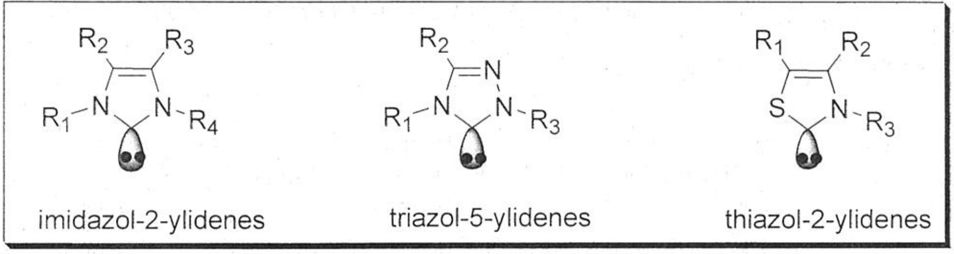
2009/7/8(Wed)
A. Nojiri(M1 part)

N-Heterocyclic(NHC) Carbenes as Organocatalysts

Review: Enders et al *Chem.Rev.* **2007**, *107*, 5606

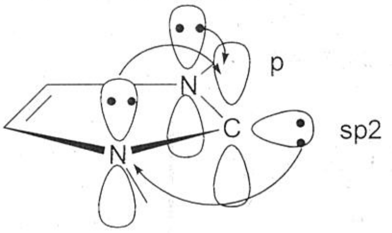
General type of N-Heterocyclic(NHC) carbenes



imidazol-2-ylidenes triazol-5-ylidenes thiazol-2-ylidenes

Introduction

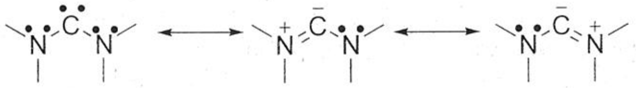
Feature of NHC carbene



\+ Singlet stable carbene
i) π-donation into the carbene out-of-plane p orbital by the electron-rich π-system
ii) Resonance form(ylide structure)
iii) σ-electronegativity effect

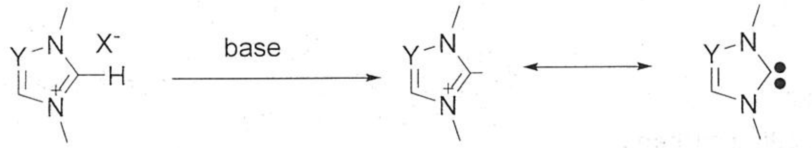
\+ Nucleophilic character
Explained by resonance form

Resonance form



Ylide structure

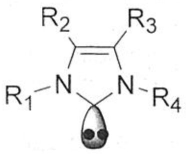
Preparative method of NHC carbene.



Azolium salt ylide carbene

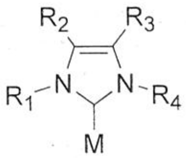
Utility

(1) As nucleophilic carbene



Topic in this literature seminar

(2) As ligand for metal-based catalyst



strong σ-donor,
poor π-acceptor
steric properties of NHCs

reaction
C-C cross-coupling
the olefin metathesis
et al

Contents

1. First isolation of carbene
2. Classical application : Umpolung reaction
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   3.1 Homoenolate addition to aldehyde or imine
   3.2 Catalytic genaration of activated carboxylates
   3.3 C-C bond formation via enol or enolate
   3.4 Cyclopentene-forming reaction(Benzoin oxi-Cope reaction)
4. Summary

1. First isolation of carbene

History of discovering stable singlet carbenes

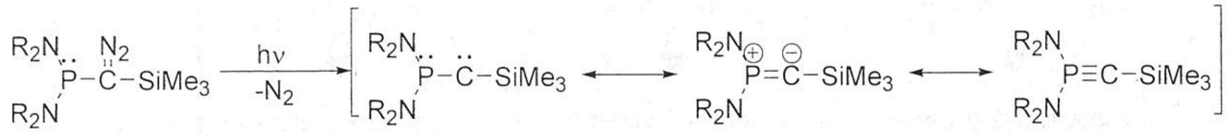
1) Bertrand work

J. Am. Chem. Soc. 1988, *110*, 6463–6466

Analogous α,α'-Bis-Carbenoid Triply Bonded Species: Synthesis of a Stable λ^3-Phosphinocarbene–λ^5-Phosphaacetylene

Alain Igau, Hansjorg Grutzmacher, Antoine Baceiredo, and Guy Bertrand*

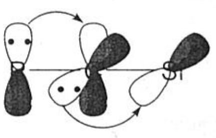
Related report
Bertrand, G rt al, *Angew. Chem. Int. Ed. Engl.* **1989**, *11*, 363
Bertrand, G rt al, *J. Am. Chem. Soc.* **2000**, *122*, 998



A. Phosphinocarbene B. Phosphorus vinyl ylide C. Phosphaacetylene

/Stable for several weeks at r.t
/Bp 75-80 °C(0.01 mmHg)
/Distillable
/Reactivity of carbene and multiple bond was observed.

Reason of stability.



Electron donation from the heteroatom lone pair into the formally empty p-orbital of the carbene center

The interaction of the carbene lone pair with the σ^* orbitals of silyl groups

This is the first report of bottle stable carbene.
But Bertrand didn't insist that point because his focus was "chemistry of C-P triple-bond".

2) Arduengo work

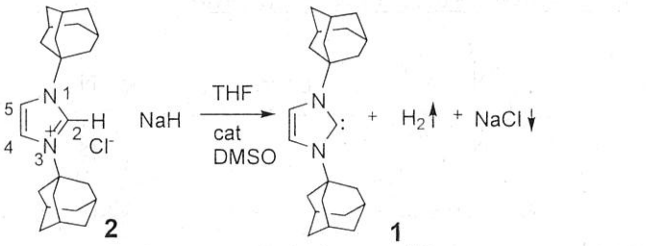
A Stable Crystalline Carbene

Anthony J. Arduengo, III,* Richard L. Harlow, and Michael Kline

J. Am. Chem. SOC. **1991**, *113*, 363

First characterization of the crystalline carbene

They insisted until now there have not been any 'bottle-able" carbenes



Colorless solid
Stable in the absent of oxygen and moisture

<Structual features of NHC carbene>

Table I. Selected Bond Lengths (pm) and Angles (deg) in 1

	bond length		bond angle
C_2–N_1	136.7 (2)	N_1–C_2–N_3	102.2 (2)
C_2–N_3	137.3 (2)	C_5–N_1–C_2	112.1 (2)
C_4–C_5	133.8 (3)	C_4–N_3–C_2	112.3 (2)
N_1–C_5	138.2 (2)	N_1–C_5–C_4	107.2 (2)
N_3–C_4	138.6 (2)	N_3–C_4–C_5	106.2 (2)
N_1–$C_{1\text{-Ad}}$	148.2 (2)	C_2–N_1–$C_{1\text{-Ad}}$	123.4 (2)
N_3–$C_{1\text{-Ad}}$	148.5 (2)	C_2–N_3–$C_{1\text{-Ad}}$	122.1 (2)

(from X- ray analysis)

Pickup

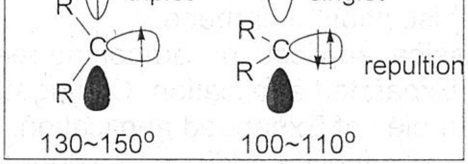
imidazolium salts(**2**)		carbene **1**
N_1-C_2 132.8 pm	⟹	N_1-C_2 136.7 pm
N_3-C_2 132.8 pm		N_3-C_2 137.3 pm
N_1-C_2-N_3 109.7°		N_1-C_2-N_3 102.2°

Difference between imdazolium ion **2** and carbene **1**

1) a diminished π-delocalization in **1** as compared to imidazolium salts

2) hybridization at the carbene center that influence bond distances
more s-orbital character is used to stabilize the in-plane lone pair of electrons at the carbene center, the N-C σ-bonds take on more p-character at the carbene center.

