Mn catalyzed Redox Cascade Reaction by Leitner's group

Literature Seminar

2020/01/11

Yuuki Watanabe

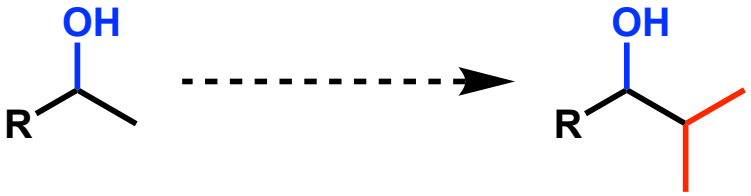
1. *β*-Methylation of alcohol
   (Methanol as C-1 unit)

2. *β*-Cycloalkylation of alcohol

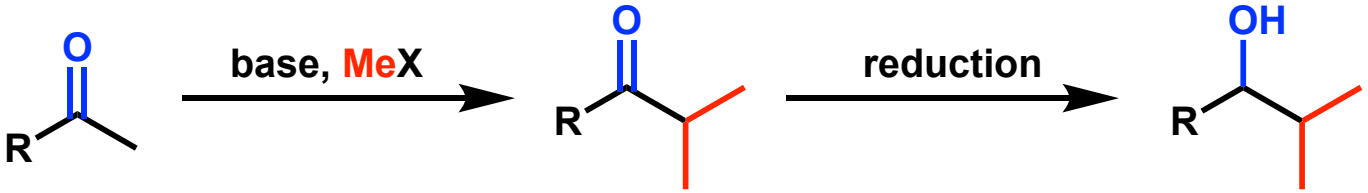
1. *β*-Methylation of alcohol (Methanol as C-1 unit)

2. *β*-Cycloalkylation of alcohol

Traditional approach: β-methylation of alcohol

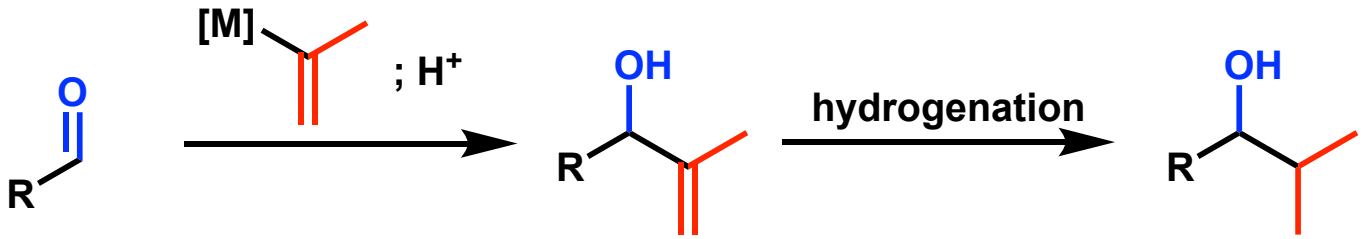


(1) enolate alkylation



X = Cl, Br, I

(2) Addition of carboanion via isopropenyl group



[M] = Li, MgBr

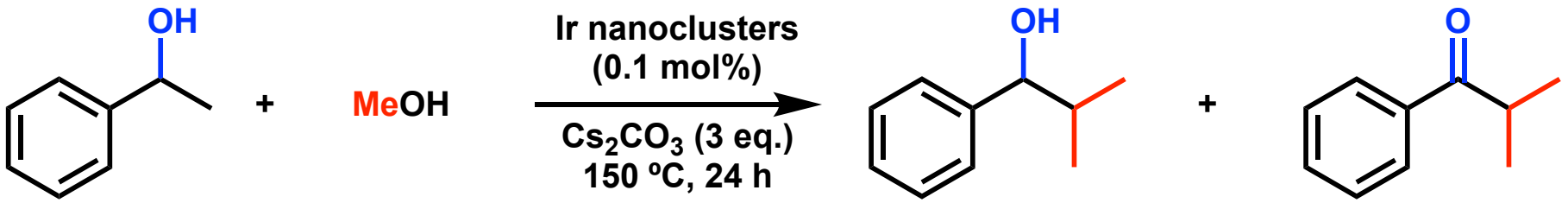
Problems:

1. **Use of highly reactive reagents**
2. **Stoichiometric amount of halide waste**
3. **Multistep**

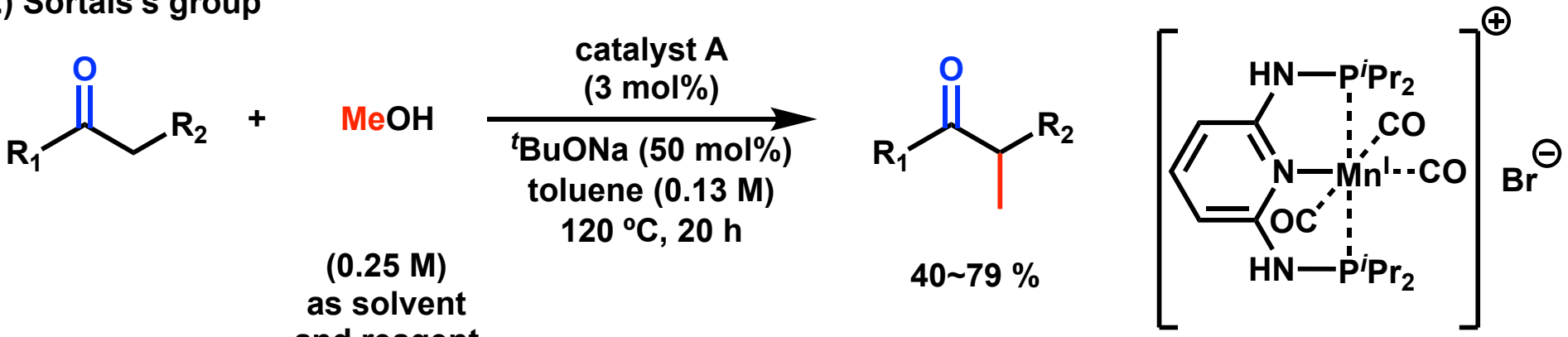
Kaithal, A.; Holscher, M.; Leitner, W. *Angew. Chem. Int. Ed.* **2020**, *59*, 215.

Methylation using methanol as C1 source by Obora's and Sortais's group

(1) Obora's group



(2) Sortais's group

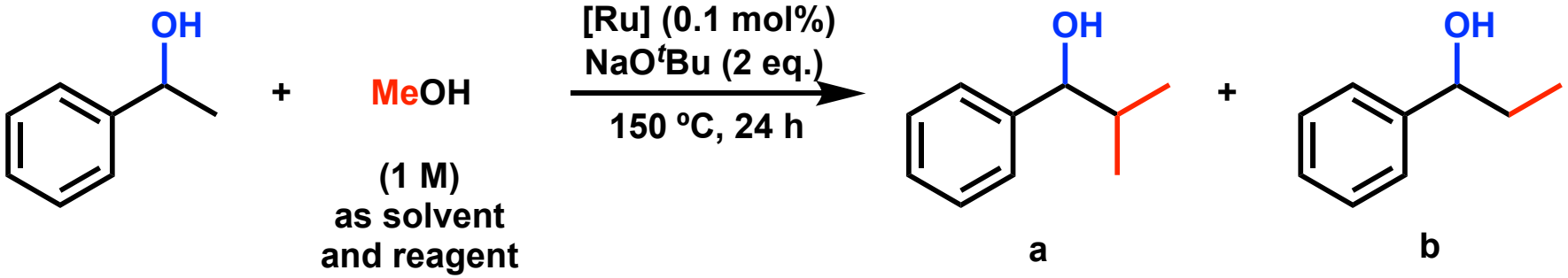


R_1 = aromatic
R_2 = aromatic or aliphatic

Oikawa, K.; Itoh, S.; Yano, H.; Kawasaki, H.; Obora, Y. *Chem. Commun.* **2017**, *53*, 1080
Bruneau-Voisine, A.; Pallova, L.; Bastin, S.; Cesar, V.; Sortais, J. -B. *Chem. Commun.* **2019**, *55*, 314

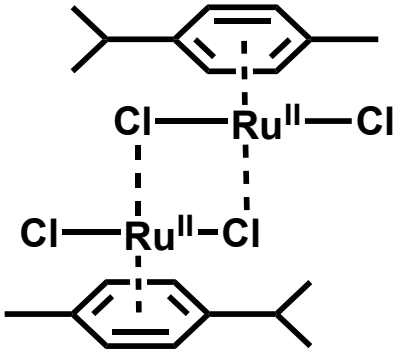
Previous work: Methylation using Ru catalyst

(3) Leitner's group

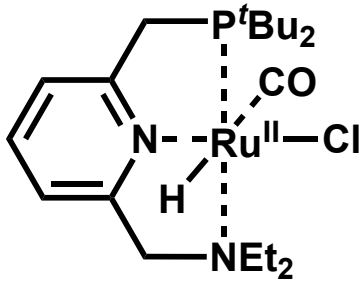


entry	[Ru]	Conv. (%)	Yield (a/b)
1	$Ru(acac)_3$	51	33/11
2	$[Ru(p\text{-cymene})Cl]_2Cl_2$	33	13/11
3	[RuHCl(CO)(PNN)]	89	40/22
4	Ru-MACHO-BH	97	75/11

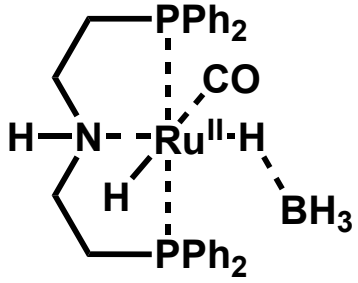
Conv. and yields were determined by NMR. Mesitylene was used as an internal standard.



$[Ru(p\text{-cymene})Cl]_2Cl_2$



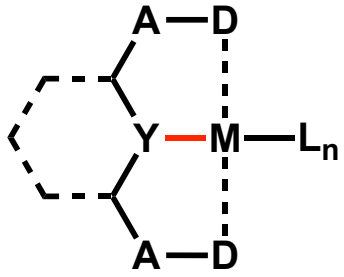
[RuHCl(CO)(PNN)]



Ru-MACHO-BH

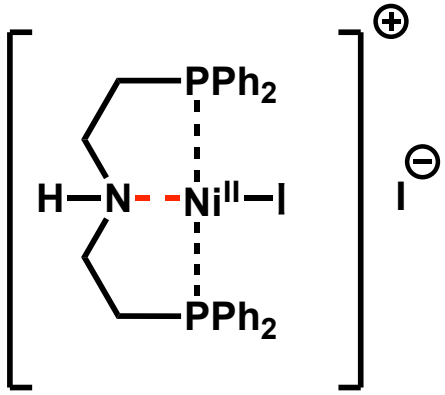
Kaithal, A.; Schmitz, M.; Holscher, M.; Leitner, W. *ChemCatChem.* **2019**, *11*, 5287.

