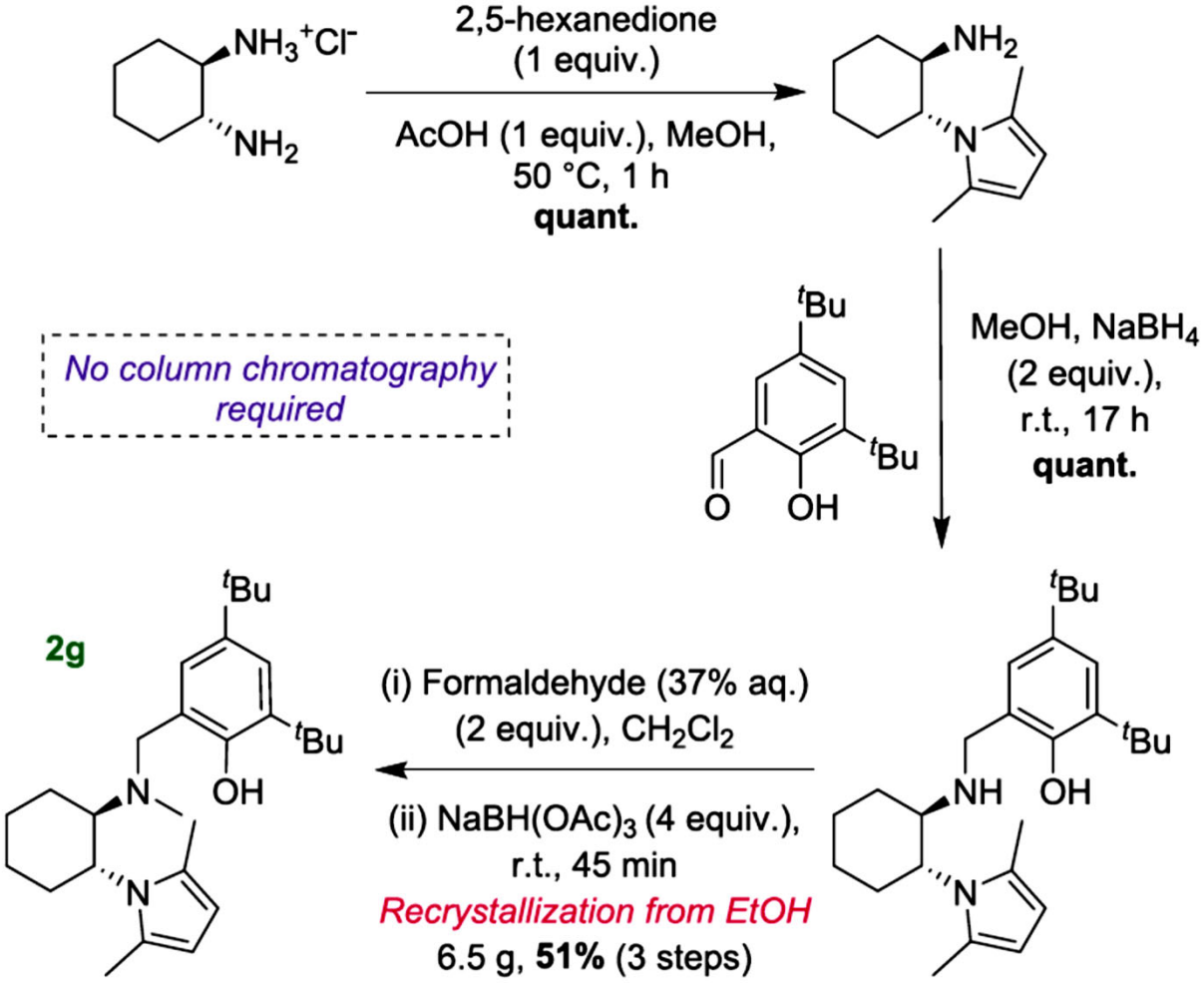
Entry	Ligand	% ee (config.)[b]	Conversion (%)[c]
1	**1**	76 (*S*)	62
2	**2a**	−70 (*R*)	34
3	**2b**	−49 (*R*)	30
4	**2c**	−39 (*R*)	44
5	**2d**	81 (*S*)	59
6	**2e**	75 (*S*)	60
7	**2f**	53 (*S*)	70
8	**2g**	93 (*S*)	80
9	**2h**	44 (*S*)	56
10	**2i**	25 (*S*)	40

[a]Solvent: toluene/ether (20:1); 0.1 mmol in ketone; overall concentration: 0.06 M; quench added at −82 °C: see Supporting Information (SI) for full procedure. [b]Measured using chiral stationary phase HPLC (see SI). [c]Calculated from HPLC data using the relative response factor of acetophenone to 2-phenyl-2-butanol; no other products visible in crude NMRs or HPLCs.

Ligand Screening!

Kavanagh, Gilheany, https://dx.doi.org/10.1021/acs.orglett.0c02629, *Org. Lett.* **2020**, *22*, 8198−8203

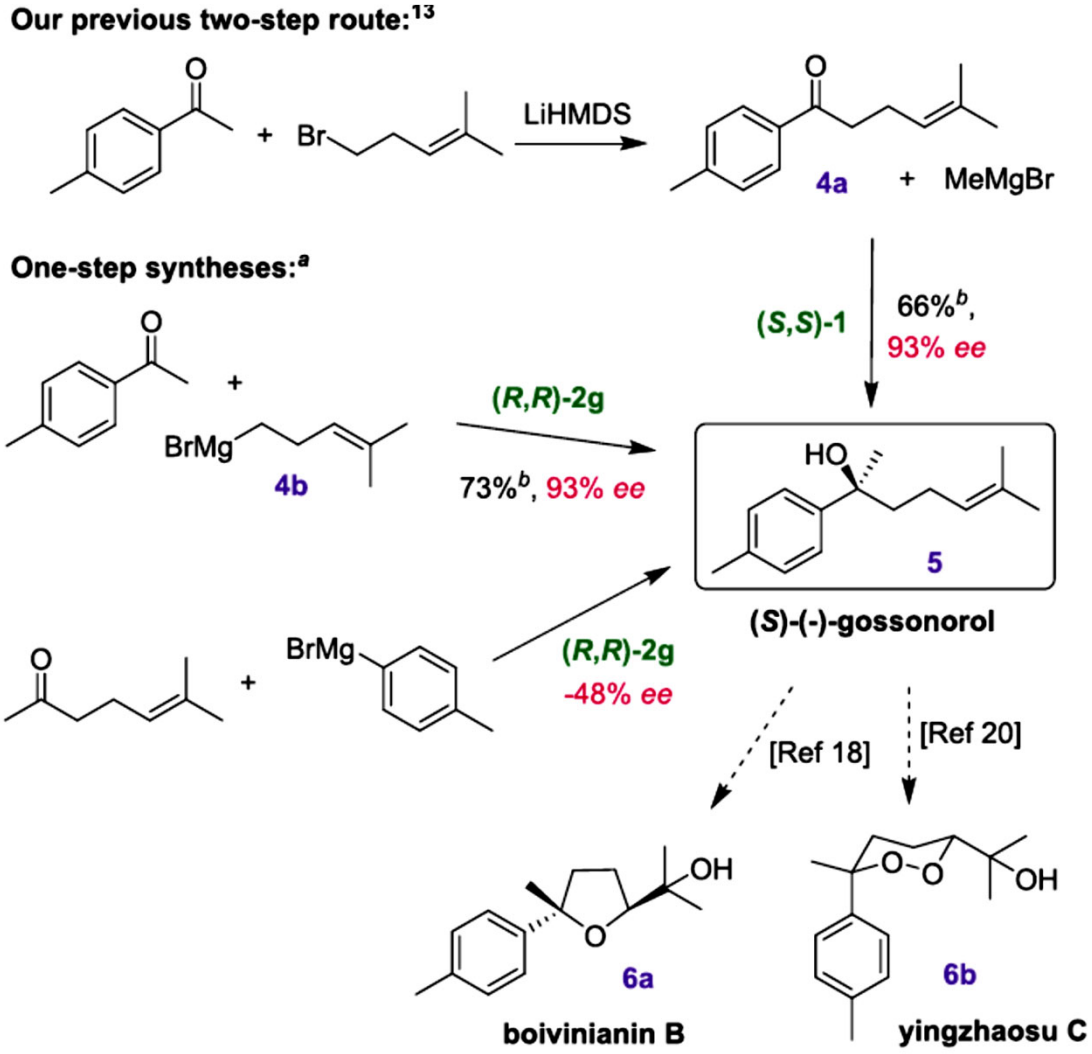
Asymmetric Grignard reaction affording tertiary alcohols



Ligand Synthesis!

Kavanagh, Gilheany, https://dx.doi.org/10.1021/acs.orglett.0c02629, *Org. Lett.* **2020**, *22*, 8198−8203

Asymmetric Grignard reaction affording tertiary alcohols

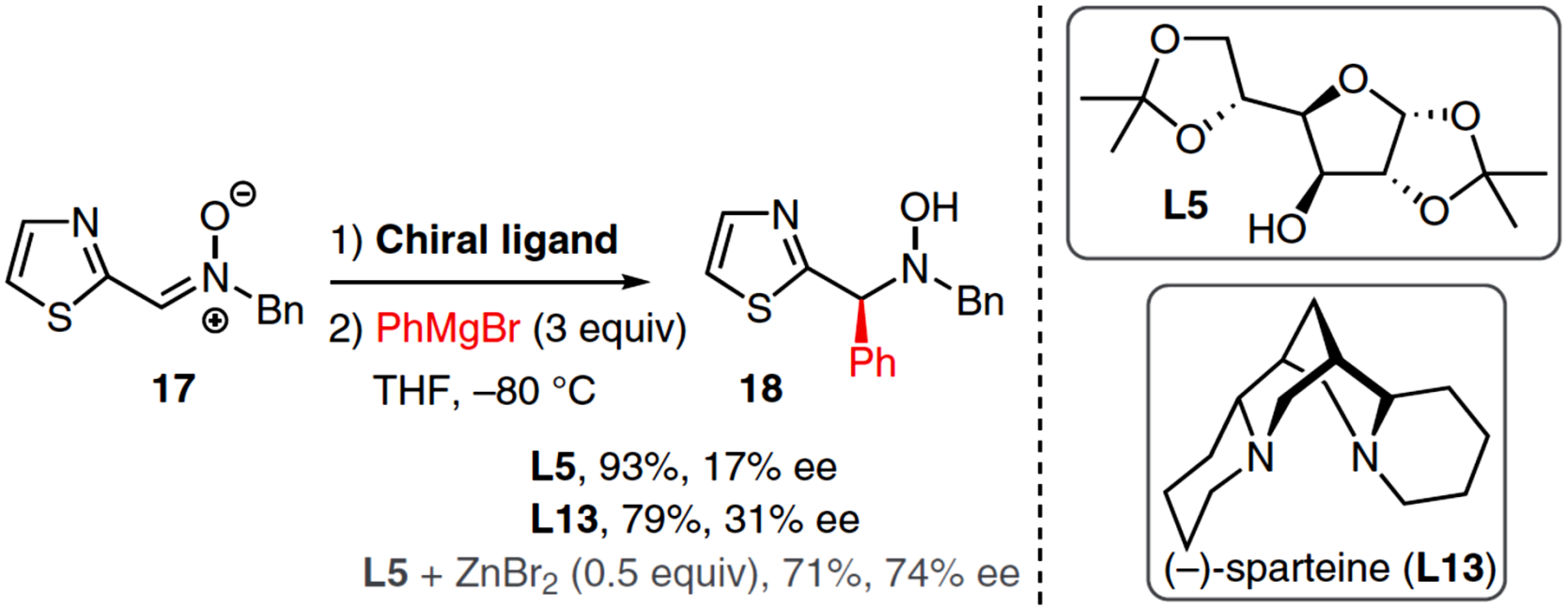


Natural product synthesis!

Org. Lett. **2020**, *22*, 8198−8203

Addition to C=N bonds: imines less reactive

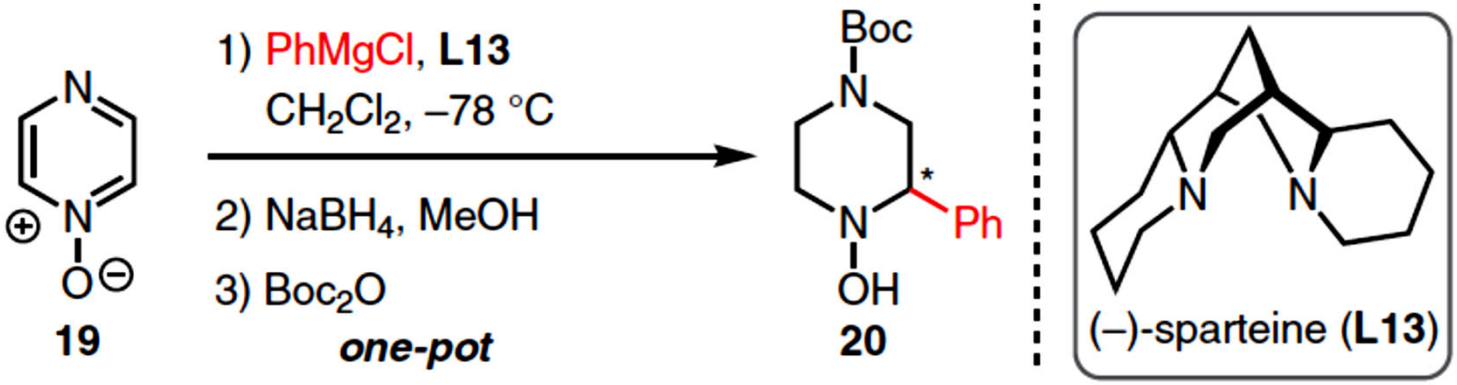
Nitrones react much faster:



from *Synthesis* **2018**, 3589

Addition to C=N bonds: imines less reactive

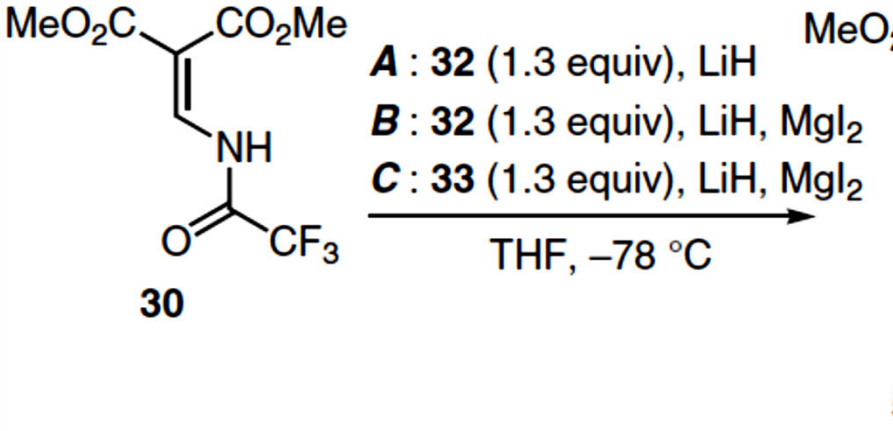
So did the pyrazine N-oxide (in low yield):

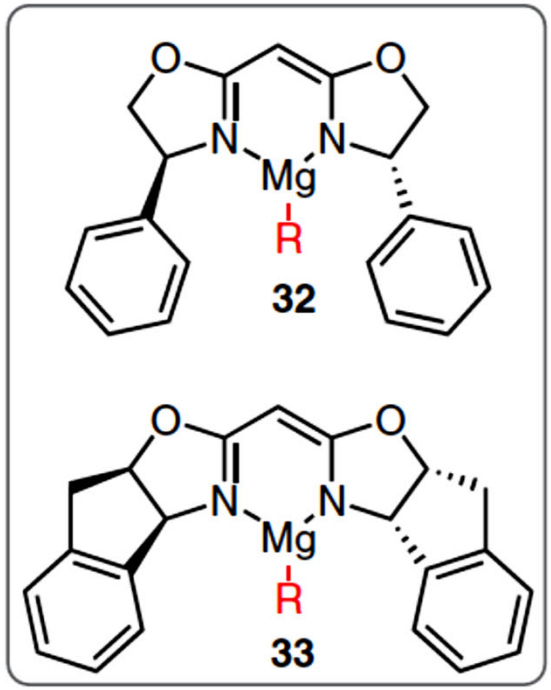


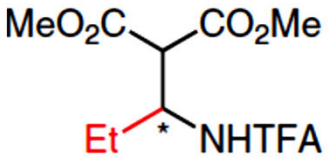
- 2.5 equiv PhMgCl, no (–)-sparteine — 91%
- 1.2 equiv PhMgCl/(–)-sparteine — 21%, 82% ee
- 3.0 equiv PhMgCl/(–)-sparteine — 26%, 62% ee
- 4.0 equiv PhMgCl/(–)-sparteine — 18%, 41% ee

from *Synthesis* **2018**, 3589

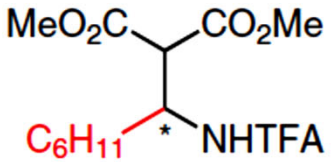
Addition to C=C bonds: uncatalyzed only for strained or α,β-unsaturated systems



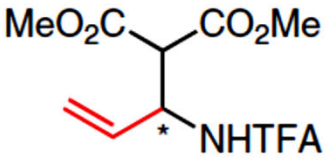




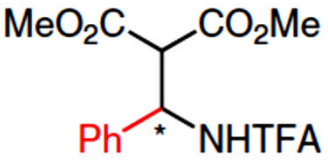
A : 86%, 83% ee
B : 79%, 78% ee
C : 65%, –78% ee



A : 82%, 94% ee
B : 69%, 93% ee
C : 64%, –74% ee



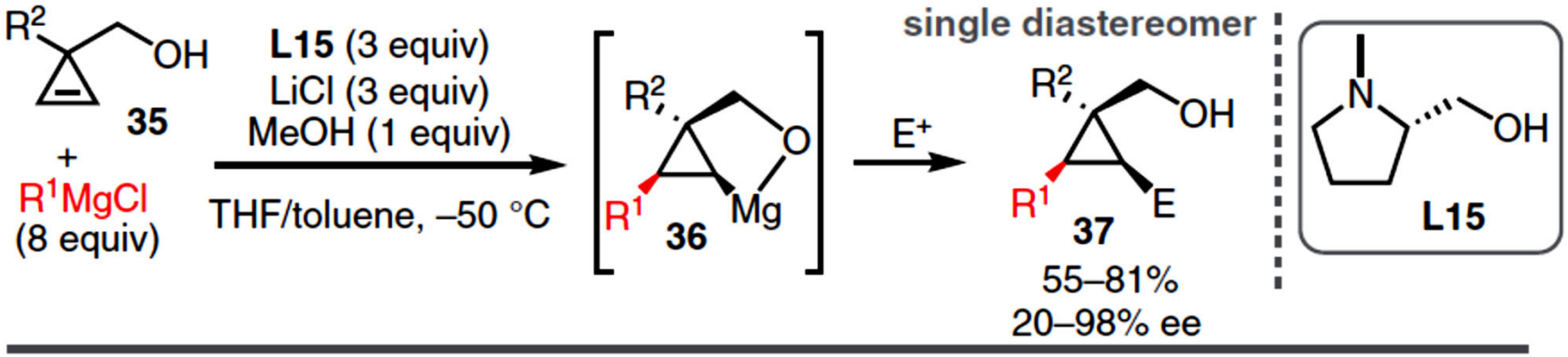
A : 80%, 82% ee
B : 65%, 86% ee
C : 58%, –59% ee



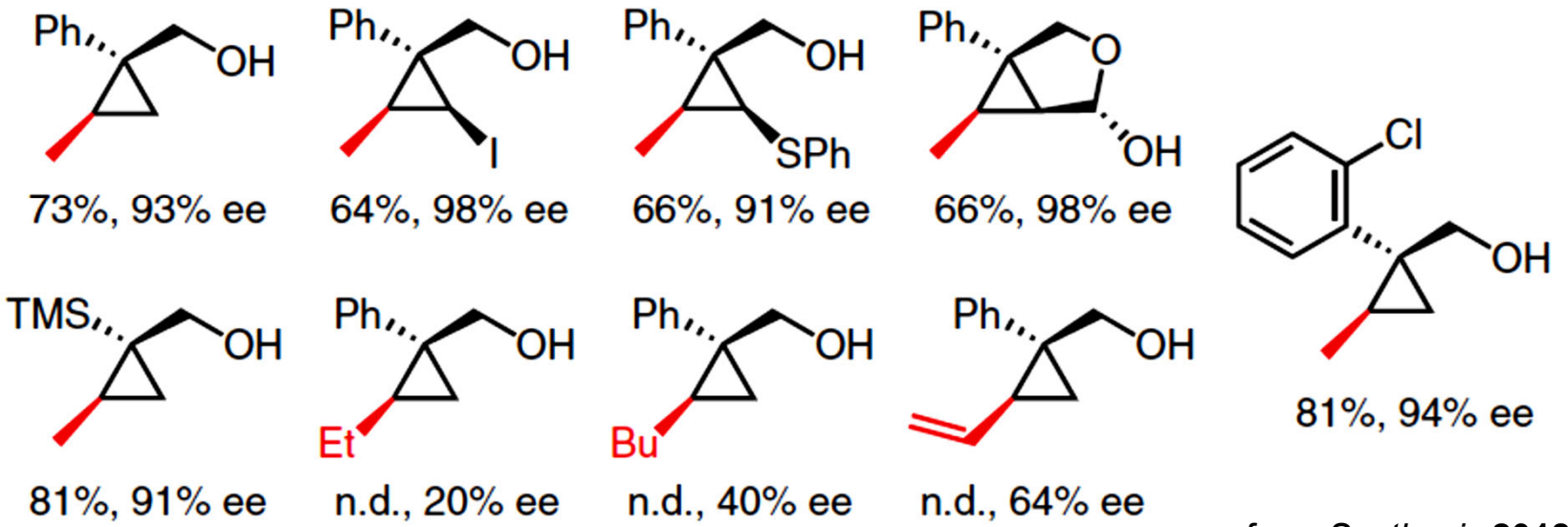
A : 88%, 71% ee
B : 70%, 81% ee
C : 65%, –56% ee

from *Synthesis* **2018**, 3589

Addition to C=C bonds: uncatalyzed only for strained or α,β-unsaturated systems



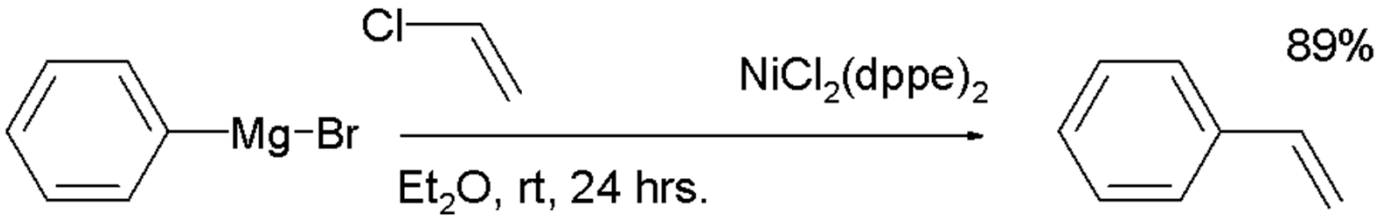
Representative examples



from *Synthesis* **2018**, 3589

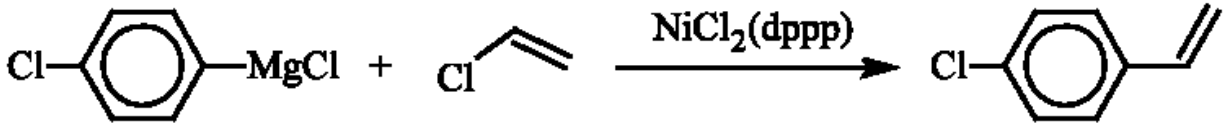
Catalysis by transition metals is often necessary!

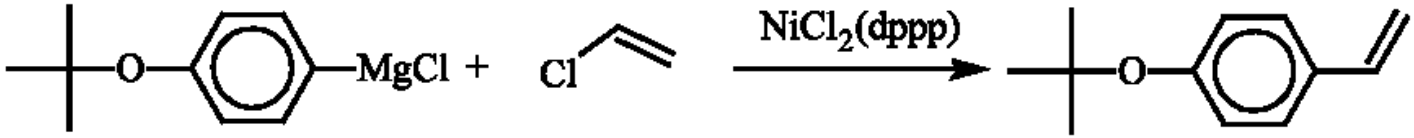
Corriu-Kumada cross coupling (1972): Ni-catalyzed coupling of RMgX to organohalides



dppe: 1,2-bis(diphenylphosphino)ethane
$NiCl_2(dppe)_2$: orange, diamagnetic, square planar

industrialized:



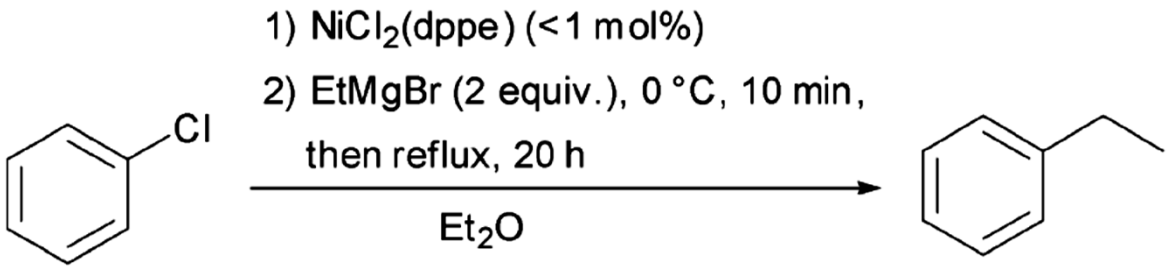


Microreview: Shinokubo et al., *Eur. J. Org. Chem.* **2004**, 2081

Catalysis by transition metals is often necessary!

Corriu-Kumada cross coupling (1972): Ni-catalyzed coupling of RMgX to organohalides

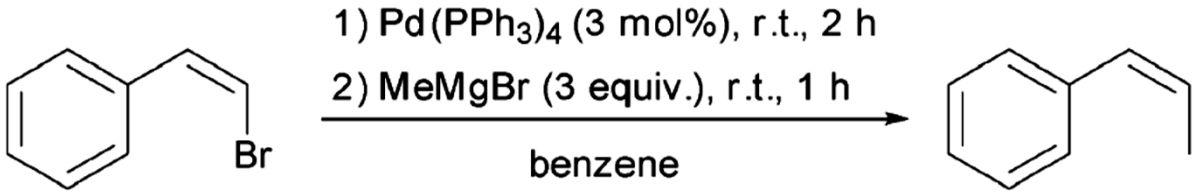
a) Example of Ni-catalyzed coupling by Kumada and Tamao:



98 %

Ni

b) Example of Pd-catalyzed coupling by Murahashi et al.:

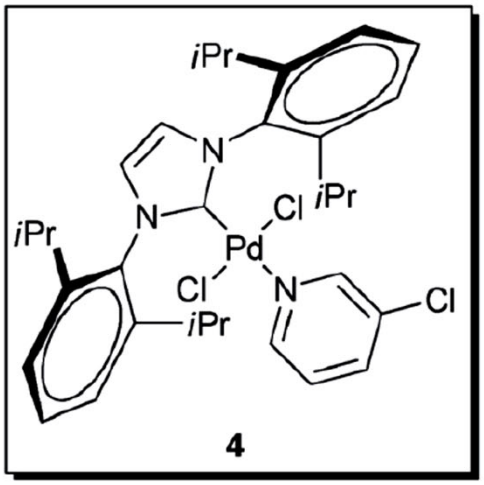


99 %

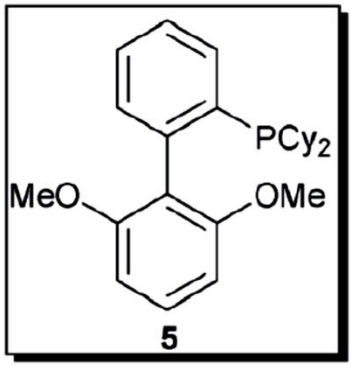
Pd

from: Jacobi von Wangelin, *Chem. Soc. Rev.* **2011**, 4948

Pd-catalyzed Grignard reactions



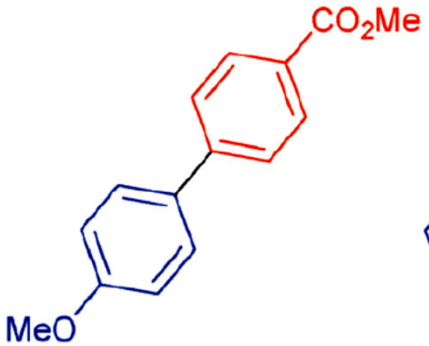
4



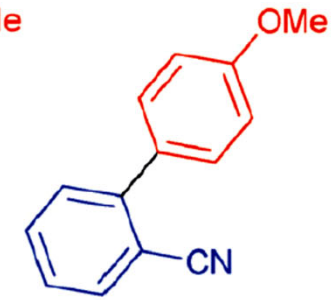
5

4 (2-3 mol%) or
$Pd(OAc)_2$ (2-4 mol%), **5** (3-6 mol%)
*i*PrI (1.1 equiv.)
THF, 25 °C, 5 min

Ar—Br + Ar'MgCl → Ar—Ar'



78 %

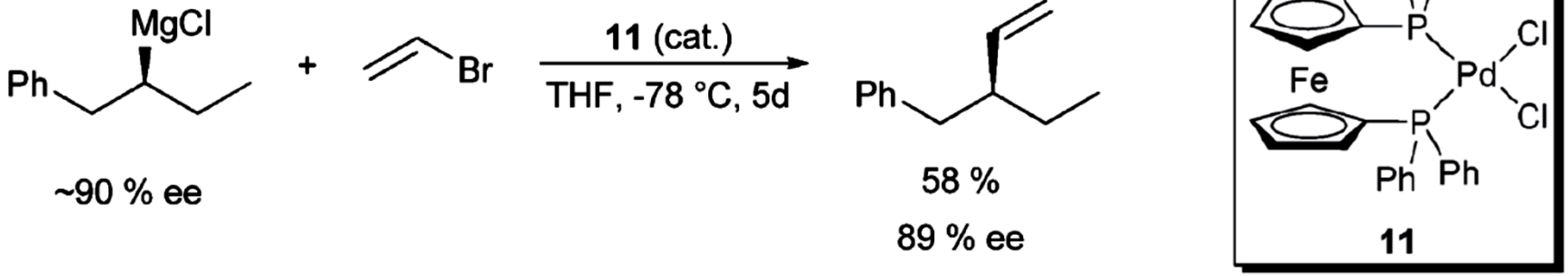


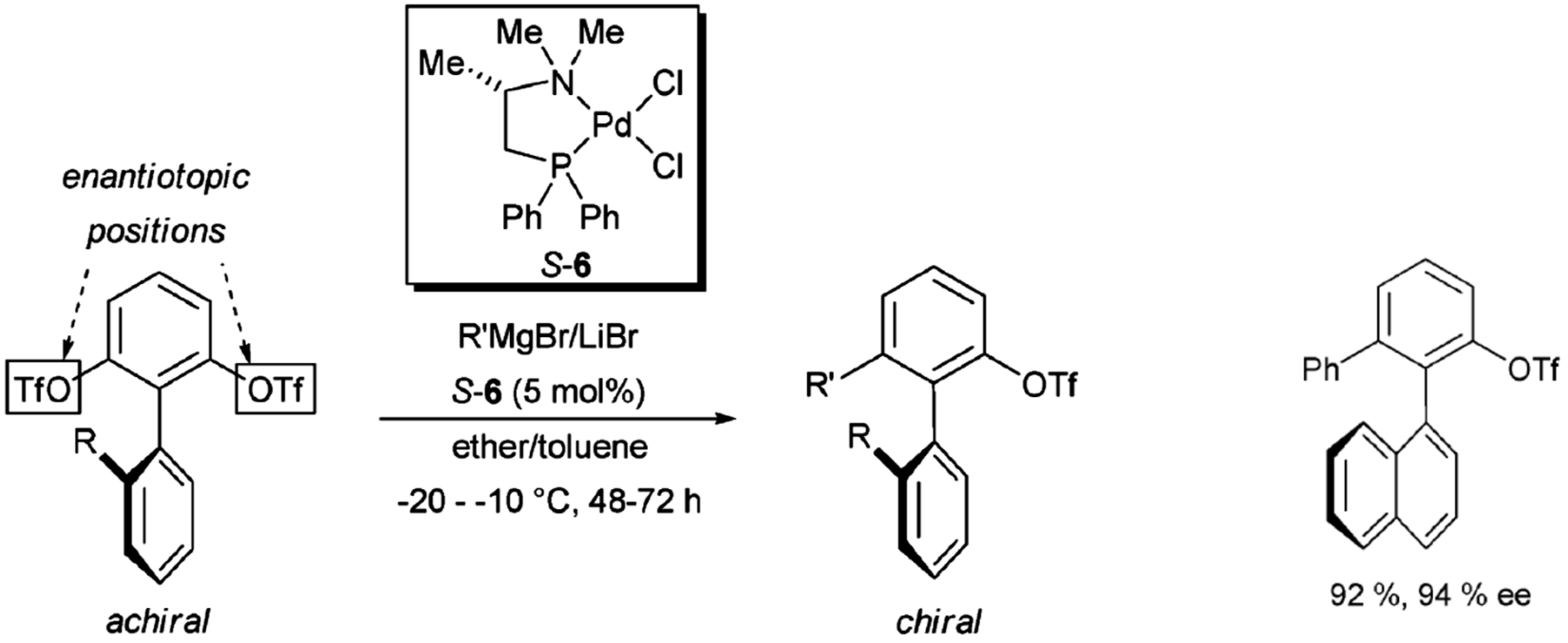
98 %

92 %

from: Jacobi von Wangelin, *Chem. Soc. Rev.* **2011**, 4948

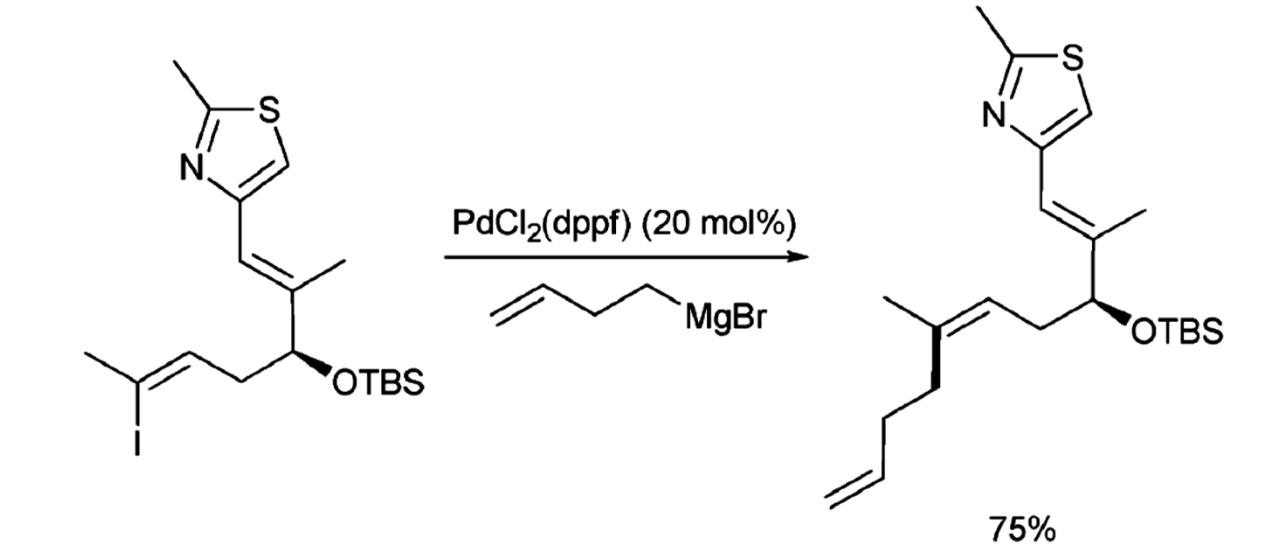
Pd-catalyzed Grignard reactions

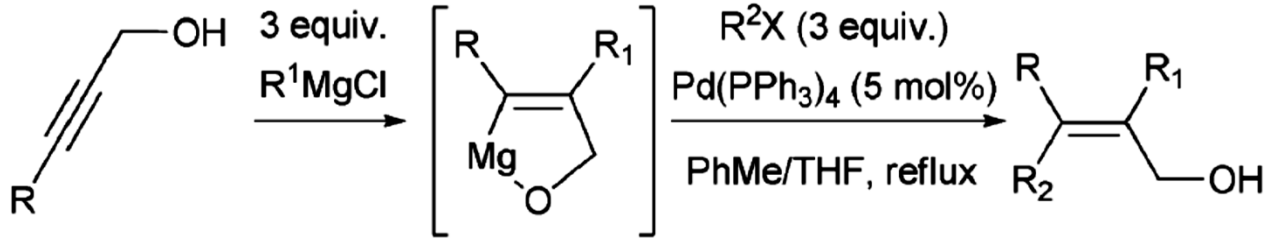




from: Jacobi von Wangelin, *Chem. Soc. Rev.* **2011**, 4948

Pd-catalyzed Grignard reactions

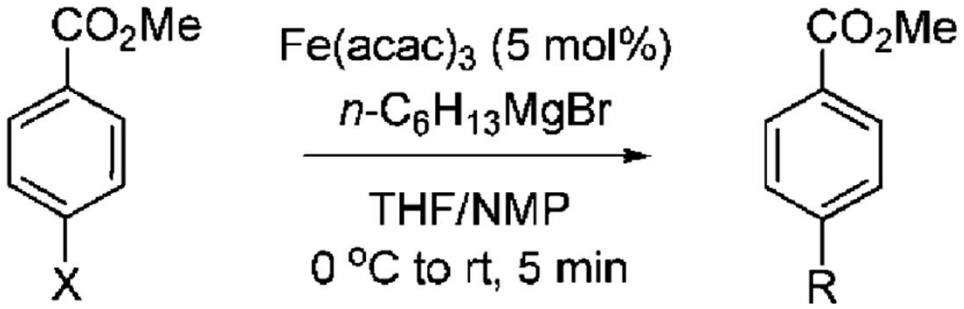




R^1, R^2 = aryl, vinyl, allyl

X = Br, I

from: Jacobi von Wangelin, *Chem. Soc. Rev.* **2011**, 4948



entry	X	yield, % (R = *n*-C_6H_{13})	yield, % (R = H)
1	I	27	46
2	Br	38	50
3	Cl	>95	
4	OTf	>95	
5	OTs	>95	

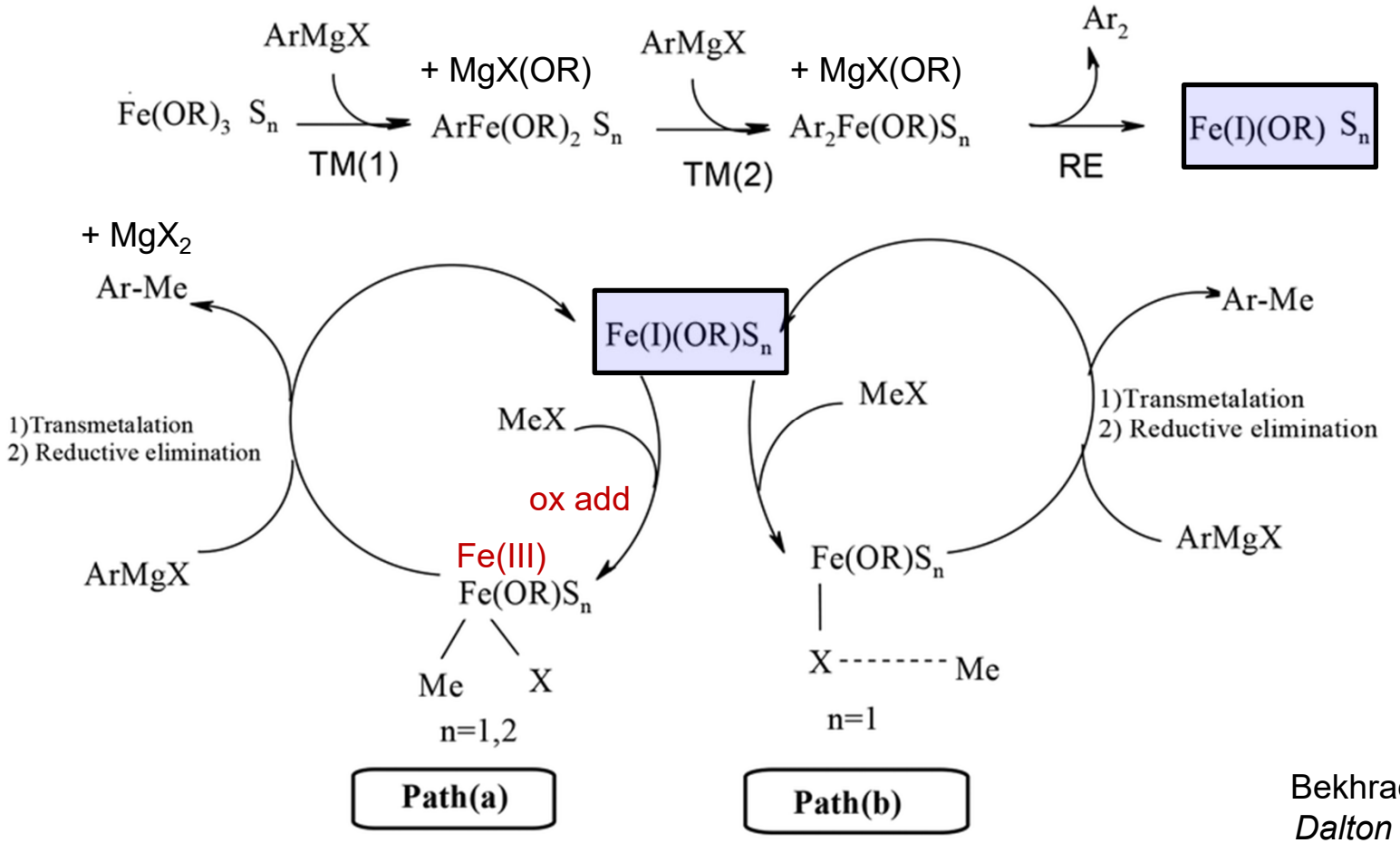
Reverted reactivity order of halides!

use of THF-NMP allows 1:1 ratio of reactants (otherwise excess Grignard reagent would be necessary; NMP: *N*-methylpyrrolidone)

Fürstner, *Acc. Chem. Res.* **2008**

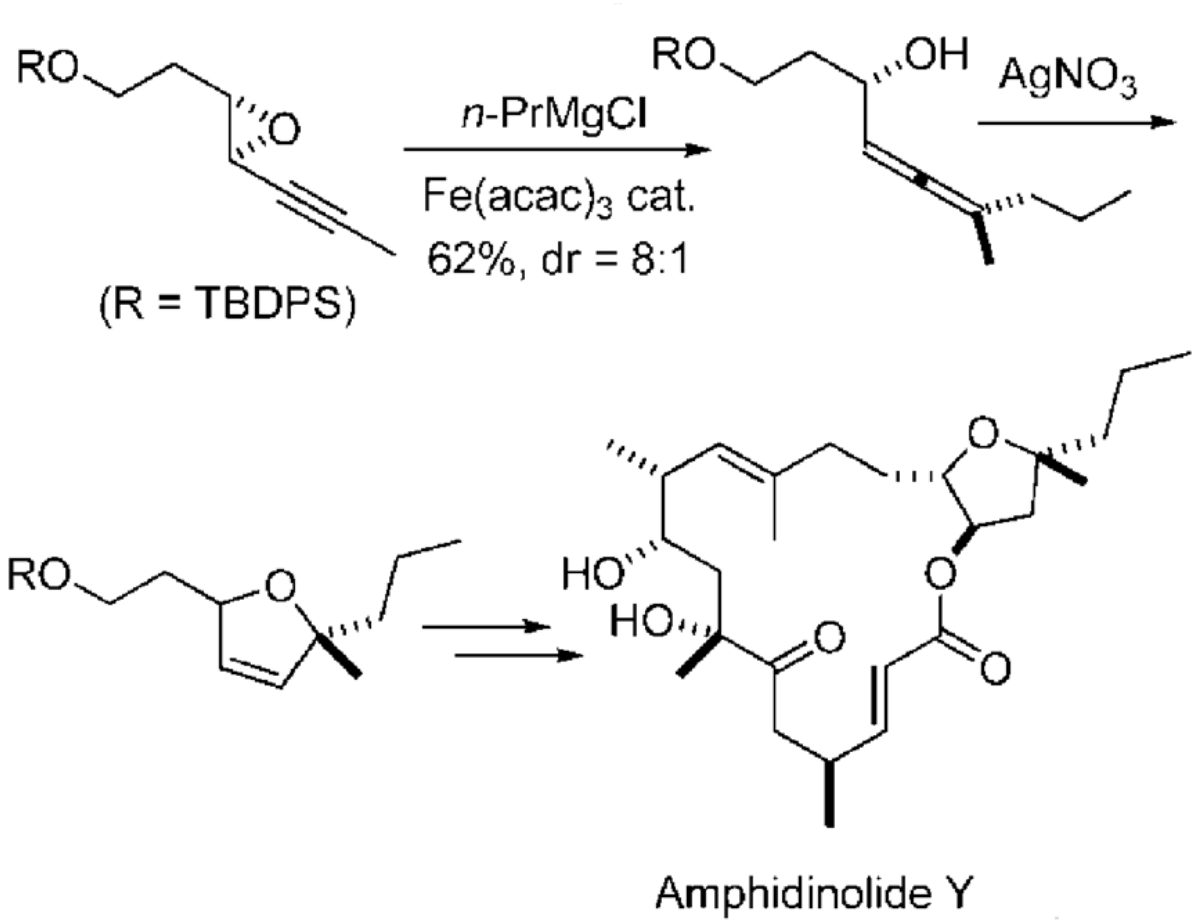
Possible mechanisms of the Fe-catalyzed Grignard reaction

Initially, formation of an Fe(I) complex occurs.



