Synthesis of 1,3-Diols *via* Controlled, Radical-Mediated C-H Functionalization

Chen, K.; Richter, J. M.; Baran, P. S.
J. Amer. Chem. Soc. **2008**, *130*, 7247-7249.

Literature Group Presentation

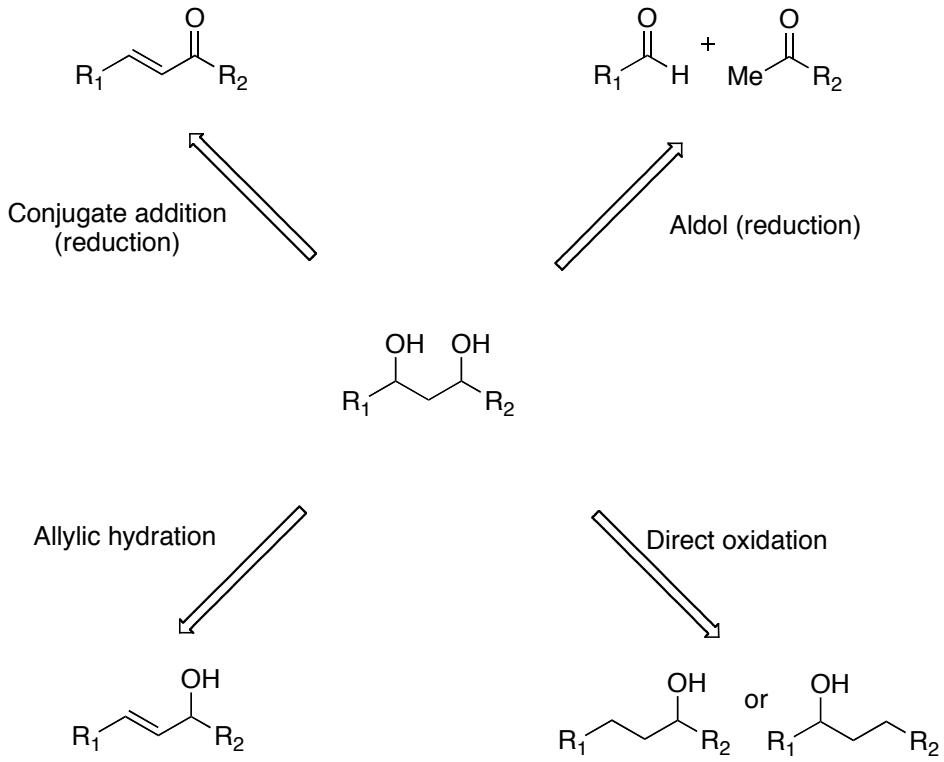
Wynter Gilson

August 1, 2008

Introduction

- Previous work on 1,3-diol synthesis.
- 1,3-diol synthesis inspired by HLF rxn.
- Challenges of this method.
- Use of this method towards synthesis of natural compounds.
- Comparison of selectivity of C-H bond activation with other methods.

Previous work on 1,3-diol synthesis



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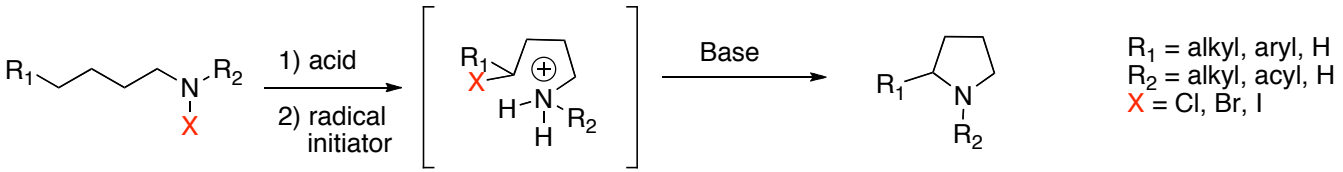
Inspiration from the Hofmann-Löffler-Freytag (HLF) reaction