Pincer ligands



Pincer-type ligand
- **Tridentate ligands**
- **two electron-donor and one central group**
- **Y-M σ-bond**

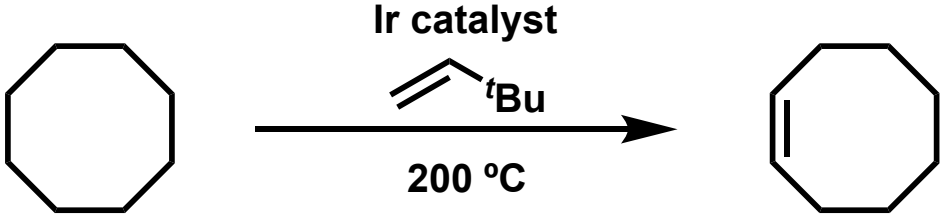
→ **High stability, activity**



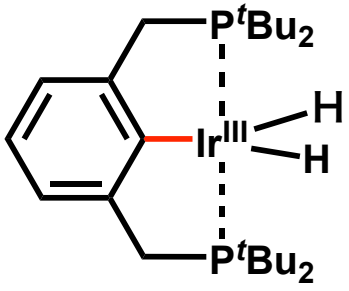
m.p. 256-260 ºC
No decompositon

Y = N, C
D = NR_2, PR_2, SR, AsR_2 …
A = CH_2, NH, O
M = Ni, Ru, Rh, Fe, Mn, Ir…

Application:
Cross coupling, (de)hydrogenation, C-H activation



transfer-hydrogenation

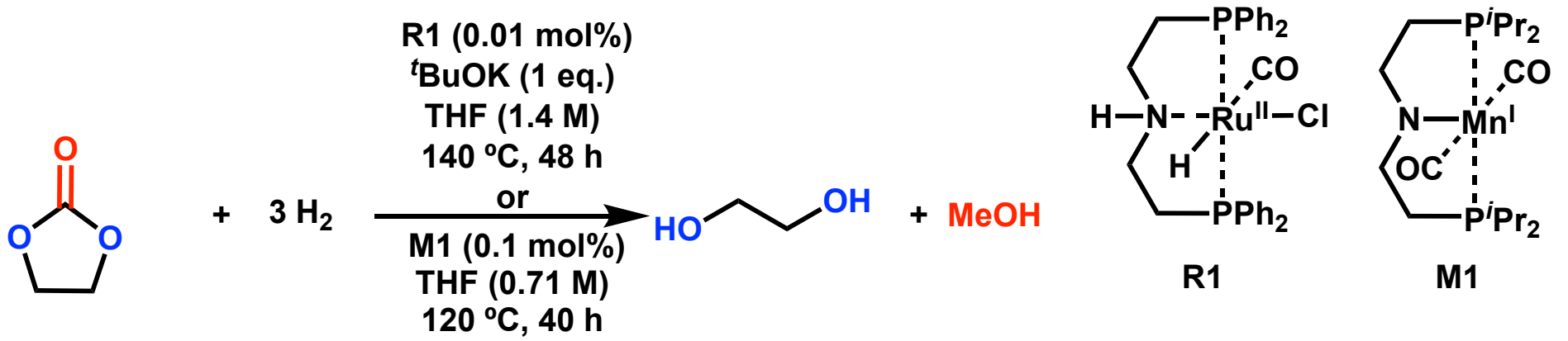


Ir catalyst

12 turnovers min^{-1} at 200ºC
No decomposition up to 1 week

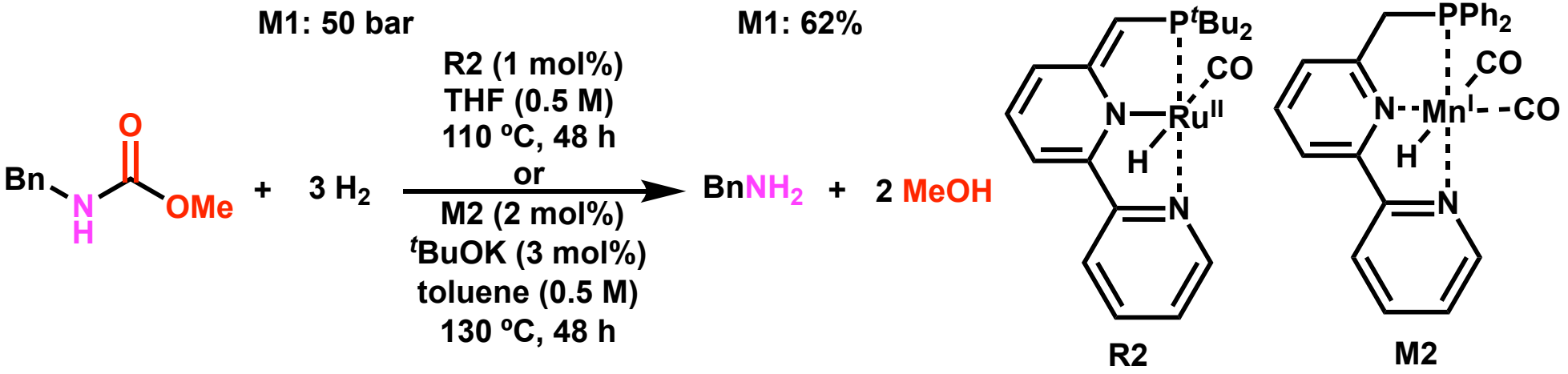
Gupta, M.; Hagen, C.;Flesher, R.J.;Kaska, W.C.; Jensen, C.M. *Chem. Commun.* **1996**, 2083
Deeming, A.J.; Shaw, B.L. *J. Chem. Soc.* ***1968***, 1887
Benito-Garagorri, D.;Kirchner, K. *A. Chem. Research.* **2008**, *41*, 201
Nelson, S. M.; Dahlhoff, W. V. *J. Chem. Soc.* **1971**, *13*, 2184

Center Metal



R1: 50 atm
M1: 50 bar

R1: >99%
M1: 62%



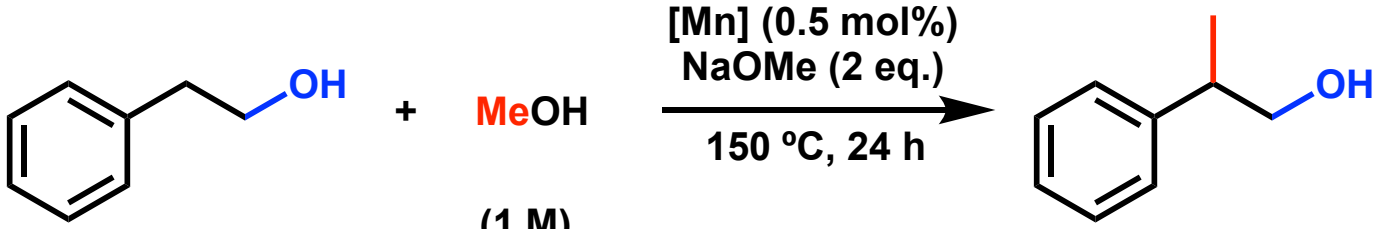
R2: 10 atm
M2: 20 bar

R2: 97%*
M2: 96%

* GC yield using *m*-xylene as an internal standard.

Han, Z.; Rong, L.;Wu, J.; Zhang, L.; Wang, Z.; Ding, K.; *Angew. Chem. Int. Ed.* **2012**, *51*, 13041.
Kaithal, A.; Holscher, M.; Leitner, W. *Angew. Chem. Int. Ed.* **2018**, *57*, 13449.
Das, U. K.; Kumar, A.; Ben-David, Y.; Iron, M. A.; Milstein, D. *J. Am. Chem. Soc*. **2019**, *141*, 12962
Balaraman, E.; Gunanathan, C.; Zhang, J.; Shimon, L. J. W.; Milstein, D. *Nature. Chem.* **2011**, *3*(8), 609

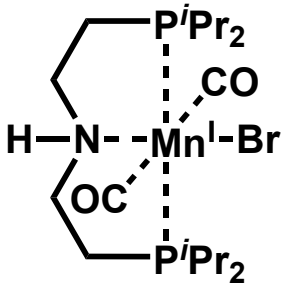
Screening of Mn catalyst



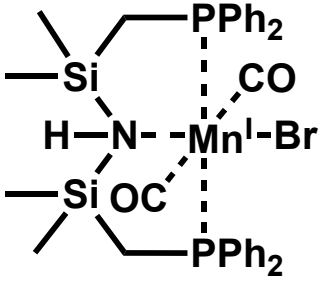
(1 M)
as solvent
and reagent

entry	[Mn]	Conv. (%)[a)]	Yield (%)[a)]
1	M1 (=C1)	97	92
2	M2	10	0
3	M3	42	21
4	M4	51	24
5	M5	23	6

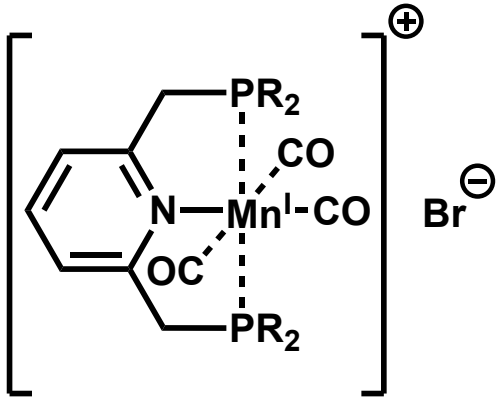
a) NMR yield using mesitylene as an internal standard.



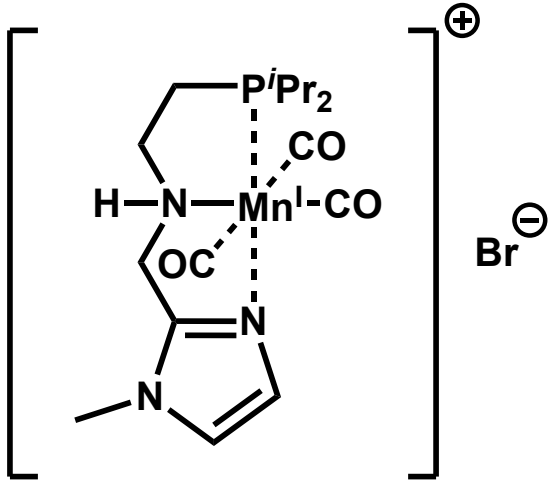
M1 (=C1)



M2



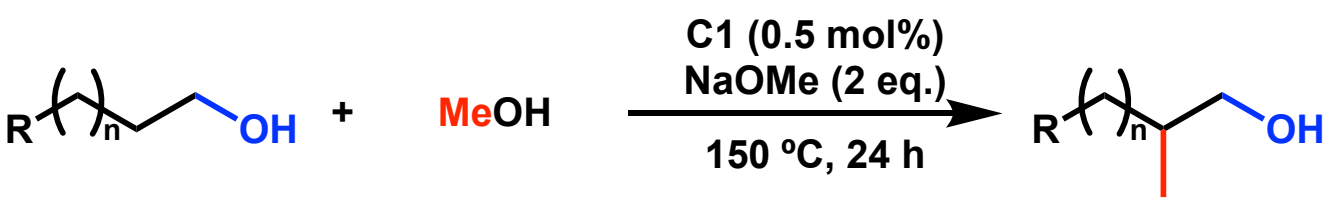
M3 : R = Ph
M4 : R = ^{t}Bu



M5

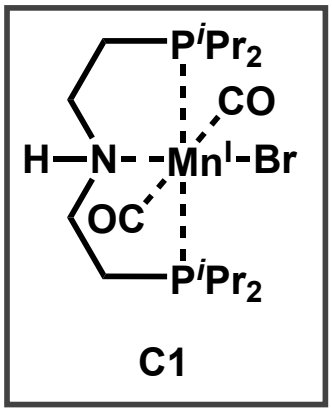
Kaithal, A.; Holscher, M.; Leitner, W. *Angew. Chem. Int. Ed.* **2020**, *59*, 215.

