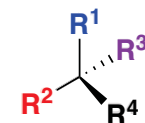


A Different View of Challenging Synthetic Problems

Ilan Marek
 Schulich Faculty of Chemistry
 Technion - Israel Institute of Technology
 Haifa, Israel

Ischia Advanced School of Organic Chemistry
 September 22-26th, 2012

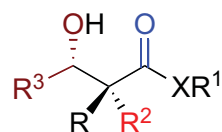


- Enantioselective conjugate addition
- Enantioselective allylic substitution
- Enantioselective nucleophilic allylation
- Enantioselective alkylation
- Enantioselective aldol reaction
- Rearrangement

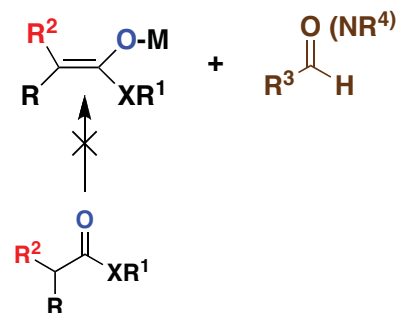
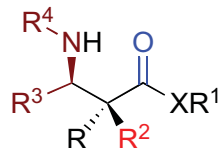
Could we consider a different approach?

Reviews: Corey (ACIE, 1998); Christoffers (ACEI, 2001); Barriault (TH, 2003); Christoffers (ASC, 2005); Trost (Synthesis, 2006); Cozzi (EJOC, 2007); Bella (Synthesis, 2009); Alexakis (CC, 2010); Marek (CC, 2011)

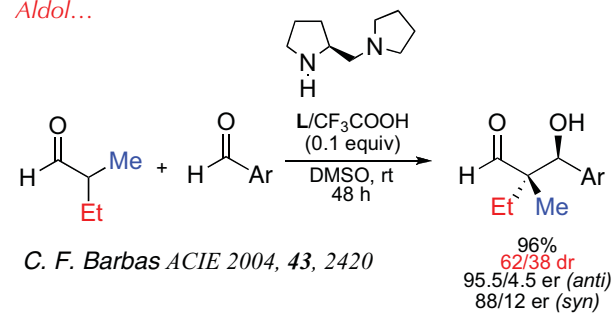
Aldol reaction



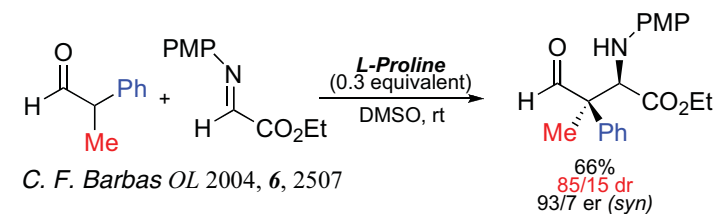
Mannich reaction



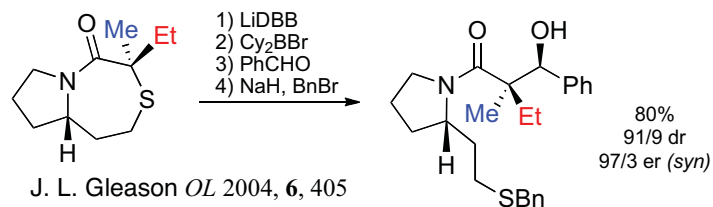
Aldol...



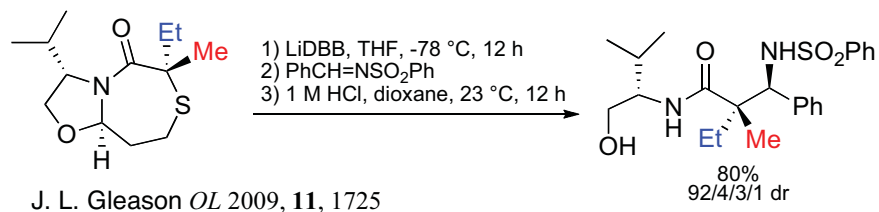
Mannich...



Aldol...

