Westfälische Wilhelms-Universität Münster

> Rhodium-Catalyzed Asymmetric Conjugate Silyl Transfer: Stereoselective Access to the C7–C16 Fragment of (+)-Neopeltolide and Synthesis of Stereodefined Polyols

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Denmark Group Meeting
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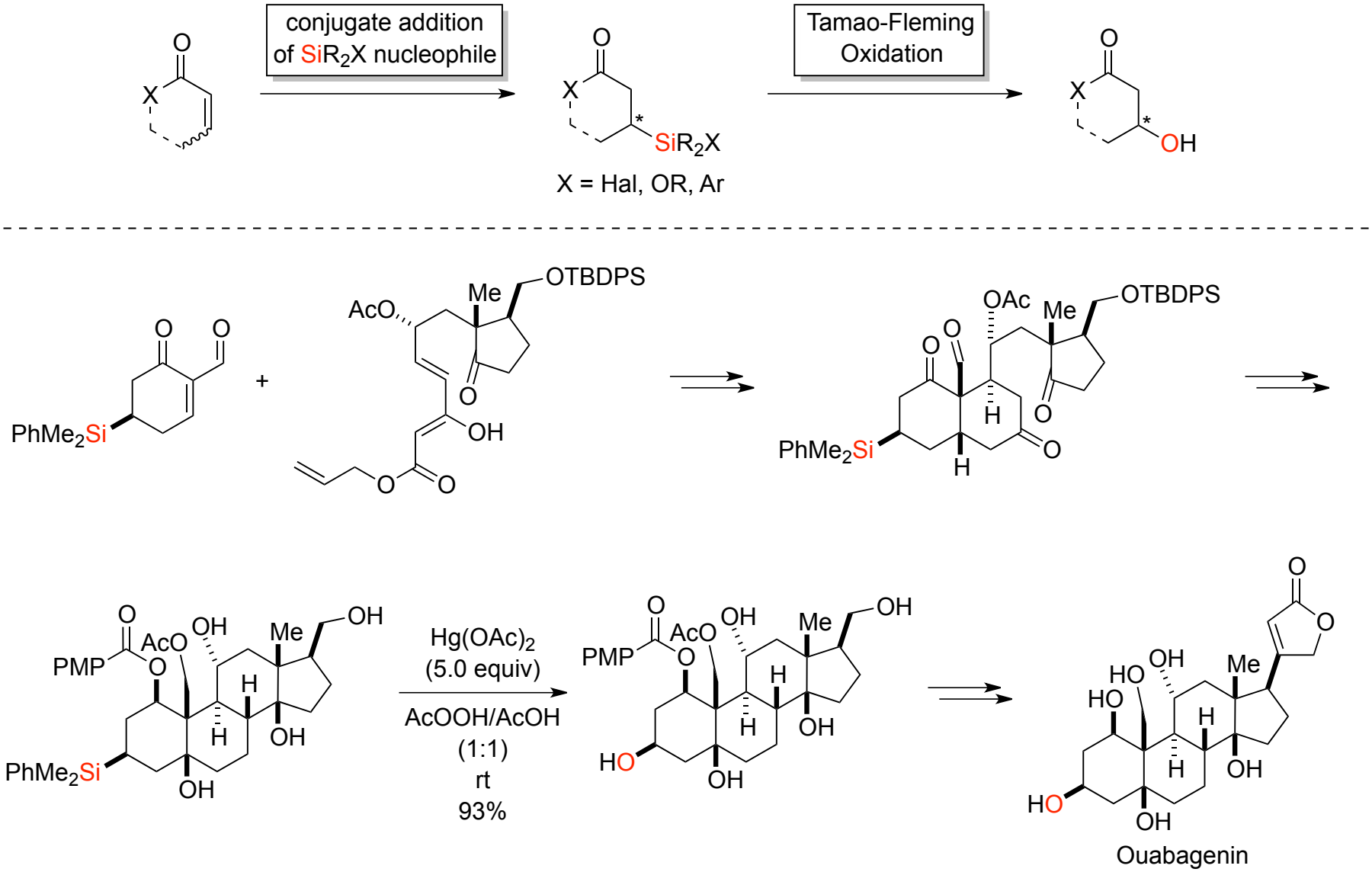
WWU Münster

Organisch-Chemisches Institut
WWU Münster

Outline

- **Stoichiometric generation of silicon nucleophiles via reductive lithiation of R_3SiCl**
- **Catalytic generation of silicon nucleophiles via activation of interelement compounds ($R_3Si–SiR_3$, $R_3Si–B(OR)_2$)**
- **Rhodium-catalyzed asymmetric conjugate silyl transfer:**
  - Stereoselective synthesis of the C7–C16 fragment of (+)-neopeltolide
  - Access to stereodefined polyols through two-directional synthesis

Stoichiometric generation of silicon nucleophiles

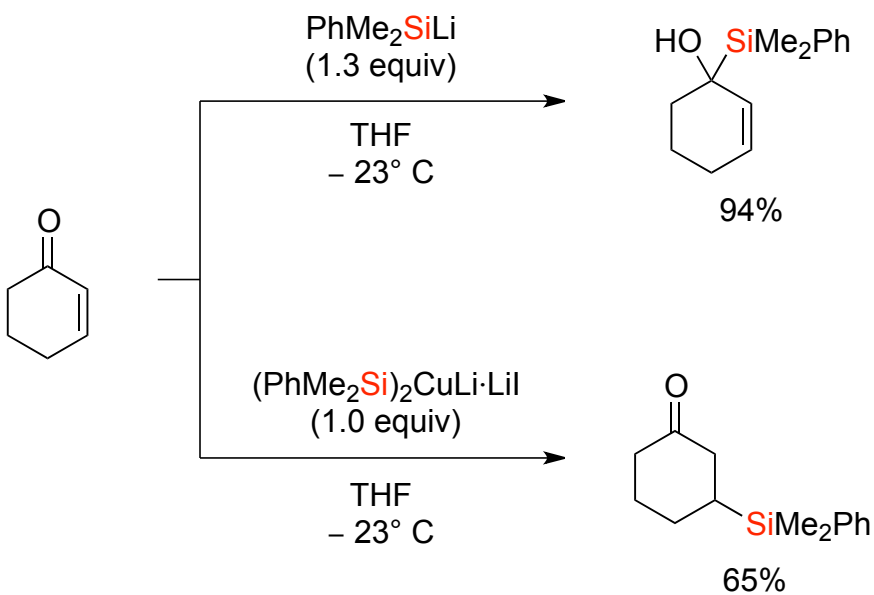


H. Zhang, M. S. Reddy, S. Phoenix, P. Deslongchamps, *Angew. Chem. Int. Ed.* **2008**, *47*, 1272–1275.

Stoichiometric generation of silicon nucleophiles

reductive lithiation:

- aryl substituents required for the reductive cleavage of the disilane
- silyllithium reagents strongly basic and nucleophilic
  → poor functional group tolerance

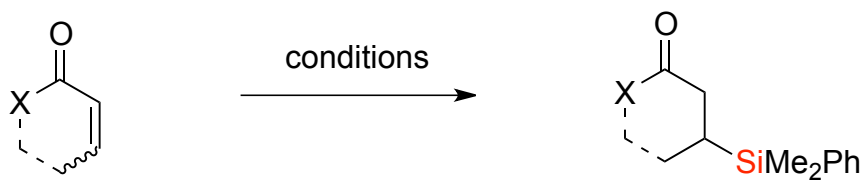


1,2-addition favored
(*Tetrahedron Lett.* **1990**, *31*, 831–834)

1,4-addition with silyl cuprates
(*J. Chem. Soc., Chem.Commun.* **1978**, 177–178)

For $PhMe_2SiLi$, see: I. Fleming, R. S. Roberts, S. C. Smith, *J. Chem. Soc., Perkin Trans. 1*, **1998**, 1209–1214.

Stoichiometric generation of silicon nucleophiles



stoichiometric in copper

FLEMING 1978
$(PhMe_2Si)_2CuLi{\cdot}LiX$ (1.0 equiv)
(from 2 $PhMe_2SiLi$ + CuX
with X = I or CN)
THF, –23°C

FLEMING 1984
$(PhMe_2Si)(Me)CuLi{\cdot}LiCN$ (1.0 equiv)
(from $PhMe_2SiLi$ + MeLi + CuCN)
THF, –23°C

catalytic in copper

LIPSHUTZ 1998
$Me_2Cu(CN)Li_2$ (3.0 mol-%)
$(PhMe_2Si)ZnMe_2Li$ (1.2 equiv)
(from $PhMe_2SiLi$ + Me_2Zn)
THF, –78°C

OESTREICH 2004
CuI or CuCN (5.0 mol-%)
$(PhMe_2Si)_2Zn$ (1.0 equiv)
(from 2 $PhMe_2SiLi$ + $ZnCl_2$)
THF/Et_2O/toluene, –78°C

copper-free

Nozaki 1986,
FLEMING 1994, SINGER 1995
$(PhMe_2Si)ZnMe_2Li$ (1.2 equiv)
(from $PhMe_2SiLi$ + Me_2Zn)
THF, –78°C

OESTREICH 2006
$(PhMe_2Si)_2Zn$ (1.0 equiv)
(from 2 $PhMe_2SiLi$ + $ZnCl_2$)
THF/Et_2O, –78°C

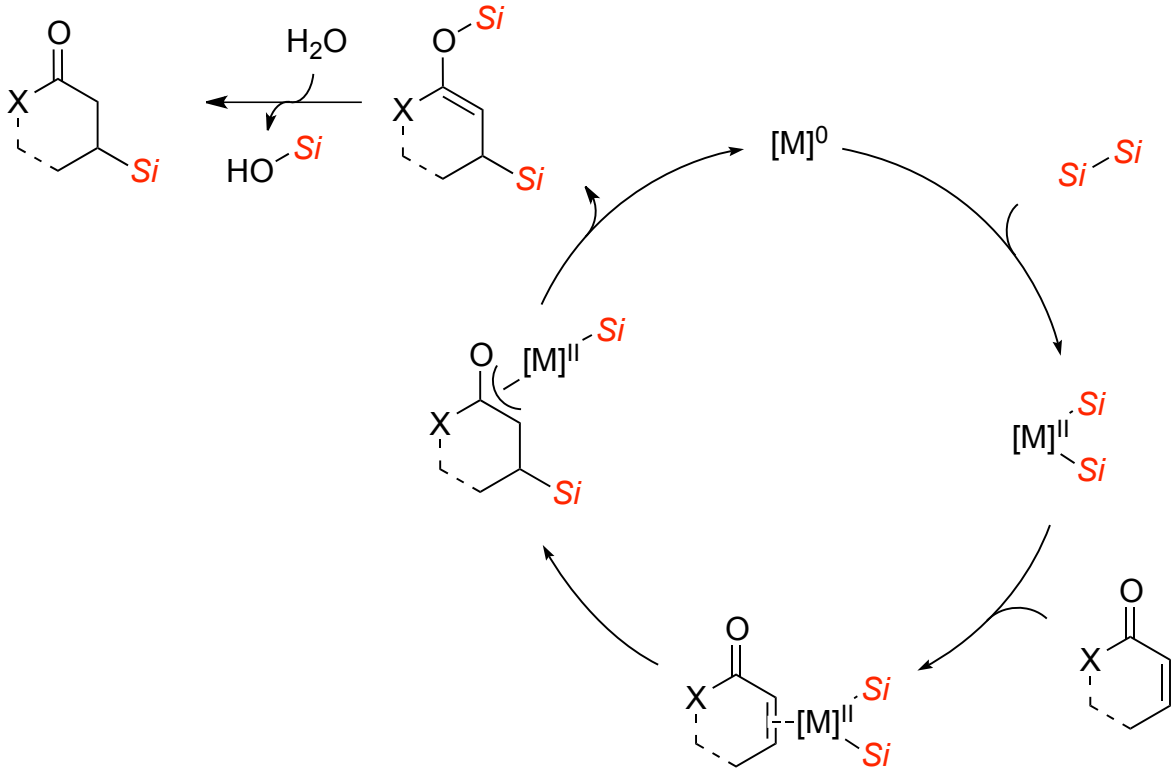
development of catalytic enantioselective protocols complicated by presence of excess LiCl and a pronounced background reaction

Overview: A. Weickgenannt, M. Oestreich, *Chem. Eur. J.* **2010**, *16*, 402–412.

Catalytic generation of silicon nucleophiles

transition metal-catalyzed activation of interelement compounds:

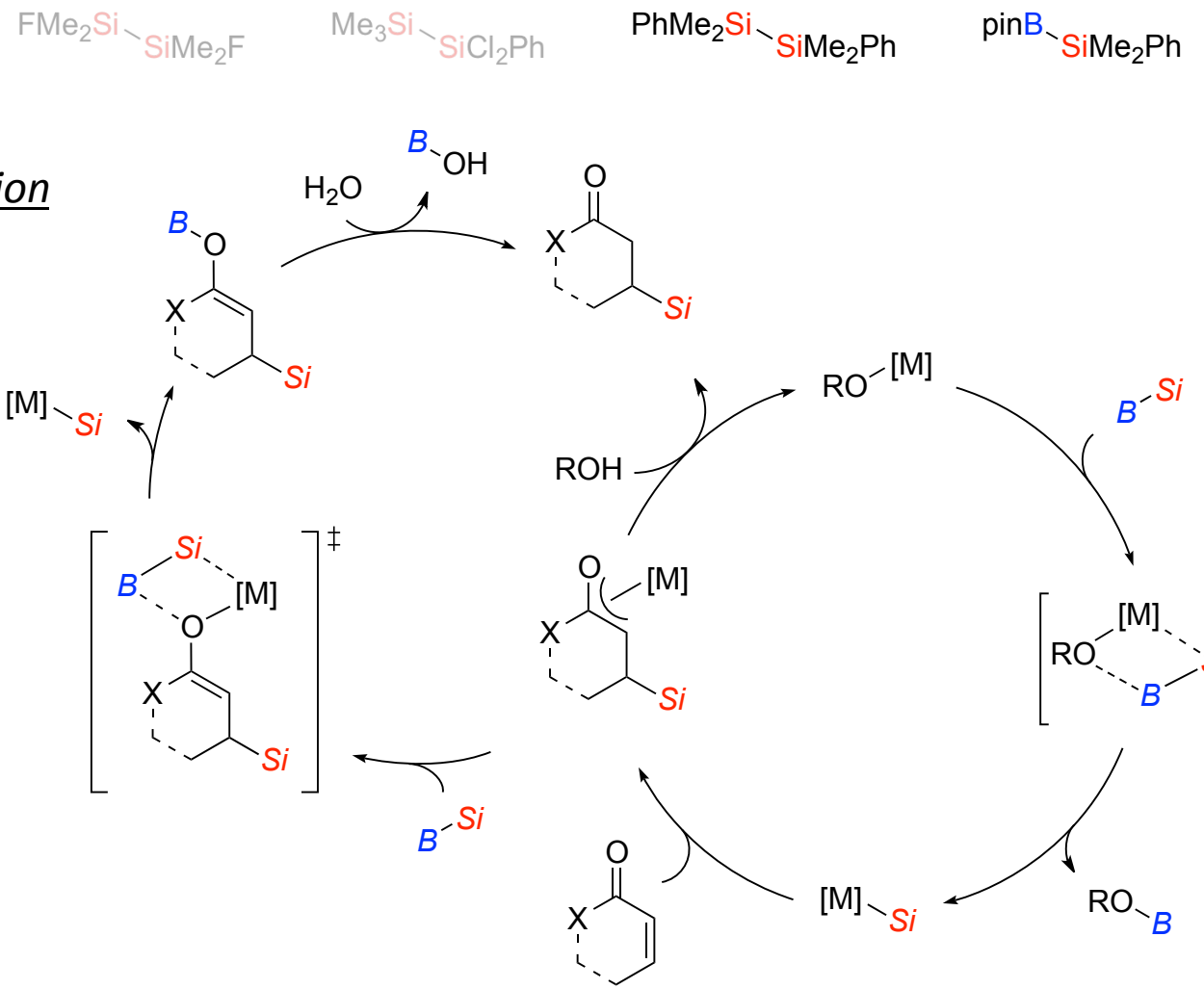
oxidative addition



H. E. Burks, J. P. Morken, *Chem. Commun.* **2007**, 4717–4725.

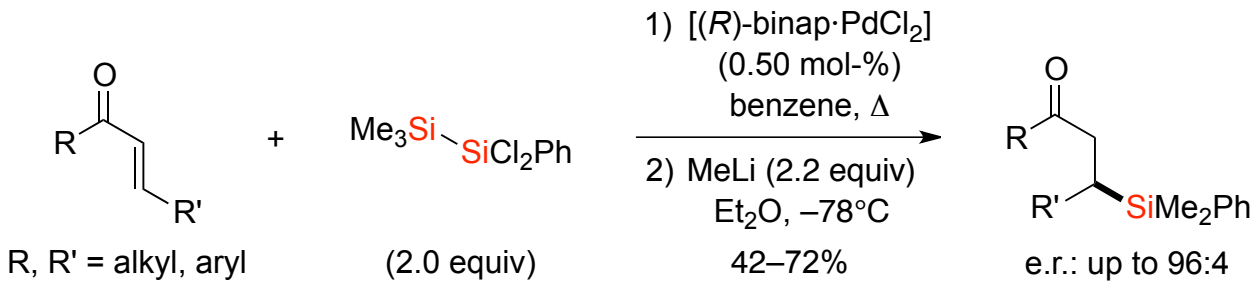
Catalytic generation of silicon nucleophiles

transition metal-catalyzed activation of interelement compounds:

