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Catalytic Asymmetric Bromoetherification and Desymmetrization of Olefinic 1,3-Diols with C_2-Symmetric Sulfides

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Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543

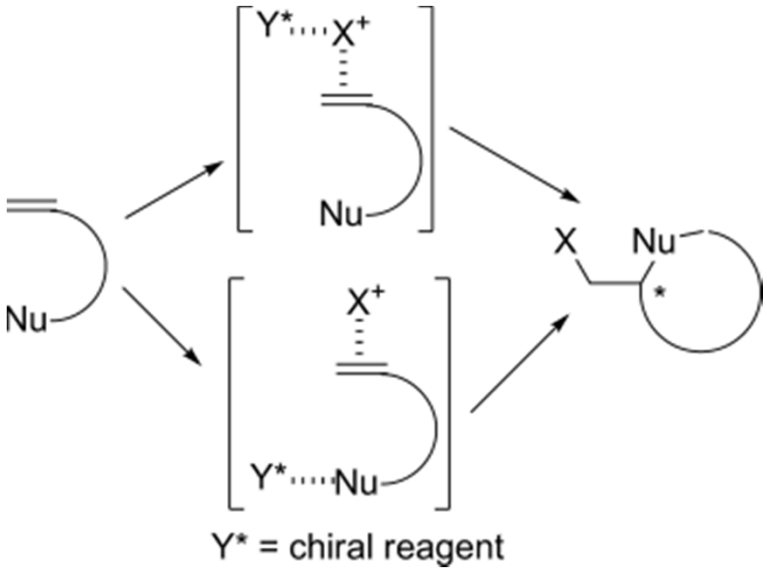
J. Am. Chem. Soc. **2014**, *136*, 5627-5630.

Vivek S. Raut

Group meeting

02 June 2014

Selected Literature Precedents

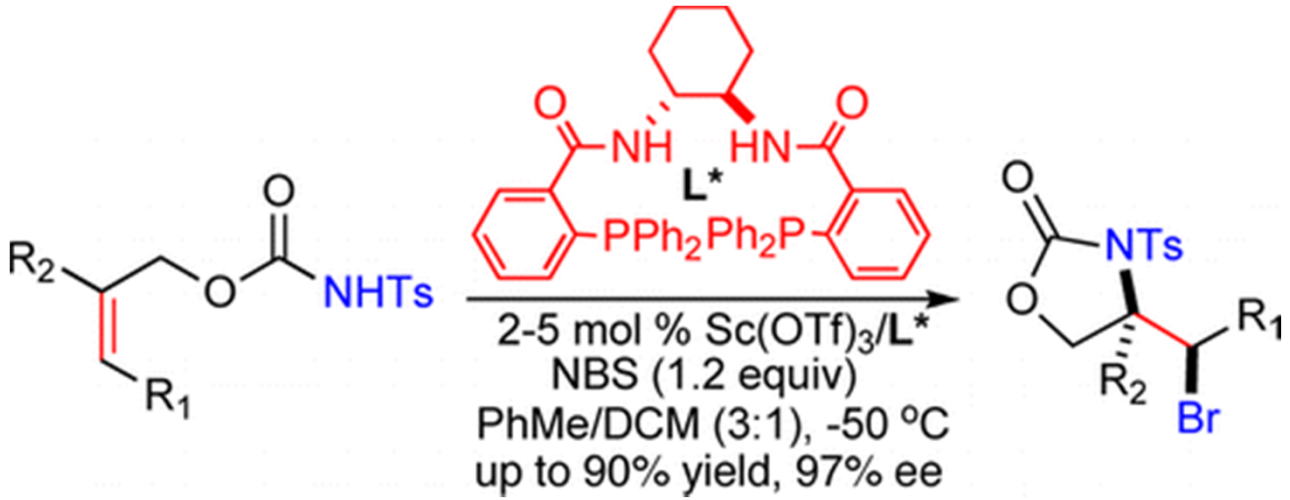


Highly enantioselective electrophilic halocyclizations based on either the interaction of a chiral Lewis acid with an unsaturated substrate or the generation of a chiral electrophilic intermediate in situ from chiral reagent

Highlight:
Enantioselective Halocyclization Reactions for the Synthesis of Chiral Cyclic Compounds

Guofei Chen and Shengming Ma *Angew. Chem. Int. Ed.* **2010**, *49*, 8306 – 8308.

