Brook Rearrangement as Trigger for Carbene Generation: Synthesis of Stereodefined and Fully Substituted Cyclobutenes

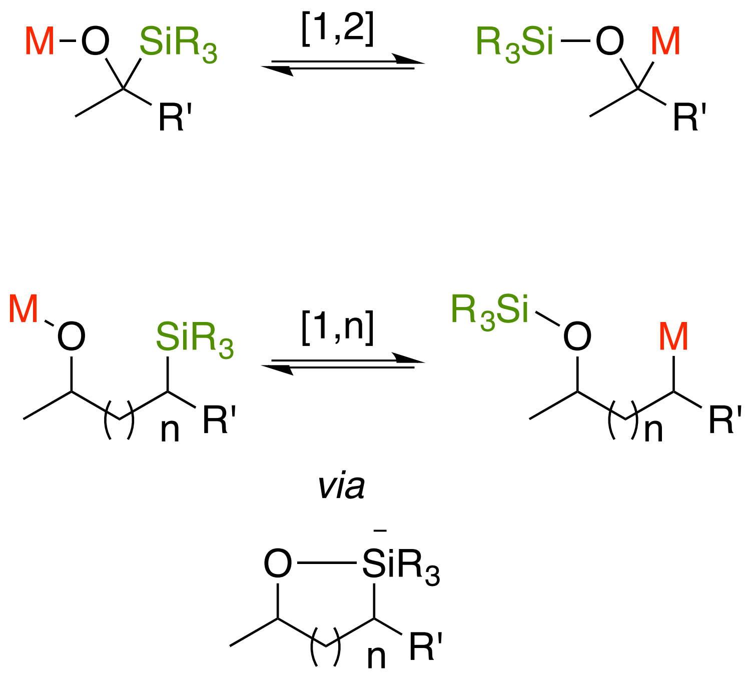
F. Ahang and Ilan Marek

J. Am. Chem. Soc. **2017**, *139*, 8364-8370.

06/24/17

Mike Frasso

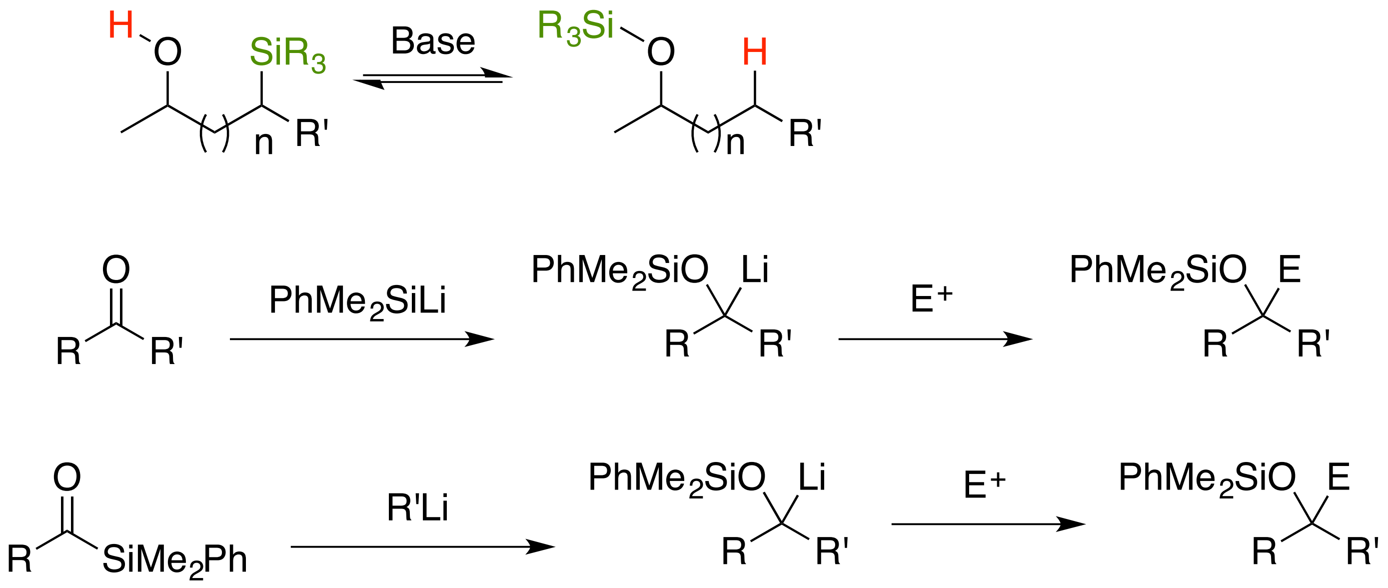
General Brook Rearrangement



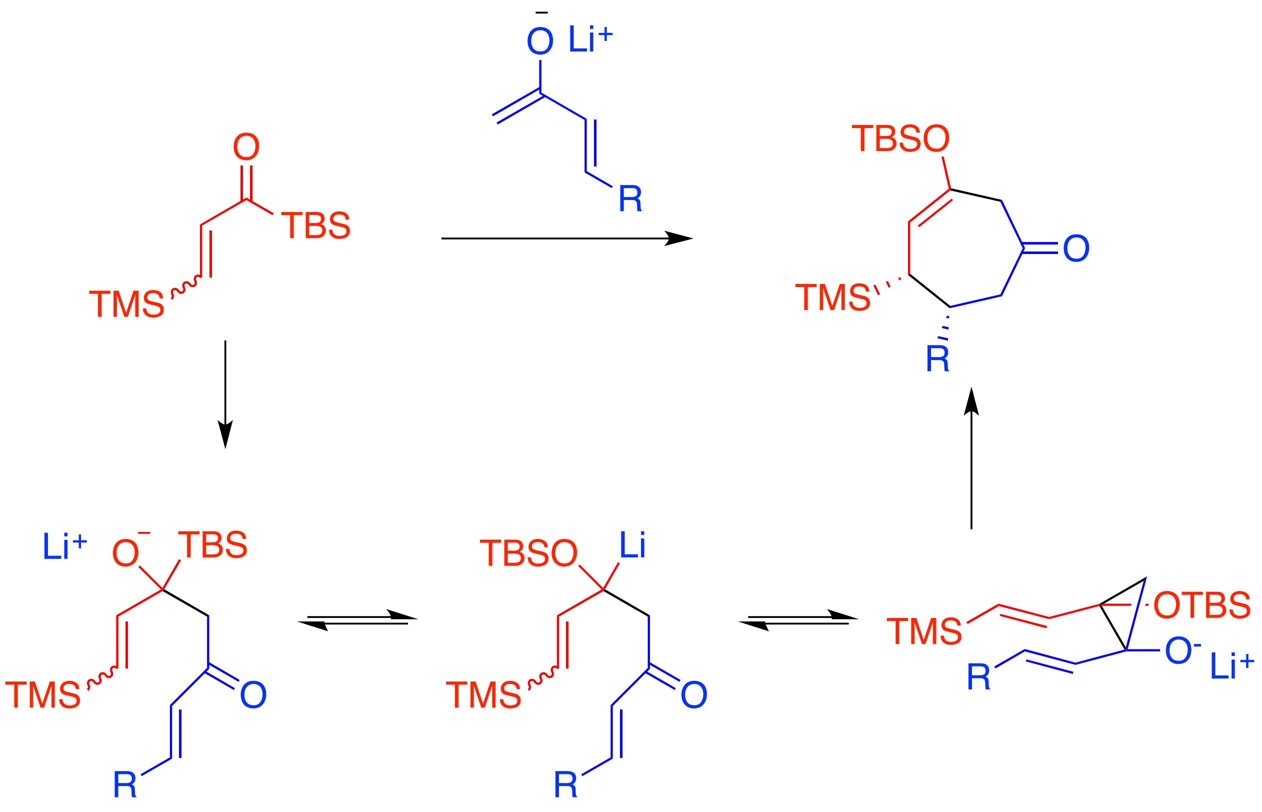
- If catalytic base used, stronger Si-O determines equilibrium
