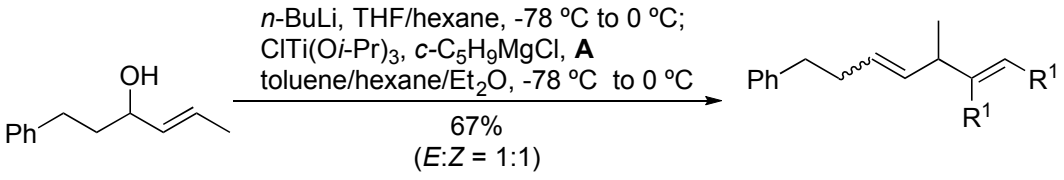
Problem Session (6)

2017/9/30 Atsushi Hayata

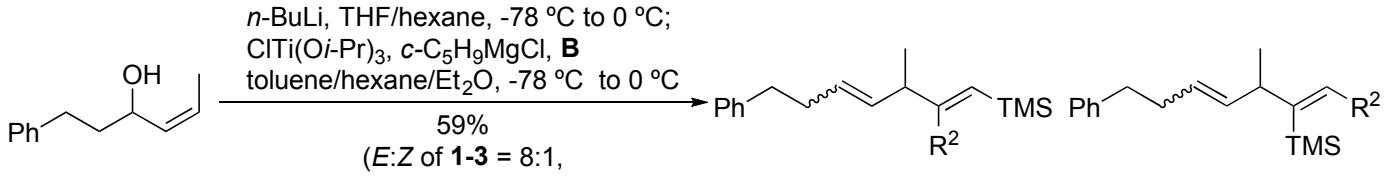
Please provide each reaction mechanisms, explain the regio/stereoselectivities and fill in the blank.

1 The solution of **1-1-Z** (**1-1-E**) and n-BuLi was cannulated to the premixed solution of $ClTi(O\textit{i}\text{-}Pr)_3$, cC_5H_9MgCl and **A** (**B**).



1-1-E

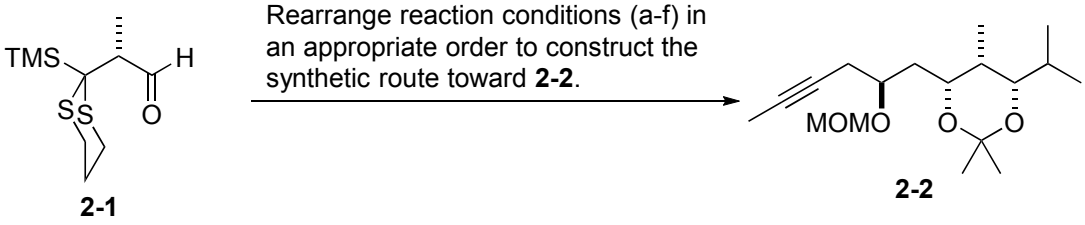
1-2: $R^1 = (CH_2)_2OPMB$



1-1-Z

1-3: $R^2 = (CH_2)_2Ph$ **1-4**: $R^2 = (CH_2)_2Ph$

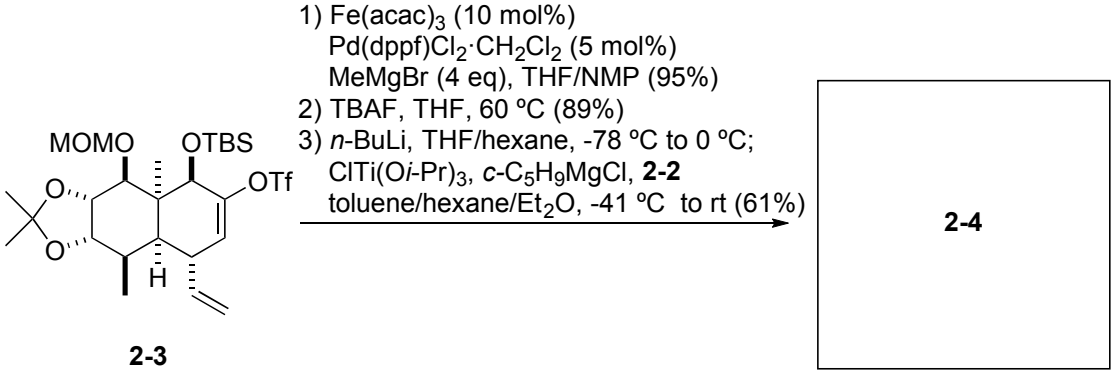
2



2-1

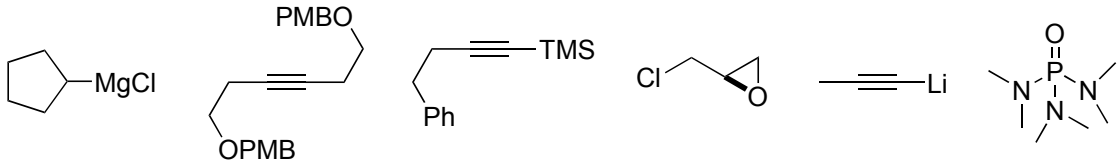
2-2

a) Et_2BOMe, $NaBH_4$, THF/MeOH, -78 ºC (75%, *d.r.* 92:8)
b) $(CH_3)_2CHLi$, Et_2O, -78 ºC; HMPA, **C,** -50 ºC to rt (76%, *d.r.* >20:1)
c) 2-methoxypropene, PPTS, CH_2Cl_2, 0 ºC (82%)
d) MOMCl, DIPEA, TBAI, CH_2Cl_2 (86%)
e) **D**, BF_3·THF, THF, -78 ºC (92%)
f) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (80%)



2-3

The solution of product from **2-3** and n-BuLi was cannulated to the premixed solution of $ClTi(O\textit{i}\text{-}Pr)_3$, cC_5H_9MgCl and **2-2**.

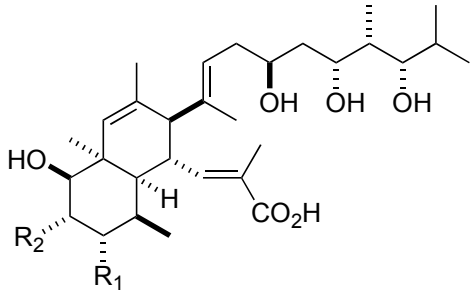


c-C_5H_9MgCl **A** **B** **C** **D** HMPA

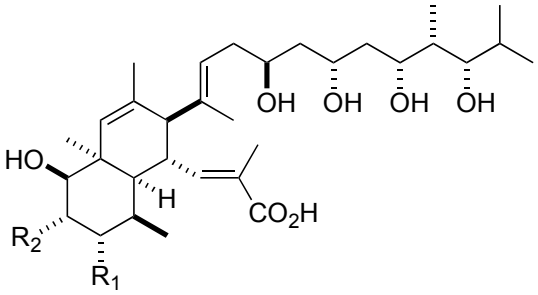
Problem Session (6) -Total synthesis of (-)-Nahuoic Acid C_i (B_{ii})-

2017/9/30 Atsushi Hayata

Introduction of (-)-Nahuoic Acid



Nahuoic Acid A: R_1 = OH, R_2 = H
B_i: R_1 = H, R_2 = OH
C_i (B_{ii}): R_1 = R_2 = OH
C_{ii}: R_1 = R_2 = H



Nahuoic Acid D_i (E_{ii}): R_1 = OH, R_2 = H
E_i: R_1 = H, R_2 = OH
D_{ii}: R_1 = R_2 = H

isolation: from *Streptomyces* sp.

