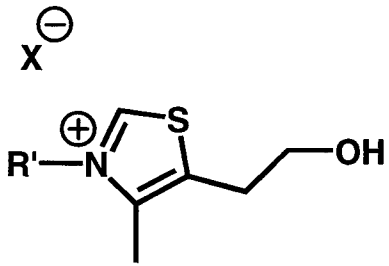
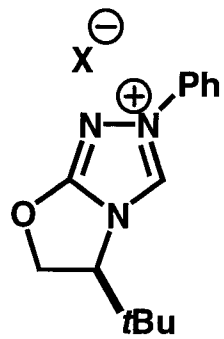
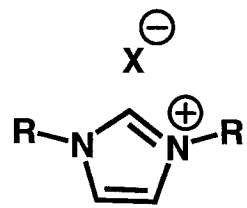
Catalytic Nucleophilic Carbenes



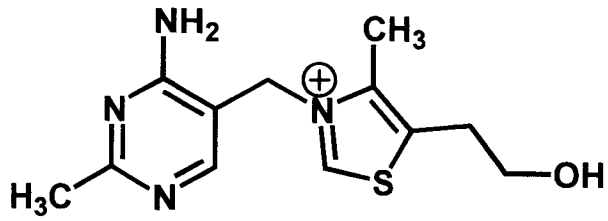




John Baird

November 12, 2002

Origins of Catalytic Activity



Thiamine (B1)

Vitamin B1 is required in the diets of most vertebrates

Deficiency of B1 results in the fatal condition **beriberi**

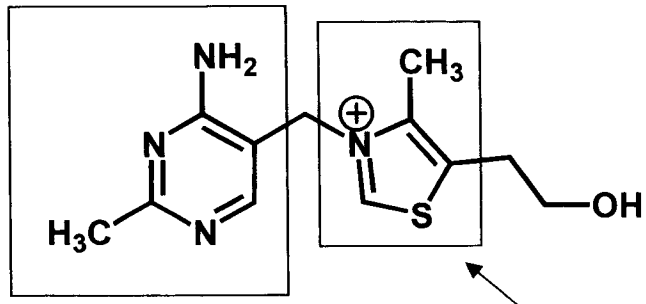
Used as a coenzyme in the decarboxylation of pyruvic acid to acetaldehyde (pyruvate decarboxylase, PD)

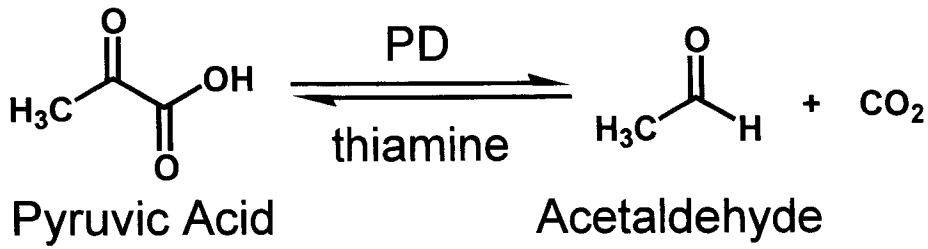
Thiamine is a biologically essential molecule

Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

Voet, D. et al. *Fundamentals of Biochemistry*. **1999**. pp403-405.

Mechanistic Understanding of thiamine





Early work focused on the amine of the aminopyrimidine ring

Other postulations included the role of the thiazolium ring

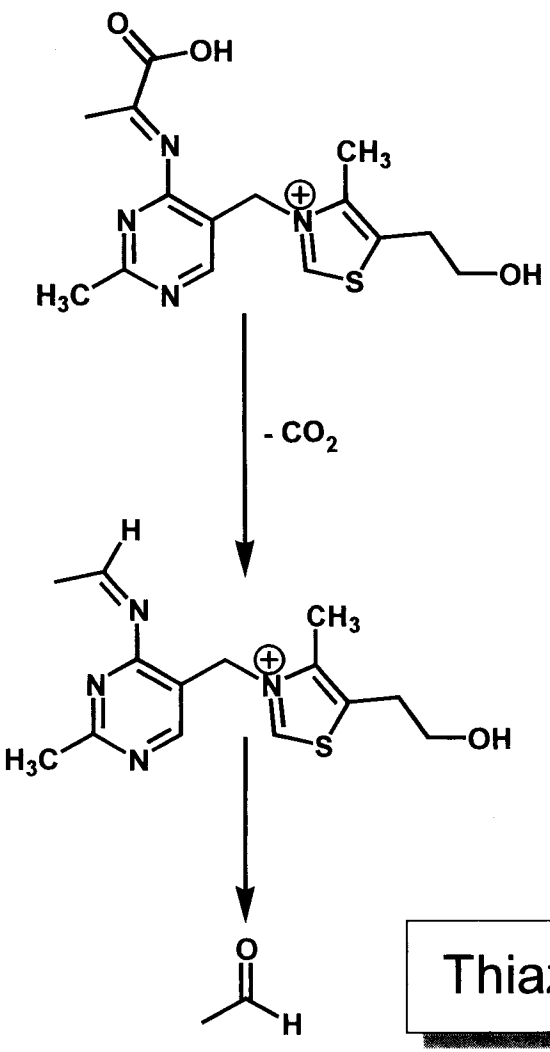
What is the catalytically active portion of thiamine?

Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

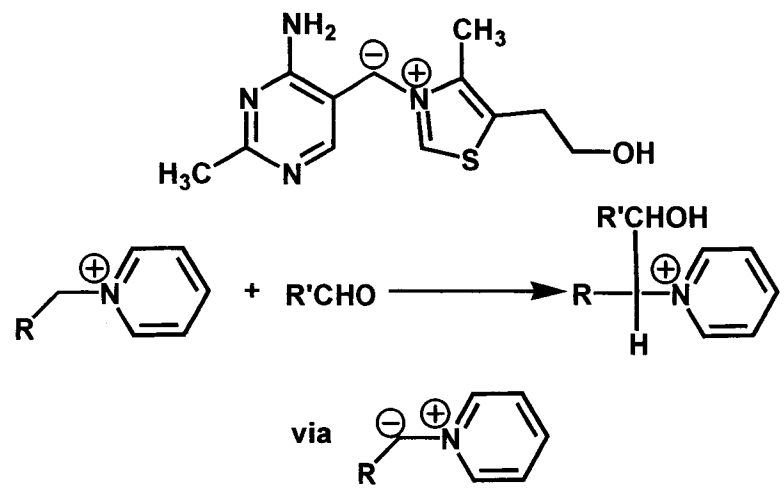
Voet, D. et al. *Fundamentals of Biochemistry*. **1999**. pp403-405.