General HLF reaction



R_1 = alkyl, aryl, H
R_2 = alkyl, acyl, H
X = Cl, Br, I

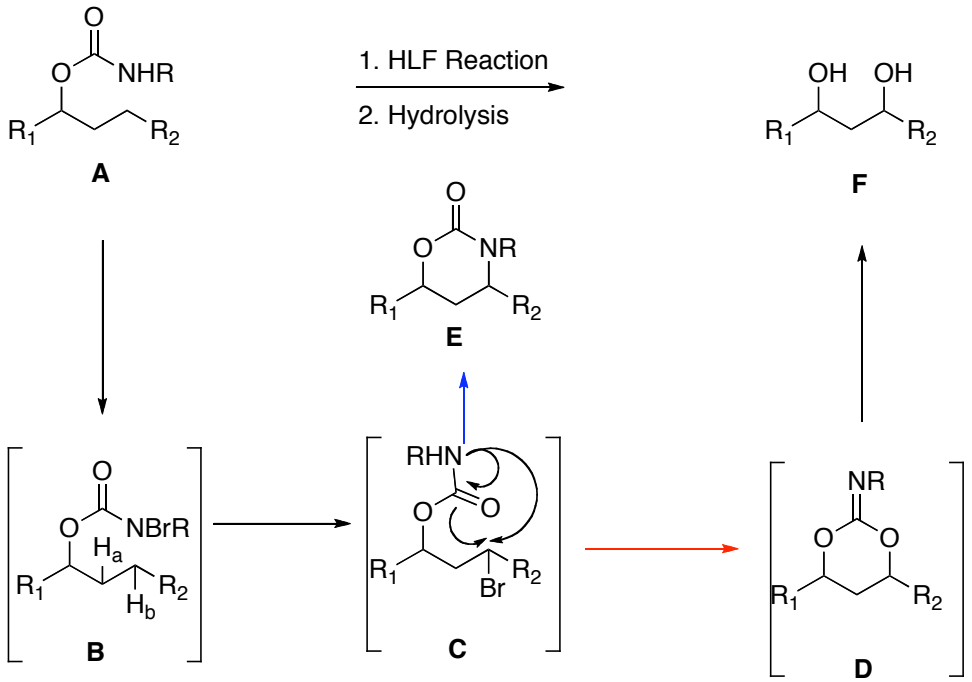
***Reaction is 99 years old.**

***Considered one of the first directed C-H activation reactions ever reported.**

Kurti, L.; Czako, B., *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier Academic Press: Burlington, MA, 2005; p 208.

Incorporating HLF rxn into 1,3-diol synthesis

Modified HLF reaction



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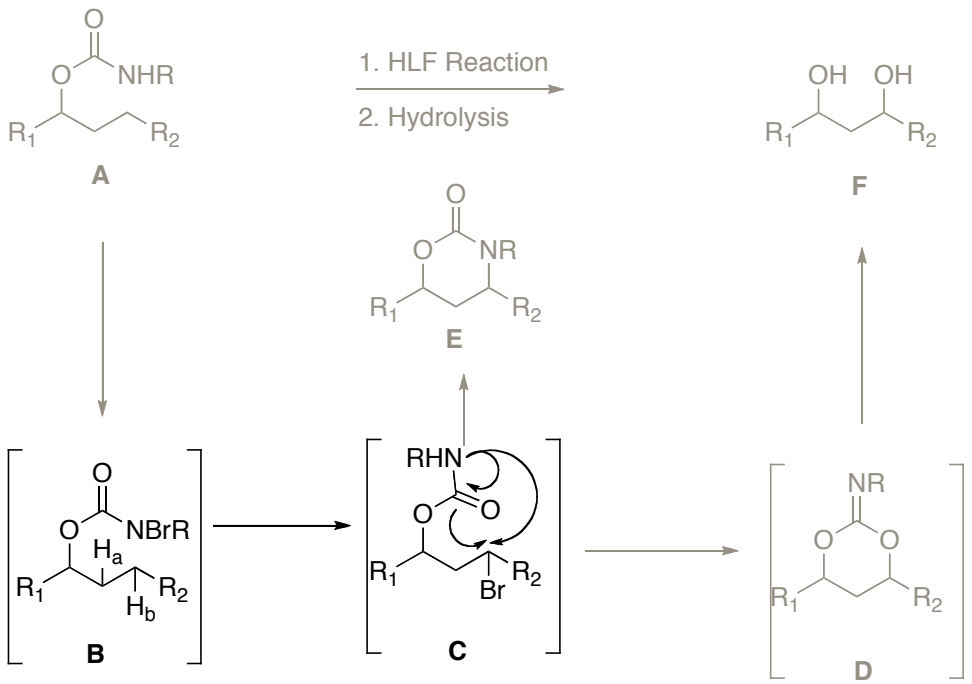
Modified HLF reaction



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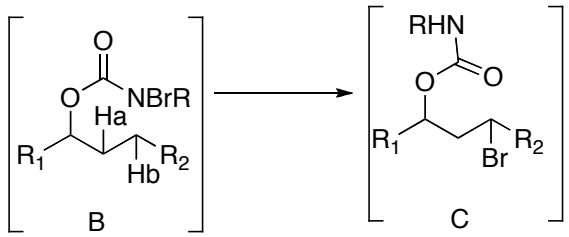
First Challenge