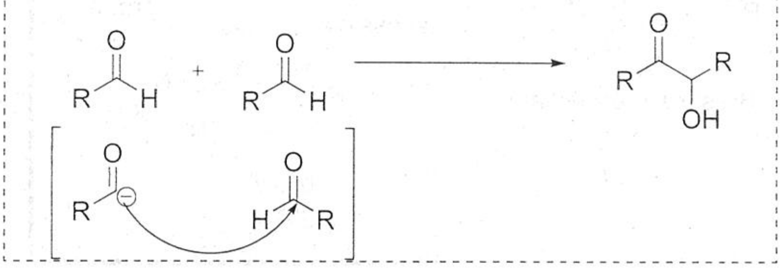
Typical angle of carbene(calculated)



2 Classical application : Umpolung reaction to Expanded application: Conjugate Umpolung reaction

See Shimizu-san(M2) lit about Umpolung

Umpolung reaction Ex. Benzoin condensation



In 1943,Ugai et al. recognized that thiazolium salts could also be used as catalysts in the benzoin condensation

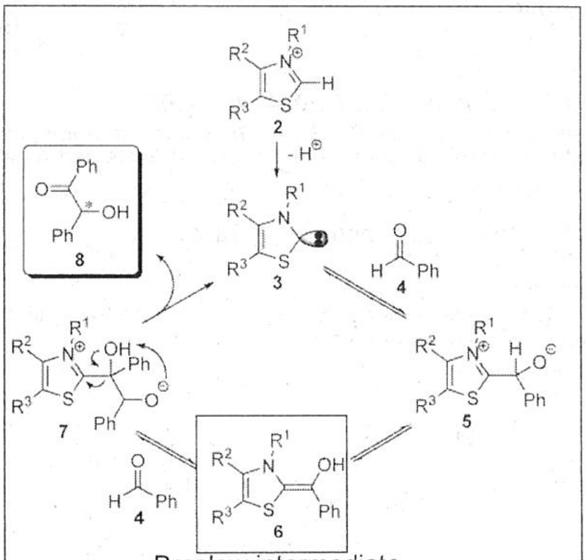
<Mechanistic proposal of benzoin condensation>

On the Mechanism of Thiamine Action. IV.[1] Evidence from Studies on Model Systems

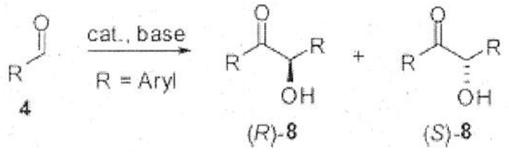
By Ronald Breslow

J. Am. Chem. SOC. **1958**, *80*, 3719

Catalytic Cycle of the Benzoin Condensation as Proposed by Breslow



Breslow intermediate

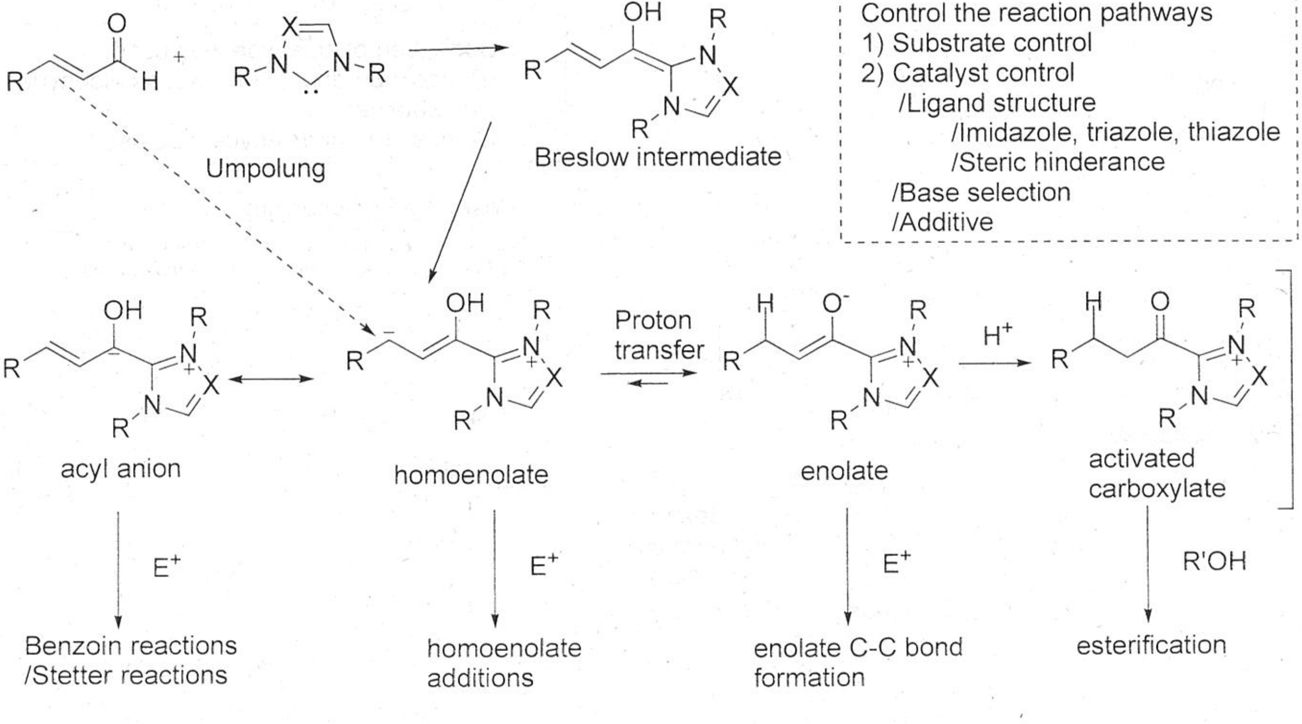


+Thiazol-2-ylidenes and triazol-5-ylidenes are used as cat.

+Asymmetric version also is developped by using chiral NHC catalyst.

Expanded application

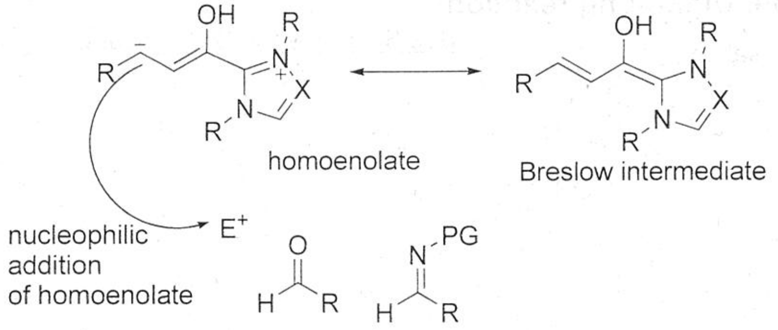
Conceptually new approach the generation of homoenolate



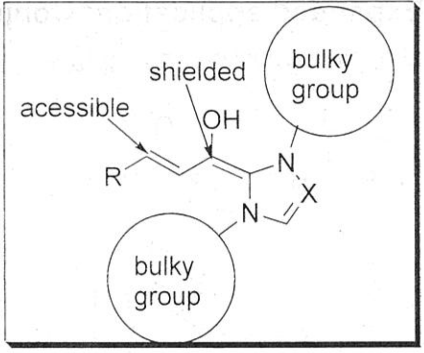
Control the reaction pathways
1) Substrate control
2) Catalyst control
  /Ligand structure
    /Imidazole, triazole, thiazole
    /Steric hinderance
  /Base selection
  /Additive

Various reactions has been developed by using this system.

3.1 Homoenolate addition to aldehyde or imine



Ligand design



3.1.1 Homoenolate addition to aldehyde

Organocatalyzed Conjugate Umpolung of α,β-Unsaturated Aldehydes for the Synthesis of γ-Butyrolactones[**]

*Christian Burstein and Frank Glorius**

Angew. Chem. Int. Ed. **2004**, *43*, 6205

Recieved date
Glorius : 2004/08/06
Bode : 2004/09/01

Same target reaction
and same catalyst
(26 days difference!)

+ Direct, catalytic generation of homoenolate

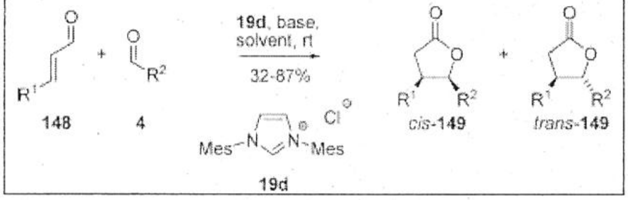
N-Heterocyclic Carbene-Catalyzed Generation of Homoenolates: γ-Butyrolactones by Direct Annulations of Enals and Aldehydes

Stephanie S. Sohn, Evelyn L. Rosen, and Jeffrey W. Bode*

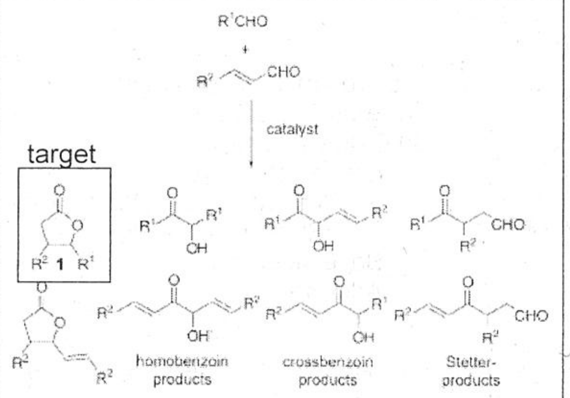
J. Am. Chem. Soc. **2004**, *126*, 14370

Reaction

Scheme 53. Generation of γ-Butyrolactones by Burstein and Glorius and Bode and Co-workers

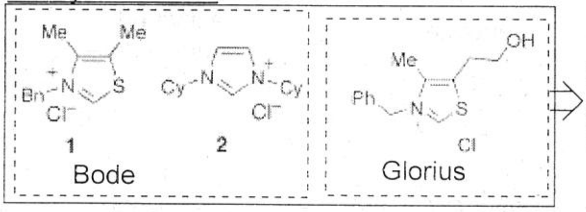


Expected byproduct

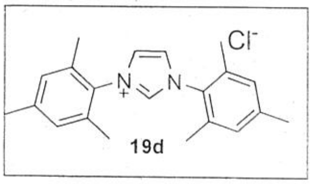


Scheme 2. Expected products of the organocatalyzed reaction of an α,β-unsaturated aldehyde with another aldehyde.

