Synthesis of Trisubstituted Alkenes by Cross-Metathesis Reactions

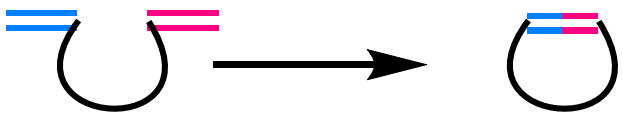
Literature Seminar
2023. 07. 29

M1 Manaka Matsumoto

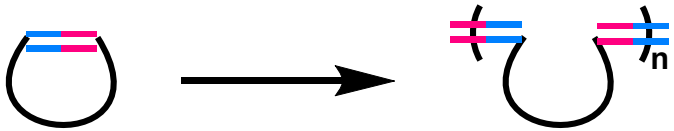
Contents

Olefin Metathesis

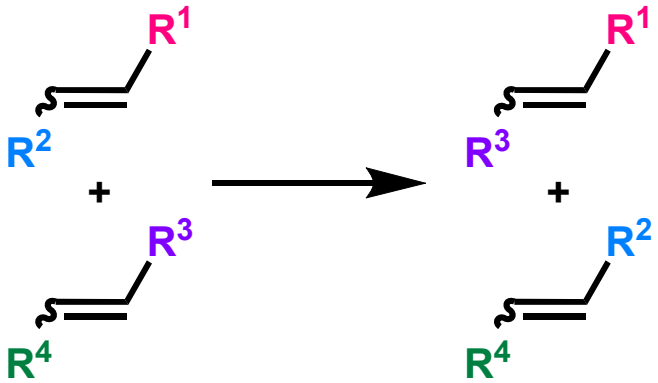
Ring Closing Metathesis (RCM)



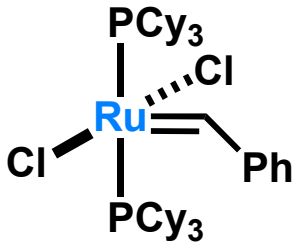
Ring Opening Metathesis Polymerization (ROMP)



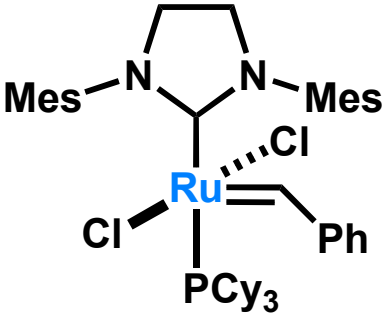
Cross Metathesis (CM)



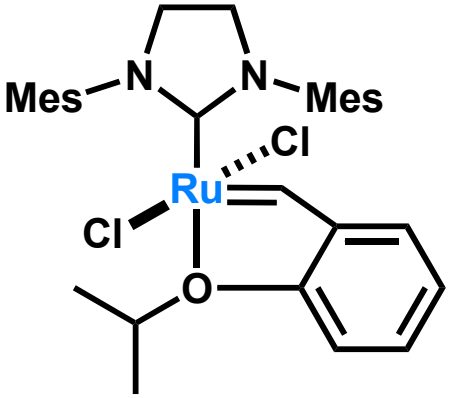
Catalysts



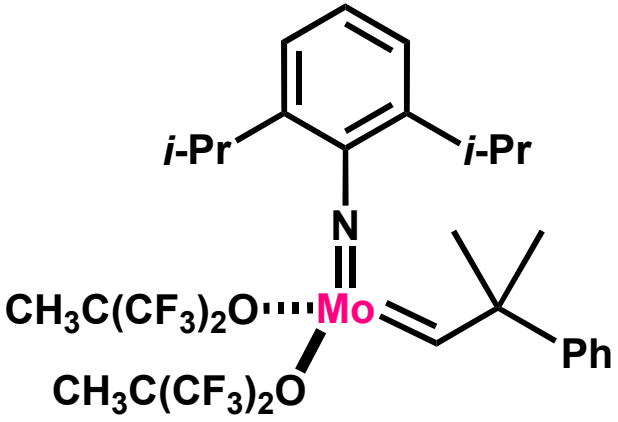
Grubbs 1st



Grubbs 2nd



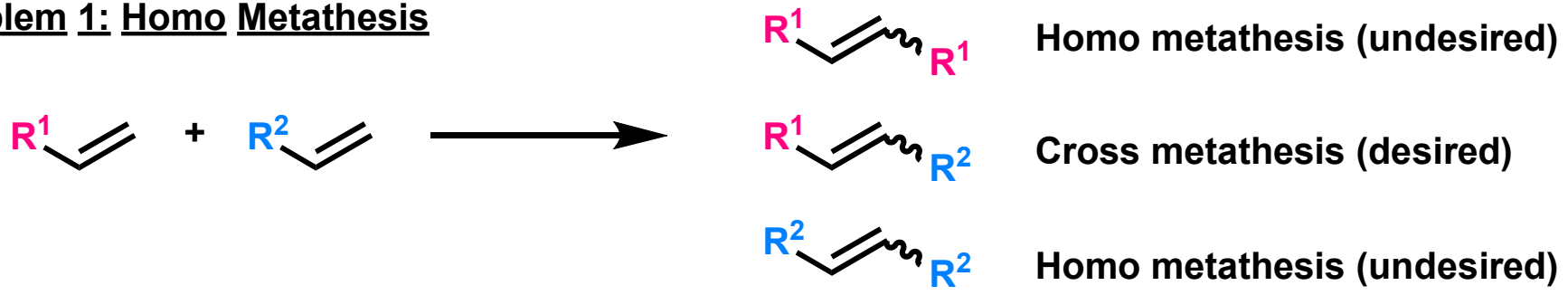
Hoveyda-Grubbs 2nd



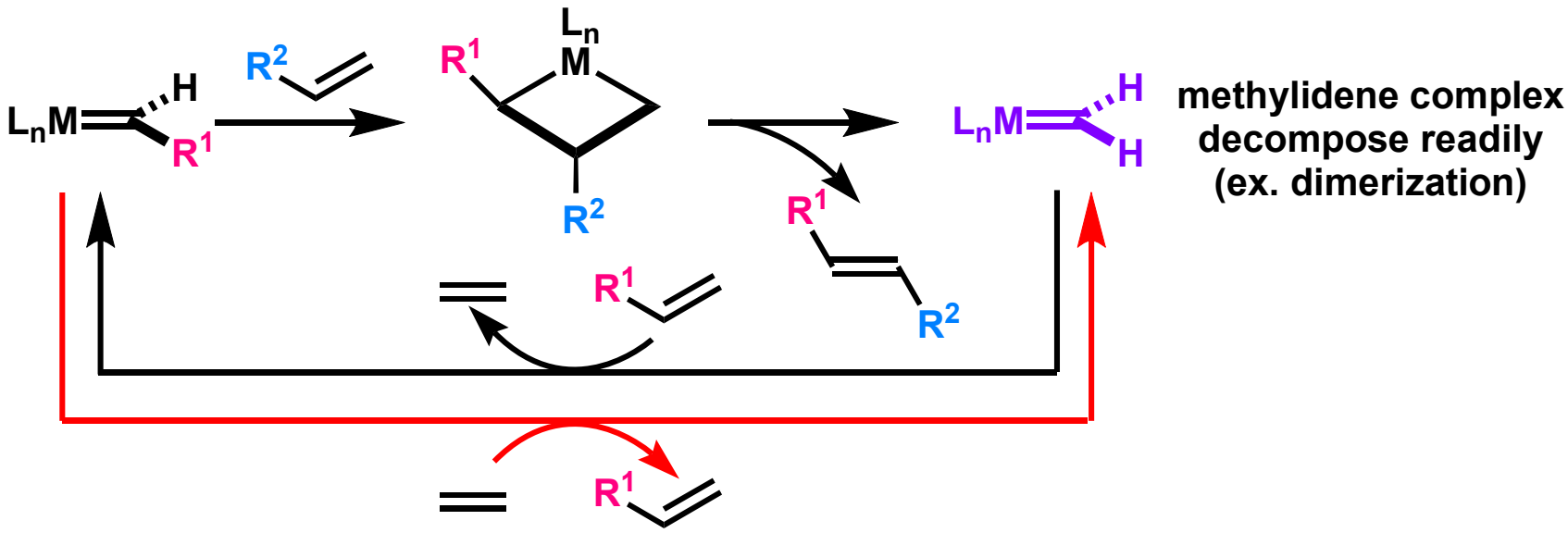
Schrock catalyst

Challenges of Cross Metathesis

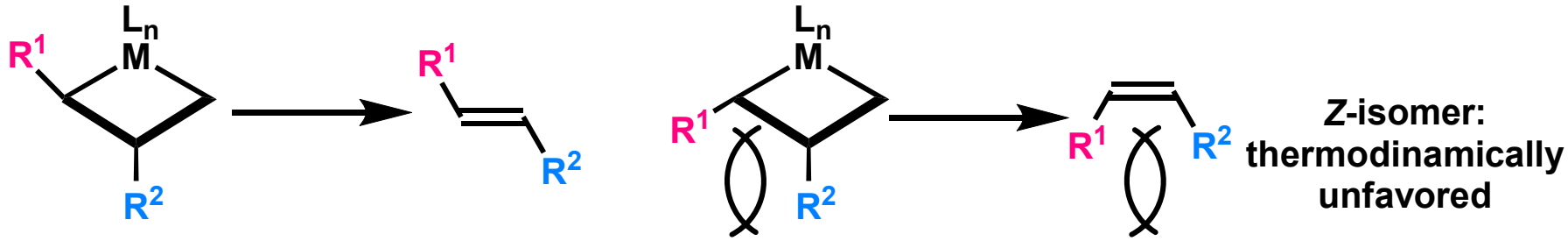
Problem 1: Homo Metathesis



Problem 2: Methylidene Complex

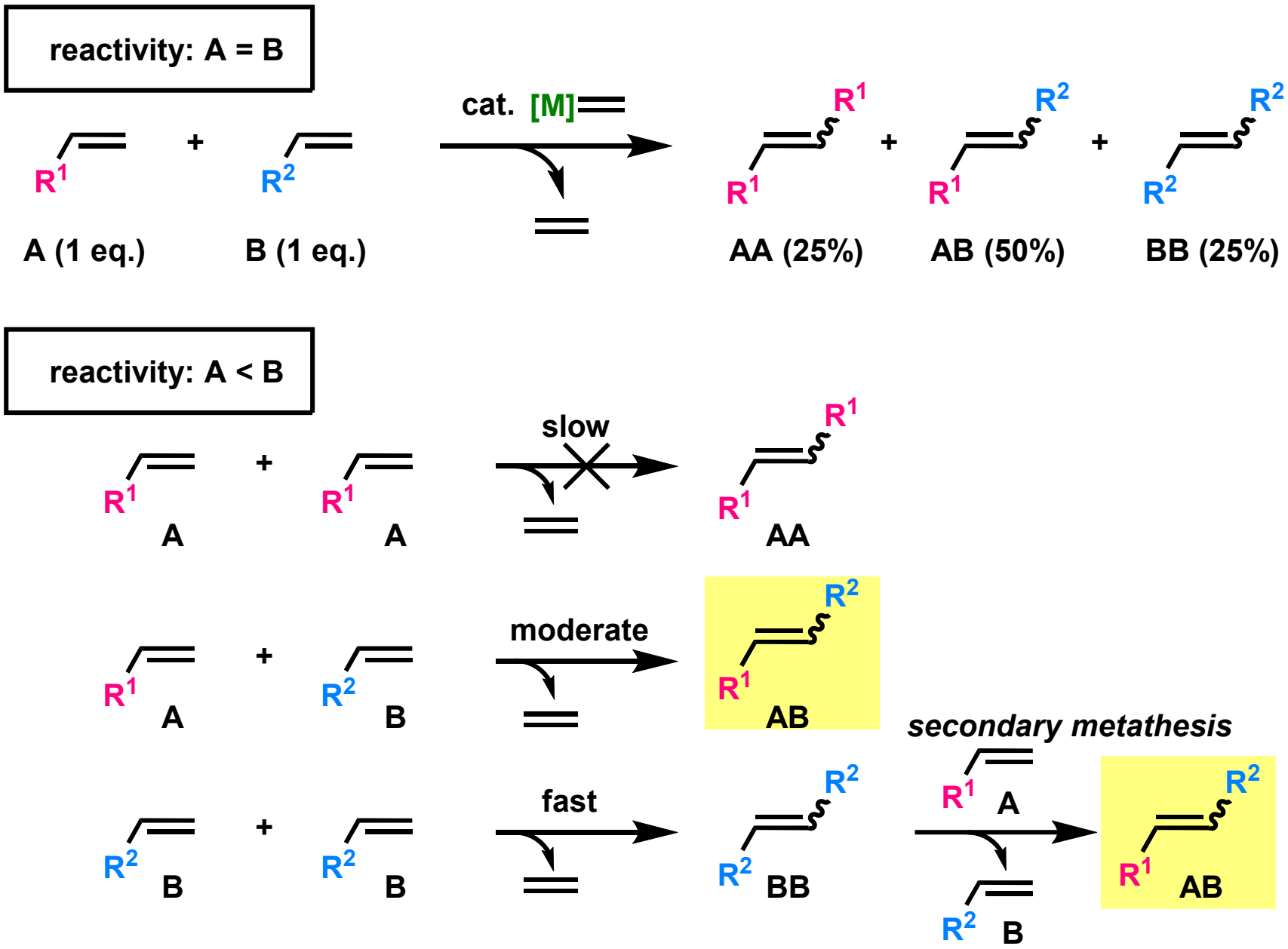


Problem 3: *E*/*Z*- Selectivity



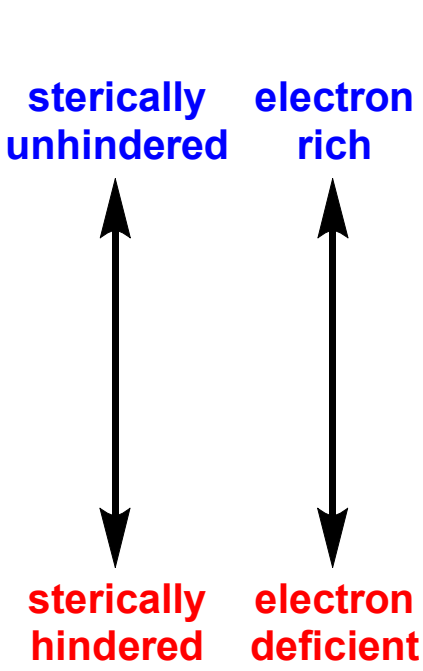
1) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
2) Xu, C.; Shen, X.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 10919.
3) Hoveyda, A. H.; Liu, Z.; Qin, C.; Koengeter, T.; Mu, Y. *Angew. Chem., Int. Ed.* **2020**, *59*, 22324.

