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RECENT ADVANCES IN LEWIS BASE-CATALYZED, STEREOSELECTIVE, TANDEM ALDOL β- AND γ-LACTONIZATIONS

Vikram C. Purohit, Andrea S. Matla, and Daniel Romo*

Department of Chemistry, Texas A&M University, P.O. Box 30012, College Station, TX, 77842-3012, USA. E-mail: romo@tamu.edu

Abstract – Stereoselective methods for the synthesis of β-lactones involving a Lewis base-promoted (nucleophile-promoted) aldol-lactonization manifold have continued to expand since the initial reports of Bormann and Wegler in the late 1960's and later by Wynberg and Staring in the early 1980's. This review will cover these developments including enantioselective versions of these processes. Cinchona alkaloids and various pyridine derivatives have been used most extensively to expand the repertoire of β-lactones accessible by this process. Furthermore, recent advances in the development of a^3-d^3-ümpolung pathways using *N*-heterocyclic carbenes have also enabled access to previously unattainable manifolds for the stereoselective synthesis of both β- and γ-lactones via aldol-lactonization pathways. This review covers literature in this area in the period from 1967- June 2008.

1 INTRODUCTION

Multiple-bond and ring forming reactions (*e.g.* Diels-Alder) that proceed with high stereochemical fidelity have been indispensible tools for synthetic chemists to build stereochemically dense, complex molecules. It is therefore not surprising, that during the last century organic chemists have continued to reap the fruits of their imagination and persistence by discovering new catalytic, asymmetric versions of these and other reactions adding to their ever increasing arsenal of enantioselective organic transformations.

"*Organocatalysis*" can be broadly classified as the changes instigated by a small organic molecule (chiral or achiral molecule containing carbon, hydrogen, nitrogen, oxygen, sulfur, or phosphorus) serving as a Lewis or Brønsted base (*electron* donicity), or a Lewis or Brønsted acid (*electron* polarizibility) during the transition state or in the ground state to achieve bond forming and/or breaking events within the same molecule or between substrates. It is interesting to note that although this important term was resurrected by Macmillan in 2000[1] to replace the term 'metal free catalysis,' this concept was introduced 80 years ago by Langenbeck in 1928.[2] Subsequent discoveries of the Hajos-Parish-Eder-Sauer-Weichert[3] process (1970's) using proline catalysis to prepare the Weiland-Mischler ketone and the application of *cinchona* alkaloids as Lewis bases by Wynberg and Staring[4] (1980's) to construct β-lactones via a net [2+2] cycloaddition pathway, mark the first truly preparatively useful examples where the stereochemical setting step was dictated by a chiral, 'all-organic' Lewis base. In retrospect, it is indeed quite spectacular that one of finest achievements in organic chemistry; the introduction of the unrivaled synthetic power of the "Noyori Asymmetric Hydrogenation" introduced in the late 1970's[5] parallels with a slow but steep rise in organocatalytic, Lewis base-catalyzed asymmetric transformations.

The topic of the current review has remained a challenging research endeavour for the past few decades: the enantioselective formation of β- and γ-lactones. Several methods for the synthesis of these lactones exist, ranging from fundamental approaches including simple lactonization and halolactonization to more convergent routes including Lewis acid promoted [2+2] cycloadditions of ketenes and aldehydes or aldol-lactonizations of ketones/aldehydes and enolates (Figure 1). As the name implies, an aldol-lactonization process merges two highly useful reactions in organic synthesis. Some of the origins, applications, and recent advances made in stereoselective, organocatalyzed aldol-lactonizations are discussed with divisions in this review based on the types of catalysts employed in these processes. In addition, the various mechanistic aspects of these processes are discussed with special emphasis on the nature of the involvement of chiral promoters in the stereochemical setting steps. A final section will cover some of the recent applications of these methods to natural and unnatural product synthesis.

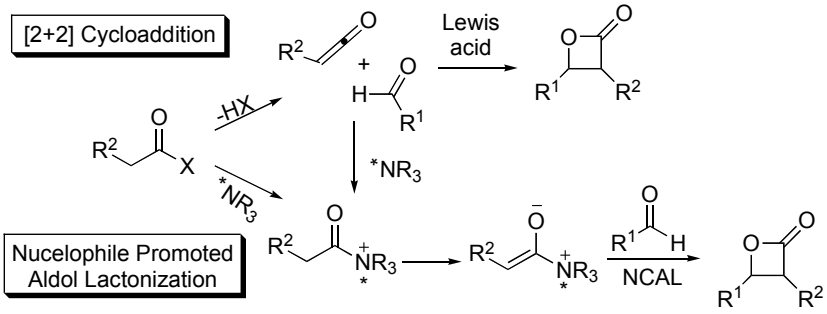
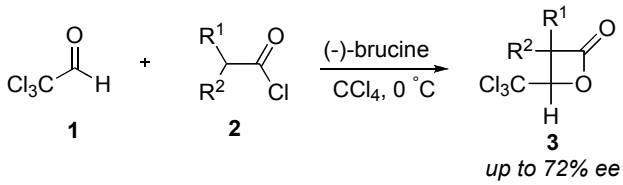


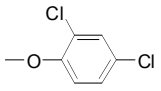
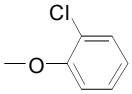
Figure 1. Convergent Routes Toward β-Lactones

2 LEWIS BASES AS CHIRAL, NUCLEOPHILIC PROMOTERS: DICHOTOMY OF [2+2] CYCLOADDITION AND ALDOL-LACTONIZATION PROCESSES

In 1966, Borrmann and Wegler[6] first synthesized optically active β-lactones via an aldol-lactonization process consisting of α-chlorinated aldehydes such as chloral **1**, a chiral Lewis base (nucleophilic promoter) (-)-Brucine and an acyl halide **2** through the intermediacy of an *in situ* generated 'ketene'. The β-lactones **3** were isolated in moderate to good yields with up to 72% ee (Table 1).

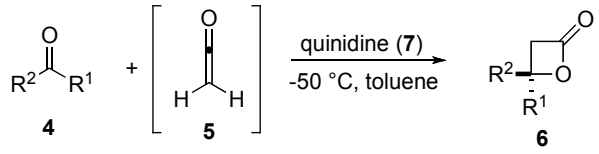
Table 1. Earliest Examples from Borrmann and Wegler[6]

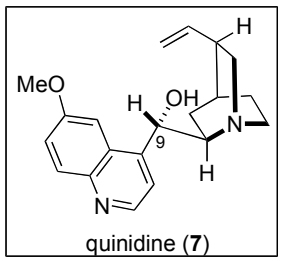


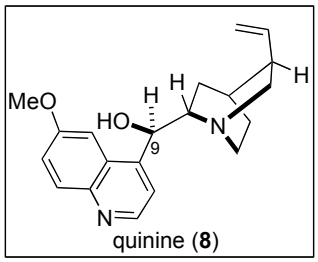
entry	R^1	R^2	% yield
1	H	H	69
2	Cl	Cl	39
3	H		63
4	H		45

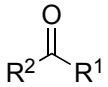
In 1982, Wynberg and Staring[7] building on the precedent of Borrmann and Wegler reported the use pseudo-enantiomeric cinchona alkaloids, specifically Quinidine (**7**) and Quinine (**8**), to catalyze the net [2+2] cycloaddition of chloral **4** and ketene **5.** Resulting β-(trichloromethyl)-β-propiolactone **6** were obtained in good yields and high enantiomeric excess. Wynberg also noted that with proper choice of catalyst (i.e. pseudo-enantiomer quinine) the enantiomeric β-lactone could be produced albeit in lower enantiomeric excess (Table 2).

Table 2. Wynberg's Seminal Studies[7]

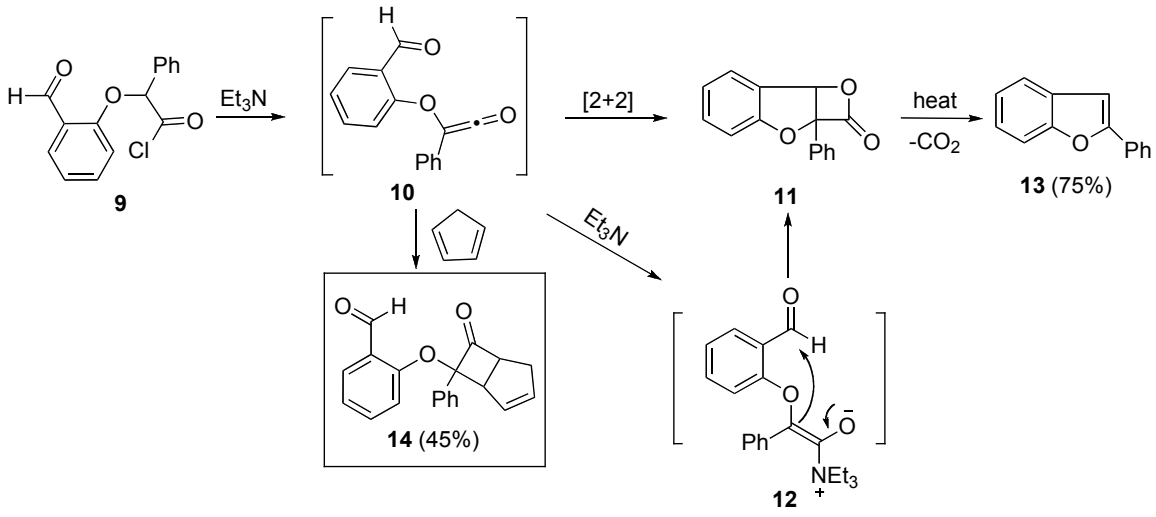






		% ee		
R^1	R^2	quinidine (**7**)	quinine (**8**)	% yield
CCl_3	H	98	76	89
CCl_2H	H	45	-	67
CCl_2CH_3	H	91	76	95
$CCl_2CH_2CH_3$	H	89	70	87
$CCl_2C_6H_5$	H	90	68	89
CCl_3	CH_3	94	85	72
CCl_3	C_6H_4Cl-*p*	90	65	68
CCl_3	$C_6H_4NO_2$-*p*	89	65	95

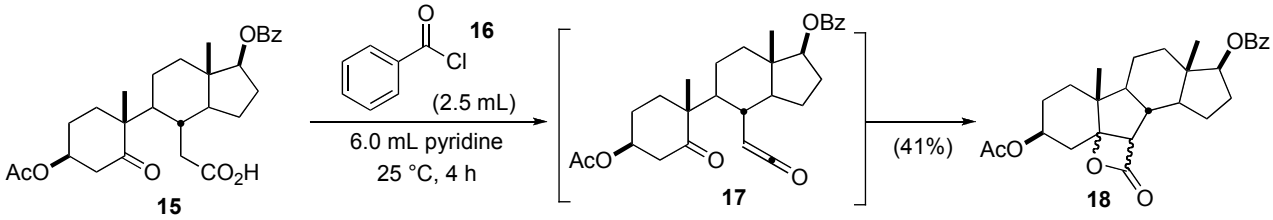
This important advance in the field of catalytic, asymmetric β-lactone synthesis reintroduced Cinchona Alkaloids as useful chiral reagents and intermediates for organic synthesis, which continues to stand as a benchmark in this area. In 1986, Brady employed ketene **10** in a presumed net [2+2] intramolecular cycloaddition to aldehydes to form substituted benzofurans **13** following the decarboxylation of unstable intermediate β-lactone **11** (Scheme 1).[8]