  - Si-O = 120-130 kcal/mol, Si-C = 75-85 kcal/mol
- If stoichiometric base used, anion stability determines equilibrium
  - R’ = EWG, polar aprotic solvents, chelating agents, and M = Na, K (but not Li) all favor Si-O bond formation

Tetrahedron, **2001**, *57,* 2065-2084.

General Brook Rearrangement

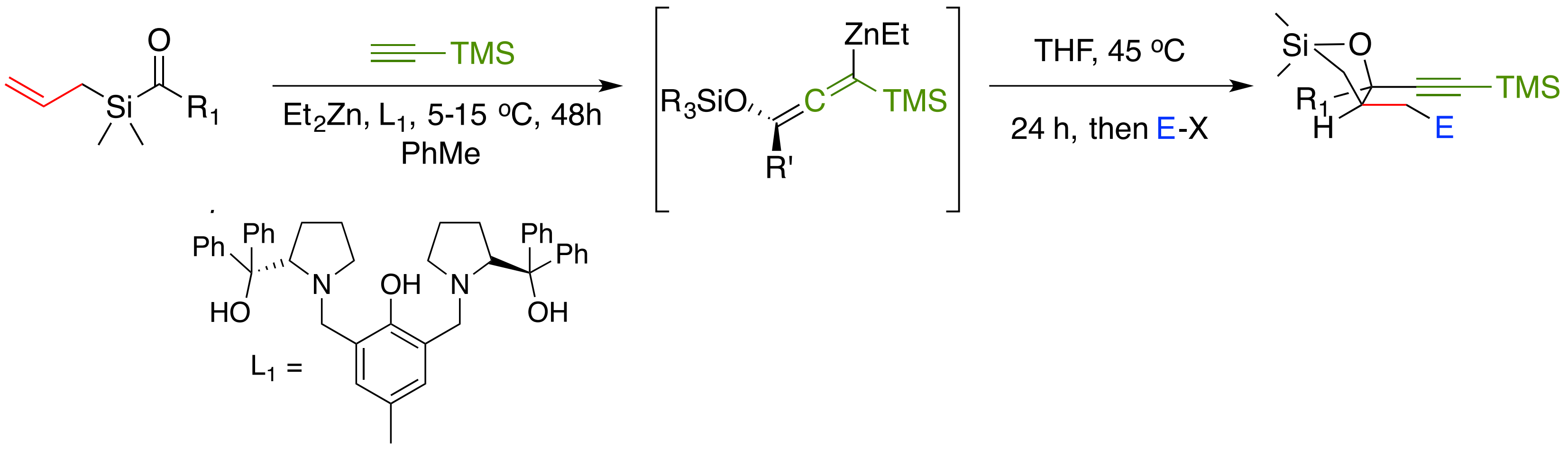


Brook Rearrangement: Formal [4+3]



Tetrahedron, **2001**, *57*, 2065-2084.
J. Am. Chem. Soc. ***1998***, *120*, 4947.

