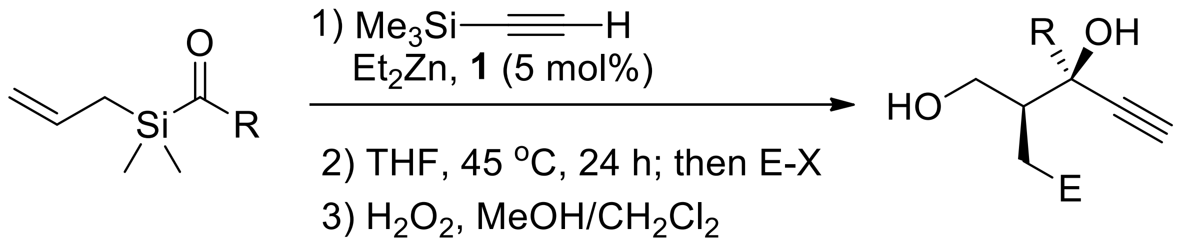
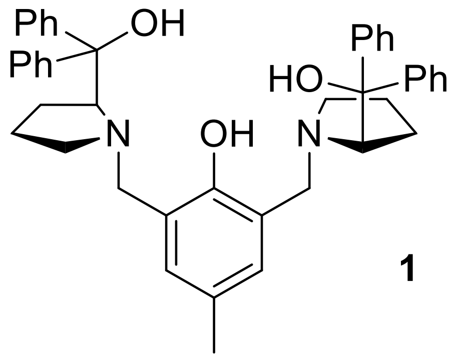
One-Pot Zinc-Promoted Asymmetric Alkynylation/Brook-Type Rearrangement/Ene-Allene Cyclization: Highly Selective Formation of Three New Bonds and Two Stereocenters in Acyclic Systems

Polina Smirnov, Jomon Mathew, Anne Nijs, Einat Katan, Miriam Karni, Casten Bolm, Yitzhak Apeloig, and Ilan Marek