Substrate scope of monomethylation



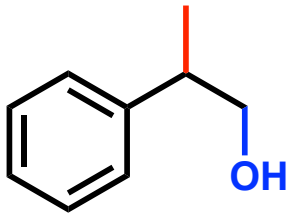
n = 0~8

(1 M)
as solvent
and reagent

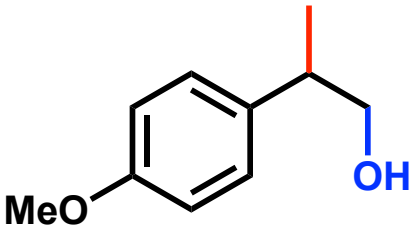


C1

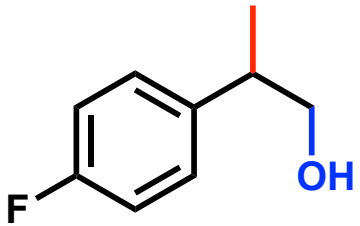
NMR Yield (Isolated Yield) (%)



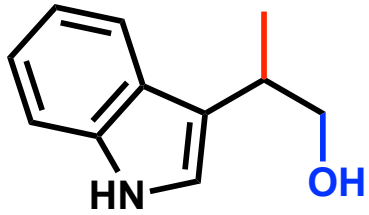
92(85)



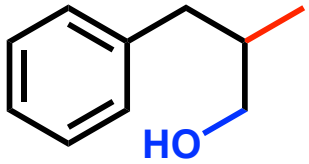
91(82)



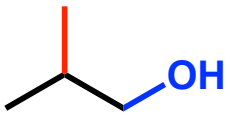
87



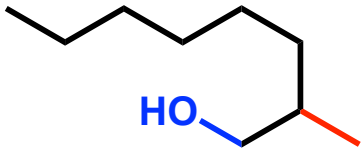
54(47)



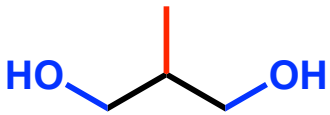
71(66)



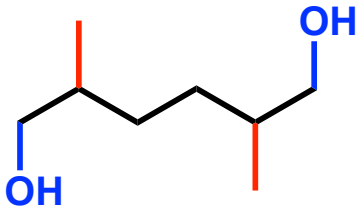
46*



75(62)*



46**



77**

* Reaction time: 36 h
** 4 eq. of NaOMe was used and reaction time was prolonged to 48 h

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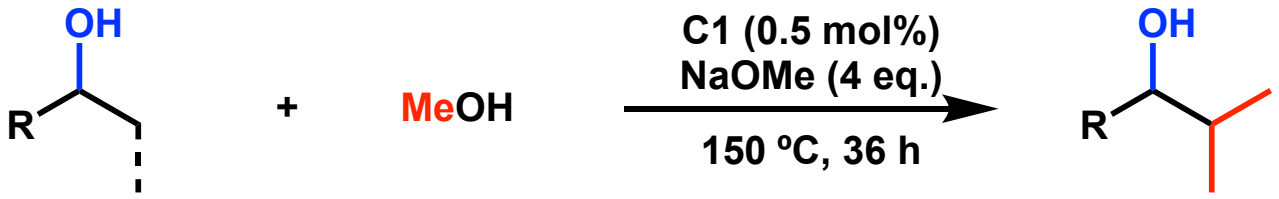
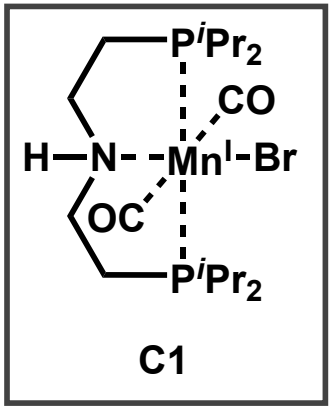
Substrate scope of dimethylation



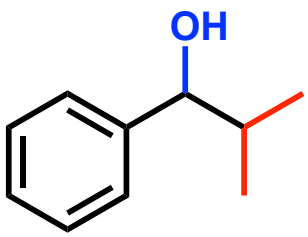
R = aryl, alkyl

(1 M) as solvent and reagent

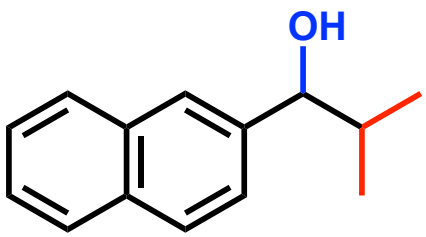


C1

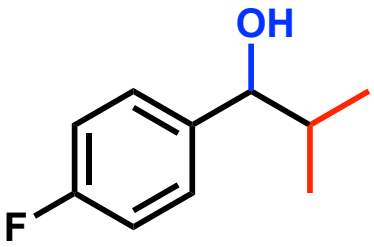
NMR Yield (Isolated Yield) (%)



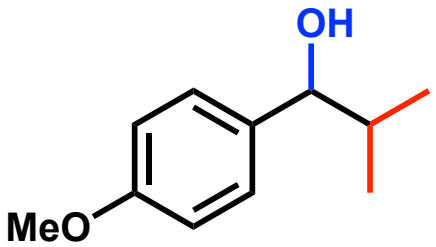
77(71)



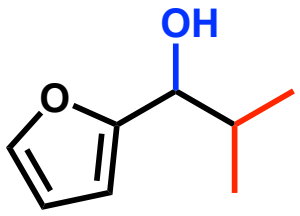
82(74)



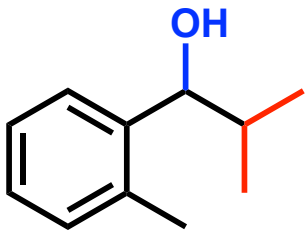
61*



57(51)



63(55)



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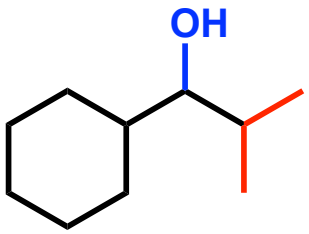

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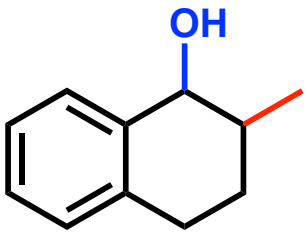

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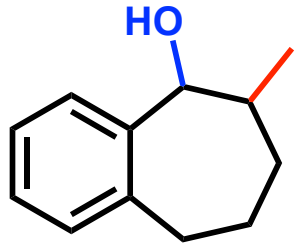

76

* Reaction time: 42 h

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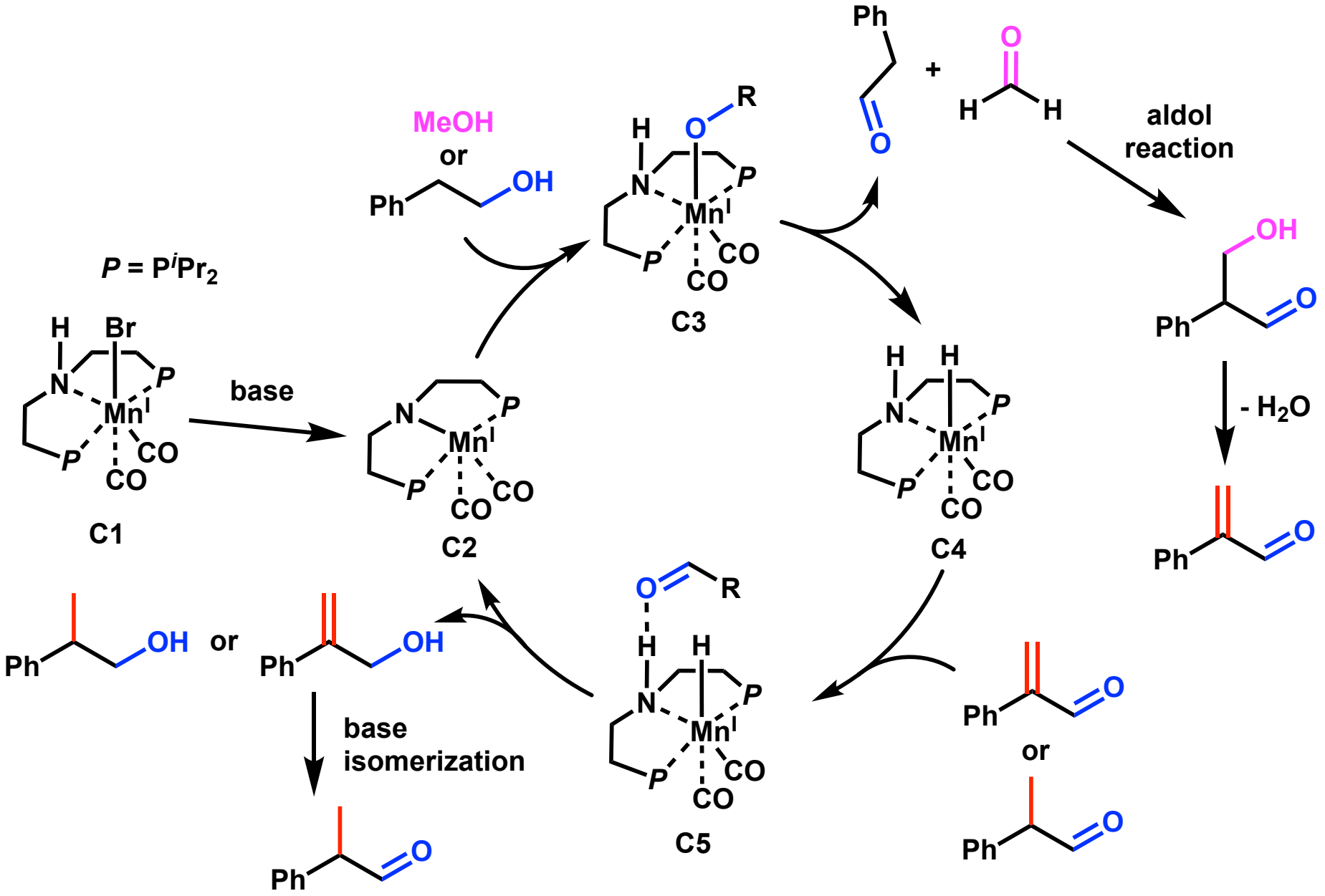
Reaction mechanism (author proposed)



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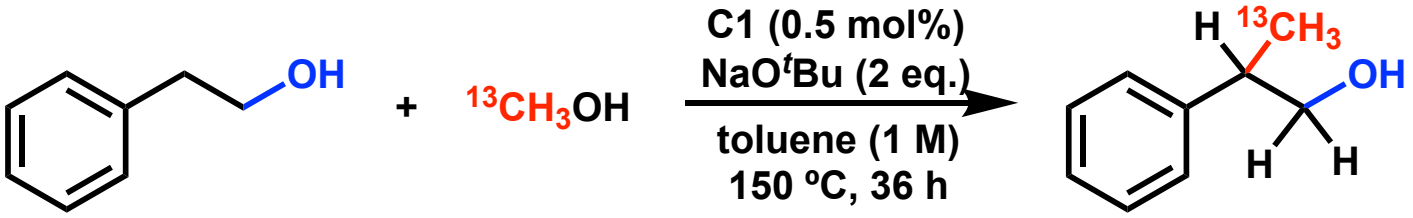
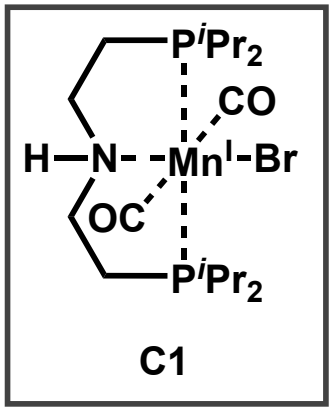
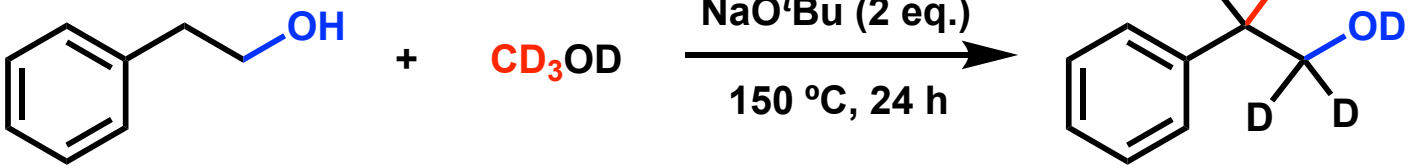
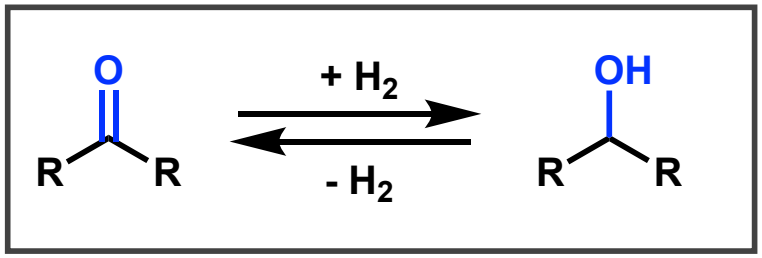
Mechanistic study (1)







