Catalytic Asymmetric Synthesis of β-Lactones and Application to the Total Synthesis of (–)-Pironetin

by

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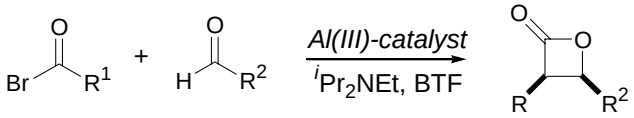
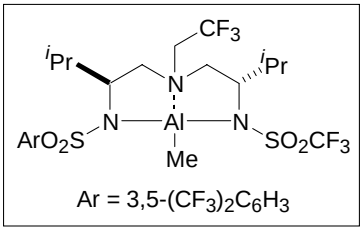
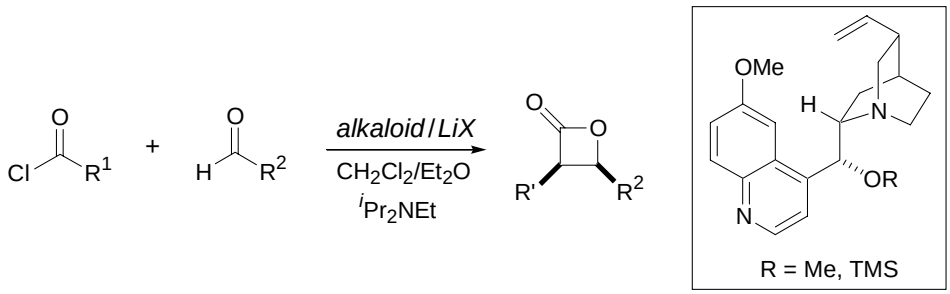
The Al-triamine complex catalyzed acyl halide-aldehyde cyclocondensation (AAC) reactions, developed previously by the Nelson group, have been extended to asymmetric AAC reactions of alkyl-substituted ketenes with structurally diverse aldehydes. By using of 2nd generation Al-triamine complex as catalyst, benzotrifluoride as solvent, the disubstituted β-lactones were synthesized in high yields and excellent enantioselectivities from readily available starting materials.

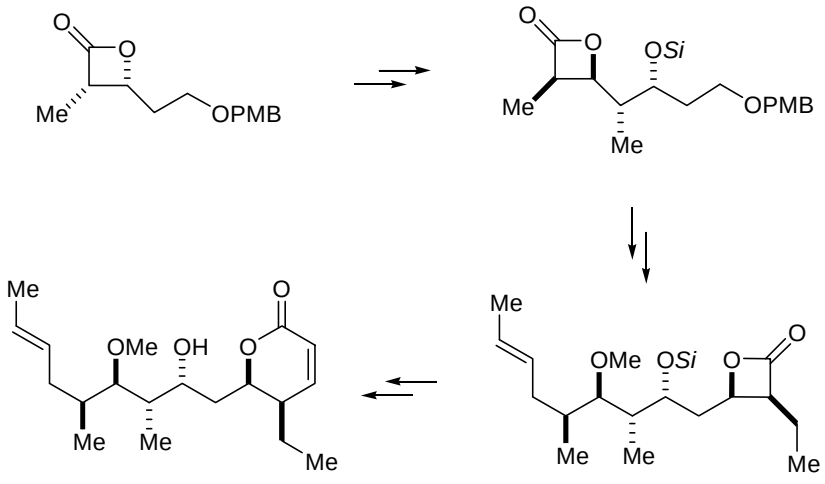




Another conceptionally different methodology has also been developed to synthesize enantioenriched β-lactones. The concept of double activation has been applied in this reaction technology to accelerate the β-lactones formation. By using of cinchona alkaloids to activate ketenes, and at the same time utilizing of lithium salts to activate aldehydes, Wynberg's [2+2] cycloaddition protocol has been greatly expanded to a variety of aldehydes.



Stereoenriched β-lactones derived from either Al-triamine or cinchona alkaloids catalyzed asymmetric acyl halide-aldehyde cyclocondensation (AAC) have been untilized in natural product synthesis. An asymmetric total synthesis of the antitumor agent pironetin was pursued using β-lactone templates for establishing all the requisite stereochemical relationships.



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AAC	Acyl halide-aldehyde cyclocondensation
Bn	Benzyl
BTF	Benzotrifluoride
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
de	Diastereomeric excess
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
equiv	Equivalent
EtOAc	Ethyl acetate
GC	Gas chromatography
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrum
LDA	Lithium diisopropylamide
Me-QN	Methyl quinine
MOM	Methoxymethyl
MsCl	Methanesulfonyl chloride
KHMDS	Potassium bis(trimethylsilyl)amide
PMB	*p*-Methoxybenzyl

TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TBSCl	*tert*-Butyldimethylsilyl chloride
TEA	Triethylamine
TES	Triethylsilyl
TESCl	Triethylsilyl chloride
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
Tf_2O	Trifluoromethanesulfonic anhydride
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
TMSCl	Chlorotrimethylsilane
TMS-QD	Trimethylsilylquinidine
TMS-QN	Trimethylsilylquinine
Ts	Tosyl

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I would like to express my sincere thanks to my advisor, Professor Scott G. Nelson, for providing me with the opportunity to work on very exciting research projects. It has been Dr. Nelson's scientific insight that has guided my research projects enabled my success. I truly appreciate the time and effort that you have devoted to helping me to become a better chemist.

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To the past and present members of the Nelson group, I wish to thank all of you for your friendship and for your help during my time at Pittsburgh. I would especially like to thank Dr. Cheng Zhu, you have been not only great teamworker but also wonderful friend, I am truly grateful.

Last but not the least, I would like to thank my dear wife, Wei Fu, for her love, care, understanding, encouragement and support over the past years. Without my wife's support, this dissertation would have been impossible.

1.0 INTRODUCTION

1.1 β-LACTONES

Enantioenriched β-lactones (2-oxetanones) are important targets for asymmetric catalysis.[1-3] β-Lactones can be viewed as 'activated aldol products' since they have an identical β-hydroxy carbonyl relation as that found in aldol products, while also having increased reactivity due to ring strain (Figure 1).[4]

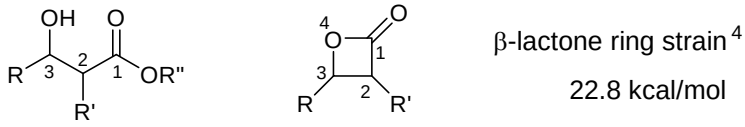


Figure 1. Comparison of β-lactones with aldol products

β-Lactones undergo reactions with nucleophiles involving either C_1-O_4 or C_3-O_4 bond cleavage. As a result, they are direct progenitors of many useful synthetic building blocks, such as enantioenriched β-amino acids,[5] allenes[6] and β,β-disubstituted carboxylic acids.[7]

Due to the important synthetic value of β-lactones, chemists have attempted to develop general methods to synthesize enantioenriched β-lactones efficiently and selectively.[3,8] There are several good reviews describing this area.[1-3] In this introduction, I will focus on the catalytic asymmetric synthesis of β-lactones and some closely related methodologies.

1.2 LEWIS BASE-CATALYZED β-LACTONE FORMATION

In 1982, Wynberg reported a remarkable example of asymmetric quinidine-catalyzed ketene-chloral cycloaddition, affording the β-lactone in 98% ee.[9] Substoichiometric amounts of a chiral Lewis base, quinidine **1**, were used as a nucleophile to attack pregenerated ketene (in toluene solution) to form a chiral acyl ammonium enolate **2** (Figure 2).

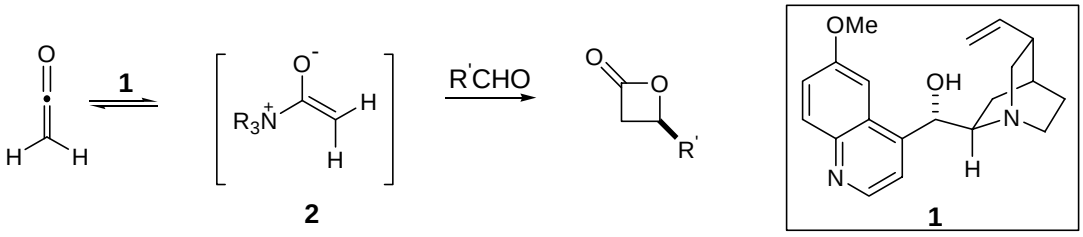
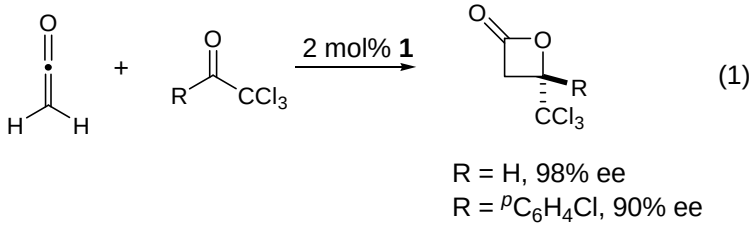


Figure 2. Wynberg [2+2] cycloaddition

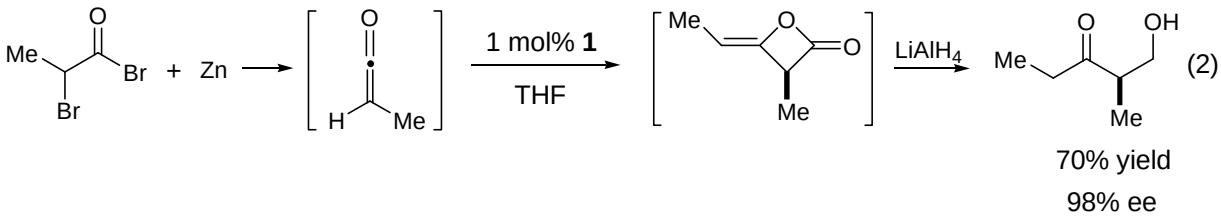
The enolate **2** was subsequently trapped by highly electrophilic aldehydes or ketones to form β-lactones in good yield and high enantioselectivity (eq 1). The success of Wynberg's system was limited to the use of highly reactive non-enolizable carbonyl electrophiles.[10]



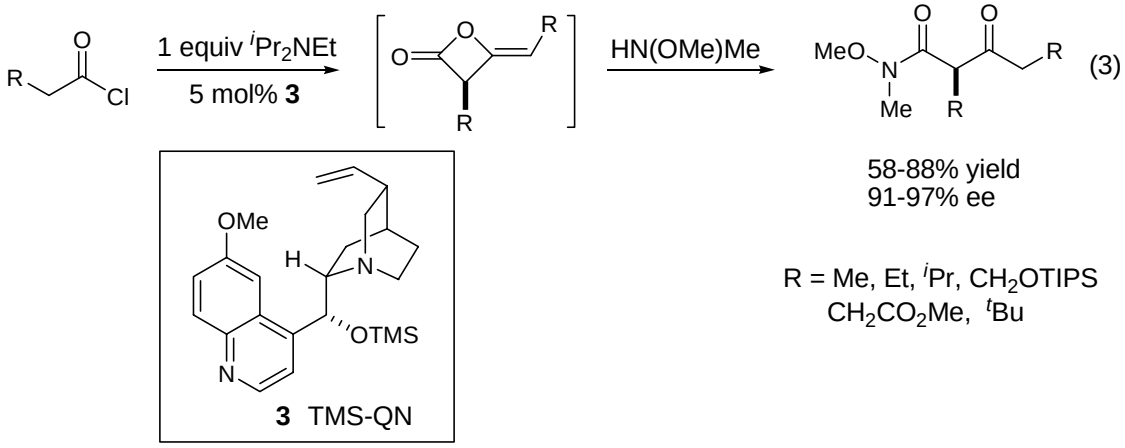
(1)

In 1996, Calter reported a catalytic, asymmetric dimerization of methyl ketene catalyzed by cinchona alkaloids.[11] In the presence of 1 mol% quinidine **1**, pregenerated methyl ketene dimerized to give β-methylene β-lactone, which was directly reduced to the corresponding alcohol due to its volatility and instability (eq 2). Either enantiomer of the product can be

produced in high enantioselectivity by judicious choice of the readily available catalysts (quinine or quinidine).

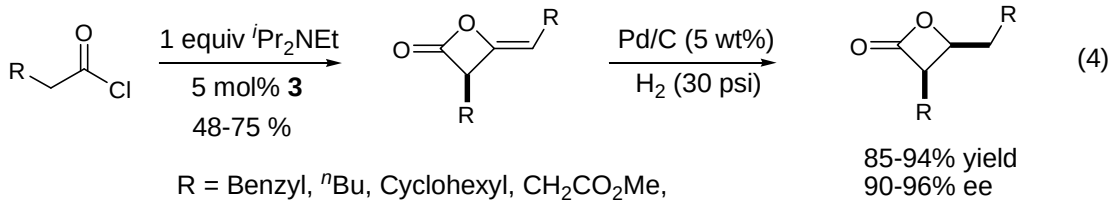


More recently, the Calter group has dramatically expanded the ketene dimerization reaction scope by utilizing *in situ* generated ketenes from acid chlorides and *N*,*N*-diisopropylethylamine. Under these new reaction conditions, the dimerization tolerates a variety of highly functionalized substituted ketenes not available from pyrolytic methods of ketene generation used previously.[12] Due to the instability, the ketene dimers were converted into the corresponding β-ketoamides without isolation (eq 3).



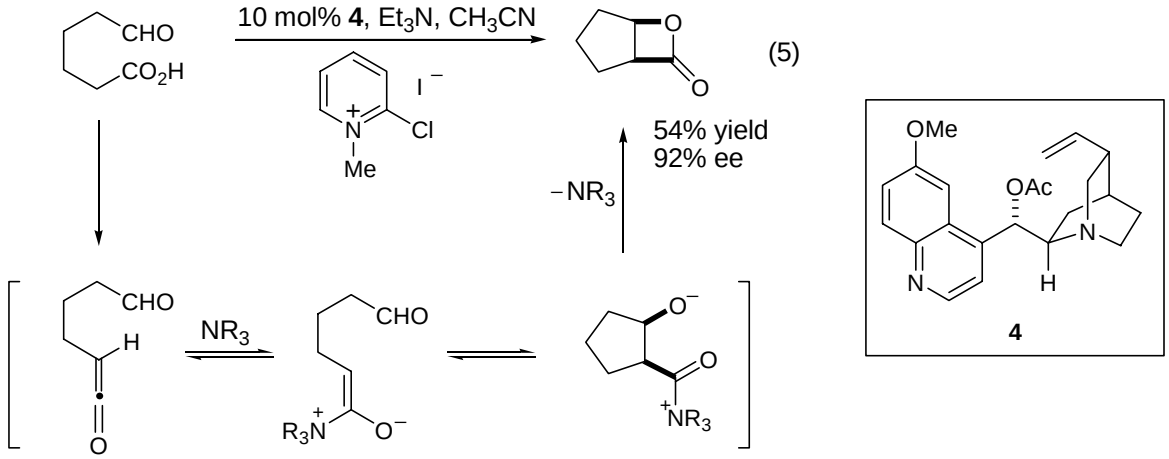
Based on Calter's cinchona alkaloid catalyzed ketene dimerization, very recently Romo reported the asymmetric synthesis of β-lactones via a sequential ketene dimerization/

hydrogenation process.[13] A variety of β-lactones were formed in good yield and high enantioselectivity (eq 4).



(4)

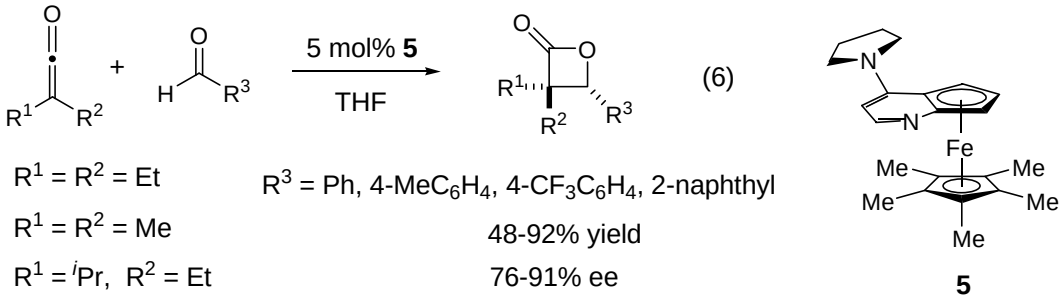
In 2001, Romo and co-workers reported an intramolecular nucleophile-catalyzed aldol-lactonization process that leads to a variety of β-lactone-fused bicyclic systems in moderate yields and very good enantioselectivities (eq 5).[14,15] They were able to generate ketene *in situ* by treating various aldehyde acids with 2-chloro-1-methylpyridinium iodide and triethylamine. The intramolecular cycloaddition allowed for the employment of unactivated aldehydes.



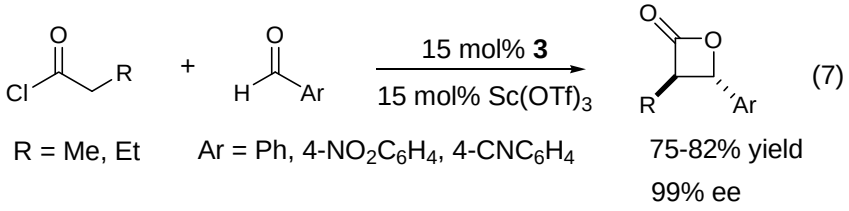
(5)

In 2004, Fu reported asymmetric synthesis of highly substituted β-lactones by planar-chiral PPY derivative **5** catalyzed [2+2] cycloadditions of disubstituted ketenes with aromatic

aldehydes (eq 6).[16] This is the first catalyst reported that is effective for enantioselective cycloadditions of disubstituted ketenes, which generate α,α-disubstituted β-lactones.



In 2005, Calter reported asymmetric synthesis of *trans* β-lactones by cinchona alkaloids and $Sc(OTf)_3$ catalyzed [2+2] cycloadditions of ketenes with aromatic aldehydes (eq 7).[17] The sense of diastereoselectivity depends on the substitution of the acid chloride, with the reactions of aliphatic acid chlorides giving predominantly *trans* isomer and those of alkoxyacetyl chlorides favoring formation of *cis* isomer.



1.3 LEWIS ACID-CATALYZED β-LACTONE FORMATION

In the aforementioned methods, chiral amines were employed as nucleophiles to activate ketenes by forming chiral acyl ammonium enolates; the resulting enolates subsequently cyclize with

aldehydes to give β-lactones (Figure 3, right). There is a conceptionally different method to synthesize β-lactones. This reaction technology utilizes chiral Lewis acids to activate electrophiles, instead of employing chiral Lewis bases to activate ketenes (Figure 3, left). And the nucleophilic ketenes react with the Lewis acid-activated aldehydes, forming the β-lactones and regenerating the Lewis acid.

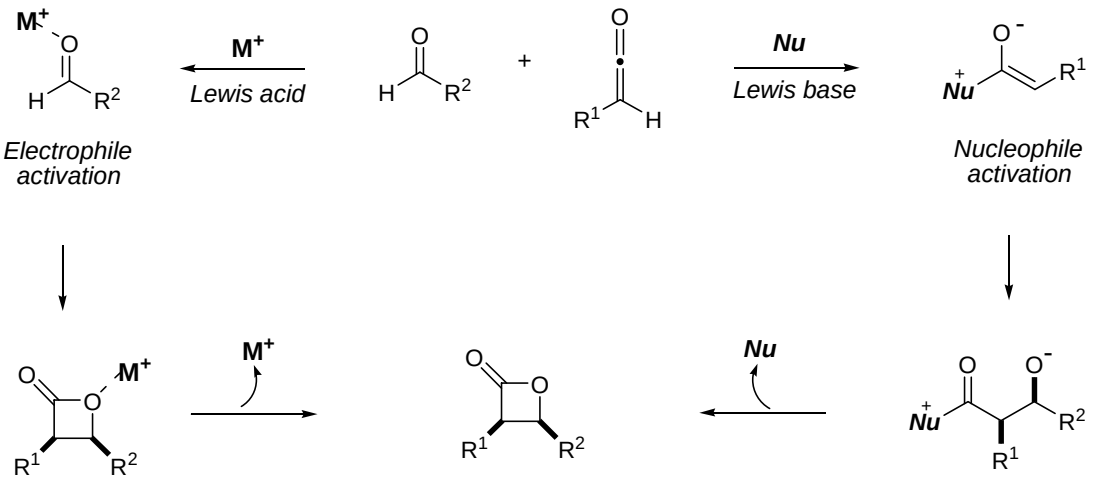
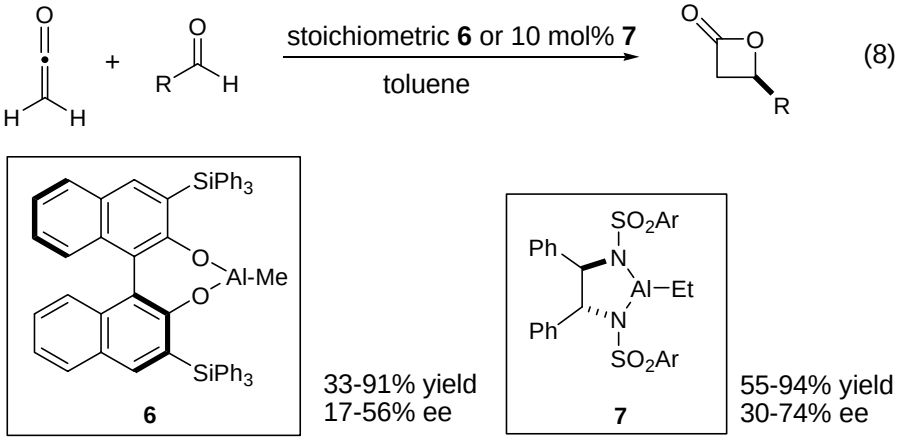


Figure 3. Comparison of Lewis acid and Lewis base-catalyzed β-lactone formation

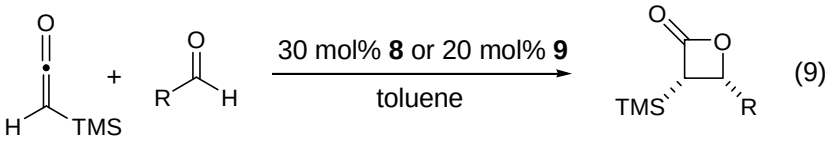
In 1994, Miyano documented the first asymmetric synthesis of β-lactones *via* [2+2] cycloaddition of ketene with aldehydes catalyzed by a stoichiometric amount of chiral aluminum-binaphthol complexes **6** (eq 8).[18] While moderate yields and enantioselectivities were reported for these stoichiometric reactions, yields and enantioselectivities greatly decreased when a substoichiometric amount of the chiral Lewis acid was employed. It was suggested that the catalyst was deactivated *via* acylation of the BINOL ligand by ketene. Catalyst deactivation by acylation could be avoided by using chiral bis-sulfonamides as ligands. Subsequently, the Miyano group reported the first catalytic, asymmetric [2+2] cycloaddition catalyzed by 10 mol%

Al(III)-bissulfonamide complexes **7** (eq 8).[19] A variety of β-lactones were obtained in good yields and moderate enantioselectivities.

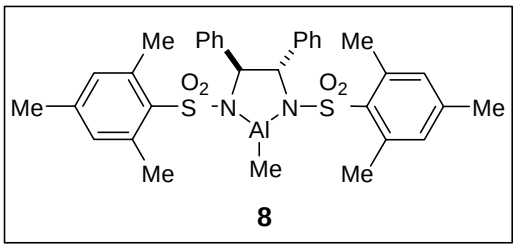


(8)

Because the generation of the ketene gas by pyrolysis of acetone is laborious, commercial trimethylsilyl ketene has been used in enantioselective ketene-aldehyde cycloaddition as an alternative to gaseous ketene. In 1996, Kocienski[20] and Romo[21] independently reported catalytic, enantioselective [2+2] cycloadditions of aldehydes with stable trimethylsilyl ketene using aluminium-based chiral Lewis acids (**8** and **9**) as catalysts (eq 9). Moderate to good yields and selectivities were obtained.

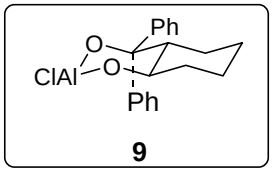


R = $PhCH_2$, $PhCH_2CH_2$, *p*-$MeOC_6H_4CH_2$, *c*-C_6H_{11}, *n*-$C_{11}H_{23}$



8

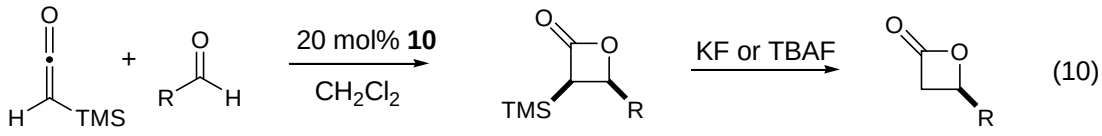
43-82% yield
36-83% ee
> 70 : 30 dr



9

45-86% yield
22-85% ee
> 19 : 1 dr

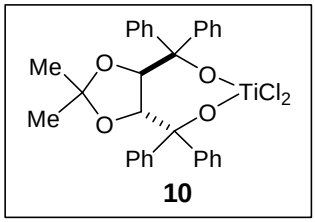
Romo also studied the [2+2] cycloaddition of trimethylsilyl ketene with various aldehydes by employing Seebach's dichlorotitanium-TADDOL catalysts **10**.[22] After desilylation, the desired β-lactones were obtained in moderate to good yield and enantioselectivity (eq 10).



R = $PhCH_2$, *n*-C_5H_{11}, *p*-$NO_2C_6H_4$, Ph
c-C_6H_{11}, $PhCH_2CH_2$, $TBSO(CH_2)_5$

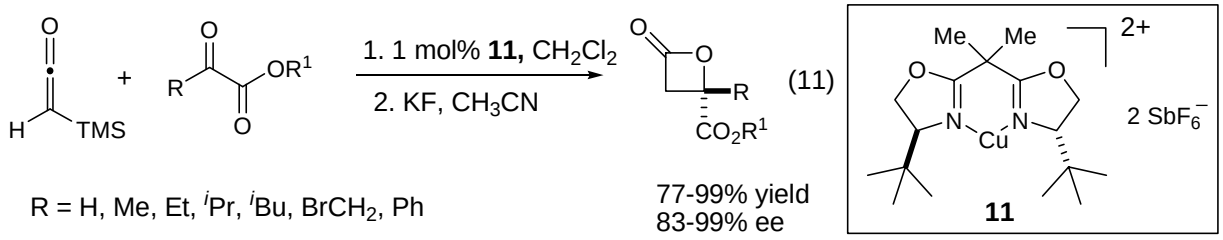
9 : 1 to
> 19 : 1 dr

49-78% yield
21-80% ee

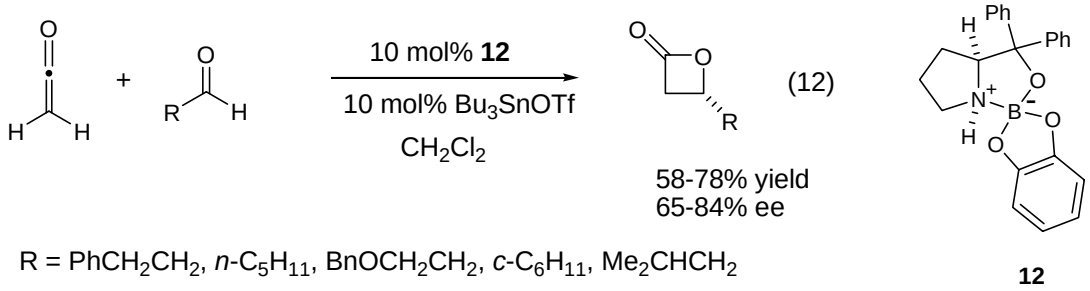


10

Evans utilized C_2-symmetric copper(II)-bisoxazoline complex (**11**) as chiral catalyst for the [2+2] cycloaddition reaction of nucleophilic silyl ketenes and chelating carbonyl substrates, which afford the enantioenriched β-lactones in excellent yield and enantioselectivity (eq 11).[23] The observed enantioselectivity is proposed to be derived from a chelation of the chiral metal complex to the both carbonyl groups of electrophiles in a square-planar geometry around the copper ion.



The Corey group very recently developed an enantioselective β-lactone formation from ketene and aldehydes catalyzed by the combination of a chiral oxazaborolidine and tributyltin triflate (eq 12).[24] The β-lactones were formed in fair yields (60-78%) and moderately good enantioselectivity (65-81% ee). In the proposed mechanism, activation of precatalyst **12** by tri-n-butyltin triflate produced the ion pair **13**, which by reaction with ketene formed the ketene acetal intermediate **14**, which coordinates with aldehyde generate transient species **15**, upon ejecting the β-lactone, completes the catalytic cycle (Figure 4).



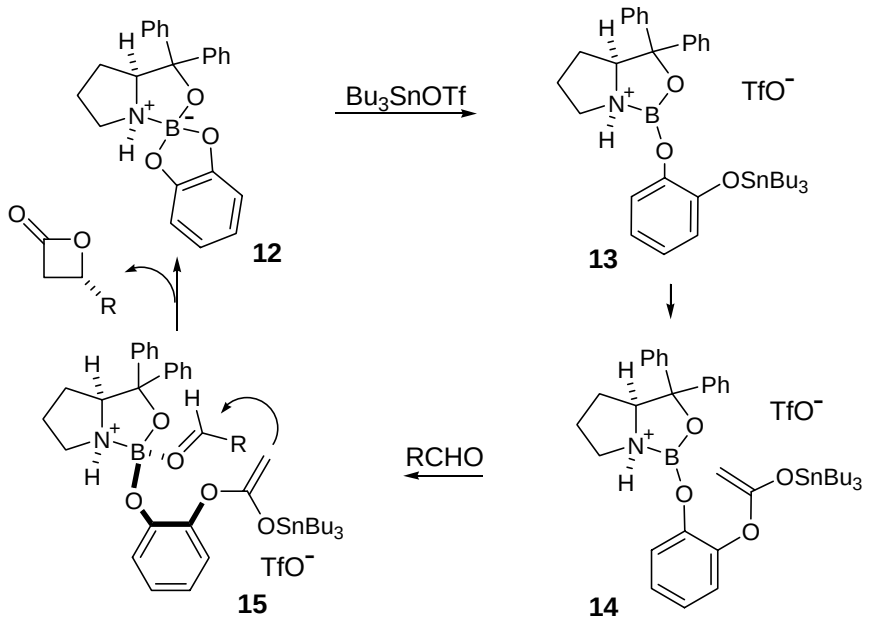
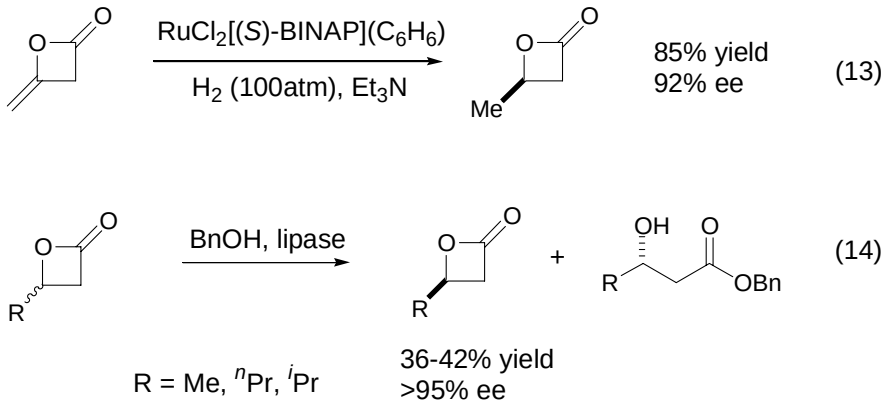


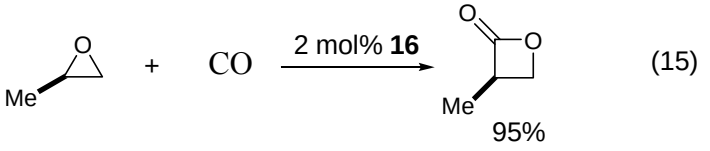
Figure 4. Corey's Sn-oxazaborolidine complex catalyzed β-lactone formation

There are several catalytic enantioselective routes to β-lactones other than ketene-aldehyde [2+2] cycloaddition. These methods include asymmetric hydrogenation of diketene (eq 13)[25] and lipase-catalyzed kinetic resolution of racemic β-lactones (eq 14).[26]



Recently, Coates developed a general method to synthesize β-lactones by carbonylation of epoxides catalyzed by cationic aluminium complexes (**16**);[27] however, enantioenriched

epoxides were used as starting materials to form enantioenriched lactones (eq 15). In the proposed mechanism, epoxides were activated by the coordination of the aluminium, backside attack by $Co(CO)_4^-$ on the less hindered carbon giving the ring-opened aluminium oxide species, insertion of CO, β-lactone extrusion and recoordination of CO to cobalt complete the catalytic cycle (Figure 5).



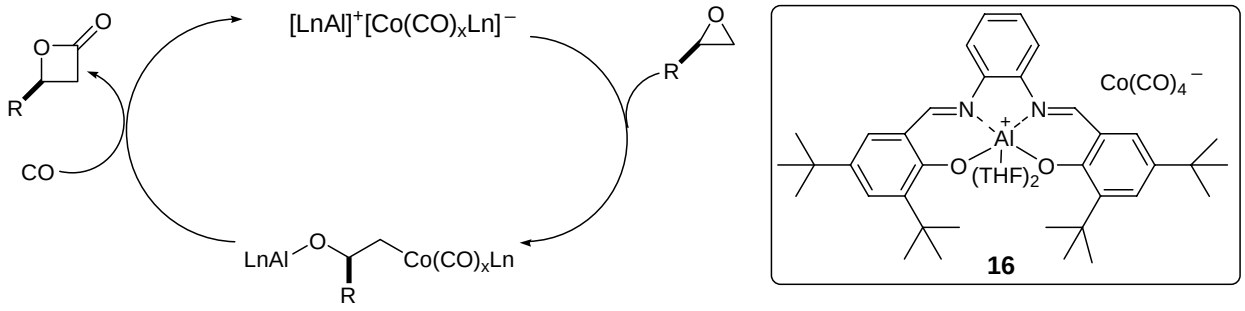


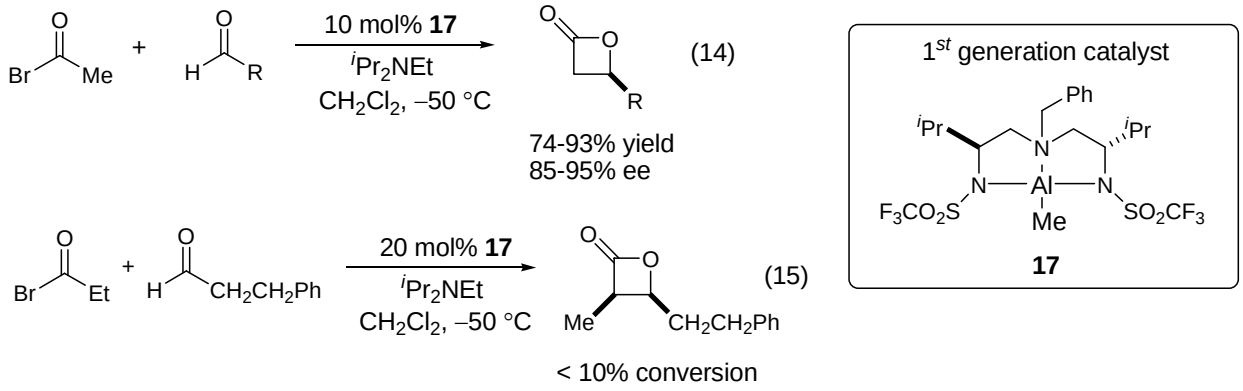
Figure 5. Coates' carbonylation approach to β-lactones

While several routes for the asymmetric synthesis of β-lactones have been developed, many of them suffer from either limited substrate compatibility or modest enantioselectivity and yields. Our goals were to develop general and convenient methods to make enantioenriched β-lactones by merging *in situ* ketene generation with asymmetric Lewis base- or Lewis acid-catalyzed [2+2] cycloaddition, and apply these methodologies to complex molecule synthesis.

2.0 AL(III)-TRIAMINE-CATALYZED AAC OF SUBSTITUTED KETENES

2.1 INITIAL STUDIES ON AL(III)-TRIAMINE-CATALYZED AAC

In 1999, the Nelson group reported the 1st generation asymmetric acyl halide aldehyde cyclocondensation (AAC) reactions (eq 14).[28] Under the influence of Al-triamine catalysts **17**, *in situ* generated ketene reacted with a variety of aldehydes to afford the β-lactones in good yields and high enantioselectivities. The 1st generation Al-triamine catalyst **17** proved to be generally useful for AAC reactions involving unsubstituted ketene. However, for substituted ketene AAC reactions, **17** was effective only for a very limited subset of activated aldehydes (such as 4-nitro benzaldehyde).[29] For example, applying **17** to the cyclocondensation of methylketene and hydrocinnamaldehyde resulted in less than 10% conversion of starting aldehyde to desired β-lactone (eq 15). Due to this limitation of 1st generation AAC reaction, the goal of this project was to develop a general solution to Lewis acid-catalyzed asymmetric AAC reactions of substituted ketenes with structurally diverse aldehydes.



The Lewis acid-catalyzed AAC reactions are complex processes.[30] There are various other reaction pathways competing with the β-lactones formation during the AAC reaction (Figure 6).

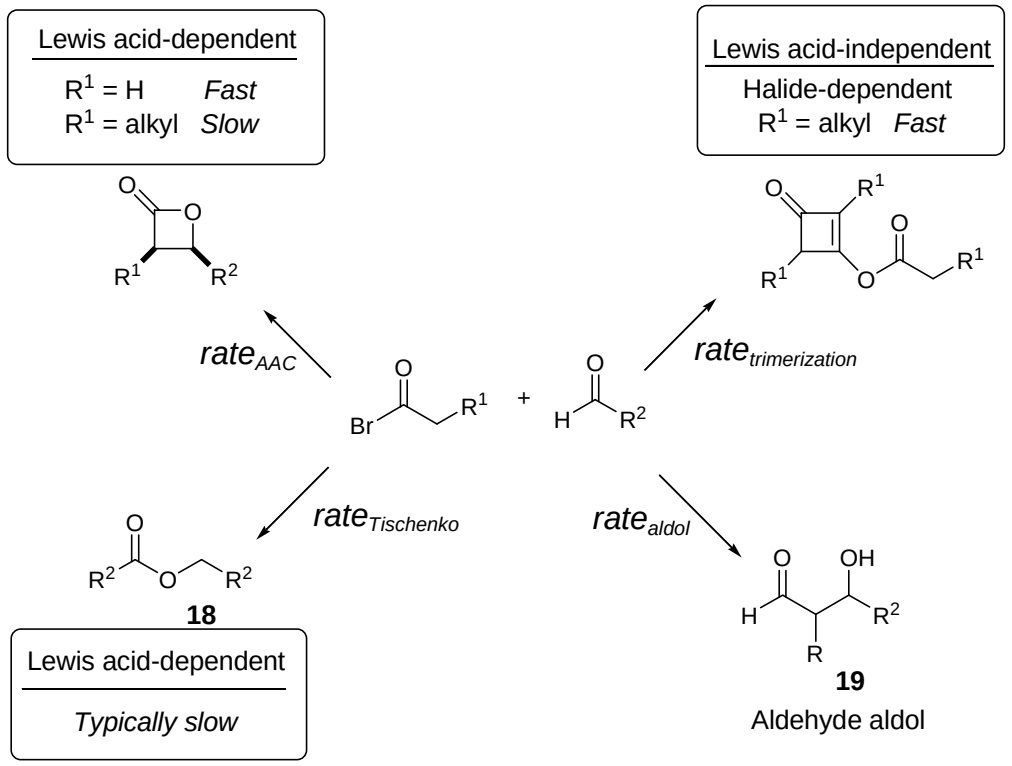


Figure 6. Competing reaction pathways in Lewis-acid-catalyzed AAC reactions

For AAC reactions with unsubstituted ketene, the desired [2+2] cyclocondensation is much faster than ketene trimerization, so the Al-triamine catalyst **17** works very well for unsubstituted ketene AAC. However, for AAC reactions with substituted ketene, the desired [2+2] cyclocondensation turns out to be much slower than ketene trimerization. Under Lewis acidic conditions, the aldehyde component may undergo the Tischenko or aldol reaction, affording the corresponding ester **18** or β-hydroxy aldehyde **19** as side products, respectively. Therefore, it was necessary to alter the reaction conditions and modify the AAC catalyst to retard the rate of unwanted pathways while facilitating the desired [2+2] cycloadditions.

Ketene trimerization is accelerated by ammonium halide salts.[31] The halide ion could add to the methyl ketene to form a halide enolate **20**, which is sufficiently nucleophilic to add to another ketene molecule resulting in the formation of the ketene dimer, this dimer reacts with another ketene eventually forming the ketene trimer **21** (Figure 7).