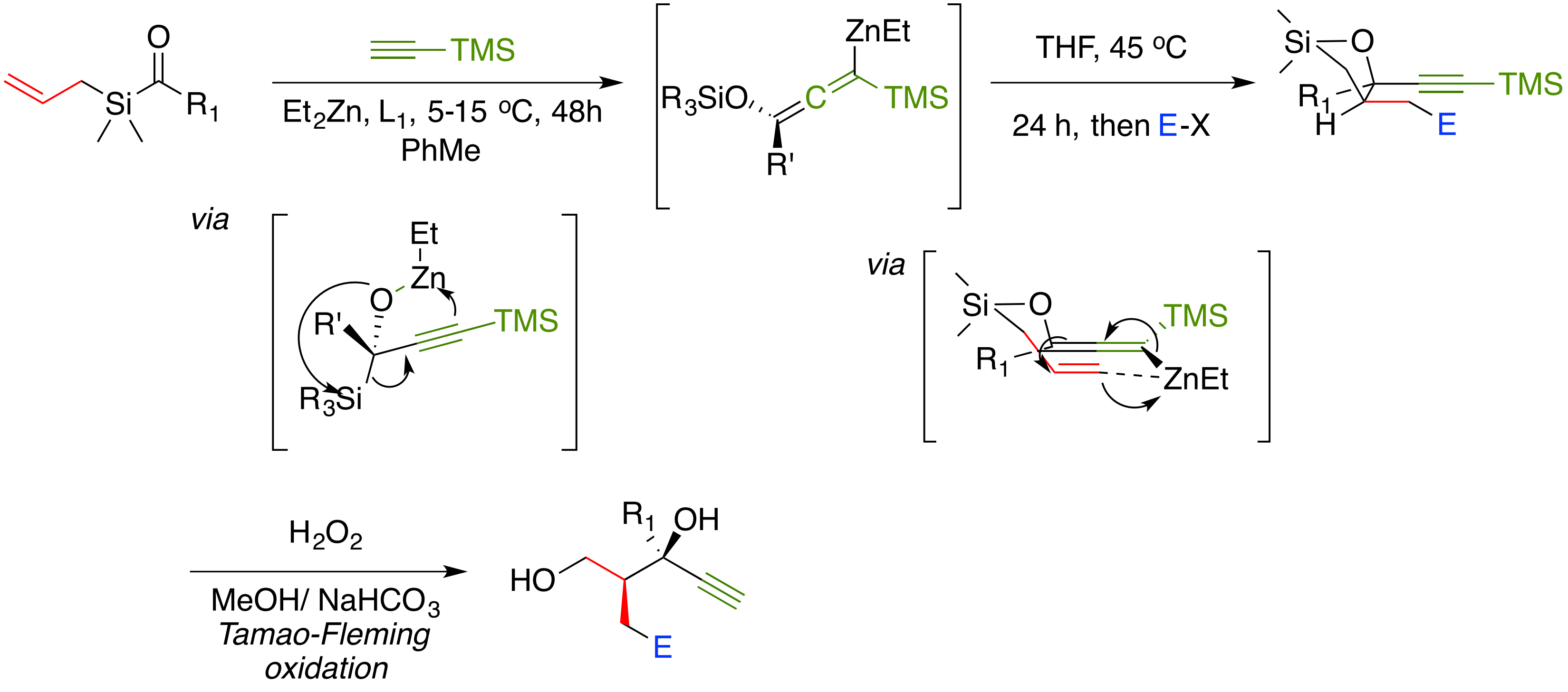
Allenyl-Zn Brook Rearrangement



- Ligand has no effect on stereochemistry after alkyne addition
- Believed to proceed directly to allenyl-Zn (configurationally stable)
    - No traditional 1,2-Brook rearrangement (alkyl-Zn not configurationally stable)

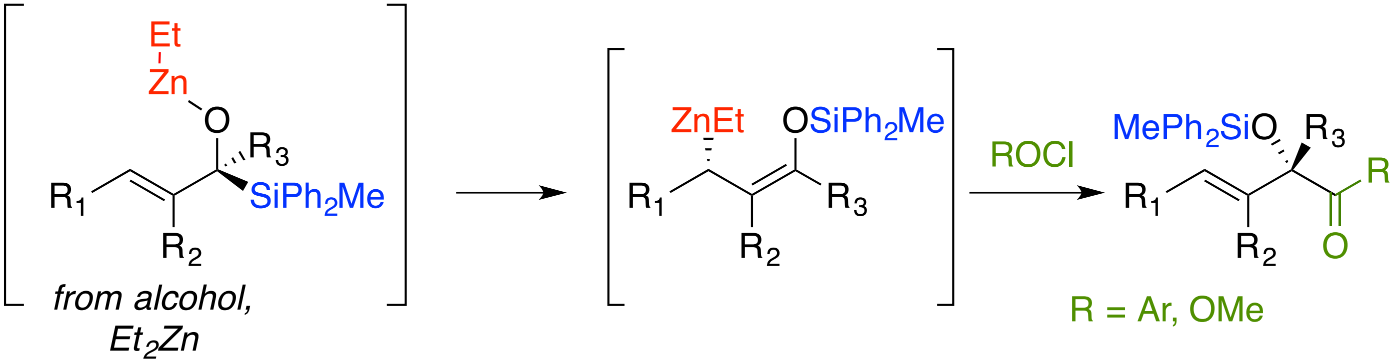
Angew. Chem. Int. Ed. **2013**, *52*, 13717–13721.

Allenyl-Zn Brook Rearrangement



Angew. Chem. Int. Ed. **2013**, *52*, 13717–13721.

