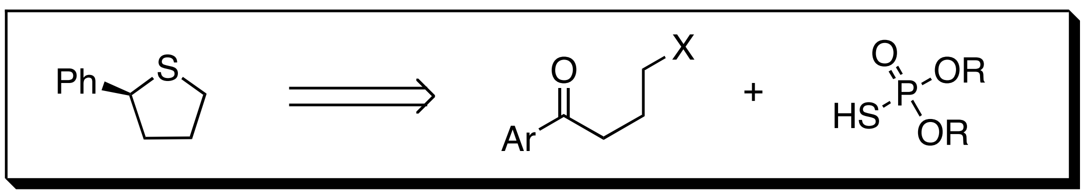
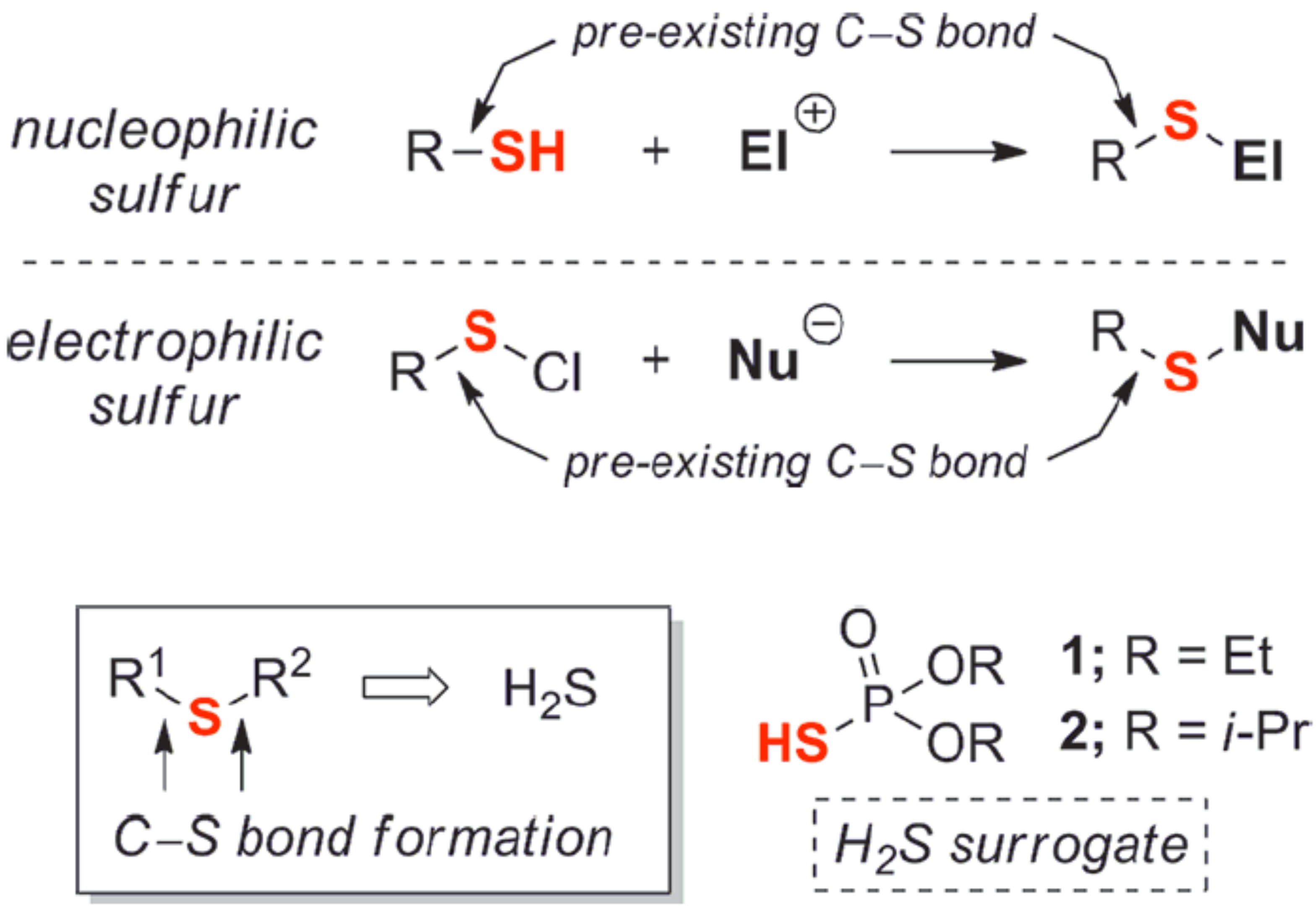
Phosphorothioic Acids and Related Compounds as Surrogates for H_2S-Synthesis of Chiral Tetrahydrothiophenes

Forest J. Robinson and Jimmy Wu *J. Am. Chem. Soc.* **2012,** *134,* 2775-2780



Melissa Sprachman
Current Literature
February 18, 2012

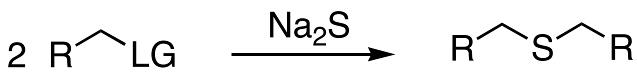
Summary of Sulfide Bond Construction



Copied from *J. Am. Chem. Soc.* **2012,** *134,* 2775-2780.

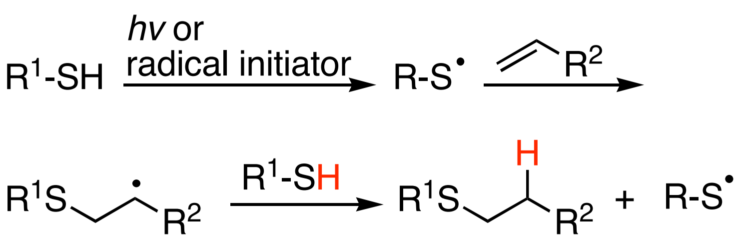
Methods for Sulfide Bond Construction

Synthesis of Symmetrical Sulfides



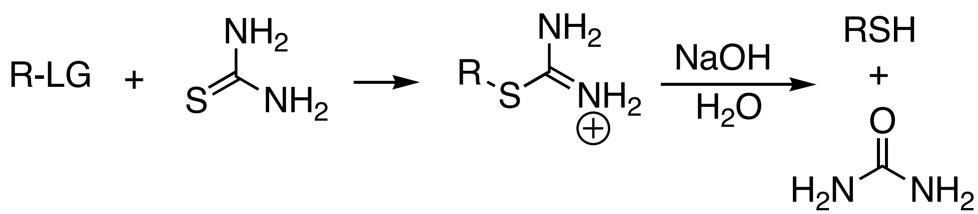
Synthesis of Asymmetrical Sulfides

The Thiol-Ene Coupling Reaction

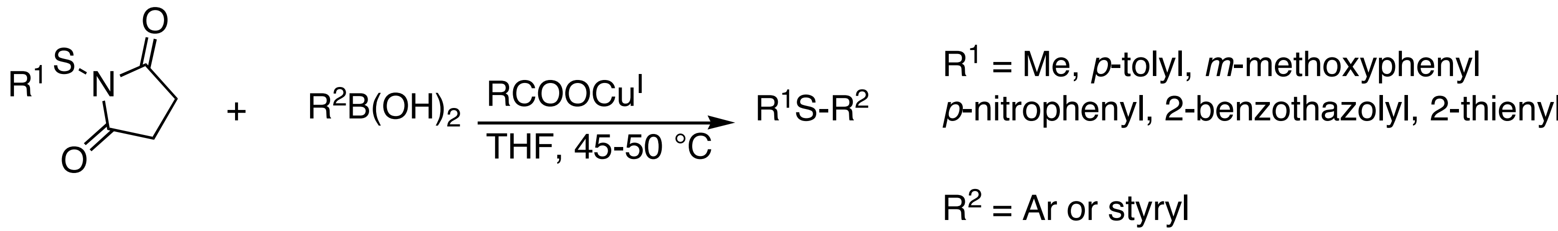


Dondoni, A. *Angew. Chem. Int. Ed.* **2008,** *47,* 8995-8997.