Bekhradnia, Norrby, *Dalton Trans.* **2015**.

Carbometalation

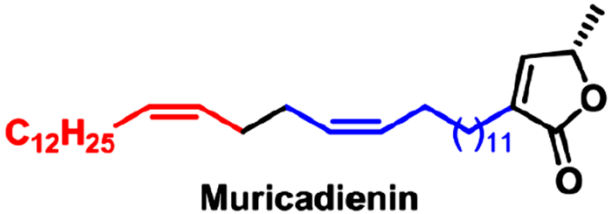


Fürstner, *Acc. Chem. Res.* **2008**

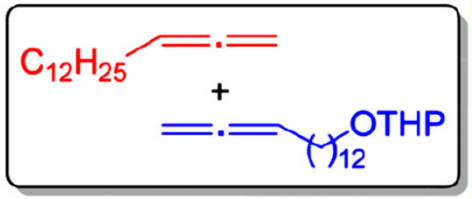
Catalytic cross-cyclomagnesiation of allenes

Roots of *Annona Muricata*

Not isolated in a pure state
(40 mg/kg of mixture)
Phytochemistry **1998**, *47*, 749



Muricadienin



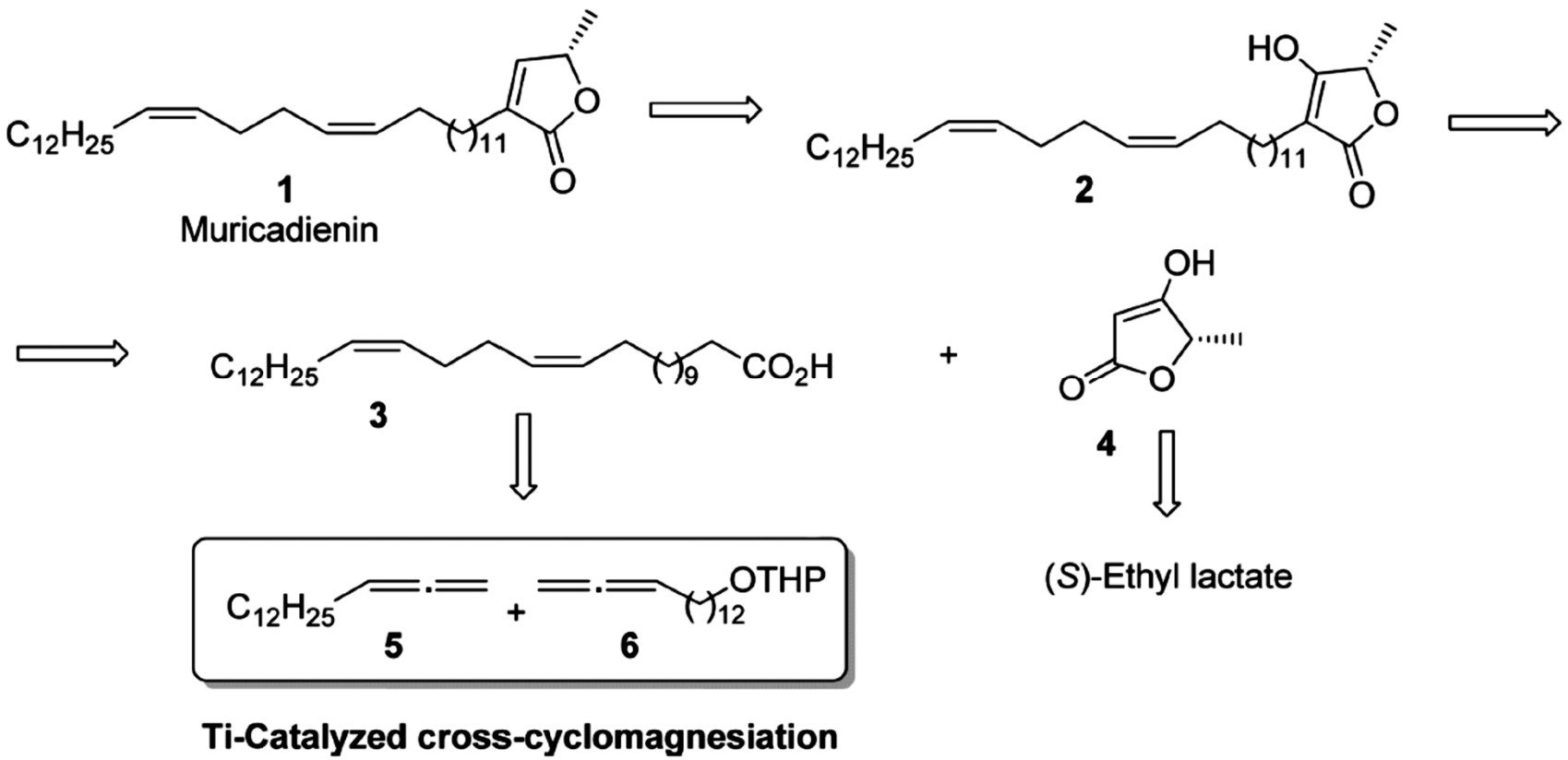
Ti-Catalyzed cross-cyclomagnesiation

1. Gram-scale five-step synthesis
2. Anti-cancer activity studies
3. Human topoisomerases I and II inhibitory activity

D'yakonov et al., DOI: 10.1021/acs.jnatprod.6b00335, *J. Nat. Prod.* **2016**, *79*, 2039−2044

Catalytic cross-cyclomagnesiation of allenes

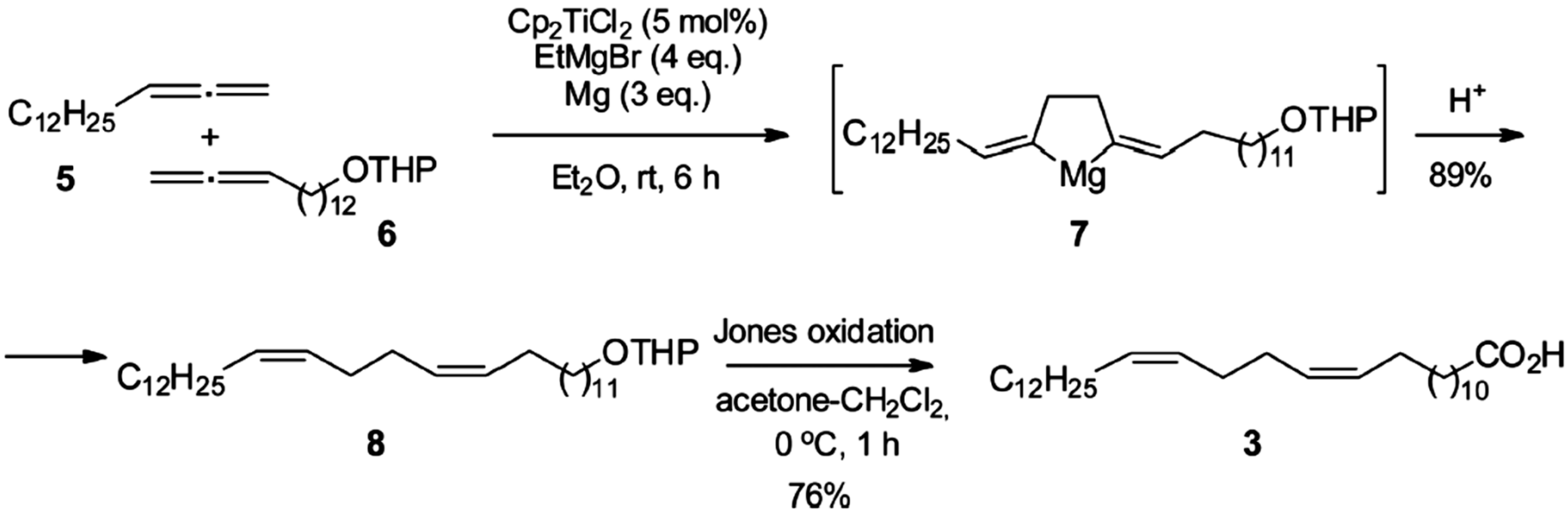
Retrosynthesis



D'yakonov et al., DOI: 10.1021/acs.jnatprod.6b00335, *J. Nat. Prod.* **2016**, *79*, 2039−2044

Catalytic cross-cyclomagnesiation of allenes

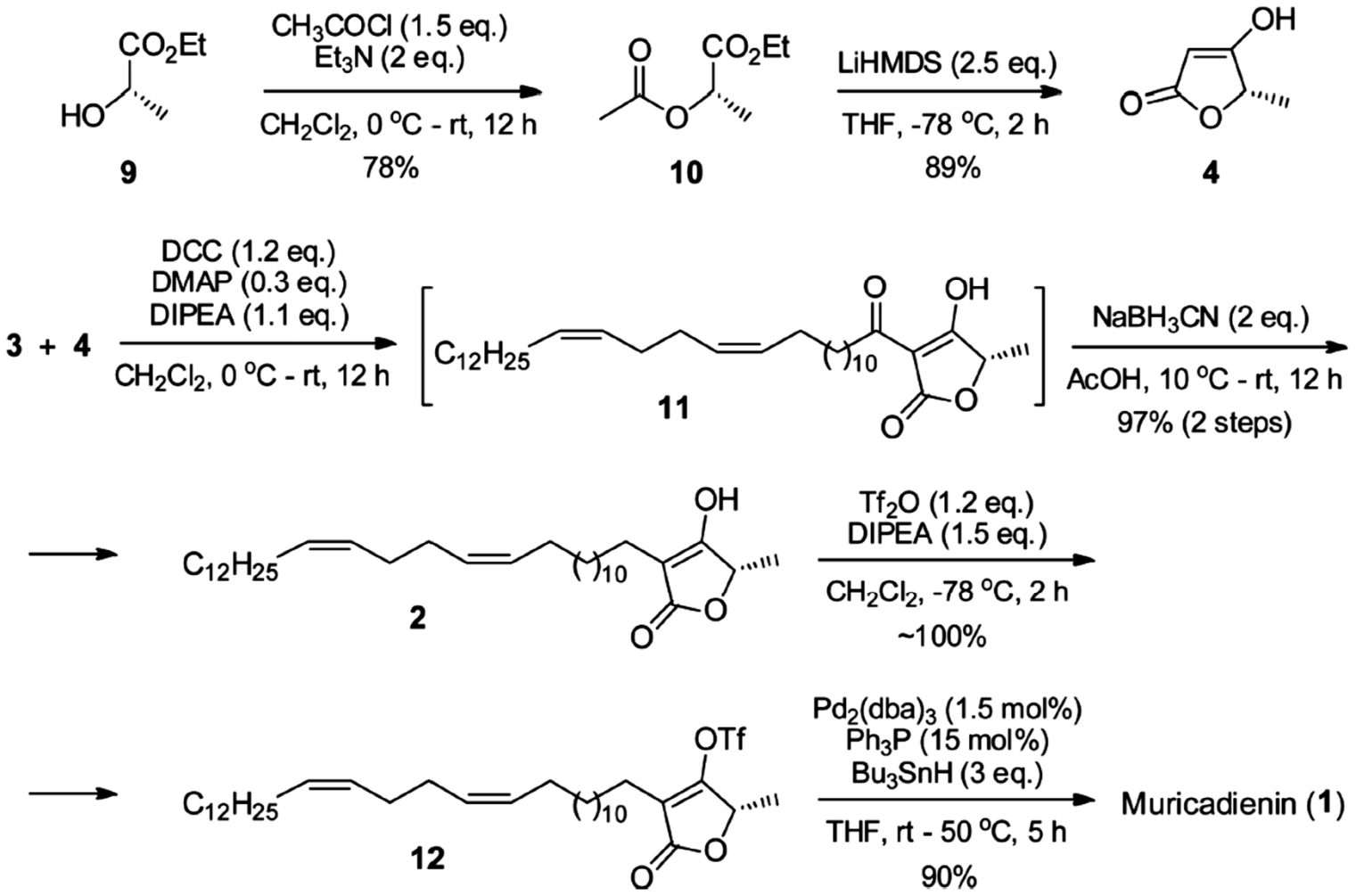
Key step



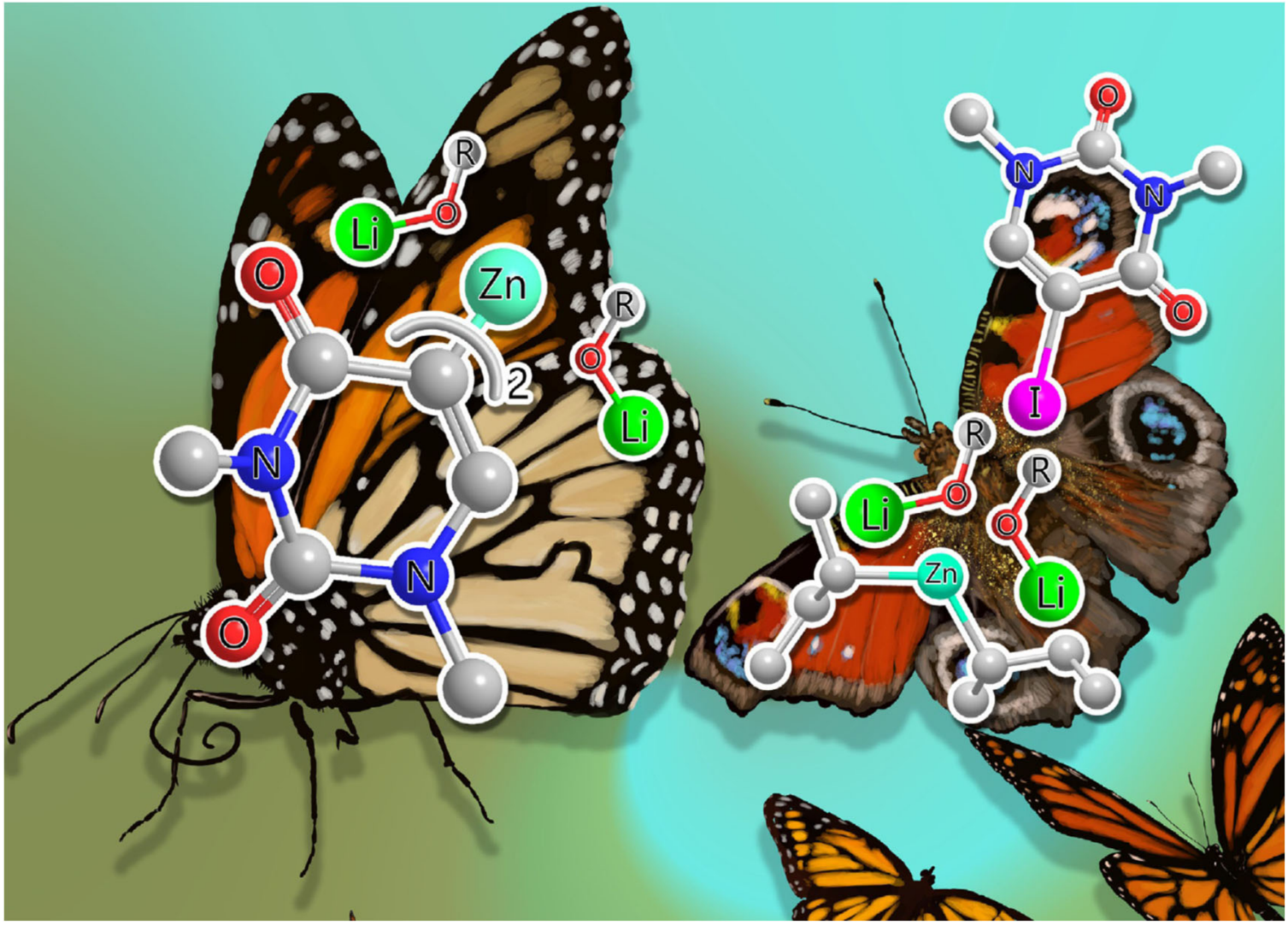
D'yakonov et al., DOI: 10.1021/acs.jnatprod.6b00335, *J. Nat. Prod.* **2016**, *79*, 2039−2044

Catalytic cross-cyclomagnesiation of allenes

Total synthesis

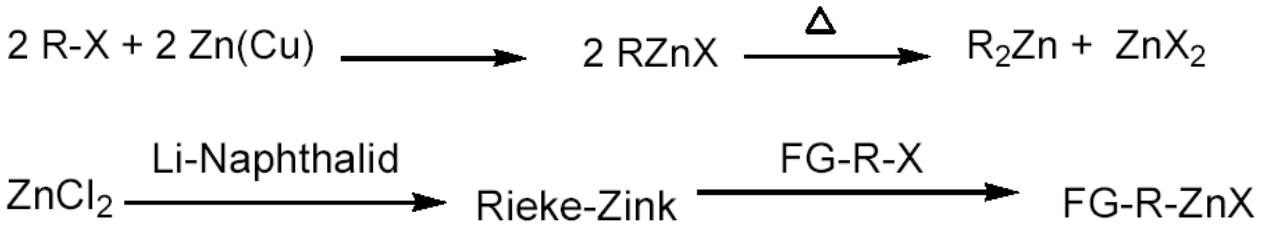


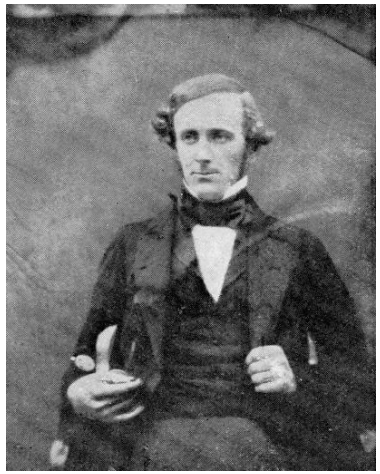
D'yakonov et al., DOI: 10.1021/acs.jnatprod.6b00335, *J. Nat. Prod.* **2016**, *79*, 2039−2044



Knochel, *Chem. Eur. J.* **2020**, 3688

Diethyl zinc (mp -28°C, bp 118 °C) by Frankland in 1849:
$2\ EtI + Zn \rightarrow Et_2Zn + I_2$





Edward Frankland (1825-99)

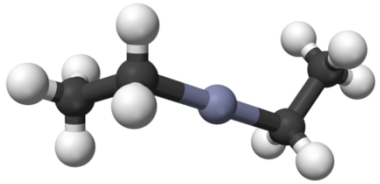
Zn dust normally not reactive enough, even for sp^3-C-Zn compounds
=> Zinc-copper pair (ca. 90% zinc) or Rieke-Zn: from $ZnCl_2$/K

Zn-C bond distances increase with the number of β-carbons in the order (from 193 to 198 pm):

$Me_2Zn \approx (Me_3SiCH_2)_2Zn < Et_2Zn \approx$ *n*-$Pr_2Zn \approx$ (neopentyl)$_2$Zn < *i*-$Pr_2Zn <$ *t*-Bu_2Zn

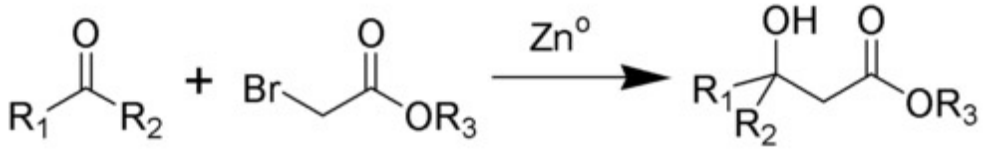
Calculated mean bond dissociation enthalpies decrease in the same order (from 186 to 116 kJ/mol).

Linear coordination of Zn:



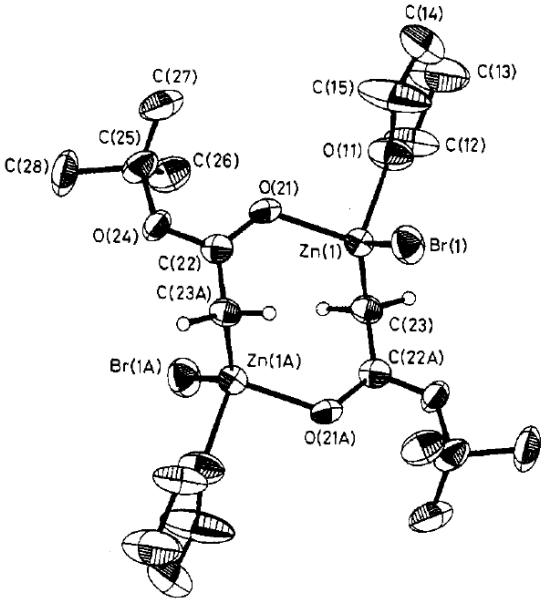
some physical data: Haaland et al., *Dalton Trans.* **2003**, 4356

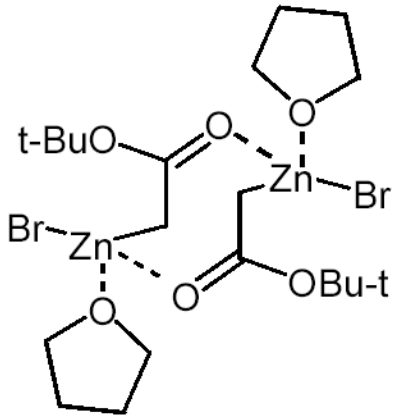
Reformatzky reaction (1887):

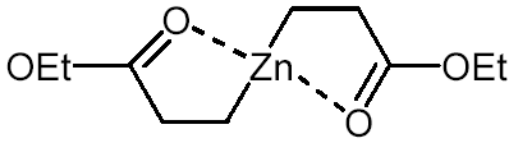


No competing Claisen condensation, because esters inert at rt.
Organozinc compounds are less reactive than organomagnesium compounds.

Alkylzinc bromide dimeric in solution, tetraedric coordination of Zn, filled up by, *e. g.*, THF.



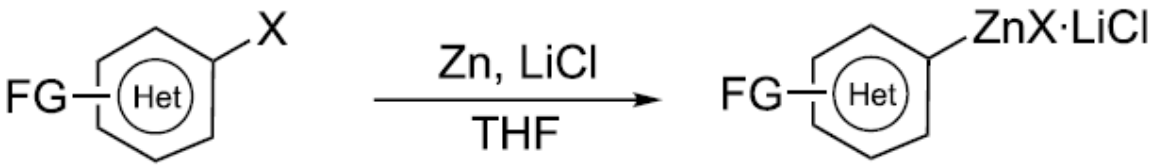




Organometallics **1984**, 3,1403

Synthesis of sp^2-C-Zn cpds needs improved strategies:

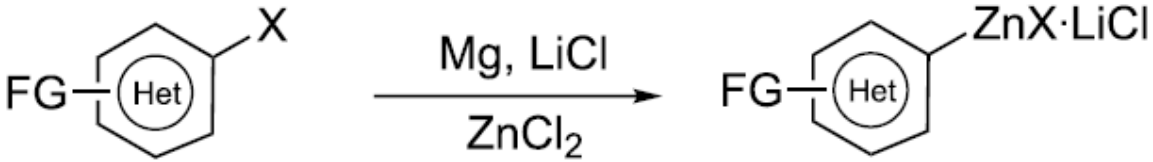
(i)



X = Br, I

LiCl greatly facilitates the insertion of zinc to aryl iodides, and in transmetalation of Grignard compounds.

(ii)

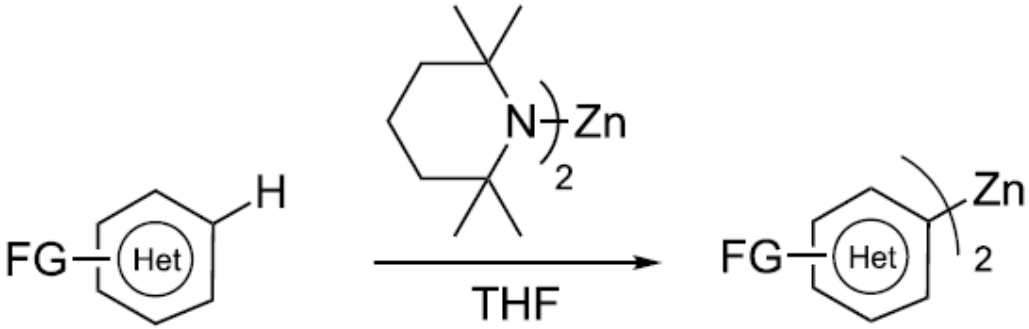


X = Cl, Br, I

Electron-poor aromates react faster.

Mg helps for electron-rich aromates.

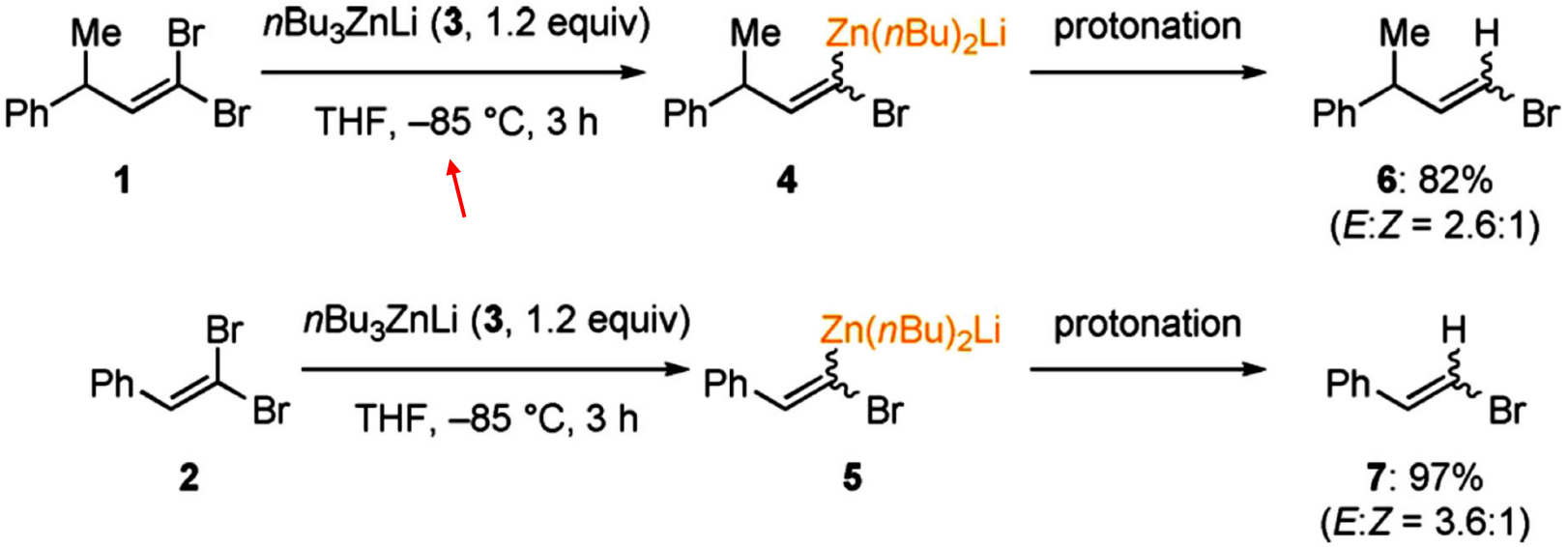
(iii)



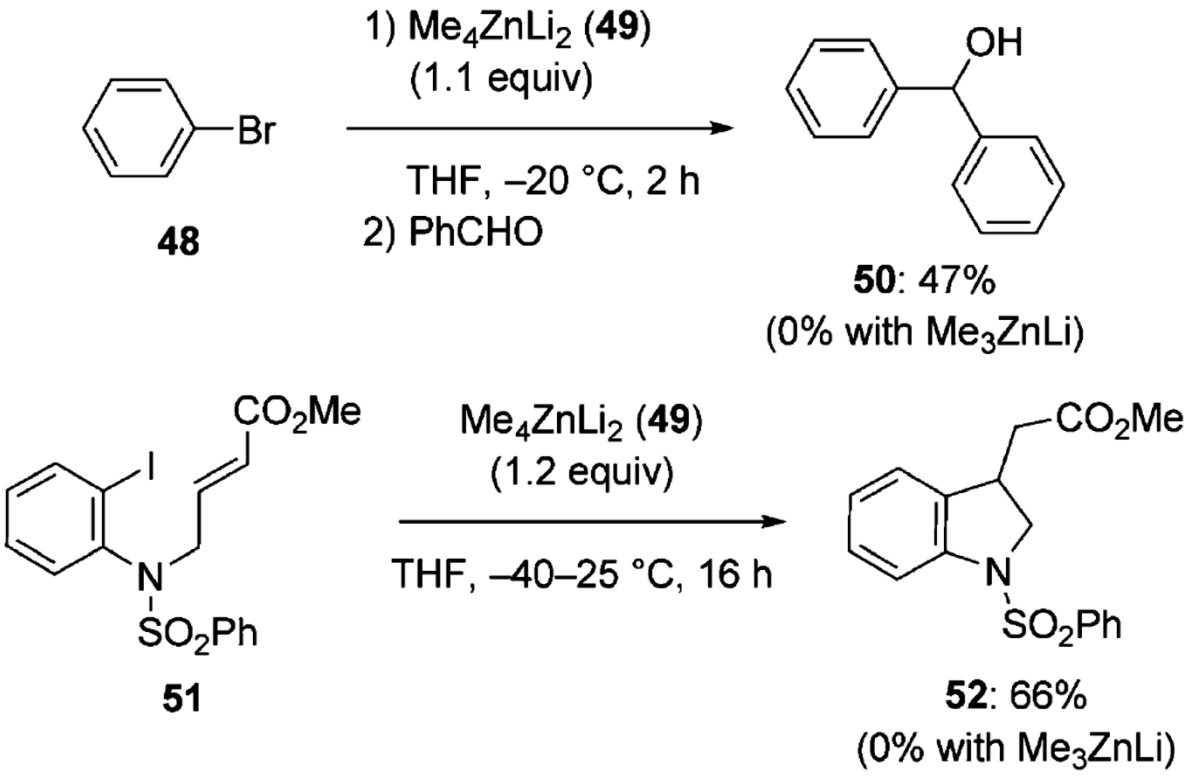
Knochel et al., *Beilstein JOC* **2011**, 1261

Knochel, *Chem. Eur. J.* **2020**, 3688: "... lithium and magnesium reagents are highly reactive and therefore often lack sensitive functional group tolerance, like nitro, azido, or triazine groups, or functionalities bearing acidic protons. Hence, zinc organometallic reagents have been developed to perform efficient and yet mild halogen–zinc exchange reactions."

R_3ZnLi: triorganozincate (from RLi + R_2Zn)
R_4ZnLi_2: tetraorganozincate (from 2 RLi + R_2Zn)

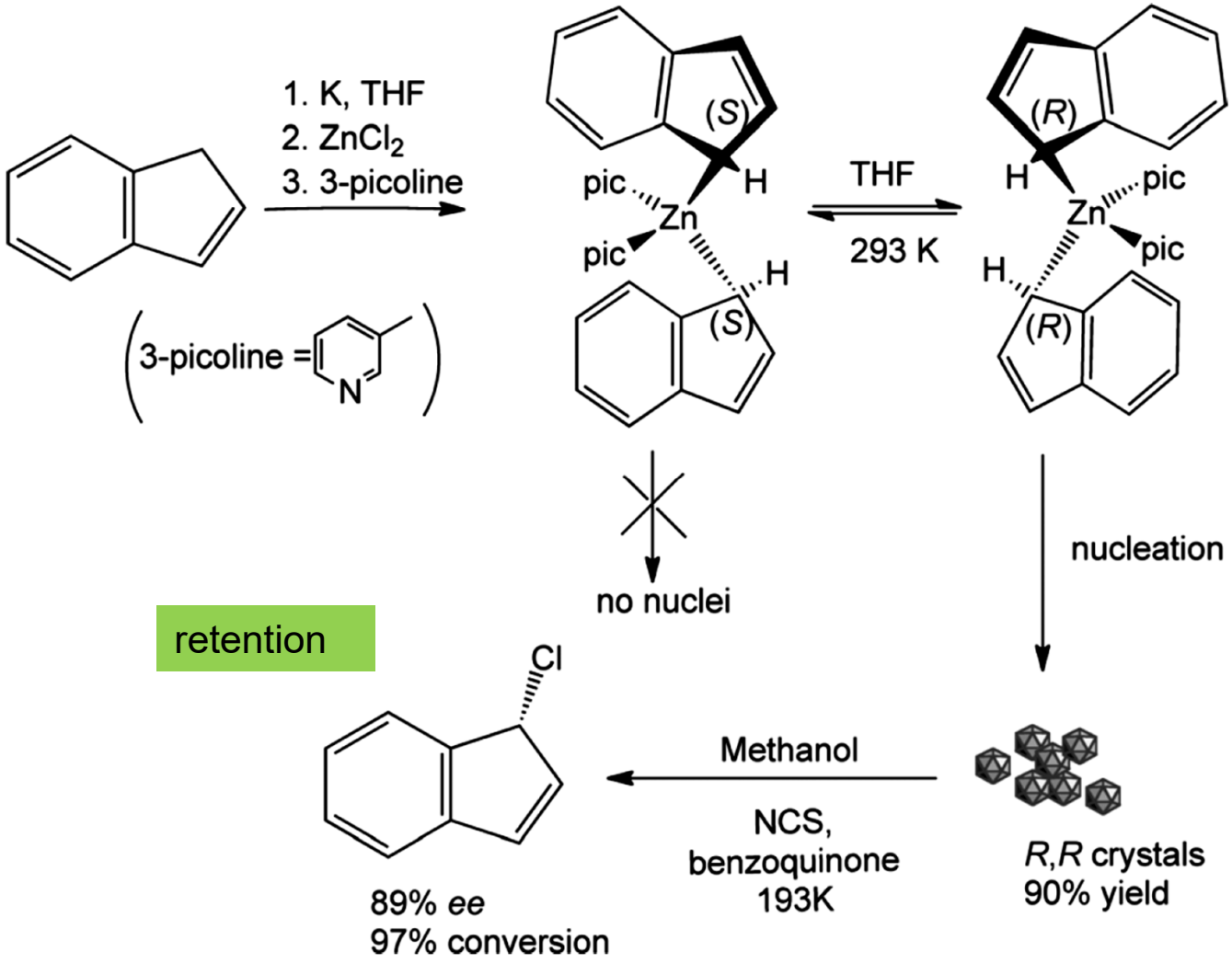


R_4ZnLi_2 is more reactive than R_3ZnLi !



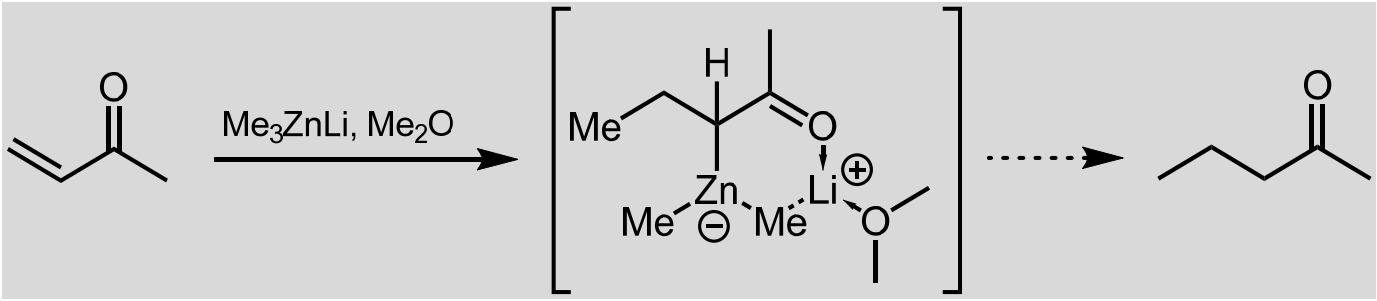
Knochel, *Chem. Eur. J.* **2020**, 3688

As expected, there are configurationally stable organozinc compounds.

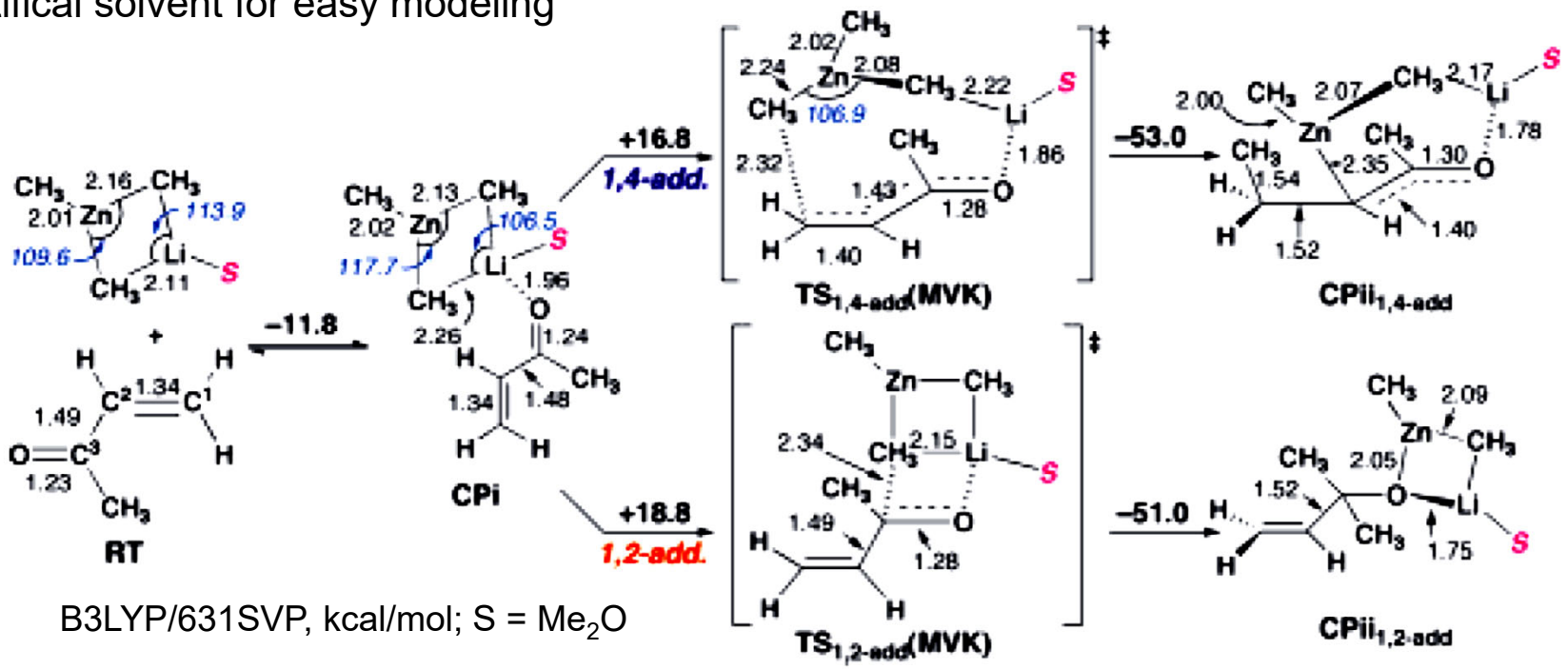


from: Håkansson et al., *CEJ* **2013**, 12415

1,4-Addition of organozincates to αβ-unsaturated ketones



artifical solvent for easy modeling

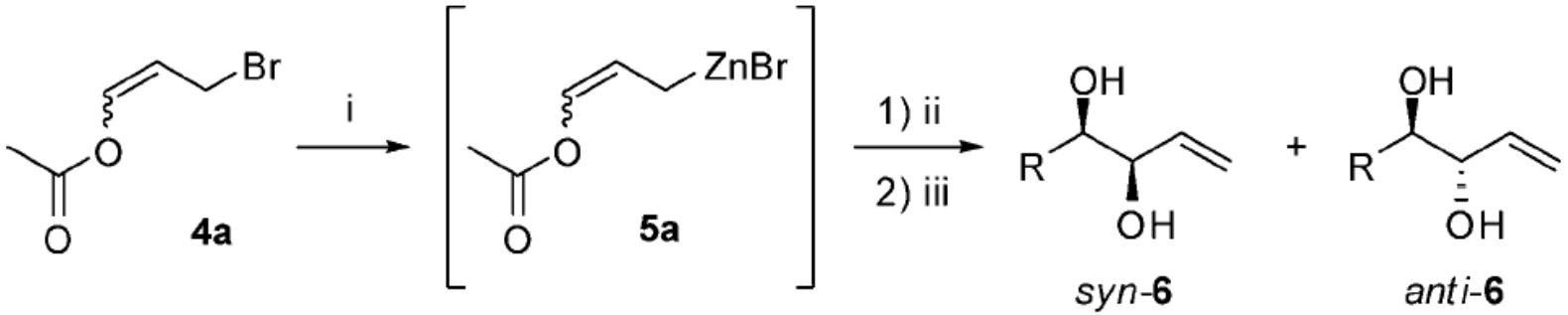


B3LYP/631SVP, kcal/mol; S = Me_2O

Uchiyama et al., *JACS* **2007**, 13360

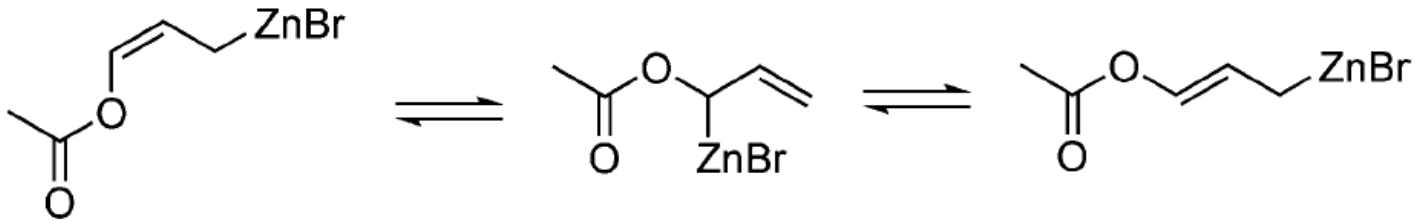
Allylzinc nucleophile (*JOC* **2008**, 418)

S_N2' attack



4a **5a** *syn*-**6** *anti*-**6**

[a] Reagents and conditions: (i) Zn, THF, 0 °C → 20 °C, 2 h; (ii) RCHO, 20 °C, 2 h; (iii) K_2CO_3 (3 equiv), CH_3OH/H_2O (4:1 v/v), 20 °C, 2 h.