Mechanistic Possibilities

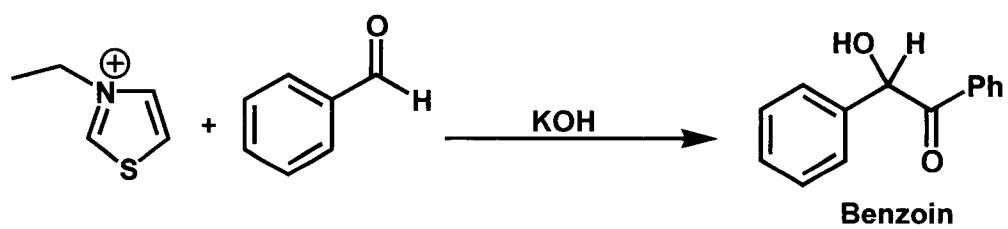
Schiff Base formation



Ylide formation



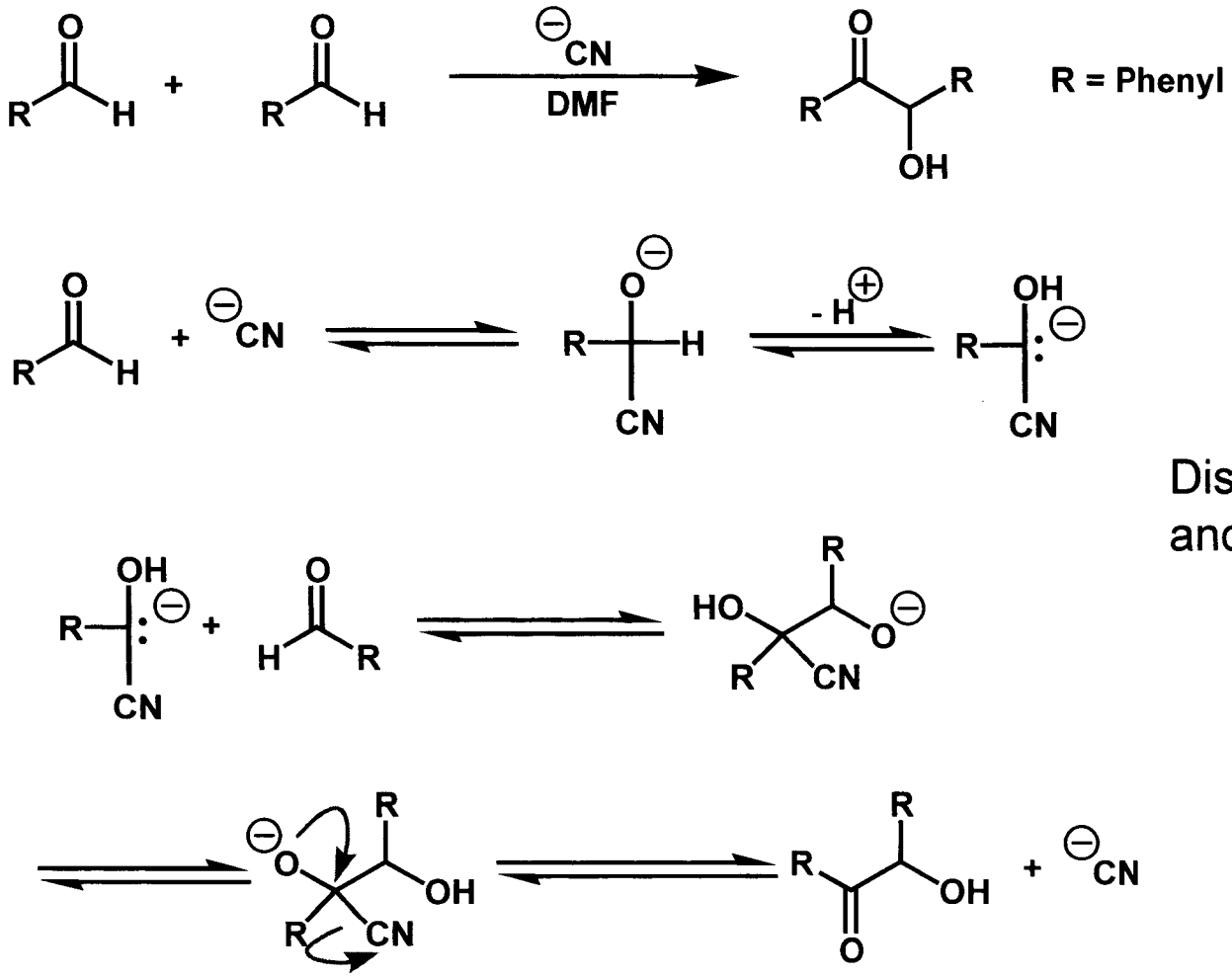
Assumed that thiazolium compounds should also condense



Thiazolium salt is able to act as a catalyst

Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

Mechanism of Benzoin Condensation

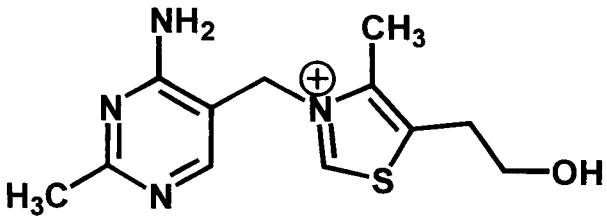


Discovered by Liebig and Wohler in 1832

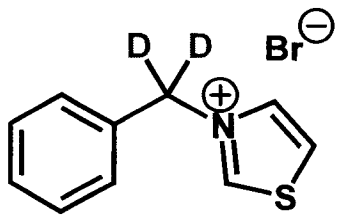
Benzoin condensation typically uses cyanide anion as a catalyst

Teles, J. H. et al. *Helvetica Chim. Act.* **1996**. *79*, 61.

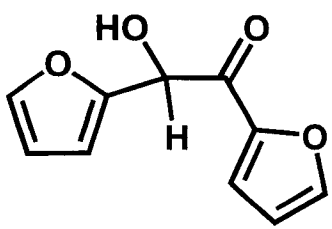
Deuterium Exchange Studies

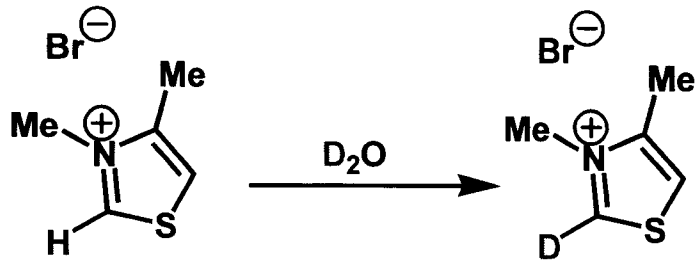


Thiamine (B1)



No deuterium exchange observed in furoin condensation





C-2 Proton exchanges with D_2O

^{1}H NMR

Disappearance of C-2 H

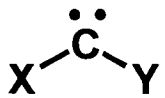
IR

Development of intense band consistent with deuterium substitution

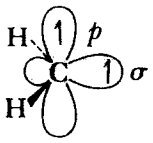
Thiazole ring of thiamine is able to stabilize negative charge

Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

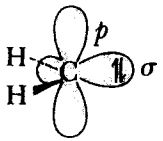
Carbene Structure



Intermediate that contains an uncharged divalent carbon

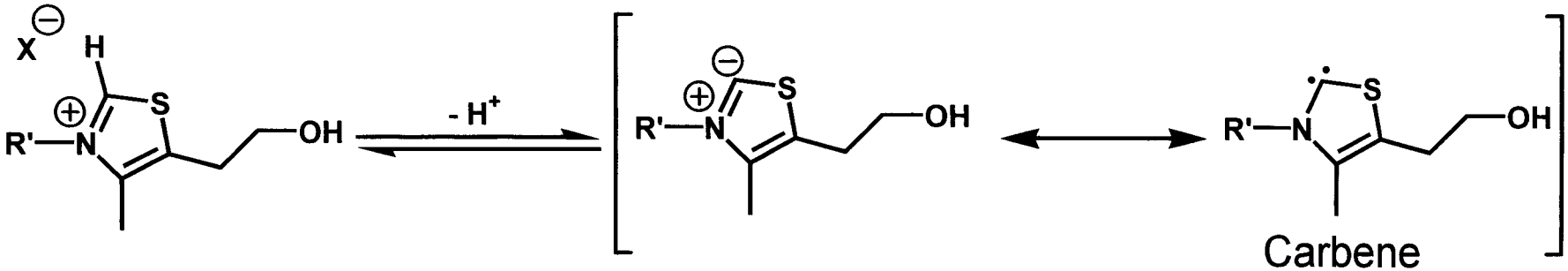


T



S

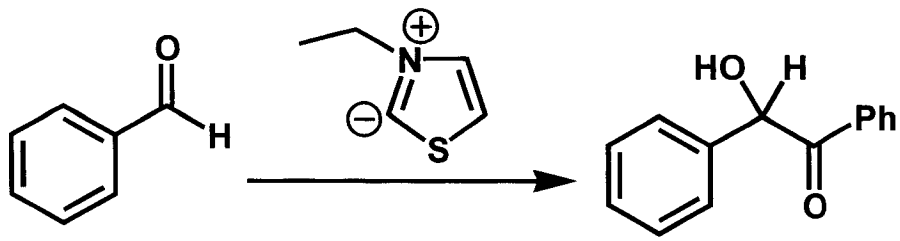
Can exist as Triplet or Singlet



N-Heterocyclic carbenes prefer the singlet state

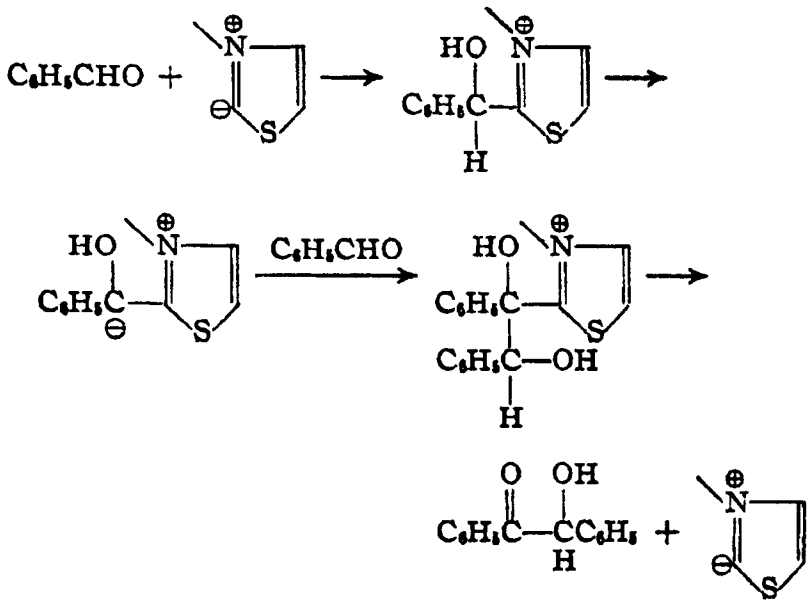
Lowry, T.H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*. **1987**. p550.

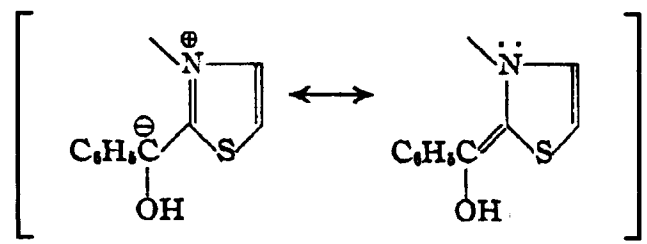
Proposed Mechanism for the Benzoin Condensation



Benzoin

Yields 50 -85%





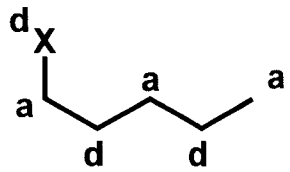
Stabilized Carbanion

Thiazole ring is able to catalyze the benzoin condensation

Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719.

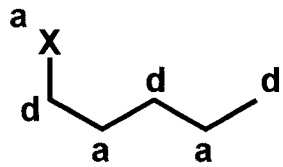
Umpolung Reactivity

"Conventional"

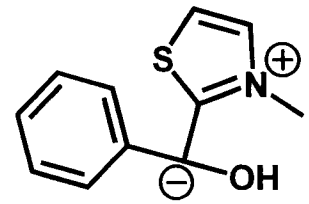


X = O, N

Umpolung Reactivity

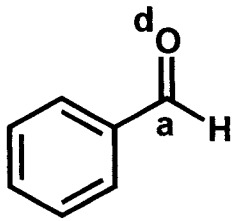


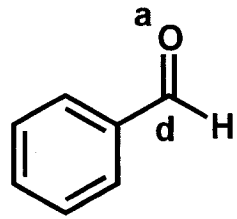
X = O, N

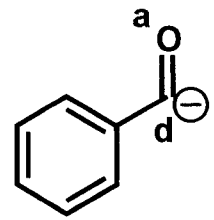


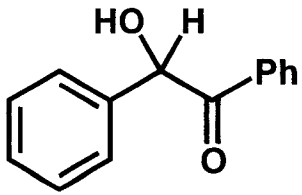
a = acceptor

d = donor









Benzoin

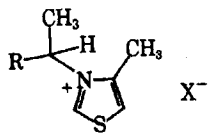
"Umpolung is the process by which donor and acceptor reactivity of an atom are interchanged"

Umpolung results in polarity reversal

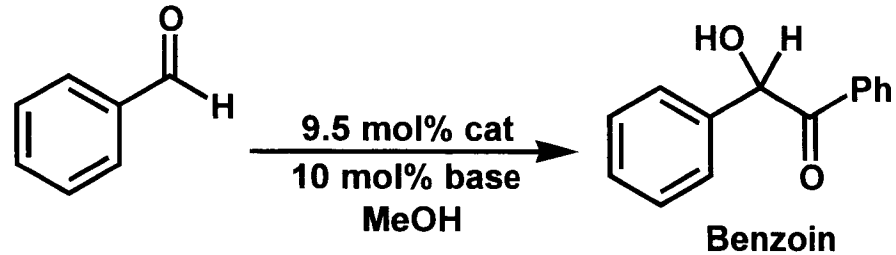
Seebach, D. *Angew. Chem. Int. Ed. Eng.* **1979**, *18*, 239.

Asymmetric Approaches-Early Work

Chiral Catalysts



4a, R = $PhCH_2$; X = Cl
b, R = 1-naphthyl; X = Br
c, R = Ph; X = (+)-3-bromocamphor 9-sulfonate
d, R = Ph; X = (−)-3-bromocamphor 9-sulfonate



Proposed Transition State

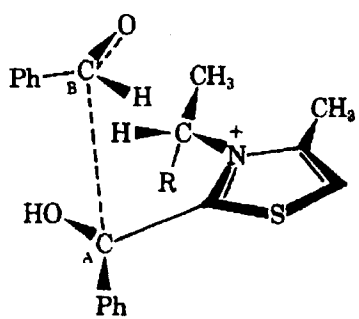


Table I
Thiazolium Salt Catalysis of the Benzoin Condensation

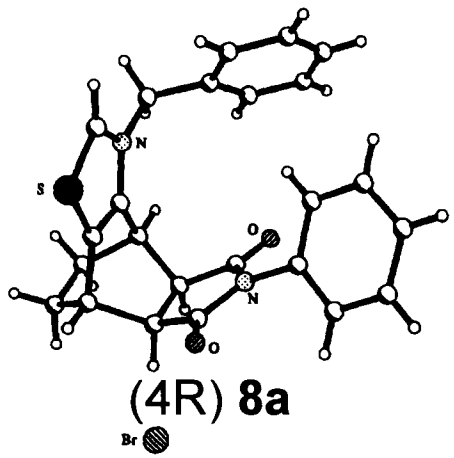
Salt	Reaction conditions,[a] solvent, base, time in hr	Yield,[b] %	Optical rotation[c] $[\alpha]_{436}$ Temp, °C	$[\alpha]$	c	Optical purity,[d] %
(*R*)-(−)-4a	MeOH, Et_3N 6	12	23	0	0.92	0
(*S*)-(+)-4b	MeOH, Et_3N 6	6.1	21	+221	0.46	51.5
(*R*)-(−)-4b	MeOH, Et_3N 24	21	23	−165	1.03	38.5
		17	20.5	−161	0.86	37.5
	MeOH, Et_3N 48	26	25	−126	1.03	29.4
	MeOH–H_2O, NaOH 24	22	23	−133	1.06	31.0
(*S*)-(+)-4c	MeOH, Et_3N 25	78	25	+33.6	1.01	7.8
(*S*)-(+)-4d	MeOH, Et_3N 25	68	20	+30.4	1.03	7.1

[a] Bath temperature, 30°. [b] Based on benzoin isolated by chromatography on silicic acid. [c] In methanol. [d] Calculated based on the following rotation of (−)-benzoin:[8] $[\alpha]_{436}^{20}$ −429 (*c* 1.01, MeOH).