Selective Cross Metathesis



1) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
2) 141213_LS_Kengo_Masuda

Classification of Olefins

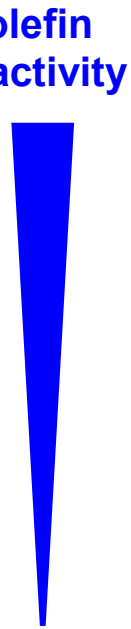


Type I - rapid homodimerization
- homodimers consumable

Type II - slow homodimerization
- homodimers sparingly consumable

Type III - no homodimerization

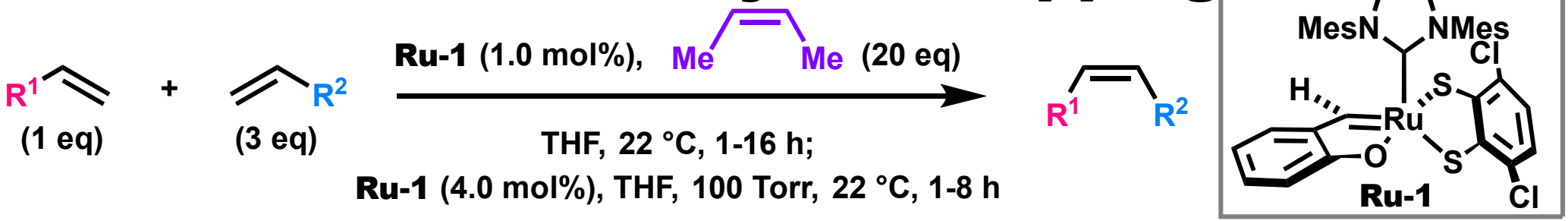
Type IV - inert to CM
- but no deactivation of cataylst

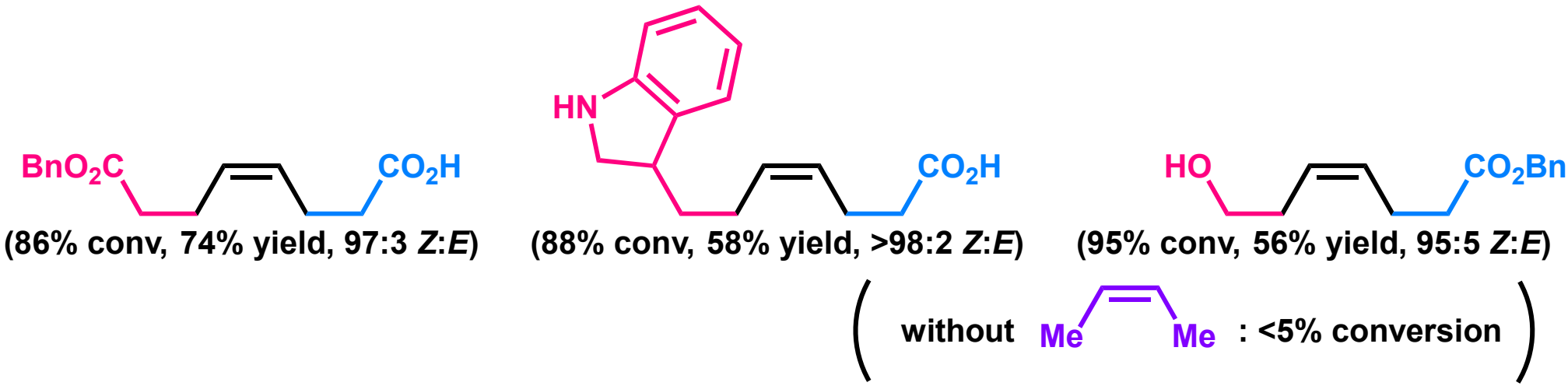


	Type I	Type II	Type III	Type IV
Type I	statistical	selective	selective	homodimerization
Type II		non-selective	selective	homodimerization
Type III			non-selective	no reaction
Type IV				no reaction

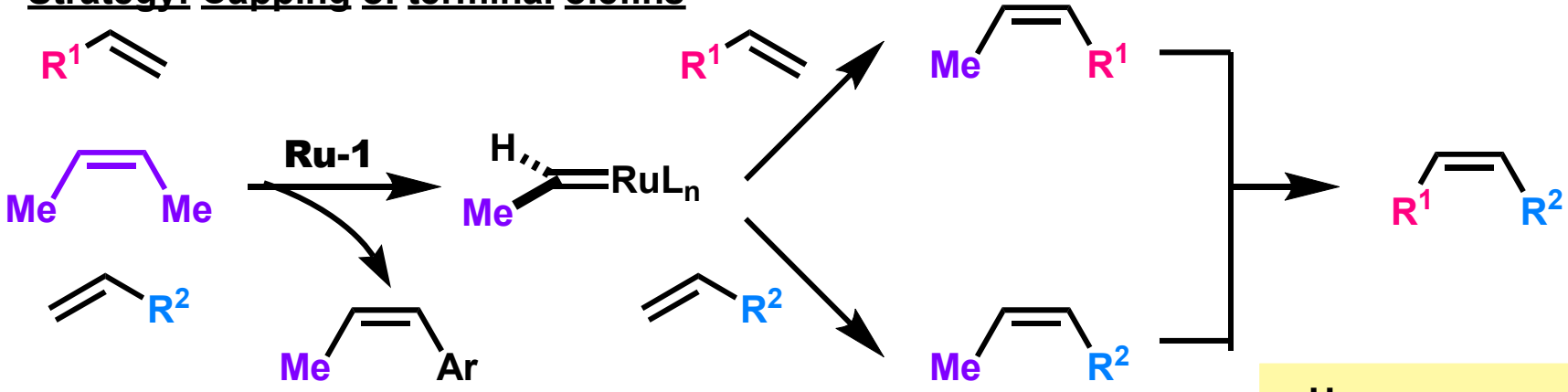
1) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.
2) 141213_LS_Kengo_Masuda

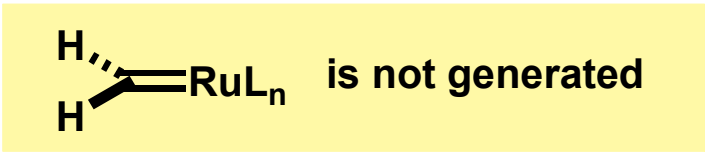
In Situ Methylene Capping





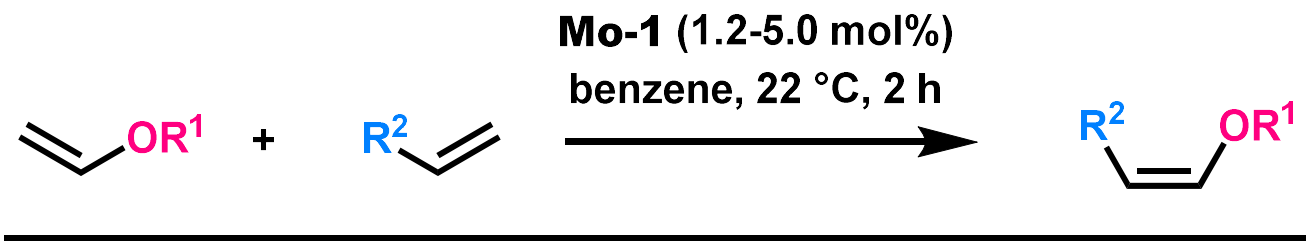
Strategy: Capping of terminal olefins



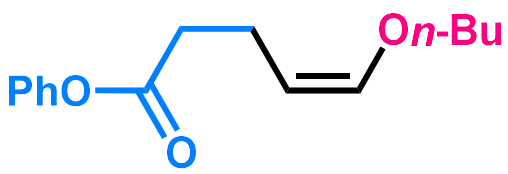


1) Xu, C.; Shen, X.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2017**, *139*, 10919.

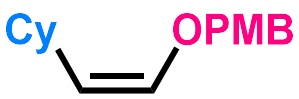
Z- Selective Cross Metathesis



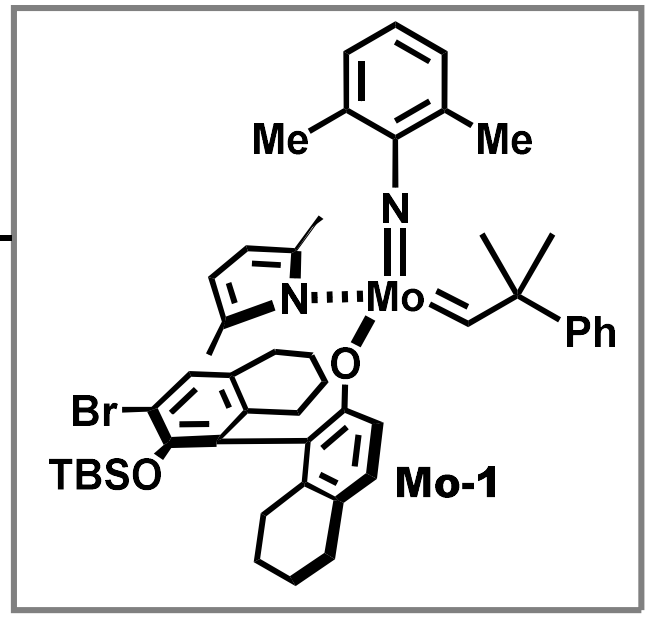
76% conv, 68% yield
98:2 *Z*:*E*

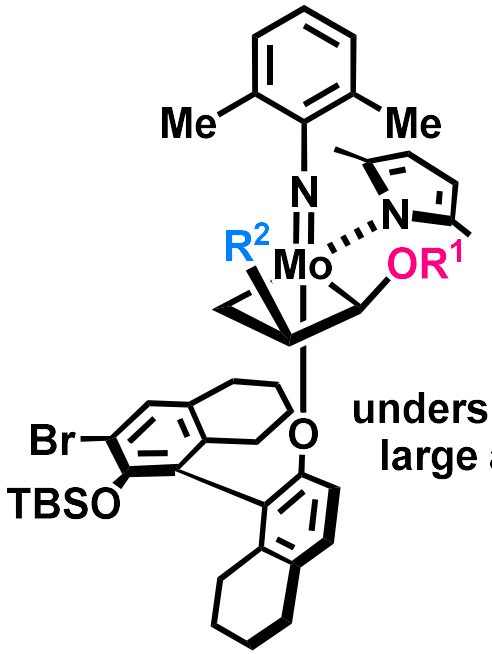


76% conv, 73% yield
98:2 *Z*:*E*

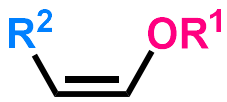


81% conv, 73% yield
>98:2 *Z*:*E*





underside is shielded by large aryloxide ligand



Z-isomer

1) Meek, S. J.; O'Brien, R. V.; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2011**, *471*, 461.

Introduction of Prof. Hoveyda

Prof. Amir H. Hoveyda

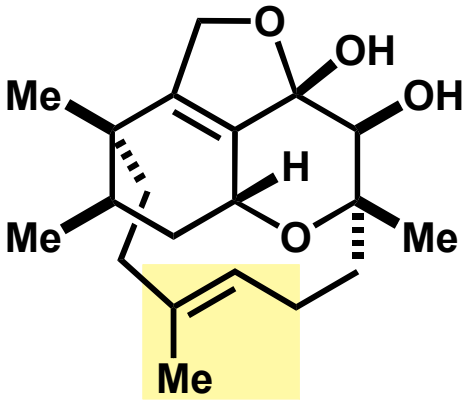
1981 B. A., @ Columbia University
1986 Ph.D., @ Yale University (Prof. Schreiber)
1986-1987, 1988-1990 Postdoctoral fellow @ Harvard University
1987-1988 Pfizer Central Research, Cancer Group
1990- Assistant Professor @ Boston University
1994- Professor @ Boston University
1998- Patricia and Joseph T. ’49 Vanderslice Millennium Professor of Chemistry @ Boston College
2014- Distinguished Visiting Professor @ Technion-Israel Institute of Technology
2019- Director of the Laboratories of Catalytic Chemical Synthesis at the University of Strasbourg

Research topic: catalysts for chemical synthesis, total synthesis of complex molecules

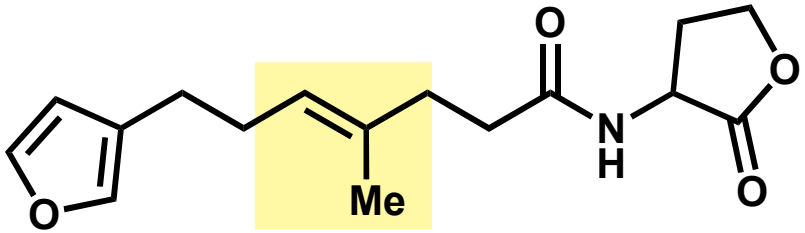
1) https://sites.bc.edu/amir-hoveyda

Contents

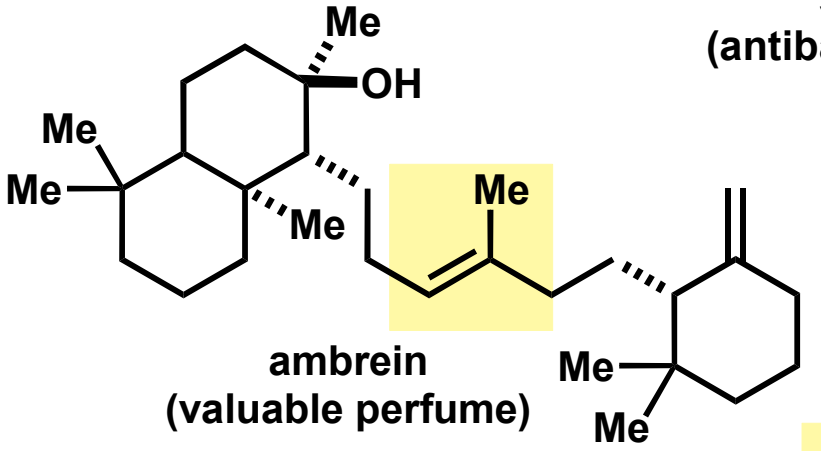
Trisubstituted Alkene in Natural Products