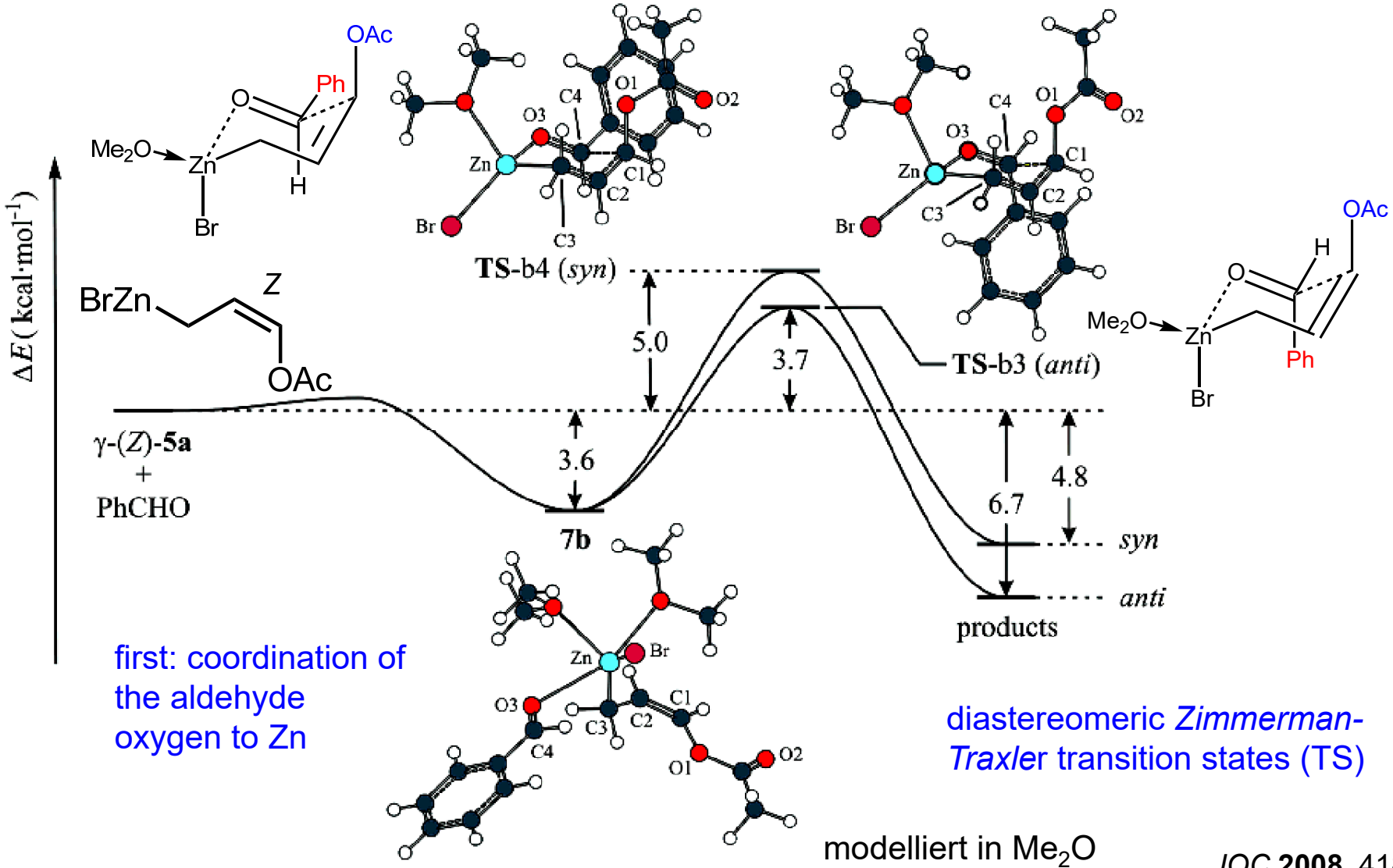


γ-(*Z*)-**5a** α-**5a** γ-(*E*)-**5a**

$\Delta E = 0.0$ kcal·mol^{-1} $\Delta E = +0.7$ kcal·mol^{-1} $\Delta E = +0.8$ kcal·mol^{-1}

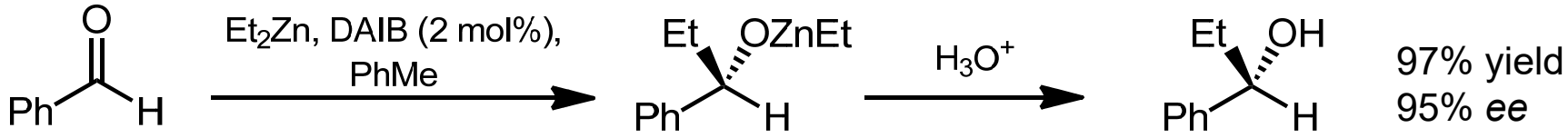
$\Delta G = 0.0$ kcal·mol^{-1} $\Delta G = +2.9$ kcal·mol^{-1} $\Delta G = +0.7$ kcal·mol^{-1}

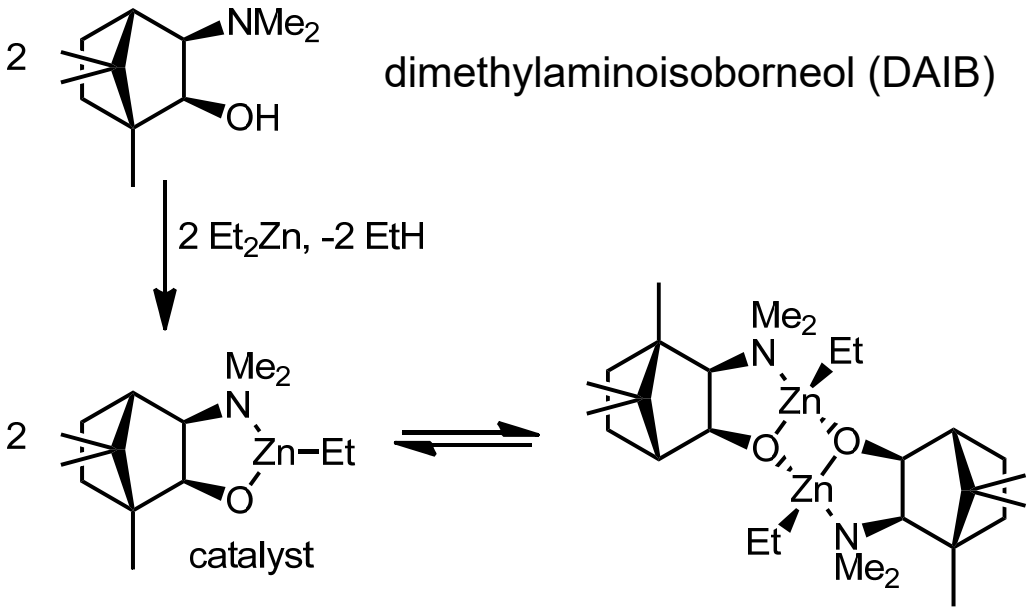
most stable


OAc
Ph
O
Me2O
Zn
H
Br
TS-b4 (syn)
TS-b3 (anti)
BrZn
Z
OAc
γ-(Z)-5a
+
PhCHO
ΔE (kcal·mol-1)
5.0
3.7
3.6
6.7
4.8
7b
syn
anti
products
first: coordination of the aldehyde oxygen to Zn
diastereomeric Zimmerman-Traxler transition states (TS)
modelliert in Me2O
JOC 2008, 418

An example of chirality enhancement

Oguni et al., *JACS* **1988**, 7877

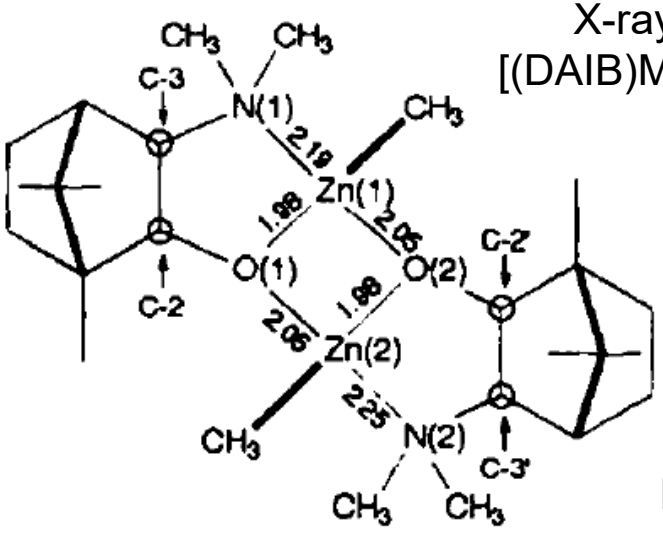




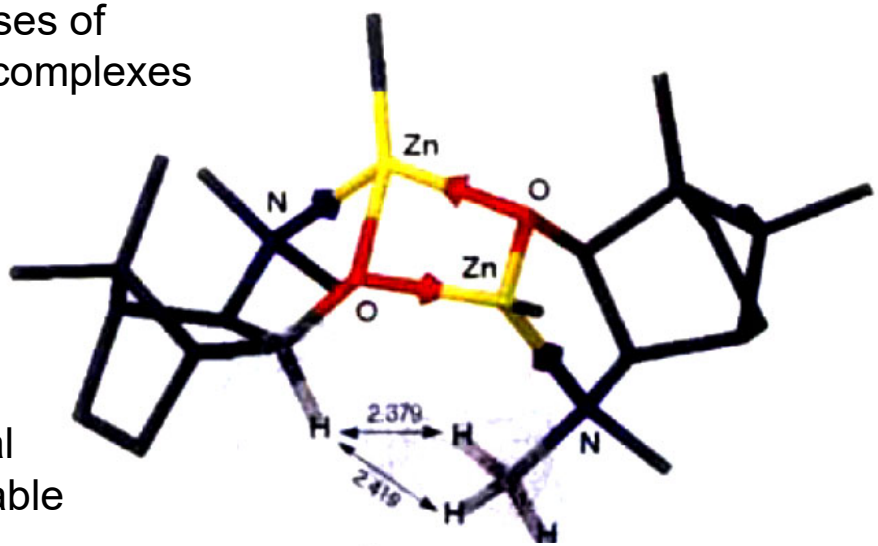
% ee (DAIB)	% ee (Produkt)
>99	98
50	97
22	96
15	95
10	90
0	0

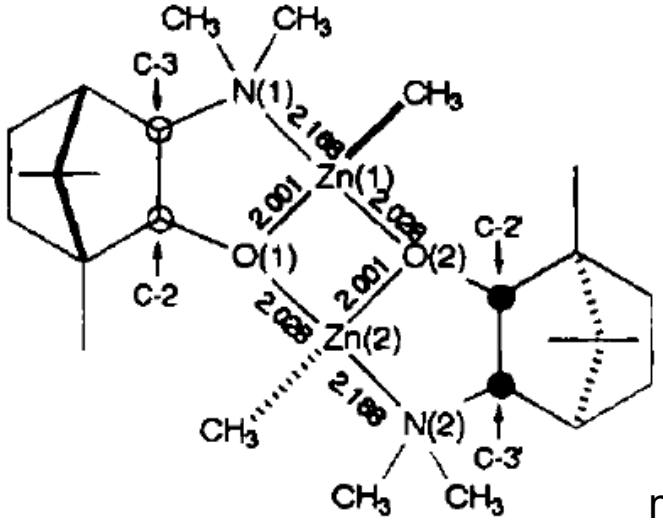
chiral dimer (above right) is less stable than *meso* dimer => major enantiomer of catalytically active monomer enriched in solution; *ee* of product higher than of the catalyst.

X-ray analyses of
$[(DAIB)MeZn]_2$ complexes

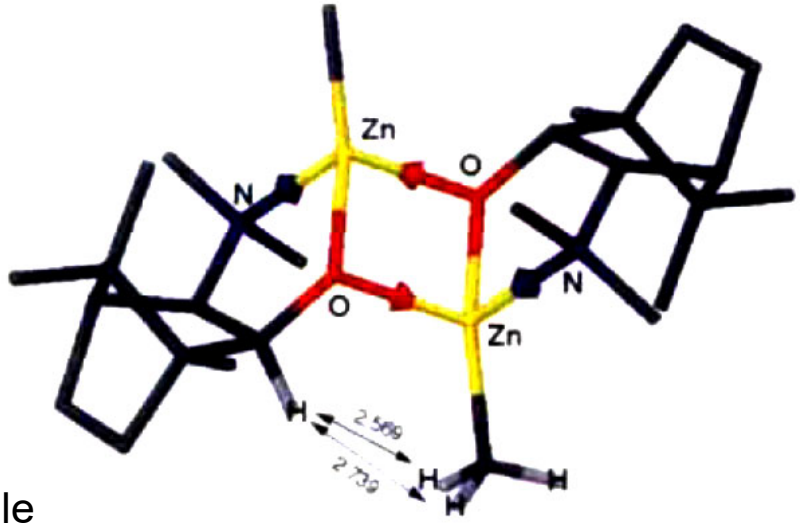


chiral
less stable



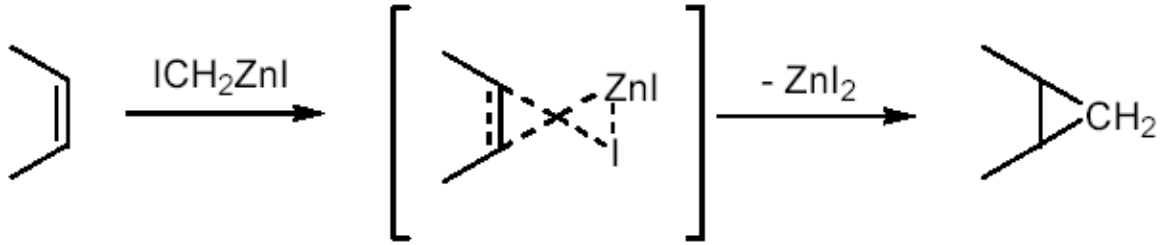


meso
more stable



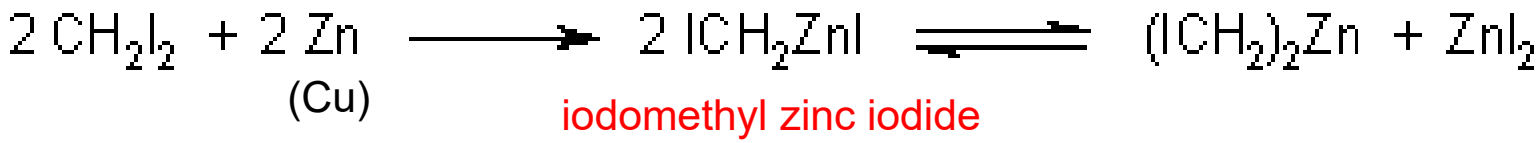
Noyori et al., *Chem. Eur. J.* **1996**, 1173

Stereospecific *Simmons-Smith* cyclopropanation via zinc carbenoid (1958):

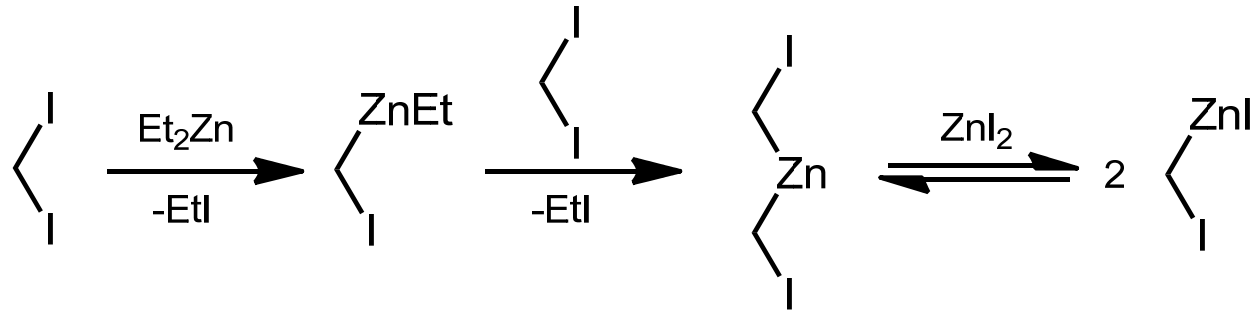


methylene transfer via butterfly transition state

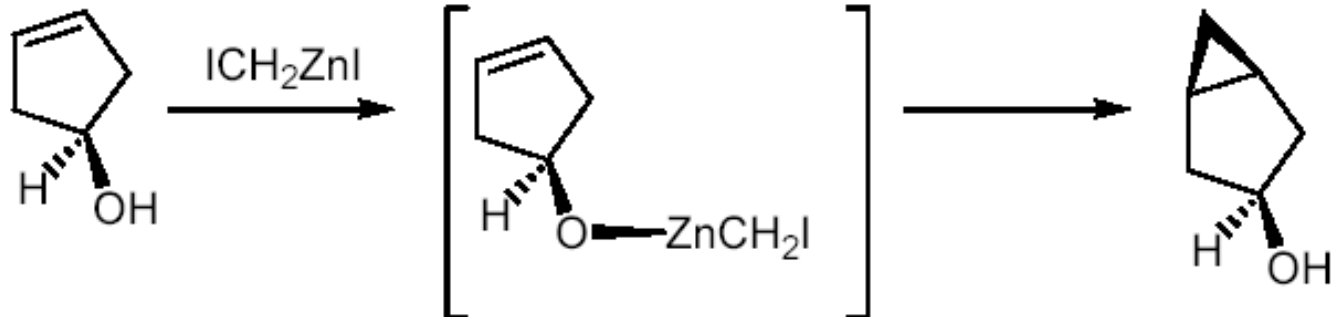
in situ formation of the reagent from Zn-Cu couple and diodomethane:



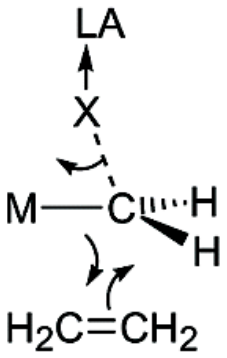
or from Et_2Zn and diodomethane (Furukawa), allows greater variation of solvent:



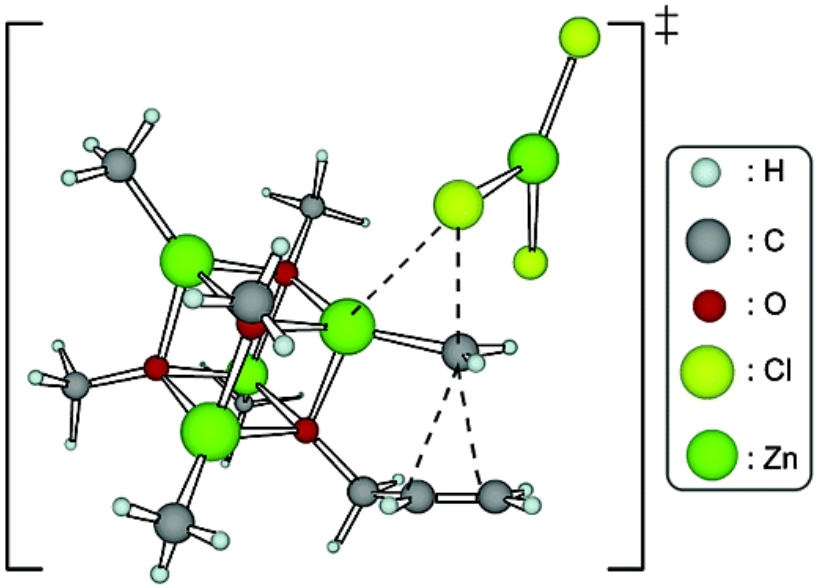
Diastereoselective *Simmons-Smith* cyclopropanation:



•leaving group activation by Lewis Acid

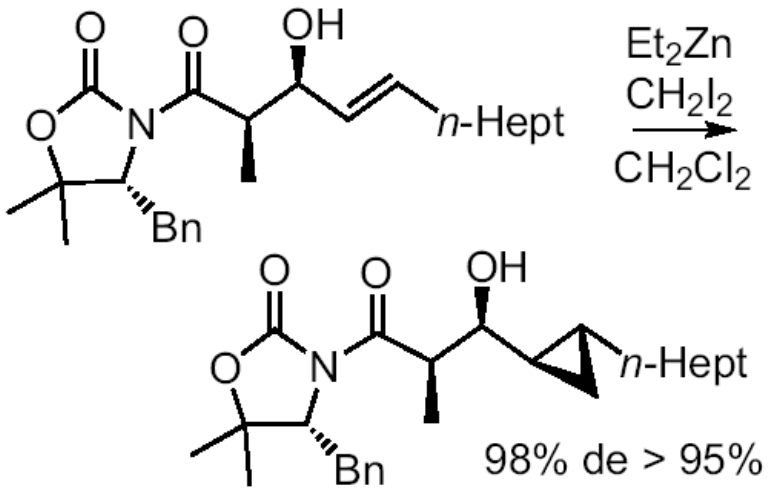


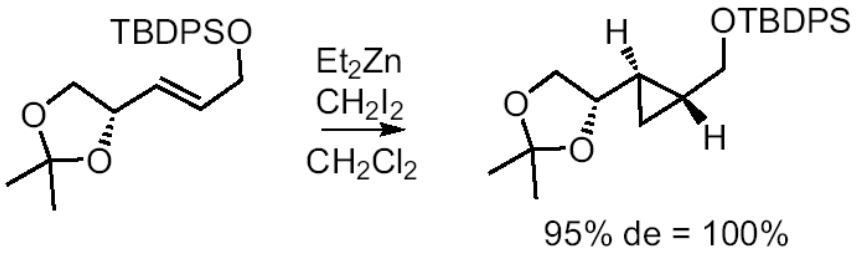
•nucleophilic attack on carbenoid carbon

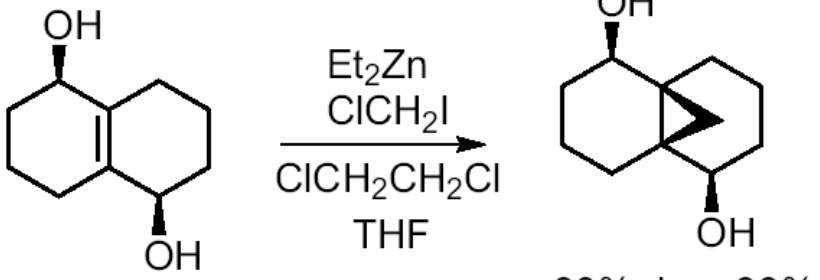


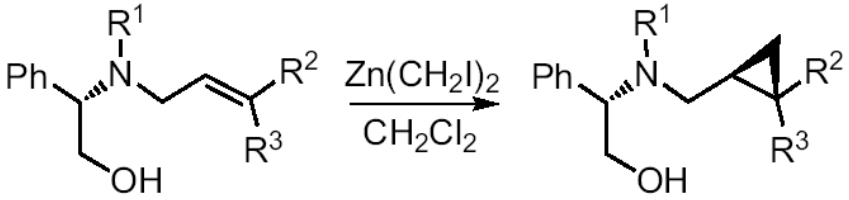
modelled for chlorine instead of iodine

Quantum chemical calculations: Nakamura et al., *JACS* **2003**, 2341





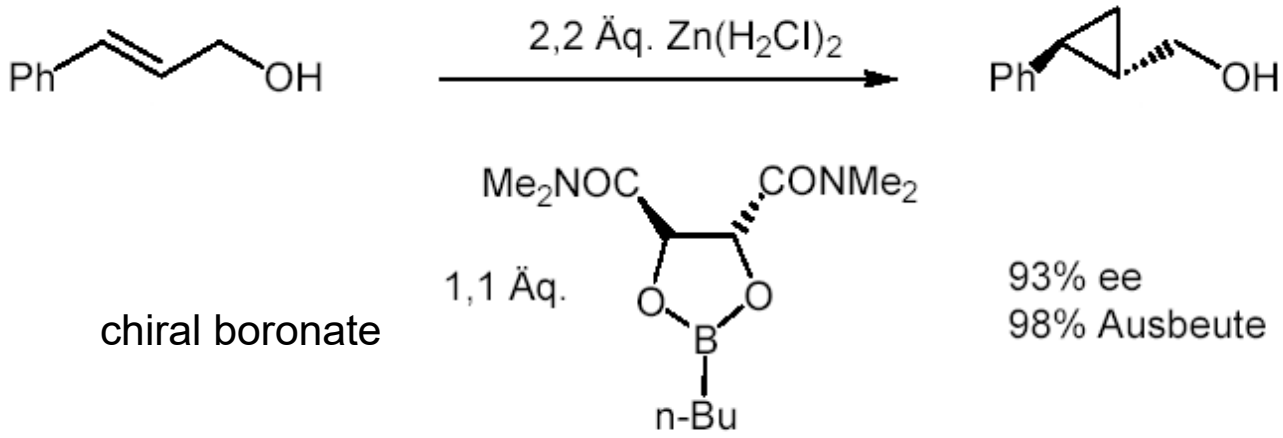




R^1 = Me, R^2 = Ph, R^3 = H: 95% de = 92%
R^1 = Bn, R^2 = Ph, R^3 = H: 87% de = 84%
R^1 = Me, R^2 = H, R^3 = *n*-Pr: 92% de = 90%
R^1 = Me, R^2 = *n*-Pr, R^3 = H: 96% de > 96%
R^1 = R^2 = R^3 = Me: 94% de = 84%

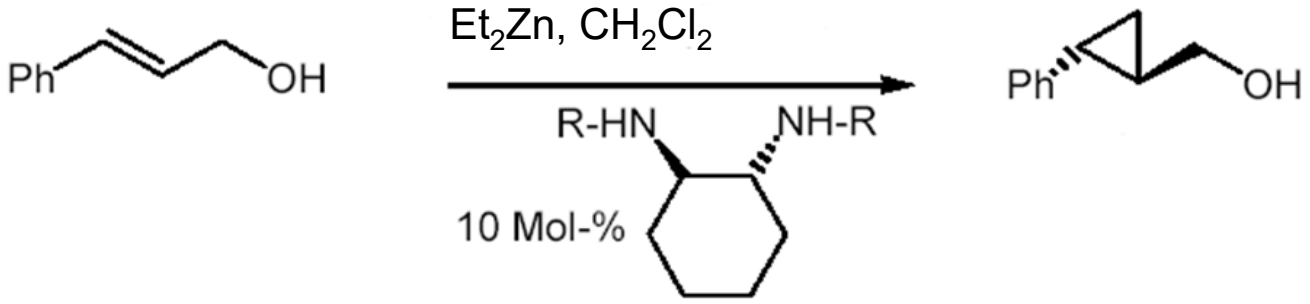
review: H. Pellissier, *Tetrahedron* **2008**, *64*, 7041

Enantioselective *Simmons-Smith* cyclopropanation of allylic alcohols with chiral Lewis acids:



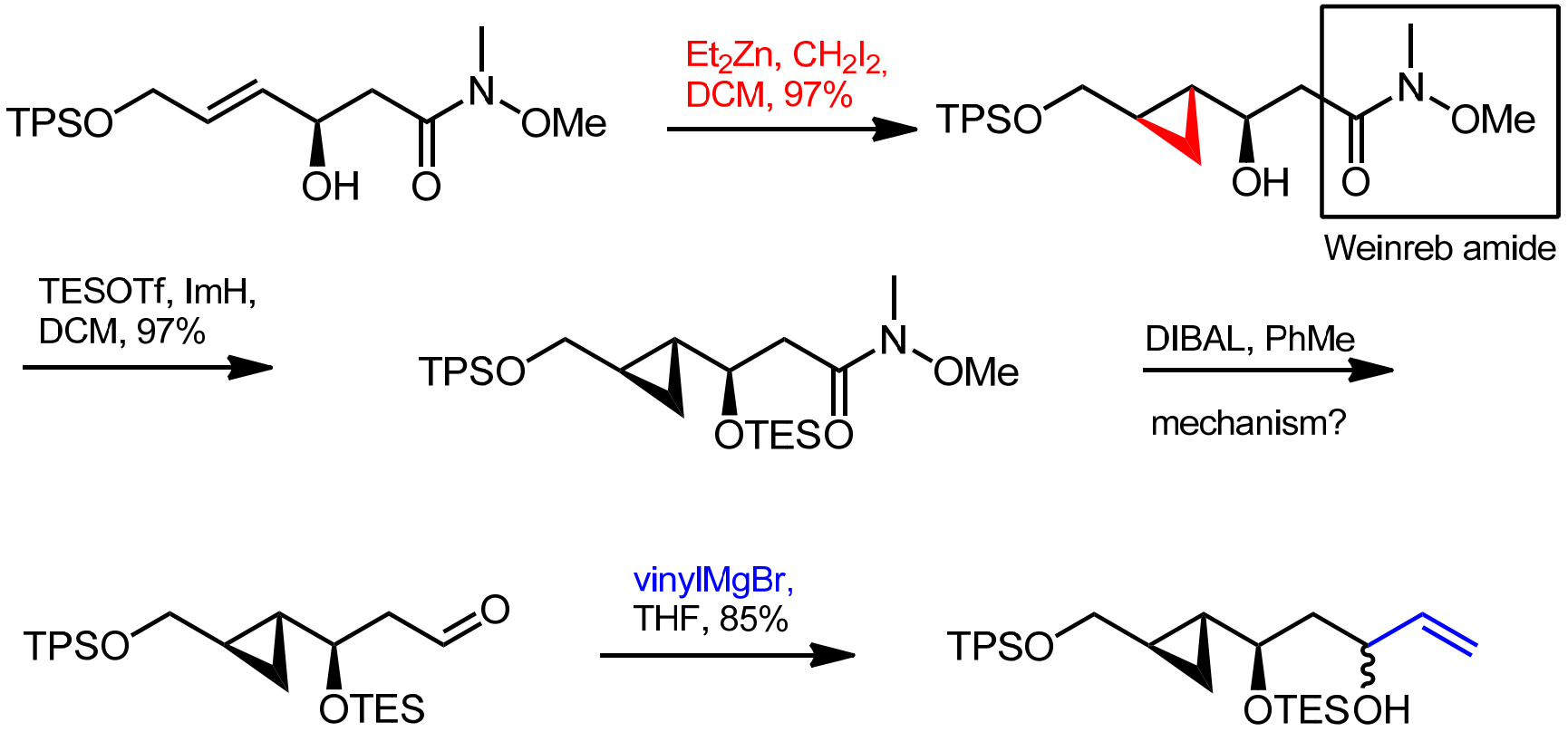
chiral boronate

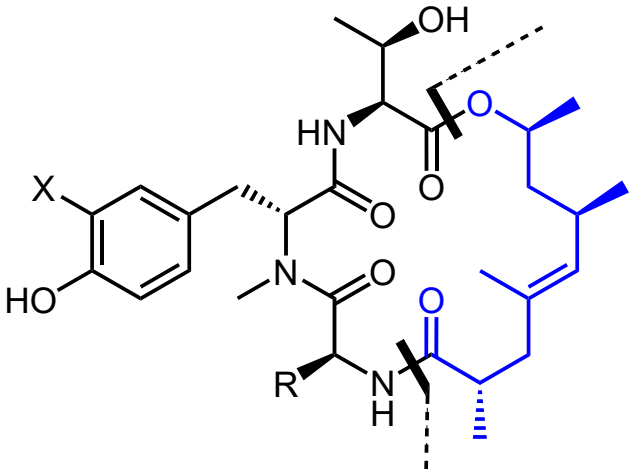
93% ee
98% Ausbeute



82% ee, 76% yield (R=Ns)

Sequence with a diastereoselective *Simmons-Smith* reaction and a *Grignard* reaction (J. D. White, *JOC* **2008**):

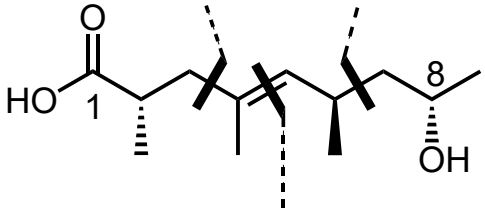




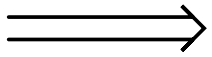
seragamide A (R = Me, X = I)
seragamide B (R = Me, X = Br)
seragamide C (R = Me, X = Cl)
seragamide D (R = H, X = I)
seragamide E (R = CH_2OH, X = I)

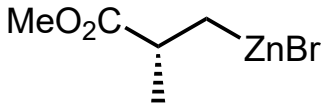
Negishi cross coupling

epoxide opening



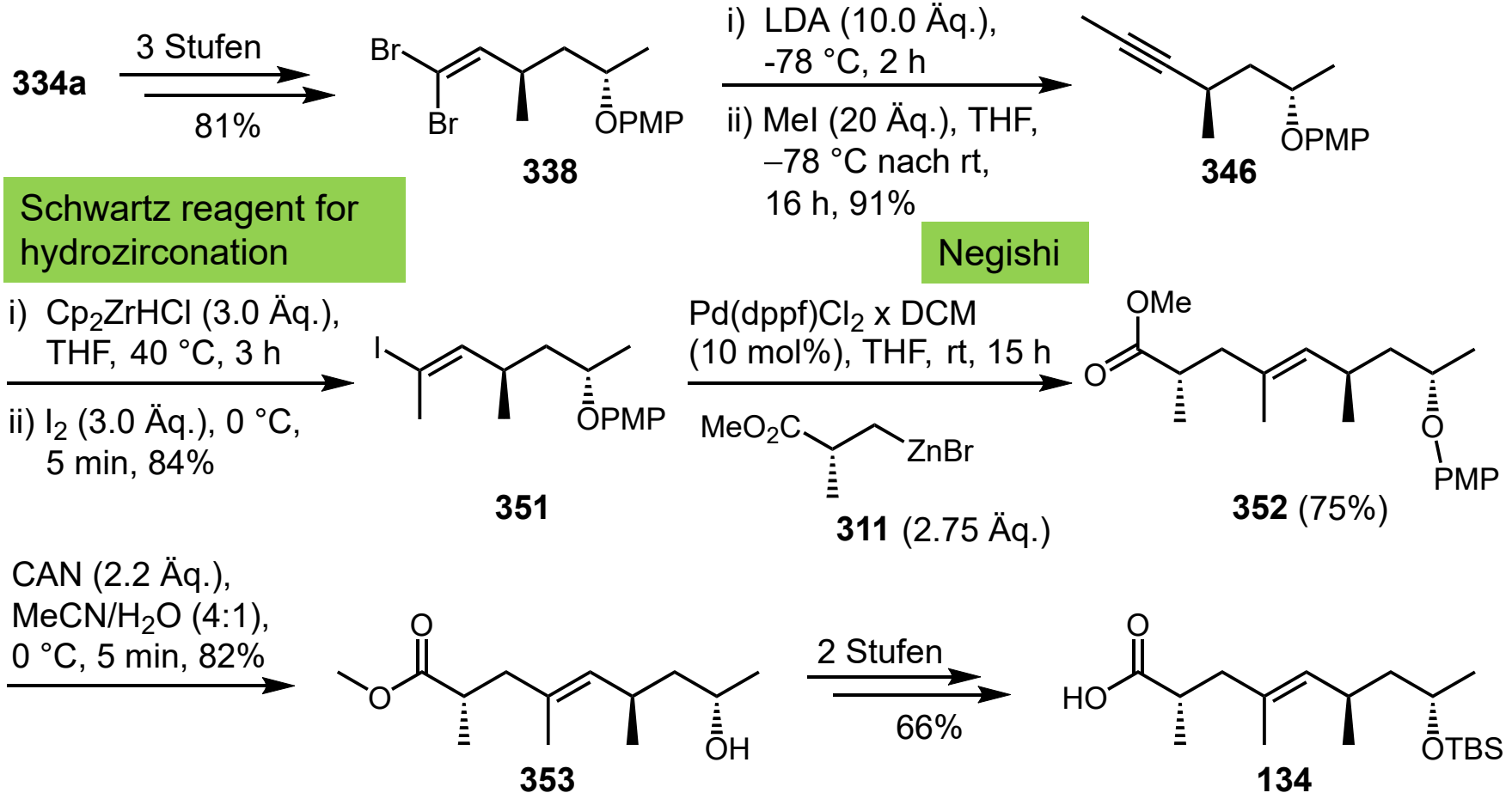
Corey-Fuchs reaction



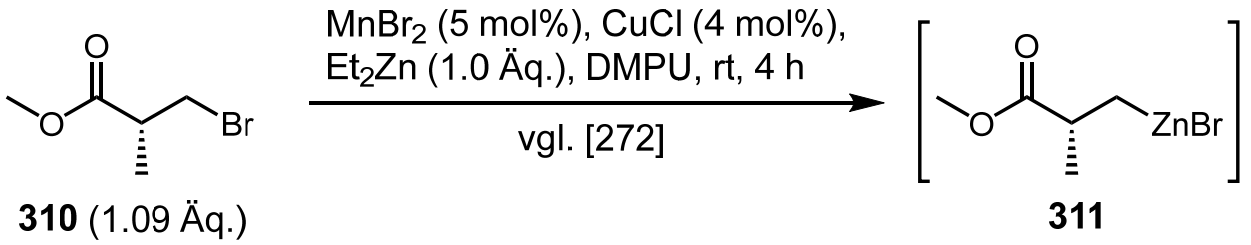


Where there is zinc, there may be Negishi (see class Reaction Mechanisms)

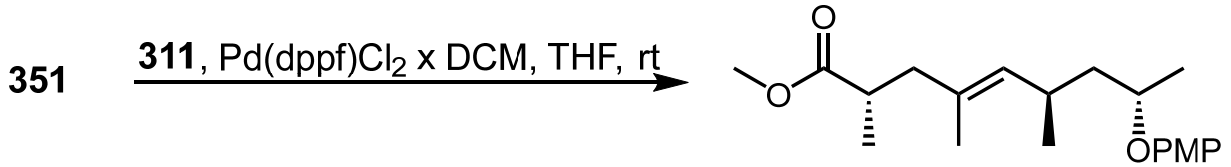
Lang, Lindel, *Beilstein J. Org. Chem.* **2019**, 577



from: Dissertation Jan Hendrik Lang, TU Braunschweig 2018



310 (1.09 Äq.) **311**



352

Tabelle 17: Ausgewählte Versuche zur Optimierung der Negishi-Kupplung.