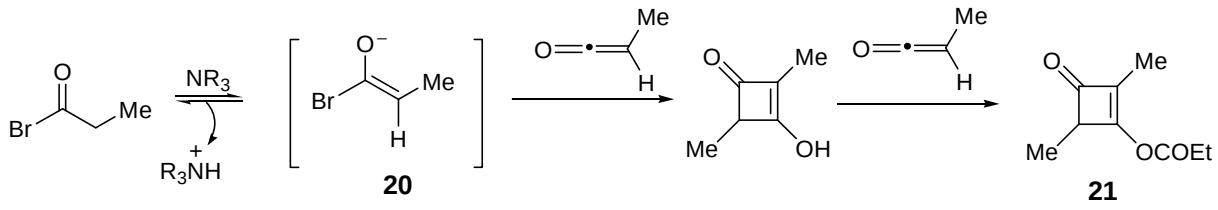
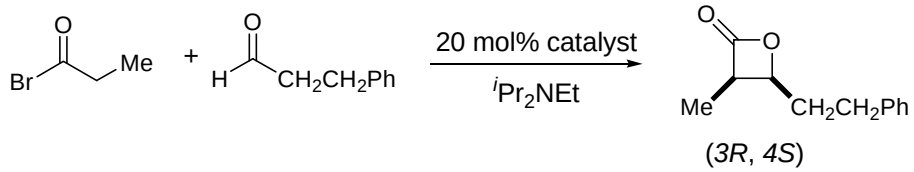


Figure 7. Halide ion-catalyzed ketene trimerization

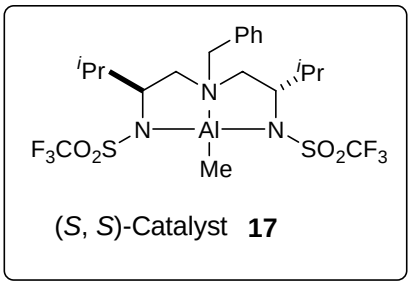
So removal of ammonium halide salts would slow unproductive methylketene trimerization. Hence, one of the essential criteria for choosing a solvent for the propionate-AAC reaction was based on how well the hydrohalide salt precipitated in that medium. An effective solvent for the AAC reactions with methyl ketene requires sufficient polarity to allow the ketene-aldehyde cycloaddition to proceed *via* a polar transition state.[32] Based on these considerations, we

screened several solvents for methylketene-hydrocinnamaldehyde cycloaddition. The standard test reactions employed hydrocinnamaldehyde (1.0 mmol) as the electrophile, propionyl bromide (4.0 mmol) as the ketene source, diisopropylethylamine (2.0 mmol) as the base, *in situ* generated Al(III)-triamine complex **17** (0.2 mmol) from trimethylaluminium and triamine ligand as the catalyst, under a N_2 atmosphere the reaction was stirred for 14 h at –25 °C. The reaction was quenched at –25 °C by adding 10 mL of Et_2O and the resulting mixture was filtered through silica gel eluting with 60 mL of Et_2O. The filtrate was concentrated *in vacuo* and the crude product mixture was used to determine the aldehyde conversion by ^{1}H NMR (the relative integration ratio of the characteristic ^{1}H NMR resonance of starting material aldehyde and product β-lactone was used to determine the percentage conversion of aldehyde to β-lactone). From these results (Table 1), we discovered that pseudo salt-free conditions could be achieved by using BTF (benzotrifluoride) as the reaction solvent.[33] In BTF, ^{i}Pr$_2$NEt·HBr salt generated from ^{i}Pr$_2$NEt and acid bromide is insoluble and the reaction mixture is heterogeneous, AAC reaction conversion was improved considerably in the standard propionyl bromide-hydrocinnamaldehyde reaction (from <10% to 47%) due to extended ketene lifetime (Table 1, entry a *vs* d). In the relatively non-polar solvent toluene, the reaction is also heterogeneous; however, the AAC reaction conversion is very low (<5 %, entry b).

Table 1. Effect of solvent on the first generation AAC reaction



(*3R*, *4S*)

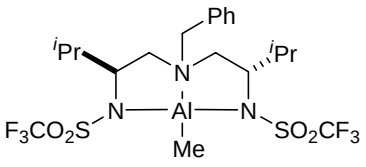


(*S*, *S*)-Catalyst **17**

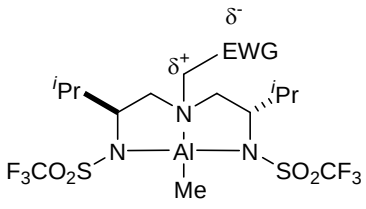
entry	catalyst	solvent	% conversion[a]	% ee[b]
a	**17**	CH_2Cl_2	<10	ND[c]
b	**17**	toluene	<5	ND
c	**17**	$CHCl_3$	<5	ND
d	**17**	BTF	47	48

[a] Conversion determined by ^{1}H NMR of crude product mixture.
[b] Enantiomer ratio assayed by chiral HPLC (Chiralcel OD-H).
[c] Not determined.

In order to further improve the conversion and obtain higher enantioselectivities for the propionyl bromide AAC, we decided to modify the ligand structures to discover more reactive and/or more selective catalysts (Figure 8). Since the ketene aldehyde cycloaddition is Lewis acid dependent, more electrophilic catalysts would make aldehydes more reactive by lowering the energy of the LUMO orbital of aldehyde after forming RCHO-Lewis acid complex.



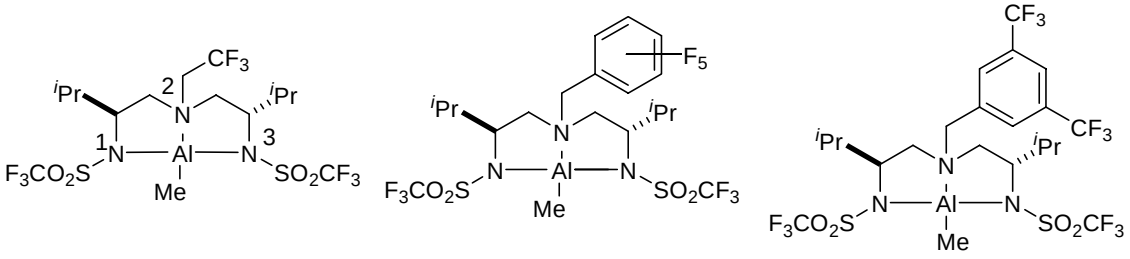
17



22

Figure 8. Concept for more reactive catalyst design

Thus, introduction of an electron-withdrawing substituent to the 1st generation catalyst **17** would render the metal center more electrophilic, enabling an accelerated AAC reaction of methyl ketene. We speculated that inductive electron withdrawal from the central nitrogen would decrease electron density at aluminum, thereby enhancing Lewis acidity of the catalyst (**17** *vs* **22**).

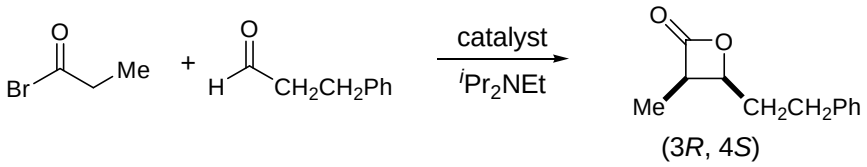


(*S*, *S*)-**23** (*S*, *S*)-**24** (*S*, *S*)-**25**

Figure 9. New catalysts with electron-withdrawing group on nitrogen

Accordingly, some modified 1st generation catalysts (**23**, **24** and **25,** Figure 9) were prepared by Cheng Zhu, in these catalysts fluorinated alkyl and aryl substituents were included at the central nitrogen of the catalyst. When evaluated in the AAC reactions, these modified catalysts exhibited improved substrate conversion in reactions involving unactivated aldehydes. For example, replacing benzyl group on the central nitrogen by trifluoroethyl group dramatically increased the reaction conversion (from 47% to 100%, Table 2, entry a *vs* b).

Table 2. Reactivity and selectivity for new catalysts



entry	catalyst	solvent	cat. loading mol %	% conversion[a]	% ee[b]
a	**17**	BTF	20	47	48
b	**23**	BTF	20	100	56
c	**24**	BTF	10[c]	51	58
d	**25**	BTF	20	100	54

[a] Conversion determined by ^{1}H NMR of crude product mixture.

[b] Enantiomer ratio assayed by chiral HPLC (Chiralcel OD-H).

[c] Because of low solubility of **24** in BTF, 10 mol% of **24** used.

The combination of BTF precipitation of ammonium bromide salts and enhancement of catalyst electrophilicity largely solved the unactivated aldehyde conversion problem in the methyl ketene AAC (Table 2, entry b and d). However, enantioselectivity of the substituted AAC reaction remained relatively low (56% ee, Table 2, entry b). Our investigation then focused on identifying modified triamine ligands that would provide the requisite levels of enantioselectivity at reaction temperatures above the freezing point of BTF (−29 ^{o}C).

2.2 DEVELOPMENT OF A 2ND GENERATION CATALYST FOR AAC

In order to design more enantioselective catalysts for substituted ketene AAC reactions, we studied the crystal structure of 1st generation catalyst (**17**). Crystallographic studies by Nelson

revealed that complex **17** adopts a four-coordinate, trigonal monopyramidal geometry with the methyl and triflamide ligands defining the equatorial plane of the bipyramidal structure.[34] The crystal structure data suggested that the distorted trigonal monopyramidal coordination geometry defined in **17** by the tridentate ligand was responsible for the observed Lewis acidity by providing a vacant apical coordination site disposed ideally to accept a fifth ligand. As shown in Figure 10, aldehydes were activated by coordination to the apical vacant orbital, nucleophilic ketene then attacked the aldehyde selectively from one face over another, forming enantioenriched β-lactones.

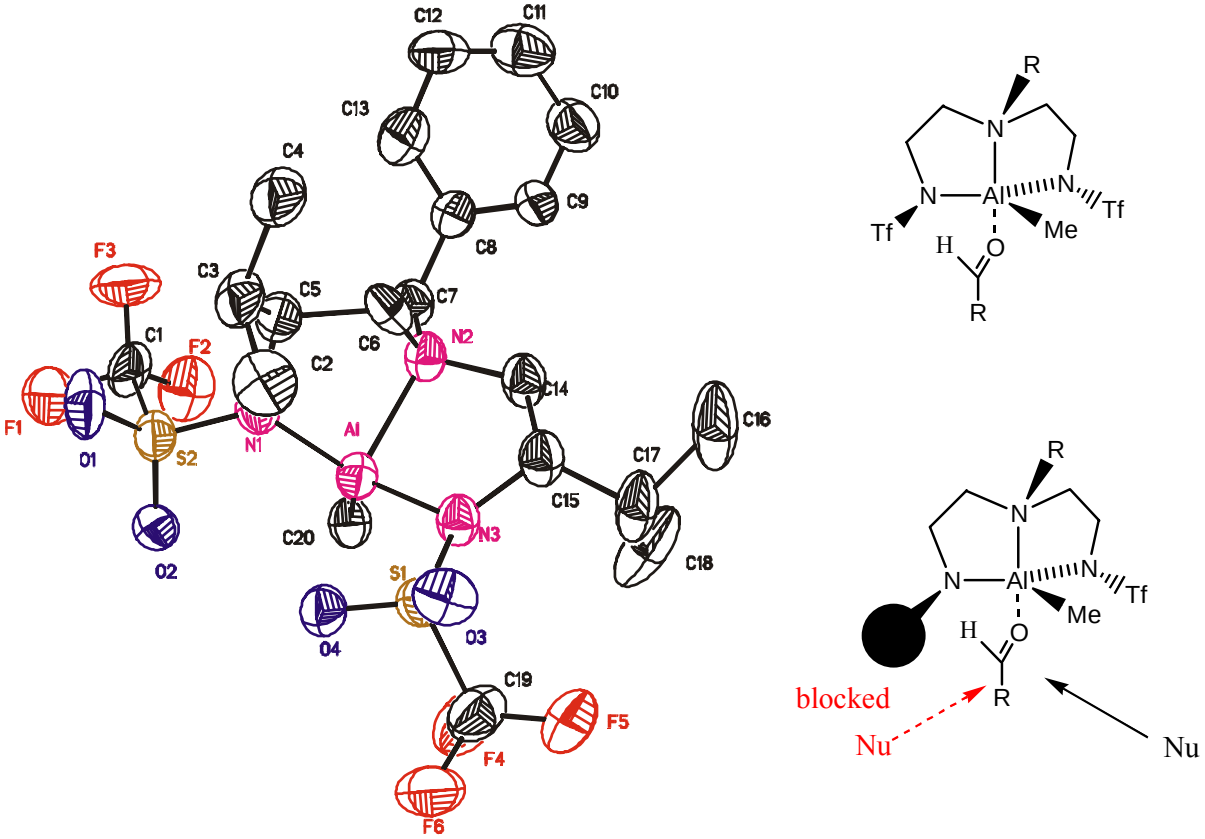
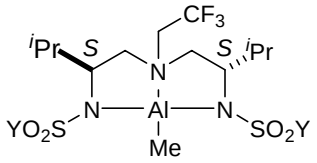
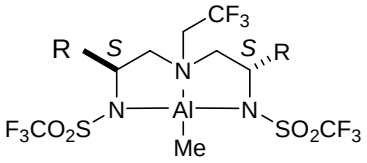


Figure 10. First generation AAC catalyst structure (from X-ray **12**)

Altering sterics or electronics of the trifluoromethanesulfonyl group in the 1st generation catalyst would be expected to have an impact on the geometry as well as the electrophilicity of the newly formed catalysts **23**, **26-29** (Figure 11). Likewise, changing the isopropyl side chain to other alkyl groups would have some effect on the orientation of the sulfonyl group (**23**, **30-33**, Figure 11), and therefore enable an effective facial bias of the aldehyde during the AAC reaction with substituted ketenes. Unfortunately, various Al(III) catalysts derived from C_2-symmetric triamine ligands differing in sulfonamide structure and backbone alkyl groups provided little improvement in enantioselectivity compared to 1st generation catalyst **17**.

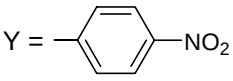


Varation in sulfonyl groups:



Varation in alkyl side chain:

Y = $-CF_3$ **23**



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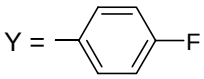

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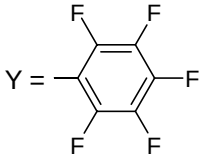

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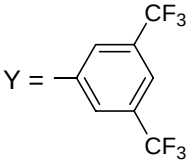


29

R = ^{i}Pr **23**

R = Bn **30**

R = Ph **31**

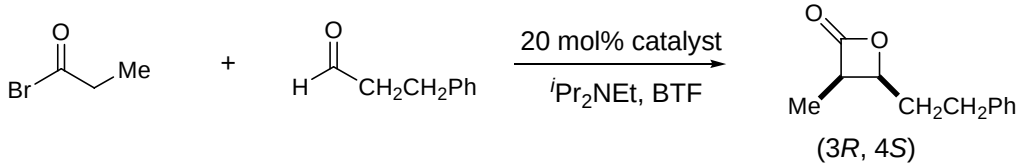
R = Et **32**

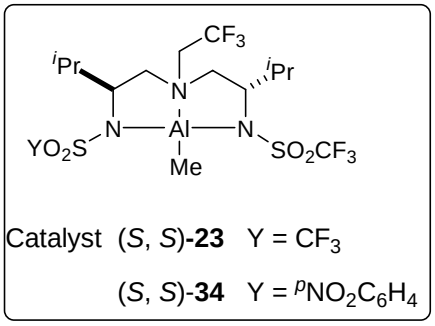
R = $^{c}C_6H_{11}$ **33**

Figure 11. Modification of 1st generation AAC catalyst

We noticed that one trifluoromethane sulfonyl group blocked one face of the aldehyde after we analyzed the crystal structure of complex **17**, we speculated that a large sulfonyl group would further increase the facial bias (Figure 10). Indeed, the catalyst derived from unsymmetric triamine provide an Al(III)-derived complex **34** exhibiting substantially improved enantioselectivity in the substituted ketene AAC (Table 3, entry a *vs* b).

Table 3. Comparison of catalysts derived from unsymmetric and symmetric ligands



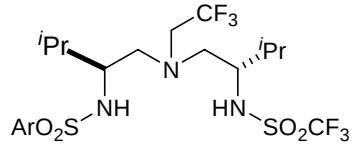


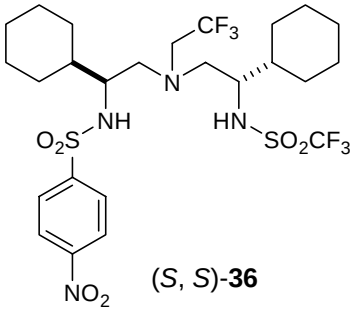
entry	catalyst	% conversion[a]	% ee[b]
a	**23**	100	56
b	**34**	100	80

[a] Conversion determined by ^{1}H NMR of crude product mixture.

[b] Enantiomer ratio assayed by chiral HPLC (Chiralcel OD-H)

Based on this result, we then turned our attention to unsymmetric ligands. We synthesized a series of unsymmetric triamine ligands **35**-**38** (Figure 12).





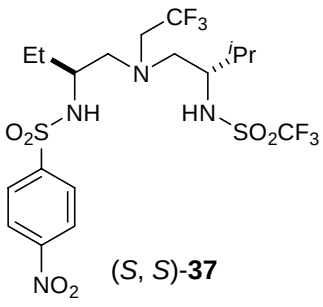
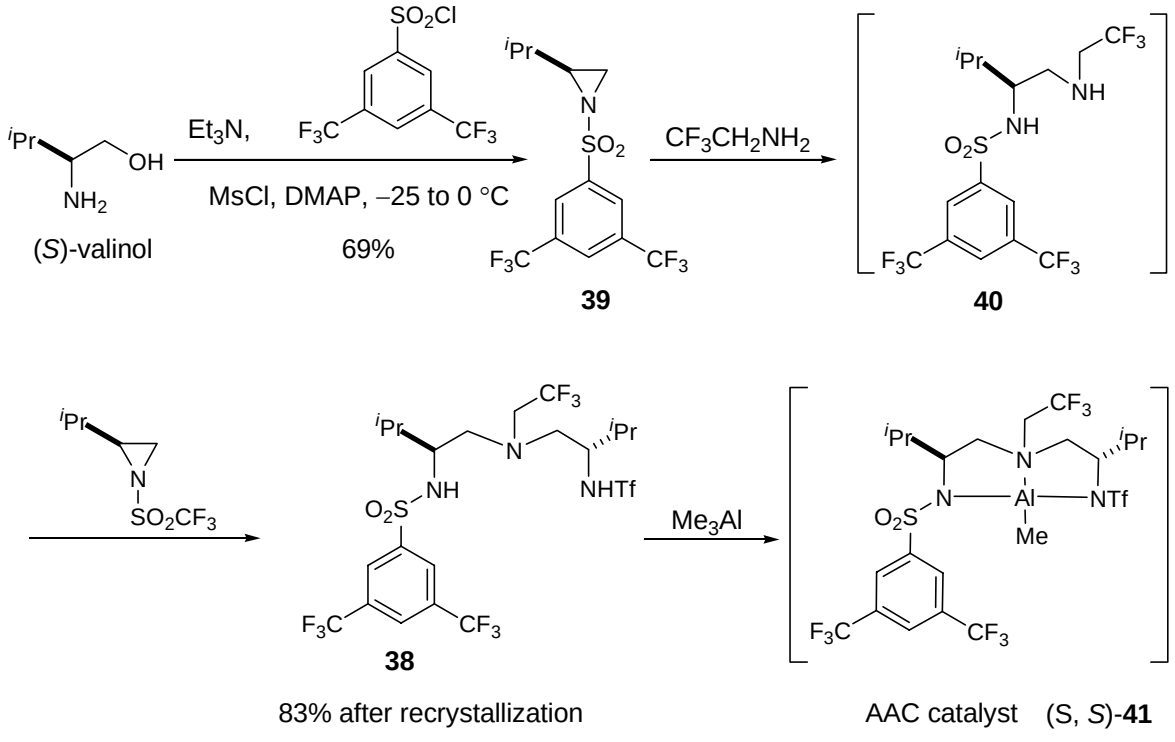


Figure 12. Unsymmetric triamine ligands

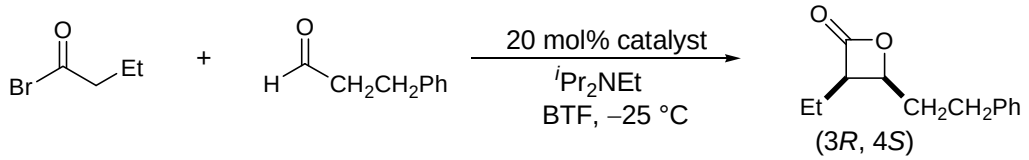
These unsymmetric ligands were easily prepared from different α-amino alcohols along a route very similar to that used in preparing the symmetric triamine ligands. For example, ligand **38** was synthesized from (*S*)-valinol (Scheme 1). Valinol was treated with 1 equiv of 3,5-bis(trifluoromethyl)benzenesulfonyl chloride and MsCl in the presence of 4 equiv of triethyl amine at 0 ^{o}C to form corresponding aziridine **39** in 69% yield. Ring-opening reactions of the aziridine employing 2,2,2-trifluoroethylamine resulted in the formation of the corresponding half-ligand **40**. Without purification, the half-ligand **40** reacted with the *N*-triflic aziridine to form unsymmetrical ligand **38**. After recrystallization, this ligand was used for *in situ* generation of the catalyst **41** with trimethylaluminium. Other unsymmetric ligands **35-37** were synthesized by similar method.

Scheme 1. Synthesis of unsymmetric ligand **38** and catalyst **41**

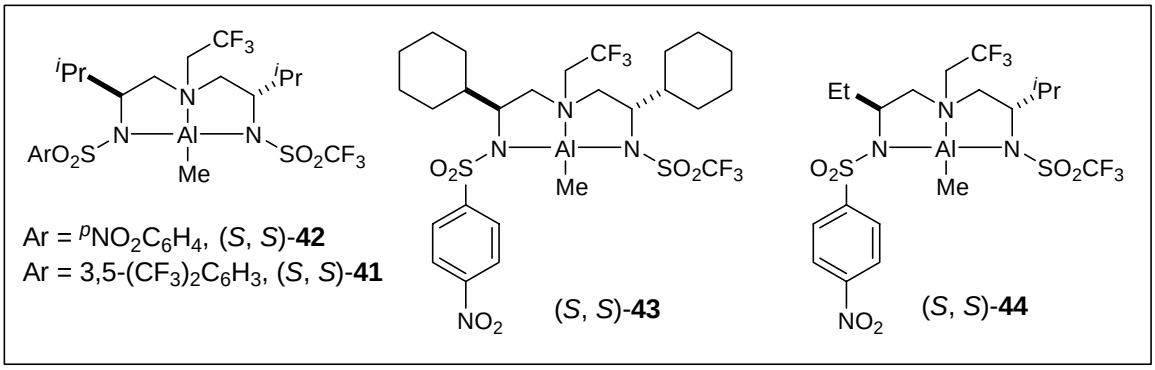


These Al(III)-triamine catalysts derived from unsymmetric ligands were screened for ethyl ketene-hydrocinnamaldehyde cycloaddition. A representative procedure consisted of following steps: a solution of triamine ligand **35-38** (0.10 mmol) in 2.0 mL of BTF at ambient temperature was slowly added 0.050 mL of a 2.0 M hexane solution of $AlMe_3$ (0.10 mmol). After stirring for 2 hours, the resulting catalyst solution was cooled to –25 °C and 0.35 mL of *N*,*N*-diisopropylethylamine (2.0 mmol) and 4 equiv of butyryl bromide were added consecutively. The resulting heterogeneous mixture was stirred 15 min at –25 °C whereupon hydrocinnamaldehyde (1.0 mmol) was added dropwise and the reaction was stirred for 15 hours at –25 °C. The reaction was workup at –25 °C by adding 10 mL of Et_2O and the resulting mixture was filtered through silica gel eluting with 60 mL of Et_2O. The filtrate was concentrated *in vacuo* and the crude product mixture was purified by flash chromatography. From the results (Table 4), we discovered catalysts **42-44** derived from ligand **35-37** giving similar selectivity (80-85% ee, entry a-c). Catalyst **41** (2^{nd} generation catalyst) derived from **38** gave the best enantioselectivity (91% ee, entry d).

Table 4. Evalution of unsymmetric ligands by the ethyl ketene-hydrocinnamaldehyde cyclocondensation



entry	catalyst	% ee[a]	% yield[b]
a	**42**	85	73
b	**43**	83	75
c	**44**	80	79
d	**41**	91	77



[a] Enantiomeric ratios assayed by chiral HPLC. [b] Isolated yield for diastereomerically pure material.

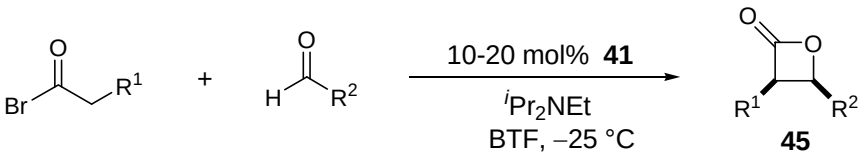
2.3 SECOND GENERATION AAC REACTIONS

For the substituted ketene AAC reactions, the 2nd generation catalyst **41** in conjunction with pseudo-salt-free reaction conditions (BTF, –25 °C) afforded a variety of β-lactones in high diastereo and enantioselectivity.[35] Methylketene seems uniquely disposed toward trimerization; as a result, slow-reacting aliphatic aldehydes require 20 mol% **41** to ensure ketene-aldehyde

cycloaddition (Table 5, entry a), unsaturated aldehydes provide sufficiently accelerated [2+2] reaction rates such that efficient AAC cross coupling is achieved with 10 mol% **41** (Table 5, entry c). Similarly, ethylketene trimerization is sufficiently retarded relative to the AAC process that 10 mol% **41** affords efficient cross coupling for both enolizable aliphatic and unsaturated aldehydes (Table 5, entries d-g). Propylketene and isopropylketene, derived from valeryl bromide and isovaleryl bromide, respectively, also participate in highly stereoselective AAC reactions under the 2nd generation reaction conditions, although isopropylketene reactions are currently limited to electron-deficient, non-enolizable aldehydes (Table 5, entries k-l).

Asymmetric catalytic acid bromide-aldehyde cyclocondensation reactions afforded a convenient method for preparing highly enantiomerically enriched β-lactones (**45a-l**) as masked propionate aldol products. This methodology provides an effective strategy for executing enantioselective C-C bond constructions that constitute surrogates for typical cross ester aldol addition reactions. These catalyzed aldol variants are characterized by their operational simplicity and their use of inexpensive, commercially available reaction components.

Table 5. Catalytic asymmetric substituted ketene-aldehyde cyclocondensation*



entry	R^1	R^2	catalyst loading mol%	% ee [a]	syn:anti [b, c]	% yield [d]
a	Me	CH_2CH_2Ph	20	90	95:5	71
b	Me	CH_2CH_2OBn	20	91	86:14	75
c	Me	Ph	10	96	98:2	80
d	Et	CH_2CH_2Ph	10	91	95:5	81
e	Et	CH_2OBn	10	93	89:11	78
f	Et	CH_2CH_2OBn	10	91	88:12	83
g	Et	Ph	10	94	98:2	83
h	^{n}Pr	CH_2CH_2Ph	10	80	95:5	91
i	^{n}Pr	CH_2CH_2OBn	10	91	91:9	88
j	^{n}Pr	Ph	10	96	98:2	85
k	^{i}Pr	$C{\equiv}CSiMe_3$	10	94	98:2	71[e]
l	^{i}Pr	Ph	10	96	98:2	84

[a] Enantiomeric ratios assayed by chiral HPLC. [b] Diastereomeric ratios determined by ^{1}H NMR of crude product mixtures. [c] Relative and absolute stereochemical assignments based on prior literature precedent; see reference 24. Absolute stereochemistry of compound **45** shown here. [d] Yields for diastereomerically pure materials except entries f and i (diastereomers were inseparable). [e] Yield for the amide derived from amine-mediated ring opening of the crude β-lactone. see experimental for details. * Investigation performed in collaboration with Dr. Cheng Zhu.

2.4 NUCLEAR MAGNETIC RESONANCE STUDIES OF 2ND GENERATION CATALYST 41

Given the trigonal monopyramidal catalyst structure, unsymmetric ligands potentially generate two diastereomeric Al complexes (Figure 13).

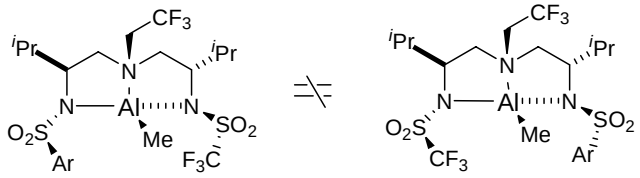
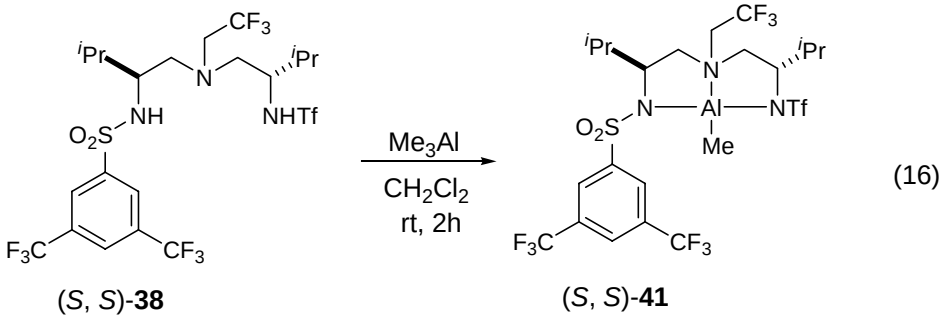


Figure 13. Diastereomers from unsymmetric ligand

To probe the diastereomeric ratio of 2nd generation catalyst, the Al-triamine complex **41** was examined by ^{1}H NMR. The catalyst **41** was prepared by treating unsymmetric ligand **38** with $AlMe_3$ in CH_2Cl_2 at ambient temperature. After stirring 2 h, the solvent was removed *in vacuo* and the crude product was washed with pentane once, and the Al-triamine complex **41** was obtained as a white solid (eq 16), this white solid was stored in the glovebox and was used for ^{1}H NMR analysis (Figure 14).



(*S*, *S*)-**38** (*S*, *S*)-**41** (16)

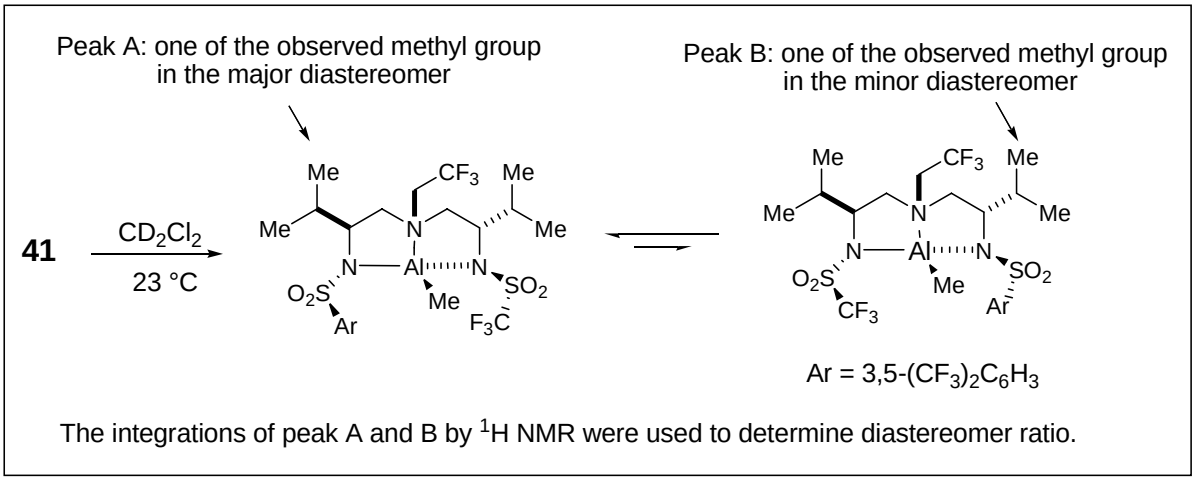


Figure 14. ^{1}H NMR spectra analysis of diastereomers

^{1}H NMR spectrum of the catalyst **41** solution in CD_2Cl_2 was taken after 25, 75 and 900 min at ambient temperature, giving about 2:1 (Figure 15), 2.5:1 (Figure 16) and 7:1 (Figure 17) diastereomeric complexes ratios respectively, and after 900 min, the diastereomeric ratio remained about 7:1.

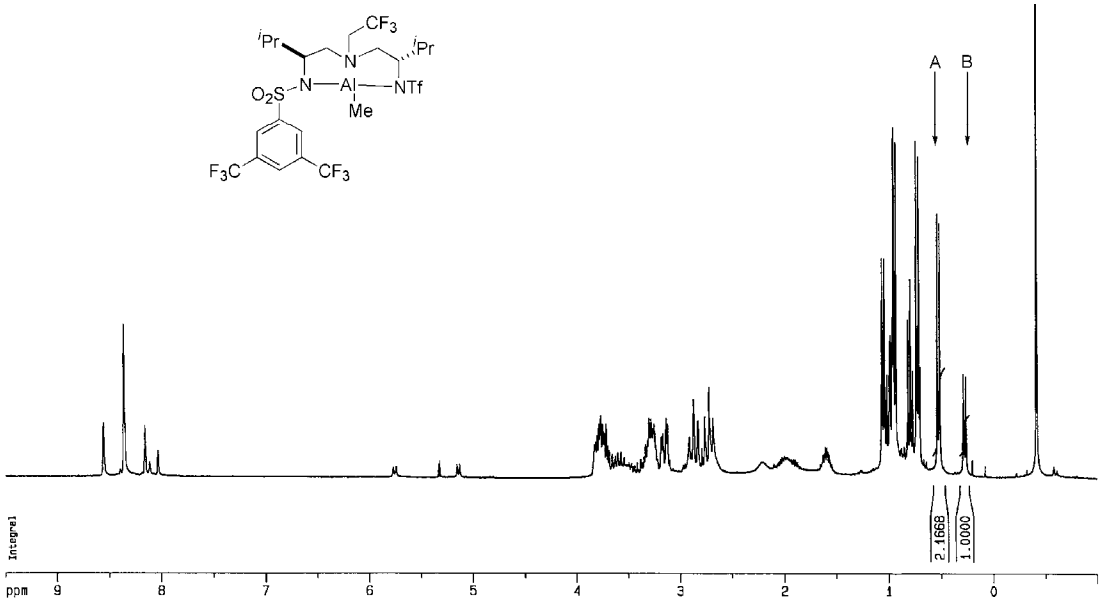


Figure 15. ^{1}H NMR spectrum of 2nd generation catalyst **41** in CD_2Cl_2, 25 min (dr = 2:1)

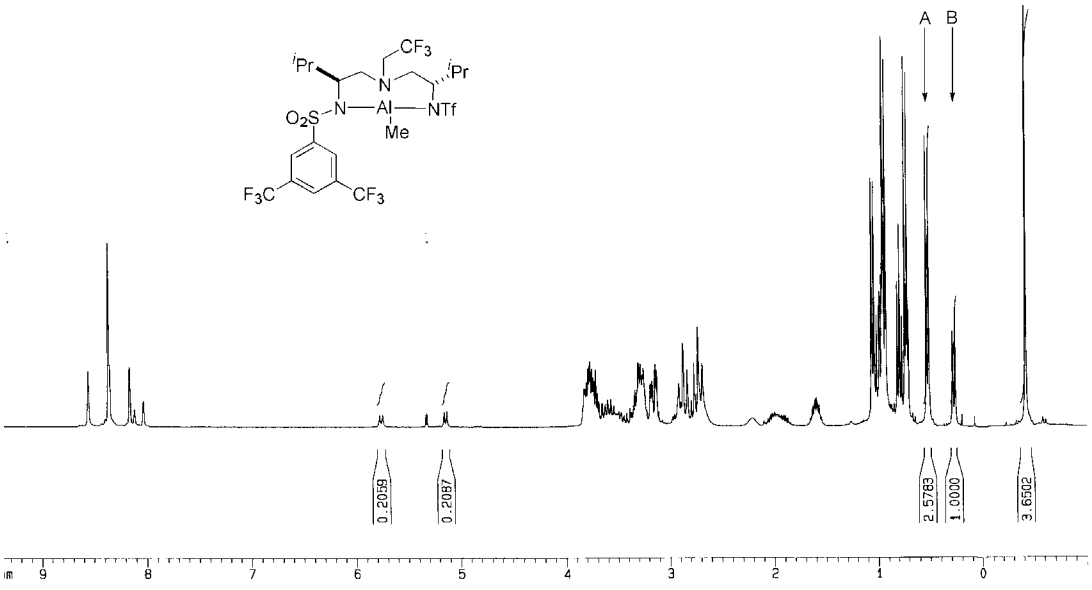


Figure 16. ^{1}H NMR spectrum of 2nd generation catalyst **41** in CD_2Cl_2, 75 min (dr = 2.5:1)

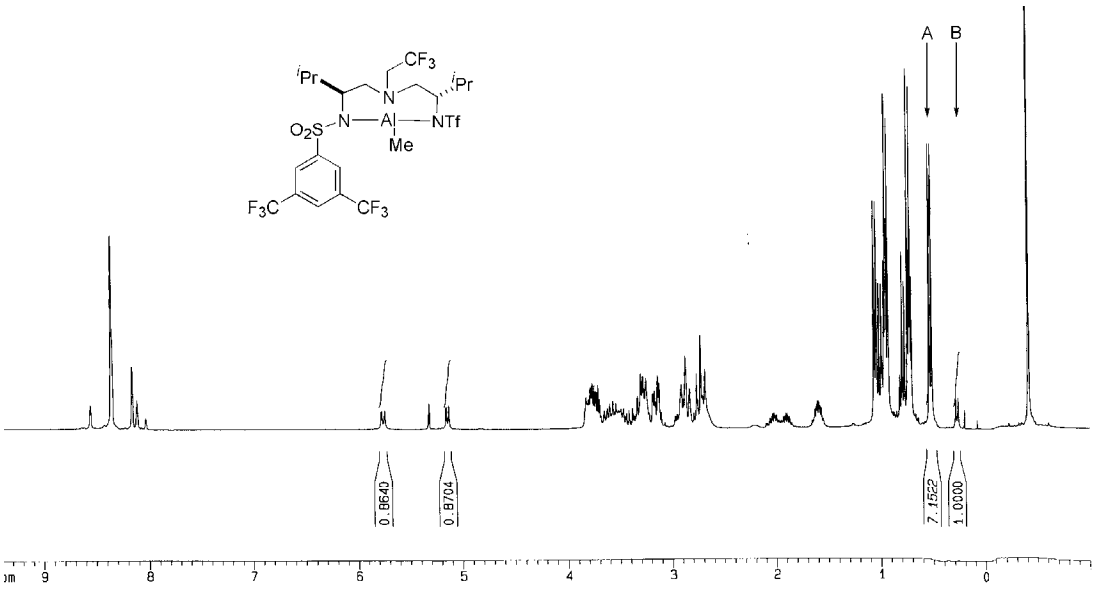


Figure 17. ^{1}H NMR spectrum of 2nd generation catalyst **41** in CD_2Cl_2, 900 min (dr = 7:1)

In order to further understand the diastereomeric Al-triamine complex, we prepared diastereomerically pure **41** by recrystallizing **41** from CH_2Cl_2 and pentane. ^{1}H NMR analysis of the recrystallized 2nd generation catalyst in CD_2Cl_2 at 5 min revealed a 30:1 bias favoring one diastereomer (Figure 18), however, after 2 h in the CD_2Cl_2, the ratio of two diastereomers went down to about 10:1 (Figure 19), and after 24 h, the diastereomeric ratio went back to 7:1. These NMR analyses of 2nd generation catalyst revealed a 7:1 bias favoring one diastereomer in CD_2Cl_2 (Figure 20).

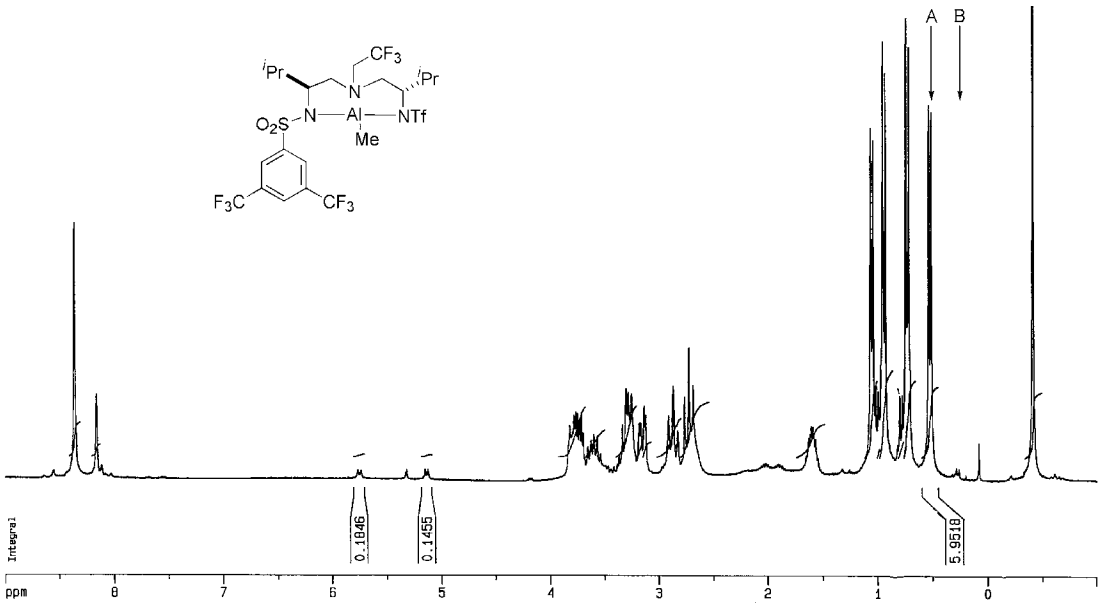


Figure 18. ^{1}H NMR spectrum of crystallized 2nd generation catalyst in CD_2Cl_2 5 min (dr = 30:1)

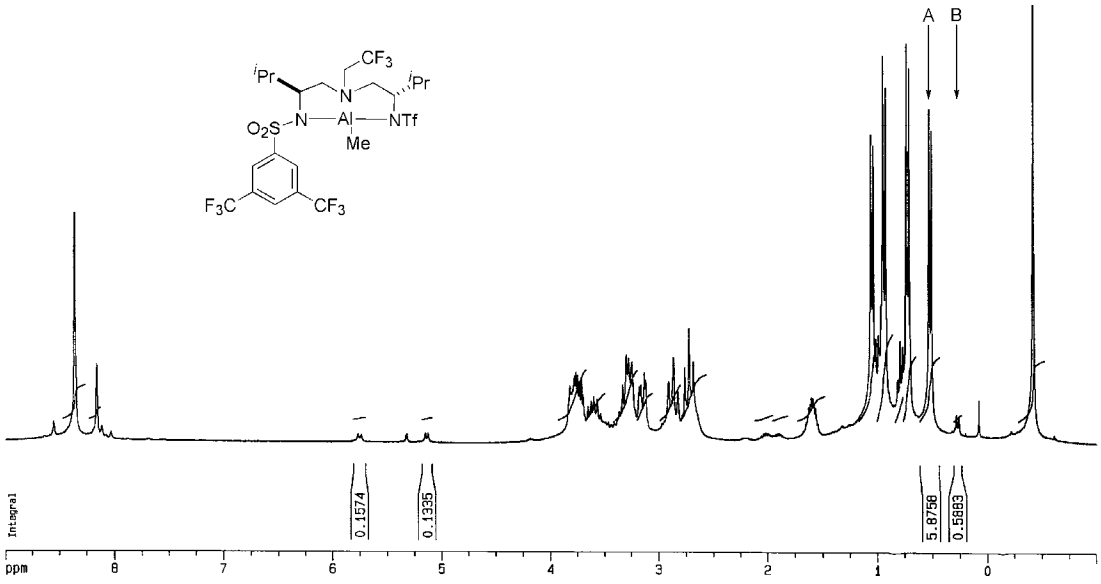


Figure 19. ^{1}H NMR spectrum of crystallized 2nd generation catalyst in CD_2Cl_2 120 min (dr = 10:1)

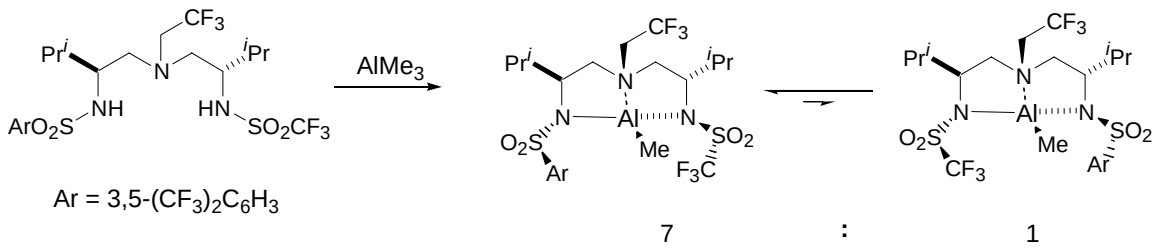


Figure 20. Equilibrium between two diastereomers

Later, crystallographic analysis of a closely related complex **46** by single crystal revealed that the major diastereomer to orient the large aryl sulfonamide group in the sterically less congested outside position relative to the [3.3.0] ring system defined by the Al-coordinated triamine ligand (Figure 21).* This indicated the major diastereomer was the active catalyst for AAC reactions.