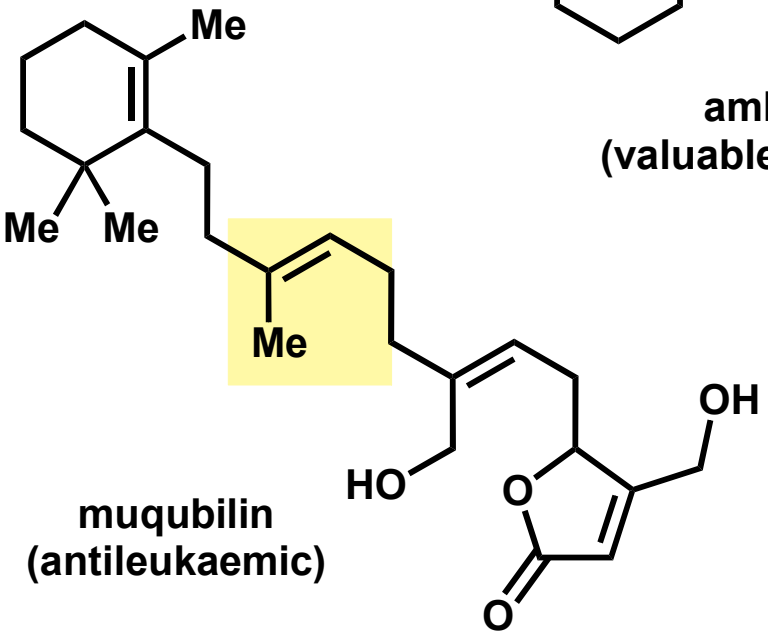
phemactin A
(PAF antagonist)



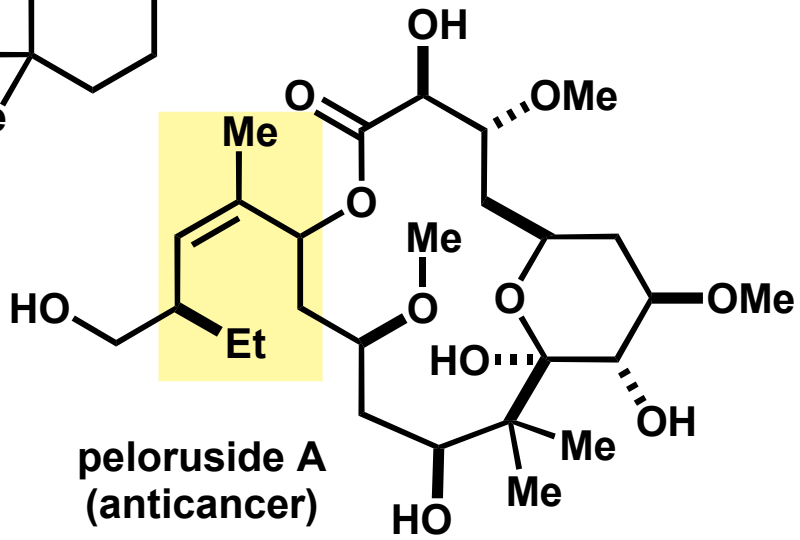
sponalisolide
(antibacterial, antifungal)



ambrein
(valuable perfume)



muqubilin
(antileukaemic)

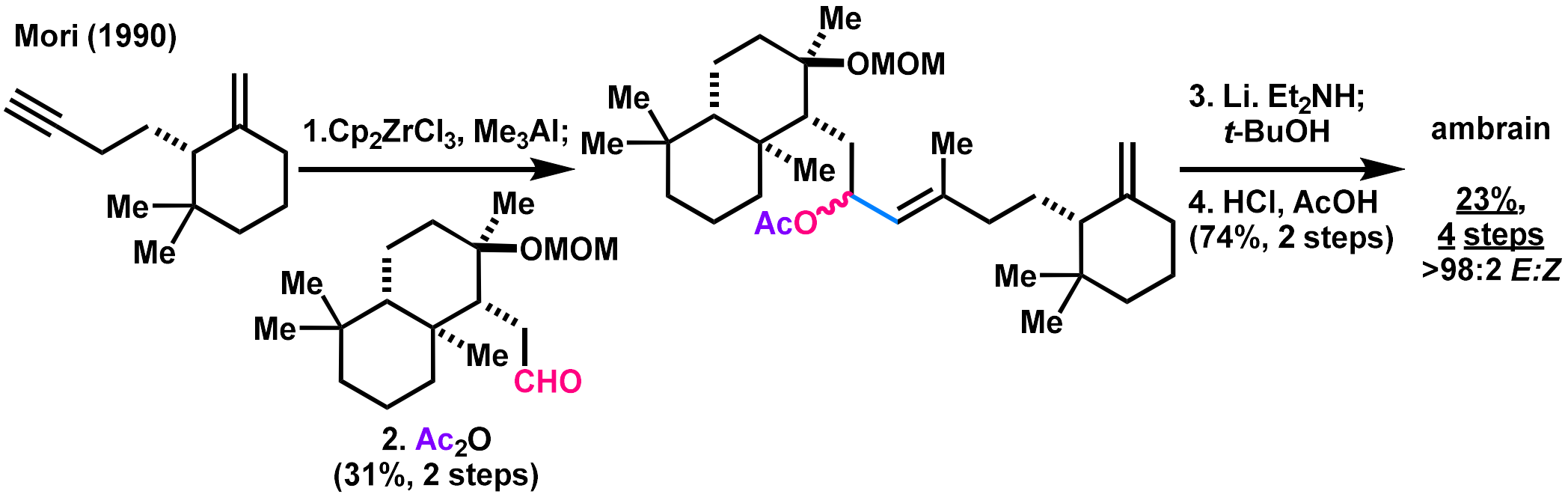


peloruside A
(anticancer)

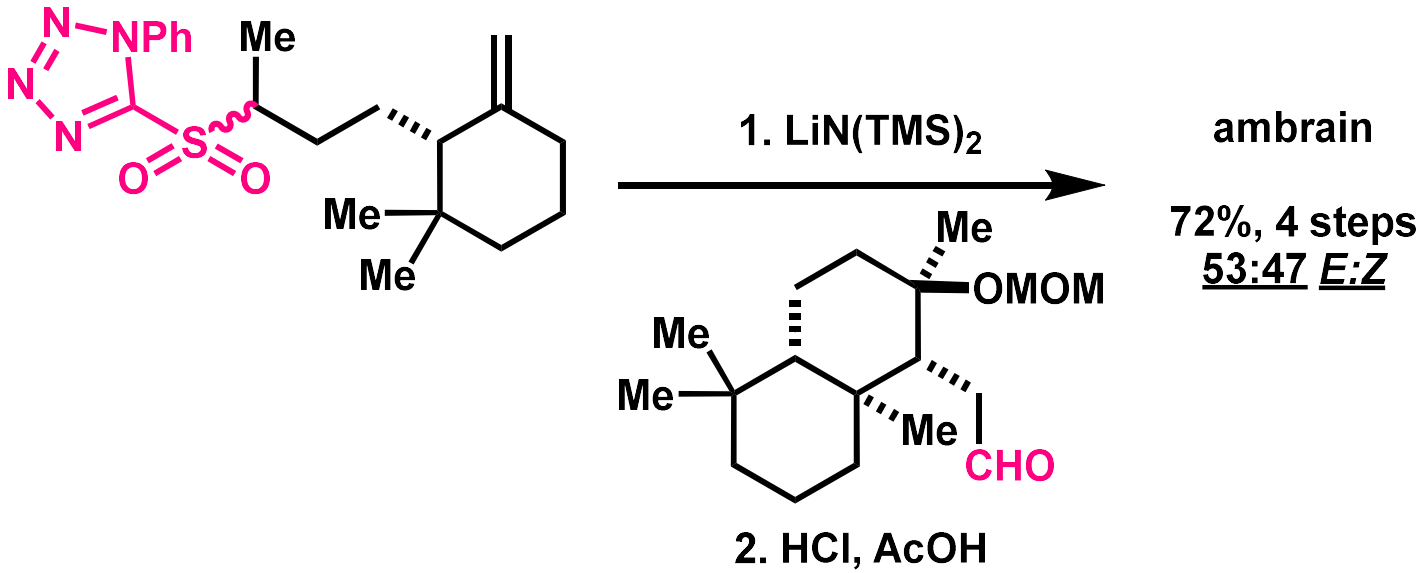
1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.

Approaches to Trisubstituted Alkene

Mori (1990)



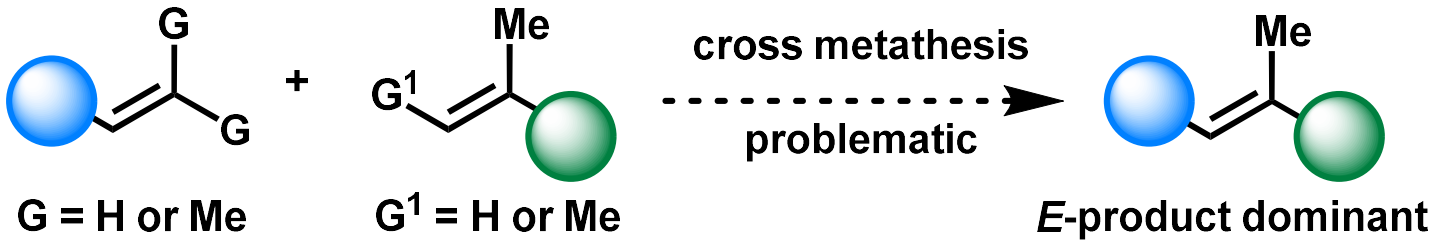
Akita (2006)



1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.
2) Mori, K.; Tamura, H. *Liebigs Ann. Chem.* **1990**, 361.
3) Fujiwara, N.; Kinoshita, M.; Akita, H. *Tetrahedron: Asymm.* **2006**, *17*, 3037.

Strategies using Cross Metathesis

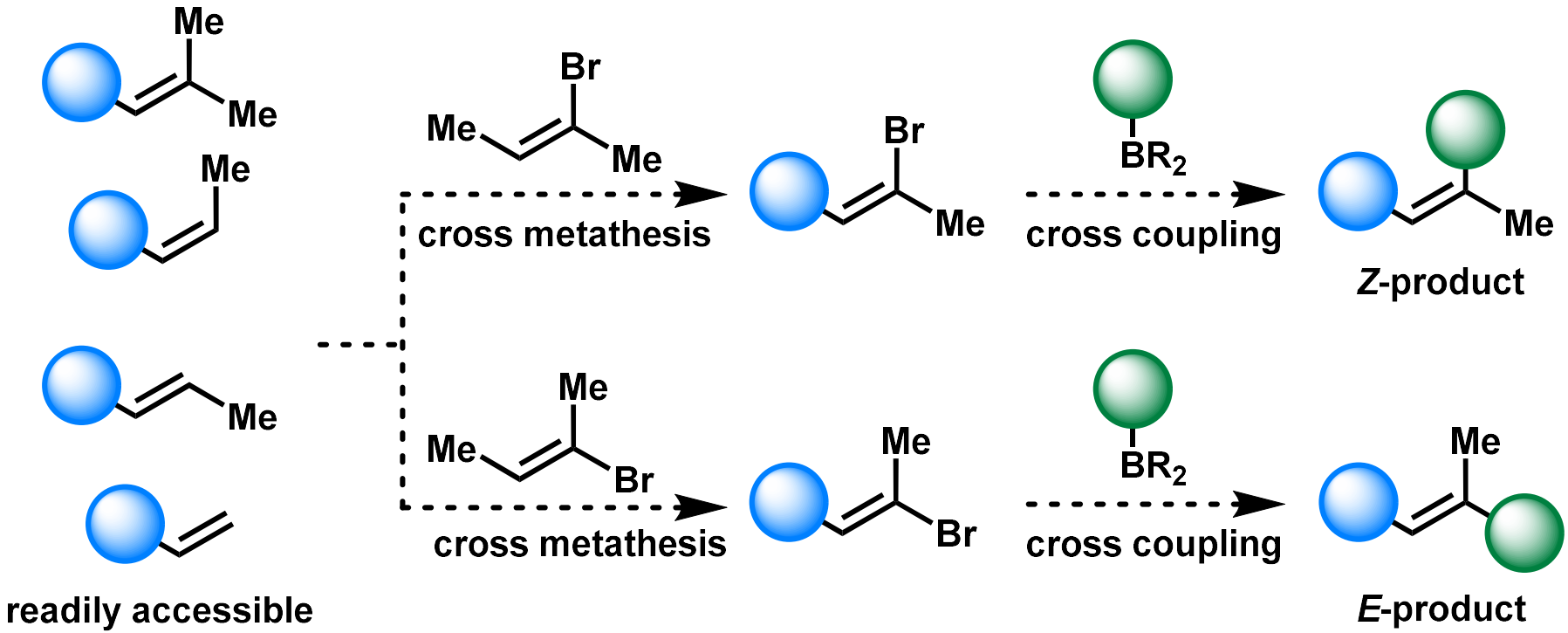
Direct cross metathesis



G or G^1= H: Homo-metathesis, unstable methylidene complex

G or G^1= Me: Low reactivity

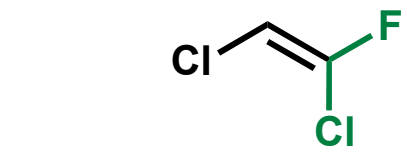
2 steps strategy



1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.