Äq. Organozink 311	Pd-Kat. [Äq.]	Reaktionszeit	Ausbeute
1.1	10 mol%	35 h	20%
1.1 + 1.1	8 mol%	1 d + 3 d	46%[a]
1.64	4 mol%	19 h	kein Umsatz[b]
2.2	10 mol%	41 h	61%
2.75	10 mol%	15 h	75%

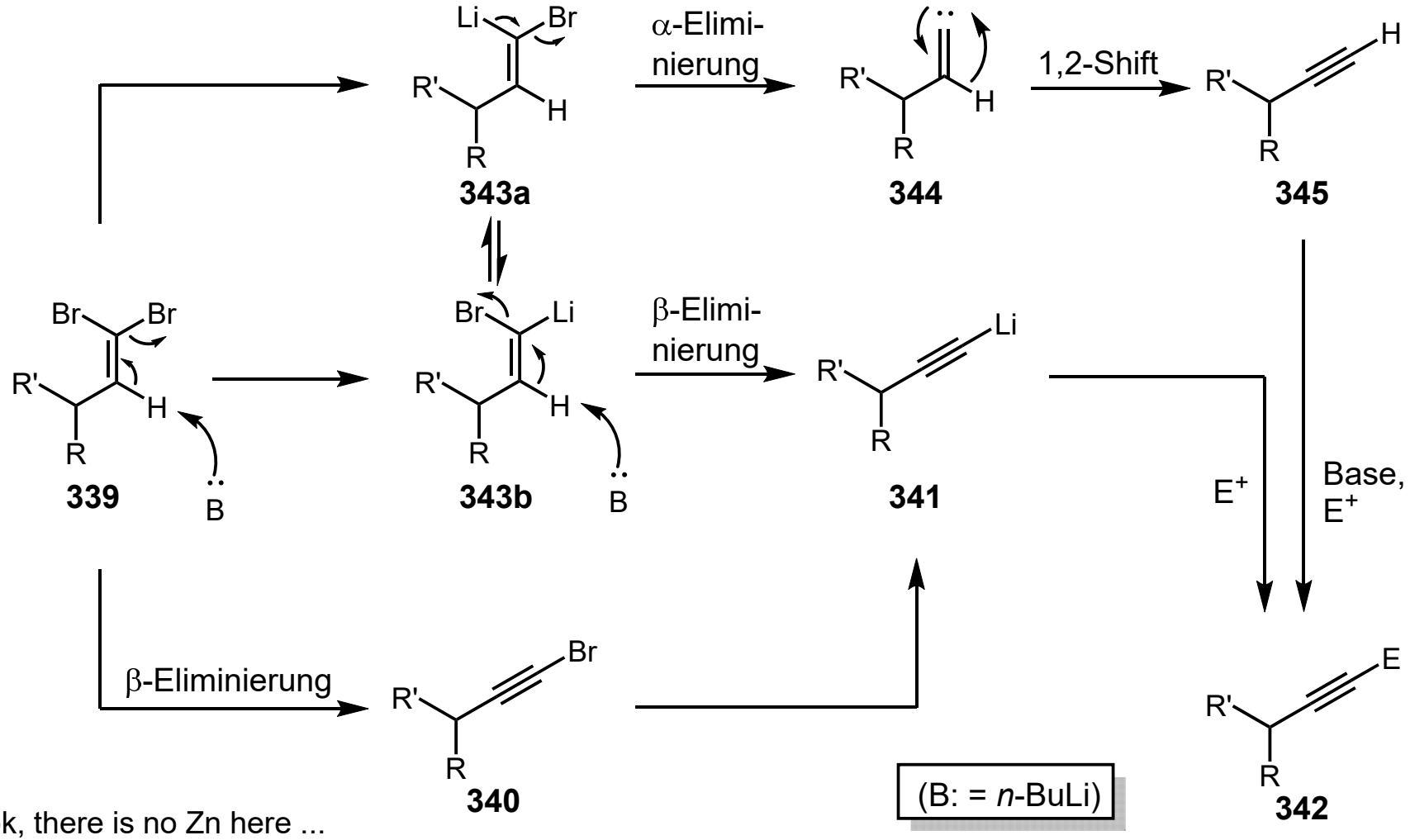
[a] Organozink **311** wurde in zwei Portionen zugegeben.

[b] Organozink-Suspension wurde vor der Zugabe über einen Spritzenfilter filtriert.

lab reality

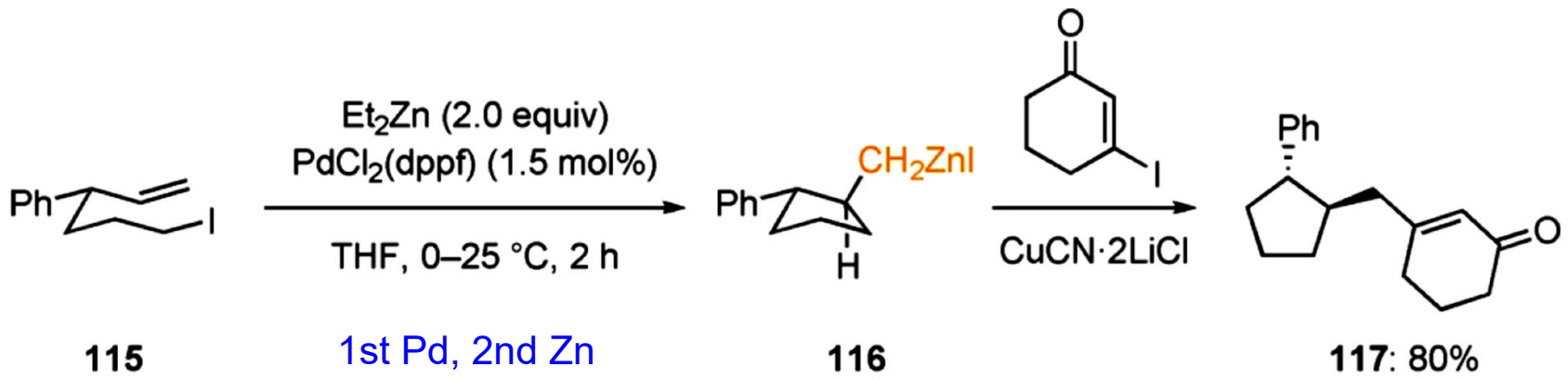
from: Dissertation Jan Hendrik Lang, TU Braunschweig 2018

Second part of the Corey-Fuchs reaction sequence

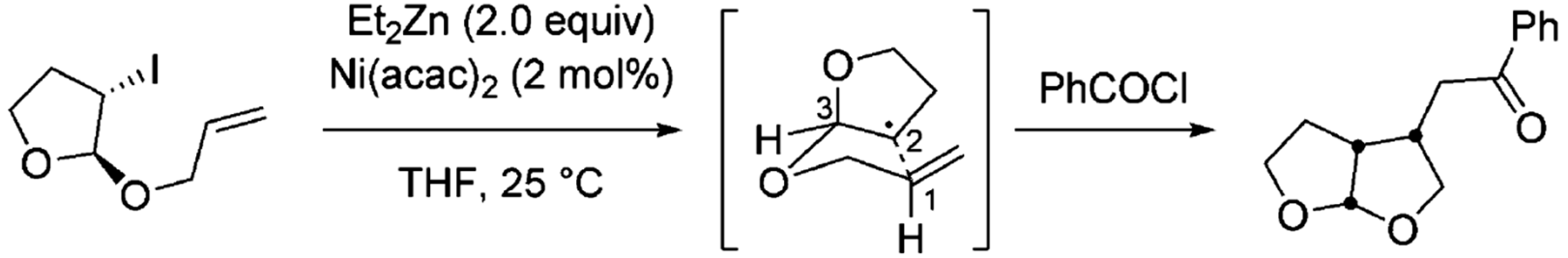


ok, there is no Zn here ...

from: Dissertation Jan Hendrik Lang, TU Braunschweig 2018



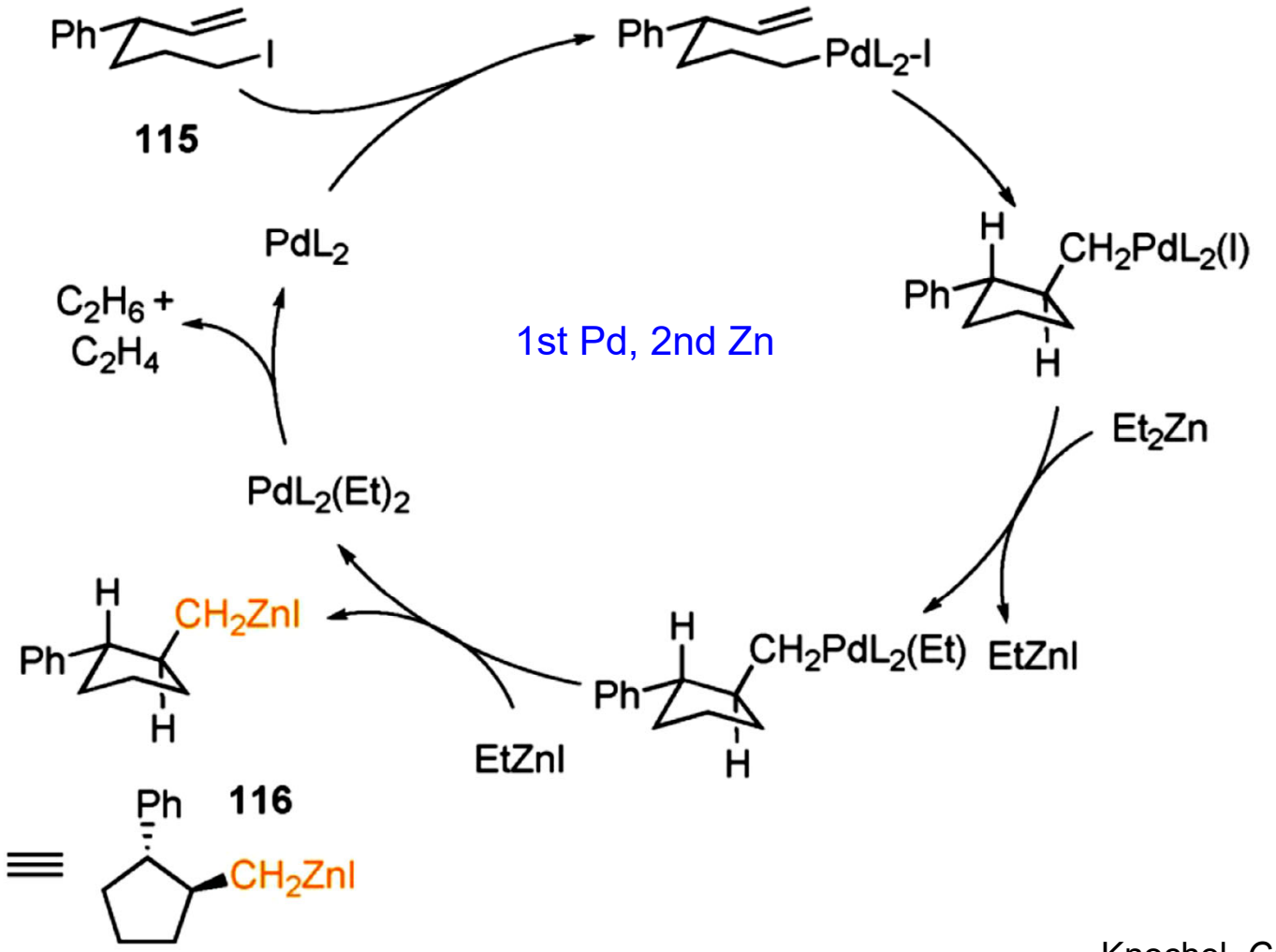
115 1st Pd, 2nd Zn **116** **117**: 80%



124 Ni-catalyzed I/Zn exchange **125** radical **126**: 64%
exo:*endo* = 2:98

Knochel, *Chem. Eur. J.* **2020**, 3688

Proposed reaction mechanism:



intramolecular carbopalladation

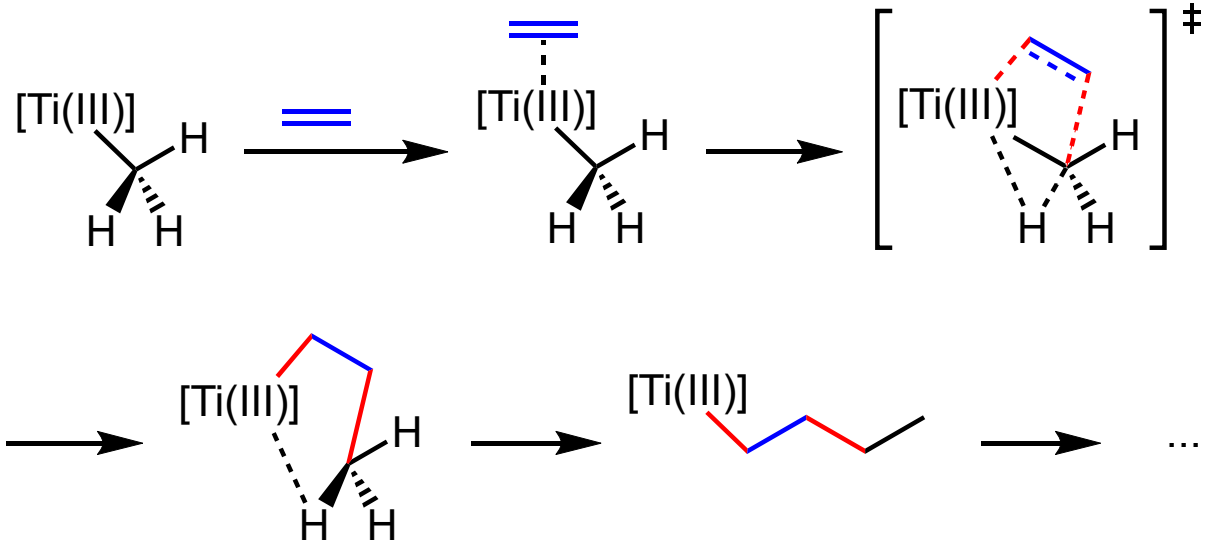
who knows whether this is correct ...

Knochel, *Chem. Eur. J.* **2020**, 3688

Ziegler-Natta polymerization: 45 Mio t/a Polypropylen

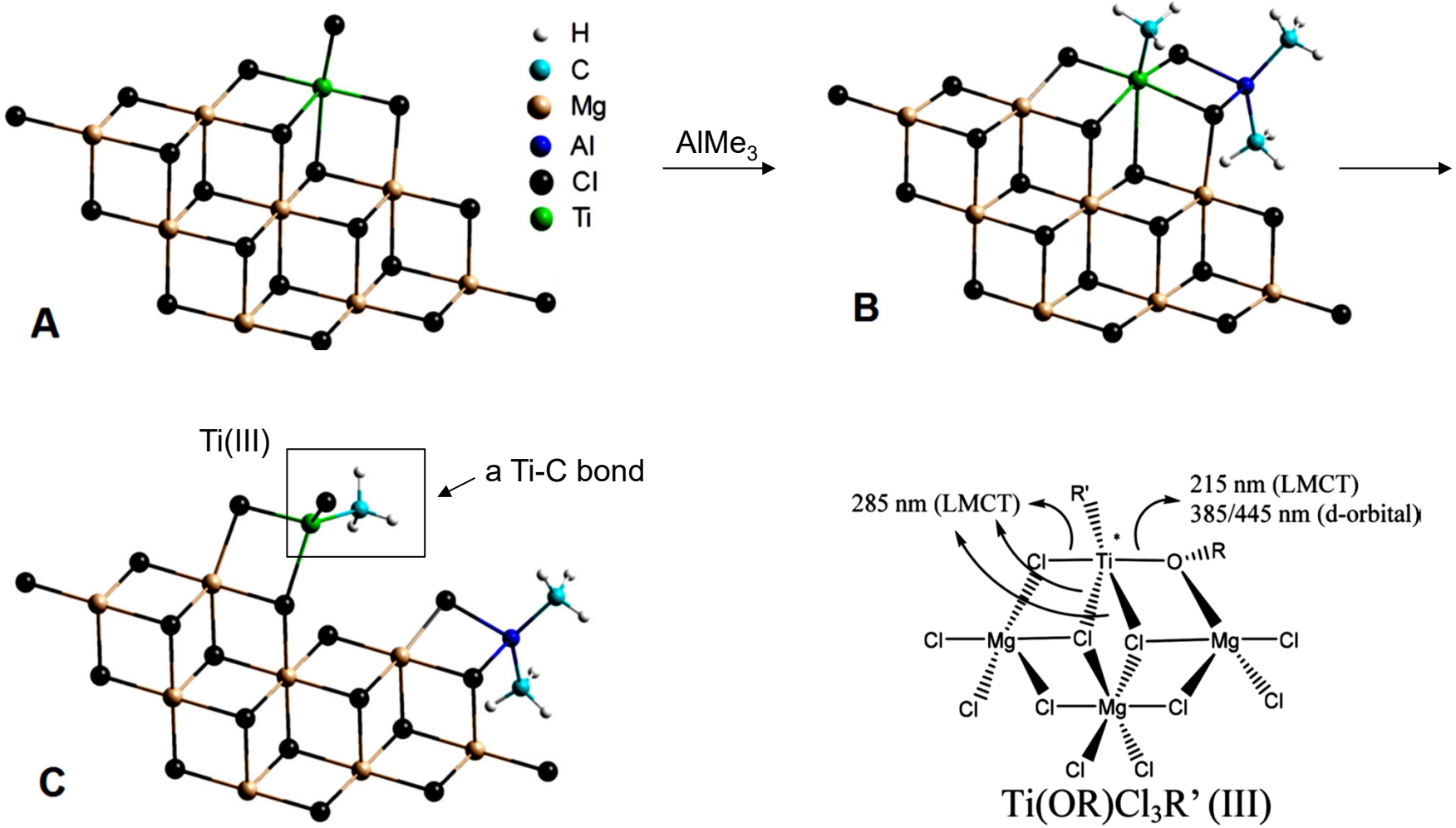
Nobel prize 1963 to
Karl Ziegler, Giulio Natta

Mechanism (shown for ethylene, 1 bar):



> 150 kg polymer per g Ti !

Ziegler-Natta catalyst: $MgCl_2$ + $TiCl_4$ + $AlMe_3$ + alkoxide



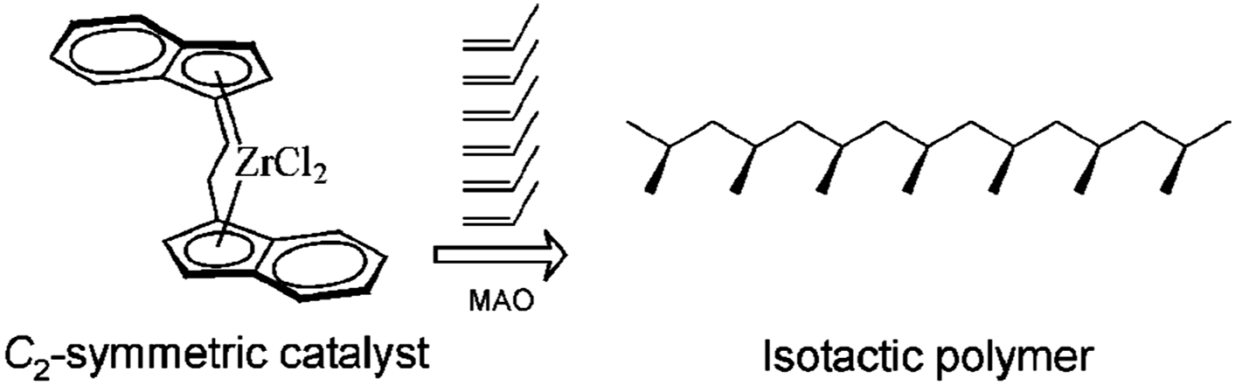
from: Koshevoy et al., *J. Phys. Chem. C* **2016**, *120*, 1121

from: Fisch, *Ind. Eng. Chem. Res.* **2018**, *57*, 6141

Ziegler-Natta polymerization

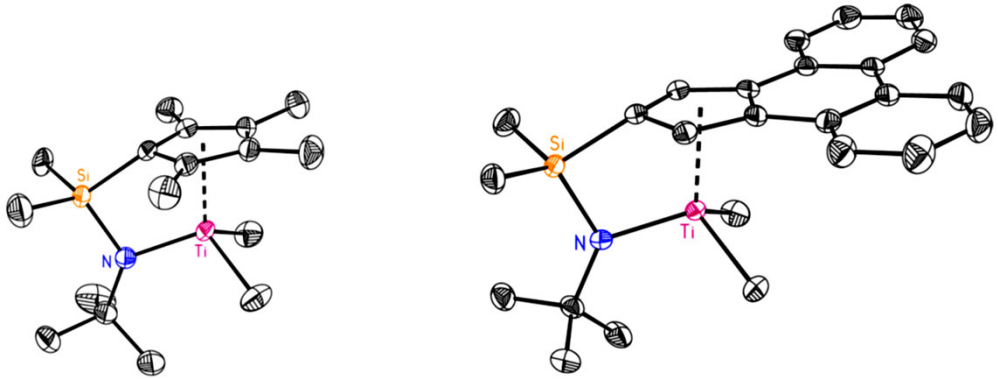
Sinn-Kaminsky catalysts: homogenous from Cp_2(Ti or Zr)X_2/$AlMe_3$ + methylalumoxane

... and further on:



syndiotactic polymers from C_s-symmetrical metallocenes

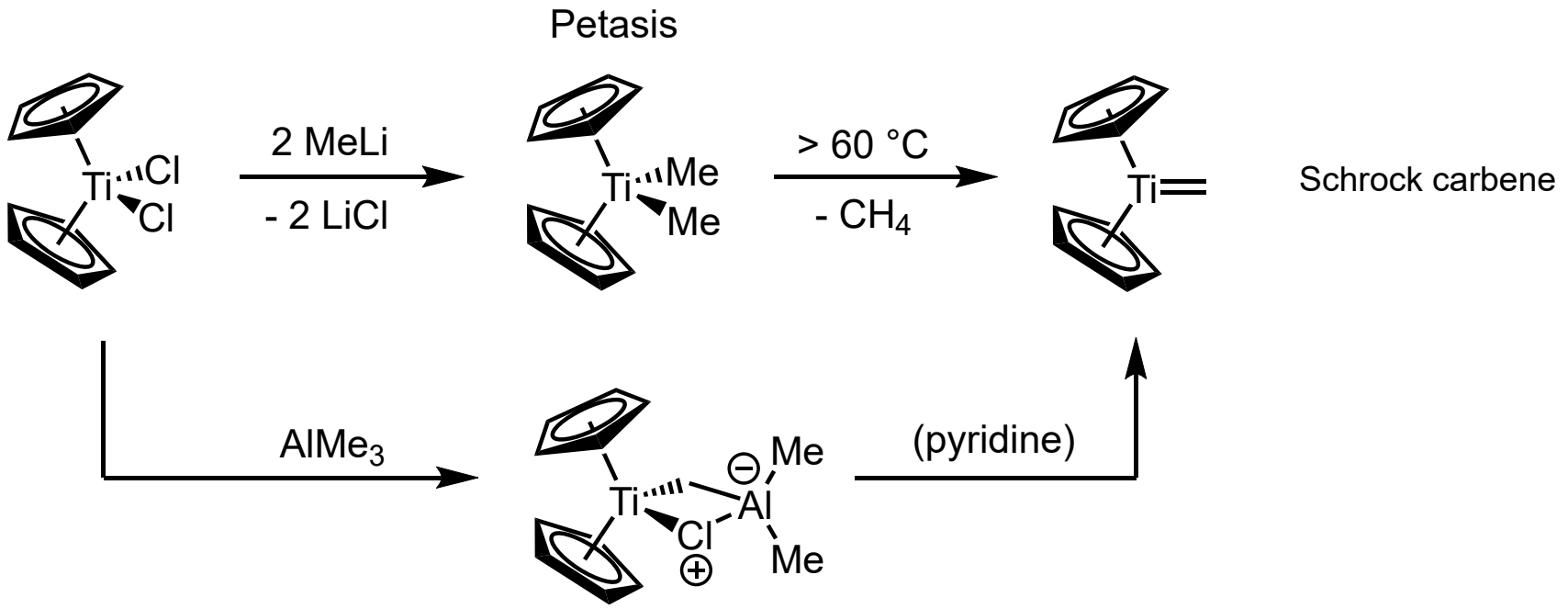
Constraint geometry catalysts: even more active



from: Klosin et al., *Acc. Chem. Res.* **2015**, *48*, 2004

Petasis and Tebbe reagents

Petasis, Bzowej, *JACS* **1990**, 6392

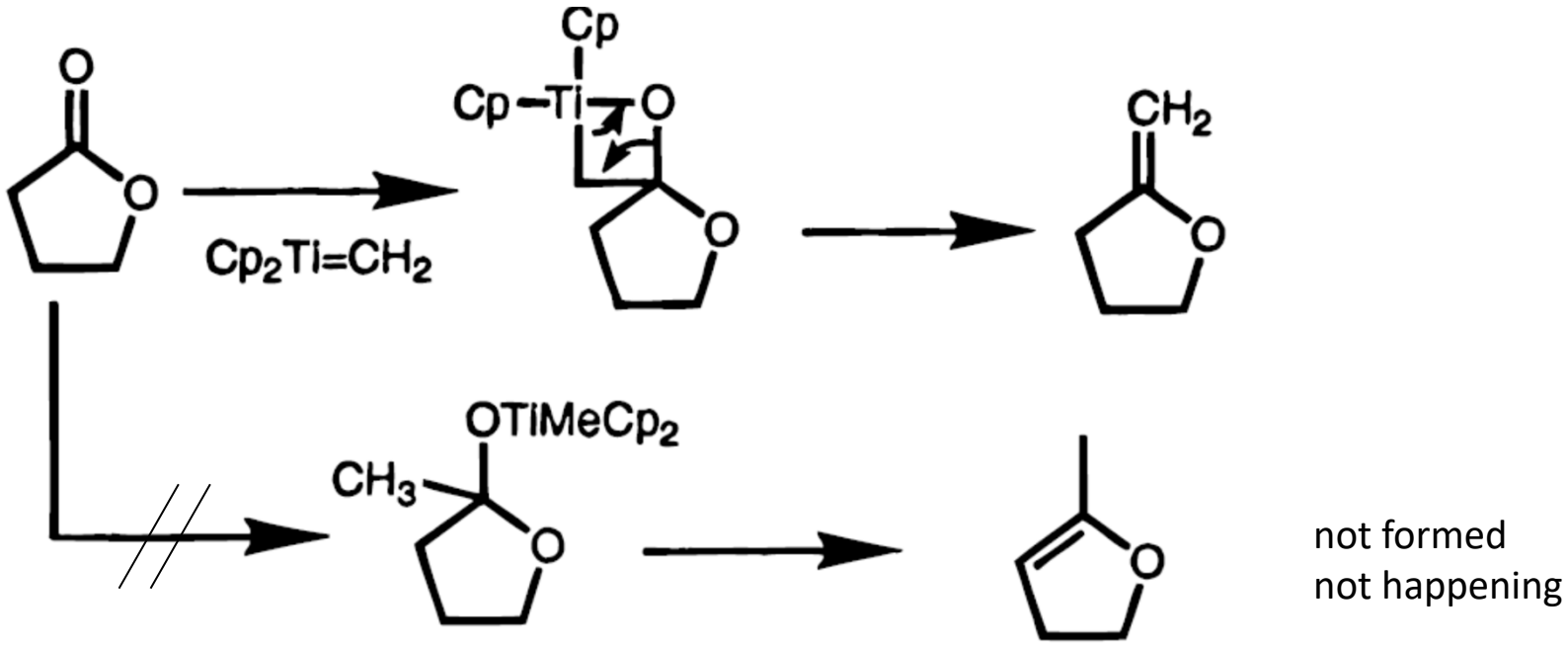


Tebbe et al., *JACS* **1978**, 3611

Petasis and Tebbe reagents

Key application: methenylation of esters or lactones affording enol ethers

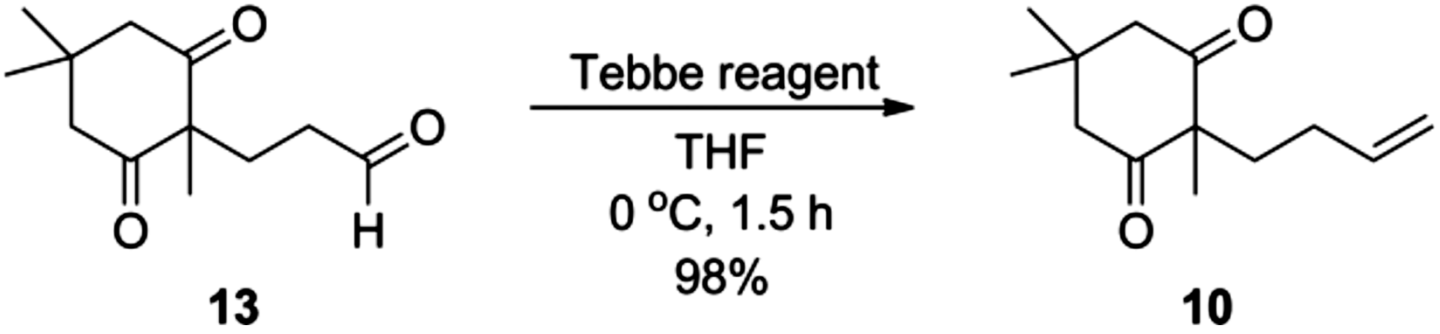
Carbene mechanism via oxatitanacyclobutane intermediate (- $Cp_2Ti=O$ -> polymer)



not formed
not happening

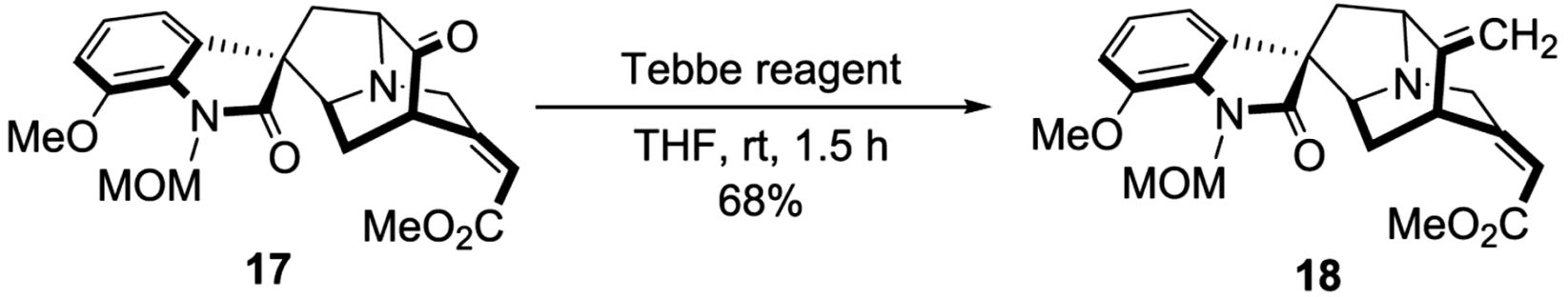
Hughes et al., *Organometallics* **1996**, *15*, 663

Tebbe olefination: not only for esters (order of reactivity as expected) ...



13 **10**

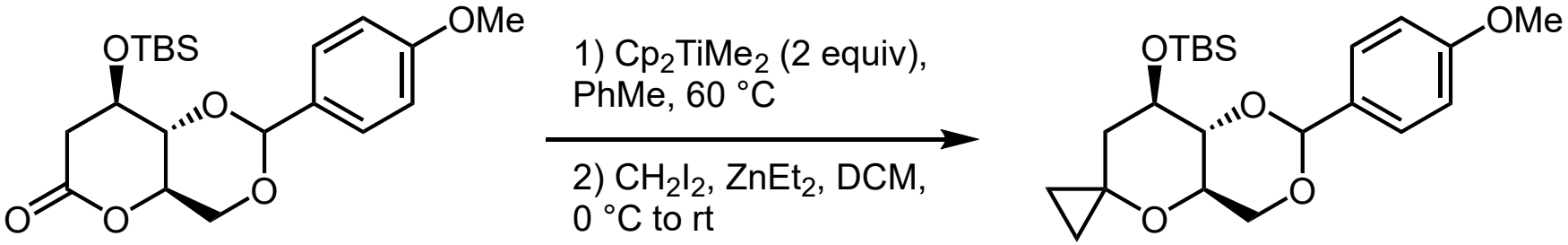
Ito et al., *EurJOC* **2017**, 6693



17 **18**

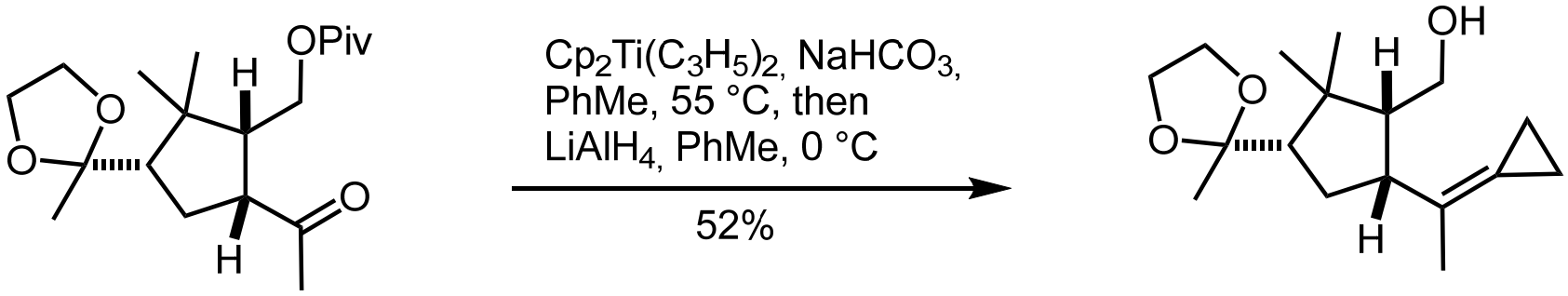
She et al., *Org. Lett.* **2020**, *22*, 2022

Petasis reagent



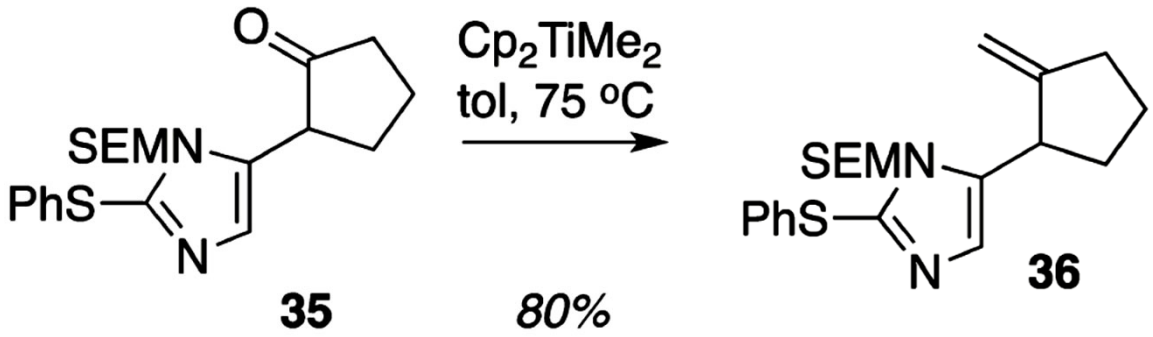
Ghosh et al., *Org. Lett.* **2018**, *20*, 7293

advantage over Tebbe: structural variability



Hönig, Carreira, *Angew. Chem. Int. Ed.* **2020**, *59*, 1192

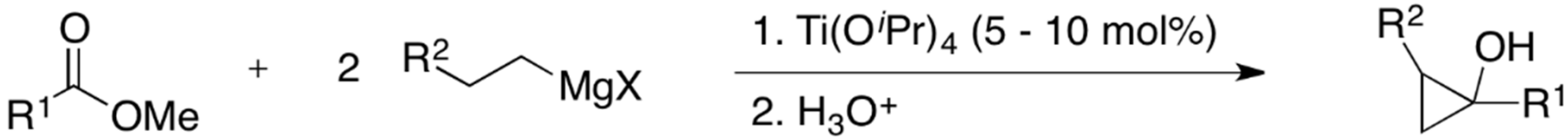
Where the Petasis reagent was superior to the Tebbe reagent:



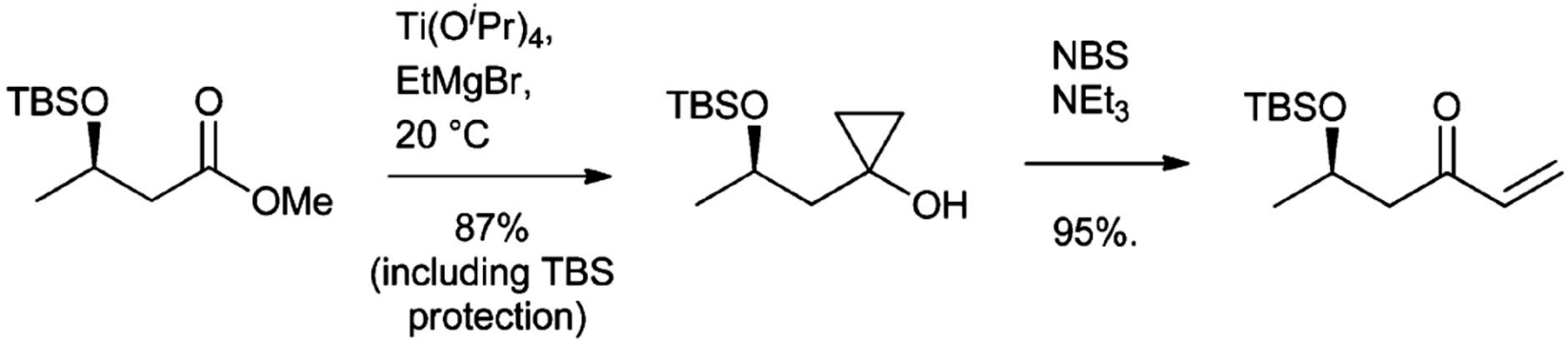
"Methylenation of the ketone within **35** was best accomplished with the Petasis reagent. Alternative methylenation approaches, such as the original Tebbe procedure (~5% of **36**) or Wittig chemistry (-> endocyclic alkene product) were not competitive."

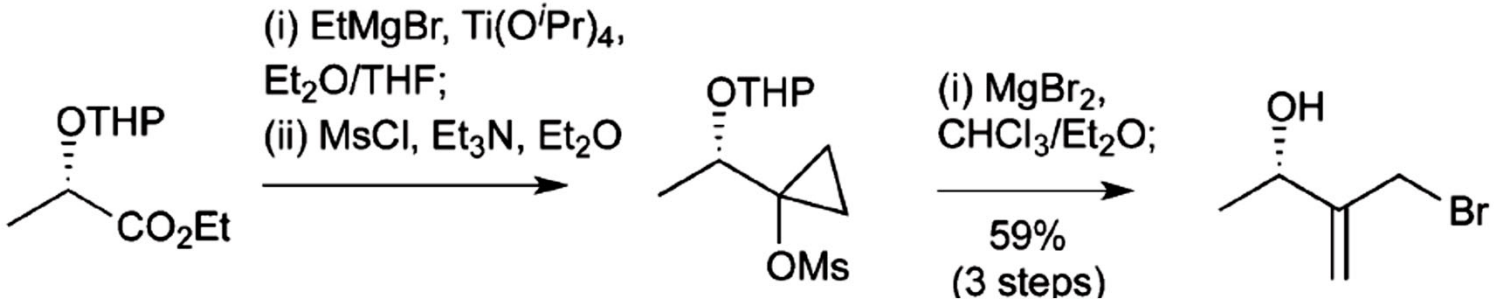
Feldman et al., *JOC* **2011**, 5042

Kulinkovich reaction: to cyclopropanols

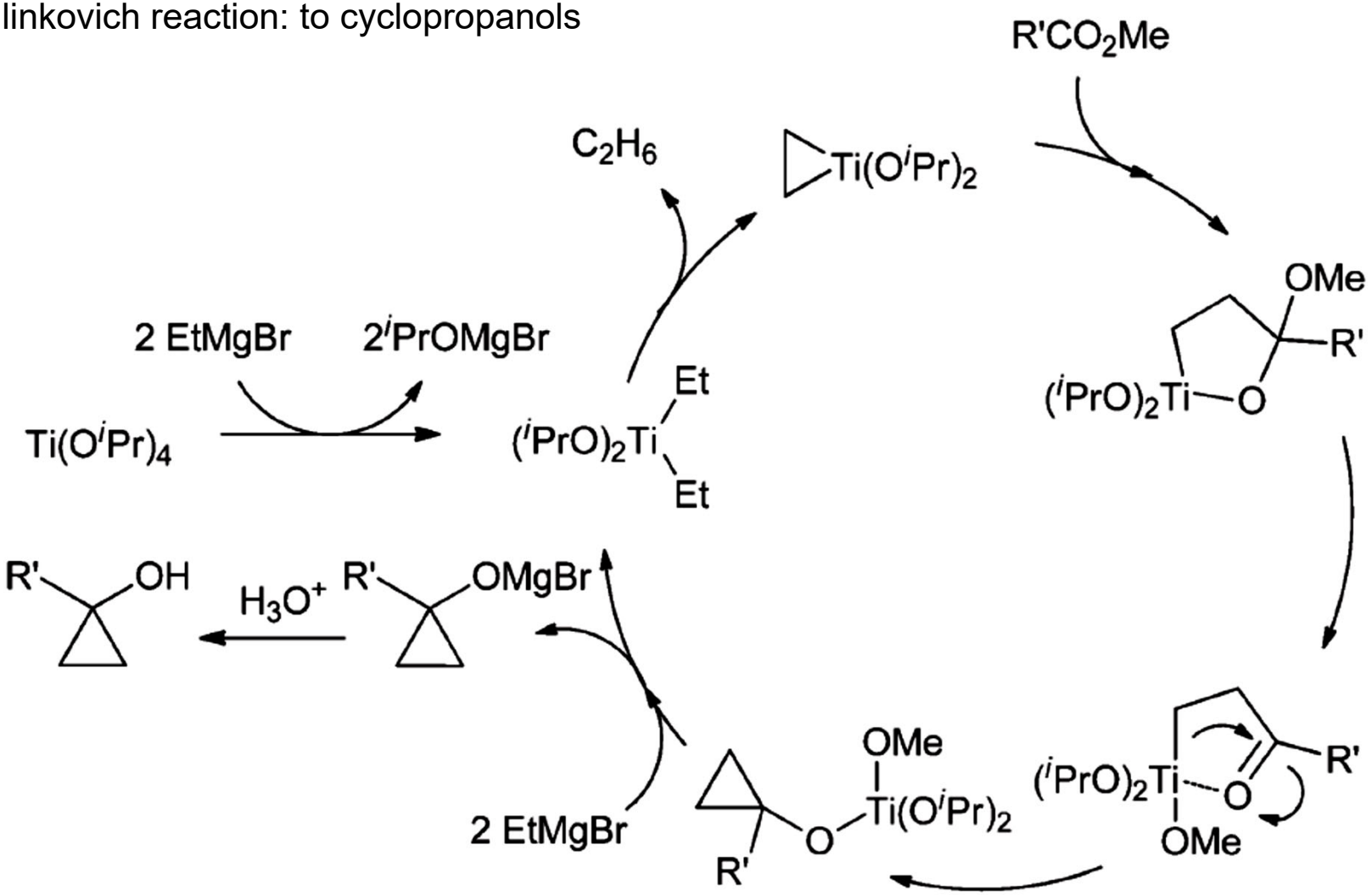


O. G. Kulinkovich, et al., *Zh. Org. Khim.* **1989**, *25*, 2244



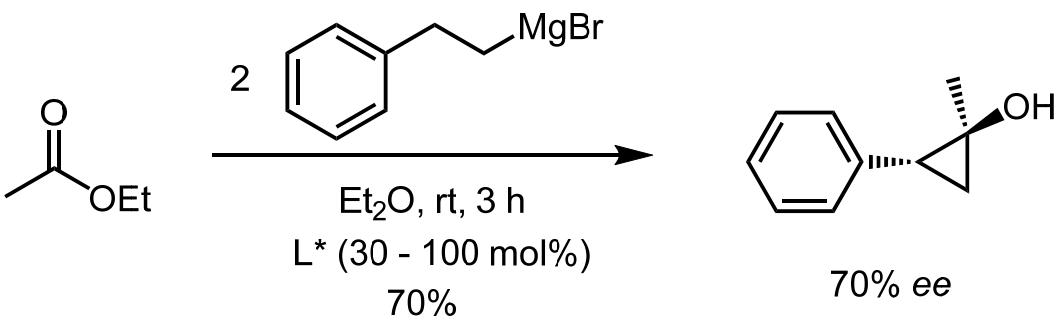


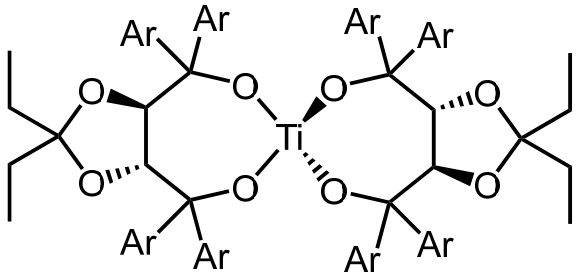
Kulinkovich reaction: to cyclopropanols



from: Brimble et al., *OBC* **2012**, 7637

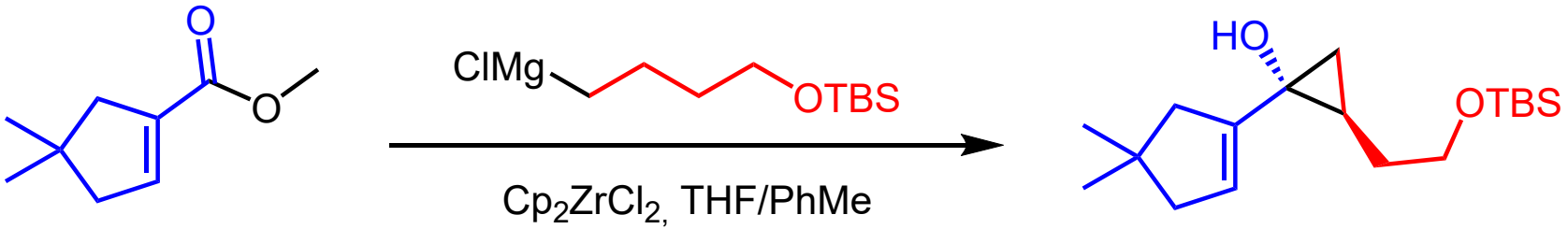
Enantioselective Kulinkovich reaction (Corey et al., *JACS* **1994**, 9345)





Ar = 3,5-bis(trifluormethyl)phenyl

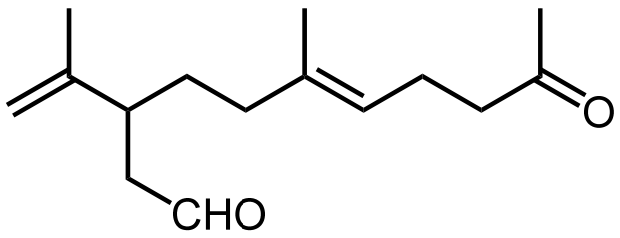
Zirconium does also work:



from: Brimble et al., *OBC* **2012**, 7637

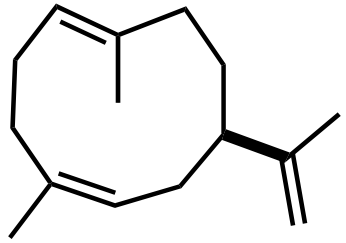
McMurry coupling (*JACS* **1974**, 4708): use of in situ formed "low-valent" titanium

Direct pathway from two aldehydes/ketones to the olefin ...