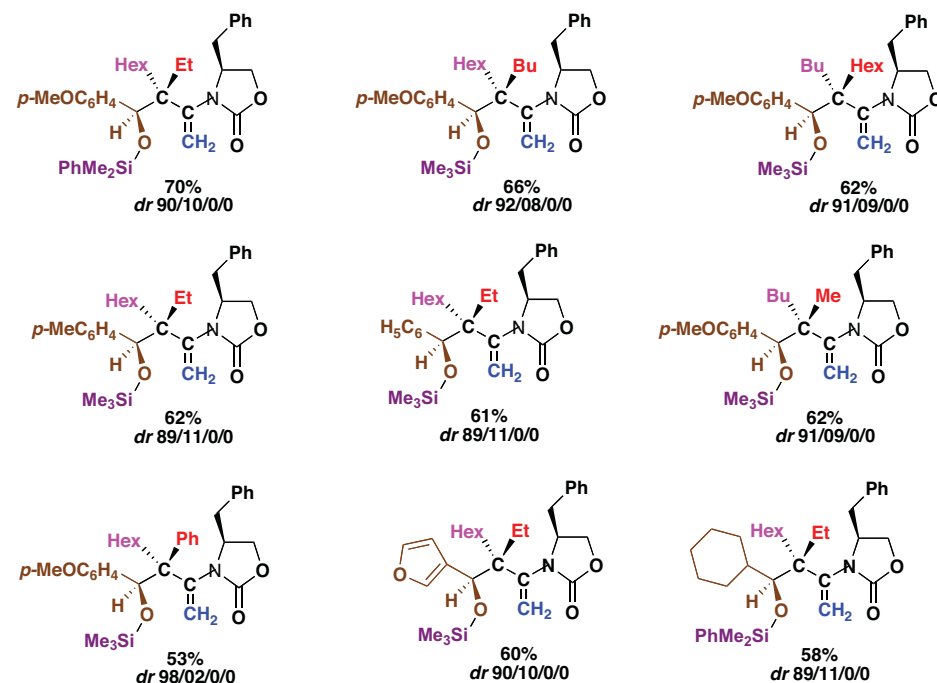
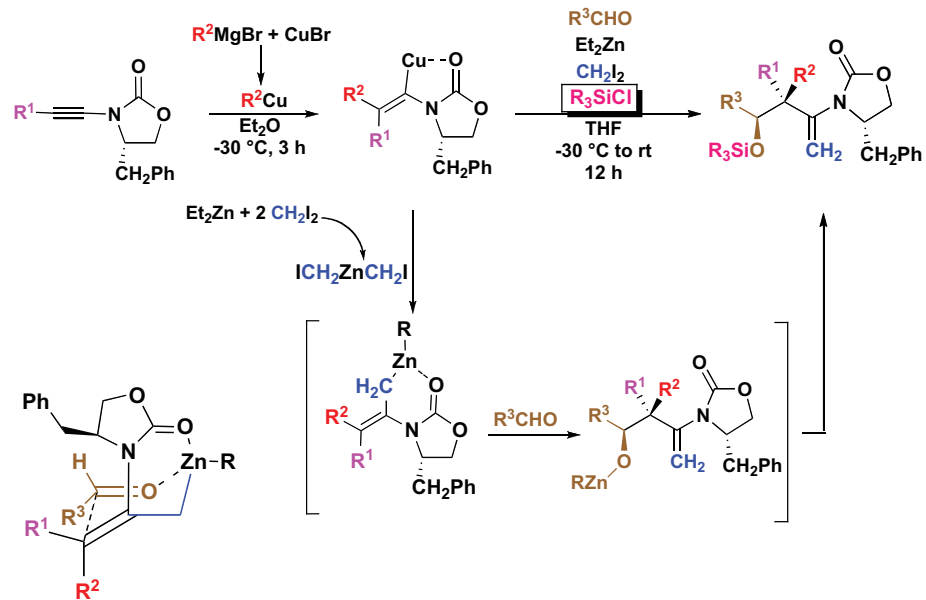
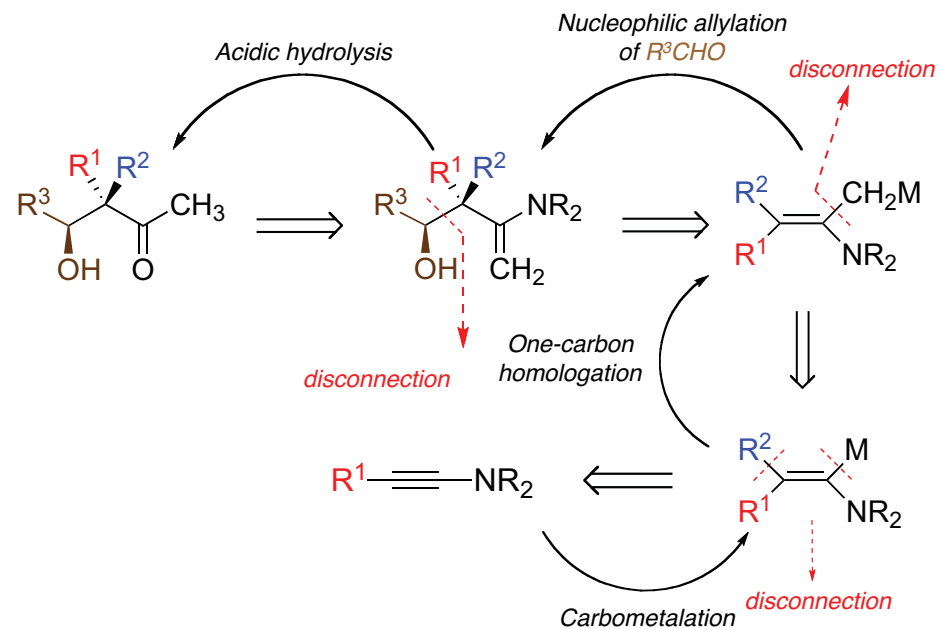


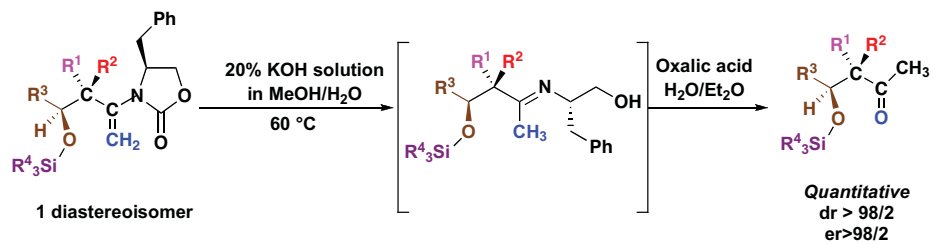
Mannich...



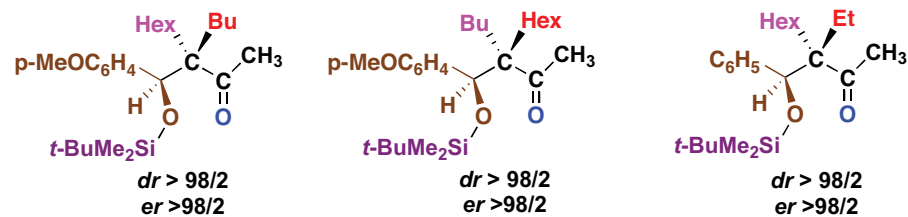
See also: A. Zakarian (*ACIE* 2007, **46**, 7466) and A. Myers (*JACS* 2008, **130**, 13231)

Our first approach....