* Most N-bromocarbamates gave < 30 % conversion

* Trifluoroethyl carbamate gave more reactive N-centered radical

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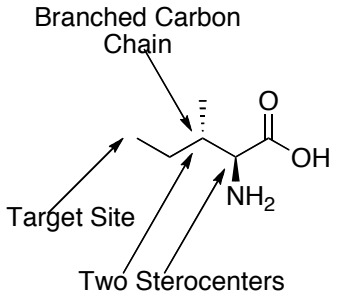
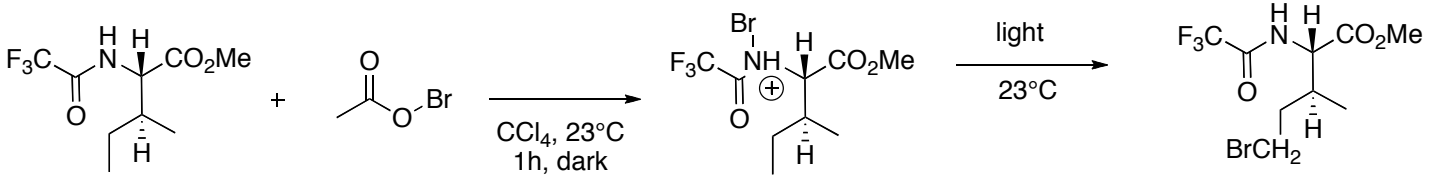
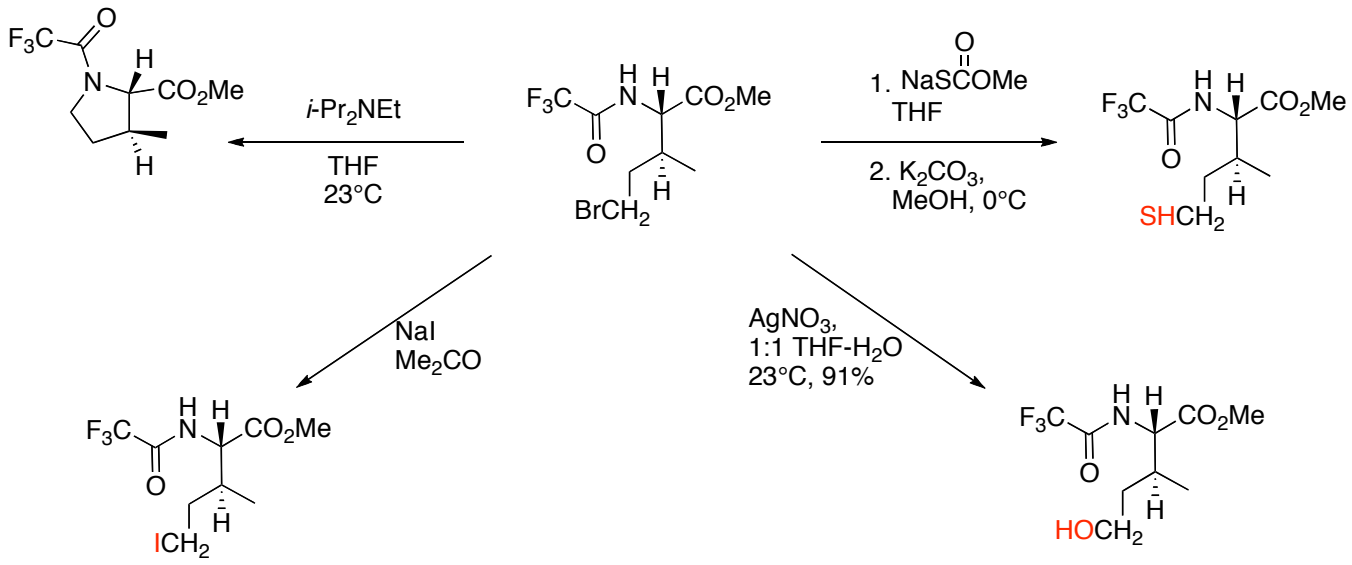
Generate more reactive radical *via* trifluoro-acetylisoleucine methyl ester





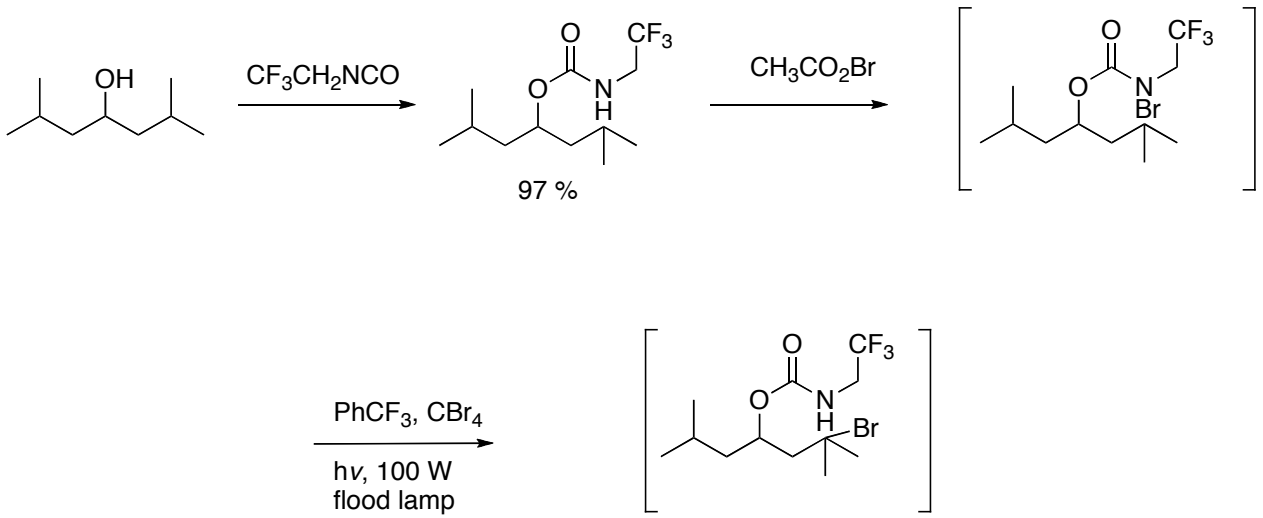
a) Reddy, L. R.; Reddy, B. V. S.; Corey, E. J. *Org. Lett.* **2006**, *8*, 2819-2821.
b) Duhamel, L.; Ple, G.; Angibaud, P. ; Desmurs, J. R. *Synth. Commun.* **1993**, *23*, 2423-2433.
c) Beebe, R.R.; Wolfe, J. W.; *J. Org. Chem.* , **1970**, *35*, 2056-2057.