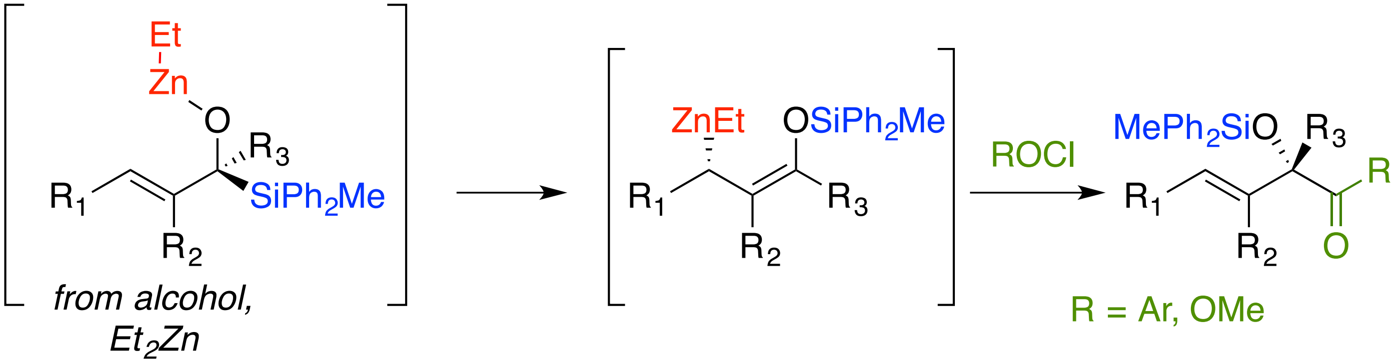
Allyl-Zn Brook Rearrangement

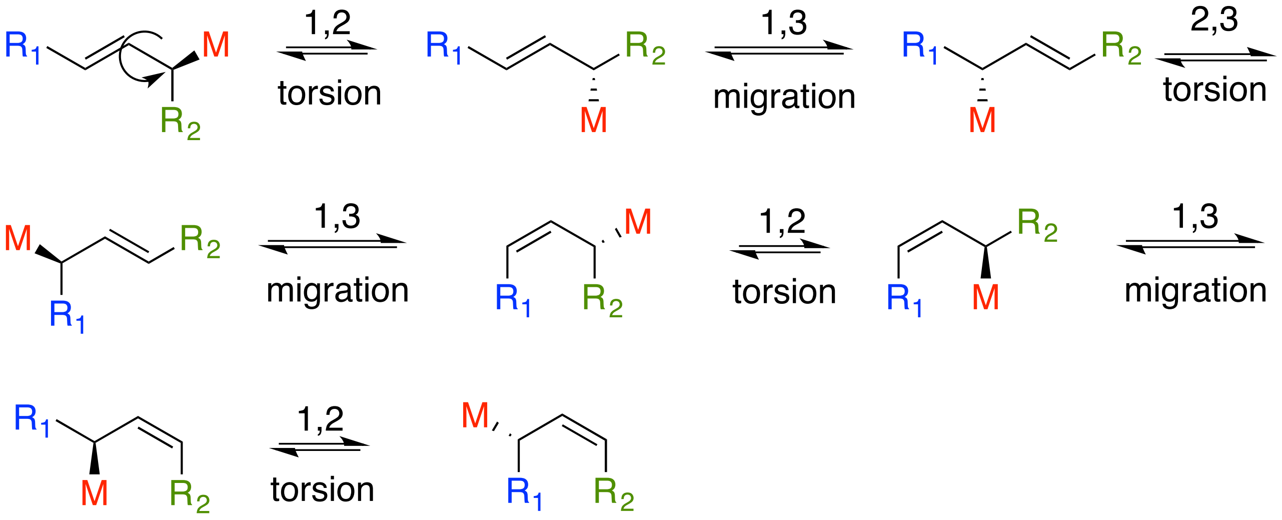


- Complete chirality transfer from starting alcohol
- 60-96% yield
- MeMgBr could also be used, but with decrease yield
- Smaller silyl groups (TMS) give *O*-acylation

Angew. Chem. Int. Ed. **2016**, *55*, 6057–6061.

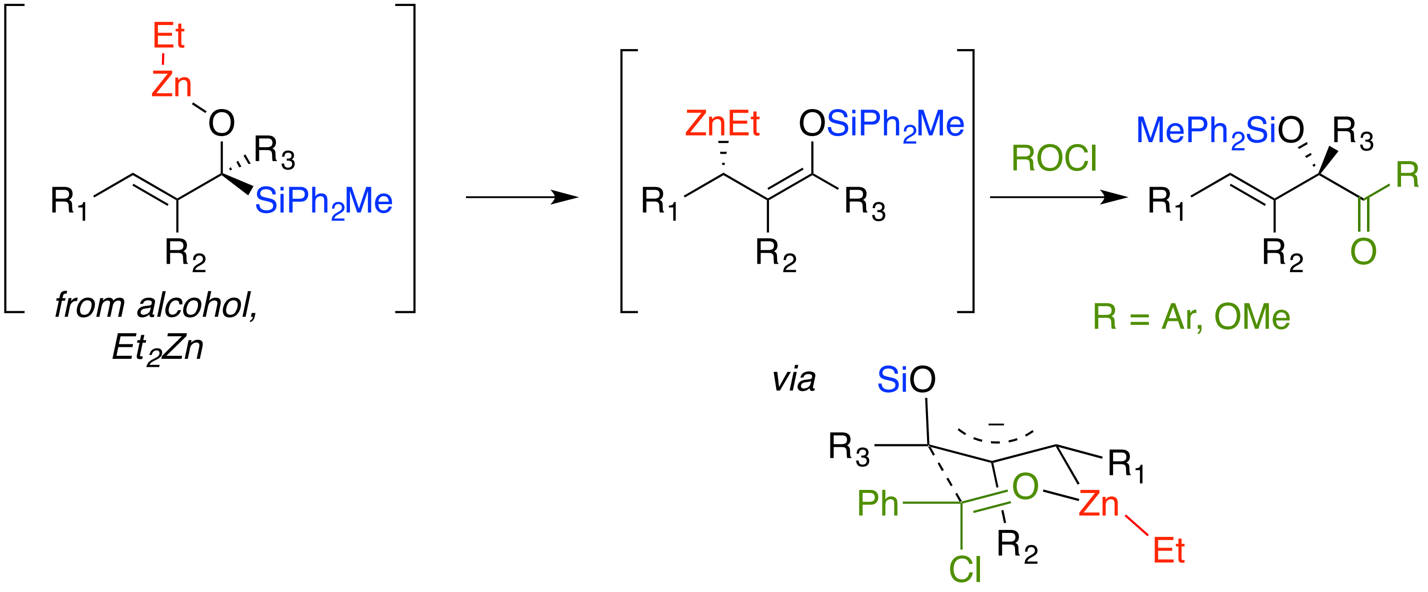
Allyl-Zn Brook Rearrangement





Angew. Chem. Int. Ed. **2016**, *55*, 6057–6061.