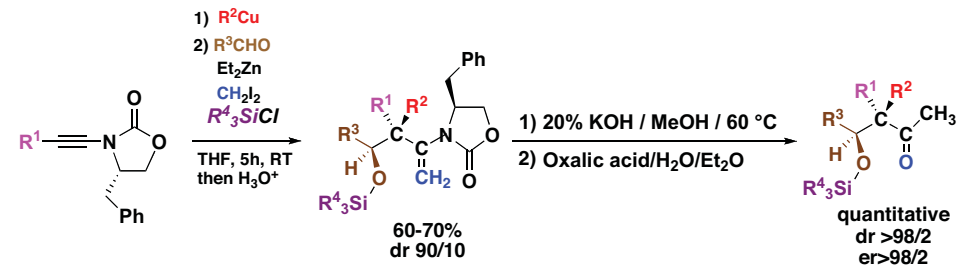




Selected examples

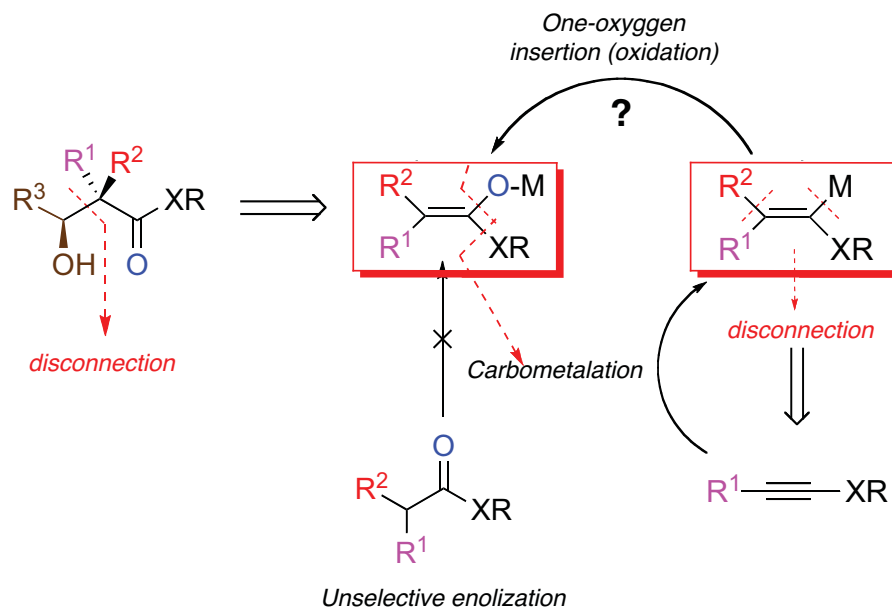


Nature Chem. 2009, 128

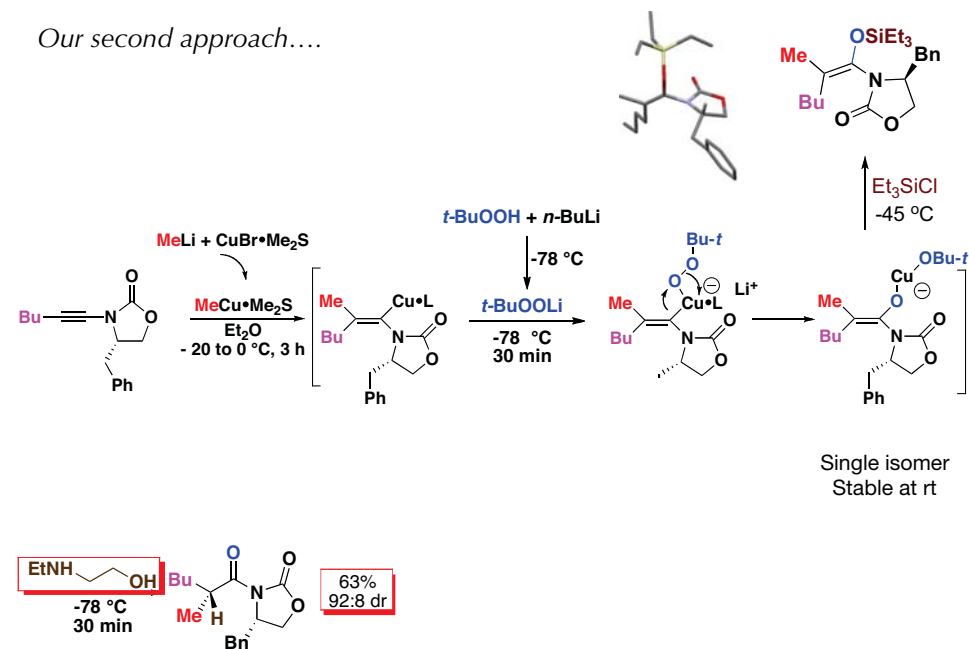


Nature Chem. 2009, 128 (highlighted Daniel Werz, ACIE 2009, 48, 7971)

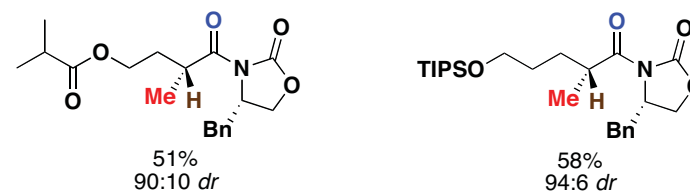
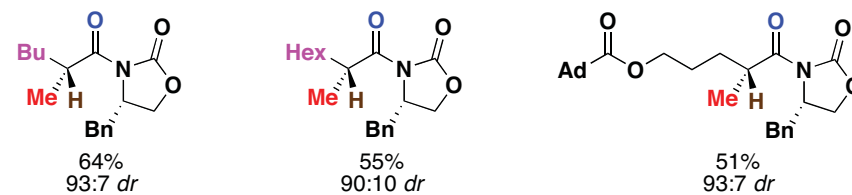
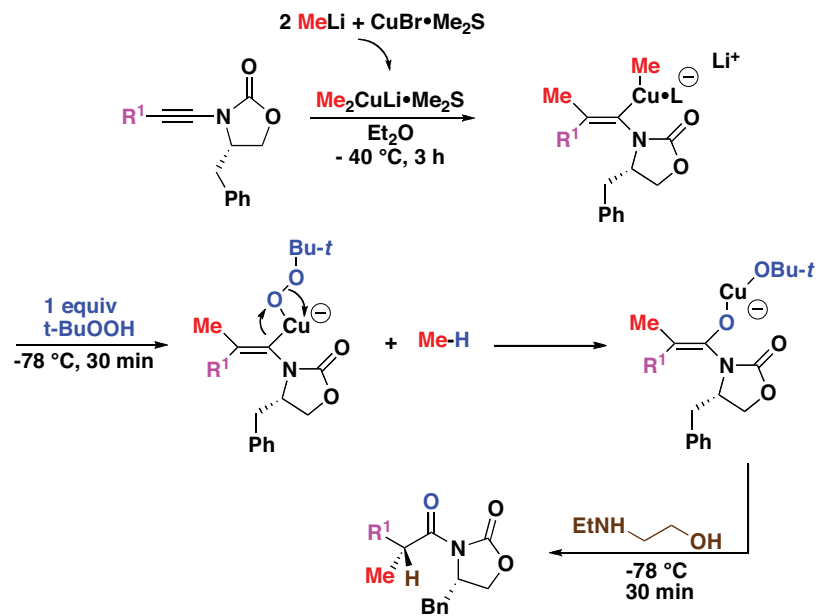
Our second (and more appealing/promising) approach....



Our second approach....