Scheme 1. Preparation of Benzofurans via Decarboxylation of β-Lactones

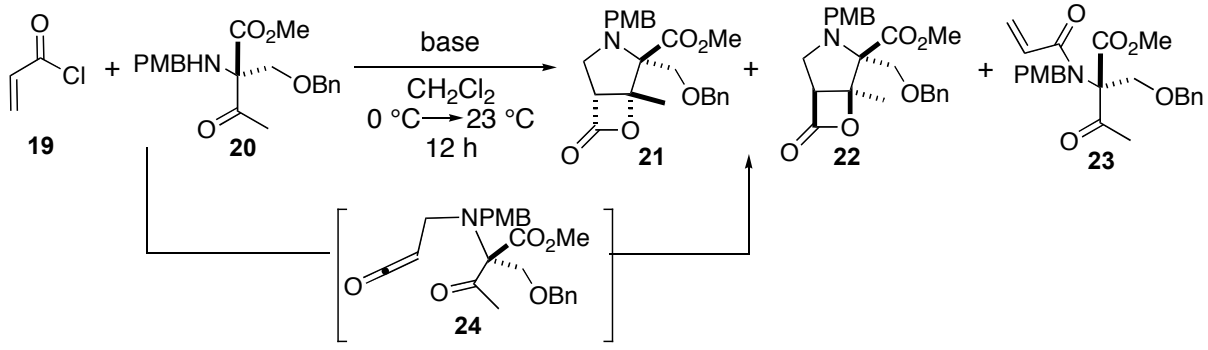
Although Brady presents this as an initial [2+2] cycloaddition, an alternate mechanism may be operative. Ketenes were never identified and excess triethylamine (TEA) could possibly lead to the formation of an ammonium enolate intermediate **12**, and subsequent aldol-lactonization process would deliver the presumed β-lactone **11**. Although Brady found evidence for a [2+2] cycloaddition from trapping the phenoxyketene **10** with cyclopentadiene, the product **14** was isolated in only 45% yield.

Another intriguingly similar and an inspiring result, dates back to the late 1950's when Boswell, Ourisson, Rull, and Dauben, Kagan and Jacques simultaneously published their early work on the isolation of a β-lactone intermediate **18** during preparation of steroid derivatives.[9] A net intramolecular [2+2] cycloaddition was envisioned between a ketone and *in situ* generated ketene **17** via the mixed anhydride derived from **15** (Scheme 2).



Scheme 2. Earliest example of a [2+2] Cycloaddition toward Steroidal β-Lactones

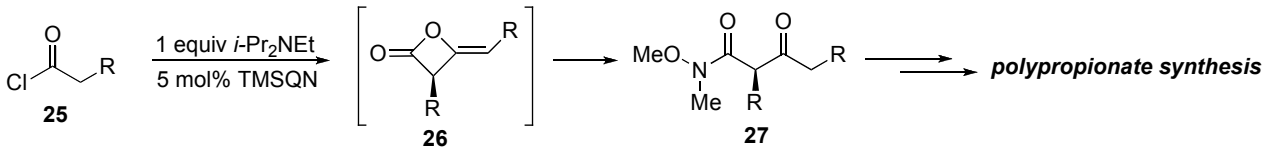
Most recently, Corey and co-workers reported a mechanistically distinct serendipitous discovery. This method allows construction of highly substituted β-lactone containing pyrrolidine rings (**21** and **22**) using a tandem Michael-[2+2] cycloaddition pathway via presumed intermediate **24** using excess pyridine (3.0 equiv) as the base.[10] Results indicate that the size of the base is crucial for executing this sequence of events toward the desired product over competitive formation of the acrylamide amide **23** (Scheme 3).



Base	2,6-lutidine	pyridine	Et_3N	2,6-di-*tert*-butylpyridine	tri isobutylamine
β-lactone **21**/ **22**	2.2	**8**	2.5	1	1
acrylamide **23**	1	1	1	**40**	14

Scheme 3. Tandem Michael-[2+2] Cycloaddition; Corey *et al.*[10]

The possibility of a simultaneous generation of an ammonium enolate intermediate in the aforementioned reactions cannot be completely disregarded since tertiary amines and nucleophilic i.e. Pyridine derivatives have shown to promote aldol-lactonization type pathways via an ammonium enolate (*vide infra*). A much more recent example of this process was illustrated by Calter in 1996 with cinchona alkaloid catalysts and their derivatives to catalyze a homodimerization reaction of *in situ* generated monosubstituted ketenes to obtain β-ketoamides **27** after ring opening of the intermediate alkylidene β-lactones **26** with high levels of enantioselection.



25 **26** **27**

Scheme 4. Calter's Homo Ketene Dimerization[11]

Given the enantioselectivity of the process, an aldol-lactonization process is clearly operative in forming **26** from **25** although alkylidene β-lactones **26** were never isolated in optically active form at that time. In 2003, Calter continuing with the ketene dimerizations reported the first examples of catalytic, asymmetric dimerization of *in situ* ketenes generated from acid halides.[11] Kinetic studies revealed that deprotonation of the acid halide was the rate determining step and that the aldol-lactonization was extremely fast based on NMR time scale.

2.1 CINCHONA ALKALOIDS CATALYSTS

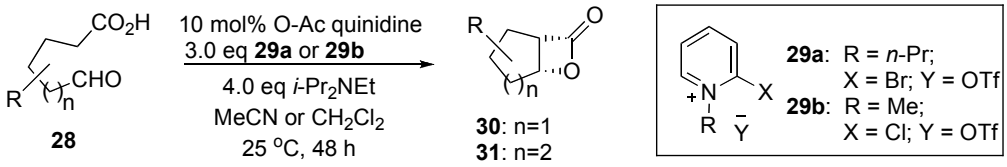
The venerable *cinchona* alkaloids are a family of natural products isolated from the bark of cinchona trees which are indigenous to the slopes of the Andes in South America.[12] Wynberg was the first to apply them in a catalytic net [2+2] cycloaddition toward optically active β-lactones. From a practical and generality standpoint, Wynberg's method requires the use of a ketene generator and highly electron deficient aldehydes and ketones requiring at least two α–chlorines for successful reactions. Although a good foundation was laid, the method was limited to activated carbonyl compounds and use of a ketene generator thus limiting its scope for practical applications. Because of these limitations, several other groups[13] including our own were prompted to expand and improve this promising advancement.

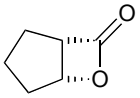
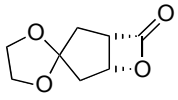
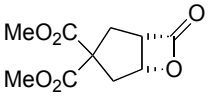
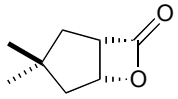
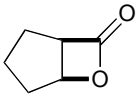
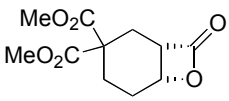
Noting the drawback in Wynberg's reaction protocol, conditions were developed to allow the *in situ* formation of ketene via the dehydrochlorination of acid chlorides. Our group was able to extend Wynberg's approach and demonstrate its efficiency to the prototypical α-chlorinated aldehydes to

produce optically active β-lactones. [14] Most importantly, use of non-activated aldehydes has been exploited in the first intramolecular nucleophile catalyzed aldol lactonization (NCAL).[15] Aldehyde-acid substrates **28** in conjunction with Mukaiyama's reagent or its modified derivatives **29** as the carboxylate activators instead of acid halides, and catalytic amounts of cinchona alkaloid derivatives delivered bicyclic β-lactones **30**/**31** with high enantiomeric excess and good yields (Table 3, Figure 2).

Based on precedented findings, either of the pseudoenantiomeric forms of, quinidine or quinine, could be employed in this protocol. Further studies indicated that although a variety of low energy conformations are operative,[16] only small variations in enantioselectivity were observed for several variations at the $\mathbf{C_9}$ position of quinidine.[17] The cinchona alkaloids have proven effective in converting aldehyde-acid to β-lactones, however their utility toward the corresponding keto-acid substrates were not as effective as pyridine derivatives (*vide infra*).

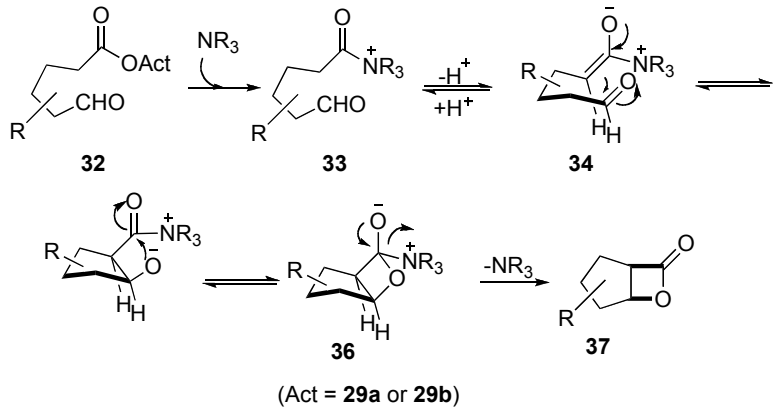
Table 3. Catalytic Asymmetric Intramolecular NCAL Reactions Leading to Bicyclic β-Lactones; Romo *et al.*[15]



entry	β-lactone	method[a]	% yield	% ee[b]	config.
1		**B**	82	92	1*R*, 2*S*[c]
2		**A**	74	92	3*R*, 4*S*[c]
3		**A**	74	91	1*R*, 2*S*[d]
4		**A**	45	90	1*R*, 2*S*[c]
5		**A**	51	86	1*S*, 2*R*[e]
6		**B**	76	98	1*R*, 2*S*[d]

[a] Method A: Pyridinium salt **29a** was employed in CH_2Cl_2 for 48 h. Method B: Pyridinium salt **29b** in CH_3CN for 108 h. [b] Enantiomeric excess was determined by chiral GC analysis. [c] Absolute configuration was assigned by reduction to the known diol and comparison of optical rotations. [d] Predicted based on analogy to that determined for β-lactones (entries 1 and 2). [e] *O*-Ac-Quinine used as the chiral catalyst.

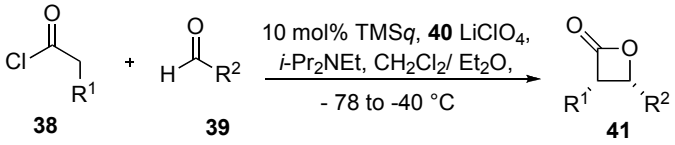
Figure 2. Proposed Nucleophile Catalyzed Aldol Lactonization Mechanism; Romo *et al.*[15]



2.2 CINCHONA ALKALOID/ LEWIS ACID COMBINATIONS

Calter reported rate enhancements in the homo ketene dimerizations when *O*-TMS protected quinine (TMS*q*) was used.[18] Nelson, combined TMS*q* with a mild Lewis acid, $LiClO_4$, to induce formation of *cis* β-lactones from acid halides **38** and aliphatic aldehydes **39**. Although somewhat mechanistically distinct, the acid chloride-aldehyde cyclocondensation (AAC) provides high enantio- and diastereoselection in the aldol-lactonization pathway leading to *cis* β-lactones.[19] After solvent optimization and manipulation of Lewis acid stoichiometry, an effective procedure for AAC reactions towards *cis* β-lactones **41** was developed (Table 4).