Variation of trifluoro-acetyl moiety



Reddy, L. R.; Reddy, B. V. S.; Corey, E. J. *Org. Lett.* **2006**, *8*, 2819-2821.

Applying trifluoro compounds to 1,3-diol synthesis



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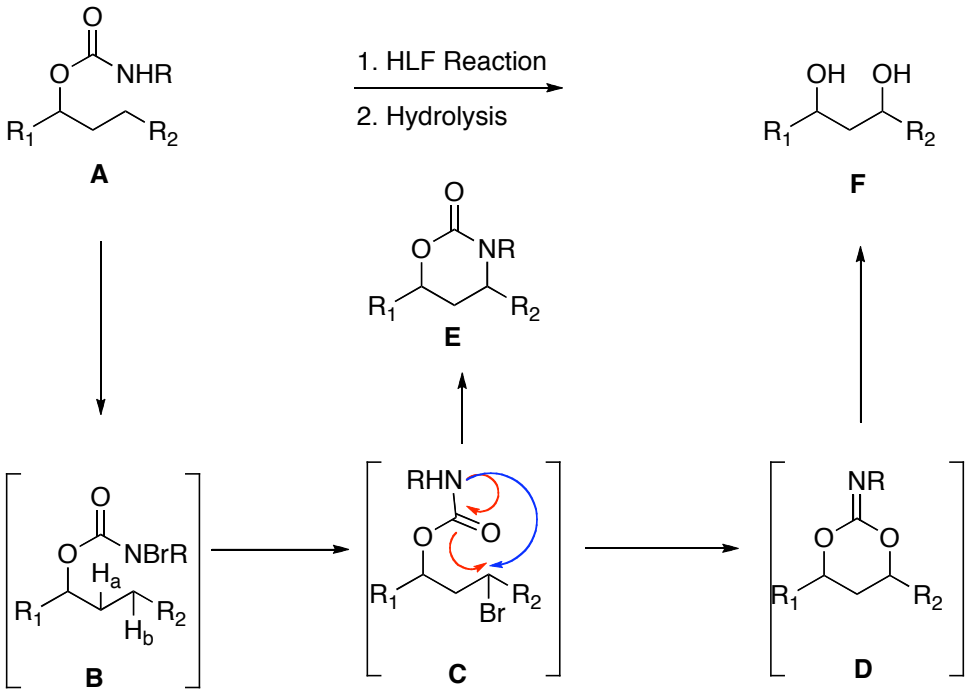
Second Challenge

Modified HLF reaction



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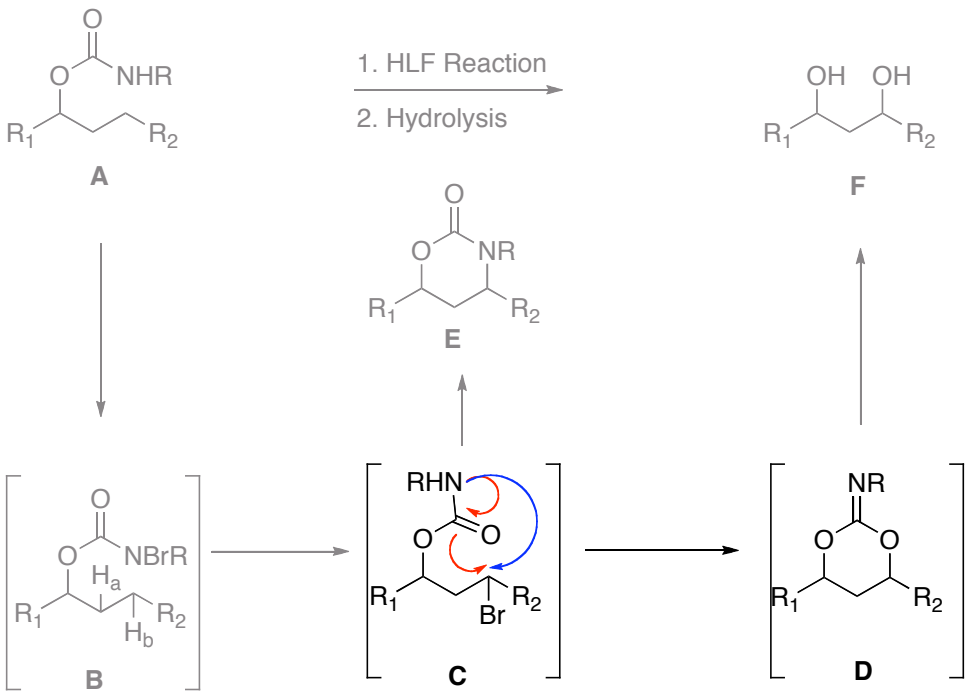
Second Challenge