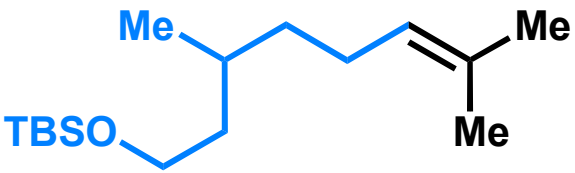
CM of Two Trisubstituted Alkenes

Previous study

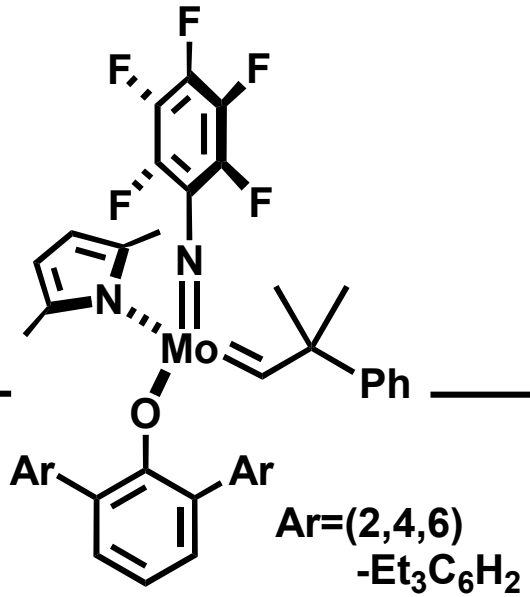


(5.0 eq, 94:6 *Z*:*E*)

+

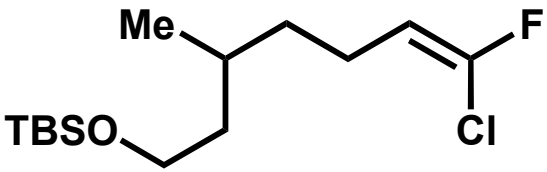


(1.0 eq)



Ar=(2,4,6)
-$Et_3C_6H_2$

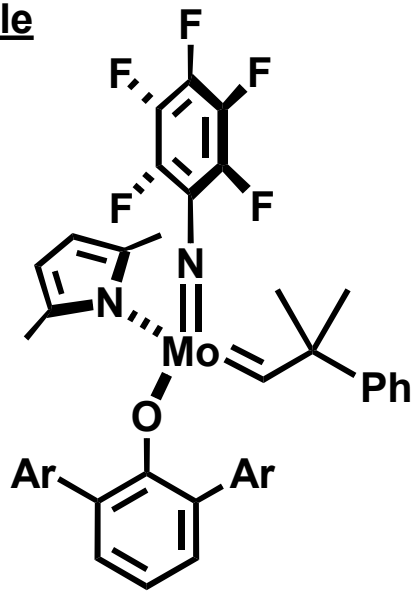
Mo-1a (5.0 mol%)
benzene, 22 °C, 12 h



without additive: 5% conv

with  (10 mol%):
76% conv, 70% yield

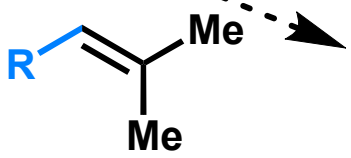
Rationale

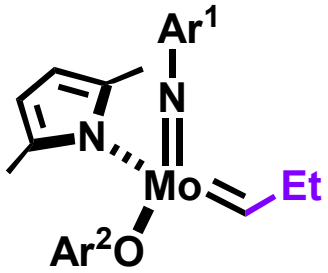


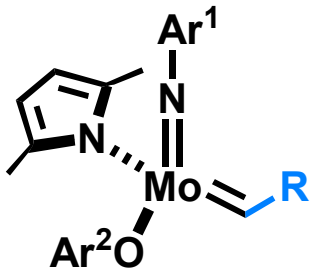
Mo-1a

fast

slow





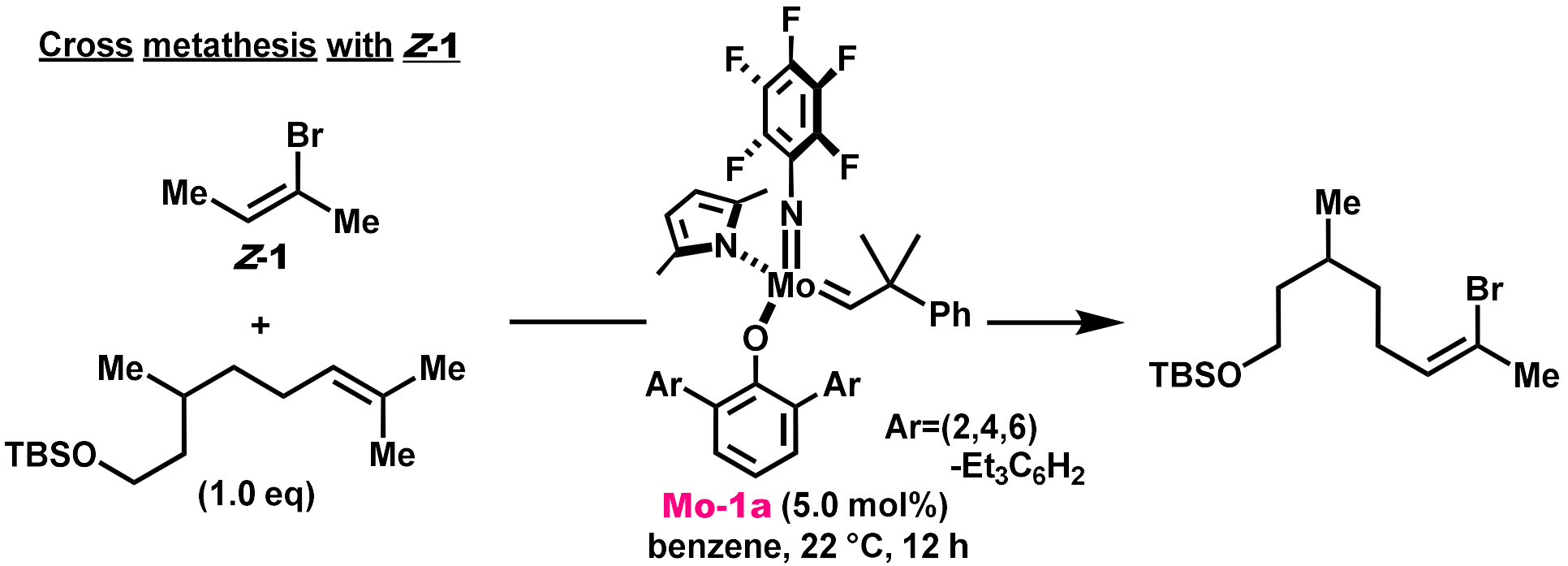


more reactive
than **Mo-1a**

1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.
2) Liu, Q.; Mu, Y.; Koengeter, T.; Schrock, R. R.; Hoveyda, A. H. *Nat. Chem.* **2022**, *14*, 463.

Small Alkene Additive

Cross metathesis with *Z*-1

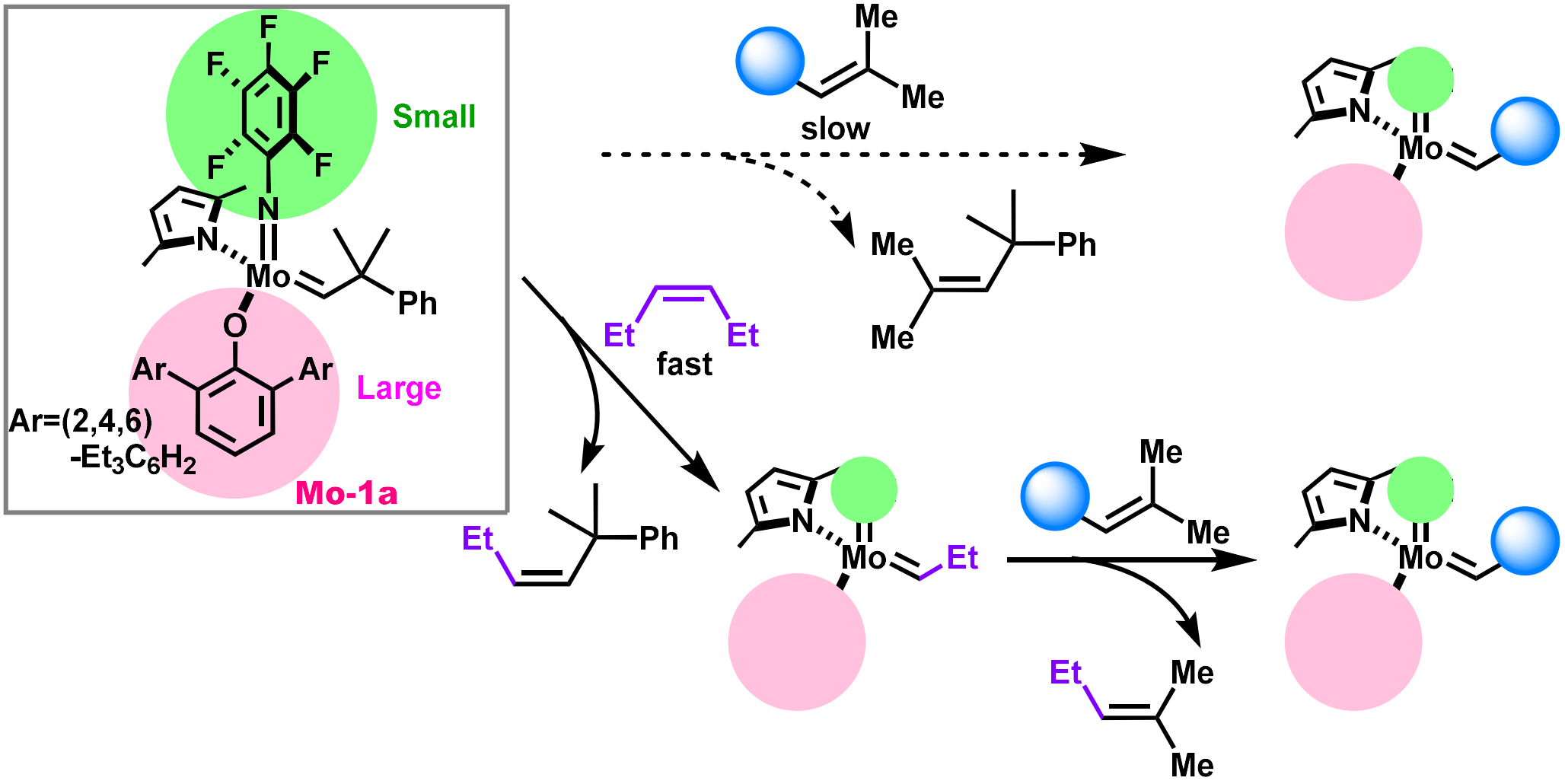


Z-1	Et Et	results
2.0 eq	-	66% conv. 59% yield, >98:2 *Z*:*E*
2.0 eq	10 mol%	71% conv. 66% yield, >98:2 *Z*:*E*
5.0 eq	-	83% conv. 68% yield, 95:5 *Z*:*E*
5.0 eq	10 mol%	89% conv. 82% yield, 95:5 *Z*:*E*

1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.

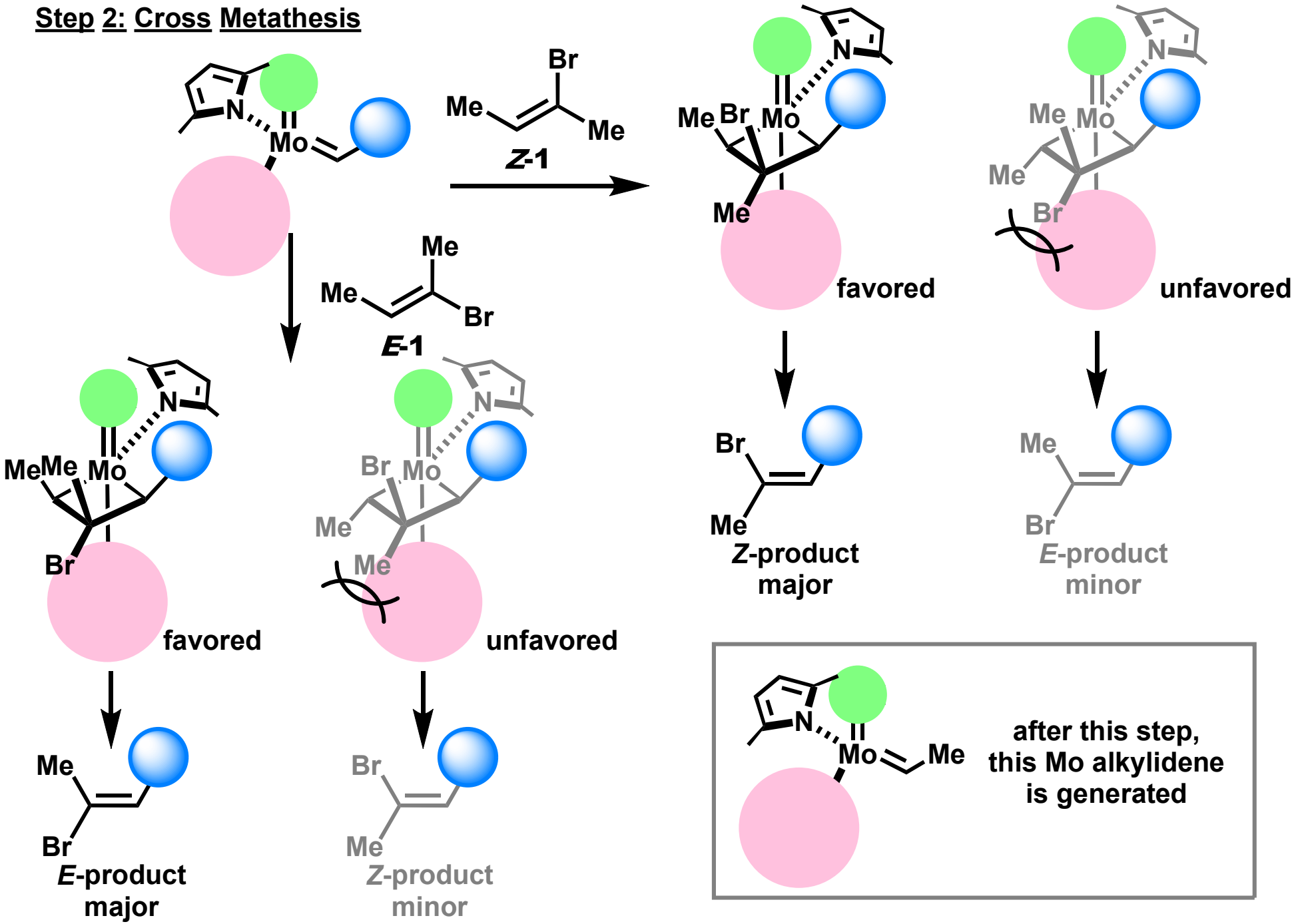
Catalytic Cycle (1)