Table 4. Cinchona Alkaloid/ $LiClO_4$-Catalyzed AAC Reactions; Nelson *et al.*[19]

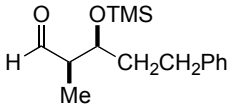
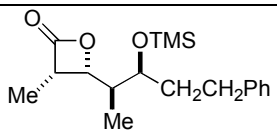
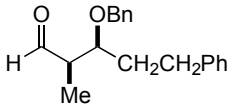
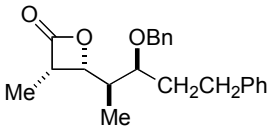
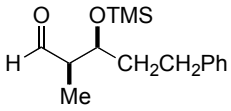
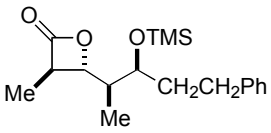
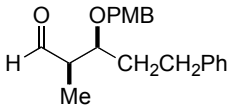
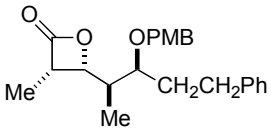


entry	R^1	R^2	%ee[a,b]	%de[c]	yield
1	H	$^cC_6H_{11}$	94[d]	-	85
2	H	CMe_3	96[e]	-	71
3	H	CH_2CH_2Ph	92	-	80
4	Me	$^cC_6H_{11}$	97[f]	>96	74
5	Me	$^oC_6H_4Cl$	>99	96	80

[a] Enantiomer ratios determined by chiral GLC or HPLC. [b] Minor enantiomer not observed for values >99%. [c] Diastereomer ratios determined by 1H NMR of crude product mixtures. [d] 90% ee using TMSq as the catalyst. [e] 95% ee using TMS*q* as the catalyst.[f] 96% ee using TMS*q* as the catalyst.

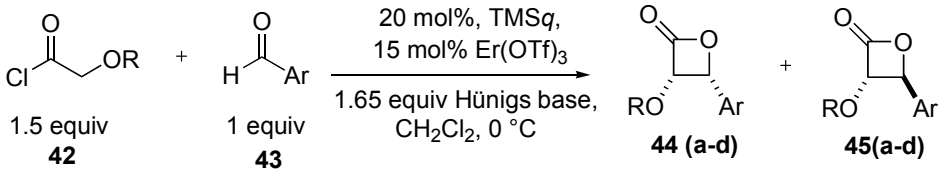
Subsequently, the Nelson group expanded their studies to include double diastereoselection with chiral aldehyde substrates providing access to *syn*- or *anti*- β-lactones. The mechanistic proposal was based upon AAC type reactions and provided access to various polypropionate substrates (Table 5).

Table 5. Matched and Mismatched AAC Reactions; Nelson *et al.*[19]

entry	aldehyde[a]	β-lactone[b]	% de (% yield)[c]
1			≥95 (83)
2			≥95 (78)
3			91 (81)
4			92 (81)

[a] Catalyst (10 mol %) TMS-quinine, entries 1 and 2; TMS-quinidine, entries 3 and 4. [b] Stereochemical asignments based on X-ray structure determinations of derivatives of entry 4's β-lactone and comparison of ^{1}H coupling constants. [c] Diastereomeric ratios determined by HPLC or ^{1}H-NMR analysis of crude reaction mixtures.

Table 6. Yields and Selectivities for the Formation of Aryl Substituted β-Lactones; Calter *et al.*[20]



products	**44**/**45**[a]	% yield of **44** [b] (% ee)[c]	% yield of **45** [b] (% ee)[c]
a: R = Ph, Ar = Ph	88:12	58 (>99)	nd
b: R = Ph, Ar = 4-bromophenyl	88:12	55 (>99)	nd
c: R = Ph, Ar = 3-chlorophenyl	92:8	88 (>99)	5 (nd)
d: R = Bn, Ar = 4-cyanophenyl	87:13	68 (>99)[d]	nd

[a] Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b] Yield of puified compound. [c] Determined by HPLC analysis of purified isomer. [d] Reaction performed with TMS-quinine as catalyst; the enantiomer of **44 d** was the major product.

Similar to Nelson's studies, Calter has used a combination of TMS*q* and achiral Lewis acids to catalyze the asymmetric condensation of aromatic aldehydes **43** with α-oxygenated acid chlorides **42**. They screened a variety of lanthanide and pseudolanthanide triflates which presumably co-catalyzed the addition of substituted ketenes to unactivated aldehydes (Table 6). In some cases, they were able to obtain the *trans* β-lactones **45**, which represented the first direct access to such systems with high diastereoselectivity.[20]

3 *N*-HETEROCYCLIC CARBENES (NHC'S)

A neutral bivalent carbon with an electronic sextet; carbenes have been the subject of numerous ground breaking discoveries in the field of synthetic organic chemistry. This is rightly so, since they were considered to be one of the most reactive intermediates known to chemists for a long time. Until very recently, due to their inherent reactivity they eluded isolation in the pure form, although their existence was documented in the late 19th and early 20th centuries by Buchner, Curtuis, Staudinger and Kupfer.[21] Discovery of a cyanide catalyzed Benzoin condensation by Woehler and Leibig as early as 1832 continued to pique the interest of organic chemists to understand its mechanistic basis.[22] On the basis of a mechanistic proposal put forward Lapworth[23] in 1903 followed by series discoveries namely: (i) the recognition of thiazolium salts as catalysts for benzoin condensation by Ugai *et al.*[24] in 1943; (ii) the area of nucleophilic acylation catalyzed by transketolase enzymes using co enzyme thiamine (Vitamin B_1) as a co-factor by Mizhura[25] in 1954, ultimately leading Breslow[26] to propose a mechanistic model in 1958 for the thiamine catalyzed benzoin condensation. The famous 'Breslow intermediate' opened new vistas for reactivity exploration and has remained a landmark inspiration in this area. Seminal contributions by Arduengo[27] (early 1990's) and Bertrand[28] (late 1980's), laid the foundation for preparation of isolable carbenes. Building on these past contributions and influential work of Stetter,[29] coupled with advent of new synthetic platforms for the preparation of asymmetric carbene catalysts, the area of NHC mediated catalysis has undoubtedly emerged as the new frontier in organometallic and most recently in organocatalysis. This can be evidenced by ever increasing number of reports in the past decade including books on the subject.[30]

3.1 BICYCLIC γ-BUTYROLACTONES VIA ALDOL-LACTONIZATIONS

3.1.1 CROSS CONDENSATION OF ENALS AND ALDEHYDES

One of the most interesting examples has been the simultaneous reports from the groups of Glorius and Bode in 2004, on the application of a^3-d^3 ümpolung (Seebach terminology[31]) to the cross-condensation of

enals and aldehydes to generate γ-butyrolactones.[32,33]

Commercially available bis-aryl (mesitylene) imidazolium chloride **45** has been the workhorse catalyst for development of various NHC mediated processes, and it was employed in both of the developmental studies since application of thiazolium salts resulted in only the competitive formation of benzoin products. Success of this manifold and others (*vide infra*) can partly be attributed to the favorable steric influence of the mesitylene CH_3's which in all probability (i) provides effective immunity to the Breslow intermediate toward self condensation in the event of attack on the aldehydic carbonyl.(ii) This reversible process thus suppresses the formation of Benzoin or Stetter type products and favors the generation of the more reactive, and steric free extended Breslow (homo enolate or dienolate) intermediate **48** which allows nucleophilic attack on the aldehyde partner to force the aldol lactonization pathway between an enal **46** and an aldehyde **49**. The mechanistic cycle involves attack of the *in situ* generated carbene **45** to an α, β-unsaturated aldehyde **46**. This zwitterinonic species then tautomerizes to species **48**, resulting in a homo enolate intermediate as a d^3- synthon for the subsequent nucleophilic capture of the aldehydic component to result in an activated acyl imidazolium aldolate **50** after tautomerization. Intramolecular lactonization with this activated species results in regeneration of the carbene catalyst. Various γ-butyrolactones **51** were synthesized by this reaction manifold in moderate to good yields with high preference for the *cis diastereomer* (Figure 3, Table 7 and 8).

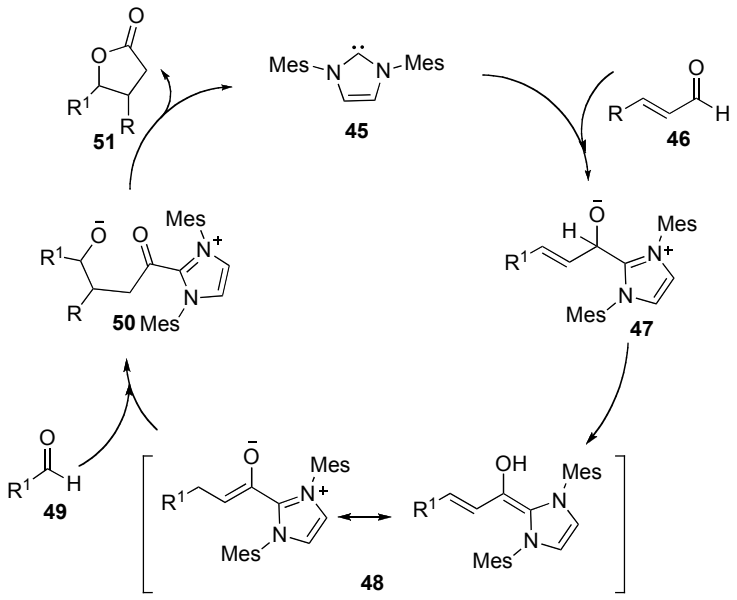
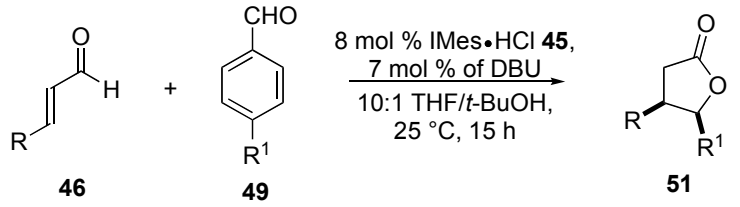


Figure 3. Proposed Catalytic Cycle with NHCs; Bode, *et al.*[33]

Table 7. Direct, Catalytic Annulations of Aldehydes and Enals; Bode, *et al.*[33]



46 49 51

entry[a]	R	R^1	*cis:trans*	%yield [c]
1	Ph	*p*-Br	4:1	79
2[b]	Ph	*p*-CO_2Me	5:1	87
3	4-$MeOC_6H_4$	*p*-Br	4:1	76
4[c]	4-$MeOC_6H_4$	H	4:1	65
5[b,d]	TIPSC≡C	*p*-CO_2Me	3:1	41
6	TIPSC≡C	TIPSC≡CH=CH	5:1	83
7[c]	1-napthyl	1-napthyl-CH=CH	5:1	67

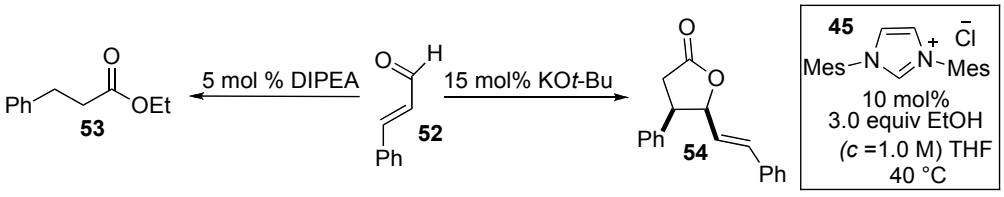
[a] Reaction conditions: 1.0 mmol enal, 0.5 M in 10:1 THF/ *t*-BuOH at 25 °C for 15 h, 8 mol % IMes•HCl, 7 mol % DBU, 2 equiv of aldehyde. [b] Concentration = 0.1 M. [c] Performed with 15 mol % IMes•HCl, 14 mol % DBU. [d] The enal was added over 3 h.