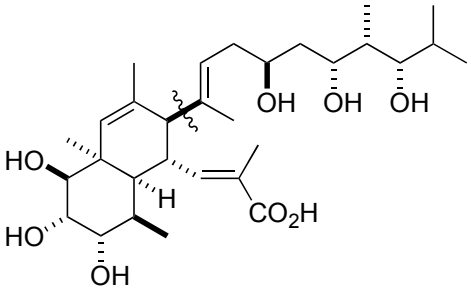
bioactivity: selective SAM-competitive inhibitor activity against the histone lysine methyltransferase SETD8 enzyme

structural feature: highly functionalized *cis*-decalin motifs in conjunction with polyol side chains

total synthesis: Smith's group *J. Am. Chem. Soc.* **2017**, DOI: 10.1021/jacs.7b08683. (problem 2)

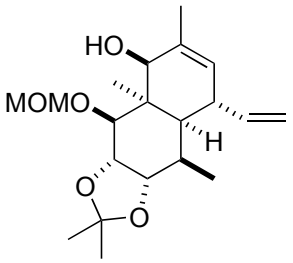
(Isolation)
Andersen's group *Org. Lett.* **2013**, *15*, 414. (Nahuoic Acid A)
J. Org. Chem. **2016**, *81*, 1324. (Nahuoic Acid B_i - E_i)
Qi's group *J. Nat. Prod.* **2016**, *79*, 141. (Nahuoic Acid B_{ii} - E_{ii})

Retrosynthetic analysis



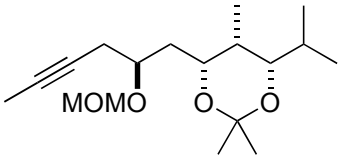
Nahuoic Acid C_i (B_{ii})
0-1

alkyne-alkene coupling (probelm 1, 2)

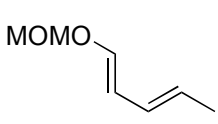


0-2

+

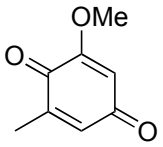


0-3 (**2-2**)



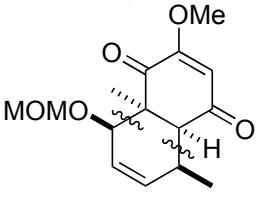
0-5

+

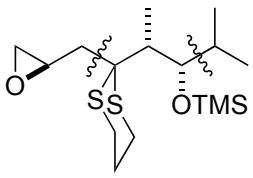


0-6

asymmetric Diels-Alder

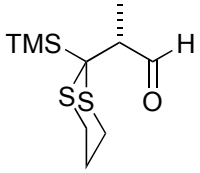


0-4



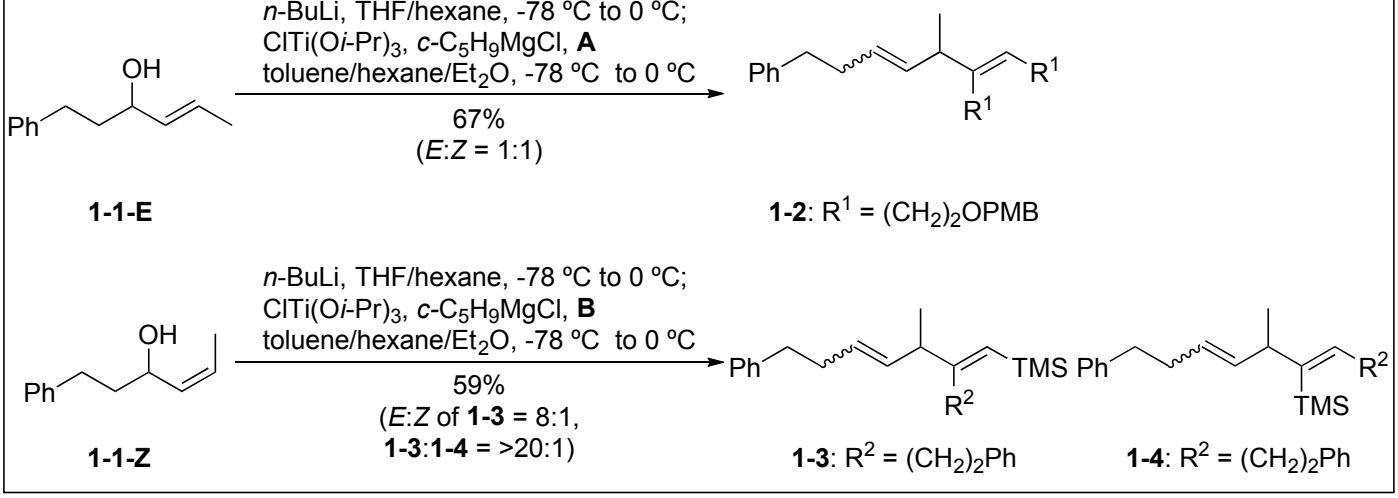
0-7

Type II Anion Relay



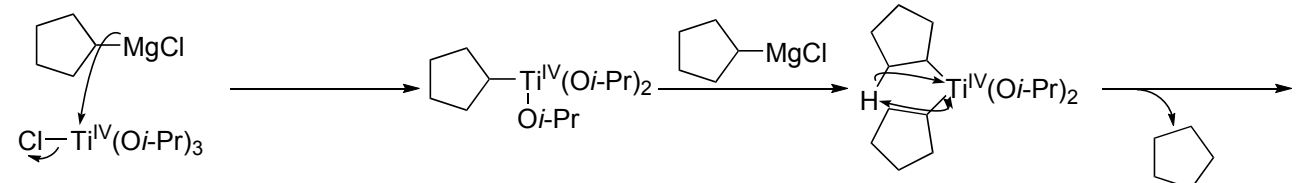
0-8 (**2-1**)

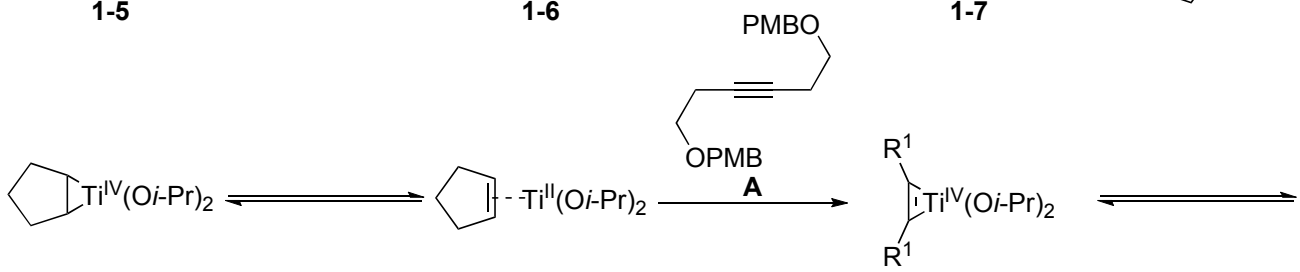
1 The solution of **1-1-Z** (**1-1-E**) and n-BuLi was cannulated to the premixed solution of $ClTi(O\textit{i}\text{-}Pr)_3$, cC_5H_9MgCl and **A** (**B**).

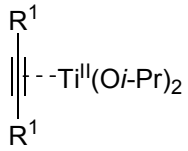


Micalizio's group *J. Am. Chem. Soc.* **2007**, *129*, 15112.

generation of active species

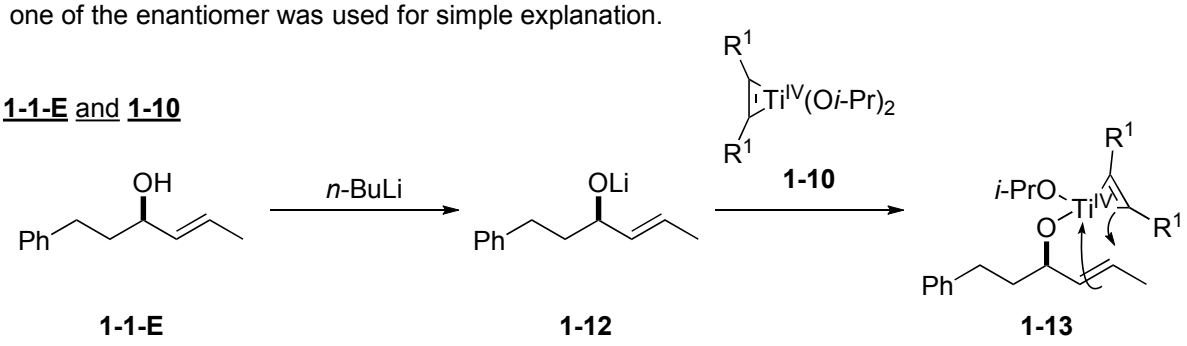






Although reaction was conducted with racemic **1-1-E/Z**, one of the enantiomer was used for simple explanation.