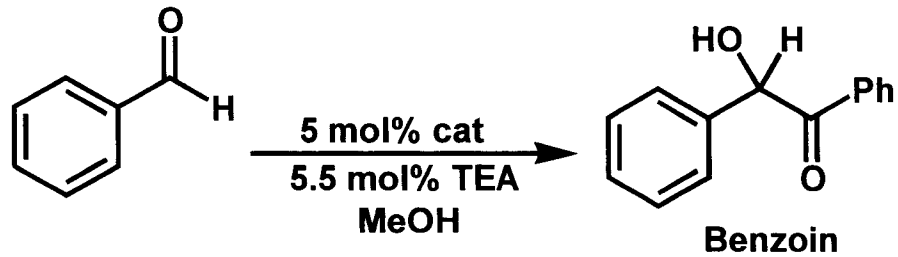
Chiral thiazolium salts are able to induce asymmetry

Sheehan, J. C.; Hara, T. *J. Org. Chem.* **1974**, *39*, 1196.

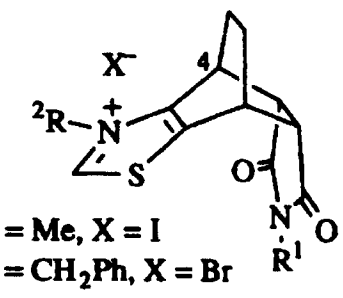
Chiral Polycyclic Thiazolium Salts



(4R) **8a**



Benzoin



7 R^2 = Me, X = I
8a R^2 = CH_2Ph, X = Br
8b R^2 = CH_2Ph, X = Cl

Table 1. Yields and Enantiomeric Excesses of the Benzoin Produced by each of the Thiazolium Salts

Thiazolium salt	Method A[a]			Method B[b]		
	Yield	Configuration	e.e.	Yield	Configuration	e.e.
(4*R*)-**7a**	50%	*R*	5%	88%	*S*	1%
(4*R*)-**8a**	70%	*S*	8%	100%	*S*	26%
(4*S*)-**7b**	47%[c]	*S*	6%	46%[c]	*S*	7%
(4*S*)-**8b**	31%[c]	*S*	13%	91%	*S*	16%

[a] PhCHO (492 μmol), Et_3N (27 μmol, 5.5%) and catalyst (24.5 μmol, 5%) in dry deoxygenated MeOH (1 ml) for 16-22 h at 20 °C.
[b] As for *a* but without any solvent at 20 °C for 1–16h. [c] Using 2.75% Et_3N and 2.5% catalyst.

Strategy of blocking one face of thiazolium ring is insufficient for high ee

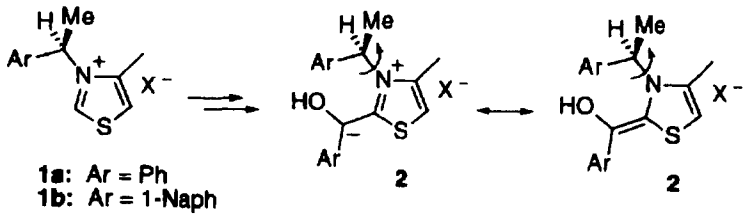
Gerhard, A., U.; Leeper, F., J. *Tetrahedron Lett.* **1997**, *38*, 3615.

Conformationally Restricted Bicyclic Salts

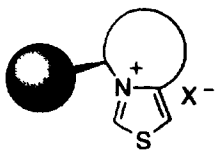
Table 1. Benzoin Condensation Using Chiral Thiazolium Salts

Entry[a]	PhCHO (mmol)	Solvent (ratio, amount)	Catalyst (9a or 9b, mmol)	Base (mmol)	Time (h)	% Yield (isolated)	% ee
1	1.17	MeOH, 0.5 mL	**9a**, 0.12	Et_3N, 0.13	0.6	< 2%	28
2	1.17	MeOH : H_2O 1 : 2.5, 0.5 mL	**9a**, 0.12	Et_3N, 0.12	8	20	24
3	1.17	" "	**9a**, 0.12	Et_3N, 0.14	12	30	23
4	2.15	MeOH : H_2O 1 : 2.5, 1.0 mL	**9a**, 0.22	Et_3N, 0.24	24	27	20
5	1.17	0.5M Na_2HPO_4 0.5 mL	**9a**, 0.14		8	13	26
6[b]	1.36	MeOH, 0.68 mL	**9a**, 0.136	Et_3N, 0.129	24	65	15
7[b,c]	1 eq.	MeOH	**1a**, 0.1 eq.	Et_3N, 0.095 eq.	24	78	7.8
8	2.54	MeOH : H_2O 1 : 2.5, 1.0 mL	**9b**, 0.25	Et_3N, 0.28	8	18	30
9	2.54	" "	**9b**, 0.22	Et_3N, 0.24	24	26	27
10[b]	0.74	MeOH, 0.2 mL	**9b**, 0.075	Et_3N, 0.078	6	45	16
11[b,c]	1 eq.	MeOH	**1b**, 0.1 eq.	Et_3N, 0.095 eq.	6	6.1	51.5
12	2.16	MeOH : H_2O 1 : 2.5, 1.0 mL	**1b**, 0.22	Et_3N, 0.24	6	52	48

[a]Unless indicated, the reactions were carried out at ambient temperature (20-23 °C). [b]Reaction carried out at 30 °C, bath temperature. [c]Data taken from Sheehan and Hara's work, reference 6e.



Proposed that conformationally locking chiral sidechain would increase enantioselectivity



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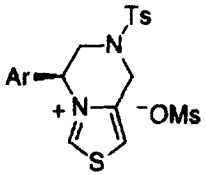
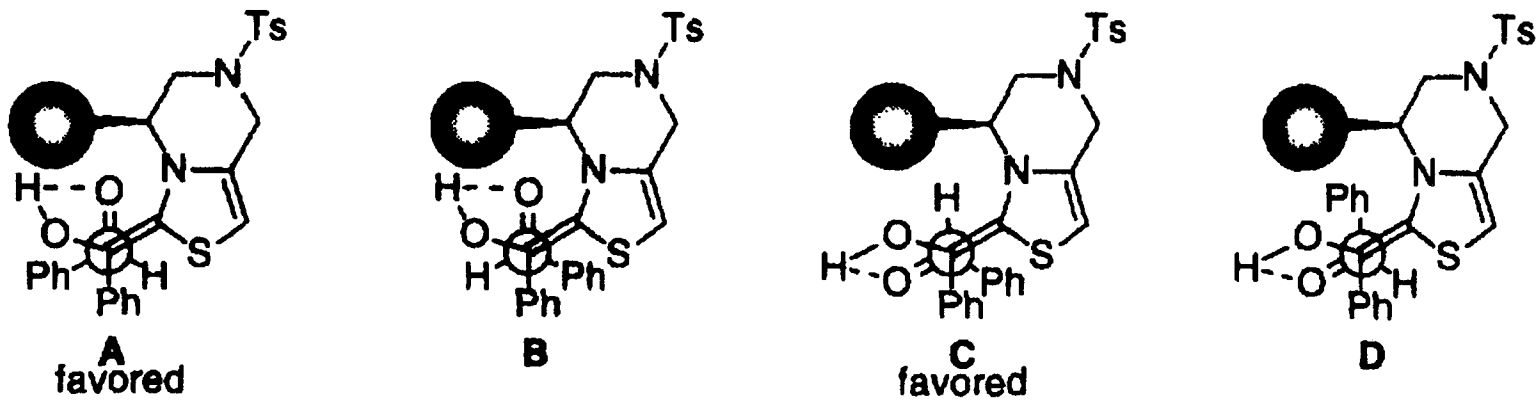


9a: R = Ph, 87%
9b: R = 1-Naph, 93%

Modification of Sheehan's conditions give ee up to 52%

Dvorak, C. A.; Rawal, V. H. *Tetrahedron. Lett.* **1998**, *39*, 2925.

