No Title

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August 07, 2008

Outline

- Bioisostere and Isostere

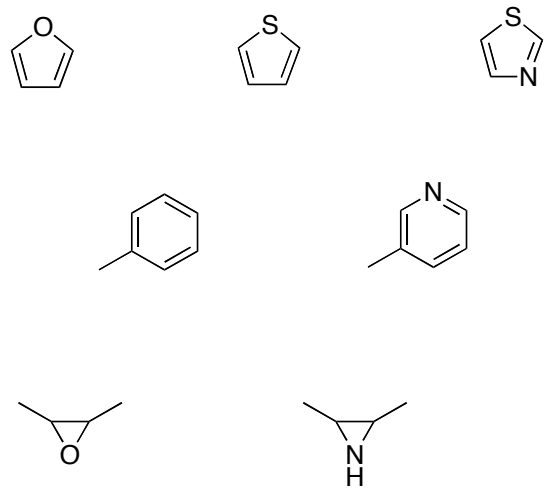
- Report on the possibility of thioureas catalyzed Claisen rearrangement

Definition of isostere

Isosteres are

molecules or ions with the same number of atoms and the same number of valence electrons.

As a result, they can exhibit similar pharmacokinetic and pharmacodynamic properties



Bioisostere

Friedman (1951):Bioisosteres are atoms or molecules that fit the broadest definition for isosteres and have the same type of biological activity.

Thornber(1979): Groups or molecules which have chemical and physical similarities producing broadly similar biological effects.

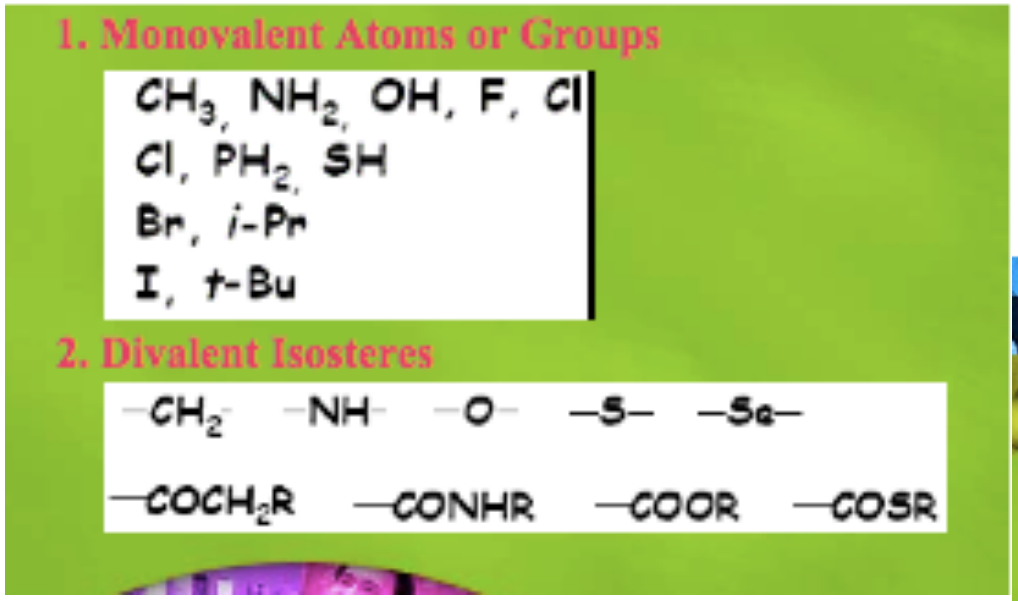
Why?

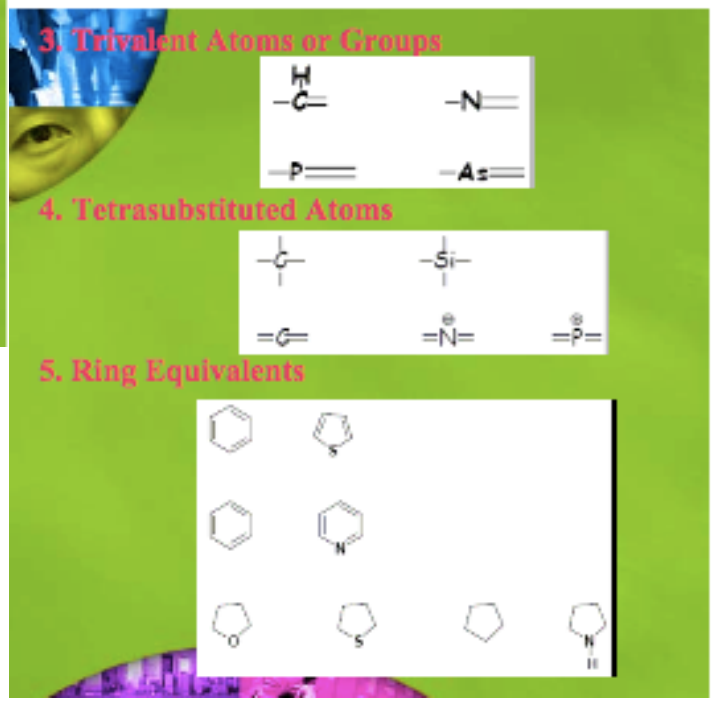
- Greater selectivity
- Less side effects
- Decreased toxicity
- Improved pharmacokinetics (solubility-hydrophobicity)
- Increased stability
- Simplified synthesis
- Patented lead compounds