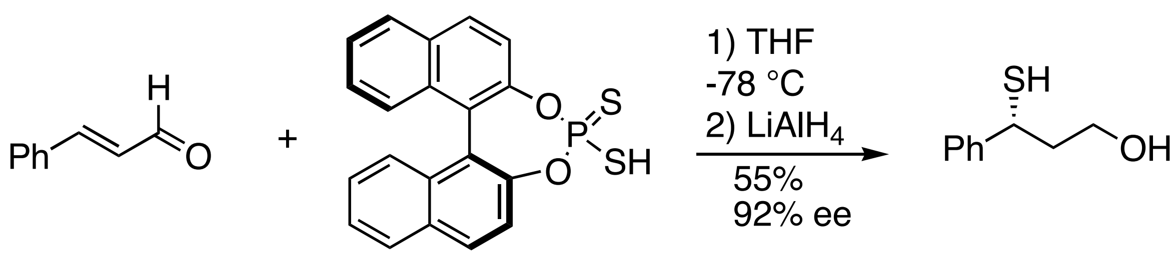
Thiol Synthesis



Additional Carbon-Sulfur Bond Constructions

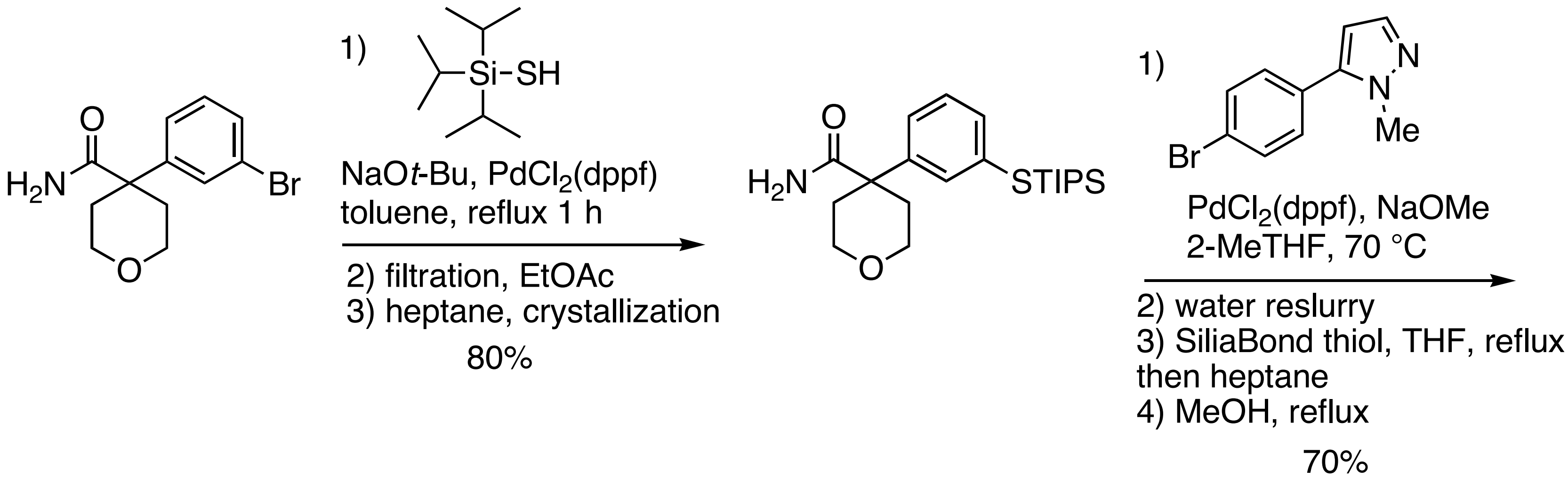


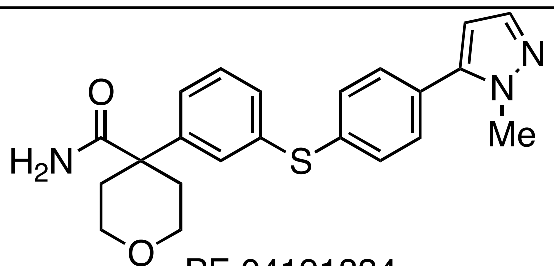
Savarin, C.; Strogl, J.; Liebeskin, L. S. *Org. Lett.* **2002,** *4,* 4309-4312.



Enders, D.; Lüttgen, K.; Narine, A. A. *Synthesis,* **2007,** *7,* 959-980.

Additional Reagents for Sulfide Bond Formation





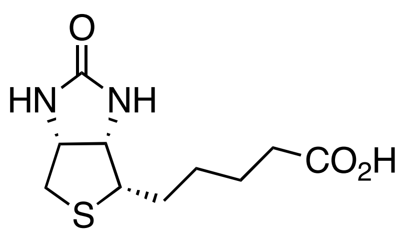
PF-04191834

(Pfizer, 5-Lipoxygenase Inhibitor)

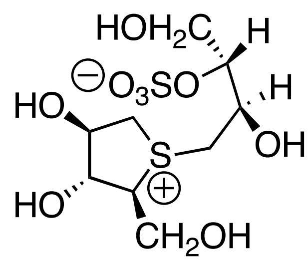
de Koning, P. D.; Murtagh, L.; Lawson, J. P.; Vonder Embse, R. A.; Kunda, S. A.; Kong, W. *Org. Process Res. Dev.* **2011,** *15,* 1046-1061.

Significance of the Tetrahydrothiophene Moeity

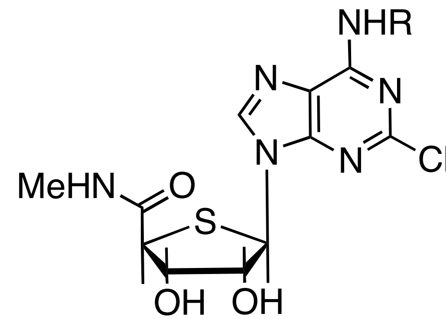
Natural Products and Medicinal Chemistry:



Biotin
For syntheses see
Chem. Rev. **1997,** *97,* 1755-1792.