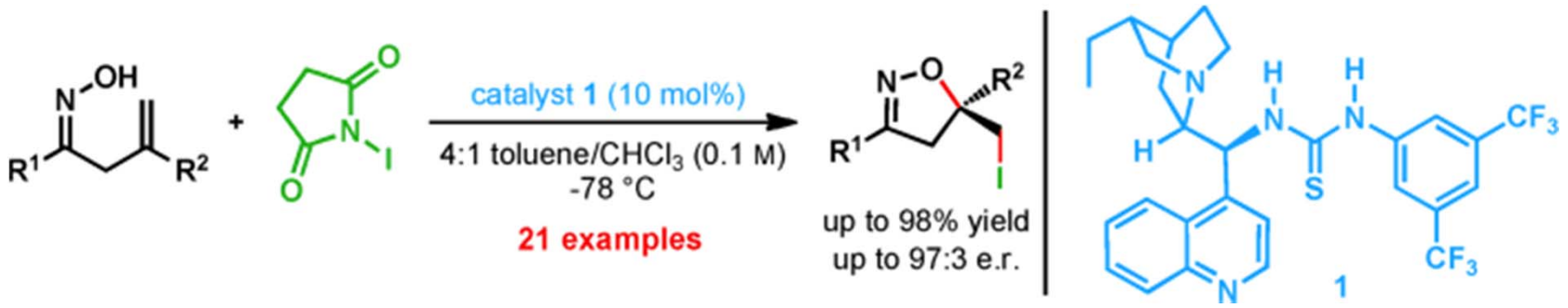
Some Recent Examples



Enantioselective Bromoaminocyclization of Allyl N-Tosylcarbamates Catalyzed by a Chiral Phosphine–$Sc(OTf)_3$ Complex

Yian Shi et al. *J. Am. Chem. Soc.* **2013**, *135,* 8101–8104.

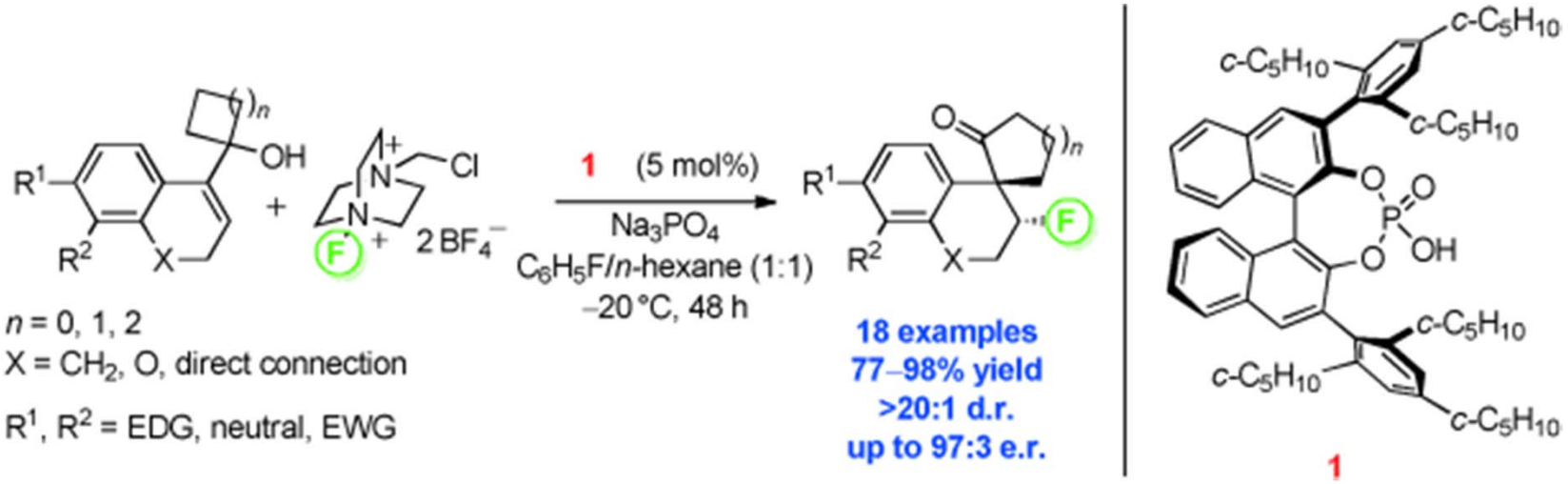
Some Recent Examples



Catalytic Enantioselective Iodoetherification of Oximes

Santanu Mukherjee et al. *Angew. Chem. Int. Ed.* **2013**, *52*, 8450 –8453.

