An Overview on Genuine Organocatalytic Reactions.

Contents:

1) Introduction.

Organocatalysts has became one of the major rapidly growing area in organic synthesis, due to its convenience, nontoxic, cheap and unique reactivity. But unfortunately in recent days, organo catalysts are became just a mimic of metal catalysts! This situation arise a doubt about the ingenuity of organo catalysts.
In this seminar i like to discuss about so called GENUINE organo catalytic reactions (the reactions that eighter cannot be achieved or not yet well established by metal based catalyst).
I hope it would show us that the organocatalyst indeed a powerful strategy for enantioselective bond constructions.

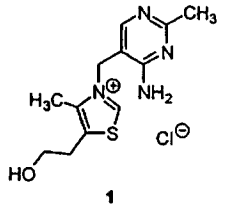
2) Thiazolium based organocatalyst: The first organocatalyst.

In the 1990s, Schneider et al revealed the structure of a transketolase enzyme that uses thiamine as a coenzyme to catalyse a number of important biochemical reactions.

Catalytic Nucleophilic Acylation Reactions

1832 when F. Wöhler and J. Liebig discovered the so-called benzoin condensation catalyzed by cyanide anions.[3] In 1903, A. Lapworth proposed a mechanism for this remarkable reaction that would proceed via a carbanion generated from the benzaldehyde substrate in a hydrogen cyanide addition followed by deprotonation.[4]

JCS, 1903, 83, 995-1005



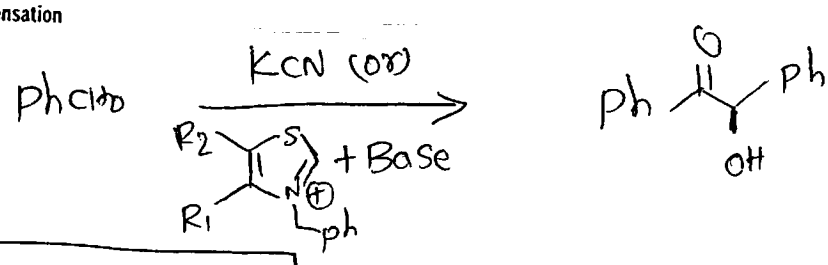
1
Thiamine (vitamin B_1), a coenzyme.

[5] Ukai et al. found in 1943 that, as well as cyanide ions, thiazolium salts can be used as catalysts for the benzoin condensation.[6] Some years later, Mizuhara et al. showed that the catalytic activity of the natural thiamine is based on its thiazolium unit as well.[7]

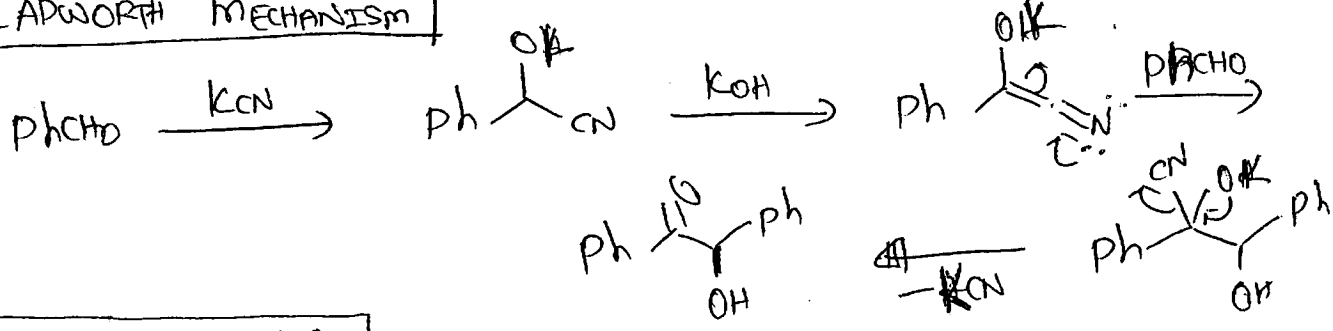
Ukai et al
J. Pharm. Soc. Jpn. 1943, 63, 296-301

Indeed, R. Breslow based his mechanistic model for the thiazolium salt catalyzed benzoin condensation on the works of Lapworth. In 1958, he presented a mechanism that has a thiazol-2-ylidene, a carbene compound, as the catalytically active species.[8]

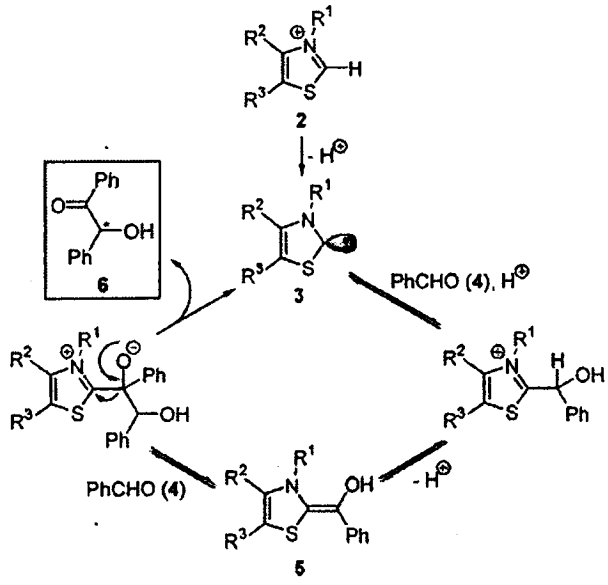
Breslow. R JACS, 1958, 80, 3719-3726



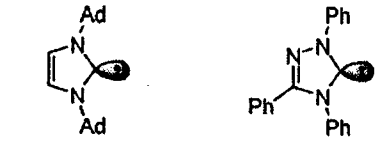
LAPWORTH MECHANISM



BRESLOW MECHANISM



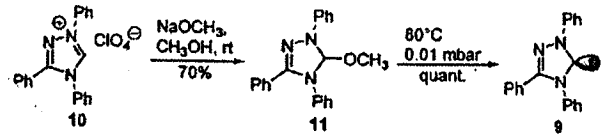
In 1980s Arduengo et al and Enders et al have shown that carbenes like imidazolyl-2-ylidene (8) and triazole-5-ylidine (9) can be prepared and stored for months in the absence of air. Ultimately this finding inspired many chemist to work on chiral triazole carbine as asymmetric catalyst.



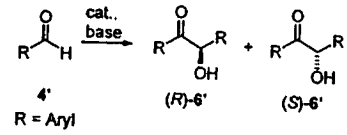
Ad = Adamantyl

8 9

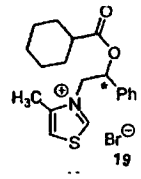
Scheme 2. Synthesis of the Stable Carbene 9 Developed by Enders et al.



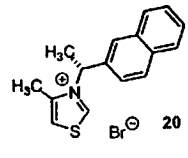
Asymmetric Catalysis with Carbenes



Sheehan etal

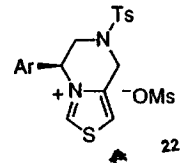


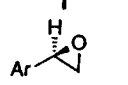
ee:-2%.
Yield:-70%.
JACS, 1966, 88, 3666-3667.



ee:-52%.
Yield:-6%.
JOC, 1974, 39, 1196-1199.

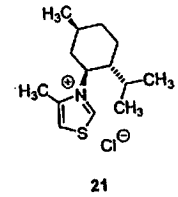
Rawal etal





ee:-48%
Yield:-52%.
TL, 1998, 39, 2925-2928.

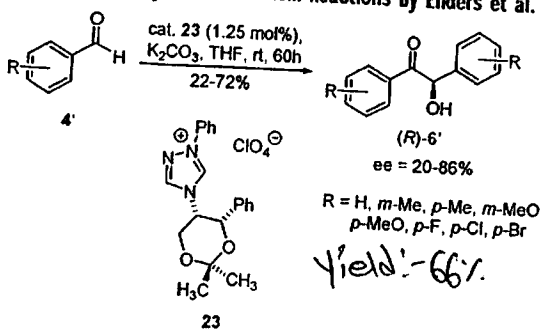
Tagaki etal



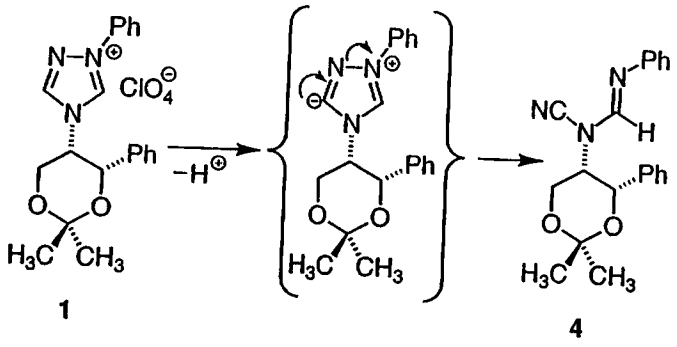
ee:-3
Yield:-20
Bull. chem. Soc. JP 1980, 53, 478-48

Generally Poor Yield and enatiomeric excess.

Asymmetric Benzoin Reactions by Enders et al.



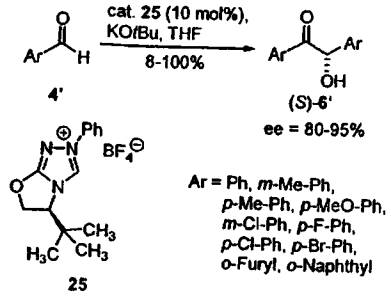
Pursuing the idea of triazolium salt catalysis, our research group synthesized a variety of chiral triazolium salts and examined their ability to catalyze the benzoin reaction.[31] However, the enantiomeric excesses and catalytic activities proved to vary strongly with slight structural changes in the substitution pattern of the triazolium system. The most active catalyst **23** provided benzoin **6** in its (*R*)-configuration with 75% ee and a satisfactory yield of 66% using a significantly reduced catalyst amount of 1.25 mol % (Scheme 6).



Enders et al Helv. Chimica. Acta 1996, 79, 1217-1221.
catalyst preparation:-
Syn. com, 1999, 29, 1-9.

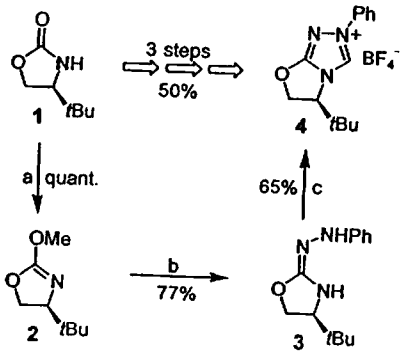
The deactivation of catalyst **1** in the course of the catalysis proceeds *via* the competing deprotonation in position 3, irreversibly leading to the formation of *N*-cyanobenzamidine **4** *via* ring opening of the triazole moiety[4]) (*Scheme 2*).

Highly Enantioselective Triazolium Salt Catalyzed Condensation of Aromatic Aldehydes Reported by Enders et al.