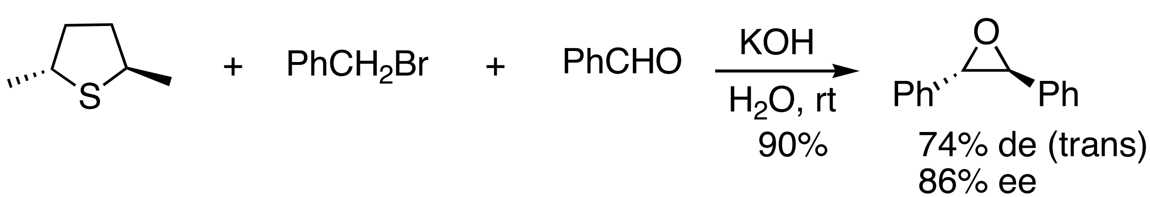


Salacinol (α-glucosidase inhibitor)
Bioorg. Med. Chem. **2002,** 10, 1547-1554.
Tetrahedron Lett. **1997,** *38,* 8367-8370.



Agonists/antagonists for adenosine receptors
J. Med. Chem. **2003,** *46,* 3775-3777.

Reagents and Ligands for Enantioselective Transformations:



Julienne, K.; Metzner, P. *J. Org. Chem.* **1998,** *63,* 4532-4534.

Significance of the Tetrahydrothiophene Moeity

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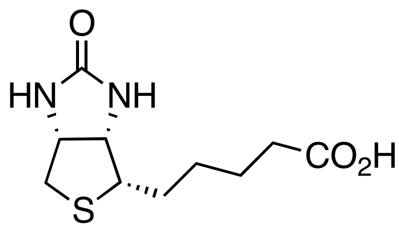
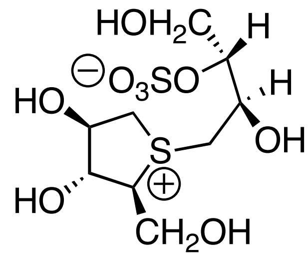
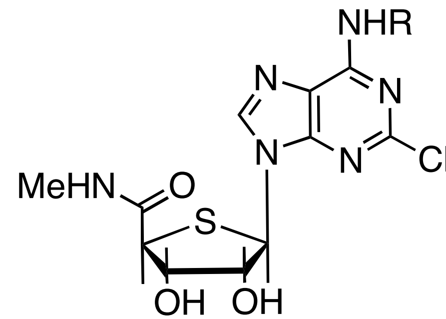


Biotin
For syntheses see
Chem. Rev. **1997,** *97,* 1755-1792.



Salacinol (α-glucosidase inhibitor)
Bioorg. Med. Chem. **2002,** 10, 1547-1554.
Tetrahedron Lett. **1997,** *38,* 8367-8370.



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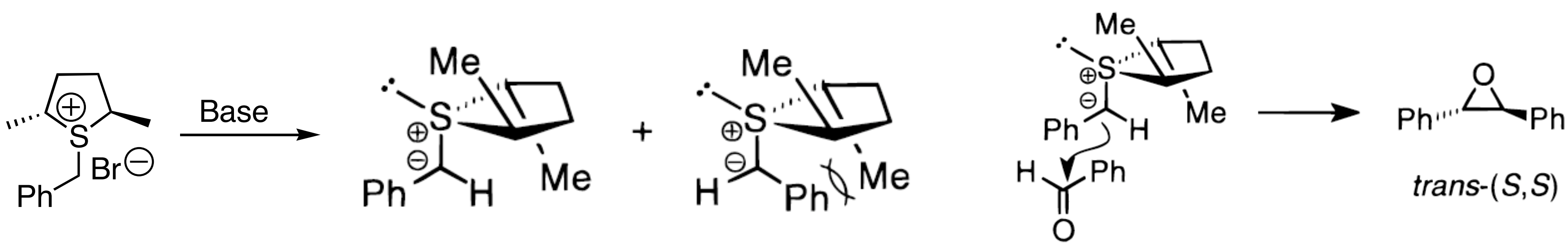
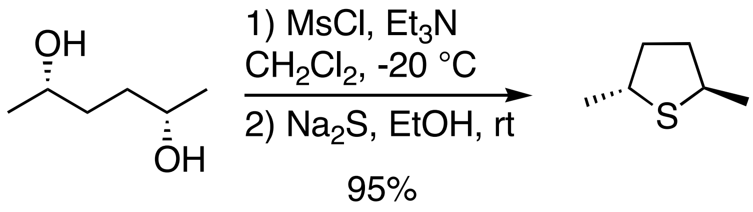
Reagents and Ligands for Enantioselective Transformations:



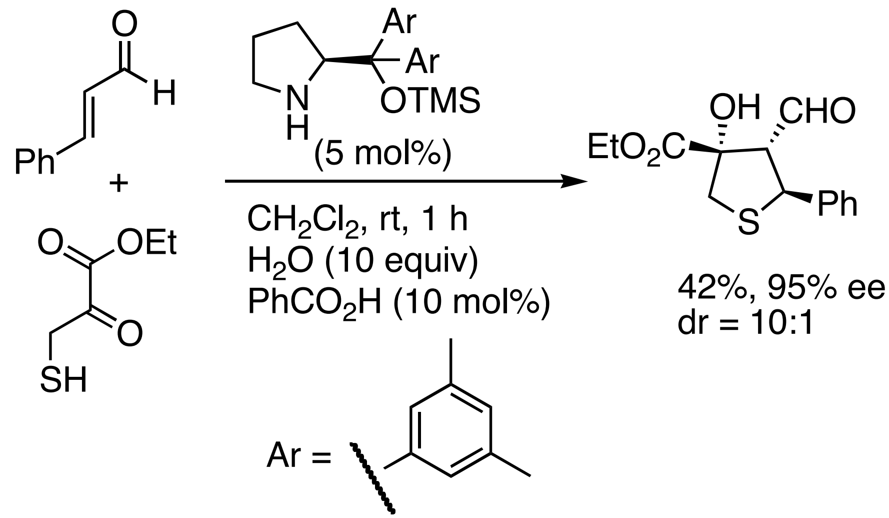
Methods for Tetrahydrothiophene Construction

Double displacement of enantiomerically pure diols:



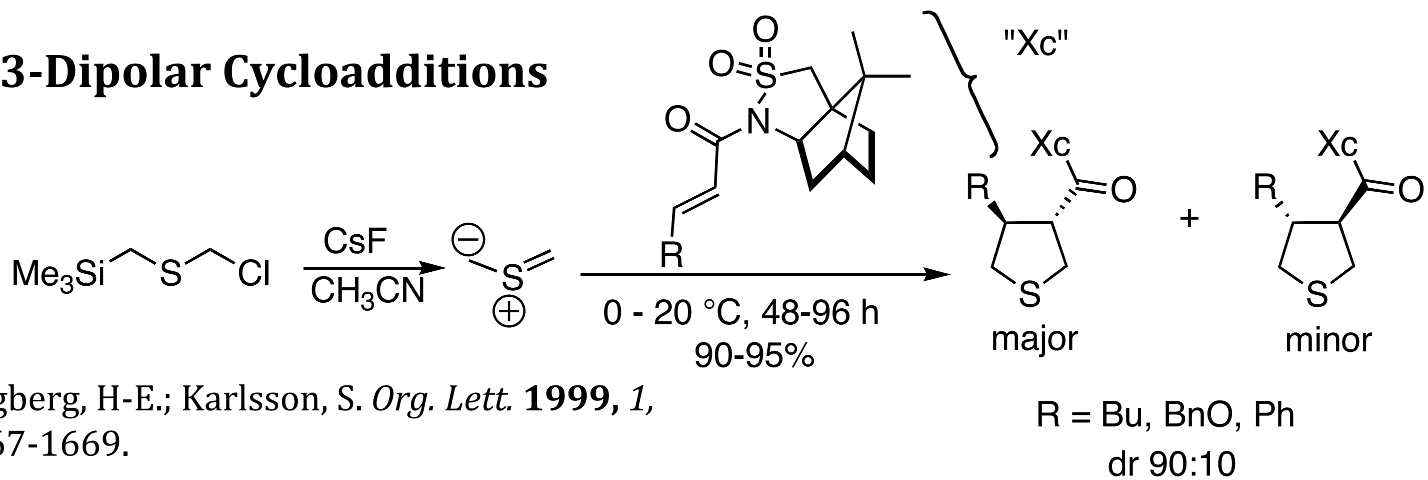
Julienne, K.; Metzner, P. *J. Org. Chem.* **1998,** *63,* 4532-4534.