Angew. Chem. Int. Ed. **2013**, *52*, 1-6





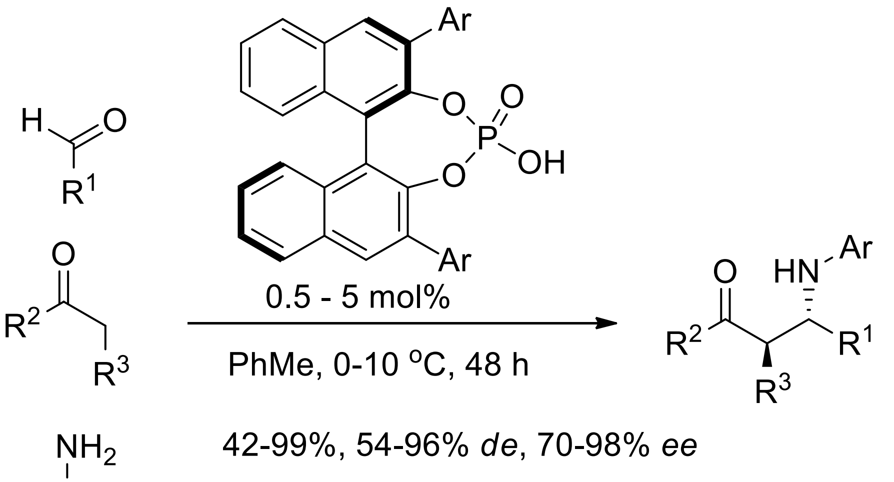
1

Nicholas Reed

Wipf Group Current Literature

June 8, 2013

Rapidly Building Complexity



0.5 - 5 mol%

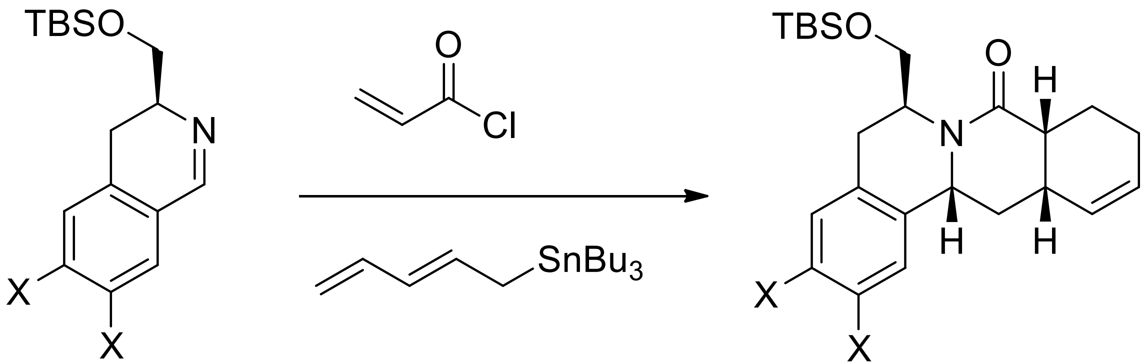
PhMe, 0-10 °C, 48 h

42-99%, 54-96% *de*, 70-98% *ee*

J. Am. Chem. Soc. **2007**, *129*, 3790

Asymmetric one-pot reactions are extremely attractive transformations for their ability to impart stereoselectivity and for their ability to rapidly build up complexity

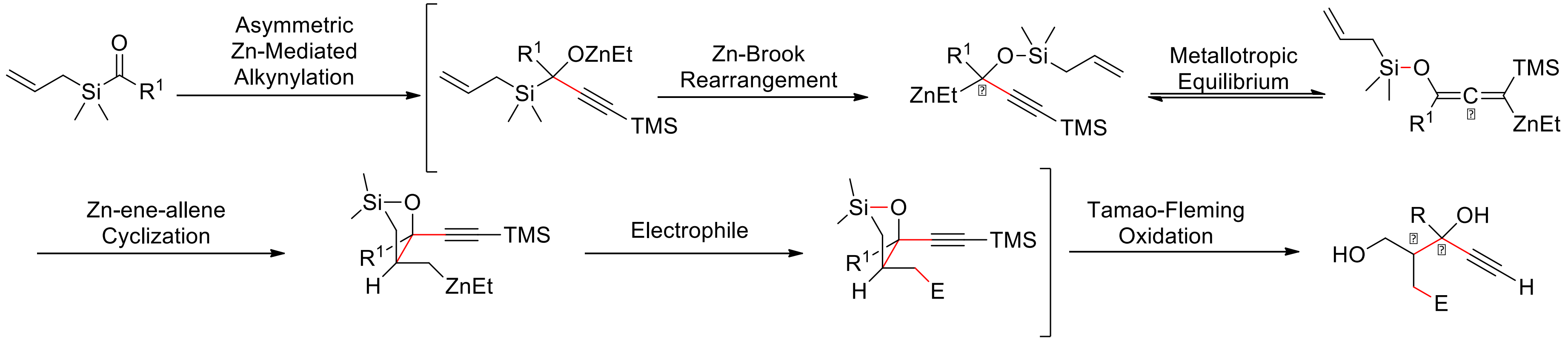
New challenges are encountered when several different types of reactions are attempted in one pot processes