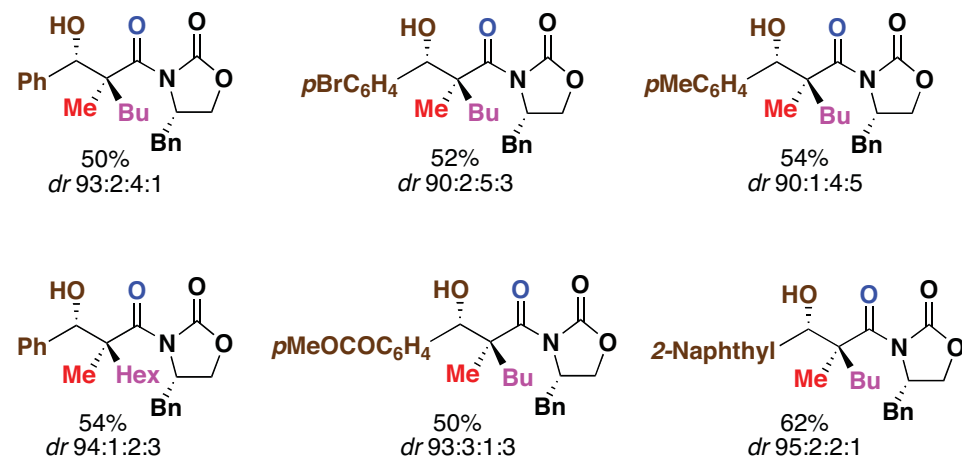
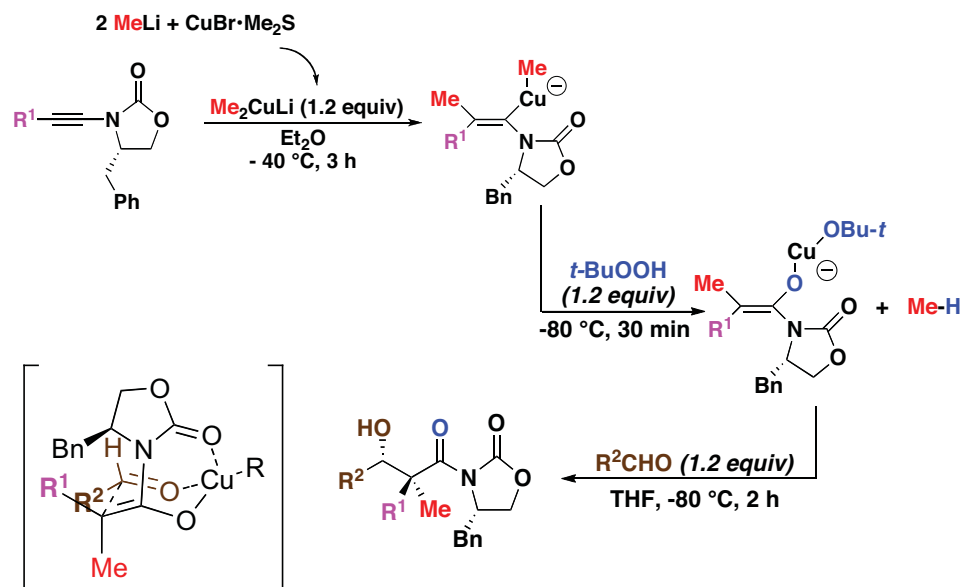


Yury Minko, Morgane Pasco, unpublished results



Yury Minko, Morgane Pasco, Accepted for publication

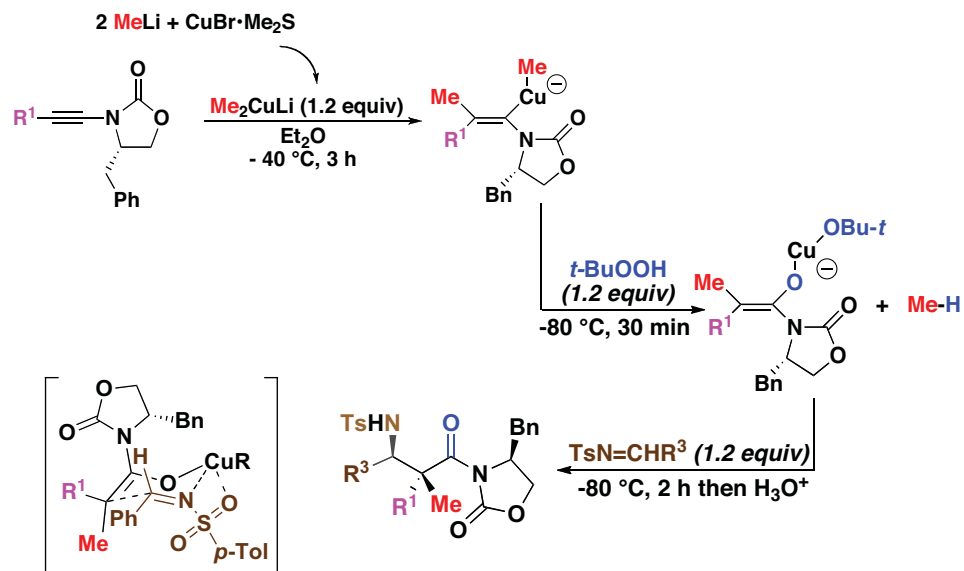
Aldol reaction....



Yury Minko, Morgane Pasco, Lukas Lercher, Accepted for publication

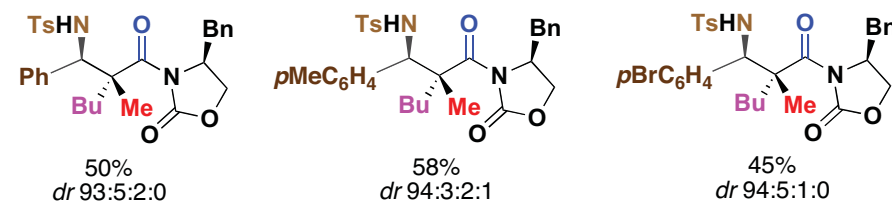
Yury Minko, Morgane Pasco, Lukas Lercher, Accepted for Publication

Mannich reaction....

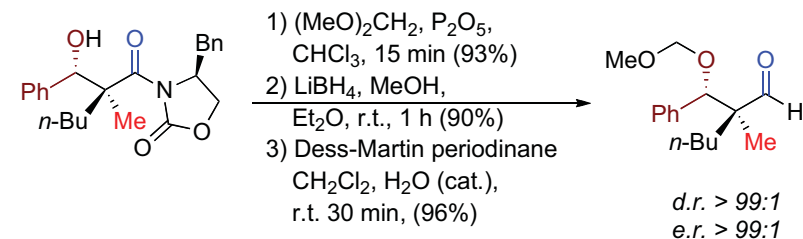


Yury Minko, Morgane Pasco, Lukas Lercher, Accepted for publication

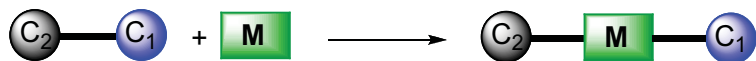
Mannich adducts....



Cleavage oxazolidinone (a selected example)....