Table 8. Direct, Catalytic Annulations of Aldehydes and Enals[a]; Glorius, *et al.*[32]

entry	R	R^1	*cis:trans*	%yield
1	*p*-Cl-Ph	H	81:19	53
2	*p*-Br-Ph	H	80:20	49
3	*p*-CO_2Me	H	79:21	70
4	*p*-CF_3-Ph	H	77:23	44
5	*p*-F-Ph	H	78:22	52
6	*m*-Cl-Ph	H	79:21	61
7	*p*-Br-Ph	H	79:21	60

[a] See Scheme in Table 7 for details.

Bode and co workers have also shown another interesting aspect of these reactions by investigating the effect of base during the development of enal aldehyde cross condensation reactions with cinnamaldehyde **52**. Weaker bases such as Hünig's base, favor protonation of the homoenolate which predominantly generates the activated carboxylic acid which is quenched by EtOH to generate ethyl ester **53**; while a stronger base, KO*t*Bu, alters the course of the reaction toward an aldol-lactonization pathway to generate the γ-lactone **54** (Scheme 5).

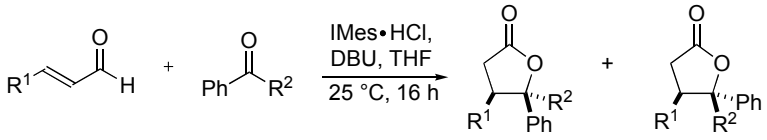


Scheme 5. Effect of Base on Enal Homo Dimerization; Bode, *et al.*[33]

3.1.2 CROSS CONDENSATION OF ENALS AND KETONES

Glorius also studied the formation of γ-lactones **57** bearing quaternary carbon centers using activated ketones **56** and aliphatic enals **55** as homoenolate equivalents in conjunction with the bulky IMes•HCl as the precatalyst (Table 9). Identical studies with α-methyl enals (Table 10, entries 9-11) and other activated ketones (entries 1-8) gave moderate diastereoselectivity with different carbene precatalysts (Figure 4), significantly expanding the scope of this process.

Table 9. Reaction of Alkyl Substituted α,β-Unsaturated Aldehydes with Ketones [a]; Glorius, *et al.*[32]



55 **56** **57a** **57b**

entry	R^1	R^2	yield (%)	ratio (**57a**/**57b**)[b]
1	Me	CF_3	82	81:19[c]
2	Pr	CF_3	90	84:16[c]
3	*i*-Pr	CF_3	66	93:7[d]
4	Me	CO_2Me	87	68:32[c]
5[e]	Pr	CO_2Me	71	67:33[c]
6[f]	*i*-Pr	CO_2Me	72	65:35[d]

[a] General reaction conditions: IMes•HCl (0.05 mmol), DBU (0.05 mmol), α, β-unsaturated aldehyde (0.5 mmol), ketone (1.0 mmol), THF (2.5 mL), r.t., 16 h. Yield given for the isolated mixture of diastereomers. [b] Determined by GC-MS. [c] **57a** = *like*, **57b** = *unlike*. [d] **57a** = *unlike*, **57b** = *like*. [e] DBU (0.25 mmol), 50 °C. [f] DBU (0.25 mmol)

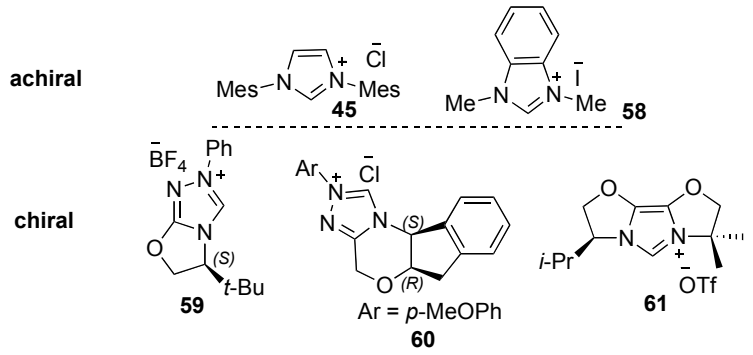
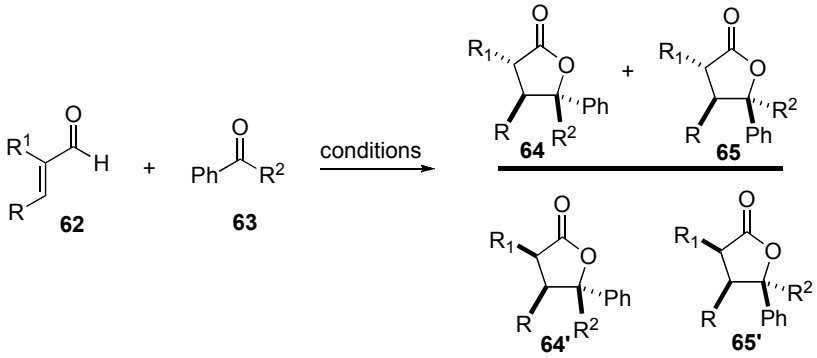


Figure 4. Carbene Precatalysts

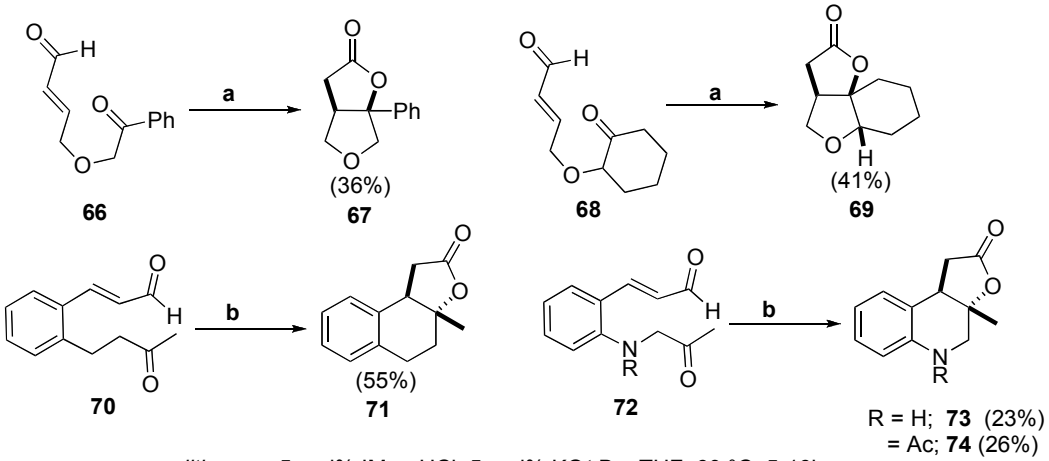
Table 10. Scope of the Enal-Ketone Cross Condensation; Glorius, *et al.*[32]



entry	R	R^1	R^2	precatalyst	yield (%)	d.r
1 [a]	Ph	H	CF_3	**45**	84	66:34
2 [a]	Ph	H	CF_3	**61**	70	74:26
3 [a]	(*m*-MeO)Ph	H	CF_3	**45**	92	66:34
4 [a]	(*m*-Me_2N)-Ph	H	CF_3	**45**	74	70:30
5 [b]	Ph	H	CO_2Me	**45**	78	50:50
6 [b]	(*m*-MeO)Ph	H	CO_2Me	**45**	94	47:53
7 [b]	(*m*-Me_2N)-Ph	H	CO_2Me	**45**	98	44:56
8 [c]	Ph	H	COMe	**45**	55	58:42
9 [d]	Ph	Me	CF_3	**61**	83	62:30:6:2
10 [d]	p-ClPh	Me	CF_3	**61**	71	63:29:6:2
11 [d]	PhCH=CH	Me	CF_3	**61**	82	32:66:2:0

[a] 10 mol%, KO*t*-Bu, THF, 23 °C, 16 h. [b] 5 mol% DBU, THF, 23 °C, 16h. [c] 5 mol% DBU, THF, 60 °C, 16h. [d] 5 mol% DBU, DMF, 75 °C, 16h

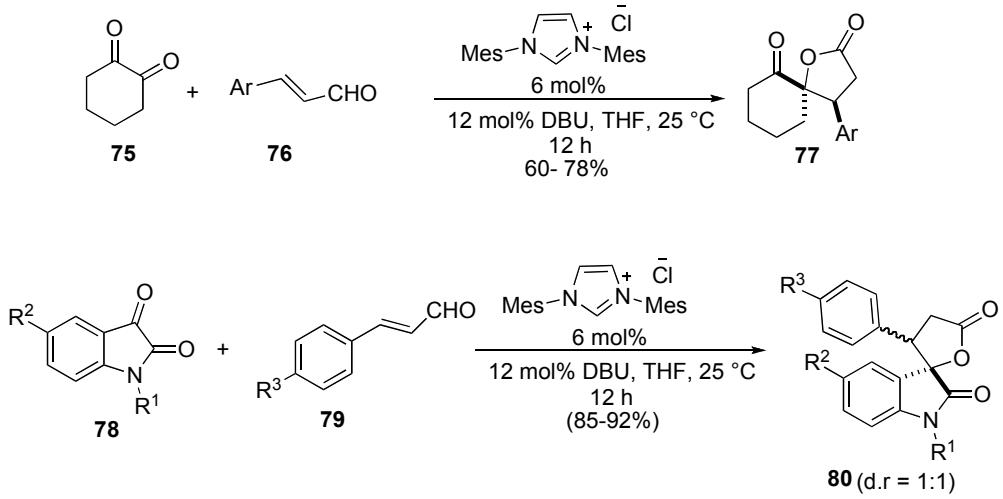
Additionally, Glorius reported an intramolecular variant of this reaction that provided straightforward access to novel heterocyclic sytems containing γ-lactones in moderate yields (Scheme 6). However, no asymmetric variants of the intramolecular annulation has been reported thus far by this group.