Step 1: Catalyst initiation



Catalytic Cycle (2) and *E/Z*- Selectivity

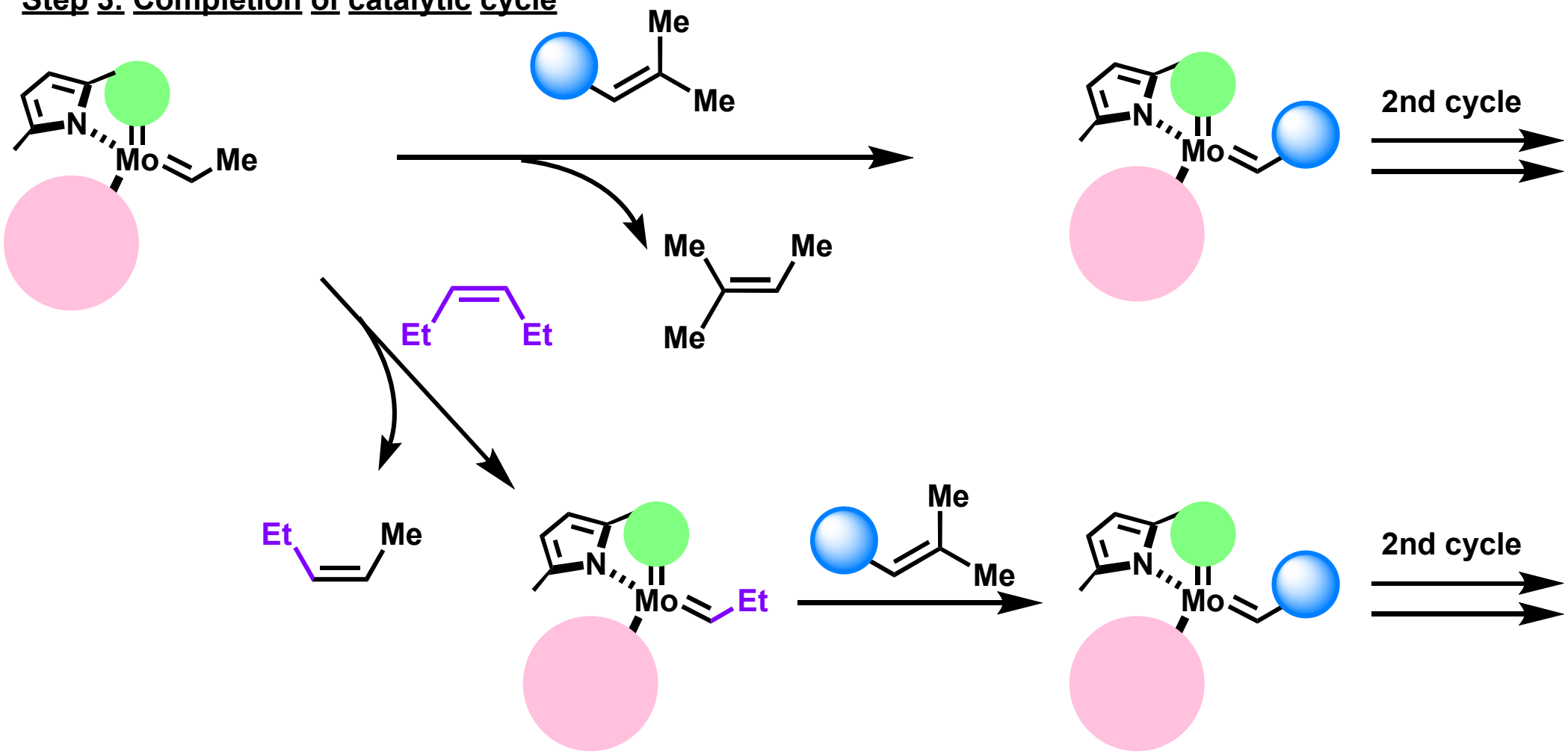
Step 2: Cross Metathesis



1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.
2) Nguyen, T. T.; Koh, M. J.; Mann, T. J.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2017**, *552*, 347.

Catalytic Cycle (3)

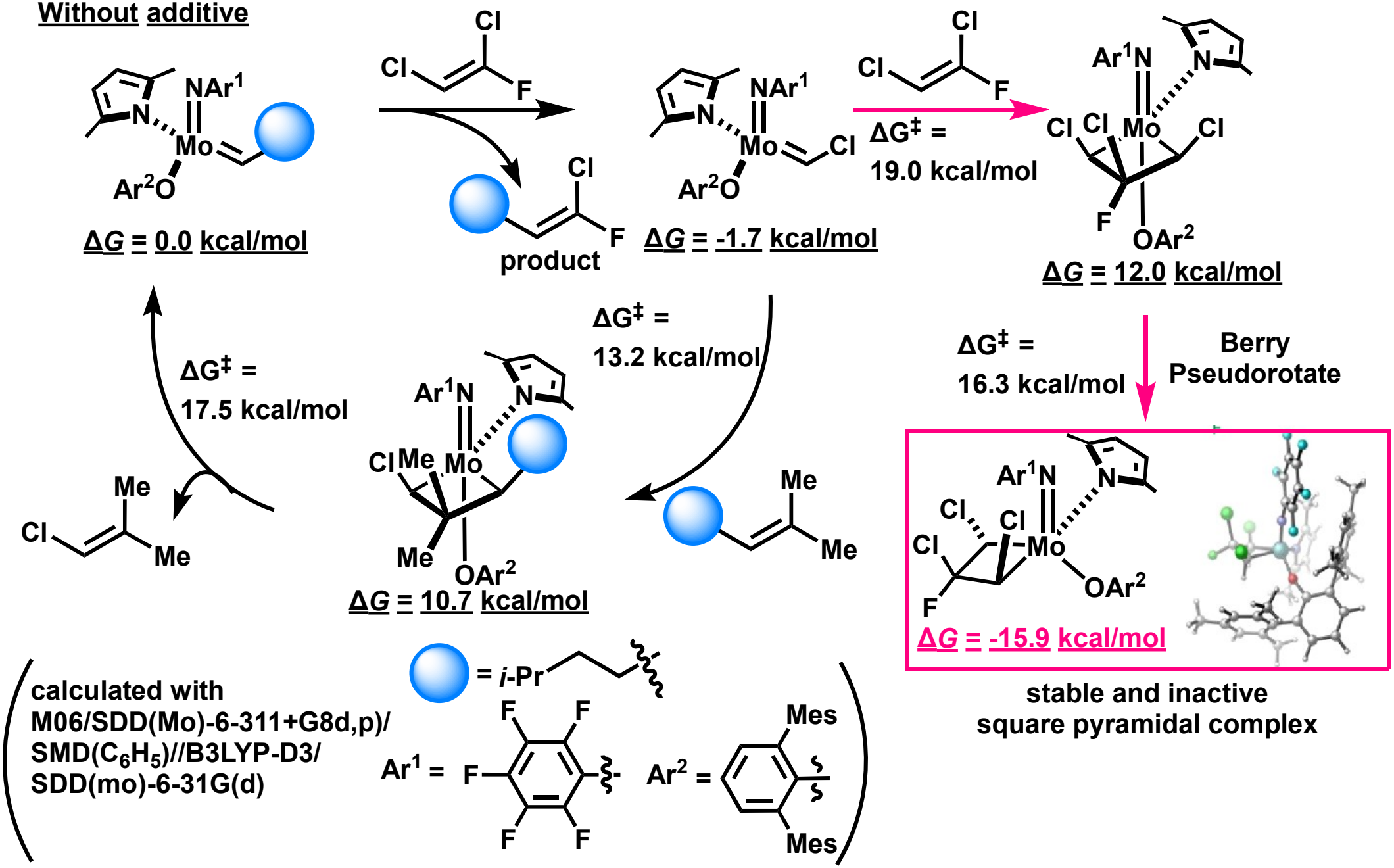
Step 3: Completion of catalytic cycle



1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.

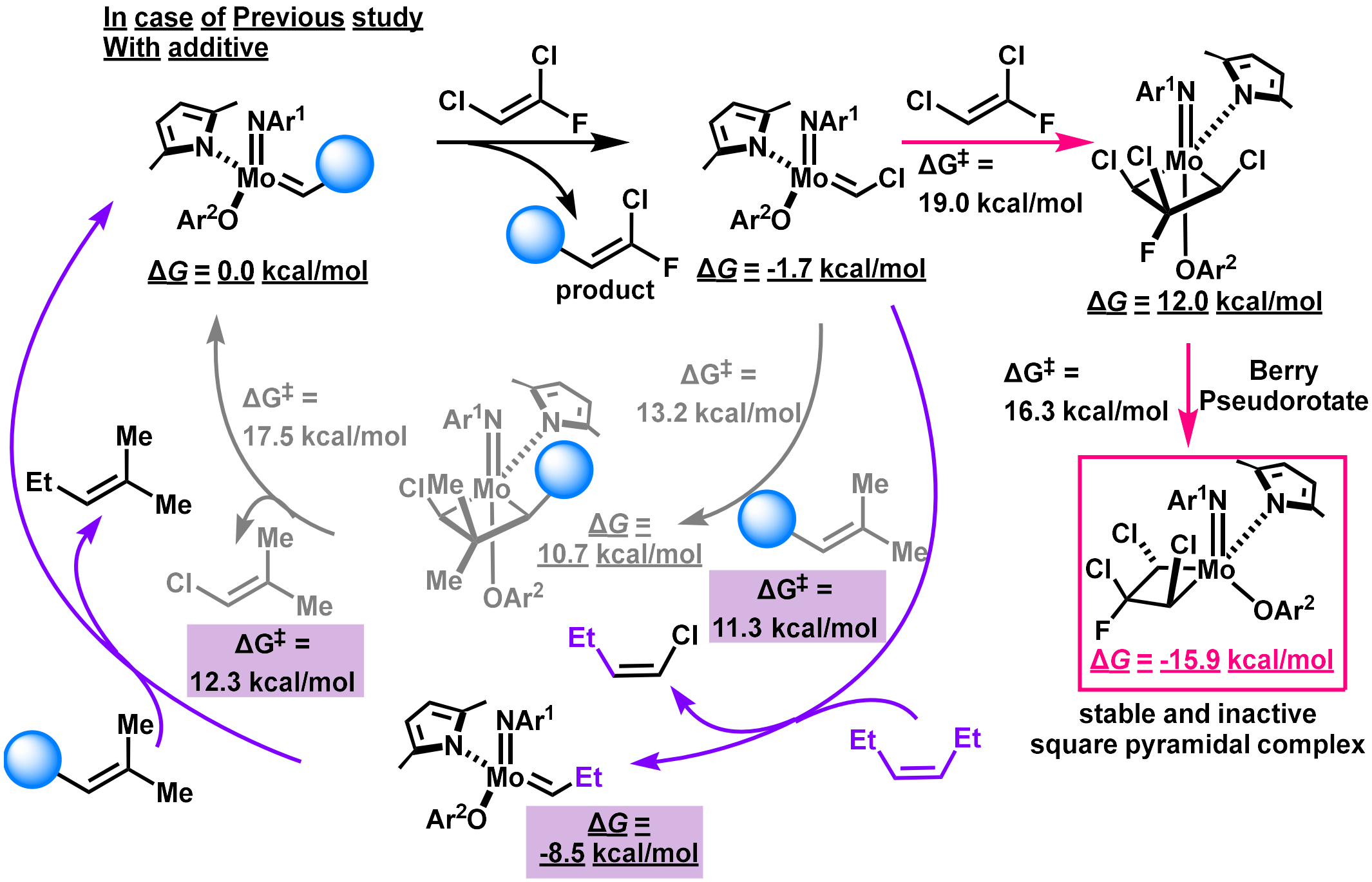
Roles of Small Alkene Additive (1)

In case of Previous study
Without additive



1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.
2) Liu, Q.; Mu, Y.; Koengeter, T.; Schrock, R. R.; Hoveyda, A. H. *Nat. Chem.* **2022**, *14*, 463

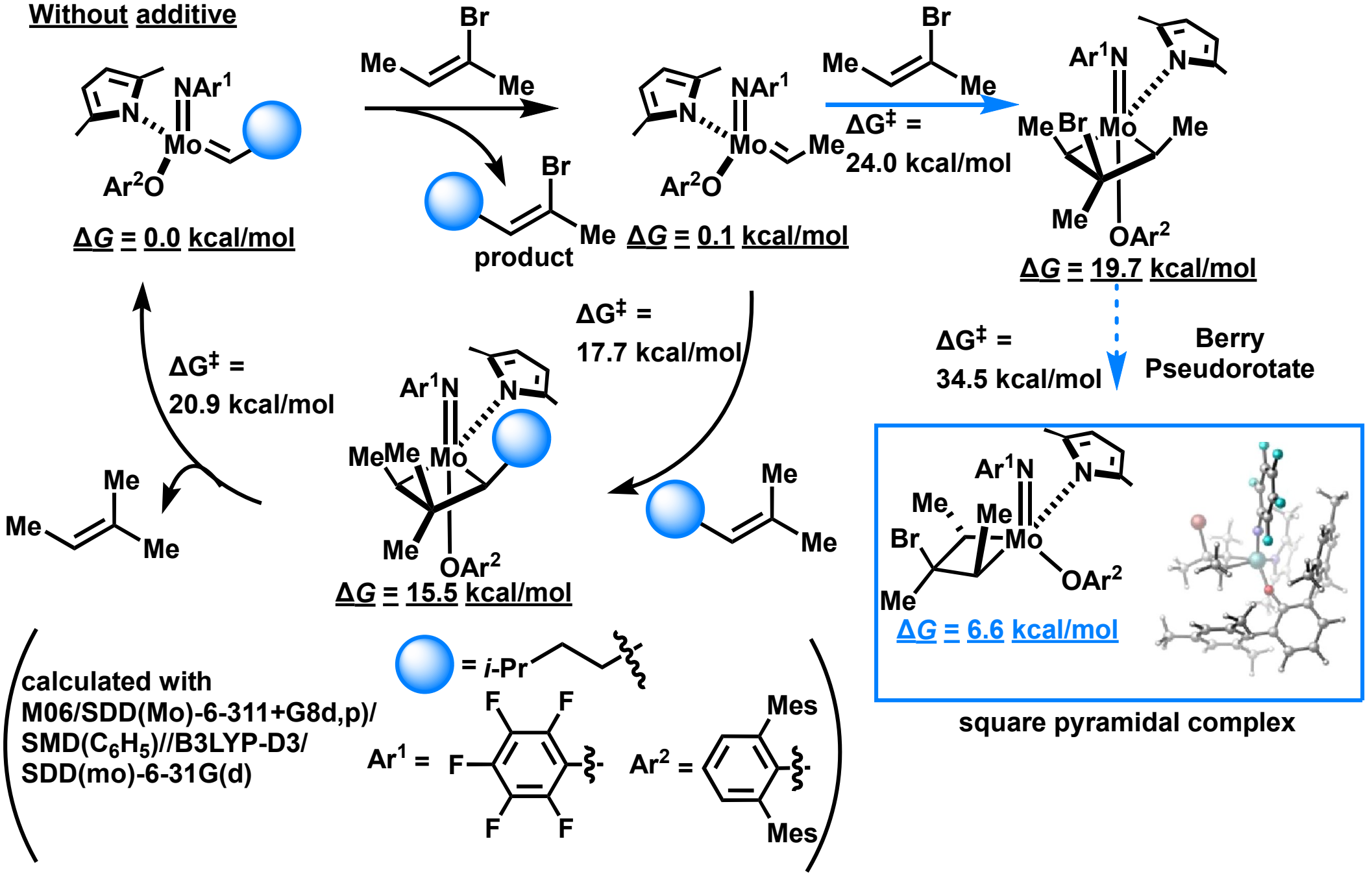
Roles of Small Alkene Additive (2)