Bicyclic Thiazolium Salts-Rationale



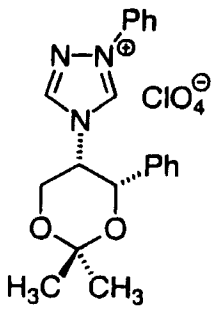
Enamine formation should give *E* geometry

Phenyl group on catalyst blocks one face

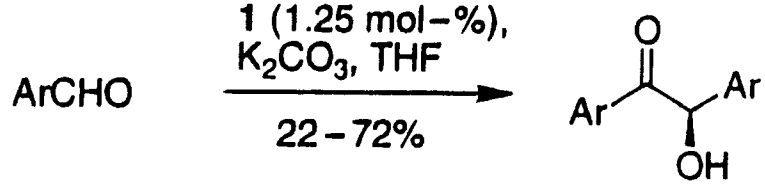
Catalyst design does not control orientation of phenyl group

Dvorak, C. A.; Rawal, V. H. *Tetrahedron. Lett.* **1998**, *39*, 2925.

Efficient Catalyst Design- Triazolium Salts



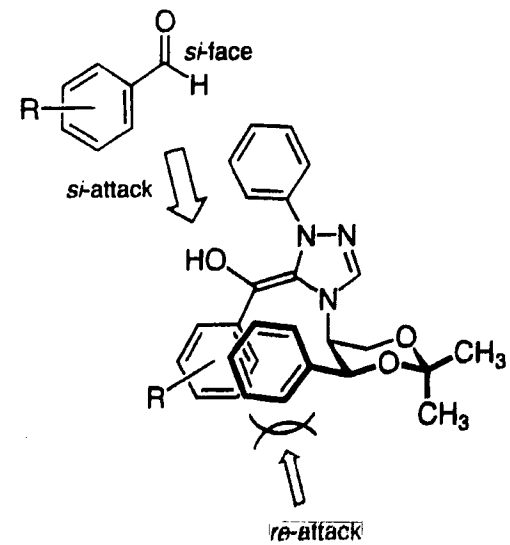
1



3	Ar	Yield [%]	ee[a]) [%]
a	Ph	66	75
b	3-$MeOC_6H_4$	41	66
c	4-$MeOC_6H_4$	22 (5)[c])	86 (87)[c])
d	3-MeC_6H_4	54	76
e	4-MeC_6H_4	46 (28)[c])	82 (84)[c])
f	4-FC_6H_4	48	44
g	4-ClC_6H_4	51	29
h	4-BrC_6H_4	72	20

Catalyst gives (R) benzoin

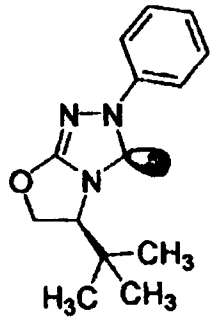
Proposed Model



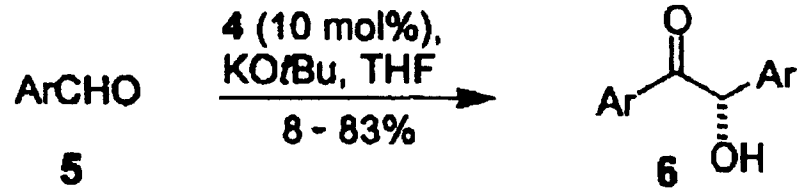
Triazolium salts provide improved yields and enantioselectivity

Enders, D.; Breuer, K. *Helv. Chim. Act.* **1996**, *79*, 1217.

Improved Triazolium Salts

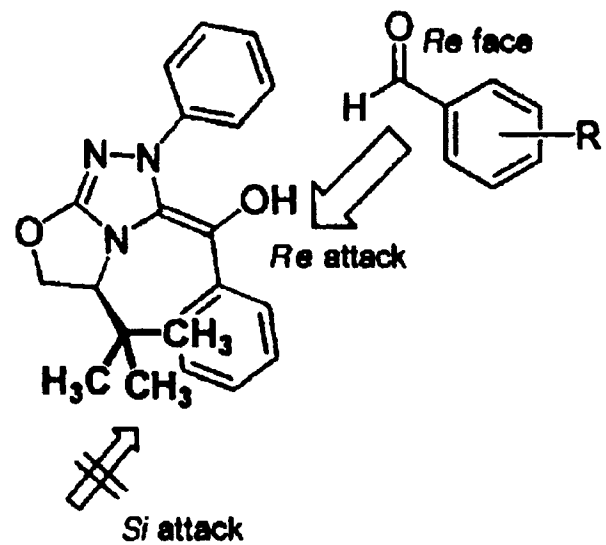


4'



6	Ar	T [°C]	Yield [%]	ee [%][c]
a	Ph	18	83	90
b	4-FC_6H_4	18	81	83
b'	4-FC_6H_4	0	61	91
c	4-ClC_6H_4	18	80	64
c'	4-ClC_6H_4	0	44	89
d	4-BrC_6H_4	18	82	53
d'	4-BrC_6H_4	0	59	91
e	3-ClC_6H_4	18	92	62
e'	3-ClC_6H_4	0	85	86
f	4-MeC_6H_4	18	16	93
g	3-MeC_6H_4	18	70	86
g'	3-MeC_6H_4	0	36	91
h	4-$MeOC_6H_4$	18	8	95
i	2-furyl	0	100	64
i'	2-furyl	−78	41	88
j	2-naphthyl	18	69	80

Proposed Model



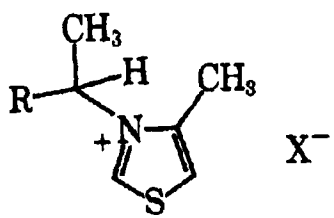
Improved triazolium catalyst provides products in good yield and high ee

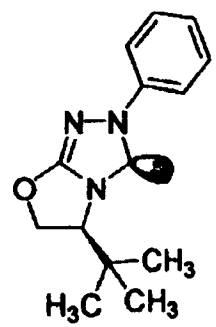
Enders, D.; Kallfass, U. *Angew. Chem. Int. Ed.* **2002**, *41*, 1743.

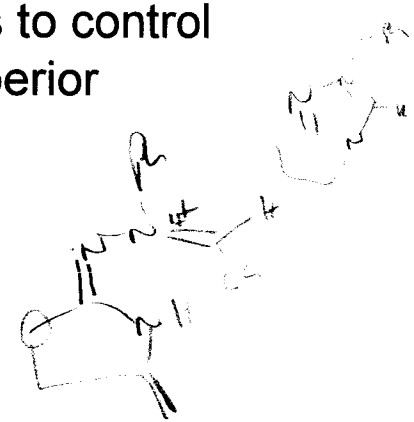
Summary for Benzoin Condensation

Thiazolium salts are able to catalyze the benzoin condensation in an anologous manner to cyanide salts

While initial work focused on the use of chiral thiazolium salts to control enantioselection, chiral triazolium salts were shown to be superior

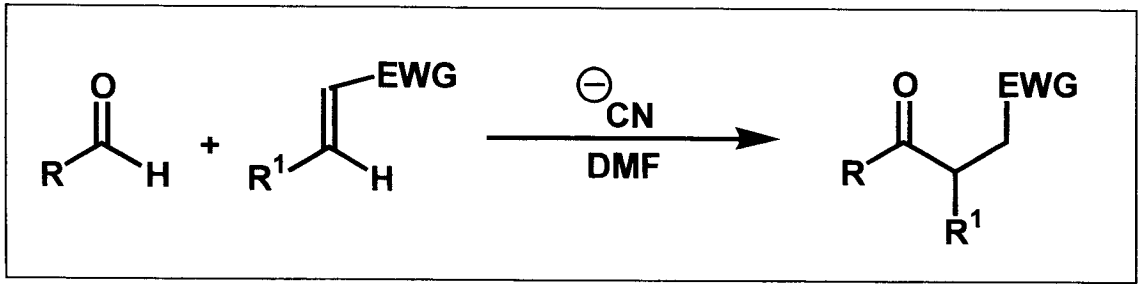






Chiral triazolium salts have given the highest ee's (up to 95%) and yields to date