Classes of Bioisosteres

- Classical bioisosteres
- Nonclassical bioisosteres

Classical bioisosteres

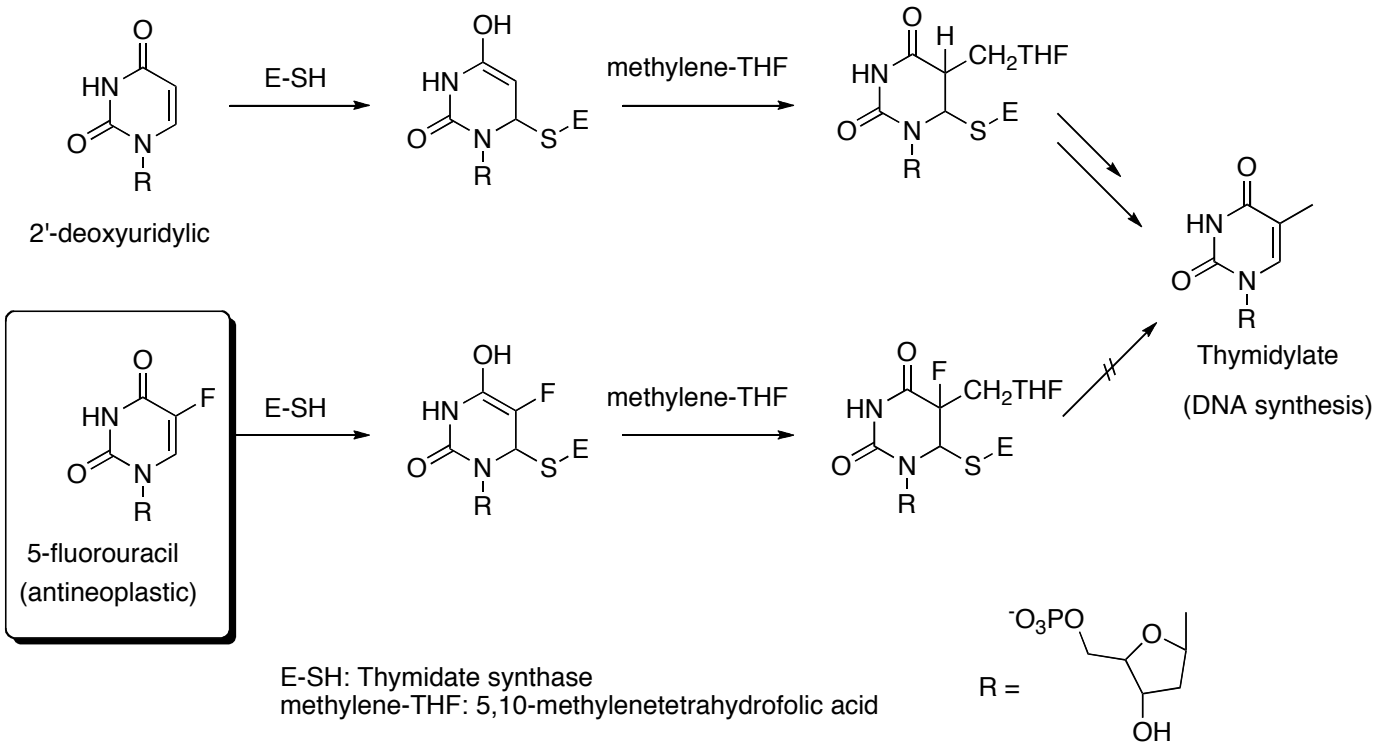




Classical bioisosteres

- H to F replacement

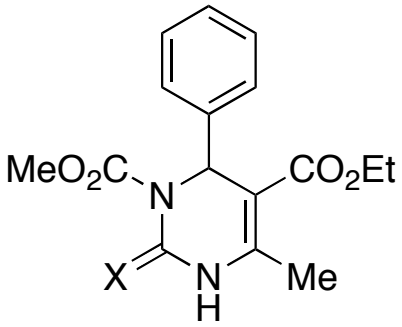
	H	F	Cl	CH_3	CF_3
Van der Waals radius	1.2	1.35	1.80	2	2
Molecular Refractivity	1.03	0.92	6.03	5.65	5.02
Inductive effect	-	3.08	2.68	0.00	2.85
Resonance effect	0.00	-0.34	-0.15	-0.13	0.19