(Deuterim ratio: Not mentioned)



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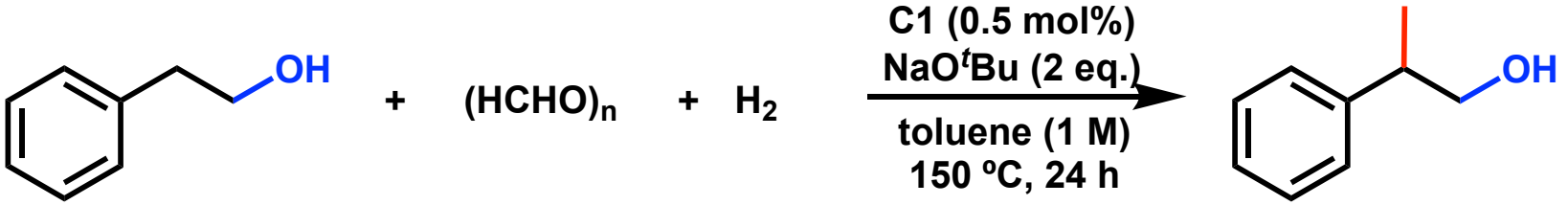
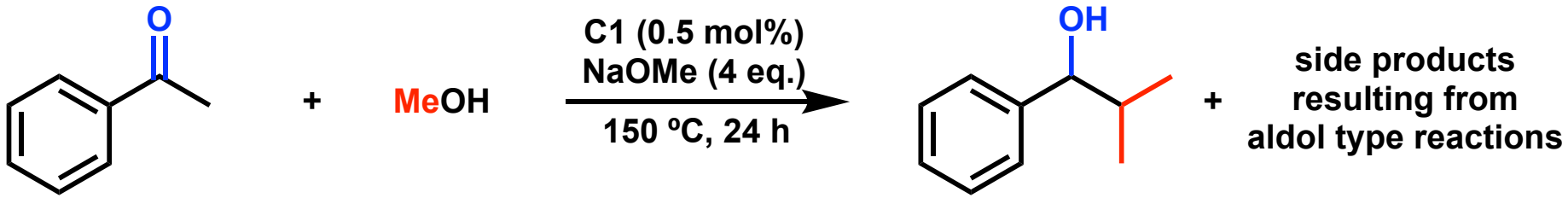
Mechanistic study (2)



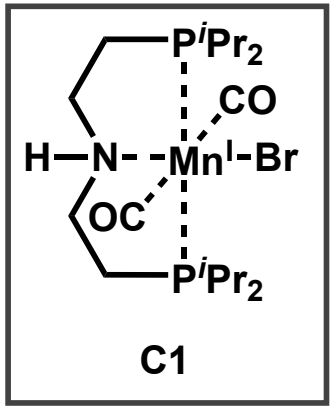
(5 eq.) (10 bar) 17 %*



(1 M) as solvent and reagent

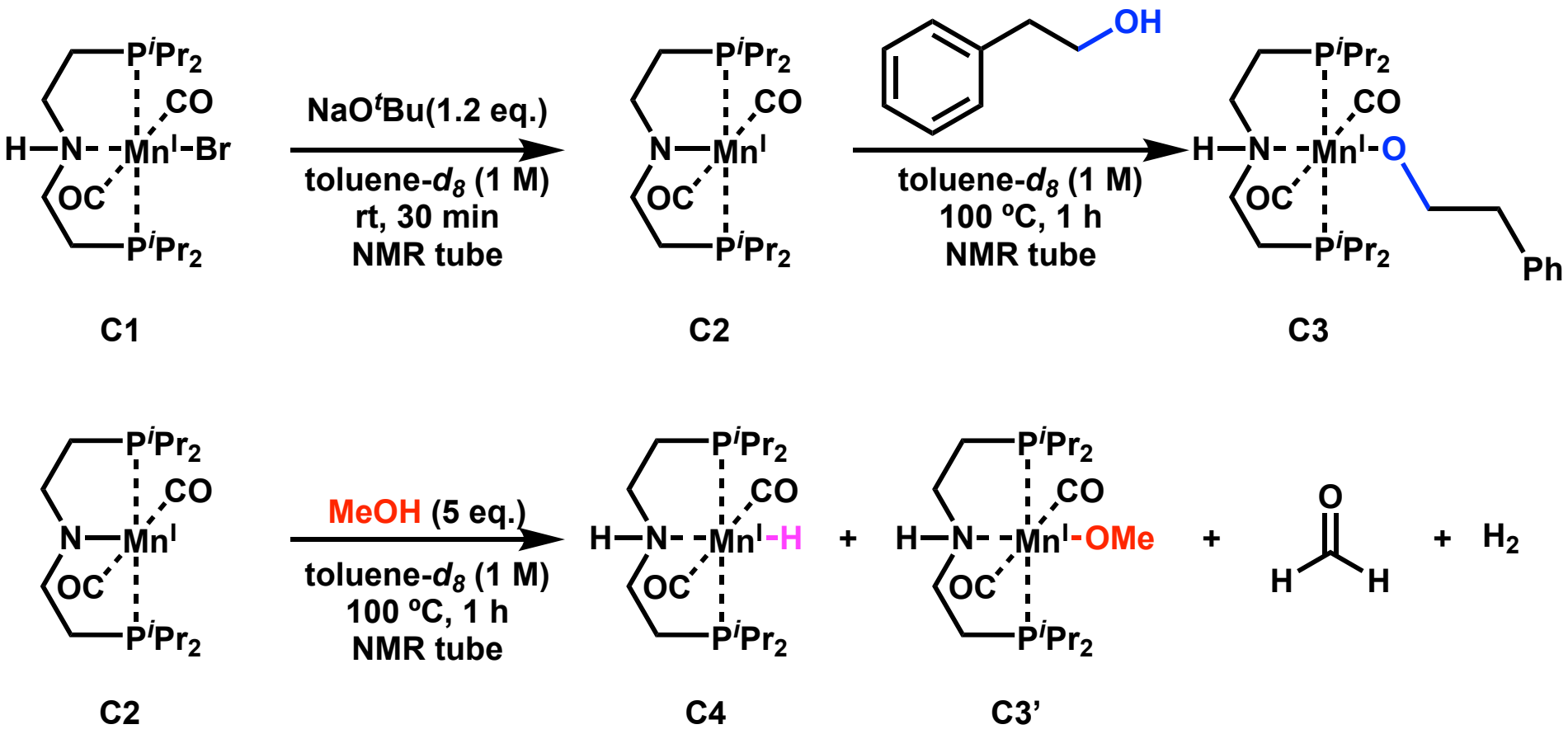
7 %*

*Yields were calculated using mesitylene as an internal standard.



Kaithal, A.; Holscher, M.; Leitner, W. *Angew. Chem. Int. Ed.* **2020**, *59*, 215.

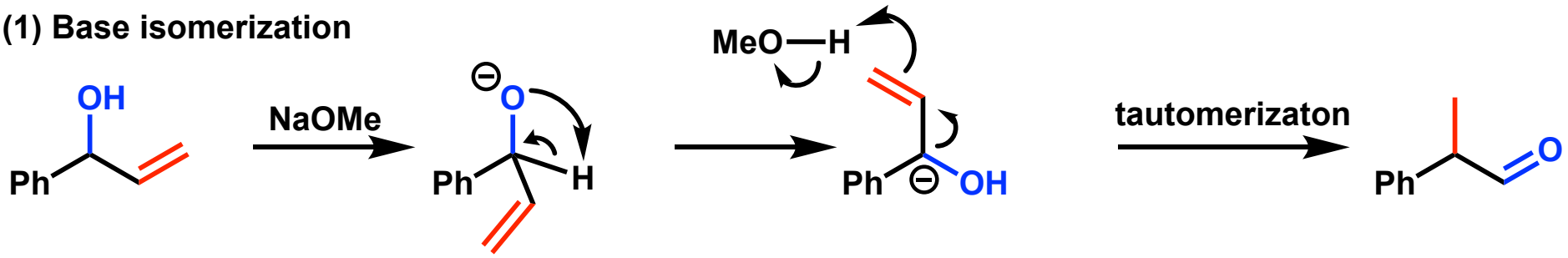
Mechanistic study (3)



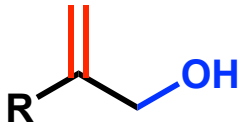
Kaithal, A.; Holscher, M.; Leitner, W. *Angew. Chem. Int. Ed.* **2020**, *59*, 215.

Problems of this mechanism

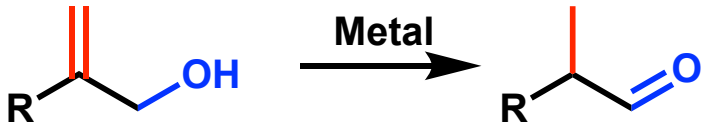
(1) Base isomerization



Is this reaction proceeded with non-aromatic substrates??

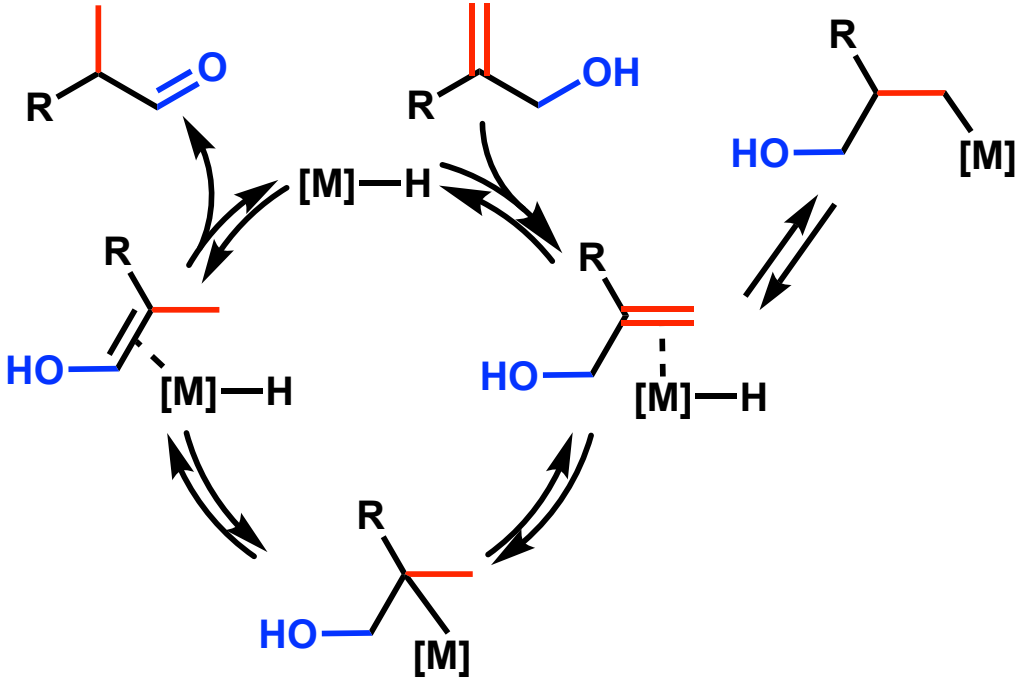


(2) Metal catalyzed isomerization



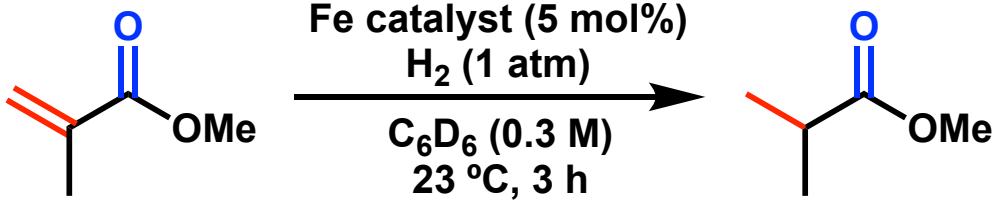
Metal: Ru^{IV}, Pd^{0}…

Is this reaction proceeded with Mn^{I} catalyst??