1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.
2) Liu, Q.; Mu, Y.; Koengeter, T.; Schrock, R. R.; Hoveyda, A. H. *Nat. Chem.* **2022**, *14*, 463

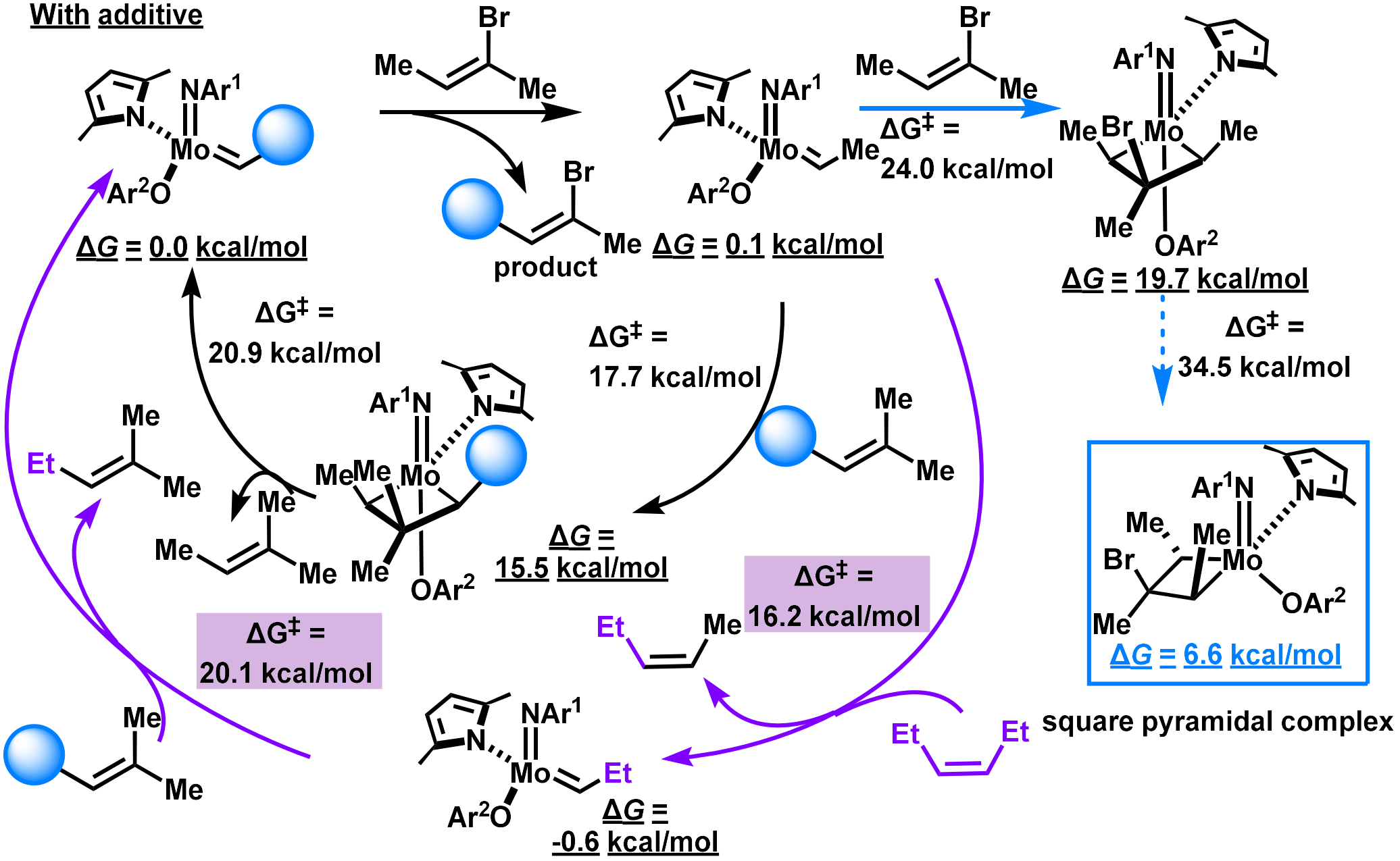
Roles of Small Alkene Additive (3)

In case of main paper
Without additive



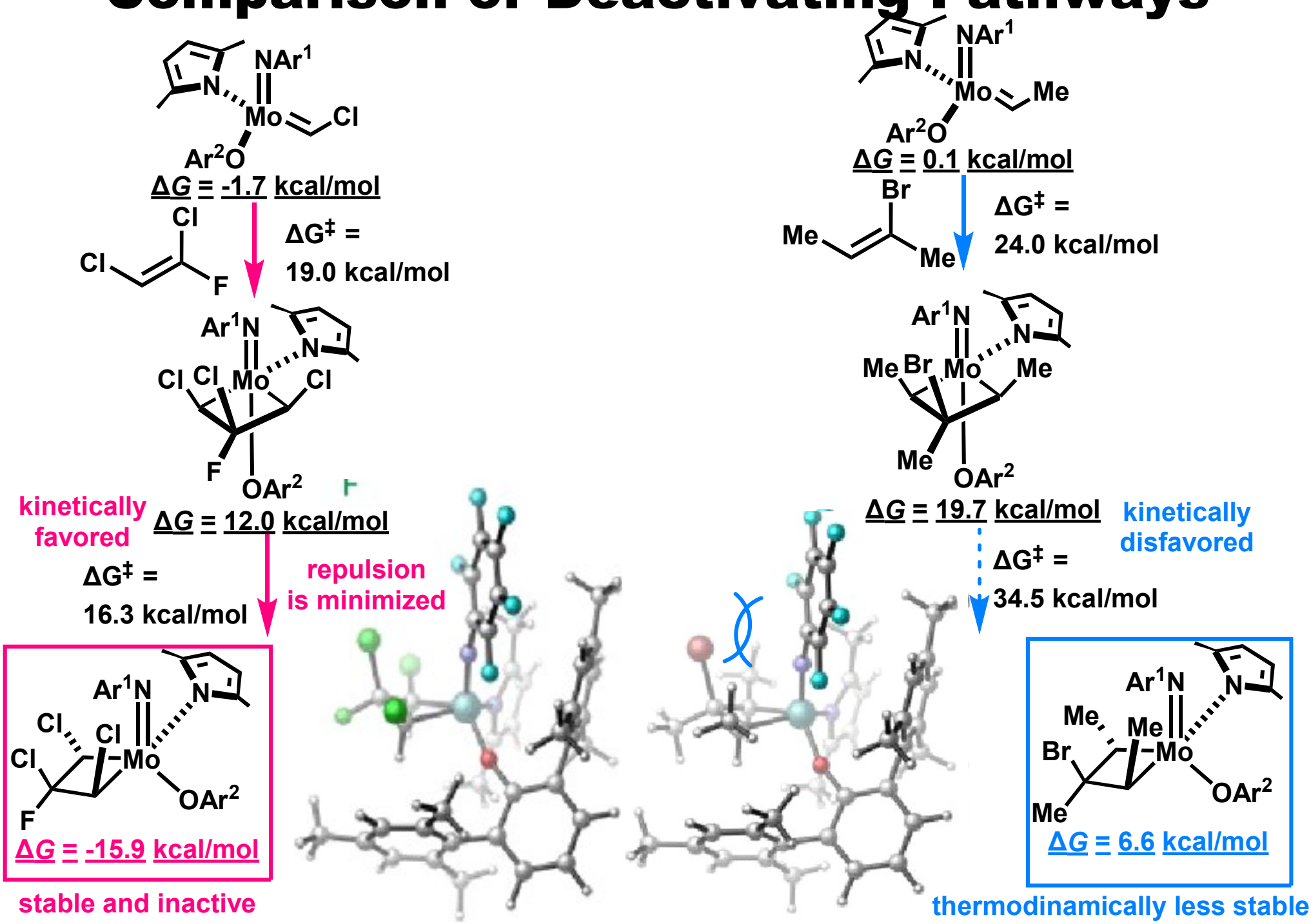
1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.

Roles of Small Alkene Additive (4)



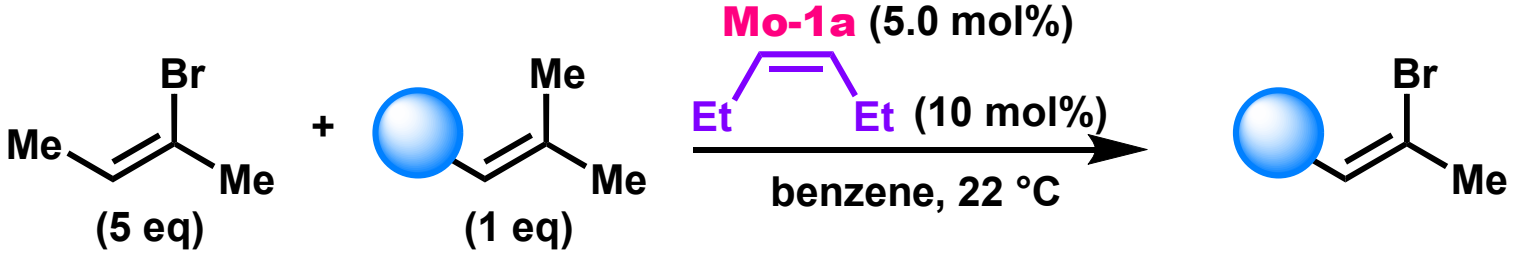
1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.

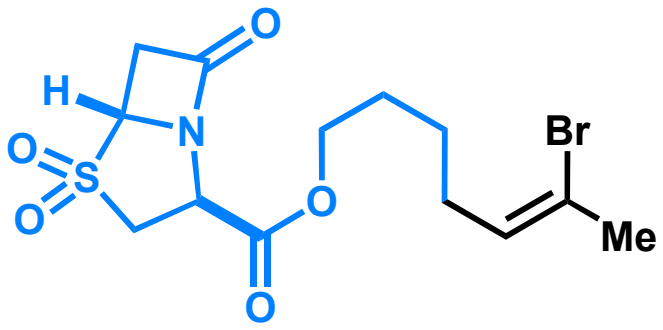
Comparison of Deactivating Pathways



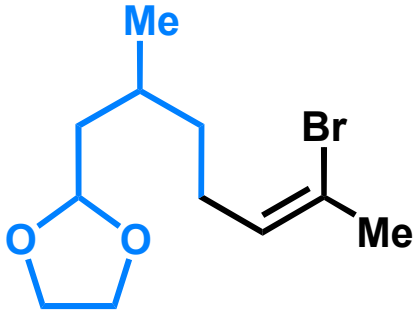
1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.
2) Liu, Q.; Mu, Y.; Koengeter, T.; Schrock, R. R.; Hoveyda, A. H. *Nat. Chem.* **2022**, *14*, 463