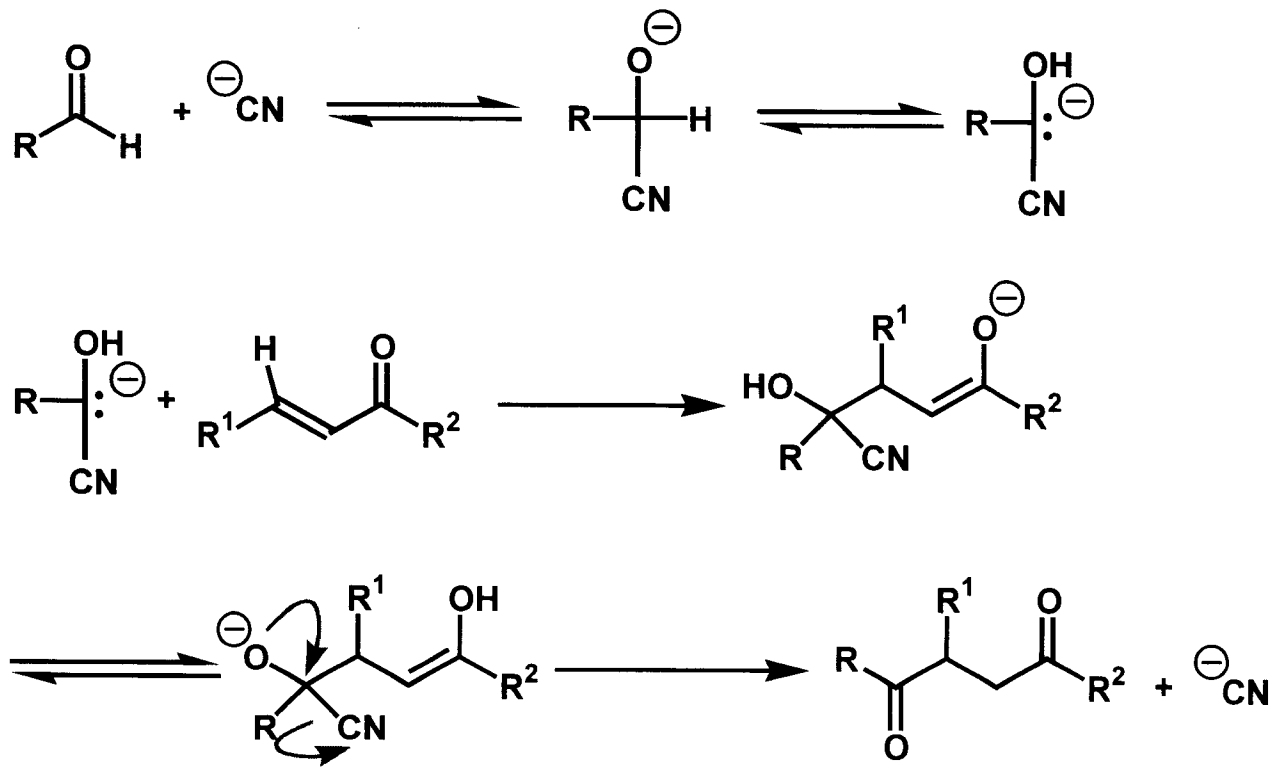
Stetter Reaction



R = aryl

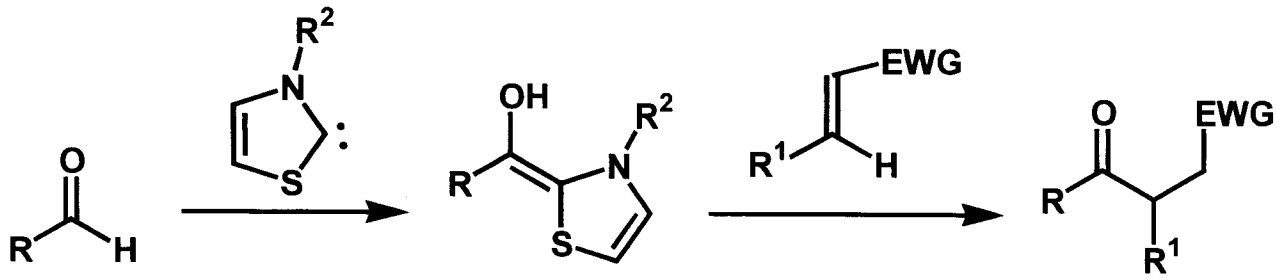
EWG = ketone, ester, nitrile

Mechanism:



Stetter, H. *Angew. Chem. Int. Ed.* **1976**, *15*, 639.

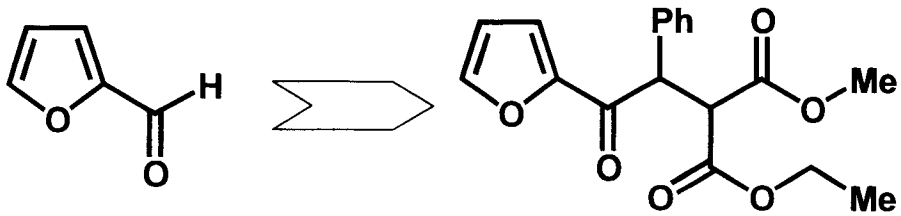
Stetter Reaction Catalyzed by Thiazolium Salts



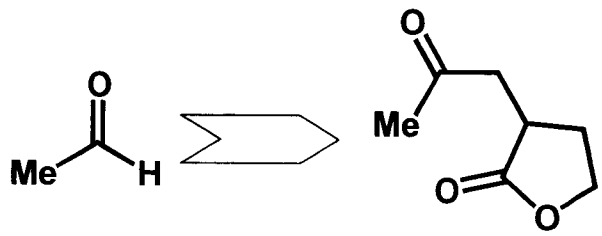
R on aldehyde can be aliphatic

Relatively mild conditions 30-35 °C, 60-80% yields

Wide range of products can be synthesized:



81%

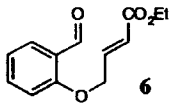
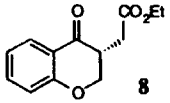
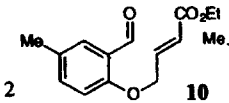
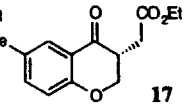
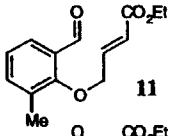
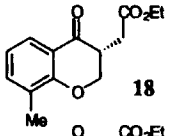
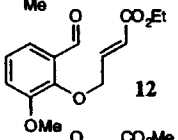
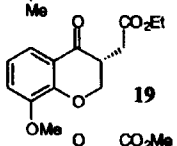
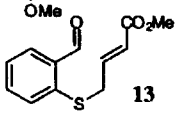
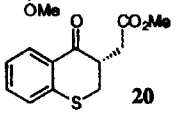
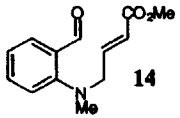
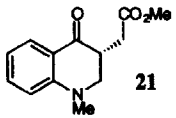
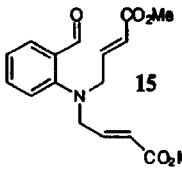
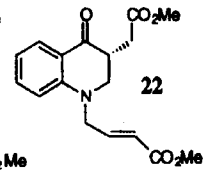


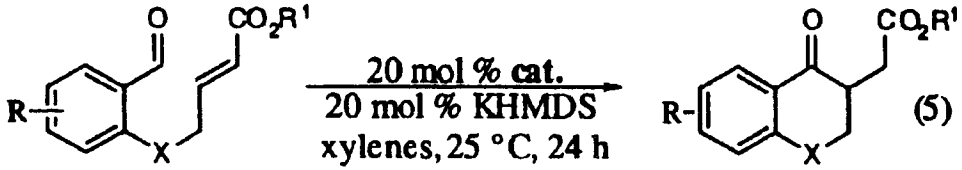
56%

Thiazolium salts permit addition of aliphatic aldehydes to Michael acceptors

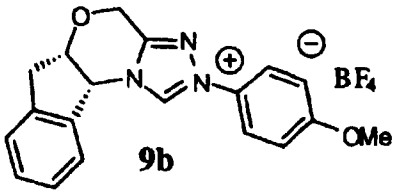
Paquette, L.A. ed. *Organic Reactions Vol. 40*, **1991**, pp407- 496.