1-1-E and **1-10**



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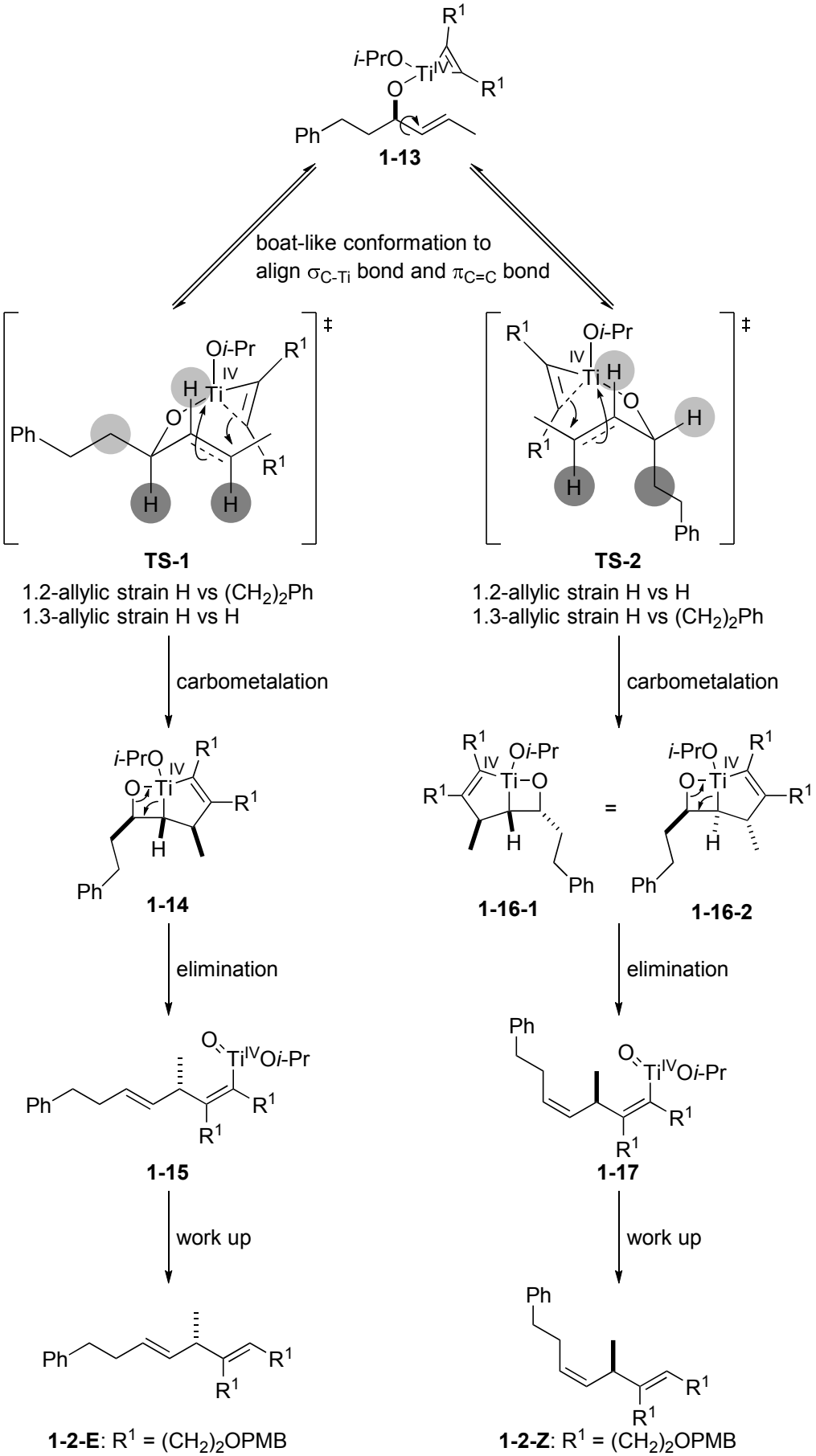
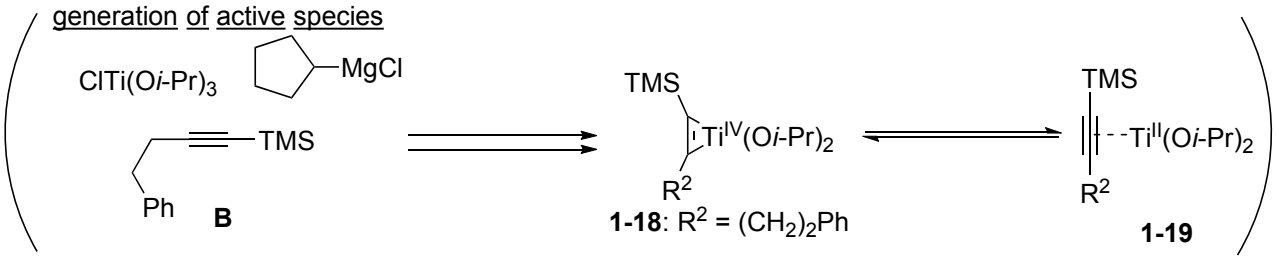
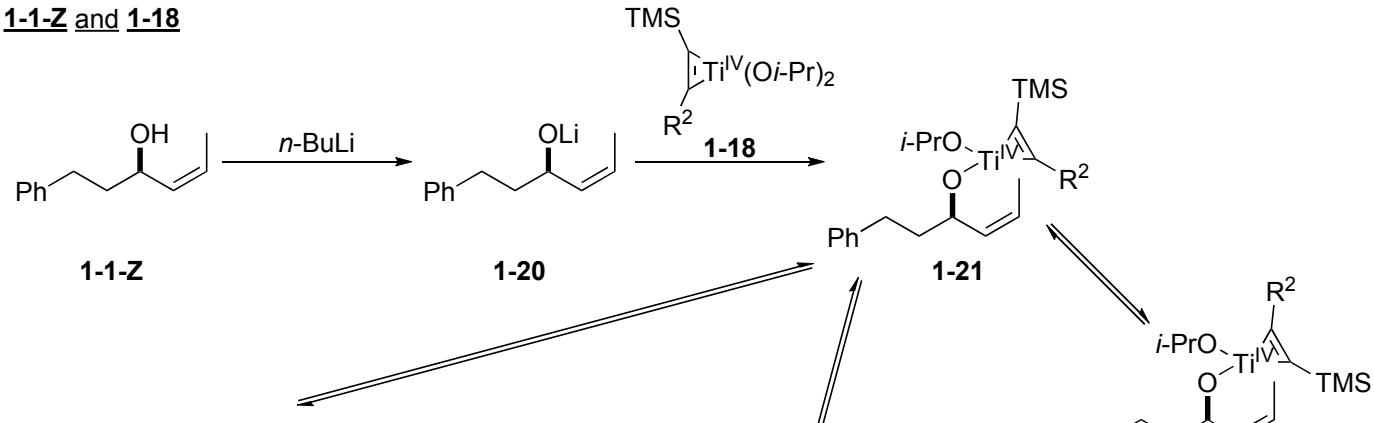


No selectivity **(1-2-E:1-2-Z** = 1:1)



1-1-Z and **1-18**



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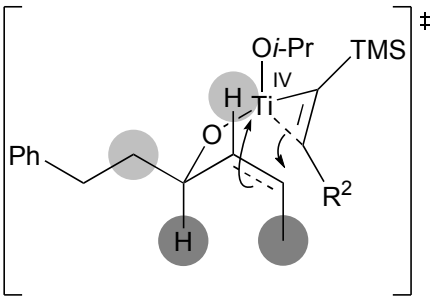
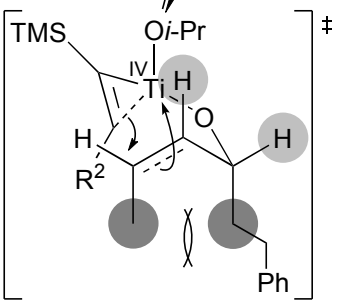
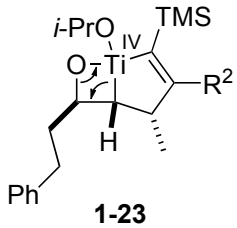