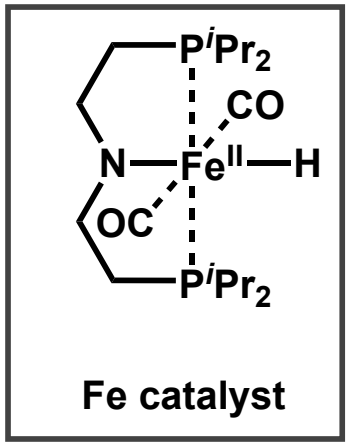


Kaithal, A.; Holscher, M.; Leitner, W. *Angew. Chem. Int. Ed.* **2020**, *59*, 215.
McGrath, D.V.; Grubbs, R.H. *Organometallics.* **1994**, *13*, 224
Rehan, M.; Maity, S.; Morya, L.K.; Pal, K.; Ghorai, P. *Angew. Chem. Int. Ed.* **2016**, *55,* 7728

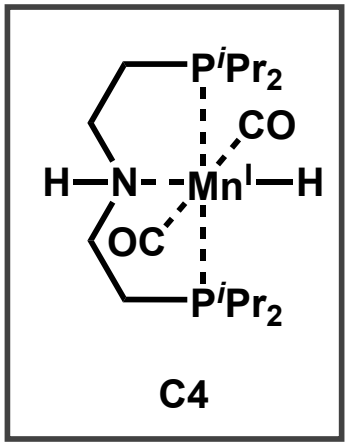
Reduction of enone by Jones' group



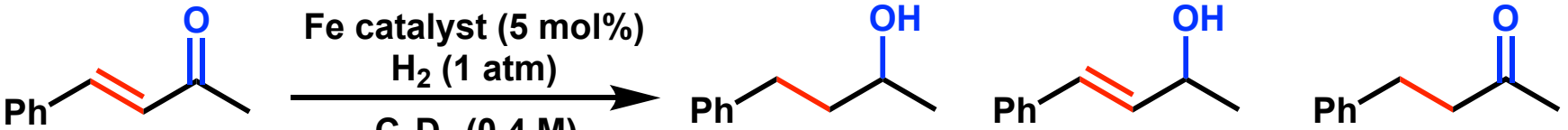
100% Conv.



Fe catalyst

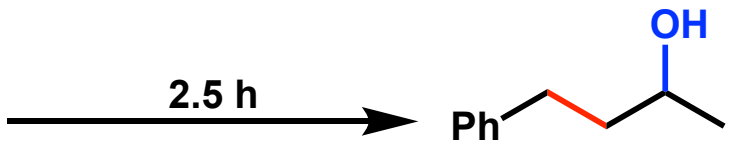


C4



a b c d

95% Conv., a : b : c : d = 1 : 7 : 10 : 1



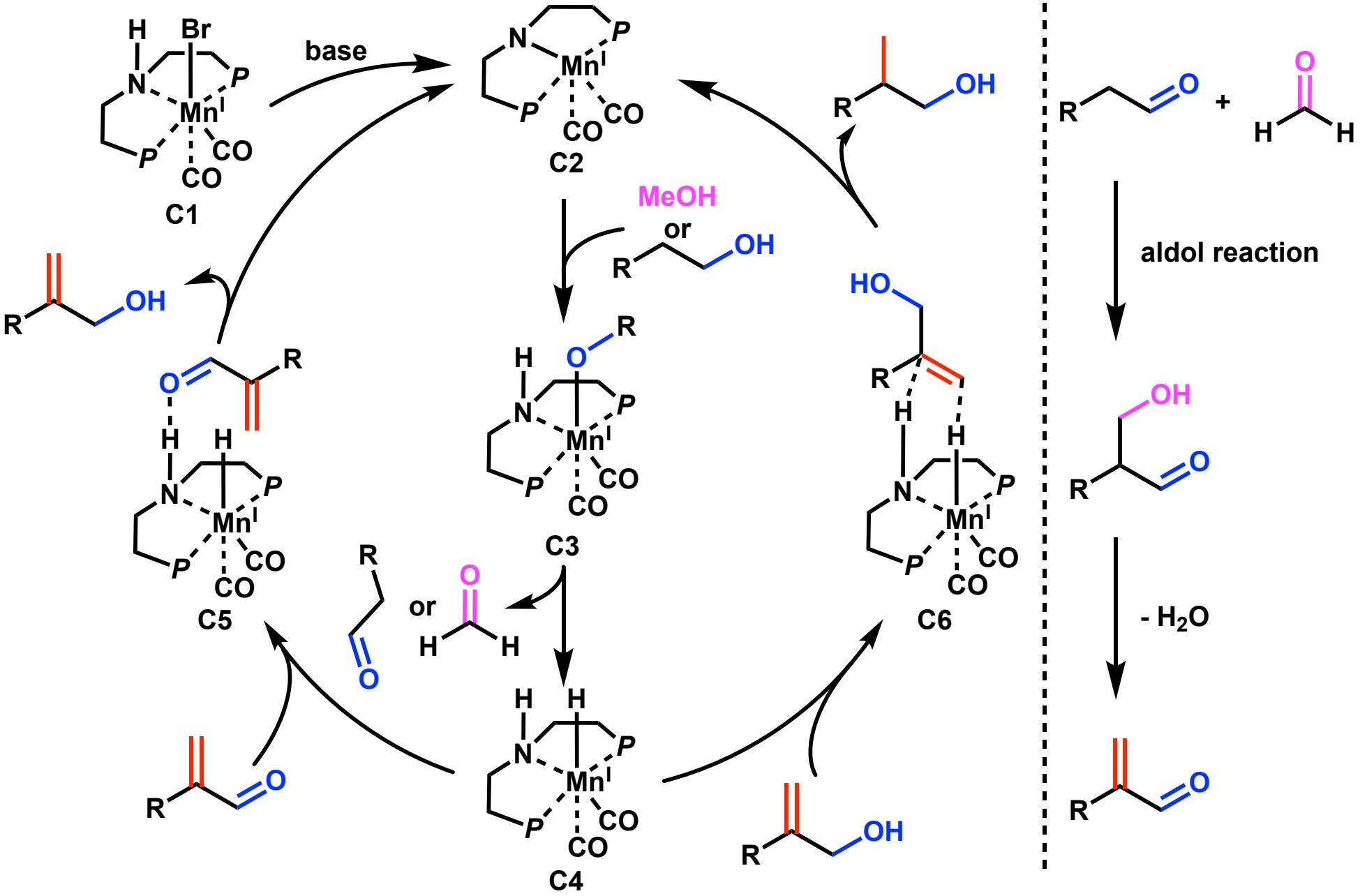
b

100% Conv.

Xu, R.; Chakraborty, S.; Bellows, S.M.; Yuan, H.; Cundari, T.R.; Jones, W.D. *ACS Catal.* **2016**, *6*, 2127

Kaithal, A.; Holscher, M.; Leitner, W. *Angew. Chem. Int. Ed.* **2020**, *59*, 215.

Reaction mechanism (my proposal)

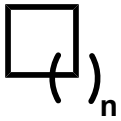


Kaithal, A.; Holscher, M.; Leitner, W. *Angew. Chem. Int. Ed.* **2020**, *59*, 215.

1. *β*-Methylation of alcohol (Methanol as C-1 unit)

2. *β*-Cycloalkylation of alcohol

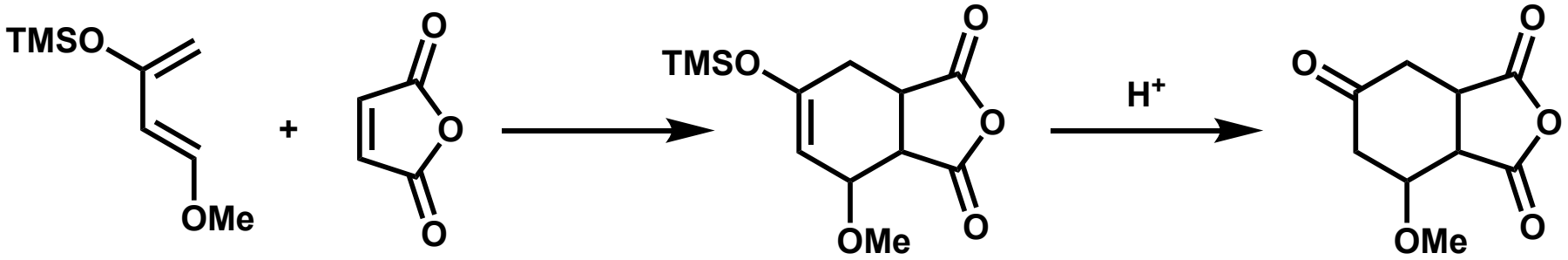
Synthesis of Cycloalkanes



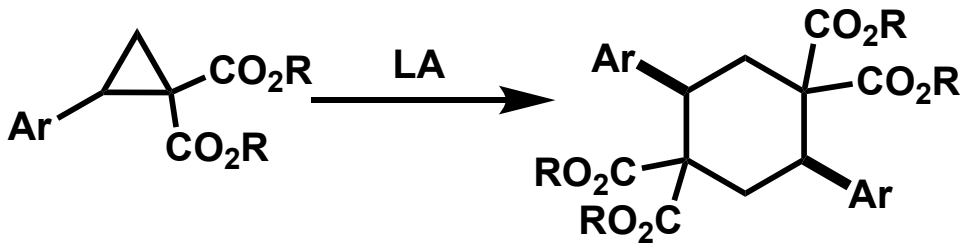
Cycloalkanes
- Ubiquitous structural motifs

(1) Cyclohexane

(1-1) Diels-Alder reaction; hydrogenation or acid



(1-2) Dimerization of cyclopropanes



ex. Michael reaction, Wurtz reaction, hydrogenation of phenyl group…

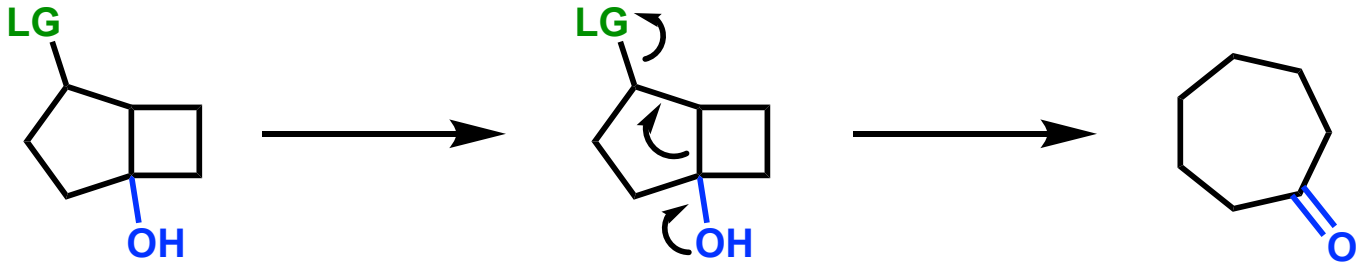
Problems:
- Multistep procedures, narrow substrate scope, poor regio- or stereoselectivity

Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974,** *96*(25), 7807
Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53*(22), 5504