Organocatalytic Michael-aldol cascade:



Luo, G.; Zhang, S.; Duan, W.; Wang, W. *Tetrahedron Lett.* **2009,** *50,* 2946-2948.

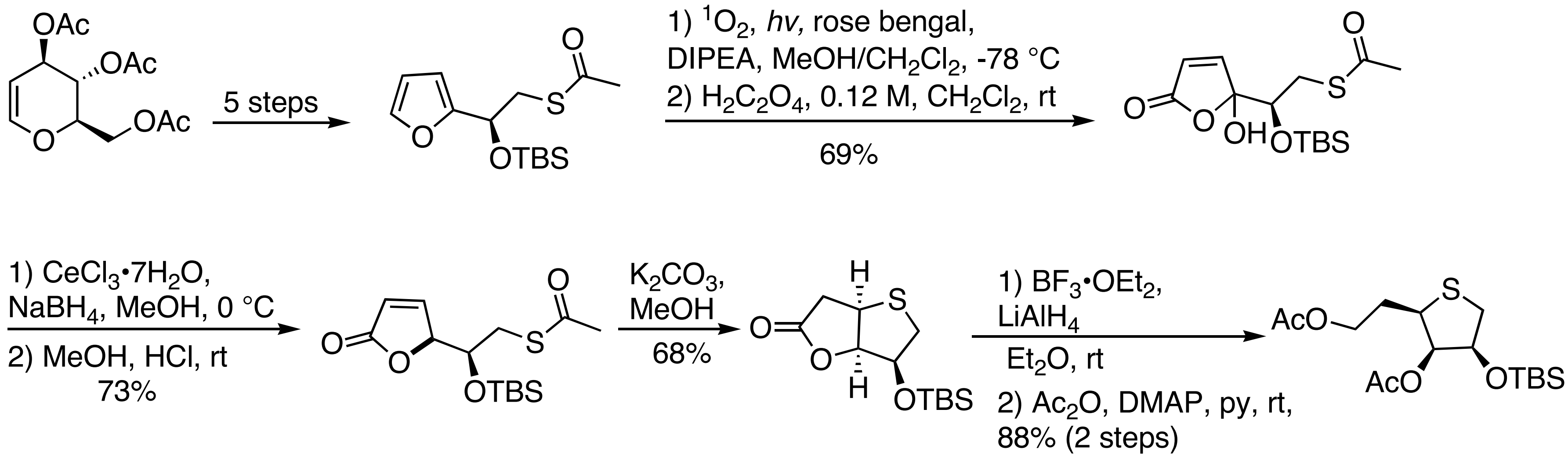
1,3-Dipolar Cycloadditions



Högberg, H-E.; Karlsson, S. *Org. Lett.* **1999,** *1,* 1667-1669.

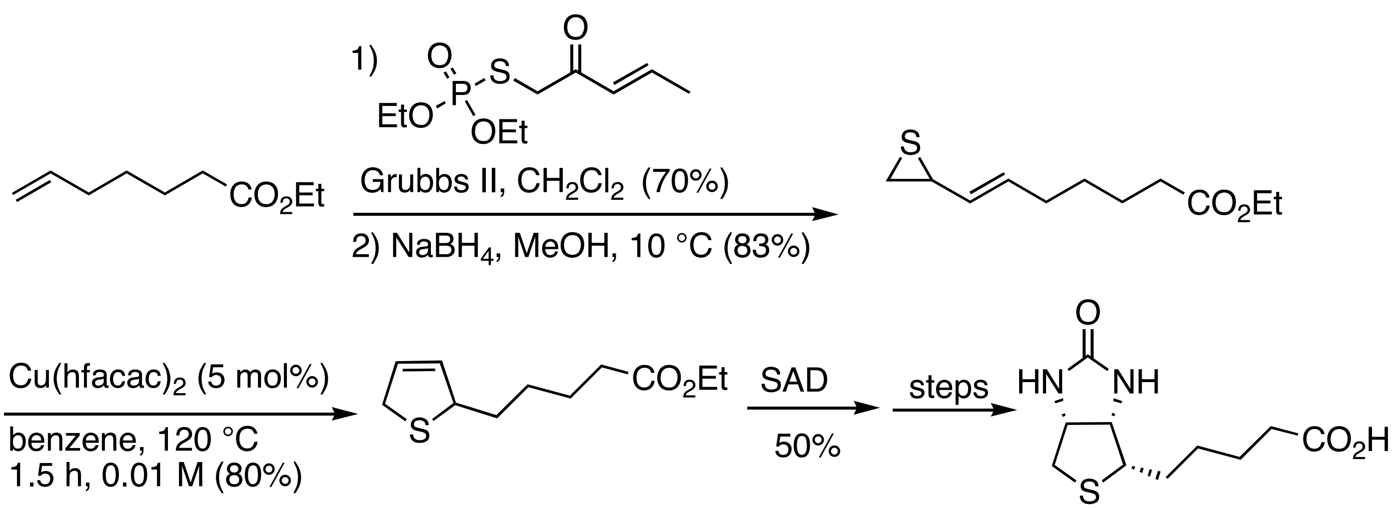
Methods for Tetrahydrothiophene Construction

Intramolecular hetero Michael addition:



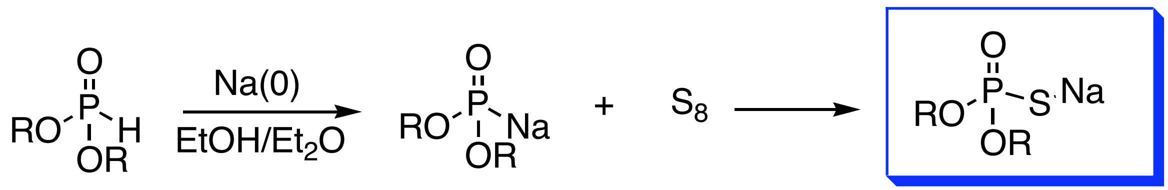
Besada, P.; Pérez, M.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2009,** *50,* 6941-6943.