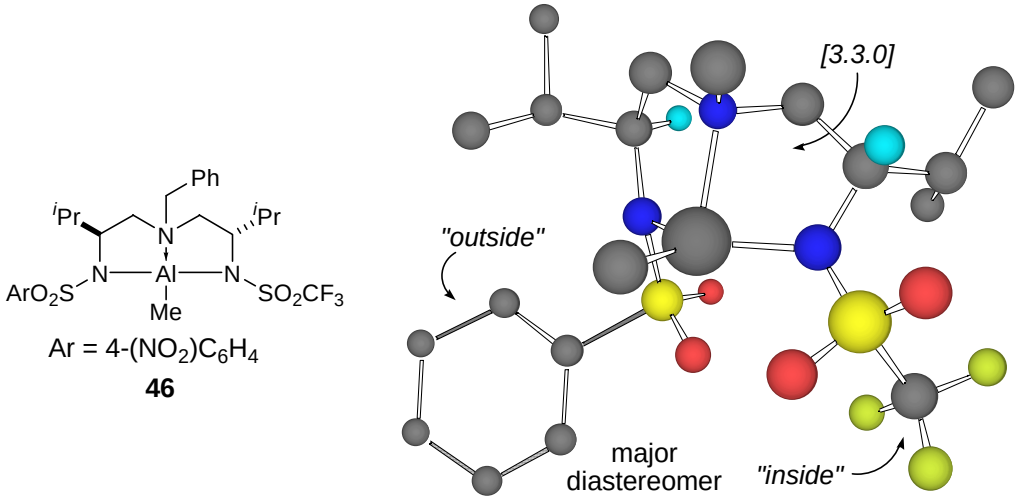


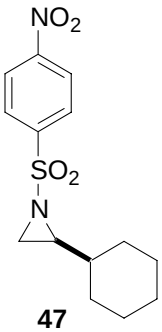
Figure 21. X-ray crystal structure **46**

2.5 EXPERIMENTALS

General Information: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature and are reported as follows: $[\alpha]_\lambda$ (c g/100mL). Infrared spectra were recorded on a Nicolet Avatar 360 FT-IR spectrometer. NMR spectra were recorded on a Bruker Avance-300 (300 MHz) spectrometer with chemical shifts reported relative to residual $CHCl_3$ (7.27 ppm) for ^1H and $CDCl_3$ (77.0 ppm) for ^{13}C NMR spectra. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp, 190-600 nm) using a Daicel Chiracel™ OD-H column (250 x 4.6 mm) (Daicel Inc.) or Daicel Chiralpak™ AD column (250 x 4.6 mm) (Daicel Inc.) and HPLC-grade isopropanol and hexanes as the eluting solvents. Analytical gas-liquid chromatography (GLC) was performed on a Varian 3900 gas chromatography equipped with a flame ionization detector and split mode capillary injection system using a Chiraldex™ G-TA column (20 m x 0.25 mm) (Advanced Separation Technologies Inc.). Helium was used as the carrier gas at the indicated pressures.

Unless otherwise stated, all reactions were carried out in dry glassware under a nitrogen atmosphere using standard inert atmosphere techniques for the manipulation of solvents and reagents. Anhydrous solvents (CH_2Cl_2, THF, DMF, diethyl ether, pentane and toluene) were obtained by passage through successive alumina and Q5 reactant-packed columns on a solvent purification system. *N*, *N*-Diisopropylethylamine and triethylamine were distilled under nitrogen from CaH_2. Trimethylaluminum (2.0M in hexane) and benzotrifluoride (BTF) were purchased from Aldrich in Sure/Seal™ bottles. $[(^cC_8H_{14})_2IrCl]_2$,[36] 3-Benzyloxypropionaldehyde[37] and

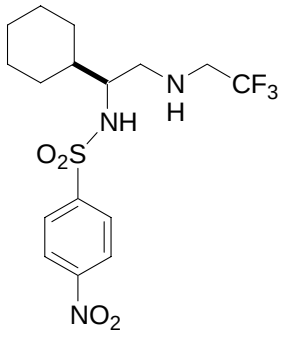
trimethylsilanylpropynal[38] were prepared according to published procedures. All commercially available aldehydes were redistilled under N_2. Anhydrous $LiClO_4$ (ReagentPlus) and LiI were purchased from Aldrich. O-trimethylsilyl quinidine (TMS-QD) and O-trimethylsilyl quinine (TMS-QN) was prepared according to the literature procedure[11](TMSCl was added at 0°C for large scale). Commercially available acetyl chloride, propionyl chloride, butyryl chloride and valeryl chloride were redistilled under N_2. Commercially available propionyl bromide and valeryl bromide were distilled from P_2O_5. Butyryl bromide and isovaleryl bromide were prepared according to literature procedures and were distilled from P_2O_5.[39] Flash chromatography was performed as previously described on EM silica gel 60 (230-240 mesh).[40]



47

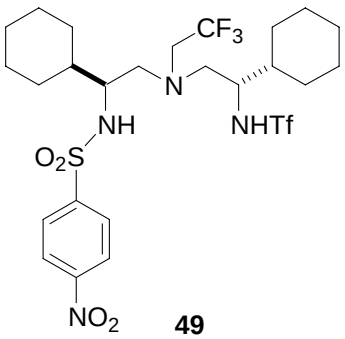
(*S*)-2-Cyclohexyl-1-(4-nitrobenzenesulfonyl)aziridine (47): To a solution of 1.00 g of (*S*)-2-amino-2-cyclohexylethanol (7.00 mmol, 1.00 eq) and 43.0 mg of DMAP (0.35 mmol, 0.05 equiv) in 25 mL of CH_2Cl_2 at 0 °C was added 3.90 mL of Et_3N (28.0 mmol, 4.00 equiv). To the resulting solution was added 3.41 g of 4-nitrobenzenesulfonyl chloride (15.4 mmol, 2.20 equiv) in portions. After addition was complete, the reaction mixture was warmed to ambient temperature and stirred for 5 h. The reaction mixture was poured into brine (50 mL) and extrated with 50 mL CH_2Cl_2 twice. The organic portion was washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography (9% ethyl acetate in hexane) to afford 1.50 g (69%) of the title compound as slightly yellow solid. $[\alpha]_D$ +15.7 (*c* 1.66, $CHCl_3$); IR (KBr Plate): 2925, 2851, 1532, 1349, 1312, 1169, 944, 887 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.8 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 2H), 2.74-2.70 (m, 2H), 2.21 (d, *J* = 4.0 Hz, 1H), 1.74-1.64 (m, 4H), 1.54-1.50 (m, 1H), 1.20-1.10 (m, 4H), 1.05-0.93 (m,

2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 144.0, 129.3, 124.2, 45.9, 39.2, 33.4, 30.1, 29.5, 25.8, 25.4, 25.2; HRMS (*ESI*) calcd for (M^++Na) $C_{14}H_{18}N_2O_4SNa$: 333.0885; found: 333.0893.



48

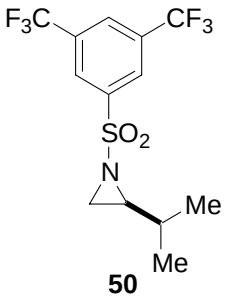
(*S*)-*N*-1-Cyclohexyl-2-(2',2',2'-trifluoroethylamino)ethyl-4-nitrobenzenesulfonamide (48): A mixture of 1.41 g of (*S*)-2-cyclohexyl-1-(4-nitrobenzenesulfonyl)aziridine **47** (4.55 mmol, 1.00 equiv) and 1.10 mL of 2,2,2-trifluoroethylamine (13.7 mmol, 3.00 equiv) was placed in a sealed Pyrex® tube and the mixture stirred at ambient temperature for 1 h, then heated at 50 °C for 15 h and finally heated at 70 °C for 4 h . The reaction mixture was then cooled to ambient temperature and the remaining 2, 2, 2-trifluoroethylamine was evaporated *in vacuo*. The resulting crude product was used directly for next step. $[\alpha]_D$ +8.90 (*c* 1.85, $CHCl_3$); IR (KBr Plate): 3413, 3252, 2930, 2855, 1528, 1351, 1336, 1310, 1263, 1155, 1110, 854, 737 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H), 5.05 (d, *J* = 8.2 Hz, 1H), 3.17-3.14 (m, 1H), 3.07 (q, *J* = 9.3 Hz, 2H), 2.84 (dd, *J* = 12.6, 5.9 Hz, 1H), 2.60 (dd, *J* = 12.6, 4.2 Hz, 1H), 1.69-1.40 (m, 8H), 1.17-1.04 (m, 2H), 0.93-0.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 146.7, 128.2 (2C), 125.2 (q, *J* = 278.2 Hz), 124.2 (2C), 59.0, 50.4 (q, *J* = 31.4 Hz), 49.8, 39.8, 29.0 (2C), 25.9 (3C); HRMS (*ESI*) calcd for (M^++H) $C_{16}H_{23}F_3N_3O_4S$: 410.1361; found: 410.1380.



49

(*1S,2'S*)-*N*-(1-Cyclohexyl-2-[(2'-cyclohexyl-2'-trifluoro-methanesulfonylaminoethyl)-(2,2,2-trifluoroethyl)amino]ethyl)-4-nitrobenzenesulfonamide (49):(*S*)-*N*-[1-Cyclohexyl-2-(2,2,2-trifluoroethyl-amino)ethyl]-4-nitrobenzenesulfonamide **48** 1.75g

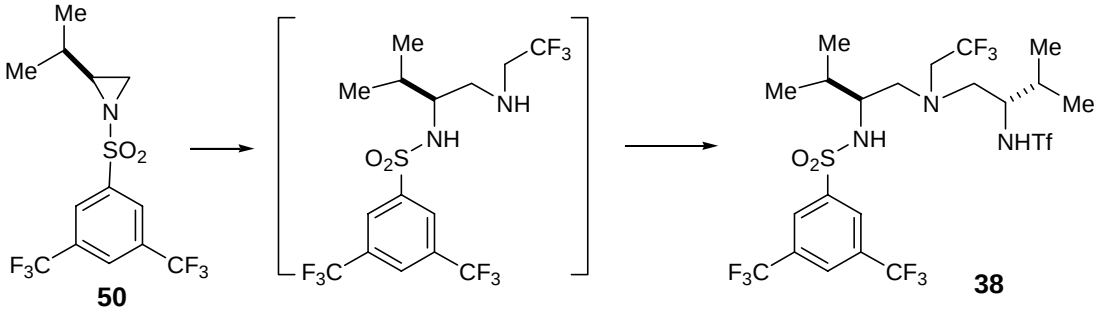
(4.28 mmol, 1.00 equiv) was combined with 1.10 g of (*S*)-2-Cyclohexyl-1-trifluoromethanesulfonyl-aziridine (4.28 mmol, 1.00 equiv)[40] and the mixture stirred at ambient temperature for 10 min then heated at 80 °C for 16 h. After cooling to ambient temperature, the crude product mixture was purified by flash chromatography (20% ethyl acetate in hexane) to afford 2.65 g (93%) of the title compound. $[\alpha]_D$ −7.10 (*c* 2.11, $CHCl_3$); IR (KBr Plate): 3309, 2931, 2857, 1534, 1451, 1351, 1229, 1197, 1148, 1093, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 8.8 Hz, 2H), 6.20 (d, *J* = 8.9 Hz, 1H), 5.28 (d, *J* = 7.7 Hz, 1H), 3.73-3.58 (m, 1H), 3.55-3.44 (m, 2H), 3.16-2.93 (m, 4H), 2.81 (dd, *J* = 14.0, 8.3 Hz, 1H), 1.93-1.50 (m, 12H), 1.32-0.93 (m, 8H), 0.88-0.70 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 146.8, 128.0 (2C), 125.9 (q, *J* = 284.2 Hz), 124.3 (2C), 119.3 (q, *J* = 318.4 Hz), 58.8, 57.0, 55.4, 55.3, 53.5 (q, *J* = 28.7 Hz), 39.6 (2C), 29.2(2C), 28.0, 27.9, 26.0 (6C); HRMS (*ESI*) calcd for (M^++Na) $C_{25}H_{36}N_4O_6F_6S_2Na$: 689.1878; found: 689.1853.



50

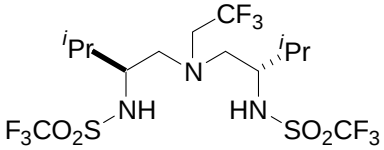
(*S*)-*N*-[3,5-(Bistrifluoromethyl)benzenesulfonyl]-2-isopropylaziridine (50): To a solution of 2.05 g of (*S*)-valinol (19.9 mmol, 1.00 eq) and 122 mg of DMAP (1.00 mmol, 0.05 equiv) in 40 mL of CH_2Cl_2 at –25 °C was added 11.0 mL of Et_3N (80.0 mmol, 4.00 equiv). To the resulting solution was added 6.84 g of 3, 5-bis(trifluoromethyl)benzenesulfonyl chloride (21.9 mmol, 1.10 equiv) in portions. After addition was complete, the reaction mixture was warmed to 0 °C and stirred for 2 h whereupon 1.85 mL of MsCl (23.9 mmol, 1.20 equiv) was added dropwise and the resulting reaction mixture was stirred an additional 2 h at 0 °C. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (50 mL) and the layers were shaken and separated. The organic portion was washed with brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The

crude product mixture was purified by flash chromatography (9% ethyl acetate in hexanes) to afford 4.96 g (69%) of the title compound as a colorless oil. $[\alpha]_D$ +14.8 (*c* 2.24, $CHCl_3$); IR (thin film): 2968, 1626, 1470, 1362, 1274, 1166 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 2H), 8.15 (s, 1H), 3.03-2.71 (m, 2H), 2.25 (d, *J* = 4.2 Hz, 1H), 1.51 (m, 1H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 133.0 (q, *J* = 34.4 Hz), 128.3, 126.9 (m), 122.4 (q, *J* = 271.7 Hz), 47.3, 33.8, 30.1, 19.4, 18.9; HRMS (*EI*) calcd for (M^+ + H) $C_{13}H_{14}NO_2F_6S$: 362.0649; found: 362.0640.



***N*-[(*S*)-*N*'-Trifluoromethylsulfonyl-2-amino-3-methylbutyl]-*N*-[(*S*)-*N*''-[3,5-bis(trifluoromethyl)benzenesulfonyl]-2'-amino-3'-methylbutyl]-2,2,2-trifluoroethyl amine (38):** A mixture of 4.96 g of (*S*)-[3,5-bis(trifluoromethyl)benzenesulfonyl]-2-iso-propylaziridine **50** (13.7 mmol, 1.00 equiv) and 3.30 mL of 2,2,2-trifluoroethylamine (41.2 mmol, 3.00 equiv) was placed in a sealed Pyrex® tube and heated at 50 °C for 12 h. The reaction was then cooled to ambient temperature and the remaining 2,2,2-trifluoroethylamine was evaporated *in vacuo*. The resulting crude (*S*)-*N*-[3,5-bis(trifluoromethyl)benzenesulfonyl]-*N*'-(2',2',2'-trifluoroethyl)-2-isopropylethylene diamine was combined with 3.43 g of (*S*)-*N*-trifluoromethylsulfonyl-2-isopropylaziridine[40] (15.8 mmol, 1.20 equiv) and the mixture stirred at ambient temperature for 1 h then heated at 80 °C for 3 h. After cooling to ambient temperature, the crude product mixture was purified by flash chromatography (25% to 33% ethyl acetate in hexane) to afford 9.00 g

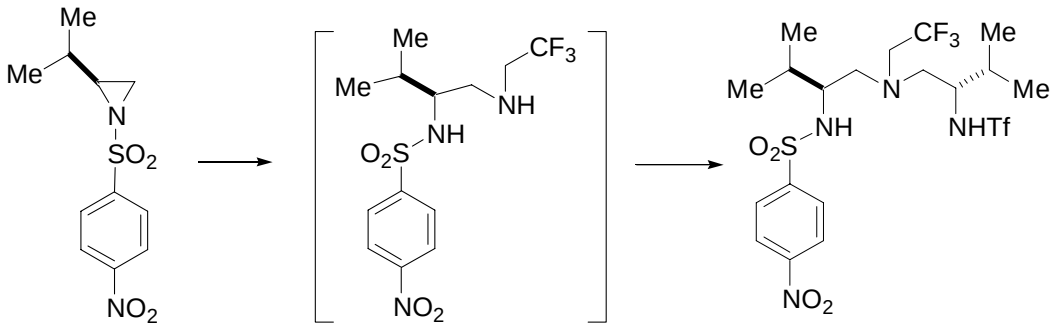
(97%) of the title compound; crystallization of purified **38** from CH_2Cl_2/hexane afforded 7.68 g of **38** (83 %) as colorless needles: mp 99-100 °C. $[\alpha]_D$ –8.50 (*c* 2.02, $CHCl_3$); IR (thin film): 3302, 1361, 1281 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 2H), 8.08 (s, 1H), 6.08 (d, *J* = 8.9 Hz, 1H), 5.35 (d, *J* = 7.4 Hz, 1H), 3.73-3.48 (m, 3H), 3.21-2.99 (m, 3H), 2.93 (dd, *J* = 14.3, 8.0 Hz, 1H), 2.79 (dd, *J* = 14.0. 8.6 Hz, 1H), 2.07-1.87 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 133.0 (q, *J* = 34.4 Hz), 127.2 (m), 126.2 (m), 126.0 (q, *J* = 284.0 Hz), 122.5 (q, *J* = 271.7 Hz), 119.4 (q, *J* = 318.1 Hz), 59.3, 57.6, 55.5, 55.2, 53.7 (q, *J* = 29.0 Hz), 29.9, 29.7, 18.43, 18.39, 17.6, 17.3; HRMS (*EI*) *m/z* calcd for (M^++H) $C_{21}H_{28}N_3O_4F_{12}S_2$: 678.1330; found: 678.1339.



51

(*S,S*)-*N*-(2-Methyl-1-([(3-methyl-2-trifluoromethanesulfonylaminobutyl)-(2,2,2-trifluoroethyl)amino]methyl)propyl)trifluoromethanesulfonamide (51) : To the (*S*)-*N*-triflic-2-isopropylaziridine 6.05g (50% purity, 13.9 mmol) was added 0.69 g of 2,2,2-trifluoroethylamine (6.96 mmol, 0.50 eq) dropwise at ambient temperature, the mixture was stirred for 4.5 h at ambient temperature, then heated at 80 ºC for 4 h. After cooling to ambient temperature, flash chromatography of the mixture (10% ethyl acetate in hexanes) and recrystallization from CH_2Cl_2/hexane gave 2.99 g of the title compound (80%) as colorless solid: $[\alpha]_D$ –9.50 (*c* 1.59, $CHCl_3$); IR (KBr Plate): 3366, 3289, 2970, 1381, 1360, 1233, 1192, 1149 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.48 (d, *J* = 8.9 Hz, 2H), 3.56 (dq, *J* = 16.4, 9.3 Hz, 1H), 3.49-3.40 (m, 2H), 3.21-3.09 (m, 1H), 3.05 (dd, *J* = 14.3, 4.9 Hz, 2H), 2.90 (dd, *J* = 14.3, 7.1 Hz, 2H), 2.05-1.89 (m, 2H), 1.02 (d, *J* = 6.8 Hz, 6H), 0.96 (d, *J* = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$)

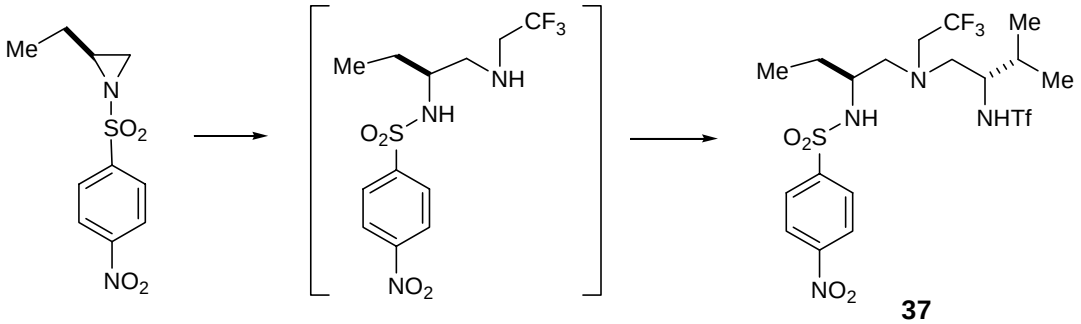
δ 125.8 (q, *J* = 283.3 Hz), 119.3 (q, *J* = 318.2 Hz), 59.4, 56.2, 53.8 (q, *J* = 29.2 Hz), 29.3, 18.6, 17.0; HRMS (*ESI*) calcd for (M^++Na) $C_{14}H_{24}F_9N_3O_4S_2Na$: 556.0962; found: 556.0967.



35

(*S,S*)-*N*-(2-Methyl-1-([(3-methyl-2-trifluoromethanesulfonylaminobutyl)-(2,2,2-trifluoroethyl)amino]methyl)propyl)-4-nitrobenzenesulfonamide (35): A mixture of (*S*)- 2-isopropyl-1-(4-nitrobenzenesulfonyl)aziridine[41] 1.62 g (6.00 mmol) and 1.78 g of 2,2,2-trifluoroethylamine (18.0 mmol, 3.00 eq) was placed in a sealed Pyrex® tube and heated at 50 °C for 12 h. The reaction was then cooled to ambient temperature and the remaining 2,2,2-trifluoroethylamine was evaporated *in vacuo*. The resulting crude (*S*)- *N*-(2-methyl-1-[(2,2,2-trifluoroethylamino)methyl]propyl)-4-nitrobenzenesulfonamide was combined with 4.23 g of (*S*)-*N*-triflic-2-isopropylaziridine (50% purity, approx. 9 mmol, 1.5 equiv) and the mixture stirred at ambient temperature for 1 h then heated at 80 °C for 3 h. After cooling to ambient temperature, the crude product mixture was purified by flash chromatography (10% ethyl acetate in hexane) to afford 2.01 g (57%, two steps) of the title compound. $[\alpha]_D$ –20.5 (*c* 1.85, $CHCl_3$); IR (KBr Plate): 3301, 3220, 2968, 1536, 1469, 1379, 1352, 1198, 1170, 1144, 1098 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.9 Hz, 2H), 8.06 (d, *J* = 8.9 Hz, 2H), 6.25 (d, *J* = 8.9 Hz, 1H), 5.31 (d, *J* = 7.6 Hz, 1H), 3.75-3.59 (m, 1H), 3.55-3.46 (m, 2H), 3.21-2.92 (m, 4H), 2.80 (dd, *J* = 13.9, 8.5 Hz, 1H), 1.99 (sextet, *J* = 6.8 Hz, 1H), 1.89-1.78 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.9

Hz, 3H), 0.77 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 146.8, 128.0, 126.0 (q, J = 288.4 Hz), 124.3, 119.3 (q, J = 318.2 Hz), 59.3, 57.4, 55.4, 55.0, 53.4 (q, J = 28.9 Hz), 29.81, 29.78, 18.50, 18.48, 17.7, 17.4; HRMS (*ESI*) calcd for (M^++Na) $C_{19}H_{28}F_6N_4O_6S_2Na$: 609.1252; found: 609.1238.



37

(*S,S*)-*N*-[1-Ethyl-6-methyl-3-(2,2,2-trifluoroethyl)-5-trifluoromethanesulfonylamino heptyl]-4-nitrobenzenesulfonamide (37): A mixture of (*S*)-2-Ethyl-1-(4-nitrobenzenesulfonyl)aziridine[41] 200 mg (0.78 mmol) and 249 mg of 2,2,2-trifluoroethylamine (2.34 mmol, 3.00 eq) was placed in a sealed Pyrex® tube and stirred at ambient temperature for 2 h, then heated at 50 °C for 17 h. The reaction was then cooled to ambient temperature and the remaining 2,2,2-trifluoroethylamine was evaporated *in vacuo*. The resulting crude (*S*)-4-nitro-*N*-(1-[(2,2,2-trifluoroethylamino)methyl]propyl)-benzenesulfonamide was combined with 170 mg of (*S*)-*N*-triflic-2-isopropylaziridine (0.78 mmol, 1.0 equiv) and the mixture stirred at ambient temperature for 1 h and heated at 45 °C for 1 h, then heated at 80 °C for 15h. After cooling to ambient temperature, the crude product mixture was purified by flash chromatography (10% ethyl acetate in hexane) to afford 410 mg (91%, two steps) of the title compound. $[\alpha]_D$ –18.2 (*c* 1.73, $CHCl_3$); IR (KBr Plate): 3328, 2973, 1542, 1351, 1195, 1167, 1092 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, J = 8.9 Hz, 2H), 8.07 (d, J = 8.9 Hz, 2H), 5.99 (d, J = 9.0 Hz, 1H), 5.39

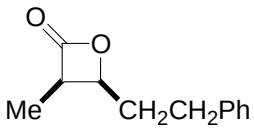
(d, J = 6.8 Hz, 1H), 3.68-3.46 (m, 3H), 3.18-3.03 (m, 3H), 2.88 (d, J = 9.5 Hz, 1H), 2.81 (dd, J = 14.5, 7.8 Hz, 1H), 2.01-1.93 (m, 1H), 1.55-1.45 (m, 2H), 1.03 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.9 Hz, 3H), 0.74 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.9, 146.7, 128.1, 125.8 (q, J = 283.4 Hz), 124.3, 119.3 (q, J = 318.2 Hz), 59.0, 58.1, 55.6, 53.9, 53.8 (q, J = 29.4 Hz), 29.8, 25.8, 18.4, 17.1, 9.6; HRMS (*ESI*) calcd for (M^++H) $C_{18}H_{27}F_6N_4O_6S_2$ 573.1276; found: 573.1257.

General procedure A: Al-triamine catalyzed asymmetric AAC reaction

To a solution of triamine ligand (0.10 mmol) in 2.0 mL of BTF at ambient temperature was slowly added 0.050 mL of a 2.0 M hexane solution of $AlMe_3$ (0.10 mmol). After stirring for 2 hours, the resulting catalyst solution was cooled to –25 °C and 0.35 mL of *N*, *N*-diisopropylethylamine (2.0 mmol) and 2-4 equiv of acid bromide were added consecutively (see table below). The resulting heterogeneous mixture was stirred 10-30 min at –25 °C (10 min: propionyl bromide; 15 min: butyryl bromide; 20 min: isovaleryl bromide; 30 min: valeryl bromide) whereupon aldehyde (1.0 mmol) was added dropwise and the reaction was stirred 14 h at –25 °C. The reaction was quenched at –25 °C by adding 10 mL of a 3% Et_3N-Et_2O solution (v/v) and the resulting mixture was filtered through silica gel (pretreated with 3% Et_3N-Et_2O) eluting with 60 mL of Et_2O. The filtrate was concentrated *in vacuo* and the crude product mixture was purified by flash chromatography (for benzaldehyde-derived lactones, the silica gel was pretreated with 2% Et_3N-hexanes).

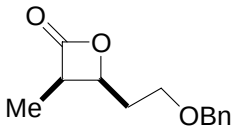
Table 6. Acid bromide and catalyst stoichiometry used for enolizable and non-enolizable aldehydes

Aldehyde / Ketene	Enolizable (catalyst, acid bromide)	Non-enolizable (catalyst, acid bromide)
Methyl ketene	20 mol %, 4 equiv	10 mol %, 2 equiv
Ethyl ketene	10 mol %, 4 equiv	10 mol %, 2 equiv
^{n}Propyl ketene	10 mol %, 4 equiv	10 mol %, 2 equiv
^{i}Propyl ketene	NA	10 mol %, 2 equiv



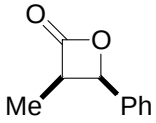
45a

***(3R, 4S)*-3-Methyl-4-phenethyloxetan-2-one (45a)**: General procedure A was followed employing 136 mg of ligand **38** (0.20 mmol, 20 mol%) and 132 μL of hydrocinnamaldehyde (1.0 mmol). Purification by flash chromatography (10% ethyl acetate in hexane) gave 135 mg (71%) of the title compound as colorless oil. Separation of enantiomers by Chiral HPLC [Daicel Chiracel^{TM} OD-H column, flow rate 1.0 mL/min, 5% ^{i}PrOH, 95% hexane T_r: 13.7 min (3*S*, 4*R*), 14.5 min (3*R*, 4*S*)] provided the enantiomer ratio (3*R*, 4*S*): (3S, 4R) = 94.5:5.5 (89% ee). $[\alpha]_D$ –42.3 (*c* 1.89, $CHCl_3$); IR (thin film): 1821, 1455 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H), 4.59 (ddd, *J* = 10.5, 6.4, 4.1 Hz, 1H), 3.76 (qd, *J* = 7.8, 6.5 Hz, 1H), 2.90 (ddd, *J* = 13.8, 9.4, 5.3 Hz, 1H), 2.72 (ddd, *J* = 13.8, 8.8, 7.5 Hz, 1H), 2.13-1.97 (m, 2H), 1.29 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 140.2, 128.4, 128.3, 126.1, 74.5, 47.0, 31.7, 31.3, 7.9; HRMS (*EI*) *m/z* calcd for (M^+) $C_{12}H_{14}O_2$: 190.0994; found: 190.0990.



45b

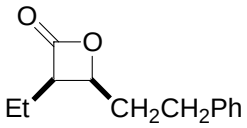
***(3R, 4S)*-4-(2-Benzyloxyethyl)-3-methyloxetan-2-one (45b)**: General procedure A was followed employing 136 mg of ligand **38** (0.20 mmol, 20 mol%) and 164 mg (1.0 mmol) of 3-benzyloxypropionaldehyde. Purification by flash chromatography (15% ethyl acetate in hexane) gave 165 mg (75%) of the title compound. Separation of the enantiomers by chiral HPLC (Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 10.6 (4*S*, 3*R*) and 15.7 (4*R*, 3*S*) min) provided the enantiomer ratio: (4*S*, 3*R*):(4*R*, 3*S*) = 95.5:4.5 (91% ee). $[\alpha]_D$ –40.4 (*c* 1.88, $CHCl_3$); IR (thin film): 2866, 1824, 1455, 1111 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.30 (m, 5H), 4.81 (ddd, *J* = 8.4, 6.5, 5.1 Hz, 1H), 4.54 (s, 2H), 3.78 (qd, *J* = 7.7, 6.7 Hz, 1H), 3.67-3.62 (m, 2H), 2.10-2.00 (m, 2H), 1.29 (d, *J* = 7.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 137.8, 128.3, 127.6, 127.5, 73.1, 72.7, 65.7, 47.2, 30.3, 8.1; HRMS (*EI*) *m/z* calcd for (M^+-CO) $C_{12}H_{16}O_2$: 192.1150; found: 192.1156.



45c

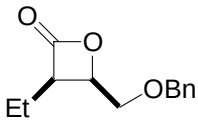
***(3R, 4R)*-3-Methyl-4-phenyloxetan-2-one (45c)**: General procedure A was followed employing 68 mg of ligand **38** (0.10 mmol, 10 mol%) and 102 μL (1.0 mmol) of benzaldehyde. Purification by flash chromatography (10% ethyl acetate in hexane) gave 130 mg (80%) of the title compound. Separation of the enantiomers by chiral HPLC (Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 3% ^{i}PrOH, 97% hexane, T_r 9.8 (3*R*, 4*R*) and 10.8 (3*S*, 4*S*) min) provided the enantiomeric ratio: (3*R*, 4*R*):(3*S*, 4*S*) = 98:2 (96% ee). $[\alpha]_D$ +138 (*c* 1.44, $CHCl_3$); IR (thin film): 2979, 1830, 1497, 1455, 1143, 1108 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.38 (m, 3H), 7.32-7.29 (m, 2H), 5.66 (d, *J* = 6.5 Hz, 1H), 4.06 (qd, *J* = 7.8,

6.5 Hz, 1H), 0.94 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2, 134.6, 128.6, 128.5, 125.7, 75.2, 50.1, 9.5; HRMS (*EI*) *m/z* calcd for (M^+) $C_{10}H_{10}O_2$: 162.0681; found: 162.0677.



45d

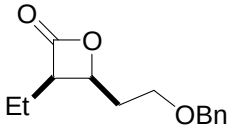
***(3R, 4S)*-3-Ethyl-4-phenethyloxetan-2-one (45d)**: General procedure A was followed employing 68 mg of ligand **38** (0.10 mmol, 10 mol%) and 132 μL (1.0 mmol) of hydrocinnamaldehyde. Purification by flash chromatography (9% ethyl acetate in hexane) gave 165 mg (81%) of the title compound. Separation of the enantiomers by chiral HPLC (Daicel Chirapak™ AD column, flow rate 0.7 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 8.4 (3*S,* 4*R*) and 9.1(3*R,* 4*S*) min) provided the enantiomer ratio: (3*S,* 4*R*):(3*R,* 4*S*) = 4.5:95.5 (91% ee). $[\alpha]_D$ –48.8 (*c* 1.37, $CHCl_3$); IR (thin film): 2969, 1821, 1497, 1455, 1106 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 4.56 (ddd, *J* = 10.1, 6.4, 3.6 Hz, 1H), 3.55 (ddd, *J* = 8.8, 7.7, 6.4 Hz, 1H), 2.91 (ddd, *J* = 14.0, 9.4, 5.1 Hz, 1H), 2.71 (ddd, *J* = 14.1, 8.7, 7.7 Hz, 1H), 2.16-1.78 (m, 3H), 1.74-1.60 (m, 1H), 1.07 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 140.4, 128.5, 128.4, 126.2, 74.4, 54.1, 31.9, 31.5, 17.3, 12.0; HRMS (*EI*) *m/z* calcd for (M^+) $C_{13}H_{16}O_2$: 204.1150; found: 204.1158.



45e

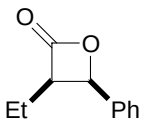
***(3R, 4R)*-4-(Benzyloxymethyl)-3-ethyloxetan-2-one (45e)**: General procedure A was followed employing 68 mg of ligand **38** (0.10 mmol, 10 mol%) and 140 μL (1.0 mmol) of benzyloxyacetaldehyde. Purification by flash chromatography (10% ethyl acetate in hexane) gave 172mg (78%) of the title compound. Separation of the enantiomers by chiral HPLC (Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 11.2 (3*R*, 4*R*) and 22.8 (3*S,* 4*S*) min) provided the enantiomeric ratio: (3*R*, 4*R*):(3*S,* 4*S*) = 96.5:3.5 (93% ee). $[\alpha]_D$ –8.00 (*c* 2.01, $CHCl_3$); IR (thin

film): 2970, 2878, 1828, 1455, 1372, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.29 (m, 5H), 4.71 (q, *J* = 5.5 Hz, 1H), 4.60 (s, 2H), 3.78 (d, *J* = 5.5 Hz, 2H), 3.64 (dt, *J* = 8.8, 6.9 Hz, 1H), 1.94-1.65 (m, 2H), 1.07 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 137.3, 128.4, 127.8, 127.6, 73.6, 72.9, 68.0, 54.2, 17.3, 12.1; HRMS (*EI*) *m/z* calcd for (M^+) $C_{13}H_{16}O_3$: 220.1099; found: 220.1109.



45f

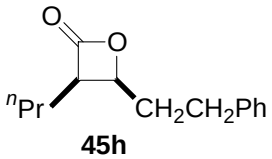
***(3R, 4S)*-4-(2-Benzyloxyethyl)-3-ethyloxetan-2-one (45f)**: General procedure A was followed employing 68 mg of ligand **38** (0.10 mmol, 10 mol%) and 164 mg (1.0 mmol) of 3-benzyloxypropionaldehyde. Purification by flash chromatography (14% ethyl acetate in hexane) gave 194 mg (83%) of the title compound as an 88:12 *syn:anti* mixture. Separation of the enantiomers by chiral HPLC (Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 8.5 (3*R*, 4*S*) and 13.3 (3*S*, 4*R*) min) provided the enantiomeric ratio: (3*R*, 4*S*):(3*S*, 4*R*) = 95.5:4.5 (91% ee). $[\alpha]_D$ –41.7 (*c* 2.06, $CHCl_3$); IR (thin film): 2969, 2877, 1824, 1496, 1455, 1116 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 4.80 (ddd, *J* = 9.8, 6.5, 4.0 Hz, 1H), 4.54 (s, 2H), 3.69-3.55 (m, 3H), 2.14-1.95 (m, 2H), 1.87-1.77 (m, 1H), 1.73-1.63 (m, 1H), 1.07 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 137.8, 128.2, 127.5, 127.4, 73.0, 72.4, 65.7, 54.0, 30.3, 17.3, 11.8; HRMS (*EI*) calcd for (M^++H) $C_{14}H_{19}O_3$: 235.1334; found: 235.1329.



45g

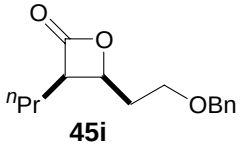
***(3R, 4R-)*-3-Ethyl-4-phenyloxetan-2-one (45g)**: General procedure A was followed employing 68 mg of ligand **38** (0.10 mmol, 10 mol%) and 102 μL (1.0 mmol) of benzaldehyde. Purification by flash chromatography (9% ethyl acetate in hexane) gave 146 mg (83%) of the title compound. Separation of the enantiomers by chiral

HPLC (Daicel Chiracel™ OD-H column, flow rate 0.5 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 13.3 (3*R,* 4*R*) and 16.1 (3*S,* 4*S*) min) provided the enantiomeric ratio: (3*R,* 4*R*):(3*S,* 4*S*) = 97:3 (94% ee). $[\alpha]_D$ +128 (*c* 2.08, $CHCl_3$); IR (thin film): 2970, 2938, 1825, 1497, 1455, 1111 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.32 (m, 5H), 5.64 (d, *J* = 6.4 Hz, 1H), 3.85 (ddd, *J* = 8.3, 8.3, 6.4 Hz, 1H), 1.57-1.41 (m, 1H), 1.35-1.21 (m, 1H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 134.7, 128.6, 128.4, 125.8, 75.1, 56.8, 18.6, 11.1; HRMS (*EI*) *m/z* calcd for (M^+) $C_{11}H_{12}O_2$: 176.0837; found: 176.0837.



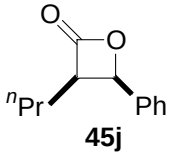
45h

***(3R, 4S)*- 4-Phenethyl-3-propyloxetan-2-one (45h)**: General procedure A was followed employing 68 mg of ligand **38** (0.10 mmol, 10 mol%) and 132 μL (1.0 mmol) of hydrocinnamaldehyde. Purification by flash chromatography (8% ethyl acetate in hexane) gave 200 mg (91%) of the title compound. Separation of the enantiomers by chiral HPLC (Daicel Chirapak™ AD column, flow rate 1.0 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 5.4 (3*S,* 4*R*) and 5.9 (3*R,* 4*S*) min) provided the enantiomeric ratio: (3*S,* 4*R*):(3*R,* 4*S*) = 10:90 (80% ee). $[\alpha]_D$ –37.1 (*c* 1.48, $CHCl_3$); IR (thin film): 2960, 1817, 1497, 1455, 1107 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 4.56 (ddd, *J* = 10.0, 6.4, 3.5 Hz, 1H), 3.63 (dt, *J* = 8.7, 6.7 Hz, 1H), 2.91 (ddd, *J* = 13.9, 9.4, 5.0 Hz, 1H), 2.71 (ddd, *J* = 14.1, 8.7, 7.7 Hz, 1H), 2.10-1.99 (m, 2H), 1.80-1.70 (m, 1H), 1.62-1.41 (m, 3H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 140.3, 128.4, 128.3, 126.1, 74.4, 52.1, 32.0, 31.4, 25.8, 20.6, 13.6; HRMS (*EI*) *m/z* calcd for (M^+) $C_{14}H_{18}O_2$: 218.1307; found: 218.1306.