TS-3 (favored)
1.2-allylic strain H vs (CH$_2$)$_2$Ph
1.3-allylic strain H vs Me



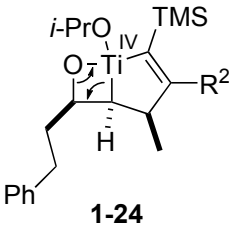
TS-4 (unfavored)
1.2-allylic strain H vs H
1.3-allylic strain Me vs (CH$_2$)$_2$Ph

carbometalation



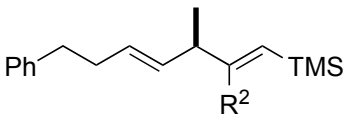
1-23

carbometalation



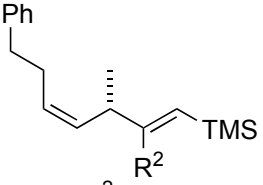
1-24

elimination and work up



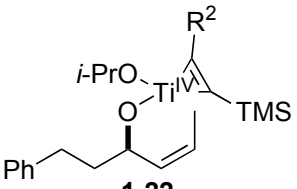
1-3-E: R^2 = (CH$_2$)$_2$Ph

elimination and work up

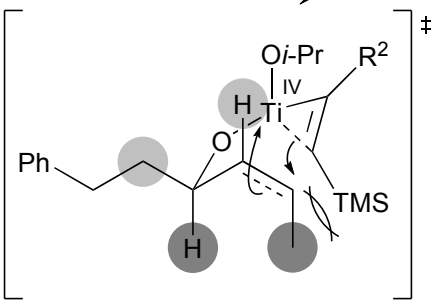


1-3-Z: R^2 = (CH$_2$)$_2$Ph

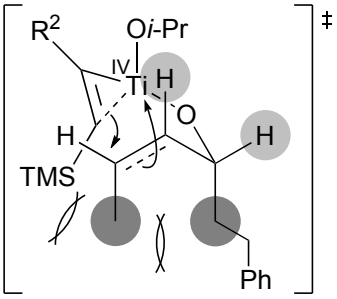
1-3-E:1-3-Z = 8:1



1-22

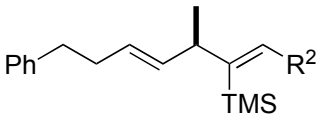


TS-5 (unfavored)
1.2-allylic strain H vs $(CH_2)_2Ph$
1.3-allylic strain H vs Me



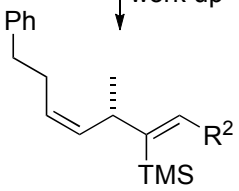
TS-6 (unfavored)
1.2-allylic strain H vs H
1.3-allylic strain Me vs $(CH_2)_2Ph$

carbometalation
elimination
and
work up



1-4-E: $R^2 = (CH_2)_2Ph$

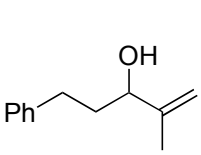
carbometalation
elimination
and
work up



1-4-Z: $R^2 = (CH_2)_2Ph$

1-3:1-4 = >20:1

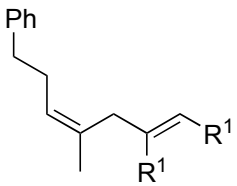
1-1) validity of model



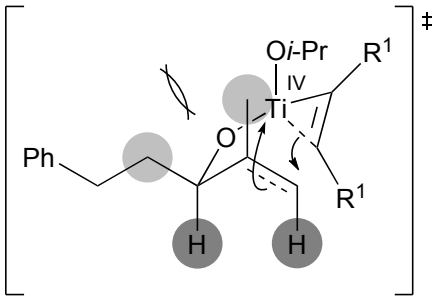
1-25

n-BuLi, THF/hexane, -78 ºC to 0 ºC;
$ClTi(O\textit{i}\text{-}Pr)_3$, *c*-$C_5H_9MgCl$, **A**
toluene/hexane/Et_2O, -78 ºC to 0 ºC

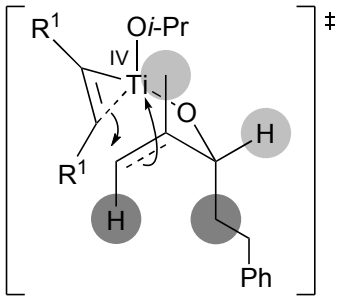
72%
(*E*:*Z* = 1:>20)



1-26-Z: $R^1 = (CH_2)_2OPMB$

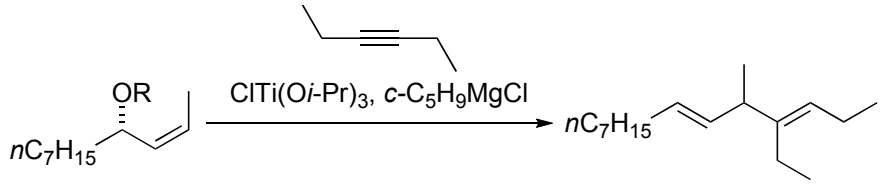


TS-7 (unfavored)
1.2-allylic strain Me vs $(CH_2)_2Ph$
1.3-allylic strain H vs H



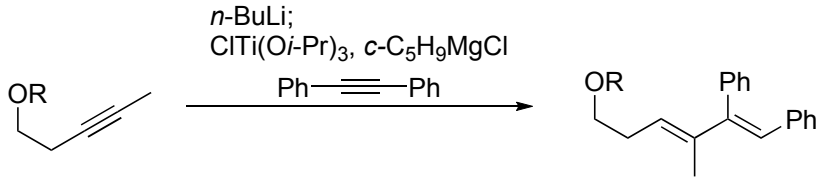
TS-8 (favored)
1.2-allylic strain H vs Me
1.3-allylic strain H vs $(CH_2)_2Ph$

1-2) necessity of Ti-O tethering



1-27 R = H: 72% (*E*:*Z* = >25:1)
R = Me or BOM: trace **1-28-E**

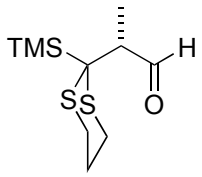
Cha's group *J. Am. Chem. Soc.* **2008**, *130*, 15997.



1-29 R = H: 68%
R = TBS: complex mixture **1-30**

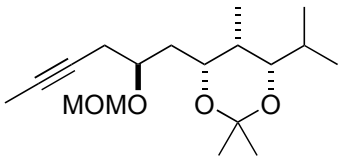
Micalizio's group *J. Am. Chem. Soc.* **2006**, *128*, 2764.

2



2-1

Rearrange reaction conditions (a-f) in an appropriate order to construct the synthetic route toward **2-2**.

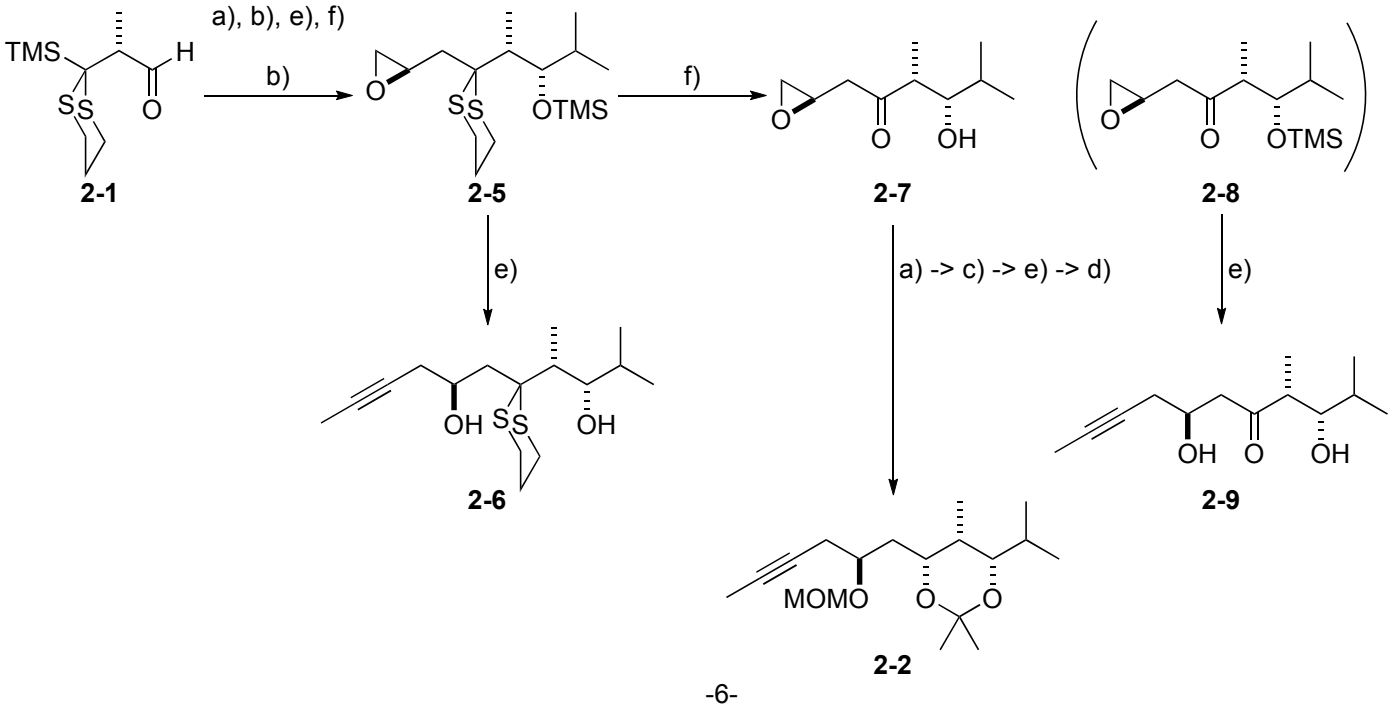


2-2

a) Et_2BOMe, $NaBH_4$, THF/MeOH, -78 ºC (75%, *d.r.* 92:8)
b) $(CH_3)_2CHLi$, Et_2O, -78 ºC; HMPA, **C,** -50 ºC to rt (76%, *d.r.* >20:1)
c) 2-methoxypropene, PPTS, CH_2Cl_2, 0 ºC (82%)
d) MOMCl, DIPEA, TBAI, CH_2Cl_2 (86%)
e) **D**, BF_3·THF, THF, -78 ºC (92%)
f) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O (80%)