Catalyst selection



Benzoin product (trace)



Desired γ-butyrolactones was obtained.

Table 15. Results of Burstein and Glorius: 5 mol % **19d**, 10 mol % KO*t*-Bu, THF, 16 h

entry	R^1	R^2	yield (%)	cis/trans
1	*p*-Cl-Ph	Ph	53	81:19
2	*p*-Br-Ph	Ph	49	80:20
3	*p*-CO_2Me-Ph	Ph	70	79:21
4	*p*-F_3C-Ph	Ph	44	77:23
5	*m*-F-Ph	Ph	52	78:22
6	*m*-Cl-Ph	Ph	61	79:21
7	*m*-Br-Ph	Ph	60	79:21

Table 16. Results of Bode and Co-workers: 8 mol % **19d**, 7 mol % DBU, THF/*t*-BuOH (10:1), 3−15 h

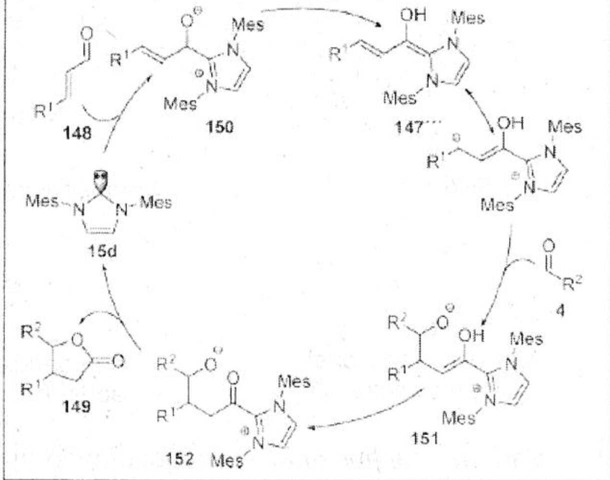
entry	R^1	R^2	yield (%)	cis/trans
1	Ph	*p*-Br-Ph	79	4:1
2[a]	Ph	*p*-CO_2Me-Ph	87	5:1
3	*p*-MeO-Ph	*p*-Br-Ph	76	4:1
4[b]	*p*-MeO-Ph	Ph	65	4:1
5[a,c]	TIPSC≡C	*p*-CO_2Me-Ph	41	3:1
6	TIPSC≡C	TIPSC≡CCH═CH	83	5:1
7[b]	1-naphthyl	1-naphthyl-CH═CH	67	5:1

[a] Concentration = 0.1 M. [b] Performed with 15 mol % **19d**, 14 mol % DBU. [c] The enal was added over a period of 3 h.

Bode: 2eq of aldehyde was used.
(Benzoin product of the excess aldehyde was obtained)
Glorius: 1eq of aldehyde was used.

Posturated mechanism

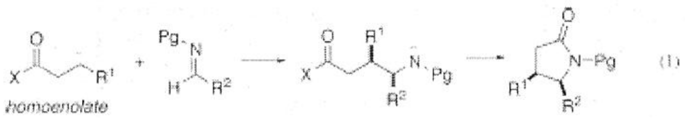
Scheme 54. Postulated Catalytic Cycle for the Carbene-Catalyzed Formation of γ-Butyrolactones

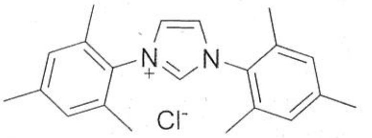


3.1.1 Homoenolate addition to imine

Catalytic Synthesis of γ-Lactams via Direct Annulations of Enals and *N*-Sulfonylimines

Ming He and Jeffrey W. Bode* *Org. Lett.* **2005**, *7*, 3131

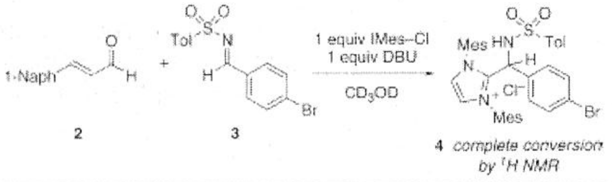


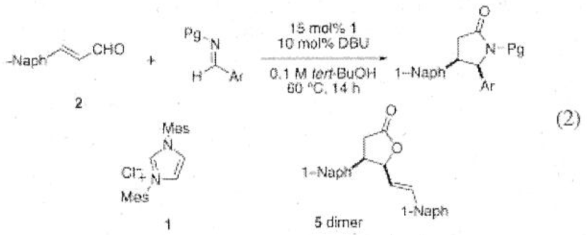


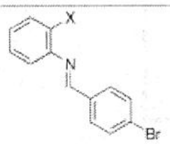
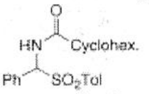
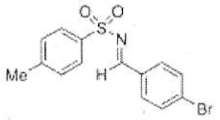
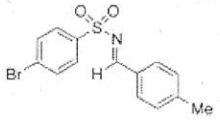
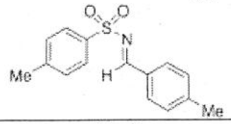
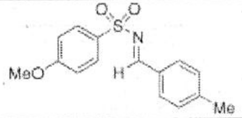
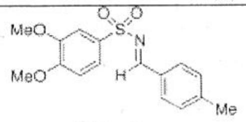
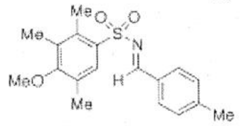
IMes-Cl Commercially available

About protecting group of imine

+N-alkyl or N-aryl imine was unreactive.
(Only dimers of enal)
+N-phosphinoyl and N- tosyl was so reactive.
(Reacted directly with catalyst)
+Moderate electrophilicity is needed about imine.
They screened electron-rich N-sulfonyl imines.



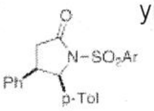
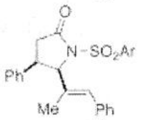
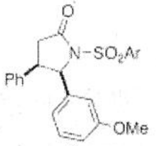
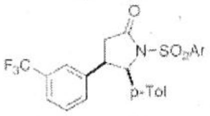
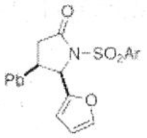
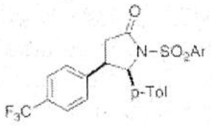
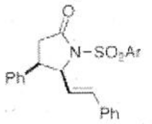
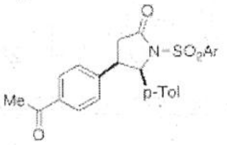


Entry	Imine		Conv.[b](%) (% dimer)[d]	Yield[c]/% (dr)
1		X=H	0 (15)	–
2		X=F	0 (91)	–
3		X=OMe	0 (69)	–
4[e]			>20 (trace)	–
5			38 (5)	11
6			14 (2)	–
7			93 (4)	64 (>10:1)
8			96 (4)	75 (>10:1)
9			73 (2)	Nd
10			0 (39)	–

[a] All reactions were performed with 1 equiv of 2, 1 equiv of imine, 15 mol % IMes-Cl, and 10 mol % DBU at 0.1 M in *tert*-BuOH at 60 °C. [b] Ratio of remaining enal to lactam and/or lactone products as measured by ¹H NMR analysis of unpurified reaction mixtures. [c] Isolated yield following silica gel chromatography. [d] Lactone homodimer. [e] Performed with 10 equiv of NEt₃.