6	Ar	T [°C]	Yield [%]	ee [%][c]	$[\alpha]_D^{20}$[d]
a	Ph	18	83	90	+146.5
b	4-FC_6H_4	18	81	83	
b'	4-FC_6H_4	0	61	91	+117.5
c	4-ClC_6H_4	18	80	64	
c'	4-ClC_6H_4	0	44	89	+39.5
d	4-BrC_6H_4	18	82	53	
d'	4-BrC_6H_4	0	59	91	+9.6
e	3-ClC_6H_4	18	92	62	
e'	3-ClC_6H_4	0	85	86	+62.2
f	4-MeC_6H_4	18	16	93	+129.8
g	3-MeC_6H_4	18	70	86	
g'	3-MeC_6H_4	0	36	91	+138.1
h	4-$MeOC_6H_4$	18	8	95	+70.0
i	2-furyl[e]	0	100	64	
i'	2-furyl	−78	41	88	+57.4
j	2-naphthyl	18	69	80	−42.9

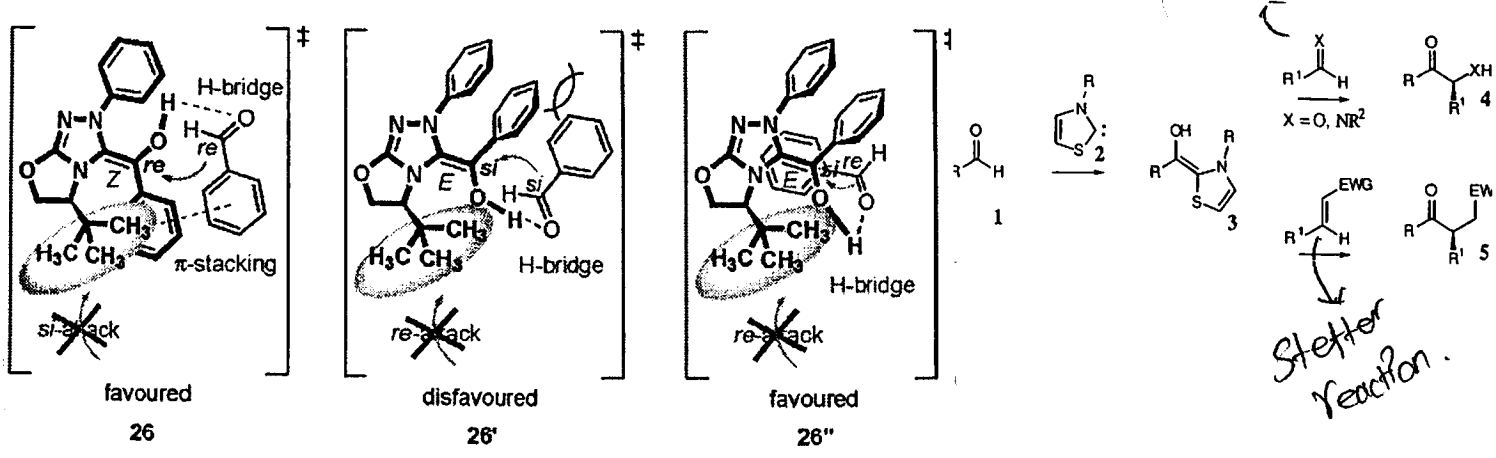
Scheme 1. Synthesis of triazolium salt **4**. a) Me_3OBF_4 (1.2 equiv), CH_2Cl_2, room temperature, 15 h; b) $PhNHNH_2$ (1 equiv), NEt_3 (1 equiv), THF, 80 °C, 7 d; c) HBF_4 (1 equiv) in diethyl ether, CH_2Cl_2, room temperature; $HC(OMe)_3$ (20 equiv), MeOH, 80 °C, 12 h.



Benzoin **6** was obtained in very good yield and with the best enantioselectivity reported so far (yield 83%; 90% ee). The condensation of numerous other aromatic aldehydes **4'** provided the corresponding α-hydroxy ketones **6'** in varying yields with excellent enantiomeric excesses up to 95%. As previously observed, electron-rich aromatic aldehydes gave significantly better asymmetric inductions than electron-deficient (i.e., activated aromatic aldehydes). Lower reaction temperatures (0 °C instead of room temperature) led to higher enantioselectivities coupled with lower yields.

Highest enantioselective Version:- Angew. Chem. Int. Ed. 2002, 41, 1713-1745.

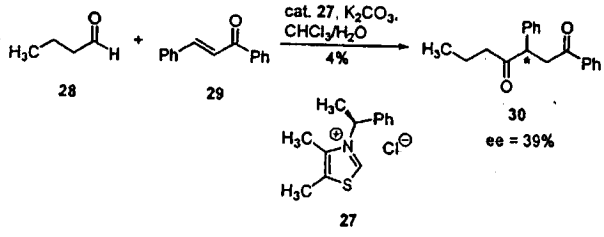
Benzoin condensation



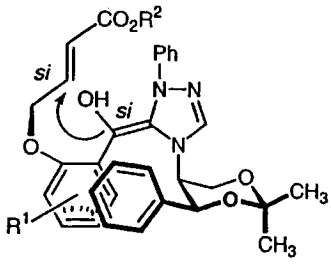
Stetter reaction:

In the 1970s, Stetter et al. succeeded in transferring the concept of thiazolium catalyzed nucleophilic acylation of aldehydes to the substrate class of Michael acceptors. The Stetter reaction, the addition of an activated aldehyde to an acceptor bearing an activated double bond, created a new catalytic pathway for the synthesis of 1,4-bifunctional molecules.[40]

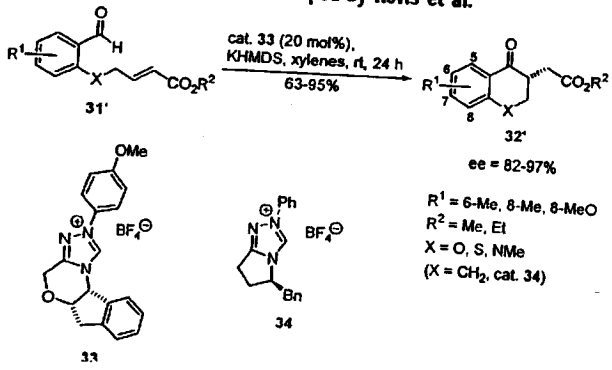
First Attempts in the Asymmetric Stetter Reaction by Enders et al.



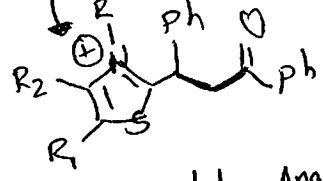
We envisaged an intramolecular variant where the reactivity of the substrate should be considerably enhanced due to entropic factors.[42] The stereoselective synthesis of various 4-chromanones via an intramolecular Stetter reaction, was performed with yields in the range of 22–73% and enantiomeric excesses of 41–74%.[31c,43]



Asymmetric Intramolecular Stetter Reaction of Aromatic Substrates Developed by Rovis et al.

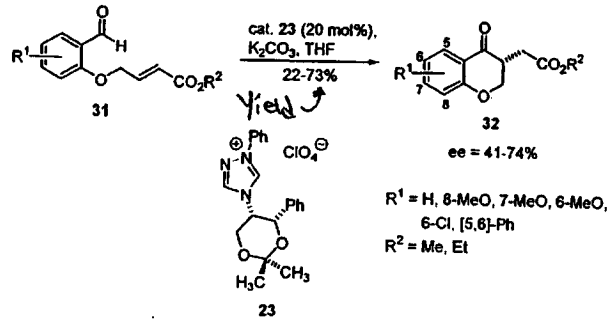


Unfortunately, the catalytic activity of thiazolium as well as triazolium salts in the Stetter reaction remained generally low,[40a] some triazol-5-ylidenes have been shown to give stable adducts with several Michael acceptors—a possible reason for their failure in catalysis.[20b]



Stetter et al Angew. chem 1976, 15, 639-648

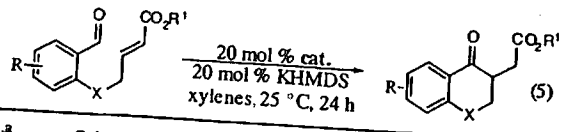
First Asymmetric Intramolecular Stetter Reactions by Enders et al.



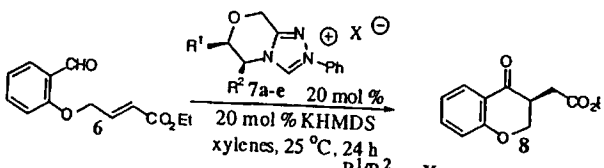
Enders et al Helv. chimica. Acta 1996, 79, 1899-1902.

Recently, Rovis et al. achieved an improvement of the asymmetric intramolecular Stetter reaction using triazolium salts. Employing catalysts of the types **33** and **34**, as depicted in Scheme 10, they obtained good enantioselectivities of 82–97% (chemical yields 63–95%) in the synthesis of numerous chromanones and aza-, thia-, and carbacyclic analogues **32'**. Thus, the scope of the reaction has been much expanded; however, it remains considerably restricted since only *E*-alkenes that are sufficiently activated for electrophilic attack can be used as Michael

Rovis et al JACS, 2002, 10298-10299.



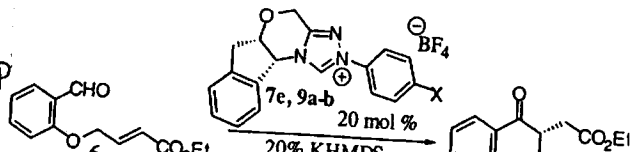
Entry[a]	Substrate	Product	cat.	Yield (%)	ee (%)[f]
1	6	8	9b	94	94
2	10	17	9b	80[b]	97
3	11	18	9b	90	84
4	12	19	9b	95[b]	87
5	13	20	9b	63	96
6	14	21	9b	64	82
7	15	22	9b	72	84
8	16	23	9b	35	94[d]
9	16	23	24	90	92[e]



	R^1/R^2	X	Yield (%)	ee (%
a	H/Bn	BF_4	85	90
b	H/*t*-Bu	BF_4	0	-
c	H/*i*-Pr	Cl	27	79
d	H/Ph*	Cl	48	80
e	Indanyl*	BF_4	58	95

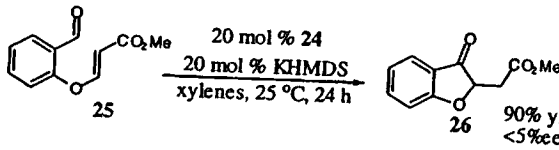
*enantiomeric catalyst was used

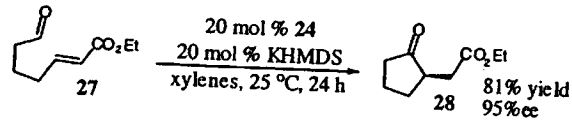
electron donating group increase the selectivity.

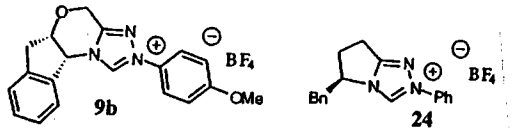


	X	Yield(%)	ee (%)
7e	H	58	95
9a	Cl	60	91
9b	OMe	94	94

Poor substrate generality.



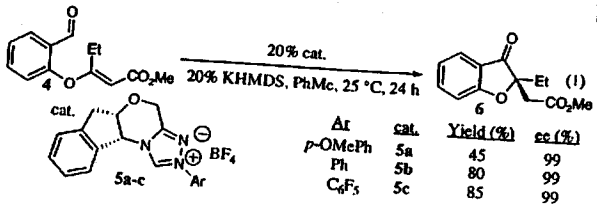




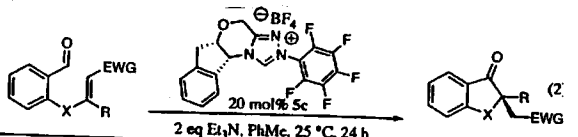
JACS ASAP.

Enantioselective Synthesis of Quaternary Stereocenters via a Catalytic Asymmetric Stetter Reaction

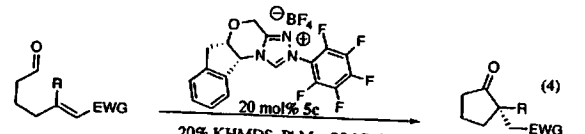
Tomislav Rovis*



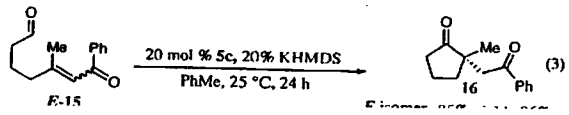
Ar	cat.	Yield (%)	ee (%)
p-OMePh	5a	45	99
Ph	5b	80	99
C_6F_5	5c	85	99

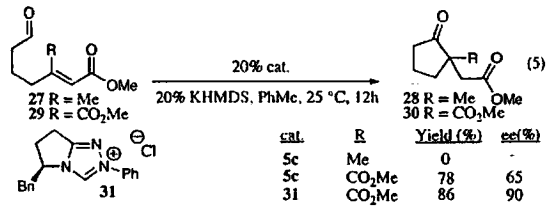


Entry	Substrate	Product[a]	Yield (%)	ee (%)[b]
1	X = H 4	X = H 6	96	97
2	Br 7	Br 8	92	89
3[c]	9	10	95	92
4	11	12	95	99
5[d]	13	14	55	99



Entry	Substrate	Product[a]	Yield (%)	ee (%)[b]
1	Ar = 4-Py 17	Ar = 4-Py 18	85	96
2	*p*-NO_2Ph 19	*p*-NO_2Ph 20	90	84
3	R = Me 21	R = Me[c] 22	81	95
4	$(CH_2)_2$Ph 23	$(CH_2)_2$Ph 24	63	99
5	25	26	71	98





cat.	R	Yield (%)	ee(%)
5c	Me	0	-
5c	CO_2Me	78	65
31	CO_2Me	86	90

Thiazolium based methodologies:

Catalytic Generation of Activated Carboxylates: Direct, Stereoselective Synthesis of β-Hydroxyesters from Epoxyaldehydes

Kenneth Yu-Kin Chow and Jeffrey W. Bode*

JACS 2004, 8126-8127.