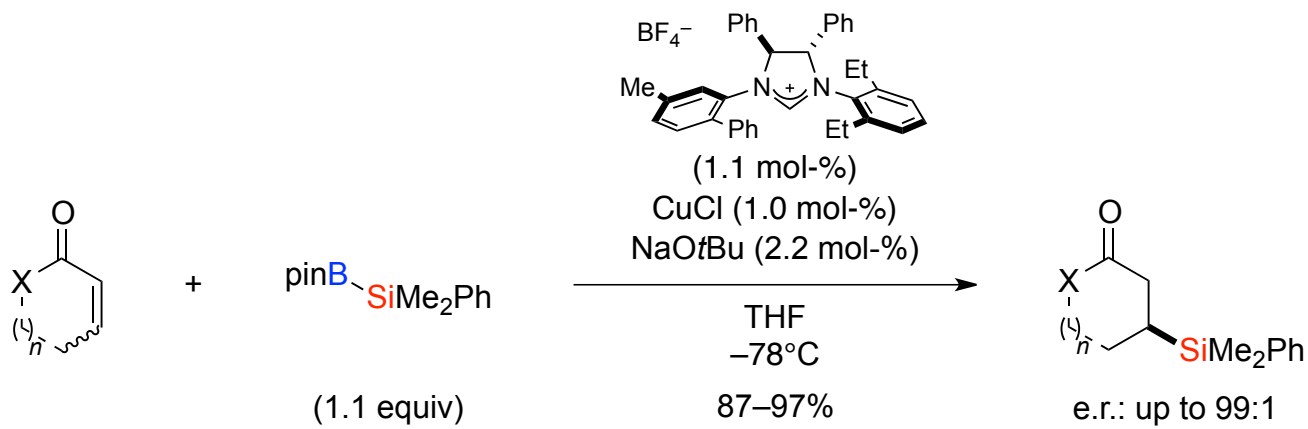


H. E. Burks, J. P. Morken, *Chem. Commun.* **2007**, 4717–4725.

Catalytic asymmetric conjugate silyl transfer

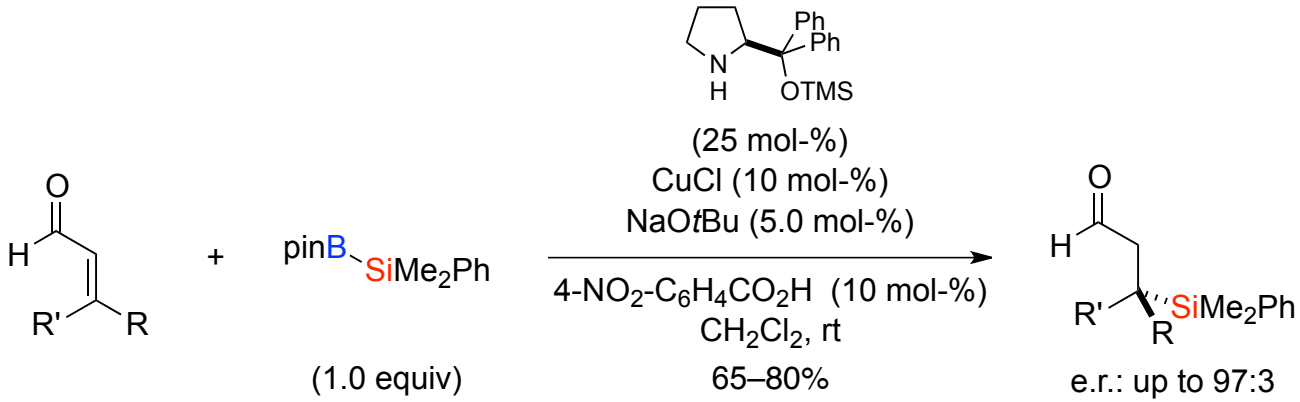


T. Hayashi, Y. Matsumoto, Y. Ito, *J. Am. Chem. Soc.* **1988**, *110*, 5579–5581.

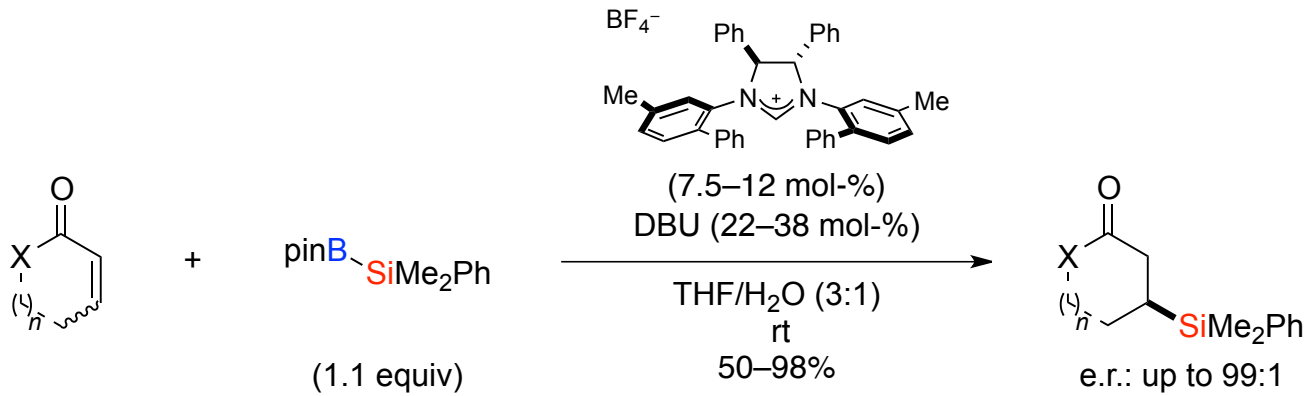


K.-s. Lee, A. H. Hoveyda, *J. Am. Chem. Soc.* **2010**, *132*, 2898–2900.

Catalytic asymmetric conjugate silyl transfer



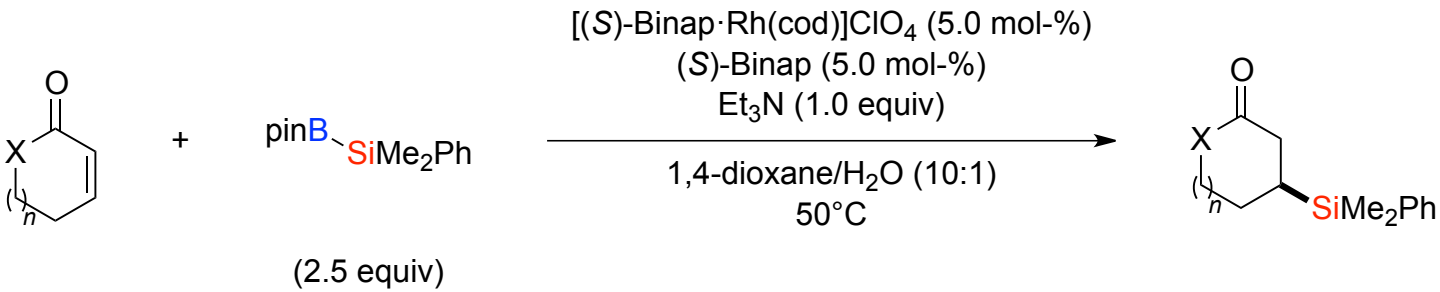
I. Ibrahem, S. Santoro, F. Himo, A. Córdova, *Adv. Synth. Catal*. **2011**, *353*, 245–252.

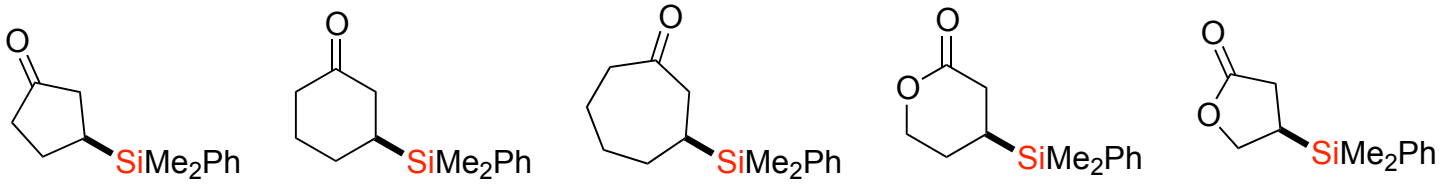


J. M. O'Brien, A. H. Hoveyda, *J. Am. Chem. Soc.* **2011**, *133*, 7712–7715.

Rhodium-catalyzed asymmetric conjugate silyl transfer

cyclic α,β-unsaturated acceptors:



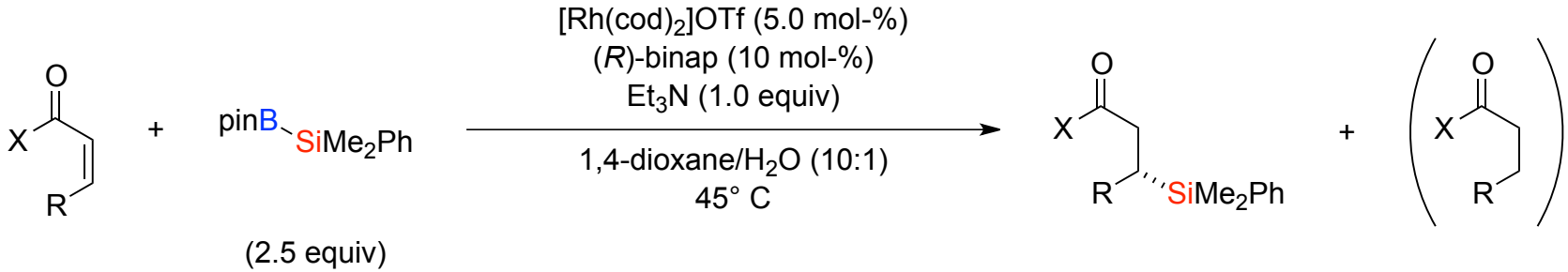


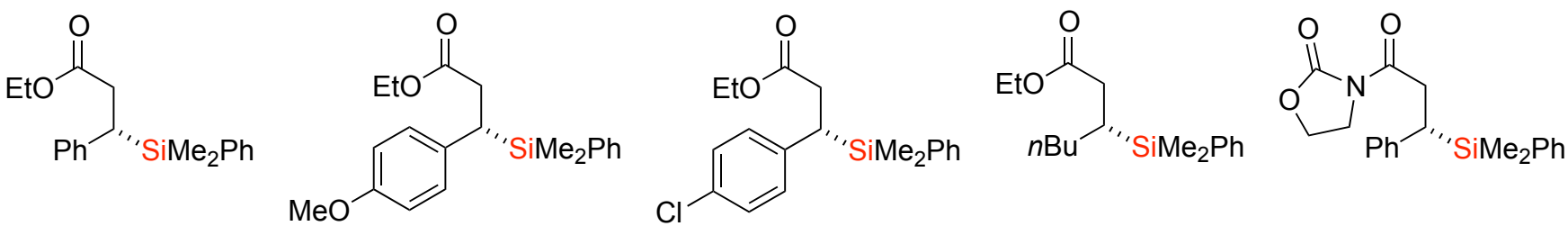
70%	45%	22%	58%	39%
e.r. = 99:1	e.r. = 98:2	e.r. = 96:4	e.r. = 99:1	e.r. > 99:1

C. Walter, G. Auer, M. Oestreich, *Angew. Chem. Int. Ed.* **2006**, *45*, 5675–5677.

Rhodium-catalyzed asymmetric conjugate silyl transfer

acyclic α,β-unsaturated acceptors:





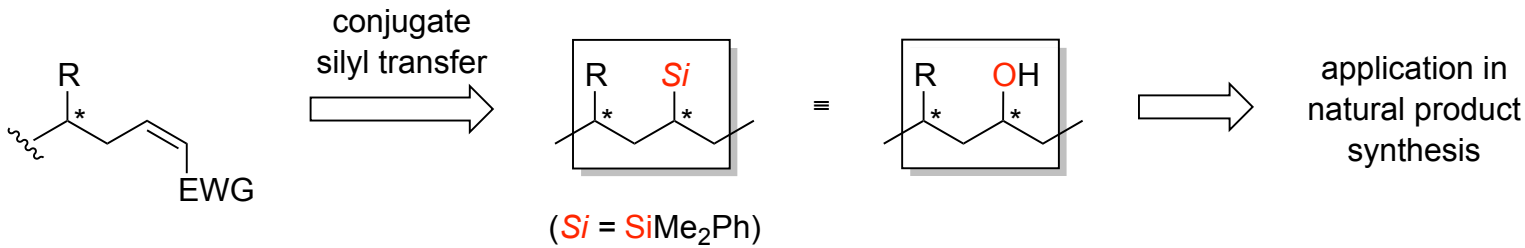
66%	50%	58%	55%	60%
e.r. > 99:1	e.r. > 99:1	e.r. > 99:1	e.r. > 99:1	e.r. > 99:1