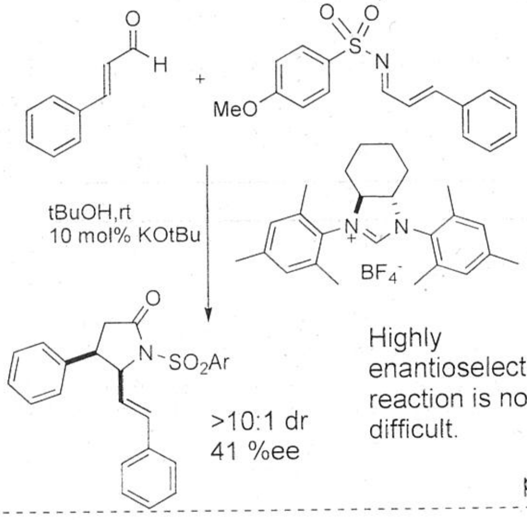
Substrate scope

Conditions
1 equiv of enal, 1 equiv of imine,
15 mol % IMes-Cl, and 10 mol % DBU
at 0.1 M in tert-BuOH at 60 °C for 14 h.
Ar = 4-MeOC6H4

	yield(%)/dr		yield(%)/dr
	70/ 4:1		62/ 5:1
	69/ 3:1		70/ 3:2
	73/ 1.7:1		70/ 3.5:1
	61/ 8:1		65/ 3.5:1

Electrondeficient aldehydes and
Electron-rich imines gave better result
⟹ To suppress the other pathways

His unpublished data(from SSOCJ Lectureship Award presentation)



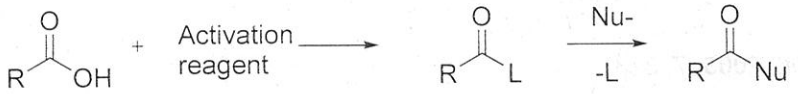
>10:1 dr
41 %ee

Highly enantioselective reaction is now difficult.

3.2 Catalytic genaration of activated carboxylates

background

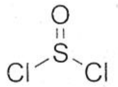
Esterification and amidation by using activation reagent(reliable method)



Activated carboxylate

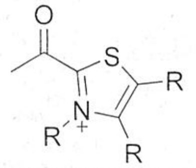
Problem
Stoichiometric use

Activation reagent = DCC



$SOCl_2$

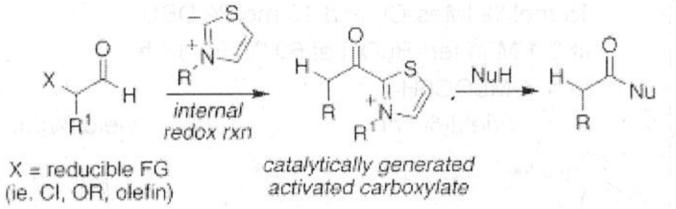
et al



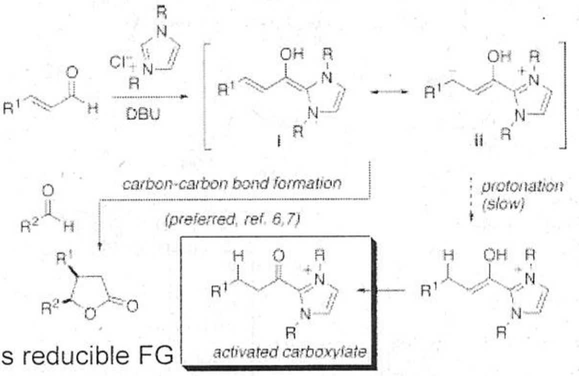
Breslow indicated 2-Acetylthiazolium salts work as active acetate
(In the Thiamine chemistry)
Breslow et al E. J. Am. Chem. Soc. 1960, 82, 2394-2395

Concepts: Catalytic generation of activeted carboxylates by NHC catalyst.

Scheme 1. Catalytic Generation of Activated Carboxylates via Internal Redox Reactions



Scheme 2. Reaction Pathways of Catalytically Generated Activated Carboxylates



Olefine is used as reducible FG

3.2.1 α,β-Unsaturated Aldehydes into Saturated Esters

Conversion of α,β-Unsaturated Aldehydes into Saturated Esters: An Umpolung Reaction Catalyzed by Nucleophilic Carbenes

Audrey Chan and Karl A. Scheidt* *Org. Lett.*, **2005**, *7*, 905

Catalyst selection and additive effect

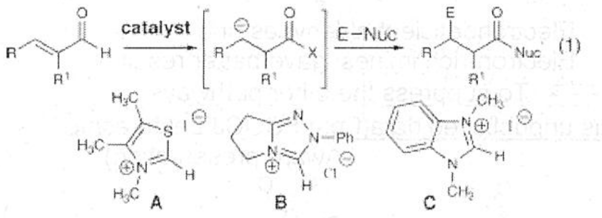
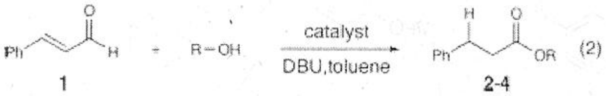


Table 1. Investigation of Homoenolate Reactivity[a]



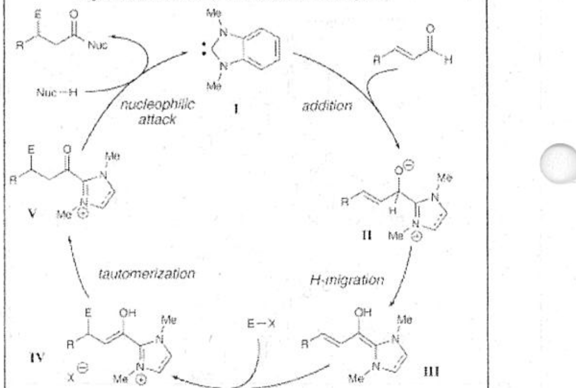
1 2-4

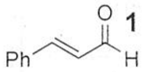
entry	ROH[b]	catalyst (mol %)	additive[c]	yield (%)
1	EtOH	A (30 mol %)		57 (2)
2	PhOH	A (30 mol %)		55 (3)
3	BnOH	B (10 mol %)	PhOH	47 (4)
4	BnOH	C (20 mol %)	PhOH	82 (4)
5	BnOH	C (5 mol %)	PhOH	82 (4)

[a] Reactions performed with a 1:1 molar ratio of catalyst to DBU at reflux temperature. [b] Performed with 5 equiv of nuclephilic alcohol. [c] Performed with 2 equiv of proton additive.

mechanism

Scheme 2. Proposed Mechanism to Generate Homoenolate Equivalents from α,β-Unsaturated Aldehydes

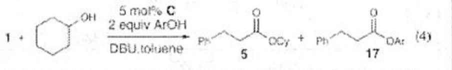




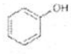
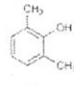
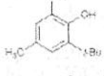
1

Suppresion of producing compound17

Table 4. Impact of Phenol Structure on Homoenolate Reaction[a]



5 17

entry	ArOH	time (h)	yield (%) of 5	yield (%) of 17
1		6	57	26
2		6	58	20
3		6	65	0%

[a] Reactions performed at 0.5 M at 100 °C with 5 equiv of cyclohexanol

By increasing the size of the substituents, production of phenyl ester can be suppressed completely.

3.2.2 α,β-Unsaturated Aldehydes into Saturated Esters

~Importance of base selection~

Catalytic Generation of Activated Carboxylates from Enals: A Product-Determining Role for the Base

Stephanie S. Sohn and Jeffrey W. Bode* *Org. Lett.*, **2005**, *7*, 3873

NHC catalyst selection

Scheme 3. Heterocyclic Precatalysts for the Catalytic Generation of Activated Carboxylates from Cinnamaldehyde

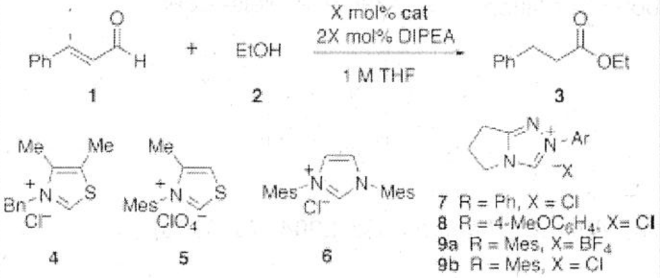
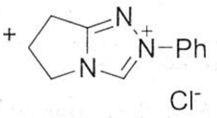


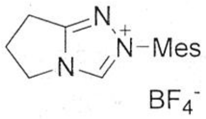
Table 1. Catalysts and Conditions for Redox Esterification[a]

entry	catalyst (mol %)	temp (°C)	conversion[b] (%)	yield[c] (%)
1	**4** (10)	40	15	
2	**5** (10)	40	trace	
3	**6** (15)	40	80	59
4	**7** (10)	40	trace	
5	**8** (10)	40	98	
6	**9a** (10)	40	99	
7	**9a** (5)	40	90	89
8	**9a** (5)	60	99	86
9	**9a** (2)	60	95	60

+ Thiazolium salt is not effective.