Classical bioisosteres

Hydride Displacement Law					
C	N	O	F	Ne	Na^+
	CH	NH	OH	FH	-
		CH_2	NH_2	OH_2	FH_2^+
			CH_3	NH_3	OH_3^+
				CH_4	NH_4^+

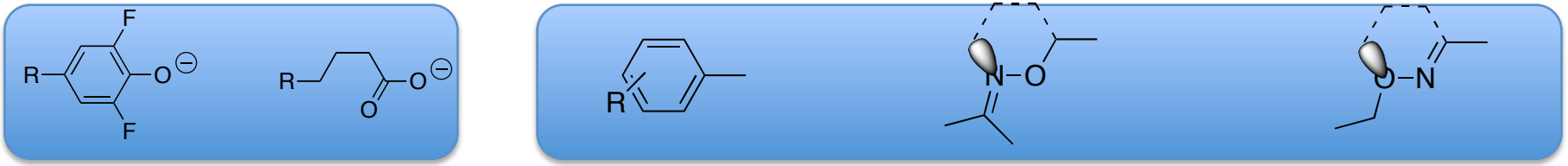
Classical bioisosteres

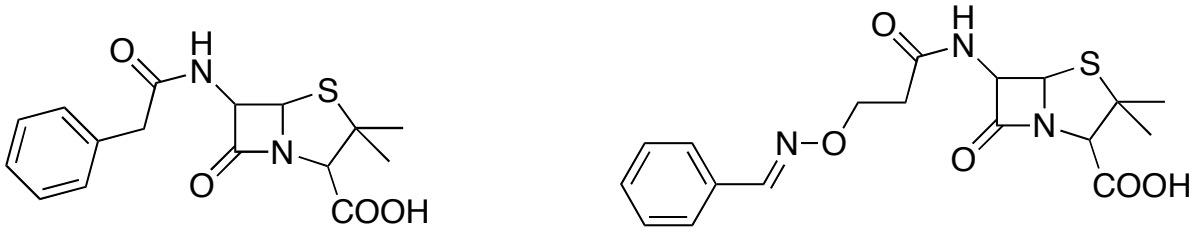


X	Van der Waals radius (A)	IC_{50} (nm)
O	1.40	140
NH	1.50	160
S	1.85	17

Nonclassical bioisosteres

- Cyclic vs Noncyclic replacement





	Minimum inhibitory concentration (MIC) (ug/mL)	
Gram positive bacteria	0.05	0.10
Gram negative bacteria	71	136

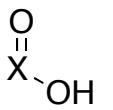
Balsamo, A.; Broccali, G.; Lapucci, A.; Maxxhia, B.; Macchia, F.; Orlandini, S.; Rossello, A. *J. Med. Chem.* **1989**, *32*, 1398.

Isosteres in catalyst design

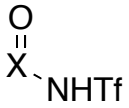
A Brønsted Acid Catalyst for the Enantioselective Protonation Reaction

Cheon, C. H.; Yamamoto, H.
J. Am. Chem. Soc. **2008**, *130*, 9246.

Catalyst design



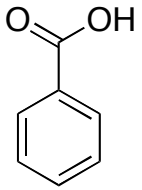
A

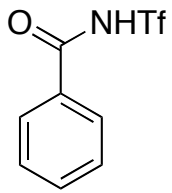


B

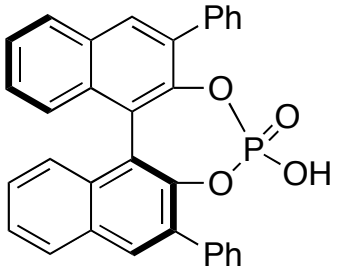
pKa of **A** > pKa of **B**

X = RC, RS=O

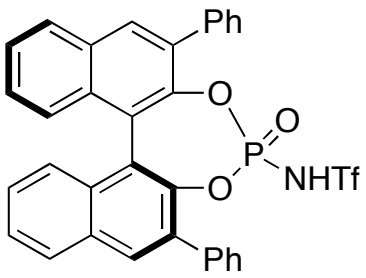




pKa(CH_3CN) 20.7 11.06



1



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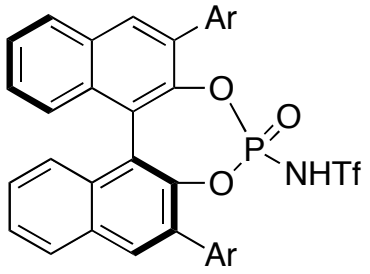
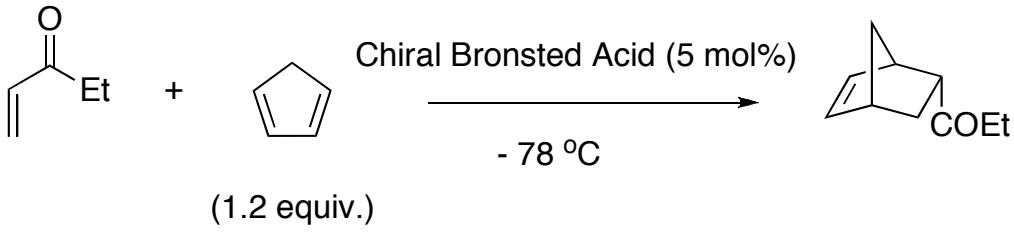