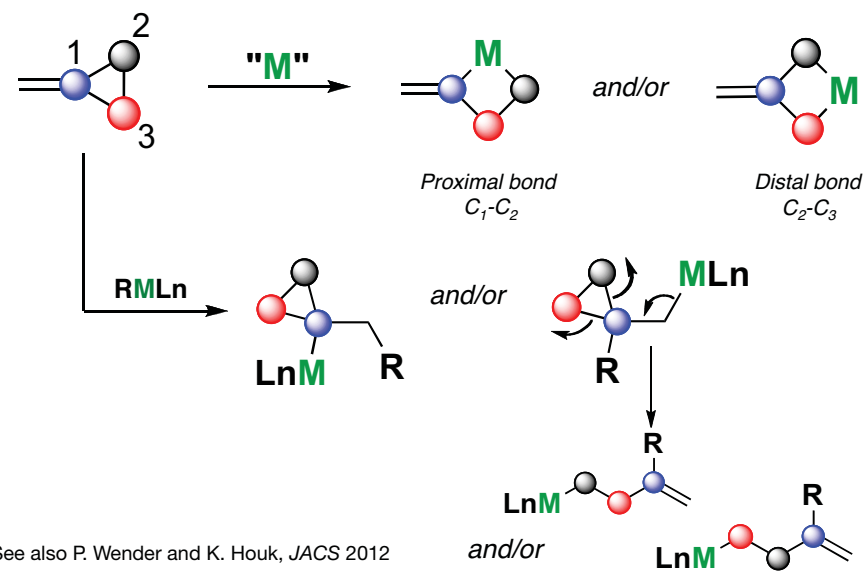
Carbon-Carbon Bond Activation



Reviews

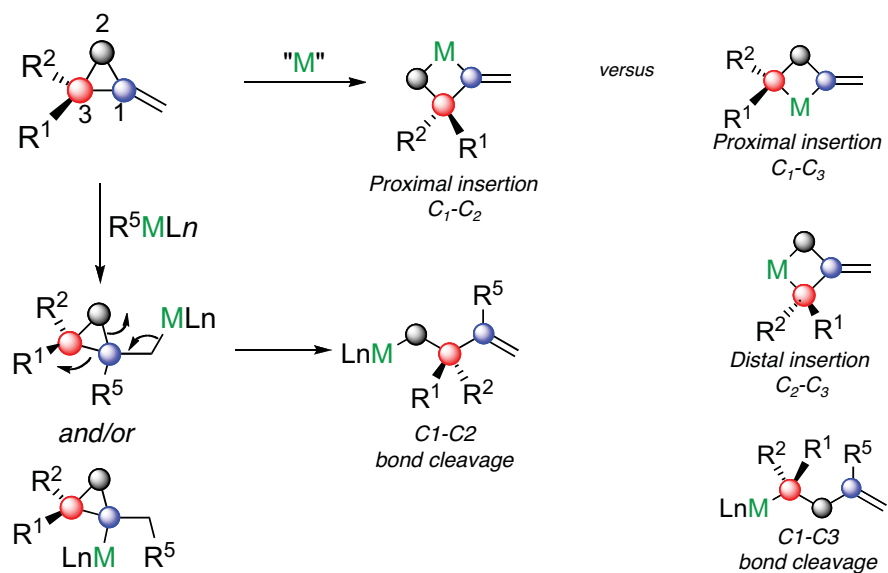
Crabtree, *CR* 1985; Jones, *Nature* 1993; Johnson, *CR* 1994; Brandi, *CR* 1998; Milstein, *ACIE* 1999; de Meijere, *TCC* 2000; Kondo, *Synlett* 2001; Yamamoto, *ASC* 2002; Milstein, *CR* 2003; Uemura, *Synlett* 2004; Jun, *CSR* 2004; Murakami, *BCSJ* 2006; Kotora, *COC* 2007; Gevorgyan, *CR* 2007; Shi, *COC* 2007; Marek, *ACIE* 2007; Cramer, *OBC*, 2009; Pelissier, *ASC* 2010; Marek, *CEJ* 2010; Murakami, *CC* 2011; Aissa, *Synthesis* 2011; Ruhland, *EJOC*, 2012.

Selectivity in Carbon-Carbon Bond Activation



See also P. Wender and K. Houk, *JACS* 2012

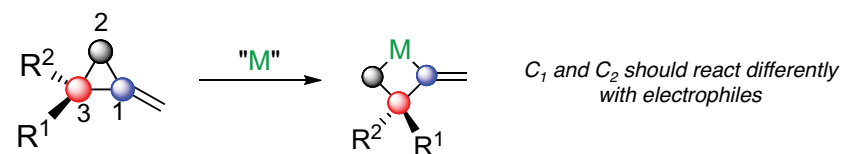
How to have a selective insertion?



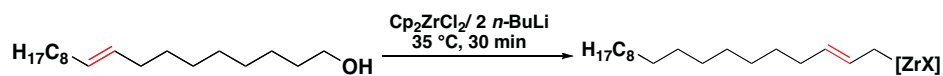
Selectivity in Carbon-Carbon Bond Activation

but also

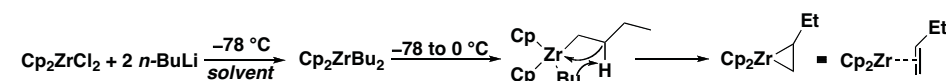
Selectivity in the reaction with electrophiles



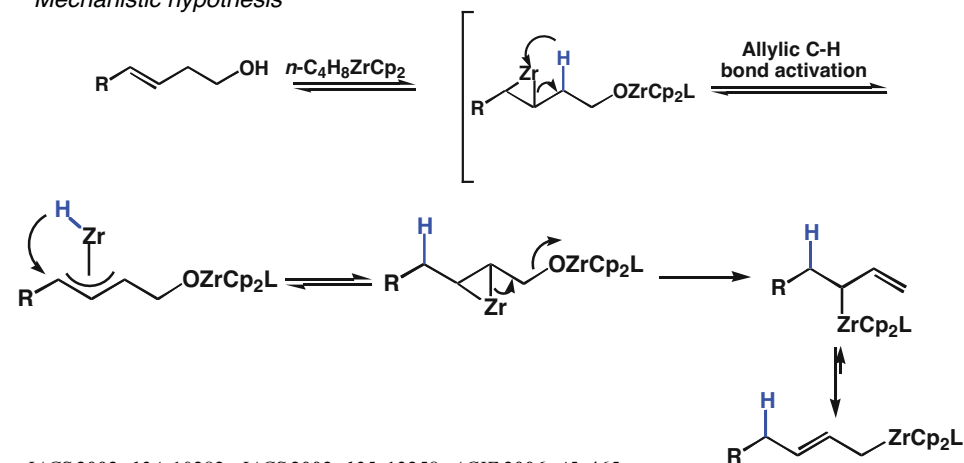
Zirconium "Walk"



With N. Chinkov, A. Levin, *JACS* **2002**, *124*, 10282; *JACS* **2003**, *125*, 13258; *ACIE* **2006**, *45*, 465