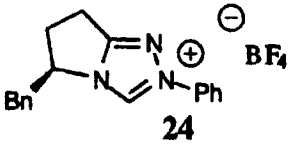
Catalytic Asymmetric Intramolecular Stetter Reaction

Entry[a]	Substrate	Product	cat.	Yield (%)	ee (%)[f]
1	 6	 8	9b	94	94
2	 10	 17	9b	80[b]	97
3	 11	 18	9b	90	84
4	 12	 19	9b	95[b]	87
5	 13	 20	9b	63	96
6	 14	 21	9b	64	82
7	 15	 22	9b	72	84



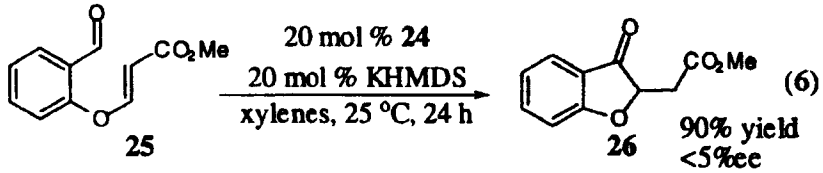
Triazolium Salts

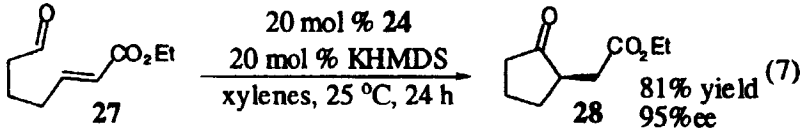




Cyclopentanones can also be accessed

Scheme 1

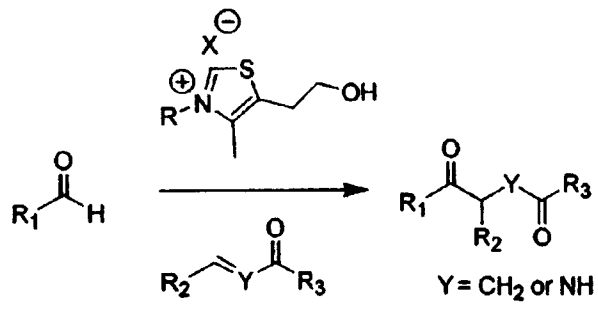




Intramolecular Stetter reaction is catalyzed by chiral triazolium salts

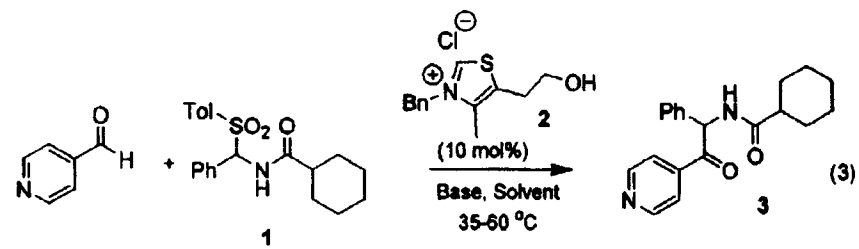
Rovis et al. *J. Am. Chem. Soc.* **2002**, *124*, 10298.

Thiazolium-Catalyzed Formation of Amido Ketones



Challenges:
Acylamine must be reactive enough to compete with another aldehyde

Acylamine must not decompose or interfere with catalyst



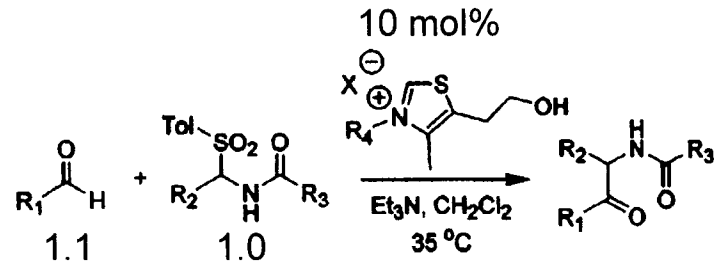
Solvent and base survey provided that triethyl amine and methylene chloride were superior

entry	solvent	base	equiv	time	yield **3** (%)
1	THF	TEA	5	24 h	66
2	Toulene	TEA	5	24 h	34
3	DMF	TEA	5	10 h	48
4	CH_3CN	TEA	5	4 h	66
5	CH_2Cl_2	TEA	5	30 min	98
6	CH_2Cl_2	TEA	2	30 min	94
7	CH_2Cl_2	K_2CO_3	5	24 h	75

Reider, P. et al. *J. Am. Chem. Soc.* **2001**, *123*, 9696.

Substrate Scope in the Synthesis of Amido Ketones

entry[b]	R_1	R_2	R_3	time	yield (%)
1	4-pyridyl	Ph	H	30 min	86
2	4-pyridyl	Ph	CH_3	30 min	93
3	4-pyridyl	Ph	c-C_6H_{11}	30 min	98
4	4-pyridyl	Ph	Ph	30 min	88
5	4-pyridyl	Ph	4-F−Ph	30 min	90
6	4-pyridyl	Ph	4-OMe-Ph	30 min	97
7	4-pyridyl	Ph	OBn	15 min	96
8	4-pyridyl	Ph	O^{t}Bu	15 min	85
9	Ph	Ph	O^{t}Bu	24 h	75
10	2-Br−Ph	Ph	O^{t}Bu	8 h	86
11[c]	3-OMe-Ph	Ph	O^{t}Bu	48 h	68
12	4-CN−Ph	Ph	O^{t}Bu	15 min	80
13	2-furyl	Ph	O^{t}Bu	24 h	73
14	3-pyridyl	Ph	O^{t}Bu	24 h	93
15	CH_3	Ph	O^{t}Bu	24 h	62
16	BnOCH2	Ph	O^{t}Bu	24 h	75
17	PhCH=CH	Ph	c-C_6H_{11}	24 h	80
18	4-pyridyl	4-F−Ph	c-C_6H_{11}	30 min	76
19	4-pyridyl	4-OMe-Ph	c-C_6H_{11}	30 min	84
20	4-pyridyl	c-C_6H_{11}	Ph	24 h	<10
21[d]	4-pyridyl	H	Ph	24 h	58



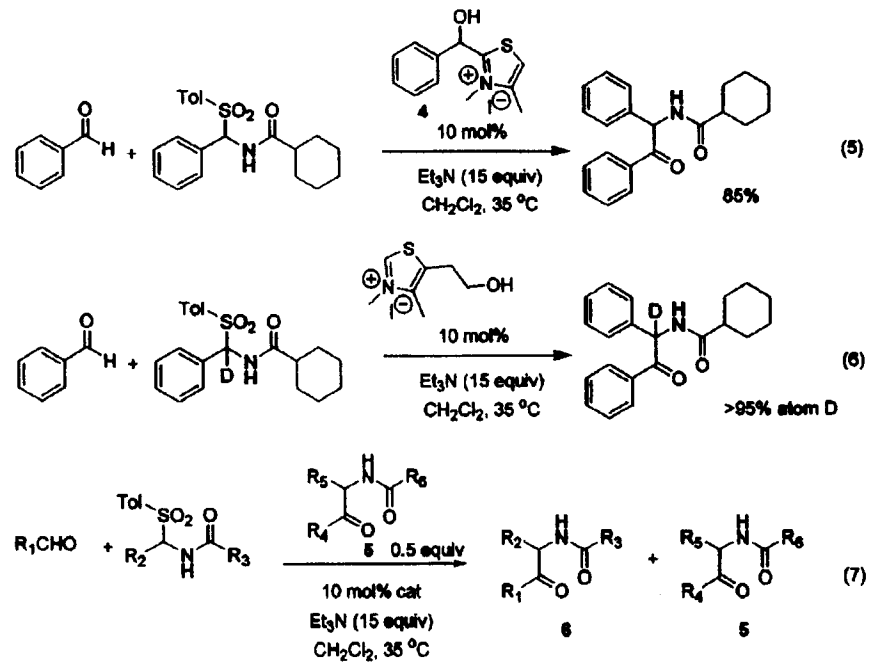
Electron deficient aldehydes are generally better than electron poor