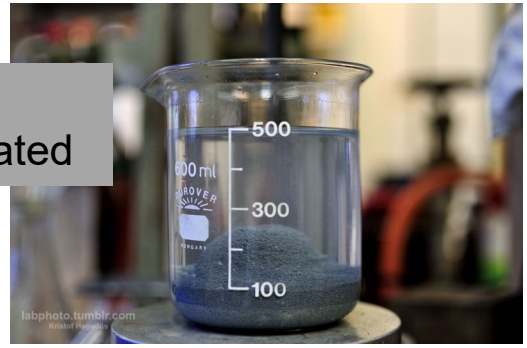
$TiCl_3$, Zn-Cu,DME,
rf, 34 h, 27%

higher temperature

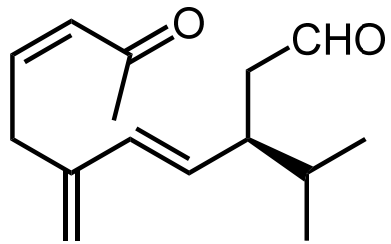


Helminthogermacren

Zn-Cu pair:
>90% Zn, activated



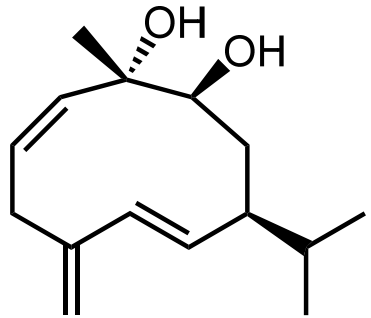
... or to the 1,2-diol



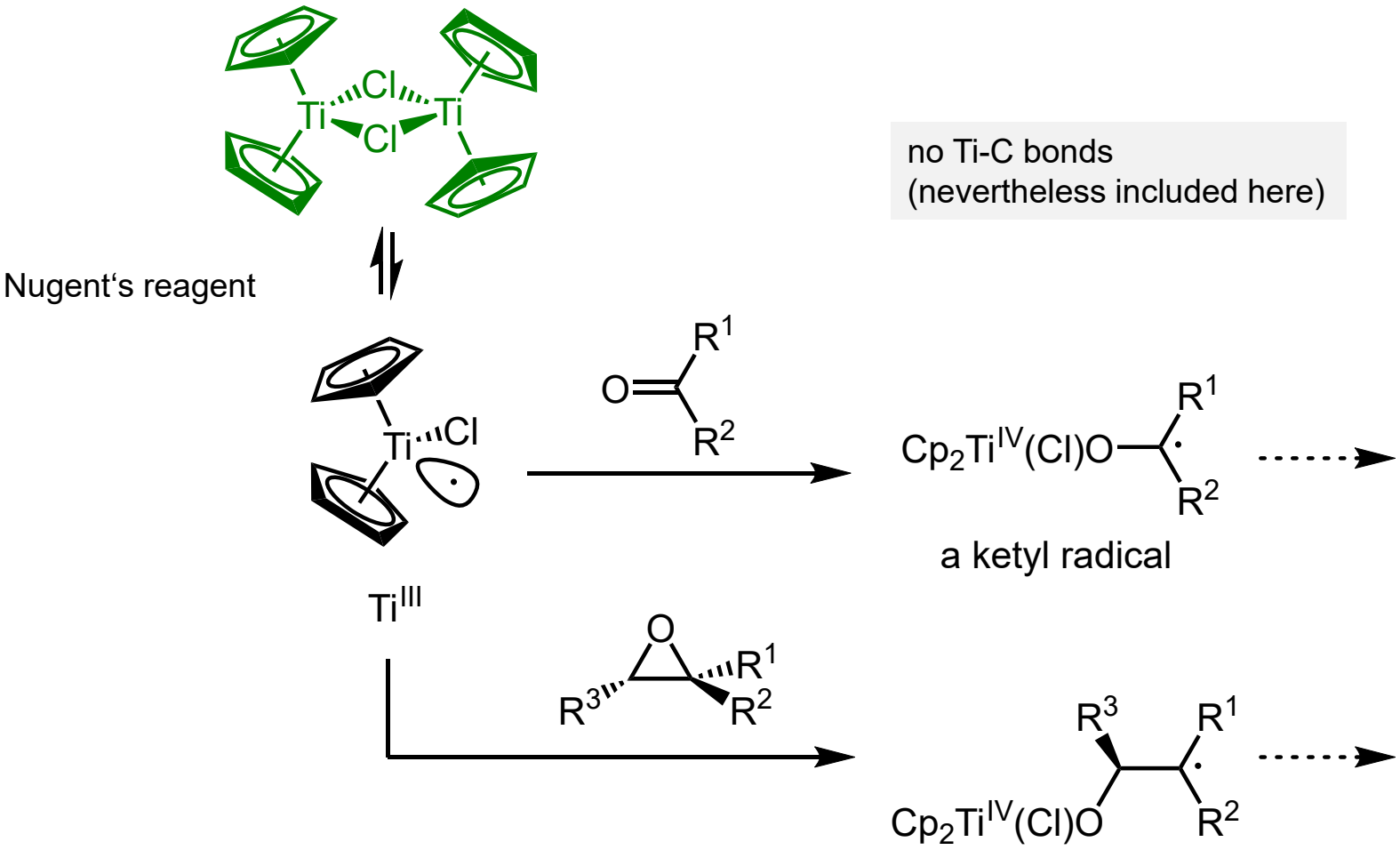
$TiCl_3$-$DME_{1.5}$, Zn-Cu,

DME, 0 °C, 36 h, 62%

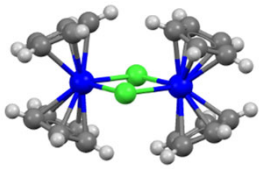
lower temperature



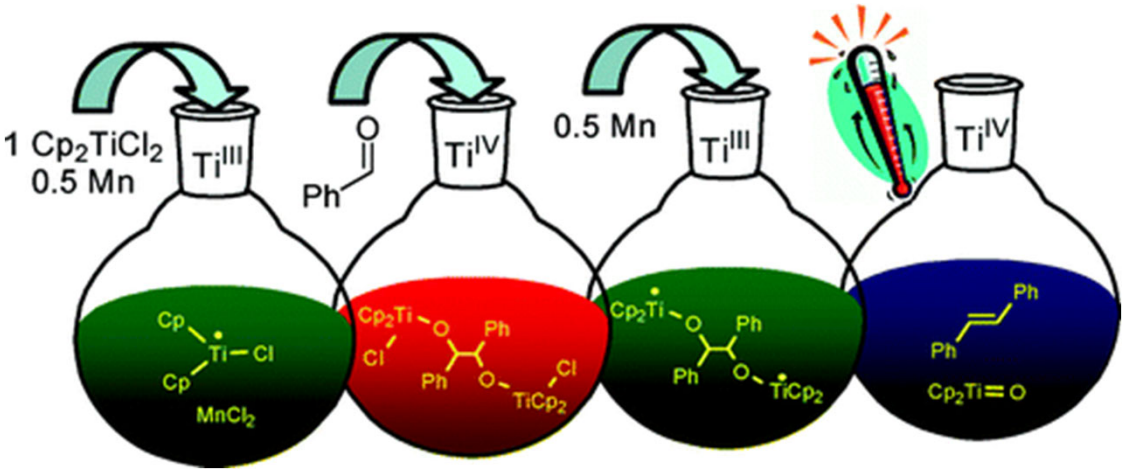
Key to McMurry et al.: Ti(III) radicals form Ti(IV)-oxygen bonds.

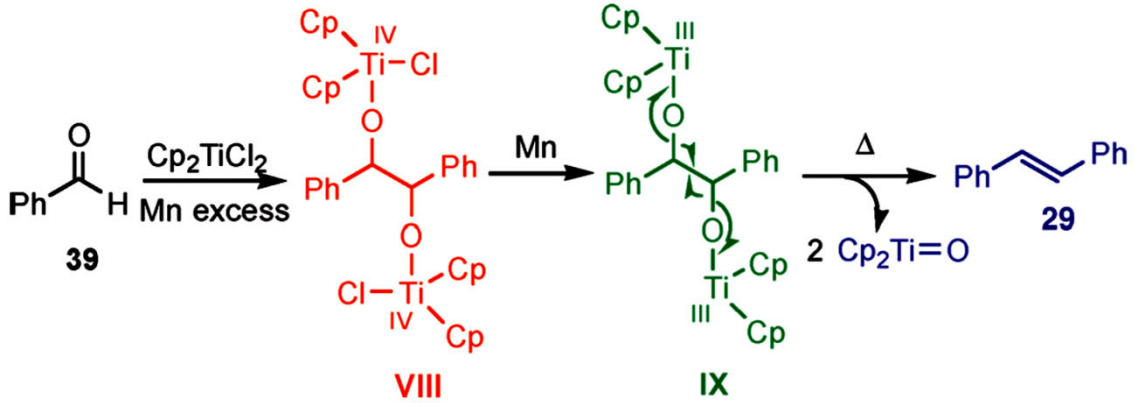


McMurry coupling: use of *in situ* formed $Cp_2Ti(III)Cl$ radicals (Nugent's reagent)



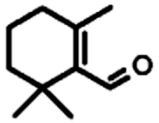
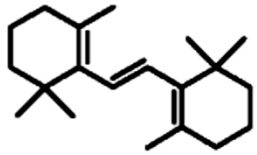
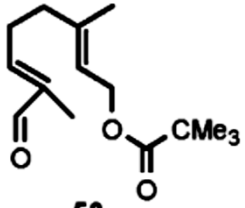
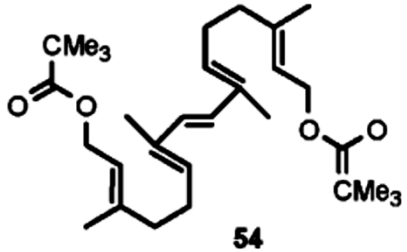
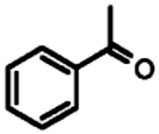
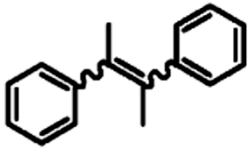
green dimer





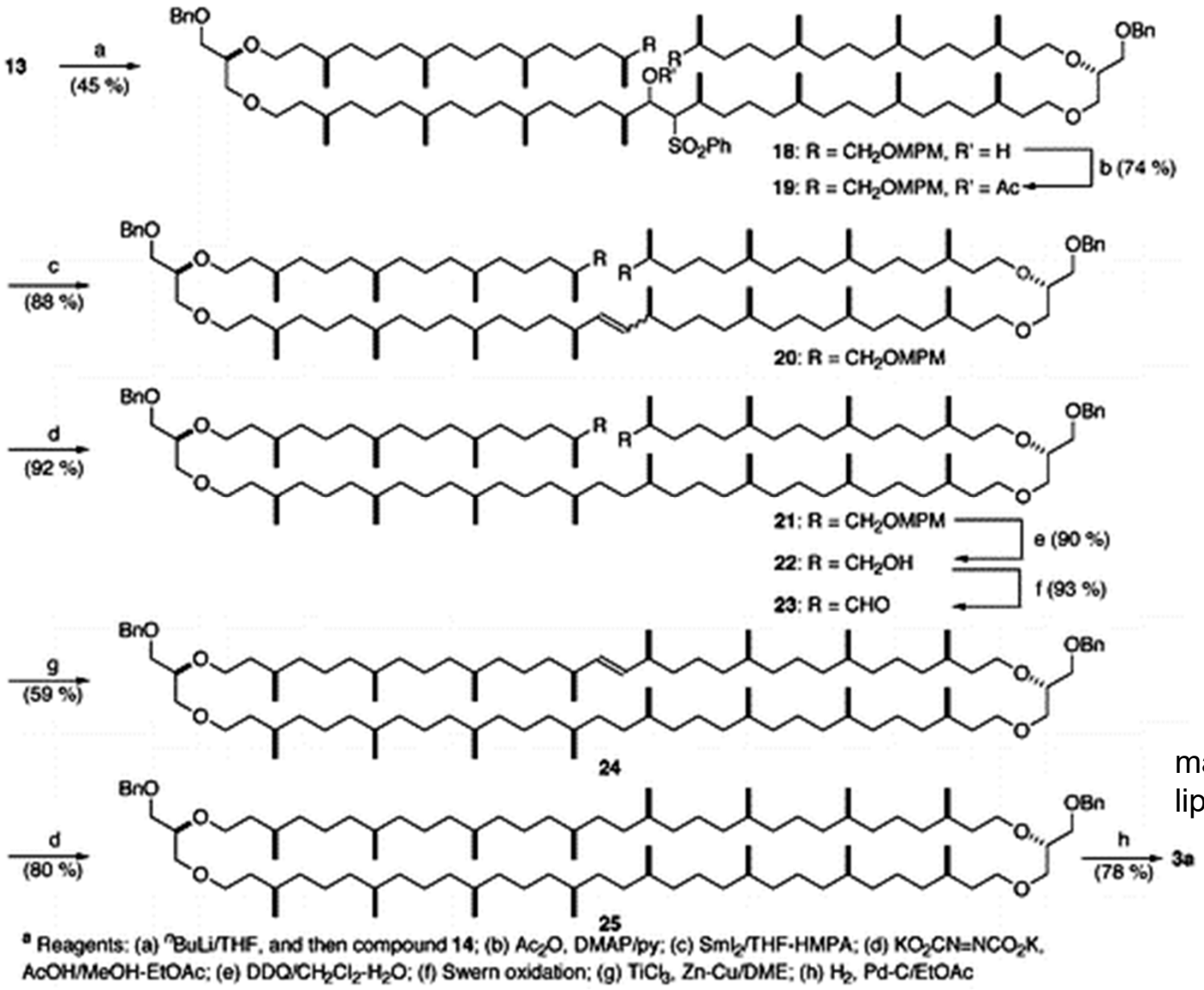
from: Barrero et al., *JACS* **2010**, 254

McMurry coupling: use of in situ formed $Cp_2Ti(III)Cl$ radicals (Nugent's reagent)

entry	substrate	product	yield (%)
9	 51	 52	74[a]
10	 53	 54	73[a]
11	 55	 56	71[a]

Cp_2TiCl (1.2 equiv), Zn or Mn (2.4 equiv), THF

from: Barrero et al., *JACS* **2010**, 254

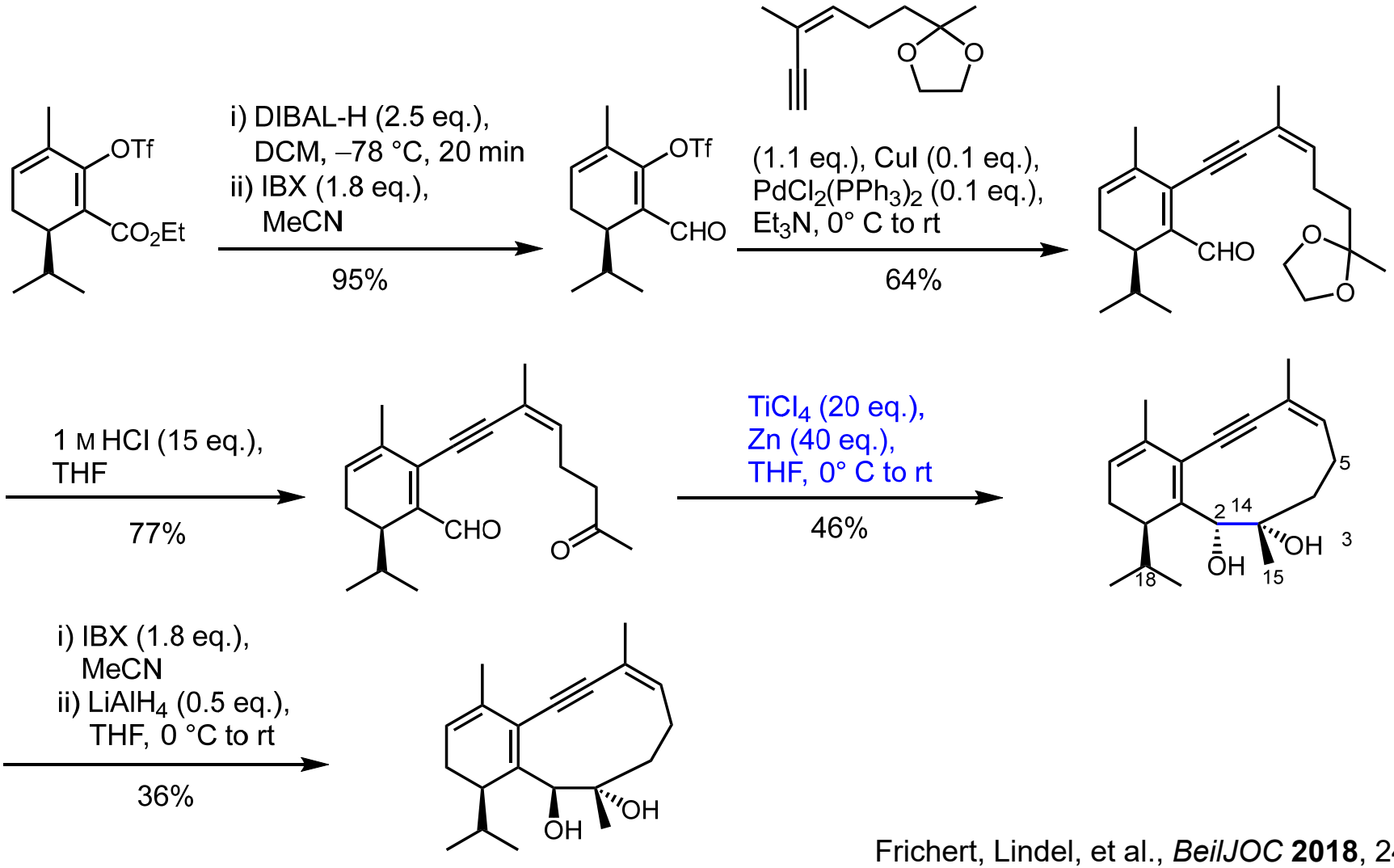


[a] Reagents: (a) ^{n}BuLi/THF, and then compound **14**; (b) Ac_2O, DMAP/py; (c) SmI_2/THF-HMPA; (d) $KO_2CN{=}NCO_2K$, AcOH/MeOH-EtOAc; (e) DDQ/CH_2Cl_2-H_2O; (f) Swern oxidation; (g) $TiCl_3$, Zn-Cu/DME; (h) H_2, Pd-C/EtOAc

macrocyclic tetraether lipid from archaebacteria

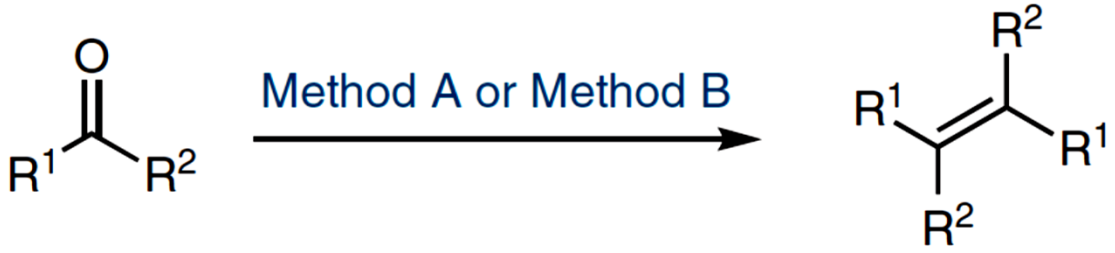
from: Kakinuma et al., *JOC* **1998**, 2689

McMurry coupling: sometimes the less reduced 1,2-diol is formed



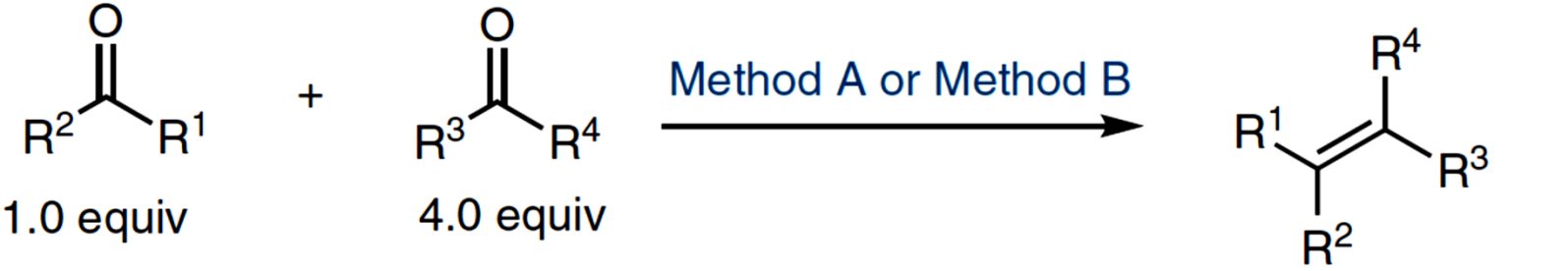
Frichert, Lindel, et al., *BeilJOC* **2018**, 2461

McMurry coupling: use of in situ formed $Cp_2Ti(III)Cl$ radicals (Nugent's reagent)



R^1 = H, Me
R^2 = alkyl, alkenyl, arom

11 examples 62–95%
E selectivity



1.0 equiv

4.0 equiv

R^1 = H, arom
R^2 = arom, alkenyl

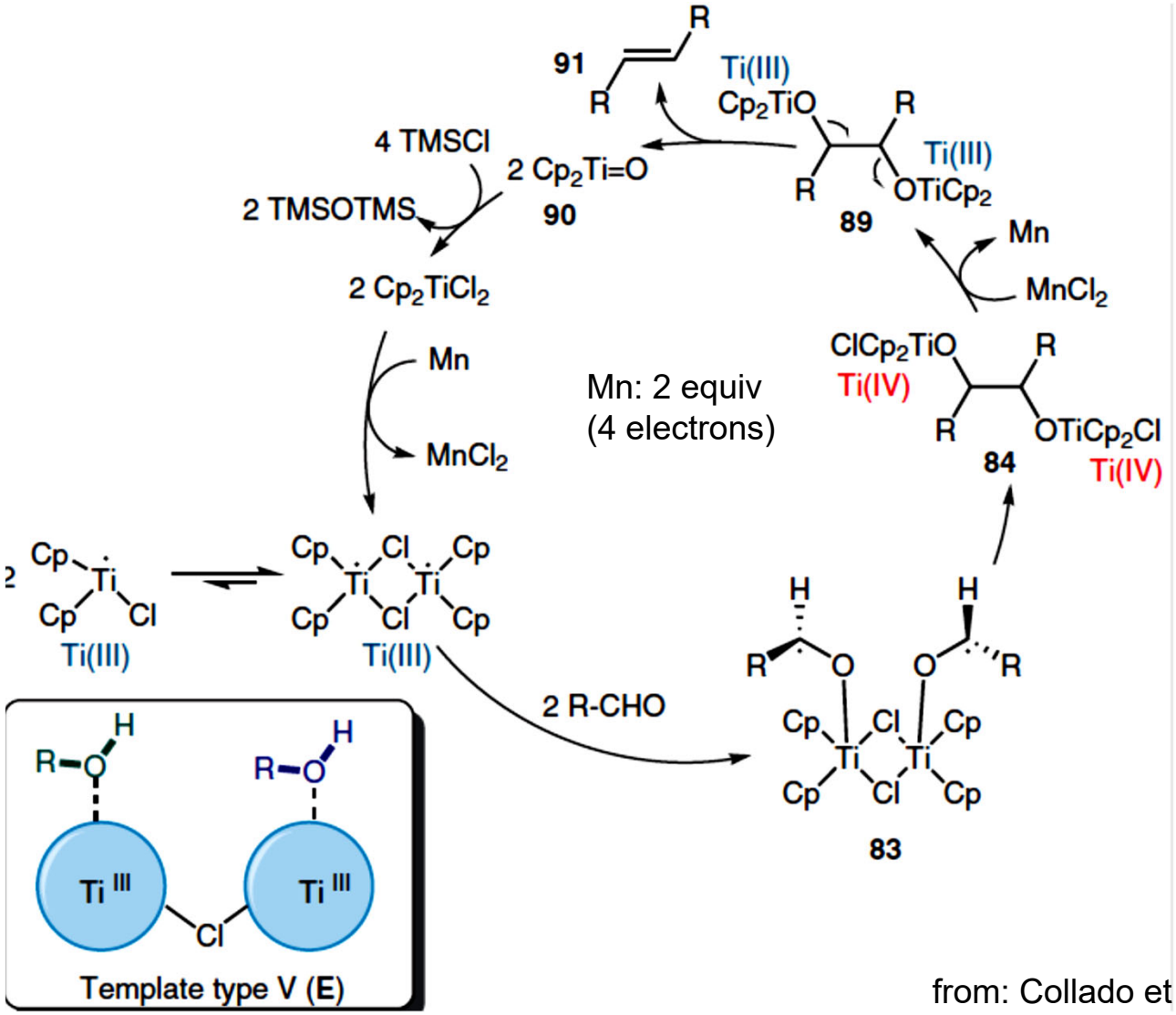
R^3 = H, alkyl
R^4 = alkyl, arom

2 examples 65–77%
E selectivity

Method A: Cp_2TiCl_2 (1.2 equiv), Mn (2.4 equiv), THF, reflux
Method B: Cp_2TiCl_2 (30 mol%), Mn (8.0 equiv), TMSCl (4.0 equiv), THF, reflux

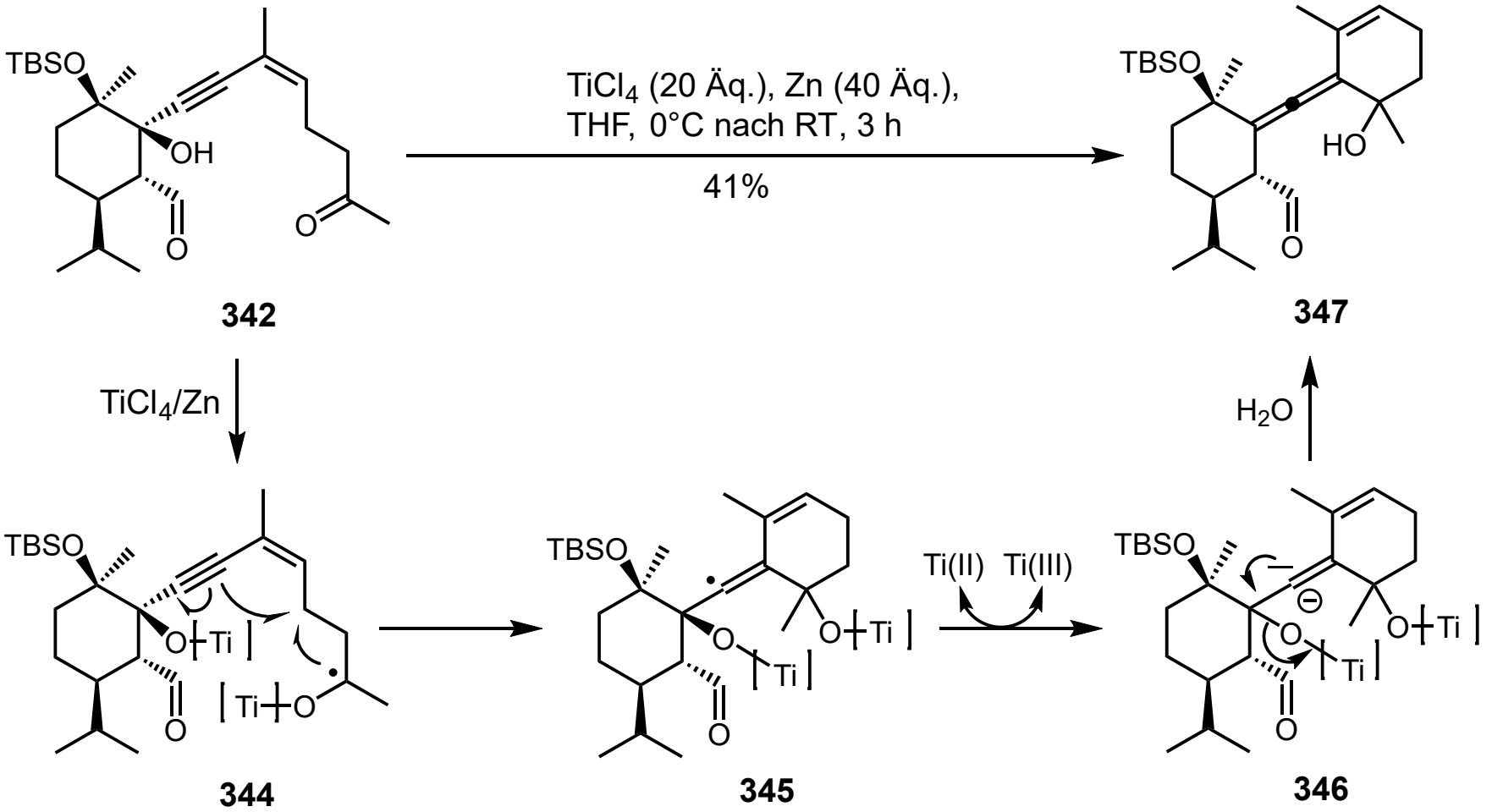
from: Collado et al., *Synthesis* **2018**, 2163

McMurry coupling: catalysis by in situ formed $Cp_2Ti(III)Cl$ radical dimers when adding TMSCl



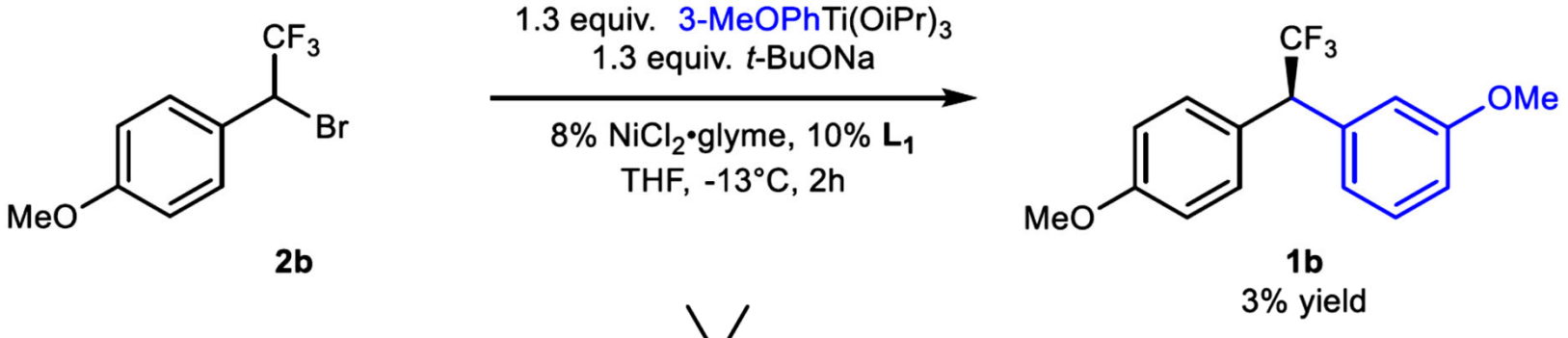
from: Collado et al., *Synthesis* **2018**, 2163

McMurry coupling: sometimes, not even the less reduced 1,2-diol is formed ...

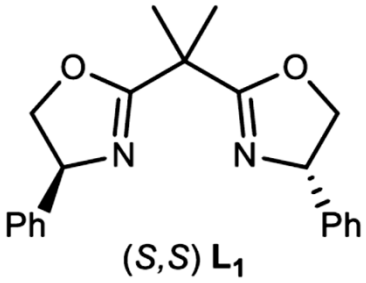


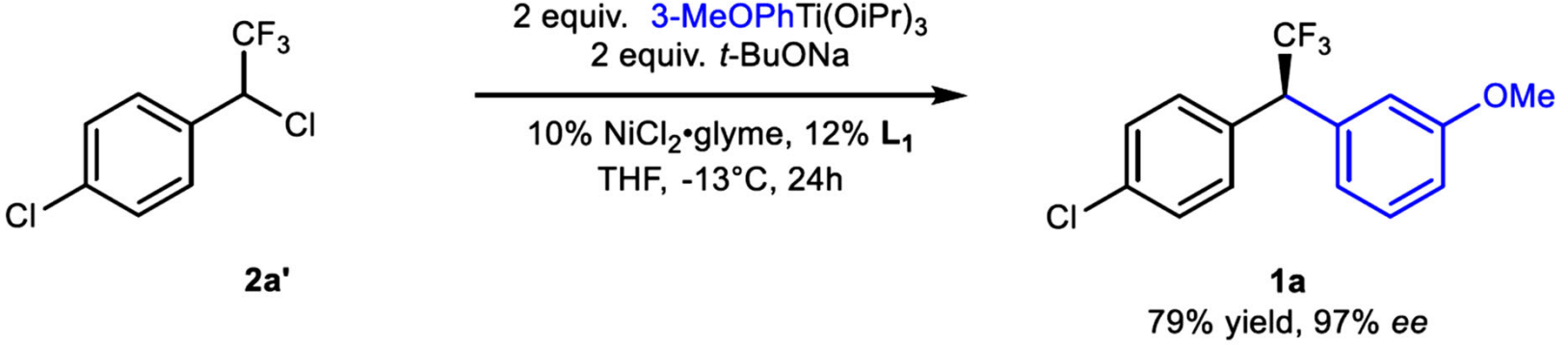
aus: Alex Frichert, Dissertation, TU Braunschweig 2018

Ni-catalyzed enantioselective arylation with an aryltitanium reagent



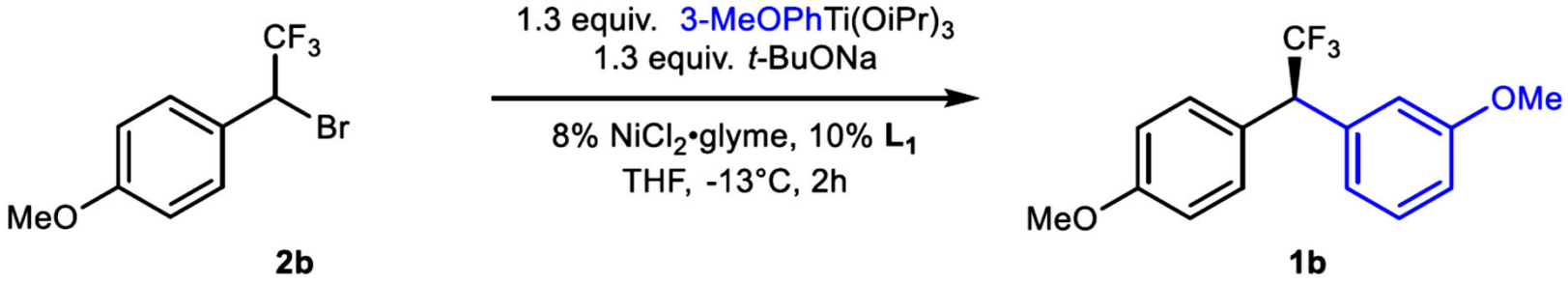
Both enantiomers are used.



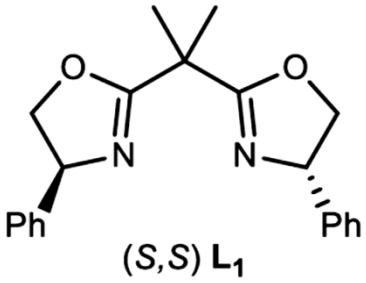


from: Gandelman et al., *OL* **2020**, doi.org/10.1021/acs.orglett.0c03673

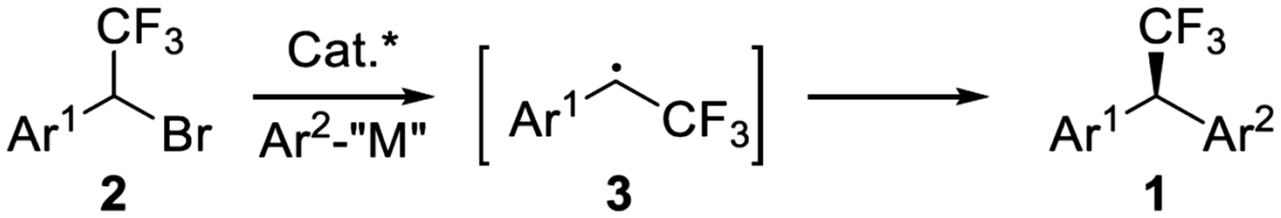
Ni-catalyzed enantioselective arylation with an aryltitanium reagent



Both enantiomers are used.