Allyl-Zn Brook Rearrangement



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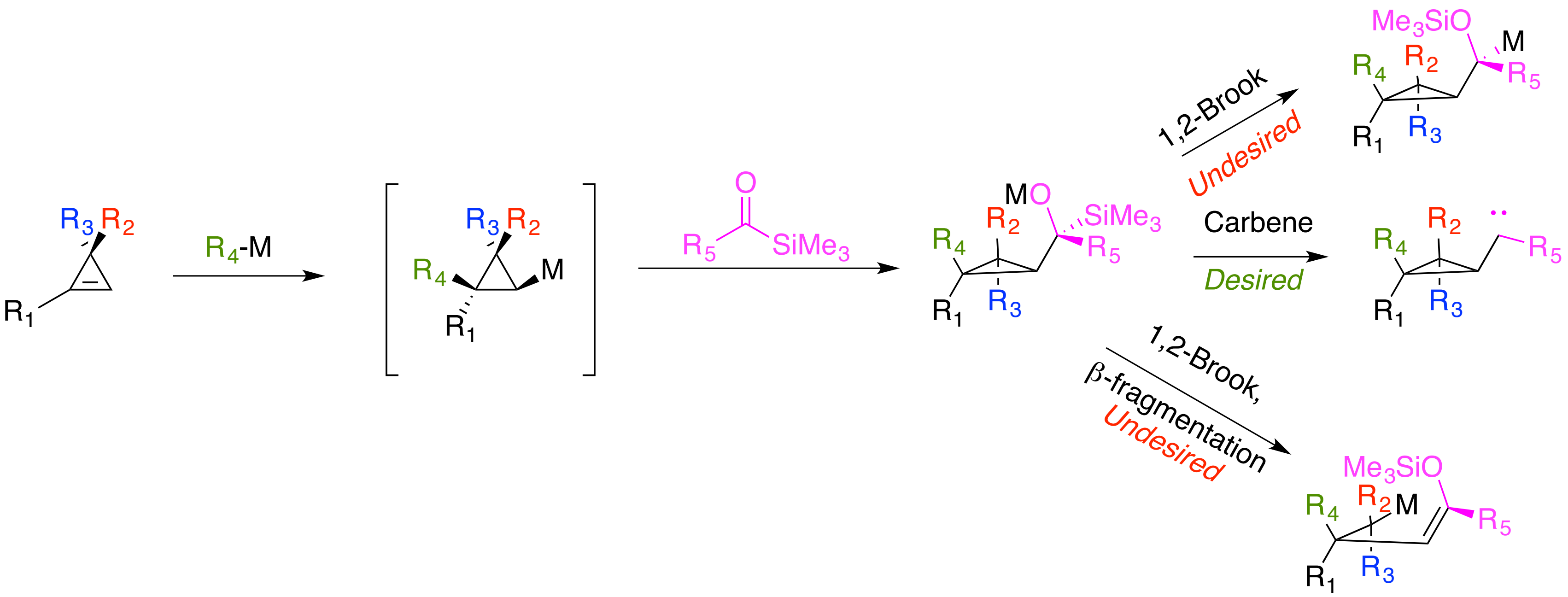
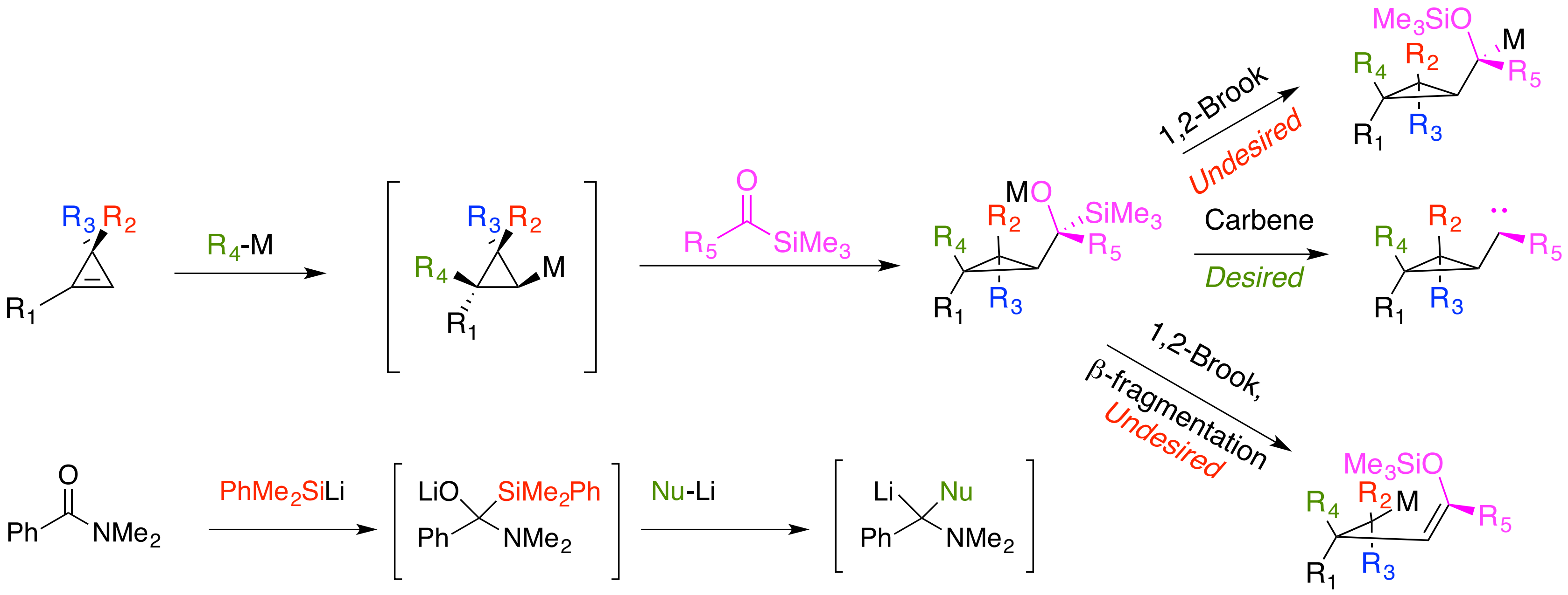
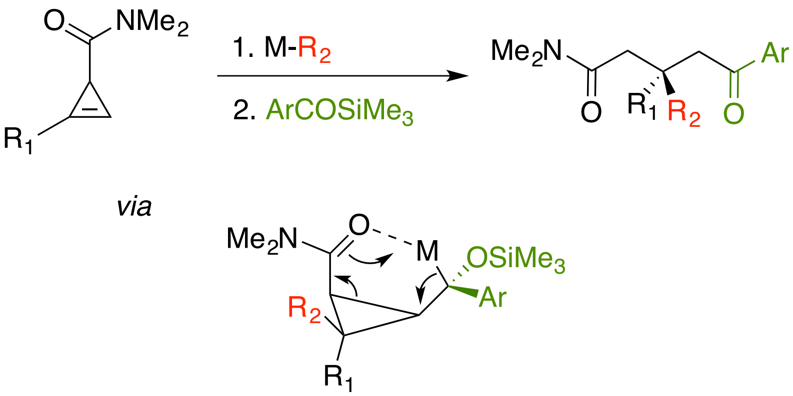
Title Work: Multiple Reaction Pathways