Tetrahedron: Asymmetry, **1996**, *7* 443

94%, d.r. <97:3

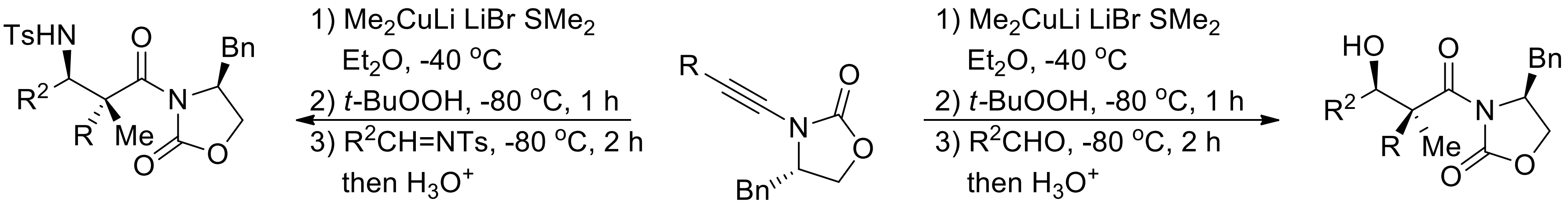
Proposed Chemical Transformation



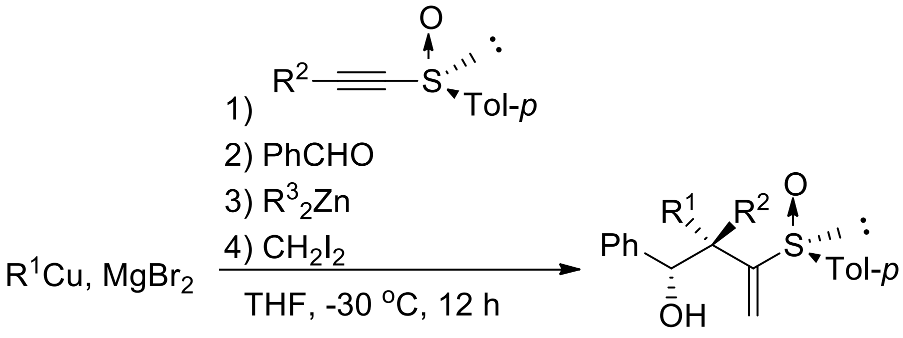
1. Does the Brook rearrangemenet proceed in the presence of stoichiometric base?
2. Does complete transfer of chirality occur?
3. Would the propargyl zinc species be configurationally stable?
4. What is the stereochemical outcome and mechanistic implications of such a transformation?
5. Would the intermediate species then undergo an enantioselective Zn-ene-allene cyclization?

Angew. Chem. Int. Ed. **2013**, *52*, 1-6

Previous Work



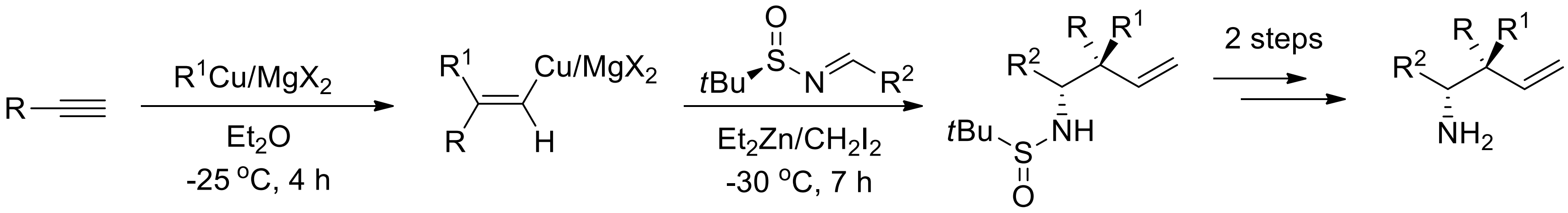
Nature Prot. **2013**, *8*, 749-754



J. Am. Chem. Soc. **2006,** *128*, 4642-4649

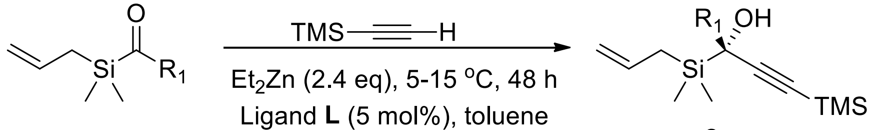
Limitations:

- Diastereoselectivity is good (>95:5 d.r. in most cases) but yields are moderate (50-70%)
- Previous methods rely on chiral auxiliaries that must be added and removed



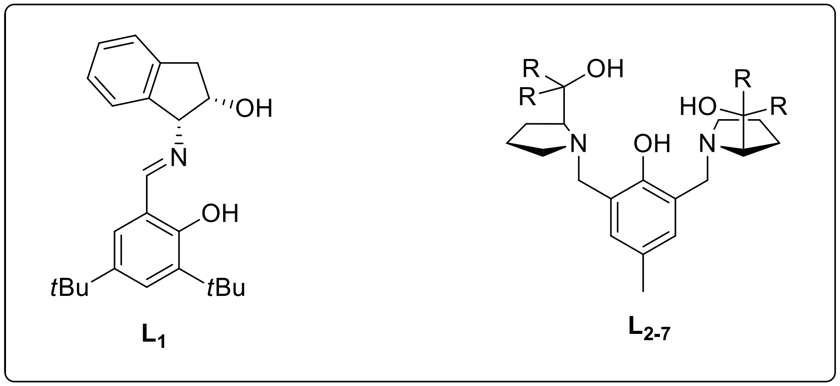
Angew. Chem. Int. Ed. **2007**, *46*, 9291-9294