Substrate Scope (1)
-Trisubstituted Alkenes (*Z*)-

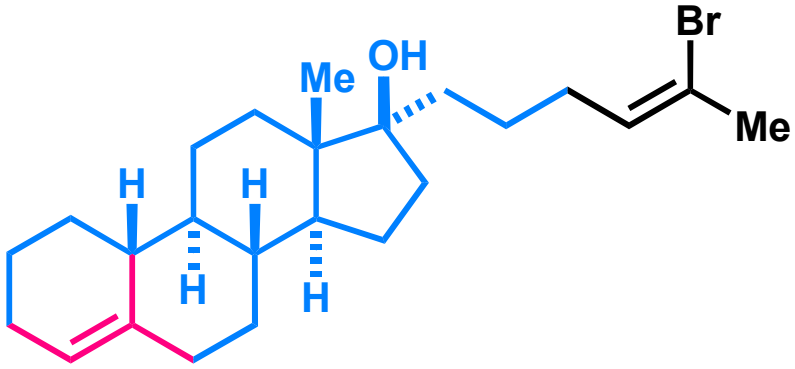




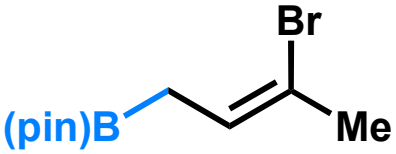
70% conv, 58% yield
>98:2 *Z*:*E*



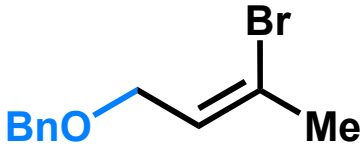
81% conv, 73% yield
95:5 *Z*:*E*



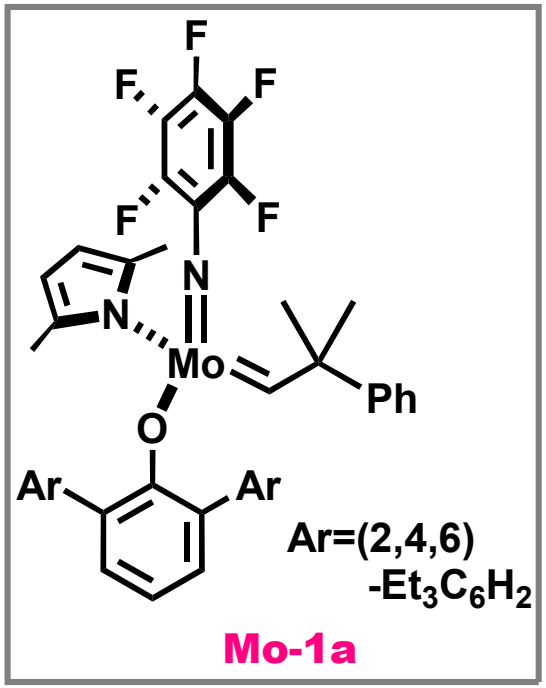
76% conv, 53% yield
93:7 *Z*:*E*



89% conv, 74% yield
95:5 *Z*:*E*

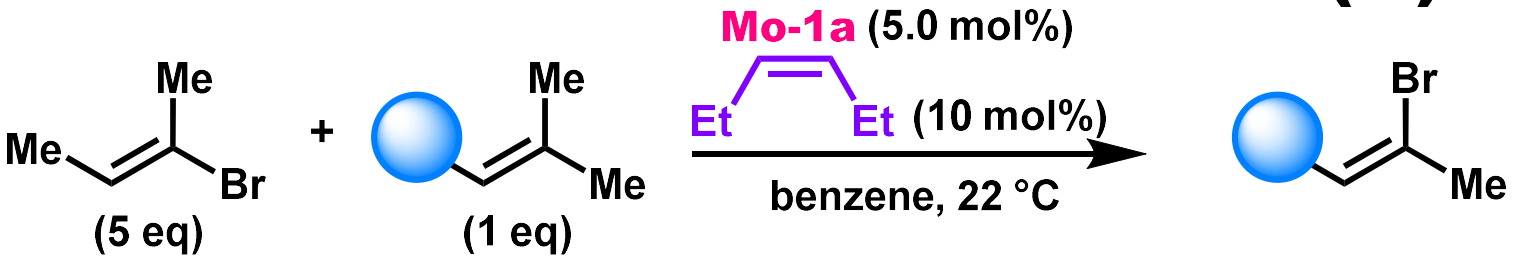


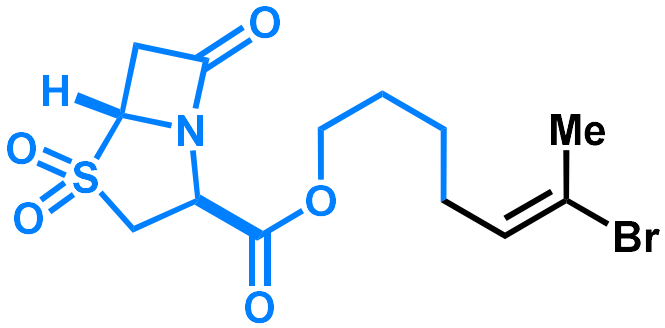
58% conv, 49% yield
97:3 *Z*:*E*



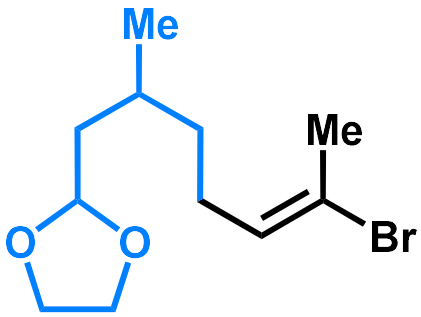
1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.

Substrate Scope (2)
-Trisubstituted Alkenes (*E*)-

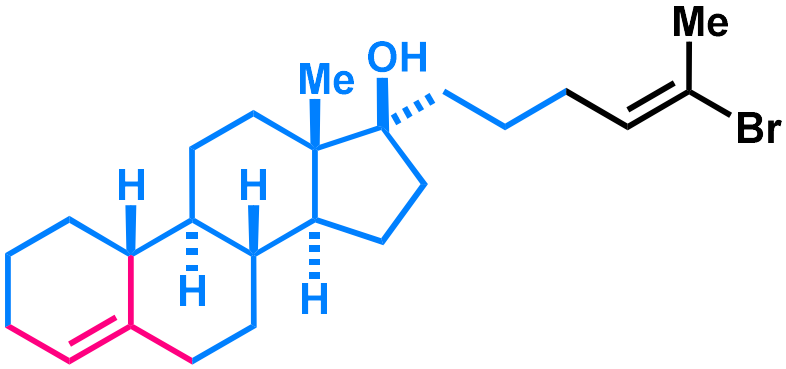




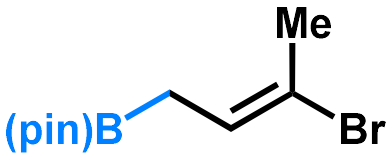
60% conv, 49% yield
98:2 *E*:*Z*



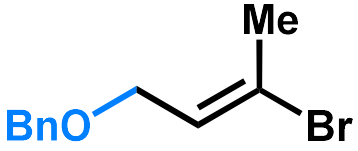
83% conv, 71% yield
>98:2 *E*:*Z*



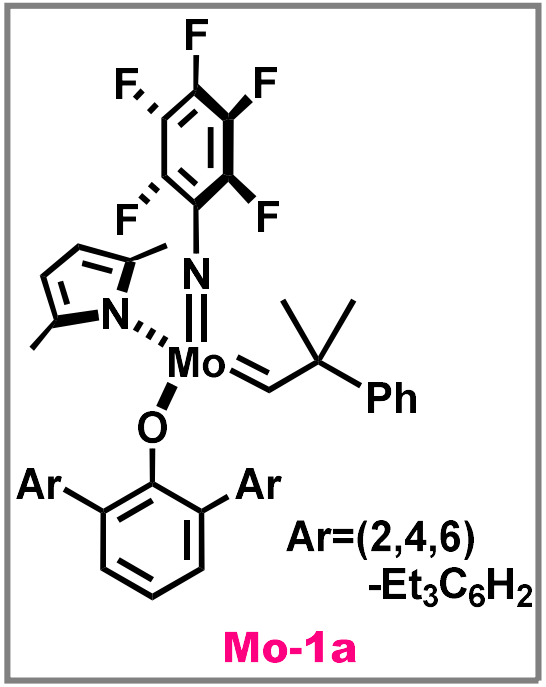
67% conv, 48% yield
>98:2 *E*:*Z*



74% conv, 55% yield
90:10 *E*:*Z*

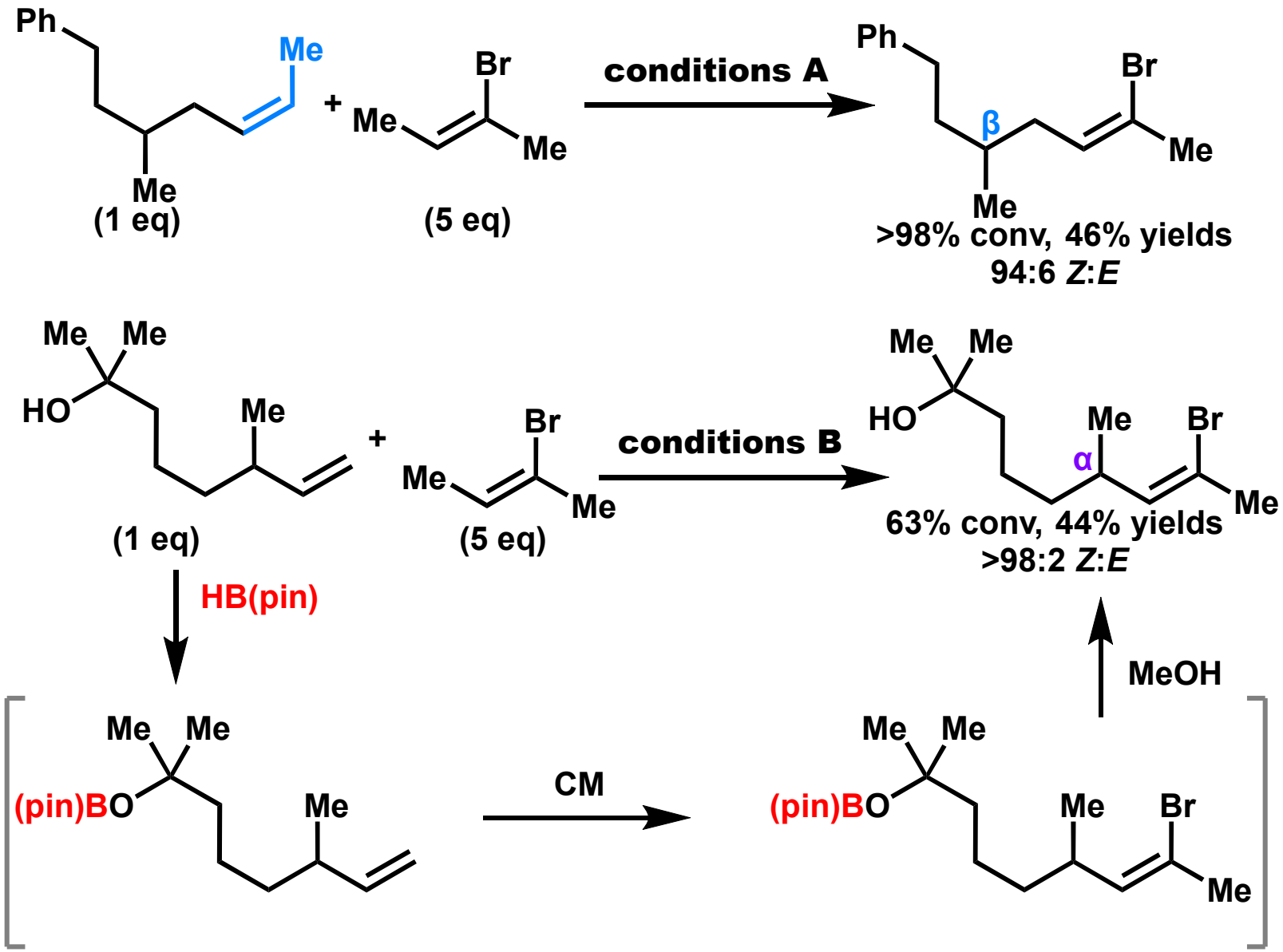


67% conv, 57% yield
>98:2 *E*:*Z*



1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.

Substrate Scope (3)
-Sterically Demanding Alkenes-



conditions A:
Mo-1a (5.0 mol%)

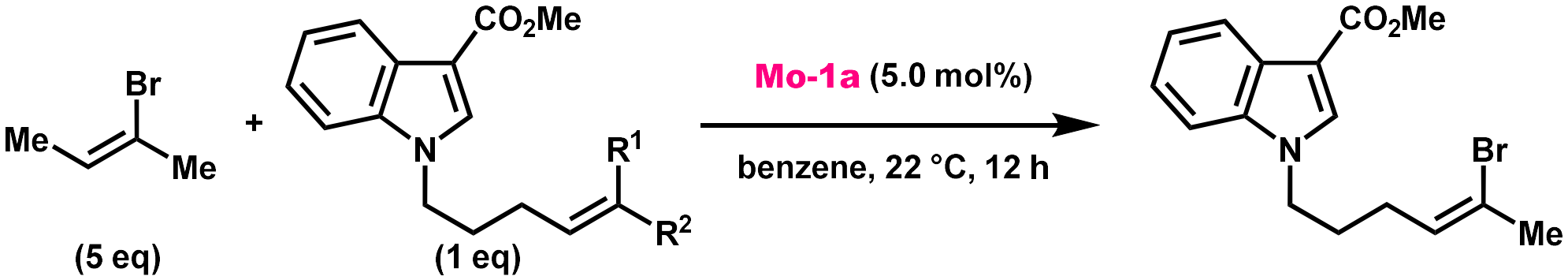
(10 mol%)
benzene, 22 °C, 12 h

conditions B:
traceless protection
HB(pin) (2 eq)
NEt_3 (10 mol%)
50 °C, 2 h;
1.0 Torr, 30 min;
Mo-1a (5.0 mol%)

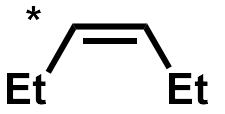
(10 mol%)
benzene, 22 °C, 12 h;
MeOH

1) Koengeter, T.; Qin, C.; Mai, B. K.: Liu, Q.; Mu, Y.; Liu, P.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2023**, *145*, 3774.