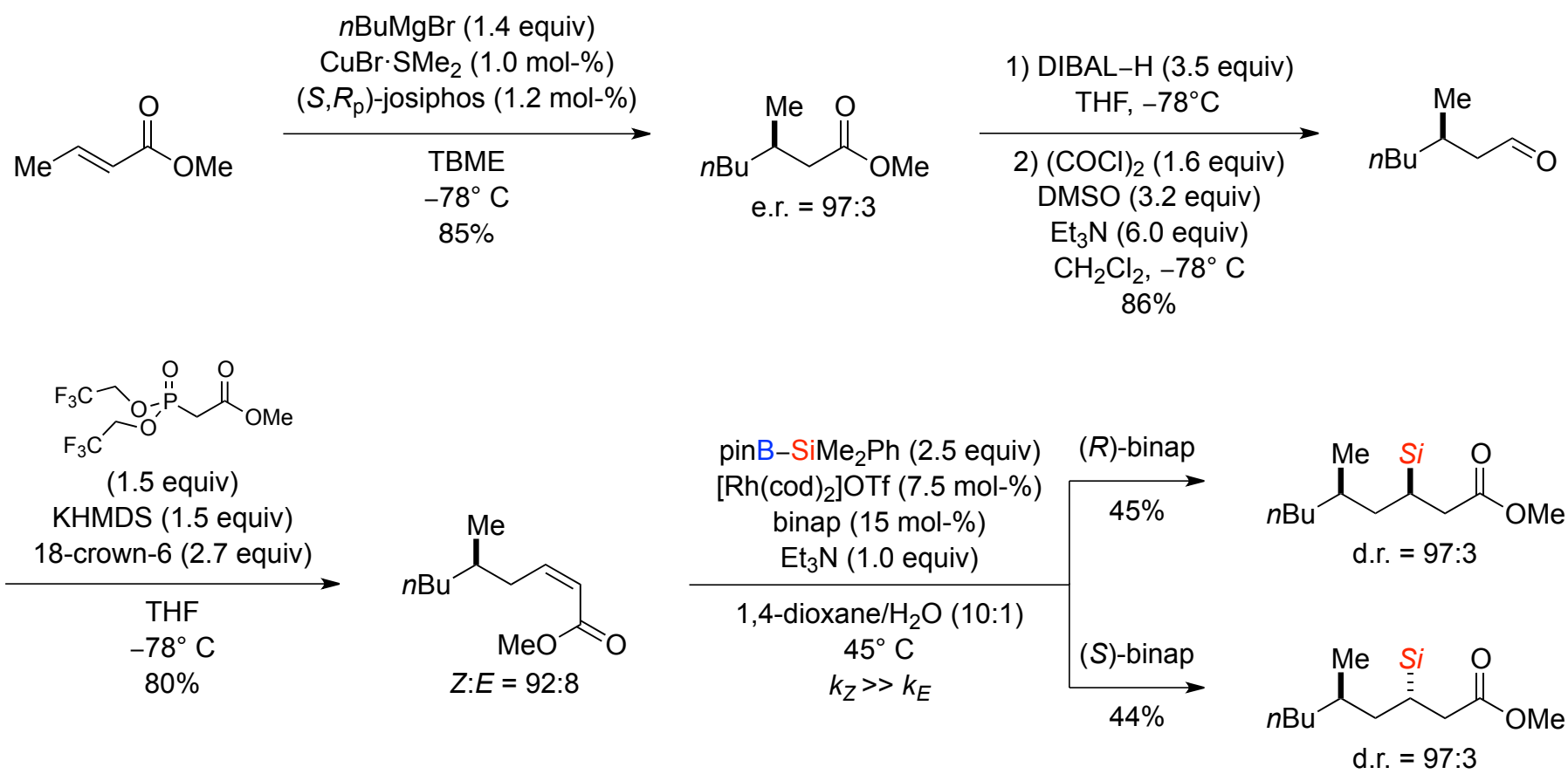
- *Z*-configured α,β-unsaturated acceptors requiered
- major byproduct: reduced acceptor

C. Walter, M. Oestreich, *Angew. Chem. Int. Ed.* **2008**, *47*, 3818–3820.

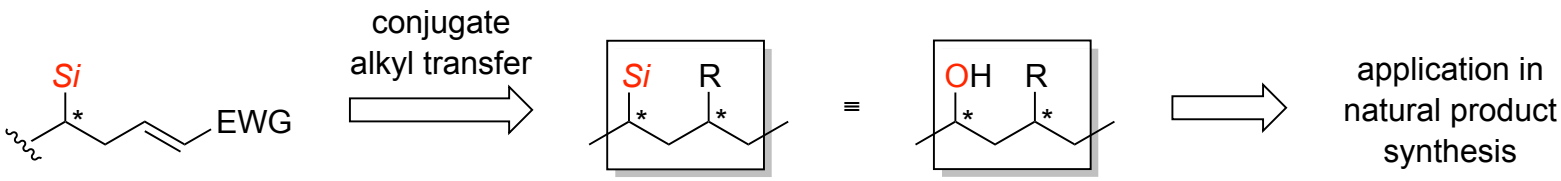
Stereoselective synthesis of the C7–C16 fragment of (+)-neopeltolide

Rhodium-catalyzed asymmetric conjugate silyl transfer

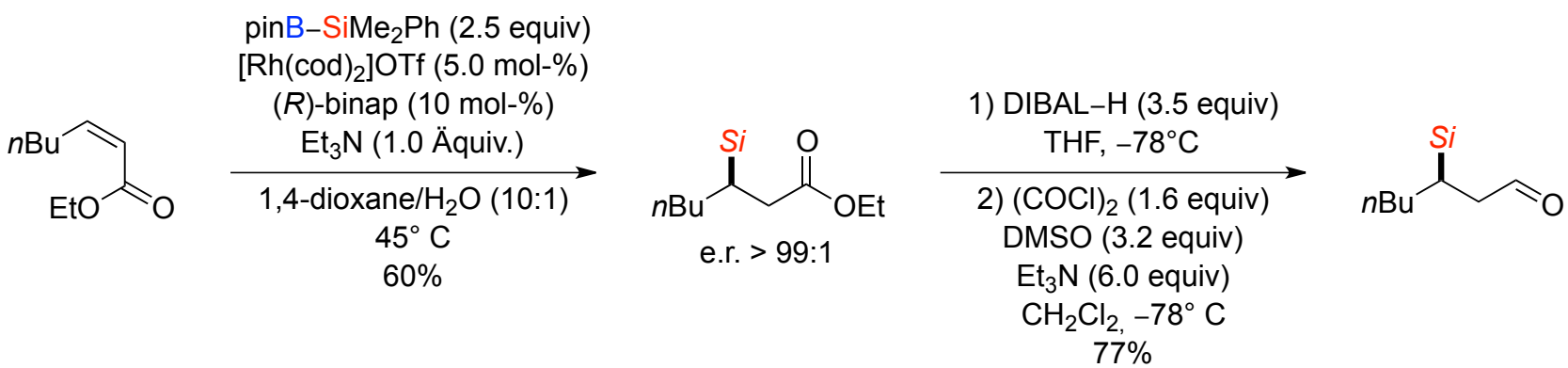


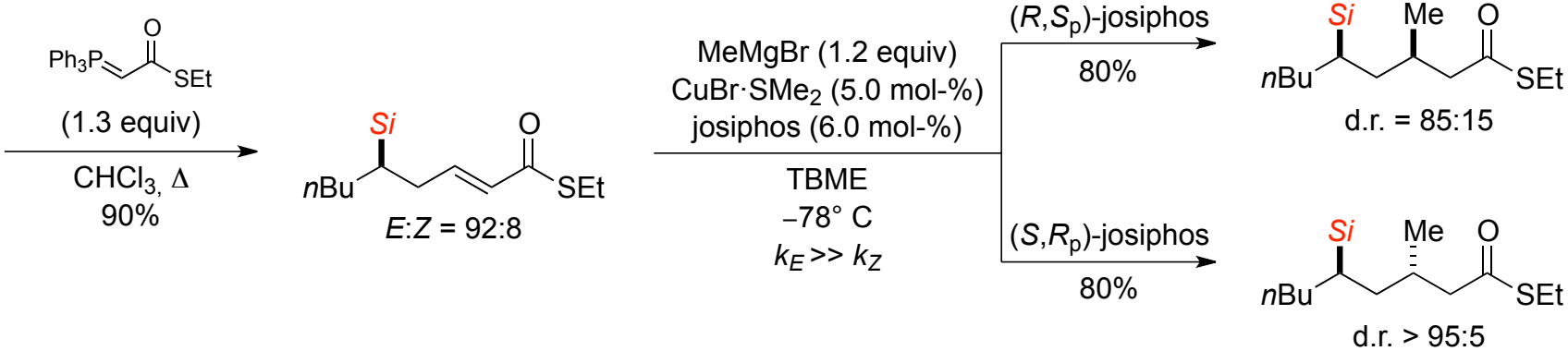


Rhodium-catalyzed asymmetric conjugate silyl transfer

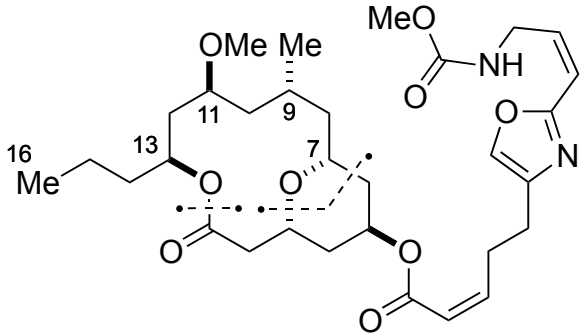


(*Si* = $SiMe_2Ph$)

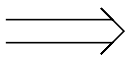


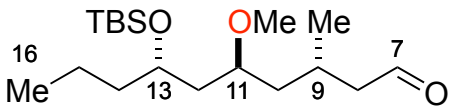


Stereoselective synthesis of the C7–C16 fragment of (+)-neopeltolide

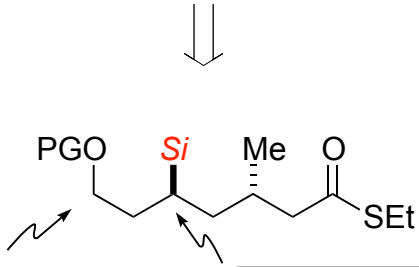


(+)-neopeltolid



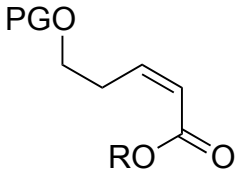


(protected C7–C16-fragment)



construction of the stereogenic center

oxidative degradation of the C–Si-bond



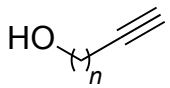
isolated from deep-water Carribbean sponge:

- activity against several cancer cell lines
- antifungal properties

(isolation: A. E. Wright *et. al.*, *J. Nat. Prod.* **2007**, *70*, 412–416)

Total synthesis using C7–C16 fragment: I. Paterson, N. A. Miller, *Chem. Commun.* **2008**, 4708–4710.

Stereoselective synthesis of the C7–C16 fragment of (+)-neopeltolide

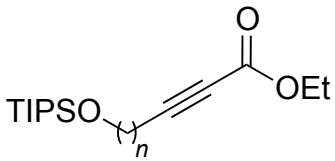


(*n* = 1)
(*n* = 2)

1) TIPSCl (1.1 equiv)
imidazole (1.1 equiv)
CH_2Cl_2, rt

2) *n*BuLi (1.1 equiv)
$ClCO_2Et$ (1.5 equiv)
–78° C → rt

82%
79%

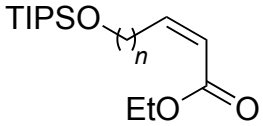


(*n* = 1)
(*n* = 2)

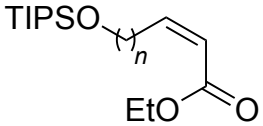
H_2 (balloon)
Pd/$CaCO_3$

quinoline
1-hexene, rt

87%
93%



Z:*E* > 95:5 (*n* = 1)
Z:*E* > 95:5 (*n* = 2)

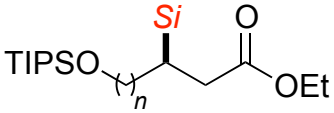


Z:*E* > 95:5 (*n* = 1)
Z:*E* > 95:5 (*n* = 2)

pinB–SiMe$_2$Ph (2.5 equiv)
[Rh(cod)$_2$]OTf (7.5 mol-%)
(*R*)-binap (15 mol-%)
Et_3N (1.0 equiv)

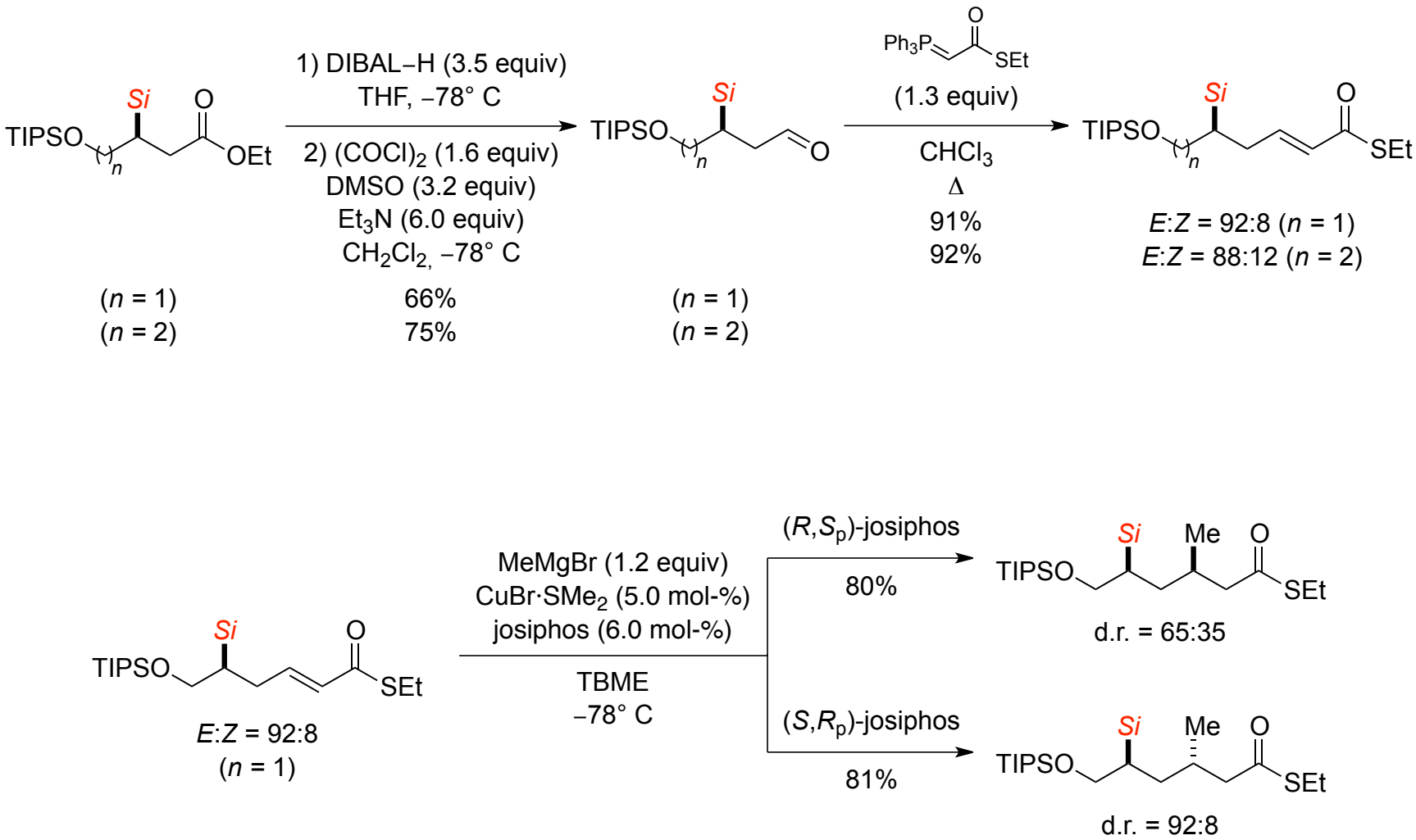
1,4-dioxane/H_2O (10:1)
45° C

73%
72%



e.r. > 99:1 (*n* = 1)
e.r. > 99:1 (*n* = 2)