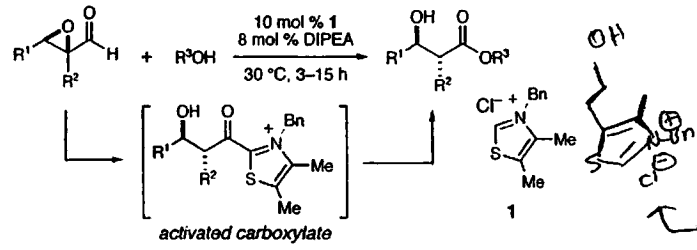
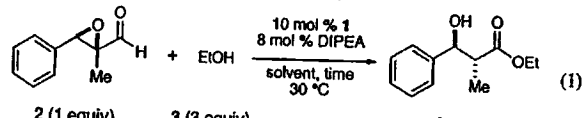


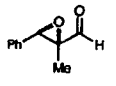
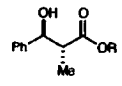
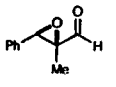
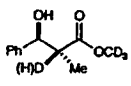
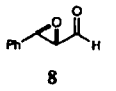
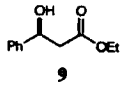
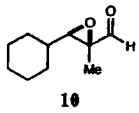
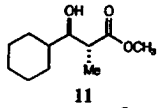
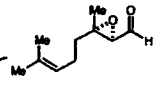
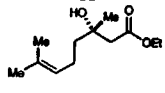
Table 1. Optimization of Reaction Conditions for the Synthesis of *anti*-β-Hydroxyesters from Epoxyaldehydes[a]



entry	solvent	time/h	yield[b] 4/%	dr 4 (*anti*:*syn*)[c]
1[d]	CH_2Cl_2	15	48	8:1
2	CH_2Cl_2	15	89	13:1
3[e]	CH_2Cl_2	4	77	12:1
4[f]	CH_2Cl_2	4	72	12:1
5	DMF	15	88	3.5:1
6	EtOH	15	68	7:1
7	CH_3CN	15	75	12:1
8	none	15	76	8:1

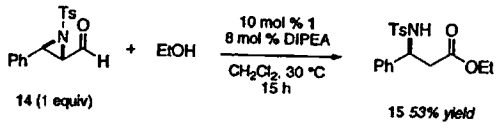
20 mol% cat DBU as base.

Table 2. Catalytic Esterifications of Epoxyaldehydes[a]

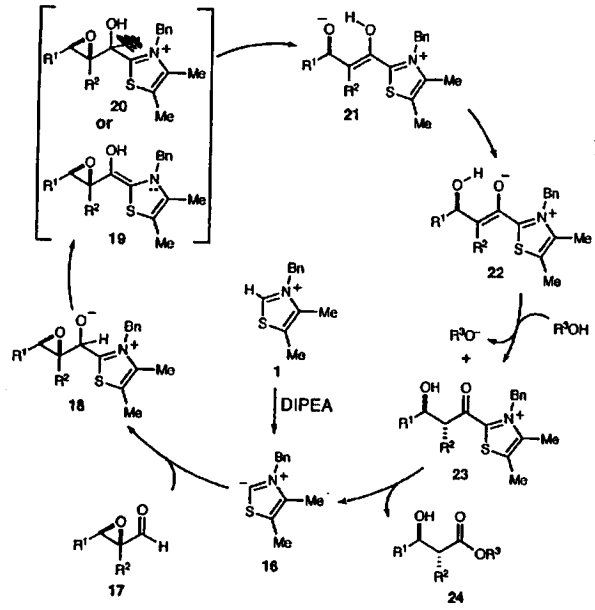
entry	epoxy-aldehyde	nu	product	dr[b]	yield /%[c]
1		BnOH		>10:1[d]	89
2	2	^iPrOH	5 (R = Bn) 6 (R = ^iPr)	>10:1[d]	79
3		CD_3OD		9:1	81[e]
	2		7		
4		EtOH		—	84
	8		9		
5		CH_3OH		7:1	82[f]
	10		11		
6[g]		EtOH		—	85
	12		13		

(Racemic epoxides)

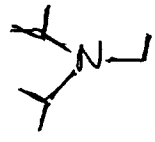
94:1 ee epoxide



Scheme 2



No Benzoin condensation type products.

DIPEA = 

JACS, ASAP

Conversion of α-Haloaldehydes into Acylating Agents by an Internal Redox Reaction Catalyzed by Nucleophilic Carbenes

Nathan T. Reynolds, Javier Read de Alaniz, and Tomislav Rovis*

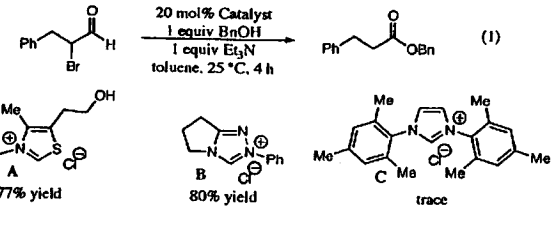
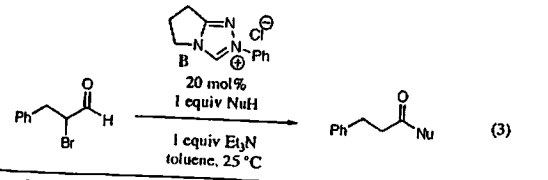
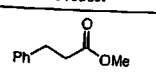
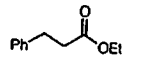
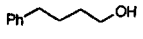
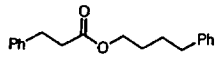
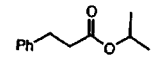
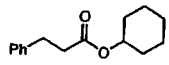
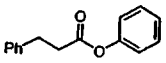
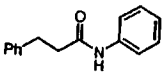
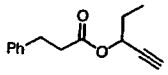
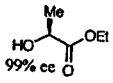
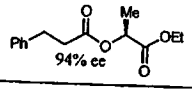
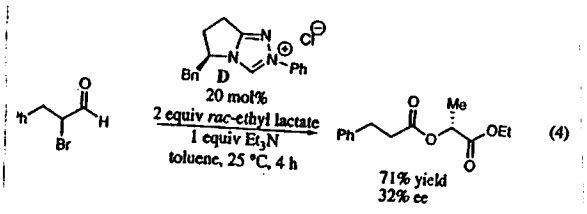


Table 2. Effect of Nucleophile Structure on the Internal Redox Reaction



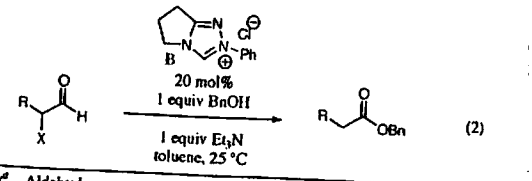
(3)

Entry[a]	Nucleophile	Time (h)	Product	Yield (%)
1	MeOH	4		78
2	EtOH	4		78
3		4		73
4		24		66
5		24		66
6		24		55
7		24		91
8		24		65
9	 99% ee	24	 94% ee	56

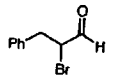
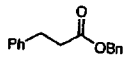
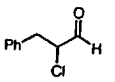
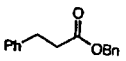
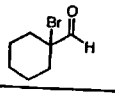
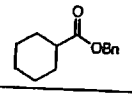


(4)

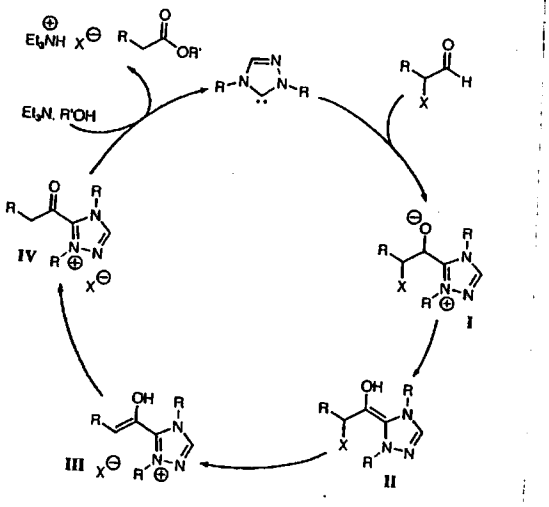
Table 1. Survey of Acylation Precursors



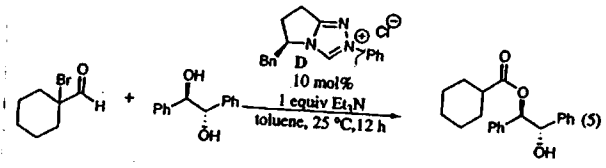
(2)

Entry[a]	Aldehyde	Time (h)	Product	Yield (%)
1		4		60
2		4		80
3		4		65
4		24		99

Scheme 1. Proposed Mechanism of the Internal Redox Reaction of α-Haloaldehydes



83% ee
75% yield



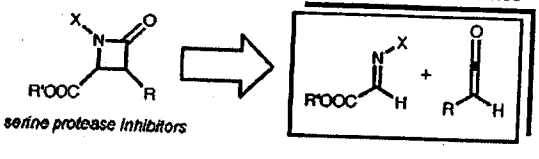
(5)

Chinchona Alkaloids.

Thomas Lectka's contribution on β-lactams synthesis:

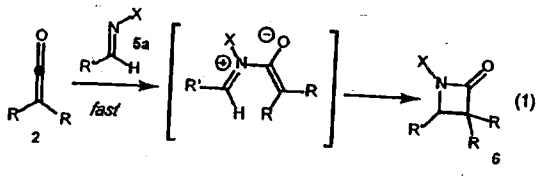
Lectka's approach:

Scheme 1. β-Lactam Disconnection into Imines and Ketenes



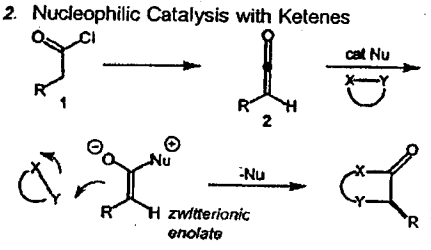
serine protease inhibitors

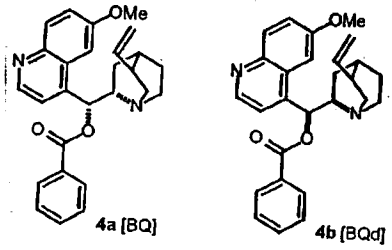
Stauginger approach:



(1)

Scheme 2. Nucleophilic Catalysis with Ketenes





JACS, 2002, 6626-6635. JACS 2000, 7921-7922

The use of tertiary amines for dehydrohalogenations of acid halides **1** to form ketenes for our reactions is complicated by the fact that they are usually too nucleophilic. The use of a stoichiometric base that is thermodynamically strong, but kinetically nonnucleophilic, could overcome this problem. This strategy, which we term "shuttle deprotonation", utilizes a catalytic, chiral nucleophile, which is kinetically active (**base k**), to dehydrohalogenate the acid chloride in the first step (Scheme 3). Exploiting the premise that proton transfers between heteroatoms are inherently fast,[36] the kinetically favored **base k** then rapidly transfers its proton to **base t**, the thermodynamically active, but kinetically restricted base, to regenerate itself for another catalytic cycle.

We found that a nucleophile such as benzoylquinine (BQ, **4a**), an inexpensive[38] and versatile asymmetric catalyst,[39] serves as an excellent shuttle base (**base k**).

Our first approach to the shuttle base synthesis of ketenes in situ was the use of the strong organic base proton sponge (**7**) as a nonnucleophilic thermodynamic base.