45i

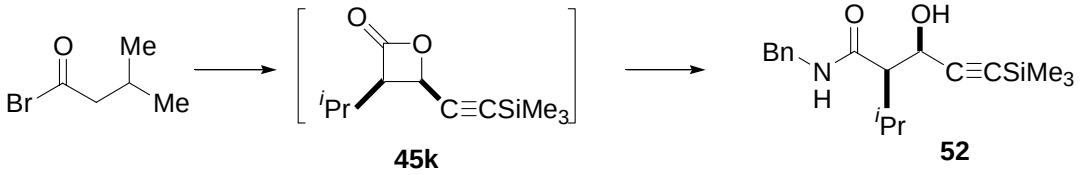
***(3R, 4S)*-4-(2-Benzyloxyethyl)-3-propyloxetan-2-one (45i)**: General procedure A was followed employing 68 mg of ligand **38** (0.10 mmol, 10 mol%) and 164 mg (1.0 mmol) of 3-benzyloxypropionaldehyde. Purification by flash chromatography (12% ethyl acetate in hexane) gave 218 mg (88%) of the title compound as a 91:9 *syn:anti* mixture. Separation of the enantiomers by chiral HPLC (Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 8.0 (3*R,* 4*S*) and 12.4 (3*S,* 4*R*) min) provided the enantiomeric ratio: (3*R,* 4*S*):(3*S,* 4*R*) = 95.5:4.5 (91% ee). $[\alpha]_D$ –37.5 (*c* 1.78, $CHCl_3$); IR (thin film): 2961, 2873, 1817, 1455, 1115 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 4.80 (ddd, *J* = 9.5, 6.4, 4.0 Hz, 1H), 4.54 (s, 2H), 3.71-3.60 (m, 3H), 2.13-1.96 (m, 2H), 1.84-1.33 (m, 4H), 0.95 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 137.8, 128.1, 127.4, 127.3, 72.9, 72.3, 65.6, 52.1, 30.4, 25.7, 20.4, 13.5; HRMS (*EI*) *m/z* calcd for (M^+-CO) $C_{14}H_{20}O_2$: 220.1463; found: 220.1466.



45j

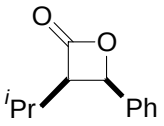
***(3R, 4R)*-4-Phenyl-3-propyloxetan-2-one (45j)**: General procedure A was followed employing 68 mg of ligand **38** (0.10 mmol, 10 mol%) and 102 μL (1.0 mmol) of benzaldehyde. Purification by flash chromatography (8% ethyl acetate in hexane) gave 161 mg (85%) of the title compound. Separation of the enantiomers by chiral HPLC (Daicel Chiracel™ OD-H column, flow rate 0.5 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 11.8 (3*R,* 4*R*) and 13.8 (3*S,* 4*S*) min) provided the enantiomeric ratio: (3*R,* 4*R*): (3*S,* 4*S*) = 98:2 (96% ee). $[\alpha]_D$ +116 (*c* 1.73, $CHCl_3$); IR (thin film): 2961, 2874, 1825, 1455, 1114 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.31 (m, 5H), 5.63 (d, *J* = 6.5 Hz, 1H), 3.93 (ddd, *J* = 8.5, 8.5, 6.5 Hz, 1H), 1.43-1.34 (m, 2H), 1.25-1.18 (m, 2H), 0.77 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 171.7, 134.7, 128.6, 128.4, 125.8, 75.1, 55.1, 27.0, 19.9, 13.5; HRMS (*EI*) *m/z* calcd for (M^+) $C_{12}H_{14}O_2$: 190.0994; found: 190.0998.



(2*R*, 3*R*)-3-Hydroxy-2-isopropyl-5-trimethylsilanylpent-4-ynoic acid, benzylamide (52) [from *(3R, 4R)*-3-isopropyl-4-trimethylsilanylethynyloxetan-2-one (**45k**)]: General procedure A was followed employing 68 mg of ligand **38** (0.10 mmol, 10 mol%) and 134 μL (1.0 mmol) of trimethylsilanylpropynal. Due to the volatility of the β-lactone, the crude product mixture was dissolved in 1 mL of CH_3CN and 109 μL of benzylamine (1.0 mmol) and DMAP (~1 mg) were added at ambient temperature. The resulting solution was stirred at ambient temperature for 15 h prior to evaoparting the volatiles *in vacuo*. The crude product mixture was purified by flash chromatography (20% ethyl acetate in hexane) to afford 225mg of (2*R*, 3*R*)-3-hydroxy-2-isopropyl-5-trimethylsilanylpent-4-ynoic acid, benzylamide (71%). Separation of the enantiomers by chiral HPLC (Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 5% ^{i}PrOH, 95% hexane, T_r 7.4 (2*S,* 3*S*) and 8.9 (2*R*, 3*R*) min) provided the enantiomeric ratio: (2*R*, 3*R*):(2*S,* 3*S*) = 97:3 (94% ee). $[\alpha]_D$ +50.4 (*c* 1.58, $CHCl_3$); IR (thin film): 3379, 3312, 2960, 2932, 2171, 1650, 1539, 1250, 1045, 845 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.30 (m, 5H), 6.38 (br, 1H), 4.73 (t, *J* = 4.9 Hz, 1H), 4.48 (d, *J* = 5.5 Hz, 2H), 3.19 (d, *J* = 4.6 Hz, 1H), 2.32 (dd, *J* = 8.5, 5.4 Hz, 1H), 2.15 (m, 1H), 1.04 (t, *J* = 7.0 Hz, 6H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

172.7, 138.0, 128.5, 127.7, 127.3, 104.4, 91.6, 62.3, 59.1, 43.4, 28.1, 21.1, 20.6, –0.5; HRMS (*EI*) *m/z* calcd for (M^+) $C_{18}H_{27}NO_2Si$: 317.1811; found: 317.1808.



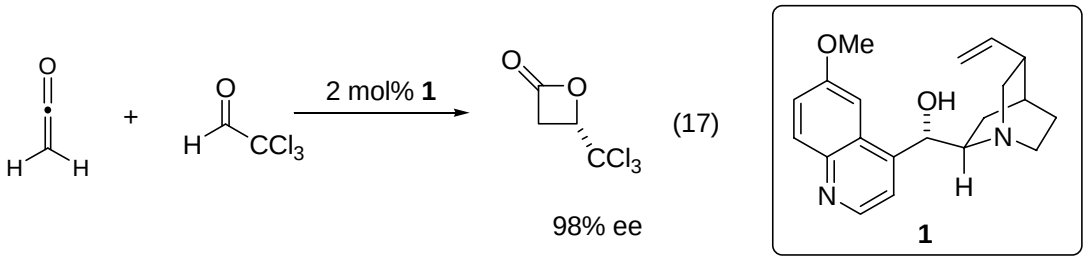
45l

***(3R, 4R)*-3-Isopropyl-4-phenyloxetan-2-one (45l):** General procedure A was followed employing 68 mg of ligand **38** (0.10 mmol, 20 mol%) and 51μL (0.50 mmol) of benzaldehyde. Purification by flash chromatography (7% ethyl acetate in hexane) gave 80 mg (84%) of the title compound. Separation of the enantiomers by chiral HPLC (Daicel Chiracel™ OD-H column, flow rate 0.5 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 11.1 (3*R,* 4*R*) and 14.1 (3*S,* 4*S*) min) provided the enantiomeric ratio: (3*R,* 4*R*): (3*S,* 4*S*) = 98:2 (96% ee). $[\alpha]_D$ +89.2 (*c* 1.50, CH_3Cl_3); IR (thin film): 2960, 1809, 1454, 1368, 1120, 881 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.39 (m, 5H), 5.60 (d, *J* = 6.4 Hz, 1H), 3.60 (dd, *J* = 11.4, 6.4 Hz, 1H), 1.82 (m, 1H), 1.07 (d, *J* = 6.6 Hz, 3H), 0.53 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1, 134.6, 128.9, 128.4, 126.7, 75.5, 62.5, 25.2, 20.2, 19.9; HRMS (*EI*) *m/z* calcd for (M^+) $C_{12}H_{14}O_2$: 190.0994; found: 190.0987.

3.0 CINCHONA ALKALOID-CATALYZED AAC

3.1 DEVELOPMENT OF LEWIS-BASE CATALYZED AAC

The 2nd generation Al-triamine complex works very well for alkyl-substituted ketenes and structurally diverse aldehydes AAC reactions, affording synthetically very useful building block disubstituted β-lactones in high yields and excellent enantioselectivities, however, this Al-triamine catalyst system does not work for α-branched aldehydes and the Al-triamine catalyst is not very easily accessible. Considering the limitations of Al-triamine catalyzed AAC reactions and based on the Wynberg's pioneering investigations on cinchona alkaloids-catalyzed ketene-chloral cycloaddition (eq 17),[9]



we attempted to develop asymmetric Lewis base-catalyzed acid chloride-aldehyde cyclocondensation (AAC) reactions applicable to a range of structurally diverse aldehydes. Extending the Wynberg ketene-aldehyde cycloadditions to structurally diverse aldehydes would afford access to more versatile enantioenriched β-lactones.

Alkaloids catalyze ketene-aldehyde addition *via* nucleophilic addition to ketene, generating the acyl ammonium enolate **53** responsible for mediating C-C bond construction (Figure 22). The specificity of Wynberg's original cycloaddition for highly electrophilic aldehydes (e.g. chloral) suggested that chiral acyl ammonium enolates **53** possess relatively limited nucleophilicity. We conceived of two potential ways to solve the limitation of the Wynberg's protocol: (1) increase nucleophilicity of the acyl ammonium enolate or (2) increase electrophilicity of the aldehyde. In our previous Al-triamine catalyzed AAC reactions, we utilized chiral Lewis acids to activate aldehydes. We speculated that addition of Lewis acid to Wynberg's system would greatly increase the electrophilicity of the aldehydes by lowering the energy of the LUMO orbital of aldehyde after forming RCHO-Lewis acid complex. Furthermore, a possible closed transition state **54** would provide entropic activation to facilitate β-lactone formation.

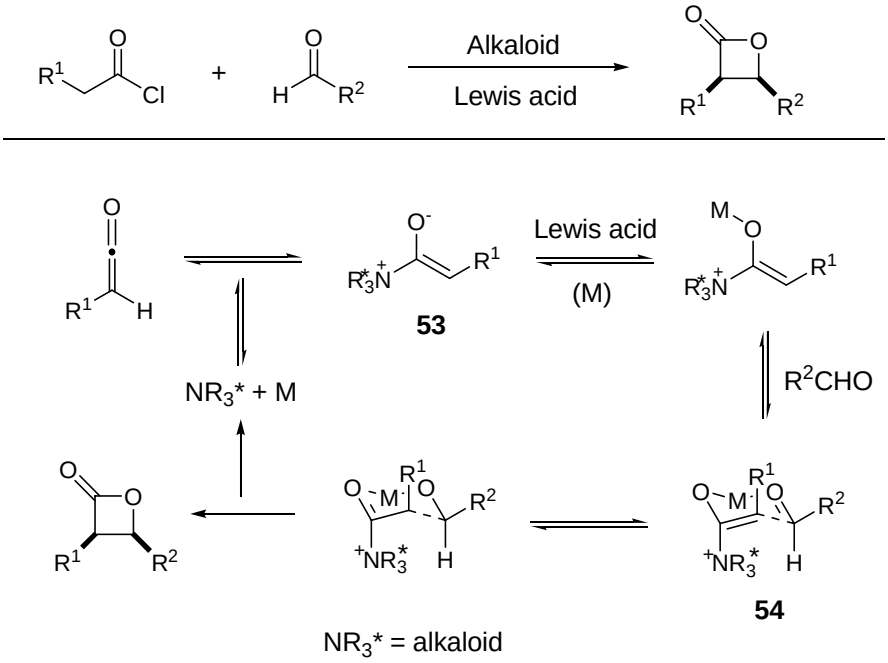


Figure 22. Postulated mechanism for alkaloid-catalyzed AAC reaction

3.2 PRELIMINARY EVALUATION OF REACTION CONDITIONS FOR ALKALOID-CATALYZED AAC

Preliminary reaction development focused on identifying a cinchona alkaloid-Lewis acid combination that would allow *in situ* ketene generation to be integrated with the catalyzed ketene-aldehyde cycloadditions. However, there are three practical problems associated with Lewis acid/alkaloid-catalyzed AAC reactions (Figure 23): (1) enolization and aldol reaction of aliphatic aldehydes in the presence of Lewis acid and base; (2) Lewis base-catalyzed ketene dimerization;[11] (3) strong Lewis acids and alkaloids forming irreversible complexes,[42] these irreversible complexes cannot act as catalysts to complete the catalytic cycle, therefore we need to find suitable Lewis acid that can form reversible complexes with alkaloids.

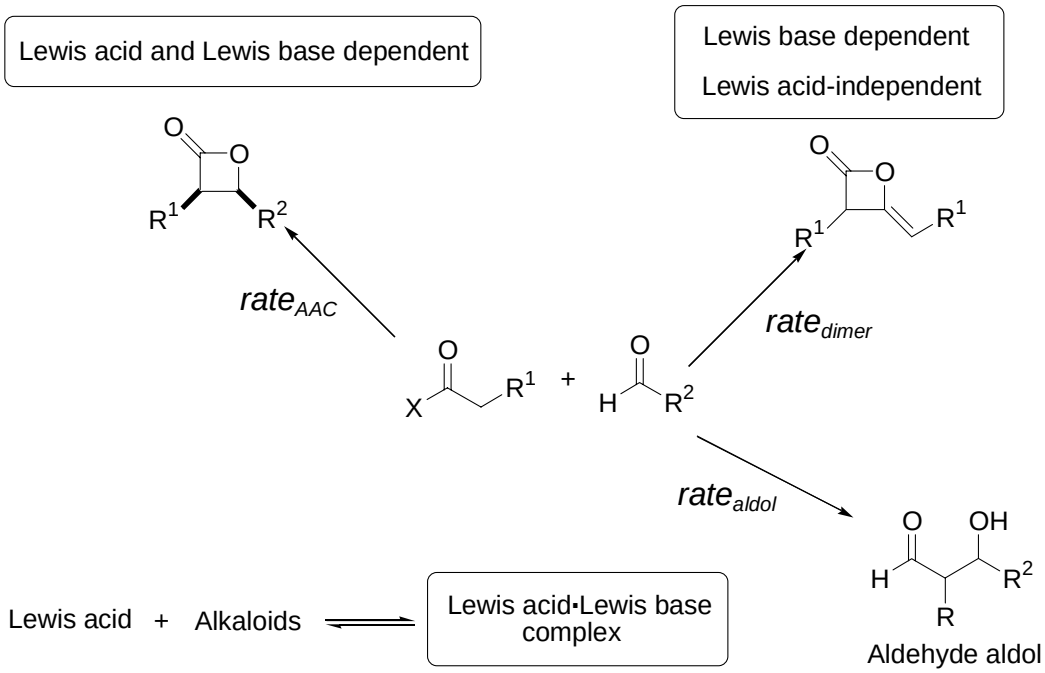


Figure 23. Competing reaction pathways in Lewis-base-catalyzed AAC reactions

In 1990, Grieco reported that 5M solutions of lithium perchlorate in diethyl ether (LPDE) can accelerate the Diels-Alder reaction dramatically.[43] It has also been found that the [2+2] cycloaddition involving nonactivated ketenes is facilitated by using 5M solution of LPDE.[44] Due to the success of using lithium perchlorate as Lewis acid activating aldehydes in these previous examples, and we speculated relatively weak Lewis acid $LiClO_4$ forming reversible complexes with cinchona alkaloids (Figure 24), $LiClO_4$ and commercially available quinidine had been examined as a co-catalyst system for acetyl chloride and hydrocinnamaldehyde cycloaddition.

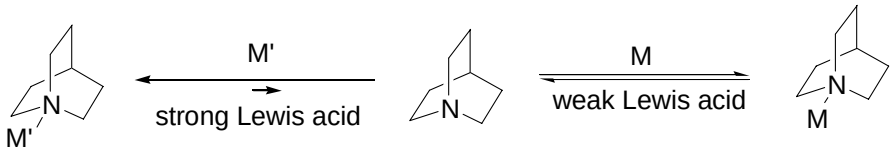
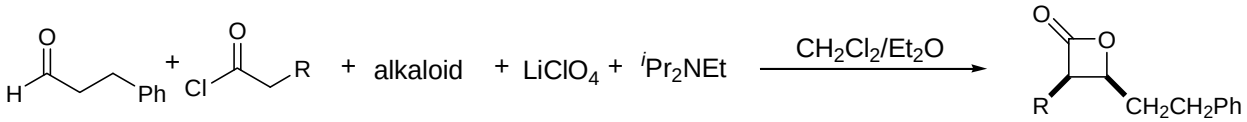


Figure 24. Complexation of Lewis acids and cinchona alkaloids

In situ ketene generation by combining *N*, *N*-diisopropylethylamine and acid halide was developed and applied successfully in the Lewis acid-catalyzed asymmetric ketene-aldehyde cycloaddition previously in our group.[28] We required that this convenient method for generating different ketenes be applied for alkaloid-catalyzed AAC reactions. Since dichloromethane is a good polar solvent for ketene generation and lithium perchlorate is soluble in diethyl ether, we use diethyl ether and dichloromethane mixed solvent for these alkaloids-catalyzed AAC reactions. In our initial study of alkaloid-catalyzed AAC reactions, 5 mol% of quinidine and 15 mol% of $LiClO_4$ were used as co-catalyst for hydrocinnaldehyde, a representative unactivated aldehyde, and acid chloride cycloaddition. The reaction was run at −25 °C and the ketene was generated over 30 min by slow addition of acid chloride to the reaction mixture. After the work up, we were pleased to find the desired cyclocondensation product was formed in 56% conversion and 62% ee (Table 7, entry a). Background AAC reactions between the ketene and

hydrocinnamaldehyde did not occur without using quinidine or lithium perchlorate (Table 7, entries b and c). These observations suggested that $LiClO_4$ and quinidine were good Lewis acid/Lewis base combination for AAC reactions. Applying 30 mol % $LiClO_4$ and 10 mol % *O*-trimethylsilyl quinine (TMS-QN) instead of *in situ* generated quinine propionate as catalyst to the cycloaddition of *in situ* generated methylketene with hydrocinnamaldehyde, gave the desired β-lactone in moderate conversion and excellent enantioselectivity (Table 7, entry d), this indicated that the trimethylsilyl protected quinidine gave much higher enantioselectivity than the quinidine propionate.

Table 7. Initial observations for alkaloid-catalyzed AAC reactions



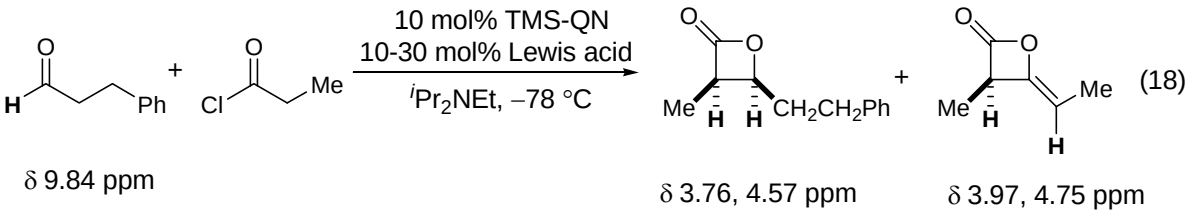
1.0 mmol 2.0 eq 2.5 eq

entry	R	temp (°C)	alkaloid (mol%)	$LiClO_4$(mol%)	% conversion[a]	% ee[b]
a	H	–25	quinidine (5)	15	56	62
b	H	–25	quinidine (0)	15	0	-
c	H	–25	quinidine (5)	0	0	-
d	Me	–78	TMS-QN (10)	30	60	99

[a] Conversion determined by ^{1}H NMR of crude product mixture. [b] Enantiomer ratio assayed by chiral HPLC.

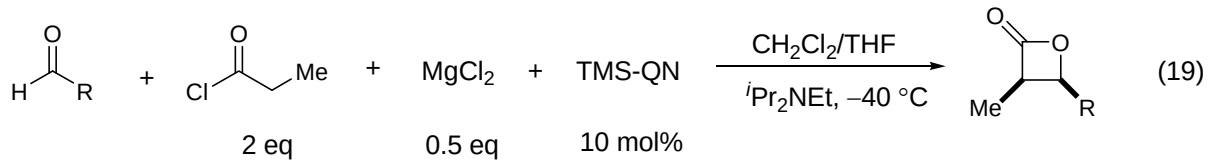
After finding that $LiClO_4$ is an efficient co-catalyst for cinchona alkaloids catalyzed acyl-chloride aldehyde cyclocondensations, we screened various commercially available Lewis acids

in order to identify other effective Lewis acids. A standard test reaction consisted of: hydrocinnamaldehyde (1.0 mmol) as the electrophile, propionyl chloride (2.0 mmol) as the ketene source, *N*, *N*-diisopropylethylamine (2.5 mmol) as the base, dichloromethane and diethyl ether as the mixed solvent and TMS-QN (0.10 mmol) as the catalyst, under a N_2 atmosphere at –78 ^{o}C (eq 18). The reaction mixture was stirred for 15 h at –78 °C. After work up, the crude product mixture was used to determine the aldehyde conversion by ^{1}H NMR, the relative integration ratio of the characteristic ^{1}H NMR resonance of starting aldehydes and resulting products was used to determine the reaction conversion and β-lactone ketene dimer ratio. The characteristic ^{1}H NMR resonance of the starting aldehyde and the resulting products used for analysis were chosen as depicted in eq 18.



(18)

Unfortunately, various Lewis acids ($Sc(OTf)_3$, $Y(OTf)_3$, $La(OTf)_3$, $Sn(OTf)_2$, $Zn(OTf)_2$, $Mg(OTf)_2$, $Mg(ClO_4)_2$, $MgBr_2$, $SmCl_3$, $AlCl_3$, Me_2AlCl, $SiCl_4$, $BF_3{\cdot}OEt$) gave no desired product β-lctone in this standard test reaction. We speculated that these relatively strong Lewis acids either form irreversible complexes with the alkaloid or speed the decomposition of aldehydes by self-aldol reaction. Less Lewis acidic species $MgCl_2$ in THF/CH_2Cl_2 ($MgCl_2$ is much more soluble in THF than Et_2O) gave promising results, however the diastereoselectivity of the reaction is only about 4-5: 1 (eq 19).



(19)

R = Ph 100% conversion dr = 5.5 : 1 97% ee

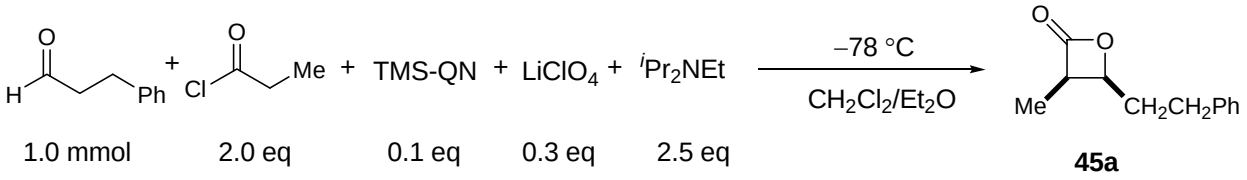
R = CH_2CH_2Ph 100% conversion dr = 4 : 1 99% ee

3.3 REACTION OPTIMIZATION

To optimize these AAC reactions, we systematically investigated Lewis acid stoichiometry, solvent complexation and Lewis base reactivity. Given the results up to this point, lithium perchlorate appeared to be an effective Lewis acid for alkaloid-catalyzed AAC reaction. The stoichiometry of $LiClO_4$ emerged as a crucial variable that could be conveniently modulated in order to maximize reaction efficiency depending on the aldehyde structure. For sterically hindered aldehydes (e.g. cyclohexanecarboxaldehyde) and aromatic aldehydes, 2 equiv of $LiClO_4$ were required to activate the aldehydes, while for sterically less hindered aliphatic aldehydes (e.g. hydrocinnamaldehyde), 0.5 equiv of $LiClO_4$ were required for activating aldehydes.

We then investigated the solvent effect on cinchona alkaloid/$LiClO_4$ system-catalyzed AAC reactions. Experimental data (Table 8) indicated that small amounts of Et_2O were necessary to ensure solubility of the $LiClO_4$ at low temperature given its insolubility in dichloromethane (entry a *vs* b-f). However, too much diethyl ether decreases the reaction conversion (entry g *vs* b-f) by competitive coordination with lithium. Based on the reaction conversion, we choose Et_2O/CH_2Cl_2 (V/V = 1: 2) as reaction solvent in later studies.

Table 8. Solvent effect on TMS-QN catalyzed AAC reaction



1.0 mmol 2.0 eq 0.1 eq 0.3 eq 2.5 eq **45a**

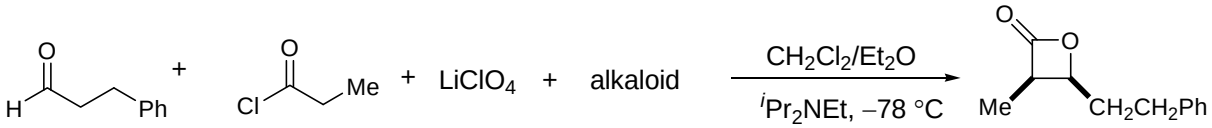
entry	Et_2O (mL)	CH_2Cl_2 (mL)	% conversion[a]
a	0	3.0	0
b	0.2	2.8	85
c	0.4	2.6	77
d	0.6	2.4	93
e	1.2	1.8	77
f	1.8	1.2	49
g	2.4	0.6	5

[a] Conversion determined by ^{1}H NMR of crude product mixture.

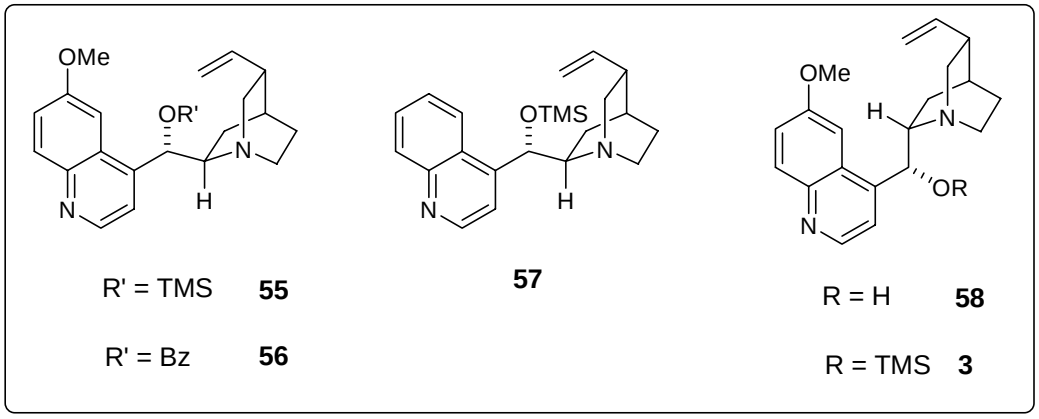
The next study conducted for optimization was focused on improving the reactivity of the Lewis base catalyst. Catalyst candidates for AAC reactions were drawn from easily accessed cinchona alkaloid derivatives differing in the C_9 oxygen substitution (Table 9). Investigation of AAC efficiency as a function of the catalyst revealed that the *O*-trimethylsilyl alkaloid **3** afforded optimum reaction yields and enantioselectivities (Table 9, entry e). In the presence of 10 mol% *O*-trimethylsilyl quinine **3**, 50 mol% $LiClO_4$, cyclocondensation between methyl ketene and hydrocinnamaldehyde gave the desired β-lactone in high conversion and enantioselectivity (entry

e). Interestingly, the AAC reaction catalyzed by *O*-trimethylsilyl cinchonine **57** only went to 30% conversion (entry c), the methoxy group at quinoline played an important but not yet understood role in these cycloaddition. The quinidine benzoate **56** and *O*-trimethylsilyl cinchonine **55** gave very similar results (entry a and b).

Table 9. Effect of alkaloids on the methyl ketene-hydrocinnamaldehyde cycloaddition



entry	$LiClO_4$ (mol%)	alkaloid	% conversion[a]	% ee[b, c]
a	30	**55**	87	99
b	30	**56**	82	99
c	30	**57**	30	ND
d	50	**58**	59	99
e	50	**3**	98	99



[a] Conversion determined by ^1H NMR of crude product mixture. [b] Enantiomer ratio assayed by chiral HPLC.

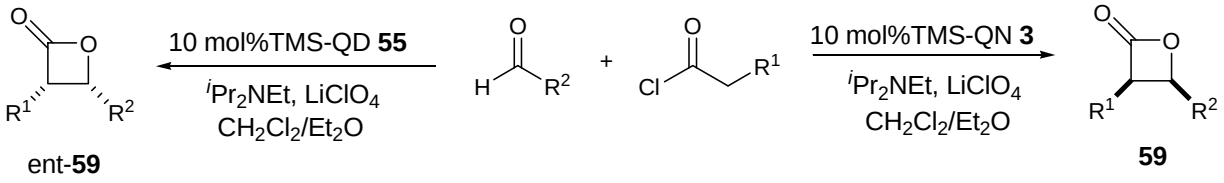
[c] Ent-**45a** provided using **55**, **56** and **57** as catalyst.

Based on these investigations, slow addition of acid chloride (2 equiv over 1-4 h to minimize ketene dimerization) to a CH_2Cl_2/Et_2O (2:1) solution containing TMS-QN **3** (10 mol %), $LiClO_4$ (for benzyloxyacetaldehyde 30 mol%, hydrocinnamaldehyde 50 mol%, aromatic

aldehydes and sterically hindered aldehydes 200 mol%) and $^{i}Pr_2NEt$ (2.5 equiv) provided the optimized conditions for AAC reactions employing a variety of aldehydes.[45]

After identifying the optimal asymmetric AAC reaction condition, we then explored reaction scope as a function of aldehyde structure for the alkaloid-catalyzed asymmetric AAC reactions. These investigations indicated that TMS-QN/$LiClO_4$ or TMS-QD/$LiClO_4$ catalyst system render a variety of structurally diverse aldehydes as suitable substrates for the AAC reaction (Table 10). Straight chain, β-branched, and alkoxy-substituted aliphatic aldehydes (entries a-g), a variety of substituted aromatic aldehydes (entries h-k), afforded the β-lactones with uniformly high yield and enantioselectivity (84-99% ee). Conjugated enals and very electron-rich aromatic aldehydes such as *p*-anisaldehyde are not effective substrates for the alkaloid-catalyzed asymmetric cycloaddition.

Table 10. TMS-QN/TMS-QD catalyzed AAC reactions*



ent-**59** **59**

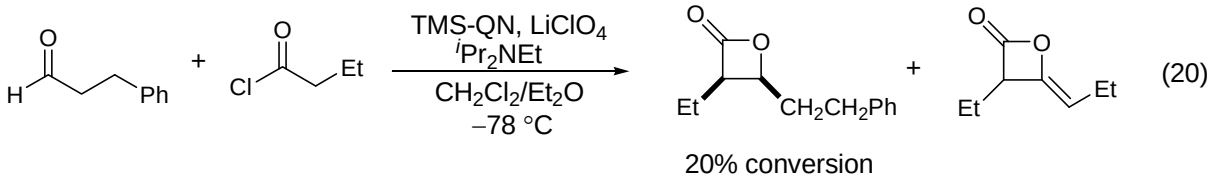
entry	R^1	R^2	catalyst	% ee[a]	syn:anti[b,c]	% yield[d]
a	H	$^{c}C_6H_{11}$	**55**	94	-	85
b	H	CH_2CH_2Ph	**55**	92	-	80
c	H	CH_2OBn	**3**	84	-	70
d	Me	CH_2CH_2Ph	**3**	>99	98:2	84
e	Me	CH_2OBn	**3**	99	88:12	68
f	Me	$CH_2CH(CH_3)_2$	**3**	99	95:5	72
g	Me	$^{c}C_6H_{11}$	**55**	97	>98:2	74
h	Me	Ph	**3**	>99	98:2	78
i	Me	$^{o}C_6H_4Cl$	**3**	>99	98:2	80
j	Me	$^{o}C_6H_4CH_3$	**3**	>99	>98:2	76
k	Me	$^{p}C_6H_4CH_3$	**3**	>99	98:2	68

[a] Enantiomeric ratios determined by chiral HPLC or GLC. [b] Diastereomeric ratios determined by ^{1}H NMR of crude product mixtures. [c] Relative and absolute stereochemical assignments based on prior literature precedent; see 3.7 for detail. Absolute stereochemistry of compound **59** shown here. [d] Yields for diastereomerically pure materials. * Investigation performed in collaboration with Dr. Cheng Zhu.

Although these alkaloid-catalyzed AAC reactions are superficially related to the Al(III)-catalyzed variants previously developed, the alkaloid-$LiClO_4$ system offers several notable advantages. In reactions involving acetyl chloride-derived ketene, even sterically hindered aldehydes such as cyclohexanecarboxaldehyde served as effective substrates providing the β-lactone in 94% ee (Table 10, entry a). Similar α-branched aldehydes are unreactive under Al(III) catalyst conditions. Methylketene is also an effective AAC reaction partner. In fact, enantioselectivity in reactions employing propionyl chloride-derived methylketene is significantly higher than the simple ketene cyclocondensation (Table 10, entry d *vs* b, e *vs* c). A variety of aldehydes reacted with propionyl chloride affording 3,4-*cis* disubstituted β-lactones with near perfect enantio- and diastereoselectivities (Table 10).

3.4 MAGNESIUM CHLORIDE/ALKALOID-CATALYZED AAC FOR ETHYLKETENE

The $LiClO_4$/TMS-QN system works well for ketene and methyl ketene AAC reactions. However, only small amounts of desired β-lactones were formed when the optimized conditions were applied to the butyryl chloride-derived ethyl ketene AAC reaction with ethyl ketene dimer being the major side product (eq 20 and 21).



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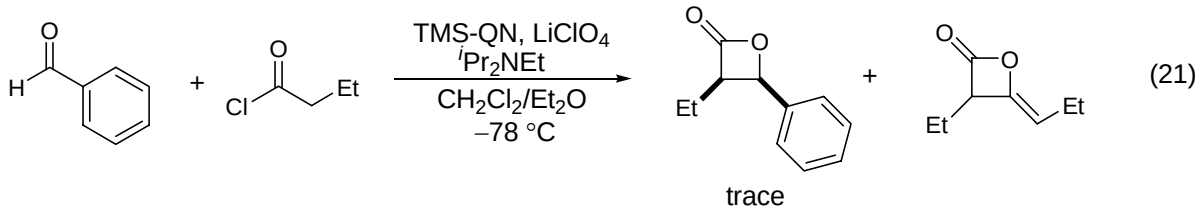
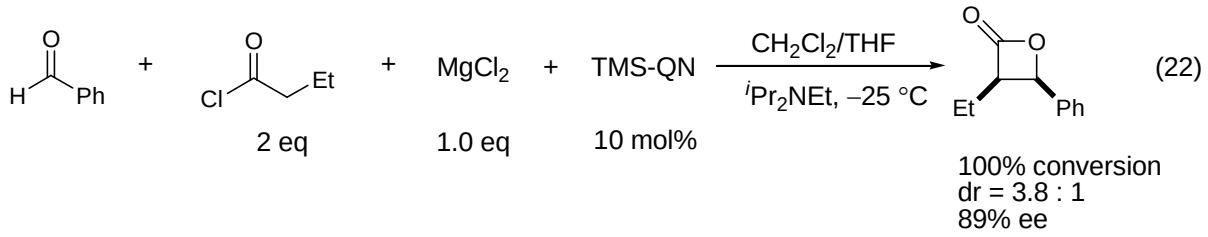


(21)

It was clear that we needed to improve the TMS-QN/$LiClO_4$ system for less reactive substituted ketenes. From previous results, $MgCl_2$ was shown to be a more reactive Lewis acid than $LiClO_4$ for the AAC reactions. We revisited this Lewis acid as a potential solution for unreactive ketene systems. Magnesium dichloride was found to allow for full conversion in the ethyl ketene-benzaldehyde cycloaddtion, though the diastereoselectivity is low (3.8:1, eq 22). For aliphatic aldehydes, under the $MgCl_2$/TMS-QN reaction conditions, the aldehyde was consumed, giving trace amount of desired β-lactones (eq 23).



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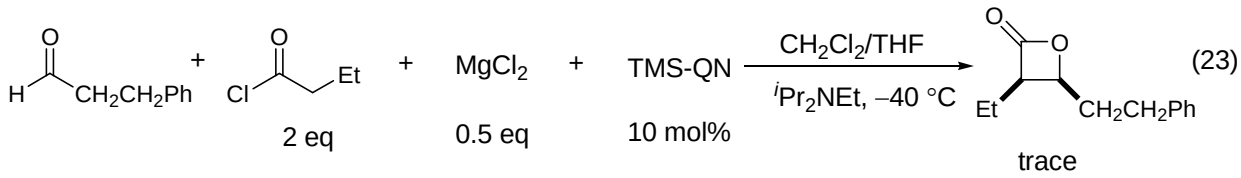
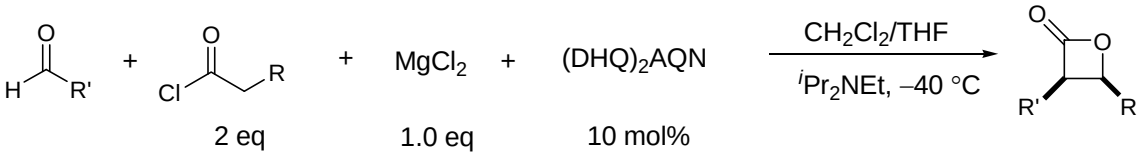


(23)

We speculated that altering the coordination between alkaloids and $MgCl_2$ might change the reactivity of catalyst system, so dimeric-quinine such as $(DHQ)_2AQN$ (**60**) and $MgCl_2$ were

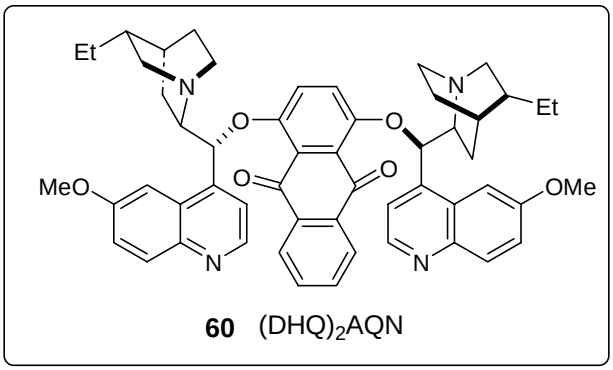
utilized to catalyze the substituted ketene AAC (Table 11). This system gave better conversions for aliphatic aldehydes compared to TMS-QN/$MgCl_2$ system; however, the diastereoselectivity was still low for aromatic aldehydes (Table 11, entry b and d). So, the diastereoselectivity of AAC reaction catalyzed by $MgCl_2$/alkaloid system was not as good as $LiClO_4$/alkaloid system, although the reactivity of the $MgCl_2$/alkaloid system is a little better than the $LiClO_4$/alkaloid system, future studies needed to find better alkaloid for $MgCl_2$.

Table 11. $(DHQ)_2AQN/MgCl_2$ catalyzed AAC reaction



entry	R	R'	% conversion[a]	syn:anti[b]	% ee[c]
a	Me	CH_2CH_2Ph	100	95 : 5	99
b	Me	Ph	85	5 : 1	ND
c	Et	CH_2CH_2Ph	75	10 : 1	95
d	Et	Ph	85	3 : 1	ND

[a] Conversion determined by ^1H NMR of crude product mixture. [b] Diastereomer ratios determined by ^1H NMR of crude product mixtures. [c] Enantiomer ratios assayed by chiral HPLC.

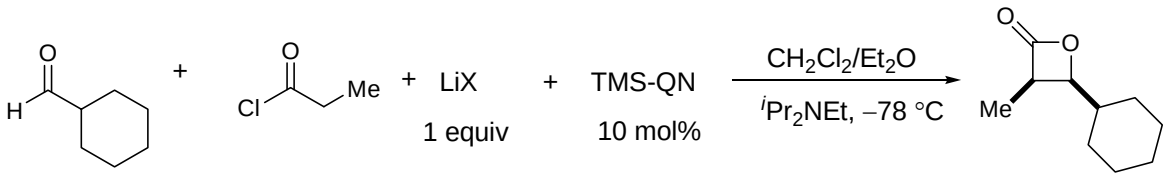


60 $(DHQ)_2AQN$

3.5 LITHIUM IODIDE/*O*-METHYL QUININE-CATALYZED AAC FOR ETHYLKETENE

It has been reported that concentrated lithium perchlorate in diethyl ether solution can be potentially explosive.[46] In order to avoid this potential hazard, we systematically investigated other lithium salts to find a more convenient Lewis acid co-catalyst for our AAC reactions. In the presence of one equiv of lithium salt and 10 mol% TMS-QN, we tested the reactivity of various lithium salts for the cycloaddition of cyclohexanecarboxaldehyde with methyl ketene in 2: 1 CH_2Cl_2/Et_2O (Table 12). These investigations revealed several lithium salts were active Lewis acids for the AAC (entry a-e) with lithium trifluoromethanesulfonimide and lithium iodide being more efficient Lewis acids than $LiClO_4$ for the AAC reactions (entry d, e *vs* c). One added advantage of LiI in the AAC reaction is its increased solubility in diethyl ether as compared to $LiClO_4$. Based on these investigations, for sterically hindered aldehydes and α-branched aldehydes, lithium iodide was selected as the Lewis acid co-catalyst in the alkaloid-catalyzed AAC reactions. For reactive aldehydes and easily enolizable aldehydes, litium perchlorate was still used as the optimal Lewis acid.