answer

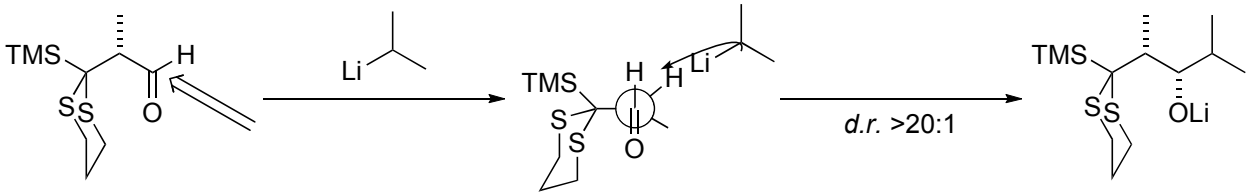
b) -> f) -> a) -> c) -> e) -> d)



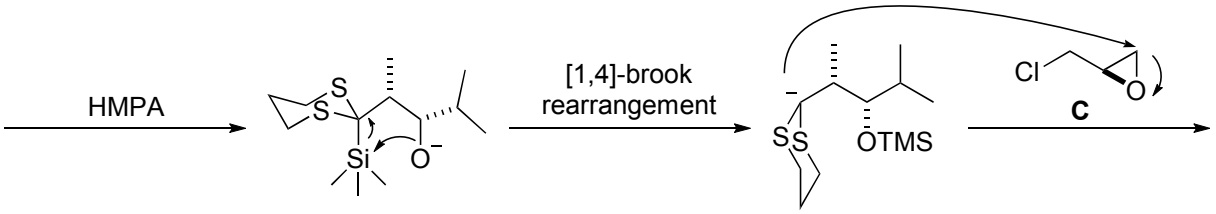
2-1 **2-5** **2-7** **2-8**

2-6 **2-9**

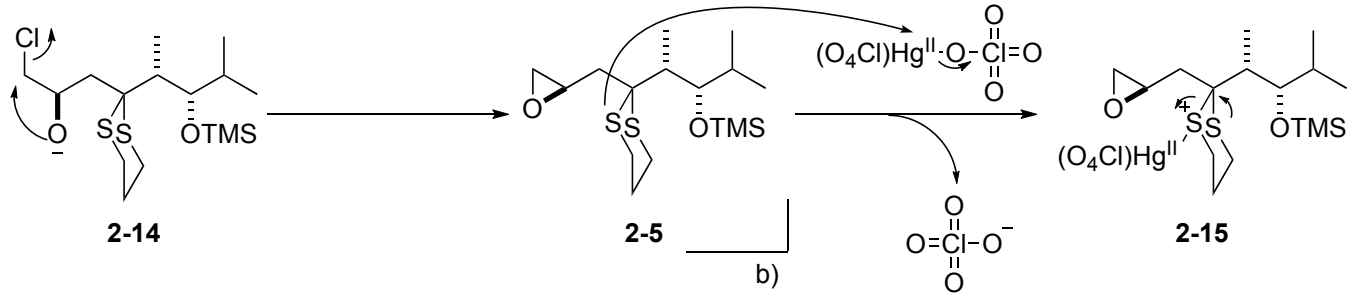
2-2



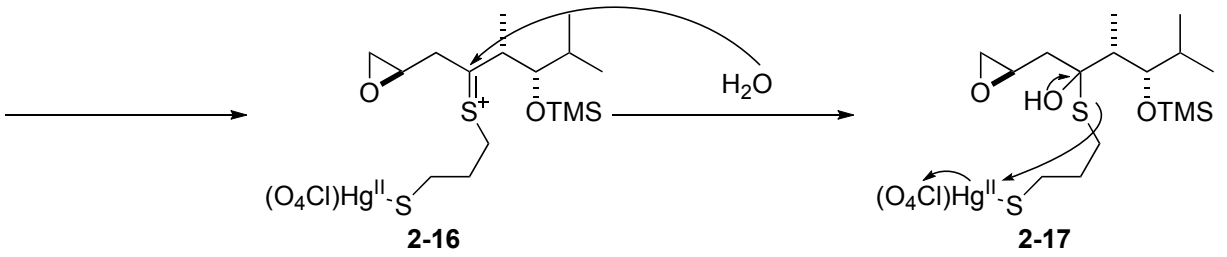
2-1 **2-10** Felkin-Anh Model **2-11**



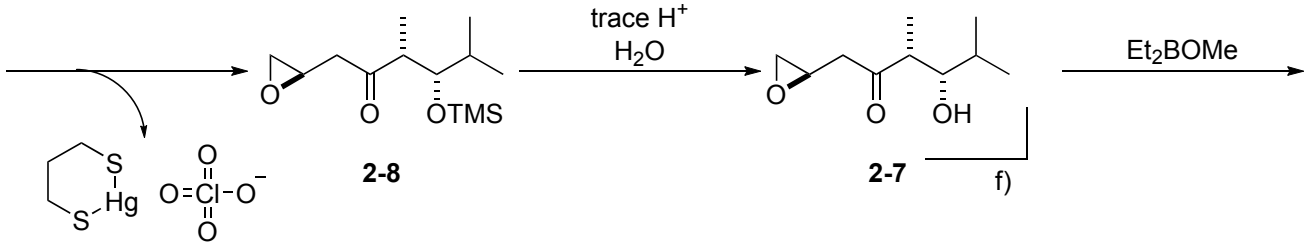
2-12 **2-13**



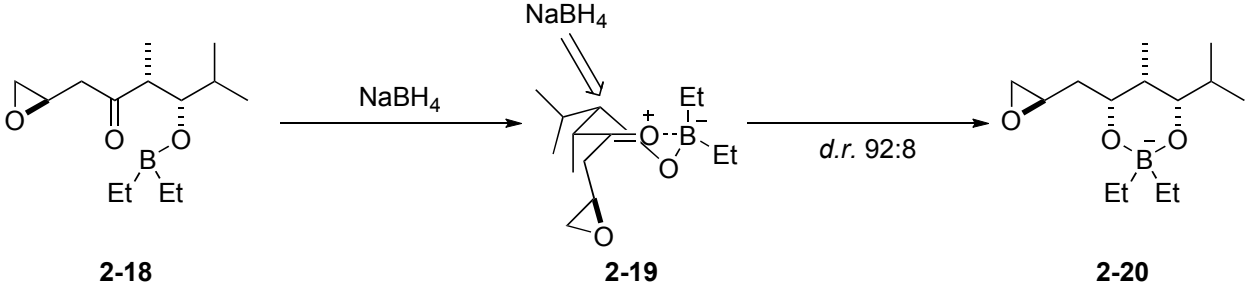
2-14 **2-5** **2-15**



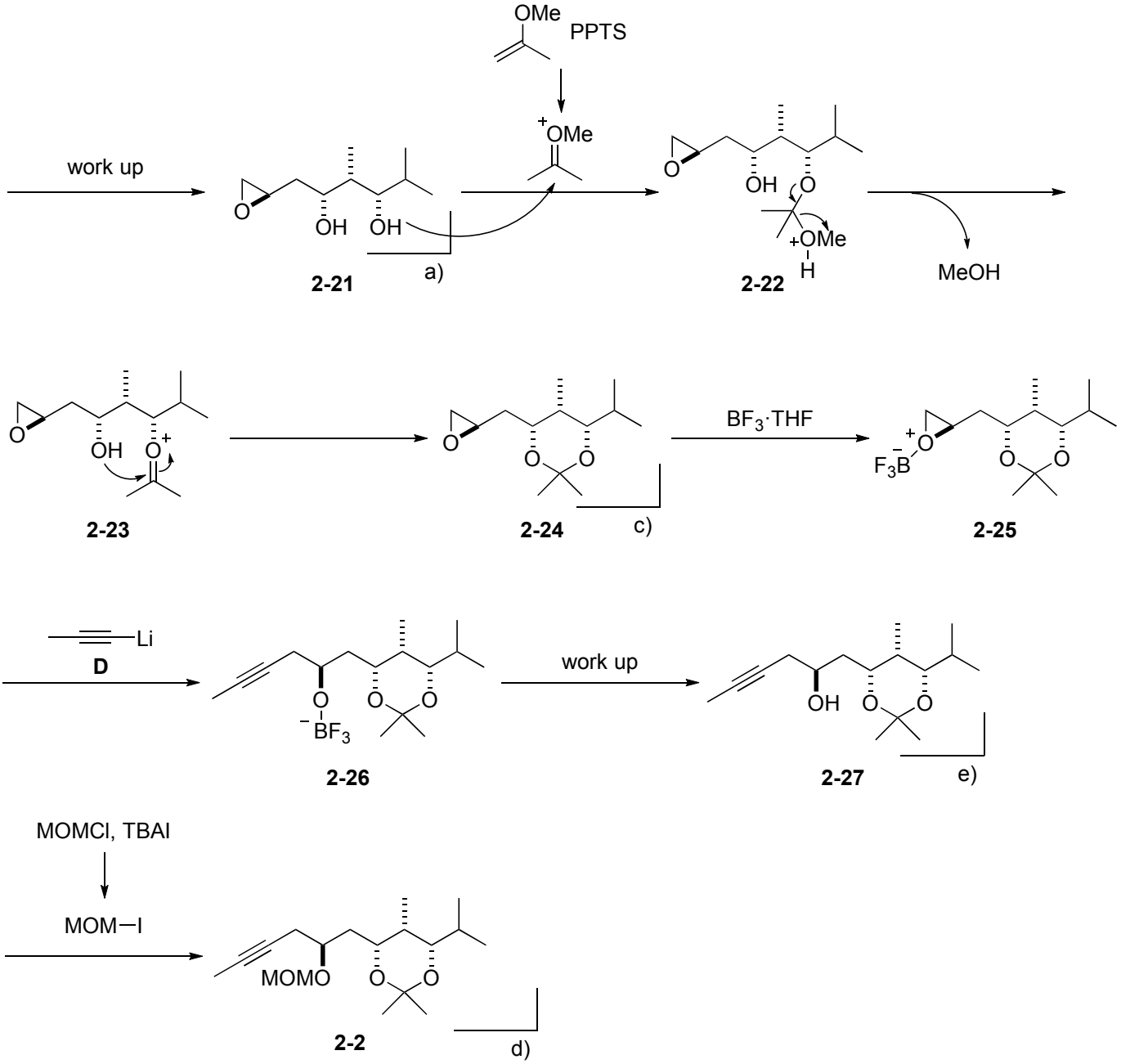
2-16 **2-17**