Scheme 3. Shuttle Deprotonation with Kinetic and Thermodynamic Bases

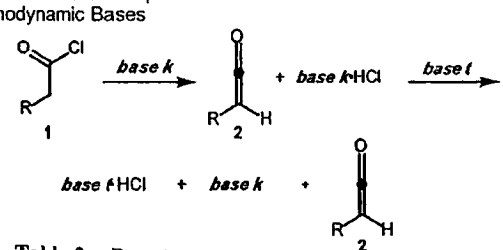
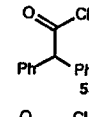
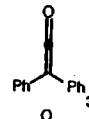
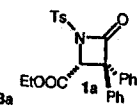
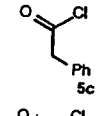
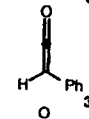
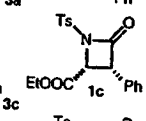
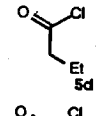
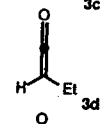
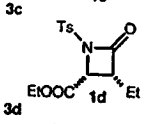
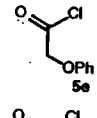
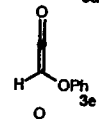
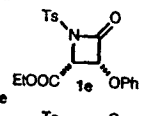
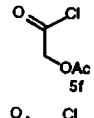
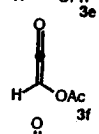
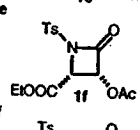
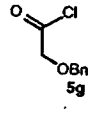
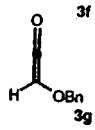
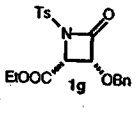
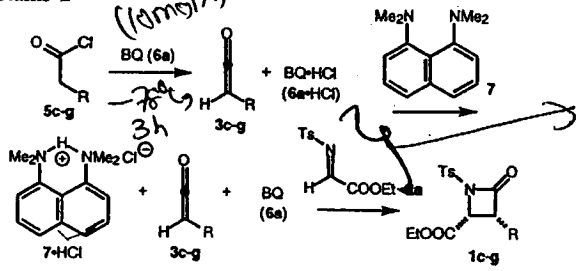


Table 2. Reaction of Ketenes **3** and Imine **2a** Catalyzed by BQ (**4a**) to Form β-Lactams **1**[a]

entry	acid chloride	ketene	product	% ee	dr (cis/trans)[c]	% yield[d]
1	 **5a**[b]	 **3a**	 **1a**	99	–	36
2	 **5c**	 **3c**	 **1c**	96	99/1	65
3	 **5d**	 **3d**	 **1d**	99	99/1	57
4	 **5e**	 **3e**	 **1e**	99	99/1	45
5	 **5f**	 **3f**	 **1f**	98	>99/1	61
6	 **5g**	 **3g**	 **1g**	95	99/1	56

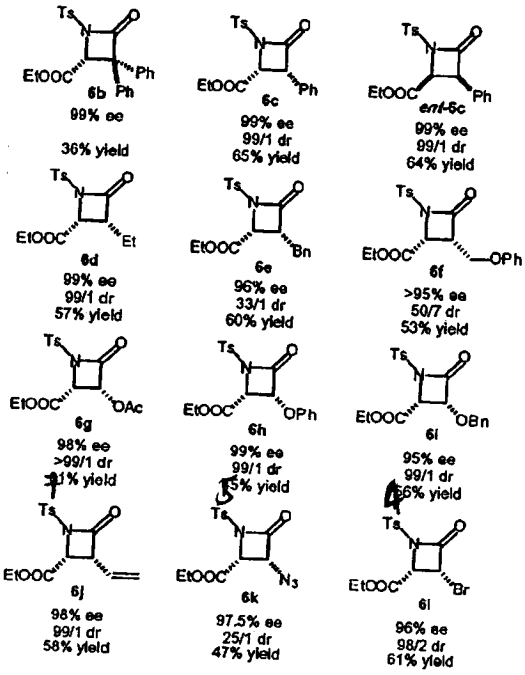
Scheme 1. Catalytic, Shuttle-Base Route to Optically Active β-Lactams **1**



JACS, 2000, 7831-7832.

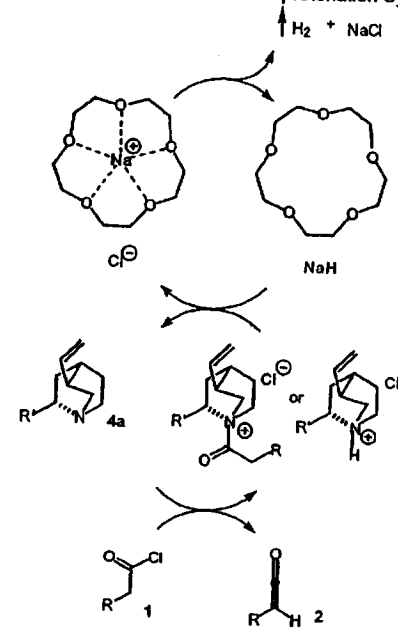
Improved method:

The main drawbacks to the use of the proton sponge-shuttle procedure include economical aspects (although proton sponge is a moderately priced chemical, in large quantities its use may be a cost factor) as well as the possibility that in rare instances the sponge itself may react in undesirable ways.

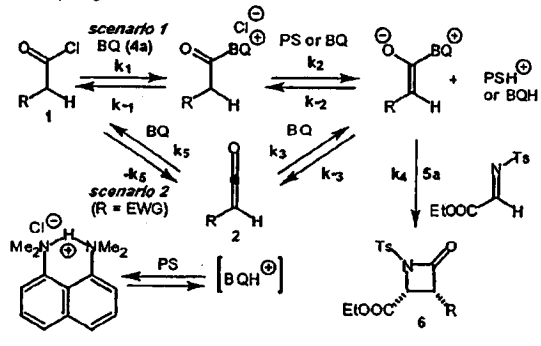


JACS, 2002, 6626-6635.

Scheme 5. Sodium Hydride Shuttle Deprotonation System



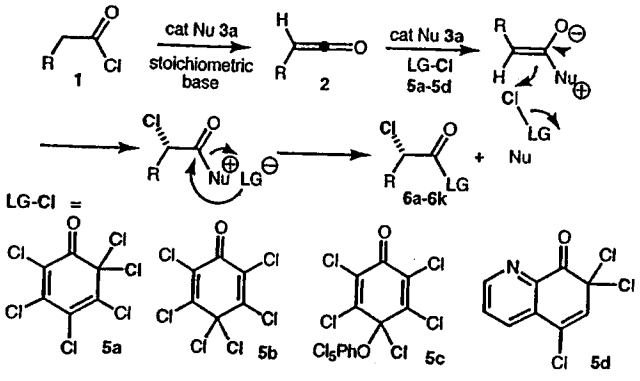
Scheme 7. Proposed Mechanism of β-Lactam Formation with Proton Sponge



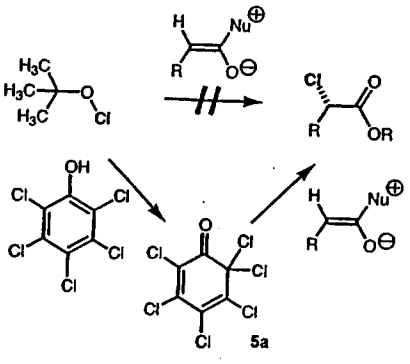
ACYL HALIDES.

Thomas Lectka's contribution on α-chlorination of ~~aldehydes~~:

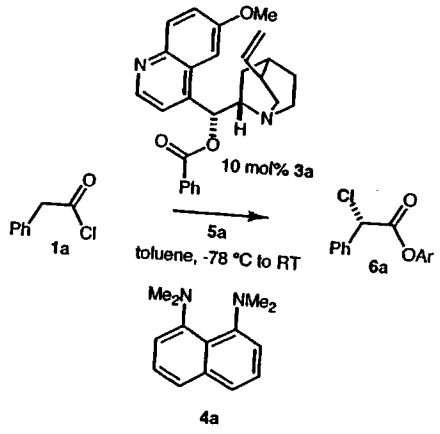
Scheme 1. Tandem Catalytic Asymmetric Chlorination/ Esterification



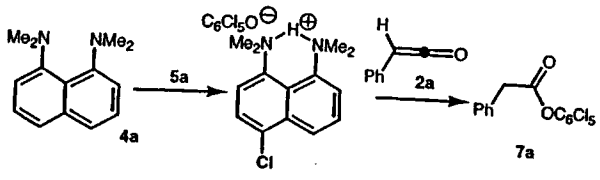
Chlorination Using *t*-BuOCl



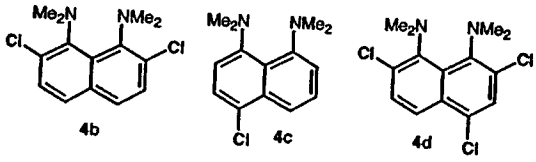
In the beginning, the most important question concerned the choice of chlorinating agent. Diatomic chlorine was deemed too reactive, whereas most other agents proved to be completely unreactive. Surprisingly, sources of halogen that are too mild pose the biggest problem, as they are unable to react with the weakly nucleophilic zwitterionic enolate. *N*-halosuccinimides and *N*-chloroamides were unsuccessful, yielding no detectible products, as were a multitude of other candidates, such as chlorinated pyridones, iodanes, and sulfonamides. *tert*-Butylhypochlorite, on the other hand, proved to be too reactive, chlorinating almost anything in the reaction mixture, including solvent (Scheme 2). After much effort, we finally turned our attention to the polyhaloquinone-derived reagents, including **5a**–**5d**.[19] For example, pentachlorophenol reacts readily with *tert*-butylhypochlorite to produce quinone **5a** in quantitative yield;[20] this substance is available commercially.



first attempt using the perchlorinated quinone **5a** and phenylacetyl chloride, with 10 mol % BQ as catalyst and 1.1 equiv of proton sponge, α-chloroester **6a** was formed in moderate yield (40%) but with high enantioselectivity (95% ee). Also isolated from the reaction mixture, however, was a fair amount of the achiral ester **7a**, the product resulting from the formal alcoholysis of phenylketene by pentachlorophenol (eq 6). Further investigation revealed that pentachlorophenol was being generated *in situ* by an undesired side reaction, the chlorination of electron-rich proton sponge by the quinone **5a**. These results constituted our first (and very ominous) encounter with byproduct halogenations that ultimately result in undesired ketene phenolysis and prompted us to investigate intensively other "clean" methods of ketene generation that would result in minimal exposure of the halogenating agents to other substrates

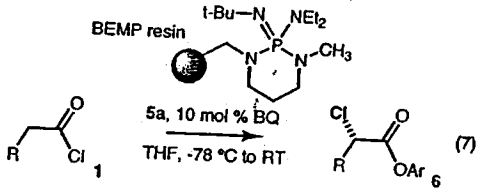


We started by using various chlorinated proton sponge derivatives **4b**–**d**[22] as stoichiometric bases, reasoning that they would be resistant to further halogenation. However, they proved to be deactivated as bases, affording products in low yield,



mation I: Generation Using BEMP.

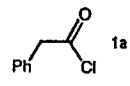
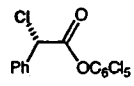
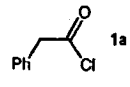
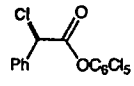
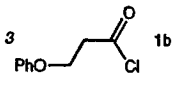
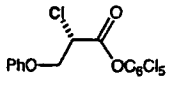
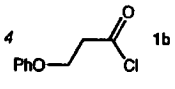
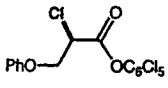
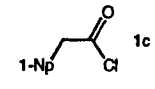
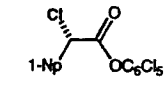
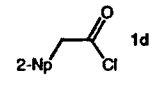
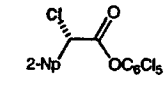
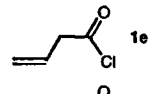
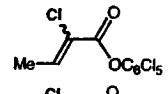
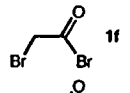
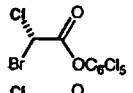
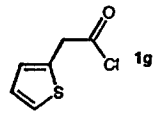
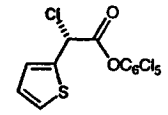
We found that when a solution of phenylacetyl chloride in THF is passed through an addition funnel containing at least 1 equiv of BEMP at −78 °C, phenylketene is produced quantitatively.[23] The ketene solution was allowed to drip slowly into a flask (−78 °C) containing **3a** (10 mol %), and to this was added a solution of **5a**. After this solution had stirred at −78 °C for 4 h, quenching and column chromatography yielded the product (*S*)-**6a**[24] in 80% yield and 99% ee (eq 7).[25] A number of other acid chlorides were screened using this procedure with similar results as summarized in Table 1. As can be seen, a wide range of acid chlorides was successfully employed, including those that possess either aliphatic or aromatic substituents, to afford products in high enantioselectivity and moderate to good chemical yields.



(7)

JACS, 2001, 1531-1532.