Table 12. Evalution of lithium salts by the methyl ketene-cyclohexanecarboxaldehyde cycloaddition



(3*R*, 4*S*)

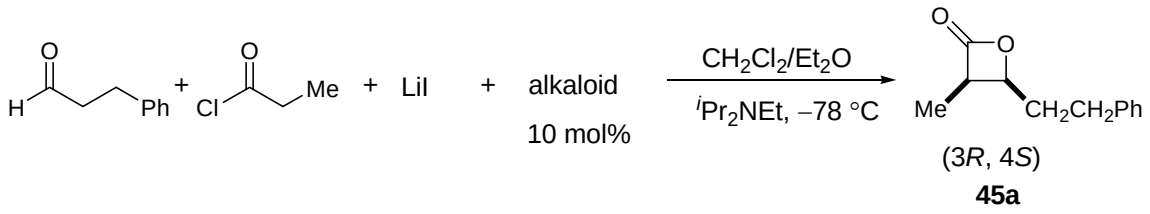
entry	X	% conversion[a]	entry	X	% conversion[a]
a	Br	25	f	SbF_6	0
b	PF_6	30	g	OTf	0
c	ClO_4	35	h	$OCOCF_3$	0
d	NTf_2	45	i	BF_4	0
e	I	50			
j[b]	ClO_4	100			
k[b]	NTf_2	100			
l[b]	I	100			

[a] Conversion determined by ^{1}H NMR of crude product mixtures. [b] 2 eq of lithium salts were used.

In order to solve the reactivity problem observed for lithium-alkaloid system catalyzed ethyl ketene AAC reaction, we attempted to increase the nucleophilicity of acyl ammonium enolate by modifying the structure of the alkaloid. Based on the premise that less sterically hindering protecting groups on the quinine would possibly increase the reactivity of the alkaloid, several sterically different protected quinine were synthesized to investigate the reactivity. Using LiI as Lewis acid and 8:1 CH_2Cl_2/Et_2O (small amounts of Et_2O was used to dissolve LiI) as

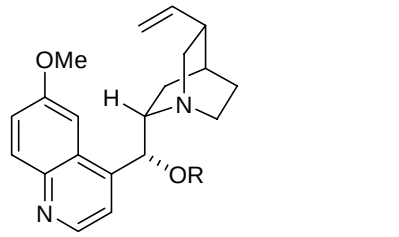
solvent, we used methylketene-hydrocinnamaldehyde cycloaddition to test the reactivities of several different alkaloids (Table 13). From these results, we concluded that bulky protection groups decrease the reactivity of alkaloids (entry e, g, *vs* a), the olefin functional group on the quinuclidine ring has little effect on reactivity (entry a *vs* f), the Me-QN **61** and TMS-QN gave similar results for methyl ketene-hydrocinnamaldehyde cycloaddition (entry a *vs* b).

Table 13. Effect of alkaloids on methyl ketene-hydrocinnamaldehyde cycloaddition

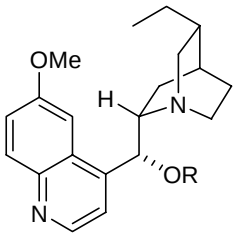


(3*R*, 4*S*)
45a

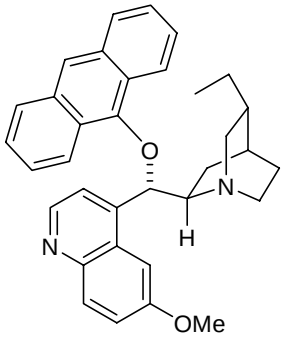
entry	LiI (mol%)	alkaloid	% conversion[a]	% ee[b]
a	50	**3**	100	99
b	50	**61**	100	99
c	50	**62**	75	ND
d	50	**63**	65	ND
e	50	**64**	70	ND
f	50	**65**	100	99
g	50	**66**	70	97[c]



R = TMS **3** R = Bn **63**
R = Me **61** R = Piv **64**
R = MOM **62**



R = TMS **65**



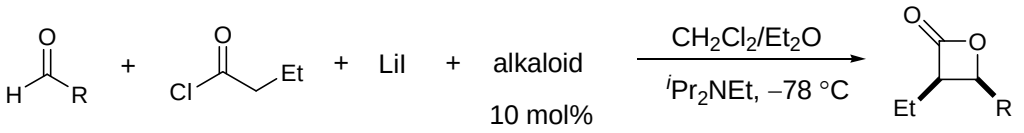
66

[a] Conversion determined by ^{1}H NMR of crude product mixture. [b] Enantiomer ratios assayed by chiral HPLC.
[c] Ent-**45a** provided using **66** as catalyst.

We further compared the reactivity of *O*-methylated quinine **61** and *O*-trimethylsilyl quinidine **55** in side by side ethyl ketene AAC reactions, as shown in Table 14, we found that using Me-

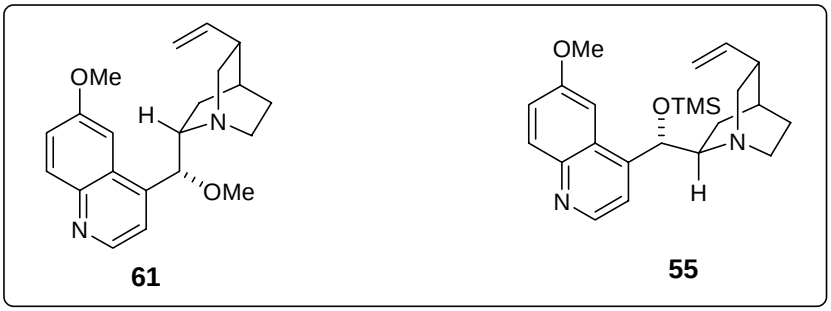
QN as a catalyst gave higher aldehyde conversion than TMS-QD in these reactions (entry a *vs* b and c *vs* d).

Table 14. Comparison of Me-QN and TMS-QD on the ethyl ketene AAC reaction



entry	LiI (mol%)	R	alkaloid[a]	% conversion[b]	% ee[c]
a	300	$^{p}C_6H_4F$	**61**	100	99
b	300	$^{p}C_6H_4F$	**55**	70	ND
c	300	$^{o}C_6H_4Cl$	**61**	100	99
d	300	$^{o}C_6H_4Cl$	**55**	80	ND

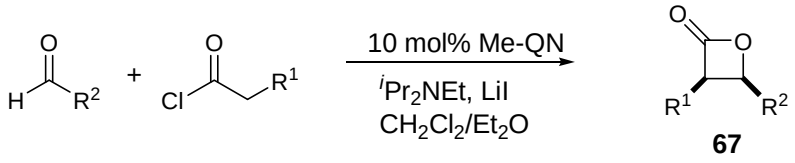
[a] **61** and **55** provided different enantiomers, **61** gave (3*R*, 4*R*) enantiomer. [b] Conversion determined by ^{1}H NMR of crude product mixtures. [c] Enantiomer ratios assayed by chiral HPLC.



The newly discovered LiI/Me-QN system worked well for the cyclocondensation of aromatic aldehydes (Table 15 entry c-f and h). Although preliminary results look promising, further improvements are still needed for the cycloaddition involving aliphatic aldehydes (entry a,

b and g), since these reactions did not go to completion by using 1 equiv of LiI, if we increased the amount of LiI, aliphatic aldehydes started to be consumed without producing desired β-lactones, while we can use 3 equiv of LiI for non-enolizable aldehydes to achieve good conversion and yield.

Table 15. LiI/Me-QN system catalyzed ethyl ketene AAC reactions



entry	R^1	R^2	% ee[a]	syn:anti[b]	% yield[c]
a	Et	CH_2CH_2Ph	ND	94:6	30
b	Et	$^{c}C_6H_{11}$	ND	95:5	30
c	Et	Ph	>99	98:2	84
d	Et	$^{p}C_6H_4F$	>99	98:2	75
e	Et	$^{o}C_6H_4Cl$	>99	98:2	83
f	Et	$^{o}C_6H_4CH_3$	>99	98:2	70
g	^{n}Pr	CH_2CH_2Ph	ND	94:6	40
h	^{n}Pr	Ph	>99	98:2	70

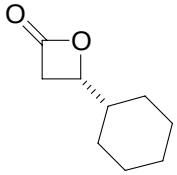
[a] Enantiomer ratios assayed by chiral HPLC, absolute stereochemistry of **67** shown here. [b] Diastereomer ratios determined by ^{1}H NMR of crude product mixtures. [c] Isolated yield for diastereomerically pure materials.

In summary, the cinchona alkaloid-Lewis acid catalyzed AAC reaction dramatically expands the scope of Wynberg's original cycloaddition between ketene and chloral. By

modulating the protecting group on the alkaloid and by careful selection of a Lewis acid and solvent, a broad spectrum of β-lactones can be expediently assembled. The cinchona alkaloid-Lewis acid catalyzed AAC reaction is a mechanistically distinct process that serves as a complimentary system to the aluminium-triamine-catalyzed AAC reaction variant. Together, these two subsets of AAC tolerate a vast array of molecular diversity. Selection of the AAC variant can provide a desired β-lactone in good yields with high enantioselectivities.

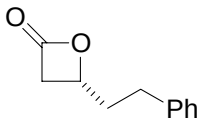
3.6 EXPERIMENTALS

General procedure B: TMS-QN/$LiClO_4$ catalyzed asymmetric ketene-aldehyde cycloadditions: To a solution of TMS-QD/TMS-QN (0.10 mmol) and $LiClO_4$ (0.30-3.0 mmol, weighed in glovebox) in 1.0 mL of diethyl ether at ambient temperature was slowly added 2.0 mL of CH_2Cl_2. The resulting mixture was cooled to −78 °C (several reactions at –40 °C) and 0.44 mL of *N*, *N*-diisopropylethylamine (2.5 mmol) was added, then aldehyde (1.0 mmol) was added dropwise followed by the addition of 2.0 mmol of acid chloride in 0.5 mL CH_2Cl_2 over 1-4 h by syringe pump (the tip of syringe was put into the reaction mixture). The reaction mixture was stirred for 14-16 h at –78 °C (or –40 °C). The reaction was quenched at –78 °C (or –40 °C) by adding 10 mL of Et_2O and the resulting mixture was filtered through silica gel eluting with 3 x 20 mL of Et_2O. The filtrate was concentrated *in vacuo* and the crude product mixture was purified by flash chromatography.



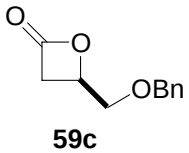
ent-59a

***(S)*-4-Cyclohexyloxetan-2-one (ent-59a)**:[28] General procedure B was followed employing 40 mg of TMS-QD (0.10 mmol, 10 mol%), 212 mg $LiClO_4$ (2.0 mmol, 200 mol%) and 120 μL of cyclohexanecarboxaldehyde (1.0 mmol). Reaction was run at –40 °C. Purification by flash chromatography (15% diethyl ether in pentane) gave 129 mg (84%) of the title compound as white crystalline solid. Separation of enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 100 °C for 10 min, ramp @ 15.0 °C/min to 130 °C for 8.0 min, ramp @ 15.0 °C/min to 160 °C for 10.0 min, T_r: 24.5 min (4*S*), 26.2 min (4*R*)] provided the enantiomeric ratio (4*S*):(4*R*) = 97.2:2.8 (94% ee). $[\alpha]_D$ +19.8 (*c* 1.48, $CHCl_3$).



ent-59b

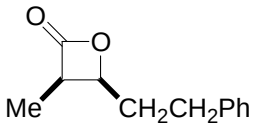
***(R)*-4-Phenethyloxetan-2-one (ent-59b)**:[28] General procedure B was followed employing 40 mg of TMS-QD (0.10 mmol, 10 mol%), 53 mg $LiClO_4$ (0.50 mmol, 50 mol%) and 132 μL of hydrocinnamaldehyde (1.0 mmol). The reaction mixture was stirred at –78 °C for 7 h. Purification by flash chromatography (25% diethyl ether in pentane) gave 141 mg (80%) of the title compound as colorless oil. Separation of the enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 15.5 min (*S*) and 17.3 min (*R*)] provided the enantiomeric ratio: (*R*):(*S*) = 96:4 (92% ee). $[\alpha]_D$ +37.8 (*c* 2.40, $CHCl_3$).



59c

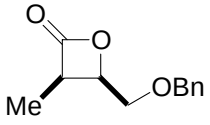
***(R)*-4-(Benzyloxy)methyl)oxetan-2-one (59c)**:[28] General procedure B was followed employing 40 mg of TMS-QN (0.10 mmol, 10 mol%), 32 mg $LiClO_4$ (0.3 mmol, 30 mol%) and 140 μL of benzyloxyacetaldehyde (1.0 mmol). Purification by flash chromatography (25% ethyl acetate in hexane) gave 134 mg (70%) of the

title compound as colorless oil. Separation of the enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 0.9 mL/min, 15% ^{i}PrOH, 85% hexane, T_r 13.9 min (*R*) and 24.8 min (*S*)] provided the enantiomer ratio: (*R*):(*S*) = 92:8 (84% ee). $[\alpha]_D$ –13.9 (*c* 1.80, $CHCl_3$).



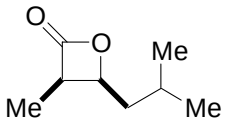
59d

***(3R, 4S)*-3-Methyl-4-phenethyloxetan-2-one (59d)**: General procedure B was followed employing 40 mg of TMS-QN (0.10 mmol, 10 mol%), 53 mg $LiClO_4$ (0.5 mmol, 50 mol%) and 132 µL of hydrocinnamaldehyde (1.0 mmol). Purification by flash chromatography (10% ethyl acetate in hexane) gave 161 mg (84%) of the title compound as colorless oil. Separation of enantiomers by Chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 5% ^{i}PrOH, 95% hexane T_r: 12.9 min (3*S*, 4*R*), 14.0 min (3*R*, 4*S*)] provided only one enantiomer (3*R*, 4*S*) (≥99% ee). $[\alpha]_D$ –47.2 (*c* 2.04, $CHCl_3$). Spectra data as reported on page 42.



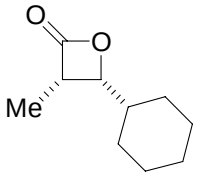
59e

***(3R, 4R)*-4-(Benzyloxy)methyl)-3-methyloxetan-2-one (59e):**[29] General procedure B was followed employing 40 mg of TMS-QN (0.10 mmol, 10 mol%), 32 mg $LiClO_4$ (0.3 mmol, 30 mol%) and 140 µL of benzyloxyacetaldehyde (1.0 mmol). Purification by flash chromatography (20% ethyl acetate in hexane) gave 140 mg (68%) of the title compound as colorless oil. Separation of the enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 13.4 min (3*R*, 4*R*) , 31.4 min (3*S*, 4*S*)] provided the enantiomeric ratio: (3*R*, 4*R*):(3*S*, 4*S*) ≥ 99.5:0.5 (≥99% ee). $[\alpha]_D$ –7.60 (*c* 1.58, $CHCl_3$).



59f

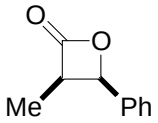
***(3R, 4S)*-4-Isobutyl-3-methyloxetan-2-one (59f)**: General procedure B was followed employing 1.0 g of TMS-QN (2.5 mmol, 10 mol%), 5.3 g $LiClO_4$ (50.0 mmol, 200 mol%) and 2.68 mL of isovaleraldehyde (25.0 mmol). Purification by flash chromatography (9% diethyl ether in pentane) gave 2.55 g (72%) of the title compound as colorless oil. Separation of enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.6 mL/min, method: 80 °C for 5.0 min, ramp @ 5.0 °C/min to 100 °C for 10.0 min, ramp @ 5.0 °C/min to 130 °C for 5.0 min, T_r: 23.9 min (3*R*, 4*S*) and 25.0 min (3*S*, 4*R*)] provided the enantiomeric ratio (3*R*, 4*S)*: (3*S*, 4*R*) = 99.7:0.3 (99% ee). $[\alpha]_D$ –41.8 (*c* 1.88, $CHCl_3$). IR (thin film): 1824, 1465, 1124 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.67 (ddd, *J* = 9.7, 6.5, 3.8 Hz, 1H), 3.77 (qd, *J* = 7.8, 6.5 Hz, 1H), 1.82 (m, 1H), 1.71 (ddd, *J* = 14.3, 9.7, 6.0 Hz, 1H), 1.51 (ddd, *J* = 14.3, 7.6, 3.8 Hz, 1H), 1.29 (d, *J* = 7.8 Hz, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 74.2, 47.4, 38.5, 25.2, 22.8, 22.0, 8.1; HRMS (*EI*) *m/z* calcd for (M^+) $C_8H_{14}O_2$: 142.0994; found: 142.0988.



ent-59g

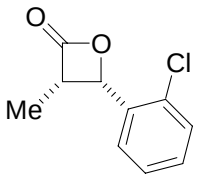
***(3S, 4R)*-4-Cyclohexyl-3-methyloxetan-2-one (ent-59g)**: General procedure B was followed employing 40 mg of TMS-QD (0.10 mmol, 10 mol%), 212 mg $LiClO_4$ (2.0 mmol, 200 mol%) and 120 µL of cyclohexanecarboxaldehyde (1.0 mmol). Reaction was run at –40 °C. Purification by flash chromatography (15% diethyl ether in pentane) gave 124 mg (74%) of the title compound as white crystalline solid. Separation of enantiomers by chiral GLC [Chiraldex™ G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min, method: 100 °C for 10 min, ramp @ 15.0 °C/min to 130 °C for 8.0 min, ramp @ 15.0 °C/min to 160 °C for 15.0 min, T_r: 26.8 min (3*S*, 4*R*), 27.7 min (3*R*, 4*S*)] provided the enantiomer ratio (3*S*, 4*R*): (3*R*, 4*S*) = 98.3: 1.7 (97% ee). $[\alpha]_D$ –13.4 (*c* 1.45,

$CHCl_3$). IR (thin film): 2932, 2854, 1825, 1132 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.18 (dd, *J* = 10.6, 6.3 Hz, 1H), 3.72 (qd, *J* = 7.8, 6.3 Hz, 1H), 2.01-1.92 (m, 1H), 1.82-1.52 (m, 5H), 1.34 (d, *J* = 7.8 Hz, 3H), 1.32-1.19 (m, 3H), 1.07-0.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 79.0, 46.8, 37.7, 28.9, 28.1, 26.0, 25.0 (2C), 8.4; HRMS (*EI*) *m/z* calcd for (M^+) $C_{10}H_{16}O_2$: 168.1150; found: 168.1158.



59h

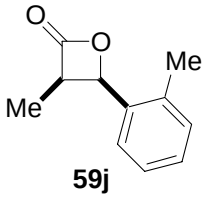
***(3R, 4R)*-3-Methyl-4-phenyloxetan-2-one (59h)**: General procedure B was followed employing 40 mg of TMS-QN (0.10 mmol, 10 mol%), 212 mg $LiClO_4$ (2.0 mmol, 200 mol%) and 102 μL of benzaldehyde (1.0 mmol). Purification by flash chromatography (10% ethyl acetate in hexane) gave 126 mg (78%) of the title compound as colorless oil. Separation of the enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 3% ^{i}PrOH, 97% hexane, T_r 10.8 min (3*R,* 4*R*), 11.7 min (3*S,* 4*S*)] provided only one enantiomer (≥99% ee). $[\alpha]_D$ +139 (*c* 1.79, $CHCl_3$). Spectra data as reported on page 43.



ent-59i

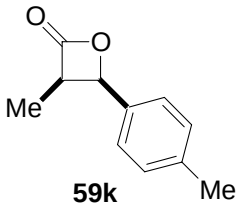
(3*S*, 4*S*)-4-(2-Chlorophenyl)-3-methyloxetan-2-one (ent-59i): General procedure B was followed employing 40 mg of TMS-QD (0.10 mmol, 10 mol%), 212 mg $LiClO_4$ (2.0 mmol, 200 mol%) and 113 μL of 2-chlorobenzaldehyde (1.0 mmol). Purification by flash chromatography (10% diethyl ether in pentane) gave 158 mg (80%) of the title compound as colorless oil. Separation of enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 0.6 mL/min, 2% ^{i}PrOH, 98% hexane, T_r 13.4 min (3*R,* 4*R*), 14.1 min (3*S,* 4*S*)] provided only one enantiomer (≥99% ee). $[\alpha]_D$ –201 (*c* 1.68, $CHCl_3$); IR (thin film): 2979, 1827, 1472, 1444, 1289, 1055, 946, 880, 755 cm^{-1}; ^1H NMR

(300 MHz, $CDCl_3$) δ 7.55-7.52 (m, 1H), 7.43-7.31 (m, 3H), 5.86 (d, *J* = 6.3 Hz, 1H), 4.16 (qd, *J* = 7.7, 6.3 Hz, 1H), 0.98 (d, *J* = 7.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 133.0, 131.2, 129.6, 129.3, 127.2, 126.9, 73.3, 50.3, 9.1; HRMS (*EI*) *m/z* calcd for (M^+) $C_{10}H_9ClO_2$: 196.0291; found: 196.0299.



59j

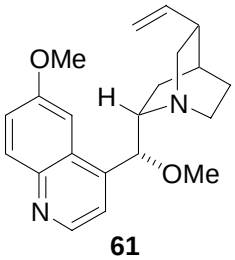
(3*R*, 4*R*)-3-Methyl-4-o-tolyloxetan-2-one (59j): General procedure B was followed employing 40 mg of TMS-QN (0.10 mmol, 10 mol %), 212 mg $LiClO_4$ (2.0 mmol, 200 mol%) and 116 μL of 2-methylbenzaldehyde (1.0 mmol). Reaction was run at –40 °C. Purification by flash chromatography (10% ethyl acetate in hexane) gave 134 mg (76%) of the title compound as white crystalline solid. Separation of enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 0.5 mL/min, 4% ^{i}PrOH, 96% hexane, T_r 18.1 min (3*R,* 4*R*), 19.1 min (3*S,* 4*S*)] provided only one enantiomer (≥99% ee). $[\alpha]_D$ +201 (*c* 1.49, $CHCl_3$); IR (thin film): 2978, 1829, 1493, 1260 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48-7.45 (m, 1H), 7.31-7.20 (m, 3H), 5.78 (d, *J* = 6.3 Hz, 1H), 4.08 (qd, *J* = 7.7, 6.3 Hz, 1H), 2.22 (s, 3H), 0.91 (d, *J* = 7.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 133.8, 132.9, 130.2, 128.2, 126.3, 124.9, 73.7, 49.5, 18.7, 9.2; HRMS (*EI*) *m/z* calcd for (M^+) $C_{11}H_{12}O_2$: 176.0837; found: 176.0831.



59k

(3*R*, 4*R*)- 3-Methyl-4-p-tolyloxetan-2-one (59k): General procedure B was followed employing 40 mg of TMS-QN (0.10 mmol, 10 mol %), 212 mg $LiClO_4$ (2.0 mmol, 200 mol %) and 118 μL of 4-methylbenzaldehyde (1.0 mmol). Reaction was run at –40 °C. Purification by flash chromatography (hexanes: ethyl acetate: Et_3N = 10:1: 0.1) gave 120 mg (68%) of the title

compound as white crystal. Separation of enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 3% ^{i}PrOH, 97% hexane, T_r 8.1 min (3*R*, 4*R*), 9.0 min (3*S*, 4*S*)] provided only one enantiomer (≥99% ee). $[\alpha]_D$ +118 (*c* 1.46, $CHCl_3$); IR (thin film): 3023, 1826, 1216, 940, 756 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.11 (m, 4H), 5.63 (d, *J* = 6.3 Hz, 1H), 4.03 (qd, *J* = 7.7, 6.3 Hz, 1H), 2.38 (s, 3H), 0.95 (d, *J* = 7.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 138.2, 131.4, 129.1, 125.5, 75.2, 49.8, 20.9, 9.3; HRMS (*EI*) *m/z* calcd for (M^+) $C_{11}H_{12}O_2$: 176.0837; found: 176.0834.



61

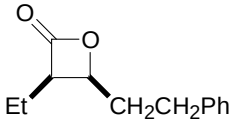
6-Methoxy-4-[methoxy-(5-vinyl-1-aza-bicyclo[2.2.2]oct-2-yl)methyl]quinoline (61):[50] 250 mg NaH (6.47 mmol, 1.05eq, 60% suspended in oil) was washed twice with 10 mL of pentane and suspended in 10 mL of THF. The suspension was cooled to 0 °C and a solution of 2.0 g of quinine (6.17 mmol) in 18 mL THF was added dropwise. The reaction mixture was stirred at 0 °C for 1 h and then ambient temperature for 6 h. The reaction mixture was recooled to 0 °C and 403 uL of methyl iodide (6.47 mmol, 1.05 eq) was added dropwise and stirred at 0 °C for 1 h and then ambient temperature for 14 h. The resulting mixture was filtered through silica gel eluting with 2 x 100 ml of Et_2O. The filtrate was concentrated *in vacuo* and the crude product mixture was purified by flash chromatography (2% methanol in ethyl acetate) and recrystallization (CH_2Cl_2/ethyl acetate), giving 810 mg (39%) of title compound as crystalline solid. $[\alpha]_D$ –83.6 (*c* 1.51, $CHCl_3$); IR (KBr Plate): 1735, 1619, 1506, 1474, 1429, 1239, 1227 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.43 (br, 1H), 8.79 (d, *J* = 4.5 Hz, 1H), 8.06 (d, *J* = 9.2 Hz, 1H), 7.50 (d, *J* = 2.6 Hz, 1H), 7.46 (d, *J* = 4.4 Hz, 1H), 7.44 (dd, *J* = 9.2, 2.6 Hz, 1H), 6.48 (br, 1H), 5.59 (ddd, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.11 (t, *J* = 1.3 Hz, 1H), 5.06 (dd, *J* = 7.1, 1.1 Hz, 1H), 4.25-4.19 (m,

1H), 4.18 (s, 3H), 3.53-3.39 (m, 2H), 3.51 (s, 3H), 3.29-3.16 (m, 2H), 2.78 (br, 1H), 2.23-2.14 (m, 3H), 1.98-1.88 (m, 1H), 1.54-1.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 146.9, 144.6, 139.7, 136.8, 131.8, 126.6, 123.1, 118.2, 117.4, 100.3, 75.7, 59.6, 58.8, 56.9, 54.5, 44.1, 36.4, 26.7, 23.9, 19.1; HRMS (*ESI*) calcd for $C_{21}H_{27}N_2O_2$ (M^++H): 339.2073; found: 339.2079.

Later, by switching base from NaH to KH, much higher yield was obtained. Here is the procedure: 247 mg KH (1.85 mmol, 1.20 eq, 30% suspended in oil) was washed three times with 5 mL pentane and suspended in 5 mL of THF. The suspension was cooled to 0 °C and stirred for 10 min. Then a solution of 0.5 g of quinine (1.54 mmol) in 4 mL THF was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and then 50 °C for 30 min. The reaction mixture was cooled down to ambient temperature and 101 uL of methyl iodide (1.62 mmol, 1.05 eq) was added dropwise and stirred at ambient temperature for 1 h. The resulting mixture was recooled down to 0 °C and quenched with water. The resulting mixture was extracted by ethyl acetate (3 x 15 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography (2% methanol in ethyl acetate), giving 490 mg (94%) of title compound as crystalline solid.

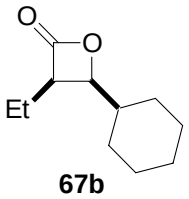
General procedure C: Me-QN/LiI-catalyzed asymmetric ketene-aldehyde cycloadditions: To a solution of Me-QN (0.10 mmol) and LiI (1.0-3.5 mmol, weighed in glovebox) in 0.25 mL of diethyl ether at ambient temperature was slowly added 2.0 mL of CH_2Cl_2. The resulting mixture was cooled to −78 °C and 0.44 mL of *N*, *N*-diisopropylethylamine (2.5 mmol) was added, and then aldehyde (1.0 mmol) was added dropwise, then a solution of acid chloride (2mmol) in 0.5 mL CH_2Cl_2 was added over 1-4 h by syringe pump (the tip of syringe was put into the reaction mixture). The reaction mixture was stirred for 14-16 h at −78 °C.

The reaction was quenched at −78 °C by adding 10 mL of Et_2O and the resulting mixture was filtered through silica gel eluting with 3 x 20 ml of Et_2O. The filtrate was concentrated *in vacuo* and the crude product mixture was purified by flash chromatography.



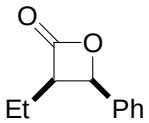
67a

***(3R, 4S)*-3-Ethyl-4-phenethyloxetan-2-one (67a)**: General procedure C was followed employing 20 mg of Me-QN (0.06 mmol, 10 mol%), 67 mg LiI (0.50 mmol, 100 mol%) and 66 μL of hydrocinnamaldehyde (0.50 mmol). Purification by flash chromatography (9% ethyl acetate in hexane) gave 31 mg (30%) of the title compound as colorless oil (reaction conversion 65% was determined by ^{1}H NMR of crude product mixtures). Spectra data as reported on page 44.



67b

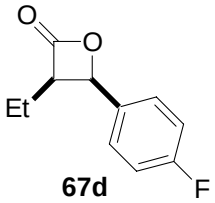
***(3S, 4R)*-4-Cyclohexyl-3-ethyloxetan-2-one (67b)**: General procedure C was followed employing 34 mg of Me-QN (0.10 mmol, 10 mol%), 402 mg LiI (3.0 mmol, 300 mol%) and 120 μL of cyclohexanecarboxaldehyde (1.0 mmol). Purification by flash chromatography (14% diethyl ether in pentane) gave 55 mg (30%) of the title compound as white crystalline solid (reaction conversion 50% was determined by ^{1}H NMR of crude product mixtures). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (dd, J = 10.2, 6.2 Hz, 1H), 3.53 (dt, J = 10.7, 5.9 Hz, 1H), 1.98-1.65 (m, 8H), 1.35-1.22 (m, 3H), 1.14 (t, J = 7.4 Hz, 3H), 1.10-0.88 (m, 2H); HRMS (*EI*) calcd for (M^+-CO_2) $C_{10}H_{18}$: 138.1409; found: 138.1406.



67c

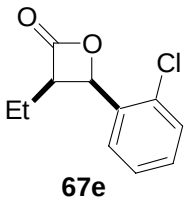
***(3R, 4R)*-3-Ethyl-4-phenyloxetan-2-one (67c)**: General procedure C was followed employing 34 mg of Me-QN (0.10 mmol, 10 mol%), 402 mg LiI (3.0

mmol, 300 mol%) and 102 μL of benzaldehyde (1.0 mmol). Purification by flash chromatography (6% ethyl acetate in hexane) gave 148 mg (84%) of the title compound as colorless oil. Separation of the enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 0.5 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 13.3 min (3*R,* 4*R*), 16.1 min (3*S,* 4*S*)] provided only one enantiomer (≥99% ee). $[\alpha]_D$ +134 (*c* 2.27, $CHCl_3$). Spectra data as reported on page 46.



67d

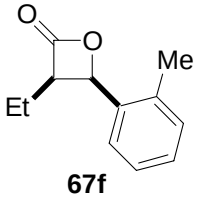
(3*R*, 4*R*)-3-Ethyl-4-(4-fluorophenyl)oxetan-2-one (67d): General procedure C was followed employing 34 mg of Me-QN (0.10 mmol, 10 mol%), 402 mg LiI (3.0 mmol, 300 mol%) and 108 μL of 4-fluorobenzaldehyde (1.0 mmol). Purification by flash chromatography (9% ethyl acetate in hexane) gave 146 mg (75%) of the title compound as colorless oil. Separation of enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 5% ^{i}PrOH, 95% hexane, T_r 7.7 min (3*R,* 4*R*), 8.5 min (3*S,* 4*S*)] provided only one enantiomer (≥99% ee). $[\alpha]_D$ +122 (*c* 2.01, $CHCl_3$); IR (thin film): 2979, 2938, 1827, 1601, 1144, 1112 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.30-7.27 (m, 2H), 5.77 (d, *J* = 6.4 Hz, 1H), 3.99 (td, *J* = 8.3, 6.4 Hz, 1H), 1.68-1.58 (m, 1H), 1.46-1.36 (m, 1H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 162.7 (d, *J* = 246.0 Hz), 130.5, 127.6 (d, *J* = 8.3 Hz), 115.5 (d, *J* = 21.6 Hz), 74.5, 56.9, 18.5, 11.1; HRMS (*EI*) *m/z* calcd for (M^+) $C_{11}H_{11}FO_2$: 194.0743; found: 194.0739.



67e

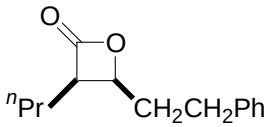
(3*R*, 4*R*)-4-(2-Chlorophenyl)-3-ethyloxetan-2-one (67e): General procedure C was followed employing 34 mg of Me-QN (0.10 mmol, 10 mol%), 402 mg LiI (3.0 mmol, 300 mol%) and 113 μL of 2-chlorobenzaldehyde (1.0

mmol). Purification by flash chromatography (4% diethyl ether in pentane) gave 174 mg (83%) of the title compound as colorless oil. Separation of enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 1.0 mL/min, 2% ^{i}PrOH, 98% hexane, T_r 6.9 min (3*R,* 4*R*), 7.8 min (3*S,* 4*S*)] provided only one enantiomer (≥99% ee). $[\alpha]_D$ +221 (*c* 2.30, $CHCl_3$); IR (thin film): 2971, 2938, 1832, 1473, 1444, 1145, 942, 897 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57-7.51 (m, 1H), 7.42-7.30 (m, 3H), 5.87 (d, *J* = 6.3 Hz, 1H), 3.96 (ddd, *J* = 8.9, 7.6, 6.3 Hz, 1H), 1.42-1.34 (m, 2H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 133.0, 131.2, 129.5, 129.2, 127.0, 126.8, 72.6, 56.6, 18.5, 11.1; HRMS (*EI*) *m/z* calcd for (M^+) $C_{11}H_{11}ClO_2$: 210.0448; found: 210.0458.



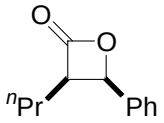
67f

(3*R*, 4*R*)-3-Ethyl-4-o-tolyloxetan-2-one (67f): General procedure C was followed employing 34 mg of Me-QN (0.10 mmol, 10 mol%), 452 mg LiI (3.4 mmol, 340 mol%) and 116 μL of 2-methylbenzaldehyde (1.0 mmol). Purification by flash chromatography (5% ethyl acetate in hexane) gave 133 mg (70%) of the title compound as colorless oil. Separation of enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 0.5 mL/min, 4% ^{i}PrOH, 96% hexane, T_r 14.9 min (3*R,* 4*R*), 17.8 min (3*S,* 4*S*)] provided only one enantiomer (≥99% ee). $[\alpha]_D$ +210 (*c* 1.98, $CHCl_3$); IR (thin film): 2971, 2938, 1825, 1462, 1148, 939, 891 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54-7.51 (m, 1H), 7.38-7.33 (m, 2H), 7.30-7.27 (m, 1H), 5.85 (d, *J* = 6.3 Hz, 1H), 3.95 (dt, *J* = 9.8, 6.4 Hz, 1H), 2.33 (s, 3H), 1.37-1.23 (m, 1H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 133.9, 133.1, 130.1, 128.2, 126.2, 125.1, 73.2, 56.3, 18.7, 18.6, 11.2; HRMS (*EI*) *m/z* calcd for (M^+) $C_{12}H_{14}O_2$: 190.0994; found: 190.0990.



67g

***(3R, 4S)-* 4-Phenethyl-3-propyloxetan-2-one (67g)**: General procedure C was followed employing 20 mg of Me-QN (0.06 mmol, 10 mol%), 67 mg LiI (0.50 mmol, 100 mol%) and 66 μL of hydrocinnamaldehyde (0.50 mmol). Purification by flash chromatography (6% ethyl acetate in hexane) gave 44 mg (40%) of the title compound as colorless oil (reaction conversion 80% was determined by ^{1}H NMR of crude product mixtures). Spectra data as reported on page 46.



67h

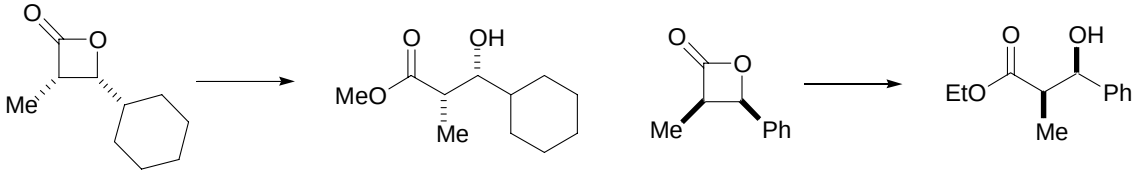
***(3R, 4R)*-4-Phenyl-3-propyloxetan-2-one (67h)**: General procedure C was followed employing 34 mg of Me-QN (0.10 mmol, 10 mol%), 470 mg LiI (3.5 mmol, 350 mol%) and 102 μL of benzaldehyde (1.0 mmol). Purification by flash chromatography (5% ethyl acetate in hexane) gave 133 mg (70%) of the title compound as colorless oil. Separation of the enantiomers by chiral HPLC [Daicel Chiracel™ OD-H column, flow rate 0.5 mL/min, 10% ^{i}PrOH, 90% hexane, T_r 11.7 min (3*R,* 4*R*), 13.6 min (3*S,* 4*S*)] provided only one enantiomer (≥99% ee). $[\alpha]_D$ +117 (*c* 1.80, $CHCl_3$). Spectra data as reported on page 47.

3.7 STEREOCHEMICAL PROOFS FOR β-LACTONES

The absolute configuration of β-lactones **ent-59g** was established by conversion to the corresponding methyl ester **68** using the published procedure ($La(O^tBu)_3$, MeOH)[47] and correlating the ester's specific rotations to those of authentic samples of known configuration: **68** $[\alpha]_D^{23}$ = +5.2 (2*S*, 3*R*) (*c* 1.64, $CHCl_3$) [lit $[\alpha]_D^{23}$ = –5.5 (2*R*, 3*S*) (*c* 0.3, $CHCl_3$).[48] The configuration of lactone **59h** was established similarly by conversion to corresponding ethyl ester

69 according to the literature procedure ($La(O^tBu)_3$, EtOH)[47] and correlating the ester's specific rotations to those of authentic samples of known configuration: **69** $[\alpha]_D^{23}$ = +20.6 (2*R*, 3*R*) (*c* 1.07, $CHCl_3$) [lit $[\alpha]_D^{23}$ = –22.0 (2*S*, 3*S*) (*c* 0.87, $CHCl_3$).[49]

Scheme 2. Absolute stereochemistry



ent-59g **68** **59h** **69**

4.0 ENANTIOSELECTIVE TOTAL SYNTHESIS OF (−)-PIRONETIN

4.1 BACKGROUND

4.1.1 Isolation and Biological Activity

Pironetin or PA-48153C (Figure 25) is an unsaturated δ-lactone derivative that was isolated in 1993 independently by two research groups from the fermentation broths of *Streptomyces prunicolor* PA-48153 [51] and *Streptomyces sp*. NK 10958.[52,53] Pironetin shows potent immunosuppressive and plant growth regulator activity. More importantly, it has recently been identified as a strong antitumor agent, that inhibts the tubulin assembly by its ability to bind covalently to the α-subunit of tubulin at Lys-352, this is the first compound that covalently binds to the α-subunit of tubulin and inhibits the interaction of tubulin heterodimers.[54] Structure elucidation and relative as well as absolutely stereochemical assignments for pironetin were achieved by spectral methods, X-ray crystallographic analysis, and further confirmed by total synthesis.[55] Based on the potential value of pironetin as a lead compound for cancer therapy and as a demonstration of our AAC methodology, we targeted a catalytic asymmetric total synthesis of the natural product that would be amenable to scale-up and derivatization.

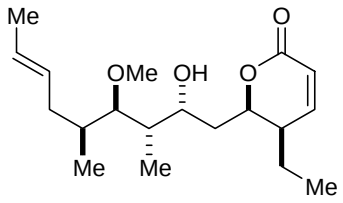


Figure 25. (–)-Pironetin

4.1.2 Previous Total Synthesis of (–)-Pironetin

To date, eight total syntheses of (–)-pironetin have been reported by eight different synthetic groups. The first total synthesis of pironetin was reported by Kawada[56] in 1995 starting from methyl-4,6-*O*-benzylidene-α-glucopyranoside **70** and (*S*)-methyl-3-hydroxyl-2-methylpropionate **71** (Figure 26). The key steps in this synthesis were achieved by *trans*-diaxial ring opening of epoxy mesylate **72** to introduce the ethyl group,[57] Wittig reaction of aldehyde **73** with a phosphorous ylide **74** derived from epoxide **75**, which was made from the methyl propionate **71**.

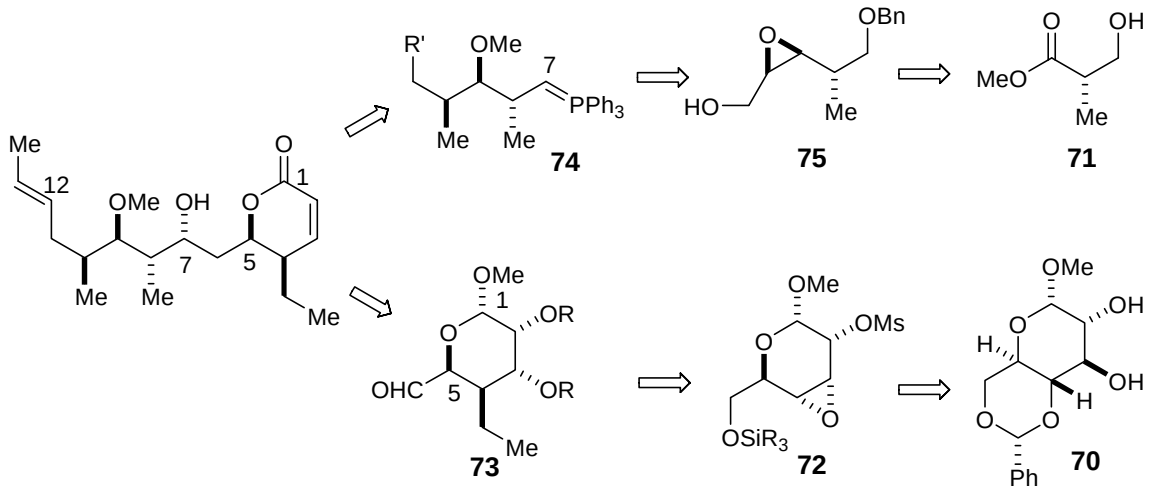


Figure 26. Retrosynthesis of (–)-Pironetin: Kawada Approach

Gurjar[58,59] published his synthesis of pironetin that involves the aldol reaction between aldehyde **76** and 4-benzyl-3-butyryl-2-oxazolidinone **77** (Figure 27). (*Z*)-Double bond in the

pyranone was achieved by modified Horner-Wadsworth-Emmons reaction.[60] The preparation of aldehyde **76** was involved a regio-selective reduction of epoxide **78** with Red-Al. Synthesis of epoxide **78** from epoxide **79** was achieved by this sequence: Me_2CuLi ring opening of epoxide **79**, protection of primary alcohol as TBS ether, methylation of secondary alcohol, deprotection of TBS ether, oxidation, olefination, DIBAL reduction and asymmetric Sharpless epoxidation. The similar sequence was used for converting of alcohol **80** to epoxide **79**.