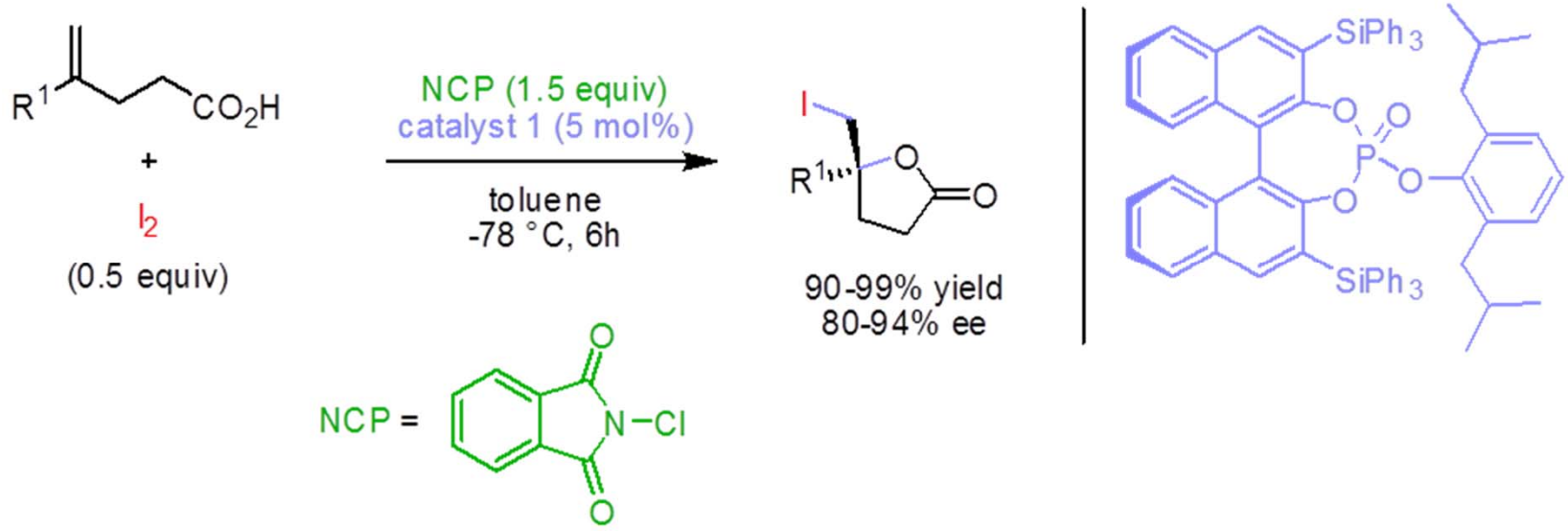
Some recent Examples



Enantioselective Organocatalytic Fluorination-Induced Wagner–Meerwein Rearrangement

Alexandre Alexakis et al. *Angew. Chem. Int. Ed.* **2013**, *52*, 9266 –9270.