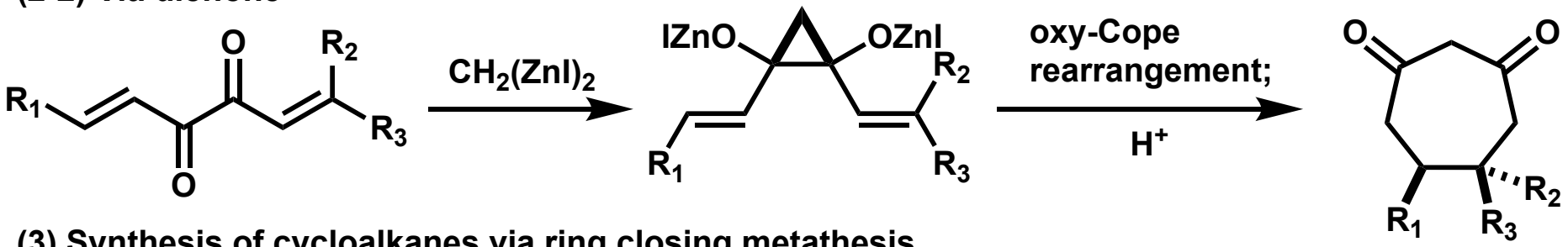
Synthesis of Cycloalkanes

(2) Cycloheptane

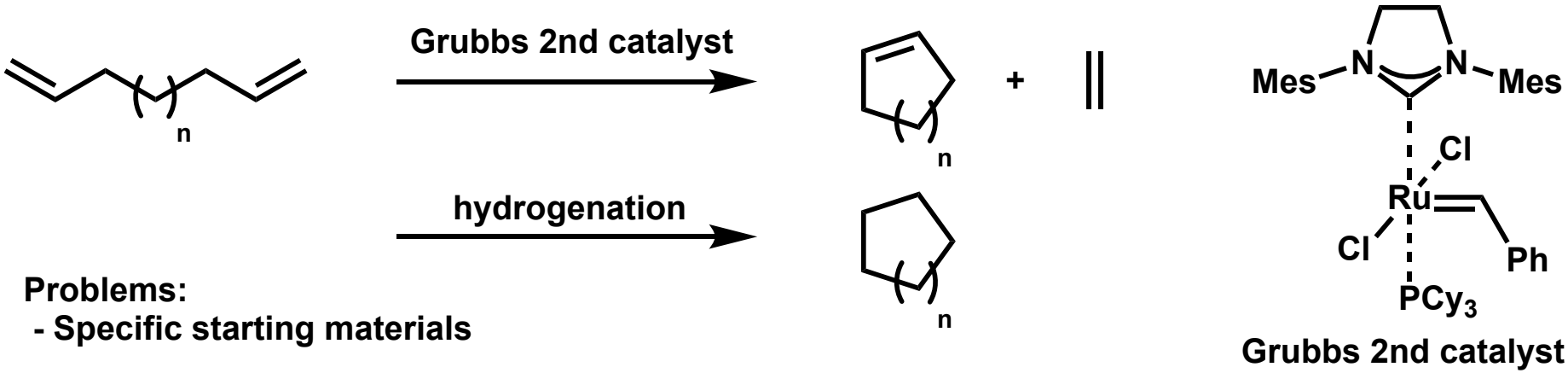
(2-1) Via bicyclo[3.2.0] heptane



(2-2) Via dienone



(3) Synthesis of cycloalkanes via ring closing metathesis



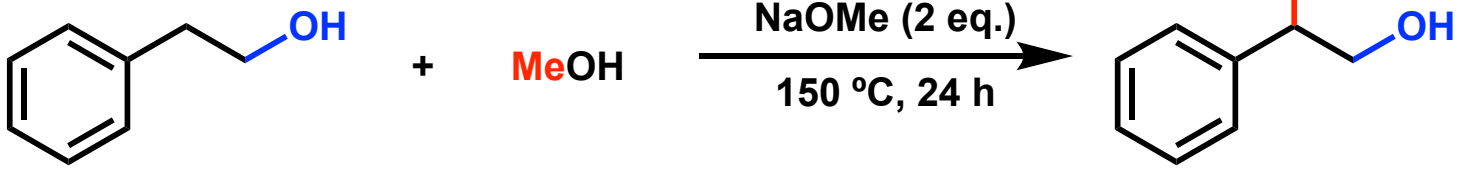
Problems:
- Specific starting materials

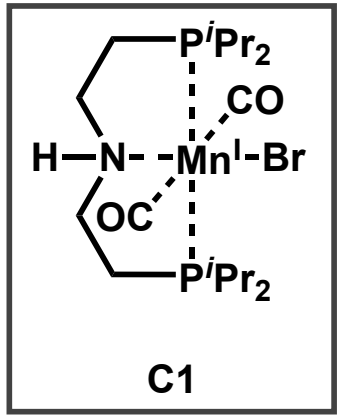
Grubbs 2nd catalyst

Oppolzer, W. *ACC. Chem. Res.* **1982,** *15*(5), 135
Haraguchi, R.;Takada, Y.; Matsubara, S. *Org. Biomol. Chem.* **2015**, *13*(1), 241
Hillier, H.; Pandian, S.; Percy, J. M.; Vincent, M. A. *R. Soc. Chem.* **2011**, *40*, 1061

Approach for direct synthesis of cycloalkanes

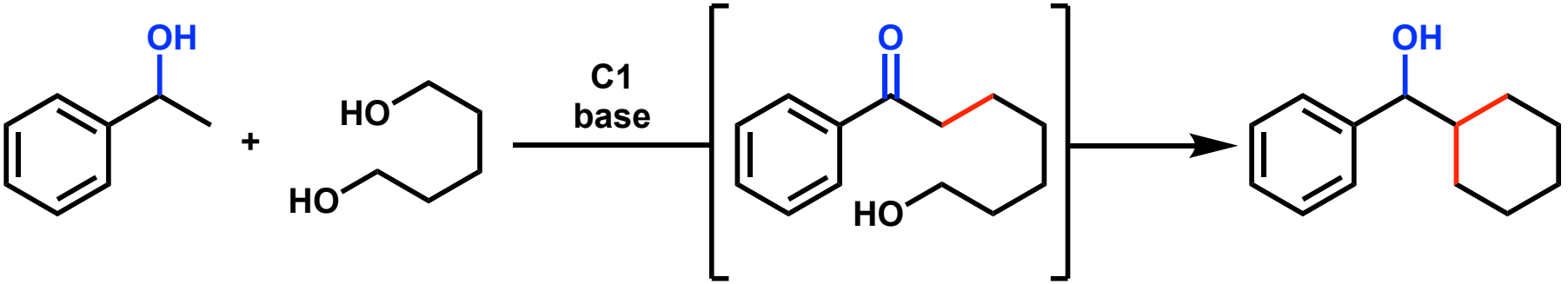
(1) Previous results





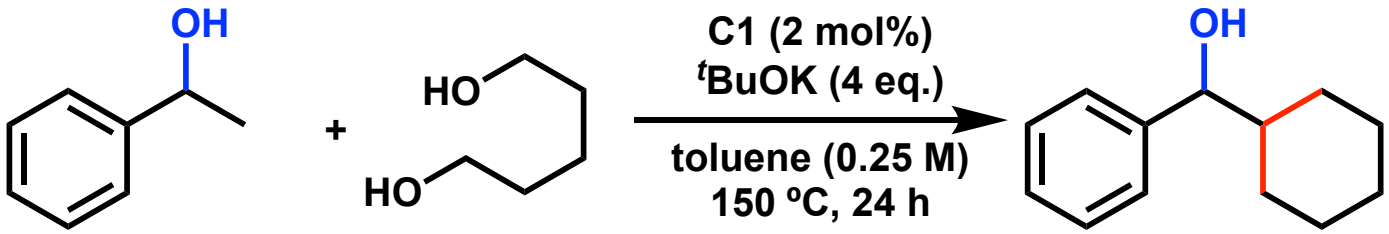
(2) Approach for direct cycloalkylation

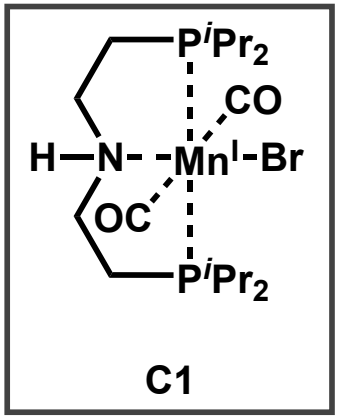
via Diol



Kaithal, A.; Gracia, L. -L; Camp, C.; Quadrelli, E. A.; Leitner, W. *J. Am. Chem. Soc.* **2019**, *141*, 17487.

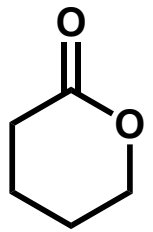
Optimization of Reaction Conditions (1)





entry	4 (equiv.)	Conv. (%)[a)]	Yield (%)[a)]
1	1	70	16
2	2	89	47
3	3	>99	60
4	4	82	62
5	5	84	35

a) Calculated by GC-MS. Mesitylene was used as an internal standard.

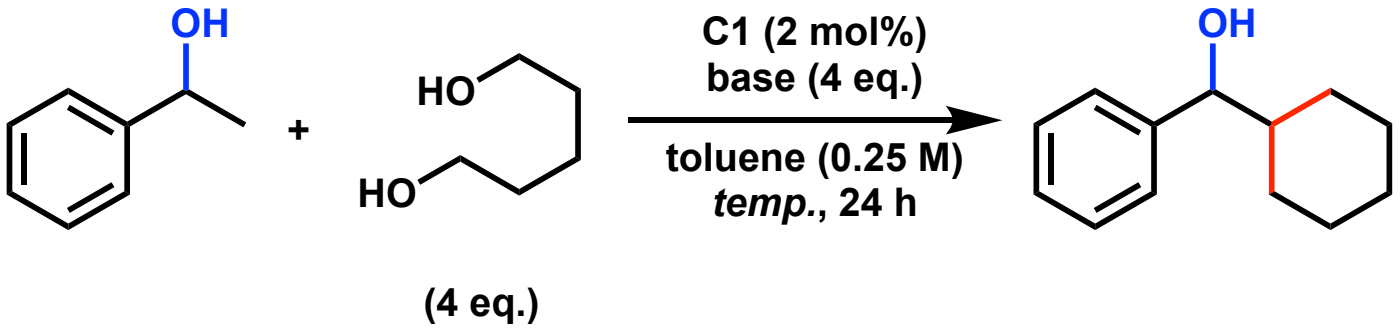


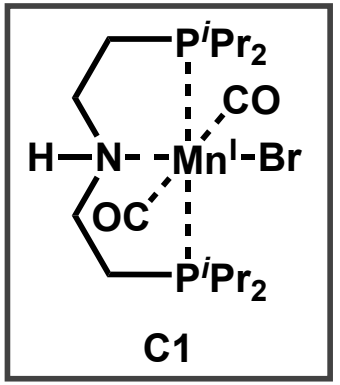
Increasing diol-to-alcohol ratio of 4 : 1 gave the best yield.

Self-condensation of glycol is the major side reaction.

Kaithal, A.; Gracia, L. -L; Camp, C.; Quadrelli, E. A.; Leitner, W. *J. Am. Chem. Soc.* **2019**, *141*, 17487.

Optimization of Reaction Conditions (2)





entry	base	*temp.* (ºC)	Conv. (%)[a)]	Yield (%)[a)]
4	^{t}BuOK	150	82	62
6	^{t}BuOK	120	60	10
7[b)]	Cs_2CO_3	150	78	2
8	^{t}BuONa	150	69	12
9[c)]	^{t}BuOK	150	>99	80

a) GC-MS yield using mesitylene as an internal standard.
b) 2 eq. of Cs_2CO_3 was used.
c) Reaction time: 32 h

From entry 4,6:

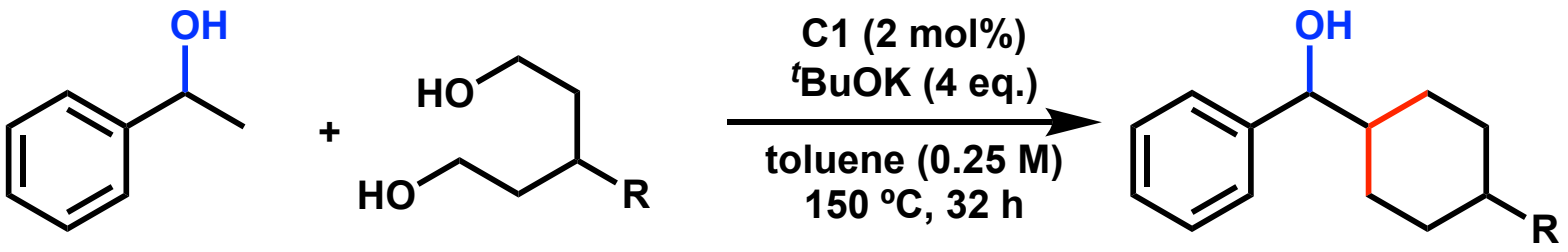
Reaction temperature should be >150 ºC.