Table 1. Alkaloid-Catalyzed Reactions of Acyl Halides **1** Using BEMP as a Dehydrohalogenating Agent

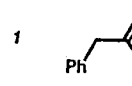
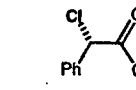
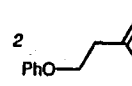
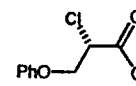
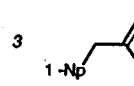
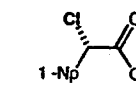
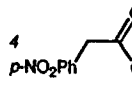
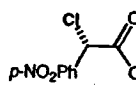
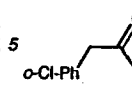
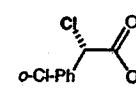
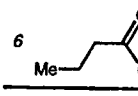
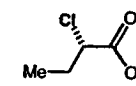
entry	acid chloride		product		% ee	% yield[a]
1		1a		(S)-6a	99	80
2		1a		(R)-6a	99	81
3		1b		(S)-6b	97	57
4		1b		(R)-6b	96	58
5		1c		(S)-6c	95	57
6		1d		(S)-6d	94	63
7		1e		6e	–	65
8		1f		(S)-6f	97	51
9		1g		(S)-6g	80	66

Ketene Formation II: "Shuttle" Deprotonation Using the Sodium Hydride/Crown Ether System.

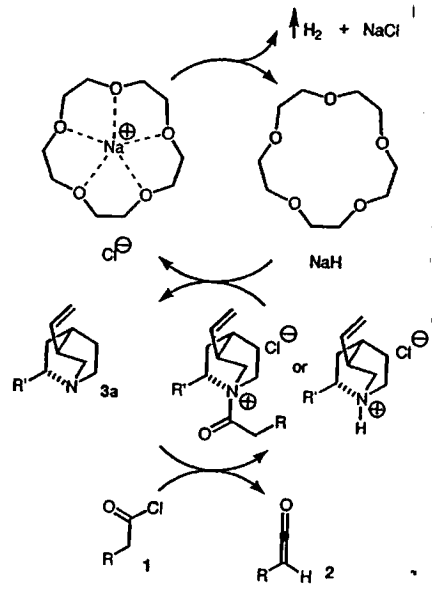
we began to test hydride salts that could act as stoichiometric bases in the dehydrohalogenation of acid chlorides. We also sought a procedure that is amenable to larger scale halogenations (in large amounts, BEMP, besides being costly, is difficult to handle and "gums" up reaction flasks preventing smooth stirring); we examined the use of the inexpensive and low molecular weight sodium hydride as a stoichiometric base for ketene generation.

In this case, ketene is generated through a shuttle deprotonation system that employs BQ and 15-crown-5 as a phase transfer cocatalyst to help solubilize NaH (Scheme 3). Phenylacetyl chloride was added to a stirred suspension of NaH and catalytic amounts of 15-crown-5 and BQ in THF at −78 °C. A solution of **5a** in THF was added slowly over 3 h by syringe pump, and the reaction was warmed to room temperature over 4 h (eq 8).[26] Workup and chromatography yielded the α-chlorinated product (*S*)-**6a** in 63% yield and 95% ee. We proceeded to examine the system on other acid chloride substrates (Table 2) with results that are comparable to BEMP (ee's 90−99%; yields 58−79%), but at a fraction of the cost. Most importantly, we were able to prepare compound **6a** on a larger, multigram scale using this methodology.

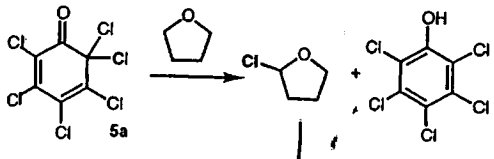
Table 2. Alkaloid-Catalyzed Reactions of Acyl Halides **1** Using NaH

entry	acid chloride		product		% ee	% yield[a]
1		1a		(S)-6a	95	63
2		1b		(S)-6b	92	61
3		1c		(S)-6c	92	61
4		1h		(S)-6h	99	58
5		1i		(S)-6i	90	79
6		1j		(S)-6j	98	43

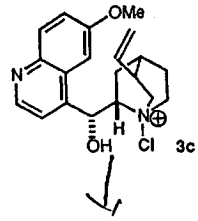
Sodium Hydride Shuttle Deprotonation S



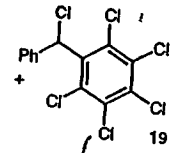
Reasons for the poor yield:



Obtained in trace amount (halogenation of solvent)

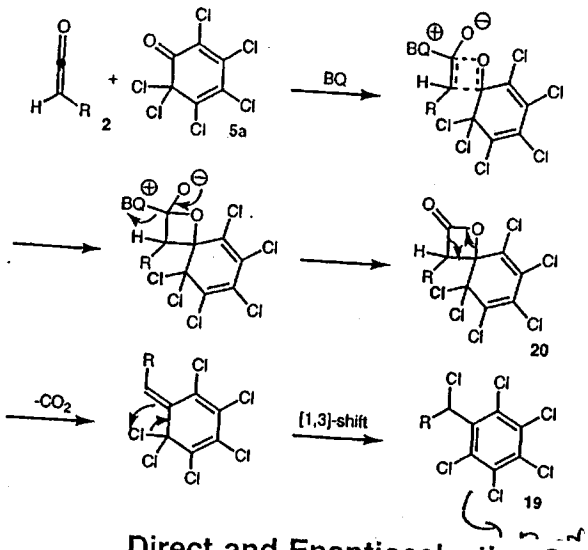


Trance amount (halogenation of catalyst)

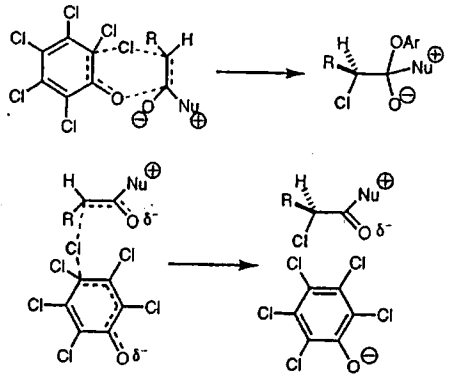


10% → 15% yield

JACS, 2004, 4245-4255.



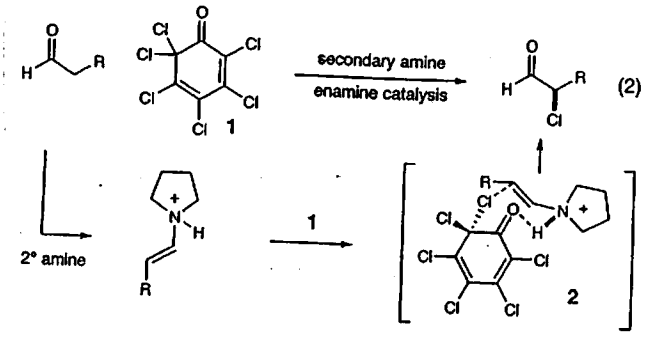
5. Proposed Transition States of Chlorination Using 5a



Direct and Enantioselective Organocatalytic α-Chlorination of Aldehydes

Michael P. Brochu, Sean P. Brown, and David W. C. MacMillan*

JACS, 2004; 4168-4169



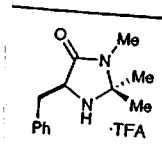
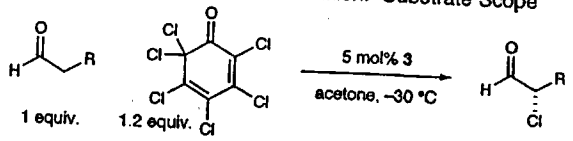


Table 3. Enantioselective α-Chlorination: Substrate Scope



Yield :- 71% → 94%

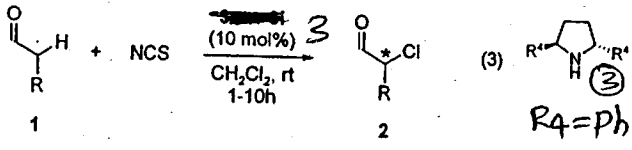
ee :- 80 – 95%.

R :- 1° alkyl, 2° alkyl, Bn, ad etc.

Direct Organocatalytic Asymmetric α-Chlorination of Aldehydes

Nis Halland, Alan Braunton, Stephan Bachmann, Mauro Marigo, and Karl Anker Jørgensen*

JACS, 2004 4790-47



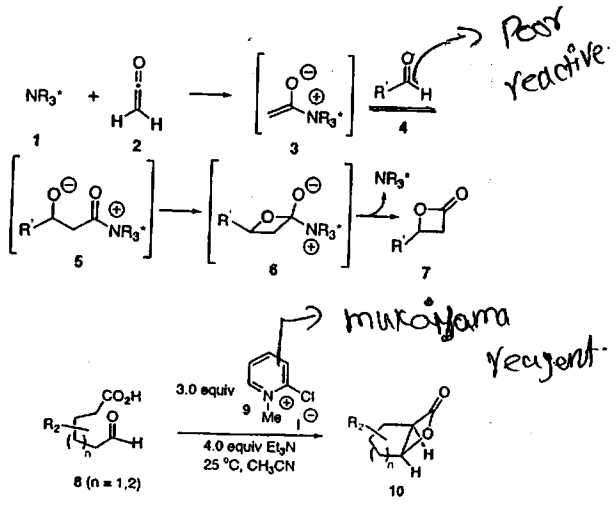
Yield :- 90 – 100%.

ee :- 87 – 97%.

R = me, i-pr, t-bu, n-hex, Allyl, Bn, 1° alkyl

Enantioselective ketene–Aldehyde cycloaddition: intramolecular.

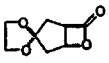
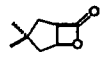
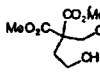
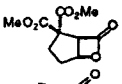
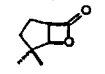
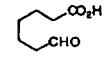
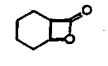
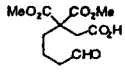
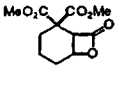
Intramolecular, Nucleophile-Catalyzed Aldol-Lactonization (NCAL) Reactions: Catalytic, Asymmetric Synthesis of Bicyclic β-Lactones



Poor reactive

Muroyama reagent

Table 1. Racemic Bicyclic β-lactones Obtained via the Intramolecular NCAL Reaction

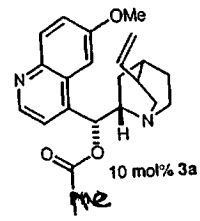
entry	oxo-acid precursor	cmpd. no.	bicyclic-β-lactones	cmpd. no.	% yield[a]
1		8a		10a	55
2		8b		10b	66
3		8c		10c	68
4		8d		10d	62
5		8e		10e	62
6		8f		10f	36[b]
7		8g		10g	57

(JACS, 2001, 7945-7946)

(First example for ketene-aldehyde)

Table 2. Catalytic, Asymmetric Intramolecular NCAL Reactions[a]

entry	bicyclic β-lactones	% yield	% ee[b]	config.
1	(+)-10a	54	92	1*R*,2*S*[c]
2	(−)-10a[d]	51	86	1*S*,2*R*
3	(+)-10b	37	92	3*R*,4*S*[e]
4	(+)-10c	45	90	1*R*,2*S*[f]



Intermolecular. JACS, 2004, 5352-5353.

Cinchona Alkaloid-Lewis Acid Catalyst Systems for Enantioselective Ketene–Aldehyde Cycloadditions

Cheng Zhu, Xiaoqiang Shen, and Scott G. Nelson*

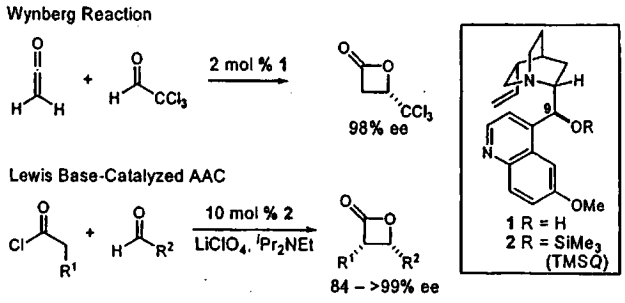


Figure 1. Alkaloid-Catalyzed Ketene–Aldehyde Cycloadditions.

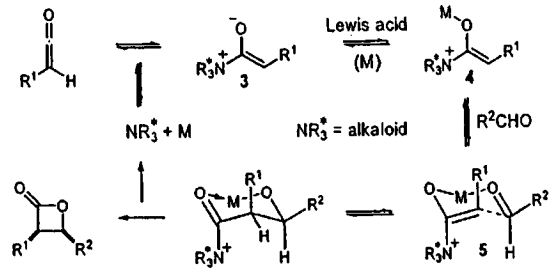


Figure 2. Postulated Mechanism for Alkaloid-Catalyzed AAC Reactions.