Modified HLF reaction



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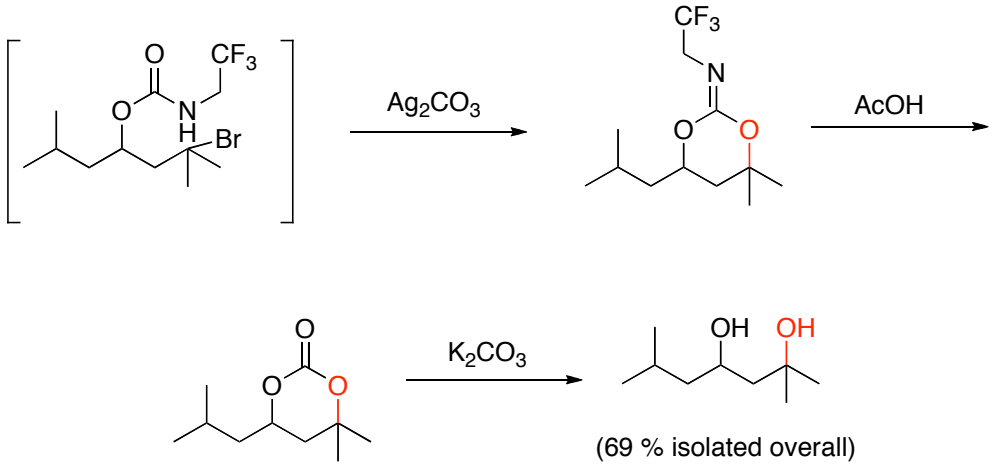
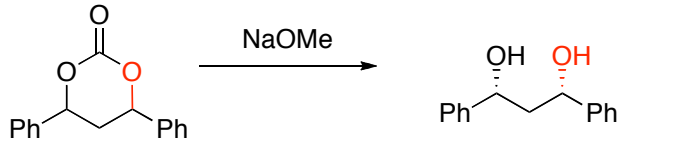
Second Challenge

Aliphatic Cases:



(69 % isolated overall)

Benzylic Cases:



(91 % isolated, *dr* 1:1)

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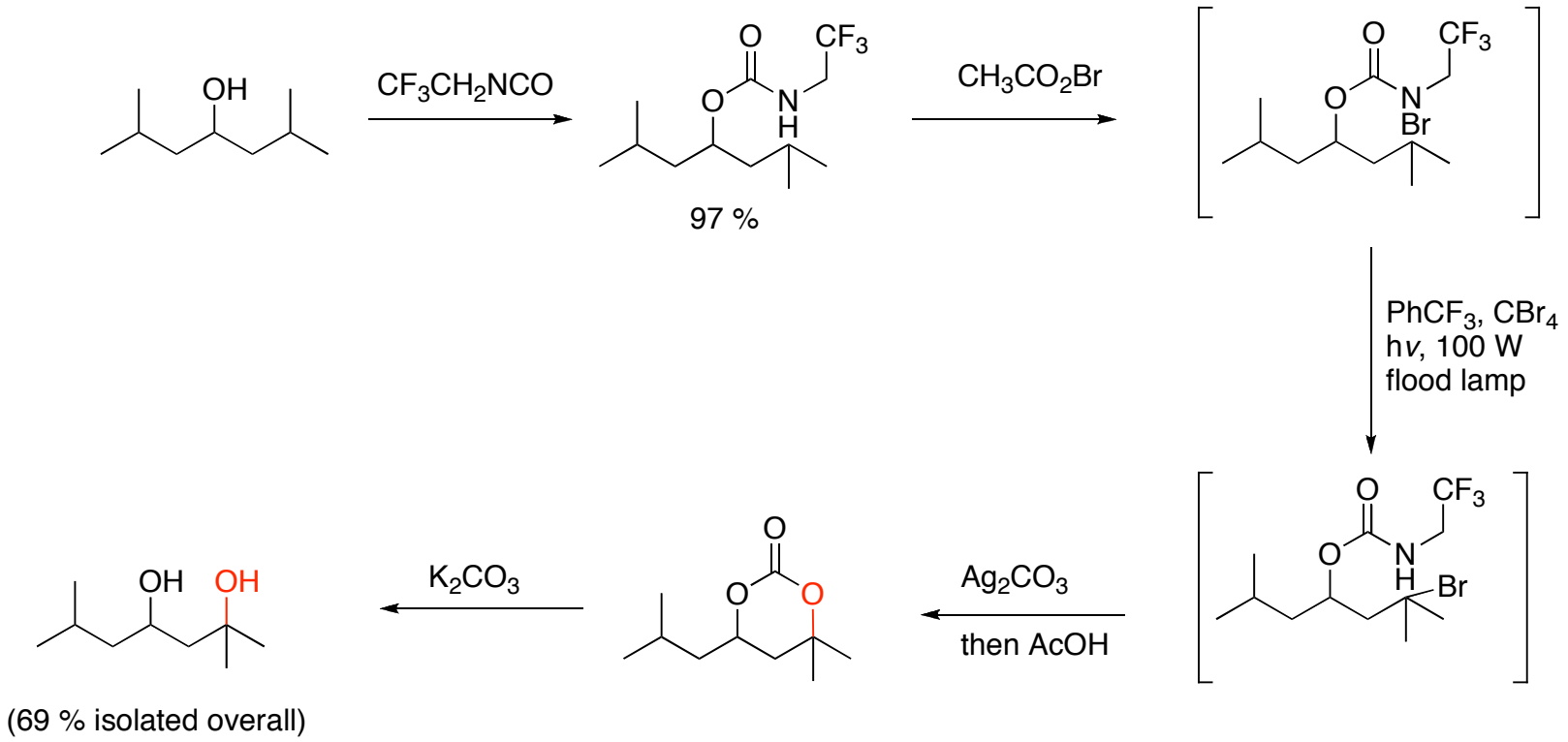
Synthesis of 1,3-diol