From entry 4,7,8:

^{t}BuOK was best as a base in this reaction.

Kaithal, A.; Gracia, L. -L; Camp, C.; Quadrelli, E. A.; Leitner, W. *J. Am. Chem. Soc.* **2019**, *141*, 17487.

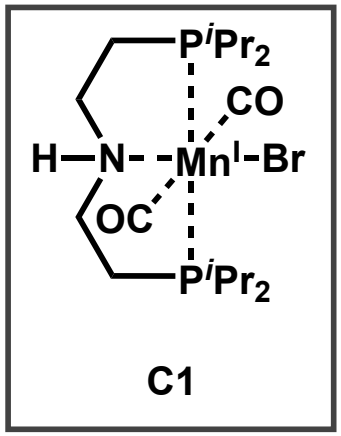
Optimization of Reaction Conditions (3)



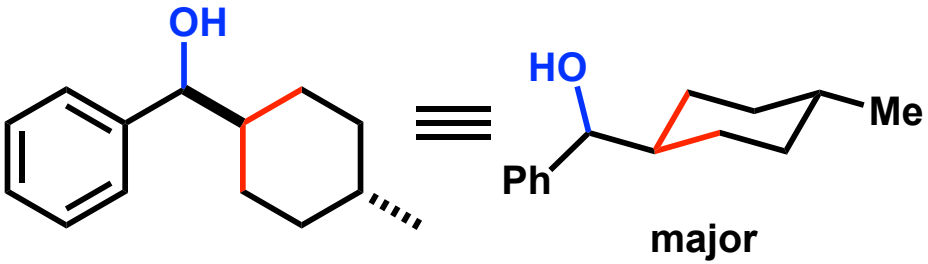
R = H or Me
(4 eq.)

entry	R	Conv. (%)[a]	Yield (%)[a]
9	H	>99	80
10	Me	>99	92 dr = 90 : 10

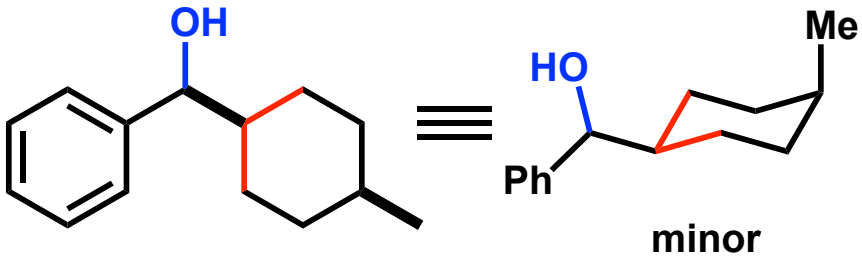
a) Calculated by GC-MS. Mesitylene was used as an internal standard.



C1



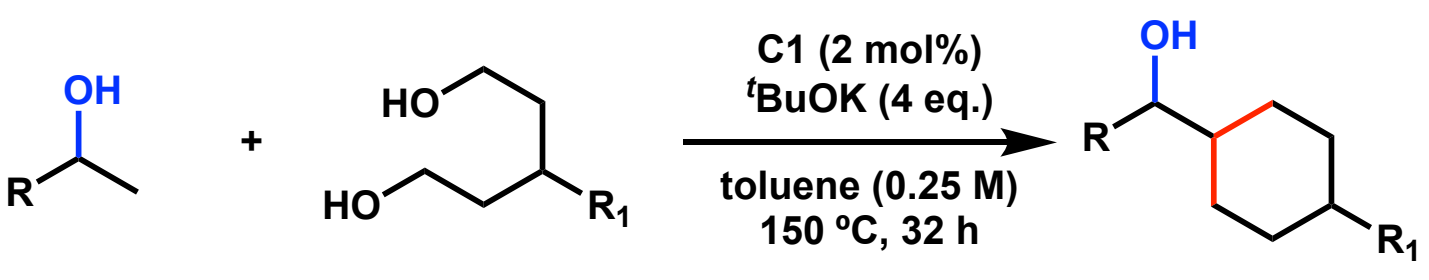
major



minor

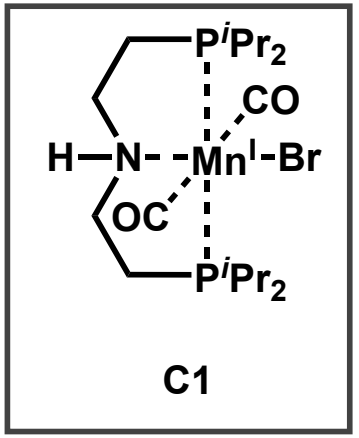
Kaithal, A.; Gracia, L. -L; Camp, C.; Quadrelli, E. A.; Leitner, W. *J. Am. Chem. Soc.* **2019**, *141*, 17487.

Substrate scope (1)



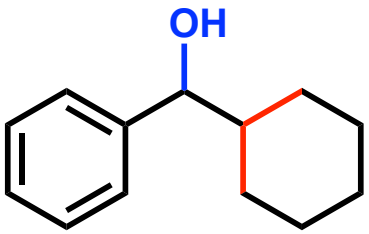
R = aryl, alkyl

(4 eq.)
R_1 = H, alkyl, aryl

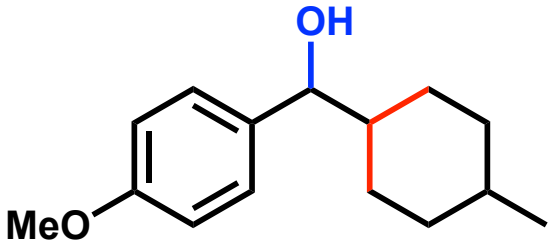


C1

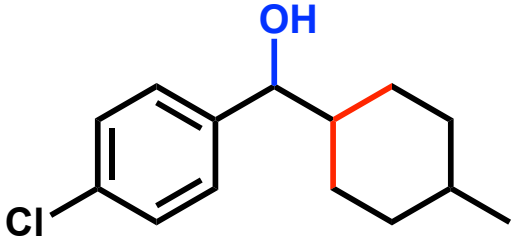
Conv. (%) / GC Yield (Isolated Yield)



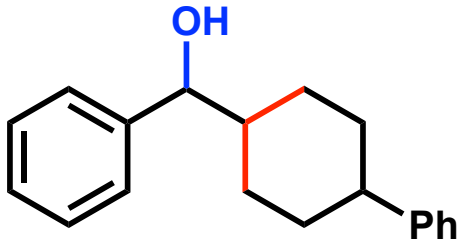
>99/80(72)



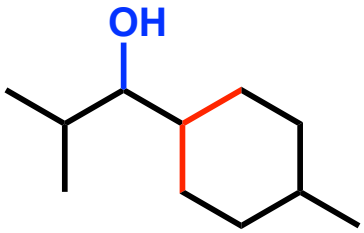
>99/78(71)
dr = 87 : 13



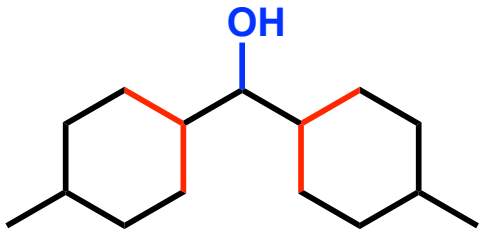
>99/70(61)
dr = 93 : 7



>99/88(83)
dr = 83 : 17



>99/n.d.(67)[a]
dr = 88 : 12

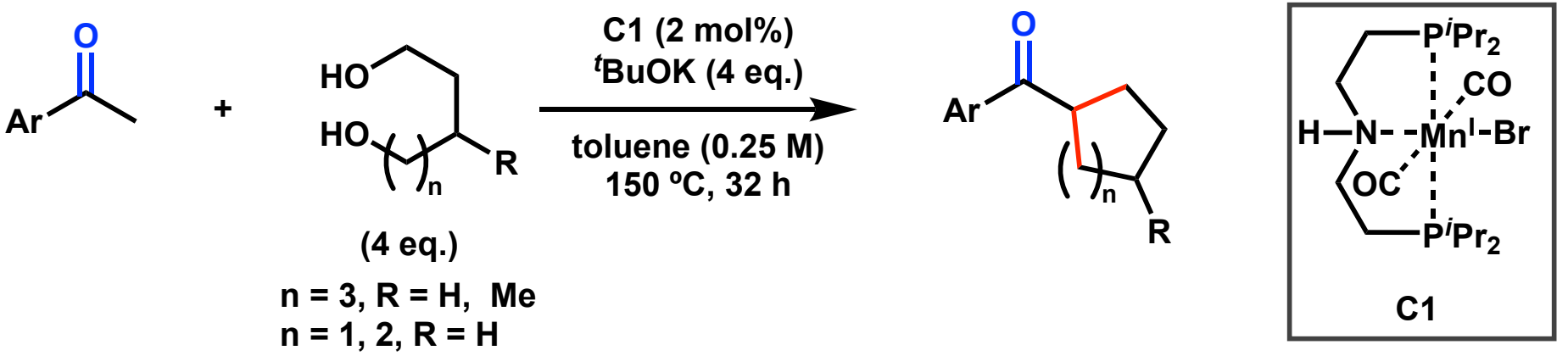


>99/n.d.(51)[b]
dr = 78 : 22 : 0

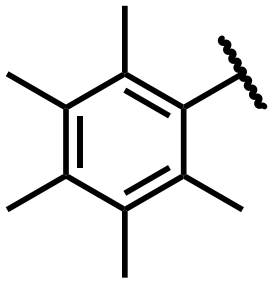
a) 3 eq. of diol was used.
b) 6 eq. of diol and 8 eq. of tBuOK were used.

Kaithal, A.; Gracia, L. -L; Camp, C.; Quadrelli, E. A.; Leitner, W. *J. Am. Chem. Soc.* **2019**, *141*, 17487.

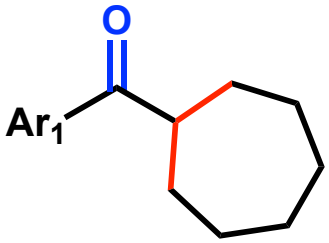
Substrate scope (2)



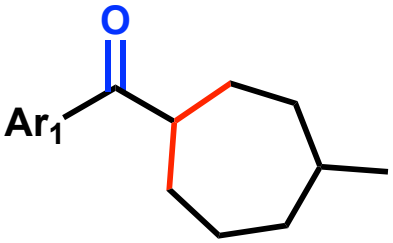
Conv. (%) / GC Yield (Isolated Yield)



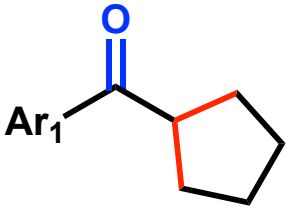
Ar_1



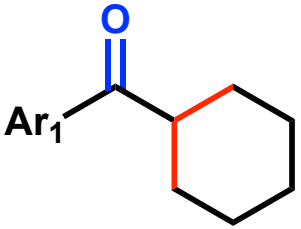
>99/78(66)



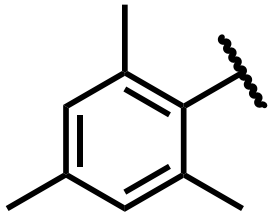
>99/98(93)
dr = 57 : 42



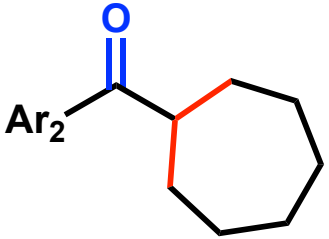
>99/46(42)