Stereoselective synthesis of the C7–C16 fragment of (+)-neopeltolide



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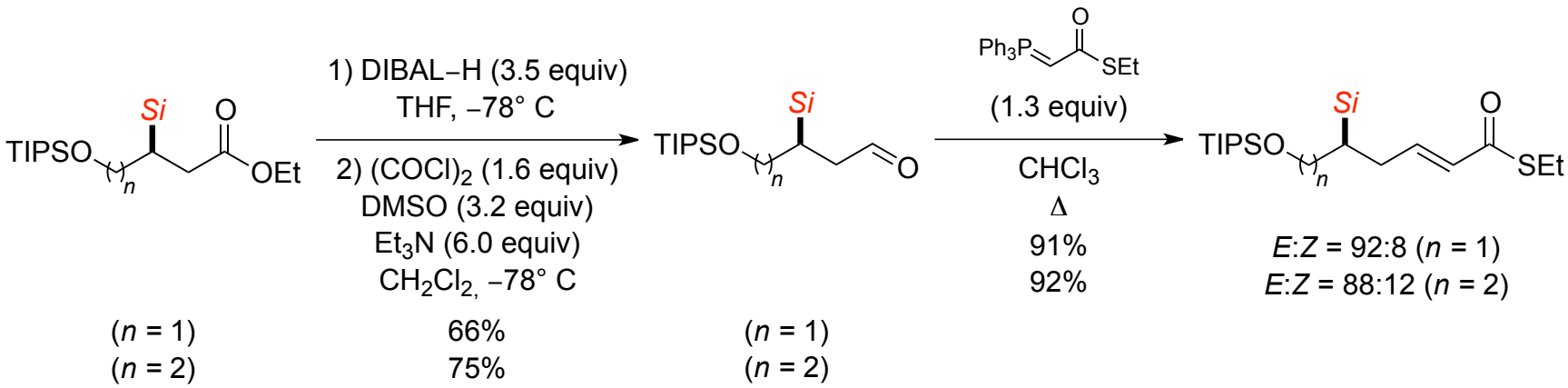

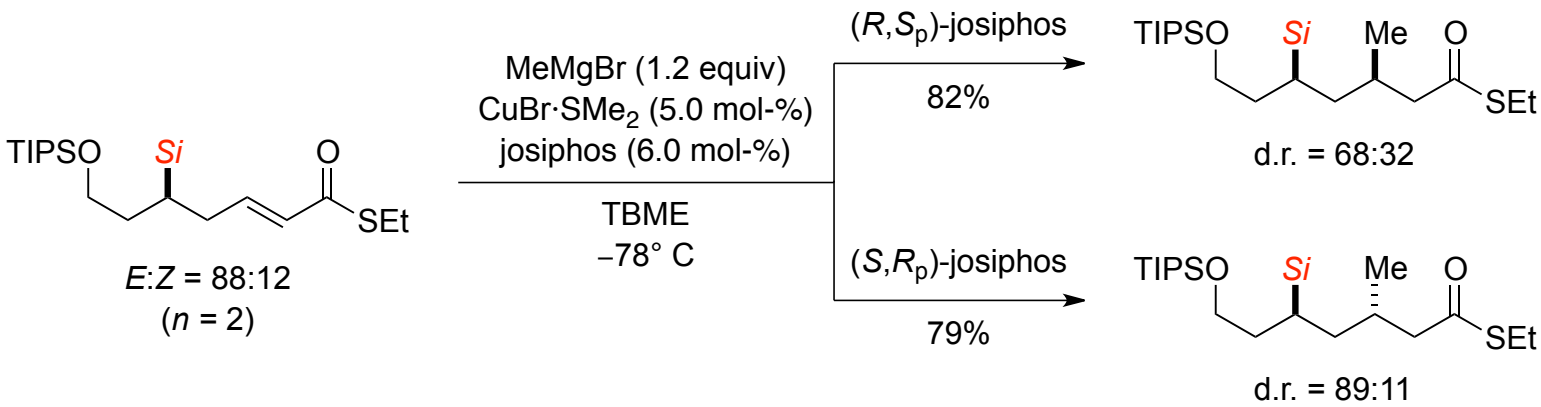

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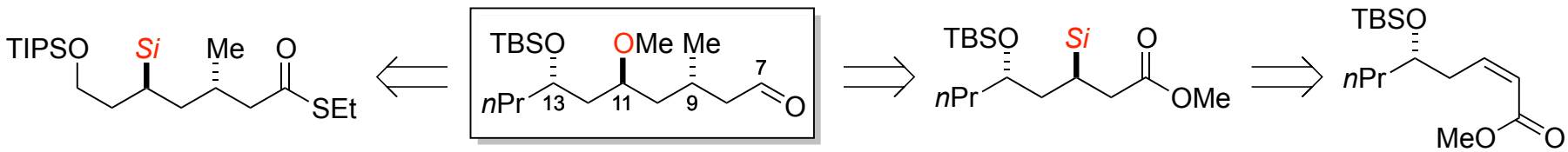

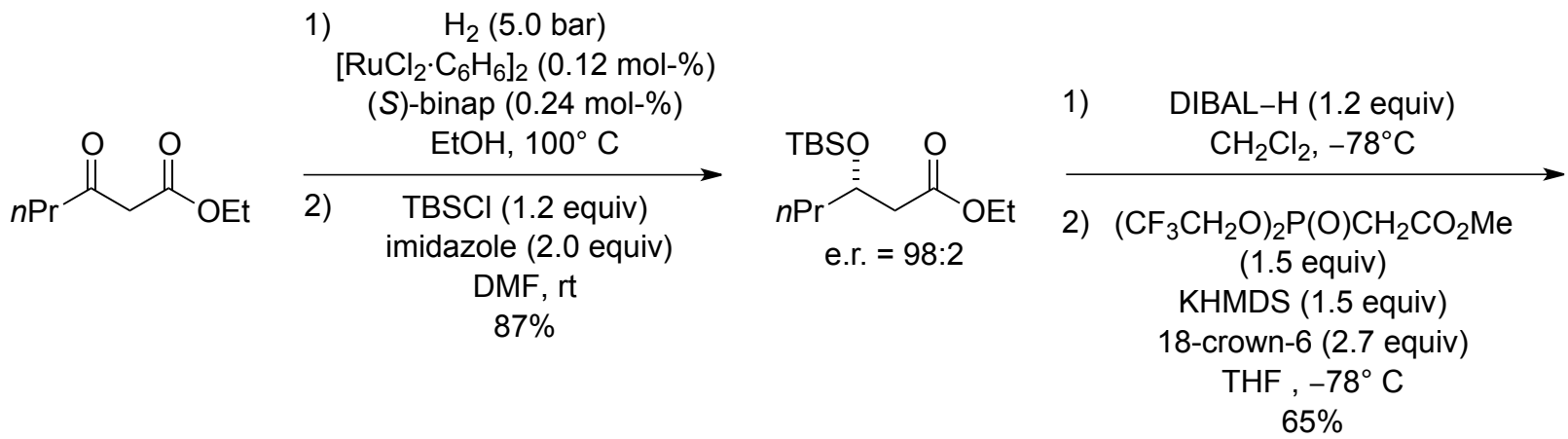

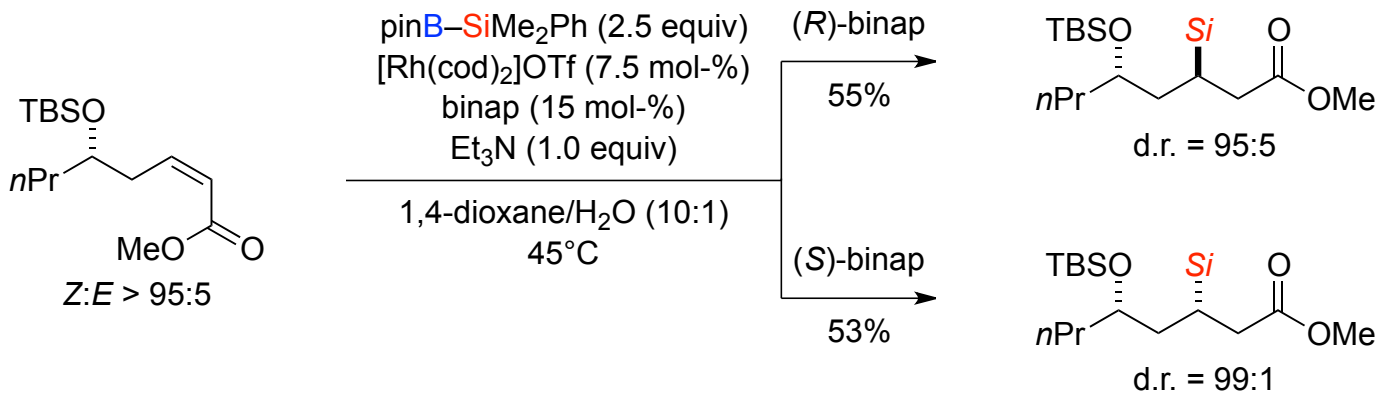

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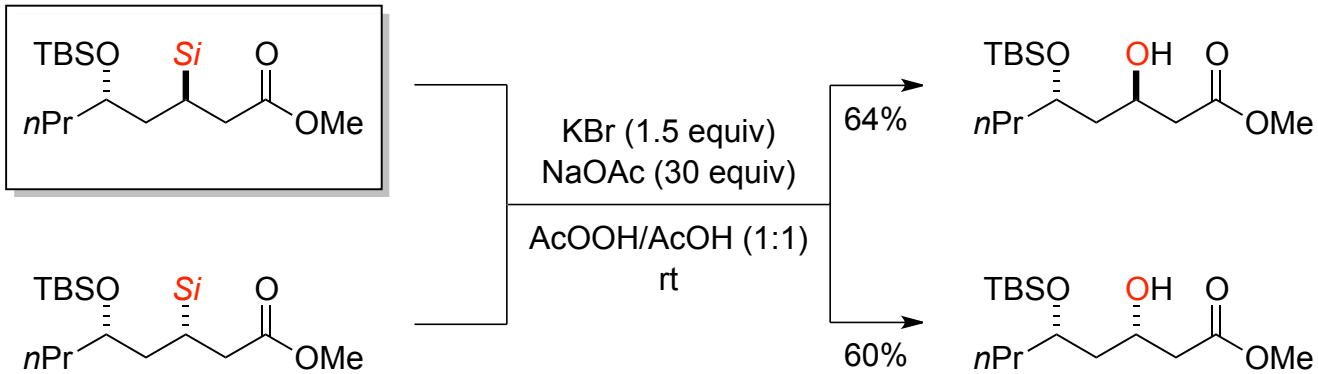
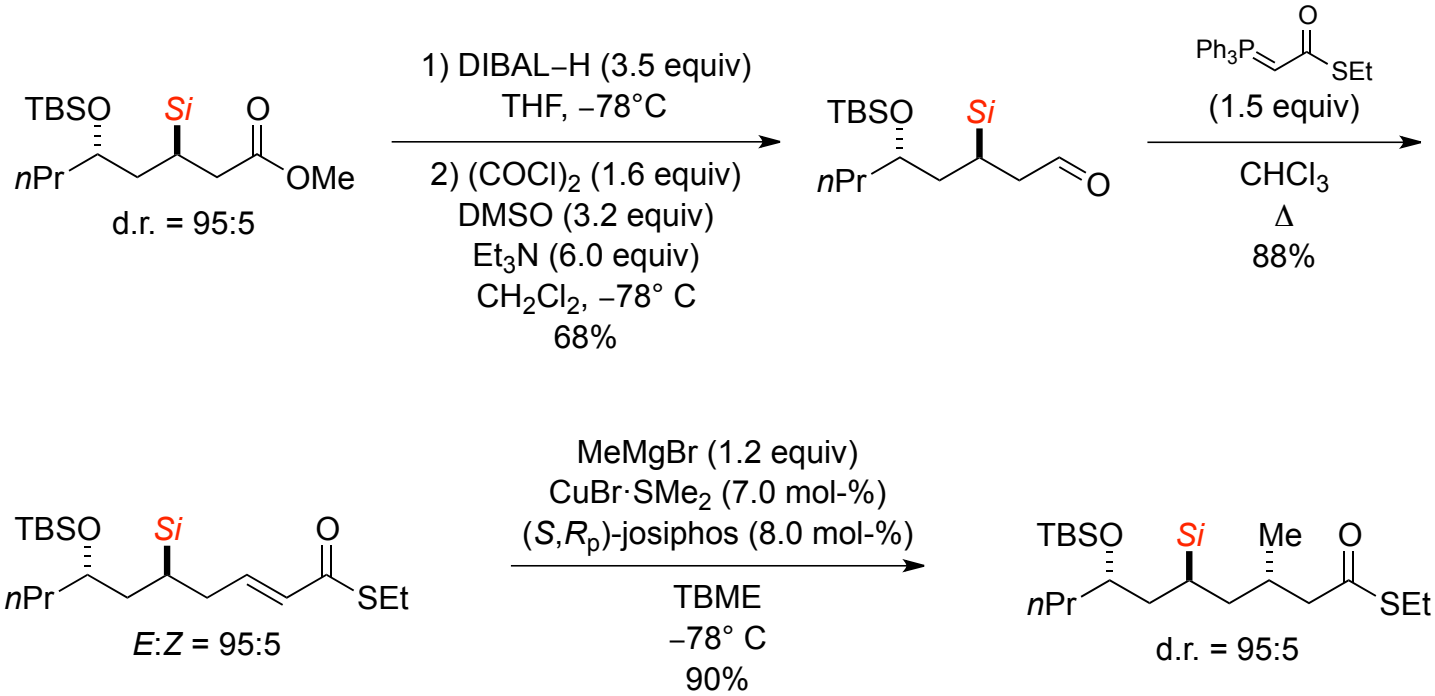
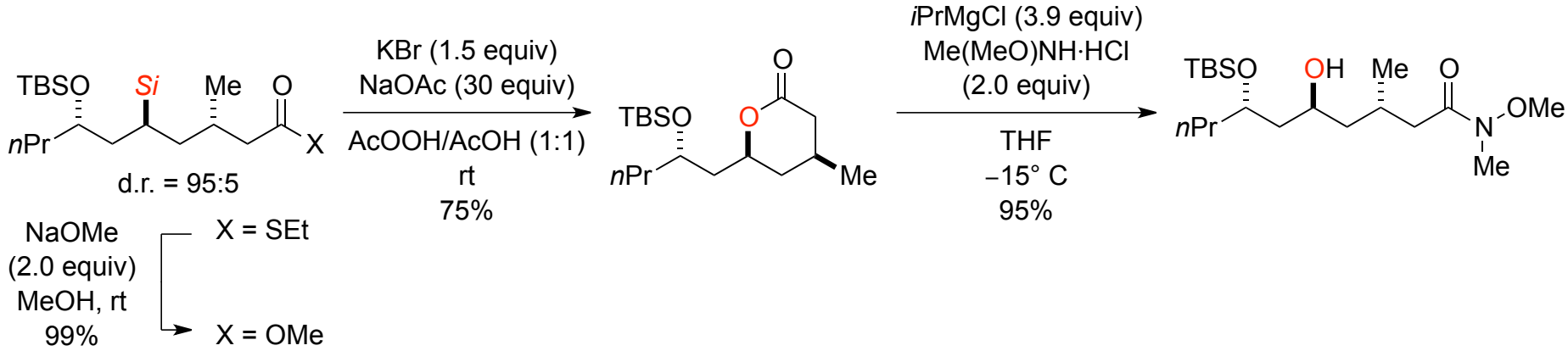
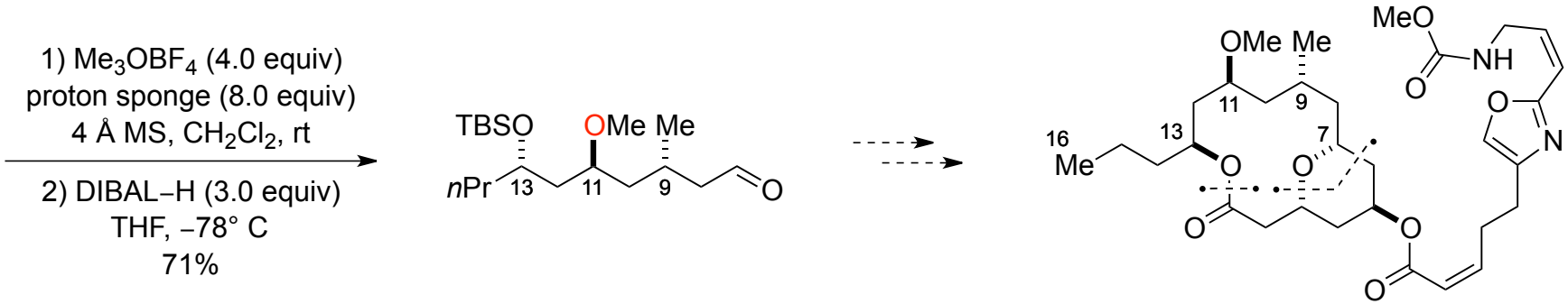