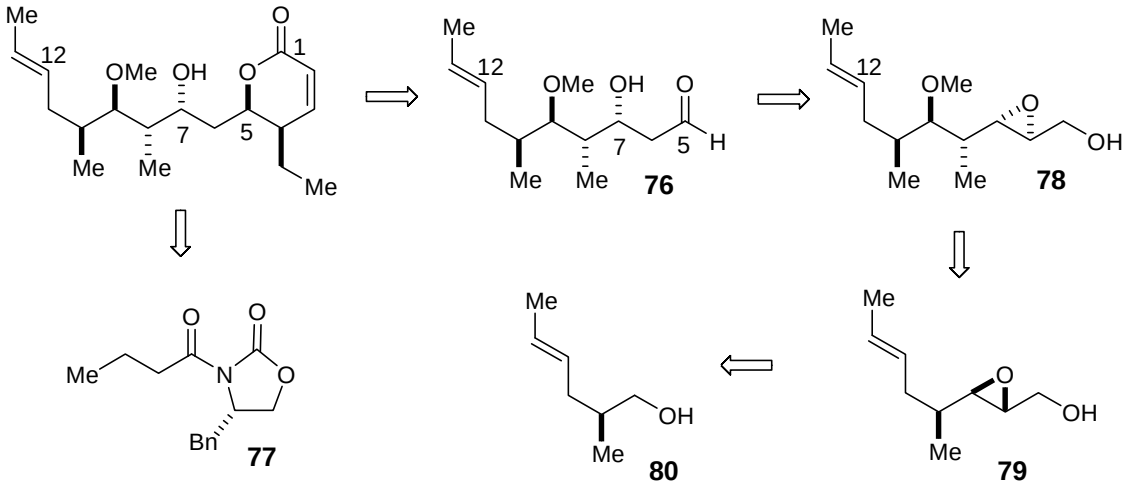


Figure 27. Retrosynthesis of (–)-Pironetin: Gurjar Approach

In his 1997 publication, Chida[61] disclosed his synthesis of pironetin by addition of dithiane anion derived from **81** to the epoxide **82** (Figure 28). The key steps involved in the formation of dithiane **81** from alcohol **83** were glycol cleavage and Still-Gennari olefination.[62] Alcohol **83** was obtained from L-malic acid in 6 steps. The epoxide **82** which has four contiguous stereocenters was constructed stereoselectively from L-quebrachitol. The key step involved here is *trans*-diaxial opening of epoxide **84** by trimethylaluminium.

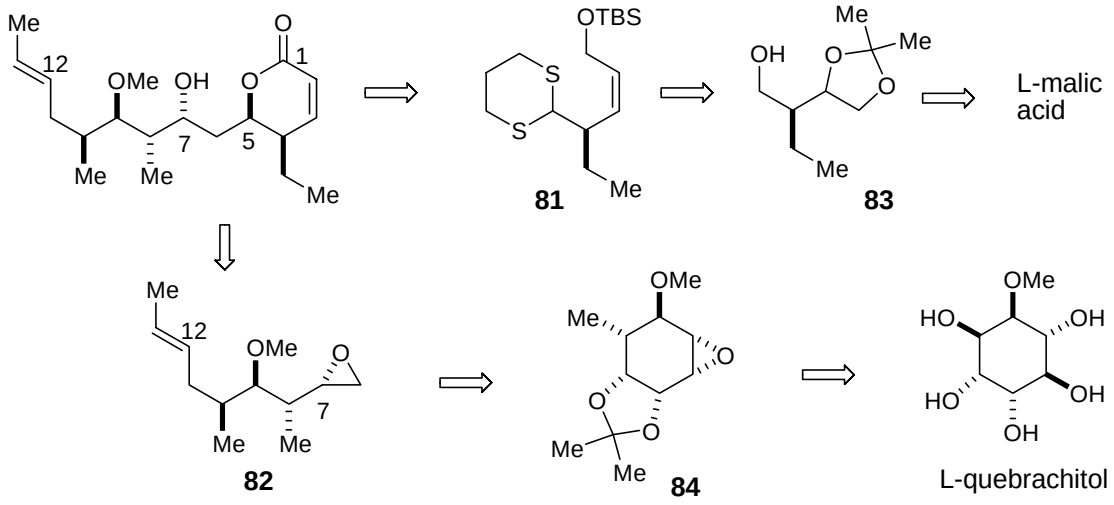


Figure 28. Retrosynthesis of (–)-Pironetin: Chida Approach

Published in 1998, Kitahara's[63,64] synthetic approach to pironetin also involved a nucloephilic addition of dathiane anion derived from **85** to epoxide **86** (Figure 29). Dithiane **85** was synthesized from a chiral building block 5-hydroxy-bicyclo[4.1.0]heptan-2-one **87**, and epoxide **86** was prepared from the benzylate **88**, which was made from epoxy alcohol **89**.

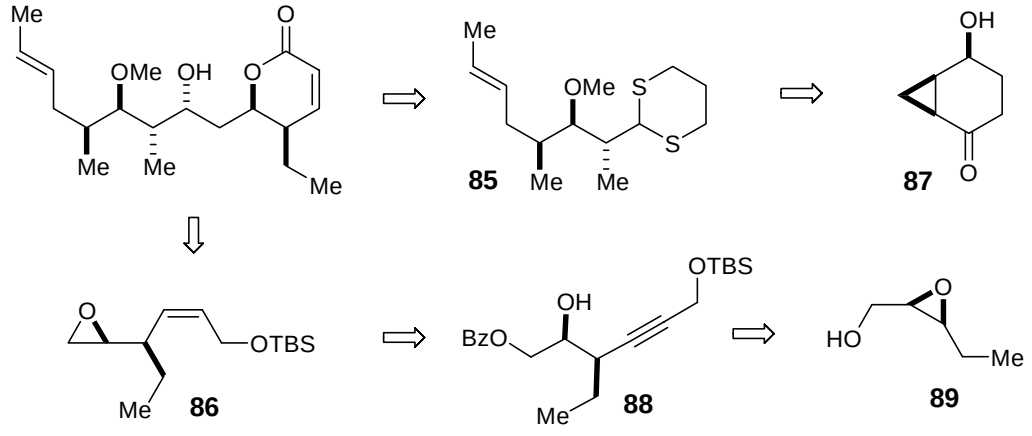


Figure 29. Retrosynthesis of (–)-Pironetin: Kitahara Approach

In 2001, Keck[65] reported a convergent total synthesis of pironetin. Key step included a highly selective BF_3 promoted Mukaiyama aldol reaction between silyl enol ether **90** and aldehyde **91**, which was obtained by a diastereoselective $TiCl_4$ mediated addition of crotylstannane **92** to aldehyde **93** [66] (Figure 30). Silyl enol ether **90** was obtained by using asymmetric alkylation protocol developed by Meyers[67] from chiral auxiliary **94**.

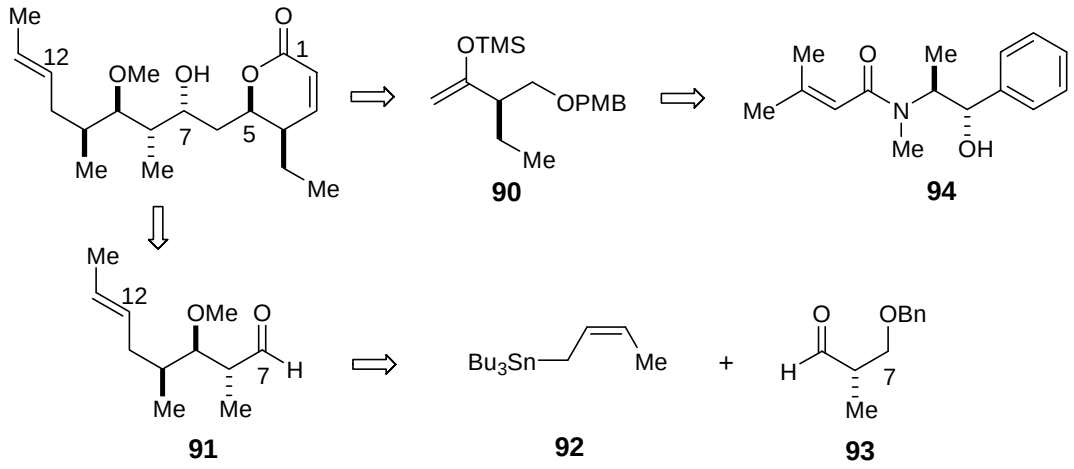


Figure 30. Retrosynthesis of (–)-Pironetin: Keck Approach

More recently 2003, Dias[68,69] reported the asymmetric synthesis of pronetin by using of three very efficient Evans oxazolidinone-mediated *syn*-aldol condensations,[70] a high-yield coupling between lithium acetylide ethylenediamine[71] complex and tosylate **97** and a selective reduction to establish C12-C13 (*E*) double bond (Figure 31).

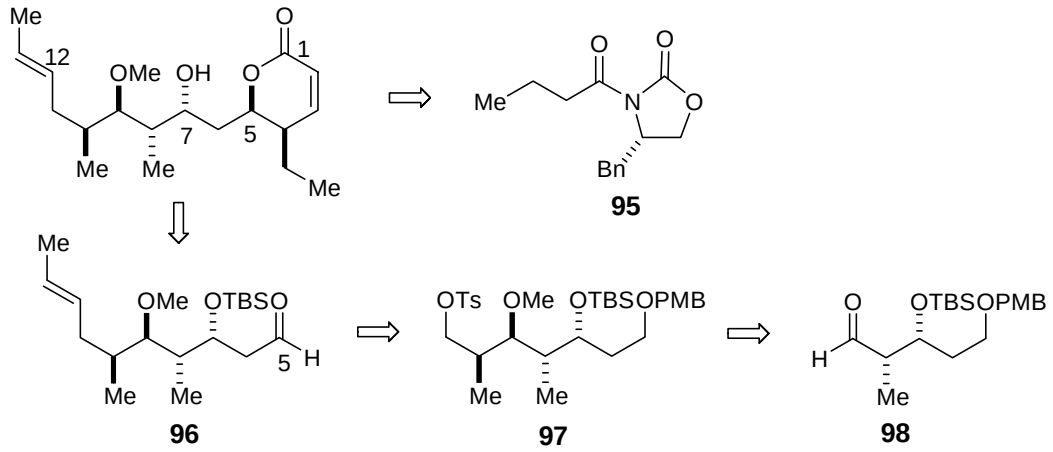


Figure 31. Retrosynthesis of (–)-Pironetin: Dias Approach

The most recent total synthesis of (−)-pironetin was published by Enders in 2007.[72] The α,β-unsaturated-δ-lactone fragement was installed by ring-closing metathesis of triene **99**, which was synthesized by coupling between the ketone **101** and aldehyde **102** by using a Mukaiyama-aldol reaction. The stereogenic centers of **101** and **102** were generated by employing the SAMP/RAMP (SAMP = (S)-1-amino-2-methoxymethylpyrrolidine, RAMP = (R)-1-amino-2-methoxymethyl-pyrrolidine) hydrazone methodology (Figure 32).

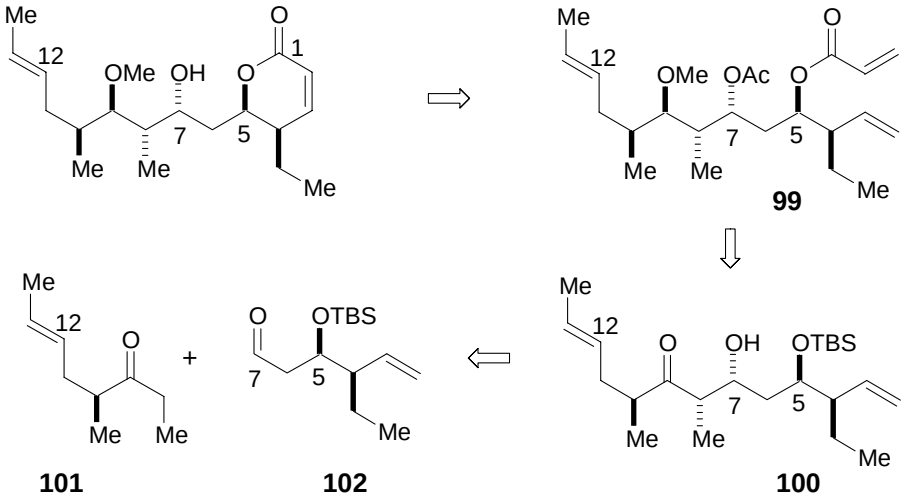


Figure 32. Retrosynthesis of (–)-Pironetin: Enders Approach

4.2 RETROSYNTHETIC ANALYSIS OF (−)-PIRONETIN

Our retrosynthetic analysis of pironetin is based on the novel approach of creating all stereocenters using our AAC methodologies (Figure 33). We envisioned that the α,β-unsaturated δ-lactone moiety in pironetin could be installed via a ring expansion of β-lactone **103**. The C12-C13 propenyl unit could be made via an allylic cuprate addition to tosylate **104** followed by olefin isomerization. Four contiguous *syn*, *anti*, *syn* stereocenters in the tosylate **104** will be made from masked dipropionate β-lactone **105** which will be made from β-lactone **106**. The β-lactone **106** will be synthesized by [2+2] cycloaddition of 3-(4-methoxybenzyloxy)-propionaldehyde **107** and *in situ* generated methyl ketene.

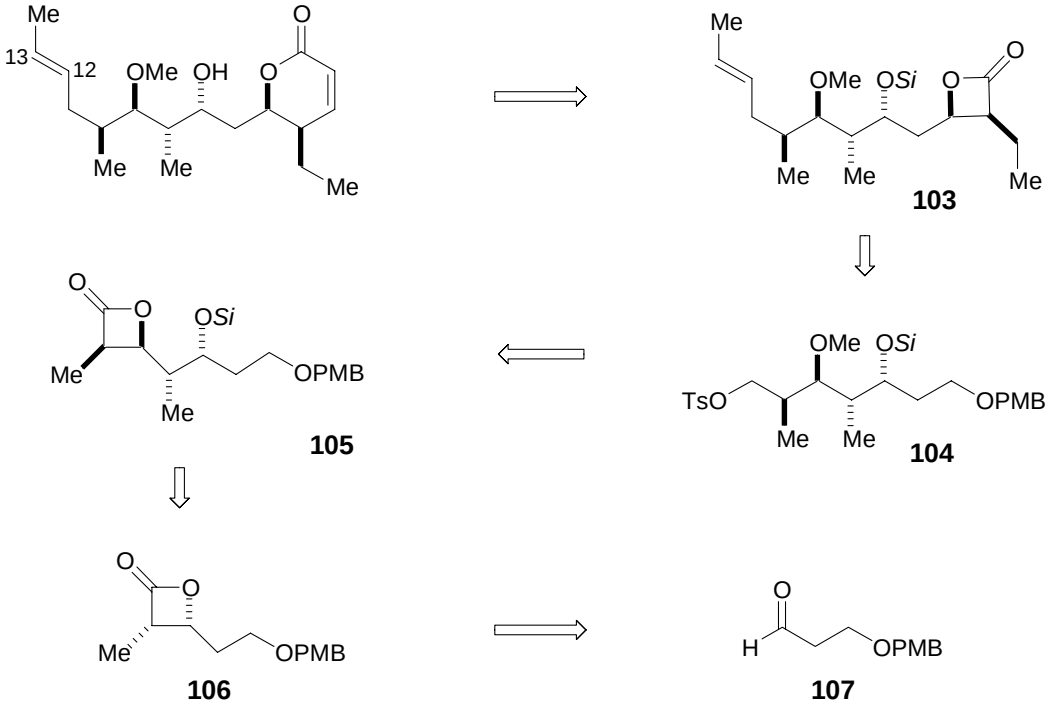
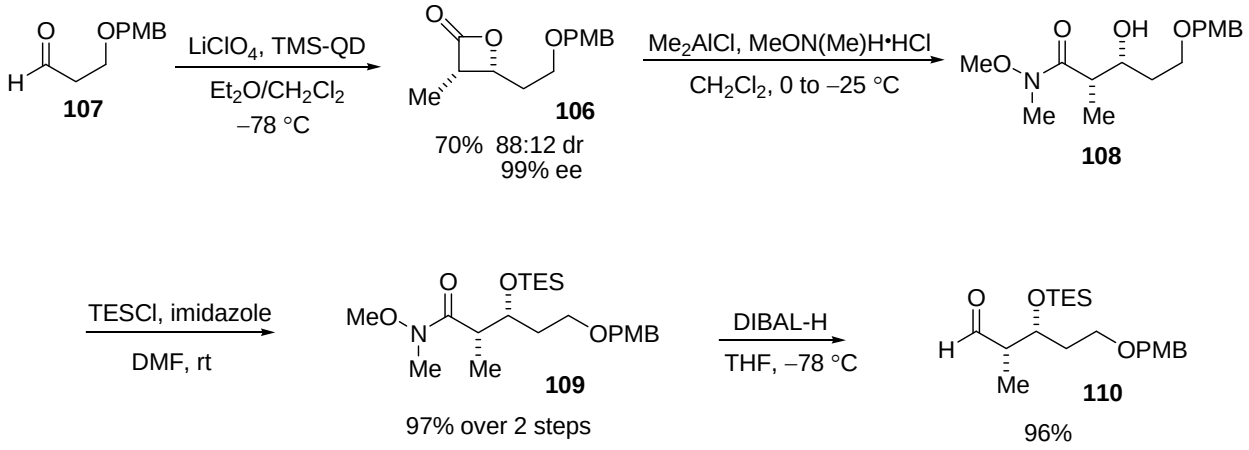


Figure 33. Retrosynthetic analysis of (−)-Pironetin

4.3 SYNTHESIS OF (−)-PIRONETIN

The synthesis of (–)-pironetin began from 3-(4-methoxybenzyloxy)-propionaldehyde **107** which was prepared according to the published procedure.[73,74] Lactone **106** was prepared in 70% yield (99% ee) from aldehyde **107** under standard alkaloid-catalyzed AAC conditions ($LiClO_4$, EtCOCl, $^{i}Pr_2NEt$, CH_2Cl_2/Et_2O, –78 °C) employing 10 mol % of the TMS-QD (Scheme 3). Ring opening of the enantioenriched β-lactone **106** by *N*,*O*-dimethylhydroxyl amine[75] followed by triethylsilyl (TES) protection of secondary alcohol afforded the β-silyloxy amide **109** in 97% yield over 2 steps. Amide **109** was then reduced with $^{i}Bu_2AlH$ to α-chiral aldehyde **110** in 96% yield.

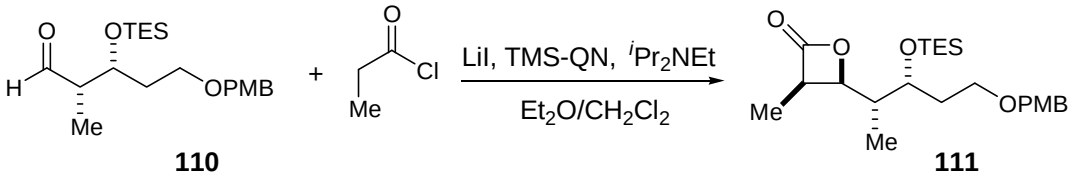
Scheme 3. Synthesis of α-methyl β-triethylsiloxy chiral aldehyde



Aldehyde **110** was then used as the coupling partner in a double diastereoselective AAC reaction (Table 16). The first test reaction consisted of 2.0 equiv of LiI and 10 mol% of TMS-QN, 2.5 equiv of $^{i}Pr_2NEt$, 2.0 equiv of propionyl chloride and at –40 °C, under these conditions,

aldehyde **110** underwent facile [2+2] cycloaddition with *in situ* generated methyl ketene to afford β-lactone **111** in 62% yield as single diastereomer (^{1}H NMR of crude reaction mixture); however, reaction did not proceed to full conversion and a small amount of α, β-unsaturated aldehyde was formed via β−elimination. By changing the reaction temperature to –78 °C and increasing the LiI to 3 equiv, the [2+2] cycloaddition proceeded to full conversion and produced *syn*, *anti*, *syn* β-lactone **111** in 87% yield as a single diastereomer.

Table 16. Effect of LiI stoichiometry on the AAC reaction



entry	Lewis Acid	Temp (°C)	Yield (%)	dr
a	2.0 equiv LiI	–40	62	>95:5
b	3.0 equiv LiI	–78	87	>95:5

[a] Isolated yields of purified products. [b] Reaction was performed using 10 mol% TMS-QN, 2.5 equiv of ^{i}Pr$_2$NEt and 2.0 equiv of propionyl chloride.

Using the mechanism we proposed for achiral aldehyde AAC reaction, we have interpreted this AAC reaction involving chiral aldehyde electrophiles using the well-established models that accurately predict and rationalize the stereochemical outcome of analogous aldol additions.[76] Due to the steric bulk of the alkaloid, the activated acyl ammonium enolate derived from methyl ketene and alkaloid is a *Z*-isomer.[11] With the nucleophilic addition of *Z*-enolate to an α-substituted aldehyde, anti-Felkin-Anh induction is generally adopted to avoid the *syn*-pentane non-bonding interaction involved in the Felkin-Anh model.[76] So transition state **A** for

the double diastereoselective AAC reaction in Figure 34 would be expected to be lower energy than transition state **B**, thus the β-lactone **111** was formed in high yield and excellent diastereoselctivity.

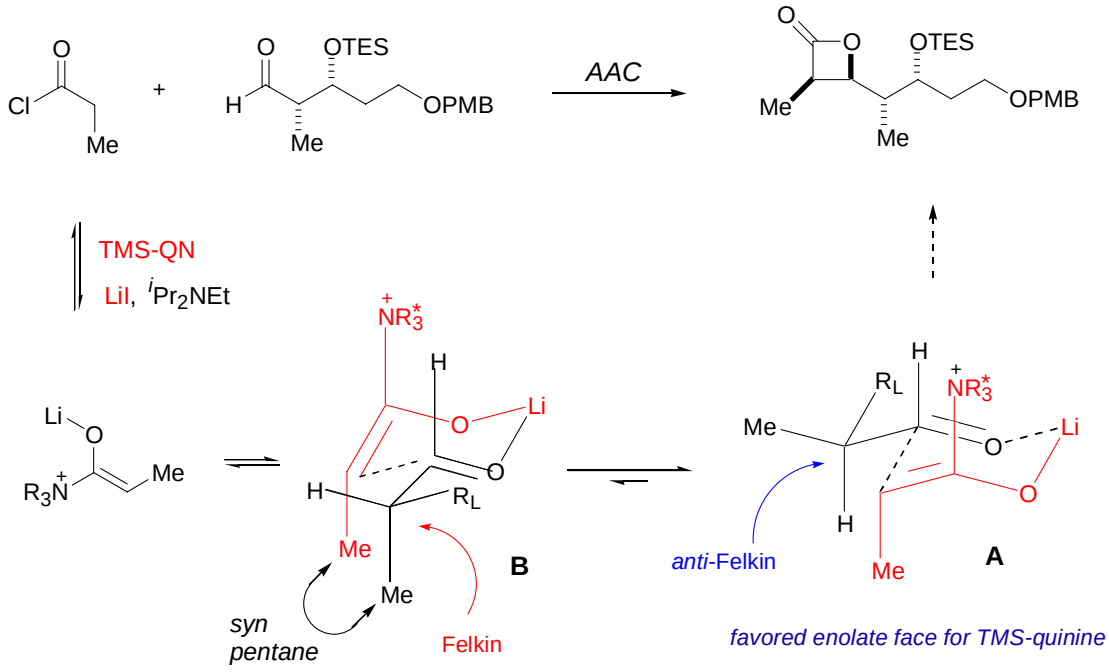
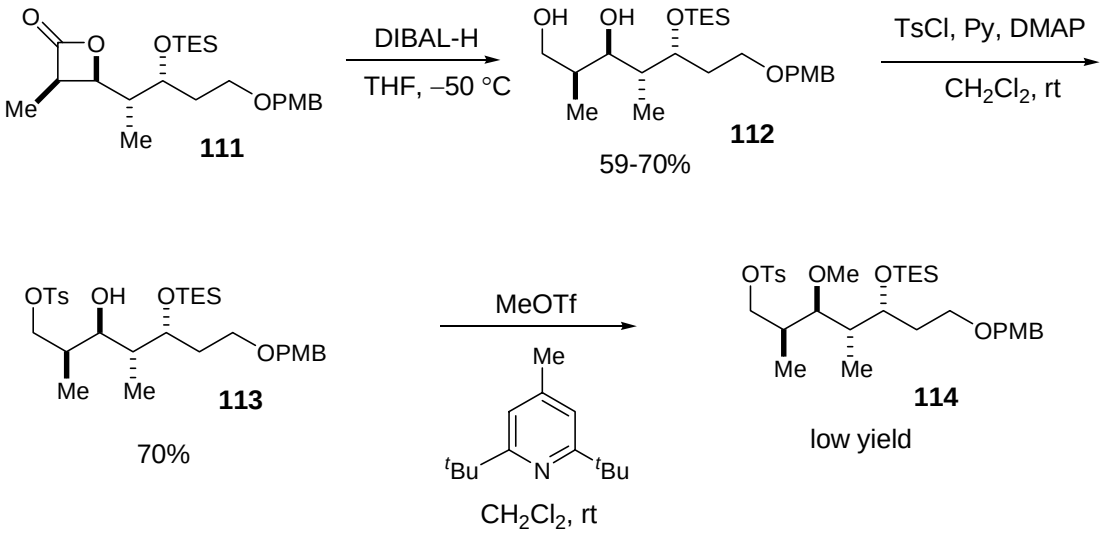


Figure 34. Postulated transition state for AAC reaction

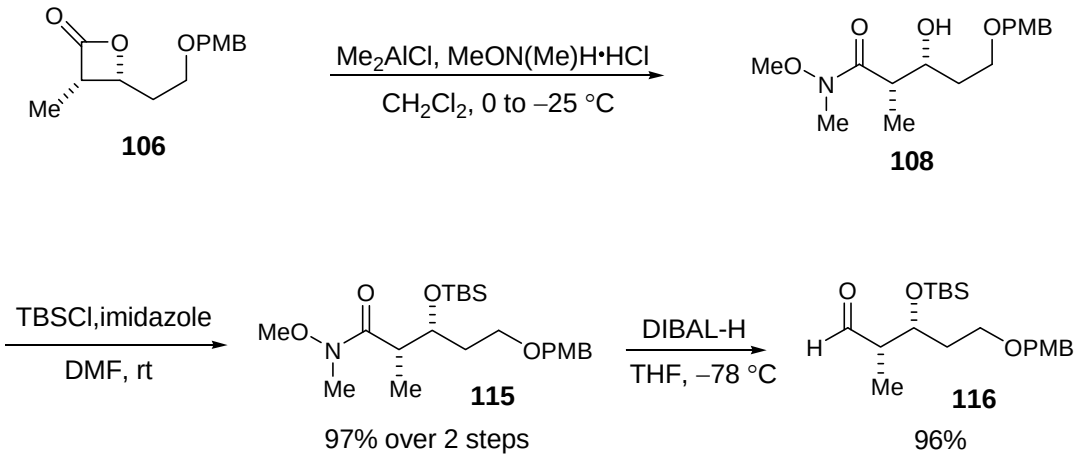
Having successfully established the four contiguous stereogenic centers in pironetin, the next phase of our synthesis focused on installing the terminal C12-C13 propenyl unit. Reduction of β-lactone **111** by $^{i}Bu_2AlH$ generated 1,3-diol **112** in 59-70% yield. Selective tosylation of primary hydroxyl group provided tosylate **113** in 70% yield.[77] In the presence of 2,6-di-tert-butyl-4-methyl-pyridine, methylation of secondary alcohol by methyl triflate[78] produced the methyl ether **114** in low yield with the concomitant deprotection of TES ether (Scheme 4).

Scheme 4. Synthesis of protected tetraol



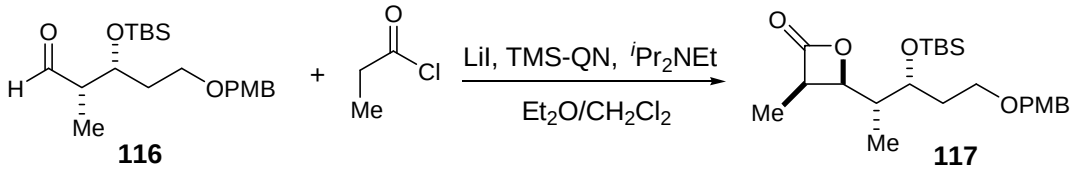
Since the TES protection group found to be labile under reaction conditions, we examined more robust protection group *tert*-butyldimethylsilyl (TBS). The synthesis of α-methyl β-*tert*-butyldimethylsiloxyl chiral aldehyde **116** was straightforward. Ring opening of highly enantioenriched β-lactone **106** by *in situ* generated *N*,*O*-dimethylhydroxyl amine-aluminium salt followed by TBS protection of secondary alcohol afforded the β-silyloxy amide **115** in 97% yield over 2 steps. Amide **115** was reduced to α-chiral aldehyde **116** on treatment with $^{i}Bu_2AlH$ in 96% yield (Scheme 5).

Scheme 5. Synthesis of α-methyl β-tert-butyl-dimethylsiloxy chiral aldehyde



This more steric bulky aldehyde **116** was then employed as the coupling partner in the double diastereoselective AAC reaction (Table 17). Subjecting aldehyde **116** to the aboved mentioned optimal AAC reaction conditions for TES-protected aldehyde **110** (3.0 equiv of LiI, 10 mol% TMS-QN, 2.5 equiv of $^{i}Pr_2NEt$, and 2.0 equiv of propionyl chloride at –40 °C), however, under these conditions, the reaction only proceeded to 60% conversion and 30% yield. Again, by adjusting the reaction condition to –78 °C and 5 equiv of LiI, the [2+2] cycloaddition proceeded to completion and the desired β-lactone **117** was formed in 95% yield as single diastereomer (^{1}H NMR of crude reaction mixture).

Table 17. Effect of β-protection group on AAC reaction

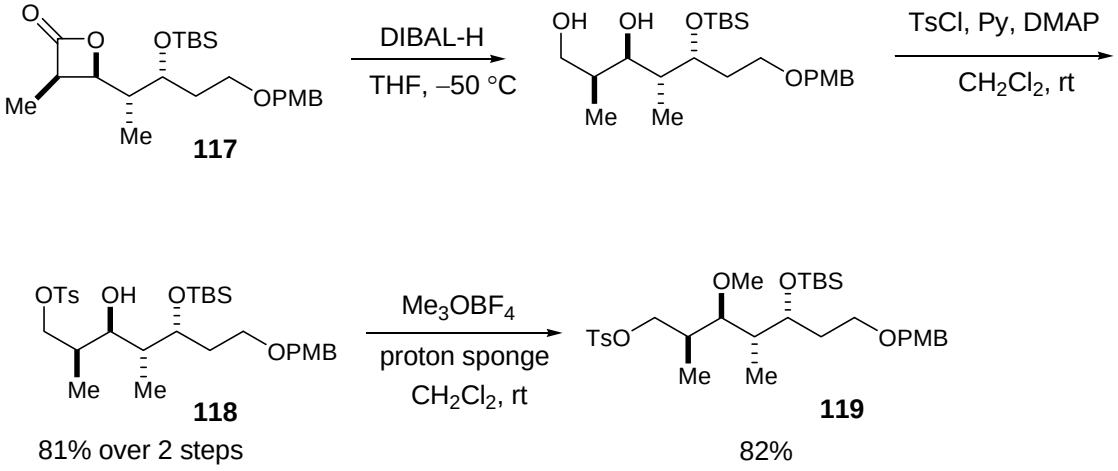


entry	Lewis Acid	Temp (°C)	Yield (%)	dr
a	3.0 equiv LiI	–40	30	>95:5
b	5.0 equiv LiI	–78	95	>95:5

[a] Isolated yields of purified products. [b] Reaction was performed using 10 mol% TMS-QN, 2.5 equiv of $^{i}Pr_2NEt$ and 2.0 equiv of propionyl chloride.

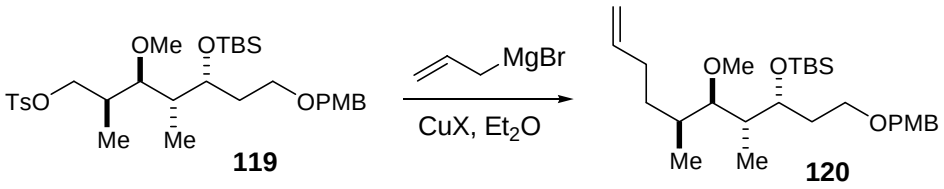
Compare to the TES-protected β-lactone **111**, the yield for $^{i}Bu_2AlH$ reduction of TBS-protected β-lactone **116** and the following tosylation of primary alcohol became much higher, the tosylate **118** was formed in 81% yield over 2 steps (Scheme 6). Then the methylation of secondary alcohol **118** was investigated,[79] under the optimal conditions (6 equiv of proton sponge and Meerwein's salt), the protected tetraol **119** was produced in 82% yield (Scheme 6).

Scheme 6. Synthesis of new protected tetraol



With the protected tetraol **119**, several *in situ* generated allylic cuprates were screened to establish the optimal reaction conditions for effecting the introduction of the terminal olefin (Table 18). Treatment of tosylate with excess amount of *in situ* generated cuprates was envisioned to result in nucleophilic attack of cuprates to tosylate to form terminal olefin **120**.[80] Cuprates derived from copper cyanide and copper iodide provided the desired olefin product **120**, but in modest yields (50-62%, entry a, b). The cuprate derived from 5 equiv of copper bromide and 10 equiv of allyl magnesium bromide afforded the product **120** in 85% yield (entry c).

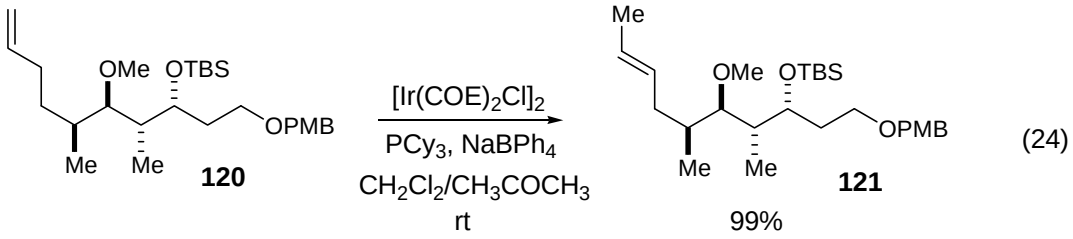
Table 18. Effect of copper salts on the substitution reaction



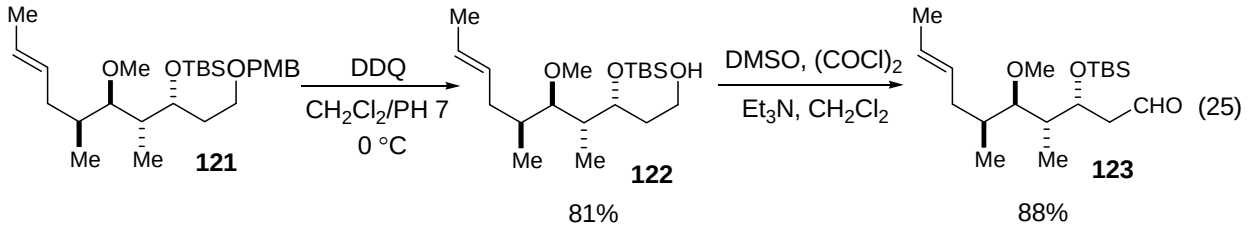
entry	CuX	MgBr	Yield (%)
a	3.0 equiv CuCN	6 equiv	50
b	3.0 equiv CuI	6 equiv	60-62
c	5.0 equiv CuBr	10 equiv	85

[a] Isolated yields of purified products. [b] Reaction was performed (–20 to 0 °C)

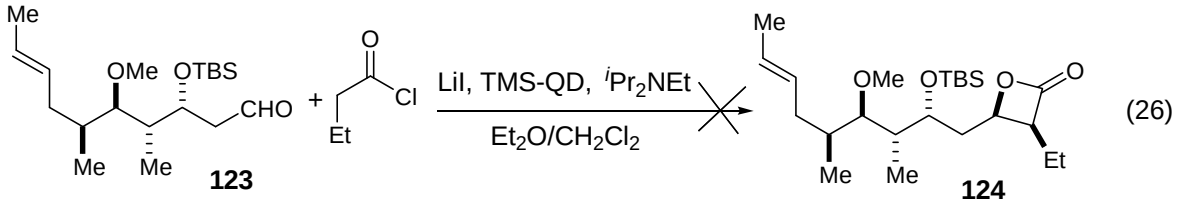
Then by using iridium-catalyzed olefin isomerization developed by the Nelson group,[81] this terminal olefin **120** was regioselectively and quantitatively converted to internal olefin **121** catalyzed by *in situ* generated iridium cation from 1 mol% $[Ir(COE)_2Cl]_2$, 6 mol% PCy_3 and 2 mol% $NaBPh_4$ (eq 24).



Deprotection of PMB ether **121** by DDQ[82] formed the primary alcohol **122** in 81% yield which was converted to the aldehyde **123** by Swern oxidation in 88% yield (eq 25).

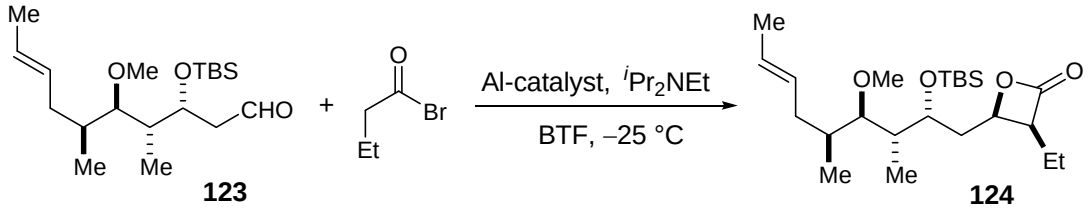


Having obtained the chiral aldehyde **123**, the AAC reaction for this aldehyde **123** was examined to set up the last two stereocenters. First, the standard alkaloid-catalyzed AAC reaction condition (10 mol% of TMS-QD, 1.0 equiv of LiI, 2.5 equiv of $^{i}Pr_2NEt$ and 2 equiv of butyryl chloride) was employed for the chiral aldehyde **123** and *in situ* generated ethyl ketene [2+2] cycloaddition (eq 26), however, there was no β-lactone **124** formation, the starting aldehyde was almost untouched and the major side product is ethyl ketene dimer.



Since the alkaloid/LiI system did not catalyzed the [2+2] cycloaddition between aldehyde **123** and ethyl ketene, the 2nd generation Al-catalyzed AAC reaction conditions was tried for the [2+2] cyclocondensation between aldehyde **123** and ethyl ketene. We were pleased to find that the chiral aldehyde **123** was converted to β-lactone **124** in 25% yield under the 2nd generation Al-triamine catalyzed AAC reaction condition (20 mol% Al-triamine, ^{n}PrCOBr, $^{i}Pr_2NEt$, BTF, –25 °C (Table 19). The yield of β-lactone could be increased to 65% by increasing the catalyst loading to 50 mol%, and the diastereoselectivity is excellent (>90% de, ^{1}H NMR of crude reaction mixture).

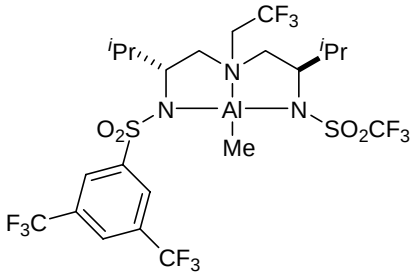
Table 19. Ethyl ketene AAC reaction



entry	Al (mol%)	Yield (%)	dr
a	20	25	>95:5
b	50	65	>95:5

[a] Isolated yields of purified products. [b] Reaction was performed using 2.5 equiv of $^{i}Pr_2NEt$ and 2.0 equiv of butyral bromide.

Al(III) Catalyst



Having set up all stereocenters for pironetin, only the extension of β-lactone **124** to α,β-unsaturated-δ-lactone **128** was necessary to complete the total synthesis. We proposed following procedure to achieve this transformation (β-lactone to α,β-unsaturated-δ-lactone, Figure 35). Ring-opening of the β-lactone by *in situ* generated ester enloate would produce β-keto ester,

which would exit as the mixture of β-keto ester and its tautomer enol ester, reduction of β-keto ester would give β-hydro ester, then under acidic conditions, β-hydro ester would be expected to undergo lactonization and dehydration, forming the α,β-unsaturated-δ-lactone.