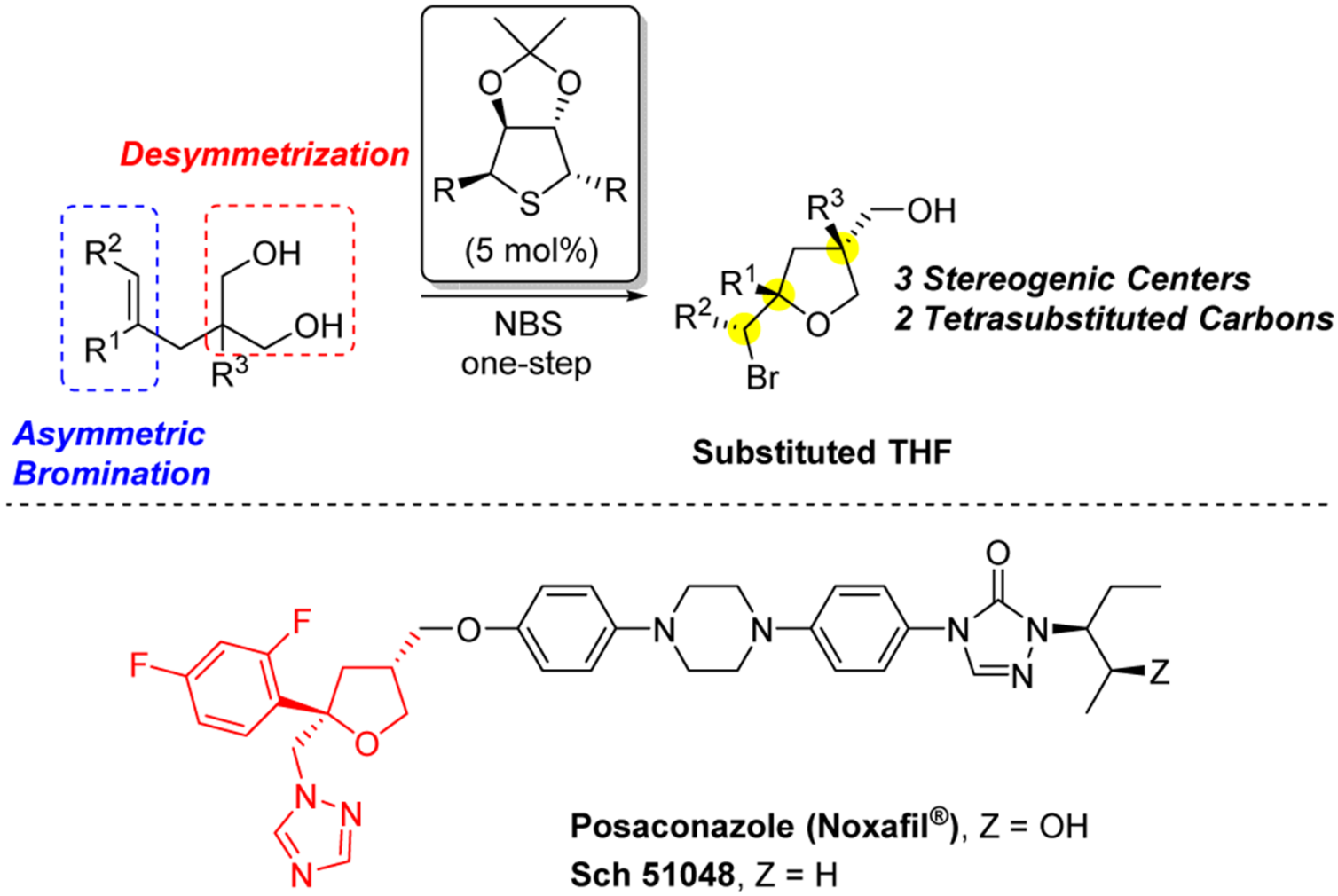
Some Recent Examples



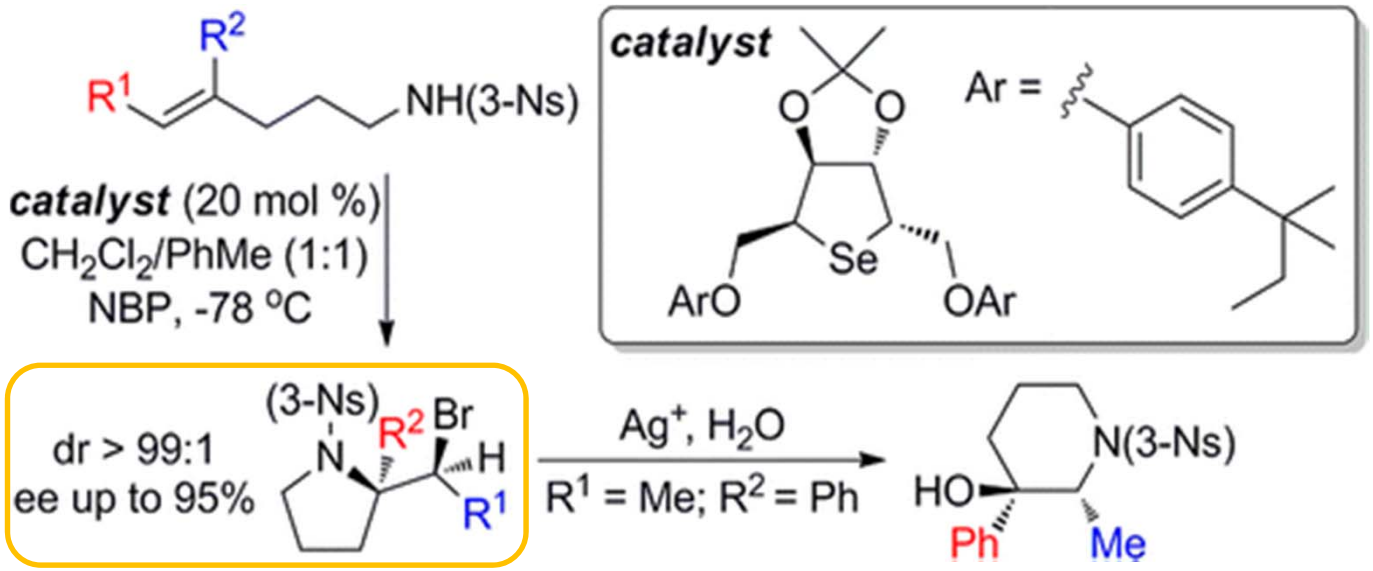
Cooperative Activation with Chiral Nucleophilic Catalysts and N-Haloimides: Enantioselective Iodolactonization of 4-Arylmethyl-4-pentenoic Acids

Kazuaki Ishihara et al. *Angew. Chem. Int. Ed.* **2014**, DOI: 10.1002/ange.201400946.