Stereoselective synthesis of the C7–C16 fragment of (+)-neopeltolide



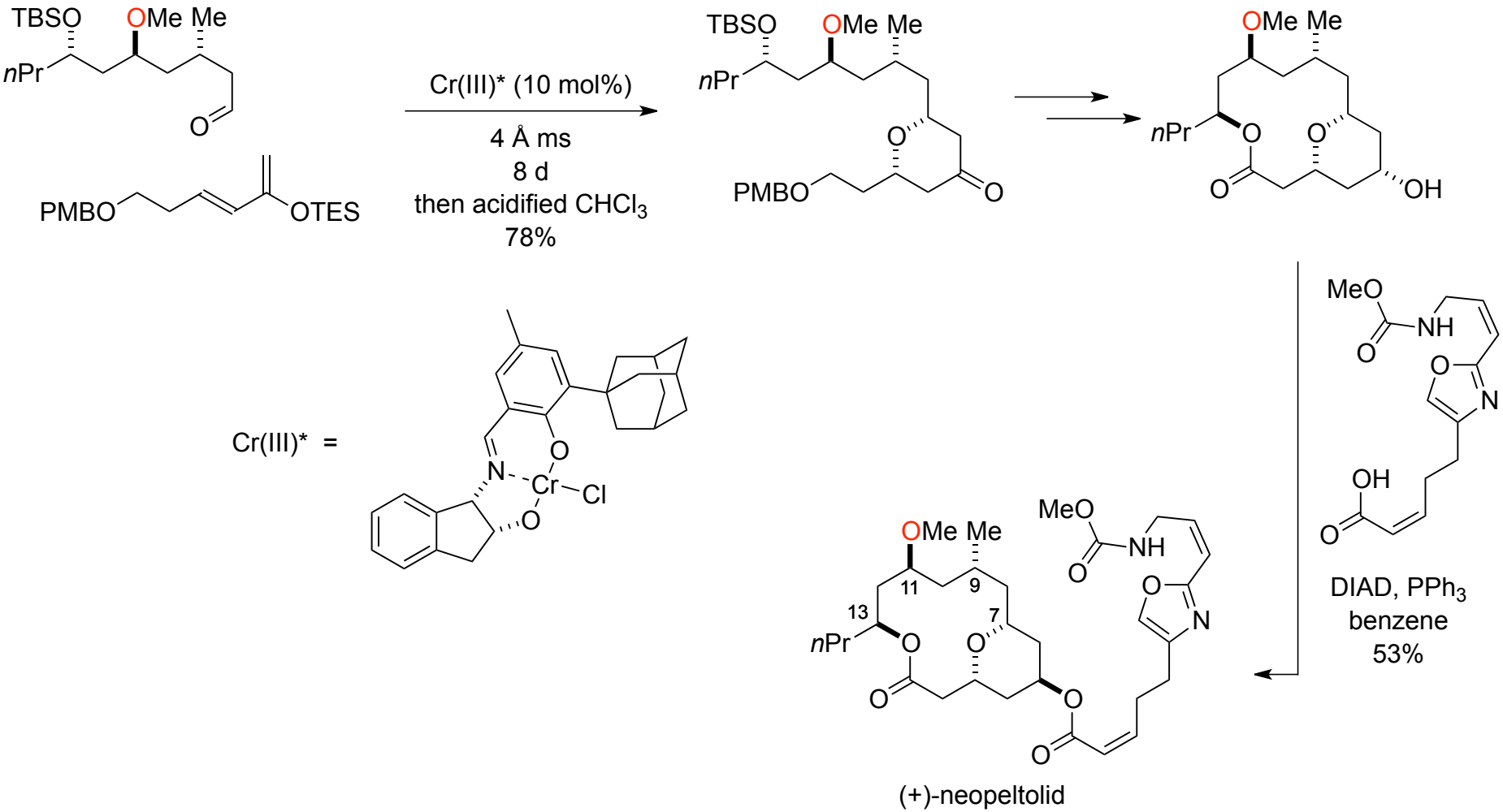


(+)-neopeltolid

I. Paterson, N. A. Miller,
Chem. Commun. **2008**, 4708–4710.

E. Hartmann, M. Oestreich, *Angew. Chem. Int. Ed.* **2010**, *49*, 6195–6198.

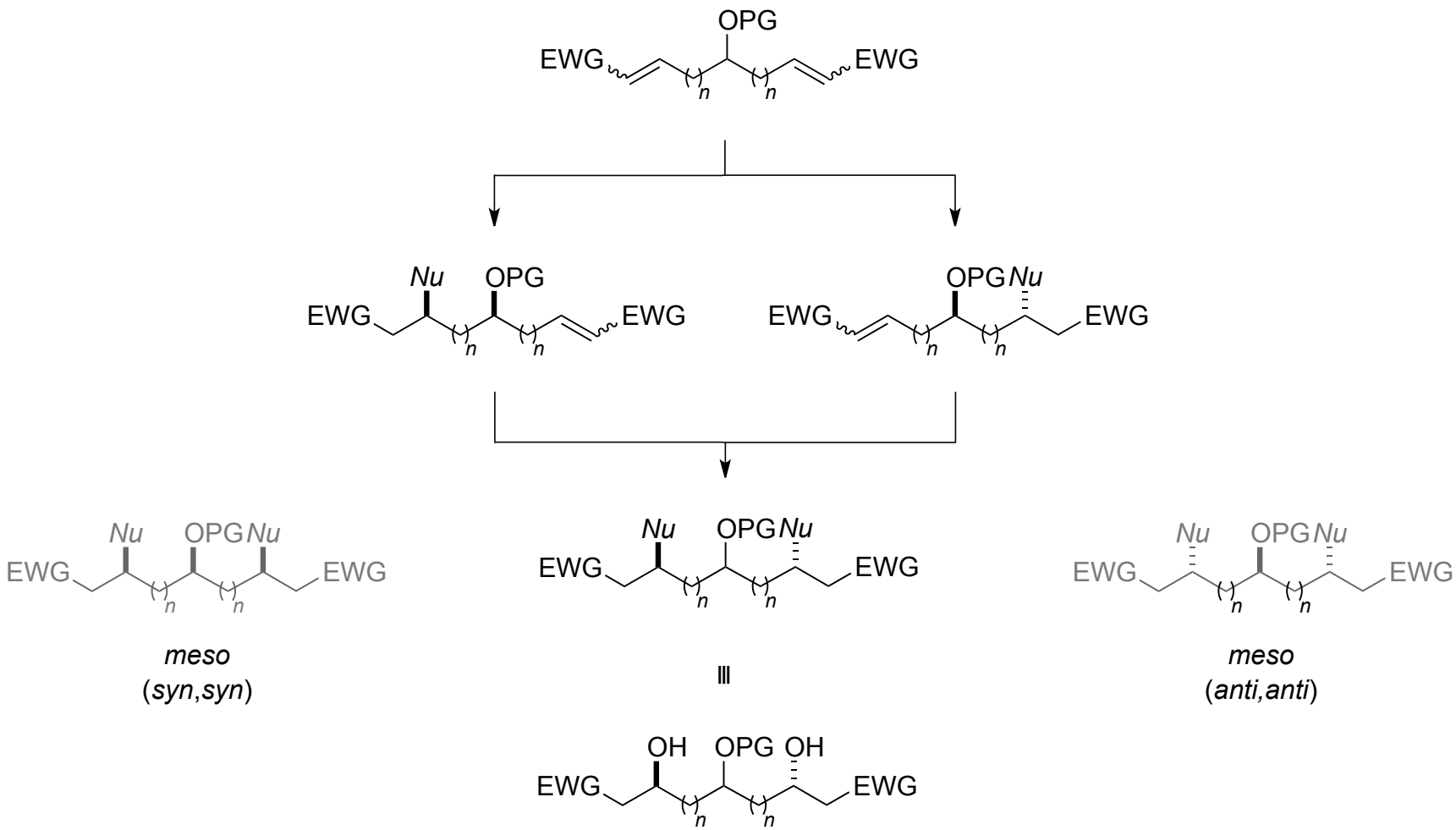
Stereoselective synthesis of the C7–C16 fragment of (+)-neopeltolide



I. Paterson, N. A. Miller, *Chem. Commun.* **2008**, 4708–4710.

Access to stereodefined polyols through two-directional synthesis

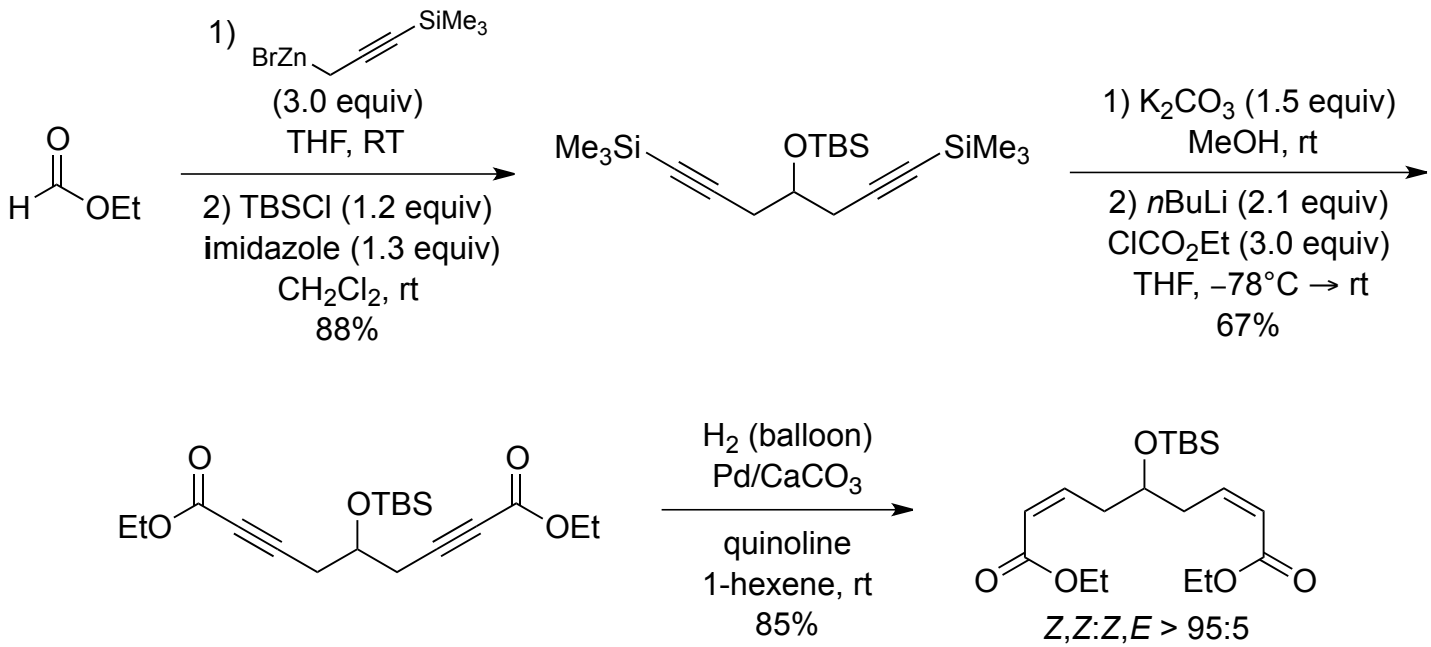
Two-directional synthesis

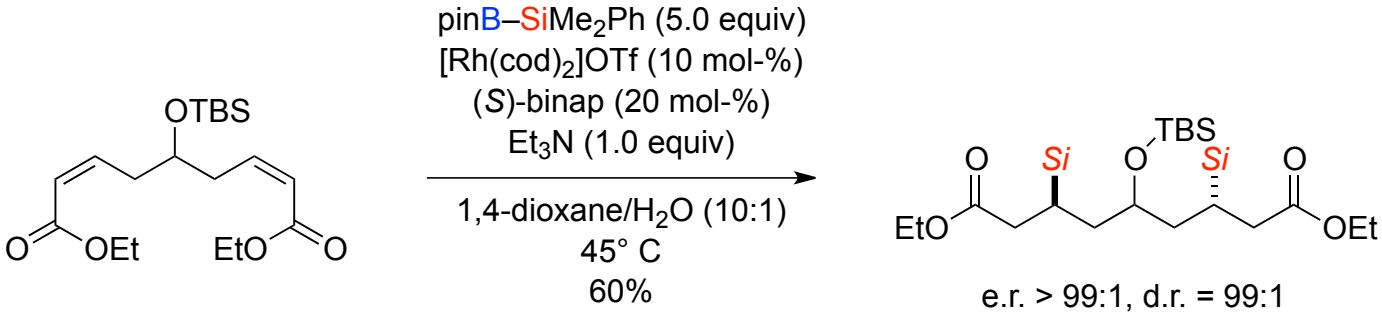


1,3,5-triol (n = 1)
1,4,7-triol (n = 2)