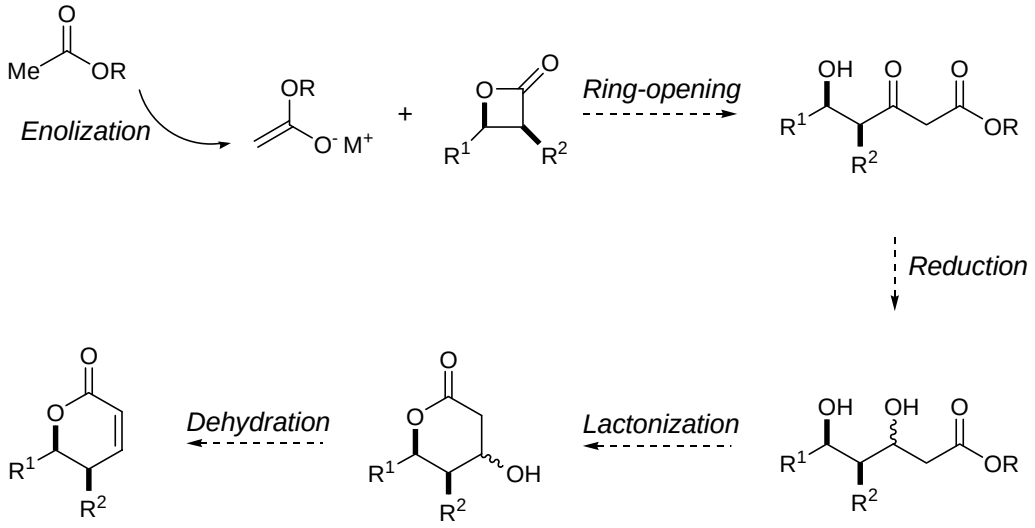
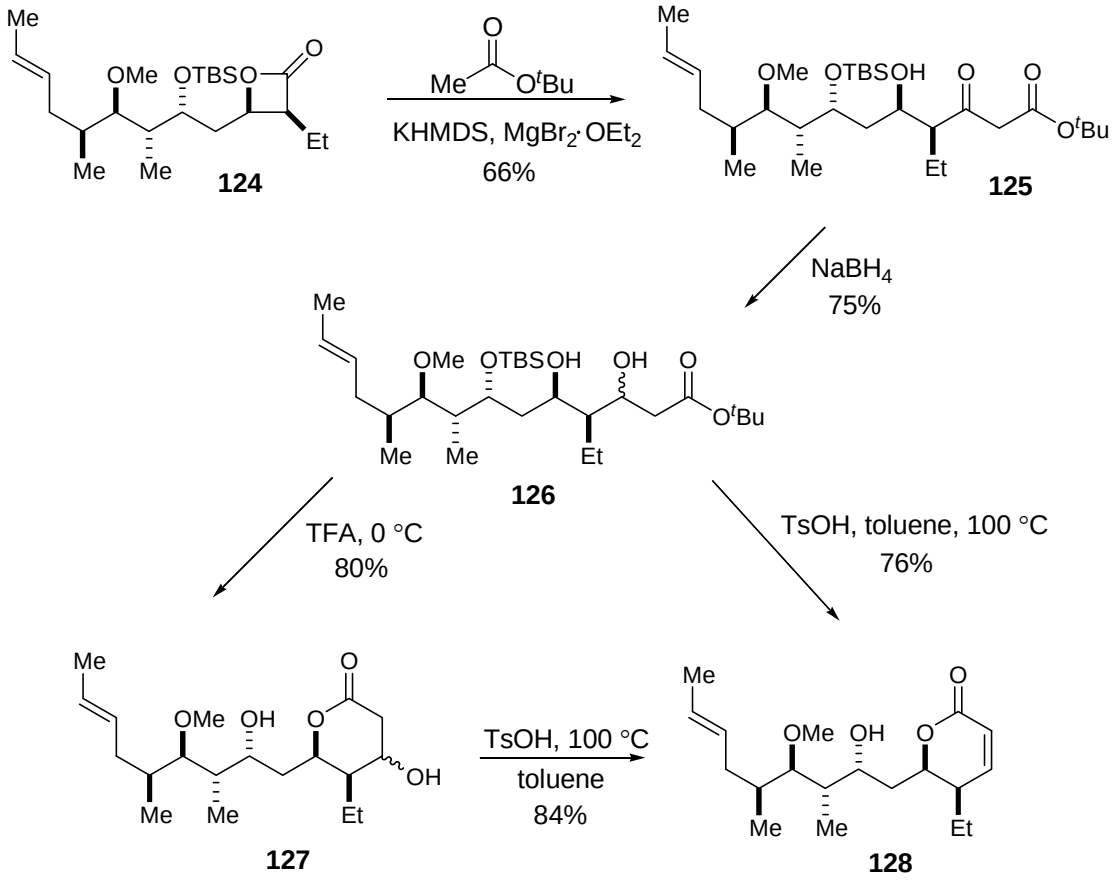


Figure 35. Synthesis of α, β-unsaturated δ-lactone from β-lactone

Then this proposed route for synthesizing of α,β-unsaturated-δ-lactone from β-lactone was applied to our synthesis (Scheme 8). Ring opening of β-lactone **124** by *in situ* generated *tert*-butyl acetate magnesium enolate gave β-keto ester **125** in 66% yield. Sodium borohydride reduction of β-keto ester **125** gave the β-hydro ester **126** in 75% yield. TFA mediated deprotection of *tert*-butyl ester and TBS ether, lactonization forming β-hydroxy σ-lactone **127** in 80% yield, after dehydration of the β-hydroxy σ-lactone **127**, pironetin **128** was obtained in 84% yield. The β-hydroester **126** can also be directly transformed to (–)-pironetin **128** in 75% yield by treated with TsOH at 100 °C, deprotection of *tert*-butyl group, TBS group, lactonization and dehydration occurred in the last step.

Scheme 7. Complete the synthesis of pironetin

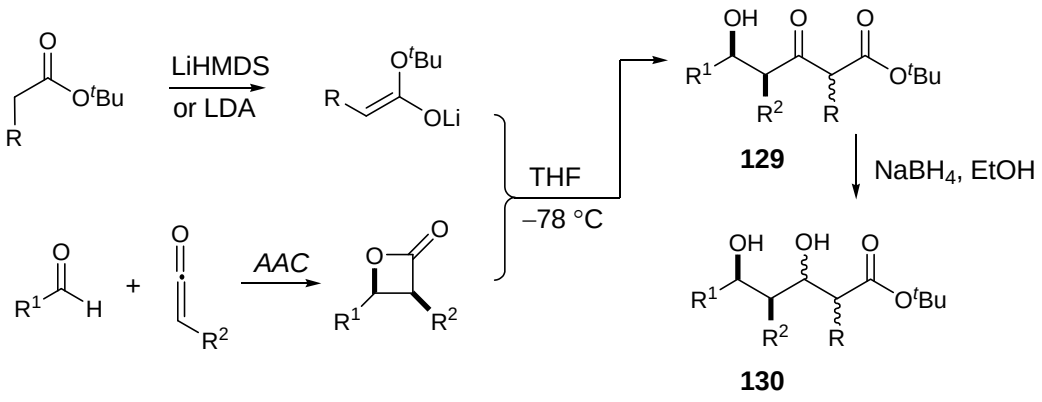


In summary, catalytic asymmetric synthesis of β-lactones methodologies have been successfully applied to the total synthesis of the potent antitumor agent (–)-pironetin. The route encompassed 16 steps and afforded pironetin in 5.9% overall yield from the inexpensive and readily available starting material 3-(4-methoxybenzyloxy)-propionaldehyde **107**. Asymmetric AAC reactions were responsible for directly establishing all the stereogenic centers in (–)-pironetin. Highlights of the synthesis include an efficient iridium-catalyzed olefin isomerization and a facile transformation of β-lactone to α,β-unsaturated δ-lactone.

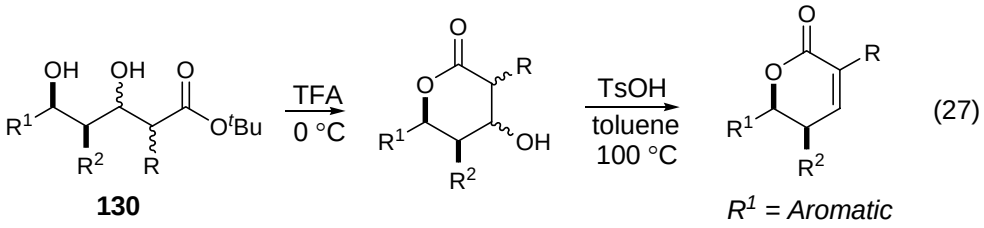
4.4 SYNTHESIS OF α,β-UNSATURATED δ-LACTONES FROM β-LACTONES

Enantioenriched α,β-unsaturated δ-lactones are key structural subunit of widely occurring natural products, the synthesis of which have generated considerable interest. During the synthesis of pironetin, a facile transformation of β-lactone to α,β-unsaturated δ-lactone was developed to complete the synthesis. This method was then used for a variety of simple β-lactones to generate a small δ-lactone library. Ring-opening of β-lactones by *in situ* generated ester enloate formed the β-keto esters **129**, which were then reduced by $NaBH_4$ to form β-hydroxy esters **130** (Scheme 7).

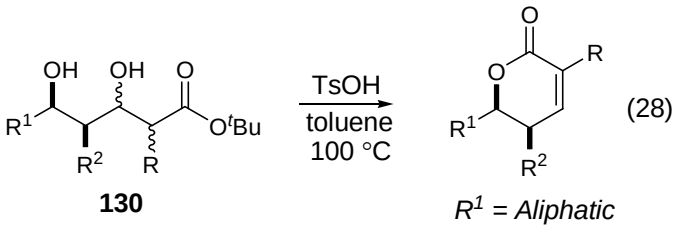
Scheme 8. Synthesis of β-hydroxy-ester



Then depend on the property of the R^1 group (aromatic or aliphatic), two different procedures were employed to convert these β-hydroxy esters **130** to α,β-unsaturated δ-lactones. When the R^1 is aromatic group, 2 step-procedure was used: 1. Trifluoroacetic acid mediated deprotection of *tert*-butyl ester and lactonization; 2. TsOH catalyzed dehydration (eq 27).



When the R^1 is aliphatic group, 1 step-procedure can be used: TsOH catalyzed deprotection of *tert*-butyl ester, lactonization and dehydration directly forming δ-lactone (eq 28).[83] When R^1 is aromatic group, we had to use 2 step-procedure, because if we use 1 step-procedure, under TsOH and high temperature, the δ benzylic position in **130** is very easy to form benzyl cation, thus the δ-chiral center is epimerized.



After identifying the optimal reaction procedures, we then explored reaction scope as a function of β-lactones structure for β-lactone to δ-lactone transformation. Table 20 listed some specific examples. Ring opening of the β-lactones derived from aliphatic aldehydes (chain or α-branched) by different *tert*-butyl ester derived lithium enolate formed different β-keto esters (**131**-**134**) in moderate to excellent yield (51-92%). Then by using the 2 step proceures I mentioned above, these different β-keto esters was converted to α, β unsaturated δ-lactones (**135**-**138**) in good yield (50-68%).

Table 20. α, β-unsaturated δ-lactones from aliphatic aldehyde derived β-lactones

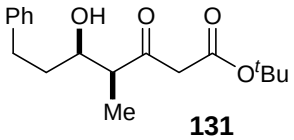
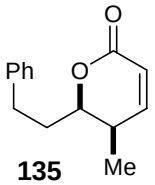
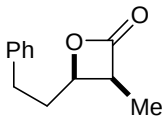
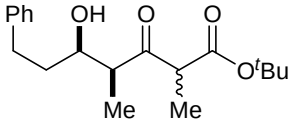
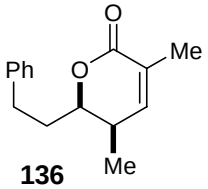
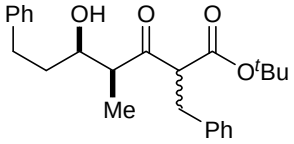
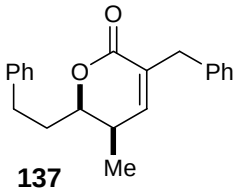
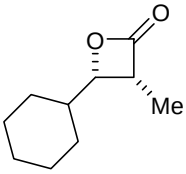
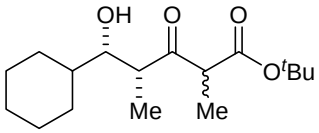
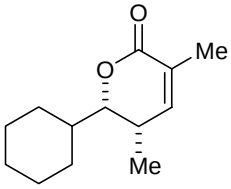
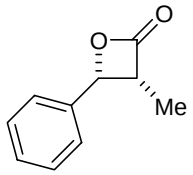
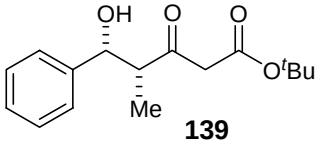
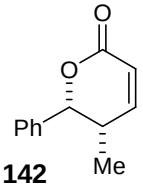
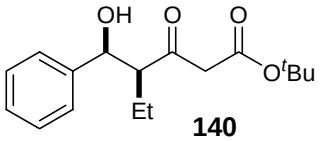
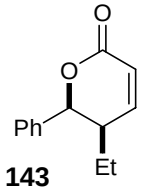
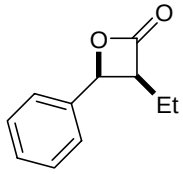
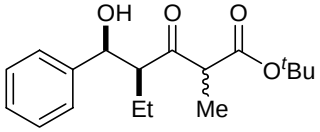
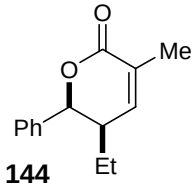
β-lactone	β-keto ester (% yield)	δ-lactone (% yield over 2 steps)
	 **131** 92%	 **135** 68%
	 **132** 74%	 **136** 58%
	 **133** 51%	 **137** 50%
	 **134** 71%	 **138** 53%

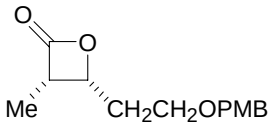
Table 21 listed some examples for benzyladehyde derived β-lactones. Again by using the 3 steps proceure I mentioned above, these β-lactones were converted to β-keto esters (**139-141**) in good yield (70-83%), and then to α, β-unsaturated δ-lactones (**142-144**) in 53-64% yield.

Table 21. α, β-unsaturated δ-lactones from aromatic aldehyde derived β-lactones

β-lactone	β-keto ester (% yield)		δ-lactone (% yield over 3 steps)	
	 **139**	72%	 **142**	59%
	 **140**	83%	 **143**	64%
	 **141**	70%	 **144**	53%

In summary, an efficient method for transforming of β-lactones to α,β-unsaturated δ-lactones was developed, a series of syntnetic useful building block α,β-unsaturated δ-lactones has been easily synthesized in moderate yield.

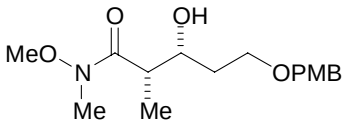
4.5 EXPERIMENTALS



106

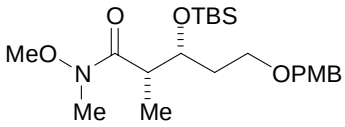
(3*S*, 4*R*)-4-[2-(4-Methoxy-benzyloxy)ethyl]-3-methyloxetan-2-one 106: To a solution of TMS-QD (0.926 g, 2.32 mmol) and $LiClO_4$ (0.737 g, 6.95 mmol) in 23 mL of diethyl ether was added 46 mL of CH_2Cl_2 and the reaction mixture was cooled to −78 °C. To the resulting mixture was added *N*, *N*-diisopropylethylamine (10.0 mL, 57.9 mmol) followed by 3-(4-methoxy-benzyloxy)-propionaldehyde **107** (4.49 g, 23.2 mmol). A solution of propionyl chloride (4.0 mL, 46.4 mmol) in 6.0 mL of CH_2Cl_2 was then added over 1 h by syringe pump. The reaction mixture was stirred for 18 h then was quenched at the −78 °C by adding 100 mL of Et_2O and 100 mL saturated aqueous NH_4Cl solution. The mixture was extracted by Et_2O (3 x 100 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography (15% ethyl acetate in hexane) gave 4.06 g (70%) of the title compound as a colorless oil (*syn*: *anti* = 89: 11). Separation of enantiomers by Chiral HPLC [Daicel Chiracel^{TM} OD-H column, flow rate 1.0 mL/min, 10% ^{i}PrOH, 90% hexane, T_r: 13.3 min (3*R*, 4*S*), 18.7 min (3*S*, 4*R*)] provided the only one enantiomer (3*S*, 4*R*) (99% ee). $[\alpha]_D$ +38.8 (*c* 1.81, $CHCl_3$); IR (thin film): 1817, 1613, 1514, 1248cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.79 (ddd, J = 8.2, 6.5, 5.2 Hz, 1H), 4.46 (s, 2H), 3.82 (s, 3H), 3.77(dq, J = 7.7, 6.5 Hz, 1H), 3.67-3.56 (m, 2H), 2.05-1.96 (m, 2H), 1.28 (d, J

= 7.8 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 158.8, 129.7, 128.8, 113.3, 72.5, 72.3, 65.2, 54.7, 46.8, 30.0, 7.7; HRMS (*EI*) *m/z* calcd for (M^+) $C_{14}H_{18}O_4$: 250.1205; found: 250.1203.



145

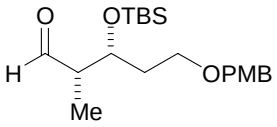
(2*S*, 3*R*)-3-Hydroxy-5-(4-methoxy-benzyloxy)-2-methyl-pentanoic acid methoxy-methyl-amide 145: To a suspension of *N*, *O*-Dimethyl-hydroxylamine hydrochloride (2.26 g, 23.2 mmol) in 40 mL of CH_2Cl_2 at 0 °C was added dimethylaluminium chloride (23.2 mL, 1.0 M solution in hexanes, 23.2 mmol) dropwise. The resulting mixture was warmed to ambient temperature and stirred for 2 h, then cooled to –25 °C and a solution of **106** (2.90 g, 11.6 mmol) in 30 mL CH_2Cl_2 was added dropwise. The reaction mixture was stirred 2h then was quenched at the –25 °C by adding 50 mL of aqueous Rochelle solution. The mixture was extracted by CH_2Cl_2 (3 x 100 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was used without purification. $[\alpha]_D$ +10.1 (*c* 1.92, $CHCl_3$); IR (thin film): 3459 (br), 1655, 1248cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, J = 8.6 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.45 (s, 2H), 4.05 (dt, J = 9.1, 3.7 Hz, 1H), 3.93 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H), 3.67-3.63 (m, 2H), 3.19 (s, 3H), 2.92 (br, 1H), 1.89-1.78 (m, 1H), 1.73-1.63 (m, 1H), 1.20 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.1, 158.8, 130.0, 128.8, 113.3, 72.4, 70.1, 67.6, 61.1, 54.8, 39.3, 33.7, 31.5, 11.1; HRMS (*EI*) *m/z* calcd for (M^+) $C_{16}H_{25}NO_5$: 311.1733; found: 311.1733.



115

(2*S*, 3*R*)-3-(tert-Butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-2-methyl-pentanoic acid methoxy-methyl-amide 115: To a solution of **145** (11.6 mmol crude product from last step) in 35

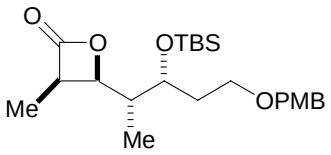
mL of DMF at ambient temperature was added imidazole (1.71 g, 25.1 mmol) followed by TBSCl (3.15 g, 20.9 mmol) and DMAP (142 mg, 1.16 mmol). The reaction mixture was stirred for 20 h then was quenched by adding 100 mL saturated aqueous NH_4Cl solution. The mixture was extracted by CH_2Cl_2 (3 x 150 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography (10% ethyl acetate in hexane) gave 4.80 g (97% over 2 steps) of the title compound as a colorless oil. $[\alpha]_D$ +0.30 (*c* 1.76, $CHCl_3$); IR (thin film): 1661, 1514, 1250, 837, 776cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.41 (s, 2H), 4.03 (dt, J = 7.9, 4.9 Hz, 1H), 3.81 (s, 3H), 3.61 (s, 3H), 3.58-3.49 (m, 2H), 3.15 (s, 3H), 3.04-2.96 (m, 1H), 1.86-1.80 (m, 2H), 1.14 (d, J = 6.9, 3H), 0.89 (s, 9H), 0.062 (s, 3H), 0.050 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.1, 159.1, 130.6, 129.2, 113.6, 72.4, 71.3, 66.2, 61.1, 55.2, 41.2, 35.4, 32.1, 25.9, 18.0, 14.3, –4.4, –4.5; HRMS (*ESI*) *m/z* calcd for (M^++Na) $C_{22}H_{39}NO_5SiNa$: 448.2495; found: 448.2452.



116

(2*S*, 3*R*)-3-(tert-Butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-2-methyl-pentanal 116: To a solution of **115** (4.45 g, 10.45 mmol) in 50 mL of THF at –50 °C was added DIBAL-H (13.0 mL, 1.0 M in hexanes, 13.0 mmol) over 30 min by syringe pump. The reaction mixture was stirred for 30 min then was quenched by adding 100 mL aqueous Rochelle solution. The mixture was extracted by Et_2O (3 x 100 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography (11% ethyl acetate in hexane) gave 3.68 g (96%) of the title compound as a colorless oil. $[\alpha]_D$ +47.7 (*c* 1.46, $CHCl_3$); IR (thin film): 1726, 1613, 1514, 1250, 837, 776cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$)

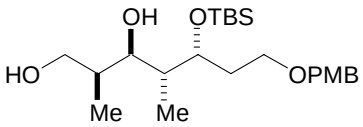
δ 9.78 (s, 1H), 7.26 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.45 (d, J = 11.5 Hz, 1H), 4.39 (d, J = 11.5 Hz, 1H), 4.31 (ddd, J = 7.2, 5.7, 3.7 Hz, 1H), 3.82 (s, 3H), 3.49 (t, J = 5.7 Hz, 2H), 2.53-2.44 (m, 1H), 1.82-1.77 (m, 2H), 1. 06 (d, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.072 (s, 3H), 0.047 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 159.0, 130.1, 129.0, 113.5, 72.4, 69.0, 65.9, 54.8, 51.3, 34.4, 25.5, 17.7, 7.5, –4.7, –4.9; HRMS (*ESI*) *m/z* calcd for (M^++Na) $C_{20}H_{34}O_4SiNa$: 389.2124; found: 389.2114.



117

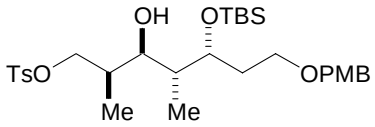
4-(2-(tert-Butyl-dimethyl-silanyloxy)-4-(4-methoxy-benzyloxy)-1-methylbutyl)-3-methyl-oxetan-2-one 117: To a suspension of TMS-QN (397 mg, 0.99 mmol) and LiI (6.64 g, 49.59 mmol) in 4.5 mL of diethyl ether was added 40.0 mL of CH_2Cl_2 and the reaction mixture was cooled to –78 °C. To the resulting mixture was added *N*, *N*-diisopropylethylamine (4.3 mL, 24.9 mmol) followed by a solution of **116** (3.43 g, 9.92 mmol) in 8.0 mL CH_2Cl_2. A solution of propionyl chloride (1.73 mL, 20.0 mmol) in 6.0 mL CH_2Cl_2 was then added over 3 h by syringe pump. After the addition of propionyl chloride the reaction mixture was quenched at the –78 °C by adding 100 mL of Et_2O and 100 mL saturated aqueous NH_4Cl solution. The mixture was extracted by Et_2O (3 x 100 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography (9% ethyl acetate in hexane) gave 3.60 g (91%) of the title compound as a single diastereomer. $[\alpha]_D$ –20.3 (*c* 2.28, $CHCl_3$); IR (thin film): 1824, 1613, 1250cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.47 (d, J = 11.6 Hz, 1H), 4.41 (dd, J = 11.1, 6.3 Hz, 1H), 4.36 (d, J = 11.4 Hz, 1H), 4.10 (t, J = 6.2 Hz, 1H), 3.82 (s, 3H), 3.75 (m, 1H), 3.43 (t, J = 6.4 Hz, 2H), 1.88-1.78 (m, 3H), 1.26 (d, J = 7.7 Hz, 3H), 0.89 (s, 9H), 0.81 (d, J = 6.7 Hz,

3H), 0.065 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 159.0, 130.2, 129.1, 113.7, 75.9, 72.5, 67.5, 66.4, 55.1, 46.3, 37.0, 35.0, 25.8, 18.0, 8.2, 7.3, –4.5, –5.0; HRMS (*EI*) *m/z* calcd for (M^+–^{t}Bu) $C_{19}H_{29}O_5Si$: 365.1784; found: 365.1786.



146

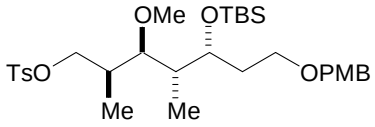
(2*S*,3*R*,4*R*,5*R*)-5-(tert-Butyl-dimethyl-silanyloxy)-7-(4-methoxy-benzyloxy)-2,4-dimethyl-heptane-1,3-diol 146: To a solution of **117** (3.60 g, 8.52 mmol) in 60 mL of THF at –50 °C was added DIBAL-H (25.6 mL, 1.0 M in hexanes, 25.6 mmol) over 30 min by syringe pump. The reaction mixture was stirred for 10 min then was quenched by adding 50 mL of Et_2O and 50 mL aqueous Rochelle solution. The mixture was extracted by Et_2O (3 x 100 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was used without purification. $[\alpha]_D$ +33.0 (*c* 1.99, $CHCl_3$); IR (thin film): 3465 (br), 1514, 1250, 837, 778cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26, (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.46 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 11.4 Hz, 1H), 4.00-3.96 (m, 1H), 3.94 (dd, J = 10.3, 2.0 Hz, 1H), 3.82 (s, 3H), 3.80 (dd, J = 10.5, 3.6 Hz, 1H), 3.68 (dd, J = 10.6, 5.4 Hz, 1H), 3.60-3.48 (m, 2H), 1.94-1.83 (m, 3H), 1.66-1.63 (m, 1H), 0.96 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.75 (d, J = 7.1 Hz, 3H), 0.133 (s, 3H), 0.074 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.4, 129.2, 113.7, 76.0, 74.9, 72.5, 67.8, 66.6, 55.2, 39.7, 36.2, 31.1, 25.6, 17.8, 13.4, 8.3, –4.5, –5.1; HRMS (*ESI*) *m/z* calcd for (M^++Na) $C_{23}H_{42}O_5SiNa$: 449.2699; found: 446.2668.



118

(2*S*,3*R*,4*R*,5*R*)-Toluene-4-sulfonic acid 5-(tert-butyldimethyl-silanyloxy)-3-hydroxy-7-(4-methoxy-benzyloxy)-2,4-dimethyl-heptyl ester 118: To a solution of **146**

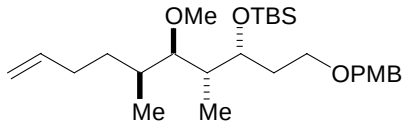
(1.81 g, 4.24 mmol) in 40 mL of CH_2Cl_2 at ambient temperature was added pyridine (840 mg, 10.61 mmol) followed by DMAP (104 mg, 0.85 mmol) and TsCl (1.21 g, 6.37 mmol). The reaction mixture was stirred for 22 h then was quenched by adding 40 mL CH_2Cl_2 and 50 mL saturated aqueous NH_4Cl solution. The mixture was extracted by CH_2Cl_2 (3 x 80 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography (7% ethyl acetate in hexane) gave 2.05 g (83% over 2 steps) of the title compound as a colorless oil. $[\alpha]_D$ +18.6 (*c* 1.86, $CHCl_3$); IR (thin film): 3469 (br), 1613, 1514, 1361, 1249, 964, 838cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 4.45 (d, J = 11.5 Hz, 1H), 4.39 (d, J = 11.5 Hz, 1H), 4.12 (d, J = 7.3 Hz, 1H), 4.09 (d, J = 7.2 Hz, 1H), 3.98-3.91 (m, 2H), 3.82 (s, 3H), 3.70 (dd, J = 10.2, 1.7 Hz, 1H), 3.56-3.47 (m, 2H), 2.44 (s, 3H), 1.92-1.70 (m, 4H), 0.87 (s, 9H), 0.84 (d, J = 6.8 Hz, 3H), 0.69 (d, J = 7.1 Hz, 3H), 0.094 (s, 3H), 0.057 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 144.3, 133.2, 130.3, 129.6, 129.1, 127.7, 113.6, 74.6, 73.5, 72.4, 71.7, 66.4, 55.1, 39.3, 35.2, 31.0, 25.6, 21.4, 17.7, 13.0, 8.1, –4.6, –5.2; HRMS (*ESI*) *m/z* calcd for (M^++Na) $C_{30}H_{48}O_7SSiNa$: 603.2788; found: 603.2778.



119

(2*S*,3*R*,4*R*,5*R*)-Toluene-4-sulfonic acid 5-(tert-butyldimethyl-silanyloxy)-3-methoxy-7-(4-methoxy-benzyloxy)-2,4-dimethyl-heptyl ester 119: To a solution of **118** (2.09 g, 3.60 mmol) in 40 mL of CH_2Cl_2 at ambient temperature was added Proton Sponge (3.20 g, 21.6 mmol) followed by Me_3OBF_4 (4.626 g, 21.6 mmol). The reaction mixture was stirred for 8 h (prevention from light by covered flask with aluminum foil) then was quenched by adding 100 mL of CH_2Cl_2 and 150 mL of saturated aqueous NH_4Cl solution. The mixture was extracted

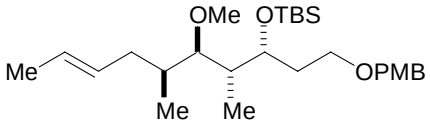
by CH_2Cl_2 (3 x 100 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography (8% ethyl acetate in hexane) gave 1.73 g (81%) of the title compound as a colorless oil. $[\alpha]_D$ –0.67 (*c* 1.79, $CHCl_3$); IR (thin film): 1514, 1365, 1249, 1189, 1178, 835cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.44 (d, J = 11.6 Hz, 1H), 4.38 (d, J = 11.6 Hz, 1H), 4.09-4.04 (m, 2H), 4.02-3.94 (m, 1H), 3.81 (s, 3H), 3.41 (td, J = 6.8, 1.0 Hz, 2H), 3.33 (s, 3H), 3.26 (dd, J = 9.4, 1.7 Hz, 1H), 2.46 (s, 3H), 2.02-1.95 (m, 1H), 1.86-1.75 (m, 2H), 1.56-1.50 (m, 1H), 0.87 (s, 9H), 0.77 (d, J = 6.8 Hz, 3H), 0.67 (d, J = 6.9 Hz, 3H), 0.068 (s, 3H), 0.062 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 144.3, 133.0, 130.2, 129.4, 128.6, 127.5, 113.3, 80.0, 72.3, 72.2, 69.0, 66.5, 60.3, 54.7, 39.8, 35.4, 34.7, 25.7, 21.1, 17.9, 9.0, 8.8, –3.7, –4.6; HRMS (*EI*) *m/z* calcd for (M^+–^{t}Bu) $C_{27}H_{41}O_7SSi$: 537.2342; found: 537.2316.



120

(3*R*,4*R*,5*R*,6*S*)-tert-Butyl-(3-methoxy-1-(2-(4-methoxy-benzyloxy)-ethyl)-2,4-dimethyloct-7-enyloxy)-dimethyl-silane 120: To a suspension of CuBr (825 mg, 5.75 mmol) in 2.5 mL of Et_2O at –20 °C was added allylmagnesium bromide (11.5 mL, 1.0 M in Et_2O, 11.5 mmol) dropwise and the reaction mixture was stirred for 30 min. To the resulting mixture was added a solution of **119** (683 mg, 1.15 mmol) in 4.0 mL Et_2O. The reaction mixture was stirred 10 min at –20 °C, then warmed to ambient temperature and stirred for 4.5 h. The reaction mixture was quenched by adding 20 mL of saturated aqueous NH_4Cl solution. The mixture was extracted by Et_2O (3 x 40 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography

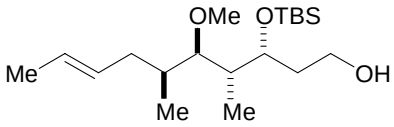
(6% ethyl acetate in hexane) gave 454 mg (85%) of the title compound as an oil. $[\alpha]_D$ –12.4 (*c* 1.65, $CHCl_3$); IR (thin film): 1640, 1614, 1514, 1249, 1097, 835cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.83 (ddt, 17.0, 10.2, 6.7 Hz, 1H), 5.0 (m, 2H), 4.45 (d, J = 11.5 Hz, 1H), 4.40 (d, J = 11.5 Hz, 1H), 4.13 (td, J = 6.9, 1.4 Hz, 1H), 3.81 (s, 3H), 3.47 (s, 3H), 3.43 (td, J = 6.8, 1.7 Hz, 2H), 3.13 (dd, J = 9.4, 1.7 Hz, 1H), 2.23-2.02 (m, 2H), 1.89-1.82 (m, 2H), 1.69-1.40 (m, 4H), 0.89 (s, 9H), 0.83 (d, J = 6.7 Hz, 3H), 0.73 (d, J = 6.9 Hz, 3H), 0.091 (s, 3H), 0.083 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 139.0, 130.6, 129.1, 114.3, 113.7, 84.7, 72.6, 69.3, 67.2, 60.8, 55.2, 40.7, 35.9, 34.4, 32.0, 26.0, 18.3, 12.8, 9.5, –3.4, –4.3; HRMS (*EI*) *m/z* calcd for (M^+) $C_{27}H_{48}O_4Si$: 464.3322; found: 464.3304.



121

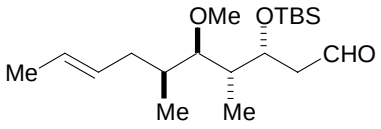
(3*R*,4*R*,5*R*,6*S*)-tert-Butyl-(3-methoxy-1-(2-(4-methoxy-benzyloxy)-ethyl)-2,4-dimethyl-oct-6-enyloxy)-dimethyl-silane 121: To a solution of $NaBPh_4$ (7.7 mg, 0.0225 mmol) in 0.2 mL of CH_3COCH_3 at ambient temperature was added a solution of $[(^cC_8H_{14})_2IrCl]_2$ (10.2 mg, 0.0113 mmol) and PCy_3(19.0 mg, 0.0678 mmol) in 10.8 mL of CH_2Cl_2. The reaction mixture was stirred for 5 min, then this catalyst solution was added to **120** (550 mg, 1.185 mmol). The reaction mixture was stirred for 3 h then was filtered through silica gel eluting with 120 ml of Et_2O. The filtrate was concentrated *in vacuo* and the crude product mixture was purified by flash chromatography (6% ethyl acetate in hexane) gave 539 mg (98%) of the title compound as a colorless oil. $[\alpha]_D$ –8.5 (*c* 1.02, $CHCl_3$); IR (thin film): 1614, 1249, 1097, 835cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.7 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 5.51-5.36 (m, 2H), 4.45 (d, J = 11.6 Hz, 1H), 4.40 (d, J = 11.6 Hz, 1H), 4.12 (t, J = 6.2 Hz, 1H), 3.81 (s, 3H), 3.48 (s, 3H), 3.43 (td, J = 7.7, 2.4 Hz, 2H), 3.18 (dd, J = 9.4, 1.6 Hz, 1H), 2.15 (m,

1H), 2.01 (m,1H), 1.87 (dd, J = 6.8, 2.2 Hz, 1H), 1.82 (dd, J = 7.3, 3.6 Hz, 1H), 1.67 (d, J = 5.0 Hz, 3H), 1.58 (br, 1H), 1.54-1.46 (m, 1H), 0.89 (s, 9H), 0.81 (d, J = 6.8 Hz, 3H), 0.73 (d, J = 6.9 Hz, 3H), 0.079 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 130.5, 128.9, 126.0, 113.5, 83.6, 72.4, 69.3, 67.0, 60.6, 54.9, 40.7, 38.2, 35.9, 35.5, 25.9, 18.2, 17.8, 12.7, 9.4, –3.5, –4.5; HRMS (*EI*) *m/z* calcd for (M^+) $C_{27}H_{48}O_4Si$: 464.3322; found: 464.3345.



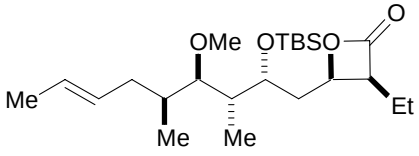
122

(3*R*,4*R*,5*R*,6*S*)-3-(tert-Butyl-dimethyl-silanyloxy)-5-methoxy-4,6-dimethyl-dec-8-en-1-ol 122: To a solution of DDQ (282 mg, 1.24 mmol) in 2.2 mL of CH_2Cl_2 and 0.45 mL of PH 7 buffer at 0 °C was added a solution of **121** (486 mg, 1.05 mmol) in 7.0 mL of CH_2Cl_2. The resulting mixture was stirred for 40 min and then quenched by adding 10 mL of H_2O. The mixture was extracted by Et_2O (3 x 40 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography (gradient 6% ➛ 10% ➛ 20% ethyl acetate in hexane) gave 291 mg (81%) of the title compound as a oil. $[\alpha]_D$ –9.3 (*c* 1.40, $CHCl_3$); IR (thin film): 3401(br), 1253, 1077, 835, 774cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.51-5.35 (m, 2H), 4.15-4.10 (m, 1H), 3.69 (td, J = 6.5, 1.4 Hz, 2H), 3.49 (s, 3H), 3.16 (dd, J = 9.2, 1.8 Hz, 1H), 2.15 (m, 1H), 2.01 (m, 1H), 1.84-1.76 (m, 2H), 1.67 (d, J = 5.3 Hz, 3H), 1.64-1.59 (m, 2H), 0.91 (s, 9H), 0.83 (d, J = 6.8 Hz, 3H), 0.77 (d, J = 7.0 Hz, 3H), 0.113 (s, 3H), 0.107 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.3, 126.3, 84.2, 69.2, 60.8, 59.4, 40.2, 38.5, 38.2, 35.5, 25.9, 18.2, 17.9, 12.6, 9.6, –3.4, –4.4; HRMS (*EI*) *m/z* calcd for (M^+–^{t}Bu) $C_{15}H_{31}O_3Si$: 287.2042; found: 287.2050.



123

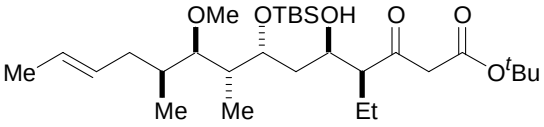
(3*R*,4*R*,5*R*,6*S*)-3-(tert-Butyl-dimethyl-silanyloxy)-5-methoxy-4,6-dimethyl-dec-8-enal 123: To a solution of DMSO (139 uL, 1.96 mmol) in 5.0 mL of CH_2Cl_2 at −78 °C was added $(COCl)_2$ (490 uL, 2 M in CH_2Cl_2, 0.98 mmol) dropwise. The reaction mixture was stirred for 40 min before adding a solution of **122** (270 mg, 0.785 mmol) in 2.5 mL of CH_2Cl_2. The resulting mixture was stirred for 30 min then Et_3N (548 uL, 3.92 mmol) was added dropwise, the reaction mixture was stirred for another 30 min then warmed to ambient temperature and quenched by adding 10 mL of saturated aqueous NH_4Cl solution. The mixture was extracted by CH_2Cl_2 (3 x 40 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography (6% ethyl acetate in hexane) gave 235 mg (88%) of the title compound as an oil. $[\alpha]_D$ –6.2 (*c* 1.62, $CHCl_3$); IR (thin film): 2718, 1728, 1472, 1134, 1089, 836, 775cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.79 (t, J = 2.4 Hz, 1H), 5.53-5.35 (m, 2H), 4.63 (td, J = 6.2, 1.8 Hz, 1H), 3.50 (s, 3H), 3.17 (dd, J = 9.2, 1.8 Hz, 1H), 2.67 (ddd, J = 16.1, 6.2, 2.5 Hz, 1H), 2.55 (ddd, J = 16.1, 6.2, 2.3 Hz, 1H), 2.15 (m, 1H), 2.05 (m, 1H), 1.76-1.66 (m, 1H), 1.67 (d, J = 4.9 Hz, 3H), 1.60-1.50 (m, 1H), 0.89 (s, 9H), 0.82 (d, J = 6.9 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H), 0.13 (s, 3H), 0. 07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.1, 130.3, 126.3, 83.9, 66.9, 60.6, 50.8, 42.6, 38.2, 35.5, 25.8, 18.2, 17.9, 12.8, 10.1, –3.8, –4.5; HRMS (*EI*) *m/z* calcd for (M^+) $C_{19}H_{38}O_3Si$: 342.2590; found: 342.2584.