Asymmetric Alkynylation



2a-c

1a R_1 = Hex
1b R_1 = Bu
1c R_1 = $(CH_2)_2Ph$



L_1 **L_{2-7}**

L_1 R_1 = Hex: **2a** (e.r. 61:39), 96%
L_2 R = Ph, R_1 = Hex: **2a** (e.r. 98:02, 90%)
L_3 R = Me, R_1 = Hex: **2a** (e.r. 80:20, 57%)
L_4 R = 3-$MeOC_6H_4$, R_1 = Hex: **2a** (e.r. 90:10, 22%)
L_5 R = 3,5-$(CF_3)_2C_6H_3$, R_1 = Hex: **2a** (e.r. 63:37, 50%)
L_6 R = 2-thienyl, R_1 = Hex: **2a** (e.r. 56:44, 15%)
L_7 R = 2-napthyl, R_1 = Hex: **2a** (e.r. 98:02, 41%)
L_2 R = Ph, R_1 = Bu: **2b** (e.r. 97:03, 89%)
L_2 R = Ph, R_1 = $(CH_2)_2Ph$: **2c** (e.r. 98:08, 70%)

•Catalyst sensitive to:

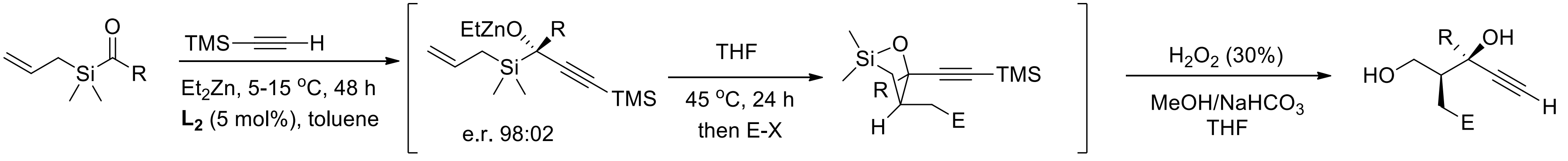
  Size of R: Reducing the steric bulk lowers e.r., increasing steric bulk lowers yield

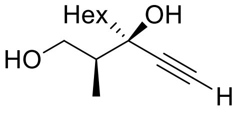
  Electronic environment: Electron-donating/electron-withdrawing groups lower yield and e.r.

•Tolerates some different substitution on silyl ketone with similar levels of stereoinduction

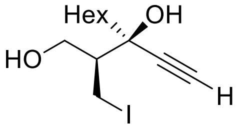
Angew. Chem. Int. Ed. **2013**, *52*, 1-6