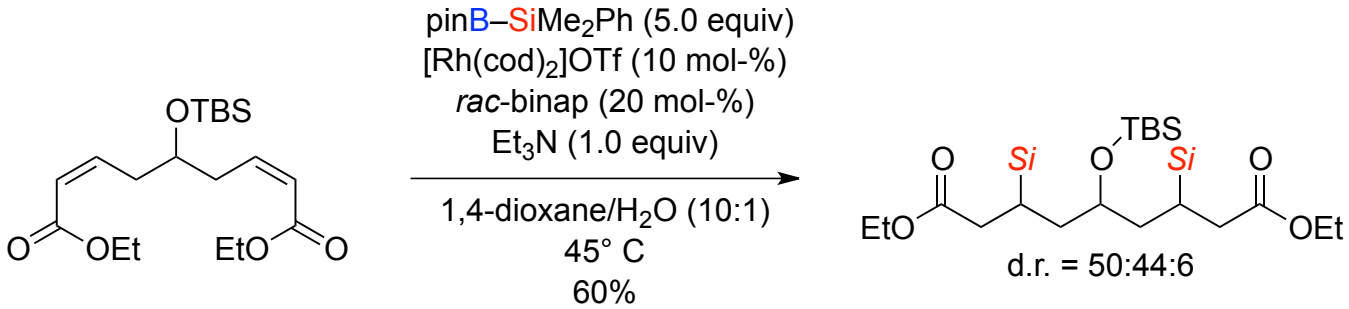
Nu = $SiMe_2Ph$ or Bpin

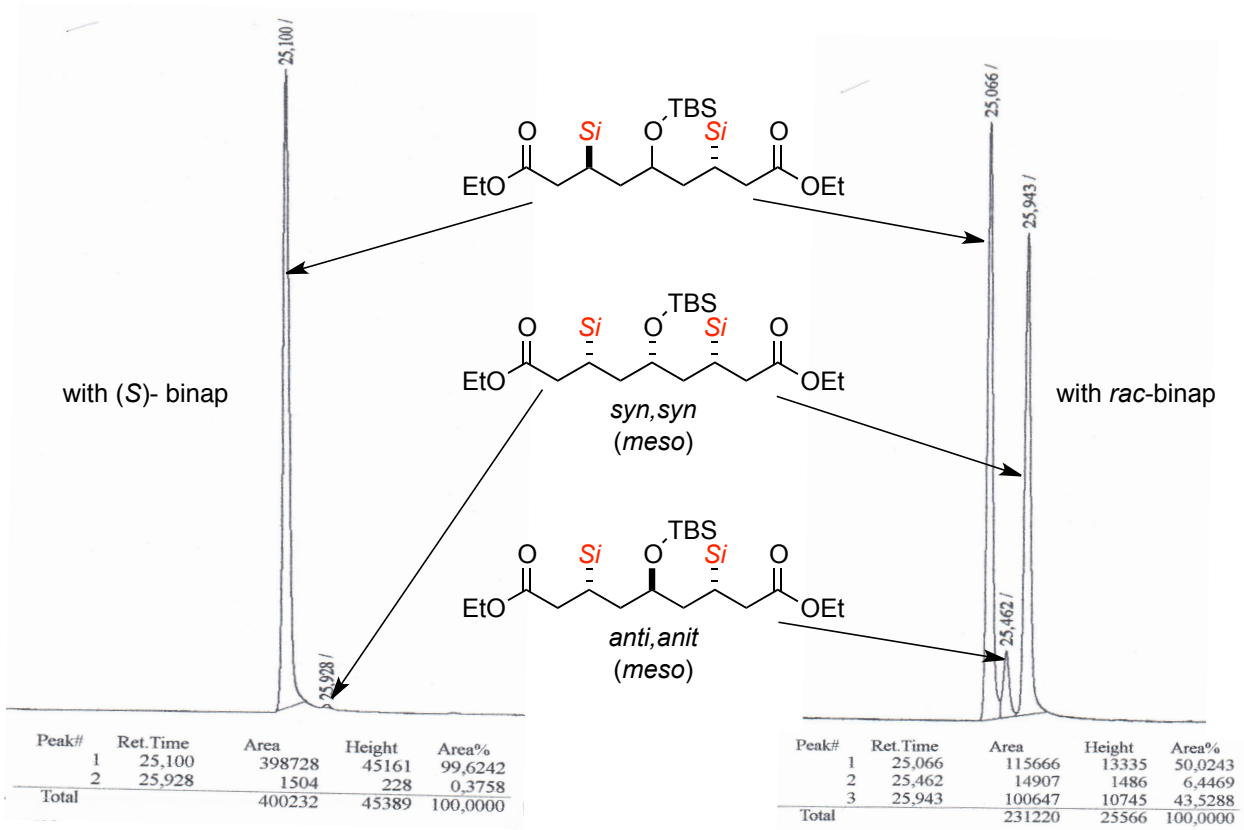
Double 1,4-addition of silicon nucleophiles



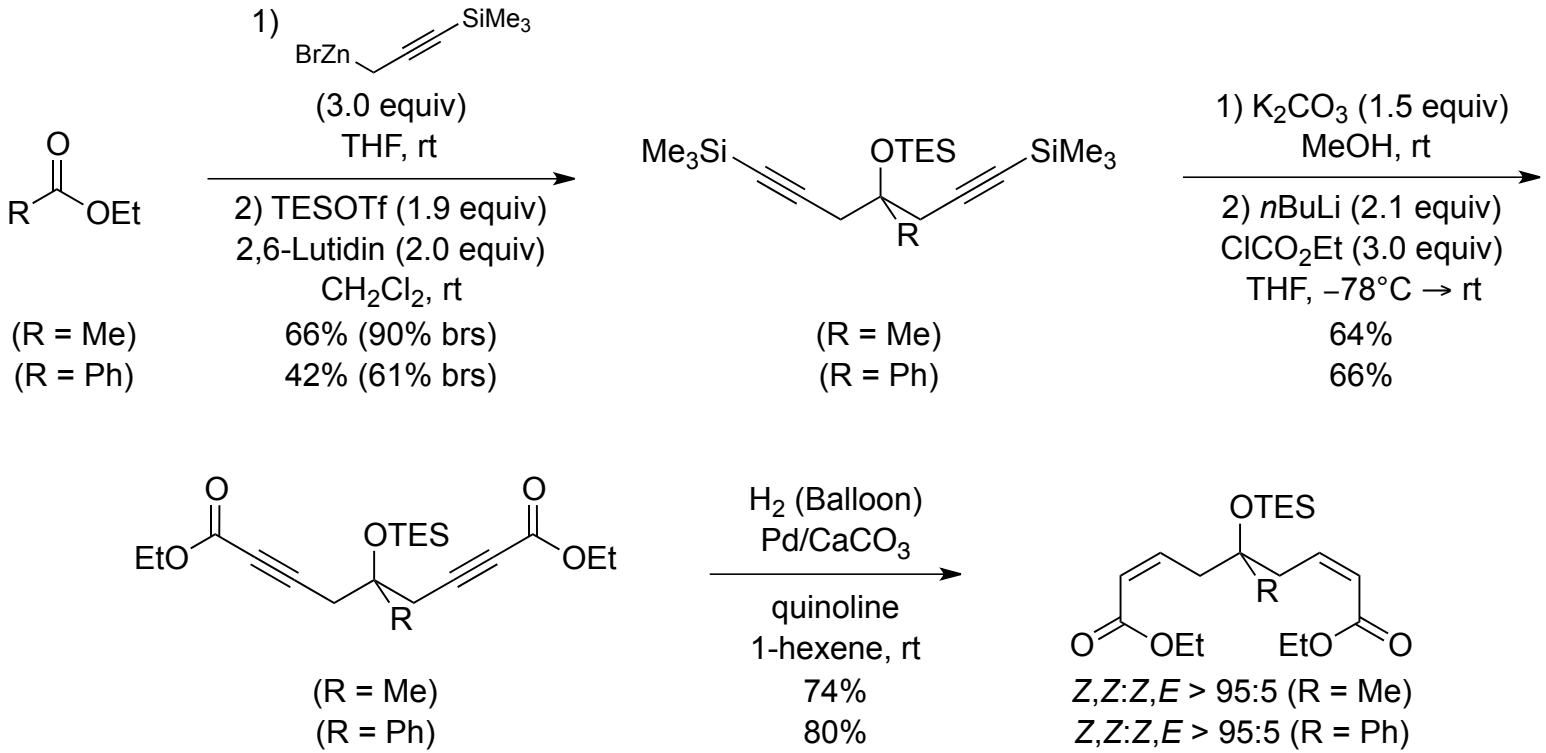


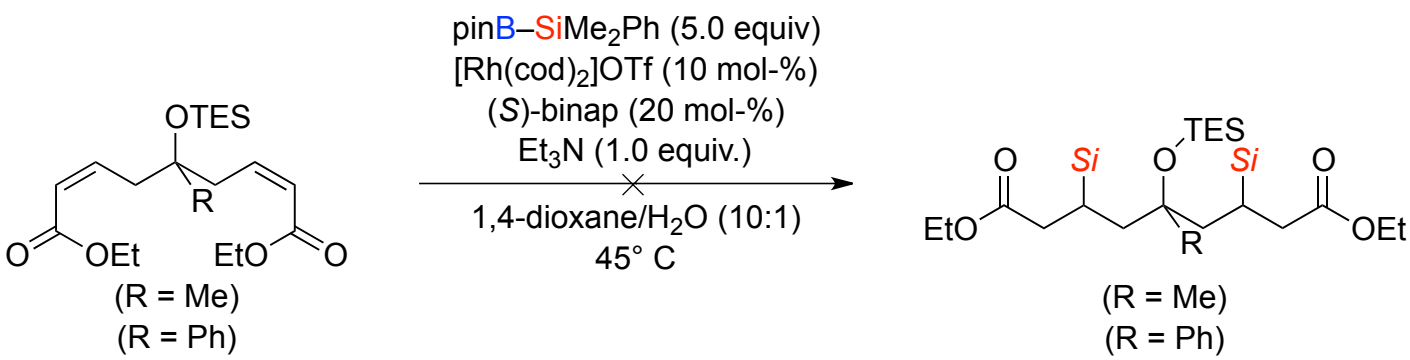
Double 1,4-addition of silicon nucleophiles



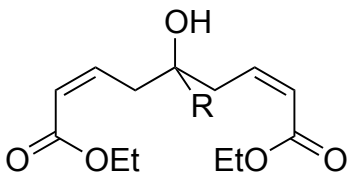


Double 1,4-addition of silicon nucleophiles





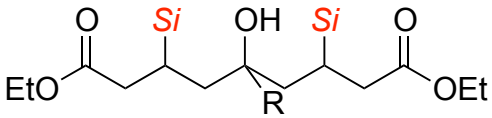
Double 1,4-addition of silicon nucleophiles



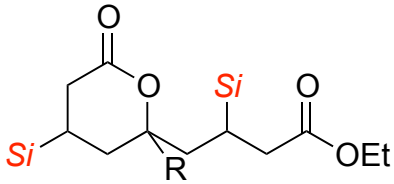
(R = Me)
(R = Ph)

pinB–SiMe$_2$Ph (5.0 equiv)
[Rh(cod)$_2$]OTf (10 mol-%)
(*S*)-binap (20 mol-%)
Et$_3$N (1.0 equiv.)

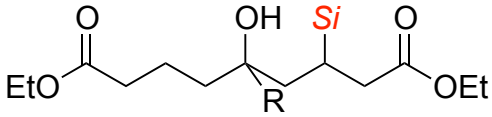
1,4-dioxane/H$_2$O (10:1)
45° C



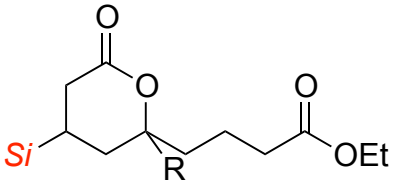
(R = Me)
(R = Ph)



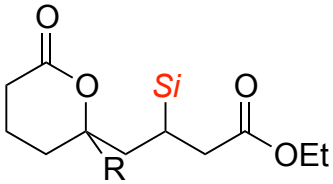
(R = Me)
(R = Ph)



(R = Me)
(R = Ph)

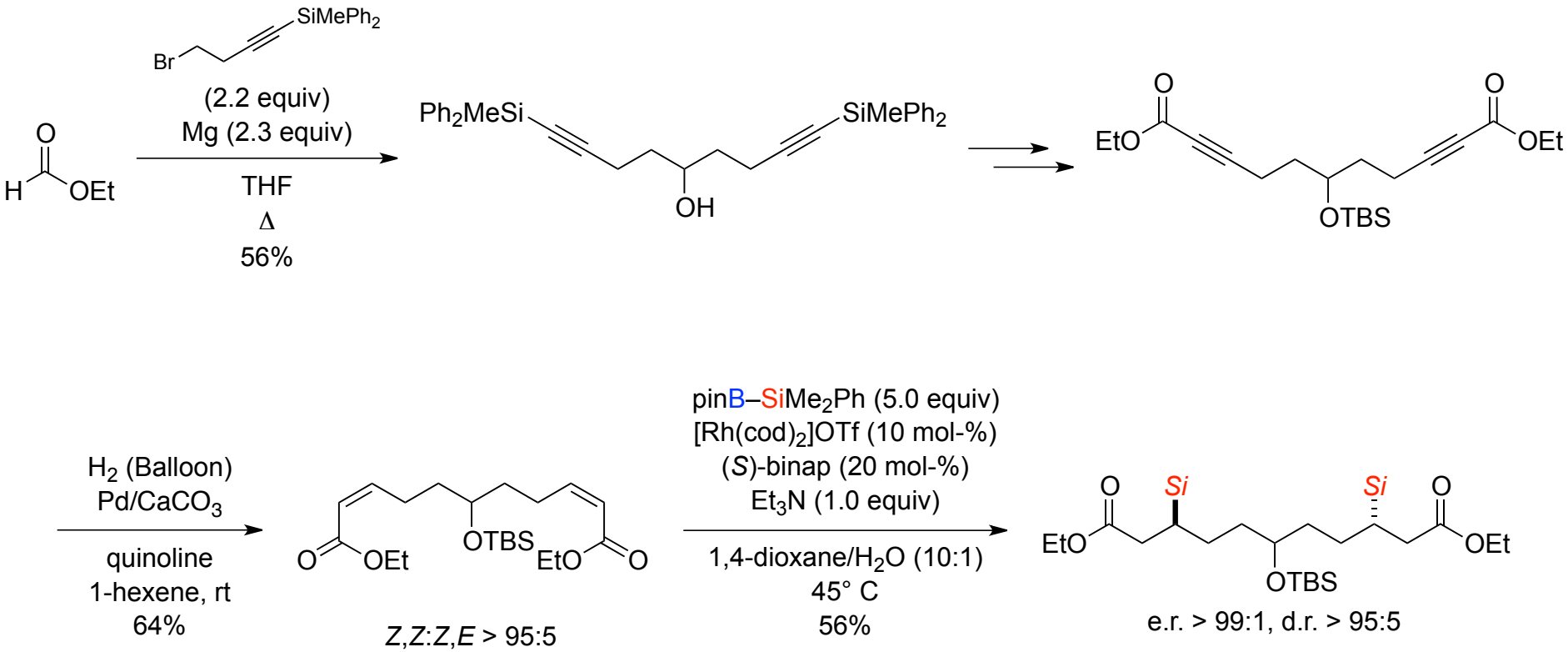


(R = Me)
(R = Ph)