Scheme 6. Intramolecular Enal-Aldehyde Cross Condensation; Glorius, *et al.*[32(b)]

3.1.3 CROSS CONDENSATION OF ENALS AND 1, 2-DIONES

In 2005, Nair and co workers reported the highly stereoselective synthesis of spiro γ butyrolactones from a reaction between 1, 2-cyclohexanedione **75** and various α, β unsaturated aldehydes **76** via homoenolate aldol lactonization pathway. Although the reaction proceeded sluggishly, acceptable yields (60-78%) of spiro lactones **77** were obtained. Interestingly, extension of this methodology toward substituted isatin derivatives **78,** which provided spiro annulated oxindoles **80** in excellent yields (85-92%), resulted in no preferential diastereoselection (Scheme 7).[34]



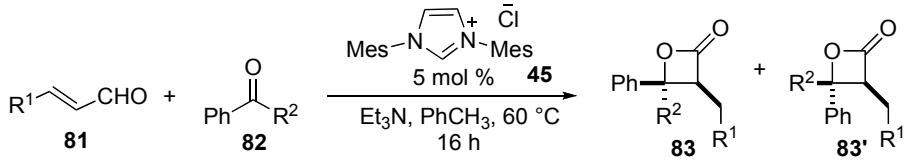
Scheme 7. Cross Condensation of 1, 2 Diones with Aromatic Enals; Nair, *et al.*[34]

3.2 BICYCLIC β-LACTONES VIA ALDOL-LACTONIZATIONS

3.2.1 CROSS CONDENSATION OF ENALS AND KETONES

Recently, during their course of studies toward cross condensation of enals **81** and ketones **82** to deliver γ-lactones, Glorius and co-workers observed formation of β-lactones **83/83'** as a by product under heating conditions using catalytic amounts of IMes•HCl. Et_3N was found to be a moderately effective auxillary base for the transformation of trifluoro acetophenone. Whereas DBU gave only 22% of the corresponding β-lactone with phenmethyl glyoxylate (Table 11, Figure 5).

Table 11. β-Lactone Formation via Conjugate Ümpolung[a]; Glorius, *et al.*[32]



entry	R^1	R^2	% yield	ratio[b]
1	Me	CF_3	34	60:40
2	Pr	CF_3	45	55:45
3	*i*-Pr	CF_3	48	62:38
4	Ph	CF_3	30	70:30
5	*i*-Pr	CO_2Me	22[c]	71:29

[a] General reaction conditions: IMes•HCl (0.05 mmol), TEA (2.0 mmol), toluene (2.5 mL), α, *β*-unsaturated aldehyde (1.0 mmol), ketone (1.0 mmol), 60 °C, 16 h. [b] Determined by GC-MS. [c] IMes•HCl (0.1 mmol), DBU (0.1 mmol)

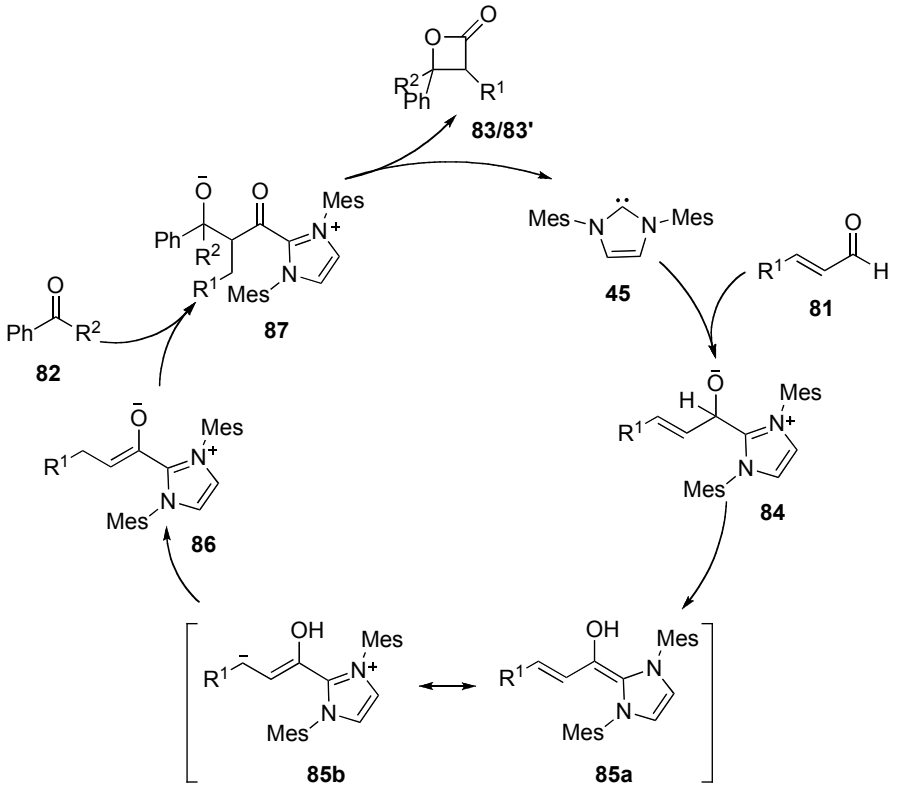
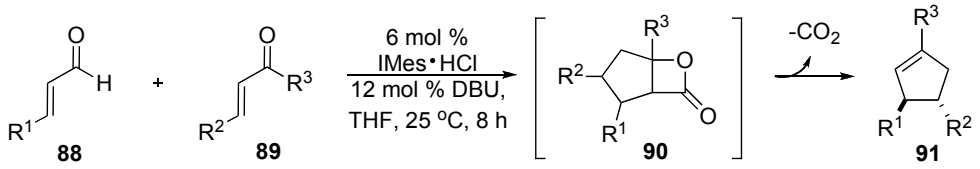


Figure 5. Proposed Catalytic Cycle; Glorius, *et al.*[32]

3.2.2 CROSS CONDENSATION OF ENALS AND α, β UNSATURATED KETONES

Nair and co-workers also reported a rather intriguing result during the course of their discovery of a new (NHC) IMes catalyzed cyclopentanulation sequence (Scheme 8). The combination of homo enolate equivalent **88** and an enone **89** did not result in the formation of the anticipated 1,3 diketone, but instead lead to the formation of the an unstable β-lactone **90,** which undergoes a retro [2+2] to the decarboxylated cyclopentene **91**.[35] The mechanistic proposal invokes intermediacy of β-lactone, as evidenced by an IR

stretching frequency at 1822 cm^{-1} from aliquot samples of the reaction (Figure 6, Table 12).



Scheme 8. Proposed β–Lactone Intermediate in a Cyclopentene Annulation; Nair, *et al.*[35]

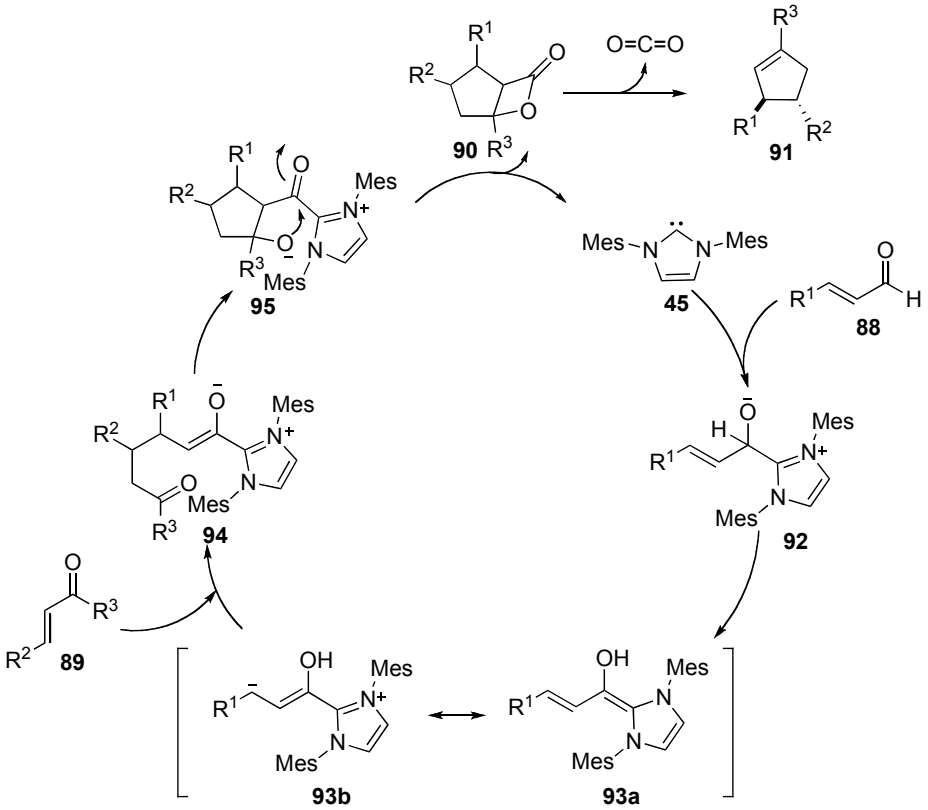


Figure 6. Proposed Catalytic Cycle; Nair, *et al.*[35]

Table 12. Scope of the Cyclopentannulation Sequence[a]

entry	R^1	R^2	R^3	% yield
1	(*o*-MeO) Ph	2-thienyl	(*p*-Cl)Ph	88
2	Ph	1-napthyl	(*p*-Cl)Ph	76
3	(*p*-MeO) Ph	(*p*-CN)Ph	(*p*-Me)Ph	85
4	(*p*-MeO) Ph	Ph	(*p*-Cl)Ph	76
5	(*p*-MeO) Ph	Ph	Ph	88
6	Ph	Ph	Ph	78
7	(*p*-MeO) Ph	(*p*-F)Ph	(*p*-Cl)Ph	78
8	(*p*-MeO) Ph	(*p*-Cl)Ph	(*p*-Cl)Ph	76
9	(*p*-MeO) Ph	2-thienyl	Ph	86
10	(*p*-MeO) Ph	2-furyl	(*p*-Cl)Ph	70
11	(*p*-MeO) Ph	Me	(*p*-Cl)Ph	55
12	Me	2-thienyl	(*p*-Cl)Ph	73

[a] See Scheme 8 for details.

Bode and co-workers have proposed an alternate mechanism for Nair's cyclopentannulation sequence.[36] Mechanistic studies provide evidence for invoking a reversible benzoin type condensation to result in anionic species **98,** which undergoes an NHC Oxy-Cope event to produce **99,** which is in accordance to Nair's findings, that undergoes tautomerization-aldol reaction to produce aldolate **100.** Upon lactonization and decarboxylation of **100** produces *cis* as opposed to *trans* cyclopentenes **102** using 4-oxo enoates **97** (Figure 7, Table 13).