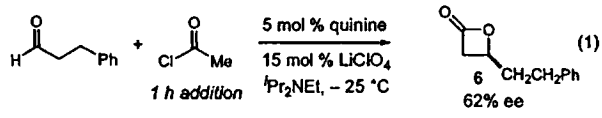
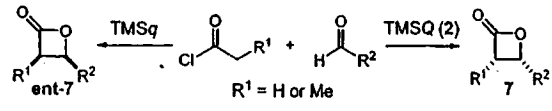


Table 1. Cinchona Alkaloid/$LiClO_4$-Catalyzed AAC Reactions



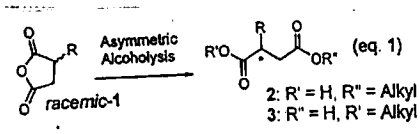
TMSQ = O-trimethylsilylquinidine; TMSq = O-trimethylsilylquinine

entry	product	R^1	R^2	% ee[a,b]	% de[c]	% yield
a	7a	H	$^cC_6H_{11}$	94[d]	–	85
b	7b	H	CMe_3	96[e]	–	71
c	7c	H	CH_2CH_2Ph	92	–	80
d	ent-7d	H	CH_2OBn	84	–	70
e	ent-7e	Me	CH_2CH_2Ph	>99	96	84
f	ent-7f	Me	$(CH_2)_8CHCH_2$	99	90	74
g	ent-7g	Me	CH_2OBn	99	76	68
h	ent-7h	Me	$CH_2CH(CH_3)_2$	99	90	72
i	7i	Me	$^cC_6H_{11}$	97[f]	>96	74
j	ent-7j	Me	C_6H_5	>99	96	78
k	ent-7k	Me	$^pC_6H_4F$	>99	>96	85
l	7l	Me	$^oC_6H_4Cl$	>99	96	80
m	ent-7m	Me	$^oC_6H_4CH_3$	>99	>96	76

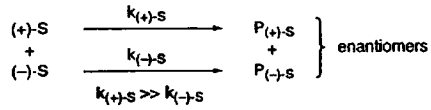
① Wynberg reaction need activated aldehyde.
② Nelson could use ordinary aldehyde by using lewis acid such as $LiClO_4$.
③ Prolong slow addition (1-4h) improved selectivity.
④ "ee" and "dr" were extremely high!! best reported so far.

Deng's research on chinchona alkaloid JACS, 2001, 11302-11303

Parallel Kinetic Resolutions of Monosubstituted Succinic Anhydrides Catalyzed by a Modified Cinchona Alkaloid



an example of a "simple" kinetic resolution:



an example of a parallel kinetic resolution:

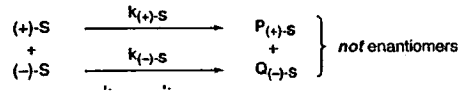
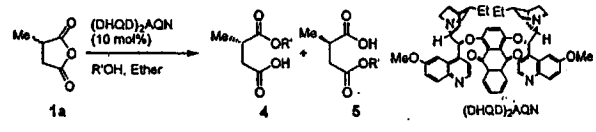


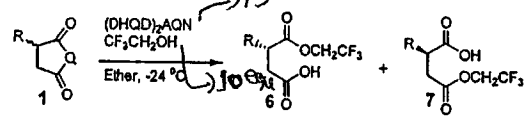
Table 1. $(DHQD)_2AQN$-Catalyzed Parallel Kinetic Resolution of Methylsuccinic Anhydride



entry	R'OH	temp/°C	% conv[a]	4/5[b]	% ee, 4[b]	% ee, 5[b]
1	MeOH	25	100	39/61	74	67
2	EtOH	25	100	49/51	82	67
3	*n*-PrOH	25	100	45/55	81	72
4	*i*-PrOH	25	<2	–	–	–
5	CF_3CH_2OH	25	100	49/51	85[c]	72[c]
6	CF_3CH_2OH	−25	100	44/56	91[c]	80[c]

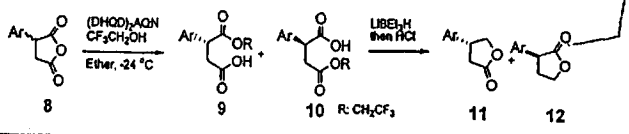
BACLOFEN Synthesis

Table 2. $(DHQD)_2AQN$-Catalyzed Parallel Kinetic Resolution of 2-Alkyl Succinic Anhydrides[a,b]



entry	substrate	6/7	% ee[d] 6	% ee[d] 7	% yield[c] 6	% yield[c] 7
1[e]	1a: R = −Me	44/55	93	80	36	41
2	1b: R = −Et	40/60	91	70	38	50
3	1c: R = $-n$-C_8H_{17}	42/56	98	66	38	41
4	1d: R = $-CH_2CH{=}CH_2$	46/53	96	82	40	49

Table 3. Asymmetric Synthesis of β-Aryl-γ-Lactones (11) via Parallel Kinetic Resolution of 2-Aryl-Succinic Anhydrides (8)[a]

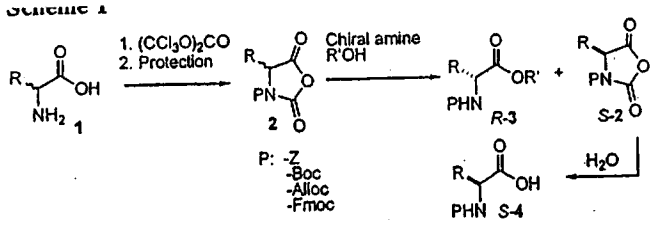


entry	substrate	% ee[b,c] 9	% ee[b,c] 10	% ee[b,c] (yield[d]) 11	% ee[b,c] (yield[d]) 12
1[e]	8a: Ar = Ph	95	87	95 (44)	82 (32)
2	8b: Ar = 3-MeO−C_6H_4	96	83	95 (45)	83 (30)
3	8c: Ar = 4-Cl−C_6H_4	96	76	96 (44)	63 (29)

JACS, 2001, 12696-12697.

Asymmetric Synthesis of α-Amino Acids via Cinchona Alkaloid-Catalyzed Kinetic Resolution of Urethane-Protected α-Amino Acid *N*-Carboxyanhydrides

Scheme 1

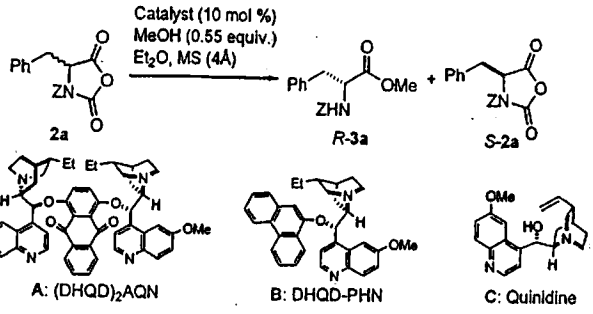


conv (c) = $100 \times ee_2/(ee_3+ee_2)$

Table 3. Kinetic Resolution of UNCA (2) via Modified Cinchona Alkaloid-Catalyzed Alcoholysis[a]

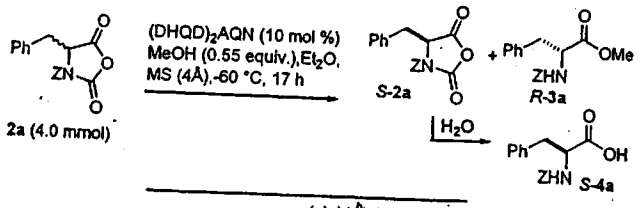
entry	UNCA 2	R	P	temp (°C)	time (h)	conv[b] (%)	ee[c] (yield)/%[d] (*S*)-4	ee[c] (yield)/%[d] (*R*)-3	*s*[e]
1	a	$PhCH_2$[f]	Cbz	−60	17	51	98 (48)	93 (48)	114
2	b	4-F−$C_6H_4CH_2$	Cbz	−78	31	50	93 (42)	92 (48)	79
3	c	4-Cl−$C_6H_4CH_2$	Cbz	−60	18	52	97[f] (43)	88 (52)	59
4	d	4-Br−$C_6H_4CH_2$	Cbz	−78	45	51	92[f] (39)	87 (51)	45
5	e	2-thienylmethyl	Cbz	−78	25	50	95 (47)	94 (49)	115
6	f	$CH_3(CH_2)_5$	Cbz	−60	37	51	94[f] (42)	91 (49)	78[f]
7	g	$BnOCH_2$	Cbz	−78	72	52	96 (44)	89 (49)	69
8	h	$(CH_3)_2CH$[g]	Cbz	0	22	59	96 (40)	67 (58)	19
9	i	Ph[h]	Cbz	−78	16	46	84 (46)	97 (45)	170
10	j	4-MeO−C_6H_4[h]	Cbz	−78	85	56	95 (43)	74 (56)	23
11	k	$PhCH_2$	Fmoc	−78	46	51	96 (47)	92 (50)	93
12	l	$PhCH_2$	Boc	−40	15	59	98 (41)	67 (56)	19
13	m	$PhCH_2$	Alloc	−60	15	50	91 (45)	91 (45)	67
14	n	$PhCH_2CH_2$	Alloc	−60	36	54	96[f] (41)	81 (53)	35

Table 1. Kinetic Resolution of UNCA 2a with Cinchona Alkaloids[a,b]



entry	catalyst	T/°C	conv/%	ee of 3a/%	*s*[c]
1	A	25	42	80	16
2	A	-60	50	92	79
3	B	-60	45	91	47
4	C[d]	-60	44	86	27

$s = k_f/k_s = \ln[1-c(1+ee)]/\ln[1-c(1-e$



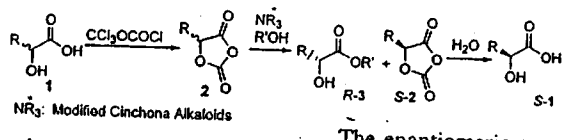
cycle	conv[a]	ee (yield[b]) /% 3a	ee (yield[b]) /% 4a	*s*
1	51	93 (48)	97 (48)	114
2[c]	52	91 (49)	98 (47)	104

JACS, 2002, 2870-2871.

Dynamic Kinetic Resolution via Dual-Function Catalysis of Modified Cinchona Alkaloids: Asymmetric Synthesis of α-Hydroxy Carboxylic Acids

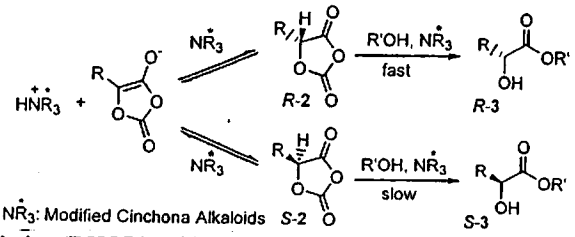
Liang Tang and Li Deng*

Scheme 1



The enantiomeric excesses of the product (3a) and the starting material (2a) were determined at various conversions and were found to remain constant at 95% and nearly 0%, respectively. In control experiments, we found that treatment of optically pure 2a with $(DHQD)_2AQN$ generated the corresponding racemic mixture within minutes. Also the $(DHQD)_2AQN$-catalyzed alcoholysis of either (*R*)- or (*S*)-2a gave the same product, (*R*)-3a, in 95% ee. Neither racemization nor alcoholysis occurred without the amine catalyst. These results

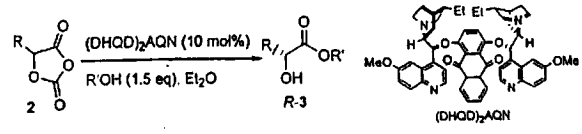
Scheme 2



establish that $(DHQD)_2AQN$ serves a dual role, mediating both the in situ racemization of 2a and the enantioselective alcoholysis of (*R*)-2a. The racemization is much faster than the alcoholysis. Consequently, both enantiomers of racemic 2a are converted to a single optically active product (3a) via an efficient dynamic kinetic resolution mediated by a single catalyst, $(DHQD)_2AQN$.

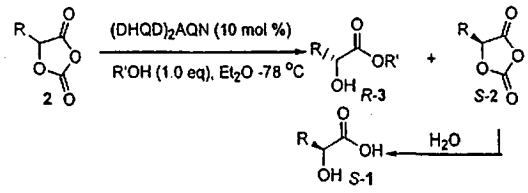
No dynamic resolution on aliphatic substrates.