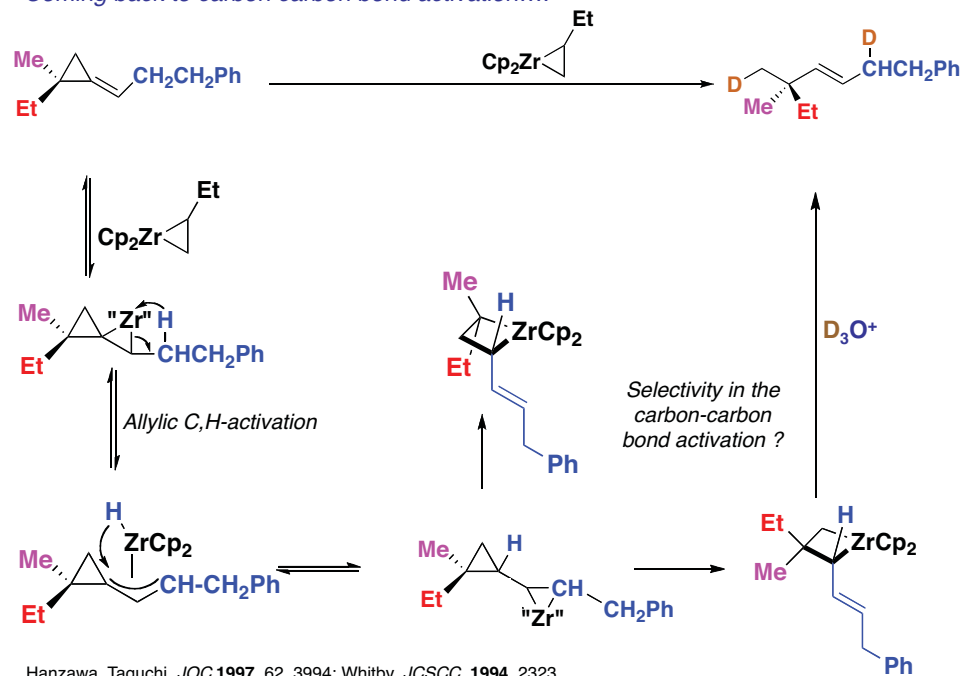


Mechanistic hypothesis

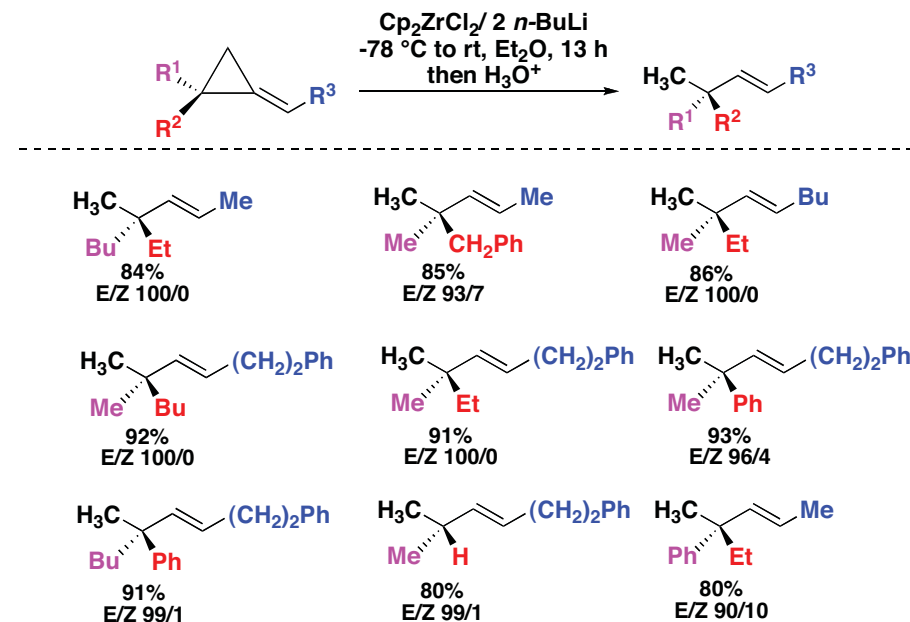


JACS **2002**, *124*, 10282; *JACS* **2003**, *125*, 13258; *ACIE* **2006**, *45*, 465.

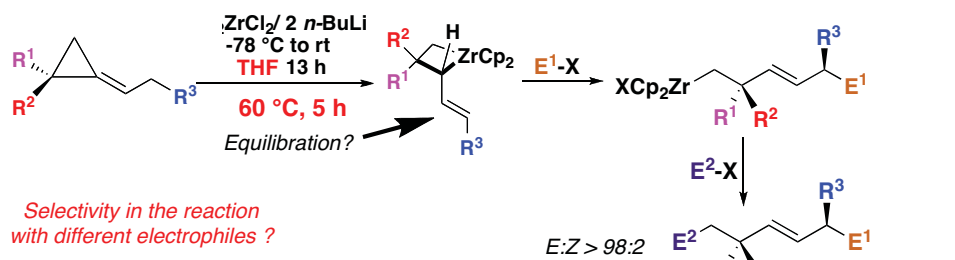
Coming back to carbon carbon bond activation....



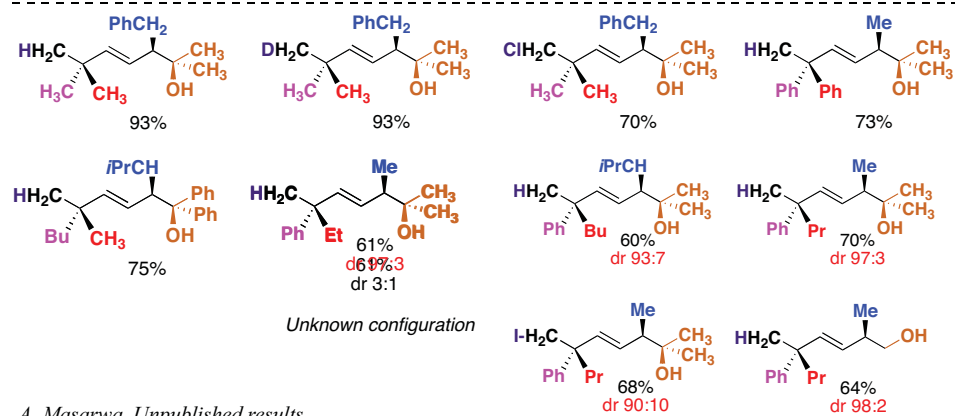
Zirconocene-mediated selective carbon-carbon bond cleavage