J. Am. Chem. Soc., **2017**, *139*, 8364–8370.
Org. Bio. Mol. Chem. **2004**, *4*, 3006–3017.
Angew. Chem. Int. Ed. **2016**, *55*, 714 –718.

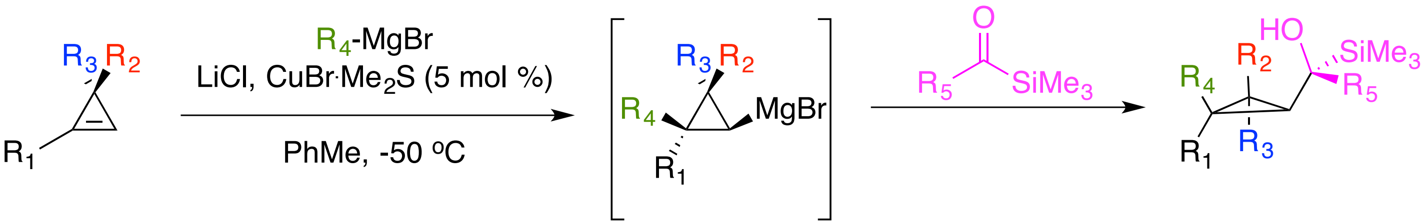
Title Work: Multiple Reaction Pathways

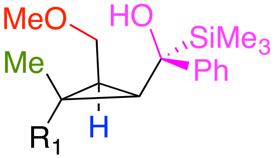




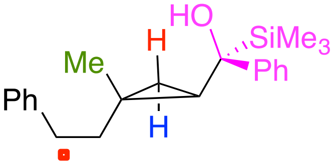
J. Am. Chem. Soc., **2017**, *139*, 8364–8370.
Org. Bio. Mol. Chem. **2004**, *4*, 3006–3017.
Angew. Chem. Int. Ed. **2016**, *55*, 714 –718.

Title Work: Carbometallation/Acyl Silane Addition

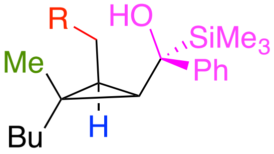




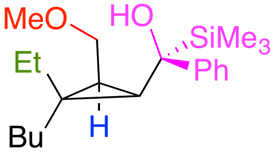
R_1 = Bu; 75%, *dr* = 95:5
R_1 = Et; 78%, *dr* = 95:5
R_1 = Hex; 72%, *dr* = 95:5
R_1 = $Ph(CH_2)_2$; 64%, *dr* = 98:2
R_1 = $BnO(CH_2)_2$; 71%, *dr* = 98:2



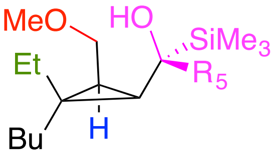
51%, *dr* =75:25



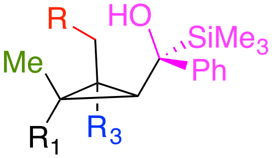
R = OBn; 65%, *dr* = 98:2
R = OH; 84%, *dr* = 98:2



51%, *dr* = 92:8



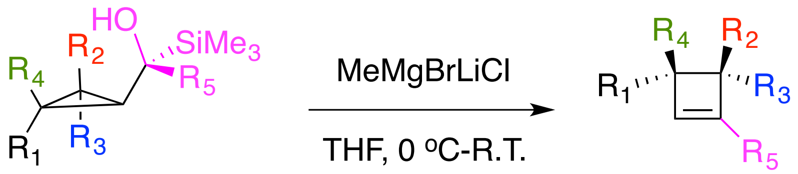
R_5 = Tol; 75%, *dr* = 95:5
R_5 = $Ph(CH_2)_2$; 80%, *dr* = 86:14
R_5 =CO_2tBu; 50%, *dr* = 66:33