Asymmetric Bromoetherification and Desymmetrization of Diols



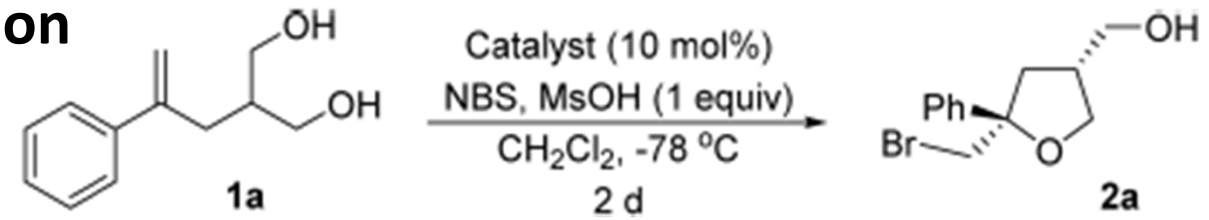
Previous Result

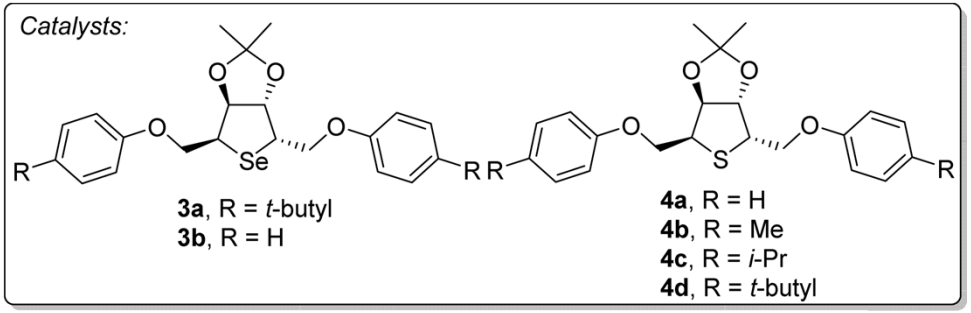


C_2-Symmetric Cyclic Selenium-Catalyzed Enantioselective Bromoaminocyclization

Ying-Yeung Yeung et al. *J. Am. Chem. Soc.* **2013**, *135*, 1232−1235.

Optimization

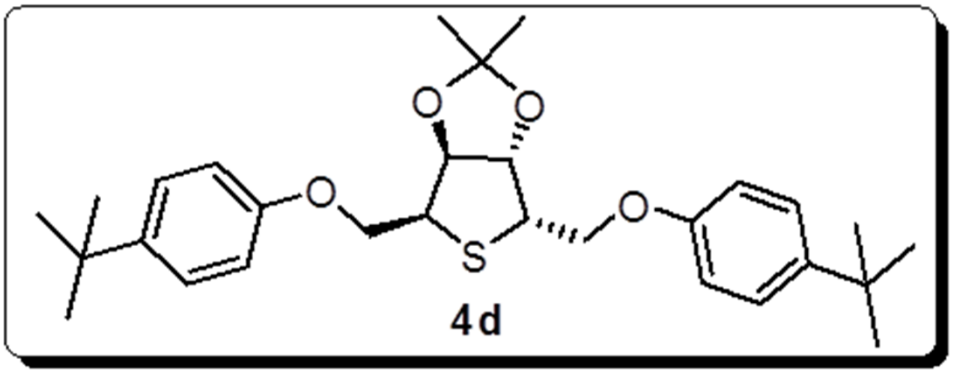


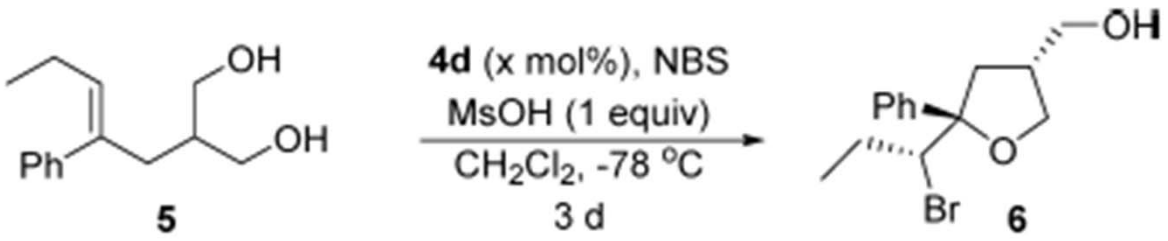


entry	catalyst	Yield (%)	dr	er
1[a]		57	84:16	
2[a]	K_2CO_3	51	64:36	
3[a]	Et_3N	53	68:32	
4		72	88:12	
5[a]	3a	Trace		
6	3a	29	92:8	65.5:34.5
7	3b	99	88:12	83:17
8	4a	73	93:7	82.5:17.5
9	4b	55	93:7	82:18
10	4c	59	92:8	82:18
11	4d	81	92:8	85.5:14.5