Table 2. Dynamic Kinetic Resolution of 5-Aryl-1,3-Dioxolane-2,4-Diones[a]



entry		R	R'OH	T/°C	time/h	yield/%[d]	ee/%
1	a	C_6H_5[b]	EtOH	−78	24	71	95
2	b	4-Cl−C_6H_4	EtOH	−78	24	70	96
3	c	4-Br−C_6H_4	EtOH	−78	24	80	96
4	d	4-F−C_6H_4	EtOH	−78	24	65	95
5	e	4-CF_3-C_6H_4	EtOH	−78	24	85	93
6	f	4-^{i}Pr−C_6H_4	EtOH	−20	8	68	91
7	g	3,4-F_2-C_6H_3	EtOH	−78	24	65	94
8	h	1-naphthyl[c]	^{n}PrOH	−40	14	74	91
9	i	2-Cl−C_6H_4	EtOH	−60	10	66	62
10	j	2-Me-C_6H_4	EtOH	−20	4	61	60

Table 3. Kinetic Resolution of 5-Alkyl 1,3-Dioxolane-2,4-diones[a]



					ee (yield)[b]/%		
entry		R	R'	time/h	S-1	R-3	s[c]
1	k	$PhCH_2$	Et	12	95 (39)	96 (47)	133
2	l	$PhCH_2CH_2$	Et	24	85 (40)	93 (46)	67
3	m	$CH_3(CH_2)_3$	Et	36	95 (36)	92 (46)	57
4	n	$(CH_3)_2CH$	Allyl	6	93 (32)	90 (48)	49

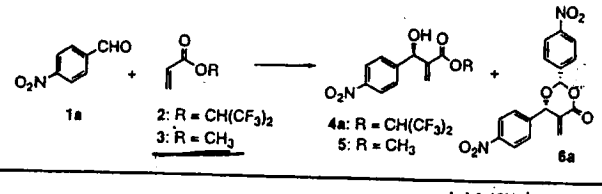
$$S = k_f/k_S = \frac{\ln[(1-C)(1+ee)]}{\ln[(1-C)(1-ee)]}$$

JACS, 1999, 10219-10220.

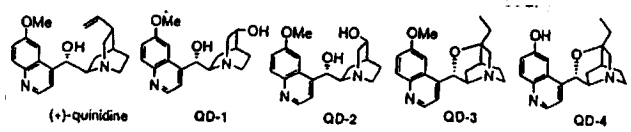
Chiral Amine-Catalyzed Asymmetric Baylis−Hillman Reaction: A Reliable Route to Highly Enantiomerically Enriched (α-Methylene-β-hydroxy)esters

Yoshiharu Iwabuchi, Mari Nakatani, Nobiko Yokoyama, and Susumi Hatakeyama*

Table 1. Asymmetric Baylis−Hillman Reaction of *p*-Nitrobenzaldehyde (1a) with Acrylates Catalyzed by Quinidine Derivatives[a]



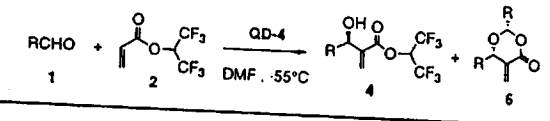
				temp	time	yield (%),[b] config[c] (% ee[d])	
entry	acrylate	catalyst	solvent	(°C)	(h)	ester	dioxanone[e]
1	2	quinidine	THF	2	24	12, nd[f]	22, *R* (33)
2	2	QD-1[g]	THF	2	72	2, nd	32, *R* (35)
3	2	QD-2[g]	THF−DMF[h]	2	72	10, nd	26, *R* (10)
4	2	QD-3	THF	2	1	63, *R* (35)	10, *R* (33)
5	2	QD-3[i]	DMF	−55	1	74, *R* (10)	7, nd
6	2	QD-4[i]	DMF	−55	1	58, *R* (91)	11, *R* (4)
7	2	QD-4[i]	DMF	0	1.5	52, *R* (64)	11, *S* (10)
8	3	QD-4	DMF	20	14	69, *S* (8)	–



H_2SO_4/Δ

7 days.

Table 2. QD-4-Catalyzed Asymmetric Baylis−Hillman Reaction of Various Aldehydes with 2[a]



				yield (%),[b] config[c] (% ee[d])	
entry	aldehyde	R	time (h)	ester 4	dioxanone 6[e]
1	1a	*p*-NO_2Ph	1	58, *R* (91)	11, *R* (4)
2	1b	Ph	48	57, *R* (95)	–
3	1c	(*E*)-PhCH=CH	72	50,[f] *R*[g] (92)	–
4	1d	CH_3CH_2	4	40, *R* (97)	22, *S* (27)
5[h]	1e	$(CH_3)_2CHCH_2$	4	51, *R* (99)	18, *S* (85)
6	1f	$(CH_3)_2CH$	16	36, *R* (99)	25, *S* (70)
7	1g	*c*-Hex	72	31, *R* (99)	23, *S* (76)
8	1h	*t*-Bu	72	–	–

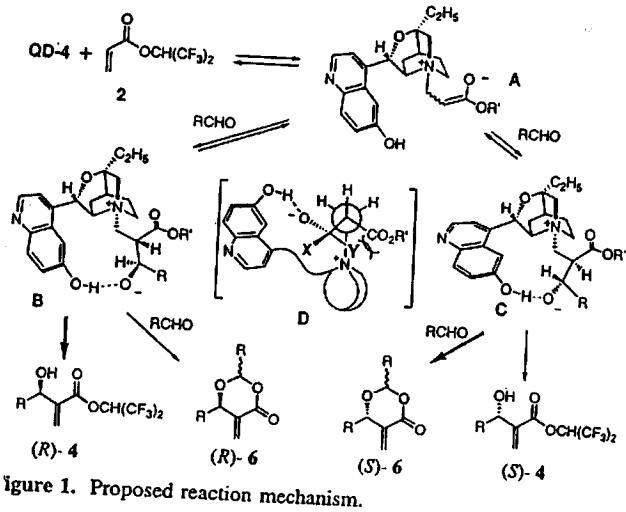


Figure 1. Proposed reaction mechanism.

JACS, 2002, 6798-6799.

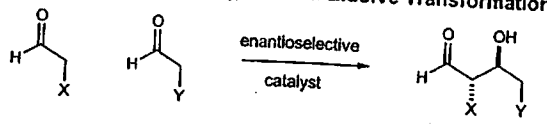
Proline.

Macmillan's 7 substrate cross-Aldol reaction:

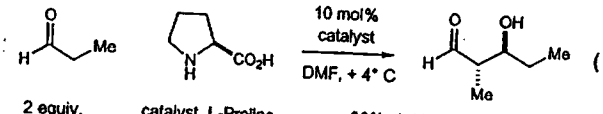
The First Direct and Enantioselective Cross-Aldol Reaction of Aldehydes

Alan B. Northrup and David W. C. MacMillan*

Enantioselective Aldehyde Aldol: Elusive Transformation

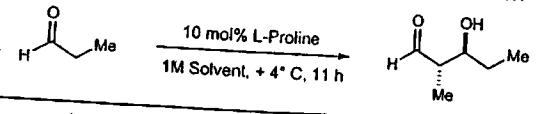


Proline Catalyzed Aldehyde Aldol Dimerization



2 equiv. catalyst L-Proline 80% yield, 4:1 *anti:syn*, 99% ee

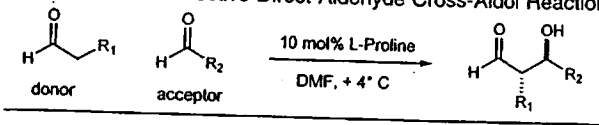
Table 1. Effect of Solvent on the Propionaldehyde Dimerization

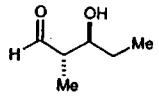
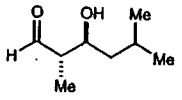
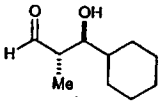
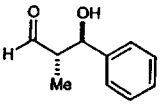
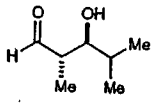
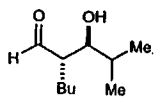
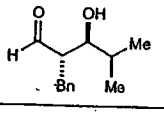


entry	solvent	conversion[a]	*anti:syn*[b]	% ee[c] (*anti*)
1	Ph-H	32	5:1	>99
2	$CHCl_3$	29	4:1	98
3	EtOAc	41	5:1	99
4	THF	36	4:1	98
5	dioxane	41	4:1	98
6	CH_3CN	42	3:1	96
7	DMSO	38	3:1	>99
8	NMP	62	3:1	98
9	DMF	91	3:1	99

Increasing catalyst loading gave poor results!!

Table 2. Enantioselective Direct Aldehyde Cross-Aldol Reaction



entry	R_1	R_2	Product	% yield[a]	*anti:syn*[b]	% ee[c,d]
1	Me	Et		80	4:1	99
2	Me	*i*-Bu		88	3:1	97
3	Me	*c*-C_6H_{11}		87	14:1	99
4	Me	Ph		81	3:1	99
5	Me	*i*-Pr		82	24:1	>99
6[e]	*n*-Bu	*i*-Pr		80	24:1	98
7[e]	Bn	*i*-Pr		75	19:1	91

Conc, amount of donor, amount of acceptor, addition time - all found to be very critical!!

2M Conc 4°C for 10h.

2 equ of EtCHO added over 2.5h.

2 equ of C_6H_{11}CHO was used.

1o equ of PhCHO was used.

2 equ of iPrCHO was used

3 equ of iPrCHO was used.

3 equ of BnCHO was used.

Conc 1M 4°C 16h.

1 equ of EtCHO was added over 20h 0.5M conc.

1 equ of EtCHO was added over 16h 0.1M conc.

1 equ of EtCHO was added over 20h 1M conc.

1 equ of hexanal was added 24h 1M conc.

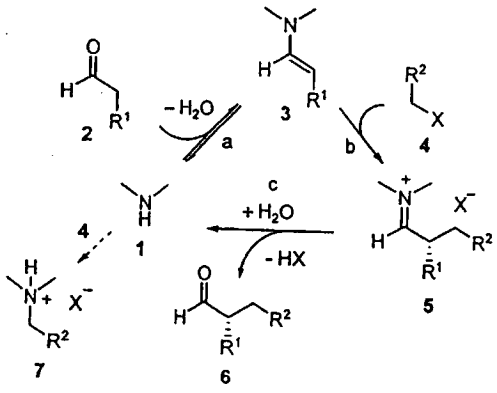
1 equ of BnCHO was added over 24h. 1M conc.

Less hindered substrates gave poor dr.

JACS, 2004, 450-451

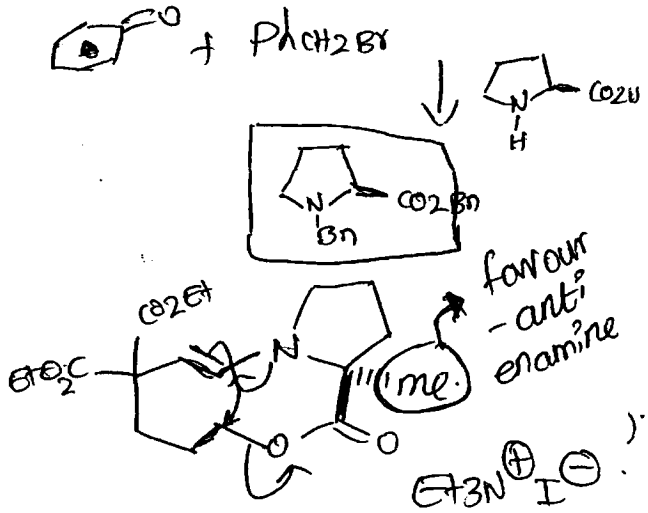
Catalytic Asymmetric Intramolecular α-Alkylation of Aldehydes

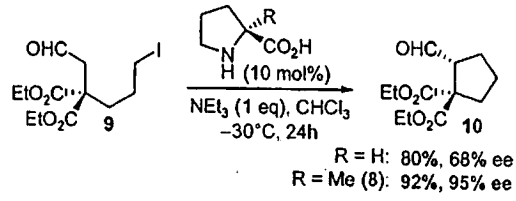
Nicola Vignola and Benjamin List*



Even stoichiometric α-alkylations of preformed aldehyde enolate equivalents are very difficult to control, and several side reactions usually occur. For example, in the reactions of metal enolates or enamines of aldehydes with alkyl halides, self-aldolization, Cannizzaro or Tischchenko reactions, and N- or O-alkylations are competing processes.[8,9] Designing a catalytic asymmetric α-alkylation of aldehydes is further complicated by the susceptibility of the nucleophilic Lewis- or Brønsted-base catalyst toward an unproductive alkylation reaction with the electrophile. In addition, racemization of the product could be a serious problem.