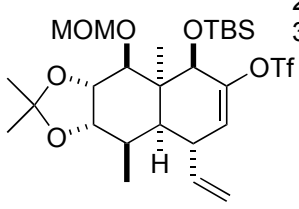


2-8 **2-7**



2-18 **2-19** **2-20**



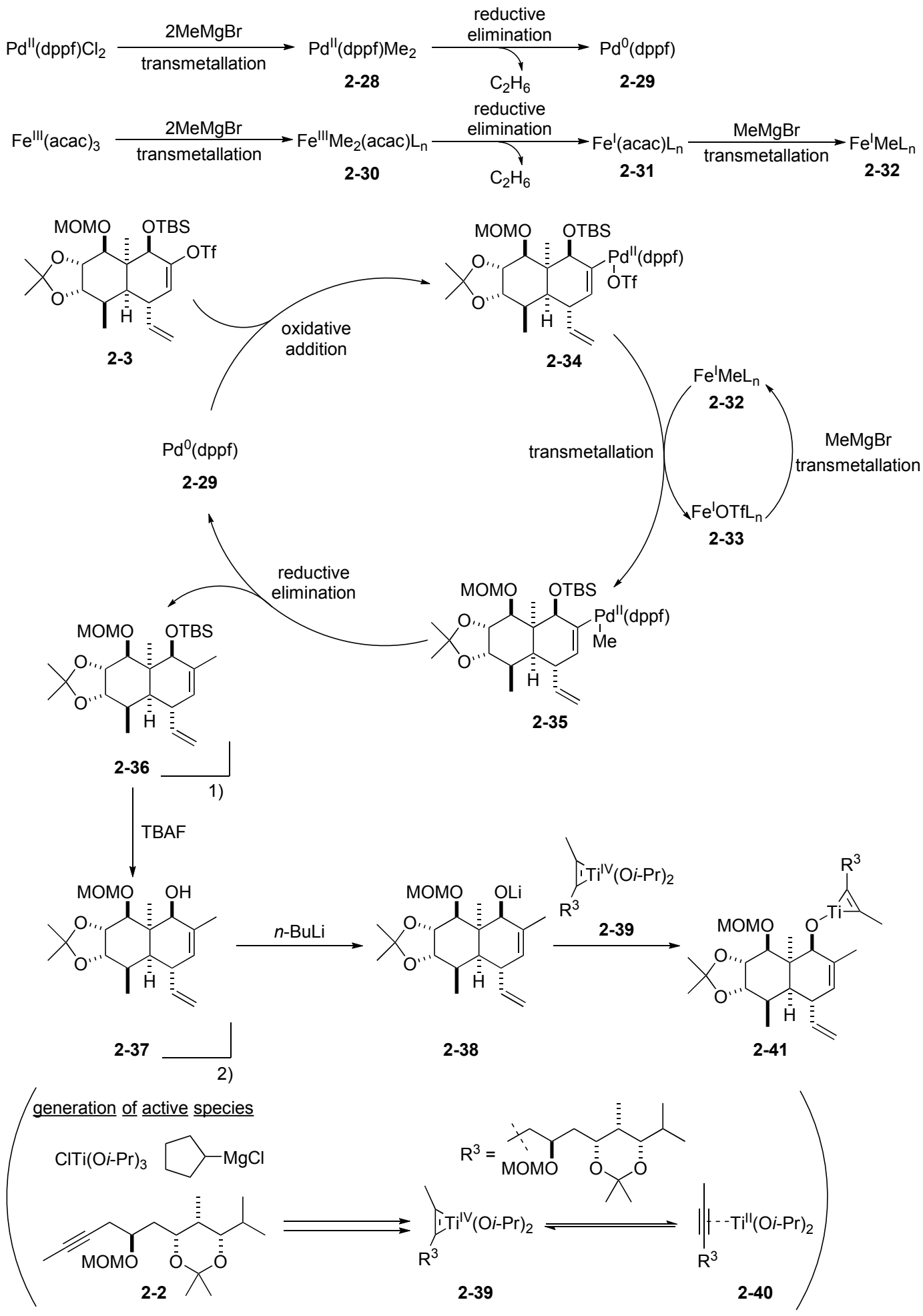


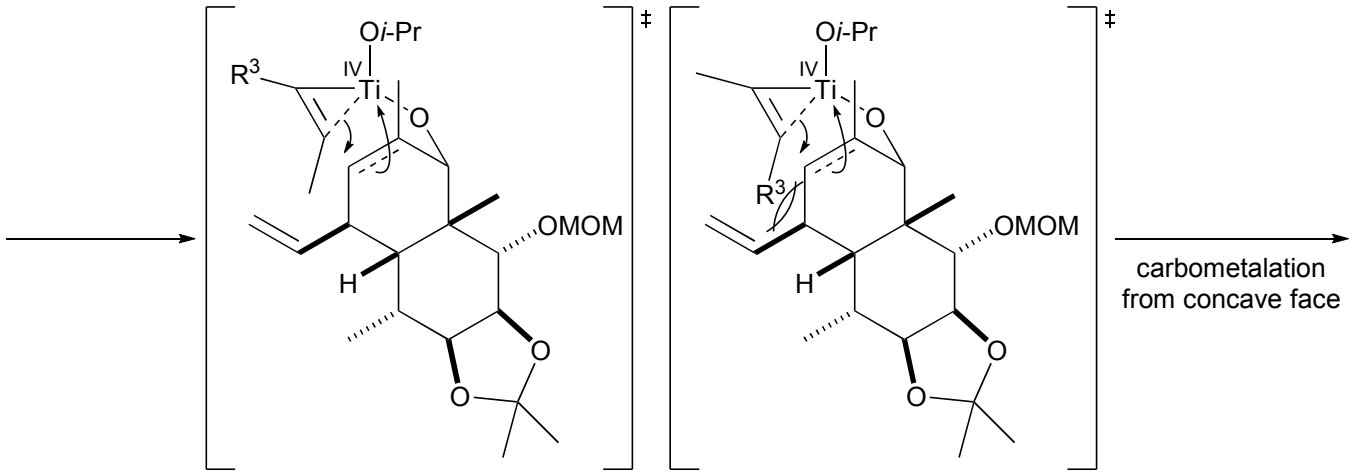
2-3

1) $Fe(acac)_3$ (10 mol%)
   $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5 mol%)
   MeMgBr (4 eq), THF/NMP (95%)
2) TBAF, THF, 60 ºC (89%)
3) n-BuLi, THF/hexane, -78 ºC to 0 ºC;
   $ClTi(O\textit{i}\text{-}Pr)_3$, *c*-$C_5H_9MgCl$, **2-2**
   toluene/hexane/Et_2O, -41 ºC to rt (61%)