Reaction is tolerant to the amide portion of the tosylamide

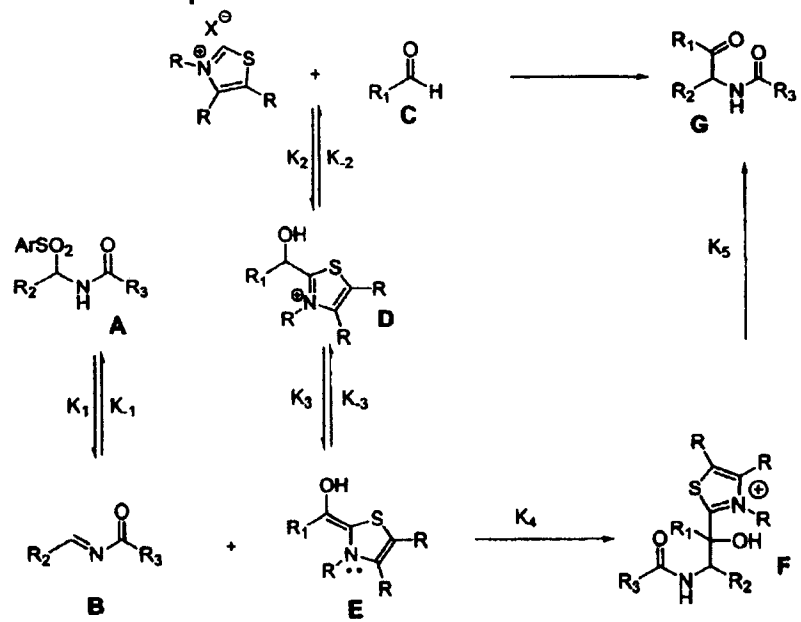
Reaction demonstrates wide scope with various aldehydes

Reider, P. et al. *J. Am. Chem. Soc.* **2001**, *123*, 9696.

Mechanistic Studies



Proposed Mechanism

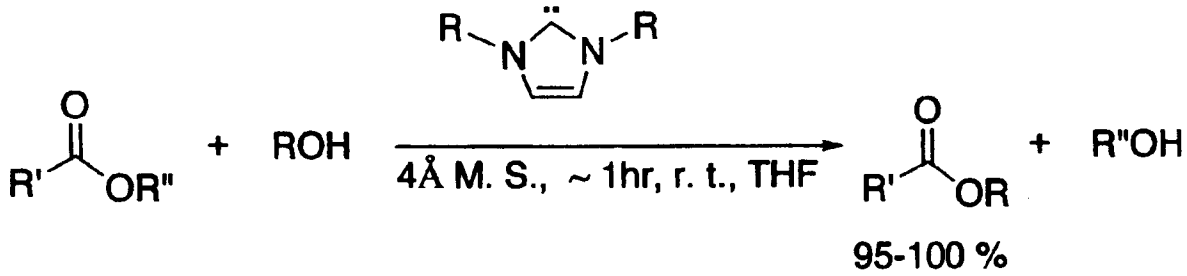


Proceeds through stabilized carbanion intermediate

Proposed mechanism is anologous to the benzoin and Stetter reactions

Reider, P. et al. *J. Am. Chem. Soc.* **2001**, *123*, 9696.

Transesterification Reactions using Imidazol-2-ylidenes

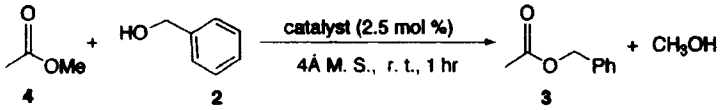


Scheme 1. Various *N*-Heterocyclic Carbenes

R		R'	
2,4,6-trimethylphenyl	IMes	2,4,6-trimethylphenyl	SIMes
2,6-di-*iso*-propylphenyl	IPr	2,6-di-*iso*-propylphenyl	SIPr
tert-butyl	I^{t}Bu		
adamantyl	IAd		
cyclohexyl	ICy		

Optimization studies showed Icy, I^{t}Bu, and IAd performed best

Table 1. Transesterification of Methyl Acetate with Benzyl Alcohol Catalyzed by Various Nucleophiles



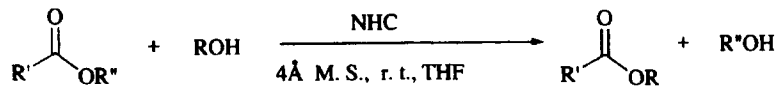
entry	catalyst	yield[a] (%)
1	IMes	93
2	IPr	45
3	SIMes	21
4	SIPr	21
5	ICy	100
6	ICy	84[b]
7	IAd	100
8	I^{t}Bu	100
9	DMAP	15
10	DABCO	45
11	DBU	24
12	NaH	95
13	KO^{t}Bu	95

[a] GC yield, average of two runs. [b] Molecular sieves were not used.

Nolan, S. P. et al. *Org. Lett.* **2002.** *4*, 3583.

Transesterification Reactions using Imidazol-2-ylidenes- Reaction Scope

Table 2. ICy-Catalyzed Transesterification of Various Esters and Alcohols



entry	ester	aclohol	product	cat/mol%	time(min)	yield(%)[e]	entry	ester	aclohol	product	cat/mol%	time min)	yield(%)[e]
1	1	5	6	IMes/1.0	60	99[a]	7	13	2	14	ICy/2.5	15	96[c]
2	1	7	8	IMes/1.0	15	96[a]	8	15	2	16	ICy/2.5	180	97[c]
3	1	9	10	IMes/0.5	15	100[a]	9	17	2	18	ICy/2.5	30	99[c]
4	4	2	3	ICy/2.5	60	95[b]	10	19	2	3	ICy/2.5	30	94[d]
5	4	9	10	ICy/2.5	30	90[b]	11	19	7	8	ICy/2.5	60	93[c]
6	11	2	12	ICy/2.5	30	95[c]	12	20	2	21	ICy/5	15	95[a]

[a] 1 mmol of alcohol, 1.2 mmol of vinyl acetate, 0.5−1 mol % of IMes, 1 mL of THF, room temperature. [b] 1 mmol of alcohol, 1 mL of methyl acetate, 2.5 mol % of ICy, 0.5 g of 4 Å molecular sieves, room temperature. [c] 1 mmol of methyl ester, 2 mmol of benzyl alcohol, 1 mL of THF, 2.5 mol % of ICy, 0.5 g of 4 Å molecular sieves, room temperature. [d] 1 mmol of alcohol, 1 mL of ethyl acetate, 2.5 mol % of ICy, 0.5 g of 5 Å molecular sieves, room temperature. [e] Isolated yield, average of two runs.

Nolan, S. P. et al. *Org. Lett.* **2002.** *4*, 3583.

Conclusions

Nucleophilic carbenes are able to catalyze a wide range of different reactions

Stabilized carbenes take advantage of umpolung reactivity

Chiral triazolium salts provided superior enantioselection in the benzoin condensation

Stetter reaction is useful in the formation of 1,4 difunctionalized carbonyl Compounds and the intramolecular variant can be done asymmetrically

Imidazol-2-ylidenes are useful in transesterification reactions under mild conditions