Copper-Catalyzed Ring Expansion of Vinyl Thiiranes:

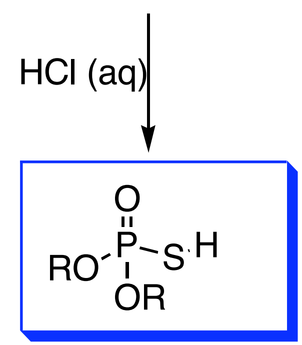


Rogers, E.; Araki, H.; Batory, L. A.; McInnis, C. E.; Njardarson, J. T. *J. Am. Chem. Soc.* **2007,** *129,* 2768-2769.

Synthesis of *O,O*-Dialkyl Phosphorothioic Acids



isolated by filtration through Celite



isolated after acidic workup/extraction

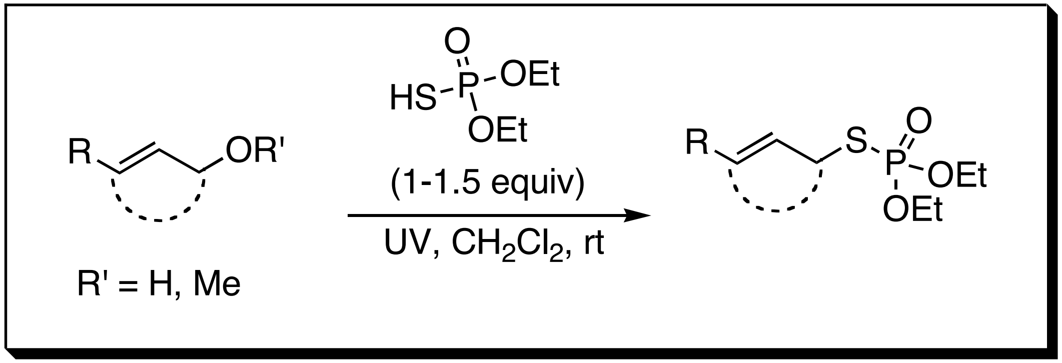
Diethyl phosphite: \$23.60/250 g (Aldrich)

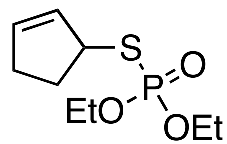
LD_{50} (oral, rat): 3,900 mg/kg
LD_{50} (dermal, rabbit): 2,167 mg/kg

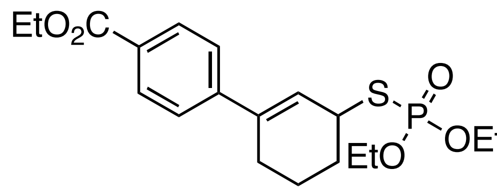
Sulfur: \$102/1 kg (Aldrich)
LD_{50} (oral, rabbit): 175 mg/kg
LD_{50} (oral, rat): 2,000 mg/kg
LC_{50} (inhalation, rat) - 4 h :9.23 mg/L
LD_{50} (dermal, rabbit) - 2,000 mg/kg

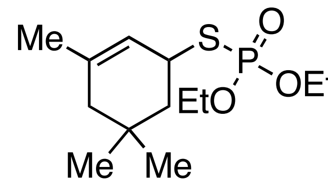
Hydrogen Sulfide: \$308/(lecture bottle?); Health Hazard 4 Gas
NaSH•xH_2O: \$63.20/kg (Aldrich); **KSAc:** \$137/g (Aldrich)