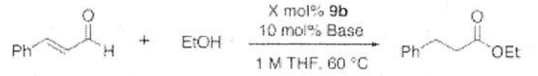
Not effective
entry4



best catalyst
entry 6

Base selection

Table 3. Effect of the Amine Base of Catalytic Esterifications[a]



entry	X (mol %)	base	pK_a of conjugate acid in THF[13]	relative yield (%)[b]
1	5	NEt$_3$	12.5	99
2	5	DIPEA	~13	99
3	5	DBU	16.8	15
4	5	P2-*t*-Bu	20.9	>5
5	5	KO*t*Bu	29.4[c]	>5
6	20	KO*t*Bu		75
7	20	DIPEA		99

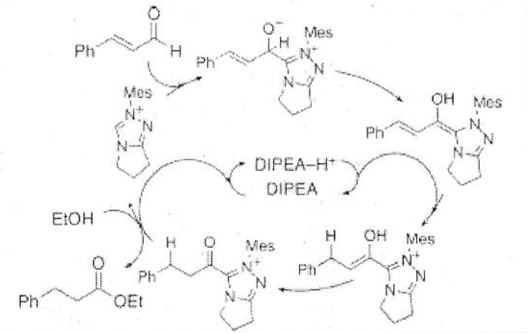
[a] Reaction conditions: X mol % of **9b**, 10 mol % of base, 0.2 mmol of enal, 1 M THF, 3 equiv of ROH, 60 °C, 15 h. [b] Relative yield of ester to starting material and other products, as determined by ^1H NMR or GC analysis of unpuried reaction mixtures. [c] In DMSO.

+ A clear correlation between the success of the reaction and the pKa of the conjugate acid emerged
+ Excess triazolium salt gave good result.

⇒ Triazolium salt itself may serve as the catalytic proton shuttle

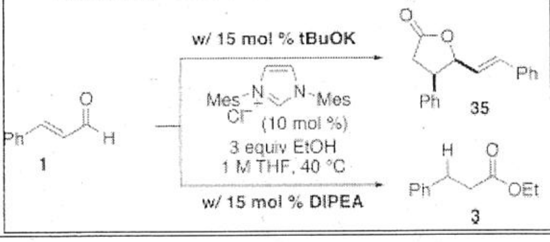
Mechanism

Scheme 5. Postulated Catalytic Cycle for Catalytic Redox Esterifications of Enals



Effect of catalytic base to rusulting product.

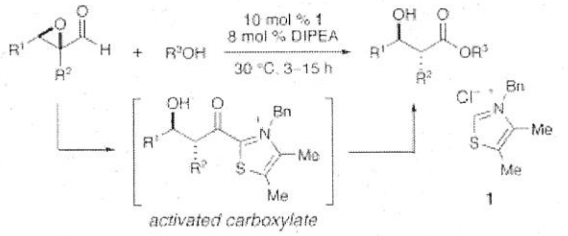
Scheme 4. Effect of Catalytic Base on the Fate of Catalytically Generated Homoenolate Equivalents



Other example

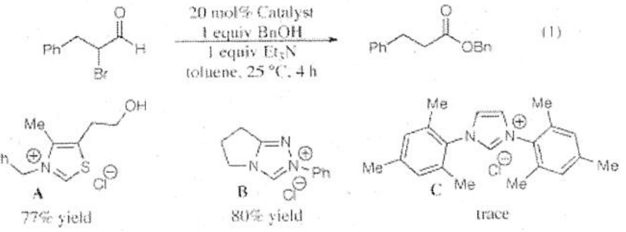
Reductive FG :epoxide
conversion:β-hydroxyester from α,β-epoxyaldehyde

Scheme 1



Bode et al. *J. Am. Chem. Soc.* **2004,** *126*, 8126-8127

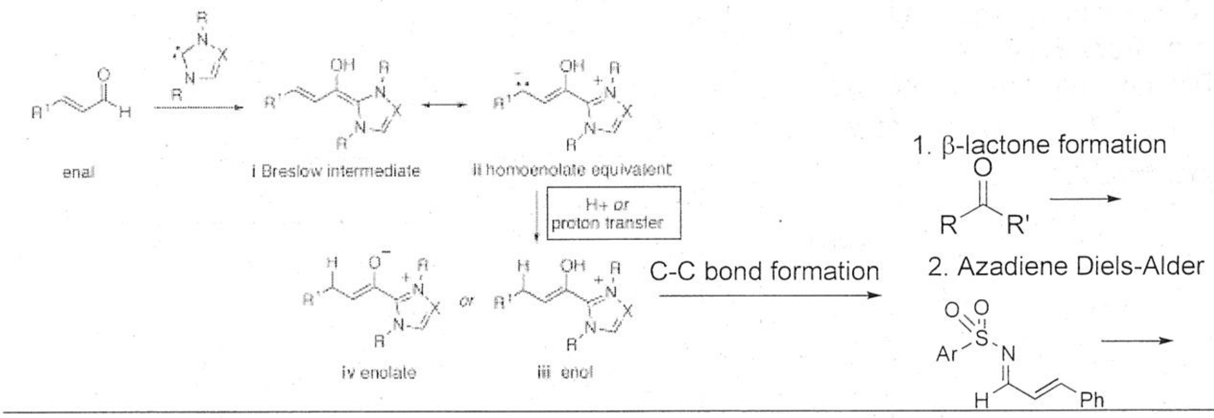
Reductive FG :α-harogen
conversion:ester from α-haroaldehyde



Rovis et al. *J. Am. Chem. Soc.* **2004,** *126*, 9518

3.3 C-C bond formation via enol or enolate

Scheme 1. Proposed NHC-Mediated Enolate Generation



C-C bond formation

1. β-lactone formation

2. Azadiene Diels-Alder

3.3.1 β-lactone forming reaction

Glorius work Synthesis 2006, No. 14, 2418.(related work :*Angew. Chem. Int. Ed.* **2004**, *43*, 6205)

Scheme 55. Conditions for the Generation of γ-Butyrolactones from Ketones by Glorius and Co-workers

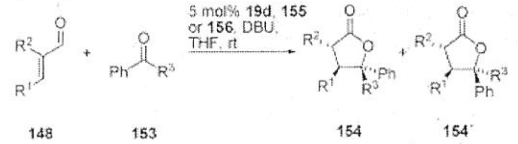


Table 17. Generation of γ-Butyrolactones from Ketones by Glorius and Co-workers

entry[a]	R^1	R^2	R^3	precat.	yield (%)	dr
1[b]	Ph	H	CF_3	19d	84	66:34
2[b]	Ph	H	CF_3	(*S*)-156	70	74:26
3[b]	*m*-MeO-Ph	H	CF_3	19d	92	66:34
4[b]	*m*-Me_2N-Ph	H	CF_3	19d	74	70:30
5[c]	Ph	H	COMe	19d	55	58:42
6	Ph	H	CO_2Me	19d	78	50:50
7	*m*-MeO-Ph	H	CO_2Me	19d	94	47:53
8	*m*-Me_2N-Ph	H	CO_2Me	19d	98	44:56
9	Me	H	CF_3	19d	82	81:19
10	Pr	H	CF_3	19d	90	84:16
11	*i*-Pr	H	CF_3	19d	66	93:7
12	Me	H	CO_2Me	19d	87	68:32
13	Pr	H	CO_2Me	19d	71	67:33

[a] General reaction conditions: 5 mol % DBU, THF, rt, 16 h. [b] Reaction conditions: 10 mol % KO*t*-Bu, THF, rt, 16 h. [c] Reaction conditions: 5 mol % DBU, THF, 60 °C, 16 h. [d] Reaction conditions: 5 mol % DBU, DMF, 75 °C, 16 h.

Scheme 56. Synthesis of β-Lactones by Glorius and Co-workers

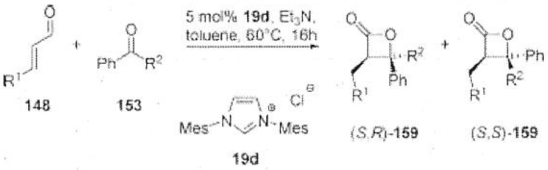
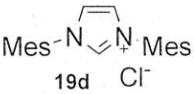


Table 18. Substrate Scope for the Synthesis of β-Lactones by Glorius and Co-workers

R^1	R^2	yield (%)	dr
Me	CF_3	34	60:40
Pr	CF_3	45	55:45
i-Pr	CF_3	48	62:38
Ph	CF_3	30	70:30
i-Pr	CO_2Me	22[a]	71:29

[a] Reaction was performed with 10 mol % 19d and 10 mol % DBU.