Scope

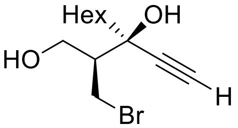




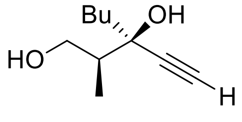
80%
d.r. > 98:02
e.r. 93:07



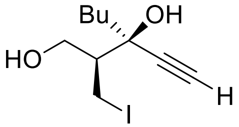
75%
d.r. > 98:02
e.r. 93:07



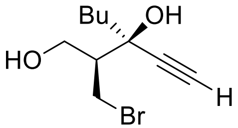
79%
d.r. > 98:02
e.r. 94:06



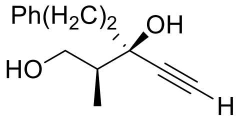
82%
d.r. > 98:02
e.r. 95:05



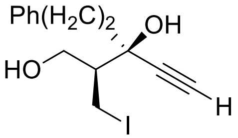
83%
d.r. > 98:02
e.r. 95:05



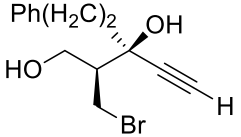
66%
d.r. > 98:02
e.r. 95:05



65%
d.r. > 98:02
e.r. 88:12



56%
d.r. > 98:02
e.r. 88:12

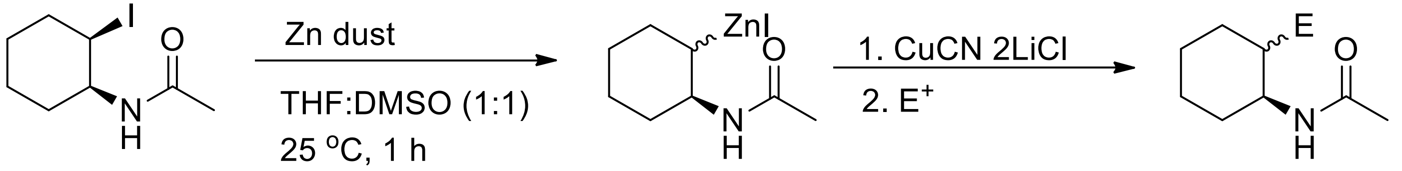


59%
d.r. > 98:02
e.r. 88:12

- Relatively small number of examples with homogeneous substrates
- Difficult to determine limits of promising methodology

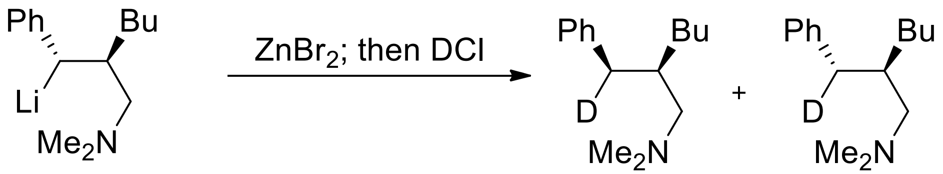
Angew. Chem. Int. Ed. **2013**, *52*, 1-6

Configurational Stability of Propargyl Zinc Species and its Implications



$E = CH_2C(CO_2Et){=}CH_2$, 93%
$E = SnMe_3$, 76%

Tetrahedron, **1994**, *50*, 2415-2432



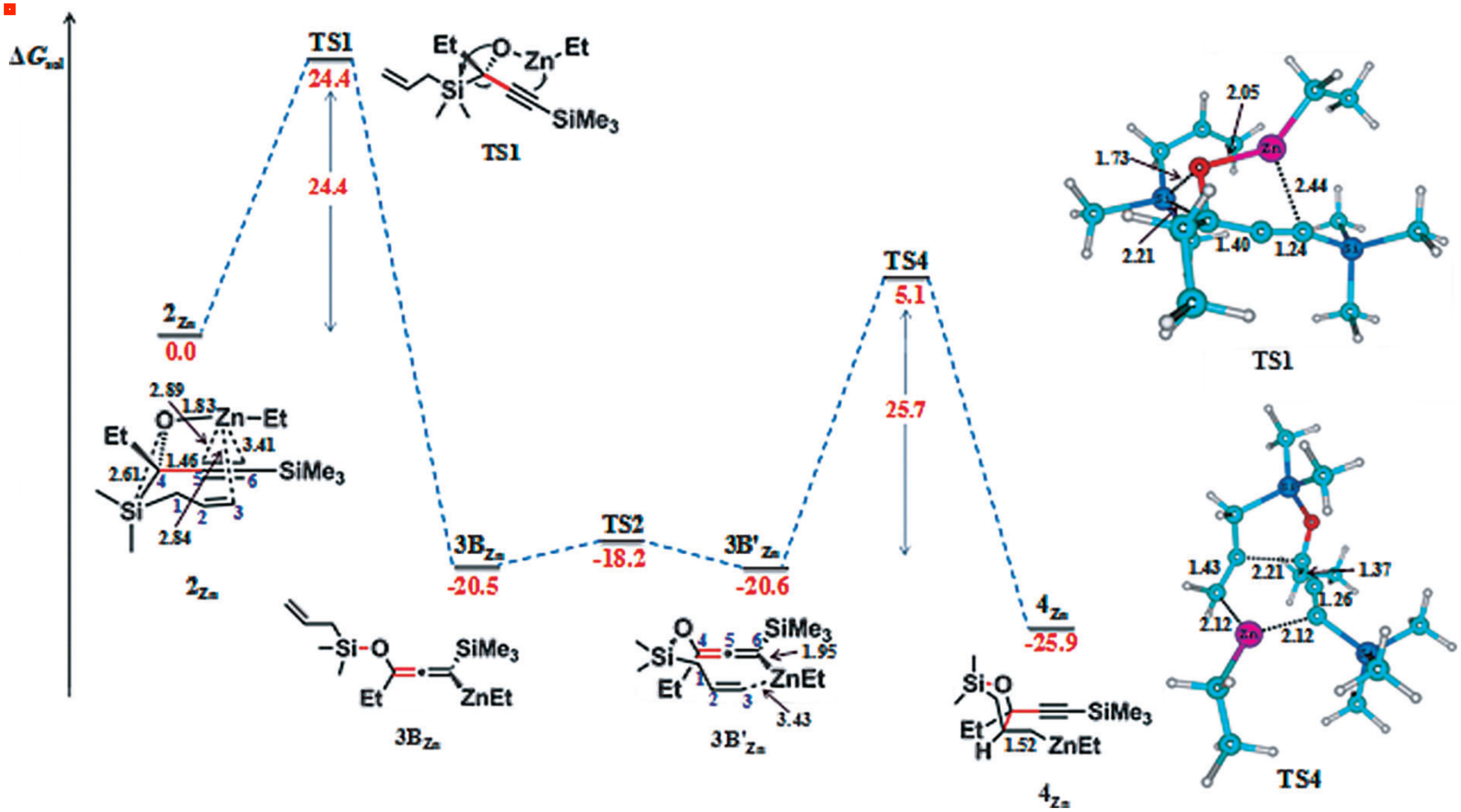
Temperature	***Syn/Anti***
-30 °C	95/5
0 °C	50/50
50 °C	5/95