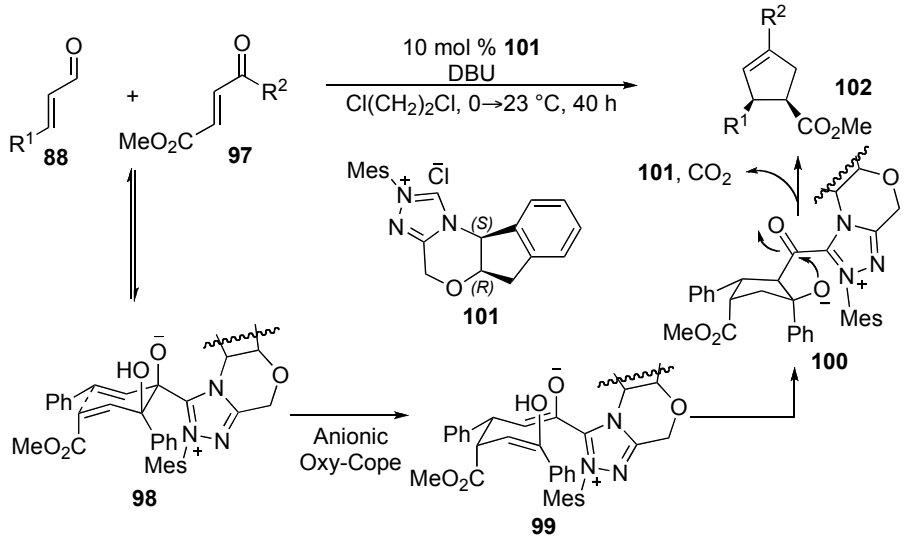


Figure 7. Proposed Anionic-Oxy Cope Manifold; Bode, *et al.*[33]

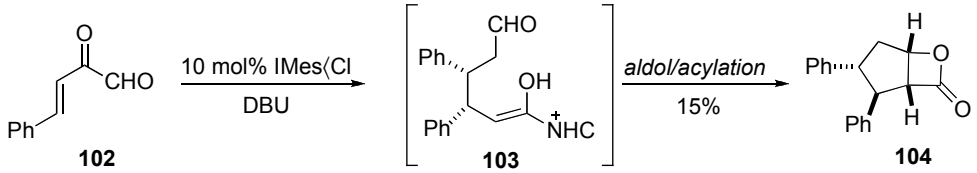
Table 13. Scope of Bode's Cyclopentannulation Sequence

entry	R^1	R^2	% yield[a]	*cis:trans*[b]	%ee[c]
1	Ph	Ph	78	11:1	99(68)[d]
2[e]	Ph	(*p*-MeO) Ph	58	5:1	99(68)[d]
3	Ph	(*p*-Br) Ph	50	11:1	99(79)[d]
4	Ph	2-furyl	93	> 20:1	98
5	(*p*-Br) Ph	Ph	58	6:1	99(67)[d]
6	(*p*-CF_3) Ph	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]

[a] Isolated yield. [b] Approximate ratio of cis:trans diastereomers. [c] HPLC analysis. [d] % e.e of the minor diastereomer. [e] Et ester instead of Me ester of the 4-oxoenoate.

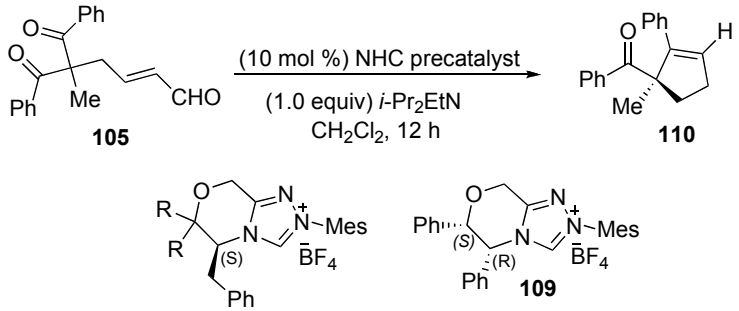
Further studies have led them to claim that chalcone susbtrates as in Nair's report under go an identical sequence of events under the influence of a chair Oxy-Cope transition state with the *s-trans* configuration to result in *trans* configured products. Whereas 4-oxoenoates maintain *s-cis* configuration in a boat-like Oxy-Cope transition state to produce *cis* cyclopentenes.

Scheidt and co-workers later expanded upon their own unpublished result and that of Glorius, Bode, and Nair toward a similar cyclopentannulation (Scheme 9). They reported that several triazolium salts (**106**-**109**) were efficient in the enantioselective formation of cyclopentene **110** from *meso* 1,3-diketone **105** (Table 14).[37]



Scheme 9. Homo Dimerization of Cinnamaldehdye; Scheidt, *et al.*[37]

Table 14. Optimization of Cyclopentannulation **105→110**



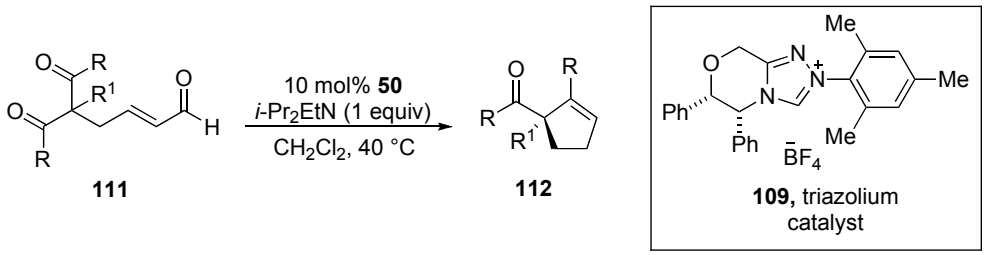
entry	temperature (°C)	NHC precat	% yield	% ee
1	23	**106**	47	-83
2	23	**107**	38	-76
3	23	**108**	45	51
4	23	**109**	40	94
5[a]	23	**109**	66	94
6[a]	40	**109**	80	93
7[a,b]	40	**109**	70	93

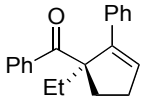
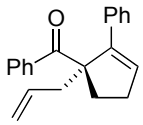
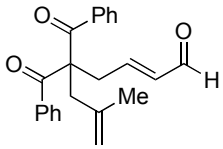
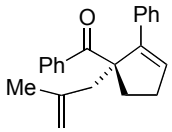
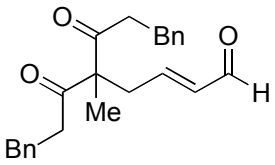
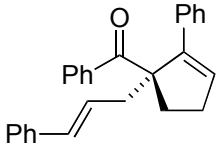
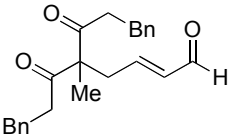
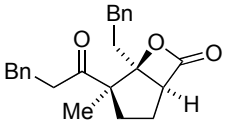
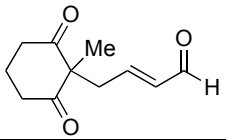
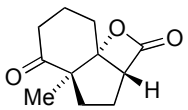
[a] careful exclusion of oxygen. [b] 5 mol% **109**.

Optimized conditions were successfully translated to the enantioselective desymmetrization of various 1,3 diketones **111** using triazolium NHC precursor **109** to produce cyclopentenes (Table 15, entries 1-4) and intermediate β-lactones (entries 5 and 6). The products were obtained in accepatable yields (51-73 %) and

good to high enantioselectivities (82-96%). A model invoking internal hydrogen bonding to alleviate non-bonding interactions has also been proposed to rationalize the high stereoinduction observed.

Table 15. Susbtrate Scope of Scheidt's Enantioselective Desymmetrization[37]



entry	R	R^1	cyclopentene	yield (%)	ee (%)[a]
1	Ph	Et		73	90
2	Ph	allyl		70	83
3				69	83
4[b]				64	82
5[b]				65[c]	93
6[b]				51[c]	96

[a] Determined by HPLC Chiracel AD-H. [b] 20 mol % of the triazolium catalyst. [c] Diastereomeric ratio = 20:1. Relative stereochemistry of β-lactones determined by nOe or X-ray crystallography.

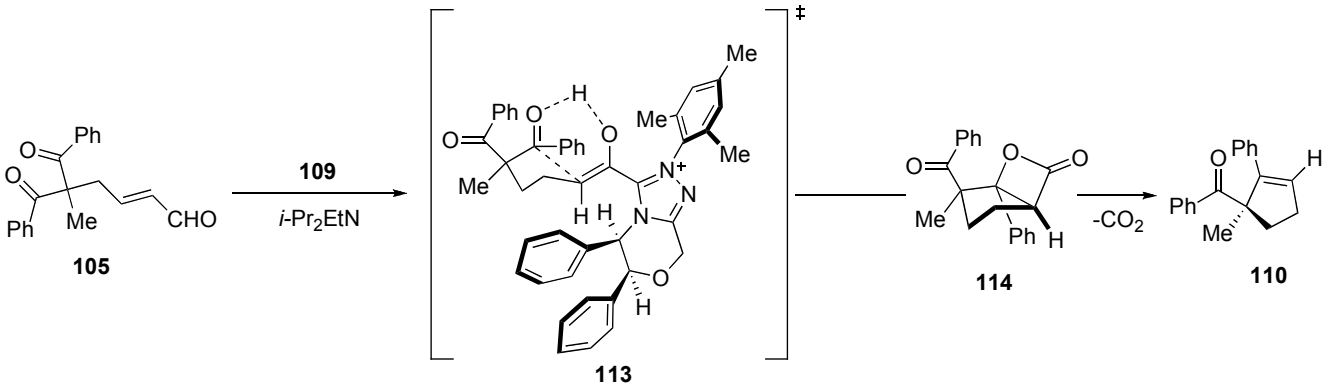


Figure 8. Proposed Model for Stereoinduction; Scheidt, *et al.*[37]

They favor a catalytic cycle similar to one that proposed by Nair involving β-protonation of homoenolate **115** to provide enol **116** which undergoes aldol-acylation (*i.e.* aldol lactonization) to give β-lactone **114** that is either isolated or undergoes decarboxylation to produce cyclopentene **110** (Figure 9).