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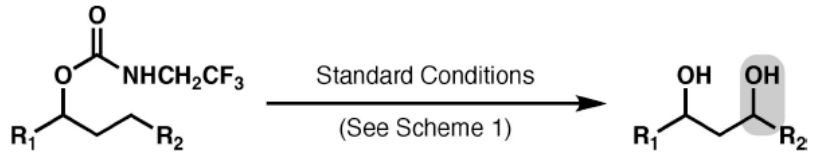
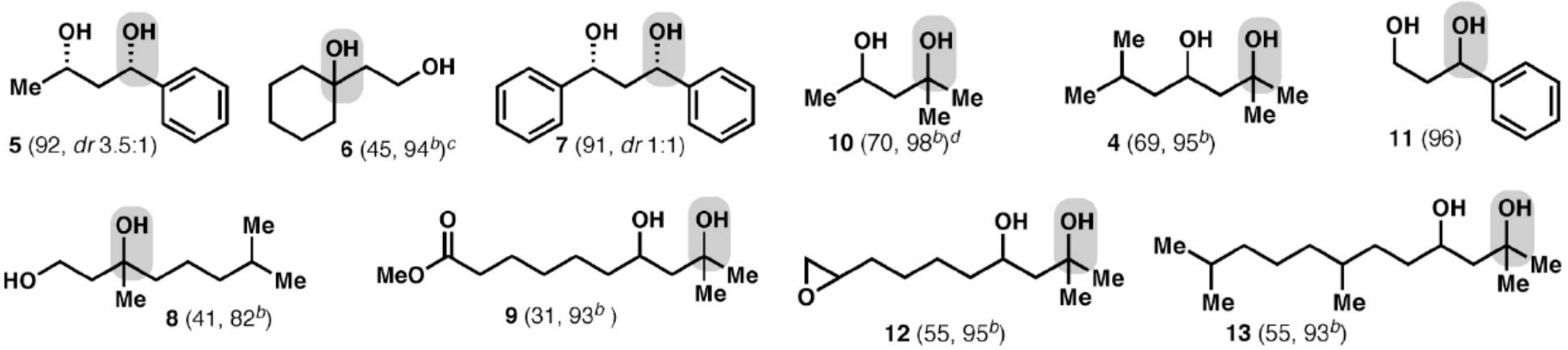
Scope of 1,3-diol synthesis

Table 1. Scope of Directed C–H Oxidation



Diol Yield (%)[a]



[a] Isolated yield. [b] Yield brsm. [c] CBr_4 is not necessary. [d] A 56% isolated yield on gram scale; 88% yield brsm.

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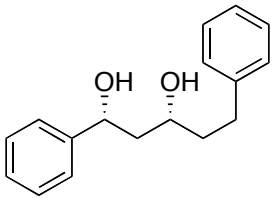
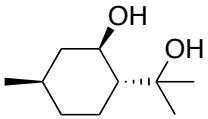
Synthesis of natural products



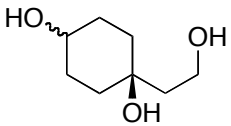
70 %, *dr* 8:1

Previous synthesis: 4 steps, 12%



42 %

9 Previous synthesis



36 % *dr* 3:2

Previous synthesis: 13 steps, 29 %

8 steps, 3.2%, *dr* 3:1

α = isorengyol
β = rengyol

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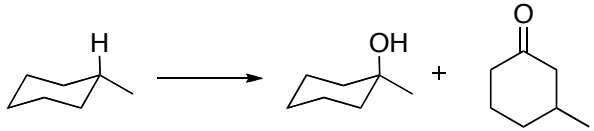
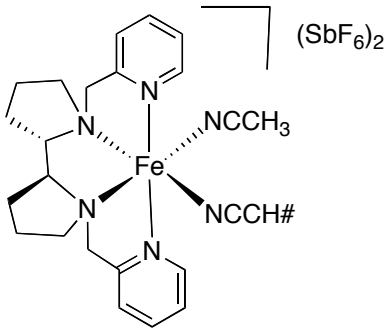
Comparison of selectivity of tertiary C-H bond activation

Curci [O] (dioxirane)

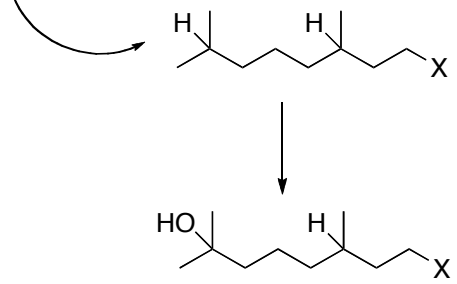
Gives both alchohol and ketone products.