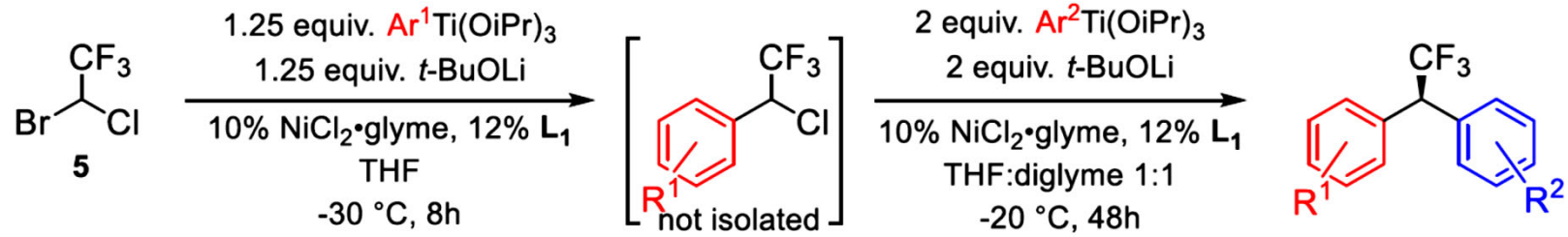
Prior deracemization of the benzhydryl bromides:

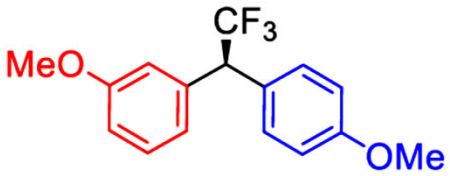


from: Gandelman et al., *OL* **2020**, doi.org/10.1021/acs.orglett.0c03673

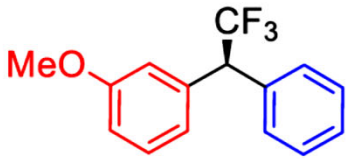
Ni-catalyzed enantioselective arylation with an aryltitanium reagent

Do it stepwise from halothane

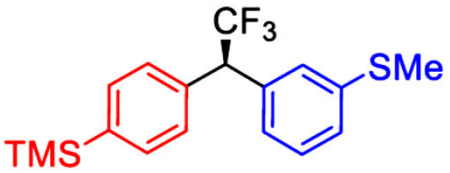




1b
70%, [77%], 94% ee



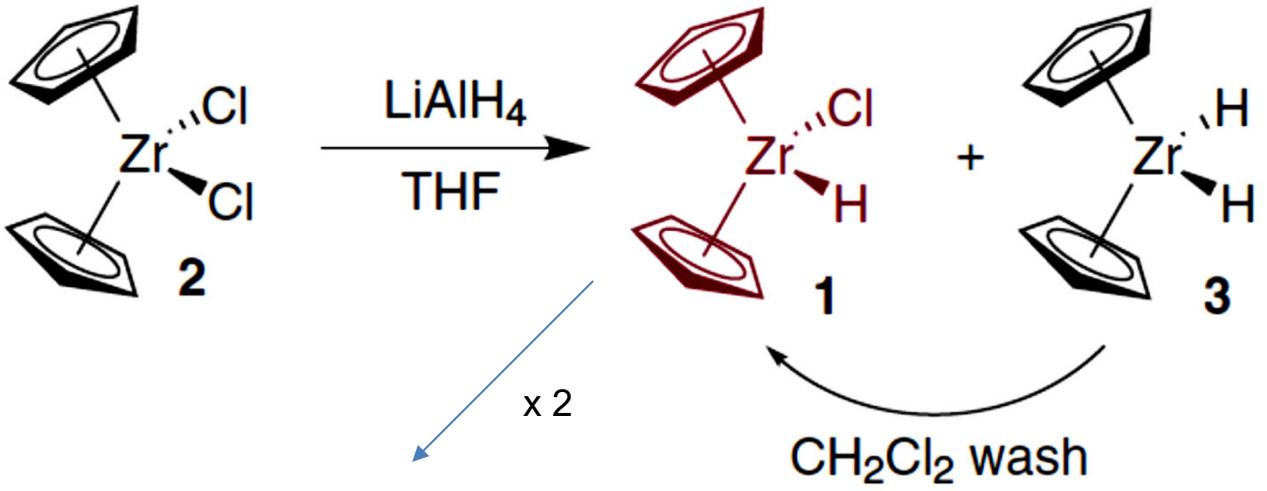
1ba
58%, [72%], 94% ee



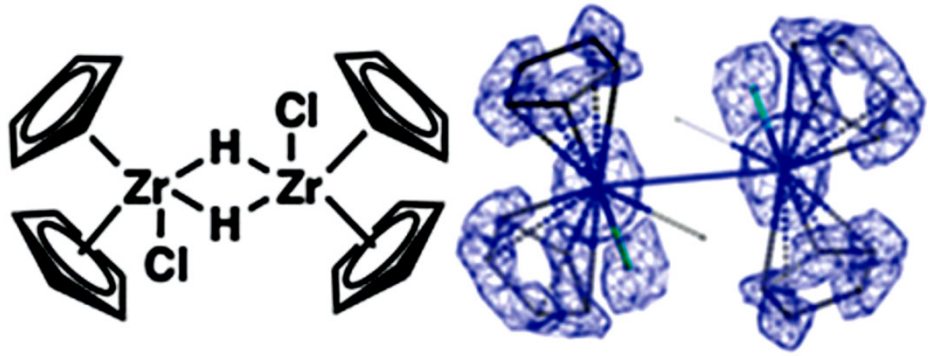
1c
58%, [69%], 93% ee

from: Gandelman et al., *OL* **2020**, doi.org/10.1021/acs.orglett.0c03673

Schwartz reagent (*JACS* **1974**, 8115)



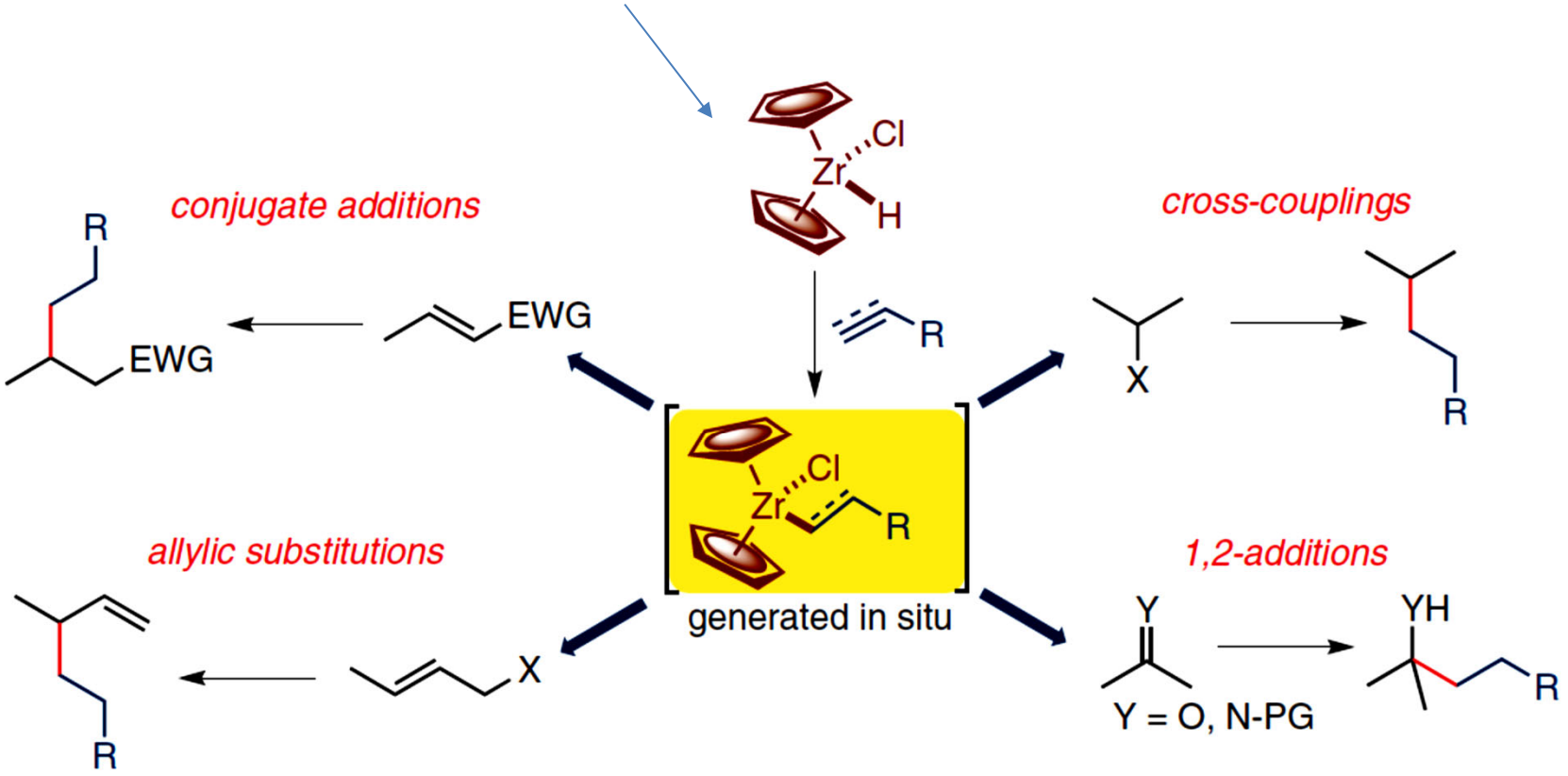
from: Jones, *ChemRxiv* **2019**, search for it



microcrystal electron defraction (microED)

Némethová et al., *Synthesis* **2020**, DOI: 10.1055/s-0040-1706055

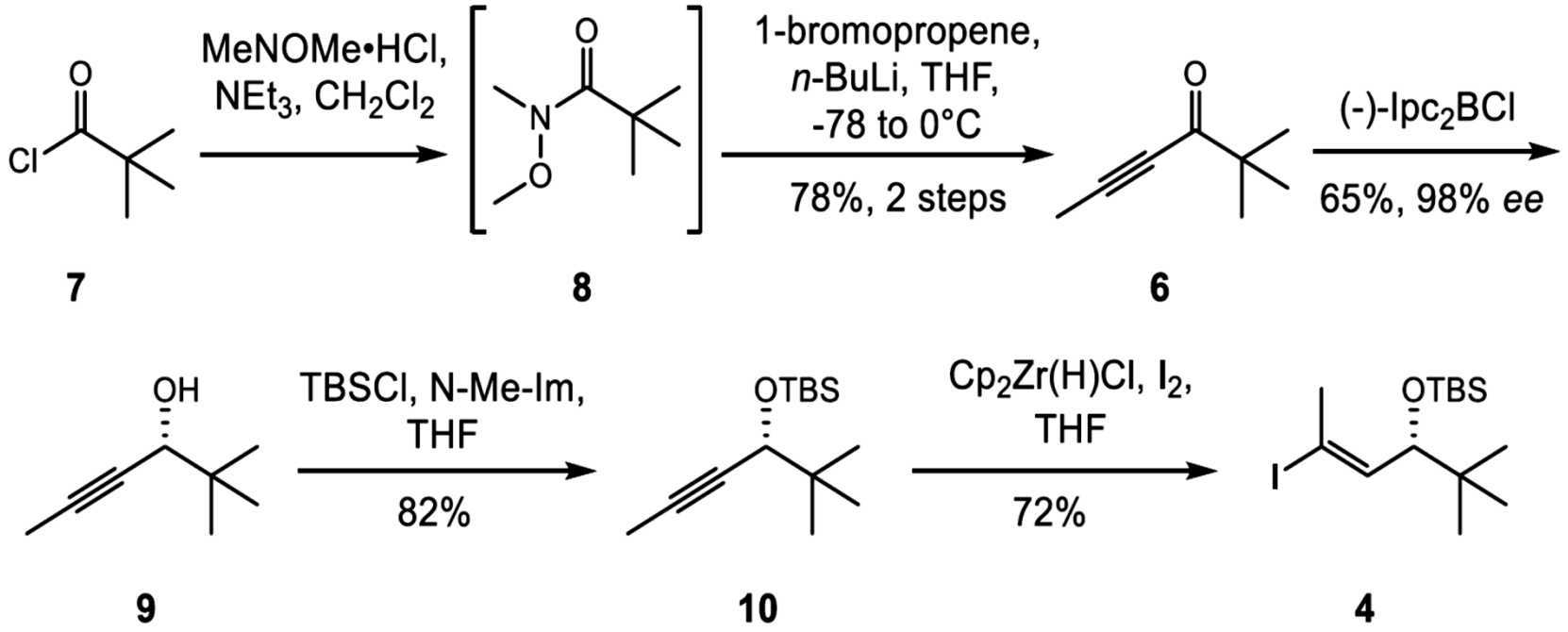
Schwartz reagent



nucleophilicity comparable to that of silylenolethers

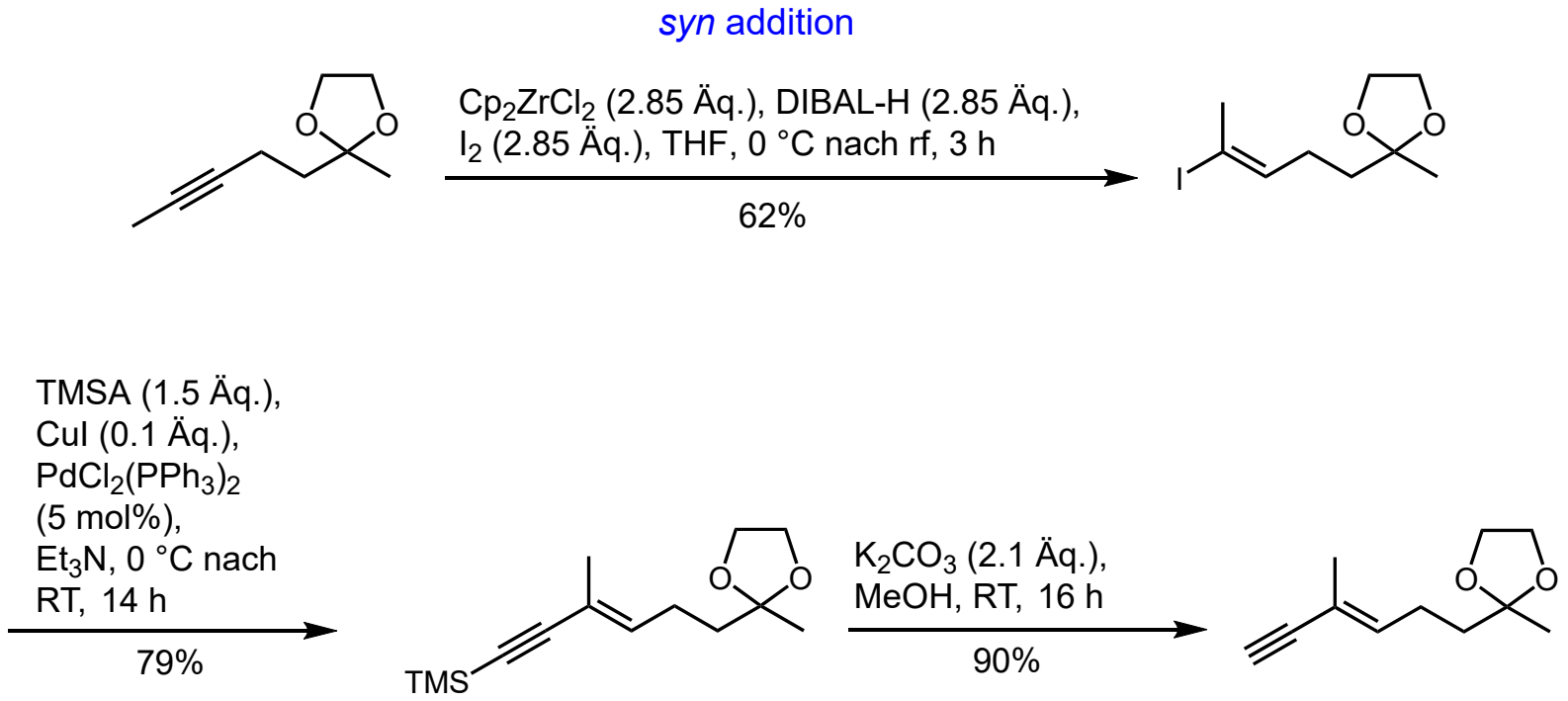
from: Némethová et al., *Synthesis* **2020**, DOI: 10.1055/s-0040-1706055

Schwartz reagent: hydrozirconation, frequently followed by iodination and cross coupling



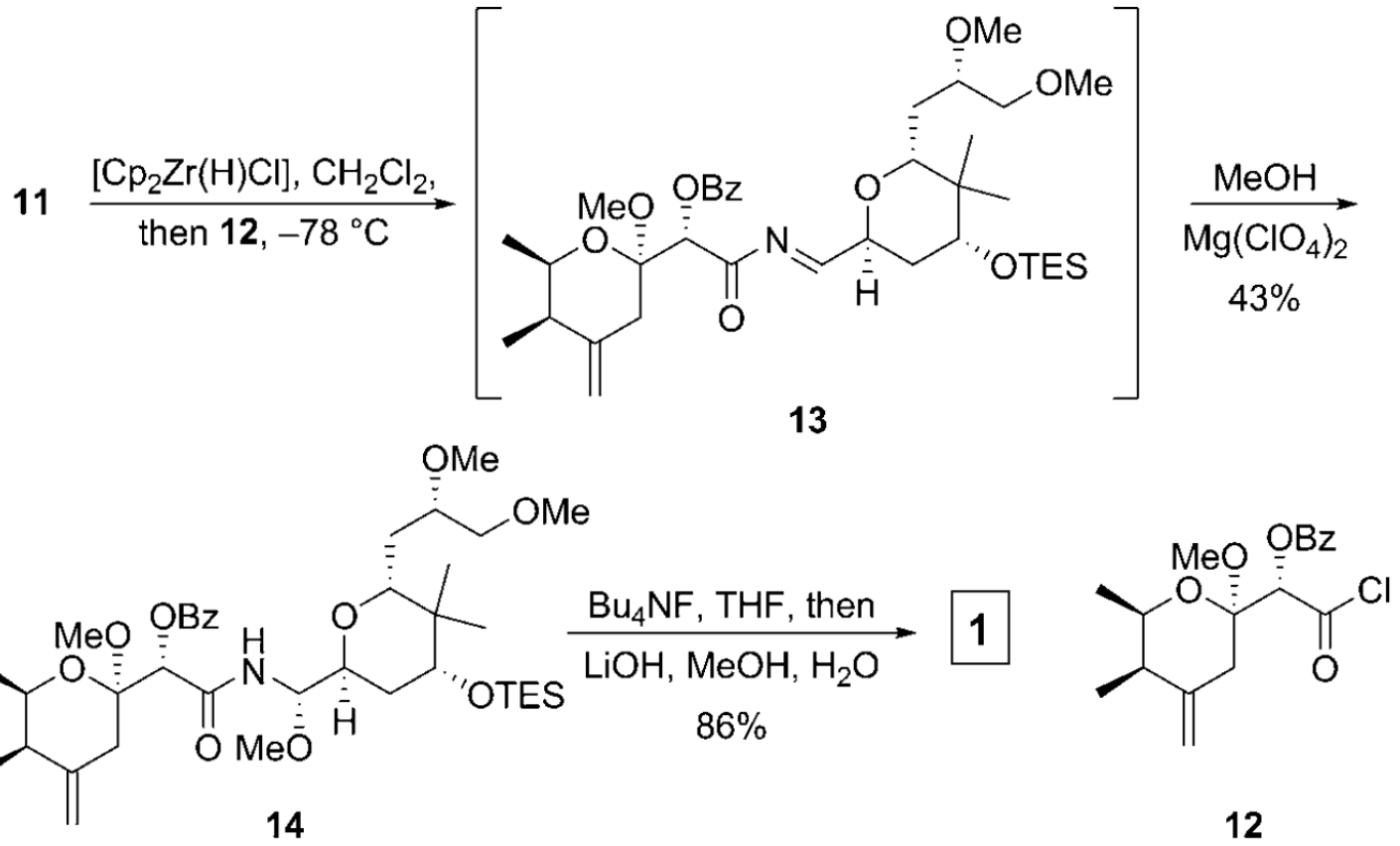
Payne et al., *OL* **2020**, 3089; DOI: dx.doi.org/10.1021/acs.orglett.0c00840

Schwartz reagent: hydrozirconation, frequently followed by iodination and cross coupling



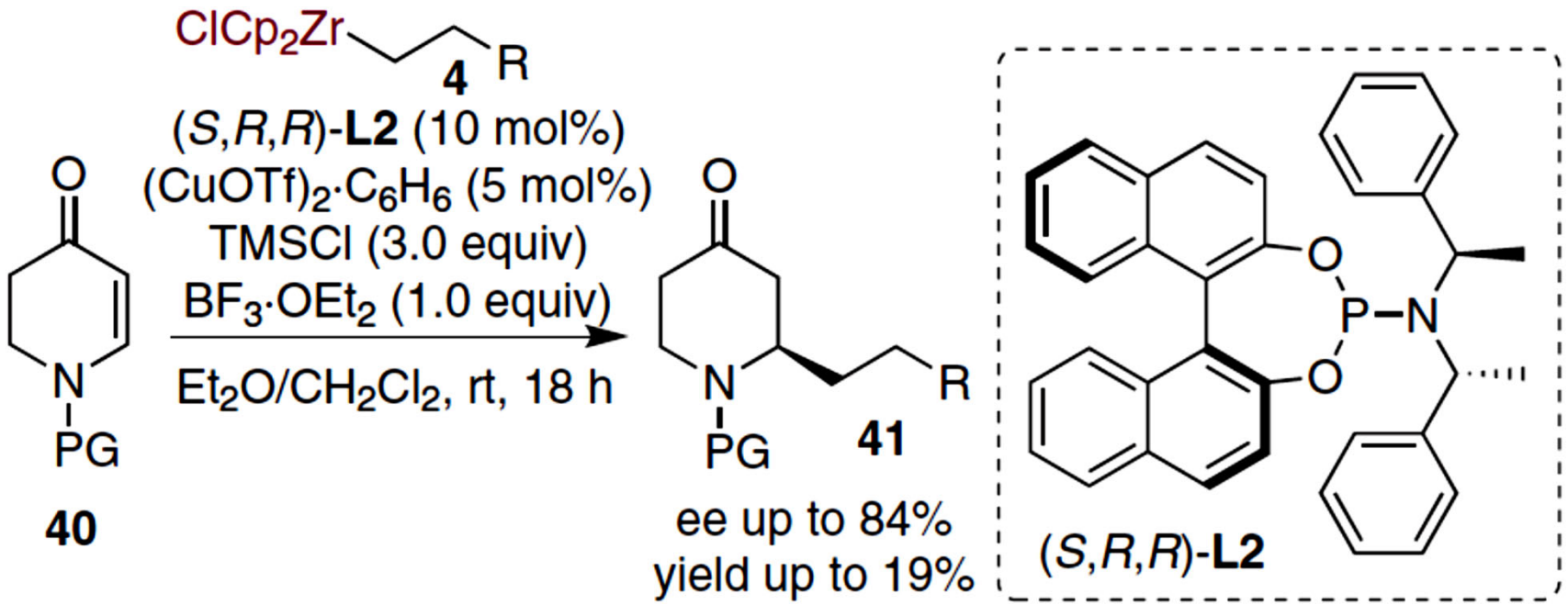
aus: Alex Frichert, Dissertation, TU Braunschweig 2018

Schwartz reagent: reduction of nitriles to imines



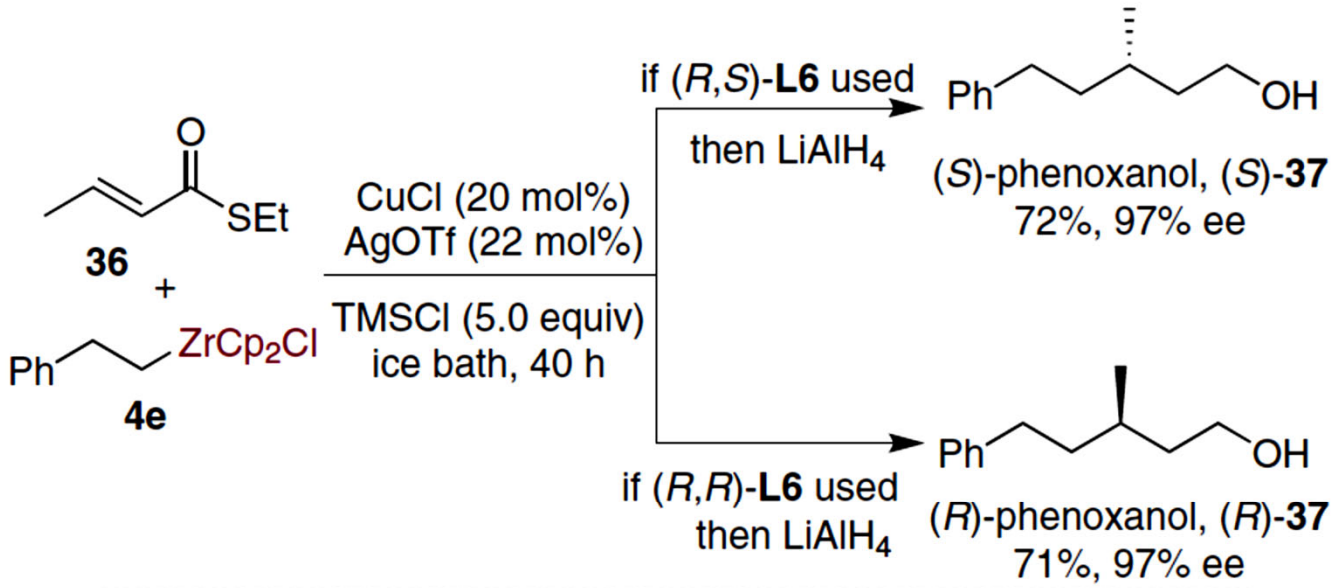
Floreancig et al., *ACIE* **2011**, 1131

Schwartz reagent: enantioselective Cu-catalyzed conjugate addition (behaves like a cuprate)



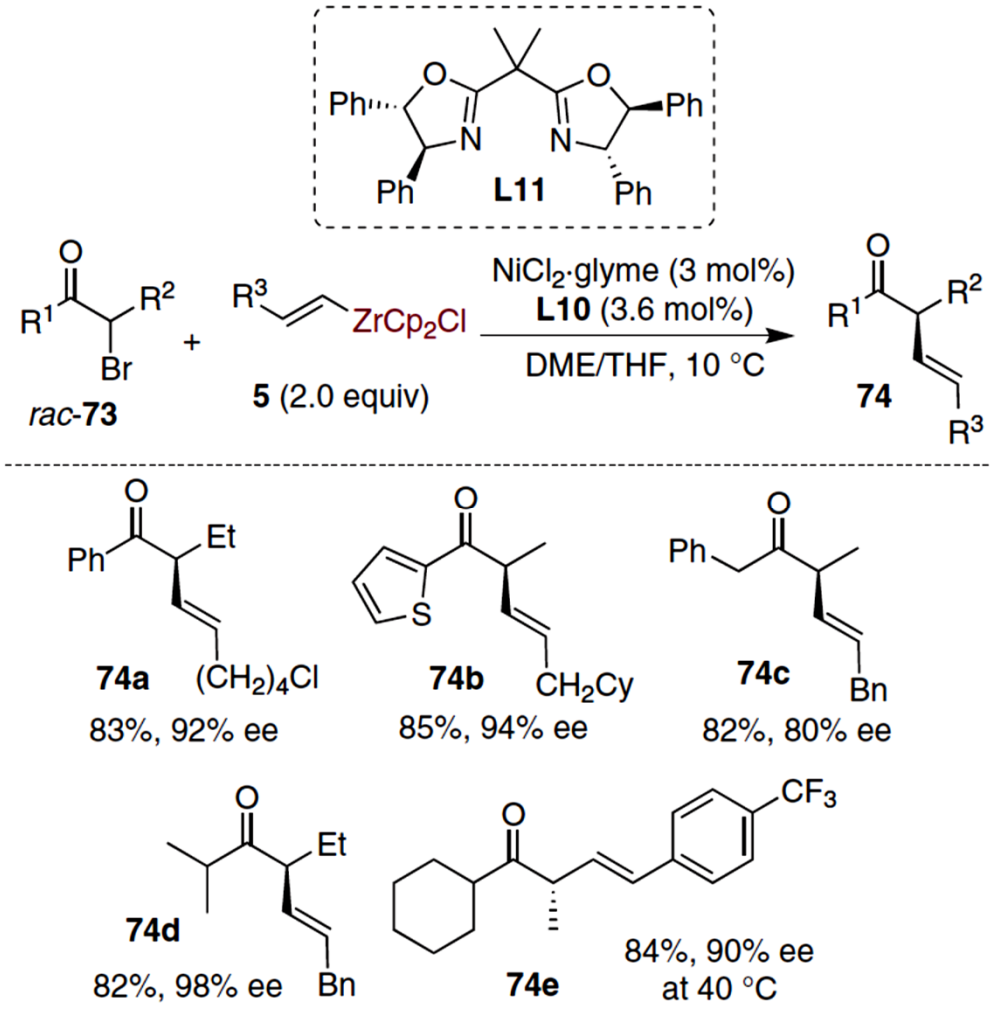
from: Némethová et al., *Synthesis* **2020**, DOI: 10.1055/s-0040-1706055

Schwartz reagent: enantioselective Cu-catalyzed conjugate addition to thiolesters



from: Némethová et al., *Synthesis* **2020**, DOI: 10.1055/s-0040-1706055

Schwartz reagent: enantioselective Ni-catalyzed α-alkenylation (enolate cross coupling)



from: Némethová et al., *Synthesis* **2020**, DOI: 10.1055/s-0040-1706055

SmI_2

introduction to organic synthesis:
Henri B. Kagan (mid 1970s)

$E^0(Sm^{+II}/Sm^{+III})$ = –1.55 V
(in water *vs.* NHE)

$Sm + I_2 \rightarrow SmI_2$

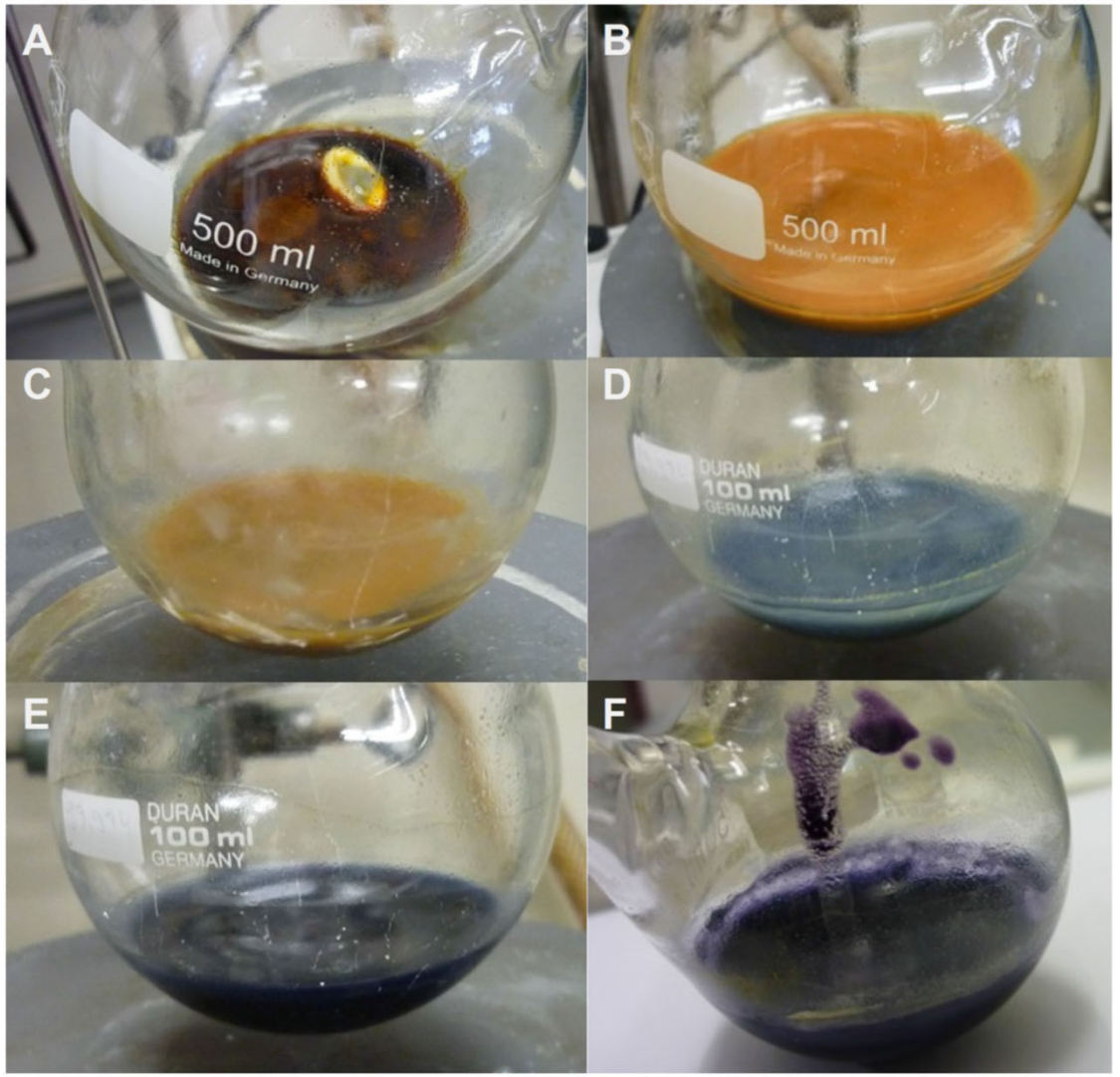
A: I_2 in THF

B: + Sm (-> SmI_3)

C, D: + Sm (-> SmI_2 + SmI_3)

E: SmI_2

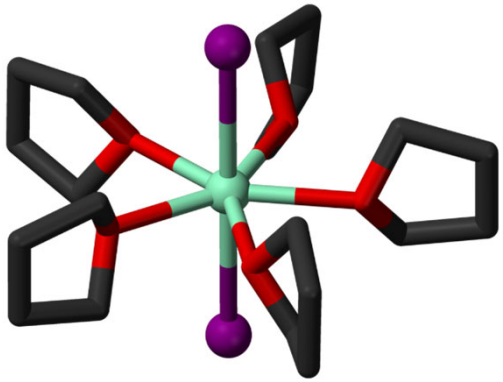
F: + DMPU



aus: Johannes Wefer, Dissertation, TU Braunschweig 2015

Redox potentials of SmX_2 in different environments (against SCE)

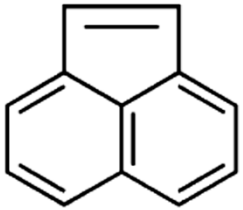
Sm(II) reductant	$-E_{1/2}$ [a]	electrode	solvent
SmI_2	0.89 ± 0.08 [b]	SCE	THF
SmI_2–HMPA	1.79 ± 0.08	SCE	THF
SmI_2–DMPU	1.61 ± 0.01 [c]	SCE	THF
$SmBr_2$	1.55 ± 0.07 [d]	SCE	THF
$SmCl_2$	1.78 ± 0.10 [e]	SCE	THF
$Sm(HMDS)_2$	1.5 ± 0.1 [f]	SCE	THF
$SmBr_2$–HMPA	2.03 ± 0.01 [g]	SCE	THF
$SmI_2(H_2O)_n$ ($n = 60$)	1.0 ± 0.1 [h]	SCE	THF/DME
$SmI_2(H_2O)_n$ ($n = 500$)	1.3 ± 0.1 [i]	SCE	THF/DME



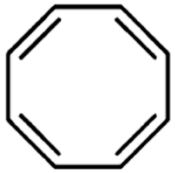
E_0(NHE) = E_0(SCE) + 0.24 V

Procter et al., *JOC* **2014**, 2522

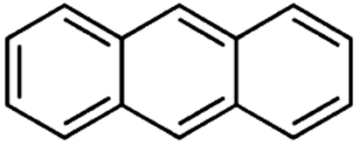
Redox potentials of hydrocarbons and halides in DMF (against SCE)



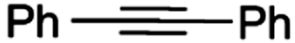
1, -1.65 V



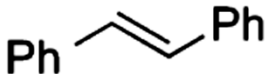
2, -1.83 V



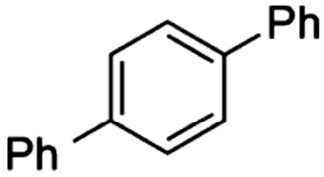
3, -1.98 V



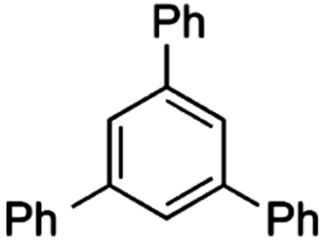
4, -2.11 V



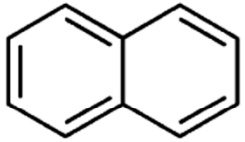
5, -2.21 V



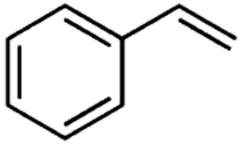
6, -2.40 V



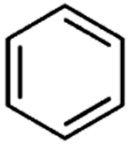
7, -2.51 V



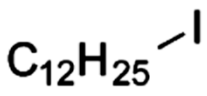
8, -2.61 V



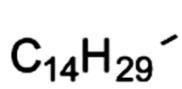
9, -2.65 V



10, -3.42 V



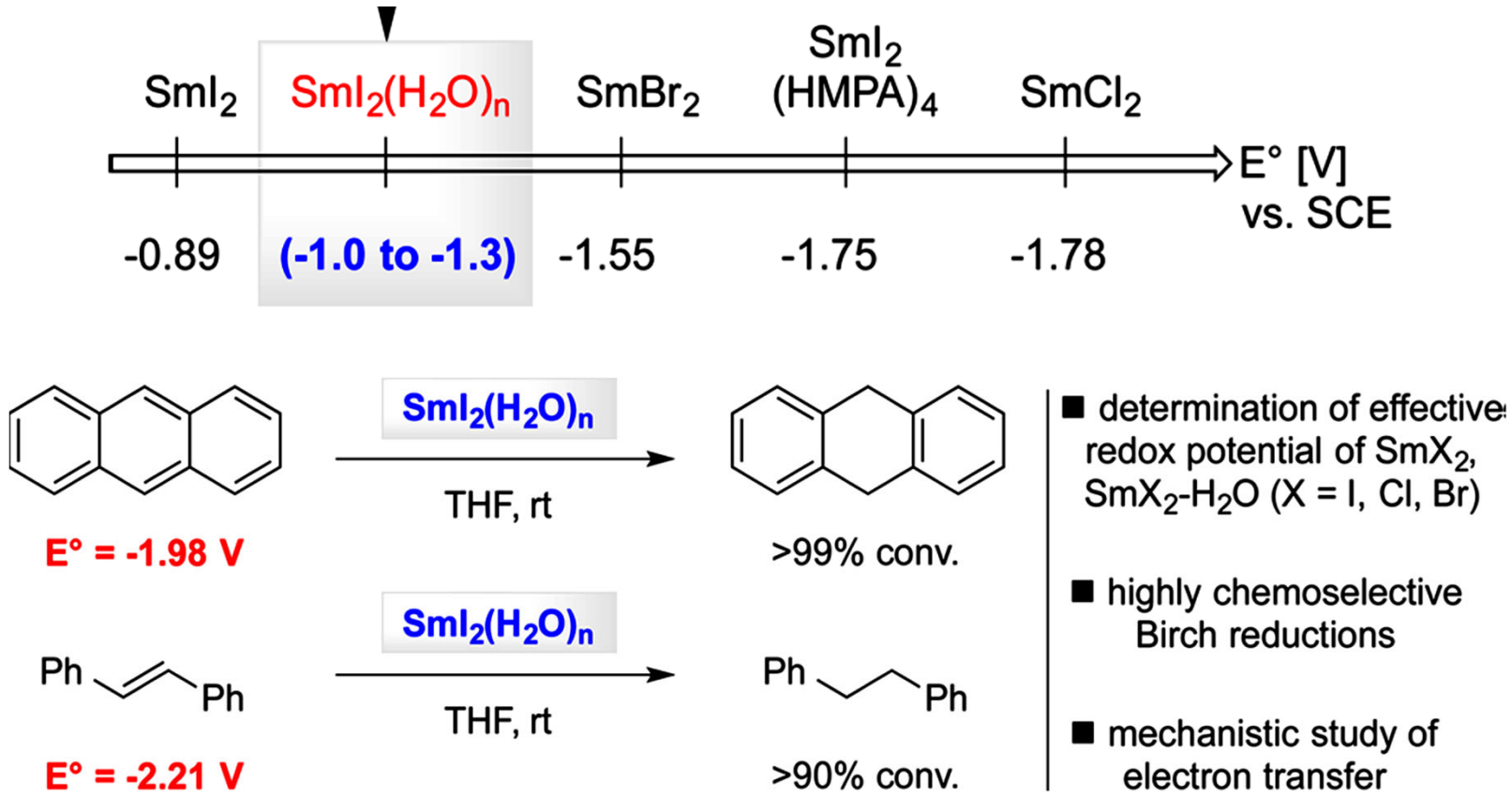
11, -1.30 V



12, X = Br, -2.29 V
13, X = Cl, -2.79 V
14, X = F, -2.97 V

Procter et al., *JOC* **2014**, 2522

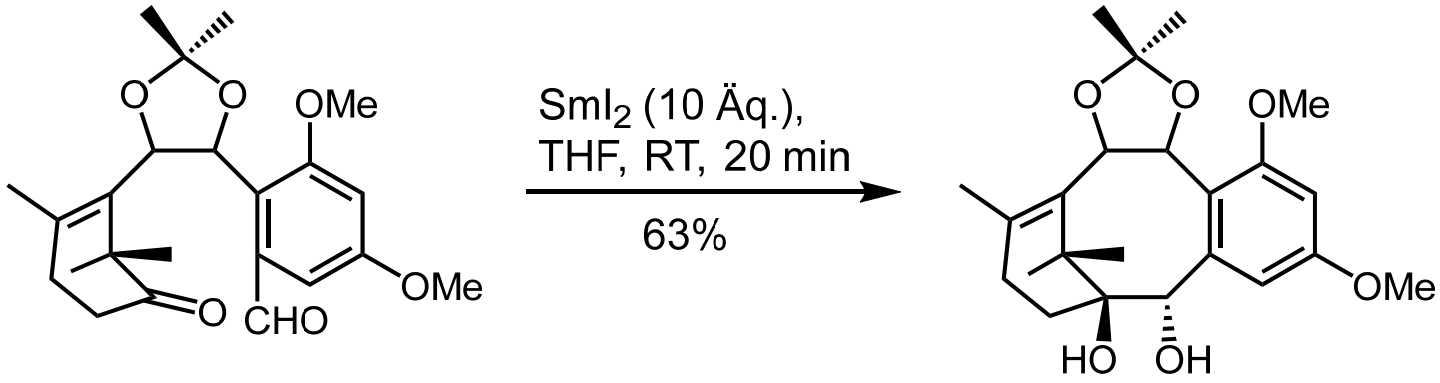
Reduction potentials inconsistency

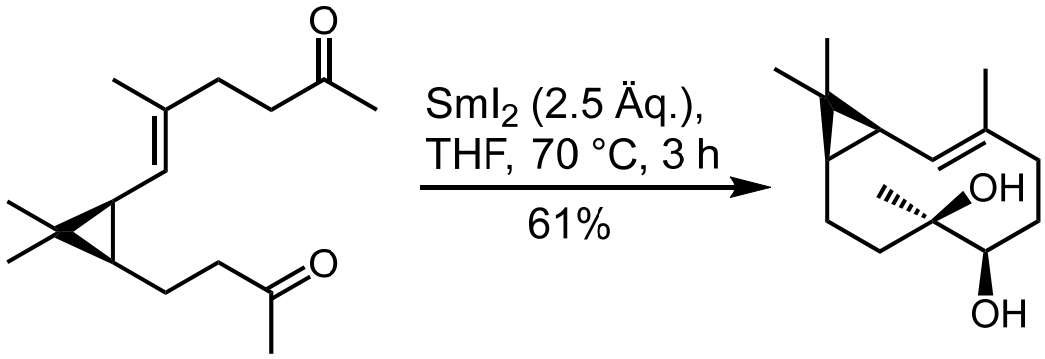


$SmI_2(H_2O)n$ is capable of reducing substrates with $E_0 > -2.2$ V.