Effects of Alkene-Substitution

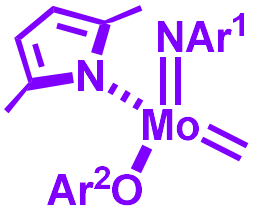


substitution	conv, conv to CM product	selectivity	yield
$R^1 = R^2 = H$	89%, 52%	>98:2 *Z*:*E*	54%
$R^1 = Me, R^2 = H$	>98%, 77%	97:3 *Z*:*E*	80%
$R^1 = H, R^2 = Me$	>98%, 62%	98:2 *Z*:*E*	64%
$R^1 = R^2 = Me^*$	66%, 61%	98:2 *Z*:*E*	62%



(6.0 mol%) was added

substitutions	efficiency	homo metathesis
$R^1 = R^2 = H$	high	much, generates methylidene
$R^1 = Me, R^2 = H$ and $R^1 = H, R^2 = Me$	middle	less, no methyliedne
$R^1 = R^2 = Me$	low	none



methylidene complex (unstable)

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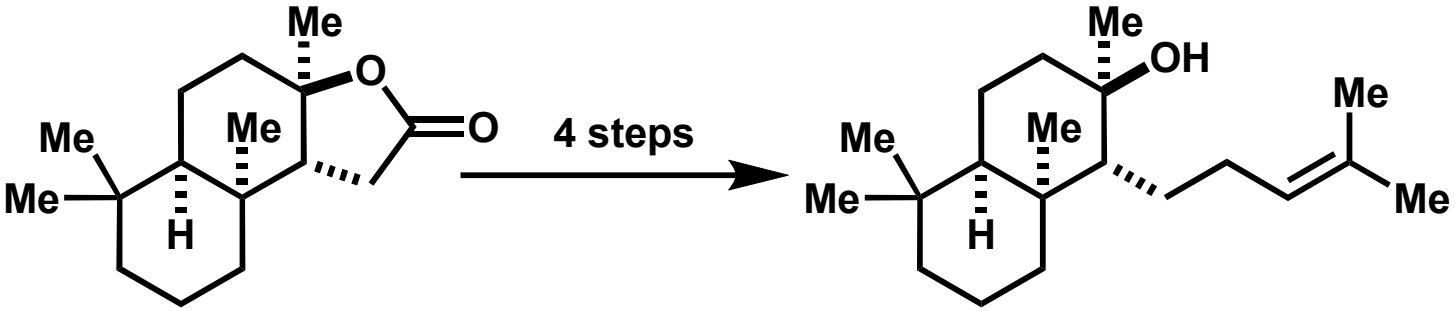
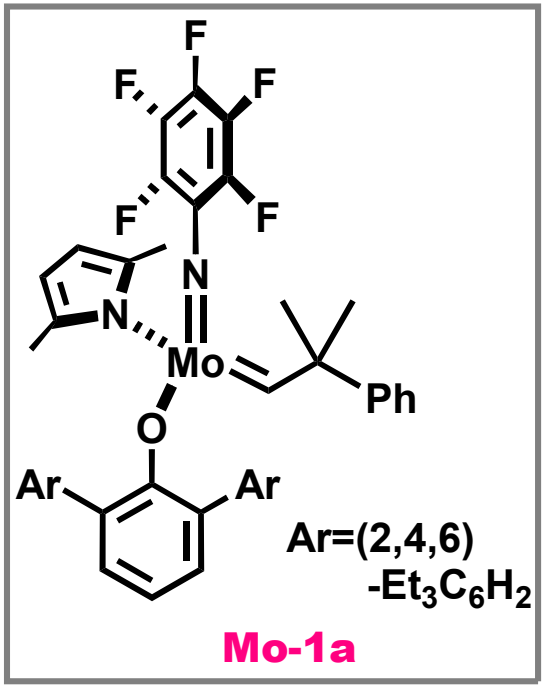
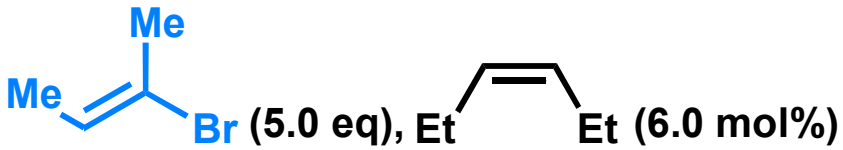
Total Synthesis of Ambrein (1)





1. HB(pin), NEt_3 (cat.), 80 °C, 2 h
   1.0 Torr, 50 °C, 15 min;
   Mo-1a (2.0 mol%),

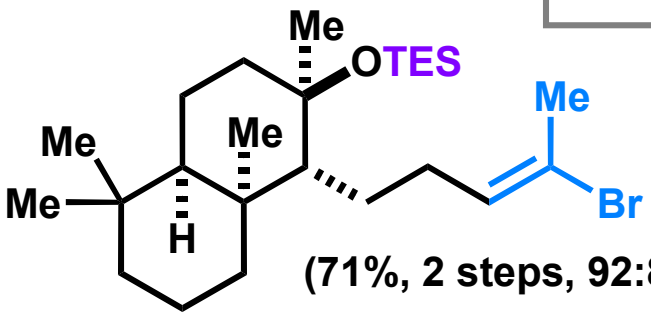


(5.0 eq),

(6.0 mol%)

benzene, 22 °C; MeOH

2. TESCl, imodazole, DMF, 22 °C



(71%, 2 steps, 92:8 *E*:*Z*)

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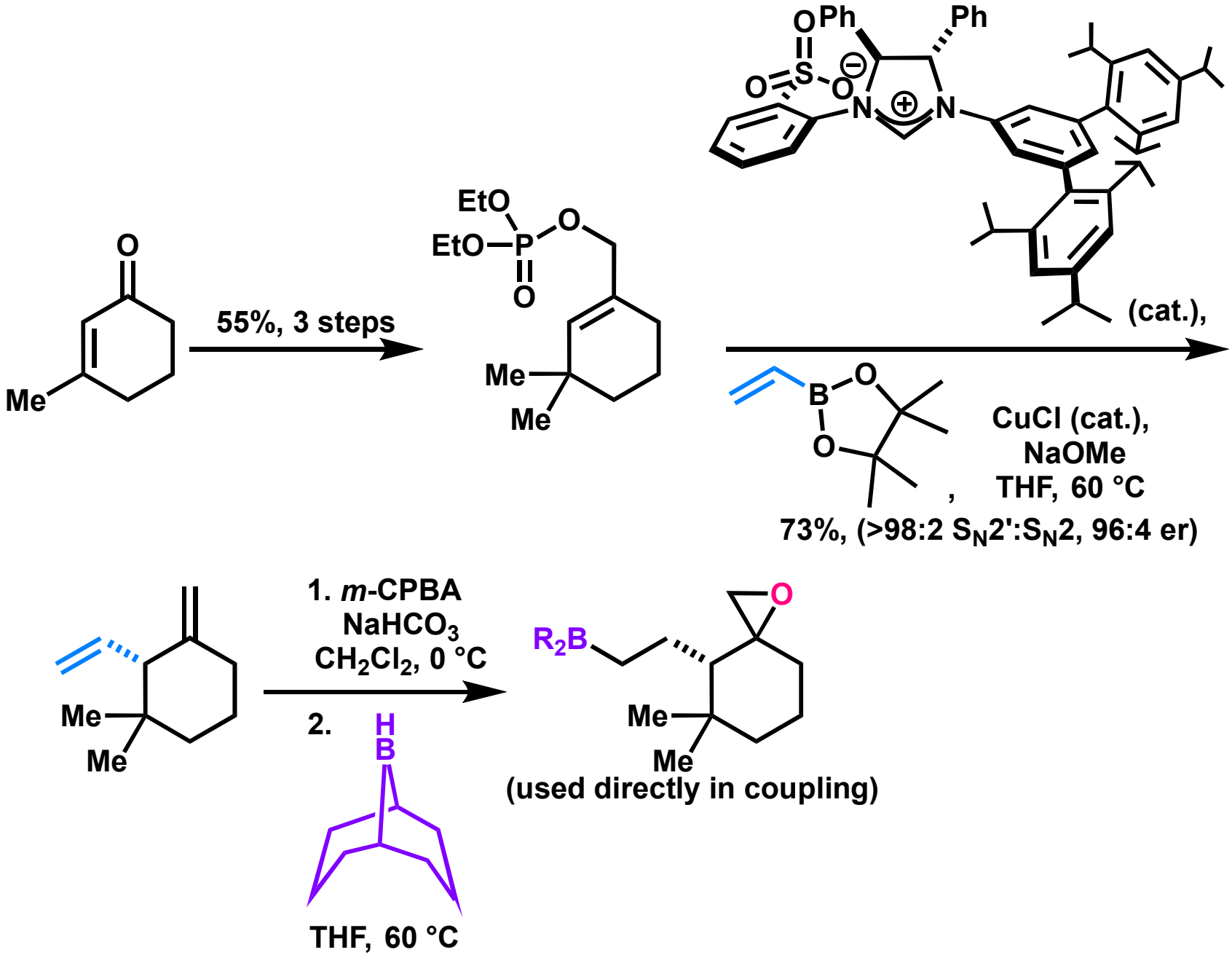
Total Synthesis of Ambrein (2)



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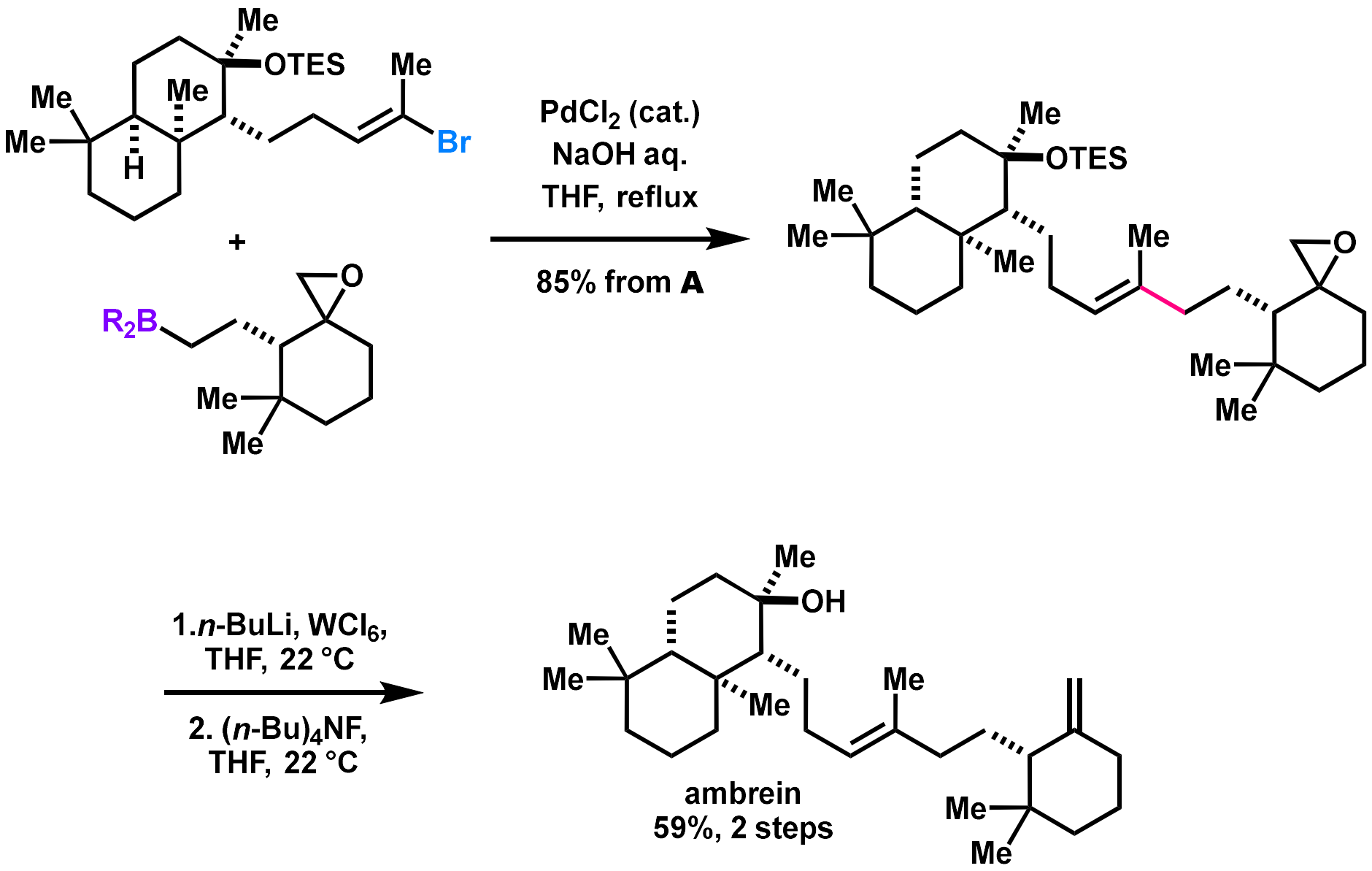
Total Synthesis of Ambrein (3)



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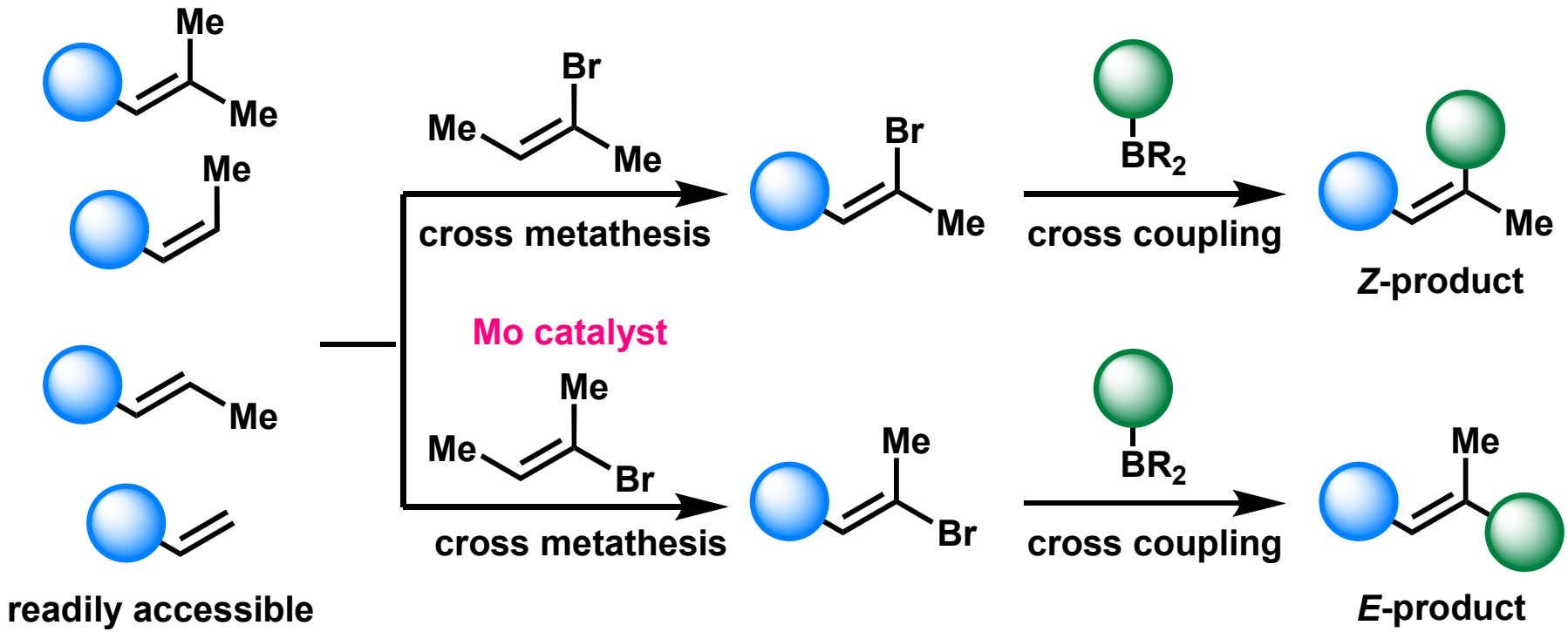
Summary



Total synthesis of ambrein