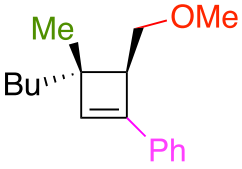


R_1 = Bu, R = OH, R_3 = Me; 95%, *dr* = 98:2
R_1 = Bu, R = OMe, R_3 = Me; 77%, *dr* = 98:2
R_1 = Bu, R = OMe, R_3 = Ph; 72%, *dr* = 98:2
R_1 = H, R = OBn, R_3 = Me; 45%, *dr* = 98:2
R_1 = Bu, R = H, R_3 = Me; 40%, *dr* = 58:42

J. Am. Chem. Soc., **2017**, *139*, 8364–8370.

Title Work: Ring Expansion





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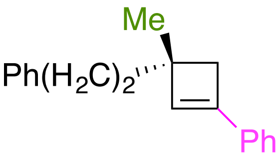

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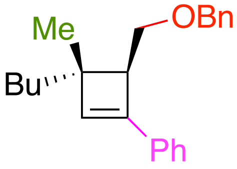

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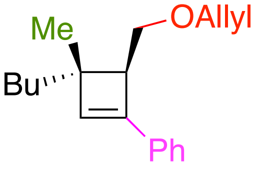

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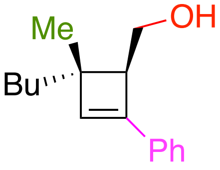

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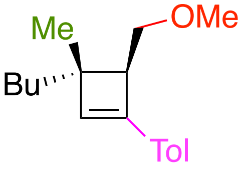

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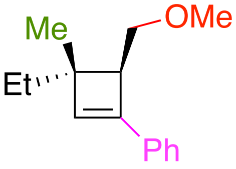

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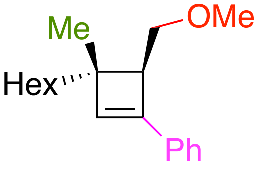

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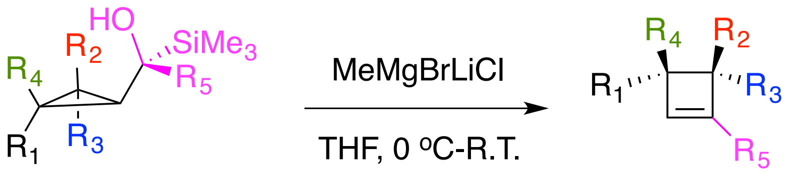
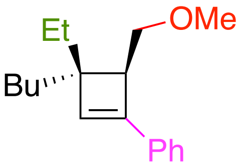
Title Work: Ring Expansion





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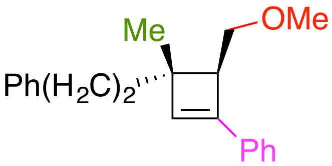

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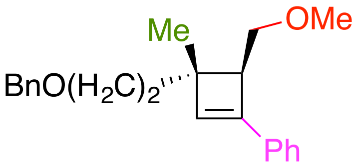

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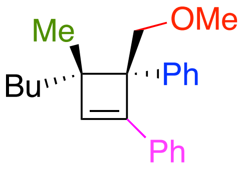

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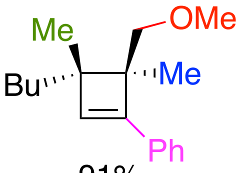

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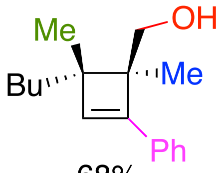

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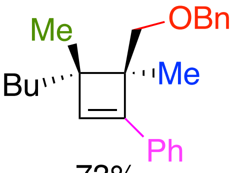

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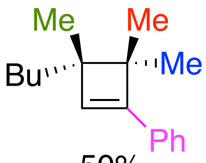
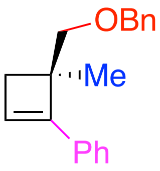
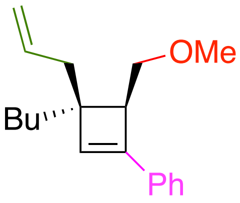


50%
rr = 7:1



53%
rr = 5:1



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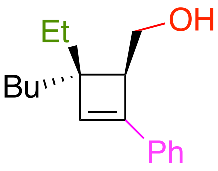

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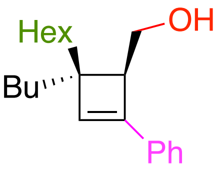

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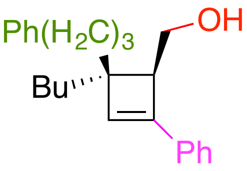

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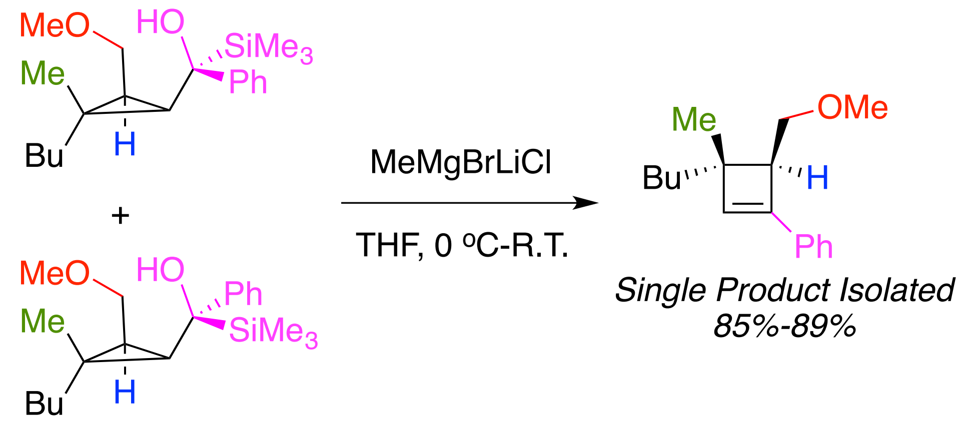
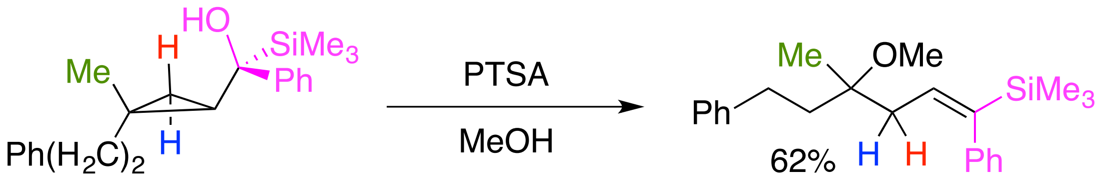
Probing the Mechanism