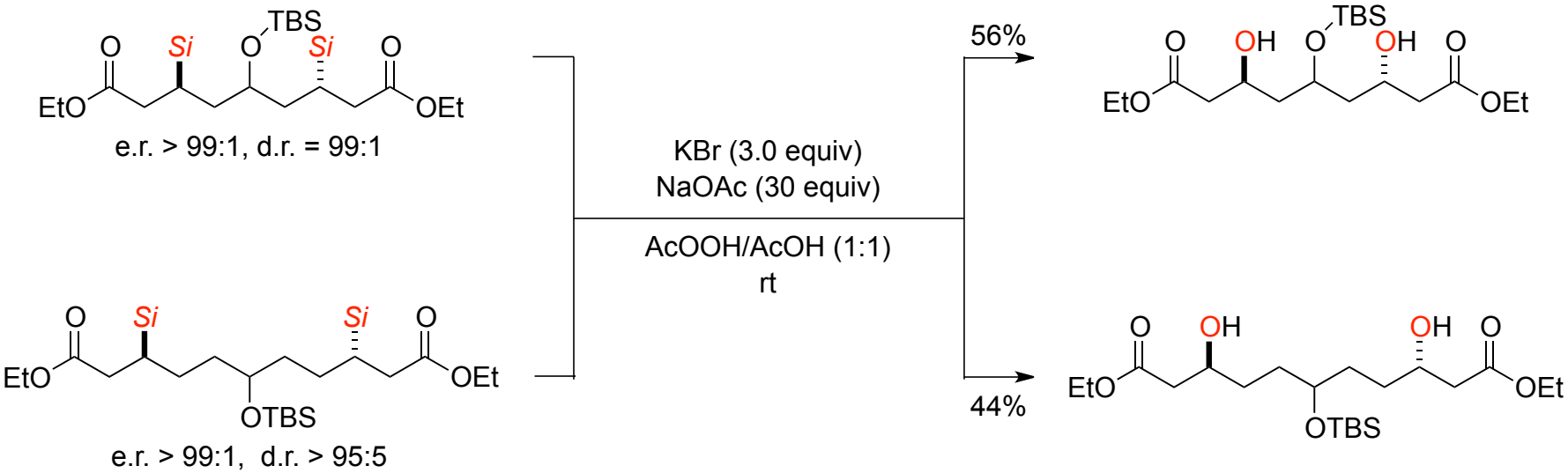


(R = Me)
(R = Ph)

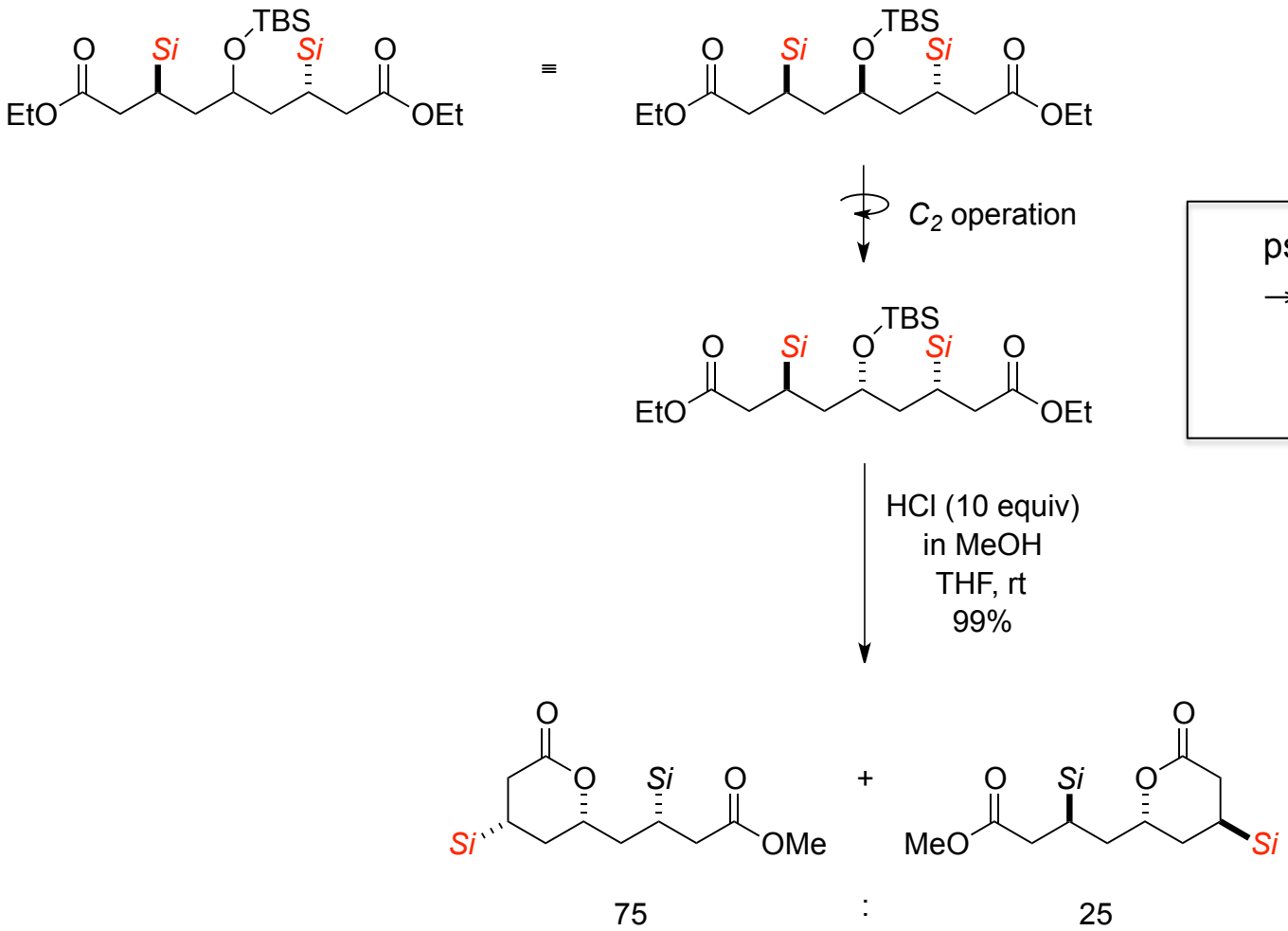
Double 1,4-addition of silicon nucleophiles



Double 1,4-addition of silicon nucleophiles

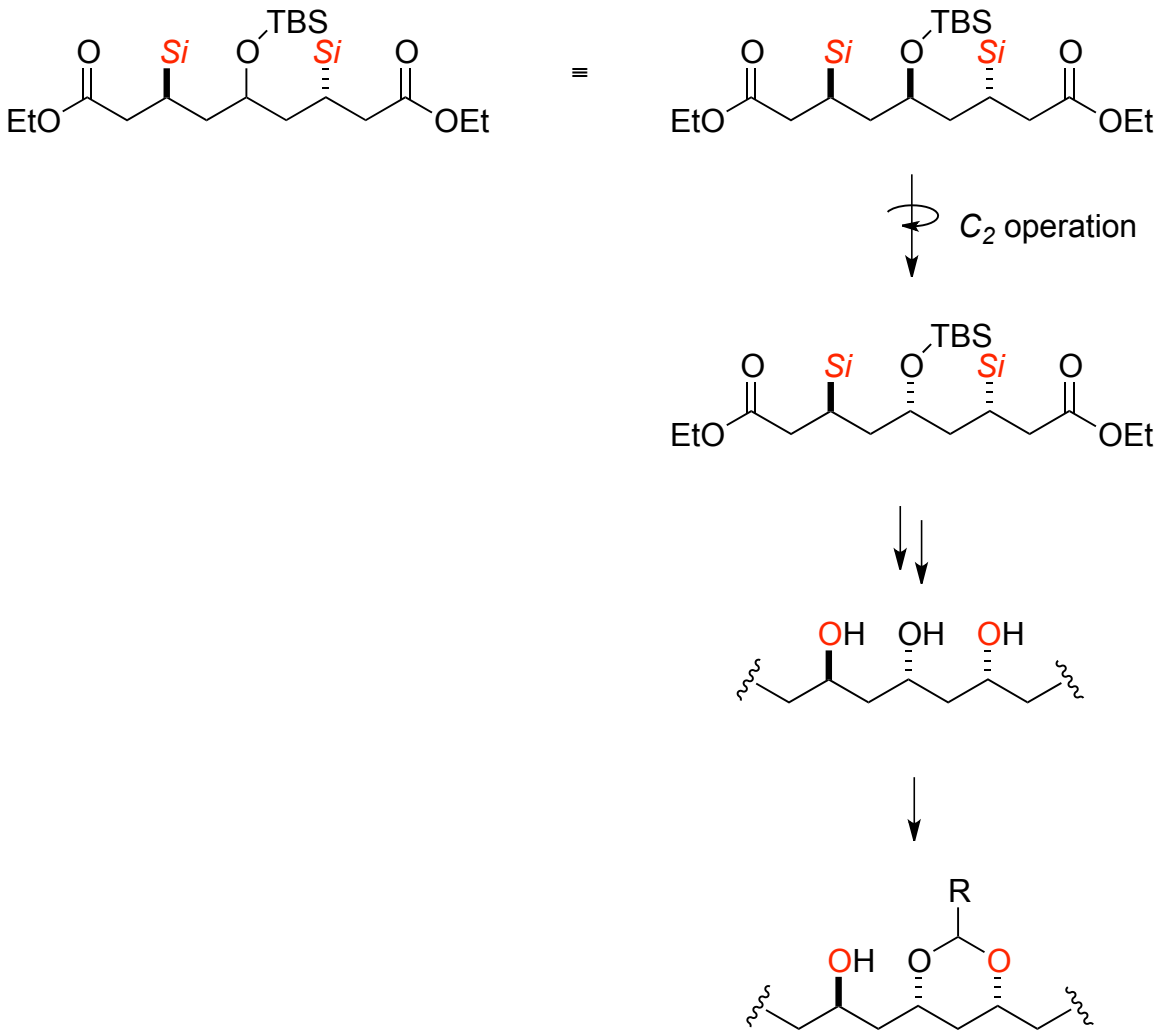


Differentiation of pseudo C_2-symmetric compounds



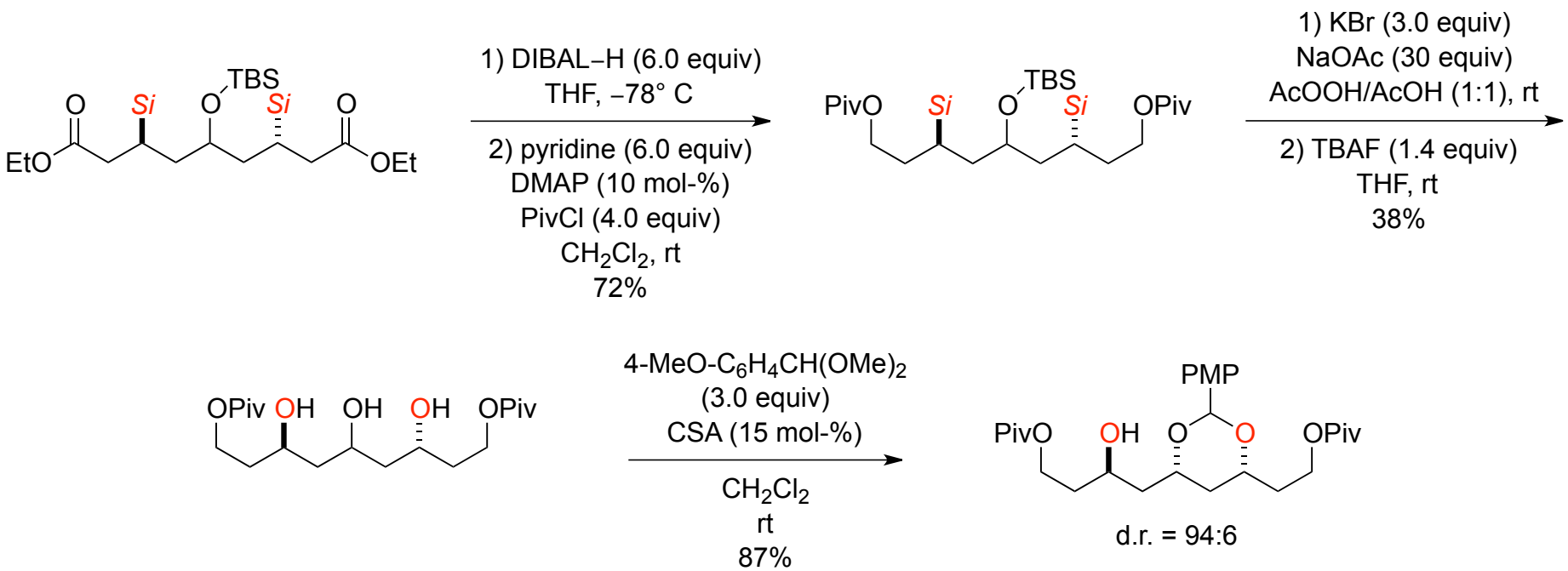
pseudo C_2-symmetric
→ differentiation of diastereotopic groups required

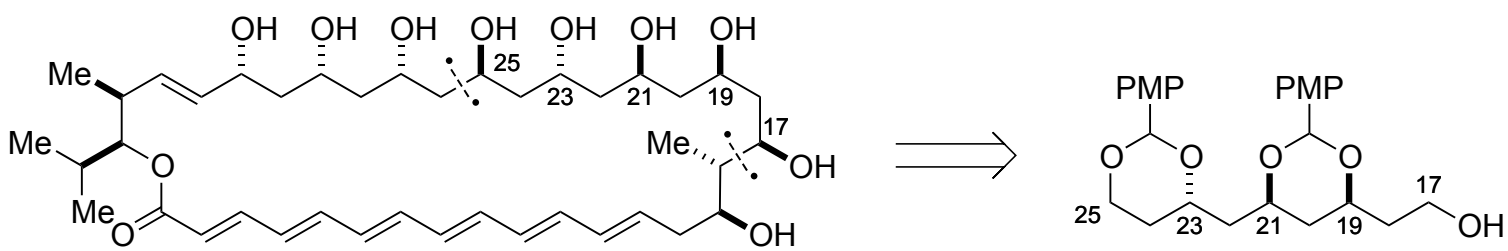
Differentiation of pseudo C_2-symmetric compounds