124

4-[2-(tert-Butyl-dimethyl-silanyloxy)-4-methoxy-3,5-dimethyl-non-7-enyl]-3-ethyl-oxetan-2-one 124: To a solution of Triamine ligand (169.5 mg, 0.25 mmol) in 2.0 ml of BTF at ambient temperature was slowly added a solution of $AlMe_3$ (0.125 ml, 2.0 M in hexane,

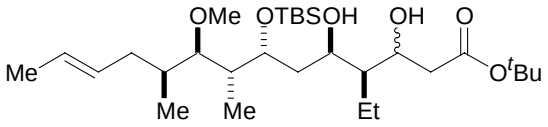
0.25 mmol). After stirring for 2 h, the resulting catalyst solution was cooled to –25 °C and *N*, *N*-diisopropylethylamine (0.173 mL, 1.0 mmol) and butyryl bromide (0.212 mL, 2.0 mmol) were added consecutively. The resulting heterogeneous mixture was stirred 20 min at –25 °C whereupon **123** (170 mg, 0.50 mmol) in 1.0 mL of BTF was added dropwise and the reaction was stirred 21 h at –25 °C. The reaction was quenched at –25 °C by adding 10 ml of a 3% Et_3N-Et_2O solution (v/v) and the resulting mixture was filtered through silica gel eluting with 60 ml of Et_2O. The filtrate was concentrated *in vacuo* and the crude product mixture was purified by flash chromatography (gradient 4% ➛ 6% ethyl acetate in hexane) gave 135 mg (65%) of the title compound. $[\alpha]_D$ +20.2 (*c* 1.06, $CHCl_3$); IR (thin film): 1828, 1462, 1254, 836, 775cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.53-5.35 (m, 2H), 4.64 (dt, J = 6.5, 6.5 Hz, 1H), 4.20 (td, J = 6.9, 1.1 Hz, 1H), 3.57(dt, J = 9.1, 7.4 Hz, 1H), 3.48 (s, 3H), 3.16 (dd, J = 9.5, 1.5 Hz, 1H), 2.15 (m, 1H), 2.02 (m, 1H), 1.89 (t, J = 6.5 Hz, 2H), 1.85-1.79 (m, 1H), 1.74-1.66 (m, 1H), 1.67 (d, J = 4.7 Hz, 3H), 1.62-1.60 (m, 2H), 1.09 (t, J = 7.4 Hz, 3H), 0.91 (s, 9H), 0.82 (d, J = 6.8 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 130.4, 126.4, 83.8, 72.6, 69.2, 60.8, 54.2, 41.6, 38.3, 36.6, 35.6, 25.9, 18.3, 18.0, 17.6, 12.7, 12.1, 9.9, –3.7, –3.9; HRMS (*EI*) *m/z* calcd for (M^+–^{t}Bu) $C_{19}H_{35}O_4Si$: 355.2305; found: 355.2311.



125

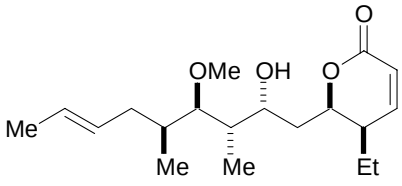
(4*S*,5*R*,7*R*,8*R*,9*R*,10*S*)-7-(tert-Butyl-dimethyl-silanyloxy)-4-ethyl-5-hydroxy-9-methoxy-8,10-dimethyl-3-oxo-tetradec-12-enoic acid tert-butyl ester 125: To a solution of KHMDS (1.14 mL, 0.5 M in toluene, 0.57 mmol) in 1.0 mL of THF at –78 °C was added tert-butyl acetate (66.2 mg, 0.57 mmol). The reaction mixture was stirred for 1h. Then this enolate solution was transferred to a suspension of

$MgBr_2 \cdot OEt_2$ (147 mg, 0.57 mmol) in 1.0 mL of THF. The resulting mixture was stirred for another 1h. Then **124** (47 mg, 0.114 mmol) was added to this mixture and stirred for 30 min. The reaction mixture was quenched by adding 10 mL of saturated aqueous NH_4Cl solution. The mixture was extracted by Et_2O (3 x 30 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography (15% ethyl acetate in hexanes) gave 40 mg (66%) of the title compound and its tautomer as inseperatable mixture. IR (thin film): 3467 (br), 1733, 1709cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.50-5.33 (m, 2H), 4.14-4.10 (m, 1H), 4.04 (q, J = 4.9 Hz, 1H), 3.48 (d, J = 1.6 Hz, 2H), 3.44 (s, 3H), 3.06 (dd, J = 8.2, 1.9 Hz, 1H), 2.75 (dt, J = 8.9, 4.3 Hz, 1H), 2.16-2.07 (m, 1H), 2.02-1.93 (m, 1H), 1.88-1.73 (m, 3H), 1.67 (d, J = 5.2 Hz, 3H), 1.63-1.58 (m, 4H), 1.47 (s, 9H), 0.92 (t, J = 7.4 Hz, 3H), 0.90 (s, 9H), 0.85 (d, J = 6.8 Hz, 3H), 0.84 (d, J = 6.9 Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.6, 166.5, 130.2, 126.5, 84.7, 81.7, 71.6, 69.3, 60.2, 59.0, 52.0, 40.7, 39.2, 38.6, 35.5, 28.3, 28.0, 26.0, 19.8, 17.9, 13.4, 12.2, 11.5, –3.8, –4.3; HRMS (*EI*) *m/z* calcd for (M^+) $C_{29}H_{56}O_6Si$: 528.3846; found: 528.3842.



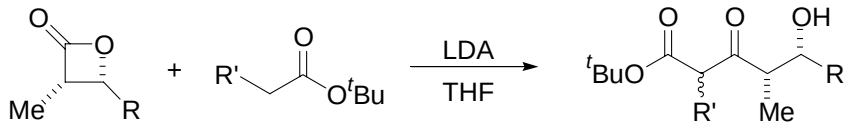
126

(4*S*,5*R*,7*R*,8*R*,9*R*,10*S*)-7-(tert-Butyl-dimethyl-silanyloxy)-4-ethyl-3,5-dihydroxy-9-methoxy-8,10-dimethyl-tetradec-12-enoic acid tert-butyl ester 126: To a solution of **125** (27 mg, 0.05 mmol) in 1.0 mL of EtOH at 0 °C was added $NaBH_4$ (6 mg, 0.16 mmol). The resulting mixture was stirred for 40 min and then quenched by adding 50 uL acetic acid. The mixture was extracted by ethyl acetate (3 x 30 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product used without purification.



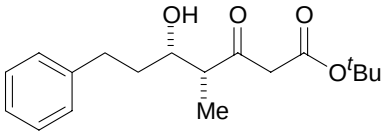
128

(–)-Pironetin 128: A solution of **126** (15 mg crude product from last step) and $TsOH{\cdot}H_2O$ (5 mg) in 1.0 mL of toluene was heated at 110 °C for 30 min. The mixture was then cooled down to ambient temperature and diluted by adding 50 mL of ethyl acetate. The resulting mixture was washed with 10 mL of aqueous $NaHCO_3$ solution and brine consecutively; the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography (40% ethyl acetate in hexanes) gave 4.6 mg (56% over two steps) of the title compound as a white solid. $[\alpha]_D$ –135 (*c* 0.35, $CHCl_3$) {lit.[53] $[\alpha]_D$ –144 (*c* 0.50, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (dd, J = 9.8, 6.0 Hz, 1H), 6.03 (d, J = 9.8 Hz, 1H), 5.51-5.32 (m, 2H), 4.74 (m, 1H), 4.21 (brd, 1H), 3.48 (s, 3H), 3.45 (d, J = 2.3 Hz, 1H), 2.99 (dd, J = 6.1, 4.4 Hz, 1H), 2.33-2.25 (m, 1H), 2.13-2.06 (m, 1H), 1.92-1.84 (m, 2H), 1.81-1.76 (m, 1H), 1.74-1.65 (m, 3H), 1.67(d, J = 5.3 Hz, 3H), 1.58-1.46 (m, 1H), 1.01 (d, J = 7.1 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H), 0.96 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 150.6, 128.8, 126.9, 120.9, 91.1, 77.8, 67.5, 61.5, 39.1, 39.0, 37.3, 36.7, 36.2, 20.8, 17.9, 15.2, 12.2, 11.0; HRMS (*EI*) *m/z* calcd for (M^+–H_2O) $C_{19}H_{30}O_3$: 306.2195; found: 306.2185.



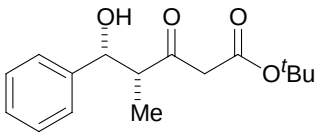
R' = H, Me, Bn; R = CH_2CH_2Ph, $^cC_6H_{11}$, Ph

General Procedure D for Ring Opening of β-lactone by Lithium Enolate: To a solution of $^{i}Pr_2NH$ (0.35 mL, 2.50 mmol) in 1.0 mL of THF at −78 °C was added $^{n}BuLi$ (1.56 mL, 2.50 mmol), the resulting solution was stirred for 5 min. Then *tert*-butyl ester (2.50 mmol) was added to this solution and stirred for 45 min. Then a solution of β-lactone (0.5 mmol in 1.0 mL THF) was added to this enolate mixture and stirred for 1-2 h. The reaction mixture was quenched by adding 20 mL of saturated aqueous NH_4Cl solution. The mixture was extracted by Et_2O (3 x 30 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography gave β-keto ester (major) and its tautomer (minor) as an inseperatable mixture. The ^{1}H NMR and ^{13}C NMR data were reported for major isomer.



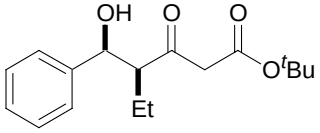
131

5-Hydroxy-4-methyl-3-oxo-7-phenyl-heptanoic acid tert-butyl ester 131: The General procedure D was followed employing 95 mg of β-lactone (0.50 mmol) and 338 μL (2.50 mmol) of *tert*-butyl acetate. Purification by flash chromatography (16% ethyl acetate in hexane) gave 130 mg (85%) of the title compound. IR (thin film): 3467, 1732, 1708 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.20 (m, 5H), 4.02 (dt, J = 6.5, 2.9 Hz, 1H), 3.47 (d, J = 15.4 Hz, 1H), 3.46 (d, J = 15.4 Hz, 1H), 2.86 (ddd, J = 14.8, 9.4, 5.0 Hz, 1H), 2.75-2.60 (m, 2H), 1.92-1.81 (m, 1H), 1.68-1.59 (m, 1H), 1.46 (s, 9H), 1.17 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8, 166.4, 141.6, 128.4, 128.3, 125.8, 82.1, 70.1, 50.9, 49.4, 35.7, 32.2, 27.9, 9.5; HRMS (*EI*) *m/z* calcd for (M^{+}) $C_{18}H_{26}O_4$: 306.1831; found:306.1829.



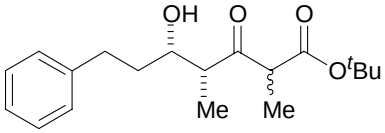
139

5-Hydroxy-4-methyl-3-oxo-5-phenyl-pentanoic acid tert-butyl ester 139: The General procedure D was followed employing 80 mg of β-lactone (0.494 mmol) and 334 μL (2.469 mmol) of *tert*-butyl acetate. Purification by flash chromatography (16% ethyl acetate in hexane) gave 100 mg (72%) of the title compound. IR (thin film): 3497, 1732, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43-7.34 (m, 5H), 5.21 (dd, J = 3.1, 3.0 Hz, 1H), 3.47 (d, J = 15.6 Hz, 1H), 3.46 (d, J = 15.6 Hz, 1H), 3.07 (d, J = 3.0 Hz, 1H), 3.06 (qd, J = 7.1, 3.8 Hz, 1H), 1.55 (s, 9H), 1.17 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.7, 166.3, 141.4, 128.3, 127.4, 125.8, 82.2, 72.9, 52.9, 49.7, 27.9, 9.8; HRMS (*EI*) *m/z* calcd for (M^+) $C_{16}H_{22}O_4$: 278.1518; found:278.1524.



140

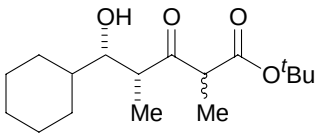
4-(Hydroxy-phenyl-methyl)-3-oxo-hexanoic acid tert-butyl ester 140: The General procedure D was followed employing 176 mg of β-lactone (1.0 mmol) and 700 μL (2.5 mmol) of *tert*-butyl acetate. Purification by flash chromatography (14% ethyl acetate in hexane) gave 242 mg (83%) of the title compound. IR (thin film): 3468, 1732, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.28 (m, 5H), 4.97 (dd, J = 5.5, 2.8 Hz, 1H), 3.29 (d, J = 15.5 Hz, 1H), 3.20 (d, J = 15.5 Hz, 1H), 3.13-3.11 (m, 1H), 2.99 (ddd, J = 9.5, 5.6, 4.1Hz, 1H), 1.90-1.79 (m, 1H), 1.74-1.66 (m, 1H), 1.51 (s, 9H), 0.91 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.8, 166.1, 141.7, 128.3, 127.6, 126.0, 81.8, 73.6, 60.5, 51.7, 27.8, 19.8, 11.9.



132

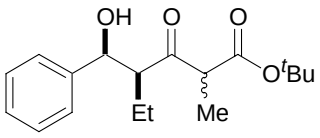
5-Hydroxy-2,4-dimethyl-3-oxo-7-phenyl-heptanoic acid tert-butyl ester 132: The General procedure D was followed employing 95 mg of β-lactone (0.50 mmol) and 377 μL

(2.50 mmol) of *tert*-butyl propionate. Purification by flash chromatography (16% ethyl acetate in hexane) gave 111 mg (70%) of the title compound as 1: 1 diastereomer mixture. IR (thin film): 3524, 1737, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.23 (m, 10H), 4.04 (dt, J = 9.0, 3.4 Hz, 1H), 3.95 (dt, J = 9.3, 3.4 Hz, 1H), 3.67 (q, J = 7.1 Hz, 1H), 3.65 (q, J = 7.1 Hz, 1H), 2.96-2.80 (m, 4H), 2.76-2.66 (m, 2H), 1.99-1.83 (m, 2H), 1.74-1.62 (m, 2H), 1.49 (s, 9H), 1.44 (s, 9H), 1.33 (d, J = 7.1 Hz, 3H), 1.32 (d, J = 7.1 Hz, 3H), 1.23 (d, J = 7.1 Hz, 3H), 1.21 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.6, 210.9, 169.3, 169.2, 141.7, 141.6, 128.4, 128.33 (2C), 128.28, 125.83, 125.76, 82.0, 81.8, 70.6, 69.9, 53.1, 52.2, 49.9 (2C), 35.7 (2C), 32.3, 32.2, 27.8, 27.7, 12.8, 12.5, 10.1, 9.8; HRMS (*EI*) *m/z* calcd for [M^+-^{t}Bu] $C_{15}H_{20}O_4$: 264.1362; found:264.1350.



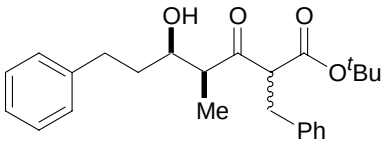
134

5-Cyclohexyl-5-hydroxy-2,4-dimethyl-3-oxo-pentanoic acid tert-butyl ester 134: The General procedure D was followed employing 84 mg of β-lactone (0.50 mmol) and 377 μL (2.50 mmol) of *tert*-butyl propionate. Purification by flash chromatography (11% ethyl acetate in hexane) gave 105 mg (71%) of the title compound as 1: 1 diastereomer mixture. IR (thin film): 3534, 1739, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.68-3.52 (m, 4H), 3.01-2.91 (m, 2H), 2.10 (t, J = 1.4, Hz, 2H), 1.74 (m, 4H), 1.69 (m, 2H), 1.56 (m, 2H), 1.45 (s, 18H), 1.29 (d, J = 7.1 Hz, 3 H), 1.28 (d, J = 7.1 Hz, 3 H), 1.22 (m, 4H), 1.12 (d, J = 7.0 Hz, 3 H), 1.11 (d, J = 7.2 Hz, 3 H), 0.95 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.0, 211.0, 169.4, 169.3, 82.0, 81.8, 75.1, 74.6, 52.5, 52.0, 46.6, 46.4, 40.2, 39.6, 29.6, 29.3, 28.9, 28.8, 26.24, 26.19, 25.94, 25.90, 25.72, 25.69, 12.8, 12.7, 9.0, 8.9; HRMS (*EI*) *m/z* calcd for (M^+) $C_{17}H_{30}O_4$: 298.2144; found:298.2136.



141

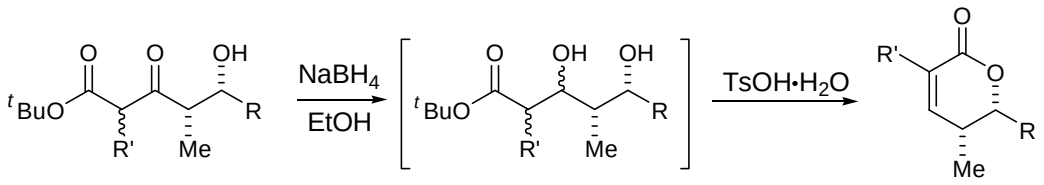
4-(Hydroxy-phenyl-methyl)-2-methyl-3-oxo-hexanoic acid tert-butyl ester 141: The General procedure D was followed employing 88 mg of β-lactone (0.50 mmol) and 377 μL (2.50 mmol) of *tert*-butyl propionate. Purification by flash chromatography (11% ethyl acetate in hexane) gave 92 mg (69%) of the title compound. IR (thin film): 3501, 1736, 1707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.35 (m, 5H), 4.92 (dd, J = 6.3, 2.8 Hz, 1H), 3.30 (q, J = 7.0 Hz, 1H), 3.15 (ddd, J = 10.0, 6.3, 3.9 Hz, 1H), 2.80 (d, J = 2.9 Hz, 1H), 1.98-1.85 (m, 1H), 1.76-1.66 (m, 1H), 1.51 (s, 9H), 1.04 (d, J = 7.0 Hz, 3 H), 0.93 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 169.0, 142.0, 128.3, 127.7, 126.2, 81.7, 74.0, 59.9, 54.8, 27.9, 20.2, 12.1, 11.7; HRMS (*ESI*) *m/z* calcd for (M^++Na) $C_{18}H_{26}O_4Na$: 329.1729; found:329.1703.



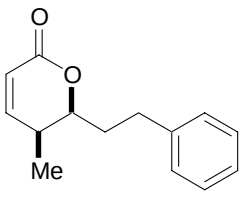
133

2-Benzyl-5-hydroxy-4-methyl-3-oxo-7-phenyl-heptanoic acid tert-butyl ester 133: The General procedure D was followed employing 145 mg of β-lactone (0.76 mmol) and 470 mg (2.28 mmol) of 3-Phenyl-propionic acid *tert*-butyl ester. Purification by flash chromatography (9% ethyl acetate in hexane) gave 155 mg (51%) of the title compound as 1: 1 diastereomer mixture. IR (thin film): 3466, 1738, 1708 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.14 (m, 20H), 4.00-3.93 (m, 1H), 3.92-3.86 (m, 2H), 3.65-3.59 (m, 1H), 3.20-3.06 (m, 4H), 2.87-2.78 (m, 2H), 2.74-2.59 (m, 3H), 2.56-2.46 (m, 2H), 2.17 (d, J = 3.0 Hz, 1H), 1.88-1.76 (m, 1H), 1.74-1.62 (m, 2H), 1.41 (s, 9H), 1.36 (s, 9H), 1.10 (d, J = 7.1 Hz, 3H), 0.85 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.1, 209.7, 167.8 (2C), 141.7, 141.6, 138.3, 138.2, 128.9 (2C), 128.5 (2C), 128.3 (4C), 126.63, 126.57, 125.84, 125.80, 82.5, 82.2, 69.9, 69.8, 60.6, 60.3,

51.3, 50.9, 35.7, 35.4, 34.3, 33.9, 32.19, 32.15, 27.80, 27.75, 9.3, 8.7; HRMS (*ESI*) *m/z* calcd for (M^++Na) $C_{25}H_{32}O_4Na$: 419.2198; found:419.2192.



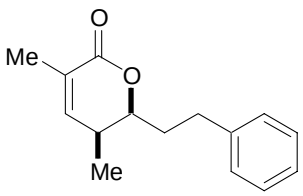
General Procedure E for Preparation of δ-lactone (R = Aliphatic group): To a solution of β-keto ester (1.85 mmol) in 9 mL of EtOH at 0 °C was added $NaBH_4$ (70 mg, 1.85 mmol). The resulting mixture was stirred for 40 min and then quenched by slowly adding acetic acid until no gas evolution. The mixture was extracted by ethyl acetate (3 x 40 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product used without purification. A solution of β-hydro ester (crude product from $NaBH_4$ reduction) and $TsOH{\cdot}H_2O$ (175.6 mg, 0.923 mmol) in 15 mL of toluene was heated at 110 °C for 45 min. The mixture was then cooled down to ambient temperature and diluted by adding 100 mL of ethyl acetate. The resulting mixture was washed with 20 mL of aqueous $NaHCO_3$ solution and brine consecutively; the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography gave δ-lactone as single diasteromer (based on ^{1}H NMR of crude product mixture).



135

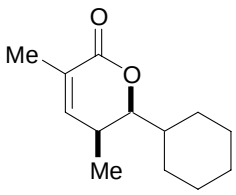
5-Methyl-6-phenethyl-5,6-dihydro-pyran-2-one 135: The general procedure E was followed employing 55 mg of β-keto ester (0.18 mmol)

and 6.8 mg (0.18 mmol) of $NaBH_4$ and 17 mg (0.09 mmol) of $TsOH \cdot H_2O$. Purification by flash chromatography (25% ethyl acetate in hexane) gave 23 mg (58% over 2 steps) of the title compound. IR (thin film): 1721 cm^{-1}; $[\alpha]_D$ +155 (*c* 0.63, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H), 6.94 (dd, J = 9.7, 6.1 Hz, 1H), 5.97 (dd, J = 9.7, 0.8 Hz, 1H), 4.41 (dt, J = 9.3, 3.9 Hz, 1H), 2.93 (ddd, J = 14.2, 9.5, 5.3 Hz, 1H), 2.73 (ddd, J = 13.8, 9.1, 7.2 Hz, 1H), 2.41-2.31 (m, 1H), 2.22-2.10 (m, 1H), 1.87-1.75 (m, 1H), 1.06 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 151.5, 140.9, 128.50, 128.45, 126.1, 119.9, 79.0, 33.2, 32.2, 31.3, 11.3; HRMS (*EI*) *m/z* calcd for (M^+) $C_{14}H_{16}O_2$: 216.1150; found: 216.1154.



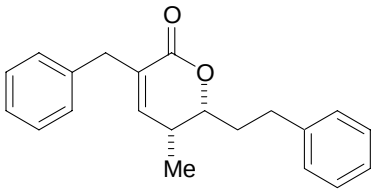
136

3,5-Dimethyl-6-phenethyl-5,6-dihydro-pyran-2-one 136: The general procedure E was followed employing 34 mg of β-keto ester (0.106mmol) and 5.0 mg (0.13 mmol) of $NaBH_4$ for 1st step and 16 mg crude β-hydro ester (0.05 mmol) and 9.5 mg (0.10 mmol) of $TsOH \cdot H_2O$ for 2nd step. Purification by flash chromatography (16% ethyl acetate in hexane) gave 13 mg (55% over 2 steps) of the title compound. IR (thin film): 1716 cm^{-1}; $[\alpha]_D$ +53.6 (*c* 1.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.20 (m, 5H), 6.64 (dq, J = 6.3, 1.5 Hz, 1H), 4.38 (dt, J = 8.9, 3.9 Hz, 1H), 2.92 (ddd, J = 14.6, 9.1, 5.0 Hz, 1H), 2.72 (ddd, J = 13.9, 9.3, 7.1 Hz, 1H), 2.34-2.26 (m, 1H), 2.20-2.08 (m, 1H), 1.91 (dd, J = 1.4, 1.0 Hz, 3H), 1.83-1.74 (m, 1H), 1.02 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 145.6, 141.1, 128.51, 128.47, 127.1, 126.1, 79.1, 33.25, 32.59, 31.4, 16.9, 11.5; HRMS (*EI*) *m/z* calcd for (M^+) $C_{15}H_{18}O_2$: 230.1307; found: 230.1314.



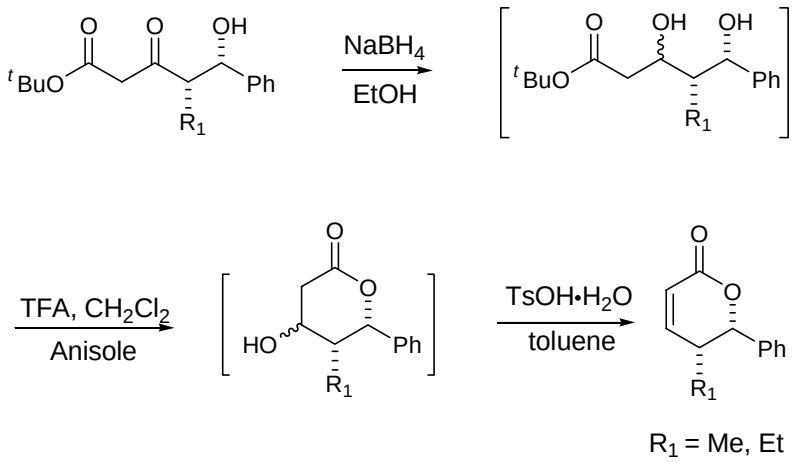
138

6-Cyclohexyl-3,5-dimethyl-5,6-dihydro-pyran-2-one 138: The general procedure E was followed employing 65 mg of β-keto ester (0.218mmol) and 8.3 mg (0.218 mmol) of $NaBH_4$ and 20 mg (0.105 mmol) of $TsOH{\cdot}H_2O$. Purification by flash chromatography (9% ethyl acetate in hexane) gave 24 mg (53% over 2 steps) of the title compound. IR (thin film): 1742 cm^{-1}; $[\alpha]_D$ +169 (*c* 1.77, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 6.67 (dq, J = 6.6, 1.4 Hz, 1H), 3.97 (dd, J = 10.0, 3.0 Hz, 1H), 2.42-2.37 (m, 1H), 2.34-2.26 (m, 1H), 1.91 (dd, J = 1.1, 1.0 Hz, 3H), 1.78-1.59 (m, 5H), 1.33-1.19 (m, 4H), 0.99 (d, J = 7.0 Hz, 3H), 0.93-0.88 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 145.8, 127.1, 84.2, 38.1, 30.3, 29.5, 27.9, 26.3, 25.6, 25.3, 16.8, 11.0; HRMS (*EI*) *m/z* calcd for (M^+) $C_{13}H_{20}O_2$: 208.1463; found: 208.1454.

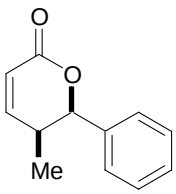


137

3-Benzyl-5-methyl-6-phenethyl-5,6-dihydro-pyran-2-one 137: The general procedure E was followed employing 71 mg of β-keto ester (0.18 mmol) and 6.8 mg (0.18 mmol) of $NaBH_4$ for 1st step and 17.1 mg (0.09 mmol) of $TsOH{\cdot}H_2O$ for 2nd step. Purification by flash chromatography (14% ethyl acetate in hexane) gave 27 mg (50% over 2 steps) of the title compound. IR (thin film): 1716, 1495, 1454 cm^{-1}; $[\alpha]_D$ −66.6 (*c* 0.98, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.18 (m, 5H), 6.42 (dt, J = 6.3, 1.1 Hz, 1H), 4.36 (dt, J = 9.1, 3.9 Hz, 1H), 3.66 (d, J = 15.9 Hz, 1H), 3.58 (d, J = 15.9 Hz, 1H), 2.90 (ddd, J = 14.7, 9.8, 5.3 Hz, 1H), 2.69 (ddd, J = 13.9, 9.4, 6.9 Hz, 1H), 2.36-2.25 (m, 1H), 1.83-1.71 (m, 1H), 1.00 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 146.1, 141.0, 138.3, 131.2, 129.2, 128.5 (2C), 128.4, 126.4, 126.1, 78.9, 36.4, 33.2, 32.6, 31.4, 11.4; HRMS (*ESI*) *m/z* calcd for (M^++Na) $C_{21}H_{22}O_2Na$: 329.1517; found:329.1511.

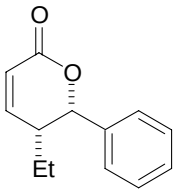


General Procedure F for Preparation of δ-lactone (R = Ph): To a solution of β-keto ester (0.15 M in EtOH) at 0 °C was added $NaBH_4$ (1.0 eq). The resulting mixture was stirred for 40 min and then quenched by slowly adding acetic acid until no gas evolution. The mixture was extracted by ethyl acetate (3 x 30 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was dissolved in methylene chloride and anisole (0.1M, 5: 1 CH_2Cl_2: anisole) and the solution was cooled down to 0 °C and TFA (2 mL/mmol diol) was added dropwise, then the resulting mixture was stirred at 0 °C for 2 h. The mixture was concentrated in *vacuo.* Then the crude mixture and $TsOH{\cdot}H_2O$ (0.5 eq) in toluene (about 0.1 M) was heated at 110 °C for 30 min. The mixture was then cooled down to ambient temperature and diluted by adding 50 mL of ethyl acetate. The resulting mixture was washed with 10 mL of aqueous $NaHCO_3$ solution and brine consecutively; the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography gave δ-lactone (dr based on crude ^1H NMR).



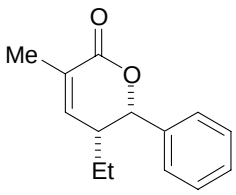
142

5-Methyl-6-phenyl-5,6-dihydro-pyran-2-one 142: The general procedure F was followed employing 17.7 mg of β-keto ester (0.0632 mmol) and 3.0 mg (0.0793 mmol) of $NaBH_4$ for 1st step and 0.12 mL TFA for 2nd step and 6.0 mg (0.0316 mmol) of $TsOH{\cdot}H_2O$ for 3rd step. Purification by flash chromatography (16% ethyl acetate in hexane) gave 7 mg (59% over 3 steps) of the title compound (8:1 dr). IR (thin film): 1728 cm^{-1}; $[\alpha]_D$ +471 (*c* 0.41, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.33 (m, 5H), 7.11 (dd, J = 9.6, 6.2 Hz, 1H), 6.10 (d, J = 9.7 Hz, 1H), 5.61 (d, J = 3.5 Hz, 1H), 2.68-2.63 (m, 1H), 0.83 (d, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.4, 151.7, 137.0, 128.5, 127.9, 125.5, 120.1, 81.0, 34.8, 11.8; HRMS (*EI*) *m/z* calcd for (M^+) $C_{12}H_{12}O_2$: 188.0837; found:188.0845.



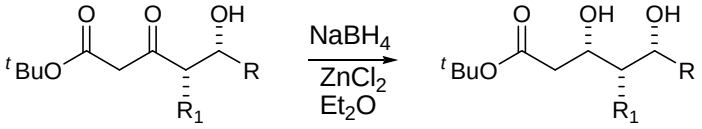
143

5-Ethyl-6-phenyl-5,6-dihydro-pyran-2-one 143: The general procedure F was followed employing 36 mg of β-keto ester (0.123 mmol) and 5.6 mg (0.148 mmol) of $NaBH_4$ for 1st step and 0.24 mL TFA for 2nd step and 11.7 mg (0.062 mmol) of $TsOH{\cdot}H_2O$ for 3rd step. Purification by flash chromatography (16% ethyl acetate in hexane) gave 16 mg (64% over 3 steps) of the title compound (9:1 dr). IR (thin film): 1732 cm^{-1}; $[\alpha]_D$ −442 (*c* 0.90, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.30 (m, 5H), 7.18 (dd, J = 9.8, 6.2 Hz, 1H), 6.16 (q, J = 9.8 Hz, 1H), 5.62 (d, J = 3.7 Hz, 1H), 2.56-2.48 (m, 1H), 1.37-1.27 (m, 2H), 0.81 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 150.8, 136.9, 128.4, 127.9, 125.5, 120.8, 81.3, 41.0, 20.9, 10.9; HRMS (*EI*) *m/z* calcd for (M^+) $C_{13}H_{14}O_2$: 202.0994; found:202.0996.



144

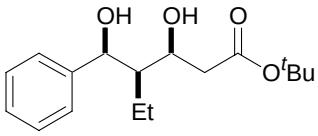
5-Ethyl-3-methyl-6-phenyl-5,6-dihydro-pyran-2-one 144: The general procedure F was followed employing 70 mg of β-keto ester (0.229 mmol) and 34.6 mg (0.915 mmol) of $NaBH_4$, 62.4 mg $ZnCl_2$ (0.456 mmol) for 1st step and 0.48 mL TFA for 2nd step and 21.8 mg (0.114 mmol) of $TsOH{\cdot}H_2O$ for 3rd step. Purification by flash chromatography (11% ethyl acetate in hexane) gave 25 mg (53% over 3 steps) of the title compound (>19:1 dr). IR (thin film): 1725 cm^{-1}; $[\alpha]_D$ −343 (*c* 2.36, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.32 (m, 5H), 6.87 (dq, J = 6.3, 1.5 Hz, 1H), 5.58 (d, J = 3.7 Hz, 1H), 2.47-2.42 (m, 1H), 2.02 (t, J = 1.2 Hz, 3H), 1.35-1.21 (m, 2H), 0.78 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.8, 144.6, 137.1, 128.3, 127.9, 127.7, 125.5, 81.3, 41.3, 20.8, 17.1, 11.0; HRMS (*EI*) *m/z* calcd for (M^+) $C_{14}H_{16}O_2$: 216.1150; found:216.1157.



R_1 = Me, Et; R = Ph, CH_2CH_2Ph

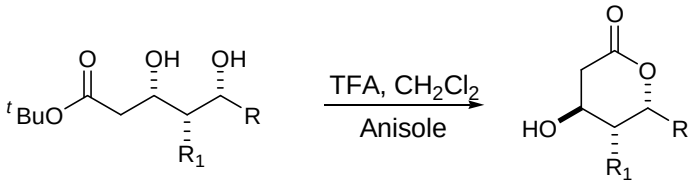
General Procedure G for 1, 3 *syn* reduction of β-keto ester:[84] A suspension of $ZnCl_2$ (0.4 mmol, 2 eq.) and $NaBH_4$ (0.8 mmol, 4 eq) in 2 mL of ether was stirred at ambient temperature for 15 min, then the mixture was cooled down to 0 °C and a solution of β-keto ester (0.2 mmol) in 1.0 mL ether was added, the resulting mixture was stirred for 2 h before quenched by slowly adding 20 mL of saturated aqueous NH_4Cl solution, The mixture was extracted by ether (3 x 30 mL). The organic layer was washed by brine and dried over Na_2SO_4 and

concentrated *in vacuo*. The crude product mixture was purified by flash chromatography gave diol (dr based on ^{1}H NMR of crude product mixture).



147

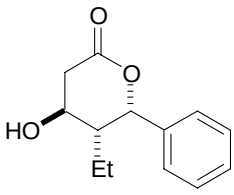
3-Hydroxy-4-(hydroxy-phenyl-methyl)-hexanoic acid tert-butyl ester 147: The general procedure G was followed employing 29 mg of β-keto ester (0.10 mmol) and 20.5 mg (0.15 mmol) of $ZnCl_2$ and 11.3 mg (0.30 mmol) of $NaBH_4$. Purification by flash chromatography (16% ethyl acetate in hexane) gave 19.5 mg (67%) of the title compound (8:1 dr). IR (thin film): 3427(br), 1720 cm^{-1}; $[\alpha]_D$ −26.3 (*c* 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45-7.41 (m, 5H), 5.19 (s, 1H), 4.46 (dq, J = 12.5, 2.6 Hz, 1H), 3.67 (d, J = 2.3 Hz, 1H), 3.36 (d, J = 2.0 Hz, 1H), 2.70 (dd, J = 16.5, 10.0 Hz, 1H), 2.48 (dd, J = 16.5, 3.0 Hz, 1H), 1.67-1.60 (m, 2H), 1.56 (s, 9H), 0.74 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 143.5, 128.1, 126.9, 125.6, 81.5, 71.9, 51.3(2C), 40.3, 28.1, 14.7, 14.6; HRMS (*EI*) *m/z* calcd for (M^+) $C_{17}H_{26}O_4$: 294.1831; found:294.1844.



R$_1$ = Me, Et; R = Ph, CH$_2$CH$_2$Ph

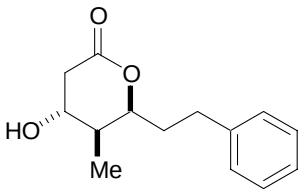
General Procedure H for cyclization of diol: The diol was dissolved in methylene chloride and anisole (0.1 M, 5: 1 CH_2Cl_2: anisole) and the solution was cooled down to 0 °C and TFA (2 mL/mmol diol) was added dropwise, then the resulting mixture was stirred at 0 °C for 2

h. The mixture was concentrated in *vacuo* and purified by flash chromatography gave β-hydroxyl-δ-lactone (dr based on ^{1}H NMR of crude product mixture).



148

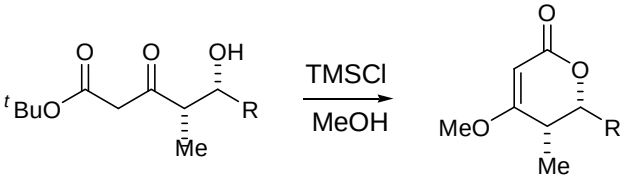
5-Ethyl-4-hydroxy-6-phenyl-tetrahydro-pyran-2-one 148: The general procedure H was followed employing 18.2 mg of diol (0.062 mmol) and 0.12 mL of TFA. Purification by flash chromatography (50% ethyl acetate in hexane) gave 11.5 mg (84%) of the title compound (>9:1 dr). IR (thin film): 3434, 1716 cm^{-1}; $[\alpha]_D$ −16.4 (*c* 0.84, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.30 (m, 5H), 5.97 (d, J = 2.8, Hz, 1H), 4.37-4.32 (m, 1H), 2.92 (dd, J = 18.4, 5.4 Hz, 1H), 2.71 (dd, J = 18.3, 3.0 Hz, 1H), 2.63 (br, 1H), 2.02-1.95 (m, 1H), 1.33-1.24 (m, 1H), 1.12-1.02 (m, 1H), 0.76 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 137.6, 128.4, 127.6, 125.4, 78.7, 65.6, 47.1, 35.9, 17.4, 11.6; HRMS (*EI*) *m/z* calcd for (M^+) $C_{13}H_{16}O_3$: 220.1099; found:220.1099.



149

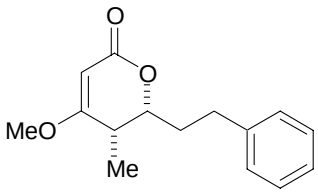
4-Hydroxy-5-methyl-6-phenethyl-tetrahydro-pyran-2-one 149: The general procedure H was followed employing 15.4 mg of diol (0.050 mmol) and 0.10 mL of TFA. Purification by flash chromatography (55% ethyl acetate in hexane) gave 8.6 mg (74%) of the title compound (>9:1 dr). IR (thin film): 3433(br), 1714 cm^{-1}; $[\alpha]_D$ +21.5 (*c* 0.75, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.19 (m, 5H), 4.74 (ddd, J = 9.5, 3.9, 2.9 Hz, 1H), 4.05 (dt, J = 5.4, 3.4 Hz, 1H), 2.93 (ddd, J = 15.0, 10.2, 5.2 Hz, 1H), 2.83 (dd, J = 18.3, 5.4 Hz, 1H), 2.71 (ddd, J = 13.8, 9.7, 6.7 Hz, 1H), 2.56 (dd, J = 18.2, 3.2 Hz, 1H), 2.15 (br, 1H), 2.13-2.03 (m, 1H), 1.98-1.90 (m, 1H), 1.84-1.74 (m, 1H), 0.97 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

170.3, 141.1, 128.5, 128.4, 126.1, 77.3, 68.7, 37.7, 35.9, 33.8, 31.8, 10.4; HRMS (*ESI*) *m/z* calcd for (M^++Na) $C_{14}H_{18}O_3Na$: 257.1154; found:257.1136.



R = CH_2CH_2Ph, Ph

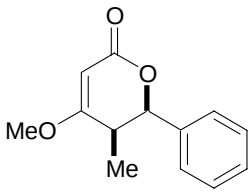
General Procedure I for TMSCl mediated β-methoxy-δ-lactone formation:[85] To a solution of β-keto ester (0.10 mmol) in 1.0 mL CH_2Cl_2 at –78 °C was slowly added MeOH (30 eq) and TMSCl (4 eq) consecutively, The resulting mixture was warmed up to 0 °C and stirred for overnight (about 16 h), then the reaction mixture was quenched by slowly adding saturated aqueous $NaHCO_3$ solution, the mixture was extracted by CH_2Cl_2 (3 x 30 mL). The organic layer was washed by brine and dried over Na_2SO_4 and concentrated *in vacuo*. The crude product mixture was purified by flash chromatography gave β-methoxy-δ-lactone.



150

4-Methoxy-5-methyl-6-phenethyl-5,6-dihydro-pyran-2-one 150: The general procedure I was followed employing 30.6 mg of β-keto ester (0.10 mmol), 121 uL of MeOH (3.0 mmol) and 50.6 uL of TMSCl (0.40 mmol). Purification by flash chromatography (20% ethyl acetate in hexane) gave 16 mg (65%) of the title compound. IR (thin film): 1713, 1622 cm^{-1}; $[\alpha]_D$ −86.8 (*c* 0.49, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.27 (m, 5H), 5.15 (s, 1H), 4.42 (dt, J = 9.2, 3.9 Hz, 1H), 3.80 (s, 3H), 2.99 (ddd, J = 14.4, 9.5, 5.4 Hz, 1H), 2.85-2.73 (m, 1H), 2.36 (qd, J = 7.1, 3.2 Hz, 1H), 2.29-2.15 (m, 1H), 1.91-1.78 (m, 1H), 1.22 (d, J = 7.1 Hz,

3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 167.2, 140.9, 128.52, 128.47, 126.1, 89.3, 77.2, 56.1, 36.4, 32.8, 31.4, 10.8 ; HRMS (*EI*) *m/z* calcd for (M^+) $C_{15}H_{18}O_3$: 246.1256; found: 246.1255.



151

4-Methoxy-5-methyl-6-phenyl-5,6-dihydro-pyran-2-one 151: The general procedure I was followed employing 42 mg of β-keto ester (0.151 mmol), 183 uL of MeOH (4.53 mmol) and 76.4 uL of TMSCl (0.604 mmol). Purification by flash chromatography (33% ethyl acetate in hexane) gave 28 mg (85%) of the title compound. IR (thin film): 1713, 1624 cm^{-1}; $[\alpha]_D$ +331 (*c* 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.27 (m, 5H), 5.56 (d, J = 3.4 Hz, 1H), 5.19 (s, 1H), 3.79 (s, 3H), 2.58 (qd, J = 7.2, 3.4 Hz, 1H), 0.90 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 166.8, 136.5, 128.4, 127.9, 125.6, 89.3, 79.5, 56.2, 38.6, 11.3; HRMS (*ESI*) *m/z* calcd for (M^++Na) $C_{13}H_{14}O_3Na$: 241.0841; found: 241.0850.

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