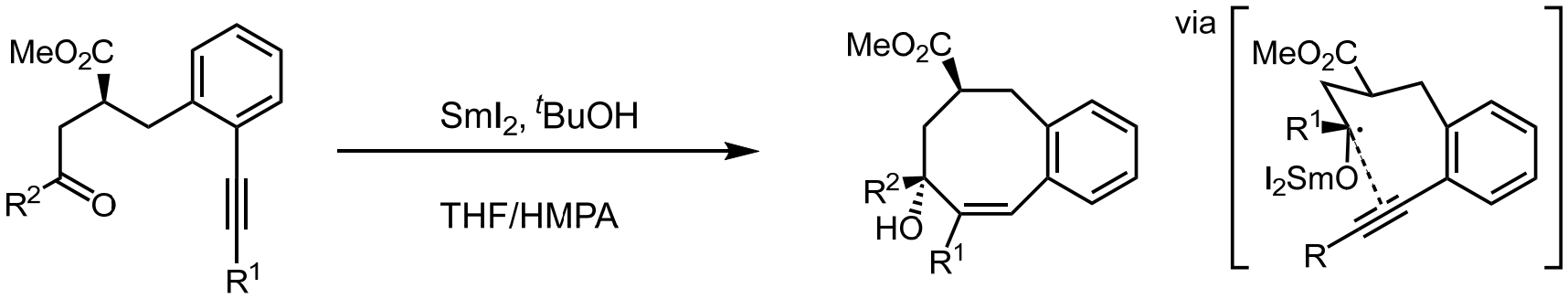
Procter et al., *JOC* **2014**, 2522

SmI_2: pinacol coupling via the ketyl radicals





SmI_2: carbonyl-alkyne cyclization

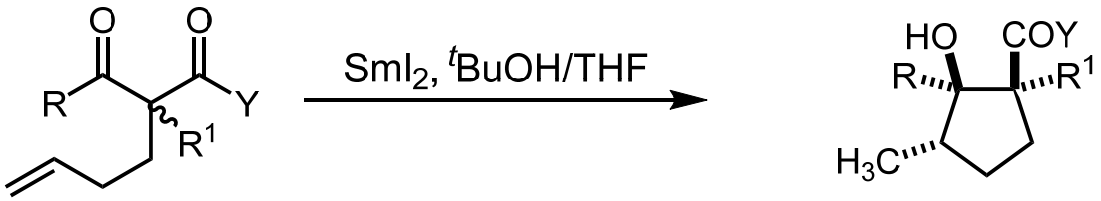


R^1 = H, $SiMe_3$, ^{n}Bu, CH_2OMe
R^2 = Me, ^{i}Pr

61-78%

Reißig et al., *Tetrahedron* **2000**, 4267

SmI_2: carbonyl-olefin cyclization

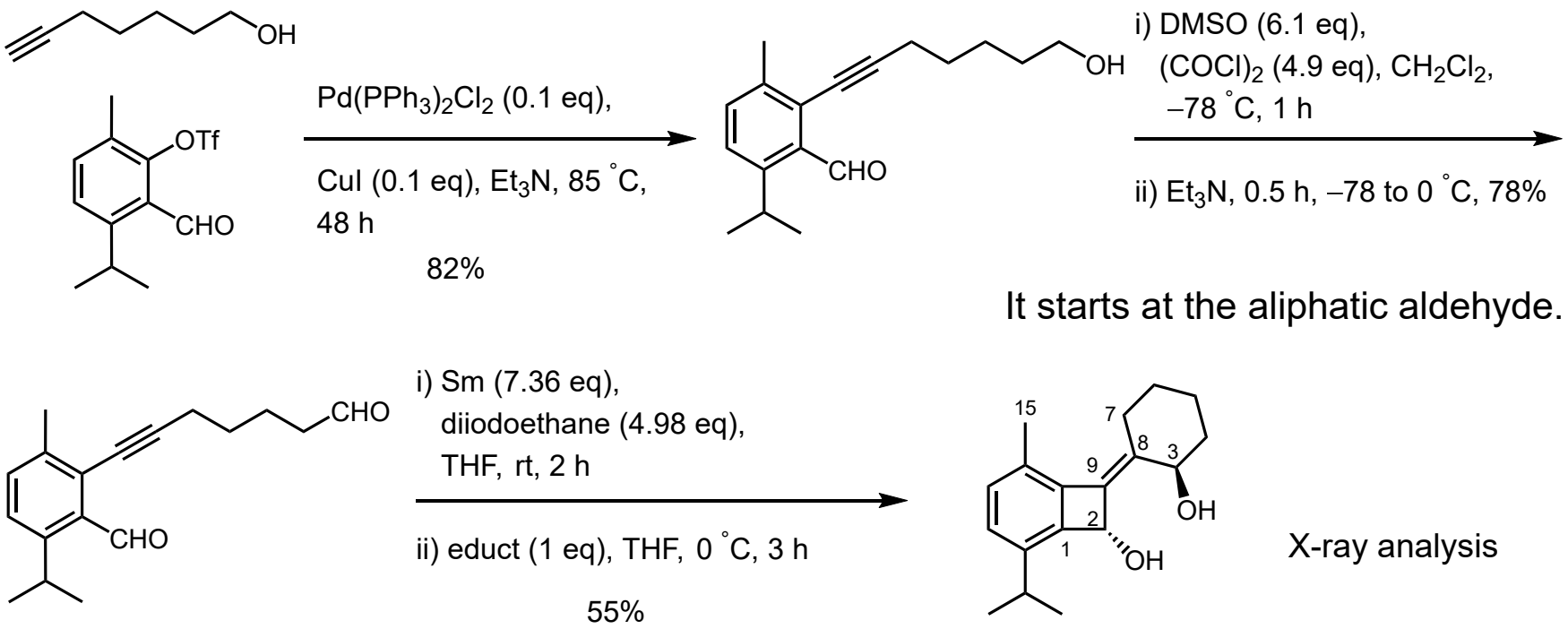


Y = OEt, OMe, R = Me, Et, ^{i}Pr, R^1 = Me, H
Y = OEt, R = Me, R^1 = Et

60-75%, *dr* up to 30:1
51%, *dr* 200:1

Molander et al., *JACS* **1989**, 8236

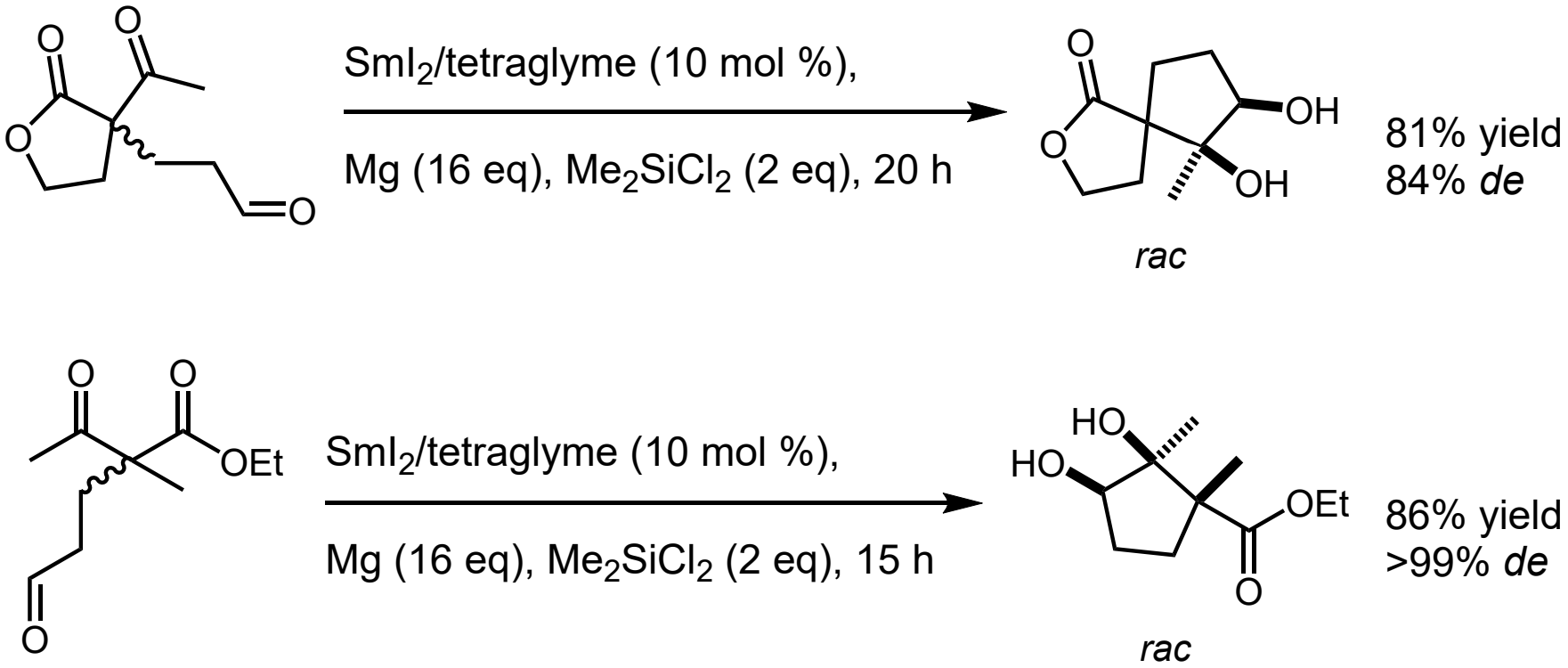
SmI_2: carbonyl-alkyne cyclization



The (*Z*)-olefin gave pinacol coupling!

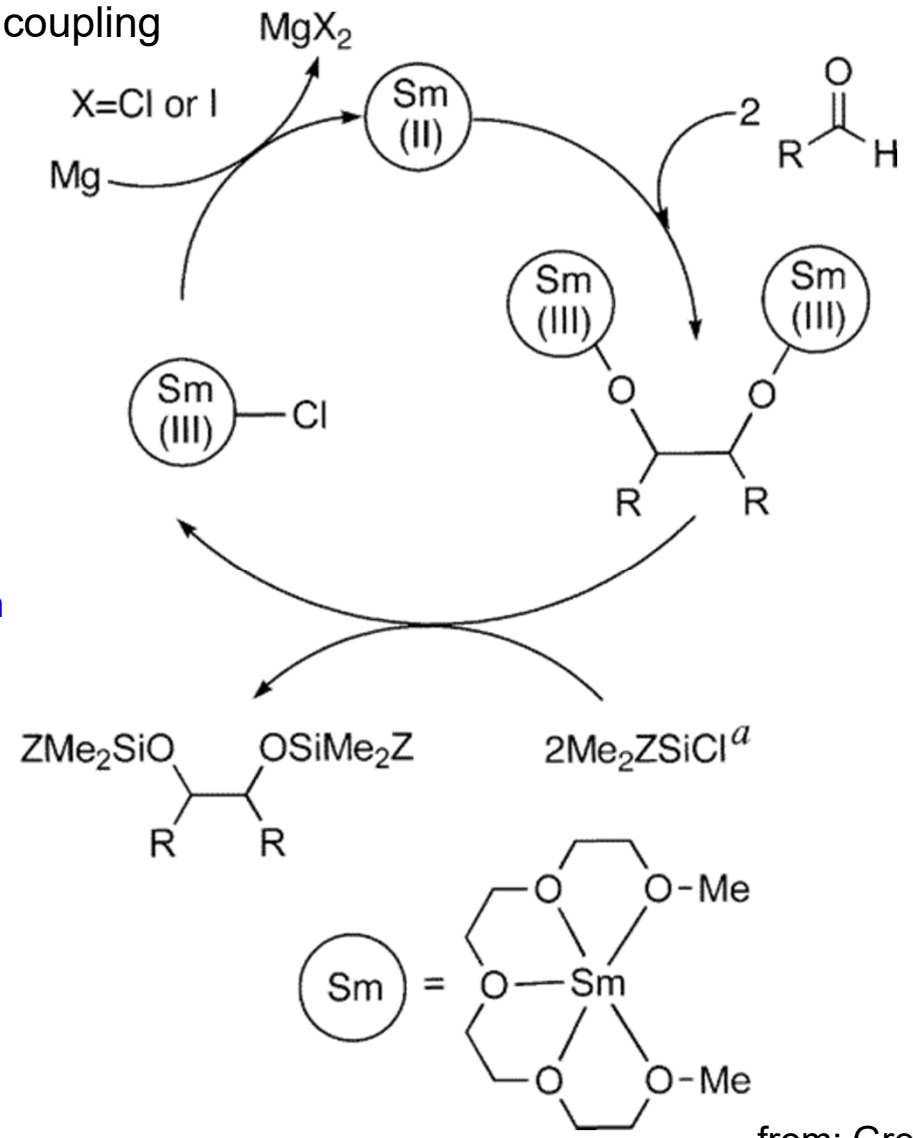
Al Batal, Lindel, *EurJOC* **2013**, 2533; Dissertation, TU Braunschweig, 2012

Catalytic SmI_2: pinacol coupling



Greeves et al., *OL* **2005**, 1919

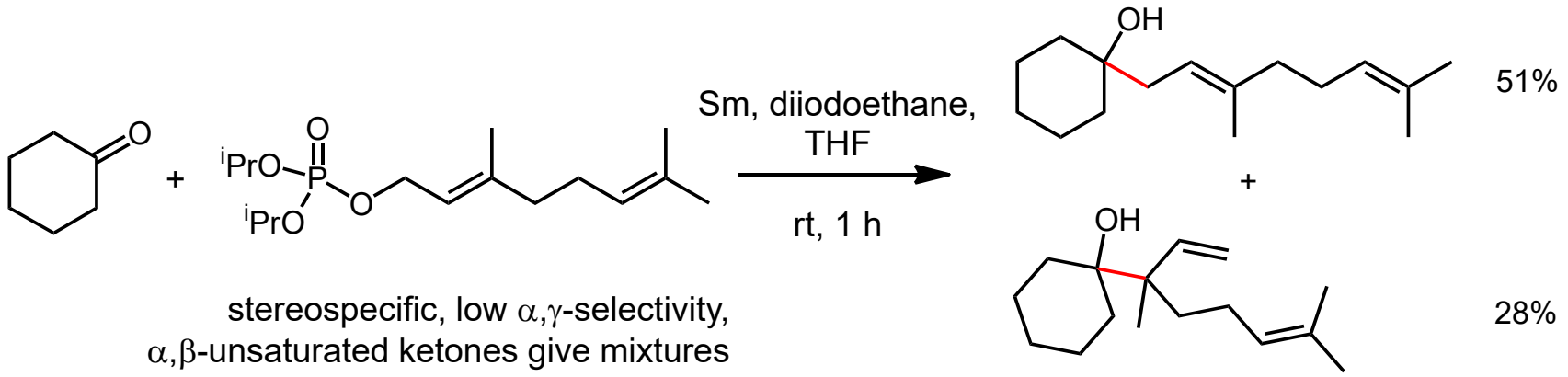
Catalytic SmI_2: pinacol coupling



proposed mechanism

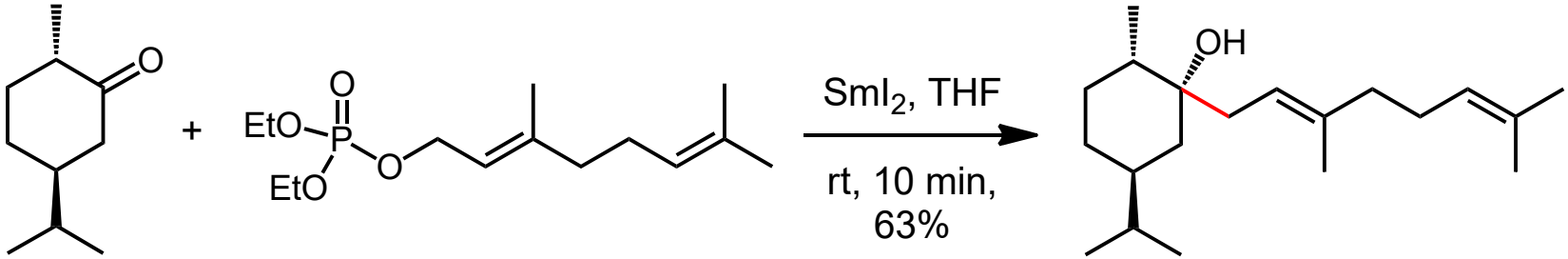
from: Greeves et al., *OL* **2005**, 1919

Sm-Barbier reaction



stereospecific, low α,γ-selectivity,
α,β-unsaturated ketones give mixtures

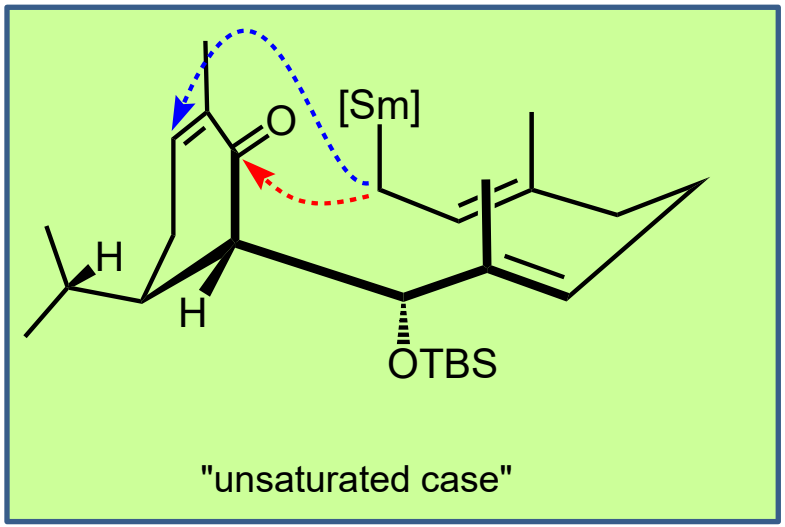
Butsugan et al., *J. Organomet. Chem.* **1987**, *333*, 329

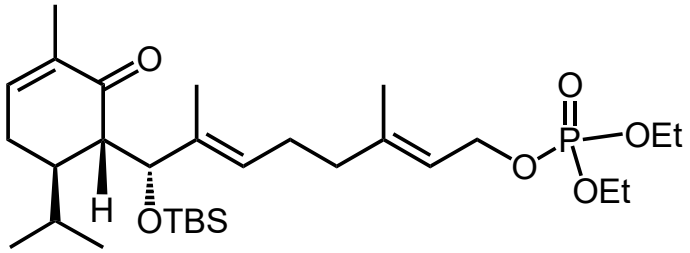


+ 5% γ-isomers

stereospecific, good α,γ-selectivity,
equatorial position

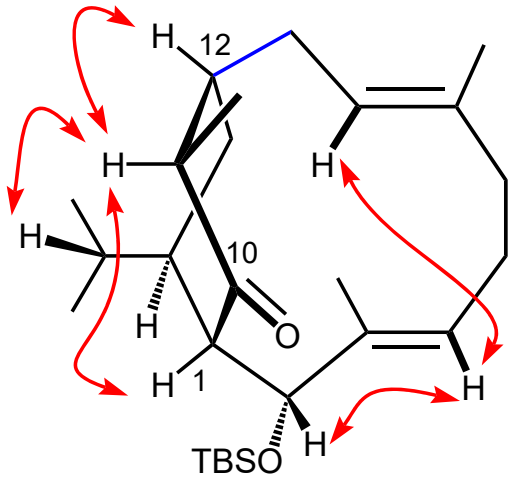
Friedel, Lindel, et al., *TETL* **2005**, 1623





46%

(i) Sm (6 equiv), diiodoethane (5 equiv), THF, rt, 4 h
(ii) start. mat., rt, 60 min



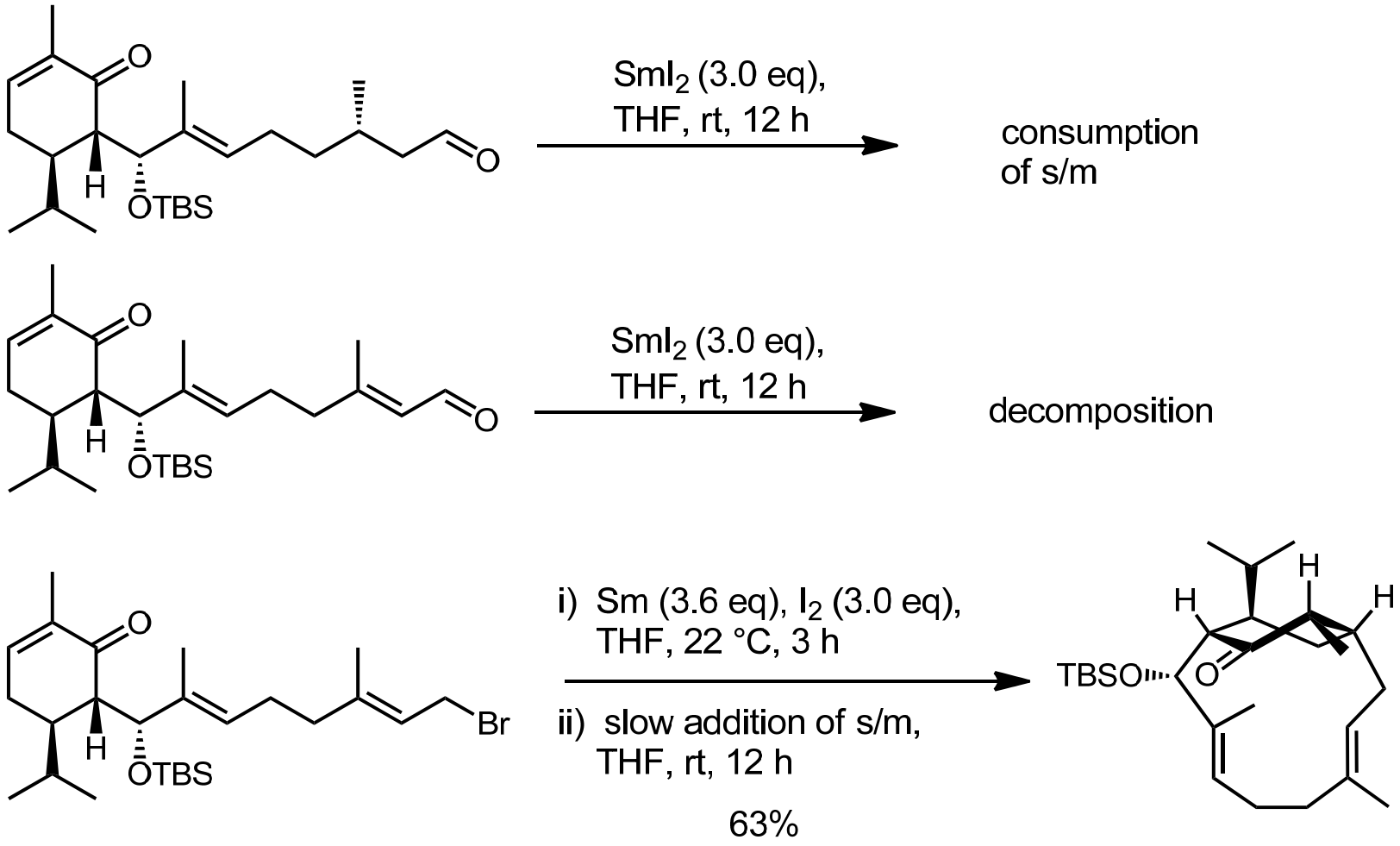
twist boat

[8.2.2], not [8.4.0]

decisive NOESY correlations

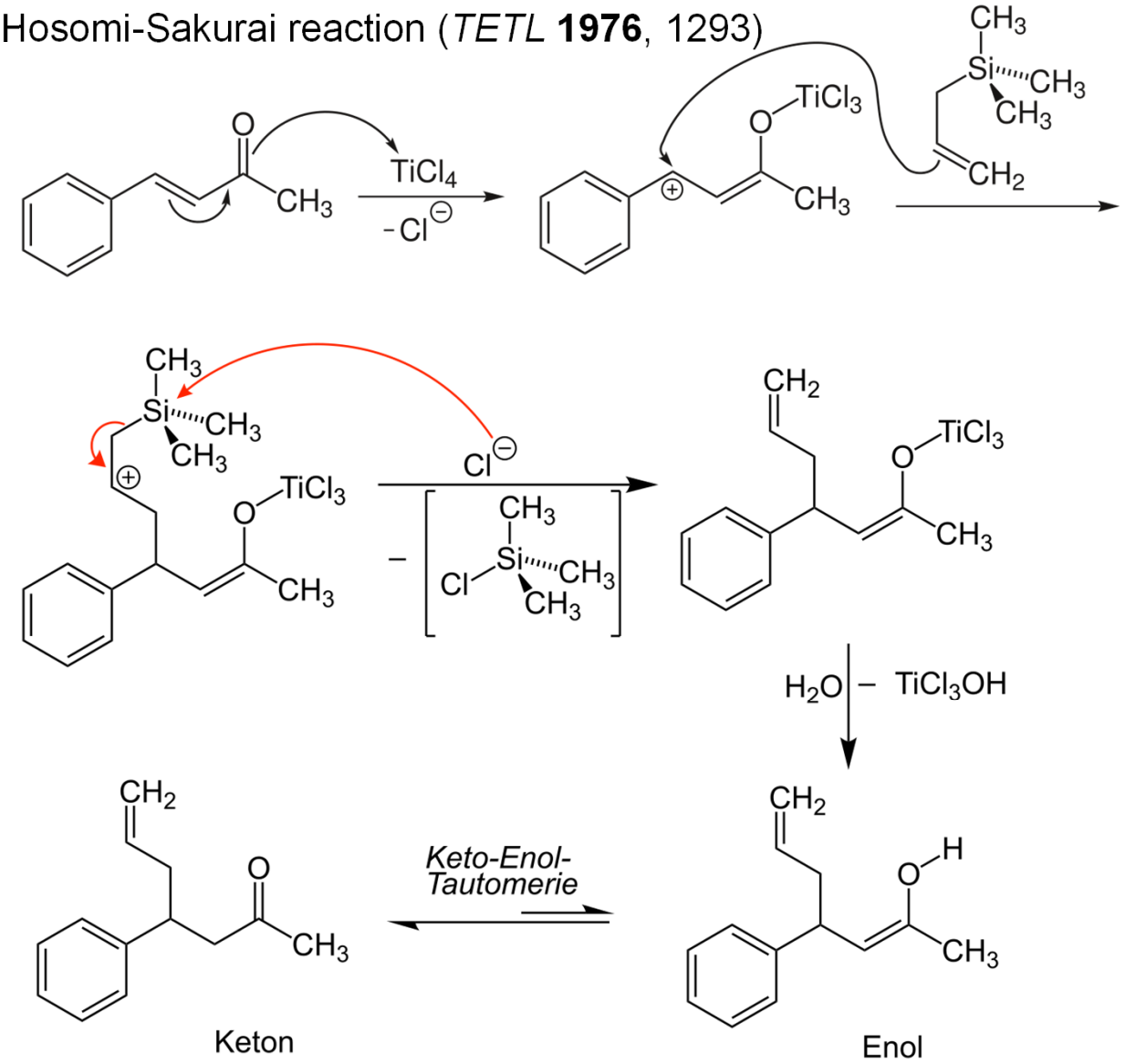
Schöttner, Lindel, et al., *Synthesis* **2009**, 3941

Sm-Barbier reaction



Johannes Wefer, Dissertation, TU Braunschweig 2015

Hosomi-Sakurai reaction (*TETL* **1976**, 1293)



Lewis acid-mediated nucleophilic attack of *allylsilicon reagents* at carbonyl compounds, imines or epoxides

Secondary carbocation stabilized by silicon β-effect (hyperconjugation)

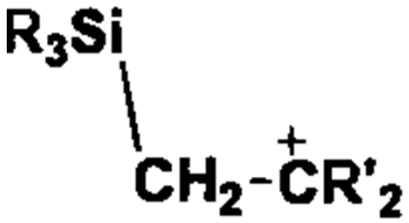
here: attack at an αβ-unsaturated ketone

direct attack at the carbonyl carbon also possible (and more common)

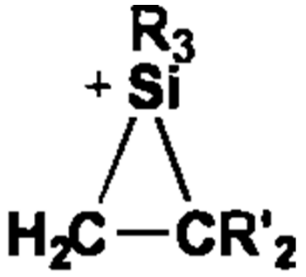
Hosomi-Sakurai reaction (*TETL* **1976**, 1293)

Silicon β-effect:
hyperconjugation between filled σ-MO of Si-R and the empty p-AO of the sp^2 carbocation)

"The ideal σ donor bond is highly polarizable and has sufficiently low energy to match that of the empty p orbital, and the atom R is electropositive in order to receive the positive charge better." (Lambert et al., *Acc. Chem. Res.* **1999**, 183; doi.org/10.1021/ar970296m)

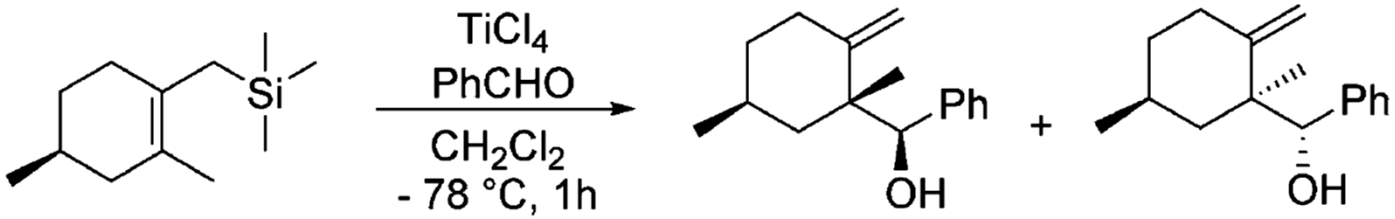


3



4

Hosomi-Sakurai reaction



3a **8a** **8a'**

(relative stereochemistry)

Entry	Allylsilane [M]	Benzaldehyde [M]	$TiCl_4$ [M]	d.r.[a]
1	0.03	0.03	0.03	3:1
2	0.10	0.10	0.10	5:1
3	0.22	0.26	0.26	12:1
4	**0.60**	**0.73**	**0.73**	**30:1**
5	0.30	0.60	0.30	2:1
6	0.30	0.30	0.60	45:1

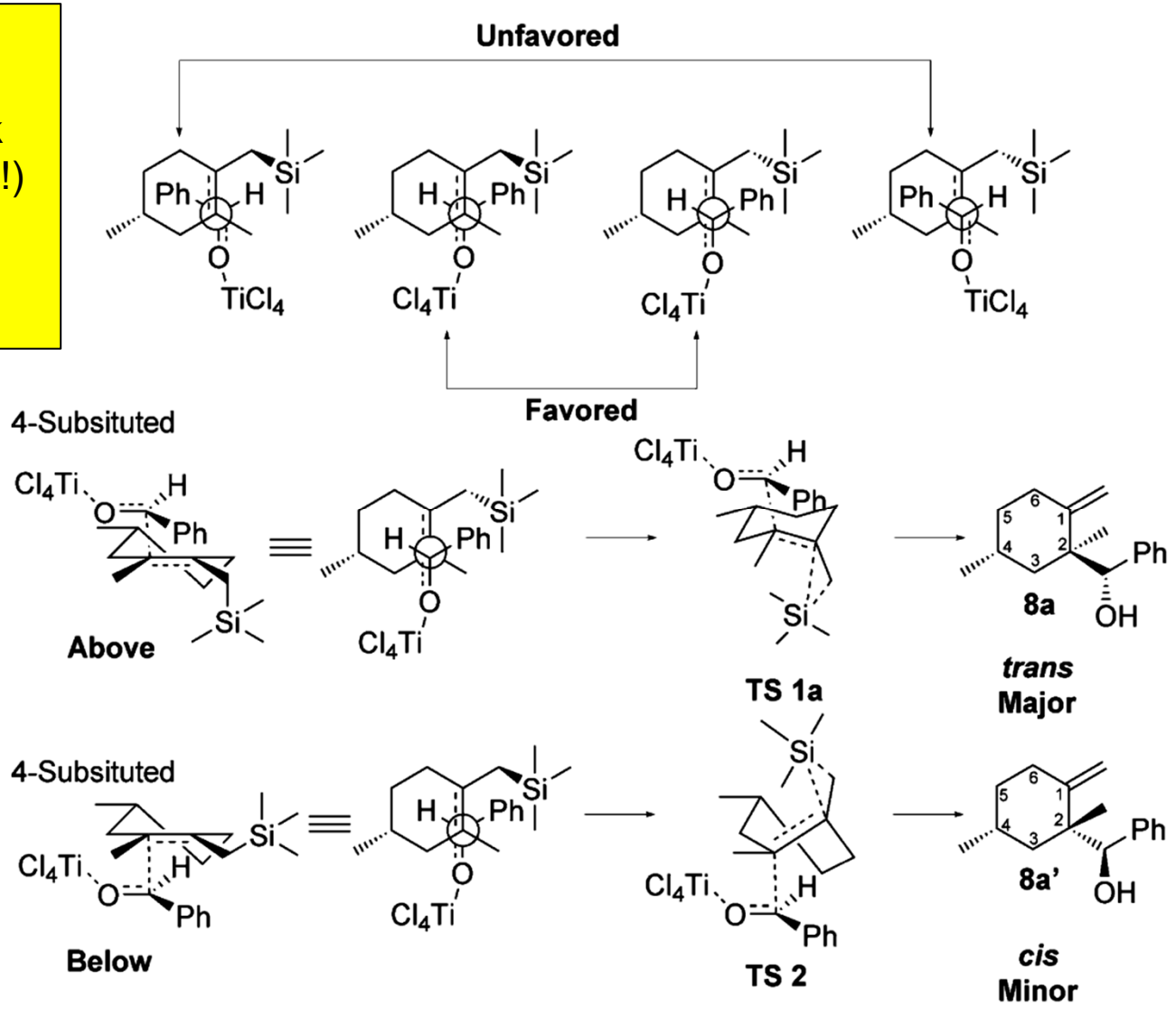
[a] Diastereomeric ratio determined by ^{1}H NMR spectroscopy.

from: Andersson et al., *CEJ* **2018**, 1681

Diastereoselectivity:

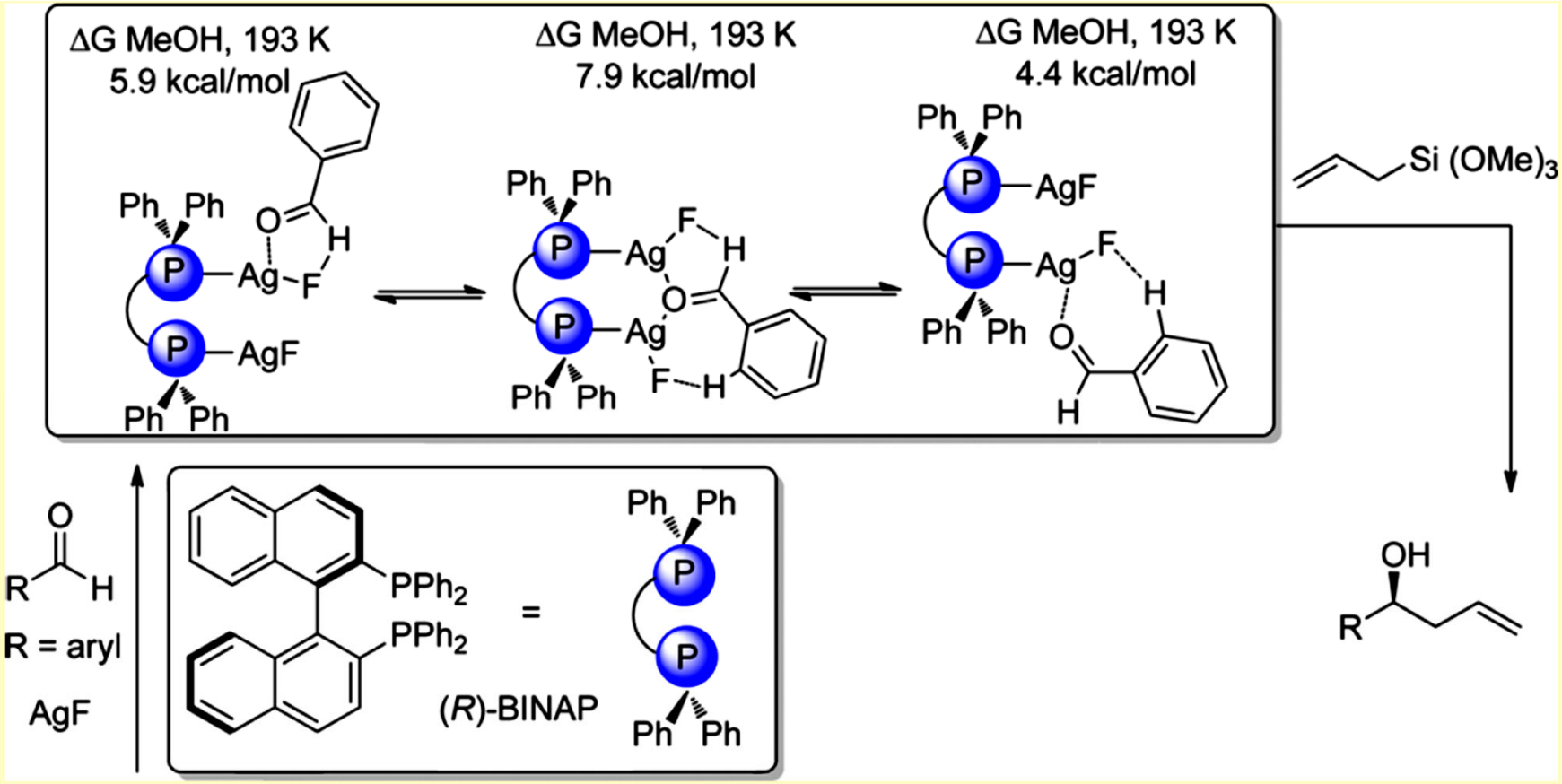
antiperiplanar attack
(no 6-membered TS!)

aldehyde R on the
less hindered side



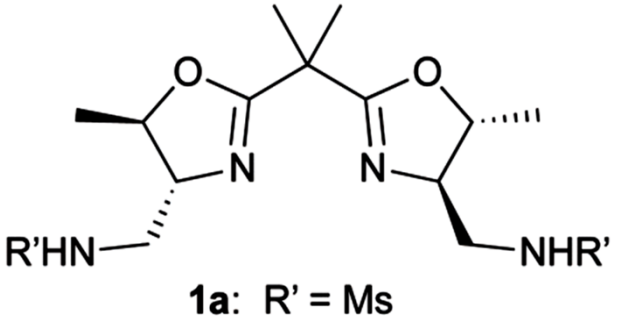
from: Andersson et al., *CEJ* **2018**, 1681

Sakurai-Hosomi-Yamamoto: enantioselective (1999)



from: Dudding et al., *JOC* **2013**, 4440

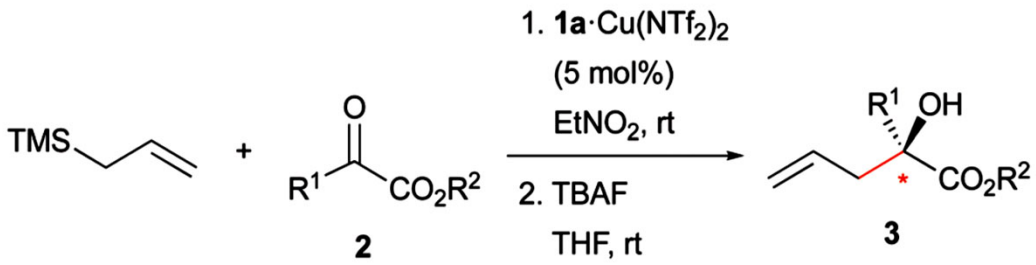
Hosomi-Sakurai reaction: enantioselective



1a: R' = Ms

chiral bisoxazoline ligand

Table 2 **1a**·Cu(NTf$_2$)$_2$-catalyzed Hosomi–Sakurai reaction of **2** with allyltrimethylsilane[a]

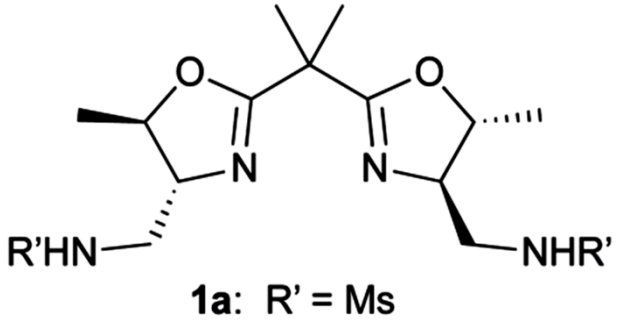


Entry	2	R^1	R^2	Yield[b] (%)	ee[c] (%)
1	**2b**	Me	Bn	**3b**, 71	65 (*R*)
2	**2c**	$CH_3(CH_2)_5$	Et	**3c**, 74	74
3	**2d**	$CH_2{=}CH(CH_2)_2$	Et	**3d**, 41	74
4	**2e**	$BnO(CH_2)_3$	Et	**3e**, 75	73
5	**2f**	*c*-C_5H_9	Et	**3f**, 67	69
6	**2g**	*c*-C_6H_{11}	Et	**3g**, 0	—
7	**2h**	Ph	Me	**3h**, 0	—
8	**2i**	4-$CF_3C_6H_4$	Et	**3j**, 72	79

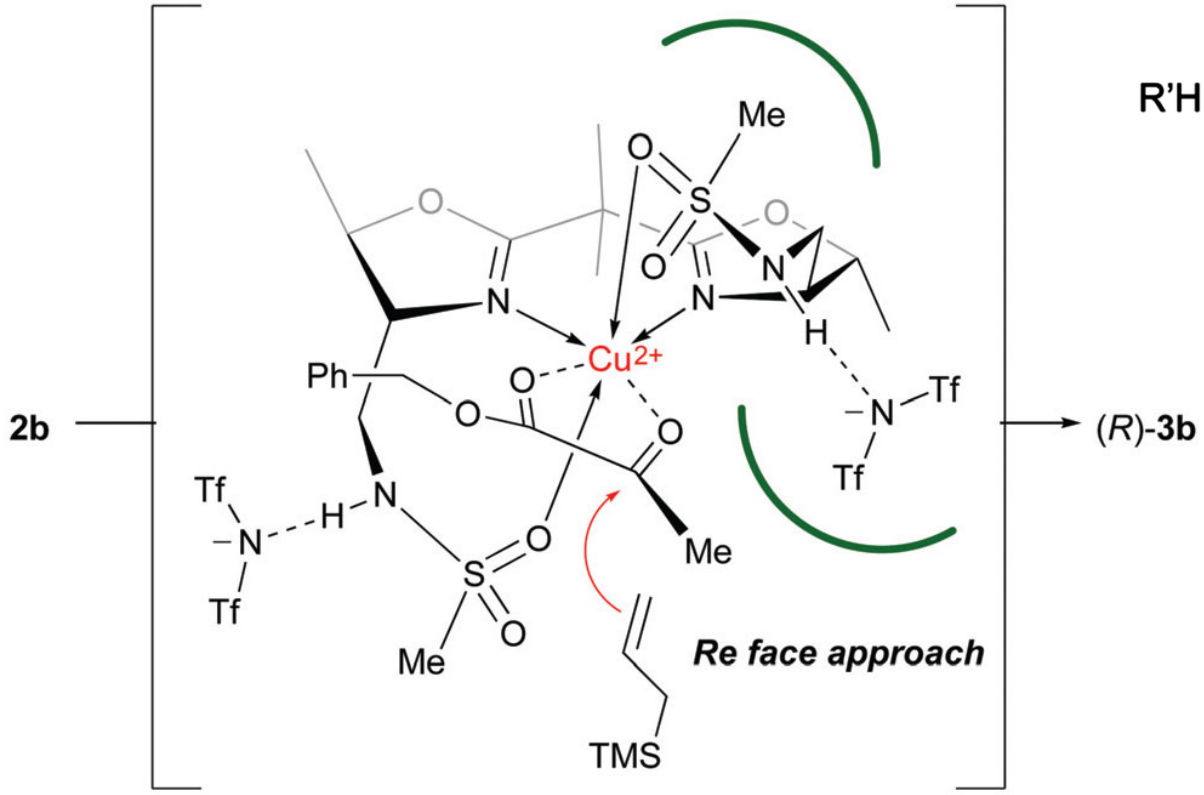
[a] The reaction of **2** (0.2 mmol) with allyltrimethylsilane (3 equiv.) was conducted in the presence of **1**·Cu(NTf$_2$)$_2$ (5 mol%) in EtNO$_2$ at ambient temperature for 1–24 h. The crude product was treated with TBAF (1 equiv.) in THF at ambient temperature. [b] Isolated yield. [c] Evaluated by chiral HPLC analysis.

from: Sakakura et al., *ChemComm* **2019**, 3923

Hosomi-Sakurai reaction: enantioselective



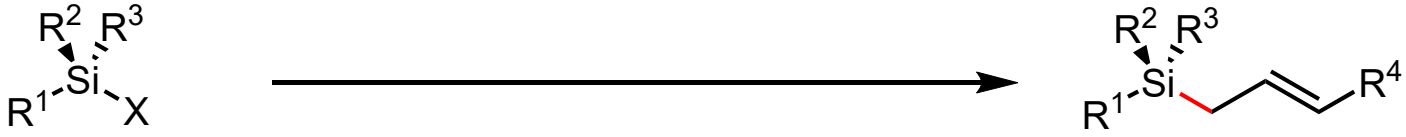
chiral bisoxazoline ligand



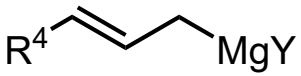
Scheme 1 Proposed transition state assembly for the **1a**·$Cu(NTf_2)_2$-catalyzed allylation of **2b**.

from: Sakakura et al., *ChemComm* **2019**, 3923

Hosomi-Sakurai reaction: synthesis of allylsilanes

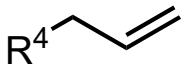


X=Cl



cat. $ZnCl_2$-TMEDA

X=I

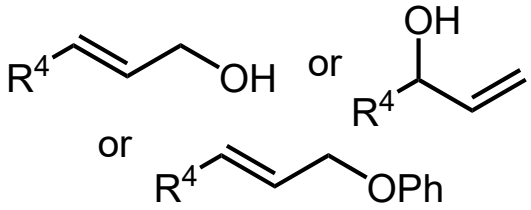


cat. $(COD)Pd(CH_2TMS)_2$, *t*$BuPAr_2$, NEt_3

X=SiR_3

X=Bpin

X=ZnCl

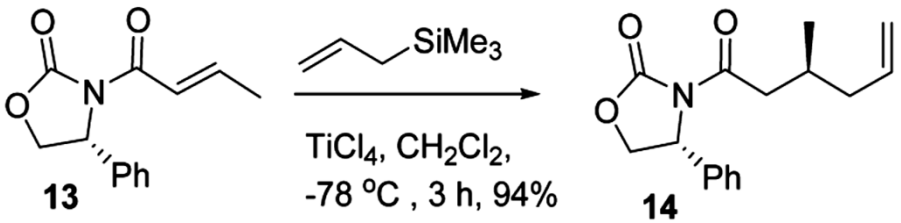


cat. $Pd(BF_4)_2(MeCN)_4$, DMSO, MeOH
or
cat. $PdCl_2$(DPEphos), NEt_3, cat. H_2O

cat. $Ni(COD)_2$, CuF_2, PR_3

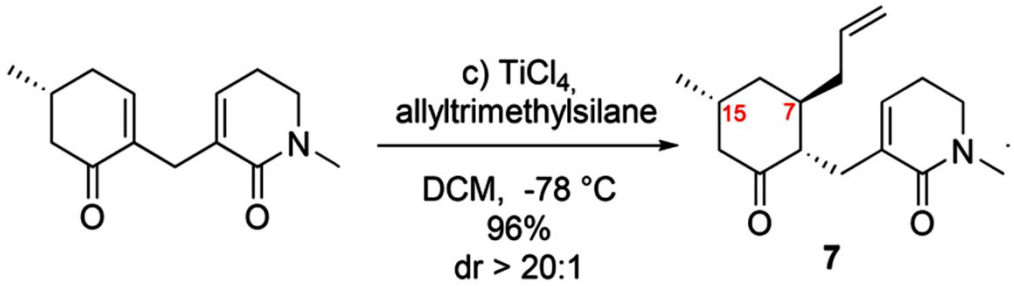
cat. $Ni(PMe_2)_2Cl_2$, MeZnCl (1.2 equiv.)