Previous Work: Allylic Thiolation Reactions



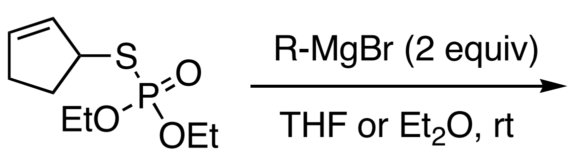


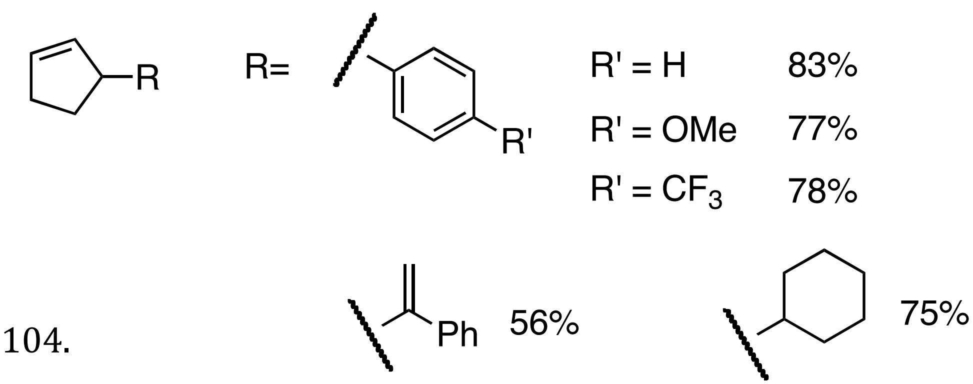




From the allylic alcohol:	72%	62%	83%
From the allylic ether:	73%	70%	91%

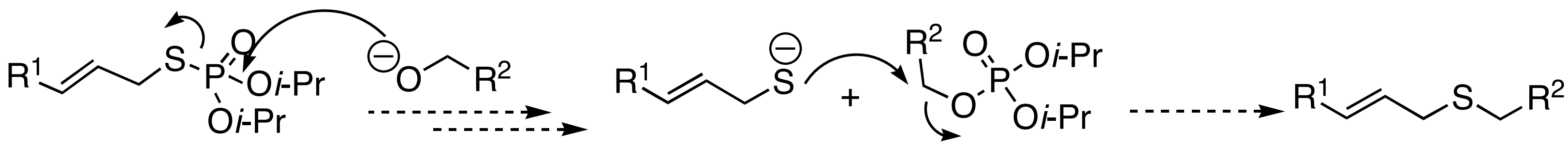
Application to C-C Bond Formation

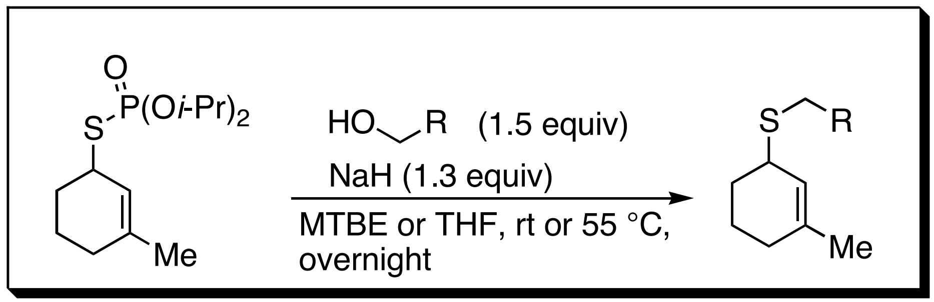


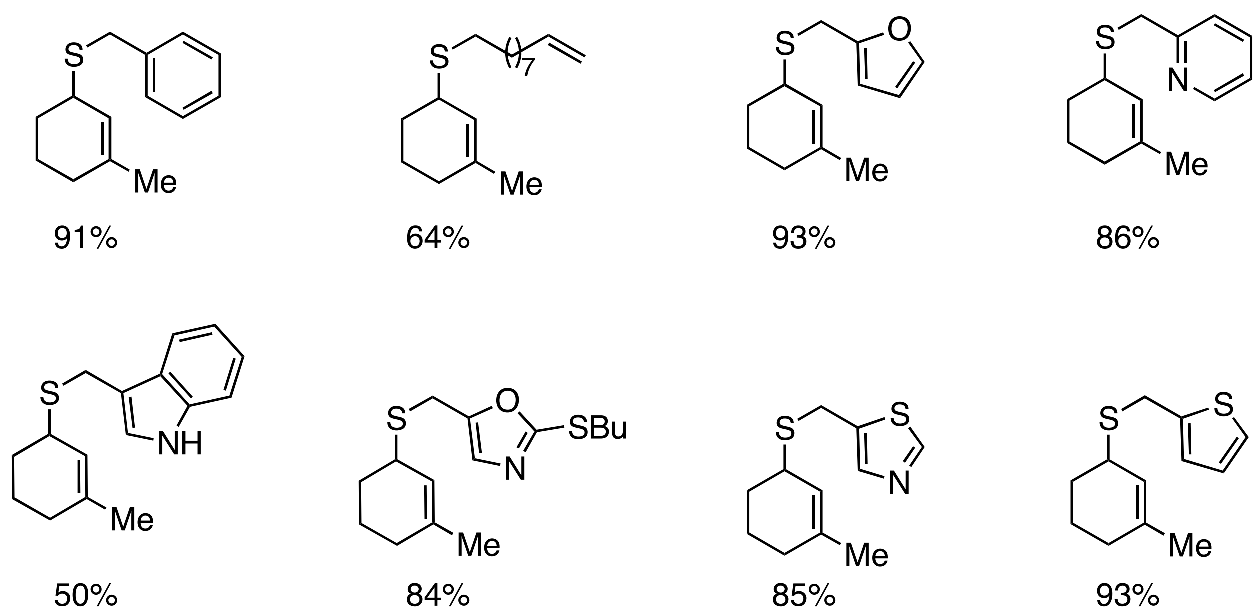


Han, X.; Zhang, Y.; Wu, J. *J. Am. Chem. Soc.* **2010,** *132,* 4104.

Previous Work: Synthesis of Allylic Thioethers

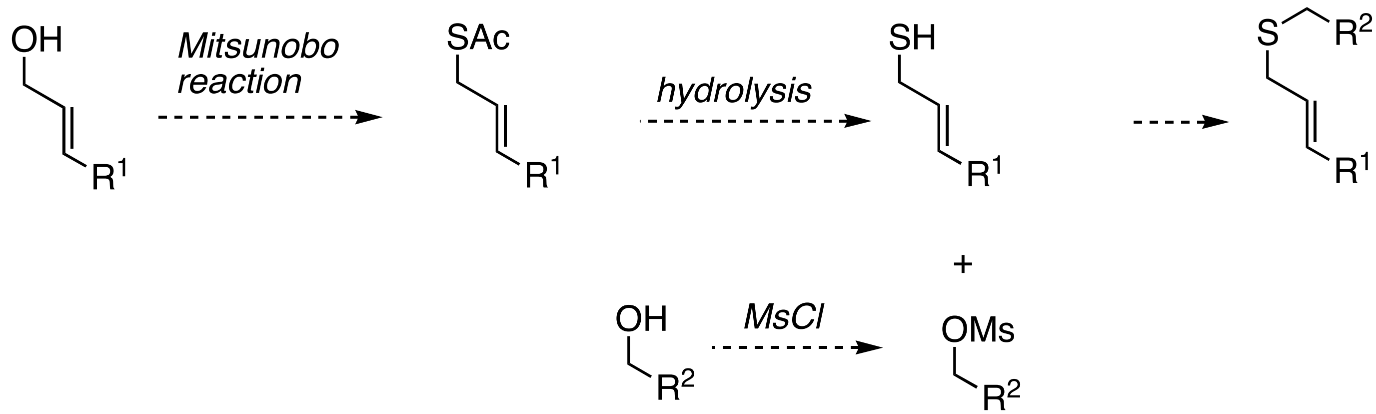






Robertson, F.; Wu, J. *Org. Lett.* **2010,** *12,* 2668.

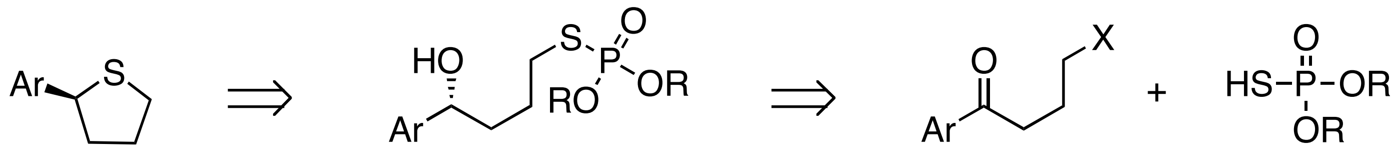
Synthesis of Allylic Thioethers



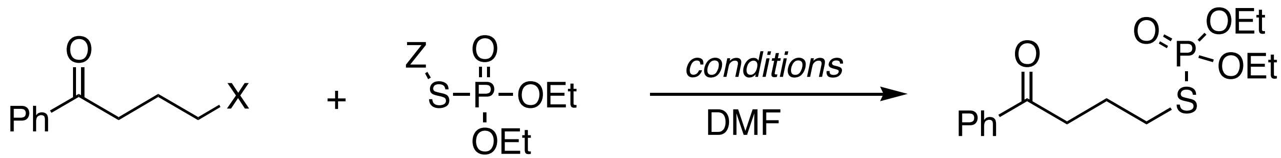
Research Area	Number of Roundtable companies voting for this research area as a priority area
Amide formation avoiding poor atom economy reagents	6 votes
OH activation for nucleophilic substitution	5 votes
Reduction of amides without hydride reagents	4 votes
Oxidation/Epoxidation methods w/out use of chlorinated solvents	4 votes
Safer and more environmentally friendly Mitsunobu reactions	3 votes
Friedel-Crafts reaction on unactivated systems	2 votes
Nitrations	2 votes

Green Chem. **2007,** *9,* 411-420.