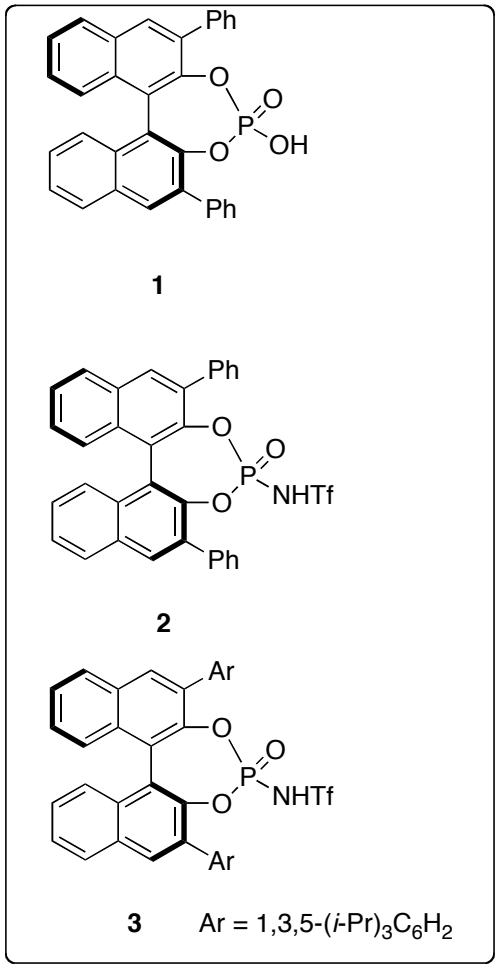
3 Ar = 1,3,5-(*i*-Pr)$_3$C$_6$H$_2$

Nakashima, D.; Yamamoto, H. J. Am. Chem. Soc. **2006**, *128*, 9626.

Reactivity of the catalysts

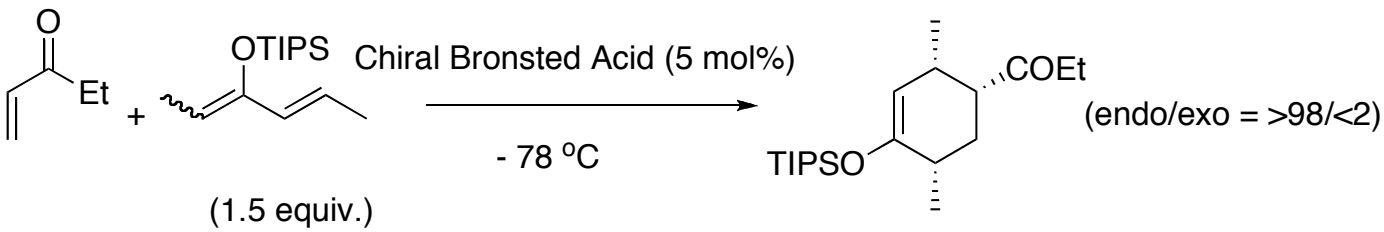


chiral bronsted acid	Solvent	Time (h)	Yield	*ee*(%)
1	CH_2Cl_2	2	0	n.d.
2	CH_2Cl_2	2	91	9 (*S*)
3	CH_2Cl_2	1	86	32 (*R*)