a = without MsOH

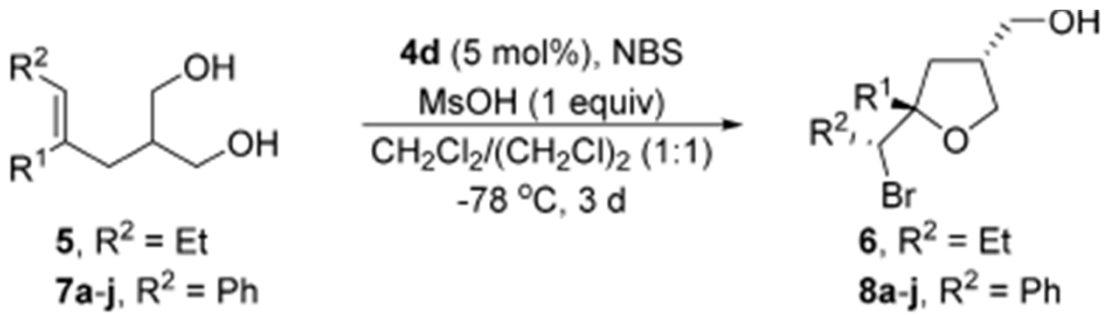
Catalyst Loading





entry[a]	4d (mol %)	yield (%)[b]	dr[c]	er
1	10	88	>99:1	90:10
2	5	97	>99:1	90:10
3	2	92	94:6	86.5:13.5

Scope

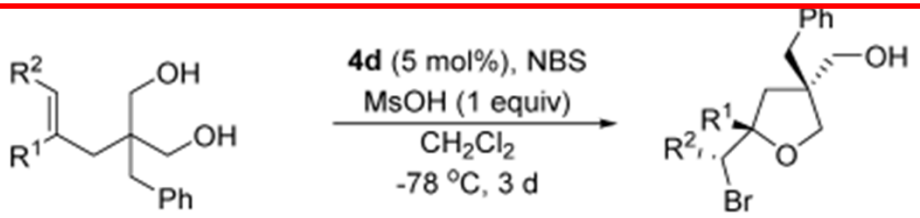


5, R^2 = Et
7a-j, R^2 = Ph

6, R^2 = Et
8a-j, R^2 = Ph

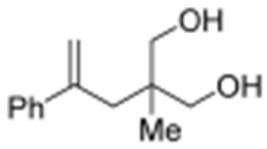
entry	diol, R^1, R^2	yield (%)[b]	dr[c]	er
1	5, Ph, Et	99	>99:1	90.5:9.5
2	7a, Ph, Ph	99	>99:1	96.5:3.5
3	7b, 2-Me-C_6H_4, Ph	95	>99:1	55:45
4	7c, 4-Et-C_6H_4, Ph	99	>99:1	96:4
5	7d, 3,5-Me_2-C_6H_3, Ph	99	>99:1	95:5
6	7e, 3-MeO-C_6H_4, Ph	98	>99:1	86:14
7	7f, 4-Ph-C_6H_4, Ph	96	92:8	73:27
8	7g, 4-F-C_6H_4, Ph	92	>99:1	97.5:2.5
9	7h, 4-CF_3O-C_6H_4, Ph	91	95:5	67:33
10	7i, 4-*i*Pr-C_6H_4, Ph	99	>99:1	97:3
11[d]	7a, Ph, Ph	94	>99:1	96:4