pseudo C_2-symmetric
→ differentiation of diastereotopic groups required

Differentiation of pseudo C_2-symmetric compounds





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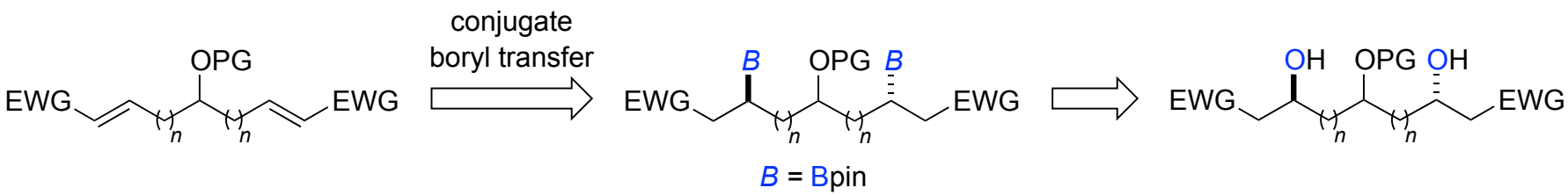
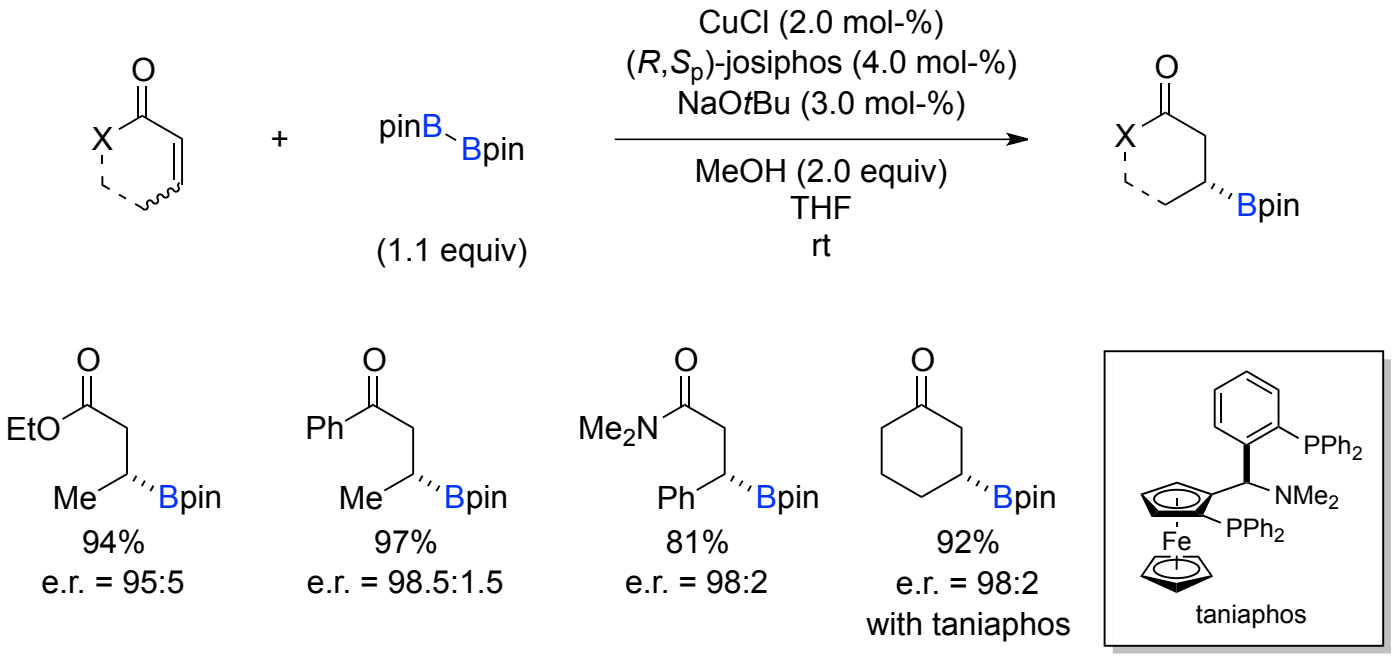
Double 1,4-addition of boron nucleophiles





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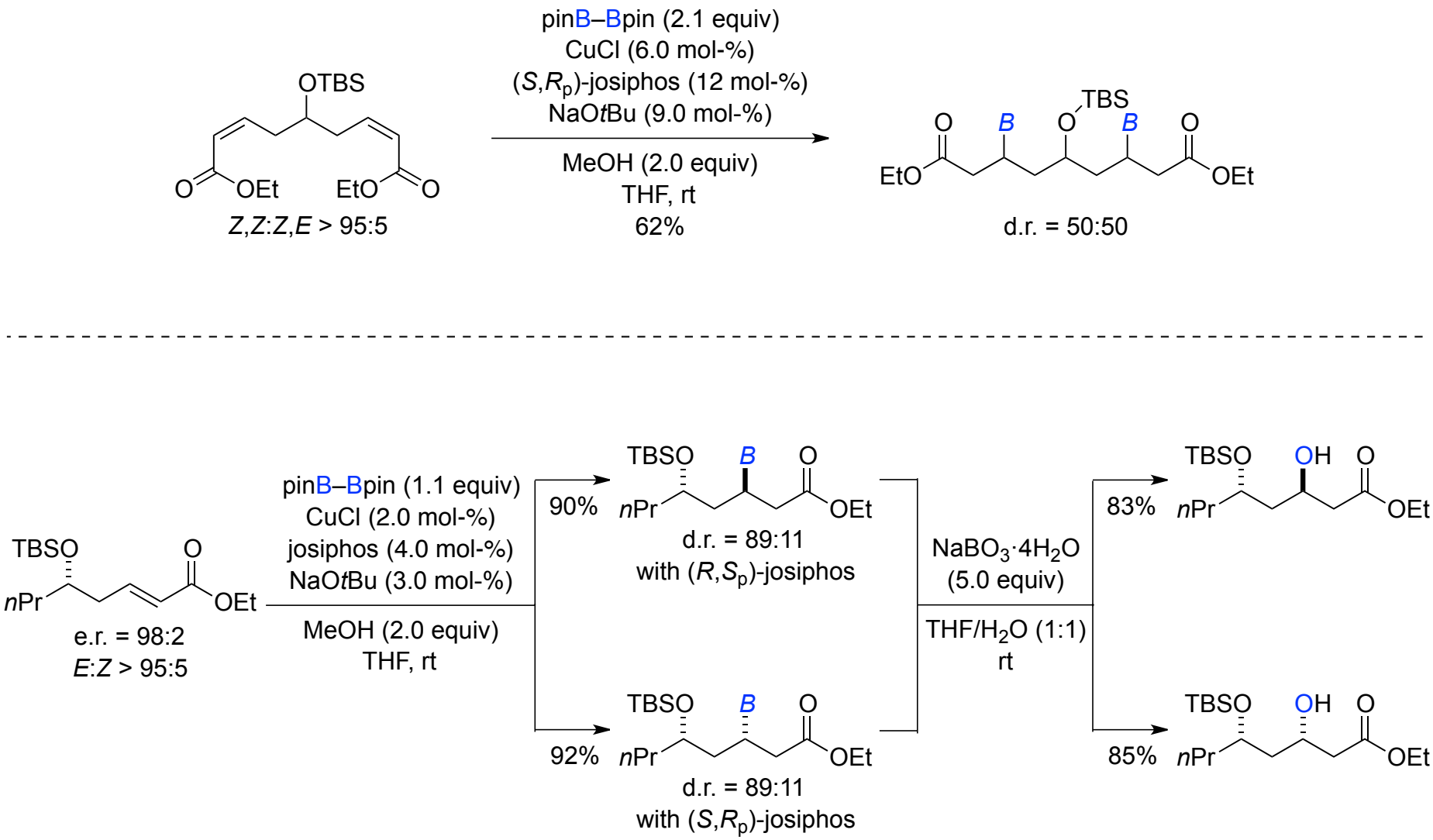
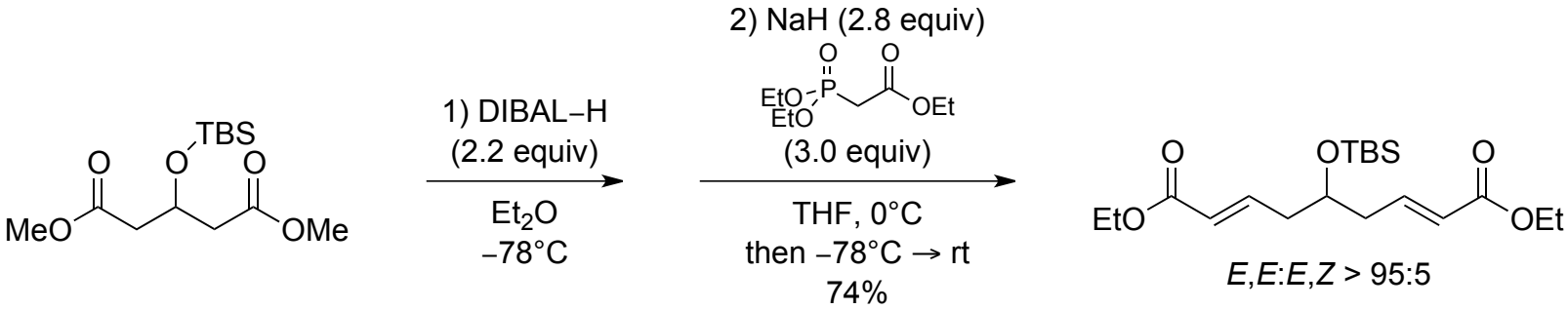
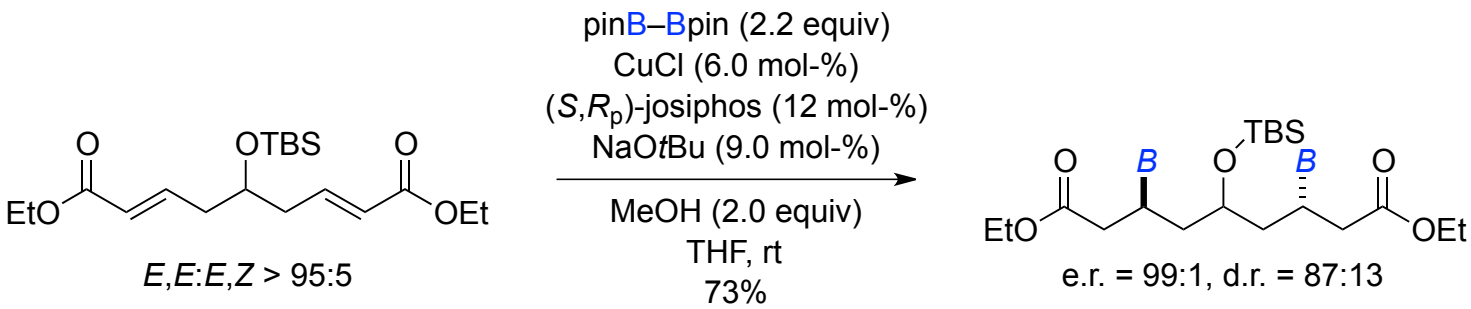
Double 1,4-addition of boron nucleophiles

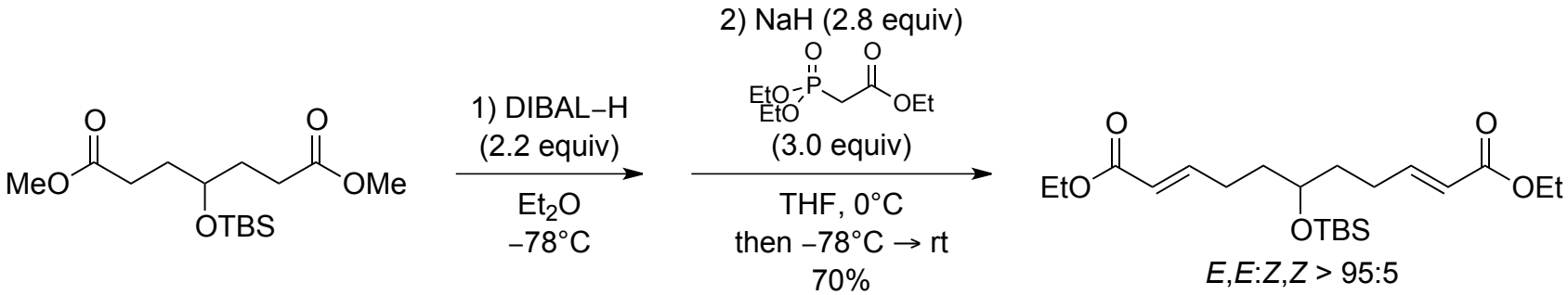


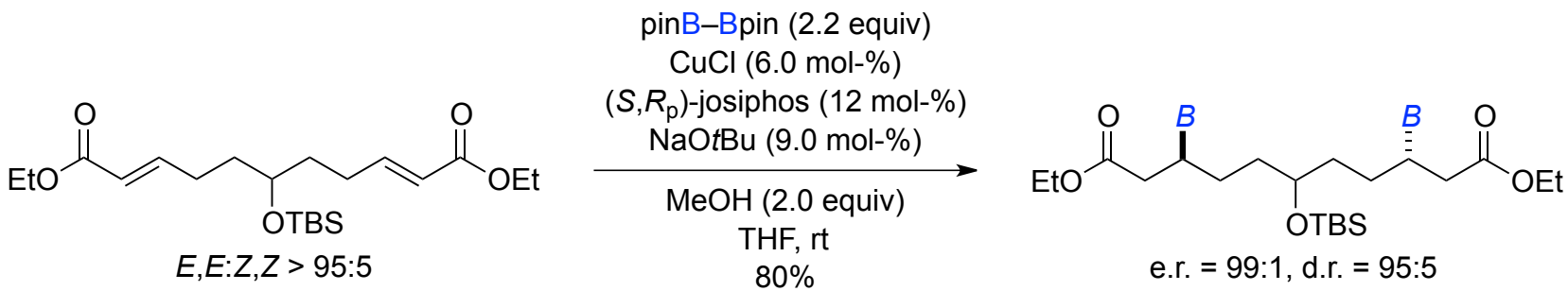
Double 1,4-addition of boron nucleophiles



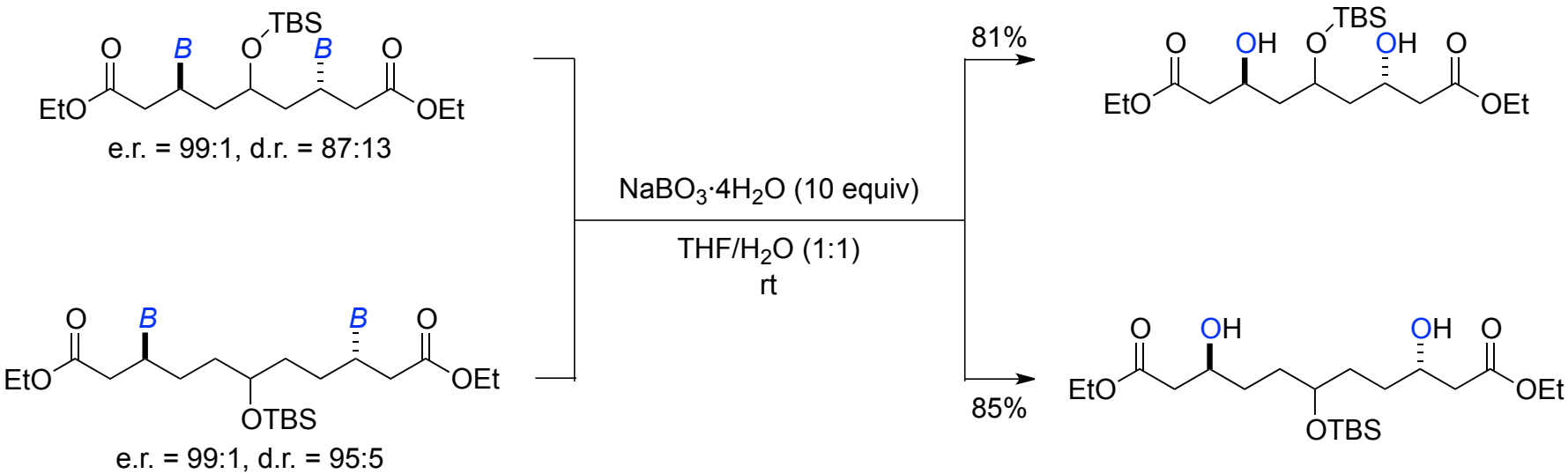


Double 1,4-addition of boron nucleophiles





Double 1,4-addition of boron nucleophiles



E. Hartmann, M. Oestreich, *Org. Lett.* **2012**, *14*, 2406–2409.