J. Org. Chem. **1994***, 59*, 2925-2926

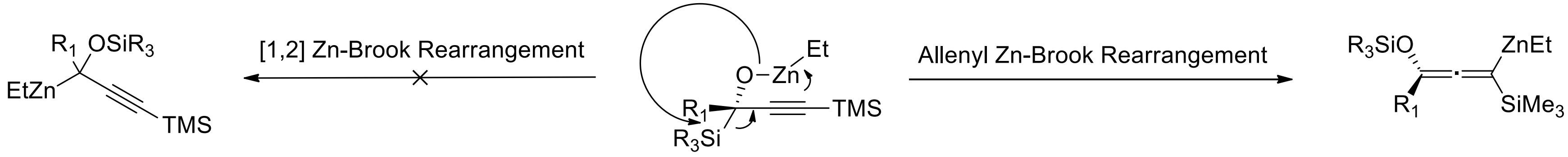
Alkyl zincs are usually unstable in the absence of a heteroatom or at high temperatures!

Why is the proposed propargyl zinc species configurationally stable?

Calculated Mechanistic Pathway



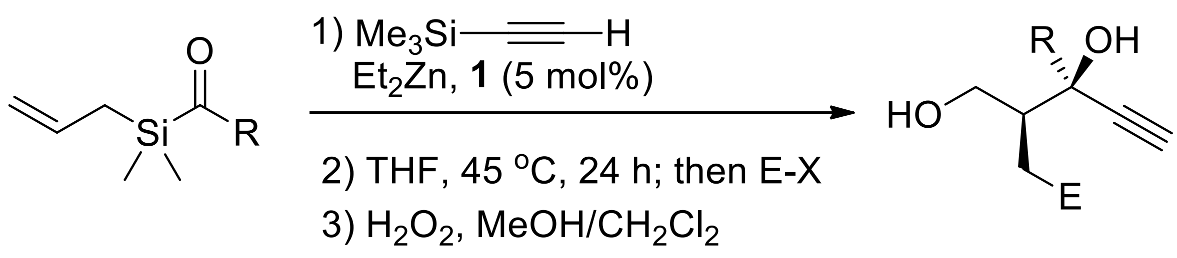
Hybrid PBE0 functional, 6-311G(d,p) basis set