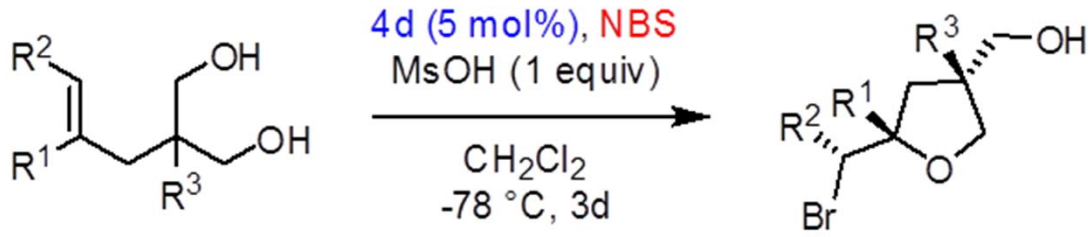
Scope



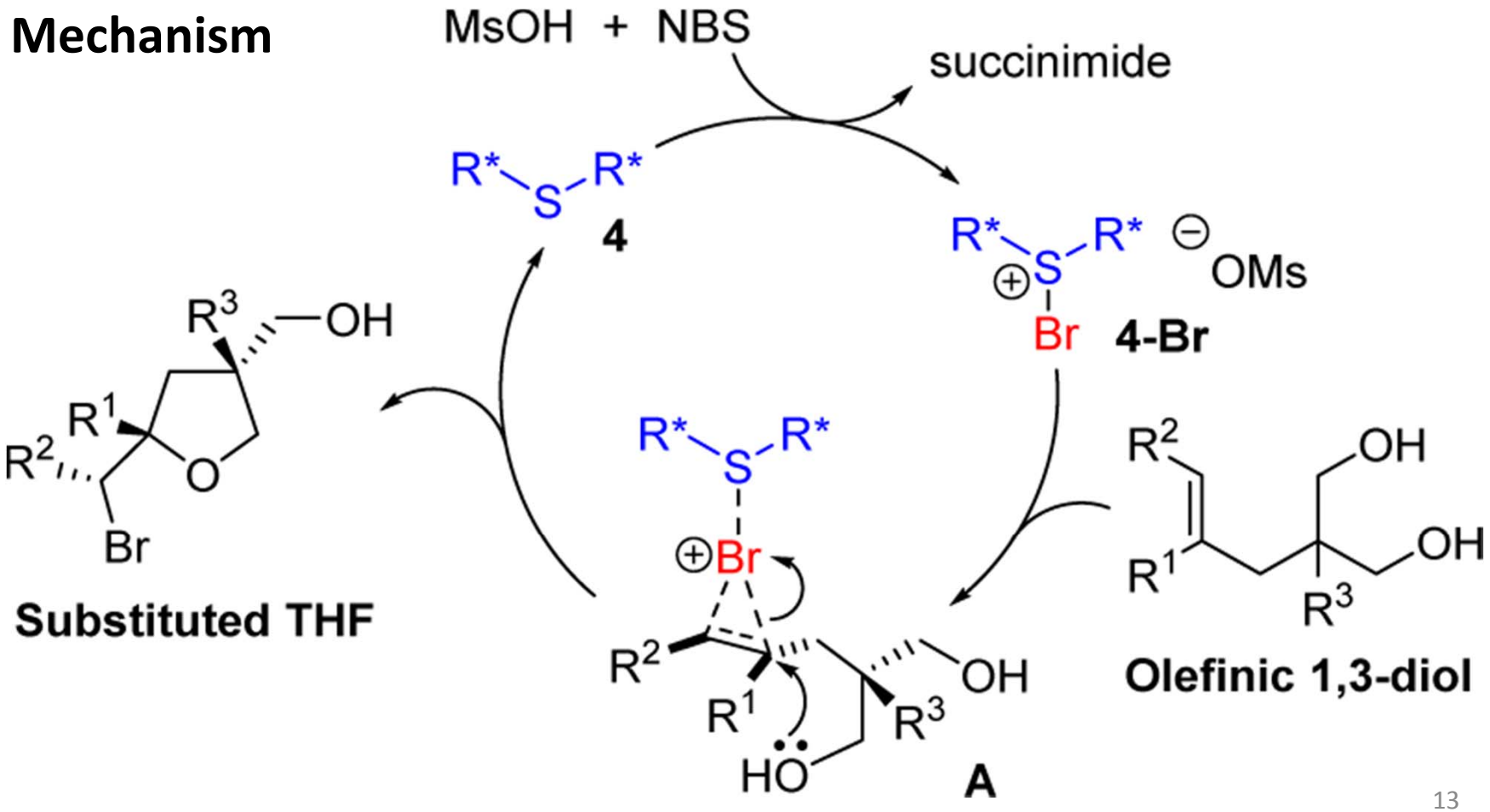
9a-f, R^2 = H
11a-e, R^2 = Ph
13, R^1 = Ph, R^2 = Et