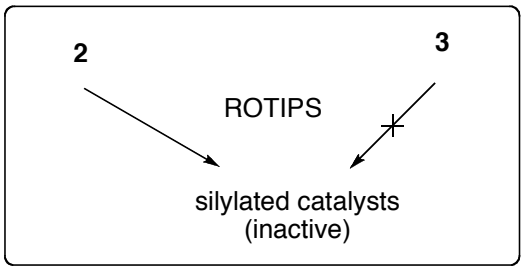


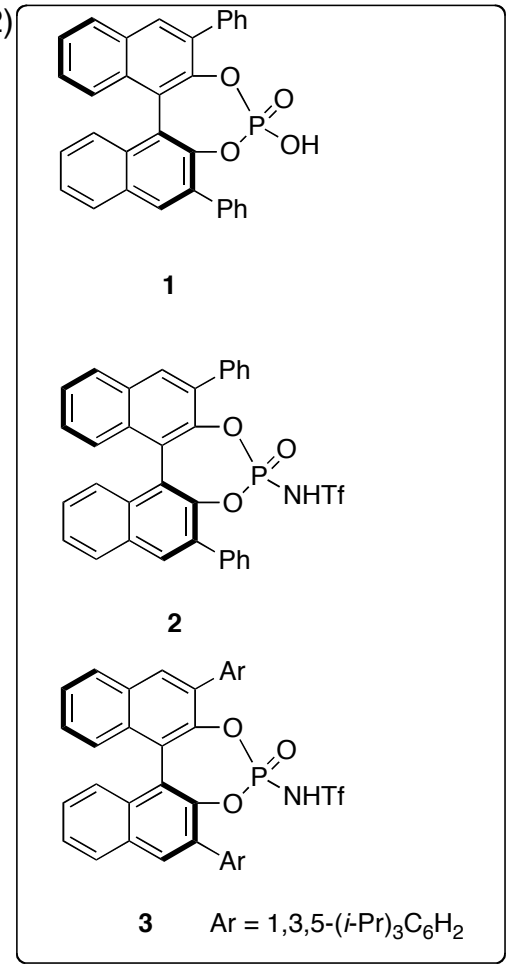
Nakashima, D.; Yamamoto, H. J. Am. Chem. Soc. **2006**, *128*, 9626.

Reactivity of the catalysts



chiral bronsted acid	Solvent	Time (h)	Yield	*ee*(%)
1	Toluene	3	0	n.d.
2	Toluene	3	<10	n.d.
3	Toluene	3	95	92

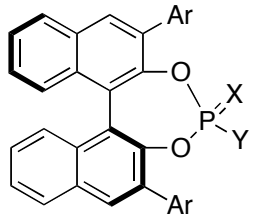




Nakashima, D.; Yamamoto, H. J. Am. Chem. Soc. **2006**, *128*, 9626.

Isostere in catalyst design

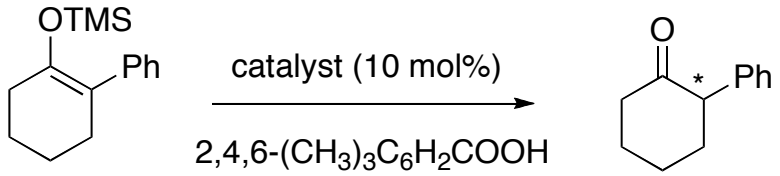
	PhOH	$PhNHSO_2Me$	PhSH	PhSeH
pKa (DMSO)	18.0	12.9	10.3	7.1

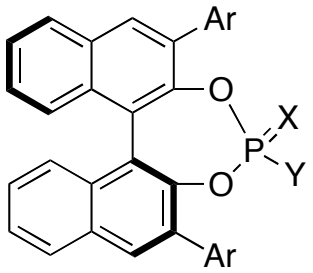


Ar = 1,3,5-(*i*-Pr)$_3$C$_6$H$_2$

	X	Y
3a	O	OH
3b	O	SH
3c	O	NHTf
3d	S	NHTf
3e	Se	NHTf

Catalyst reactivity

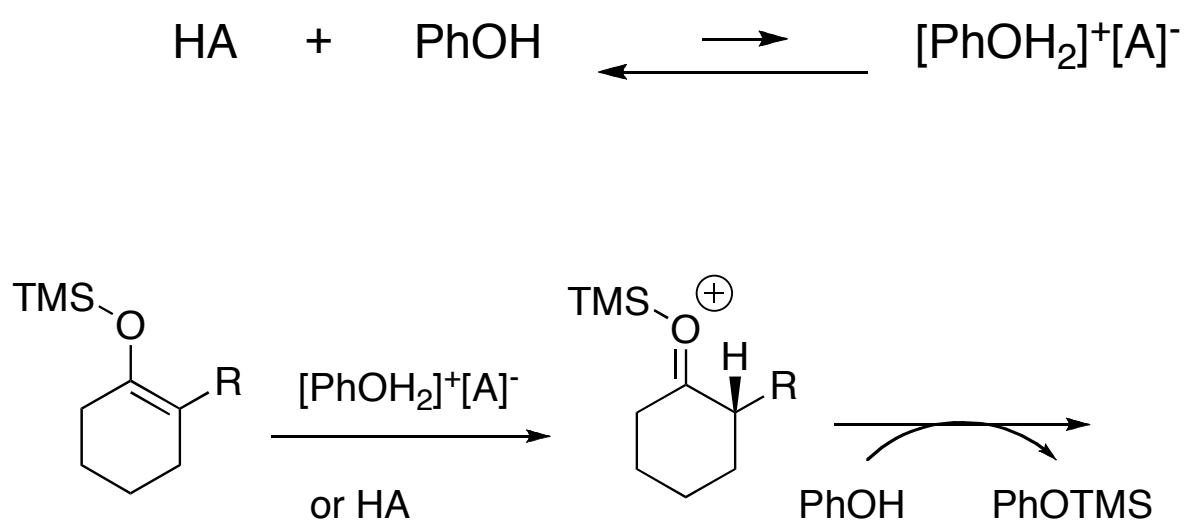




Ar = 1,3,5-(*i*-Pr)$_3$C$_6$H$_2$

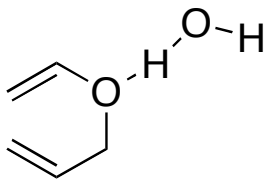
	X	Y	time (h)	Yield (%)	er
3a	O	OH	96	NR	ND
3b	O	SH	96	trace	ND
3c	O	NHTf	4.5	>99(98)	77:23
3d	S	NHTf	3.5	>99(97)	89:11
3e	Se	NHTf	3.5	>99(97)	86:14