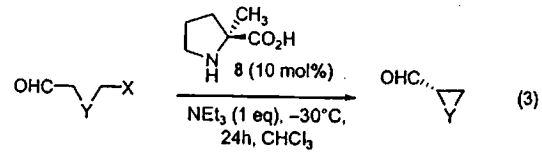
INTERMOLECULAR

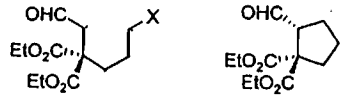
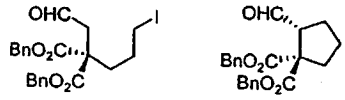
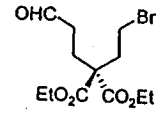
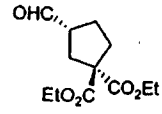
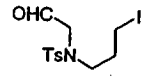
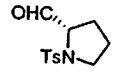
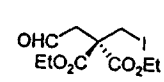
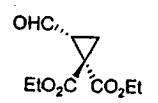




R = H: 80%, 68% ee
R = Me (8): 92%, 95% ee

Table 1. (*S*)-α-Methyl Proline-Catalyzed Direct Asymmetric Intramolecular α-Alkylation of Aldehydes

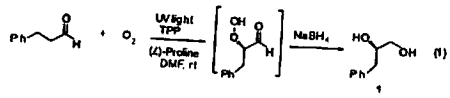


Entry	Substrate	Product	Yield (%)	ee (%)[a]
(1)	 9 (X = I) (5mol%)	10	92[b]	95
(2)	11 (X = Br) (15mol%)	10	90[c]	94
(3)	12 (X = OTs) (20mol%)	10	20[d]	91
(4)	 13	14	94	95
(5)	 15	 16	92[e] 93[c]	96 84
(6)	 17	 18	52[f]	91
(7)	 19	 20	70[e]	86

JACS ASAP

The Direct Amino Acid-Catalyzed Asymmetric Incorporation of Molecular Oxygen to Organic Compounds

Armando Córdova,* Henrik Sundén, Magnus Engqvist, Ismail Ibrahem, and Jesús Casas

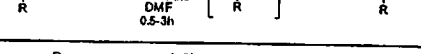


States of the oxygen molecule	Occupancy of highest orbitals	Energy above ground state
Second excited state ($^1\Sigma_g^+$)	↑↓	37 kcal
First excited state ($^1\Delta_g$)	⇅ —	22 kcal
Ground state ($^3\Sigma_g^-$)	↑↑	

singlet state ($^1O_2$)

triplet state ($^3O_2$)

Table 1. Direct Catalytic Asymmetric Incorporation of $^1O_2$ to Aldehydes[a]



entry	R	temp (°C)	yield (%)[b]	er (*R*/*S*)[c]	cmpd
1	CH_2Ph	27	45	61/39	1
2	CH_2Ph	−5	91	74/26	1
3	Ph	−20	92	62/38	2
4	*i*-Pr	−5	95	71/29	3
5	*i*-Pr[d]	−5[d]	93[d]	28/69[d]	ent-3
6	*n*-Pent	−5	91	58/42	4
7	*n*-Bu	−5	92	61/39	5

① No catalyst = No reaction

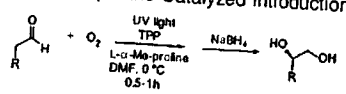
② O_2 = No reaction.

③ $^3O_2$ = No reaction.

④ Sunlight = Good Yield. Poor ee.

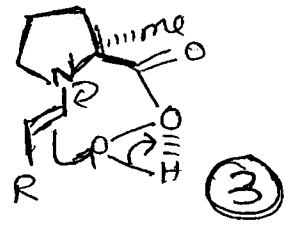
⑤ D-α-Me-Proline ⇒ opposite enantiomer (Same ee).

Table 2. Direct L-α-Me-proline Catalyzed Introduction of $^1O_2$[a]

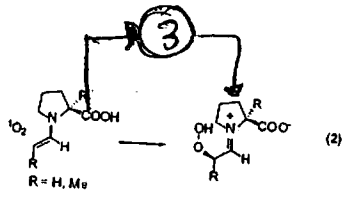


entry	R	cmpd	yield (%)[b]	ee (%)[c]
1	CH_2Ph	1	77	66
2	CH_2Ph[d]	1	72[d]	66[d]
3	*i*-Pr	3	75	57
4	*n*-Pent	4	77	54
5	*n*-Bu	5	73	57

[a] In a typical experiment, the amino acid (20 mol %) was stirred in the DMF (1 mL) for 20 min followed by addition of tetraphenylprophine (TPP) (5 mol %) and the aldehyde (1 mmol). The reaction was initiated and performed by bubbling a continuous flow of molecular oxygen or air for 0.5−3 h in the presence of visible light by a 250-W high-pressure sodium lamp. [b] Isolated yield after silica gel column chromatography. [c] Determined by chiral-phase HPLC or GC. [d] The reaction performed with air as the oxygen provider.

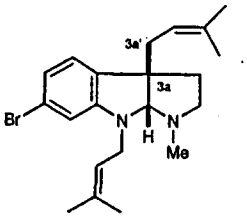


SPCULATIVE ACTIVE SPECIES.

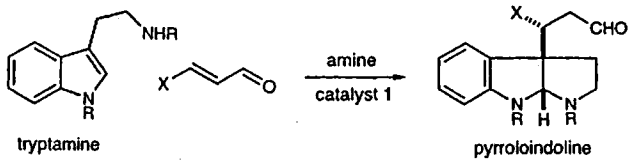


Enantioselective organocatalytic construction of pyrroloindolines by a cascade addition–cyclization strategy: Synthesis of (−)-flustramine B

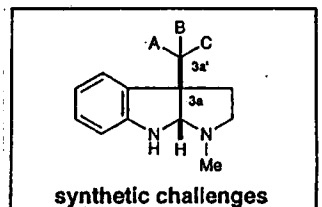
Joel F. Austin, Sung-Gon Kim, Christopher J. Sinz, Wen-Jing Xiao, and David W. C. MacMillan*

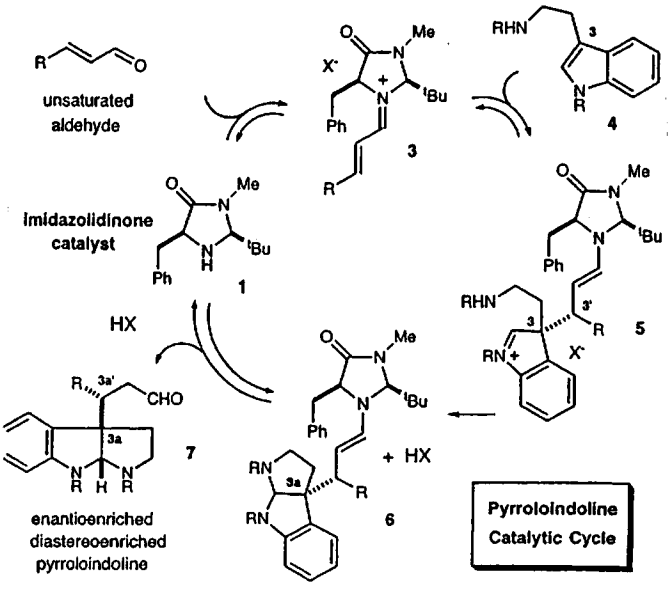


(−)-Flustramine B

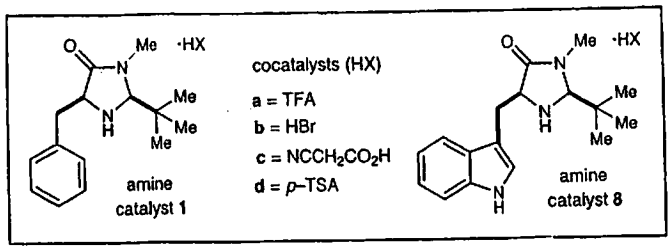


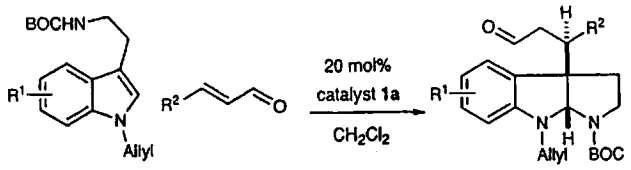
Scheme 4.



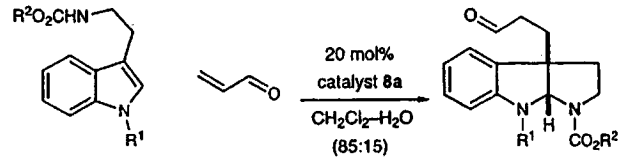


PNAS, 2004, 5482-5487.



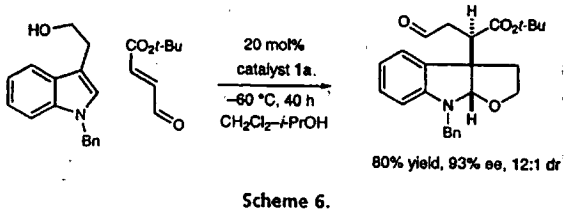


Entry	R^1	R^2	Time, h	Yield, %	ee,* %	dr†
1	H	COPh	64	92	94	13:1
2	H	CH_2OBz	44	66	91	22:1
3	H	CO_2Me	28	93	91	44:1‡
4	5-Me	CO_2Me	18	94	92	50:1
5	5-MeO	CO_2Me	20	99	90	10:1
6	6-Br	CO_2Me	36	86	97	31:1
7	7-Me	CO_2Me	30	97	99	17:1

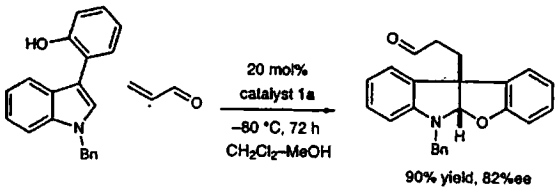


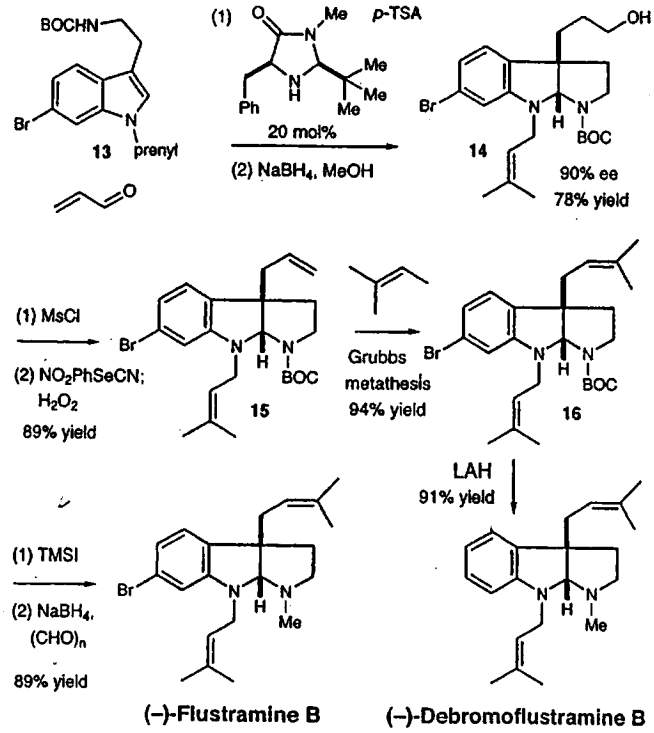
Entry	R^1	R^2	Time, h	Yield, %	ee,* %
1	Allyl	*t*-Bu	25	85	89
2	Allyl	Et	26	89	89
3	Prenyl	Et	24	89	89
4	Benzyl	Allyl	48	83	89
5	Benzyl	*t*-Bu	30	82	90†

Dainshefsky etal used Tryptophan based starting materials. (long steps).



Scheme 6.





① Overman group :- enantioselective bis-Heck technology. JACS, 1999, 7702-03.

only 7 steps!