10a-f, R^2 = H
12a-e, R^2 = Ph
14, R^1 = Ph, R^2 = Et

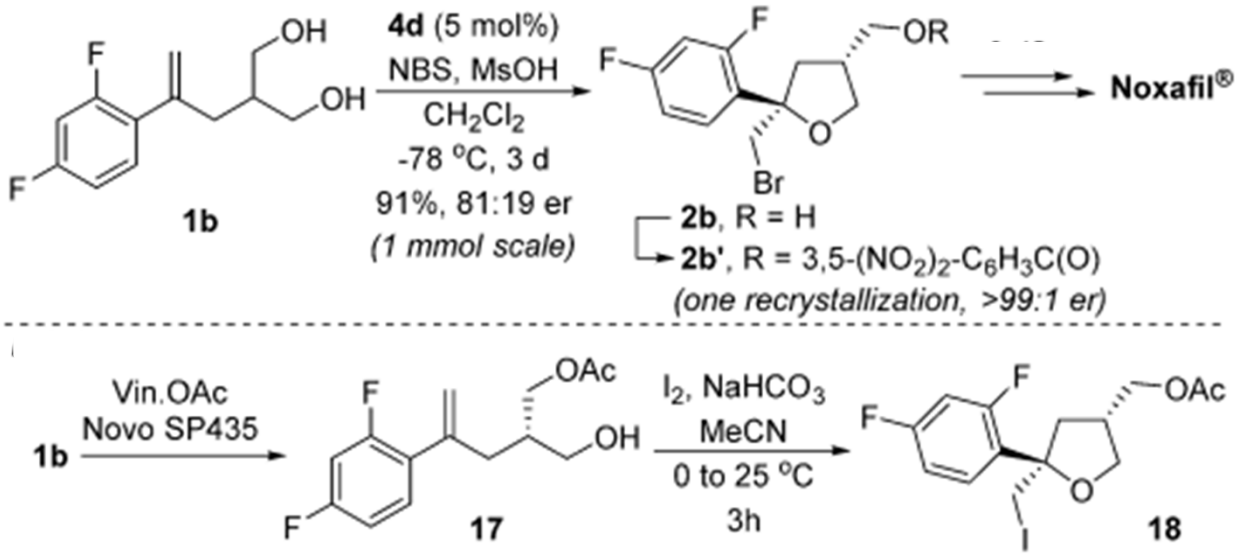
entry	diol, R^1, R^2	yield (%)[b]	dr[c]	er
1	**9a**, Ph, H	92	93:7	93.5:6.5
2	**9b**, 4-Me-C_6H_4, H	96	>99:1	90:10
3	**9c**, 2-Naphthyl, H	97	92:8	82:18
4	**9d**, 4-F-C_6H_4, H	91	95:5	93:7
5	**9e**, 4-CF_3O-C_6H_4, H	93	85:15	80:20
6	**9f**, 4-Cl-C_6H_4, H	86	89:11	94:6
7	**11a**, 4-Et-C_6H_4, Ph	96	92:8	95:5
8	**11b**, 3-MeO-C_6H_4, Ph	99	71:29	97.5:2.5
9	**11c**, 4-Ph-C_6H_4, Ph	98	91:9	96:4
10	**11d**, 4-F-C_6H_4, Ph	94	>99:1	91:9
11	**11e**, 4-CF_3O-C_6H_4, Ph	93	>99:1	92:8
12	**13**, Ph, Et	99	>99:1	92.5:7.5
13[d]	**9a**, Ph, H	91	93:7	93:7
14	 **15**	73	75:25	91:9

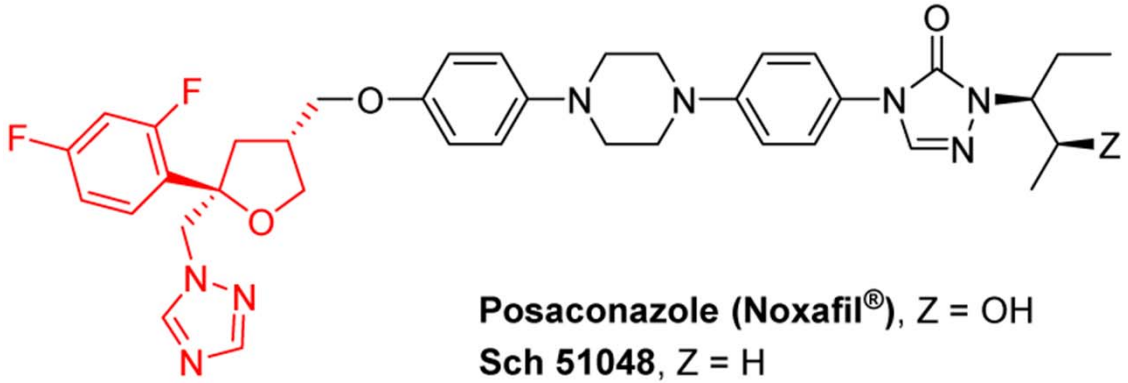

4d (5 mol%), NBS
MsOH (1 equiv)
CH2Cl2
-78 °C, 3d

Mechanism


MsOH + NBS
succinimide
4
4-Br
OMs
Substituted THF
Olefinic 1,3-diol
A

Application

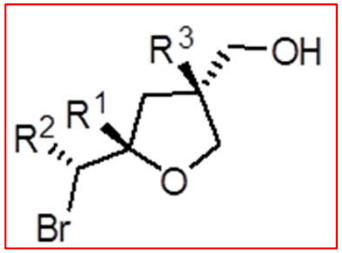




highly active azole antifungals

Summary

- A facile enantioselective and diastereoselective bromoetherification and desymmetrization of olefinic 1,3-diols has been developed using a cyclic sulfide catalyst
- The process allows for the construction of substituted THFs with up to three stereogenic centers with two tetrasubstituted carbons
- Applicable to the synthesis of a key intermediate of the orally active antifungal drug posaconazole (Noxafil)
- Combination of concept catalytic asymmetric halocyclization and desymmetrization with application



Thank You