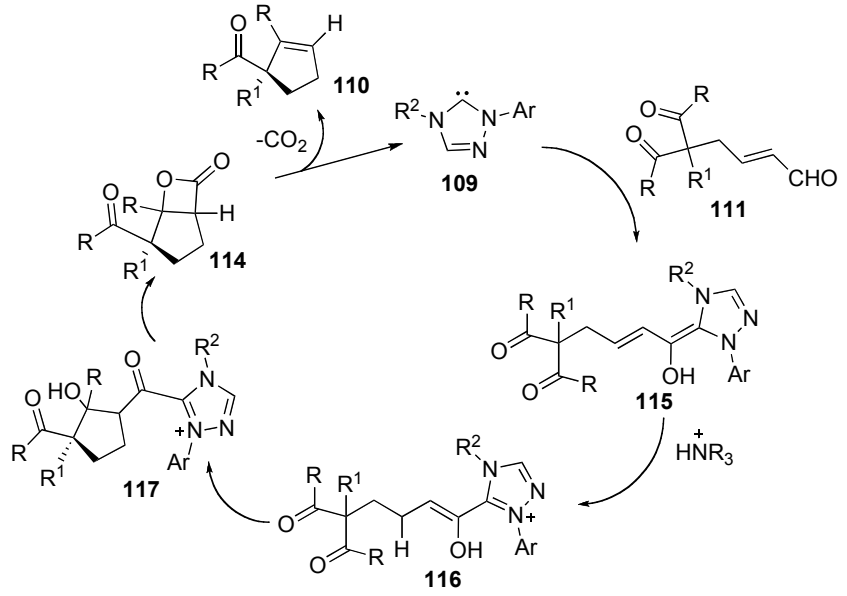


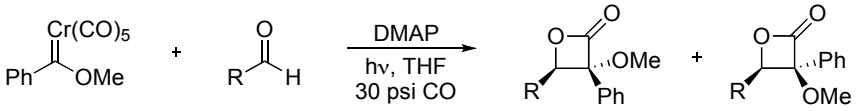
Figure 9. Proposed Catalytic Cycle for β-Lactone and Cyclopentene Formation; Scheidt, *et al.*[37]

4 PYRIDINE DERIVATIVES

Introduction of 4-(*N,N'*-dimethyl)amino pyridine by Litvinenko and Kirichenko[38] in 1967 and further studies by Steglich and Höfle[39] thereafter, have dramatically altered the scope of acylation chemistry being the subject of many exhaustive reviews.[40] Zipse's contribution toward understanding the stabilization achieved during 'acyl pyridinium' formation and hence the efficiency of the catalyst for acylation in general, via computational calculations, provides a very useful guide for planning new catalyst design.[41]

Although, pyridine has been presumed to serve as a general base in many reactions proceeding via a net [2+2] cycloaddition pathway involving ketenes (*vide supra*, Sec. 2), one early example that provides some credence as to the role of pyridine derivatives in a net [2+2] cycloaddition, actually aldol-lactonization pathway, comes from the work of Merlic *et al.*[42] Electron-rich aldehydes **119** were reacted with ketenes derived from 'CO' trapping of chromium carbene complexes **118** to yield the β-lactones **120** in presence of a lewis base (nucleophile) (Table 16). A number of catalysts were screened including cinchona-like alkaloids, which have been known to catalyze such reactions with activated aldehydes. Most of the Lewis bases failed except for diazabicycloundecane (DBU), diazabicyclooctane (DABCO), and DMAP, which delivered the highest yields and the best diastereoselectivities.

Table 16. Results of DMAP Ketene-Aldehyde Aldol-Lactonization; Merlic, *et al.*[42]

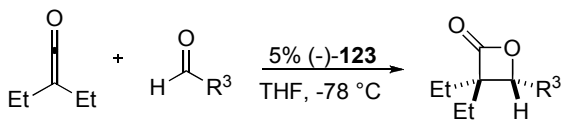


118 **119** **120**(syn) **120'**(anti)

entry	aldehyde	product	% yield **120** (*syn*/*anti*)
1	propionaldehyde	**120a/120a'**	53 (15/1)
2	acetaldehyde	**120b/120b'**	55 (8/1)
3	*n*-butyraldehyde	**120c/120c'**	43 (23/1)
4	isobutyraldehyde	**120d/120d'**	35 (4/1)
5	benzaldehyde	**120e/120e'**	33 (15/1)

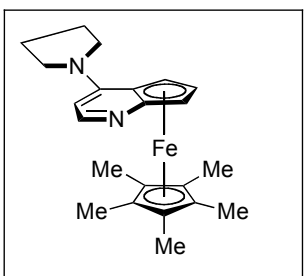
Fu and co-workers explored the use of planar-chiral derivatives of DMAP as nucleophilic catalysts for enantioselective processes.[43] This idea was then applied towards C-acylation processes leading to the observation that several pyridine derivatives catalyze the asymmetric synthesis of β-lactones from disubstituted ketenes. Chiral 4-pyrrolidinopyridine (PPY) derivative **123**, gave the best enantioselectivity, which is the first catalyst to date to promote the synthesis of α,α-disubstituted β-lactones **124** from disubstitued ketenes **121** (Table 17).

Table 17. Catalytic Asymmetric Synthesis of β-Lactones by Cycloadditions of Disubstituted Ketenes with Aldehydes; Fu, *et al.*[43]



121 **122** **124**

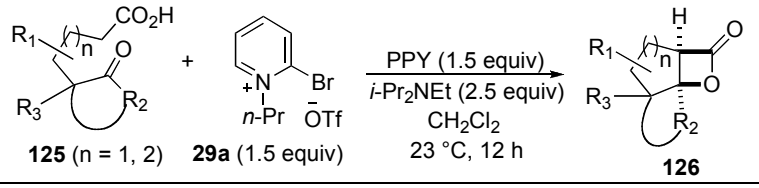
entry	R^3	ee (%)[a]	yield (%)[a]
1	Ph	91	92
2	2-naphthyl	89	77
3	4-$(CF_3)C_6H_4$	80	74
4	4-$(MeCO)C_6H_4$	81	76
5	4-MeC_6H_4	89	67

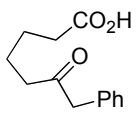
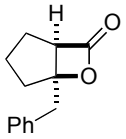
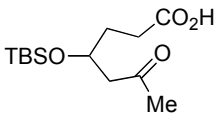
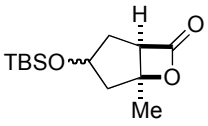
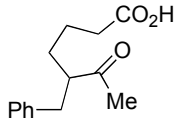
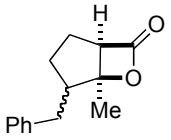
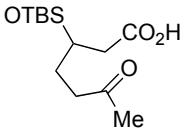
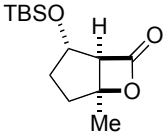
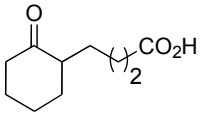
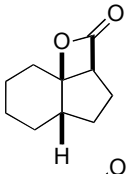
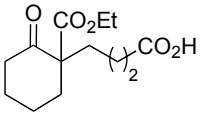
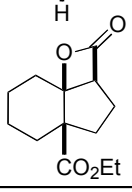


123
Fu's chiral PPY derivative

Romo and co-workers recently developed a bis-cyclization protocol to synthesize bicyclic and tricyclic β-lactones **126** starting with more tractable keto-acids **125** building on their previous work with acid aldehydes (see Section 2.1 above). 4-Pyrrolopyridine (PPY) was found to be an effective stoichiometric promoter of this transfomation in conjunction with modified Mukaiyama's reagent **29a** and *N-N'* diisopropyl ethyl amine as an auxillary base (Table 18).

Table 18. Nucleophile Promoted Bis-cyclization of Keto-Acids; Romo, *et al.*[44]



entry	keto acid	β-lactone[a]	% yield[b]	dr[d]
1			58	-
2			51	2:1
3			75[c]	~1:1
4			67	>19:1
5			61	>19:1
6			70	>19:1

[a] Yields refer to isolated (silica gel), purified product. [b] 1.5 equiv PPY, 1.5 equiv **29a**, and 2.5 equiv Hünig's base were employed. [c] Relative stereochemical assignment of bicyclic β-lactones was based on either strain arguments, nOe, X-ray analysis, or coupling constant analysis of derivatives.

An aldol-lactonization pathway was proposed since high diastereoselection (dr, >19:1) with β-substituted keto-acid substrates (entry 4) points to avoidance of $A^{1,3}$ strain during the transition state in a nucleophile promoted process. However, a [2+2] cycloaddition pathway would be expected to lead to low or no

diastereoselectivity (Figure 10).[44] Furthermore, initial studies with dimethylamino pyridine (DMAP) (1.0 equiv) using (slow addition of substrate over 1 h via syringe pump, 0.05 M final concentration, 25 °C) and the modified Mukaiyama reagent led to a >5-fold increase in conversion of β-lactone (19%) over pyridine. Further conversion (48%) was observed with the more nucleophilic promoter, 4-pyrrolidino pyridine (PPY) (1.0 equiv). However, under the identical conditions, pyridine, DABCO, DBU, and phosphorus nucleophiles (PPh_3 and PBu_3) provided no β-lactone. Importantly, use of only Hünig's base gave no β-lactone, suggestive of a nucleophile-promoted process. Attempts to locate fleeting ketene intermediates via *in situ* IR spectroscopy were unsuccessful, however this does not rule out their existence.

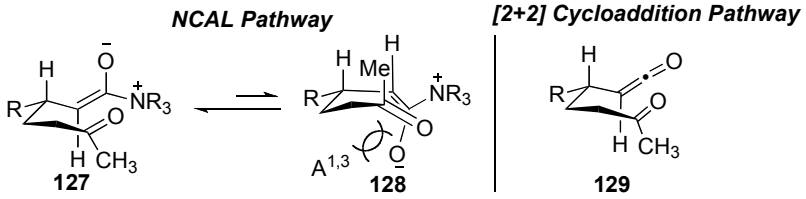


Figure 10. Rationale for High Diastereoselection in β-Substituted Keto-Acids

5 APPLICATIONS

β-Lactones are highly versatile scaffolds, are found in a number of bioactive natural products, and are also useful intermediates toward the synthesis of natural products.[45] Over the past 10 years, there has been an increase in the application of β-lactones as intermediates and especially those derived from an organocatalyzed aldol-lactonization pathway. Some recent examples of applications of β-lactones, derived from an aldol-lactonization manifold, to natural product synthesis are shown below (Figure 11).[46]

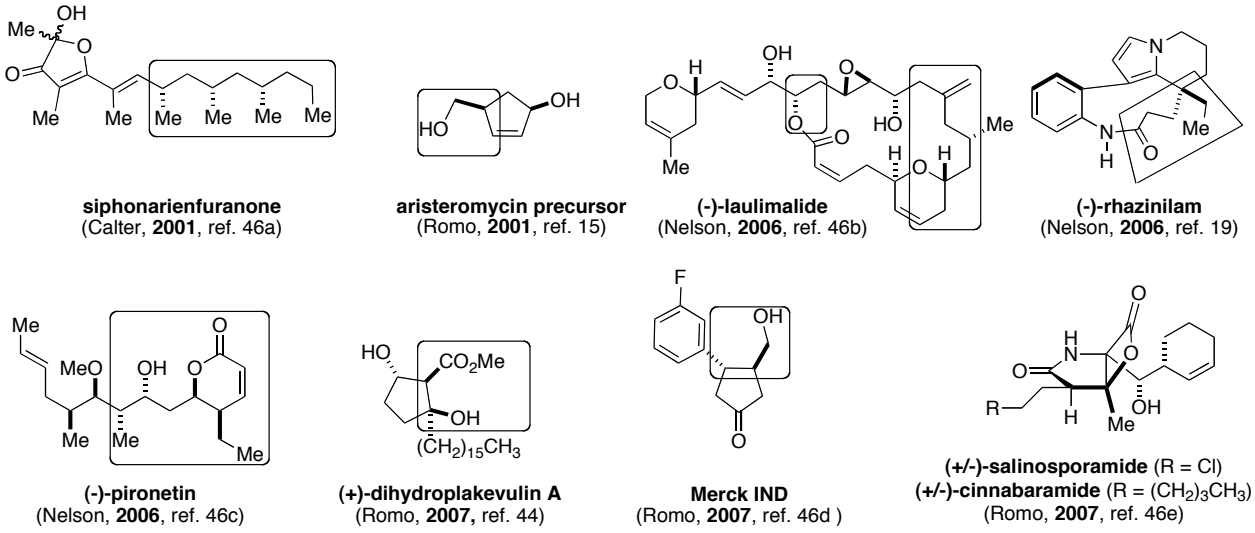


Figure 11. Natural Products or Intermediates Derived from β-Lactones Prepared via an Organocatalyzed Aldol-Lactonization-Type Manifold (Fragments Derived from β-Lactones are Boxed)