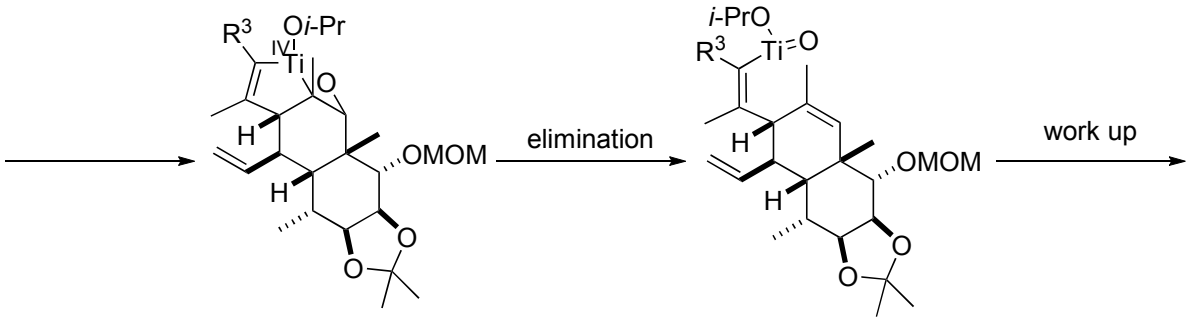
2-4

The solution of product from **2-3** and n-BuLi was cannulated to the premixed solution of $ClTi(O\textit{i}\text{-}Pr)_3$, cC_5H_9MgCl and **2-2**.

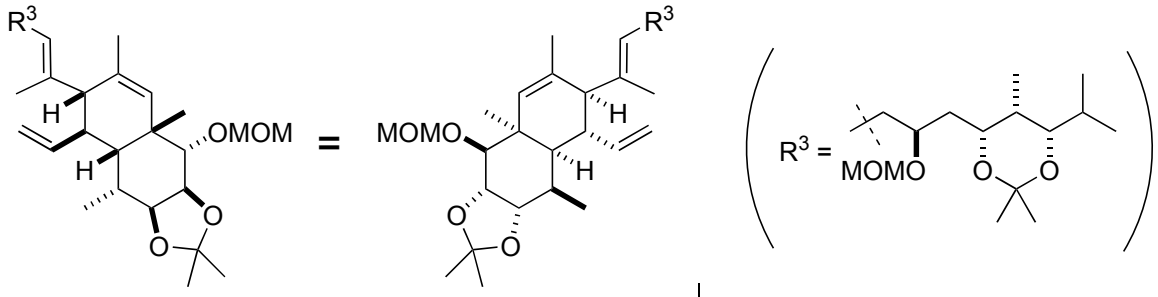

generation of active species
Pd^II(dppf)Cl2
2MeMgBr
transmetallation
Pd^II(dppf)Me2
2-28
reductive elimination
C2H6
Pd^0(dppf)
2-29
Fe^III(acac)3
2MeMgBr
transmetallation
Fe^IIIMe2(acac)Ln
2-30
reductive elimination
C2H6
Fe^I(acac)Ln
2-31
MeMgBr
transmetallation
Fe^IMeLn
2-32
MOMO
OTBS
OTf
2-3
oxidative addition
Pd^II(dppf)
OTf
2-34
Fe^IMeLn
2-32
MeMgBr
transmetallation
transmetallation
Fe^IOTfLn
2-33
Pd^0(dppf)
2-29
reductive elimination
Pd^II(dppf)
Me
2-35
2-36
1)
TBAF
MOMO
OH
2-37
2)
n-BuLi
MOMO
OLi
2-38
Ti^IV(Oi-Pr)2
R3
2-39
R3
Ti
MOMO
O
2-41
generation of active species
ClTi(Oi-Pr)3
MgCl
R3 =
MOMO
2-2
Ti^IV(Oi-Pr)2
R3
2-39
Ti^II(Oi-Pr)2
R3
2-40



TS-9 (favored) **TS-10** (unfavored)



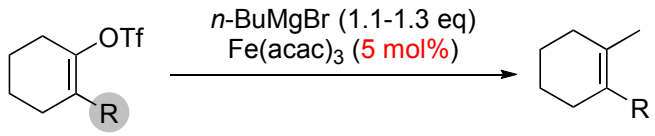
2-42 **2-43**



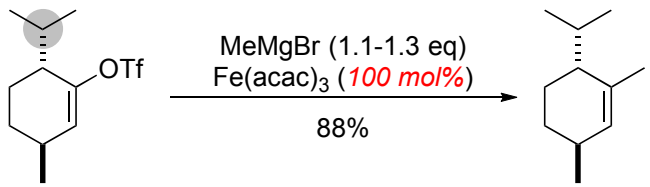
2-4-1 **2-4-2**

3)

2-1) Kochi-Fürstner coupling (Fe and grignard reagent)

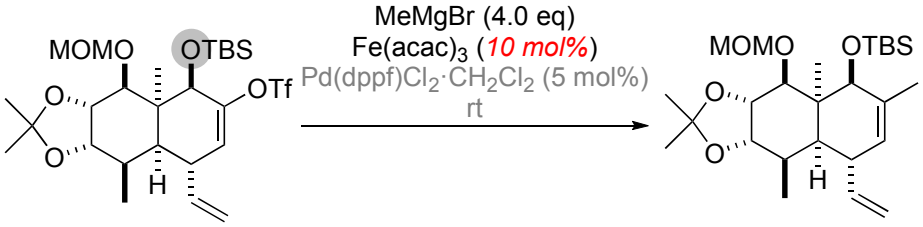


2-44 R = H: 80% R = Me: 53% **2-45**



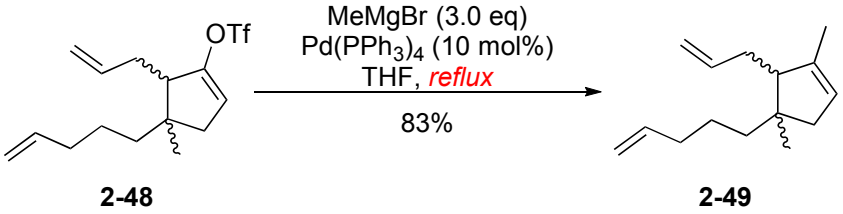
2-46 sensitive to steric hindrance **2-47**

Fürstner's group *J. Org. Chem.* **2004**, *69*, 3943.

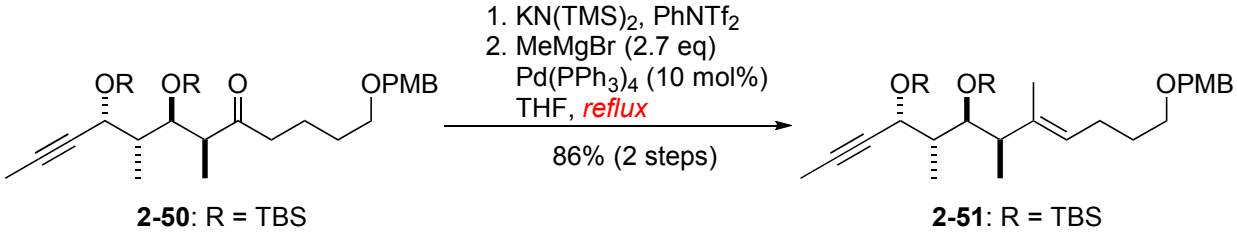


Not suitable for Kochi-Fürstner coupling

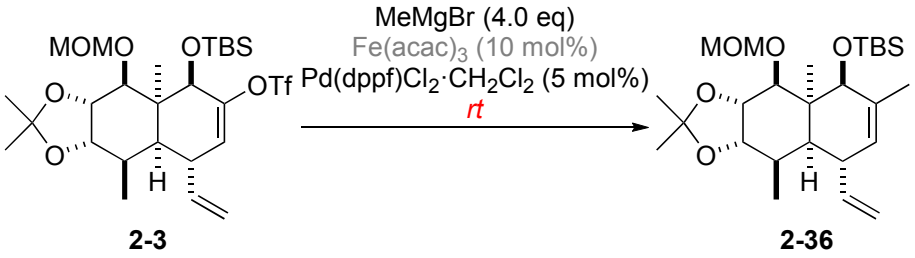
2-2) Kumada coupling (Pd and grignard reagent)



Williams's group *Eur. J. Org. Chem.* **2002**, 3145.