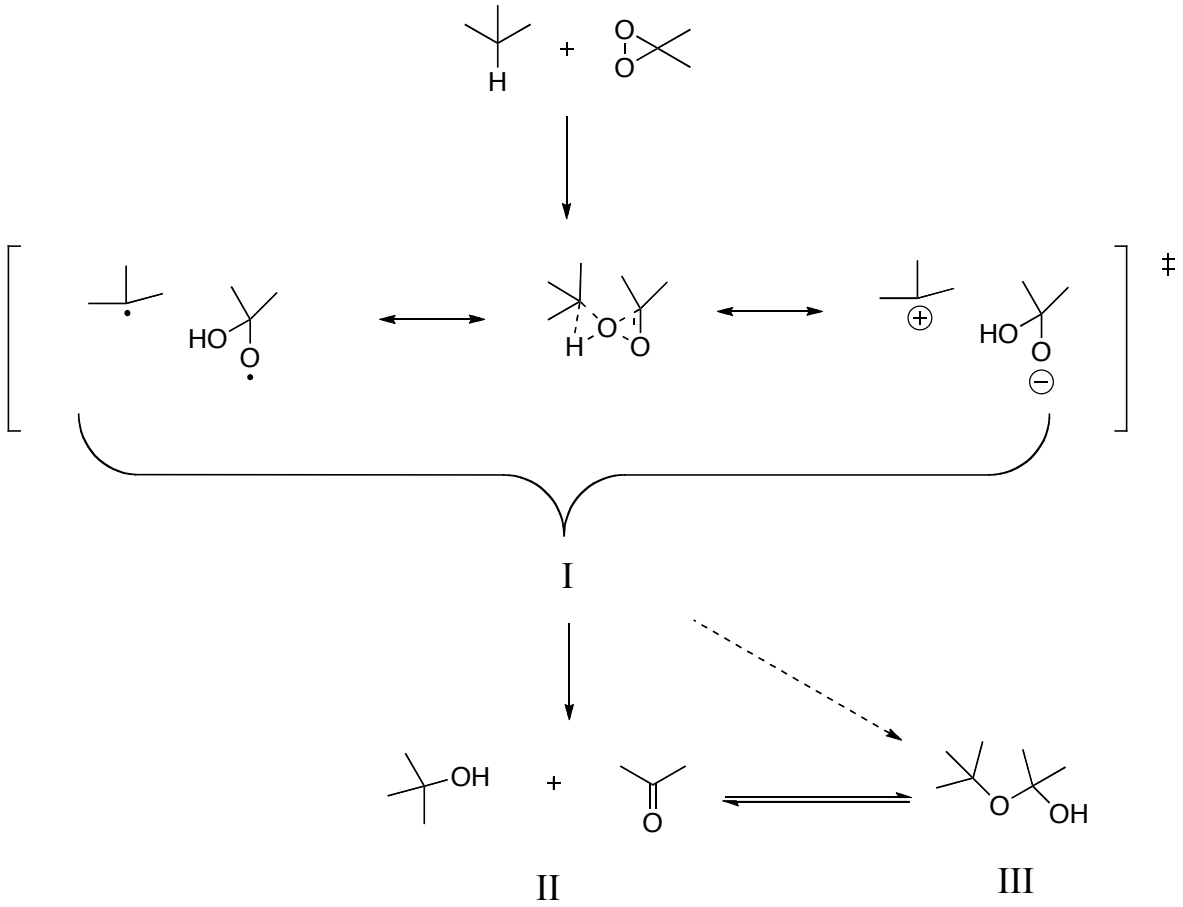
White Fe-based catalyst

Targets remote tertiary position

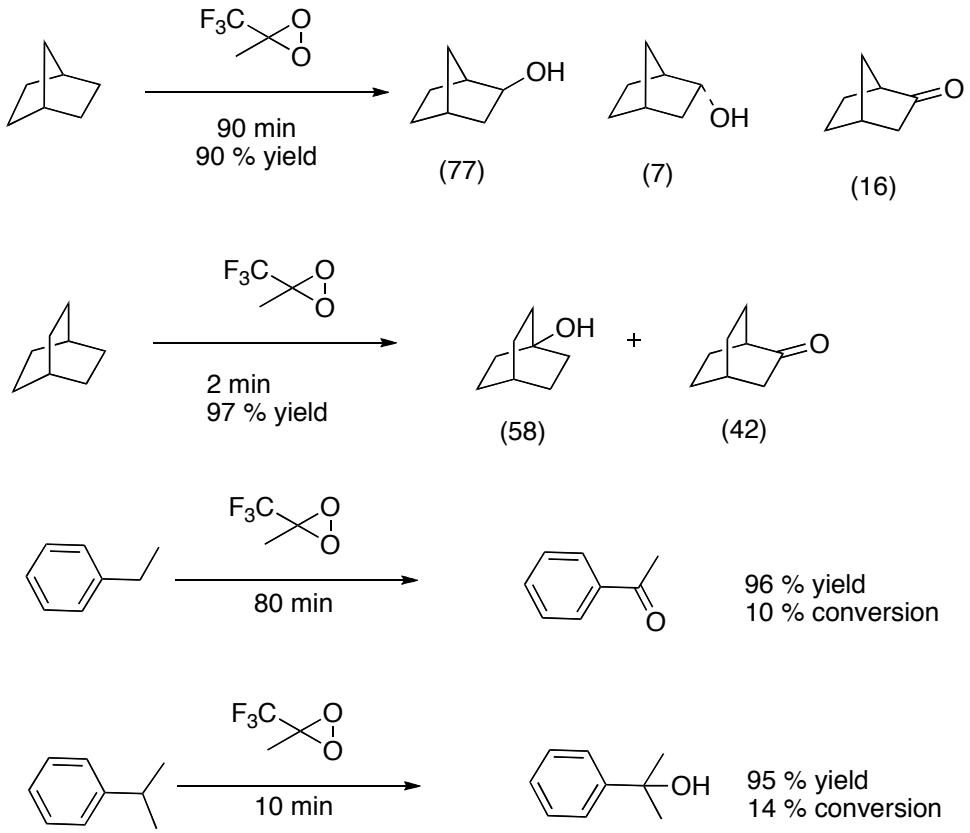


a) Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Amer. Chem.* **1989**, *111*, 6749-6757.
b) Chen. M. S.; White, M. C. *Science* **2007**, *318*, 783-787.

Curci method's proposed mechanism

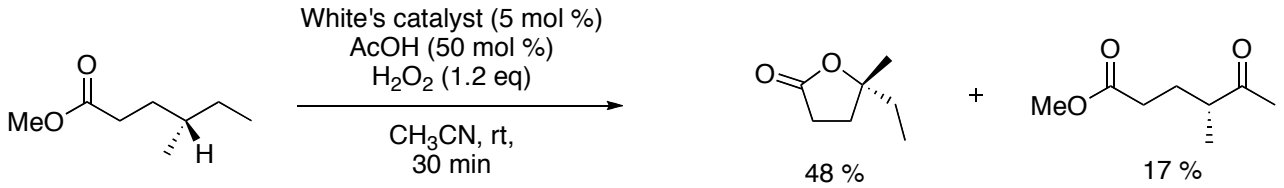


Curci method

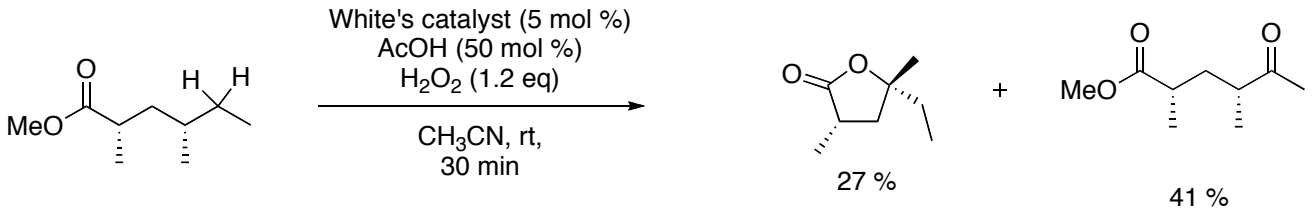


White's method

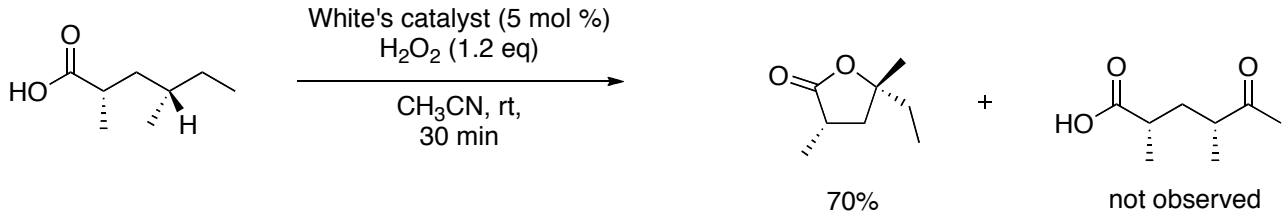
Electronic:



Steric:



Directed:



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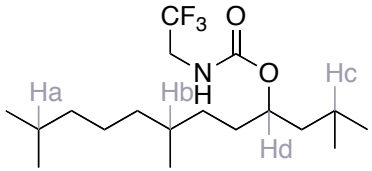
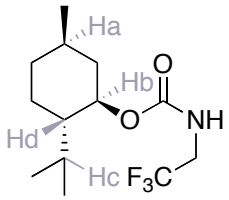
Comparison of selectivity of tertiary C-H bond activation





- White catalyst selective for H_a.
- Curci non-selective
- This work selective for H_c.

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Conclusion

- Only method for conversion of alcohols to 1,3-diols.
- Practical method using simple reagents.
- Capable of installing hydroxy functionality in a late stage thereby reducing unproductive chemical manipulations.