6 SUMMARY AND OUTLOOK

Both inter- and intramolecular β- and more recently γ-aldol-lactonizations can now be promoted by a variety of organocatalysts that proceed by various reaction manifolds. Utilizing different types of catalysts and under varied conditions, a particular absolute stereochemistry can now be achieved, however further improvements are clearly needed. Whether it be *cinchona* alkaloids, pyridine derivatives or the more recent *N*-heterocyclic carbenes, methods to accomplish aldol-lactonizations are proving to be diverse and highly preparatively useful. The synthetic community will require further improvements in these methods as our synthetic targets become more complex and the need for efficiency for reaching these targets in a concise manner continues to increase. While our current state of the art in methodology development, toward β- and γ-lactones employing organocatalysis has increased by leaps and bounds in the past two decades, this is necessary as these heterocycles continue to find wider application and utility in organic synthesis, especially inherently strained β-lactones, and this will undoubtedly continue to increase in the future.

ADDENDUM: RECENT REPORTS ADDED IN PROOF

Romo and coworkers recently reported additional ketoacids derived from readily available dione acids that were found to be excellent substrates for diastereoselective nucleophile promoted bis-cylization with 4-PPY leading to tricyclic β-lactones **130a-e** (Figure 12).[47] Subsequent dyotropic rearrangements of these rigid β-lactones provided a complexity generating process for the construction of unique spirocyclic γ-lactones.

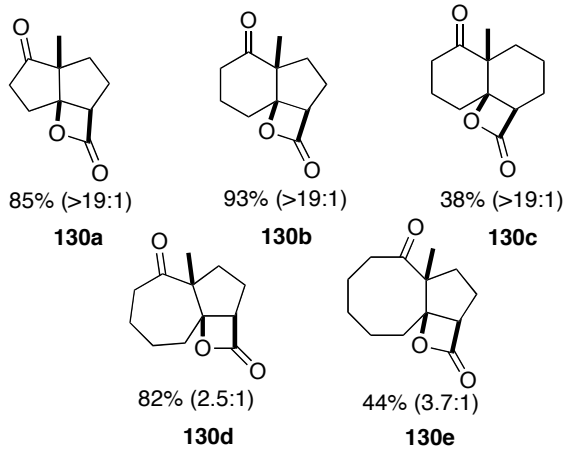


Figure 12. Tricyclic β-Lactones Dervied from 1,3-Dione acids, Romo *et al.* [47]

Furthermore, the hypothesis that the bis-cyclization process with ketoacid substrates proceeds through the intermediacy of an ammonium enolate (*cf.* **132**) leading to an aldol-lactonization pathway was proven

experimentally by use of stoichiometric (R)-tetramisole•HCl (**133**) under identical reaction conditions which provided β-lactone (-)-**130b** in 97% ee, a result incompatible with a [2+2] cycloaddition pathway (Figure 13).

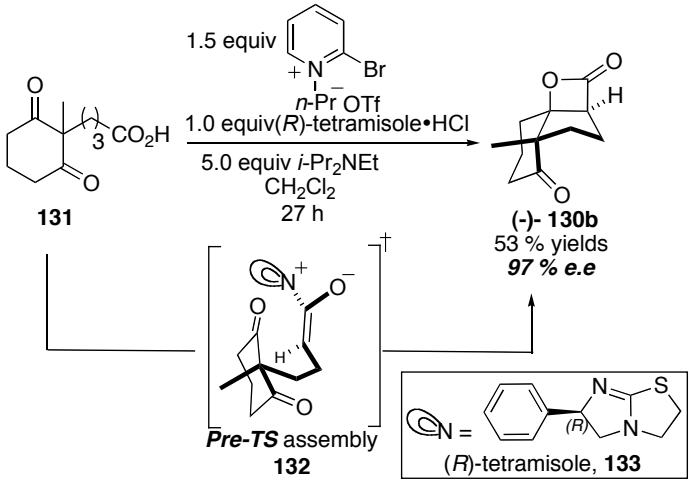


Figure13. Enantioselective Bis-cyclization of 1,3-Dione Acid **131**, *Romo et al.*[47]

Peters and coworkers recently described a bifunctional catalyst based on an Al-SALEN backbone **137** that was proposed to provide two sites for binding of reactants via (i) generation of an octahedral complex upon binding of an aliphatic aldehyde with the Al center and (ii) and formation of an aprotic contact ion pair with the pendant pyridinium ring upon formation of a discrete bromo enolate (Figure 14).[48] This provides a stereocomplimentary route to methods developed by Nelson[19] providing *trans*-β-lactones **136**, via a net [2+2] cyclocondensation (Scheme 10, Table 19).

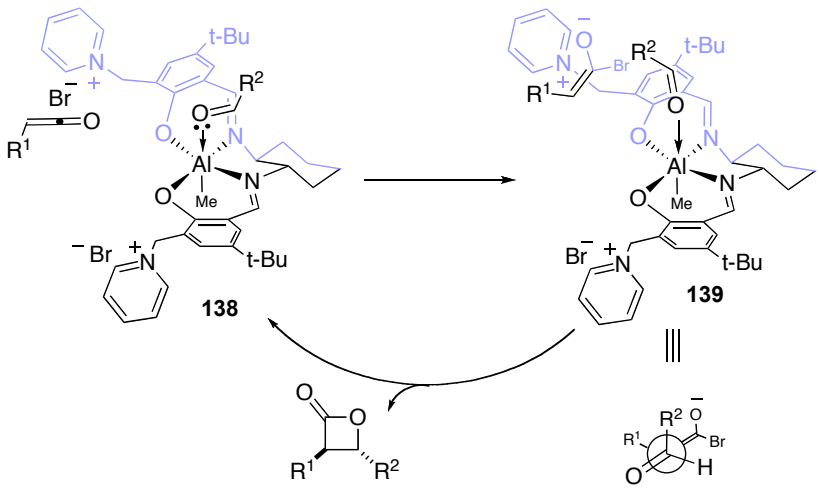


Figure 14. Proposed Mechanistic Model for the Bifunctional Catalyst **137**, Peters *et al.*[48]

Scheme 10. Asymmetric Synthesis of *trans* β-Lactones using Bifunctional Al-SALEN Catalyst; Peters, *et al.*[48]

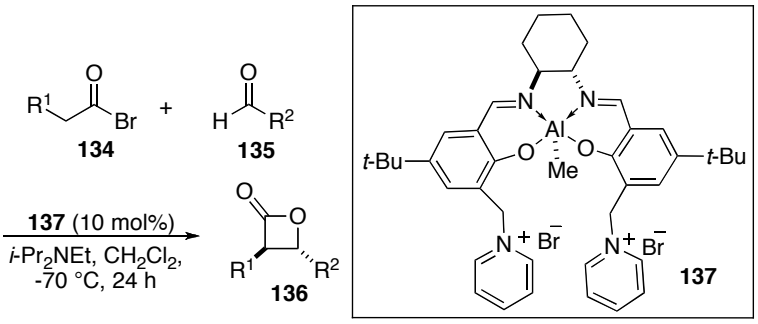


Table 19. Scope of the Bifunctional Catalytic System

entry	R^1	R^2	% yields[a]	% ee[b]	*trans:cis*[c]
1	Me	$(CH_2)_2Ph$	82[d]	88	97:3
2	Me	*n*-Hept	77	87	96:4
3	Me	$(CH_2)_3CH{=}CH_2$	74[d]	88	96:4
4	Me	$(CH_2)_8CH{=}CH_2$	62[d]	87	94:6
5	Me	Et	76	87	95:5
6	Me	*n*-Pr	67	93	97:3
7	Me	*n*-Bu	64	89	97:3
8	Me	*i*-Bu	76[d]	87	94:6
9	*n*-Pr	$(CH_2)_2Ph$	91	94	98:2
10	*n*-Pr	$(CH_2)_3CH{=}CH_2$	96	95	98:2
11	*n*-Pr	Et	63	94	97:3
12	*n*-Pr	*n*-Pr	93	95	98:2
13	*n*-Pr	*n*-Bu	92	93	96:4
14	*n*-Pr	*i*-Bu	76	94	96:4

[a] yield of isolated product if not indicated otherwise. [b] Determined by HPLC or GC on a chiral support. [c] Ratio determined by ^{1}HNMR spectroscopy. [d] Determined by ^{1}HNMR spectroscopy.

ACKNOWLEDGEMENTS

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Vikram Chandrakant Purohit is fulfilling his Ph.D candidacy at Texas A&M University-College Station, USA. He obtained his B.E (Chemical Engineering) from University of Pune, India in 1998. In 2002, he recieved his M.S in organic chemistry under direction of Prof. Dr. Apurba Bhattacharya from Texas A&M University-Kingsville discovering green and patent free, atom economical synthesis of pharmaceutical building blocks under Industry-Academia Collaboration with Bristol-Myers Squibb. He is a recipient of Robert A. Welch Fellowship, and Bristol-Myers Squibb Sponsorship. His current Ph.D. studies focus on the development new efficient stereoselective protocols for construction of β-lactones and novel transformations of these heterocycles including novel variants of the dyotropic rearrangment under the auspices of Prof. Daniel Romo.

Andrea Matla was born in Philadelphia, Pennsylvania in 1983. She graduated with a BS in chemistry from University of Pittsburgh in 2005. She completed her MS (under the supervision of Prof. Daniel Romo) at Texas A&M University in 2007. She is currently pursuing other interests in the United States and abroad focused on teaching.

Daniel Romo received his B.A. in chemistry/biology from Texas A&M and a Ph.D. in Chemistry from Colorado State University as a NSF Minority Graduate Fellow under the tutelage of the late Prof. Albert I. Meyers. Following postdoctoral studies at Harvard as an American Cancer Society Fellow, with Prof. Stuart L. Schreiber he began his independent career at Texas A&M in 1993 and is currently Professor of Chemistry. Research interests in the Romo Group are at the interface of chemistry and biology focused on total synthesis and biomechanistic studies of natural products and the asymmetric synthesis and application of b-lactones in organic synthesis and as potential drug candidates.