Hosomi-Sakurai reaction: examples



β-attack

from: Ghosh et al., *ACS Omega* **2018**, 16563

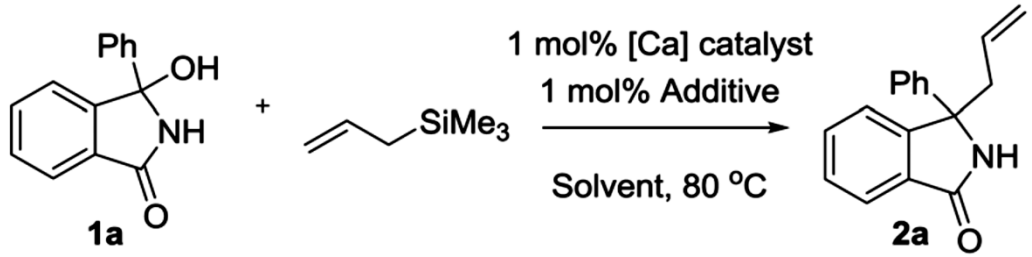


β-attack

from: Qiu et al., *AdvSynthCatal* **2019**, *361*, 3514

Michael-type attack preferred on the ketone side and over 1,2-addition

Hosomi-Sakurai reaction: examples

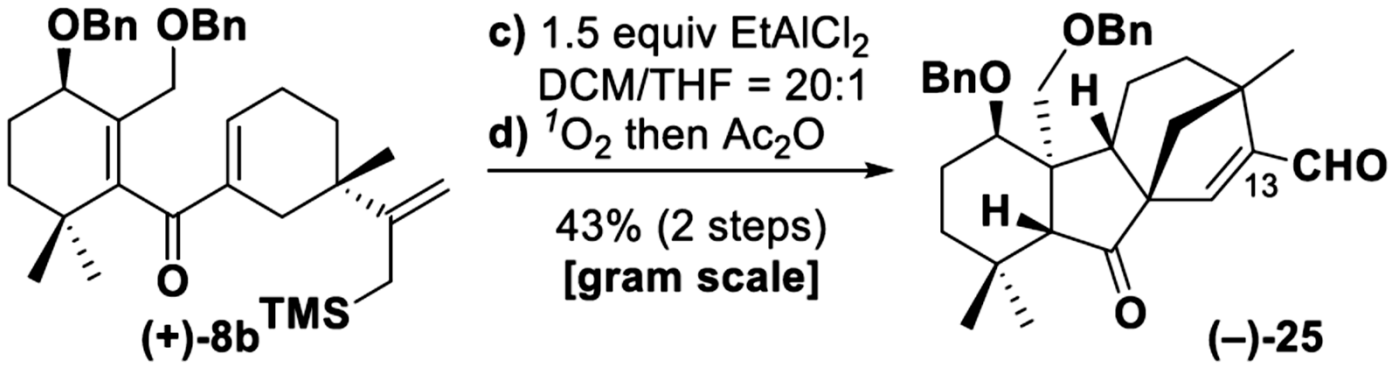


Entry	Calcium source	Additive	Solvent	Yield[a]
1	$CaCl_2$	None	THF	n.r
2	Ca(OH)	None	THF	n.r
3	$Ca(OiPr)_2$	None	THF	9%[b]
4	$Ca(NTf_2)_2$	None	CH_2Cl_2	15%
5	$Ca(NTf_2)_2$	nBu_4NPF_6	CH_2Cl_2	69%
6	**$Ca(NTf_2)_2$**	**nBu_4NPF_6**	**1,2-DCE**	**98%**
7	$Ca(NTf_2)_2$	nBu_4NPF_6	1,2-DCE[c]	25%
8	$Ca(NTf_2)_2$	nBu_4NPF_6	DCE:DME	88%

N,O-hemiketals

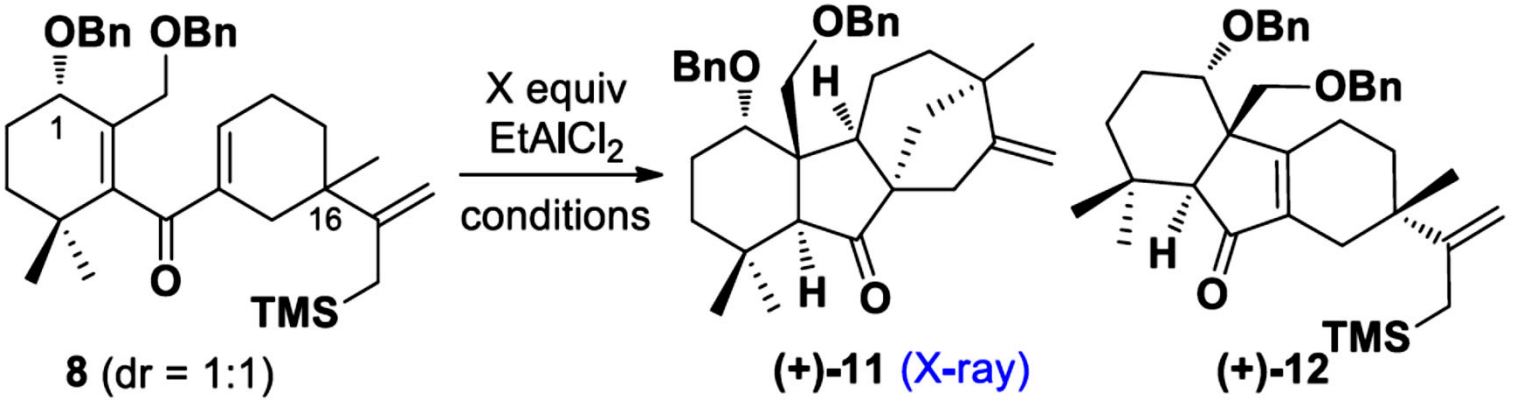
from: McLaughlin et al., *ChemComm* **2019**, 8317

Interrupted Nazarov / Hosomi-Sakurai cascade, followed by ene reaction



from: Tuoping Luo et al., *JACS* **2019**, 20048

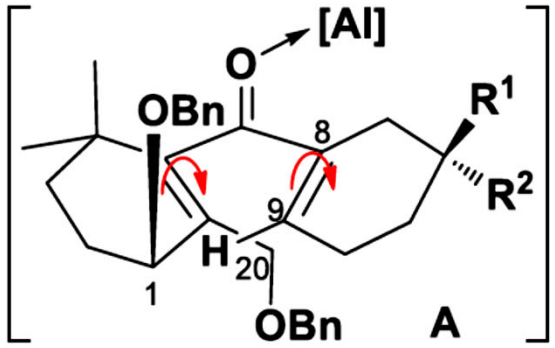
Interrupted Nazarov / Hosomi-Sakurai cascade, followed by ene reaction

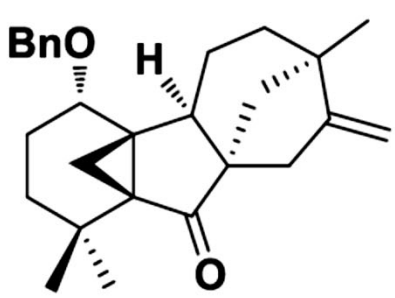


8 (dr = 1:1)

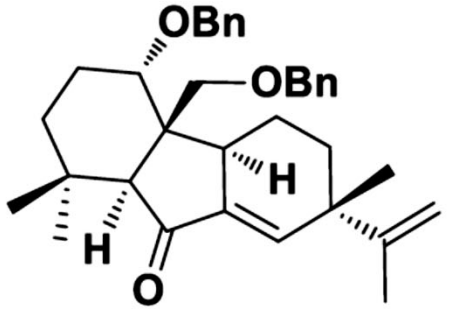
(+)-11 (X-ray)

(+)-12





13



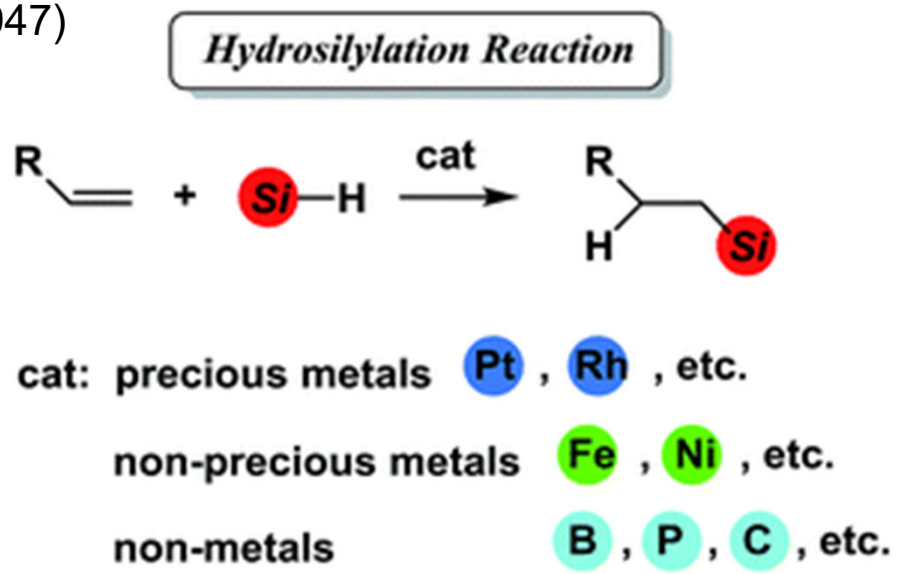
(–)-14

8a: R^1 = -$C(CH_2)CH_2TMS$, R^2 = -Me

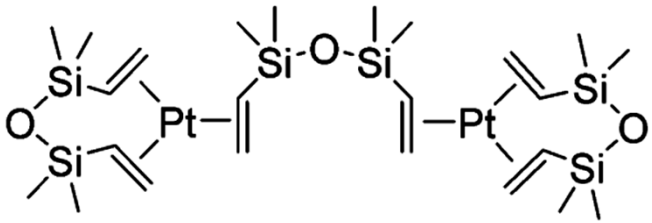
8b: R^1 = -Me, R^2 = -$C(CH_2)CH_2TMS$

from: Tuoping Luo et al., *JACS* **2019**, 20048

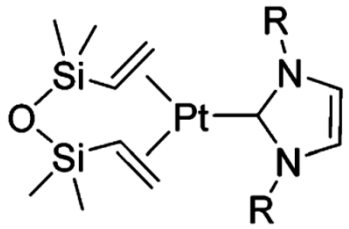
Hydrosilylation (since 1947)



Karstedt's cat (1973)



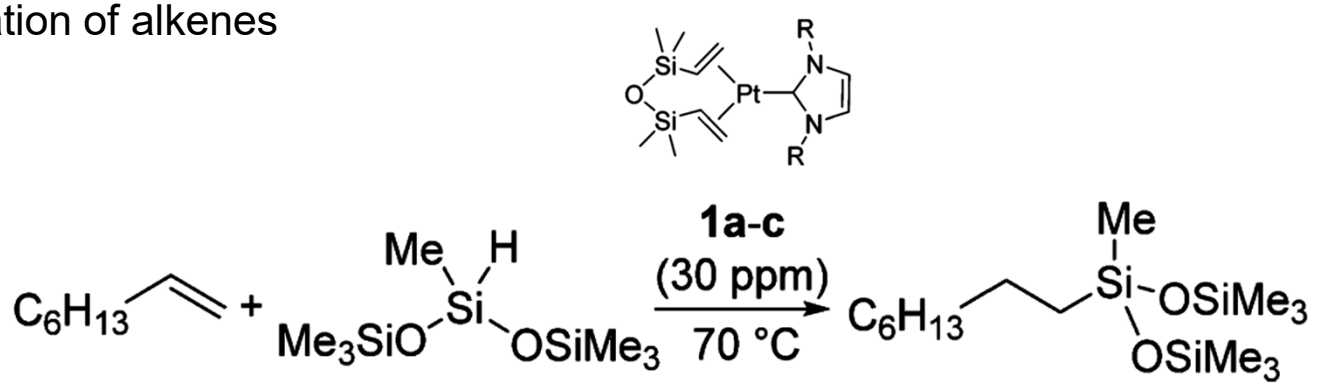
Marko's cat (2002)

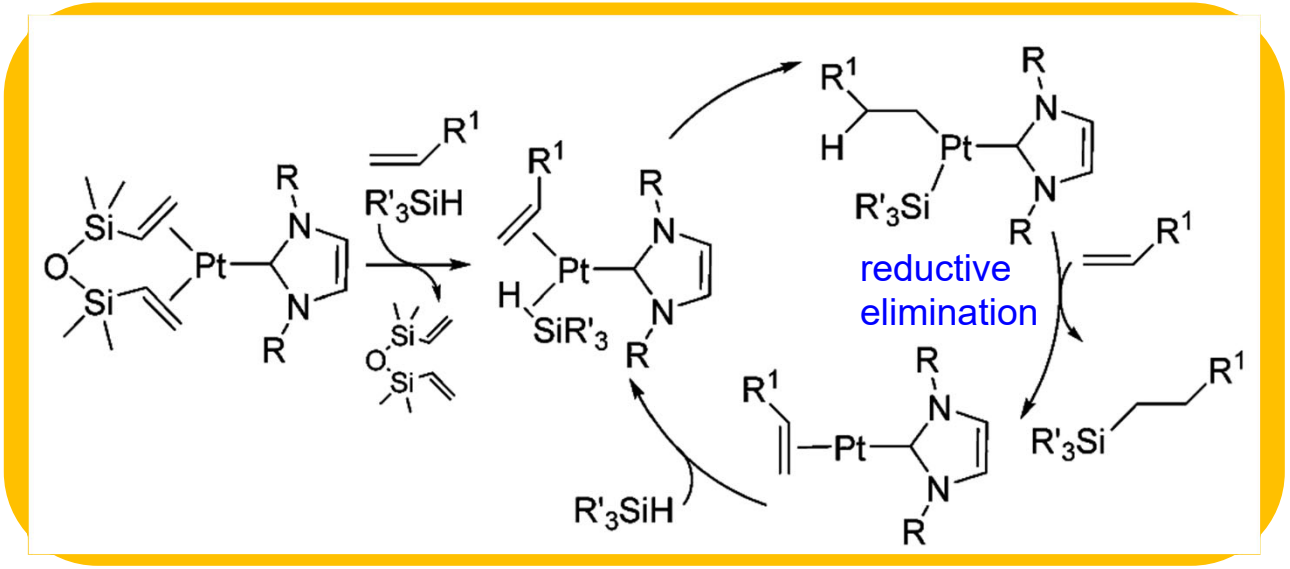


R = Me (**1a**), Cyclohexyl (**1b**), ^{t}Bu (**1c**)

from: Nakajima, Shimada, *RSC Adv.* **2015**, 20603

Hydrosilylation of alkenes

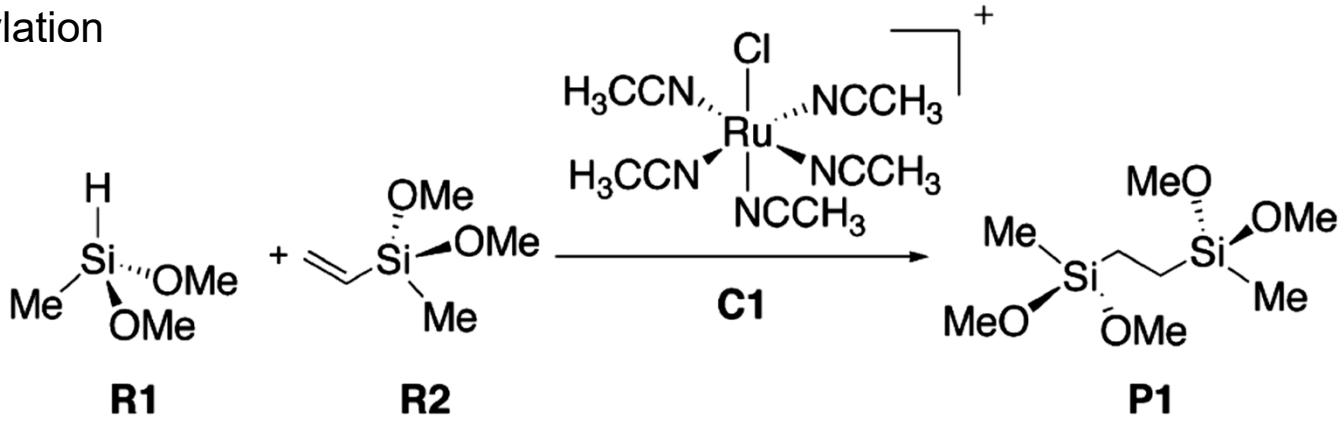


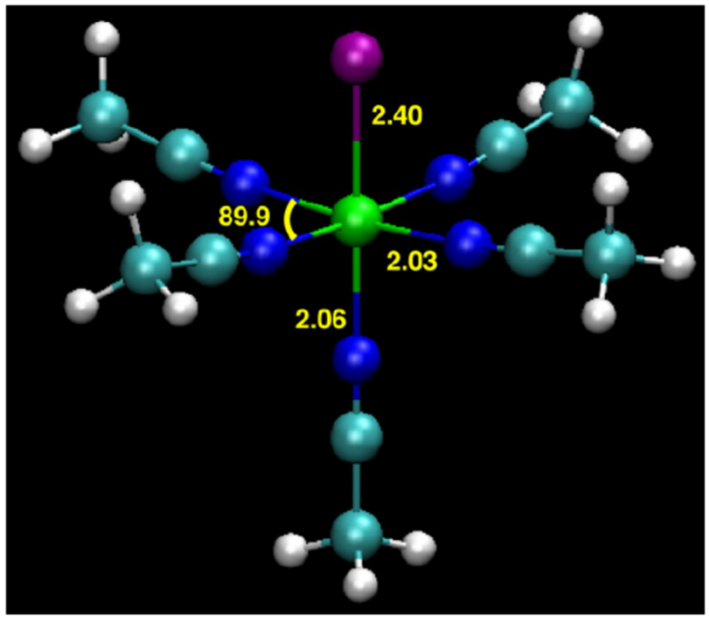


Chalk-Harrod-Mechanism

from: Nakajima, Shimada, *RSC Adv.* **2015**, 20603

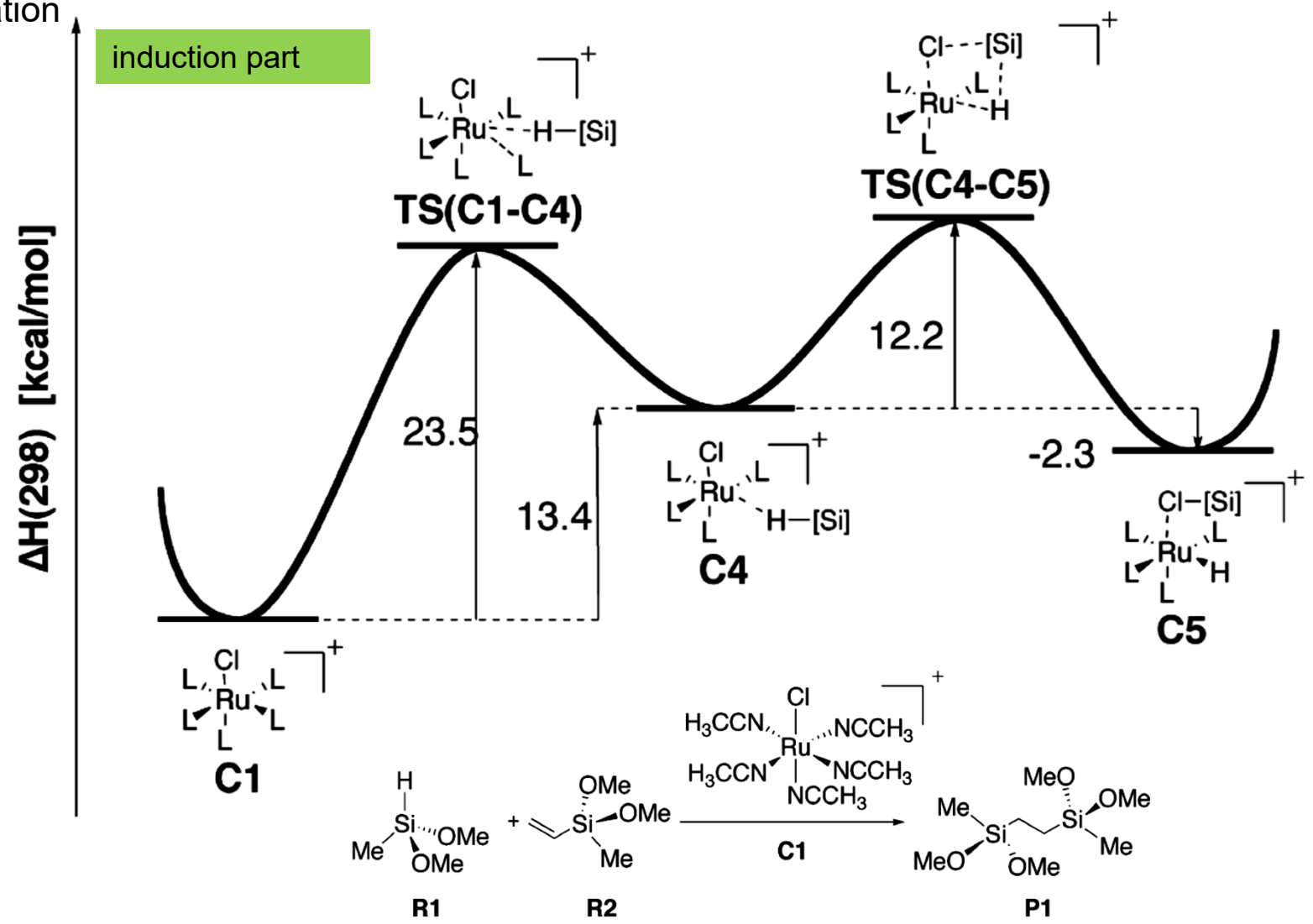
Hydrosilylation





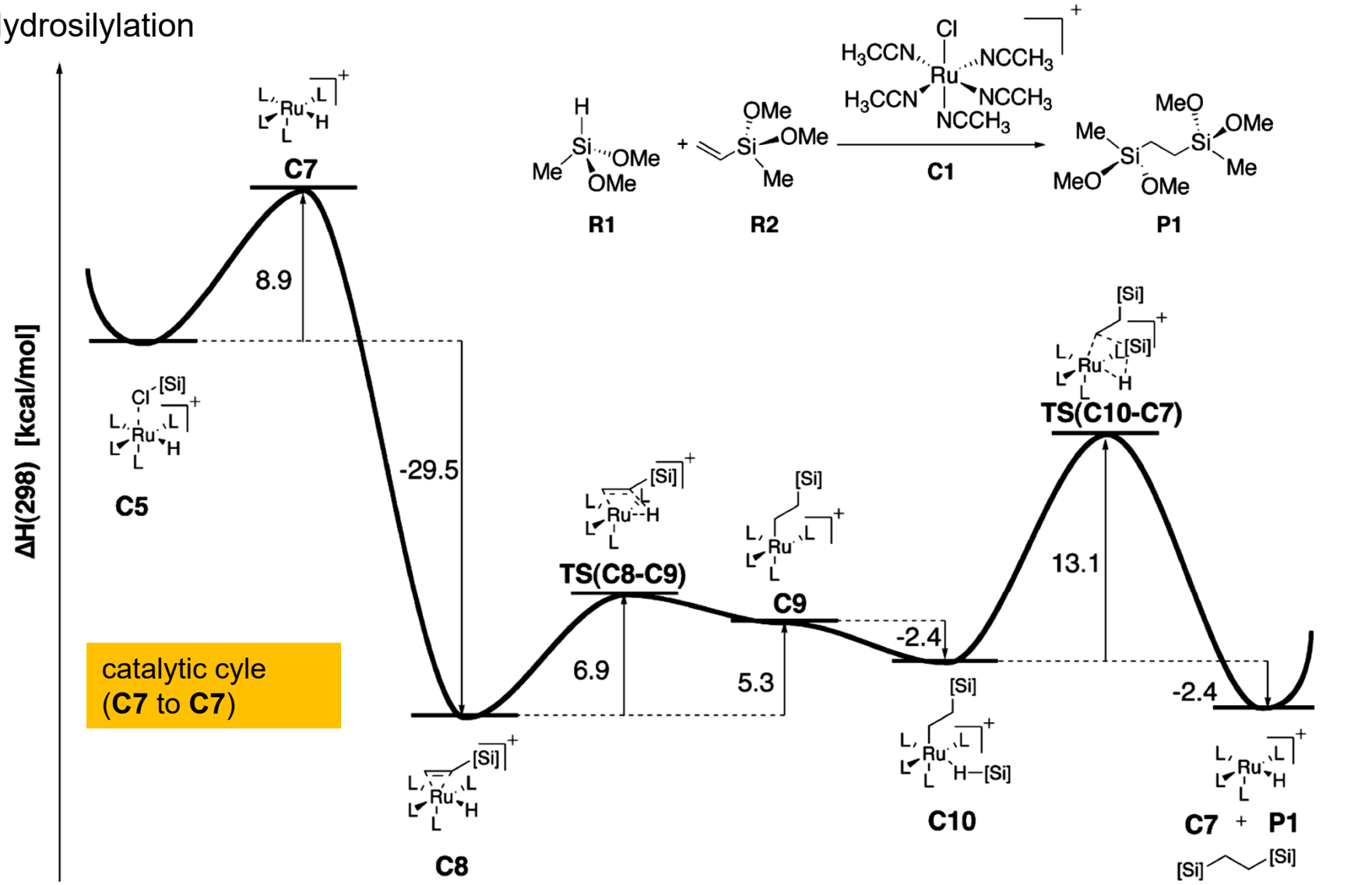
from: Tuttle et al., *J. Organomet. Chem.* **2007**, 2282

Hydrosilylation



from: Tuttle et al., *J. Organomet. Chem.* **2007**, 2282

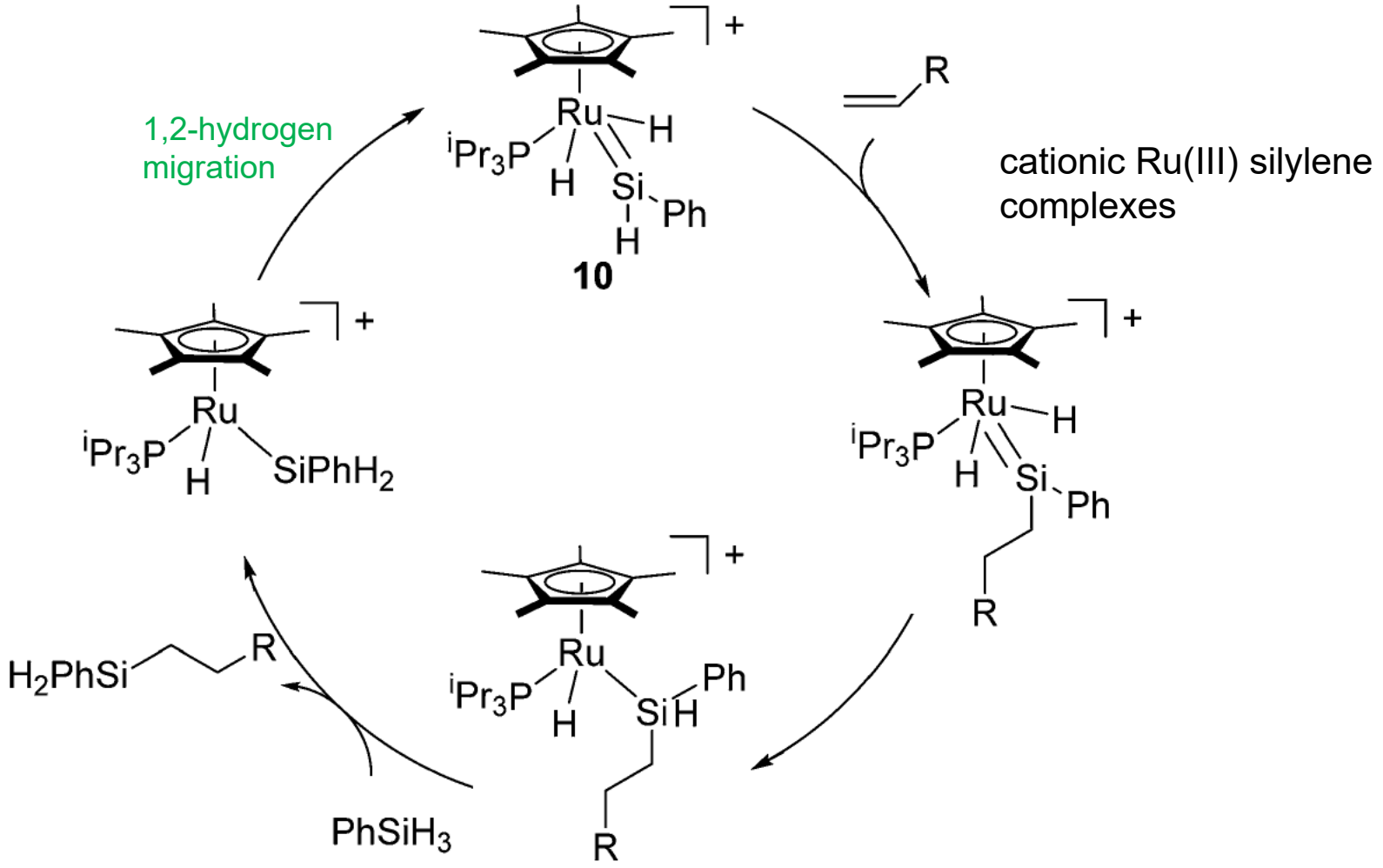
Hydrosilylation



from: Tuttle et al., *J. Organomet. Chem.* **2007**, 2282

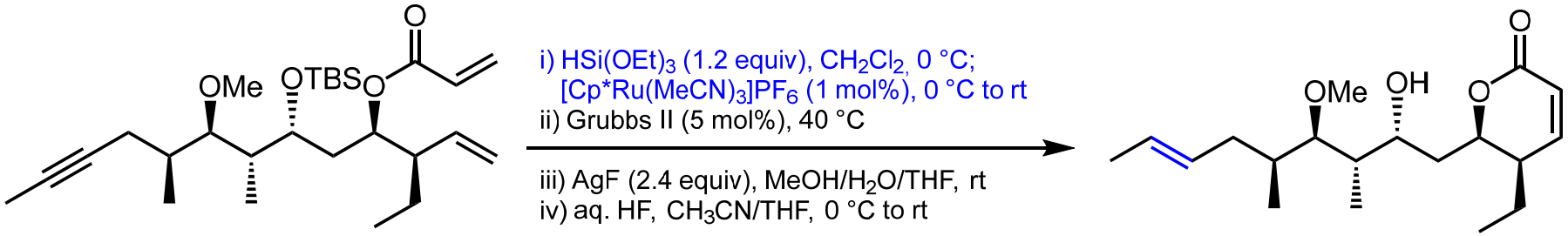
Hydrosilylation: there are more mechanisms ...

Glaser-Tilley mechanism



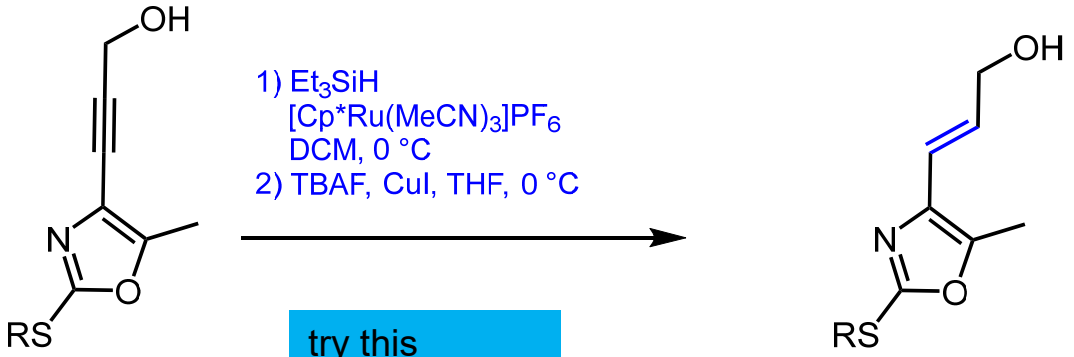
from: Nakajima, Shimada, *RSC Adv.* **2015**, 20603

Hydrosilylation of alkynes -> (*E*) (Trost et al., *JACS* **2005**, 17644)



64%

(-)-Pironetin (Cossy et al., *ACIE* **2008**, 10137)



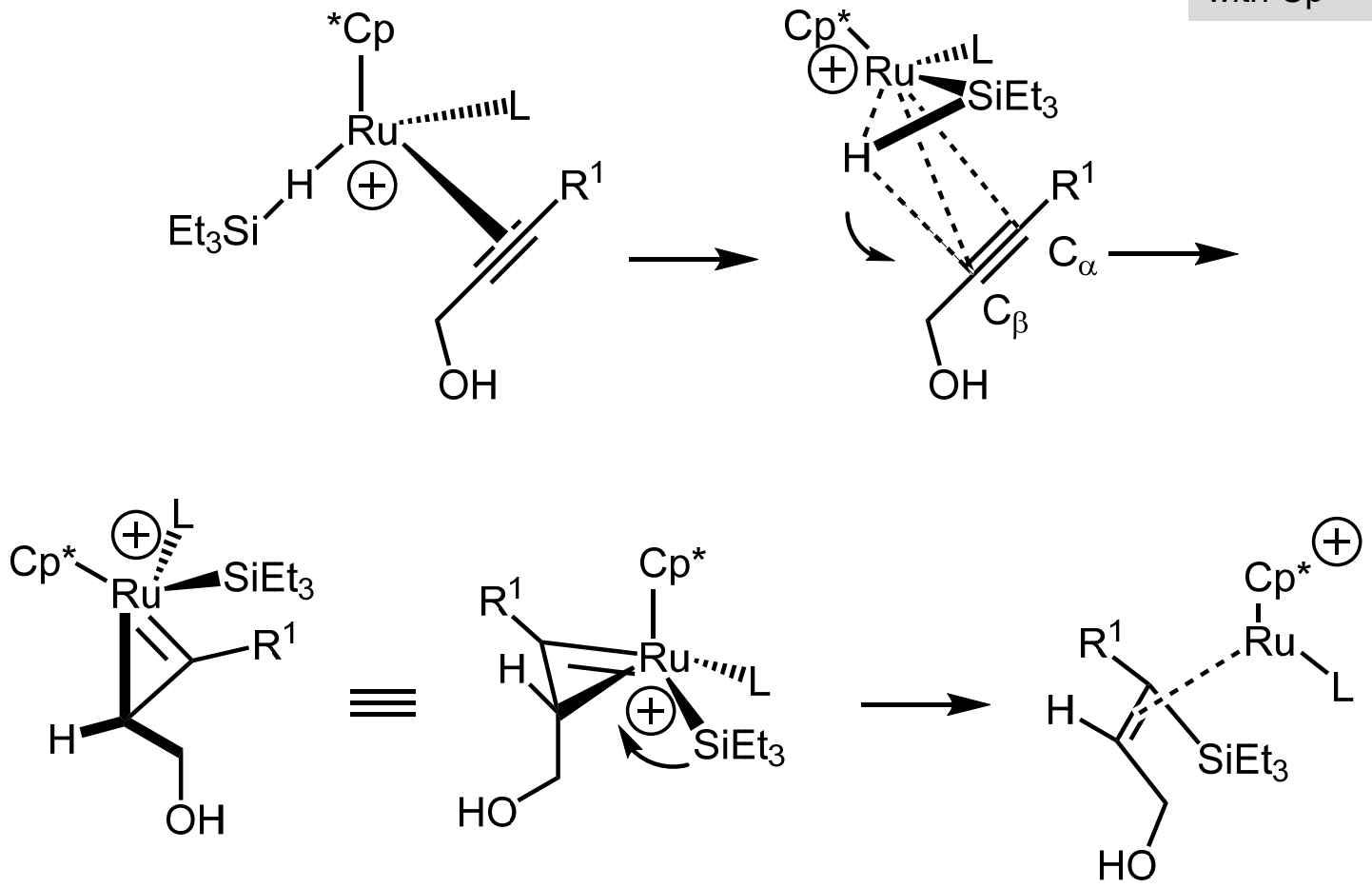
try this instead of $Na/NH_3(l)$ ... !

R = *n*-Bu (80%, 2 steps)
R = Ph (43%, 2 steps)

Schäckermann, Lindel, *Org. Lett.* **2017**, 2306

Hydrosilylation of alkynes -> (*E*) (Trost et al., *JACS* **2005**, 17644)

Cp*: better regioselectivity than with Cp



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