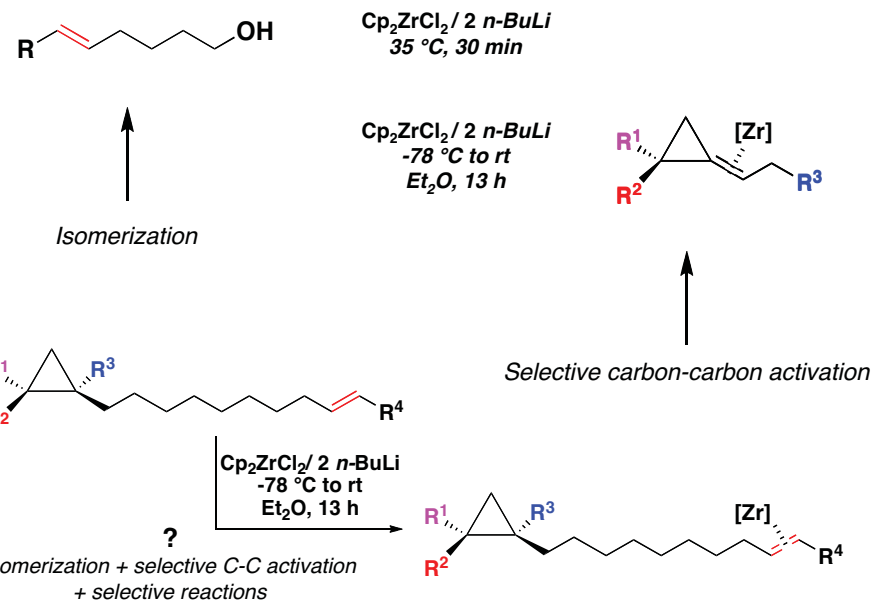
A. Masarwa, Unpublished results



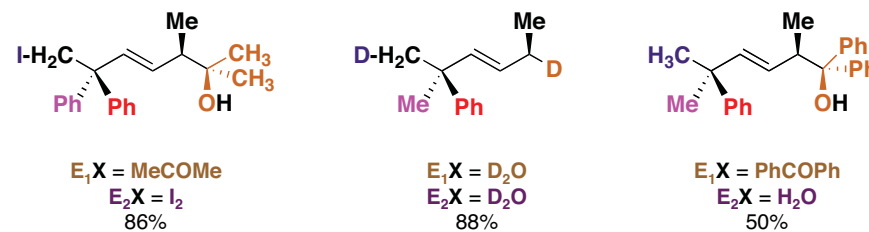
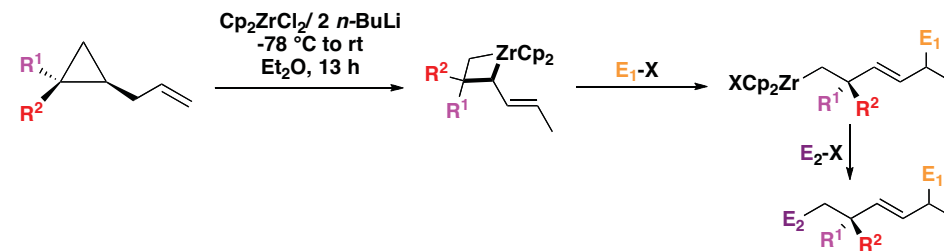
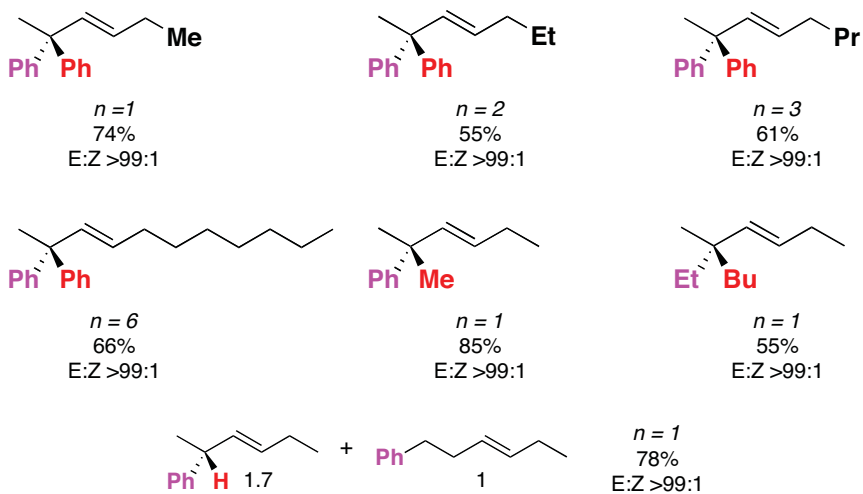
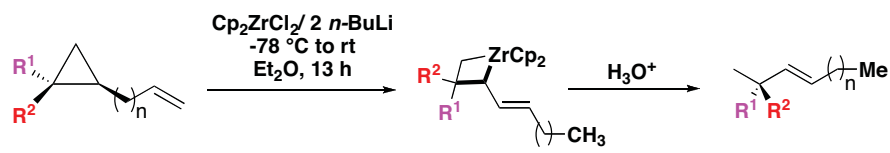
Selectivity in the reaction with different electrophiles ?



A. Masarwa, Unpublished results



Isomerization + selective C-C activation + selective reactions

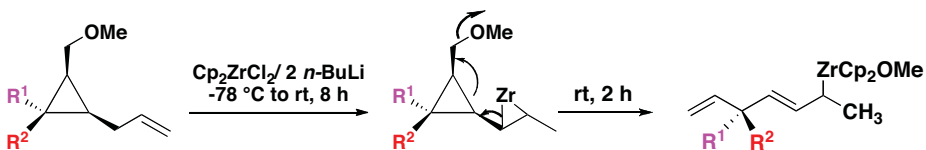


A. Masarwa, T. Zabrodski Unpublished results

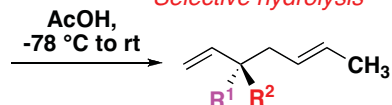
Extension of our "Zr walk" to enantiomerically enriched dienes....

C,H-allylic activation

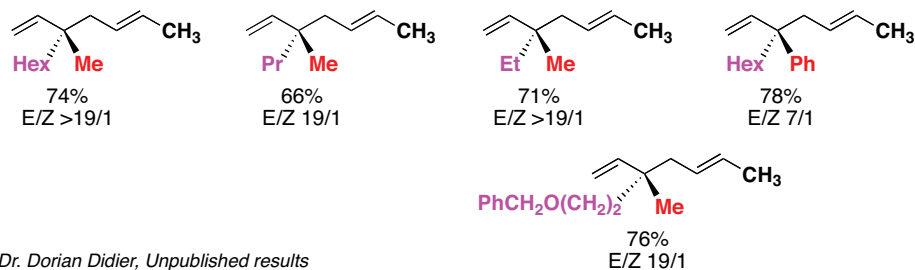
Selective ring-opening



Selective hydrolysis



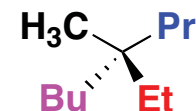
Corey, Davis, Zhang, Katsuki, Doyle, Muller, Pfaltz



Dr. Dorian Didier, Unpublished results

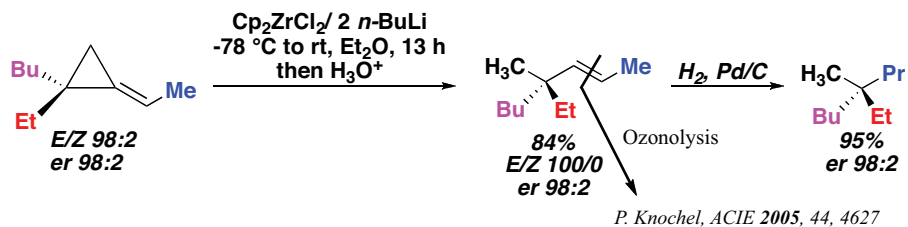
Applications.....