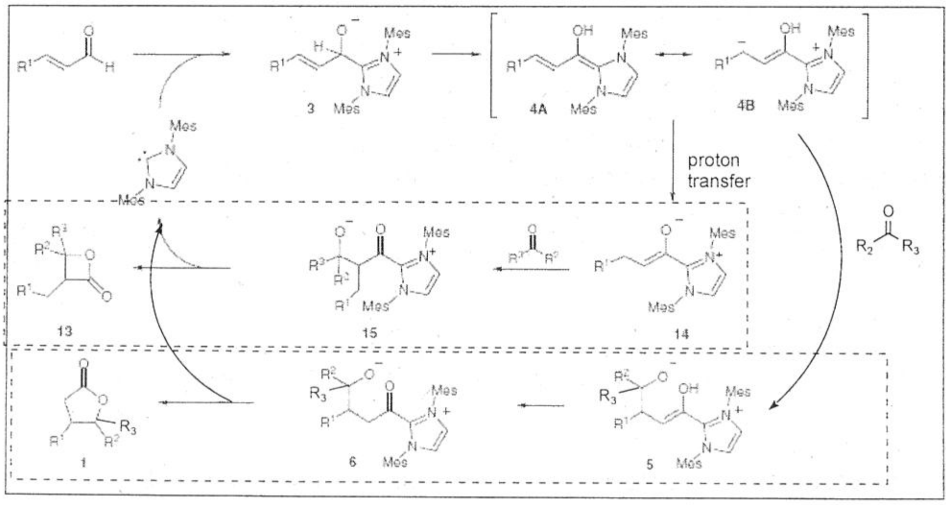
NHC catalyst



19d

Differnce	γ-lactones	β-lactones
Base	KOtBu or DBU	**NEt_3(less basic)**
solvent	THF	toluene
temperature	rt	60 °C

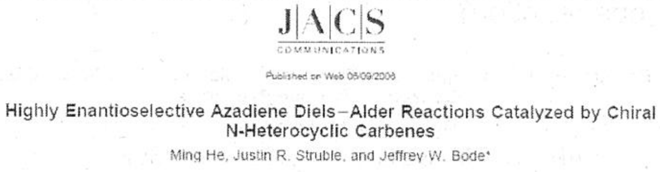
Mechanism



+ Weak base promote proton transfer
$\Rightarrow$ β-lactones

+ Addition to ketone of homoenolate
$\Rightarrow$ γ-lactones

3.3.2 Highly Enantioselective Azadiene Diels-Alder Reactions



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Published on Web 06/09/2006

Highly Enantioselective Azadiene Diels–Alder Reactions Catalyzed by Chiral N-Heterocyclic Carbenes

Ming He, Justin R. Struble, and Jeffrey W. Bode*

J. AM. CHEM. SOC. **2006**, *128*, 8418

His focus was extending the mechanistic pathways available
the formation of a catalyst-bound enol
or enolate poised for carbon-carbon bond formation

-First example :NHC-catalyzed generation of a highly reactive dienophile that participates in LUMOdiene-controlled Diels-Alder cyclizations

Investigation of conditions

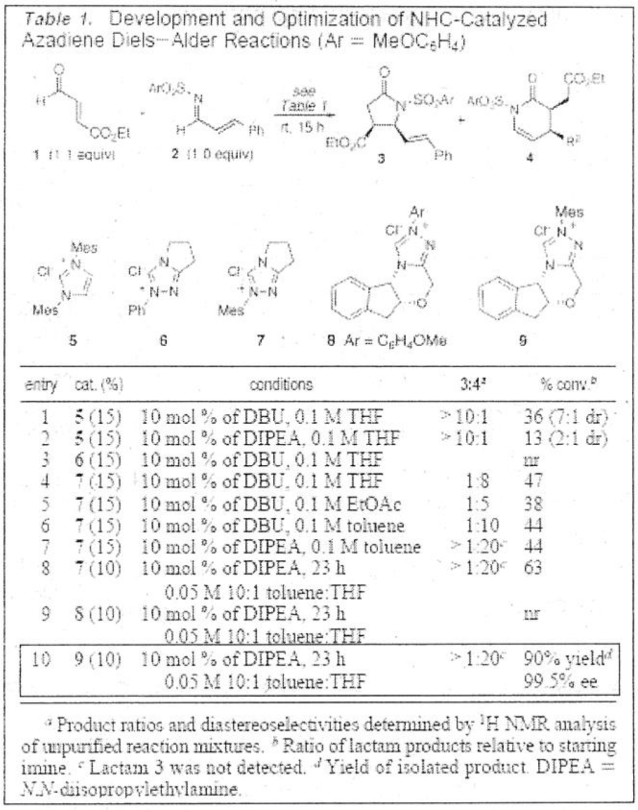
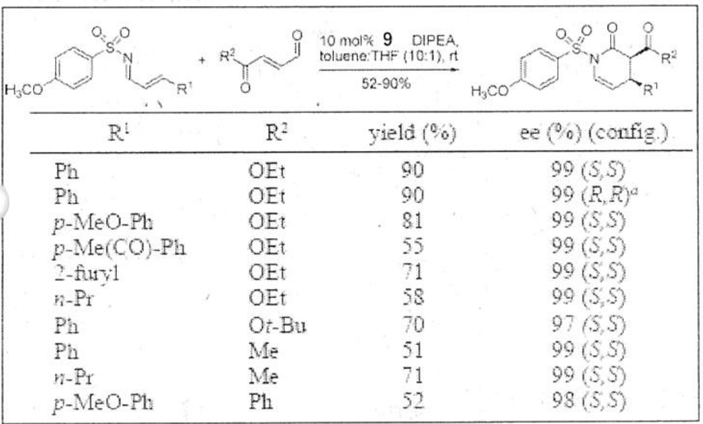


Table 1. Development and Optimization of NHC-Catalyzed Azadiene Diels–Alder Reactions (Ar = $MeOC_6H_4$)

entry	cat. (%)	conditions	3:4[a]	% conv.[b]
1	5 (15)	10 mol % of DBU, 0.1 M THF	>10:1	36 (7:1 dr)
2	5 (15)	10 mol % of DIPEA, 0.1 M THF	>10:1	13 (2:1 dr)
3	6 (15)	10 mol % of DBU, 0.1 M THF		nr
4	7 (15)	10 mol % of DBU, 0.1 M THF	1:8	47
5	7 (15)	10 mol % of DBU, 0.1 M EtOAc	1:5	38
6	7 (15)	10 mol % of DBU, 0.1 M toluene	1:10	44
7	7 (15)	10 mol % of DIPEA, 0.1 M toluene	>1:20[c]	44
8	7 (10)	10 mol % of DIPEA, 23 h 0.05 M 10:1 toluene:THF	>1:20[c]	63
9	8 (10)	10 mol % of DIPEA, 23 h 0.05 M 10:1 toluene:THF		nr
10	9 (10)	10 mol % of DIPEA, 23 h 0.05 M 10:1 toluene:THF	>1:20[c]	90% yield[d] 99.5% ee

[a] Product ratios and diastereoselectivities determined by ^{1}H NMR analysis of unpurified reaction mixtures. [b] Ratio of lactam products relative to starting imine. [c] Lactam 3 was not detected. [d] Yield of isolated product. DIPEA = *N,N*-diisopropylethylamine.

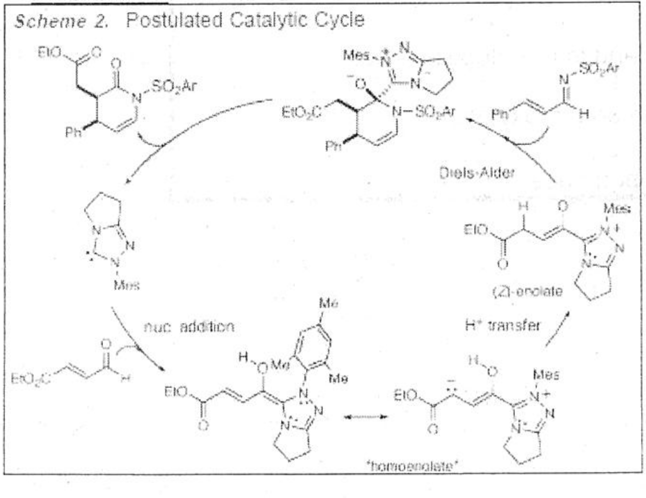
Substrate scope



R¹	R²	yield (%)	ee (%) (config.)
Ph	OEt	90	99 (*S,S*)
Ph	OEt	90	99 (*R,R*)[a]
p-MeO-Ph	OEt	81	99 (*S,S*)
p-Me(CO)-Ph	OEt	55	99 (*S,S*)
2-furyl	OEt	71	99 (*S,S*)
n-Pr	OEt	58	99 (*S,S*)
Ph	O*t*-Bu	70	97 (*S,S*)
Ph	Me	51	99 (*S,S*)
n-Pr	Me	71	99 (*S,S*)
p-MeO-Ph	Ph	52	98 (*S,S*)

Mechanism

Scheme 2. Postulated Catalytic Cycle



(Z)-enolate formation

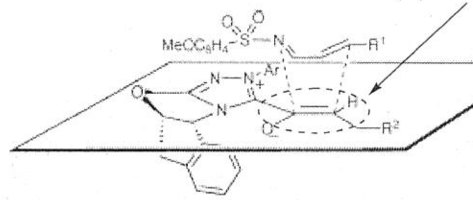
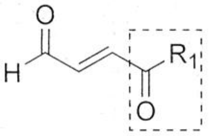
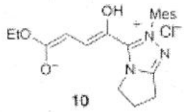


Figure 1. Stereochemical model for **endo**-Diels-Alder cycloaddition

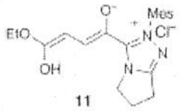


Electrowithdrawing group is essential (from substrate scope)

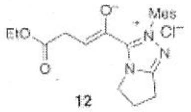
+ supposable reason 1
[tautomeric form shown below is essential]



10

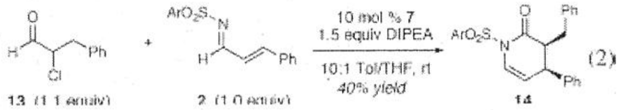


11



12

<Test reaction>



(2)

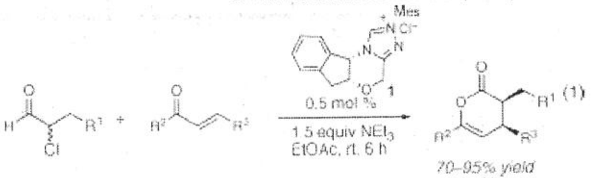
reaction proceeded.