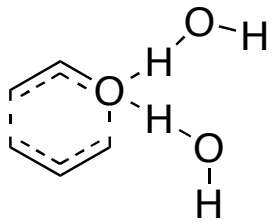
Mechanism for protonation reaction

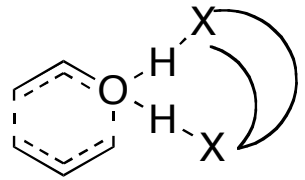


Possibilities on thioureas catalyzed Claisen rearrangement

Claisen rearrangement was accelerated by protic solvents or Bronsted Acids.

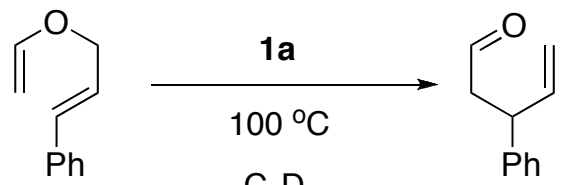






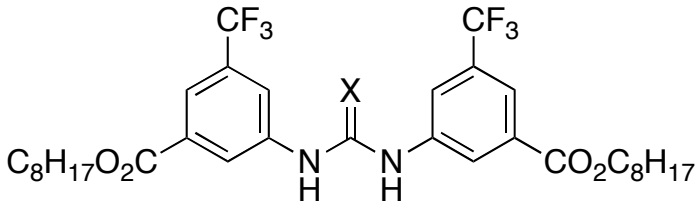
Kristen, M.; Rehbein, J.; Hiersemann, M.; Strassner, T. *J. Org. Chem.* **2007***, 72*, 4001-4011.
Severance, D. L.; Jorgensen, W. L. *J. Am. Chem. Soc*. **1992**, *114*, 10966.

Rate acceleration of Claisen rearrangement



4 (*E*) **5**

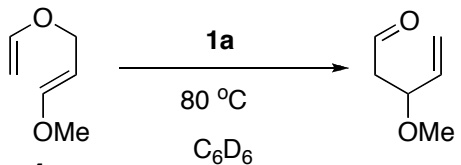
equiv (**1a**)	k_{rel}
none	1
0.2	1.7
0.5	3.1
1.0	4.2



1a X = O
1b X = S

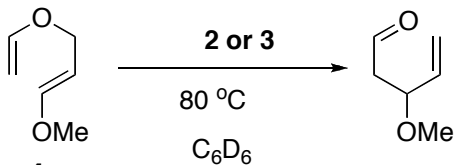
Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, *36(37)*, 6647.

Rate acceleration of Claisen rearrangement



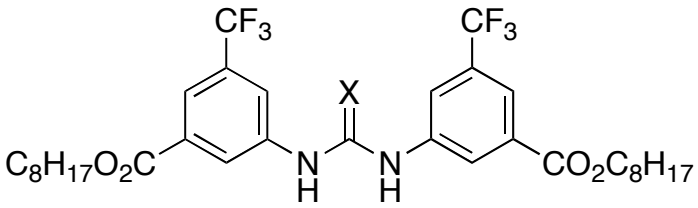
4 (*E/Z 2.6:1*) **5**

equiv (**1a**)	k_{rel}
none	1
0.2	2.7
0.5	5.0
1.0	22.4

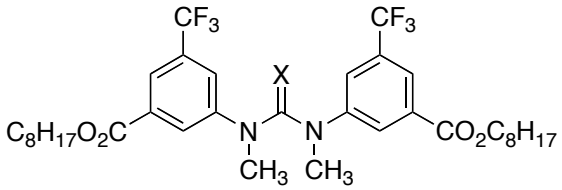


4 (*E/Z 2.6:1*) **5**

equiv	k_{rel}
none	1
2 (1.0 equiv.)	1.0
3 (1.0 equiv.)	1.6
DMSO (5.0 equiv.)	1.9



1a X = O
1b X = S



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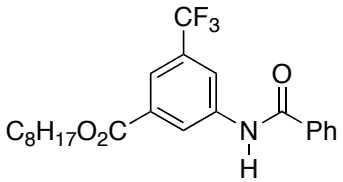
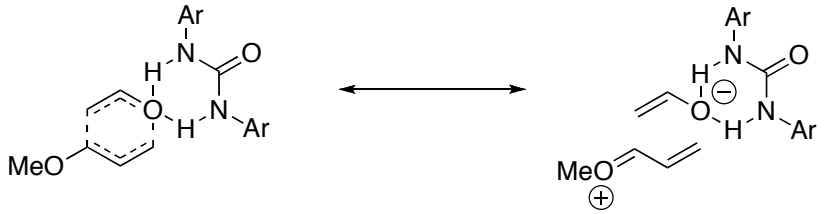


3

Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, *36(37)*, 6647.