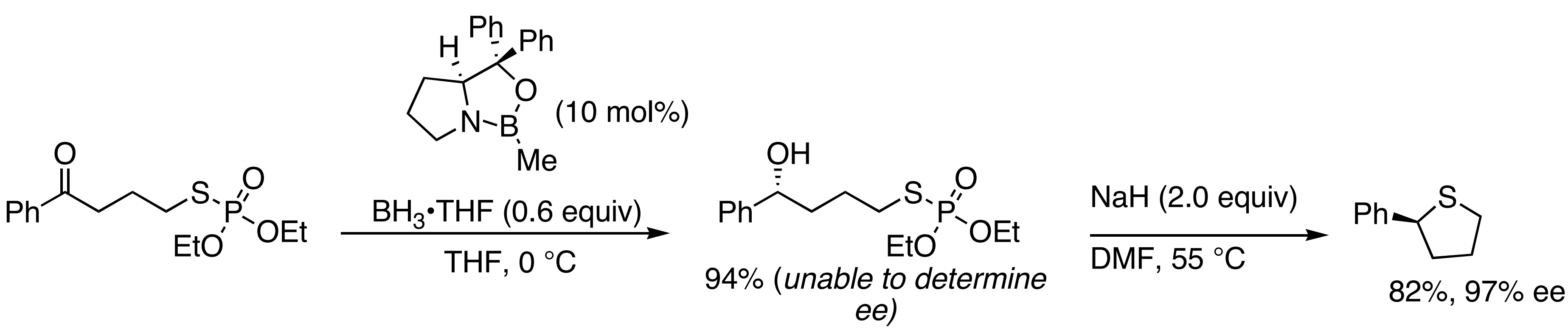
Synthesis of Chiral Tetrahydrothiophenes



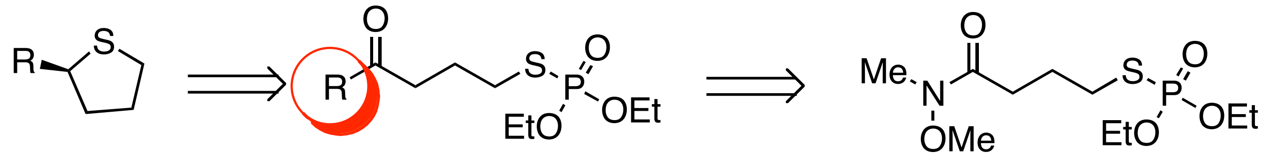
Initial C–S Bond Formation Strategy:

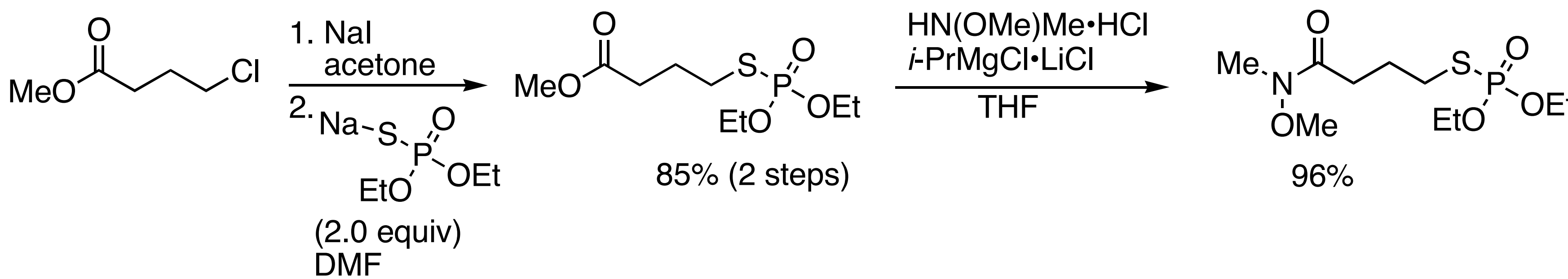


Entry	X	Z	Conditions	Yield
1	Cl	H	K_2CO_3 (2 equiv), 80 °C	49%
2	Cl	Na	No additive, 70 °C	63%
3	I	Na	No additive, rt	98%

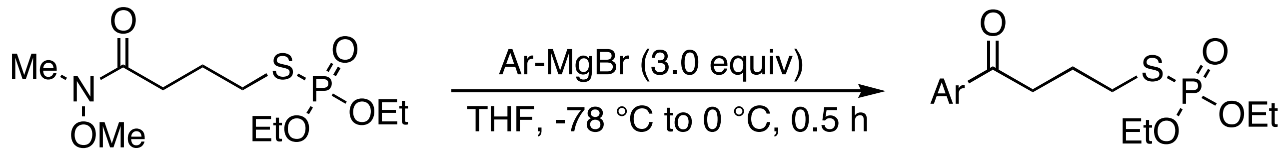


General Approach to Aromatic Tetrahydrothiophenes

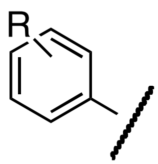




Scope of Grignard Addition to Weinreb Amide



Ar =



H, 98%

4-Me, 96%

2-OMe, 61%

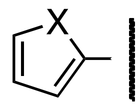
3,4-Me, 94%

4-*t*-Bu, 89%

4-F, 89%

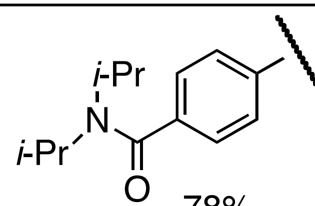
4-Cl, 90%

4-MeO, 80%

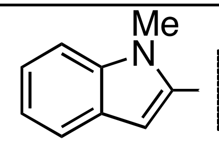


X = O, 91%

X = S, 99%



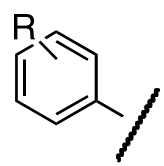
78%



49%

required additional ArMgBr, warming to rt and 3 h reaction time required 12 equiv LiCl

Ar =

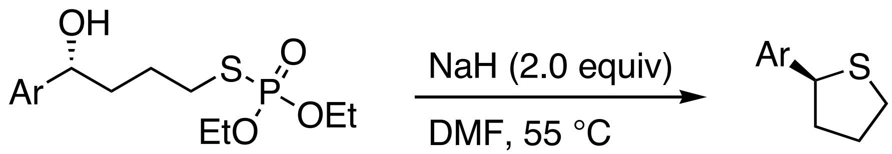


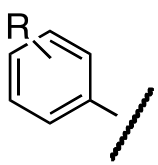
R = 4-NC, 79%

R = *t*-BuO_2C, 97%

required additional ArMgBr (3.0 equiv) and warming to rt

Scope of Chiral Tetrahydrothiophene Formation



Ar = 

H, 82% (97% ee)

4-Me, 84% (97% ee)

2-OMe, 79% (89% ee)

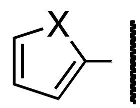
3,4-Me, 80% (92% ee)

4-*t*-Bu, 84% (91% ee)

4-F, 79% (97% ee)

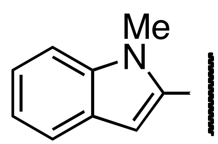
4-Cl, 89% (97% ee)

4-MeO, 73% (94% ee)

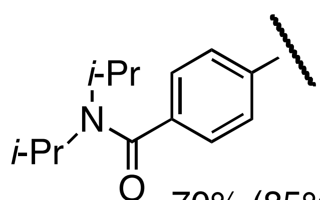


X = O, 74% (96% ee)

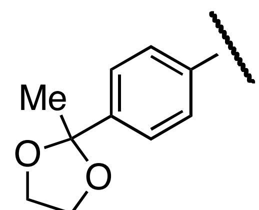
X = S, 94% (91% ee)



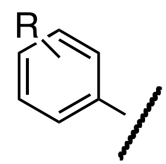
86% (74% ee)



70% (85% ee)