⟹ supposable reason1 is not so important

+ supposable reason 2
[Only increase electrophilicity of enal]
When less electrophilic enals are employed,
the NHC catalyst reacts preferentially
with the electrophilic imine.

<Related work>

Chiral N-Heterocyclic Carbene Catalyzed, Enantioselective Oxodiene Diels-Alder Reactions with Low Catalyst Loadings
Ming He, Gerson J. Uc, and Jeffrey W. Bode*
J. AM. CHEM. SOC. **2006**, *128*, 15088



Similar reaction system.
(To trap HCl, 1.5 eq of Et3N is used)

3.4 Cyclopentene-forming reaction(Benzoin oxi-Cope reaction)

N-Heterocyclic Carbene-Catalyzed Reaction of Chalcones and Enals via Homoenolate: an Efficient Synthesis of 1,3,4-Trisubstituted Cyclopentenes

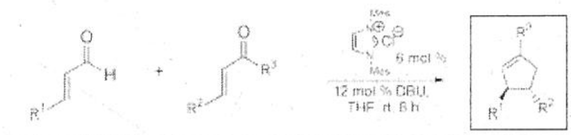
Vijay Nair,*,† Sreekumar Vellalath,† Manojkumar Poonoth,† and Eringathodi Suresh‡

J. AM. CHEM. SOC. 2006, 128, 8736-8737

Nair's work(racemi)

Substrate

Cinnamaldehyde and **chalcone**

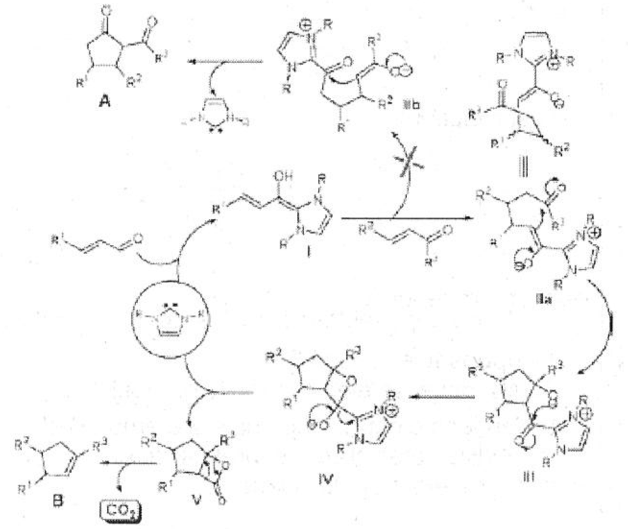


Trans only

entry	R¹	R²	R³	product	yield (%)
1	2-MP^b	2-thienyl	4-chlorophenyl	4b	88
2	phenyl	1-naphthyl	4-chlorophenyl	4c	76
3	4-MP^b	2-thienyl	4-methylphenyl	4d	85
4	4-MP^b	4-cyanophenyl	4-chlorophenyl	4e	76
5	4-MP^b	phenyl	phenyl	4f	88
6	phenyl	phenyl	phenyl	4g	78
7	4-MP^b	4-fluorophenyl	4-chlorophenyl	4h	78
8	4-MP^b	4-chlorophenyl	4-chlorophenyl	4i	76
9	4-MP^b	2-thienyl	phenyl	4j	86
10	4-MP^b	2-furyl	4-chlorophenyl	4k	70
11	4-MP^b	methyl	4-chlorophenyl	4l	55
12	methyl	2-thienyl	4-chlorophenyl	4m	73

^{a} Isolated yield. ^{b} MP = methoxy phenyl.

Scheme 3. Postulated Catalytic Cycle Involving NHC



Enantioselective, Cyclopentene-Forming Annulations via NHC-Catalyzed Benzoin–Oxy-Cope Reactions

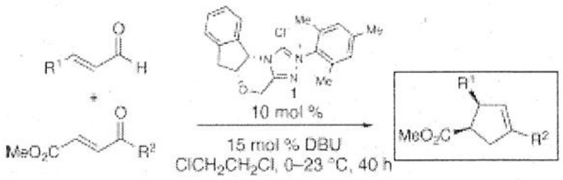
Pei-Chen Chiang, Juthanat Kaeobamrung, and Jeffrey W. Bode*

J. AM. CHEM. SOC. 2007, 129, 3520-3521

Bode's work(asymmetric)

Substrate

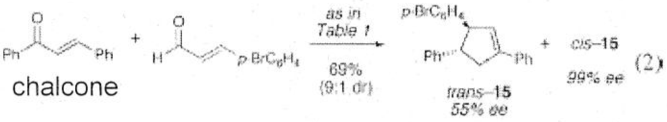
Cinnamaldehyde and **4-oxoenone**



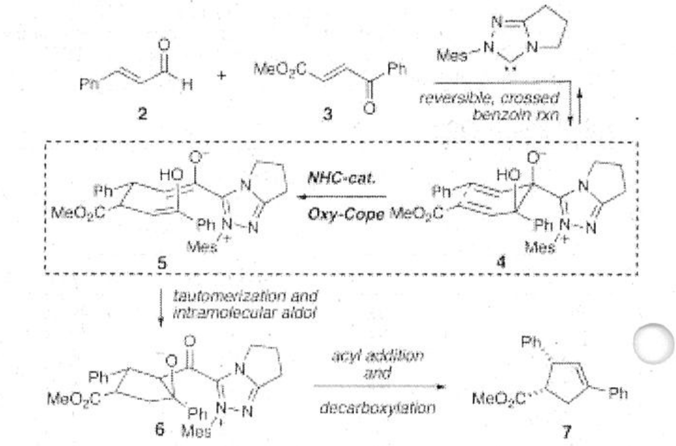
(1)

Cis

entry	R¹	R²	% yield^a	cis:trans^b	% ee^c
1	Ph	Ph	78	11:1	99 (68)^d
2^e	Ph	p-MeOC$_6$H$_4$	58	5:1	99 (68)^d
3	Ph	p-BrC$_6$H$_4$	50	11:1	99 (79)^d
4	Ph	2-furyl	93	>20:1	98
5	p-BrC$_6$H$_4$	Ph	58	6:1	99 (67)^d
6	p-CF$_3$C$_6$H$_4$	Ph	68	4:1	98 (67)^d
7	2-furyl	Ph	53	5:1	99 (82)^d
8	n-Pr	Ph	25	14:1	96 (32)^d