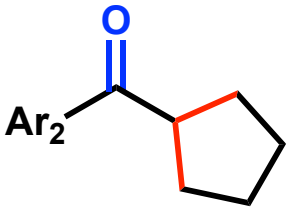
>99/56(52)



Ar_2



>99/78(62)



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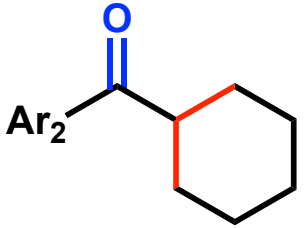
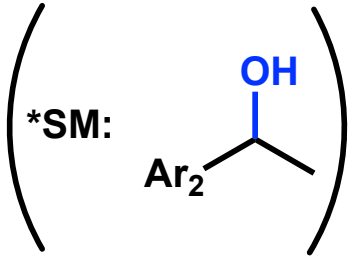


n.d./n.d.(37)*



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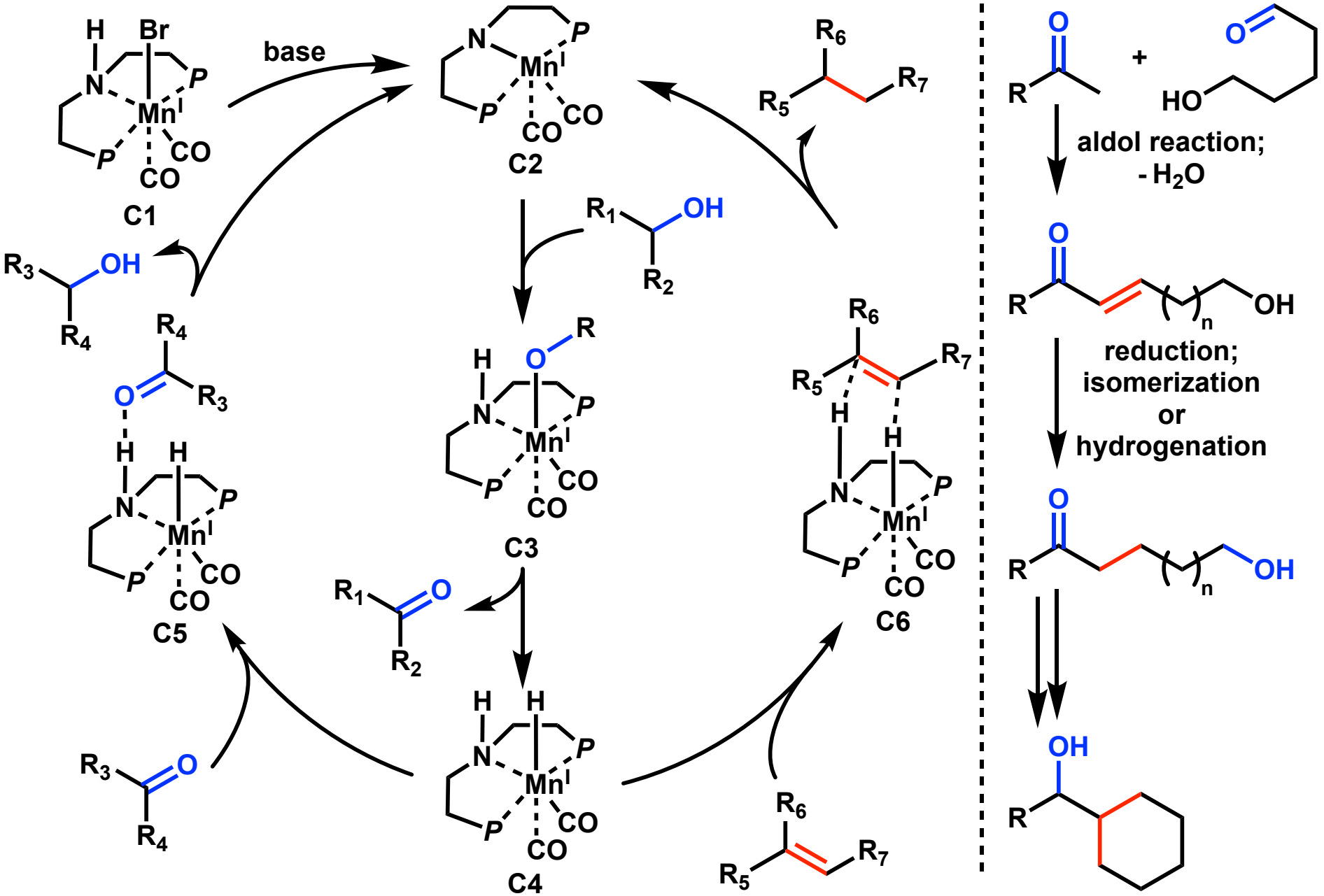
Reaction mechanism



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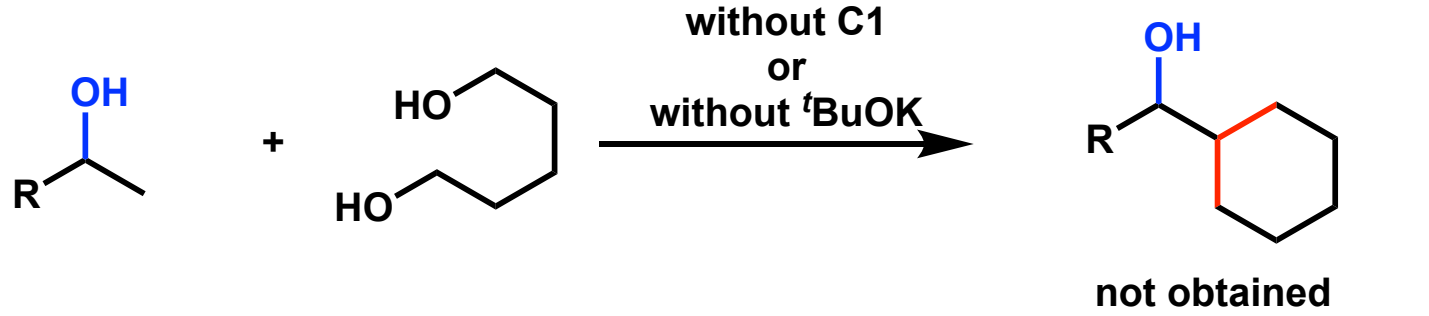
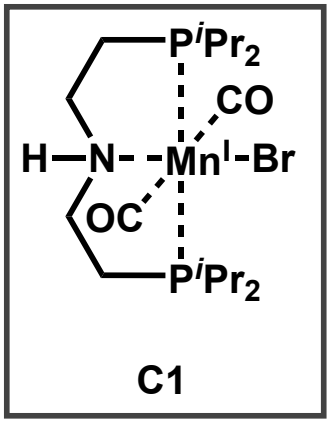
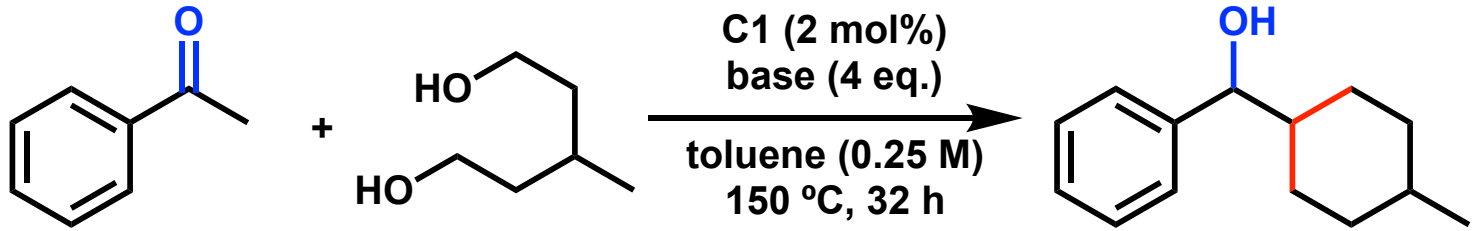
Mechanistic study

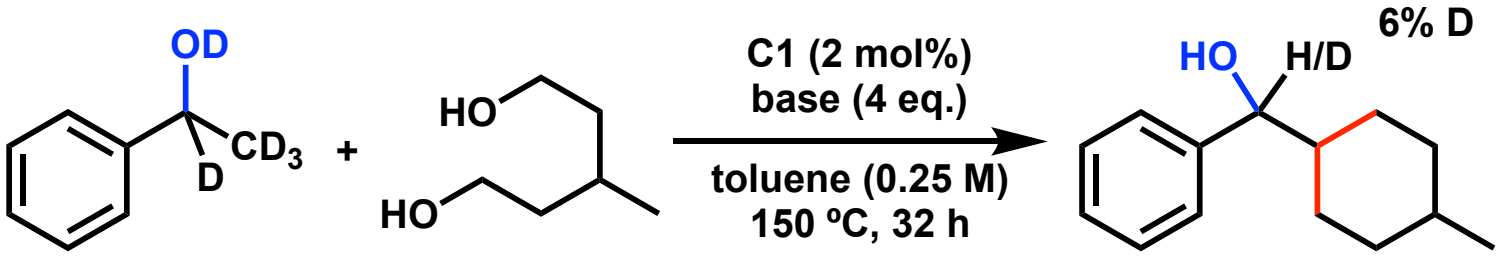






(4 eq.)

90%
d.r. = 86 :14



α and β = 92 %

(4 eq.)

86%
d.r. = 85 :15

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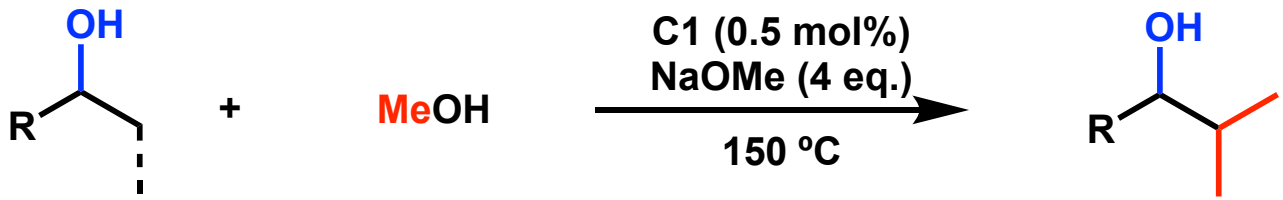
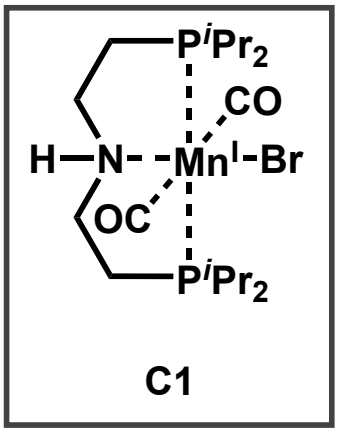
Summary

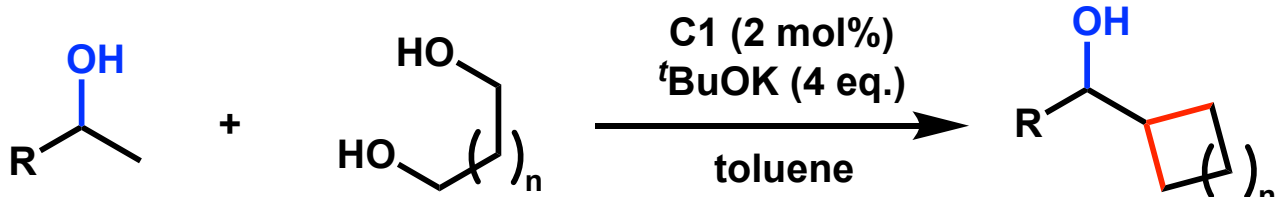
(1) Methylation of alcohols using Methanol as C_1 source





- Methanol as C1 source
- No highly reactive reagents
- No stoichiometric amount of halide waste
- Earth abundant metal

(2) Direct cycloalkylation of alcohols



n = 2~4

- Alcohols and diols: biogenic and cheap feedstocks
- Direct synthesis of substituted cycloalkanes
- Earth abundant metal