Single Product Isolated
85%-89%



- Different diastereomers give same product
    - Suggests that carbene pathway possible
- PTSA reaction: Test if cationic reaction pathway is operative

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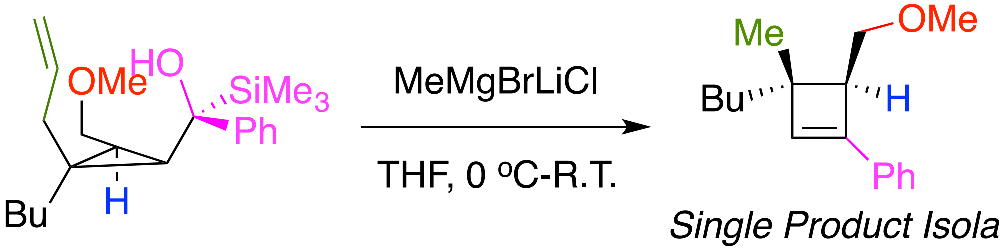
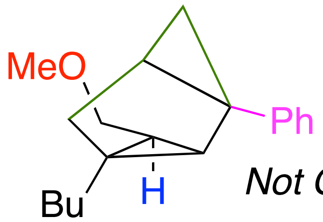
Probing the Mechanism

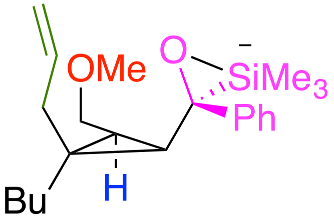


Single Product Isolated
86%



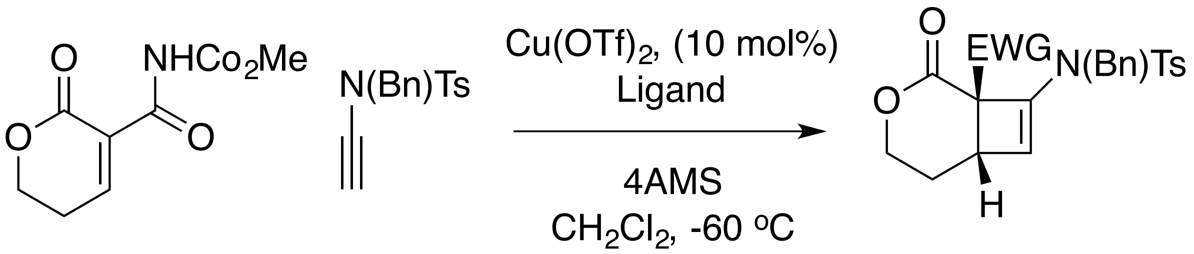
Not Observed

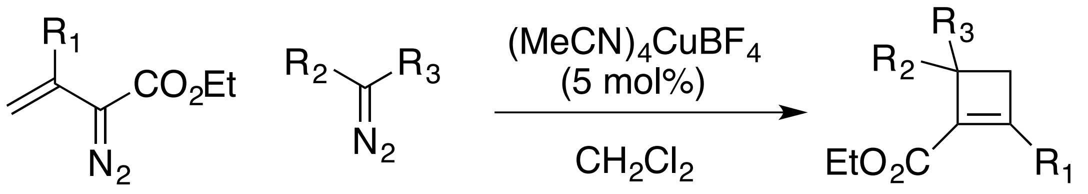
- Attempts to trap carbene fail
  - Analogous to similar previous report
  - Possible alternative?

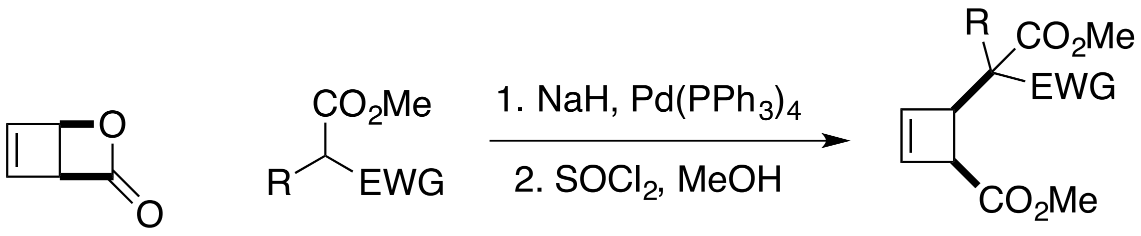


J. Am. Chem. Soc., **2017**, *139*, 8364–8370.
Org. Bio. Mol. Chem. **2004**, *4*, 3006–3017.

Other Cyclobutene Methods







Org. Lett., **2010**, *17*, 3780-3783.
Angew. Chem. Int. Ed. **2009**, *48*, 7569-7572.
Angew. Chem. Int. Ed. **2010**, *49*, 5762-5766.

Conclusion

- One-pot synthesis of cyclobutenes from cylcopropenes was developed
- Good diastereoselectivity
- Simple protocol