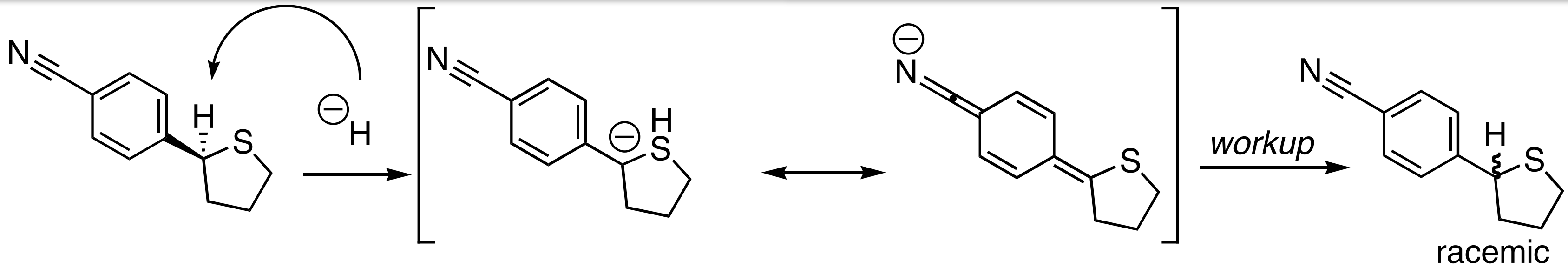
83% (92% ee)

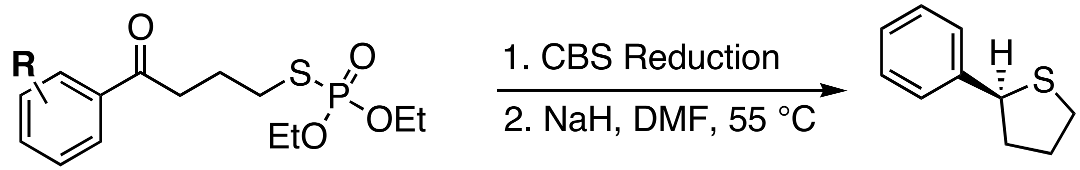
Ar = 

R = 4-NC, 60% (0% ee)

R = *t*-BuO_2C, 50% (10% ee)

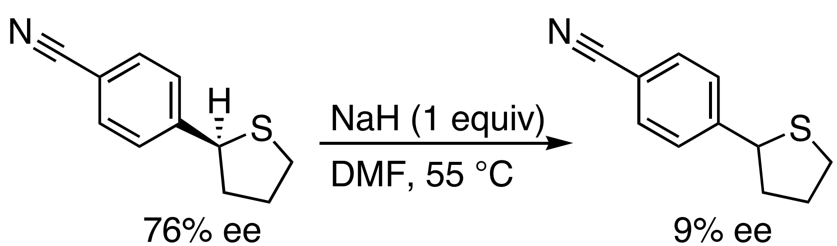
Proposed Racemization Mechanism and Support



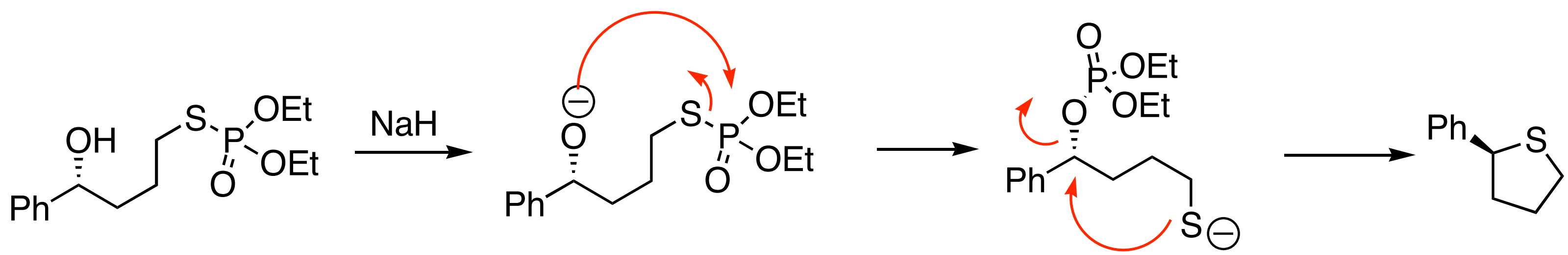


Entry	**R**	Conditions	Yield	ee (%)
1	3-CN	2.0 equiv NaH	70	74
2	3-CN	1.2 equiv NaH	81	82
3	4-CN	1.2 equiv NaH	82	76
4	4-*t*-BuO_2C	1.2 equiv NaH	81	93

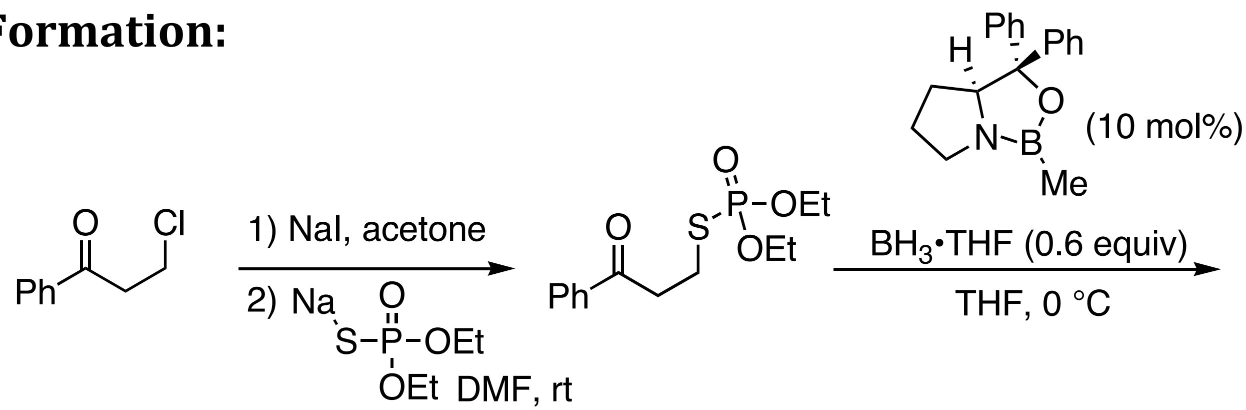
Subjection of the enantioenriched tetrahydrothiophene to the reaction conditions:

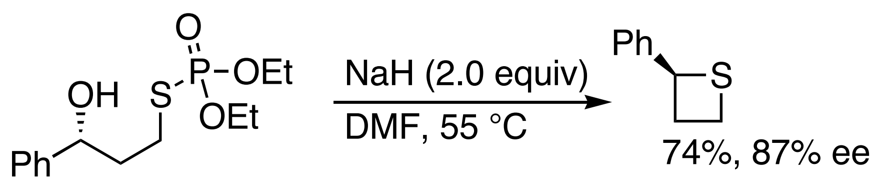


Mechanism and Extension of Methodology



Thietane Formation:





Attempts to form thianes using an analogous sequence were unsuccessful.

Summary

-A general, functional group-tolerant methodology for construction of 2-substituted enantioenriched tetrahydrothiophenes was developed.

-Extensions involving substitution of the alkyl tether or oxidation to the sulfoxide may be of interest.