Scheme 1. Cyclopentenes via NHC-Catalyzed Oxy-Cope RAR



Proposed mechanism

Nair

Conjugate addition of homoenolate to enone

Bode

Benzoin-Oxy Cope reactions

↘ ↙

tautomerization and intramolecular aldol

↓

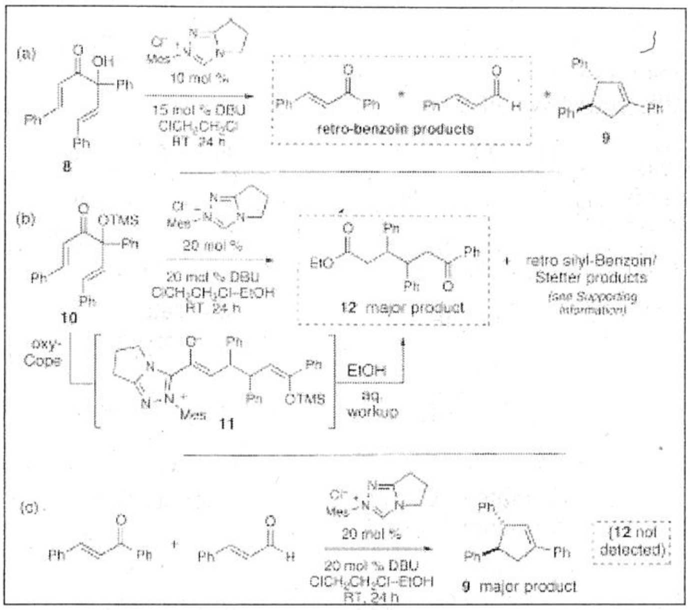
lactonization and decarboxylation

↓

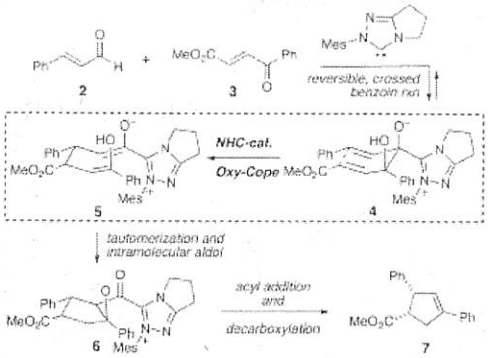
cyclopentenes

<Explanation by Bode(2007)>

Control experiments to explain Oxy-cope reaction



Scheme 1. Cyclopentenes via NHC-Catalyzed Oxy-Cope RAR



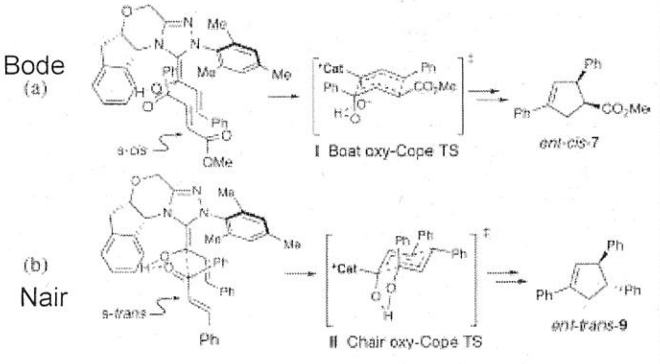
(a) Benzoin type reaction can take place reversibly.

(b)**12** can be obtained.

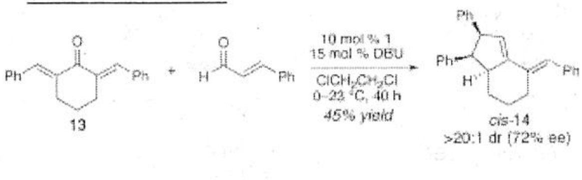
(c) (+ EtOH standard conditions)**12** was not detected.
>>Tautomerization and aldol reaction is fast compared to nucleophilic addition of EtOH.

About result of (b)
If oxy-Cope reaction doesn't take place,
retro benzoin followed by catalytic homoenolate addition is mechanism.
But from (c), **12** was not detected.So, oxy-Cope reaction should take place.

Explanation for different diastereoselectivity to different substrate

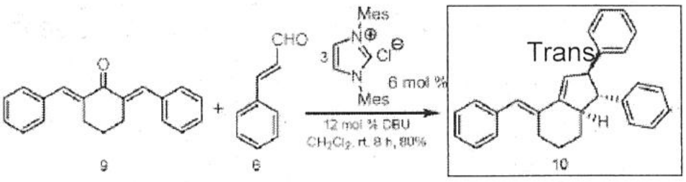


s-cis fixed enone



Reactive conformation of the enone determined the relative stereochemistry of the annulation products

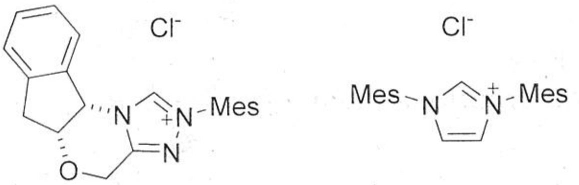
<Result by Nair(2008)> Chem. Commun., 2008, 747



This result cannot be explained by the explanation of Bode.

Conclusion

Bode Nair

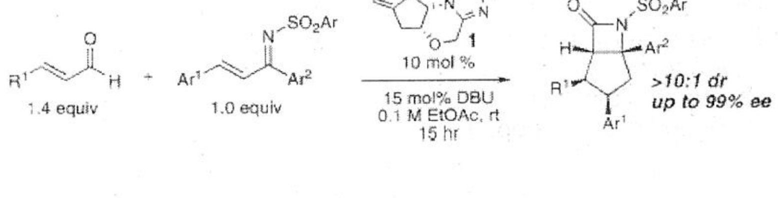


Two catalysts show different reaction pathways

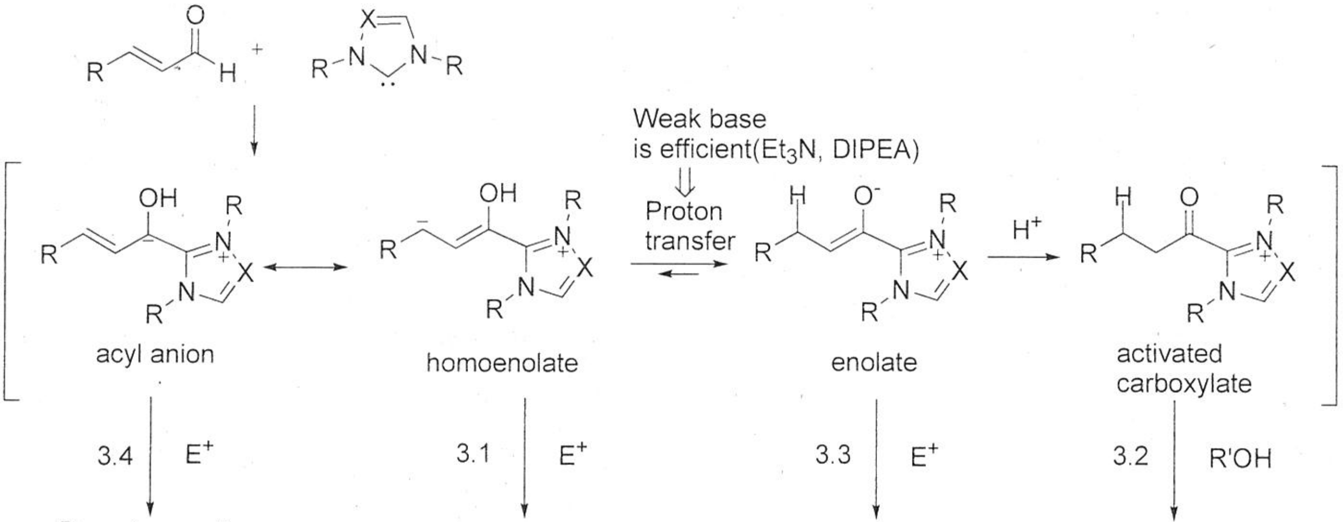
<related work>

Enantioselective, NHC-Catalyzed Bicyclo-a-Lactam Formation via Direct Annulations of Enals and Unsaturated N-Sulfonyl Ketimines

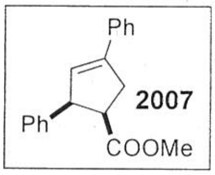
Ming He and Jeffrey W. Bode J. AM. CHEM. SOC. 2008, 130, 418

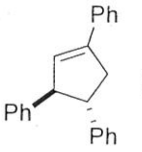


4. Summary

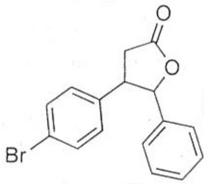


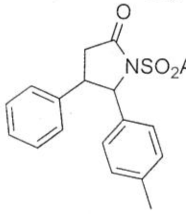
Benzoin reactions /Stetter reactions


2007

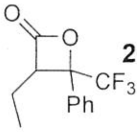

2006

Homoenolate additions


2004


2005

Enolate C-C bond formation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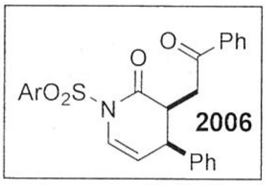
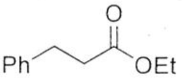
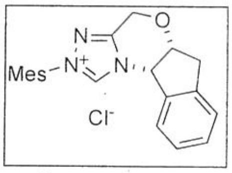
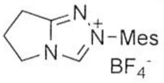

2006

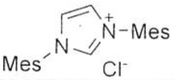
Esterification

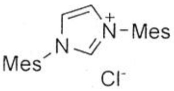

2005

enantioselective reaction

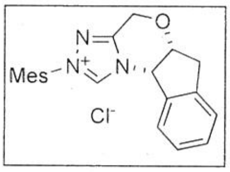


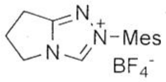


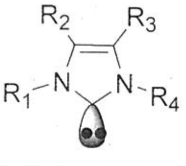
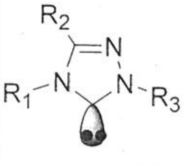
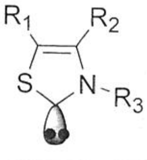




Enantioselective reaction





Utility as organocatalyst			
Homoenolate Chemistry (Conjugate umpolung)	Best catalyst of homoenolate additions	Widely used	Not Effective
Benzoin and Stetter (Umpolung)	scarcely used	Widely used	Widely used
Asymmetric Version	Few highly enantioselective reactions are reported. (Almost is C-2 symmetric catalyst. Now another type of asymmetric catalyst is needed and developed.)	Widely used to various reactions	Used to Benzoin and Stetter reaction