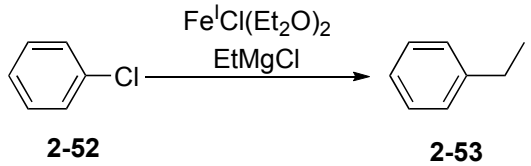
Maier's group *Org. Lett.* **2016**, *18*, 3146.

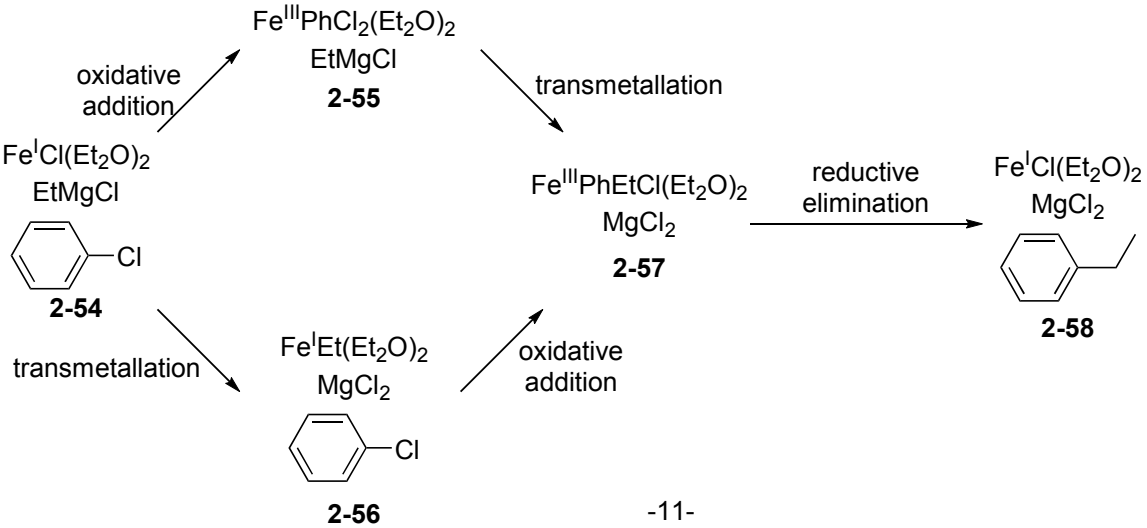


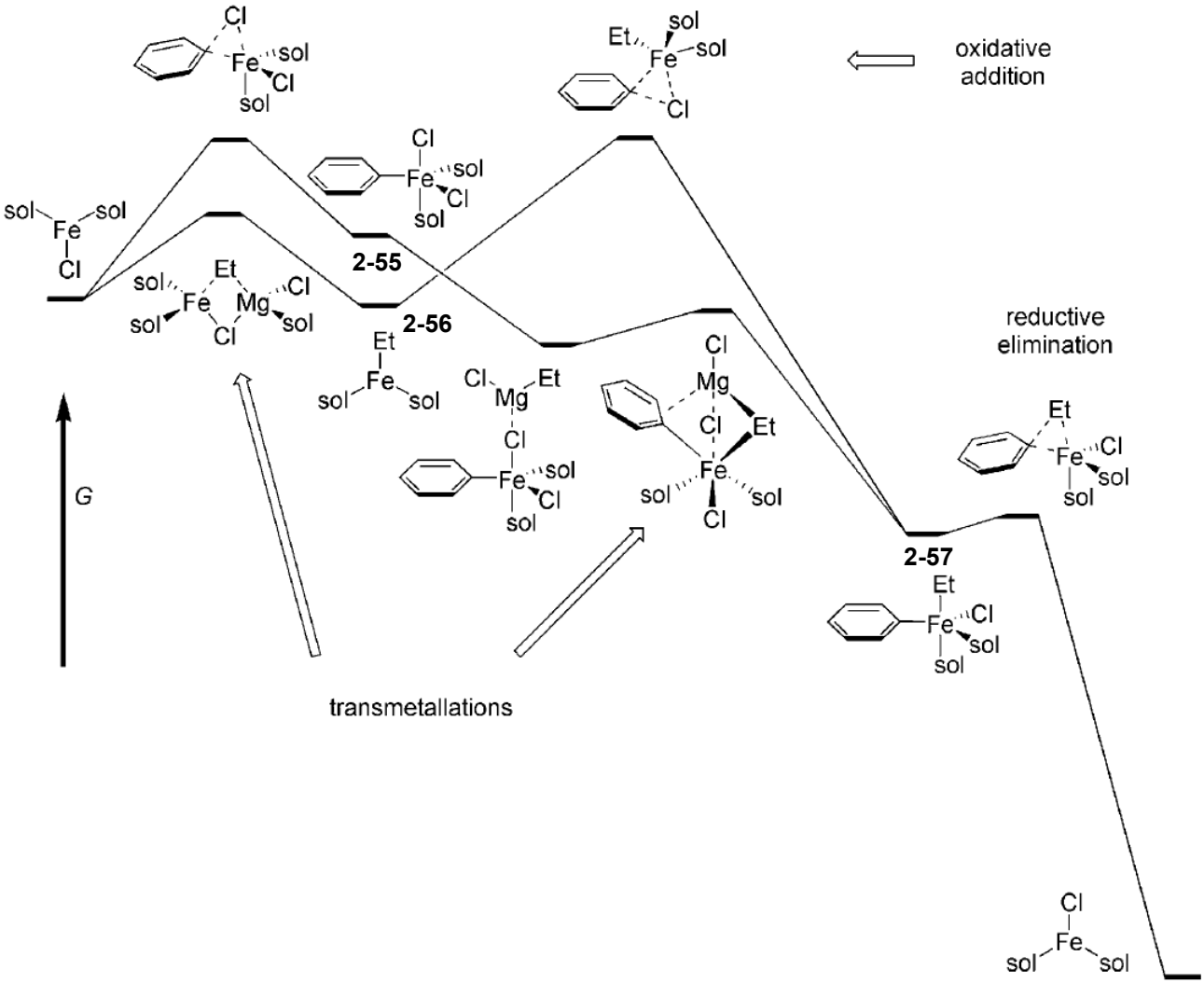
Fe(acac)$_3$ activated Kumada coupling?

2-3) DFT calculation

Norrby's group *ChemCatChem* **2009**, *1*, 152.
Chem. Eur. J. **2015**, *21*, 5946.
(review) *ACS Catal.* **2016**, *6*, 1640.



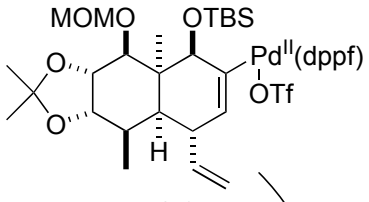




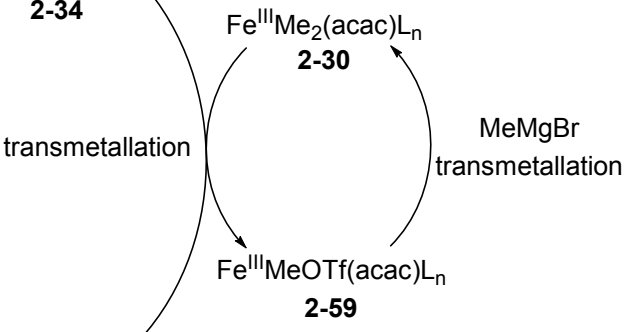
- Oxidative addition is rate-determining step in both route ($\Delta G^{\ddagger}$: 65 kJ/mol from **2-54**, 69 kJ/mol from **2-56**)

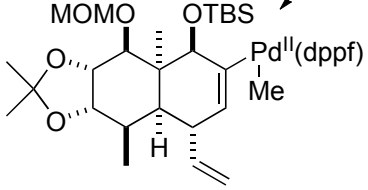
2-4) other possible explanation

transmetallation via Fe^{III}



2-34





2-35

ligand exchange to accelerate oxidative addition

Pd^0(dppf) **2-29** —ligand exchange (Fe^{III} or Fe^{I})→ Pd^0 **2-60**