Simplest enantiomerically pure saturated hydrocarbon....



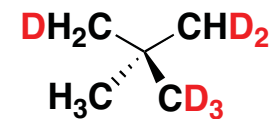
Wynberg, *JOC* 1980; Harada, *TL* 2007; Grimme, *Chirality* 2008; Cramer, *JACS* 2010

Simplest enantiomerically pure saturated hydrocarbon.....



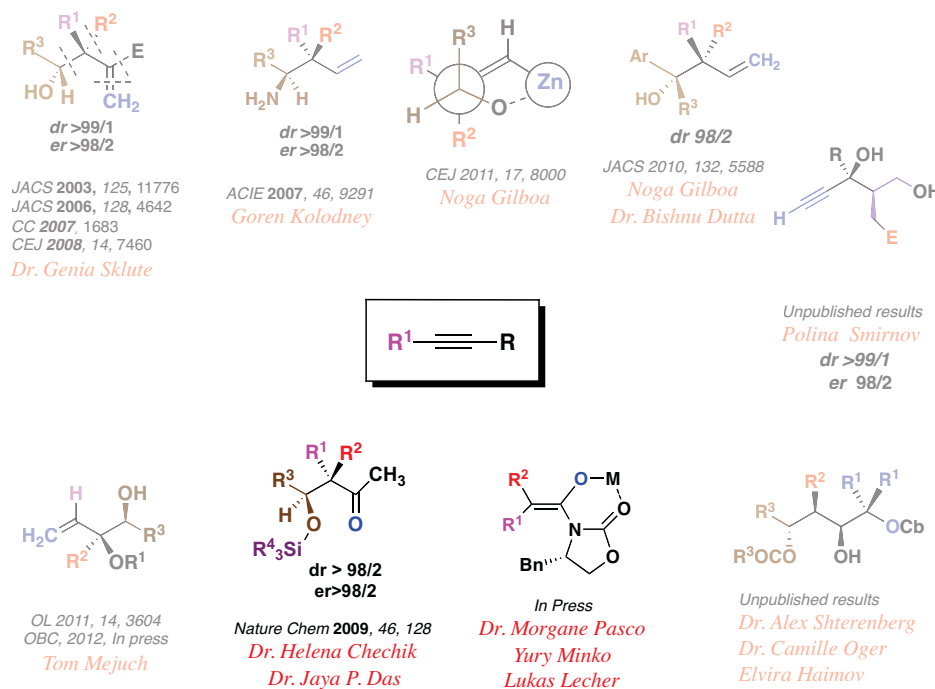
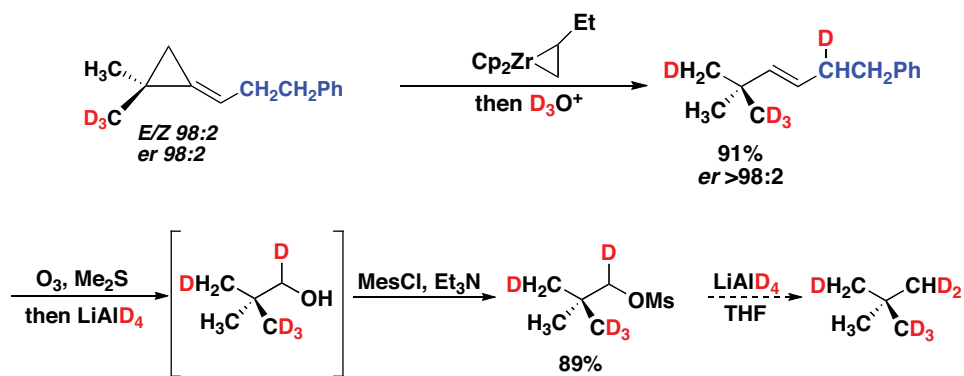
Application to the synthesis of an even more beautiful molecule.....(top-model)

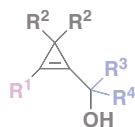
Enantiomerically pure deuterated neopentane....



For determination of absolute configuration, see:
 Haesler, Schindeholz, Riguët, Bochet, Hug, *Nature*, 2007, 446, 526

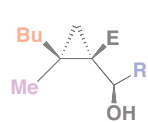
Enantiomerically pure deuterated neopentane....



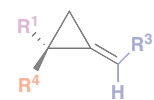


ACIE 2006, 45, 3963
ACIE 2007, 46, 7364
CEJ 2009, 15, 8449

Dr. Samah Simaan
Prof. Philippe Bertus
Ahmad Masarwa

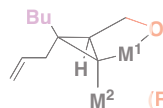


OL 2007, 9, 2569
Dr. Samah Simaan

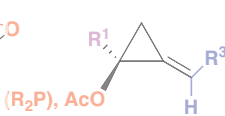


ACIE 2006, 45, 3963
ACIE 2007, 46, 7364
CEJ 2009, 15, 8449

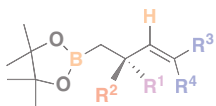
Dr. Samah Simaan
Prof. Philippe Bertus
Ahmad Masarwa



CC 2008, 4300
Dr. Anat Levin

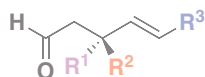


ACIE 2007, 46, 8039
Ahmad Masarwa



CEJ 2010, 16, 774
CEJ 2010, 16, 9712

Dr. Samah Simaan
Alex F. G. Goldberg



JACS 2010, 132, 4066
CEJ 2010, 16, 9712

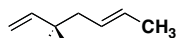
Dr. Samah Simaan



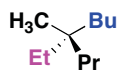
CC 2009, 5760
Ahmad Masarwa



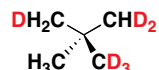
OL 2011, 13, 4076
Dr. Ahmad Basheer



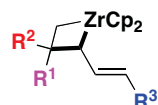
Unpublished
Dr. Dorian Didier



Unpublished
Ahmad Masarwa



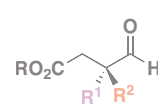
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Tamara Zabrodski
Ahmad Masarwa



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Quantum Chemistry

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Houk (UCLA), Prof. Odile Eisenstein (Montpellier), Prof.
Philippe Lesot (Orsay), Prof. Paul Knochel (Munich),
Prof. Peter Schreiner (Giessen).

Sunset in Haifa