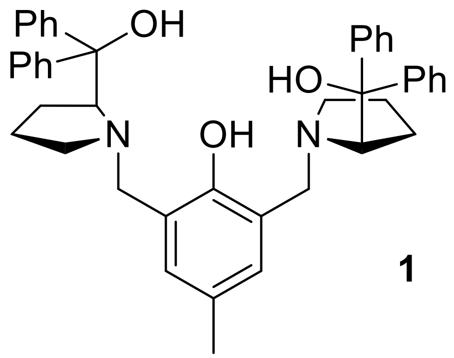


Angew. Chem. Int. Ed. **2013**, *52*, 1-6

Conclusions and Future Work

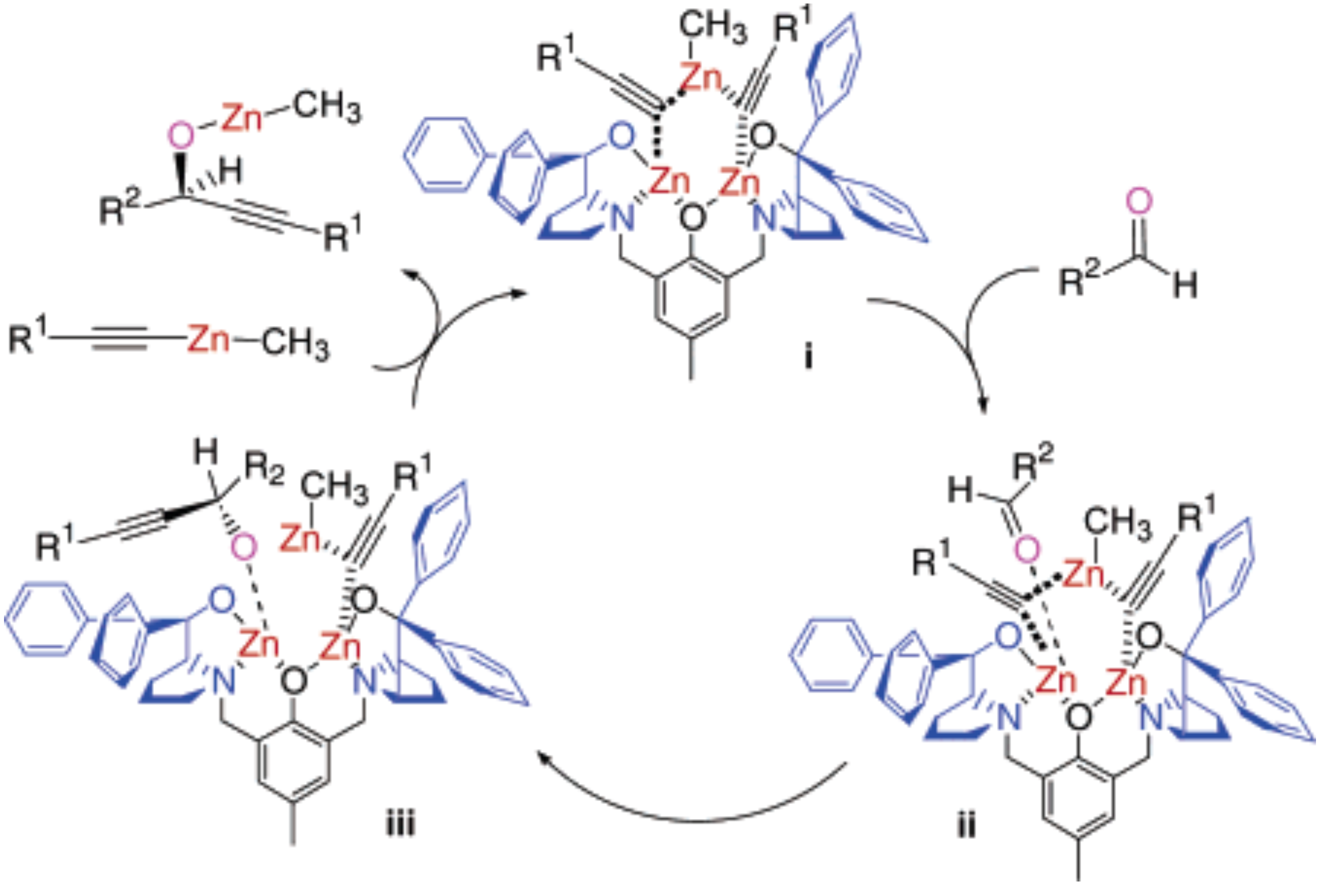
- Initial development of an attractive cascade process that forms three new bonds and two stereocenters
- Uses a catalytic amount of chiral organo-catalyst as the only source of chirality
- Calculations suggest an allenyl Zn-Brook rearrangement as the operative mechanistic pathway (in agreement with observed experimental results).
- Limited substrate scope makes it difficult to know the limits of such an attractive transformation





1

Asymmetric Alkynylation Catalytic Cycle



J. Am. Chem. Soc. **2006**, *128*, 8-9