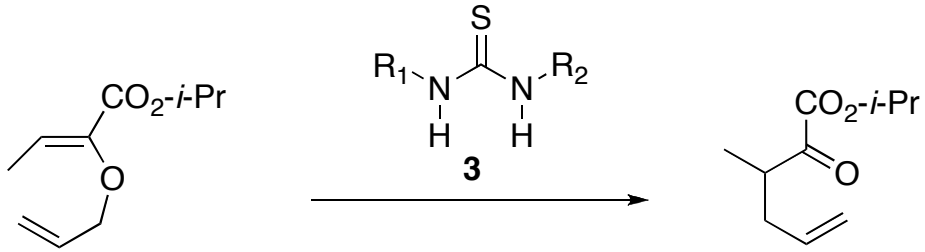
Bis-hydrogen bonded model



Thiourea has weaker accelerating effect than urea

Hydrogen bonding is crucial instead of acidity

Claisen rearrangement catalyzed by thiourea

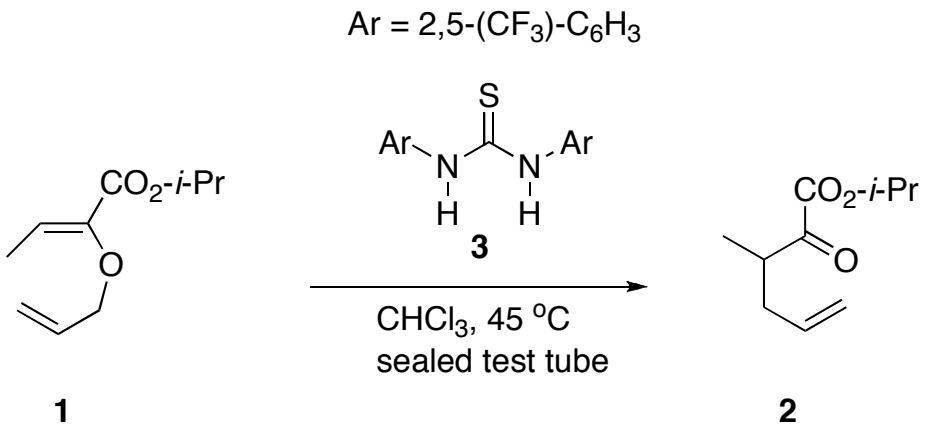


1 **2**

entry	thiourea	mol%	solvent	T (°C)	time	Conv. (%)
1	3	20	CHCl3	25	5 d	17
2	3	20	CF_3CH_2OH	25	5 d	44
3	3	20	CF_3CH_2OH	45	6 h	44
4	3	20	DCE	25	5 d	14
5			CHCl3	25	5 d	10
6			CF_3CH_2OH	25	5 d	41
7			CF_3CH_2OH	45	6 h	41
8			DCE	25	5 d	7

Kristen, M.; Rehbein, J.; Hiersemann, M.; Strassner, T. *J. Org. Chem.* **2007**, *72*, 4001-4011

Claisen rearrangement catalyzed by thiourea



		Conversion (%)	
entry	t (d)	100 mol% **3**	no **3**
1	1	41	23
2	2	63	41
3	3	72	52
4	5	84	57
5	7	87	74

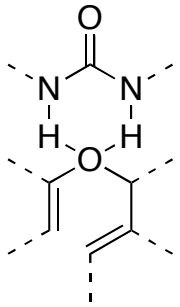
Conclusion

✧ Thioureas are ineffective as catalysts for the Claisen rearrangement of 2-alkoxylcarbonyl-substituted allyl vinyl ethers.

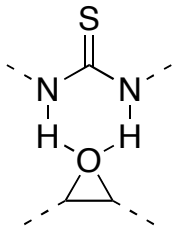
✧ It is important to have a suitable catalyst/substrate combination.

✧ The transition model proposed is useful in catalyst design.

Bis(hydrogen) bond binding models of thiourea catalysts



A



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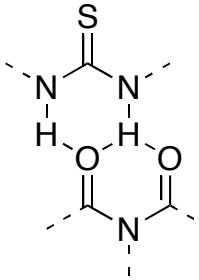


C

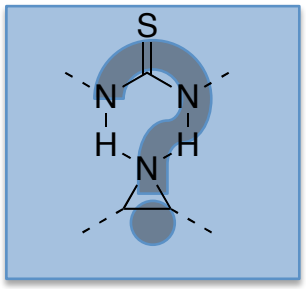
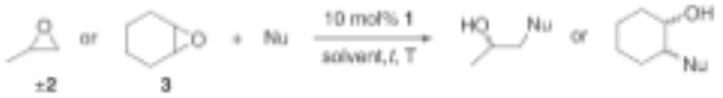
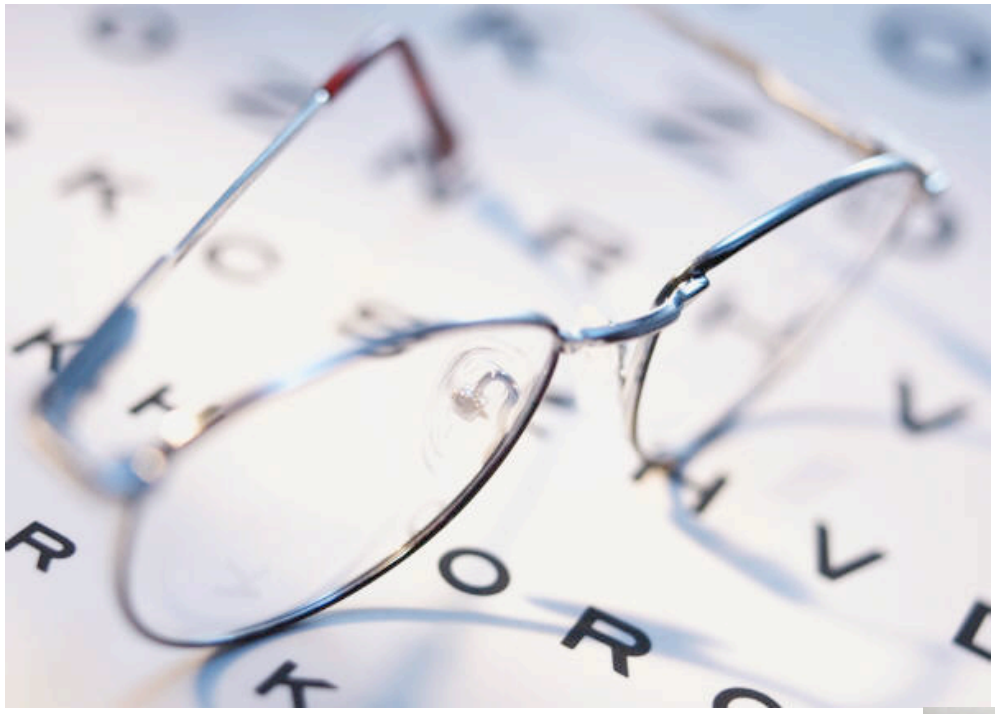


Table 1 Organocatalytic nucleophilic ring opening of oxiranes in water: reactions of ±**2** run at rt; of **3** at 40 °C. Nu = nucleophile



Oxirane	Nu	Yield (%) DCM no cat.	DCM cat.	H_2O no cat.	H_2O cat.
±**2**	*t*-$BuNH_2$	<0.5	37	29	**94**
±**2**	*n*-Bu_2NH	17	70	73	**90**
±**2**	*n*-Pr_2NH	36	48	30	**91**
±**2**	*i*-Pr_2NH	<1	47	30	**64**
±**2**	$(C_3H_5)_2NH$	63	85	78	**87**
±**2**	Morpholine	52	62	25	**83**
±**2**	Piperidine	45	57	83	**87**
±**2**	Pyrrolidine	63	85	82	**90**
3	*n*-$BuNH_2$	9	27	89	**95**
3	*t*-$BuNH_2$	<0.5	14	59	**68**
3	*i*-Pr_2NH	<1	10	11	**62**
3	$(C_3H_5)_2NH$	4	11	54	**60**
3	Morpholine	24	37	84	**85**
3	Piperidine	15	47	72	**94**
3	Pyrrolidine	63	70	75	**97**

Kleiner, C. M.; Schreiner, P. R. *Chem. Commun*., **2006**, 4315.



Thanks!

同一个世界 同一个梦想

One World One Dream

Beijing Olympics 2008

One World One dream


www.beijing2008.cn

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福娃 Fuwa

Fish and Lotus	Giant panda	Fire	Tibetan antelope	swallow
Blue	Black	Red	Yellow	Green
Water	Forest	Fire	Earth	Sky
Prosperity	happiness	passion	health	Good fortune

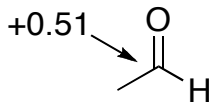
Reactivity of Imine

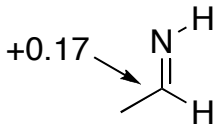
C=O

2.3 D

C=N

0.9 D





- Attaching activating groups on the imine N